A study of frailty, falls, bone mineral density and fractures among HIV-positive and HIV-negative controls in England and Ireland, the POPPY study

THESIS

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Declaration

I, Emmanouil Bagkeris, confirm that the work presented in this thesis is my own. When information has been derived from other sources, I confirm that this has been indicated in the thesis.

Acknowledgments

I would like to dedicate this work to my niece Zenia and my nephew Antonis with the hope that they will get the inspiration to strive and work hard to achieve big goals in their lives.

This work would not be possible without the support of my family, my good friends and of course my partner Austen. From the beginning of this long journey in 2016 until its end in 2020 I have been blessed to have met great people that have helped me and inspired me to complete this task. I want to deeply thank Claire Thorne, Mario Cortina Borja, Angie Wade, and Deborah Ridout and Tim Cole that helped to start this PhD and always stood by me at the beginning of my career in the UK. I owe a lot to my primary supervisor Caroline Sabin for being such a great inspiration and my secondary supervisor Paddy Mallon for his support. I want to thank Ioannis Tsakiris for his financial advice and my office colleagues for having such a smooth and pleasant 3.5 years in the "almost devil" 667 office. Davide De Francesco, Milensu Shanyinde, Ada Miltz, Helen Mebrahtu, Kathryn Roberts, Reynie Purnama, Sophia Rein, Kasonde Mwaba you have been great office buddies. I want to also thank the rest of the people (students and staff) from the Royal Free campus for their support and friendship.

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I could not have this thesis completed without the help of all my good friends and colleagues that devoted time to read and comment on chapters of my thesis. Thank you, Pantos and Konstantina Yantsides, Alison Rodger, Amanda Mocroft, Sanjay Bhagani, Colette Smith, Marina Daskalopoulou, Hajra Okhai, Eirini Koutoumanou, Jane Ahn, Claire Townsend, Anna Pearce, Arturo Gonzalez-Izquierdo and Katie Harron.

Abstract

Effective antiretroviral therapy (ART) has prolonged life expectancy among people living with HIV (PLWH) in most parts of Europe, but as PLWH are ageing, this group is now starting to experience signs of compromised health, with particular concerns around possible increased rates of frailty, falls and fractures.

In this thesis I use data from the Pharmacokinetic and Clinical Observations in People Over Fifty (POPPY) study (699 older (≥50 years) PLWH, 374 younger (<50 years) PLWH and 304 HIV-negative controls (≥50 years)) to examine some of the challenges of ageing in PLWH in England and Ireland. In particular, I investigate frailty, falls, bone mineral density (BMD), fractures and fracture (hip and major-osteoporotic) risk among PLWH and HIV-negative controls, and examine their associations with demographic, clinical, lifestyle and HIV-specific factors.

Results highlight that older PLWH experience increased frailty, a higher prevalence of falls and a greater loss of BMD than younger PLWH and similarly-aged HIV-negative controls. Furthermore, this thesis highlights the importance of demographic characteristics, lifestyle traits, depressive symptoms, physical functioning and HIV-specific factors for the development of frailty, falls and low BMD in PLWH.

Among PLWH, I also explore whether the effect of age on the prevalence of frailty could be explained by the effect of HIV parameters by investigating the association of HIV-specific parameters with each of the outcomes considered. Finally, I explore the link between pharmacokinetic (PK) parameters of commonly used nucleoside reverse transcriptase inhibitors (NRTIs) with BMD and with the 10-year probability of fracture.

This thesis identified groups at heightened risk for frailty, falls and low BMD, fractures and fracture risk experiencing poor health outcomes against the backdrop of overall improvement of life span among PLWH and aims to inform policy for optimising treatment, tailored to the needs of this population.

Impact statement

Findings of this thesis provide identification of avoidable risk factors to promote a healthier ageing and enhance the quality of life among PLWH who are at risk for frailty, falls, low BMD and fractures. Both the clinical and the research settings may benefit from utilising findings from this thesis. The findings can impact on the future development of sensitive frailty tools for the early identification of people at risk of decreased physical functioning and the improvement of healthcare services. This can lead to updating guidelines and strategies to prevent the development of frailty. Similarly, the identification of risk factors for falls and fractures can navigate the direction towards the clinical practice should shift to early identify individuals at risk and aid the development of interventions aiming to secure a healthier ageing among PLWH.

The research settings may also benefit from the findings of this thesis by evaluating the four definitions of frailty and the two definitions of fracture risk scores presented and by examining their advantages and disadvantages in resource limited settings. Further, the identification of risk factors for falls and fractures can facilitate an early diagnosis for better monitoring of those at risk. The comparison of all findings between PLWH and HIV-negative controls helped to confirm existing knowledge and highlighted evidence concerning the role of HIV among the ageing cohort. The findings from the work on BMD may be used to identify HIV-associated risk factors for low BMD. In particular, the findings regarding the association of PK parameters of HIV treatment with bone demineralisation highlights the importance of revising the routinely used regimens and explore their potential interaction with treatments for non-communicable diseases in the cohort of ageing PLWH.

During this research, I was involved in delivering talks within the wider study team including study participants which enabled an effective two-way communication to better understand their needs and concerns. I also attended two international conferences presenting my work and I authored and co-authored a number of publications in subjects related to several aspects of the HIV and ageing which highlighted the importance of disseminate recommendations to a cohort that is predicted to increase significantly in the following years.

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Abbreviations

A&E	Accident & Emergency
AIDS	Acquired Immunodeficiency Syndrome
ART	Antiretroviral therapy
ADL	Activities of daily living
aFRP	Adapted frailty-related phenotype
ATZ	Atazanavir
$AUC_{0\text{-}24h}$	Area under the curve during 24 hours
AZT	Zidovudine
BHIVA	British HIV association
BIC	Bictegravir
BMC	Bone mineral content
BMD	Bone mineral density
BMI	Body mass index
BUA	Broadband ultrasound attenuation
CDC	Centers for Disease Control and Prevention
cART	Combination antiretroviral therapy
CRBRS	Crichton Royal Behavioural Rating Scale
CIND	Chronic Immunological and Neurological Disease
CRP	C-reactive protein
CHS	Cardiovascular Health Study
CNS	Central nervous system
CVD	Cardiovascular disease
CWH	Chelsea and Westminster Hospital
CES-D	Center for Epidemiological Studies Depression
C_{max}	Maximum concentration
C_{min}	Trough concentration
CL_{24h}	Clearance over 24 hours
COBI	Cobicistat
COPD	Chronic obstructive pulmonary disease
CSV	Comma-separated values
ddC	Zalcitabine
DEXA	Dual-energy X-ray absorptiometry
DRV	Darunavir
DUH	Dublin University Hospital
DMP	Data Management Plan
DTG	Dolutegravir
d4T	Stavudine
EFV	Efavirenz
ETR	Etravirine
eCRF	Electronic case report form
FDA	Food and Drug Administration
FFP	Fried's frailty phenotype
FIR	Fracture incidence rate
FN	Femoral neck
FRAMO	Fracture and Mortality index

FRC	Fracture Risk Calculator
FRISC	Fracture and Immobilization Score
FRISK	Fracture Risk score
FS	Femoral shaft
FTC	Emtricitabine
GSS	Geriatric status scale
GP	General practitioner
HR	Hazard ratio
HU	Hounsfield units
HCV	Hepatitis C virus
HUH	Homerton University Hospital
HIV	Human Immunodeficiency Virus
IL	Interleukin
IADL	Instrumental activities of daily living
IBS	Irritable bowel syndrome
ICD9	International Classification of Diseases version 9
ICTU	Imperial College Clinical Trials Unit
ICH-GCP	International Conference on Harmonisation-Good Clinical Practice
IHD	Ischaemic heart disease
INSTI	Integrase Strand Transfer Inhibitors
IQR	Interquartile range
IRR	Incidence rate ratio
ITM	Integrated Trial Management
KCH	Kings College Hospital
KS	Kaposi's Sarcoma
LS	lumbar spine
LLQ	Limit of quantification
L_1	First lumbar vertebra
LPV	Lopinavir
MI	Myocardial infarction
MSM	Men who have sex with men
MeSH	Medical subject headings
MHMC	Modena HIV Metabolic Clinic cohort
MMC	Mortimer Market Centre
MDMA	Methylenedioxymethamphetamine
MCAR	Missing completely at random
MAR	Missing at random
MNAR	Missing not at random
MACS	Multicenter AIDS Cohort Study
NRTI	Nucleoside Reverse Transcriptase Inhibitor
NSAIDs	Non-steroidal anti-inflammatory drugs
OR	Odds ratio
OFV	Objective function value
PHE	Public Health England
PI	Protease inhibitor
POPPY	Pharmacokinetic and clinical Observations in PeoPle over fiftY
PK	Pharmacokinetic
PMG	Project management group

PHQ-9	Patient Health Questionnaire
PPI	patients and public involvement
PPT	Physical Performance Test
PLWH	People living with HIV
pRR	Pooled rate ratio
QUS	Quantitative ultrasound
RANKL	Receptor activator of nuclear factor kappa-B ligand
RFH	Royal Free Hospital
RNA	Ribonucleic acid
RR	Rate ratio
RTG	Raltegravir
RTV	Ritonavir
RPV	Rilpivirine
RSH	Royal Sussex County Hospital
SAEs	Serious adverse events
SD	Standard deviation
SFS	Secure File Sharing
SF-36	36-Item Short Form Survey Instrument
SMH	St Marys Hospital London
SOF	Study of Osteoporotic Fractures
SOP	Standard operating procedure
SPPB	Short Physical Performance Battery
SSRI	Selective serotonin reuptake inhibitors
STDs	Sexually transmitted diseases
TMG	Team management group
TDF	Tenofovir disoproxil fumarate
TNFα	Tumour necrosis factor
Tregs	CD4+ T regulatory cells
TBS	Trabecular bone score
TH	Total hip
TB	Tuberculosis
UK CHIC	UK Collaborative HIV Cohort
VACS	Veterans Aging Cohort Study
VAT	Visceral adipose tissue
VIF	Variance inflation factor
VL	Viral load
WT	Ward trochanter
WHI	Women's Health Initiative
WHO	World Health Organisation
3TC	Lamivudine

Chapter 1 Introduction

1.1 HIV epidemic

On 5 June 1981 the United States (US) Centers for Disease Control and Prevention (CDC) reported 5 cases of a rare lung infection among young, white, previously healthy gay men in Los Angeles (1). On the same day CDC New York released a report on a case cluster of a rare and aggressive cancer, Kaposi's Sarcoma (KS), among gay men (2). Cases of these lung infections and KS continued to be reported in the following years. The CDC coined the term Acquired Immunodeficiency Syndrome (AIDS) in 1982 describing it as: "A disease at least moderately predictive of a defect in cell-mediated immunity, occurring in a person with no known cause for diminished resistance to that disease" (3). At the beginning of the epidemic, HIV infection was, in effect, a death sentence with survival as low as a few months after diagnosis. The fear of stigma resulted in low levels of testing, which allowed the epidemic to spread. By the mid-1980s, AIDS cases had been reported all over the world. Currently the number of people with HIV/AIDS according to the 2019 Joint United Nations Programme on HIV/AIDS (UNAIDS) was estimated to be 38 million of which 36.2 million were adults (4).

There are four primary routes of transmission of the Human Immunodeficiency Virus (HIV): sexual contact, vertical transmission from mother to child at birth or via breastfeeding, needle sharing and exposure to infected blood/blood products. Historically, it is believed that the HIV epidemic was introduced to humans through direct blood transmission from hunting infected macaque species; however, this accounted for only a few infections (5). The rapid mobility of human populations, the practice of needle sharing and the sexual transmission have significantly contributed to the proliferation of HIV infections globally. As HIV exhibits a long latent non-symptomatic period, its transmission remains undetected for years.

1.2 HIV treatment

Antiretroviral (ART) medication has dramatically improved the lives of people living with HIV PLWH (6). Historically, zidovudine (AZT) was the first HIV treatment approved by the Food and Drug Administration (FDA) in 1987. Although there was a

statistically significant drop in mortality rates following introduction of AZT, many treated with AZT experienced severe side effects after starting treatment (7-11).

ART drugs are divided into several classes based on which part of the cycle of life of HIV they interrupt, (12). After the approval of AZT, three other similar ART drugs were introduced, namely didanosine (ddI) in 1991, zalcitabine (ddC) in 1992 and stavudine (d4T) in 1994. Together these comprise the first approved drugs from the nucleoside reverse transcriptase inhibitors (NRTIs) class (12). At the time, NRTIs were taken either alone or in combination with drugs from at least one other class while now they are taken in combination with drugs from another class.

In 1995 saquinavir (SQV) was the first drug from the protease inhibitor (PI) class to be approved by the FDA (13). Drugs in this class interrupt the HIV life cycle by blocking the action of an enzyme (protease) that is important for HIV replication.

In 1996 a new class of ART was introduced that targets the reverse transcription step of the HIV life cycle, namely the non-nucleoside reverse transcriptase inhibitors (NNRTI). The first NNRTI drug to be approved by the FDA was nevirapine (NVP). In subsequent years two new classes of drugs were developed and several drugs were approved by the FDA for all classes, described chronologically within each drug class in Box 1.

The combined use of drugs from two or more different drug classes has been proven to offer important benefits for PLWH (14). Initially these regimens were referred to as combination antiretroviral therapy (cART) or highly active antiretroviral therapy (HAART), to differentiate them from the mono-/dual therapy regimens that had been used prior to 1996. However, the term ART is now currently used to refer to any combination of antiretroviral treatment. Many trials have been conducted to explore the most effective combinations to treat HIV (15). Several drugs have been combined into a single tablet, allowing a reduction in the pill burden with the aim of enhancing treatment adherence among PLWH (16, 17). However, several initially approved drugs were later found to cause severe side effects, be toxic or ineffective. This was either due to high dosage (18, 19) or low efficacy that led to long-term harms such as toxicity of the liver, central nervous system, and bone, and/or changes in physical

appearance. The need for alternative drugs became essential and has led to the ongoing development of drugs with improved toxicity profiles or efficacy (9, 10, 13).

The advancement of ART has reduced drug-toxicity problems and has dramatically improved the life expectancy of PLWH, such that it now has almost reached that of those living without HIV. Among those on effective ART 85-90% have been reported to achieve an undetectable viral load (VL) with ≤50 copies/mL within 6 months after ART initiation (20). Recent studies from 2017 have shown that treated PLWH with an undetectable VL cannot transmit HIV to a partner during sex. The current consensus is that "U=U" which means that those who have an undetectable VL are untransmittable as they are not able to transmit the virus (21-23). As a result, HIV is now considered by many to be a chronic disease with some researchers already starting to discuss the end of AIDS (24).

Box 1: Classes and individual antiretroviral drugs by year of approval by FDA

Class	Drug	Year approved
Nucleoside reverse-transcriptase inhibitors (NRTIs)	Zidovudine (AZT)	1987
	Didanosine (ddI)	1991
	Zalcitabine (ddC)	1992
	Stavudine (d4T)	1994
	Lamivudine (3TC)	1995
	Abacavir (ABC)	1998
	Tenofovir disoproxil fumarate (TDF)	2001
	Emtricitabine (FTC)	2003
	Tenofovir alafenamide fumarate (TAF)	2016
Protease Inhibitors (PIs)	Saquinavir hard gel (SQV)	1995
	Indinavir (IDV)	1996
	Ritonavir (RTV)	1996
	Saquinavir soft gel	1997
	Nelfinavir (NFV)	1997
	Amprenavir (APV)	1999
	Lopinavir/Ritonavir (LOP/RTV)	2000
	Atazanavir (ATV)	2003
	Fosamprenavir (fAPV)	2003
	Tipranavir (TPV)	2005
	Darunavir (DRV)	2007
Non-nucleoside reverse transcriptase inhibitors (NNRTIs)	Nevirapine (NVP)	1996
	Efavirenz (EFV)	1998
	Etravirine (ETR)	2008

Class	Drug	Year approved
	Rilpivirine (RPV)	2011
	Doravirine (DOR)	2018
Fusion/entry inhibitors	Enfuvirtide (T20)	2003
	Maraviroc (MVC)	2007
Integrase Inhibitors (INSTIs)	Raltegravir (RAL)	2007
	Elvitegravir (ETG)	2012*/2014**
	Dolutegravir (DTG)	2013
	Bictegravir (BIC)	2018
*As part of co-formulated single-table regimen Stribild **As a single pill formulation, administered with pharmacokinetic enhancer such as cobicistat or ritonavir		

1.3 Ageing among PLWH

Current estimates suggest that the number of PLWH over the age of 50 is 4 million globally. Over the following years this is expected to increase dramatically and possibly double in some cases (25-27) considering the access to effective cART in resource-rich settings. The 2018 report from Public Health England (PHE) estimates that the number of PLWH in the UK is 96,142 of which 97% (93,384/96,142) were receiving treatment, 69% (66,257/96,142) were male and 31% (29,712/96,142) were female (28). The increase in the number of older PLWH is due to two main reasons: 1. successful antiretroviral treatment (24, 29); and 2. increased HIV acquisition later in life (30-34).

Between 2004 and 2015 in sixteen countries within Europe (Belgium, Bulgaria, Czech Republic, Estonia, Germany, Greece, Hungary, Ireland, Latvia, Lithuania, Malta, Norway, Poland, Romania, Slovakia and the UK) the rate of new HIV diagnoses among those aged 50 years and older increased significantly (31) (Figure 1.1). Modelling studies suggest that the life expectancy of HIV positive men who have sex with men (MSM) in high-income countries with extensive access to ART and HIV care is 75 years (35, 36) while recent cohort studies in the UK (37) and the USA (38) have confirmed that successfully treated PLWH have near-normal life expectancy.

Life expectancy among PLWH in the UK has increased by about 10 years since the introduction of effective ART (6). Data from the UK Collaborative HIV Cohort (UK CHIC) Study have suggested that life expectancy at the age of 20 has increased from

30 (estimate for the period 1996-1999) to 46 years (estimate for the period 2006-2008) (39). Furthermore, PLWH with good responses to their initial HIV treatment have been found to have a better life expectancy than people in the general population (37).

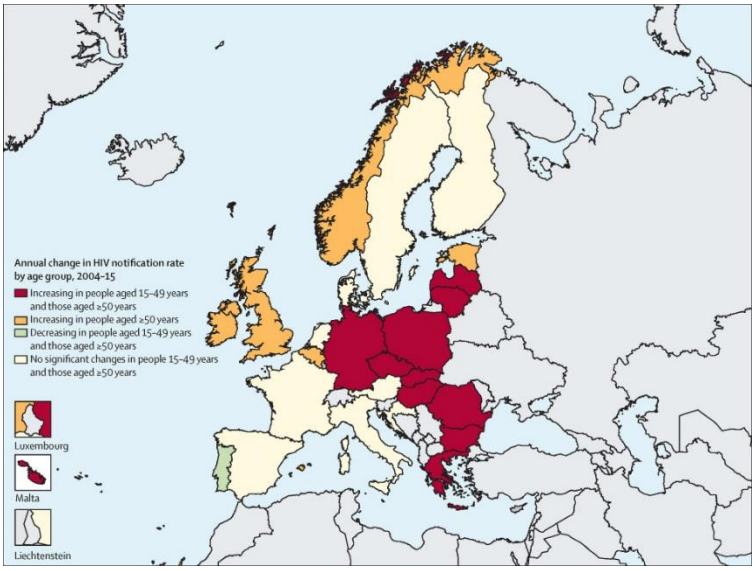


Figure 1.1: Average annual percentage change in new HIV diagnoses in people aged 50 years or older in the European Union and European Economic Area, 2004–15, taken from Tavoschi *et al.* (31)

The population of those receiving care for HIV aged below the age of 50 has been fairly stable over the last 9 years (2008-2017). However, the proportion of those receiving care for HIV who are aged 50 years and above has dramatically increased from 6% in 2008 to 34% in 2015 to 39% in 2017 (Figure 1.2). In Ireland, according to the latest annual epidemiological report in 2018, the cohort of those receiving care for HIV who are aged 50 years and older is reported to have increased from 7.1% in 2015 to 7.8% in 2016 and 13.8% in 2018 (40).

It is estimated that by 2020, 21% of PLWH globally will be over the age of 50 years (41). In developed countries such as the USA, the proportion is estimated to be 50% and is expected to rise to 70% by 2030 (42). This increased life span among PLWH has revealed some new age-related diseases (43), including cardiovascular, hepatic, and metabolic complications (44). Recent evidence suggests that cardiovascular (45, 46), neurocognitive (47), oncological (48), renal (49) and osteoporotic diseases (50) are associated with elevated rates of inflammation seen in PLWH, even if their VL is

suppressed and CD4 counts are preserved (51). These conditions present significant challenges with a detrimental effect on the quality of life of older PLWH and are reported to increase exponentially with age (52-55).

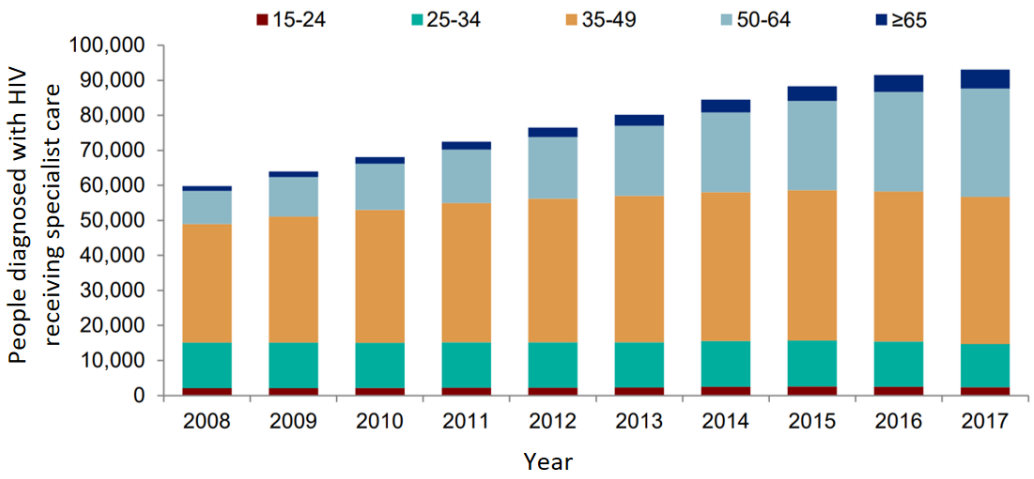


Figure 1.2: Data for the use of HIV-healthcare in the UK stratified by age between 2008-2017, taken from the 2018 report of PHE (56)

1.4 Bone health among PLWH

It has been long debated whether PLWH experience an accelerated ageing process (57). As the epidemiology of HIV changes, the healthcare priorities have shifted from treating opportunistic infections and preventing the development of AIDS-defining illnesses to treating the long-term effects of HIV and ART (38). It is predicted that by 2030, 84% of PLWH over the age of 50 will have at least one non-communicable disease and 20% will be taking 3 or more co-medications (43) and this is an estimate that is almost double compared to the prevalence of 42.2% of one or more comorbidities reported in the general population of Scotland (58) and the prevalence of 54.7% of more than 3 comorbidities reported in the general population of Australia (59).

One prevalent clinical condition observed among the population of ageing PLWH is compromised bone health, the mechanisms of which are more complex as compared to the general population and are still not fully understood. Early diagnosis of bone demineralisation is key considering the effect that low bone mass may have on

quality of life, physical functioning, and metal health (60-62). HIV-induced and ART-induced hormonal imbalances in PLWH, such as lower oestrogen, lower testosterone or high thyroxine, have been associated with higher bone metabolism (63). Poor diet, smoking, alcohol and recreational drug use and a sedentary lifestyle lead to a greater risk for compromised bone health (64). Furthermore, among PLWH use of glucocorticoids, family history of osteoporosis and history of parental hip fracture are all risk factors for poor bone turnover (65-68). In addition to the traditional risk factors for poor bone health among PLWH, ART, HIV-specific factors and increased HIV-induced inflammation have been reported to have a significant effect on bone health causing signs of frailty, increased prevalence of falls and loss of bone mineral density (BMD) which subsequently results in osteopenia, osteoporosis and the increased likelihood of fractures (69-71). Osteoclasts and osteoblasts are types of bone cells that are responsible for the maintenance, repair, and remodelling of bones. The role of osteoclasts is to resorb aged bone cells and the role of osteoblasts is to formulate new bone cells (72). An expression of HIV-induced inflammation is an elevation of cytokines of tumour necrosis factor alpha (TNFα) and interleukins (Il-1 and Il-6), which all have been associated with the activation of osteoclast and bone resorption by activating proteins such as the receptor activator of nuclear factor kappa-B ligand (RANKL) (73).

In addition to the HIV-induced chronic inflammation that has been reported to persist after initiation of ART and after achieving viral suppression (73), HIV viral proteins such as gp120 and p55gag (74) and immune system reconstruction, measured by CD4 cell recovery (75), have been associated with markers of bone turnover, calcium disposition and osteoblast function. Finnerty *et al.* have grouped the mechanisms by which HIV affects bone health in three main categories of traditional risk factors (such as female gender, older age, lower physical activity, lower bone acquisition, smoking, alcohol, opiate use, previous fractures and falls), secondary risk factors (such as comorbidities, medications, hypogonadism, malnutrition/low body mass index (BMI), co-infection) and HIV-related factors (such as ART, viral factors, systemic inflammation, ageing and frailty), described in more detail in Figure 1.3.

Early diagnosis of bone loss is crucial for the maintenance of functional status, mobility and a good quality of life among the elderly. Recent evidence suggests that a decline in functional status leads to frailty (76) and that this frailty increases the risk of falls and fractures. In a recent review by Levett *et al.* (77) the prevalence of frailty among PLWH has been reported to range from 5% up to 29%. Thus, understanding the risk factors for increased frailty, increased falls, low BMD and increased fractures is of great importance. Quantifying the scale of problem will inform gerontologists, HIV-consultants, policy makers and PLWH. A good understanding of the risk factors will aid in the development of problem-specific interventions to help maintain good bone health and promote longevity and vitality.

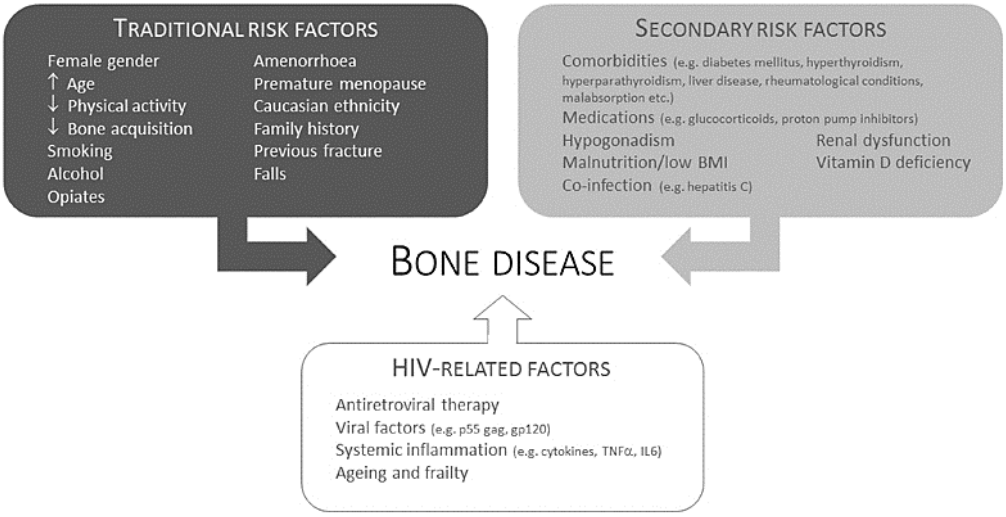


Figure 1.3: Summary of the mechanisms by which HIV impacts adversely on bone health, taken from Finnerty *et al.* (78)

1.5 Aims

The primary aim of this thesis is to assess frailty, falls, BMD, fracture rate and fracture risk among PLWH compared to HIV-negative controls and identify factors that are associated with each outcome.

The secondary aims are to identify the HIV-specific factors that are associated with changes in frailty, falls, BMD, fracture rate and fracture risk and to assess the effect of cART-specific pharmacokinetic (PK) parameters on BMD and fracture risk.

1.5.1 Thesis overview

This thesis explores the relationship between frailty, falls, BMD and fractures in the context of individuals ageing with HIV by comparing a group of older and younger PLWH with a group of HIV-negative controls. Chapter 2 describes the current literature regarding the main outcomes of interest: frailty, falls, BMD and fractures among PLWH and the general population. Chapter 3 describes the methodological approach by describing the study design as well as data management and statistical methodology used in each of the Results chapters. Chapter 4 comprises by two sections; first the description of the characteristics of the POPPY study participants and the association of the characteristics with HIV and the outcome variables of frailty, falls, BMD, fractures and FRAX score and second the method of choosing the factors that confound the association between HIV and the outcomes. Chapters 5-8 are the Results chapters and focus on the four main themes of frailty, falls, BMD and fractures among the POPPY participants in that order. Each Results chapter includes a brief introduction, followed by the chapter hypotheses and objectives, methods of analysis, the results and a short discussion. The closing chapter, Chapter 9, summarises the findings and discusses them in the context of the published literature. It also highlights the strengths and limitations of the research and concludes with recommendations for future studies.

Chapter 2 Literature review

2.1 Methodology of literature review

A separate literature review has been conducted for each of the main topics of frailty, falls, BMD and fractures using the search engine PubMed. The search terms used to identify the relevant literature are listed in Table 2.1. Medical subject headings (MeSH) terms and the option "all fields" were used for each search. The full list of the search results was saved and subsequently scanned for relevant articles. The relevant articles were saved to a reduced list. The abstracts of those articles were reviewed for relevance and the full text of any selected articles were extracted. For the articles where full text was not available, I contacted the corresponding author of the article and requested the full text. When no response was received the results were summarised from the available information in the abstract.

Table 2.1: Terms used for the literature reviews

Topic	Search terms/strategy
Frailty	
General population	("frailty"[MeSH Terms] OR "frailty"[All Fields]) AND definition[All Fields] and ("frailty"[MeSH Terms] OR "frailty"[All Fields]) AND ("aged"[MeSH Terms] OR "aged"[All Fields] OR "elderly"[All Fields])
PLWH	("frailty"[MeSH Terms] OR "frailty"[All Fields]) AND ("hiv"[MeSH Terms] OR "hiv"[All Fields]) and ("hiv"[MeSH Terms] OR "hiv"[All Fields]) AND ("frailty"[MeSH Terms] OR "frailty"[All Fields]) AND ("aging"[MeSH Terms] OR "aging"[All Fields]) AND ("ageing"[MeSH Terms] OR "ageing"[All Fields])
Falls	
General population	("accidental falls"[MeSH Terms] OR ("accidental"[All Fields] AND "falls"[All Fields]) OR "accidental falls"[All Fields] OR "falls"[All Fields]) AND ("aged"[MeSH Terms] OR "aged"[All Fields] OR "elderly"[All Fields])
PLWH	("accidental falls"[MeSH Terms] OR ("accidental"[All Fields] AND "falls"[All Fields]) OR "accidental falls"[All Fields] OR "falls"[All Fields]) AND ("hiv"[MeSH Terms] OR "hiv"[All Fields])
BMD	
General population	(((bmd[All Fields] OR ("bone density"[MeSH Terms] OR ("bone"[All Fields] AND "density"[All Fields]) OR "bone density"[All Fields] OR ("bone"[All Fields] AND "mineral"[All Fields] AND "density"[All Fields]) OR "bone mineral density"[All

Topic	Search terms/strategy
	Fields])) OR ("aging"[MeSH Terms] OR "aging"[All Fields] OR "ageing"[All Fields])) OR ("aged"[MeSH Terms] OR "aged"[All Fields] OR "elderly"[All Fields])) OR ("aging"[MeSH Terms] OR "aging"[All Fields] OR "ageing"[All Fields])
PLWH	BMD[All Fields] AND ("bone density"[MeSH Terms] OR ("bone"[All Fields] AND "density"[All Fields]) OR "bone density"[All Fields] OR ("bone"[All Fields] AND "mineral"[All Fields] AND "density"[All Fields]) OR "bone mineral density"[All Fields]) AND ("hiv"[MeSH Terms] OR "hiv"[All Fields])
Fractures	
General population	("fractures, bone"[MeSH Terms] OR ("fractures"[All Fields] AND "bone"[All Fields]) OR "bone fractures"[All Fields] OR "fractures"[All Fields]) AND ("aged"[MeSH Terms] OR "aged"[All Fields] OR "elderly"[All Fields])
PLWH	("fractures, bone"[MeSH Terms] OR ("fractures"[All Fields] AND "bone"[All Fields]) OR "bone fractures"[All Fields] OR "fractures"[All Fields]) AND ("hiv"[MeSH Terms] OR "hiv"[All Fields])

Conference abstracts that had not yet been published as a peer-reviewed paper were included in the literature review. The literature reviewed is summarised in a narrative format.

2.2 Frailty

2.2.1 What is frailty?

Biological ageing expresses itself in several ways, one of which is frailty. This is a state of decline in general health and physical function which is typically associated with weakness, physical shrinkage, and older age. The frailty process varies by person and by chronological age with various factors, such as weakness and slowness, being responsible for its development; some of these factors are reversible.

2.2.2 Nomenclature and extended definition of frailty

The first publication to use the term “frailty” in its title dates back to 1956 (79) with the concept more elaborately explained by Brocklehurst in 1973 (80), who was the first to introduce the concept of frailty in the elderly. By 1978 the Federal Council on Ageing defined the frail elderly as “persons, usually but not always, over the age of 75, who because of an accumulation of various continuing problems often require one or several supportive services in order to cope with daily life” (81). The WHO has

described frailty as the holy grail of geriatric medicine that results from age-associated declines in physiological reserve (82). Frailty has also been defined as a state of reduced physiologic reserve by Buchner in 1992 (83). Some researchers have characterised frailty as a state that gradually appears after the accumulation of deficits and is described as a dynamic process frequently worsening from mild to severe frailty over time (84).

Components of general health such as medical and functional status, malnutrition, inflammation, muscle mass and endurance, body composition and morphology, gait balance and falls have been related to frailty and have been used in its definition. Other important parameters such as mental health components, psychological variables such as anxiety, cognition and motor processing have also been used as part of the definition of frailty (85-90). Loss of vision, hearing impairment, social withdrawal, increased vulnerability to stressors, accumulation of chronic diseases and increased utilisation of resources (community, hospital, and long-term care institutions) have also been deemed important for the definition of frailty (91-94).

A well established and broadly used definition was introduced by Fried *et al*. in 2001 (95). This is the definition of frailty used in this thesis. More details for the assessment of frailty using this definition are in Section 3.5.1 of Chapter 3. In brief, persons with three or more of the following five conditions were considered to be frail: 1. unintentional weight loss (Baseline: >10 lbs lost unintentionally in prior year); 2. Slowness (Walking time/15 feet: slowest 20% (by gender, height); 3. Weakness (Grip strength: lowest 20% (by gender, BMI); 4. low physical activity (Kcals/week: lowest 20% males:<383 Kcals/week and females: <270 Kcals/week); and 5. Exhaustion (self-report). The study that developed this definition has been characterized as a landmark study by the WHO and has been incorporated in the consortium meeting on “Healthy Ageing” of WHO in 2016 (82). Numerous studies have used this definition to assess frailty and the prevalence of frailty even when it is assessed using the same definition may vary across different studies from 2.5% to 95.3%, Figure 2.1.

Rockwood *et al*. (96) and Bowels *et al*. (97) used some proxy-characteristics involving activities of daily living (ADL) to define a deficit accumulation model of frailty. A

summary assessment of functional status, related to specific health conditions, has also been used to define frailty (98, 99).

Frailty has been considered as an index of "dependency" (100) or a multidimensional concept related to one or more deficits in physical, cognitive, emotional, sensory, or social functioning (100). This has been extended to a model of the sum of diseases and health conditions, including psychiatric conditions, over the lifespan (101) with some researchers choosing from lists of 20 (102), 38 (103), 40 (104, 105) and even 92 deficits (106). This approach calculates a score by dividing the number of deficits that are present by the number of deficits taken into consideration, e.g. a score of 10/20, when a person reports having 10 deficits present of the list of 20 that have been taken into account. Frailty scores such as this have been examined through their relationship to chronological age and associations with mortality. Other definitions involved the utilisation of 10 health domains in order to construct an impairment index (107, 108). Other researchers described frailty as the state when a person experiences reduced ability to carry out the important practical and social ADL (109-111). Some research groups take account of the presence of multiple disease levels when defining frailty (85, 112, 113).

2.2.3 Variability of frailty definition in the general population

Studies that were not able to collect the information suggested by Fried to define frailty, have sometimes tailored the frailty definition to their available information. Grip strength (114, 115) or gait speed (116, 117) have been used as single markers of frailty, as they are considered to be quick, inexpensive and highly reliable measures. Bandeen-Roche *et al*. (118) introduced a definition borrowing some characteristics from Fried's definition. In particular, walking speed, grip strength and weight loss were included, while they added some new characteristics from the Minnesota Leisure Time Activity questionnaire such as walking, doing strenuous household chores, doing strenuous outdoor chores, dancing, bowling and exercise (119). Bond, using the Crichton Royal Behavioural Rating Scale (CRBRS) (120), incorporated components of mobility, ability to dress, ability to bathe, urinary and/or fecal continence, orientation, ability to communicate, ability to cooperate and restlessness

(and agitation) to derive a score (121). Winograd *et al*. (122) extended the spectrum of variables used for the frailty definition using criteria focused on geriatric conditions and ADL. Similarly, Rockwood *et al*. in 1999 (96), suggested a definition based on the classification scheme of the geriatric status scale (GSS) where people were classified at four levels accounting for walking, ability to perform basic ADL (eating, dressing, bathing, bed transfers), continence of bowel and bladder, and cognitive function.

In 2007 Rockwood *et al*. (123) used the deficit accumulation model for the definition of frailty. This method suggests a stochastic mechanism using a modified Poisson model that gives a description of transitions to worse health states, health improvements and mortality. This is expressed as the probability of transitions between *n* (at baseline) and *k* deficits (P_{nk}) and is expressed as:

$$P_{nk} = \frac{\rho_n^k}{k!} \exp(-\rho_n)(1 - P_{nd})$$

Where P_{nd} is the probability of dying between two consecutive scheduled assessments, $\rho_n = \rho_0 + b_1 n$ and $P_{nd} = P_{0d} \exp(b_2 n)$, ρ_0 and P_{0d} are the baseline characteristics and the parameters b_1 and b_2 describe the increment of the expected change in the risk of death given the current number of deficits. The authors reported that an effect of chronological age on developing adverse outcomes could be ruled out after accounting for existing deficits (107, 124-126).

Depending on the index used, the prevalence of frailty in the general population among adults 65 years and older is estimated to be 10.9%–20.3% (127) while a quarter of those aged 85 and above are reported to be frail (128). Frailty appears to be more common among women, those who are socially isolated (103), and those who live in socioeconomically disadvantaged communities (129). Frailty has been characterised as a potentially reversible health status for older adults associated with low body weight, obesity, smoking and depressive symptoms (130, 131).

Although many efforts have been made to define frailty, there is still a lack of consensus in defining it (132-134). Despite the dissimilarities between approaches, researchers agree that early diagnosis of frailty with early intervention protocols such as resistance exercise, aerobic training and training using balance-based wearable

sensor virtual-reality equipment (135-138) can lead to a reversal of its negative outcomes and may improve the quality of life of people at risk.

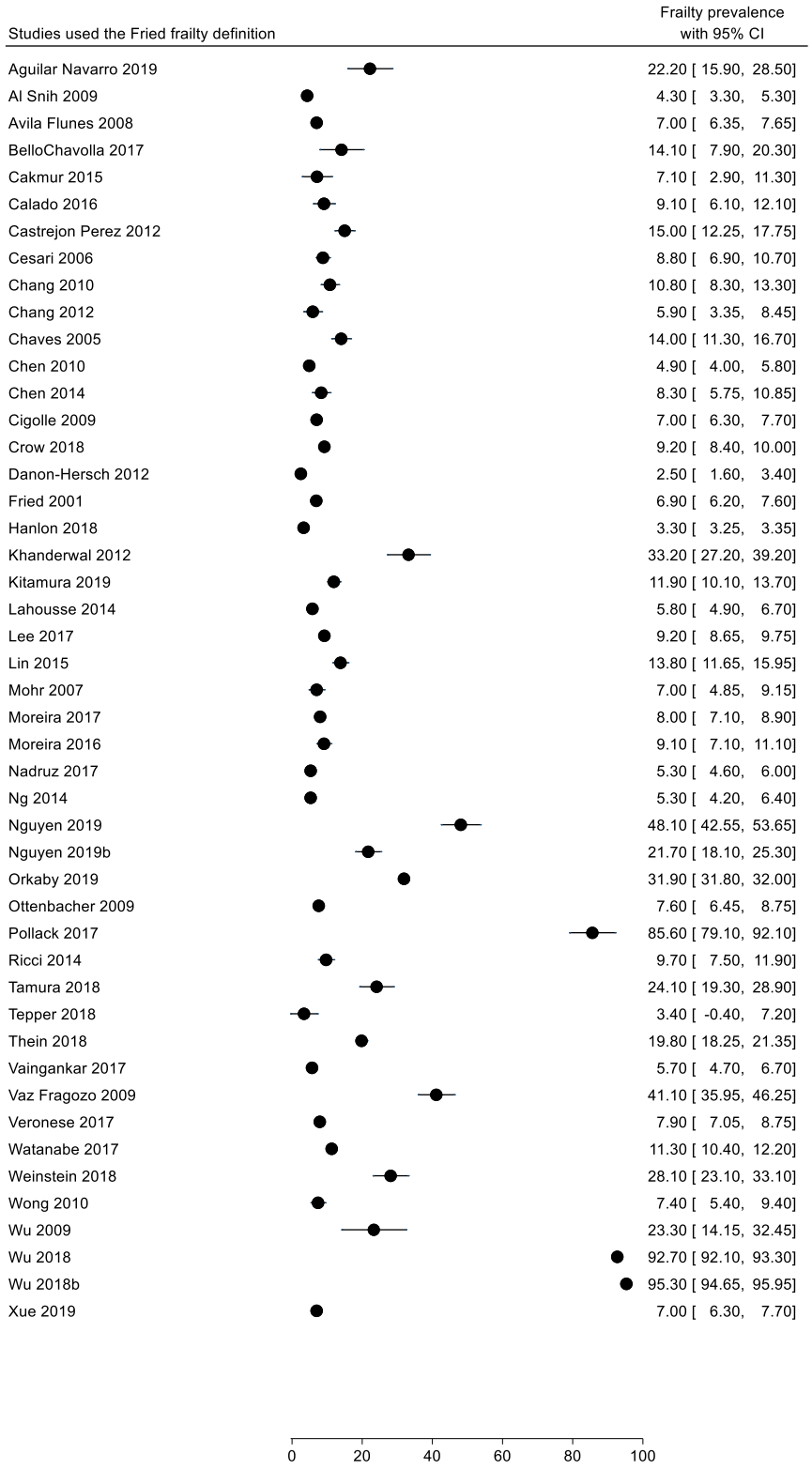


Figure 2.1: Studies that have used the Fried definition for the assessment of frailty in the general population-Details of the studies in Appendix VII

2.2.4 Frailty among PLWH

The improvement of cART has contributed to the longer survival and ageing of PLWH, with a decrease in the rates of AIDS-defining and non-AIDS-defining mortality in high-income countries (139, 140). Effros *et al.* (141) reported that HIV infection may expand morbidity and accelerate the incidence of comorbidities and frailty. Even though frailty may be present in up to half of older adults with HIV (142), it is unclear whether frailty in PLWH follows the same pathways as in the general population (143). Some researchers have referred to frailty as "the silent epidemic" (144) and suggest that among PLWH frailty is likely to develop at earlier ages than in the general population (24, 77, 145-150), especially among those with advanced HIV infection (146, 151-154). However, other researchers suggest that frailty occurs at comparable rates in older individuals with and without HIV (77, 145, 146, 149, 155-164).

There is need for consensus to define frailty among older PLWH given that several measures already exist. Despite the variable measures used to define it, parameters of functional capacity have commonly been used for its definition (165). As in the general population, frailty in PLWH is evident when a threshold of age-related physiological dysregulation is reached, also described as loss of homeostasis (166, 167). The adoption of a universal definition for frailty will allow the comparison of its magnitude across different settings and will enable mapping the barriers for prolonging homeostasis in older age and understanding the key drivers of frailty.

A suspected cause of increased frailty in PLWH is the greater number of comorbidities such as anaemia, cardiovascular disease (CVD), or metabolic abnormalities (147, 148, 167, 168). Frailty may increase with mitochondrial dysfunction, chronic inflammation, and oxidative stress (57). However, some studies have found no evidence of inflammation-associated physical impairment when comparing older PLWH and negative controls when age-related co-morbidities were carefully balanced between the groups (169). The following section outlines the different frailty definitions that have been used in studies in PLWH.

2.2.5 Definitions of frailty in PLWH

A recent review from Piggott *et al.* in 2016 (170) identified nine highly cited frailty instruments with Fried's frailty phenotype and the deficit accumulation index suggested by Mitnitski and Rockwood being the most popular.

2.2.5.1 Deviances from Fried definition in PLWH

In three publications by Desquilbet *et al.* (146, 155, 156), published in 2007, 2009 and 2011 respectively, modified Fried's frailty definitions were assessed in the Multicenter AIDS Cohort Study (MACS). Two studies (146, 156) assessed weakness and slowness using questions on difficulty in walking various distances with frailty being characterised as a participant meeting at least three of the following four components of the definition: physical shrinkage, exhaustion, slowness, and low physical activity level. The third study (155) considered as frail those who responded positively to self-reported questions regarding weight loss, exhaustion, slowness and low physical activity level. This latest frailty definition has also been adopted by Woods *et al.* and Gill *et al.* (84, 130).

Another Fried frailty definition adaptation was suggested by Olsen *et al.* (171). The authors described levels of habitual physical activity and physical capacity in PLWH initiating ART in Ethiopia. Physical capacity was defined in such a way as to share elements with the frailty definition suggested by Fried. It was assessed by grip strength, sleeping heart rate and heart rate economy. The adapted frailty-related phenotype (aFRP) was suggested by Akgun *et al.* (172) where frail individuals were considered to be those participants who satisfied three or more domains of physical shrinkage, exhaustion, slowness and low physical activity. Another adaptation of Fried's frailty definition was suggested by Kooij *et al.* (173) who defined a frail person as one exhibiting at least 3 of the 5 Fried criteria. Whilst similar to the original Fried criteria, slow walking speed and low grip strength were classified by the lowest quintile of the study population rather than using the predefined cut-off as suggested by Fried.

Grip strength has been used by Schrack *et al*. (174) as a single marker of frailty. Grip strength was measured using a Jamar hydraulic hand-held dynamometer. Study

participants were asked to squeeze the dynamometer as hard as they could on three separate occasions using their dominant hand, with a brief recovery between each assessment - an average of the three measures was used for this analysis. Tassiopoulos *et al*., in 2017 (70), assessed frailty using both the Fried definition and also introduced an additional measure for accounting for participants' slowness/gait speed using a binary ≤1 or >1 m/sec criterion. This measure of slowness in PLWH has also been used by Erlandson *et al*. (175) and was initially suggested by Studenski *et al*. (176) for use in the general population of older adults.

2.2.5.2 Fried-modified frailty definitions

Önen *et al*. (160) introduced a definition of frailty based on the presence of low physical activity. In particular, individuals reporting having limited vigorous activities such as running, lifting heavy objects or participating in strenuous sports were characterized as having a low physical activity. Similarly in two publications by Pathai *et al*. (161, 177) a frailty-like definition was used, where weight loss, physical activity and exhaustion were self-reported as suggested by Önen *et al*. (160).

In a small study of 20 participants, Ruiz *et al*. (178) grouped study participants as mildly, moderately and very frail. The categorisation was based on the number of domains that the participants failed during a geriatric screening. The domains assessed were instrumental activities of daily living (IADL), nutrition, cognitive, hearing and visual screening, depression, and mobility problems. Individuals were considered as mildly frail when they failed in one domain only; those classified as moderately frail failed in two domains and those classified as severely frail failed in three or more domains and/or died during the first year of follow up.

Shah *et al*. (150) considered frail participants as those with two or more deficits present and who reported difficulty or need of assistance with one basic ADL (basic self-care tasks) or two or more IADL (slightly more complex skills). The deficits considered were a Physical Performance Test (PPT) score of 18–32 and a VO_{2peak} of 11–18 mL/kg per minute. VO_2 peak is the peak oxygen uptake in the human body during maximum physical effort and was assessed in this study through a graded treadmill walking test. The PPT score was derived by scoring the following nine

activities from 0-4, with scores ranging from 0-36 and 36 being a perfect score: 50-foot walk, putting on and removing a coat, picking up a penny, standing up from a chair, lifting a book, climbing one flight of stairs, progressive Romberg-balance test, climbing four flights of stairs and performing a 360° turn.

Another simple measure of impaired function was suggested by Richert *et al*. (179) who determined impaired function using a sit-to-stand test repeated five times. Erlandson *et al*. (148) assessed frailty as low or high function using a mixture of the Fried definition and the Short Physical Performance Battery (SPPB). Low function was defined as a score of ≥3 on the Fried frailty phenotype or a score of <9 on the SPPB. The SPPB assessed tandem stand, walking speed, and sit-to-stand test time, scoring each from 0 to 4. Tandem stand was measured by the ability to stand heel to toe for 10 seconds, walking speed was assessed by the faster of two 4-minute walks at usual pace, and sit-to-stand test time was assessed by 5 repetitions of going from a seated position to a standing position without use of the arms (180). A score of <9 is highly predictive for subsequent disability and was considered indicative of low functional status; a score of 9–11 points of moderate functional status; and a score of 12 points (no deficits) as high functional status.

A 37-item frailty index was suggested by Guaraldi *et al*. (181). Components of this index included metabolic, hematologic, and coagulation parameters, hepatitis B and C coinfection, polypharmacy, low physical activity, and unemployment. Eight comorbidity variables and then eight additional HIV-related variables were added to this index resulting in 45 and 53-item indices, respectively. Each variable was coded as 1, indicating a health deficit, or 0, indicating no deficit. The index score was then calculated as the proportion of deficits present out of the total number of variables considered. The authors found that the 37-item frailty index was able to predict survival and incident multimorbidity independently of age, behavioural, and HIV-related variables, and the indices with added variables (45 and 53-item) discriminated mortality risk at a similar level to the original index. The 37-item frailty index has also been used by Wallace *et al*. (182).

Finally, the criteria of the Cardiovascular Health Study (CHS) index and the criteria of the Study of Osteoporotic Fractures (SOF) have been used from Bregigeon *et al*. (69) to assess frailty. The CHS index included the same criteria as the Fried frailty definition although different cut-offs were introduced: unintentional weight loss (≥4 kg during the last year), weakness (low grip strength using a hand grip dynamometer (SAEHAN Corporation, Changwon, Korea) by sex and BMI, exhaustion (self-reported on 0–10 scale), slowness (gait speed ≥1 s/m), and low physical activity (≤30 min walking, three times/week); existence of three or more of the above was indicative of frailty. For the SOF index, frailty was defined when two criteria were satisfied. The criteria considered were weight loss, exhaustion ('no' answer to the question 'do you feel full of energy?') and the inability to perform three chair stands (without arm help) in 15 seconds.

2.2.6 The prevalence of frailty among PLWH

In the pre-HAART era the prevalence of frailty was significantly higher compared to that at both the introduction and establishment of HAART (155). In the general population of elderly people it has been reported to increase from 4%-7% at age 65-69 years to 26% at age 85 years and older (128). The picture is different among PLWH where the prevalence has been reported to range from 5% to 20% at median ages between 40 and 50 years. In studies using the Fried frailty definition in PLWH frailty ranged from 6.1% to 20% while in the general population it ranged from 0% to 10% for HIV-negative participants (145, 157, 162, 163, 183-188), Table 2.2. In studies that used a modified Fried definition or introduced their own frailty definition the prevalence ranged from 1.0% to 62.5% (70, 77, 146, 148-150, 155, 156, 160, 161, 172-174, 178, 179, 181, 182). Frailty among men in the USA participating in the MACS was 13.9% (146), while at the Washington University Infectious Diseases Clinics (June 2008 to December 2008) it was 9% (160). Talukdar *et al.* (189), in a cross-sectional study of 567 newly infected PLWH aged 50 years or more at a tertiary care hospital in Kolkata in India (N=567), reported a prevalence of frailty or unexpected weight loss of 31% (142/457) in men and 14% (15/110) in women. No clear definition of frailty was provided in this study with frailty and weight loss being treated as a single entity.

Table 2.2 Description and summary of studies that have explored frailty among people with HIV

First author	Year	Study design	Frailty definition	Predictors of increased frailty	Population characteristics	Frailty prevalence
Desquilbet (146)	2007	Longitudinal	Presence of at least three of the following four components: physical shrinking, exhaustion, slowness, and low physical activity level	Years of HIV infection	2150 men (245 with incident HIV and 1905 HIV-negative) with median age 42 years (IQR) 37–47 years from the MACS in Baltimore, Washington, Chicago, Los Angeles and Pittsburgh	3.4% among 55-year old HV-positive and 3.4% among >65 years HIV-negative
Önen (160)	2009	Longitudinal	Modified Fried's definition	Unemployment, greater number of comorbid conditions and past opportunistic illnesses, higher depression severity score, receipt of antidepressants and lower serum albumin	445 men with HIV, mean age 41.7 years, 71% male, 63% African American with a mean 8.4 years since HIV diagnosis from the MACS in Baltimore/Washington, Chicago, Los Angeles and Pittsburgh	9%
Terzian (163)	2009	Longitudinal	Fried's frailty definition	CD4 count <100 and CD4/CD8 ratio <0.29	Cohort of women (1206 with HIV and 573 HIV-negative) from the WIHS cohort at six sites across five USA cities (Bronx and Brooklyn, NY, Washington, DC, the San Francisco, CA, Bay Area, Los Angeles, CA, and Chicago, IL)	8% among the HIV negative and 12% among the women with HIV with clinical AIDS and 20% in women with HIV with CD4 count <100 cells/mm^3
Desquilbet (155)	2009	Longitudinal	Presence of at least three of the following four self-reported components; Weight loss of at least 10 pounds, exhaustion in performing work or other activities, slowness in walking several blocks, and low physical activity level in performing vigorous activities	Increased age, CD4 count <350 cells/mm^3 and clinical AIDS	1046 men with HIV, 80% white non-Hispanic 52% with education greater than college, followed up for an average 9.2 years from the MACS in Baltimore/Washington, Chicago, Los Angeles and Pittsburgh	7.6% in 1994–1995 (pre cART) and 4.5% in 2000–2005 (cART era)

First author	Year	Study design	Frailty definition	Predictors of increased frailty	Population characteristics	Frailty prevalence
Desquilbet (156)	2011	Longitudinal	Presence of at least three of the following four components: physical shrinking, exhaustion, slowness, and low physical activity level	Frailty phenotype was a predictor of development of AIDS or death in PLWH prior to cART initiation	596 men with HIV, 57% with education greater than college with average age 43 years from the MACS in Baltimore/Washington, Chicago, Los Angeles and Pittsburgh	13.9%
Ruiz (178)	2011	Longitudinal	Frail by counting the number of domains failed during the initial geriatrics screening (ADL, IADL, nutrition, cognitive, hearing and visual screening, depression, and mobility problems). Mildly frail failed only in one domain, moderately frail failed in two domains and severely frail failed in three or more domains and/or died during the first year of follow up	Cognitive impairment, presence of comorbidities, high number of medications used, and history of any opportunistic infection	20 PLWH, 12 male and 8 female, mean age 63.5 years, 17 African American, 2 Caucasian, 1 Hispanic, from the HIV Outpatient Program clinic based at the Medical Center of Louisiana in New Orleans from 2007 to 2009	20% mildly, 50% moderately, and 30% severely frail
Shah (150)	2012	Cross-sectional	Physical Performance Test score of 18–32, VO_{2peak} of 11–18 mL/kg per minute and report of difficulty or need of assistance with two or more IADL or one basic ADL	hypertension, hyperlipidaemia and diabetes	40 PLWH, mean age of 58 years, 27.5% female from the academic hospital-based infectious disease clinic in Rochester NY	62.5%
Richert (179)	2011	Cross-sectional	Five-times sit-to-stand test	Years since HIV diagnosis, low BMI, older age	324 PLWH, Median age 48 years, 80% men and 89% on antiretroviral treatment from the French Agency for AIDS and Hepatitis Research CO3 Aquitaine Cohort	50% reported poor lower limb muscle performance
Ianas (159)	2012	Cross-sectional	Fried's frailty definition	Older age, low CD4 count was significantly associated with frailty in both age groups	100 PLWH, 69% white non-Hispanic, 26% female, 58% <50 years old from the University of Arizona Petersen Clinics	60% of people with CD4 counts of <200 cells/mm^3 aged ≥50 years and 39% of people younger than 50

First author	Year	Study design	Frailty definition	Predictors of increased frailty	Population characteristics	Frailty prevalence
						10% of people with CD4 counts of >350 cells/mm^3 aged ≥50 years and 4% of people younger than 50
Erlandson (157)	2012	Cross-sectional	Fried's frailty definition	Current CD4+ lymphocyte count<200 cells/mm^3, lower VACS Index score and use of NRTIs	359 PLWH, 85% male, mean age 52 years, from the Infectious Diseases Group Practice clinic at the University of Colorado Hospital	7.5%
Erlandson (148)	2013	Nested case-control	High function was defined as the ability to complete a 400m walk and no deficits on either the frailty phenotype or the Short Physical Performance Battery. Low function was defined as a score of ≥3 on the frailty phenotype or a score of <9 on the Short Physical Performance Battery with at least 1 deficit on the opposing test. Moderate function was defined as at least 1 deficit on the frailty phenotype or Short Physical Performance Battery without meeting the definition of low function	Lower proportions of CD4+ T cells, higher proportions of CD8+ T cells, higher CD38/HLA-DR expression, higher CD8+ T cells, and higher IL-6	359, 85% male, mean age 52 years, from the Infectious Diseases Group Practice clinic at the University of Colorado Hospital	9% low functional status, 52% moderate functional status, and 39% high functional status
Rees (190)	2013	Longitudinal	Frail when responding positively to 2 or 3 of the Fried's criteria	low CD4-cell	100 PLWH, 69% white non-Hispanic, 26% female, 58% <50 years old from the University of Arizona Petersen Clinics	20%

First author	Year	Study design	Frailty definition	Predictors of increased frailty	Population characteristics	Frailty prevalence
Sandakovsky (162)	2013	Cross-sectional	Fried's frailty definition	This was a pilot study to cognitive and motor function, overall activity by actigraphy and self-report, emotional wellbeing, sexual function, inflammatory biomarkers, and frailty	41 PLWH, 29.3% female, 68.3% white, 58.5% MSM from a pilot study of younger and older PLWH from the University of Nebraska Medical Center	20% in the older group and 14% in the younger group
Piggott (149)	2013	Longitudinal	Fried frailty definition with an adjustment (weight loss of ≥5% since last visit—greater weight loss than the original criteria)	HIV infection, CD4 count <350 cells/mm^3, detectable HIV ribonucleic acid (RNA), increased comorbidities, low education, non-married marital status, depressive symptoms and prescription drug abuse	1230 participants with 3365 visits (2306 visits among PLWH and 1059 visits from HIV-negative controls, median age 48 years, 29% PLWH, AIDS Linked to the Intra Venous Experience (ALIVE)	12.3%
Pathai (161)	2013	Case-control	Modified Fried frailty definition with weight loss, physical activity and exhaustion being self-reported	HIV infection, older age, female gender, smoking (among seronegative only), lower education and lower BMI Among HIV-positive individuals, age, female gender, multiparity (≥3 children), low BMI, lower socioeconomic status and alcohol consumption	504 participants (248 PLWH and 256 HIV-negative controls), 25.8% male, 15.3% had education <high school, 66.1% single from a community-based HIV treatment centre in Nyanga district of Cape Town in South Africa	19.4%, 95% CI (14.4, 24.3%) for PLWH vs. 13.3%, 95% CI (9.1, 17.5%) for HIV negative; p=0.07 Among PLWH on ART, the prevalence of frailty was 18.0%, 95% CI (13.2, 23.8%)
Guaraldi (181)	2015	Longitudinal	37-item frailty index that includes metabolic, hematologic, and coagulation parameters, hepatitis B	Frailty index scores increased 0.4% with each year of age	2720 PLWH, mean age 46 years, 32% women from northern Italy, the Modena HIV Metabolic Clinic	Frailty expressed as an index

First author	Year	Study design	Frailty definition	Predictors of increased frailty	Population characteristics	Frailty prevalence
			and C status, polypharmacy, low physical activity, and unemployment		(MHMC) cohort that included visits from June 2003 to July 2014	
Young (188)	2016	Longitudinal	Fried's frailty definition	Total body fat and HIV infection	61 PLWH and 27 HIV-negative, Hispanic and African American postmenopausal women between 2002 and 2007. Columbia University Medical Center, USA	11.5% HIV-positive and 0% in HIV-negative
Akgun (172)	2016	Cross-sectional	Adapted frailty-related phenotype (aFRP) (frail if three domains are satisfied from physical shrinking, exhaustion, slowness and low physical activity). Participants with one/two domains were classified as prefrail	Chronic obstructive pulmonary disease (COPD) and depression were associated with increased frailty. Hypertension, renal disease and congestive heart failure were associated with pre-frailty. Within HIV-positive group, CD4 cell count less than 50 cells/mm^3, and HIV RNA>400 copies/mL had increased risk for frailty.	3472 PLWH and 3043 HIV-negative from the Veterans Aging Cohort Study (VACS) between 2002 and 2012, USA	The prevalence of prefrail in HIV-positive was 32.2%, and 33.0% in HIV-negative. The prevalence of frailty was 3.0% and 2.6%, for positive and negative respectively.
Kooij (173)	2016	Longitudinal	Modified Fried frailty definition: Slow walking speed and low grip strength were classified by the per stratum lowest quintile of the study population rather than using the predefined cut-offs based on per stratum lowest quintiles in a population of elderly individuals	HIV infection, depressive symptoms and BMI<20kg/m^2 for the HIV-positive group	521 PLWH and 513 HIV-negative individuals aged at least 45, from the AGEhIV Cohort Study at the HIV outpatient clinic of the Academic Medical Center, in Amsterdam, Netherlands	Prevalence of frailty was significantly higher in HIV-positive individuals vs. HIV-negative (10.6 versus 2.7%) and prefrailty (50.7 versus 36.3%) (Ptrend<0.001)

First author	Year	Study design	Frailty definition	Predictors of increased frailty	Population characteristics	Frailty prevalence
Schrack (174)	2016	Longitudinal	Grip strength measured as an average of 3 measures using a Jamar hydraulic hand-held dynamometer	Age, BMI, education and kidney disease, HCV and viral load	1552 men (716 with HIV and 836 HIV-negative) aged at least 50 years participating in the MACS, using data from 2007 to 2014	Among the HIV-negative men, grip strength declined 0.33 kg for each 1-year increase in age (P<0.001), whereas in the men with HIV, this decline was significantly faster at 0.42 kg/year
Kallianpur (191)	2016	Longitudinal	Fried's frailty definition	Volumetric changes in cerebellar white matter and subcortical grey matter, brain regions involved in motor control and cognition	35 PLWH, median age 50.6 years SD (6.8), 89% male, 47% Caucasian from the Hawaii Aging with HIV Cohort Cardiovascular Disease study	2.8% frail 23.0% pre-frail
Erlandson (175)	2017	Longitudinal	Fried definition also introducing assessment of slowness/gait speed using a binary ≤1 or >1 m/sec criterion	Non-white ethnicity, female gender persons with Medicare/Medicaid health insurance	1016 PLWH, 44% <50 years, 19% female, 48% white non-Hispanic, from the AIDS Clinical Trials Group Study A5322, the HIV Infection, Aging, and Immune Function Long-Term Observational Study (HAILO) in Baltimore, USA	6% frail, 38% prefrail
Margolick (192)	2017	Longitudinal	Fried's frailty definition	immune activation, higher serum levels of sCD14, sIL2Rα, sTNF-R2, IL-6, and TNF-α, higher levels of C-reactive protein (CRP)	921 MSM men (714 with HIV 207 HIV-negative), 54.9% white, 30.9% smokers from the MACS in Baltimore/Washington, Chicago, Los Angeles and Pittsburgh	15.3% among PLWH and 12.6% among HIV-negative

First author	Year	Study design	Frailty definition	Predictors of increased frailty	Population characteristics	Frailty prevalence
Tassiopoulos (70)	2017	Longitudinal	Fried definition also introducing assessment of slowness/gait speed using a binary ≤1 or >1 m/sec criterion	Falls (single/recurrent)	967 PLWH, median age 51 years IQR (46, 56), 18.9% female, 48.1% white non-Hispanic from a prospective, multicenter cohort from the USA and Puerto Rico	6% were frail, 39% prefrail
Wallace (182)	2017	Cross sectional	Deficit accumulation approach by Searle *et al.* (104), (overall physiologic vulnerability)		103 PLWH, average age 56.4 years, 27.2% female, from the Modena HIV Metabolic Clinic (MHMC) at the University of Modena and Reggio Emilia in Italy	Mean frailty index was 0.26 (SD=0.10), corresponding to 9.6 deficits of a possible 37 deficits
Bregigeon (69)	2017	Cross sectional	Cardiovascular Health Study (CHS) index; Frail had three markers and prefrail 1-2; unintentional weight loss (≥4 kg during the last year), weakness (low grip strength using a hand grip Dynamometer (SAEHAN Corporation, Changwon, Korea) by sex and BMI), exhaustion (self-reported on 0–10 scale), slowness (gait speed ≥1 s/m), and low physical activity (≤30 min walking, three times/week) Study of Osteoporotic Fractures (SOF) index, frailty was at least two frailty markers out of weight loss, exhaustion ('no' answer to the question 'do you feel full of energy?') and the inability to perform three chair stands (without arm help in 15s), prefrail had one frailty markers	Low spinal BMD and femoral osteoporosis in female and male HIV-positive people	171 PLWH, 69.1% men, median age 56 years IQR (51, 64) among men and 53 years IQR (50, 56) among women from the HIV outpatient unit of the Sainte Marguerite Hospital, in Marseille, France	According to CHS (8%) were frail and 111 (63.4%) prefrail According to the SOF index, 9.7% frail and 37.1% prefrail

2.2.7 Risk factors for frailty

Frailty has been associated with several negative outcomes. Some of the outcomes are organ-specific and others involve combined deficits such as an increased number of comorbidities, depression, increased risk for falls, decreased functionality, hospitalization and death, all of which are more common among older PLWH (77, 145, 178, 193-196). This section will consider the factors associated with frailty by the following categories: Sociodemographic and lifestyle, clinical, HIV-specific and other factors.

2.2.7.1 Sociodemographic and lifestyle factors

In the general population, significant geographic differences in the prevalence of frailty have been reported across Europe (197) and Latin America (198) which potentially implies ethnic differences in the prevalence of frailty. Demographic characteristics that have been linked with increased prevalence of frailty in PLWH include older age (77, 145, 156, 161, 174) (ORs ranging from 1.5 to 2.55) non-white ethnicity, lower education (OR=1.73 , 95% CI (1.19, 2.50)) and smoking (145, 174).

Moreover, increased malnutrition has been reported among those with lower physical activity (184), which has been used as a proxy for frailty. Severe household food insecurity expressed as decreased energy intake (mean and standard deviation (SD) 5.2 (2.4) MJ/day, half of the energy intake of a healthy, balanced diet, for a male 10.5 MJ/day), has been linked with decreased grip strength, which has been used as an element of the frailty definition (171). Other demographic social factors that have been linked with an increased prevalence of frailty in PLWH include unemployment and lower education (51, 145, 160, 172)

2.2.7.2 Clinical factors

Frail PLWH have more severe lipodystrophy characteristics, particularly lower middle/upper arm circumference, and higher trunk-to-total fat and lower appendicular-to-total fat ratios, than PLWH who are not frail (150, 171). Among other diseases, hypertension (178), renal disease, anaemia, history of diabetes, depressive symptoms, symptoms of low mood, central obesity and other geriatric syndromes

and BMI <20 kg/m^2 have been reported to be associated with expression of frailty or pre-frailty among PLWH (51, 77, 145, 150, 171-173, 178, 184, 187, 193-195, 199).

Other clinical conditions that have been associated with an increased prevalence of frailty among PLWH are cognitive impairment, a greater number of comorbidities, a high number of medications used, and a history of any opportunistic infection (157, 178). Past opportunistic illnesses, increased hospitalization, receipt of antidepressants, lower serum albumin (51, 145, 160, 172). Other clinical characteristics include greater use of non-antiretroviral therapy medications (prescribed medications and over-the-counter treatments) which is a proxy for co-occurring comorbidities (184),

Finally, clinical conditions such as infection from Hepatitis C Virus (HCV) (51, 145), increased inflammation (24, 192, 200), elevated markers of blood clotting (201), vitamin D deficiency (202), sarcopenia (150, 184, 203-205), Chronic Obstructive Pulmonary Disease (COPD) (172) and lower spinal and femoral neck BMD (69) have been associated with an increased prevalence of frailty.

2.2.7.3 HIV-specific factors

HIV infection has been associated with early presentation of frailty and HIV-specific factors such as low current and nadir CD4 count, HIV WHO clinical stages III and IV, and drug toxicities have been associated with premature presentation of frailty (77, 141, 142, 146, 155, 160, 163, 171-173, 190, 192, 199).

History of an AIDS diagnosis (OR=2.26, 95% CI 1.50, 3.39) (145), longer HIV duration, and VL above 50,000 copies/mL versus a lower VL, have each been associated with increased frailty (51, 146, 155, 159, 163, 181, 189). However, a lack of difference in CD4 count and VL between frail and non-frail PLWH has been reported among other researchers (184). The lack of consensus regarding the association of low CD4 and high VL with increased frailty may be due to differences in treatment history, treatment initiation and frailty onset among the study participants. Immune reconstruction has been associated with increased frailty with those starting cART

reporting a significant decline in their physical activity and capacity at cART initiation (150, 171, 184).

HIV disease has also been associated with an increased risk of poor balance and gait speed (206, 207), both of which have been used as components of frailty definitions. Finally, a greater total amount of viral replication measured over a period of time (referred to as "cumulative VL exposure") appears to be an important driver of grip strength decline (174), which has been used as a single marker for frailty.

2.2.8 Frailty as a risk factor for clinical outcomes and AIDS-defining illnesses

Grip strength, a component of common frailty definitions associated with lower quality of life, has been reported to be significantly lower in PLWH with or without HCV coinfection, compared to HIV-negative individuals (171, 174, 208). Frailty prior to cART initiation along with older age and higher maximum plasma VL have been associated with a significantly increased risk of a composite outcome of AIDS and death in the post-cART era (156).

PLWH classified as frail have been reported to have chronic immune activation and are at increased risk for fragility fractures (209, 210). Frailty has also been associated with an inflammatory index constructed from IL-6 and TNFα receptor-1 (211), with a history of kidney disease and a history of peripheral neuropathy (131). In a study by Desquilbet *et al.,* PLWH with persistent frailty-like phenotype before HAART initiation had a worse prognosis for progression to AIDS or death (156).

Impaired function, as a proxy for frailty, has been reported to be associated with an increased risk for falls and fracture in adults with HIV (179). The frailty index has been found to be an independent predictor of all-cause mortality, incident multi-morbidity and increased hospitalization (157, 181, 186), and has been strongly associated with increased risk of recurrent falls among older adults with HIV (70).

Associations of frailty with functioning in the memory domain have also been reported among older subjects with HIV (162) and may be associated with changes in motor and cognition control through volumetric changes in cerebellar white matter and subcortical grey matter (191). PLWH deemed to be less frail have an

increased likelihood of successful cognitive ageing, defined as the absence of neurocognitive and functional impairment and absence of depression (182).

2.2.9 Interventions for frailty among PLWH

A frail state compromises the quality of life of PLWH (142). Thurn *et al.* reported that health professionals should systematically use frailty indices to evaluate health and future risks for adverse events especially among PLWH (212). Several interventions have been suggested to either prevent or reverse the onset of frailty. Exercise interventions, in particular resistance training and aerobic exercise, have been reported to be effective at preventing and/or treating components of frailty among younger PLWH (135, 136). Effective and early treatment with cART also plays a protective role against frailty (159, 190).

It has been suggested that it is essential to undertake annual screens of the functionality of PLWH over the age of 60. This may facilitate diagnosis and treatment of multiple functional problems (76) and may minimize frailty (152). The 2019 recommendations from the European AIDS Clinical Society (EACS) suggest frailty screening using the Fried Frailty Phenotype or Rockwood Frailty index definitions (213).

2.3 Falls

2.3.1 Falls definitions in the general population

Falls are an indication of severely compromised health in older people (214) and are one of the major causes of mortality and morbidity in older adults (215). Unintended moves from a higher to a lower level are considered to be falls, typically happening rapidly and without control when someone loses balance and collapses. According to WHO, falls are defined as "inadvertently coming to rest on the ground, floor or other lower level, excluding intentional change in position to rest in furniture, wall or other objects" (216). This definition has also been used by the International Classification of Diseases (ICD9) (217) and other researchers (88) while others have used a modified version e.g. by excluding stumbles (218).

Several classifications of falls have been used. They can be explained/unexplained on the basis of whether the reason for the fall is known or not, intrinsic/extrinsic on the basis of whether the cause of fall comes from the person or the environment, accidental/non-accidental on the basis of whether the fall was purely due to accident or not and injurious/non-injurious based on whether the fall resulted in an injury or not (219).

2.3.2 Falls prevalence in the general population

The frequency of falls increases with age with 30-40% of people over the age of 65 reporting at least one fall over the past year, making falls a leading cause of injury in this age group (215, 220-223). It has been reported that 25% of independent-living persons aged 70-75 years have experienced a fall over the last year (112) while the percentage is 50% for people living in institutional care (219). The prevalence of having experienced a fall increases with age. People ≥75 years have reported a prevalence of falls between 32-42% (224) while of those aged between 75 and 80 years, 50% have reported repeated falls (112, 225-227). People aged 60 years or older with a history of a fall have almost a 70% chance of falling in the subsequent year (228). The most rapidly growing segment of adults consists of those aged 85 years and older with 21.3% of them reporting to have had a fall in the past 3 months and 7.2% reporting experiencing an injury requiring treatment (229).

Indoor falls are more prevalent among the elderly over the age of 75 years and their falls are normally linked with increased frailty, while people aged <75 years mainly fall outdoors with their falls linked to compromised health (230). During winter and colder days a higher rate of falls has been reported among women (231) and only 20% of falls occur during the night-time (232). A study that summarised the results across twelve studies (227) suggests that the main cause of falls among elderly adults was accidents or environmentally-related reasons (31%, 95% confidence interval (CI) (1%, 53%)) with the second main cause being gait/balance disorder or weakness (17%, 95% CI (4%, 39%)). Other reasons for falls are dizziness/vertigo, drop attack, confusion, postural hypotension, visual disorder, syncope and other or unknown reasons (Table 2.3).

Falls represent a serious public health challenge to the elderly, considering their frequency and adverse outcomes (233) and the cost to the healthcare system and services (234).

Table 2.3: Causes of falls in elderly adults: summary of 12 studies[a] that carefully evaluated elderly persons after a fall and specified a 'most likely' cause

Cause	Mean percentage[b] (%)	Range[c] (%)
Accident/environment-related	31	1-53
Gait/balance disorders or weakness	17	4-39
Dizziness/vertigo	13	0-30
Drop attack	9	0-52
Confusion	5	0-14
Postural Hypotension	3	0-24
Visual disorder	2	0-5
Syncope	0.3	0-3
Other specified causes[d]	15	2-39
Unknown	5	0-21

[a] Taken from Rubenstein *et al.* (227)
[b] Mean percentage calculated from the 3628 falls in the 12 studies
[c] Ranges indicate the percentage reported in each of the 12 studies
[d] This category includes arthritis, acute illness, drugs, alcohol, pain, epilepsy and falling from bed

2.3.3 Falls prevalence among PLWH

In PLWH the risk for falling has been reported to be higher among middle aged adults compared to younger PLWH (194), with recurrent falls being more prevalent among frail PLWH (70). However, other researchers have reported that the rate of falls (235, 236) and the incidence of falls during a movement was similar between PLWH and HIV-negative controls (237). Among PLWH the prevalence of falls over a 12-month period has been reported to range from 11% to 18% (70, 238) while 7% of PLWH have reported recurrent falls of whom 21% required medical help and 5% reported a fracture (70).

Self-reported recall has been the main way of reporting a fall while the optimum timeframe of recall has been debated (239). Simple recall questions like "In the past month, have you had any fall including a slip or trip in which you lost your balance and landed on the floor or ground or lower level" (240) or daily fall diaries or calendars (241) have been used to collect this information. Cummings *et al.* (239) have reported that a 12-month recall period for falls in the general population is a

better recall window compared to shorter 3- or 6-month periods. Furthermore, they concluded that retrospective studies underestimate falls by 13-32% compared to prospective studies.

2.3.4 Risk factors for increased falls

Several risk factors for falls have been identified in the general population and among PLWH. Both physiological and environmental factors have been reported to contribute to falls (225, 242) and over 400 potential risk factors for falling have been identified. The Effective Health Care Bulletin classifies these into environmental factors, and factors related to medication, medical conditions, ageing and lack of exercise (243). Other researchers have grouped the risk factors for falls into categories of muscle weakness, gait and balance problems, visual impairment, cognitive impairment, depression, functional decline, and medications (244). This section will consider the factors associated with falls by the following categories: Sociodemographic and lifestyle, Clinical, HIV-specific and Other factors.

2.3.4.1 Sociodemographic and lifestyle factors

Gender differences have been reported in the risk for falls. Women have been found to have an increased risk for a nonfatal fall injury (OR=2.0, 95% CI 1.12, 3.70) (258). However, after age adjustment, men have been found to have a 46% higher rate for fatal falls (245, 246). Other researchers have reported that male sex (OR=1.41, 95% CI 1.18, 1.69), perceived insufficient sleep, health problems requiring assistive devices, alcohol consumption, malnutrition and increasing BMI were all independently associated with a greater risk of falls or fall-related injuries (229, 247). White elderly women were reported to have 2.5 times increased risk for fall-related deaths compared to black women (245). Female gender among PLWH has been reported to be the among the most significant predictors of falls (OR ≥2.5 and P≤0.05) (194).

Among women with HIV, older age (≥60 vs ≤39 years) has been associated with an increased risk for falls and recurrent falls (OR=2.26, 95% CI (1.38, 3.71) and OR=2.08, 95% CI (1.05, 4.10) respectively) (248). Other researchers reported similar findings for falls and recurrent falls when comparing older with younger PLWH (≥60 vs. 40-49

years) (OR=2.39, 95% CI (1.34, 4.23) and OR=2.45, 95% CI (1.05, 5.67), respectively) (70). Older age has been linked with an increased risk for falls (249) with the CDC reporting that adults over the age of 85 have almost a 4 times higher rate of falls/injuries compared to adults aged 65-74 in the USA (220, 250). Older people have been found to be less capable of avoiding a fall after a trip or slip, which at advanced stages of gait impairment and poor gait extremity coordination may result in walking with smaller and more unsteady steps (251-255).

Among PLWH lifestyle characteristics, such as alcohol and substance use have been linked with an increased risk for falling (248), decreased motor balance and decreased executive functioning as assessed by the Fregly Graybiel Ataxia Battery (256). In particular Sharma *et al.* found that among HIV-positive middle-aged women current substance use increased the odds of falls and recurrent falls by more than 2-fold (OR=2.19, 95% CI (1.53, 3.13) and OR=2.60, 95% CI (1.64, 4.13), respectively), while heavy alcohol use (≥14 drinks/week) versus no alcohol increased the odds of recurrent falls by more than 7-fold (aOR=7.28, 95% CI (1.91, 27.78)) (248).

However, there is no consensus in the literature regarding the association of alcohol with falls and recurrent falls among PLWH. Few other studies that defined high alcohol use as ≥14 drinks/week (257) or >7 drinks/week (194) found no association between high alcohol use with higher odds of falls and recurrent falls (OR=0.3, 95% CI (0.04, 2.7) and OR=1.60, 95% CI (0.73, 3.51), respectively).

2.3.4.2 Clinical

Disorders in balance and gait have been reported to be the leading risk factors for increased falls (226, 242, 258). Lack of coordination, balance and posture control have been reported among people over the age of 65 (251, 259). An increased odds of falling has been linked to impaired strength of the hips (259), knees and ankles (260). A meta-analysis of 30 studies concluded that lower extremity weakness (lower extremity strength, finding that declined knee extension strength, ankle dorsiflexion strength and slow chair stands) was associated with a 76% increase in the odds of falling (combined odds ratio (OR)=1.76, 95% CI (1.31, 2.37)). Upper extremity weakness (assessed by grip strength or manual muscle testing) was associated with

a 53% increase in the odds of falls (OR=1.53, 95% CI (51.01, 2.32)) and a 41% higher odds of recurrent falls (OR=1.41, 95% CI (51.25, 1.59)) (261). Difficulty with balance, exhaustion and weight loss among PLWH have been reported to be the most significant predictors of falls (all with ORs ≥2.5 and P≤0.05) (194).

Cognitive and physiological declines have been associated with natural ageing and subsequently linked with impaired functional status and increased risk for falling. Poor performance in motor and sensory systems, in particular dual tasking, executive function, information processing and reaction time, have been linked with an increased risk for falling (262-268). Elderly individuals scoring poorly on a validated speed/executive attention test had almost four times higher odds to fall than individuals in the high scoring group (OR=3.9, 95% CI (1.5, 10.1)) (269-271). Moreover a high total disease score (per one unit increase), constructed by counting the total number of diseases present (diabetes, chronic heart failure, arthritis, hypertension, depression, stroke, Parkinson's disease, COPD, myocardial infarction (MI) and angina), was associated with an increased odds for recurrent falls (OR=2.7, 95% CI (1.3, 5.7)) (265, 272).

Depression and high levels of depressive symptoms have been associated with up to five-fold increased risk for falls among older nursing home residents aged between 63 to 91 on multiple medications (273) and among men and women over the age of 60 (249). A six-fold increased falls risk has been reported among elderly (63-91 years old) depressed people using ancillary devices, while the same risk was 11-fold higher among elderly depressed participants with neurological diseases (273).

Polypharmacy in the elderly has been associated with an increased risk for falls (259). Use of psychotropic medication has been linked with an increased risk for falling (274). A recent review by Chen (275) reported that central nervous system-acting agents, cough preparations, nonsteroidal anti-inflammatory drugs, anti-Alzheimer's agents, antiplatelet agents, calcium antagonists, diuretics, α-blockers, digoxin, hypoglycaemic drugs, neurotoxic chemotherapeutic agents, nasal preparations, and antiglaucoma ophthalmic preparations can be described as fall-risk-increasing drugs. Details of the association of these drugs with falls are summarised in Table 2.4.

Table 2.4: Drugs associated with increased falls, taken from Chen *et al.* (275)

Drug	Association with falls
Central nervous system (CNS)-acting agents	Subjects on CNS-acting agents (benzodiazepines, sedatives, hypnotics, antidepressants, antipsychotic drugs, and anti-Parkinson drugs) were 9.9 times more likely to have a fall OR=9.90, 95% CI (1.6, 60.63) (276-279). Inpatient falls were significantly associated with patients taking anti-Parkinson's medication (OR about 4–5) (278, 280)
Cough preparations	Subjects with history of fall were more likely to be taking cough mixture compared with those with no history of fall (5.7% versus 1.0%, P=0.001), indicating hospitalized patients on cough preparations were more likely to fall (281)
Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)	NSAID use was a significant predictor of falls in hospitalized elderly patients and was associated with a tenfold increase in the likelihood of falling (OR=10.02, 95% CI (2.6, 38.58), P=0.001) (282)
Anti-Alzheimer's agents	The use of Alzheimer's medication (eg, donepezil, rivastigmine, galantamine, memantine) was associated with fall risk, hazard ratio (HR)=1.63, 95% CI (1.24, 2.14), P=0.0005) (283)
Antiplatelet agents	Subjects on antiplatelet agents are more likely to fall. More fallers were taking antiplatelet agents compared with non-fallers (15.9% versus 1.3%, P<0.001) (281)
Calcium antagonists	The probability of falls increased when subjects used calcium antagonists (adjusted odds ratio (aOR)=2.45, 95% CI (1.16, 4.74), P=0.02) (279)
Diuretics	Nursing home residents are at an increased risk of falls on the day following a new prescription or increased dose of a loop diuretic drug, (OR=2.46, 95% CI (1.02, 5.92)) (284). A case-control study showed that current prescribing of thiazides was associated with an increased risk of falling, and that this was strongest in the 3 weeks following the first prescription (OR=4.28, 95% CI (1.19, 15.42)) (285)
α-blockers	Current use of standard-formulation α-blockers (prazosin, doxazosin, terazosin, alfuzosin, and tamsulosin) was associated with an increased risk of hip/femur fracture, commonly due to falls (aOR=1.9, 95% CI (1.1, 3.0)). The effect was particularly strong for first prescriptions (aOR=5.1, 95% CI (1.0, 31.7)) and during the first month of treatment (aOR=4.1, 95% CI (0.7, 23.9)). Stratification analysis according to indication of use showed that current use of α-blockers was not associated with hip/femur

	fracture in men with a diagnosis of benign prostatic hyperplasia, but was associated in men who used α-blockers for cardiovascular disease (aOR=2.8, 95% CI (1.4, 5.4)) (286). No increased risk of fractures was associated with current use of modified-release doxazosin in hypertension, previous use, or the start of a treatment episode (≤28 days) (287). Caution with respect to first-dose effects related to the initiation of a new episode of α-blocker treatment is advised and modified-release doxazosin is a superior α-blocker versus standard formulation for the sake of avoiding fall risk in elderly patients
Digoxin	Digoxin therapy (35% versus 22%) was more common in hospitalized elderly patients who had fallen than in control patients (288)
Miscellaneous	Use of diabetes medications was significantly associated with an increased risk of falling (aOR=3.2, 95% CI (1.3, 7.9)) (289). The rate of fall-related injuries for patients receiving a doublet of neurotoxic chemotherapy (9.15 per 1,000 person-months) was significantly higher than for those receiving a single neurotoxic agent (7.76 per 1,000 person-months) or a non-neurotoxic agent (5.19 per 1,000 person-months) (290). Nasal preparations (eg, treatment of asthma or allergic rhinitis) (aOR=1.49, 95% CI (1.07, 2.08)) and antiglaucoma ophthalmic preparations (aOR 1.51, 95% CI (1.10, 2.09)) were significantly associated with an emergency department visit due to a recurrent fall (291)

Other researchers reported that benzodiazepines, antipsychotics, antidepressants used for bipolar disorder and anxiolytics/hypnotics treatment and psychotropic medications including drugs for dementia treatment, and antipsychotics are associated with an increased risk for falling in older adults (267, 292, 293). In contrast, other researchers report that use of antidepressants not only improves depression and cognition, but has a small but significant improvement on several gait measures (294). Among PLWH cognitive complaints, mild and moderate cognitive decline, depressive symptoms, neuropathy and a lower bone and muscle mass have been linked with increased falls (248, 257, 295, 296). Increased or premature frailty (70, 297), presence of more than three comorbidities and having a functional impairment (194, 298) have also been linked with an increased risk for falling.

Insulin-treated people from the general population have been reported to have an increased risk of falls compared to non-diabetic controls with a reported relative risk of 2.76 (95% CI (1.52, 5.01)). Although metformin has not been directly linked to falls, it has been associated with neuropathy secondary to vitamin B12 deficiency, which can place people at higher risk for falls (299).

Exposure to NSAID medication has been linked with an increased risk of falls (300) as has current cardiac medication (293, 300). Other medications associated with an increased risk for falls include digoxin (OR=1.22, 95% CI (1.05, 1.42)), type 1A anti-arrhythmic (OR=1.59, 95% CI (1.02, 2.48)) and diuretics (OR=1.08, 95% CI (1.02, 1.16)) (284, 293, 300-302). Change or dosage adjustment of diuretic medication has been linked with an increased odds of falling the day following the change (OR=2.08, 95% CI (0.89, 4.86)) (301). Antiepileptic medication has potential side effects at the CNS such as sedation, dizziness and ataxia, and these drugs have been linked with an increased risk of falling. Compared to non-users, women on anti-epileptic medication have been reported to be 75% more likely to experience a fall (OR=1.75, 95% CI (1.49, 4.41)) (303).

Among PLWH polypharmacy (298) has been linked to an increased risk of falls (60, 194), with PLWH aged between 45 and 65 having a 40% increased odds of falling for every additional medication taken (OR=1.4, 95% CI (1.3, 1.6)) (194). Use of ddI has been linked with an increased risk for falling (OR=1.9, 95% CI (1.0, 3.5)) (194) and PLWH on PI vs. non-PI containing regimens were more likely to experience medication-related side effects that are linked to falls (296). Reported side effects of the INSTIs use include neuropsychiatric symptoms, sleep disturbances and dizziness (304-308) all of which may increase the risk for falls. An increased number of concomitant medications (298) and receipt of a greater number of medications affecting the nervous system (sedative, opioid, and antidepressant medications) (248, 257, 295) have been associated with an increased risk of falls among PLWH. People on sedative medication increased their odds of falling by 30% for every additional sedative drug (OR=1.30, 95% CI (1.13, 1.50)) (295). Similarly, other researchers reported that beta-blockers, antidepressants, antipsychotics, sedatives, and opiates were independently associated with falling (all OR ≥2.7, p≤0.01) (194).

Other comorbidity factors that have been linked with increased risk for falls include below average general health (229), decline in the function of musculoskeletal system, history of cerebrovascular disease and CVD, impaired vestibular and proprioception system and other conditions such as arthritis, diabetes and incontinence (309, 310). A history of stroke has also been associated with a greater risk of falls or fall-related injuries (229). Among men and women aged 60 and over, increased falls are associated with diagnosis of at least one chronic disease, in particular, severe pain, incontinence and frailty in women (249). Every additional comorbidity reported among PLWH between 45 and 65 years of age, was associated with a 70% increased odds of falling (OR=1.7, 95% CI (1.5, 2.1)) (194).

High blood pressure and low heart rate have been found to be significantly associated with decreased balance and gait measures (311). Atrial fibrillation has been reported to be an independent risk factor for non-accidental falls in elderly people. The mechanisms that may explain this association include a decreased cardiac output, co-existing sinus-node disease, and impaired baroreflex (312). Higher odds of falls and recurrent falls in PLWH have been reported among persons with CVD, diabetes, hypertension, dementia, neuropathy, arthritis, chronic pain and psychiatric disease (194).

Compromised vision has been linked with severe functional limitation, poor balance and postural control (310). Vision-specific conditions, in particular depth perception impairment and impaired visual acuity, have been linked with increased falls among elderly people (313-315). Other visual impairments associated with increased risk for falling include age-related macular degeneration, poor stereo-accuracy, visual field loss (central and peripheral) and poor contrast sensitivity (314, 316-320). Further evidence suggests that early cataract surgery and changing bifocal and multifocal spectacles reduce the rate of falls (321-324).

Neurodegenerative diseases have also been linked with falls risk and recurrent falls both in community and institution-dwelling older adults (266, 325). Moreover, people with Alzheimer's disease have been found to have an increased gait instability and subsequently increased risk for falling (325). Similarly, people diagnosed with

Parkinson's disease with greater impairments in executive function and attention have been found to have higher incidence of falls compared to those without Parkinson's (67% vs. 18%) (326).

Older people have been found to commonly report reduction of neural and sensory hair cells linked to vestibular dysfunction (327). Precise measurements of vestibular function like asymmetry and eye and head-trunk motion have been linked with increased risk for falls (328, 329).

2.3.4.3 HIV-specific risk factors

Long-term infection with HIV, Hepatitis B Virus (HBV), untreated HCV and non-compliance to ART medication have been associated with an increased risk for falls (298, 330). PLWH walk slower and have poorer balance and both declines in gait speed and balance may intensify with disease progression (331).

2.3.4.4 Other factors

Balance confidence as a measure of self-awareness and capability has been used by the MACS. The authors asked the study participants to rate their balance confidence from 0-100% on 16 activities, ranging from walking around the house to standing on a chair to reach and walking on icy sidewalks. The average balance confidence was calculated and participants with total balance confidence ≤90% vs > 90% were more likely to report at least one fall (OR=2.1, 95% CI (1.32, 3.34)); when the analysis was restricted to PLWH, the odds of falling was more than 4-fold higher (OR=4.15, 95% CI (1.96, 8.78)) (332).

2.3.5 Interventions for falls in HIV

Validated fall risk screens and assessments are now available for older people in the general population in community, hospital, and nursing and residential care settings, and randomised controlled trials provide good evidence that falls can be prevented by tackling identified risk factors (333).

Routine assessment of falls and dizziness/imbalance symptoms should be considered as a part of routine care for PLWH to prevent falls (194, 257). Moreover

polypharmacy management and monitoring of the effect of sedating medications are suggested as potential interventions among PLWH (295). In addition to the above an effective pain symptom management has been suggested as a potential intervention to improve functional impairment and subsequently to reduce falls risk among elderly adults with HIV (157).

Interventions among older people in the general population with increased risk for falling or recurrent falls include discontinuation of high risk and psychotropic medications, exercise, physical therapy, balance training programs and home safety evaluations (334-336). In particular, a pooled analysis across 17 studies has shown a 15% risk reduction among the elderly in the general population on exercise or physical therapy programs (pooled rate ratio (pRR)=0.85, 95% CI (0.78, 0.92)) (335). Several other studies in the general population have shown that vitamin D supplementation significantly reduces the risk for falling by 17% (pRR=0.83, 95% CI (0.77, 0.89)) (335). The 2020 EACS guidelines recommend assessment of the falls risk among all PLWH above the age of 40 (337).

2.4 BMD and fractures

2.4.1 Definition of fracture

Fractures (broken bones) can range from a thin crack to a complete bone break and are mostly diagnosed using an x-ray scan. Bones can fracture crosswise, lengthwise or in several places. Most fractures happen when a bone is impacted by more force or pressure than it can support.

2.4.2 Types of fracture and prevalence

Fractures may be characterised as fragility or osteoporotic. The National Institute for Health and Care Excellence (NICE) in recent review from 2018 has characterised fragility fractures those resulting from a force such as fall, that would not ordinarily result in fracture (338). Although the definition of osteoporotic fractures varies across studies, hip fractures have been consistently considered as an osteoporotic fracture throughout the epidemiological research literature (339, 340). However, the definition of osteoporotic fractures is quite variable in epidemiological research and

accounts for fractures that occur at only some sites. Examples of variable approaches are detailed in Table 2.5.

Table 2.5: Fracture locations that have been considered for the definition of osteoporotic fractures by different researchers

	Fracture location					
Author	**Hip**	**Vertebrae**	**Wrist**	**Forearm**	**Spine**	**Shoulder/humerous**
Hippisley-Cox (341)	○	●	○	○	○	○
Gregg (342)	●	○	●	○	○	○
Jassal (343)	●	○	●	●	○	○
Berg (344)	●	●	●	●	○	○
Kanis (345-347) Leslie (348) Hodsman (349)	●	○	●	●	●	●

● considered osteoporotic
○ not considered osteoporotic

Other researchers considered as osteoporotic any fractures excluding those that occurred at the ankle, hands or feet, digits, skull, face and kneecap (350). Finally, considering that osteoporotic individuals are more likely to have a fracture compared to those without osteoporosis (351), some researchers have considered all fractures to be osteoporotic (352), and others excluded those resulting from severe trauma (motor vehicle accidents, being struck by a rapidly moving projectile, assault) (353-355).

Nine million osteoporotic fractures were estimated to have occurred in the general population worldwide in 2000 of which 1.6 million were at the hip, 1.7 million at the forearm and 1.4 million were clinical vertebral fractures with the greatest number of fractures occurring in Europe (34.8%) (340). In the general population the 10 year probability of osteoporotic fracture has been reported to vary from 2.6% to 13.1% for 45-85 year old men and from 3.8% to 27.0% for similarly-aged women (347).

2.4.3 Bone health and ageing

Bone quality and bone quantity decline in ageing men and women (356, 357) with women experiencing bone loss earlier in life and progressing at a faster rate compared to men due to menopause (358). This process involves genetic, hormonal, biochemical and environmental factors and is associated with an increased risk of

fractures. The process of slowing down of bone formation, sometimes referred to as "bone-ageing", is directly linked to changes in physical anatomy, osteoporosis, osteomalacia and fractures. People with a decreased BMD are more likely to experience a fracture (359). Older age, osteoporosis, menopause, endocrinal and intestinal disorders as well as lifestyle traits like physical inactivity, smoking and alcohol accelerate bone demineralization (360). Individuals with a history of a hip fracture have been reported to have an increased risk of institutionalization and mortality (361, 362).

2.4.4 Measures of bone health

2.4.4.1 BMD

Individuals at high risk for fracture are often identified through BMD measurement (363); WHO released the first guidance for using bone density measurements to diagnose osteoporosis before a fracture occurred in 1994 (364). BMD is the amount of bone mineral in bone tissue. Bone demineralization is affected by both genetic and lifestyle characteristics (365) and has been reported as a prevalent process among PLWH (365-377). Dual-energy X-ray absorptiometry (DEXA) scan is a commonly used method of measuring BMD. A full body scan is normally performed, and areas of interest are normally the femoral neck (FN), lumbar spine (LS), total hip (TH) or vertebrae. DEXA measures the bone mineral content (BMC) in a specific area of bone. These numbers are used to calculate the BMD, using the equation:

$$BMD(g/cm^2) = \frac{BMC\ in\ grams\ (g)}{Area\ in\ centimeters\ (cm^2)}$$

Bone mass at the LS and FN reaches its peak by the age of 20–25 in healthy men and women, with declines with increased age (378-380). The T-score is assessed cross-sectionally and provides a comparison of the individual's BMD to that of a healthy young adult reference population and is expressed in standard deviations, i.e. how much does the BMD differ compared to that of the reference population (381). It is calculated by subtracting the mean BMD of the reference group from the measured BMD of the study participant, and then dividing the difference by the standard deviation (SD) of the BMD of the reference group.

$$T\text{-score} = \frac{measured\ BMD - mean\ BMD\ of\ reference\ group}{SD\ of\ BMD\ of\ reference\ group}$$

According to WHO, a BMD T-score ≥-1 is considered to be normal, a T-score in the interval >-2.5 to <-1 is indicative of osteopenia and a T-score ≤-2.5 is indicative of osteoporosis (382).

The BMD Z-score is also used to assess bone loss and is calculated by comparing the bone density of a person to the average bone density of people of the same age and gender. It is calculated by subtracting the mean BMD of the reference group from the measured BMD of the study participant, and then dividing the difference by the standard deviation (SD) of the BMD of the reference group.

$$Z\text{-score} = \frac{measured\ BMD - mean\ BMD\ of age\text{-}gender\text{-}matched\ reference\ group}{SD\ of\ BMD\ of\ age\text{-}gender\text{-}matched\ reference\ group}$$

According to the International Society of Clinical Densitometry (ISCD), a BMD Z-score ≥-1 is considered to be normal, a Z-score in the interval >-2.0 to <-1 is indicative of osteopenia and a Z-score ≤-2.0 is indicative of osteoporosis (382).

A compromised BMD is a leading cause of increased fracture risk. In clinical practice, predicting fracture risk using BMD T-scores has been characterised as an effective method with TH measurements being superior in fracture prediction compared to measurements at the LS or other sites (339, 348, 383). The risk for osteoporotic fractures (defined as those at the vertebrae, hip or forearm) when the BMD decreases by 1 SD within an individual, has been reported to increase from 50% to 300% (354, 384, 385). The risk for hip, distal radius and proximal radius fracture has been reported to increase by 66%, 55% and 41% respectively among women for every additional standard deviation lower BMD (RR=1.66, 95% CI (1.22, 2.26), 1.55, 95% CI (1.13, 2.11) and 1.41, 95% CI (1.06, 1.88) respectively) (386).

Despite its use as a measure for assessing osteopenia and osteoporosis, BMD alone has been considered to be an inadequate sole measure of fracture risk (387). Therefore additional consideration of clinical conditions, along with BMD, has been suggested to provide a more robust prediction for fracture risk (346, 387). When BMD

measurements are not available, use of clinical conditions alone can still be used for the prediction of fracture risk (388).

2.4.4.2 The FRAX score

The FRAX score (389-391) is one of the most commonly used and validated tools to assess the 10-year probability of hip fracture and the 10-year probability of a major-osteoporotic fracture (spine, forearm or shoulder fracture) (392) and has been approved by the National Institute for Health and Care Excellence in the UK and the FDA in the U.S. (389-393). It is calculated using seven clinical risk factors (the prevalence of a prior fragility fracture, a parental history of hip fracture, smoking, use of systemic glucocorticoids, high alcohol intake, BMI, and rheumatoid arthritis), which, in addition to age and sex, contribute to fracture risk independently of BMD. Use of only clinical risk factors to assess fracture risk may introduce some bias, therefore accounting for BMD appears to improve the estimated fracture risk (346). When BMD is included in the FRAX assessment, the FN measurement can be used for optimising its calculation (394). Evidence supports the use of FRAX including BMD measurements as a more sensitive tool to identify those at intermediate risk for fractures (383, 395, 396). Those with low BMD and a ten-year risk of hip fracture of ≥3% or a ten-year risk of a major-osteoporotic fracture of ≥20%, as assessed with FRAX, should be considered for osteoporosis treatment according to the National Osteoporosis Foundation Guide (357, 397).

Several limitations regarding the use of the FRAX score have been raised. The lack of consideration of a history of falls as a risk factor has been raised as a main concern that may lead to underestimation of fracture risk (398). However, the developers of the FRAX score note that data on history of falls have been inconsistently captured in databases and that there is lack of data on the interaction of history of falls with the other risk factors considered for the calculation of the FRAX score (399). However, they suggested that falls history may be incorporated in the prediction of fracture risk when reliable data become available (400). Another limitation is that FRAX has not been validated among PLWH and it does not include HIV-specific risk factors. Recent studies suggest that the FRAX score underestimates fracture risk among men with

HIV (401, 402). Therefore, a modification has been suggested by considering 'secondary osteoporosis', one of the twelve risk factors included in the FRAX score, as being present for all PLWH. Whilst research suggests that this modified-FRAX improves the accuracy of FRAX estimates (403, 404), it continues to underestimate fracture risk among men with HIV aged 50-70 years compared to similar HIV-negative men (403). Since BMD measurements may not always be available, some researchers have explored whether FRAX score based on case report forms (CRFs) alone can provide an accurate fracture prediction. In a study among older women with HIV, the FRAX score using CRFs alone was reported to underestimate the fracture risk compared to the score of similar HIV-negative women (404). Similarly, Gazzola *et al.* reported that FRAX score based on CRFs alone underestimates the proportion of patients at higher risk for hip and major-osteoporotic fractures and suggested that the use of the modified FRAX score does not significantly change the ability to correctly identify PLWH who should undergo DEXA testing (405). Conversely, other researchers have suggested that among PLWH whilst the sensitivity of FRAX estimates improves when FRAX (without BMD) is combined with the ageing male symptoms scale, its specificity remains low (402). Others have suggested that among HIV-positive men aged ≥45 years, addition of BMD measurements to the assessment of the FRAX score may detect more candidates for therapeutic management (406). Nevertheless, the EACS currently recommends the use of FRAX as a screening tool for the assessment of fragility fracture risk among PLWH (407).

2.4.4.3 Q-Fracture

Q-Fracture is another measure used to estimate an individual's 10-year risk of developing both hip and major-osteoporotic fractures (hip, spine and wrist), utilizing information that is readily available in electronic healthcare records, without the need for a BMD measurement (408). It was developed in 2009 and updated in 2012 and has been reported to be a sensitive measure to identify those at high risk of hip fractures (409). Hip bone geometry has also been used to assess bone health by measuring the narrow neck, intertrochanter, and shaft using hip structural analysis (208).

2.4.4.4 The Garvan score

The Garvan score is intended for use by general practitioners (GPs) and other health professionals. It is based on data from the Dubbo Osteoporosis Epidemiology Study. The factors that are accounted for in the Garvan score are age, BMD, history of prior fracture and falls (387). Whilst it has been reported to be well calibrated for estimation of risk of osteoporotic fractures, it overestimates hip fracture risk (410). Its sensitivity in identifying hip fractures has been reported to be the poorest when compared to Q-Fracture and FRAX score (409). In particular, Q-Fracture identified 45.1% of those at the top 10% risk of hip fracture, FRAX 43.6%, but Garvan only 36.9% and the specificity for Q-fracture, FRAX and Garvan was 91.0%, 90.0% and 90.7% respectively, in a retrospective study from 2010 to 2014.

2.4.4.5 Other measures for risk of fracture

The trabecular bone score (TBS) has also been used as an indirect index of bone microstructure in the general population (411) and among PLWH (412). It is a visually structured index that analyses pixel grey-scale differences from a DEXA image. A low TBS value reflects a porous trabecular structure, whereas a high TBS value reflects a well-structured trabecular bone.

Broadband ultrasound attenuation (BUA) has also been used for fracture prediction. It is a measurement of the differential attenuation of sound waves transmitted through the calcaneus. Among postmenopausal women BUA has been reported to be a strong predictor of hip and all non-spine fractures (413). BUA measures both bone mass and structural features (e.g. connectivity and spacing of trabeculae) of the bone that are important for prediction of fracture risk (414).

The quantitative ultrasound (QUS) method has been extensively used for assessment of osteoporosis (415-418). It is a non-invasive method that is easy to use, does not expose the subject to ionizing radiation and is portable and cheaper to implement than DEXA (419). QUS has been found to predict fractures at the proximal femur (413, 420-422), hip (423), vertebrae (415, 424, 425) and other sites (425-430). The use of QUS is still debated despite its advantages. It is unclear how it can be used for the diagnosis of osteoporosis and how subjects at risk could be selected for treatment

based on QUS. However, QUS of calcaneus is reported to identify women at high risk for osteoporotic vertebral fractures similarly to DEXA (431).

Other measures include the Computer model for osteoporotic fracture risk, the Fracture and Mortality index (FRAMO), the Fracture Risk Calculator (FRC), the Fracture and Immobilization Score (FRISC), the Fracture Risk score (FRISK), the Score for estimating the long-term risk of fracture in post-menopausal women, the Simplified fracture risk system, the SOF and the Women's Health Initiative (WHI) hip fracture risk score described in detail in a systematic review by Marques (392), (Table 2.6).

Table 2.6: Scores available for predicting fracture risk, taken from Marques *et al.* (392)

Score name	Number of clinical conditions	Prediction time and outcome	BMD required
Computer model for osteoporotic fracture risk	8	5 years Absolute fracture risk Expected absolute risk reduction after treatment	Yes
FRC	12	10 years Hip fracture risk	Yes
FRAMO	4	2 years Hip fracture risk Mortality	No
FRISC	8	1, 3, 5 and 10 years Major-osteoporotic fracture risk Immobilisation risk	Yes
Score for estimating the long-term risk of fracture in post-menopausal women	8	5 years Clinical vertebral fracture risk Clinical osteoporotic fracture risk Hip fracture risk	No
Simplified fracture risk system	5	10 years Any fracture risk	Yes
SOF	14	5 years Hip fracture risk	No
WHI	11	5 years Hip fracture risk	No

2.4.5 Fractures and BMD in PLWH

Over the last 10 years, a higher prevalence of bone disease and a higher risk for fractures has been reported in PLWH compared to age-, ethnicity - and sex-matched HIV-negative individuals (367-369, 371, 373-377, 401, 403, 432-443). A recent review from Premaor *et al.* has suggested that the estimated incidence of osteoporotic fractures (fragility or non-fragility) among PLWH is at least twice as high as that in HIV-negative controls (444). Low BMD, indicative of osteopenia or osteoporosis, occurs in 40–90% of PLWH (445). The increased rate of fracture appears to occur a decade earlier in men living with HIV compared with HIV-negative controls (446), therefore there are predictions of an exponential increase in bone fractures among older PLWH, considering the already elevated fracture rates among young men living with HIV (24, 447). Men with HIV aged 50–59 years are reported to have a significantly higher incidence of all fractures (RR=2.06, 95% CI (1.49, 2.84)) and fragility fractures (RR=2.06, 95% CI (1.21, 3.50)) compared to HIV-negative controls of similar age (448).

Several investigators have shown that PLWH experience a 2- to 6-fold higher loss of bone mass (449) and have a greater risk for fractures (50, 398, 447, 450-469) compared to HIV-negative controls. The fracture risk has been reported to be 60% higher among PLWH compared to HIV-negative controls in a recent meta-analysis (456). The risk of osteoporotic fractures increases 1.5 to 3-fold for each standard deviation lower BMD depending on the site of assessment and the fracture of interest (339, 363, 382). A lower BMD and a longer duration of HIV infection have been associated with increased fracture risk (470-472) among PLWH and it has been reported that PLWH may experience a higher incidence of past osteoporotic fragility fractures compared to population-based controls despite a normal BMD (473). However, other researchers have found no difference between PLWH and HIV-negative study participants in the rate of fractures (474, 475).

The measures of bone health reported in the previous section have also been used to evaluate bone health among PLWH. However, there are no agreed BMD cut-offs for the FRAX score among PLWH (398) and there is no tool to assess fracture risk

utilizing information from clinical factors alone (398). Attempts to use the FRAX score on the basis of clinical conditions alone to identify PLWH at risk of osteopenia or osteoporosis, even when HIV was included as a cause of secondary osteoporosis, resulted in an underestimation of the number of people in need of treatment (401, 405). Therefore, the use of both clinical factors and measures of BMD have been utilized for fracture risk prediction among PLWH (401, 476).

Among PLWH it has been found that low TBS is associated with a high prevalence of vertebral fractures. Vertebral fractures are of interest, since they have been used by WHO to define fractures caused by injury that would be insufficient to fracture a normal bone (464, 477).

2.4.6 Risk factors for low BMD and fractures

More than 30 are the risk factors for osteoporosis (low BMD) which subsequently increases the risk for fractures. The list includes lifestyle, genetic, hypogonadal, endocrine, gastrointestinal, hematologic, rheumatologic, neurological, HIV/AIDS, respiratory and renal factors (397). This section will consider the factors associated with low BMD and fracture risk by the following categories: Sociodemographic and lifestyle, Clinical, HIV-specific and Other factors.

2.4.6.1 Sociodemographic and lifestyle factors

Older age has been associated with low BMD in the general population (RR 2.2 95% CI 1.7, 2.8) (388, 478) and among PLWH (β-coefficient = -0.05, $P < 0.001$) (461). Older women (>65 years) have been found to have a higher risk of hip, forearm, spine or proximal humerus fractures compared to men (347, 354, 479, 480). Women at the age of 50 and 80 years, have been reported to have a 14-fold and a 145-fold higher risk, respectively, of hip fracture compared to younger women (347).

Lifestyle characteristics, including smoking, use of alcohol and greater amounts of caffeine intake have been linked with an increased risk for fractures in the general population (341, 354, 386, 481) and low BMD among PLWH (472). Factors such as white ethnicity (HR=1.92, 95% CI (1.63, 2.28)), alcohol-related diagnoses (HR=1.65, 95% CI (1.26, 2.17)) and low BMI (HR=0.94, 95% CI (0.92, 0.96)) have been associated

with increased fracture risk. Other lifestyle factors such as former and current injection drug use and physical inactivity, have been associated with reduction of BMD and incident fractures in PLWH (442, 461, 467, 468, 472, 475, 482-487). Among PLWH malnutrition, decreased intake of calcium (intake <400 mg/d) and hypovitaminosis D have also been associated with increased history of fracture and low BMD (388, 488).

In the general population compared to abstainers, persons who consume 0.5 to 1.0 alcoholic drinks per day have 20% lower risk of hip fracture (RR=0.80, 95% CI (0.71, 0.91)) while persons consuming more than 2 drinks per day had almost 40% higher risk (relative risk (RR)=1.39, 95% CI (1.08, 1.79)) (344). Conversely, physical activity has been associated with a reduced risk for fractures. In particular, very active women have been found to have a 36% lower risk of hip fractures (RR=0.64, 95% CI (0.45, 0.89)) compared with women who are least active (342).

2.4.6.2 Clinical

In the general population, presence of more than three comorbidities and suffering from functional impairment that restricts leaving the house, have both been identified as risk factors for decreased BMD (388). Moreover, low BMI <19 kg/cm^2 and a history of fracture have been associated with increased loss of BMD (388). Among PLWH BMI decrease (by 1 kg/m^2) has been found to be associated with a 17% increased risk of osteopenia and a 24% increased risk for osteoporosis (OR=1.17, 95% CI (1.05, 1.31) and OR=1.24, 95% CI (1.07, 1.45), respectively), while the risk of osteopenia was approximately three-fold higher when lean mass was <61kg (OR=2.98, 95% CI (1.49, 5.97)) (71). Among men with HIV it has been reported that BMI ≥30kg/m^2 vs. <25kg/m^2 was associated with significantly increased risk of vertebral fractures (any fractures: OR=4.5, 95% CI (1.05, 19.29), P=0.043; severe fractures: OR=7.37, 95% CI (0.90, 60.78), P=0.06; multiple fractures: OR=6.44, 95% CI (1.10, 37.72), P=0.04)) (489). Excess weight loss/BMI, history of 10kg weight cycling (weight gain/ weight loss) and oligomenorrhea have been linked with increased fracture risk among PLWH (473) and decreased BMD (461). Per unit increase of BMI has been positively associated with increased LS (β-coeff.=0.3, 95% CI (0.2, 0.4),

P<0.001), FN (β-coeff.=0.2, 95% CI (0.1, 0.2), P<0.001) and TH (β-coeff.=0.2, 95% CI (0.1, 0.2), P<0.001) T-scores (461). Moreover those with history of 10kg weight cycling had an almost 3-fold higher probability of osteoporosis (OR=2.8, 95% CI (1.8, 4.3)) (473).

Clinical characteristics in the general population associated with increased risk for osteoporotic fractures include history of falls, type 2 diabetes, rheumatoid arthritis, CVD, liver disease, asthma, anxiety, use of tricyclic antidepressants and history of prior fractures (386, 481). A meta-analysis across 14 cohort studies, provided evidence that depression is associated with increased risk of fracture and bone loss, however, this association may be mediated by the use of antidepressants (490). Other researchers suggested that in the general population immune and endocrine mechanisms triggered by depression, low serotonin levels, inactivity and use of specific antidepressants are associated with bone loss and osteoporotic fractures (491, 492). Among PLWH clinical characteristics such as depression and renal insufficiency have been associated with higher risk for bone loss, fracture risk and fractures (488). In particular, men with HIV with chronic renal insufficiency have been reported to have 4-fold higher risk of any-type fractures (OR=4.3, 95% CI (1.29, 14.38), P=0.02) (489).

Among elderly people undergoing a chest or abdominal CT scan for various indications (aged ≥65), those with a history of prior fracture had a 2.35-fold increased risk for fracture (hazard ratio (HR) =2.35, 95% CI (1.55, 3.54)). Moreover attenuation of the first lumbar vertebra (L_1), scaled to Hounsfield units (HU) of 10, was associated with an almost 40% increased risk for future fragility fracture (HR=0.63, 95% CI (0.47, 0.85)) (352).

Other risk factors for osteoporotic fractures include a parental history of osteoporosis among women, use of corticosteroids, menopausal symptoms, gastrointestinal malabsorption, and other endocrine disorders (341). In a study of older white women (≥65 years) with no previous hip fracture, those whose mothers had a history of hip fracture had a 2-fold increased risk for hip fracture compared to women with no maternal hip fracture history (RR=2.0, 95% CI (1.4, 2.9)) (354). Among

postmenopausal women aged ≥45 years, wrist fractures are the most prevalent type of fracture (46.2%). History of a wrist fracture increased the risk for osteoporotic fracture by 58% (HR=1.58, 95% CI (1.29, 1.93)) while up to a 3-fold increase for osteoporotic fracture has been reported for women with primary fracture (HR for hip: 2.00, 95% CI (1.53, 2.63); spine 2.73, 95% CI (2.21, 3.36); humerus 3.18, 95% CI (2.56, 3.94) and any non-wrist site 2.66, 95% CI (2.30, 3.08)) (349). However, hormone treatment has been found to reduce the risk for osteoporotic fractures (341, 493). In particular women over the age of 50 on oestrogen treatment and women with a history of oestrogen use over the previous 2 years had a 35% and 66% reduced risk for hip fracture (RR=0.65, 95% CI (0.44, 0.98) and RR=0.34, 95% CI (0.12, 0.98), respectively) (493).

Other risk factors associated with higher risk for fractures among white older women in the general population include weight gain after the age of 25, history of previous fracture after the age of 50, being tall at the age of 25, self-rated health as fair or poor compared to excellent or good, previous hyperthyroidism, poor visual acuity or biophysical activity (4 hours a day or less on their feet). Low calcaneal bone density and prior treatment with long-acting benzodiazepines or anticonvulsant drugs have been associated with higher risk for fractures (354).

Decreased weight among older women has been identified as a risk factor for increased fracture risk. In particular women over the age of 65 years who lost 10% of their weight intentionally over a period of approximately 19 years had an increased risk for fragility fractures of 86% (RR=1.86, 95% CI (1.42, 2.43)), the association was similar among the women who did not intend to lose weight over the follow-up (RR=1.81, 95% CI (1.26, 2.61)) (494). Other studies reported that among women aged 65 years or more, those who weighed less (≤57.8 kg) had a 2.5-fold increase in the risk of hip fracture (RR=2.51, 95% CI (1.69, 3.73)) compared to heavier women (≥73.3 kg) (495).

Among men risk factors for increased osteoporotic fractures include history of rheumatoid arthritis, CVD, liver disease, type 2 diabetes, asthma, use of antidepressants, current use of corticosteroids and a history of falls (341).

Among HIV-positive males, those with diabetes mellitus had 4-fold higher odds of any-type fracture (OR=4.07, 95% CI (1.25, 13.48)), an 8-fold higher odds of severe fractures and a 6-fold higher odds of multiple fractures (OR=8.18, 95% CI (1.30, 51.43) and OR=6.10, 95% CI (1.48, 25.12), respectively) (489). Cerebrovascular disease was associated with a 95% higher risk of fractures in a study of HIV-positive male veterans (HR=1.95, 95% CI (1.14, 3.33)) (467) and hypertension was associated with a 32% higher rate of all fractures (RR=1.32, 95% CI (1.04, 1.69)) (448). Reduced BMD and a history of previous low-trauma fracture have been described as risk factors for fracture risk (474, 486). Other clinical conditions linked with increased risk for fracture include rheumatoid arthritis, family history of hip fracture, falls, frailty and higher serum creatinine (474, 486). Insulin resistance, diabetes and cerebrovascular disease may contribute to the high risk of fractures in PLWH (467, 489).

2.4.6.3 HIV-specific

HIV infection has been considered as a secondary cause of osteoporosis (496) and as a risk factor for bone demineralization (497). Several researchers have identified HIV infection as an independent risk factor for decreased BMD (63, 376, 450, 468, 470, 472, 473, 476, 498-504), osteopenia and osteoporosis (68, 366, 402, 459, 468).

The prevalence of osteopenia has been reported to vary from 22.0% to 67.5% (71, 367, 434, 439, 449), and of osteoporosis from 1.0% to 26.8% (71, 433, 436, 457, 505) among PLWH. Two of every three people presenting with HIV infection have osteopenia and PLWH have a 3.7 higher odds of developing osteoporosis compared to HIV-negative controls (506). More specifically, compared to HIV-negative controls, PLWH have been reported to have 5 to 30-fold higher odds of osteoporosis (Table 2.7) in 4 out of the 11 studies examined by Brown *et al*. but in the rest 7 studies, no significant association was identified.

Table 2.7: Odds ratios of osteoporosis (T-score≤ -2.5) in PLWH compared with HIV-negative controls, taken from Brown *et al.* (449)

Author	Odds ratio (95% CI)
Amiel (375)	5.03 (1.47, 17.27)
Brown (374)	4.26 (0.22, 82.64)
Bruera (376)	4.51 (0.26, 79.27)
Dolan (438)	2.11 (0.54, 8.28)
Huang (507)	3.52 (0.15, 81.92)
Knobel (434)	5.13 (1.80, 14.60)
Loiseau-Peres (435)	4.28 (0.46, 39.81)
Madeddu (377)	29.84 (1.80, 494.92)
Tebas (366)	3.40 (0.19, 61.67)
Teichman (371)	17.41 (0.97, 313.73)
Yin (508)	2.37 (1.09, 5.16)

Decreased CD4 count has been reported to be independently associated with increased risk of fragility fractures (483, 509) and lower BMD (401, 510). In particular, those with a CD4 cell count <200 cells/mm^3 have an almost 5-fold increased risk of fragility fractures compared to those with a CD4 cell count ≥200 cells/mm^3 (OR= 4.91, 95% CI (1.78, 13.57)) (509). Among treatment naïve PLWH who initiated cART, a low CD4 cell count was a strong independent risk factor for a lower BMD. In particular, in a 96-week follow up those who initiated cART at CD4 <50 cells/mm^3 experienced a 3.0% (95% CI (−4.0, −2.0) lower BMD compared to PLWH that initiated cART at CD4 >500 cells/mm^3 (511). Other researchers have reported conflicting results to the above, reporting no association of BMD with CD4 cell count or nadir CD4 count (512).

HCV infection commonly co-occurs with HIV. Recent data indicate that HIV/HCV coinfection is an independent risk factor for lower BMD (513) and incident fractures (50, 453, 474, 514, 515), including both low-trauma (482) and high-trauma (50) fractures. A three-fold increased fracture incidence has been reported among PLWH co-infected with HCV, compared with uninfected controls, with those who are living with both HIV and HCV being at increased risk of osteoporosis and fractures even before the development of cirrhosis (498). Long-term infection with HIV, HBV and untreated HCV have been associated with an increased risk for fragility fractures in treated PLWH (330).

HCV/HIV coinfected people have been reported to have an increased risk of hip fracture compared to HCV-mono-infected, HIV-mono-infected and uninfected persons (515). HIV/HCV-co-infection has been linked to low bone strength according to hip bone geometry. The prevalence of osteoporosis among HIV/HCV-coinfected persons has been reported to be 22% (95% CI (12, 31)) with HIV/HCV-coinfected persons being 63% more likely to have osteoporosis compared to HIV-monoinfected persons (OR=1.63, 95% CI (1.27, 2.11)). HIV/HCV-coinfected individuals had a 77% higher overall fracture risk compared with those who are HIV-monoinfected (OR=1.77, 95% CI (1.44, 2.18)). When compared to uninfected individuals, the overall fracture risk among HIV/HCV-coinfected individuals was almost 3-fold higher (OR=2.95, 95% CI (2.17, 4.01)) (442). Despite HCV/HIV coinfection being associated with BMD loss and increased fracture risk (50, 451, 454, 483, 499, 516, 517), it remains to be seen whether HCV cure with new agents will improve bone health.

2.4.6.3.1 BMD, fracture risk and cART

In the cART era, fractures are a leading cause of morbidity (518). Use and duration of cART have been associated with decreased BMD (449, 519). In a study of young PLWH and HIV-negative controls aged 14-25 years it was found that newly HIV-diagnosed men on cART had lower bone mass than controls (520). This might be linked with the increased risk for fractures and osteoporotic fractures and also reduced BMD linked with antiretroviral medication (50, 401, 447, 457, 487, 489, 521-523). Most commonly, studies have linked regimens including tenofovir disoproxil fumarate (TDF) or PI (366, 401, 449, 460, 467, 469, 482-484, 524-531) with an increased risk for fractures.

Initiation of cART has been associated with acceleration of BMD loss with the initial 12-month period being the period when the greatest decreases in BMD occur (67, 451, 499, 506, 532), potentially leaving PLWH at increased susceptibility to fractures. More specifically, the fracture incidence is higher in the first two years after cART initiation compared to that in subsequent years (482, 533). Reduced spine and hip BMD within the first 48 weeks after cART initiation have been reported to be

independent of cART type (534) and longer duration of therapy has been linked to further loss of BMD (521, 535), osteopenia and osteoporosis (433, 536-538).

More than 30% of treated PLWH experience substantial bone loss regardless of cART regimen (539), however, other researchers report that those receiving PI regimens (not including NNRTI) had a significantly lower total hip BMD Z-score compared to those receiving NNRTI regimens (not including PIs) or to those who are cART naïve or HIV-negative controls (mean (SD) -0.68 (0.15), -0.39 (0.14), -0.01 (0.10) and -0.05 (0.15), respectively, P=0.001) (520).

Other researchers report opposing findings suggesting that every additional year of cART duration decreases by 13% the odds of osteopenia (OR=0.87, 95% CI (0.80, 0.94)). Osteopenia risk decreases by 58% when the cART duration is >3 years vs. ≤3 years (OR=0.42, 95% CI (0.22, 0.80)) (71). Initiation of cART at higher CD4 counts may reduce the burden of osteoporosis and fragility fractures (450).

A protective effect of cART (vs. no cART) on all-cause fracture has been reported (540) with some researchers reporting that neither cumulative PI use nor TDF were associated with increased incidence of fractures (448, 457). Moreover no significant associations have been reported between HIV viremia, use of antiretroviral medication or cummulative exposure to cART, and risk of fracture (448, 509) or lower BMD (472, 541, 542). It is not entirely clear whether BMD loss is a direct effect (drug effect on osteoclasts and/or osteoblasts) and/or indirect (drug effect on the proximal renal tubule and/or vitamin D metabolism) (500).

2.4.6.3.2 BMD and Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

Exposure to NRTIs for less than 3 years has been significantly associated with osteopenia (71). A retrospective cohort study in Catalonia, Spain with median interquartile range (IQR) TDF exposure of 2.22 (1.06, 3.82) years reported that for every additional year on TDF BMD loss was increased by 8% (OR 1.08, 95% CI (1.03, 1.14), P=0.002). Moreover, PLWH exposed to TDF for more than 1 year had an increased rate of osteoporosis of 20% while the rate was increased by 37% among PLWH exposed to TDF for more than five years (543). Several studies have reported

that cART regimens are linked with compromising BMD after treatment initiation and the magnitude of reduction has been reported to be greater with the use of TDF-containing regimens (544-547). In particular 1-3% greater BMD loss with TDF compared with other regimens has been reported among treatment-naive PLWH, with exposure to TDF being associated with an intensified BMD loss in young adults compared to older adults (548). Among previously treatment naïve PLWH, 96 weeks after cART initiation, those on a TDF-emtricitabine (FTC) combination had significantly greater decreases in spine and hip BMD compared to PLWH on ABC-lamivudine (3TC) (-1.3% vs. -3.3% (P=0.004) and -2.6% vs. -4.0% (P=0.024), respectively), while participants on atazanavir (ATZ)/ritonavir (RTV) compared to efavirenz (EFV), had significantly lower BMD at the spine but not at the hip (-1.7% vs. -3.1% (P=0.035) and -3.1% vs. -3.4% (P=0.61), respectively) (534).

Duration of exposure to other NRTIs, such as 3TC-FTC, has also been linked with increased rates of osteopenia (71). Subjects on ABC-3TC have been reported to have a lower rate of BMD decline and bone turnover compared to those on TDF-FTC (534, 549). TDF and PI-based regimens have been linked to greater BMD loss compared to regimens including NNRTIs or Integrase Strand Transfer Inhibitors (INSTIs) (499) and some studies have suggested that BMD loss can be reduced by the selection of the NRTI-free (specifically TDF-free) regimens (550, 551). However, several switch studies have demonstrated that the BMD loss associated with TDF is largely reversible (500, 552, 553) and despite the intensified BMD drop after initiation of TDF-including regimens, BMD stabilizes after 48 weeks (365, 452, 487).

2.4.6.3.3 BMD and PIs

Current use of PIs and increased time on PIs (per 1 year increase) have been associated with 64% and 18% increased BMD loss and progression to low BMD respectively (OR=1.64, 95% CI (1.35, 2.04), P<0.0001 and OR=1.18, 95% CI (1.12, 1.24), P<0.0001) (543). Among male veterans with HIV, those on PIs vs. non-PIs (excluding those not on ART) had a 25% higher risk for fractures (HR=1.25, 95% CI (1.04, 1.50)) (467). For those exposed to PIs for less than 2 years the rate of osteoporosis was 18% while it reached 64% for those exposed for more than ten

years (543). Subjects remaining on PIs compared to those that discontinued PIs were found to have a lower LS BMD (T score -1.3 vs. -0.8, P=0.04) (554). On the other hand, longer duration of lopinavir (LPV) therapy has been shown to be protective for osteopenia among men with HIV younger than 50 (71). Use of PIs has been identified as a risk factor for fragility fractures among several researchers (461, 467, 469, 470, 485, 487, 530, 555, 556).

Hypothyroid patients on PIs have been found to have a significantly lower LS BMD compared to those with normal thyroid function taking PIs (-1.56 vs. -1.13, P=0.029) (557) and femur bone loss among those receiving PIs is greater compared to those on NNRTIs (558). In a Japanese study, longer treatment (per 1 year increase) with a PI was associated with 10% lower LS BMD and 19% lower FN BMD (OR=1.10, 95% CI (1.00, 1.21), P=0.042 and OR=1.19, 95% CI (1.04, 1.35), P=0.009, respectively) (554). Another study of cART-naïve participants of whom 34% had impaired BMD, found that after one year, the mean drop of LS BMD was 4.4% and 5.8% among participants receiving PI-containing regimens (PI and NRTI or PI and a NNRTI) compared to participants on the NNRTI/NRTIs arm that experienced a 1.5% reduction, P=0.007 and P=0.001 respectively (559).

Although the studies above have shown a significant association between use of PIs and increased bone turnover, several other studies have failed to show any difference (375, 376, 445, 560).

2.4.6.3.4 BMD and NNRTIs

EFV use has been associated with low vitamin D and osteoporosis (63). However, other researchers have reported that exposure to EFV has a protective effect against osteopenia (71). Vitamin D is a key component of bone and mineral metabolism. Effective absorption of calcium, which is essential for a good bone health can be decreased when the levels of vitamin D are low. In the general population vitamin D deficiency has been found to be on the causal pathway towards bone mass reduction (561), with hypovitaminosis D being associated with increased risk of fragility fractures (562, 563), osteopenia and osteoporosis (63, 402) and incidence of vertebral fractures among PLWH (562).

2.4.6.4 Other factors

B and T lymphocytes have been found to be potential contributors to HIV-induced bone loss (564). Although bone mass is a body characteristic that is mostly genetically predefined, hormonal imbalances like androgen/oestrogen deficiency, low testosterone and hypogonadism have been linked to BMD loss and increased fracture risk (461, 470, 485, 487, 518, 565).

2.4.7 Interventions

Effective interventions to avoid future fractures suggest prioritization of BMD monitoring and treatment among PLWH with a history of fragility fractures and significant risk factors instead of treating everyone with reduced BMD (486). Avoidance of malnutrition and adherence to cART among PLWH helps to maintain a good skeletal health (566). Dietary and lifestyle modification may improve bone health in all PLWH (454, 499, 505).

In the absence of known risk factors for fractures a common practice is to screen all women ≥65 years and men aged ≥75 years for fracture risk (398). However, in the general population of people <50 years, those with major risk factors should be screened for osteopenia and osteoporosis (567, 568). Among PLWH a recommendation is to assess fracture risk primarily using the FRAX scores with no BMD measures in all men with HIV aged 40–49 years and HIV-positive premenopausal women aged ≥40 years (66, 569) in order to identify people at early stages of osteopenia and osteoporosis. The current recommendation among PLWH suggests screening of postmenopausal women and men aged ≥ 50 years and treat for osteoporosis those with BMD T-score ≤-2.5 (337).

Other interventions suggest screening of BMD by DEXA and assessment of fracture risk in all PLWH regardless of any further specification (401, 570) while others suggest screening of all men with HIV over the age of 50 years, as well as postmenopausal women living with HIV (455). Other recommendations suggest annual or bi-annual DEXA scans after initiation of osteoporosis therapy (505, 563).

Treatment with bisphosphonate has been considered effective for treating PLWH with decreased BMD, increased risk for fractures or those who have progressed to osteoporosis (67, 452, 454, 462, 499, 525). Some researchers have found that use of the bisphosphonate alendronate combined with calcium, and vitamin D supplementation was more effective in increasing BMD compared with calcium and vitamin D supplementation alone (505, 563, 571, 572) while others found that weekly alendronate intake along with dietary counselling was more effective in reducing osteoporosis in PLWH compared to dietary counselling alone (573).

Among men with HIV combination use of calcitriol, cholecalciferol or calcium was associated with deceleration of bone turnover to a greater extent than supplementation of cholecalciferol or calcium alone (574). Finally, muscle strengthening and balance exercises have also been suggested to increase BMD and reduce fractures and osteoporosis (454, 505).

There are few published treatment studies of low BMD in PLWH, therefore treatment with bisphosphonates as first line agents is the common practice as in the general population and generally increases BMD (569). Discontinuation of PIs has been suggested as a BMD-loss recovery method, with more significant BMD recovery occurring at the LS (554).

2.5 Literature review summary

Considering the longer survival among PLWH in high-income countries due to effective cART and the decrease in the rates of AIDS-defining and non-AIDS-defining mortality (139, 140) the research of the cohort of ageing PLWH is of interest. The challenge of PLWH is that they may express frailty, falls and fractures differently comparted to HIV-negative controls.

PLWH experience frailty at earlier ages of life and the prevalence of frailty is higher among those with advanced disease. Regarding falls, it is debated whether the prevalence among PLWH and HIV-negative controls is similar or not. Finally, the prevalence of fractures is reported to be higher among PLWH compared to HIV-negative controls with PLWH reporting a higher loss of bone mass.

2.6 Gaps in the literature and thesis aims

Ageing and development of frailty, falls, low BMD and fractures in PLWH have gathered a lot of interest and emerged as major topics in HIV research. Nevertheless, several research gaps remain to be addressed. First, the main body of the literature regarding frailty, falls, low BMD and fractures is among people within the USA, therefore, the results may not be generalizable to European settings. In Western Europe, there are no studies that have explored the prevalence of frailty, falls, low BMD and fractures among PLWH that are as big as the POPPY study. Second, few studies among PLWH have explored the association between depressive symptoms assessed with more than one tool with the development of frailty, falls, low BMD and fractures among PLWH. Third, despite the finding that a good body of the literature has suggested a negative association of ART with BMD and fracture risk, few studies have investigated the association of ART assessed by PK parameters with BMD and fracture risk.

The aim of this thesis is to investigate the association of HIV with frailty, falls, BMD and fractures using data from the POPPY study described in detail in Section 3.2. The hypothesis and objectives for each specific chapter are listed at the beginning of each chapter. The chapter that follows (Chapter 3) provides a detailed description of the study design and the processes of data management and data cleaning and the statistical analysis methods that were used in this thesis.

Chapter 3 Methods

3.1 Introduction

The data included are derived from the POPPY study. This chapter describes the study design and population, the data collection, management and cleaning and, finally, the statistical methodology used. Each of the Results chapters contains a brief section to describe in more detail the statistical methods used in that particular chapter.

3.2 The POPPY study

3.2.1 Study design

This study is the first large-scale, prospective, multicentre, observational cohort study that aims to assess clinical outcomes of older and younger PLWH against older HIV-negative controls in England and Ireland. The study was set up in response to the need to understand the recent studies that had supposedly indicated an acceleration of ageing among PLWH exhibited through increased rates of several comorbidities including CVD, cancers, cognitive disorders, end-stage liver and renal diseases, frailty, falls and fractures (43, 448, 575-577).

The primary aims of the POPPY study are: i) to describe the burden of clinical conditions in older PLWH; ii) to investigate whether there is an increased burden of comorbidities among PLWH compared with demographically similar HIV-negative controls; iii) to describe the healthcare resource use required to treat some of the more common comorbidities occurring in older PLWH; and iv) to investigate whether these differ between those with and without HIV. An additional aim of the study is to investigate the impact of age on PK profiles of different antiretroviral agents.

3.2.2 Recruitment process of the study population

The POPPY study was initiated in 2013 and was originally funded to involve a screening/baseline visit and two additional annual visits (visit 2 and visit 3) approximately 12 months apart. The study participants are PLWH aged ≥50 years (older PLWH); PLWH aged <50 years (younger PLWH); and a control group of HIV-negative people aged ≥50 years. The participants are of white or black African ethnicity and the inclusion criteria required that all participants must have acquired

HIV via a sexual route (either sex between men or sex between men and women). The younger group of PLWH were frequency-matched to the group of older PLWH on gender, ethnicity, sexual orientation and participating clinic. The HIV-negative control group were required to have a documented negative HIV test in the 6 months prior to enrolment or at the time of screening and this group was frequency-matched to the group of older PLWH by age, gender, ethnicity, sexual orientation and geographical location (whether in or out of London).

Eight clinical sites are involved in the POPPY study: Chelsea and Westminster Hospital (CWH), Homerton University Hospital (HUH), Kings College Hospital (KCH), Mortimer Market Centre (MMC), Royal Free Hospital (RFH), and St. Mary's Hospital (SMH), all in London, the Royal Sussex County Hospital, Brighton (RSH), and the Mater Misericordiae University Hospital, Dublin (DUH) in Ireland (Figure 3.1). Recruitment targets were set at each participating centre based on the demographic characteristics of each clinic, using data from the UK CHIC study (578) and the Dublin ID cohort (579) to ensure the representativeness of the PLWH in the study.

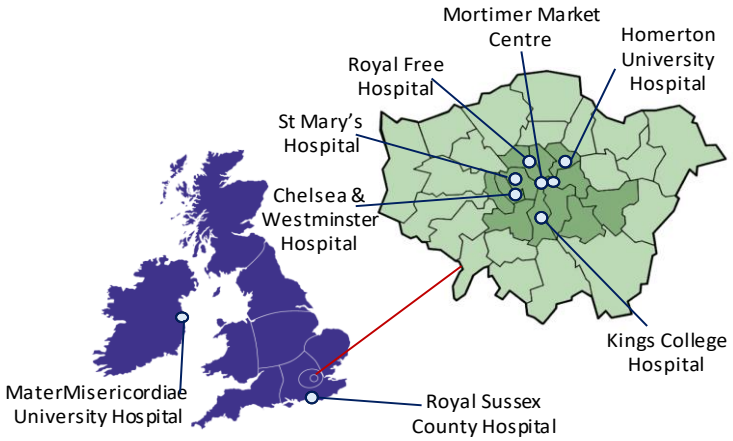


Figure 3.1: The eight sites participating in POPPY study in England and Ireland

The original plan was to recruit a sample of 2000 participants (1000 older PLWH, 500 younger PLWH and 500 HIV-negative controls). However, study recruitment was stopped after 1377 participants were enrolled, including 699 older PLWH, 374 younger PLWH and 304 HIV-negative controls (Table 3.1). The POPPY steering committee decided that achieving a larger sample size could not justify the amount of effort and resources required. Each participant provided informed consent prior

to participation. The screening visit evaluated whether the subject met the study inclusion/exclusion criteria and HIV antibody testing was undertaken for the HIV-negative cohort participants.

Table 3.1: Recruited POPPY participants stratified by study centre and group

	Recruited			Total
	HIV positive		HIV-negative	
Centre	≥50 years	<50	≥50 years	
St. Mary's Hospital	108	64	65	237
King's College Hospital	66	36	28	130
Chelsea & Westminster Hospital	192	96	75	363
Royal Free Hospital	17	8	7	32
Homerton University Hospital	17	10	10	37
Mortimer Market Centre	133	59	42	234
Royal Sussex County Hospital	135	71	57	263
Mater Misericordiae University Hospital	31	30	20	81
Total	699	374	304	1377

3.3 Data management

The Imperial Clinical Trials Unit (ICTU) trial manager was tasked with making sure that each centre met recruitment goals and was taking steps to minimise attrition rates for subsequent study visits. Dataset management was done using the InForm ITM (Integrated Trial Management) system version 4.6, a web-based data entry system built on an Oracle database. This arrangement allowed the trial manager to undertake monitoring among other functions. Two monitoring appointments were performed on a random sample of participants during the baseline visit to evaluate data quality, consistency and integrity. The ICTU trial manager prepared the Data Management Plan (DMP) and was closely involved in the data cleaning process (described below in Section 3.6) in collaboration with Professor Caroline Sabin and myself. The DMP described the data management processes employed ensuring that the study was managed and maintained in accordance with the International Conference on Harmonisation-Good Clinical Practice (ICH-GCP) guidelines.

During the second year of my PhD I published the POPPY study cohort profile in the *International Journal of Epidemiology* (580). This paper described the reasons for setting up the cohort, the baseline characteristics of the participants and study procedures and offers some of the key findings and publications at the time. I have

primarily used data from the baseline visit for this work. Therefore, I will next describe the process of data extraction and cleaning for this baseline dataset.

3.4 Data collected

During the baseline visit 1 the electronic CRF (eCRF) (Appendix I) was administered. Additionally, the self-completed questionnaire (Appendix II) was used to assess the Lawton IADL scale, two depressive symptoms scores and other patient-reported outcomes. The baseline visit 1 also included a DEXA scan and was followed by collection of biological samples.

All data were pseudonymised and study participants were allocated a unique ID in keeping with the study's data protection and ethics policies. The participants' initials and surname as well as the study centre ID were collected and stored at the study centres for participant tracking. In summary, the data collected at each study visit are described in Table 3.2.

3.4.1 eCRF

The eCRF was built in the Inform system and was managed by research nurses and research assistants. At each site they collected information on participant's demographic and social history, intoxications, anthropometric characteristics, physical functioning tests, current cART, family and personal medical event history, healthcare utilisation, co-medications and history of serious adverse events (SAEs).

Table 3.2: Information collected at each POPPY visit

	Baseline visit	Visit 2	Visit 3
eCRF			
Demographics and social history	●	●	●
Smoking, alcohol and substance use	●	●	●
Anthropometrics	●	○	●
Walk and hand grip test	●	○	●
Current antiretroviral medication	●	●	●
Family medical history	●	○	○
Medical history	●	●	●
Co-medications (non-cART)	●	○	●
Healthcare utilisation	●	●	●
SAEs	●	●	●

	Baseline visit	Visit 2	Visit 3
Self-completed questionnaire			
Quality of life	●	●	●
Depressive symptoms	●	●	●
Cognitive complaints	●	●	●
Functionality in activity of daily living	●	●	●
Fall risk	●	●	●
Pain	●	●	●
Sexual function	●	●	●
Cognitive assessment	●	○	●
Biological samples and scans			
Biochemistry and urinalysis	●	○	●
Syphilis, hepatitis B and C serology	●	○	●
Pharmacokinetic analysis	●	○	●
Fasting lipids	●	○	●
Haematology	●	○	●
DEXA scan	●	○	●

● Collected

○ Not collected

3.4.2 Self-completed questionnaire

The self-completed section of the questionnaire contained 87-items including questions on cognitive complaints, general health, feelings of anxiety or depression, history of falls, aches and pains, employment, education, housing and sexual function. The pain data were recorded using a hard copy printout of a mannequin where the study participants marked ache and pain locations. The hard copies of the pain mannequins were scanned for archive purposes and sent to Professor Caroline Sabin for coding in a separate Excel spreadsheet.

The list of questions and the pictures of the pain mannequins were used to determine the bodily site(s) of pain (Appendix II). Completion of the self-completed questionnaire required approximately 30 minutes and the research nurses were available for clarification. The data were recorded on the survey tool Qualtrics that operated independently from Inform.

3.4.2.1 The Lawton IADL scale

Functional status assessment among the study participants was done using the IADL scale which establishes the skill level required for independent living among eight key domains. Study participants were scored according to their level of functioning in each category (0; lack of ability, 1; having the ability (fully or partly)). A summary score ranging from 0 (low, dependent) to 8 (high, independent) indicated the participants' overall functionality. The eight domains measured the ability of participants to use a telephone, do their shopping, prepare their food, do their housekeeping, do their laundry, use a means of transport, take their medication and handle their finances.

3.4.2.2 Depressive symptoms

Depressive symptoms were assessed using the Center for Epidemiological Studies Depression symptoms index (CES-D) (581) and the Patient Health Questionnaire scale (PHQ-9) (582), Box 2. Both the PHQ-9 and CES-D scores are considered reliable and valid measures for assessing depressive symptoms. The advantage of PHQ-9 is that it is administered easily and takes half the time to be completed in comparison to the CES-D (583-585). However, since both PHQ-9 and CES-D have been administered in POPPY, I have explored both scales.

CES-D is a 20-item score that assesses the frequency of symptoms during the past week. The symptoms are scored using a Likert-type scale ranging from 0 to 3 ('rarely or none of the time' to 'most or all of the time', respectively). The scores for the questions 4, 8, 12 and 16 need to be reversed as they are positive statements and the total score after adding up ranges between 0 and 60. The resulting CES-D score was categorised into three groups of depressive symptomatology: none to mild (0-16), moderate (16-23) and severe (24-60) (586). The PHQ-9 rates the frequency of nine symptoms over the past two weeks on a Likert-type scale that ranges from 0 to 3 ('not at all' (0), 'several days' (1), 'more than half the days' (2), and 'nearly every day' (3)). The answers are summed with the total score ranging between 0 and 27. The resulting score was categorized as follows: No symptoms of depression/minimal (0-4), mild (5-9), moderate (10-14), moderately severe (15-19), and severe (20-27).

Box 2: Assessment of depressive symptoms in POPPY

<table>
<tr><td colspan="2">Depressive symptoms scores</td></tr>
<tr><td colspan="2">CES-D questionnaire</td></tr>
<tr><td colspan="2">20-item questionnaire</td></tr>
<tr><td>1. I was bothered by things that usually don’t bother me
2. I did not feel like eating; my appetite was poor
3. I felt that I could not shake off the blues even with help from my family or friends
4. I felt I was just as good as other people
5. I had trouble keeping my mind on what I was doing
6. I felt depressed
7. I felt that everything I did was an effort</td><td>8. I felt hopeful about the future
9. I thought my life had been a failure
10. I felt fearful
11. My sleep was restless
12. I was happy
13. I talked less than usual
14. I felt lonely
15. People were unfriendly
16. I enjoyed life
17. I had crying spells
18. I felt sad
19. I felt that people dislike me
20. I could not get “going”</td></tr>
<tr><td colspan="2">Likert scale range
0 (rarely/none of the time - less than 1 day)
3 (most/all of the time - 5 to 7 days)</td></tr>
<tr><td colspan="2">Total score range (0 to 60)</td></tr>
<tr><td colspan="2">Higher scores indicate higher levels of anxiety and depression</td></tr>
<tr><td colspan="2">Internal reliability: alpha coefficient ranges from 0.86 to 0.89</td></tr>
<tr><td colspan="2">PHQ-9 questionnaire</td></tr>
<tr><td colspan="2">9-item questionnaire
1. Little interest or pleasure in doing things
2. Feeling down, depressed, or hopeless
3. Trouble falling or staying asleep, or sleeping too much
4. Feeling tired or having little energy
5. Poor appetite or overeating
6. Feeling bad about yourself, or that you are a failure or have let yourself or your family down
7. Trouble concentrating on things, such as reading the newspaper or watching television
8. Moving or speaking so slowly that other people could have noticed? Or the opposite-being so fidgety or restless that you can have been moving around a lot more than usual?
9. Thoughts that you would be better off dead or of hurting yourself in some way</td></tr>
<tr><td colspan="2">Likert scale range
1 (none of the time)
6 (all of the time)</td></tr>
<tr><td colspan="2">Total score range (0 to 30)</td></tr>
<tr><td colspan="2">Higher scores indicate higher levels of anxiety and depression</td></tr>
<tr><td colspan="2">Internal reliability: alpha coefficient 0.85</td></tr>
</table>

3.4.2.3 Short Form Health Survey questionnaire (SF-36)

The questionnaire used to assess the health-related quality of life among the POPPY participants was the SF-36. It is a patient-reported survey consisting of 36 items in eight sections: vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning and mental health (587). The questions within each section are weighted and summed to construct eight scores, which are then mapped onto a 0-100 scale, the lower the score, the higher the disability. A score of zero is equivalent to poor functionality, and a score of 100 is equivalent to full functionality. The summary scores for physical and general health were mainly used in analyses.

3.5 Variables of main interest

3.5.1 Frailty assessment in POPPY

For descriptive analysis participants that fulfilled none of the four criteria described in Box 3 were considered robust, those who fulfilled one or two of the four criteria were considered as pre-frail and those that fulfilled three or four of the criteria were considered frail. For all subsequent analyses frail were considered those who fulfilled 3 or 4 of the frailty criteria described in Box 3 and non-frail those who fulfilled 0, 1 or 2 of the criteria. This is an adaptation of the frailty measure suggested by Fried *et al.* (95); it does not incorporate unintentional weight loss as there was no relevant question asked at the baseline POPPY visit. This frailty assessment among PLWH has also been adopted by Desquilbet *et al.* (155), Önen *et al.* (160) and Kooij *et al.* (173).

Box 3: Components of frailty definition in POPPY

1. Slowness
Decreased walking time as defined by a timed 15-foot walk test: men with a height of <173 cm and women with a height of <159 cm who walked 15 feet in >7 seconds are considered to fulfil the criteria, whereas men >173 cm or women >159 cm met the criteria if they walked the same distance in >6 seconds
2. Weakness
Decreased grip strength measured by a dynamometer: men with a BMI ≤24 kg/m^2 are considered to meet the criteria if their grip strength is ≤29 kg; for men with a BMI of 24.1 to 28 kg/m^2, the criteria is met if the grip strength is ≤30 kg; and for men with a BMI >28 kg/m^2, the criteria is met if the grip strength is ≤32 kg. For women, the thresholds are 17, 17.3, 18 and 21 kg for those with BMIs of ≤23, 23.1-26, 26.1-29 and>29 kg/m^2, respectively
3. Low physical activity
Low physical activity measured through the SF-36 quality of life questionnaire: participants responding "Yes, limited a little" or "Yes, limited a lot" to the question "Vigorous activities such as running lifting heavy objects participating in strenuous sports" were considered to fulfil the criteria
4. Exhaustion
Exhaustion measured through the SF-36 quality of life questionnaire: participants responding "Occasionally or a moderate amount of time (3-4 days)" or "Most or all of the time (5-7 days)" to either of the questions "I felt that everything I did was an effort" or "I could not get going" were considered to fulfil the criteria

3.5.2 Falls assessment in POPPY

Falls in POPPY were recorded using the CRF. Study participants were asked to respond to the following question: "Over the past 28 days have you had any falls?". They were able to select whether they had zero, one, two or three or more falls. Those who experienced more than 1 fall in the past 28 days were considered to have recurrent falls. Additional information was asked regarding the location, cause and injury caused by the falls. The questions are described in detail in the Appendix II.

3.5.3 BMD

The BMD measures (density, Z and T-score) were derived by comparing the participant's score to that of an established reference range of the peak bone mass for men and women (363, 588). BMD was assessed at several locations on the body (LS, FN, ward trochanter (WT), femoral shaft (FS) and TH). However, for Chapter 7 the BMD T-score at LS, FN and TH were considered the most complete, since some of the

sites did not perform all scans. Only results at these three sites are therefore presented in this thesis.

3.5.4 PK parameters

The PK modelling of TDF, FTC, ABC and 3TC was carried out by the University of Liverpool. The treated PLWH who consented, provided one PK aliquot at the baseline visit and visit 3 and the samples have been transferred to Liverpool from the Jefferiss Trust Laboratory. Clinical data (PK data, weight, height, BMI, ethnicity, comorbidities, co-medications, etc.) and data regarding the current use of TDF, FTC, ABC and 3TC, time since last dose and frequency of dose were provided to the University of Liverpool by the co-principal investigator (co-PI) of the study, Professor Caroline Sabin for the purposes of PK modelling.

Ultra-performance liquid chromatography was used to quantify plasma concentrations of TDF, FTC, ABC and 3TC samples taken once or twice daily. Patients with unknown dose or unknown post-dose time were excluded from the PK analysis. Other patients excluded were those with post-dose time >16h or >30h for twice or once daily regimens, respectively. The proportion of samples below the lower limit of quantification (LLQ) of the assay (<0.025 mg/L) for TDF, FTC, ABC and 3TC were 2.3% (13/555), 1.9% (10/519), 31% (34/109) and 5.6% (8/143). Samples <LLQ were given values of LLQ/2 with the exception of ABC. Given the high proportion of ABC samples with values below the LLQ, the M3 method was implemented in NONMEM (589) in order to reduce bias of parameter estimates and prevent exclusion of data. The M3 method suggests ignoring sample values below LLQ and estimating them by treating the sample as a whole in which case, values below the limit of quantification are excluded.

For each of TDF, FTC, ABC and 3TC the PK models predicted the area under the plasma concentration-time curve ($AUC_{0\text{-}24h}$) for each study participant. This estimates the body exposure to a drug in the first 24 hours after the administration of a drug dose. The maximum concentration (C_{max}) estimates the maximum measured plasma concentration over the last 24-hour dosing interval and trough concentration (C_{min}) estimates the minimum measured plasma concentration over the last 24-hour dosing

interval. Clearance (CL_{24h}) estimates the average drug concentration over the last 24-hour dosing interval (Figure 3.2). Analysis results from the University of Liverpool were sent to Professor Caroline Sabin and myself in the form of an Excel spreadsheet.

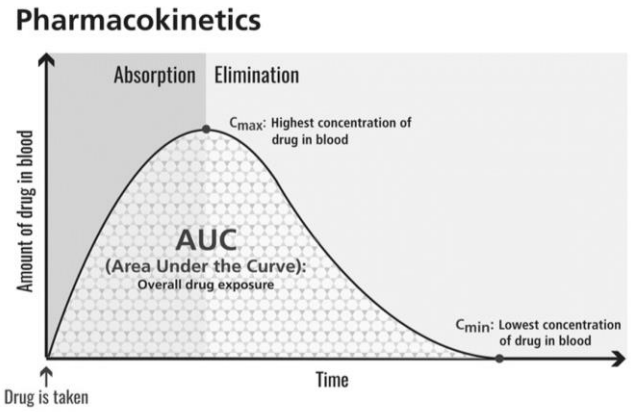


Figure 3.2: PK parameters

3.5.5 Fracture and FRAX assessment in POPPY

Within the medical history section of the CRF, there was a subsection asking participants if they have any fracture history. Those responding positively were asked to provide additional information. The year of each fracture was reported, and the location of the fracture was categorised using the codes in Box 4. Adulthood fractures were defined as those that occurred from the age of 21 years and older and childhood fractures were those occurring before the age of 21. Recent fractures were those that occurred at any site within 5-years before entering POPPY.

Fractures were also classified as either occurring at an osteoporotic or a non-osteoporotic site. Fractures at osteoporotic sites were those that occurred at the hip, upper arm, vertebrae and wrist, while fractures at a non-osteoporotic site included all others: head; upper extremities such as collar bone, elbow, forearm; hand; fingers; ribs; pelvis; lower extremities including thigh, knee, lower leg; ankle; foot; toes and those that occurred at an unknown site. Those with a fracture history were then asked to specify which side of the body the fracture occurred (left/right) and the cause of the fracture (fall from height more than your own length/fall from height less than your own length/ traffic accident/other-please specify). Finally, information on whether the fracture required an open surgery or not was recorded.

This coding employed a mixture of approaches from the relevant literature that was developed by me (341, 344-349).

FRAX scores were calculated manually by Megan Yeomans (a student from Nonsuch High School in Surrey who interned in the summer of 2018) and by myself. The FRAX® calculation tool (Figure 3.3) required 12 parameters to calculate the scores.

Box 4: Bodily location of the fracture among POPPY participants

1.	Wrist
2.	Upper arm
3.	Hand
4.	Fingers
5.	Other upper extremities (collar bone, elbow, forearm)
6.	Ribs
7.	Pelvis
8.	Ankle
9.	Foot
10.	Toes
11.	Hip
12.	Other lower extremities (thigh, knee, lower leg)
13.	Head (skull, nose, jaw)
14.	Vertebrae (back, neck)
15.	Unknown

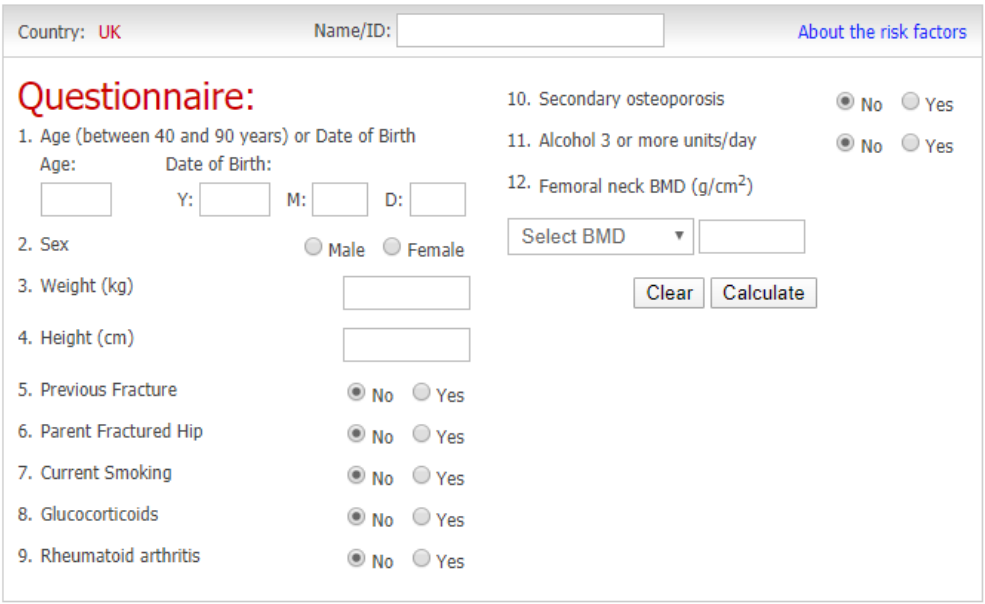


Figure 3.3: The UK-specific online FRAX® calculation tool, taken from https://www.sheffield.ac.uk/FRAX/tool.aspx

3.6 Data extraction

The exported files were provided in a Zip folder with a total of 297 comma-separated values (CSV) files and 173 STATA files. There were 11,154 variables of which 23 were repeated in each dataset and 4,323 were unique. The STATA data extract was sent to me from the InForm team on 4 April 2016 and included a total of 4,930 variables of which 3,039 were unique and relevant to the baseline visit. Both CSV and STATA format files were used to construct the final dataset of the baseline visit. I initially used the extracted STATA files in the data cleaning process and in the construction of the baseline visit dataset. However, due to some date and numeric variables not being correctly identified, I then used the CSV files which I imported to STATA.

3.7 Data coding and cleaning

Data cleaning was a two-part process. The first part was performed in collaboration with the ICTU. Values of the continuous variable that appeared out of the expected range were identified through graphical and statistical analyses. They were then queried with the study centres for cross-checking and correction. I generated a Google Drive spreadsheet and shared it with the trial manager, so that we could monitor the progress of queries raised. The spreadsheet included the following columns: Pending, Comment from Laura, Date queried, Date reported, Patient form, Query. A screenshot of the shared spreadsheet with the anomalies of the data is shown in Figure 3.4.

	Pending?	Comment from Laura	Date queried	Date reported	Patient	Form	Query
2	no	Resolved by nurse 18/02/2016	11/02/2016	11/02/2016	KCH032	Anthropometrics	42.00 cm
3	no	Resolved by nurse 15/02/2016	11/02/2016	11/02/2016	UCL1290	Anthropometrics	empty Date of visit/ No anthropometrics
4	no	Resolved by nurse 17/03/2016	12/01/2016	11/02/2016	KCH559	Anthropometrics	empty Date of visit
5	no	Patient withdrew consent before baseline visit	N/A	11/02/2016	CWH1407	Anthropometrics	Date of visit: "Not Applicable"--what does it mean?
6	no	Patient withdrew consent before baseline visit	N/A	11/02/2016	CWH1305	Anthropometrics	Date of visit: "Not Applicable"--what does it mean?
7	no	Comment saying 'not done in error'	N/A	11/02/2016	RFH1300	Anthropometrics	patient has a date of anthropomentrics (27/01/2016) but no other info reported, no (Not Done) reported
8	no	Comment saying 'not done'	N/A	11/02/2016	UCL904	Anthropometrics	Waist circ==0
9	no	Comment saying 'not done'	N/A	11/02/2016	KCH550	Anthropometrics	Waist circ==0

Figure 3.4: Sample of the 2917 queries raised to the ICTU trial manager using a Google document spreadsheet

In total, 2,917 queries were raised with the ICTU trial manager from 11 February 2016 until 26 July 2016 of which 2,381/2,917 (81.6%) were resolved by the ICTU trial manager and the remaining 536/2,917 (18.4%) were resolved by the study co-PIs and

myself (second part of data cleaning). More details on the involvement of co-PIs and myself in the data cleaning process is provided in the following sections.

3.7.1 Demographic characteristics

A detailed review of the demographic data regarding age, ethnicity and HIV status was required to ensure that those included in the study met the inclusion criteria and there was no missing data for those variables. I corrected missing visit dates or dates erroneously listed as being outside the study period by querying them to the ICTU trial manager. The study participants were asked to report their own and their parent's country of birth in a free-text field. There was great variation in the reporting of country of birth (e.g. U.K., UK, United Kingdom, GB, Great Britain, England). Some study participants also reported their city of birth. In order to provide a variable that could be analysed more readily, I created country groupings as agreed in advance with the study co-PIs: UK/Ireland, rest of Europe, Africa, North America, Southern/Central America, rest of the world and missing.

3.7.2 Anthropometric, blood pressure, grip strength and timed walk

Values of height, weight and waist circumference either below the 5th centile or above the 95th centile were cross-checked with the ICTU trial manager and were corrected where appropriate. More specifically, those with height ≤158 cm or ≥186 cm, weight ≤59 kg or ≥106 kg or with waist circumference ≤77cm or ≥115 cm were first checked for plausibility. Any anthropometric measures reported incorrectly (e.g. feet instead of centimetres) were converted as necessary.

The gait speed test measured the time needed to walk 15 feet. For 15 participants the gait speed test result was recorded as below 2 seconds (e.g. 1.2 seconds). The trial manager queried those values with the study centres, but it was not possible to retrieve the correct values. The study management group agreed that these were unrealistic values and should be corrected to 2 seconds.

3.7.3 Lifestyle characteristics

Of lifestyle characteristics, only the responses for smoking and alcohol were checked for logical errors and corrected to common units were necessary. For example,

several participants reported that they smoked 1 pack of cigarettes per day; this was then converted to 20 cigarettes per day. Extreme values (≥60 cigarettes/day) were queried with the trial manager. With regards to alcohol intake, several study participants reported drinking only on special occasions (Christmas, birthday). However, the InForm system required whole number inputs. Some research nurses reported 0 values in these cases, whereas others reported 1. To address this inconsistency, the study management group agreed that the weekly units of alcohol for these participants would be corrected to 0.5 units in the final dataset. Any extreme values (≥50 units per week) were raised as queries with the trial manager and were corrected where appropriate.

3.7.4 Laboratory measurements

Laboratory measurements that were below the 5% percentile or above the 95% percentile of the distribution of the laboratory results and deemed implausible were raised as queries with the trial manager. For example, the white blood cell count for study participant UCL864 was 51.9 $x10^9$/l and the platelet count for SMH034 was 74 $x10^9$/l). Both values were too low for someone to be physically able to attend the study site. Following the trial manager's request, the research nurses at the relevant centres checked the laboratory measurements in InForm and updated the trial manager with the correct values.

Among PLWH the values of the CD4 count, CD4 percent and VL were collected from study participants' clinical notes and this resulted in a great number of missing values. In cases where the POPPY visit was several months after the last clinical visit with available data the values of CD4 count, CD4 percent and VL were set to missing. For some study participants, instead of copying the values of the CD4 count, CD4 percent and VL that were closest to the date of the POPPY visit, the study managers mistakenly copied values from their latest visit, which for several study participants was several months after the POPPY baseline visit. The study management group agreed to use the data from the UK CHIC Study (578) and the Dublin ID cohorts (579), studies that have been established for several years and have historical data for CD4 count, CD4 percent and VL. First, I cross-checked the UK CHIC Study and Dublin ID

values against the existing InForm data and performed the appropriate corrections for those that were considered to be data entry errors. Second, I completed the data for those with missing values with data from these established cohorts. For participants with missing data for their CD4 count, CD4 percent and VL but who had UK CHIC Study or Dublin ID data available in the 6 months prior or up to 1 month after the baseline POPPY visit, the UK CHIC/Dublin ID values were used to supplement the POPPY dataset.

3.7.5 cART during the entry to POPPY

For all PLWH the research nurses were asked to report their current cART at the baseline visit. However, for several study participants their current cART was reported among the list of their current co-medications. Combining entries from both parts of the eCRF resulted in an updated record of current cART use.

Even after this update, current cART regimens remained missing for some participants and there were several inconsistencies relating to cART start/stop dates. This resulted in regimens that had apparently only been started after the baseline POPPY visit or which were highly unlikely/impossible treatment combinations based on the national guidelines.

To overcome this problem, a similar approach was adopted to that described above for the CD4 count, CD4 percent and VL. The POPPY cART data were cross-checked using data from UK CHIC Study and the Dublin ID cohorts. For the majority of participants (817/1073, 75.9% POPPY PLWH) there was agreement between the POPPY data and the cohort data with respect to cART use. For the remaining 237/1076 (22.1%) participants, however, the cART data were inconsistently reported.

For 142/237 (59.9%) of the discrepancies, the POPPY data were more up-to-date than the data from the UK CHIC and Dublin ID datasets; in these cases, the POPPY data were retained. Seventy-seven of the 237 (32.5%) disagreements were due to data transcription errors on the eCRF which I resolved myself. Finally, the remaining 18/237 (15.6%) discrepancies were more complex so the historical data and the POPPY data were examined by the co-PIs of the study who suggested the correct

current cART based on their knowledge of the most common regimens in use. The number of discrepancies between the POPPY dataset and the cohorts categorised by study centre is presented below (Table 3.3).

Table 3.3: Number of discrepancies between cART regimens as reported directly to POPPY and from the UK CHIC/Dublin ID cohort datasets

Site centre	Total PLWH	Number of discrepancies	(%) of discrepancies per site
Chelsea and Westminster Hospital	288	25	(8.7)
Homerton Hospital	27	1	(3.7)
Kings College Hospital	102	52	(51.0)
Royal Free Hospital	25	16	(64.0)
Royal Sussex County Hospital	206	55	(26.7)
St Mary's Hospital	172	14	(8.1)
Mortimer Market Centre	192	69	(35.9)
Mater Misericordiae University Hospital, Ireland	61	5	(8.2)
Total	**1073**	**237**	(22.1)

3.7.6 Co-medications (non-ART)

The POPPY participants reported their current co-medications. Co-medication indication information as well as start/stop date, dose, frequency and side effects were collected. The reported drugs were grouped into broader categories, based on treatment indication. However, this information was missing for several entries and was therefore retrieved either from online sources (Google search) or from consulting the study PIs. An added complexity was that co-medication data were stored in a file without a visit order identifier (visit 1, 2 or 3). When the first data extract was requested on 4th April 2016 some participants had already attended the study centres for visit 2. The lack of visit identifier was not an error but was a function of data collection methods in InForm. This complicated the data cleaning process and required additional coding to ensure that the visit 1 co-medications were not confused with the co-medications subsequently reported at later visits.

Twenty-one groups of co-medications were created: antihistamines, antiplatelet, antivirals, urogenital and sexually transmitted diseases (STDs), gastrointestinal, antimicrobial, neurological, mental health, sleeping, antihypertensives, lipids

lowering, analgesic, anticoagulant, chest, endocrine, steroidal, dermatological, vitamins, supplemental, rheumatological, PrEP and other. The 'other' category included any co-medications that could not be categorized into any previous categories, for example anti-malaria tablets, dry mouth gel, nasal spray, etc. Start and stop dates, as well as dose, frequency of dosing and side effects were not consistently captured for all co-medications.

3.7.7 Healthcare utilisation

A detailed list of healthcare resource use was collected. Visits to the GP, nurse, specialist, Accident & Emergency (A&E) department, psychiatrist, psychologist, counsellor and any other healthcare provider was captured, as well as information on any hospital procedures, hospital investigations, use of ambulance or community healthcare. For each of the above categories of healthcare resource use, the study participants were asked to recall their healthcare use and reasons over the 12 months prior to study entry. These were reported as an open-ended (free-text) variable. I coded healthcare use reasons to create broad categories. Any clinical conditions identified during this coding process were cross-checked with the person's clinical history to ensure that no clinical events had been missed. The process is described in more detail in section 3.7.9.2.

3.7.8 Reported family history of medical events

The data cleaning required for the participants' family medical history required detailed examination of the free text provided. Participants were asked only to provide information relating to first-degree relatives. Problematically several participants reported medical events experienced by a non-immediate family member, such as an uncle/aunt, cousin or grandparent. These entries were excluded from the list of family medical events.

3.7.9 Personal clinical history

The personal clinical history of POPPY participants is generated by combining information from four different sources: 1) direct questions about clinical conditions the participant experienced over the past 12 months; 2) healthcare utilisation section

of the CRF; 3) list of co-medications received; and 4) reporting of any SAEs. These four datasets were cross-checked to generate a complete and robustly representative dataset.

3.7.9.1 Personal clinical history

In the CRF study participants were asked whether they had experienced any of 46 pre-defined comorbidities divided into 17 clinical event categories. Sixteen of these categories also included a sub-category for "other events". For example, under AIDS-defining events, history of tuberculosis (TB) was the only pre-defined AIDS-defining event, as this was expected to be the most commonly reported. However, the section also included an option to select "History of other AIDS events" after which free-text could be added to provide further information. Prior to analysis, I examined all free-text entries for each of the sixteen categories and, together with the co-PIs, added new codes for commonly occurring (frequency >0.2%) clinical events. As a result, the number of specified comorbidities increased from 46 to 187. This allowed a detailed description of the clinical history of the POPPY participants. A full table of the clinical events reported by study participants attending visit 1, stratified by POPPY group, is provided in Appendix V. Table 3.4 shows the 17 CRF questions and the original 46 pre-defined clinical events set by the study team.

Table 3.4: The personal clinical history questions that were on the CRF with the original 46 pre-specified clinical events at baseline visit 1

1.AIDS-defining Events	
1	History of TB
2	History of other AIDS events
2.Infections and Paracytic	
3	History of STD
4	Infected with Hepatitis B
5	Infected with Hepatitis C
6	History of any other Infections
3.Endocrine disease	
7	Type 1 Diabetes
8	Type 2 Diabetes
9	History of thyroid disease
10	History of any other endocrine diseases
4.Blood Diseases	
11	Other blood or blood forming organs - provide details for each event
5.Mental Health	
12	History of depression

13	Medically diagnosed depression (treated by a doctor)
14	History of any other mental disorders
6.Nervous System	
15	Does the patient have Parkinson's disease or any other movement disorder?
16	Does patient experience dizziness or vertigo, which causes them to fall?
17	Any condition associated with loss of consciousness for 30 minutes or more
18	Any history of brain surgery?
19	History of encephalitis
20	History of epilepsy
21	History of peripheral neuropathy
22	History of any other nervous system disorders
7.Heart Failure	
23	History of heart failure
24	History of angina pectoris
25	History of narrowed blood vessels in legs or abdomen
8.Chest disease	
26	History of asthma, bronchitis (chronic or acute), pulmonary emphysema or COPD
27	History of any other chest disease
9.Gastro Intestinal	
28	Persistent bowel disorder over last 3 months
29	History of any other liver disease
30	Other gastro-intestinal disorders
10.Renal/Urinary/Reproductive	
31	History of end stage renal disease (receipt of dialysis or renal transplant)
32	Urinary incontinence requiring treatment
33	Other genitourinary disorders
11.Medical History - Related to Childbirth	
34	Is patient still menstruating?
35	Has patient had any pregnancies?
12.Skin	
36	History of any skin disorders
13.Joint, Bone and connective tissue	
37	History of any joint inflammation or rheumatoid or osteoarthritis
38	History of arthritis of knee or hip
39	History of any joint replacement
40	Has the subject suffered any fractures
41	History of congenital bone disease (osteogenesis imperfecta)
42	History of any other joint, bone or connective tissue disorders
14.Congenital	
43	History of any congenital disorders
15.Injury and Poisoning	
44	History of any injury or poisoning
16.Cancer	
45	History of any form of cancer (if not covered elsewhere)
17.Chronic Disease	
46	Does the patient think that they have any chronic diseases not recorded elsewhere?

3.7.9.2 Healthcare utilisation

The second source of personal clinical history information was derived from the reported healthcare utilisation (described in Section 3.7.7) and particularly from healthcare use reason. I used the free text variable of the healthcare utilisation reason and created codes for clinical conditions that I subsequently cross-checked with the 187 specified comorbidities described in the previous section. I added it where the healthcare utilisation reason suggested a clinical condition that had not been reported in the list of previously specified comorbidities. For example, participant CWH576 reported having visited their GP in the past 12 months for conjunctivitis. However, there was no record of eye problems in the participant's clinical history, so this information was added manually. Although this may be a legitimate method of updating the robustness of the data, it may inflate the prevalence of comorbidities among the POPPY participants as they may have required healthcare for minor self-limiting illnesses.

3.7.9.3 Co-medications

The third source of personal clinical history information was the list of co-medications. Study participants were asked to report any co-medications they were taking at study entry and the purpose for use. Just as in healthcare utilisation, I used the free text variable of the co-medications indication and created clinical condition codes that I subsequently cross-checked against the 187 comorbidities. These were updated where appropriate. For example, participant CWH363 reported taking Simvastatin at study entry to treat high cholesterol. However, there was no record of dyslipidaemia for this study participant, so the participant's personal clinical history was updated.

For several co-medications, the reason for taking the drug was not reported. For each of those records, I searched online for the named co-medications to identify possible use indication(s). I then generated a spreadsheet that included the participant's ID, the drug names and the online extracted indication for each co-medication. As some drugs have multiple indications for use, this spreadsheet was shared with the co-PIs who checked each record to ensure that it was appropriate to assume that the

medication been used for that particular reason. Following the same strategy described above, I created clinical condition codes that I subsequently cross-checked against the 187 specified comorbidities, updating personal clinical history as appropriate.

3.7.9.4 SAEs

Finally, clinical event information was extracted from the SAE data. Study participants were asked "Have there been any SAEs over the past year?". Where a SAE was reported to have occurred, additional information was captured in a free-text field. I examined the responses and created clinical condition codes that I subsequently cross-checked against the 187 comorbidities, updating personal clinical history as appropriate. For example, participant CWH107 had reported a SAE in June 2013, prior to visit 1 (October 2013). The notes for this participant stated "Patient collapsed at home and was brought to hospital by ambulance. Treated with amoxicillin for Lower Respiratory Tract Infection". This was cross-checked against the personal clinical history variable of respiratory tract infection. It was confirmed that it had already been recorded. Similarly, the use of amoxicillin and the use of ambulance were cross-checked against the participant's co-medications and healthcare utilization, respectively.

3.7.10 DEXA scan

The DEXA data required graphical inspection of each distribution measurement prior to data cleaning. Tissue, muscle and fat values that were below the 5th percentile or above the 95% percentile were identified as queries to the trial manager who then sought confirmation from the study centres. A total of 297 outliers were identified of which 186 could be easily addressed (incorrect units had been reported, e.g. from kilograms to grams); 111 data entry errors were corrected by the study centres. In addition, I checked that Z and T-scores were similar for each study participant. I performed cross-checks of the DEXA measurement at arm, leg, limb, trunk and body to confirm that the tissue values were a product of the sum of muscle and fat measurements, replacing any missing values with the calculated value. For example, study participant UCL442 was missing an arm tissue value but had their arm fat and

muscle measurements assessed (1,677g and 5,967g, respectively) so the arm tissue value was calculated as 7,644g (1,677+5,967). The cases with data anomalies that I was unable to resolve using the above method were raised with the trial manager and research nurses of the study centres for further investigation.

3.7.11 The Lawton IADL Scale

The data cleaning required for the IADL was minimal. Scales that had missing data were recoded to a new category of "unknown" and those individuals were excluded from the calculation of the summary score.

3.7.12 Depressive symptoms

For depressive symptoms, an "unknown" category was created for those who did not respond to these individual questions for the CES-D and PHQ-9 questionnaires. Individuals with missing values were excluded from the summary scores.

3.8 Statistical analysis

This section provides a brief description of the statistical analyses presented. Each results chapter will include further detailed information on the analyses that were performed in that chapter. The analysis has been performed using STATA 15 (StataCorp. 2017, Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC.).

3.8.1 Descriptive analysis

Categorical variables are summarised, reporting the total number of individuals (n) and the percentage (%) in each category. For continuous variables with normal distribution, the mean and the SD are reported, while the median and the IQR are reported for non-normally distributed numerical data.

Prevalence, incidence and rate are three statistical concepts that are discussed throughout this thesis. Prevalence is calculated as the number of individuals with a condition divided by the total number of individuals. Incidence is the number of individuals who newly develop a condition over a given period of time divided by the total number of individuals initially at risk. Finally, the rate the number of individuals

who develop a condition divided by the total person-time at risk (normally expressed as person-years) over the time period. Although the data used here are cross-sectional, the fracture data are historical which enables rate calculation (see Chapter 8, detailed calculation).

3.8.2 Statistical models

The choice of the statistical models depends on the outcome of interest. The main statistical models used in this thesis are linear regression, logistic regression and Poisson regression which are described in more detail below.

3.8.2.1 Linear regression

Linear regression models the relationship between two or more variables, the outcome variable, a numerical variable (y) and the explanatory variable(s) ($x_1, x_2 \dots x_n$). The aim of this modelling is to estimate the effect explanatory variables have on the mean of (y). The linear regression equation can be expressed as:

$$\mu = E(y) = \alpha + \beta_1 x_1 + \beta_2 x_2 + \cdots + \beta_n x_n + \varepsilon$$

Linear regression can be simple when it has one explanatory variable (x_1) or multiple/multivariable when it has more than one explanatory variable ($x_1, x_2 \dots x_n$). The components β_i are the regression coefficients that express the change in the mean of y per unit increase of the explanatory variable x_i when the explanatory variable is numeric and the difference in the mean y at each level of the explanatory variable compared to the reference group when the explanatory variable is categorical, after correcting for the effect of the other variables included in the model. The ε (residuals) is the error term that represents the difference between the expected y and the observed y ; their sum and mean are equal to zero.

Linear regression employs four main assumptions. First, that the relationship between x_i and the mean of y is linear. Second, that there is homoscedasticity, which means that the variance of ε is the same for any x_i. The third assumption is independence. All observations should be independent of each other. Lastly, the fourth assumption is that the residuals ε follow a normal distribution.

3.8.2.2 Logistic regression

Logistic regression allows assessment of the relationship between a dichotomous outcome variable (two possible outcomes) and one or more explanatory variables. π denotes the predicted probability that an individual belongs into one of the two possible outcomes, and $(1-\pi)$ the predicted probability that an individual belongs to the second possible outcome. The logit link function is the transformation of the probability of the outcome into the natural log odds:

$$logit(\pi) = \ln\left(\frac{\pi}{1-\pi}\right)$$

An iterative procedure produces the estimated logistic regression equation which is similar to that of the linear regression:

$$Log(odds) = a + \beta_1 x_1 + \beta_2 x_2 + \cdots + \beta_n x_n + \varepsilon$$

The quantity on the right-hand side of the equation is known as the linear prediction of the log-odds of the outcome, given the particular value of the n exposure variables x_1 to x_n. The β's are the regression coefficients associated with the n exposure variables. The exponential e^{β_1}, provides the OR, which is the estimated relative change in the odds of the outcome associated with a unit increase of the explanatory variable when the explanatory variable is continuous and the relative change in the odds of each level compared to the reference level when the explanatory variable is categorical, assuming all the other variables remain constant. The assumptions of the logistic regression are: (i) the dependent variable should be binary, (ii) observations should be independent of each other, (iii) there is a linear association between log(odds) and each explanatory variable.

3.8.2.3 Poisson regression

This type of regression is used when the outcome variable is a discrete numerical variable, e.g. counts of an event. The number of events (n) over a period of time (t) should follow a Poisson distribution. This type of regression may also be adapted to model the rate of an event (r). The Poisson regression equation is the following:

$$\ln(r) = \ln(n) - \ln(t) = a + \beta_1 x_1 + \beta_2 x_2 + \cdots + \beta_n x_n + \varepsilon$$

The estimated value of the mean is denoted by r while x_i is the ith explanatory variable ($i = 1,2,3, \ldots, n$). The estimate of the log rate when all x_i's are equal to zero is denoted by a and β_i's are the estimated Poisson regression coefficients. The e^{β_i} is the estimated relative rate (RR) also referred to as the relative ratio or the incidence rate ratio (IRR). If x_i is a categorical variable, then e^{β_i} is the RR or IRR for factor x_i. Poisson regression makes the following assumptions. First that the response variable is a count of positive integers per unit of time or space which follows a Poisson distribution, i.e. the mean and the variance should be the same. Second, the observations must be independent of one another. The third assumption is that the rate of the event is constant over time.

Chapter 4 Characteristics of the POPPY participants and confounding factors of the association of HIV with the outcomes of interest

4.1 Chapter's objectives

This chapter aims to describe the three groups of the POPPY study participants and explore the factors confounding the association of HIV with frailty, falls, low BMD, fractures and FRAX scores.

4.2 The POPPY participants

The POPPY study from the spring of 2013 until the winter of 2016 had enrolled 1377 participants of which 699 were in the group of older PLWH, 374 were younger PLWH and 304 were HIV-negative controls. The characteristics of each group are described in the following sections.

4.2.1 Older PLWH

The median age of the group of older PLWH was 57 years IQR (53, 62). This group was mainly comprised of white (86.3%, 603/699) men (87.6%, 612/699). The majority had an educational level of a university degree or above (42.4%, 296/699) and almost half of them were single (47.5%, 332/699). More than three quarters were non-smokers (77.0%, 538/699), almost 80% were using alcohol (79.4%, 555/699) and almost more than a quarter have used recreational drugs in the past 6-months (25.3%, 177/699).

The median BMI of the older PLWH was indicative of an overweight group (median 25.7, IQR 23.4, 28.5), the median physical functioning score was 85% (IQR 60%, 95%) and the median general health score was 60% (IQR 40%, 75%). The proportion of those taking more than 5 co-medications excluding medication for HIV was almost 30% (29.8%, 208/699).

The median time since HIV diagnosis in this group was almost 16 years (15.9, IQR (9.6, 22.4) and the median years on treatment for HIV was almost 11 years (10.7, IQR (5.3, 16.1). A good immune system reconstruction was achieved by the majority of the older PLWH (median CD4 count 610 cells/mm^3, IQR (467, 792)). Almost two thirds

had no history of previous diagnosis of AIDS-defining illness (65.5%, 458/699) and more than 90% have achieved an undetectable viral load (91.7%, 641/699) at the time of recruitment. The majority were on TFV/FTC (59.5%, 416/699), 34% were taking a boosted PI regimen (34.1%, 238/699), 24.5% were on EFV treatment (24.5%, 171/699) and less than 15% were on INSTI-containing treatment (14.5%, 101/699), Table 4.1.

Table 4.1: Characteristics of the older PLWH, n=699

	n	(%)
Age		
50-54	266	(38.1)
55-59	188	(27.0)
60-64	125	(17.9)
65-69	81	(11.6)
≥70	38	(5.4)
Gender		
Female	87	(12.5)
Male	612	(87.6)
Ethnicity		
Black African	96	(13.7)
White	603	(86.3)
Education		
Finished education with no qualifications	75	(10.7)
O levels/GCSEs (or equivalent)	115	(16.5)
A levels (or equivalent)	95	(13.6)
University degree or above	296	(42.4)
Other	88	(12.6)
Unknown	30	(4.3)
Marital status		
Single	332	(47.5)
Married/Civil Partnership/ Cohabiting	264	(37.8)
Divorced/Living separately	78	(11.2)
Widowed/Other	25	(3.6)
Current smoking		
No	538	(77.0)
Yes	158	(22.6)
Unknown	3	(0.4)
Current alcohol use		
No	57	(8.2)
Yes	555	(79.4)
In the past	87	(12.4)
Recreational drugs in the past 6 months		
No	522	(74.7)
Yes	177	(25.3)
Number of total co-medications (excluding cART)		
0	179	(25.6)
1-4	312	(44.6)
5-9	155	(22.2)
≥10	53	(7.6)
BMI (kg/m^2)		
≤22.8	143	(20.5)
22.9-24.7	132	(18.9)
24.8-26.7	153	(21.9)
26.8-29.3	132	(18.9)
≥29.4	129	(18.5)
Unknown	10	(1.4)
Physical functioning score		
≤65	180	(25.8)

	n	(%)
66-85	125	(17.9)
86-95	132	(18.9)
96-100	135	(19.3)
Unknown	127	(18.2)
General health score		
≤40	155	(22.2)
41-60	137	(19.6)
61-75	150	(21.5)
76-85	71	(10.2)
≥86	59	(8.4)
Unknown	127	(18.2)
Previous diagnosis of AIDS-defining illness		
No	458	(65.5)
Yes	241	(34.5)
CD4 count (cells/mm^3)		
≤441	148	(21.2)
442-564	130	(18.6)
565-687	144	(20.6)
688-858	130	(18.6)
≥859	128	(18.3)
Unknown	19	(2.7)
CD4 nadir (cells/mm^3)		
≤82	162	(23.2)
83-170	152	(21.7)
171-240	140	(20.0)
241-340	120	(17.2)
≥341	94	(13.5)
Unknown	31	(4.4)
VL		
Detectable	55	(7.9)
Undetectable	641	(91.7)
Unknown	3	(0.4)
Years on ART		
≤3.9	99	(14.2)
4.0-7.3	115	(16.5)
7.4-12.4	135	(19.3)
12.5-17.3	157	(22.5)
≥17.4	186	(26.6)
Unknown	7	(1.0)
Time since HIV diagnosis (yrs)		
≤6.3	102	(14.6)
6.4-10.9	114	(16.3)
11.0-16.0	132	(18.9)
16.1-22.0	161	(23.0)
≥22.1	184	(26.3)
Unknown	6	(0.9)
NRTI backbone		
None	104	(14.9)
TFV/FTC	416	(59.5)
ABC/3TC	84	(12.0)

	n	(%)
Other	95	(13.6)
PIs		
None	396	(56.6)
Boosted PIs	238	(34.1)
Unboosted PIs	65	(9.3)
NNRTIs		
None	341	(48.8)
EFV	171	(24.5)
NVP	104	(14.9)
RPV	37	(5.3)
ETR	46	(6.6)
INSTIs		
No	598	(85.5)
Yes	101	(14.5)

4.2.2 Younger PLWH

The group of younger PLWH consisted of participants with a median age of 43 years IQR (37, 47). The majority were white (80%, 299/374), male (80.8%, 302/374). Almost half of them had an educational level of university degree or above (46.3%, 173/374) and more than half were single (51.6%, 193/374). The majority were non-smokers (70.3%, 263/374), were currently using alcohol (81.0%, 303/374) and more than a third have used recreational drugs in the past 6 months (34.8%, 130/374).

The median BMI of the younger PLWH indicated an overweight group (median 25.2, IQR 23.0, 27.9), with a median physical functioning score of 95% IQR (85%, 100%) and a median general health score of 65% IQR (50%, 85%). The proportion of those taking more than 5 co-medication excluding medication for HIV was 14.2%, 53/374.

The median time since HIV diagnosis was just below 10 years (9.6, IQR (5.5, 15.2) and the median years on treatment for HIV was above 5 years (5.5, IQR (2.2, 9.9). A good immune system reconstruction was achieved by the majority of the younger PLWH (median CD4 count 661 cells/mm^3, IQR (499, 847)). More than 80% had no history of previous diagnosis of AIDS-defining illness (81.3%, 304/374) and more than 85% have achieved an undetectable viral load (86.4%, 323/699) at the time of recruitment. The majority were on TFV/FTC (69.5%, 257/374), almost 30% were on a boosted PI

regimen (27.8%, 104/374), almost a quarter were on EFV treatment (24.9%, 93/374) and less than 15% were on INSTI-containing treatment (13.1%, 48/374), Table 4.2.

Table 4.2: Characteristics of the younger PLWH, n=374

	n	(%)
Gender		
Female	72	(19.3)
Male	302	(80.8)
Age		
≤29	29	(7.8)
30-39	92	(24.6)
40-49	253	(67.7)
Ethnicity		
Black African	75	(20.0)
White	299	(80.0)
Education		
Finished education with no qualifications	29	(7.8)
O levels/GCSEs (or equivalent)	57	(15.2)
A levels (or equivalent)	59	(15.8)
University degree or above	173	(46.3)
Other	35	(9.4)
Unknown	21	(5.6)
Marital status		
Single	193	(51.6)
Married/Civil Partnership/ Cohabiting	148	(39.6)
Divorced/Living separately	28	(7.5)
Widowed/Other	5	(1.3)
Current smoking		
No	263	(70.3)
Yes	111	(29.7)
Unknown	0	(0.0)
Current alcohol use		
No	33	(8.8)
Yes	303	(81.0)
In the past	38	(10.2)
Recreational drugs in the past 6 months		
No	244	(65.2)
Yes	130	(34.8)
BMI (kg/m^2)		
≤22.8	92	(24.3)
22.9-24.7	85	(22.7)
24.8-26.7	63	(16.8)
26.8-29.3	72	(19.3)
≥29.4	60	(16.3)
Unknown	2	(0.5)
Physical functioning score		
≤65	44	(11.8)
66-85	38	(10.2)
86-95	73	(19.5)
96-100	154	(41.2)

	n	(%)
Unknown	65	(17.4)
General health score		
≤40	50	(13.4)
41-60	80	(21.4)
61-75	71	(19.0)
76-85	49	(13.1)
≥86	59	(15.8)
Unknown	65	(17.4)
Number of total co-medications (excluding cART)		
0	142	(38.0)
1-4	179	(47.9)
5-9	49	(13.1)
≥10	4	(1.1)
Previous diagnosis of AIDS-defining illness		
No	304	(81.3)
Yes	70	(18.7)
CD4 count (cells/mm^3)		
≤441	62	(16.6)
442-564	79	(21.1)
565-687	66	(17.7)
688-858	79	(21.1)
≥859	81	(21.7)
Unknown	7	(1.9)
CD4 nadir (cells/mm^3)		
≤82	51	(13.6)
83-170	50	(13.4)
171-240	71	(19.0)
241-340	79	(21.1)
≥341	111	(29.7)
Unknown	12	(3.2)
VL		
Detectable	49	(13.1)
Undetectable	323	(86.4)
Unknown	2	(0.5)
Years on ART		
≤3.9	112	(30.0)
4.0-7.3	95	(25.4)
7.4-12.4	75	(20.1)
12.5-17.3	53	(14.2)
≥17.4	24	(6.4)
Unknown	15	(4.0)
Time since HIV diagnosis (yrs)		
≤6.3	111	(29.7)
6.4-10.9	99	(26.5)
11.0-16.0	80	(21.4)
16.1-22.0	52	(13.9)
≥22.1	28	(7.5)
Unknown	4	(1.1)
NRTI backbone		
None	40	(10.7)

	n	(%)
TFV/FTC	257	(69.5)
ABC/3TC	52	(13.9)
Other	25	(5.9)
PIs		
None	233	(62.6)
Boosted Pis	104	(27.8)
Unboosted Pis	37	(9.6)
NNRTIs		
None	192	(51.3)
EFV	93	(24.9)
NVP	33	(8.8)
RPV	44	(11.8)
ETR	12	(3.2)
INSTIs		
No	326	(86.9)
Yes	48	(13.1)

4.2.3 HIV-negative controls

The group of HIV-negative controls was on median 58 years IQR 53, 63. The majority (89.8%, 273/304) were white, two thirds were male (64.1%, 195/304), had an educational level of university degree or above (48.0%, 146/304) and more than 50% were married had a civil partnership or were cohabiting (52.0%, 158/304). The majority of the HIV-negative controls were non-smokers (85.5%, 260/304), were currently using alcohol (86.2%, 262/304) and less than 15% had used recreational drugs in the past 6 months (14.5%, 44/304).

The median BMI of HIV-negative controls was indicative an overweight group (median 25.2, IQR 23.0, 27.9), and the median physical functioning score was 95% IQR (85%, 100%) while their general health score 65% IQR (50%, 85%). The proportion of those taking more than 5 co-medication excluding ART was 14.2%, 53/374, Table 4.3.

Table 4.3: Characteristics of the HIV-negative controls, n=304

	n	(%)
Age		
50-54	102	(33.6)
55-59	79	(26.0)
60-64	65	(21.4)
65-69	31	(10.2)

	n	(%)
≥70	27	(8.9)
Gender		
Female	109	(35.9)
Male	195	(64.1)
Ethnicity		
Black African	31	(10.2)
White	273	(89.8)
Education		
Finished education with no qualifications	22	(7.2)
O levels/GCSEs (or equivalent)	45	(14.8)
A levels (or equivalent)	39	(12.8)
University degree or above	146	(48.0)
Other	40	(13.2)
Unknown	12	(4.0)
Marital status		
Single	91	(29.9)
Married/Civil Partnership/ Cohabiting	158	(52.0)
Divorced/Living separately	41	(13.5)
Widowed/Other	14	(4.6)
Current smoking		
No	260	(85.5)
Yes	42	(13.8)
Unknown	2	(0.7)
Current alcohol use		
No	18	(5.9)
Yes	262	(86.2)
In the past	24	(7.9)
Recreational drugs in the past 6 months		
No	260	(85.5)
Yes	44	(14.5)
BMI (kg/m^2)		
≤22.8	42	(13.8)
22.9-24.7	58	(19.1)
24.8-26.7	51	(16.8)
26.8-29.3	71	(23.4)
≥29.4	78	(25.7)
Unknown	4	(1.3)
Physical functioning score		
≤65	33	(10.9)
66-85	52	(17.1)
86-95	85	(28.0)
96-100	93	(30.6)
Unknown	41	(13.5)
General health score		
≤40	24	(7.9)
41-60	43	(14.1)
61-75	71	(23.4)
76-85	65	(21.4)
≥86	60	(19.7)
Unknown	41	(13.5)

	n	(%)
Number of total co-medications		
0	122	(40.1)
1-4	142	(46.7)
5-9	35	(11.5)
≥10	5	(1.6)

4.3 Association between participant characteristics and the cohort of older PLWH and HIV-negative controls

The prevalence of HIV in the sub-group of older POPPY participants was significantly higher among participants who were male, married or had a civil partnership or cohabiting, had a BMI≥29.4 kg/m^2, no smokers, alcohol drinkers, no history of recreational drug use in the past 6 months and were taking no co-medications. No difference in the prevalence of HIV was observed for participants with different characteristics of age, ethnicity and education, Table 4.4

Table 4.4: Prevalence of HIV among older POPPY participants stratified by participant characteristics

	Total N=1003		Group: Older PLWH n=699		Group: HIV-negative n=304		
	n	**(%)**	**n**	**(%)**	**n**	**(%)**	**p-value**
Age							0.14
50-54	368	(100.0)	266	(72.3)	102	(27.7)	
55-59	267	(100.0)	188	(70.4)	79	(29.6)	
60-64	190	(100.0)	125	(65.8)	65	(34.2)	
65-69	112	(100.0)	81	(72.3)	31	(27.7)	
≥70	65	(100.0)	38	(58.5)	27	(41.5)	
Gender							<0.001
Female	196	(100.0)	87	(44.4)	109	(55.6)	
Male	807	(100.0)	612	(75.8)	195	(24.2)	
Ethnicity							0.12
Black African	127	(100.0)	96	(75.6)	31	(24.4)	
White	876	(100.0)	603	(68.4)	273	(31.2)	
Education							0.44
Finished education with no qualifications	97	(100.0)	75	(77.3)	22	(22.7)	
O levels/GCSEs (or equivalent)	160	(100.0)	115	(71.9)	45	(28.1)	
A levels (or equivalent)	134	(100.0)	95	(70.9)	39	(29.1)	
University degree or above	442	(100.0)	296	(67.0)	146	(33.0)	
Other	128	(100.0)	88	(68.8)	40	(31.3)	

	Total N=1003		Group: Older PLWH n=699		Group: HIV-negative n=304		
	n	(%)	n	(%)	n	(%)	p-value
Unknown	42	(100.0)	30	(71.4)	12	(28.6)	
Marital status							<0.001
Single	423	(100.0)	332	(78.5)	91	(21.5)	
Married/Civil Partnership/ Cohabiting	422	(100.0)	264	(62.6)	158	(37.4)	
Divorced/Living separately	120	(100.0)	79	(65.8)	41	(34.2)	
Widowed/Other	38	(100.0)	24	(63.2)	14	(36.8)	
BMI (kg/m^2)							0.004
≤22.8	186	(100.0)	144	(77.4)	42	(22.6)	
22.9-24.7	190	(100.0)	132	(69.5)	58	(30.5)	
24.8-26.7	203	(100.0)	152	(74.9)	51	(25.1)	
26.8-29.3	202	(100.0)	131	(64.9)	71	(35.2)	
≥29.4	208	(100.0)	130	(62.5)	78	(37.5)	
Current smoking							0.006
No	797	(100.0)	537	(67.4)	260	(32.6)	
Yes	200	(100.0)	158	(79.0)	42	(21.0)	
Unknown	6	(100.0)	4	(66.7)	2	(33.3)	
Current alcohol use							0.04
No	75	(100.0)	57	(76.0)	18	(24.0)	
Yes	817	(100.0)	555	(67.9)	262	(32.1)	
In the past	111	(100.0)	87	(78.4)	24	(21.6)	
Recreational drugs in the past 6 months							<0.001
No	782	(100.0)	522	(66.8)	260	(33.3)	
Yes	221	(100.0)	177	(80.1)	44	(19.9)	
Number of total co-medications							<0.001
0	301	(100.0)	179	(59.5)	122	(40.5)	
1-4	454	(100.0)	312	(68.7)	142	(31.3)	
5-9	190	(100.0)	155	(81.6)	35	(18.4)	
≥10	58	(100.0)	53	(91.4)	5	(8.6)	

4.4 The outcomes of interest

4.4.1 Frailty

Among the POPPY participants, 78.1% (1076/1377) provided full information for the assessment of frailty at the baseline study visit. Almost two thirds of the participants in whom frailty could not be assessed, 57.1% (172/301), were missing information on both exhaustion and low physical activity. After this, 16.6% (50/301) of participants

in whom frailty could not be assessed were missing measurements of slowness only and 8.6% (26/301) were missing exhaustion measurements only. Those missing low physical activity only and those missing both slowness and weakness represented 5.0% (15/301) and 4.7% (14/301) respectively, with 2.3% (7/301) missing information on weakness only. A further 2.3% (7/301) were missing all the frailty components; other patterns of missing data were present in 1.3% or less of those with missing frailty data. The patterns of missing data are presented in detail in Table 4.5.

Detailed information on the components of the frailty definition that were missing for participants at each study centre is shown in Appendix III. The sites with the highest proportions of complete data for the assessment of frailty were the SMH and RSH centres with complete records for 92.0% (218/237) and 85.9% (226/263), respectively. At UCL, 78.6% (184/234) participants provided information on all four components for frailty assessment with 78.5% (285/363) of the CWH site participants providing full information for the assessment of frailty. For the HUH, KCH and DUH sites, the completeness of the components for the assessment of frailty was more than 60% (67.6% (25/37), 62.3% (81/130) and 61.7% (50/81), respectively). Finally, the centre with the lowest completeness of data was the RFH where only 21.9% (7/32) of the participants provided complete data for the assessment of frailty. The components of exhaustion and low physical activity had the higher proportion of missing data.

Table 4.5: Patterns of the missing components required in order to assess frailty

Components of frailty score					
Slowness	**Weakness**	**Exhaustion**	**Low physical activity**	**Frequency in the full cohort**	**Percentage of those with any missing data**
●	●	●	●	1076 (78.1%)	-
●	●	●	○	15 (1.1%)	5.0%
●	●	○	●	26 (1.9%)	8.6%
●	○	●	●	7 (0.5%)	2.3%
○	●	●	●	50 (3.6%)	16.6%
●	●	○	○	172 (12.5%)	57.1%
○	●	●	○	1 (0.1%)	0.3%
○	○	●	●	14 (1.0%)	4.7%
○	●	○	●	1 (0.1%)	0.3%
●	○	○	○	4 (0.3%)	1.3%

○	●	○	○	3 (0.2%)	1.0%
○	○	●	○	1 (0.1%)	0.3%
○	○	○	○	7 (0.5%)	2.3%

● Present ○ Missing

At the RFH site, 23/32 (71.9%) of the study participants had incomplete information on the questions of SF-36 required to assess exhaustion and low physical activity.

In order to explore the potential for selection bias it was important to explore whether the characteristics of the participants with and without sufficient information for the assessment of frailty were similar. Significant differences were observed between those with and without complete data for the POPPY groups (older PLWH, younger PLWH, HIV-negative controls), ethnicity, BMI and the total number of co-medications received. In particular, among those with complete data in whom frailty could be assessed the proportion of older PLWH was significantly higher compared to that of older PLWH among those with missing data in whom frailty could not be assessed (52.0% (560/1076) vs. 46.2% (139/301), global P=0.04).

Among those with complete data, the proportions of those of white ethnicity and those with a BMI ≤22.8 kg/m^2 were significantly higher compared to among those with missing data (87.2% (938/1076) vs. 78.7% (237/301), P<0.001, and 21.7% (233/1076) vs. 14.3% (43/301), P<0.001). No differences were observed between those with complete data and those with missing data with regards to gender, current smoking status and current alcohol use and recreational drug use in the past 6 months and number of total co-medications, Table 4.10.

Among the POPPY participants with complete information for an assessment of frailty, 9.9% (107/1076) were deemed to be frail, 30.3% (326/1076) were categorised as pre-frail and the remaining 59.8% (643/1076) were non-frail. Hereafter I will refer to the “non-frail” group as POPPY participants that belong to either the robust or the pre-frail groups. Among participants who were classified as being frail, all (n=107) had reported low physical activity, 87% (93/107) had reported weakness, 69% (74/107) exhaustion and 53% (57/107) slowness, Figure 4.1.

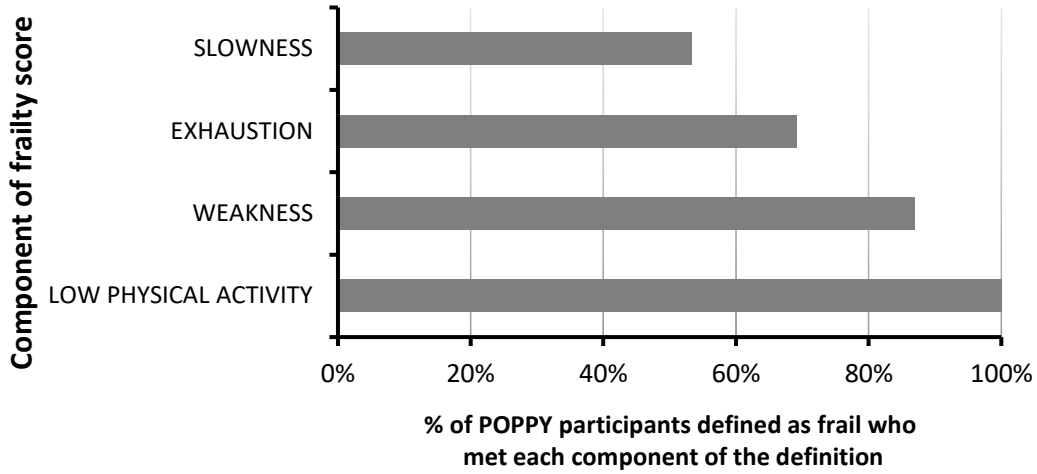


Figure 4.1: Proportion of POPPY participants defined as being frail who met each component of the frailty score

Among the older PLWH in POPPY, 13.0% (73/560) met three or more of the frailty criteria and were deemed to be frail, a significantly higher proportion compared to both younger PLWH and the HIV-negative controls (9.2% (27/294) and 3.2% (7/222), respectively, P<0.001). With regards to pre-frailty, among the older PLWH 35.9% (201/560) fulfilled one or two of the frailty criteria and were deemed to be pre-frail. This was a significantly higher proportion compared to the proportion with pre-frailty in the younger PLWH and the HIV-negative controls (22.5% (66/294) and 26.6% (59/222), respectively, P<0.001, Figure 4.2).

Table 4.6: Characteristics of POPPY participants in whom frailty could and could not be assessed

			Assessed frailty (data complete)				
	Total N=1377		No N=301		Yes N=1076		
	n	(%)	n	(%)	n	(%)	p-value
Group							0.04
Older PLWH	699	(50.8)	139	(46.2)	560	(52.0)	
Younger PLWH	374	(27.2)	80	(26.6)	294	(27.3)	
HIV-negative	304	(22.1)	82	(27.2)	222	(20.6)	
Gender							0.29
Female	268	(19.5)	65	(21.6)	203	(18.9)	
Male	1109	(80.5)	236	(78.0)	873	(81.1)	
Ethnicity							<0.001
Black African	202	(14.7)	64	(21.3)	138	(12.8)	
White	1175	(85.3)	237	(78.7)	938	(87.2)	
BMI (kg/m^2)							<0.001
≤22.8	276	(20.0)	43	(14.3)	233	(21.7)	
22.9-24.7	275	(20.0)	53	(17.6)	222	(20.6)	
24.8-26.7	267	(19.4)	66	(21.9)	201	(18.7)	

			Assessed frailty (data complete)				
	Total N=1377		No N=301		Yes N=1076		
26.8-29.3	275	(20.0)	62	(20.6)	213	(19.8)	
≥29.4	268	(19.5)	61	(20.3)	207	(19.2)	
Unknown	16	(1.2)	16	(5.3)	0	(0.0)	
Current smoking							0.82
No	1061	(77.1)	236	(78.4)	825	(76.7)	
Yes	311	(22.6)	64	(21.3)	247	(23.0)	
Unknown	5	(0.4)	1	(0.3)	4	(0.4)	
Current alcohol use							0.48
No	108	(7.8)	27	(9.0)	81	(7.8)	
Yes	1120	(81.3)	246	(81.7)	874	(81.3)	
In the past	149	(10.8)	28	(9.3)	121	(10.8)	
Recreational drug use in the past 6 months							0.68
No	1026	(74.5)	227	(75.4)	799	(74.3)	
Yes	351	(25.5)	74	(24.6)	277	(25.7)	
Total number of co-medications							0.82
0	443	(32.2)	103	(34.2)	340	(31.6)	
1-4	633	(46.0)	136	(45.2)	497	(46.2)	
5-9	239	(17.4)	50	(16.6)	189	(17.6)	
≥10	62	(4.5)	12	(4.0)	50	(4.7)	

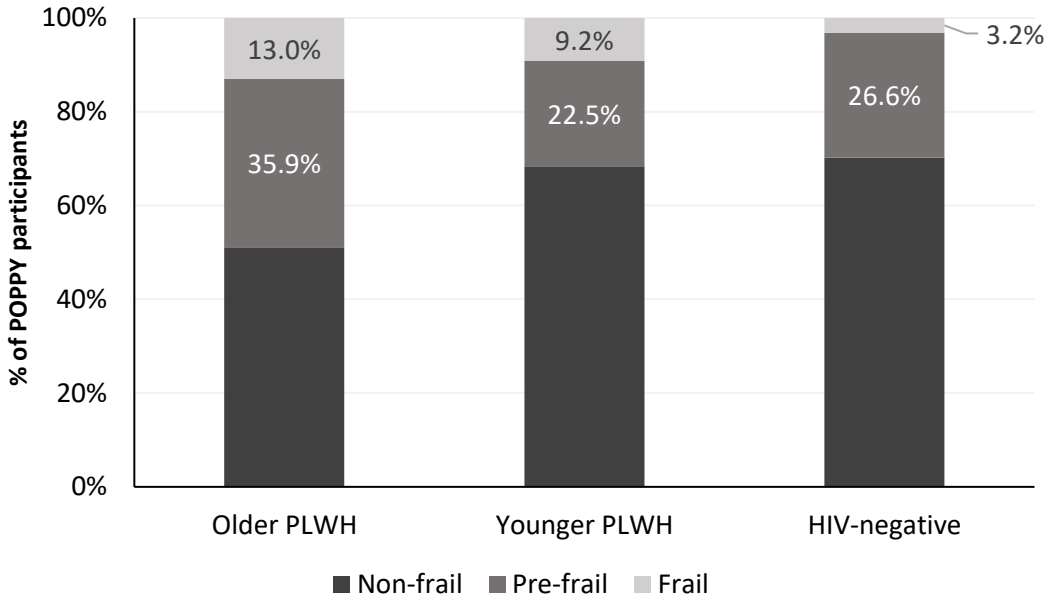


Figure 4.2: Frailty and pre-frailty prevalence stratified by POPPY group

4.4.1.1 The prevalence of frailty stratified by characteristics of the older POPPY participants

All subsequent analysis considers as frail those who fulfilled 3 or 4 of the frailty criteria described in Box 3 of Section 3.5.1 and non-frail those who fulfilled 0, 1 or 2 of the criteria.

The prevalence of frailty in the sub-group of older PLWH and HIV-negative controls was significantly higher among participants who were male, with unknown level of education, divorced or living separately to their partner, with use of recreational drugs in the past 6 months and a higher number of total co-medications. No difference in the prevalence of frailty was observed for participants with different characteristics of age, ethnicity, BMI, smoking and alcohol use, Table 4.7.

Table 4.7: Prevalence of frailty among older POPPY participants stratified by participant characteristics

			Frailty				
	Total N=782		Non frail n=702		Frail n=80		
	n	(%)	n	(%)	n	(%)	p-value
Age							0.40
50-54	276	(100.0)	253	(91.7)	23	(8.3)	
55-59	218	(100.0)	195	(89.5)	23	(10.6)	
60-64	154	(100.0)	137	(89.0)	17	(11.0)	
65-69	82	(100.0)	74	(90.2)	8	(9.8)	
≥70	52	(100.0)	43	(82.7)	9	(17.3)	
Gender							0.02
Female	147	(100.0)	140	(95.2)	7	(4.8)	
Male	635	(100.0)	562	(88.5)	73	(11.5)	
Ethnicity							0.65
Black African	86	(100.0)	76	(88.4)	10	(11.6)	
White	696	(100.0)	626	(89.9)	70	(10.1)	
Education							0.003
Finished education with no qualifications	78	(100.0)	73	(93.6)	5	(6.4)	
O levels/GCSEs (or equivalent)	130	(100.0)	116	(89.2)	14	(10.8)	
A levels (or equivalent)	111	(100.0)	99	(89.2)	12	(10.8)	
University degree or above	348	(100.0)	322	(92.5)	26	(7.5)	
Other	102	(100.0)	83	(81.4)	19	(18.6)	
Unknown	13	(100.0)	9	(69.2)	4	(30.8)	
Marital status							0.002
Single	333	(100.0)	286	(85.9)	47	(14.1)	
Married/Civil Partnership/ Cohabiting	337	(100.0)	317	(94.1)	20	(5.9)	
Divorced/Living separately	85	(100.0)	73	(85.9)	12	(14.1)	

	Total N=782		Frailty				
			Non frail n=702		Frail n=80		
	n	(%)	n	(%)	n	(%)	p-value
Widowed/Other	27	(100.0)	26	(96.3)	1	(3.7)	
BMI (kg/m^2)							0.65
≤22.8	157	(100.0)	140	(89.2)	17	(10.8)	
22.9-24.7	155	(100.0)	140	(90.3)	15	(9.7)	
24.8-26.7	152	(100.0)	141	(92.8)	11	(7.2)	
26.8-29.3	157	(100.0)	140	(89.2)	17	(10.8)	
≥29.4	161	(100.0)	141	(87.6)	20	(12.4)	
Current smoking							0.30
No	620	(100.0)	561	(90.5)	59	(9.4)	
Yes	158	(100.0)	137	(86.7)	21	(13.3)	
Unknown	4	(100.0)	4	(100.0)	0	(0.0)	
Current alcohol use							0.89
No	58	(100.0)	51	(87.9)	7	(12.1)	
Yes	634	(100.0)	570	(89.9)	64	(10.1)	
In the past	90	(100.0)	81	(90.0)	9	(10.0)	
Recreational drugs in the past 6 months							0.03
No	611	(100.0)	556	(91.0)	55	(9.0)	
Yes	171	(100.0)	146	(85.4)	25	(14.6)	
Number of total co-medications							0.002
0	222	(100.0)	207	(93.2)	15	(6.8)	
1-4	364	(100.0)	331	(90.9)	33	(9.1)	
5-9	149	(100.0)	128	(85.9)	21	(14.1)	
≥10	47	(100.0)	36	(76.6)	11	(23.4)	

4.4.2 Falls

Among the POPPY participants 96.8% (1333/1377) provided full information for falls at the baseline study visit. Significant differences were observed between those with and without complete data for the POPPY site, the POPPY groups, gender, ethnicity, sexuality/route of HIV-transmission and current use of alcohol. No evidence of associations at the 5% level were observed between those with complete data and those with missing data with regards to BMI, current smoking status, recreational drug use in the past 6 months and number of total co-medications, Table 4.8.

Table 4.8: Characteristics of POPPY participants in whom complete data on falls were and were not available

	Total N=1377		Provided falls data: No N=44		Provided falls data: Yes N=1333		
	n	(%)	n	(%)	n	(%)	p-value
Study centre							<0.001
CWH	363	(26.4)	9	(20.5)	354	(26.5)	
DUH	81	(5.9)	1	(2.3)	80	(6.0)	
HUH	37	(2.7)	0	(0.0)	37	(2.8)	
KCH	130	(9.4)	27	(61.4)	103	(7.7)	
RFH	32	(2.3)	0	(0.0)	32	(2.4)	
RSH	263	(19.1)	1	(2.3)	262	(19.7)	
SMH	237	(17.2)	1	(2.3)	236	(17.7)	
UCL	234	(17.0)	5	(11.4)	229	(17.2)	
Group							<0.001
Older PLWH	699	(50.8)	19	(43.2)	680	(51.0)	
Younger PLWH	374	(27.2)	16	(36.4)	358	(26.9)	
HIV-negative	304	(22.0)	9	(20.4)	295	(22.1)	
Gender							0.01
Female	268	(19.5)	15	(34.1)	253	(19.0)	
Male	1109	(80.5)	29	(65.9)	1080	(81.0)	
Ethnicity							<0.001
Black African	202	(14.7)	16	(36.4)	186	(13.9)	
White	1175	(85.3)	28	(63.6)	1147	(86.1)	
Marital status							0.07
Married	210	(15.3)	4	(9.1)	206	(15.5)	
Civil Partnership	176	(12.8)	1	(2.3)	175	(13.1)	
Cohabiting	184	(13.4)	6	(13.6)	178	(13.4)	
Single	616	(44.7)	24	(54.6)	592	(44.4)	
Divorced	92	(6.7)	2	(4.6)	90	(6.8)	
Living separately	56	(4.1)	3	(6.8)	53	(4.0)	
Widowed/Other	43	(3.1)	4	(9.1)	39	(2.9)	
BMI (kg/m^2)							0.30
≤22.8	276	(20.0)	7	(15.9)	269	(20.2)	
22.9-24.7	275	(20.0)	8	(18.2)	267	(20.0)	
24.8-26.7	267	(19.4)	11	(25.0)	256	(19.2)	
26.8-29.3	275	(20.0)	7	(15.9)	268	(20.1)	
≥29.4	268	(19.5)	9	(20.5)	259	(19.4)	
Unknown	16	(1.2)	2	(4.6)	14	(1.1)	
Sexuality/Route of HIV transmission							0.03
MSM	960	(69.7)	24	(54.5)	936	(70.2)	
Heterosexual	417	(30.3)	20	(45.5)	397	(29.8)	
Current smoking							0.86
No	1061	(77.0)	33	(75.0)	1028	(77.1)	
Yes	311	(22.6)	11	(25.0)	300	(22.5)	
Unknown	5	(0.4)	0	(0.0)	5	(0.4)	
Current alcohol use							0.001
No	108	(7.8)	10	(22.7)	98	(7.4)	
Yes	1120	(81.3)	29	(65.9)	1091	(81.8)	

	Total N=1377		Provided falls data: No N=44		Provided falls data: Yes N=1333		
	n	(%)	n	(%)	n	(%)	p-value
In the past	149	(10.8)	5	(11.4)	144	(10.8)	
Recreational drug use in the past 6 months							0.53
No	1026	(74.5)	31	(70.5)	995	(74.6)	
Yes	351	(25.5)	13	(29.5)	338	(25.4)	
Total number of co-medications							0.58
0	443	(32.2)	11	(25.0)	432	(32.4)	
1-4	633	(46.0)	24	(54.6)	609	(45.7)	
5-9	239	(17.4)	8	(18.2)	231	(17.3)	
≥10	62	(4.5)	1	(2.3)	61	(4.6)	

4.4.2.1 Prevalence of falls and recurrent falls in POPPY

Among the 1333 study participants with complete data on falls, 12.9% (172/1333) reported having at least 1 fall over the past 28 days. Among the older PLWH 17.9% (122/680) had a history of falls in the past 28 days, a significantly higher proportion compared to both younger PLWH and the HIV-negative controls (9.7% (35/360) and 5.1% (15/293), respectively, P<0.001).

Among the 1333 study participants with complete data on falls, 121 (9.1%) experienced recurrent falls (more than 1 fall in the past 28 days). The proportion of older PLWH who experienced recurrent falls was significantly higher than that of the younger PLWH and the HIV-negative controls (13.4% (91/680) vs. 6.1% (22/360) and 2.7% (8/293), P<0.001, respectively). In the older PLWH with at least one fall, 54.9% (67/122) had three or more falls, a higher proportion compared to both younger PLWH and the HIV-negative controls (45.7% (16/35) and 33.3% (5/15), P<0.001), Table 4.9.

Table 4.9: Falls in the past 28 days before entering POPPY, stratified by study group

	Older PLWH		Younger PLWH		HIV-negative		
	n	(%)	n	(%)	n	(%)	p-value
History of falls							<0.001
No	558	(82.1)	325	(90.3)	278	(94.9)	
Yes	122	(17.9)	35	(9.7)	15	(5.1)	
Number of falls							<0.001
Zero	558	(82.1)	325	(90.3)	278	(94.9)	
One fall	31	(25.4)	13	(37.1)	7	(46.7)	
Two falls	24	(19.7)	6	(45.7)	3	(20.0)	
Three or more	67	(54.9)	16	(45.7)	5	(33.3)	
History of recurrent falls*							<0.001
No	589	(86.6)	338	(93.9)	285	(97.3)	
Yes	91	(13.4)	22	(6.1)	8	(2.7)	

*Participants with more than 1 fall in the past 28 days

4.4.2.2 Location, cause and consequences of falls in POPPY

Among the 172 participants with a history of falls, 138 (80.2%) had experienced falls inside their home, 76 (44.2%) outside their home and 125 (72.7%) had them away from home. Three of the POPPY participants reporting a fall did not specify where they had fallen. Detailed information regarding the circumstances surrounding the falls are presented in Figure 4.3 and Table 4.10. The participants reported multiple responses for the causes of falls. In particular, 65 (37.8%) lost their balance, 59 (34.3%) tripped, 35 (20.3%) felt that their legs gave way, 31 (18.0%) slipped and in 29 (16.9%) cases they felt giddy or dizzy. Of the 172 persons reporting falls, only 6 (3.5%) reported feeling faint, with 'other' causes being reported by 16 (9.3%) persons. Finally, only 10 (5.8%) persons were not sure about the cause of their falls. Fewer than half of the people reporting falls, 75 (43.6%), stated that their falls resulted in injury, 91 (52.9%) stated that their falls did not result in injury, and 6 (3.5%) had an unknown injury status. The majority of those with injuries (n=91), reported bruises (69, 75.8%) or cuts or grazes (22, 43.6%); only 3 (3.3%) reported fractures and 16 (17.6%) had an injury that resulted in back pain, Table 4.11.

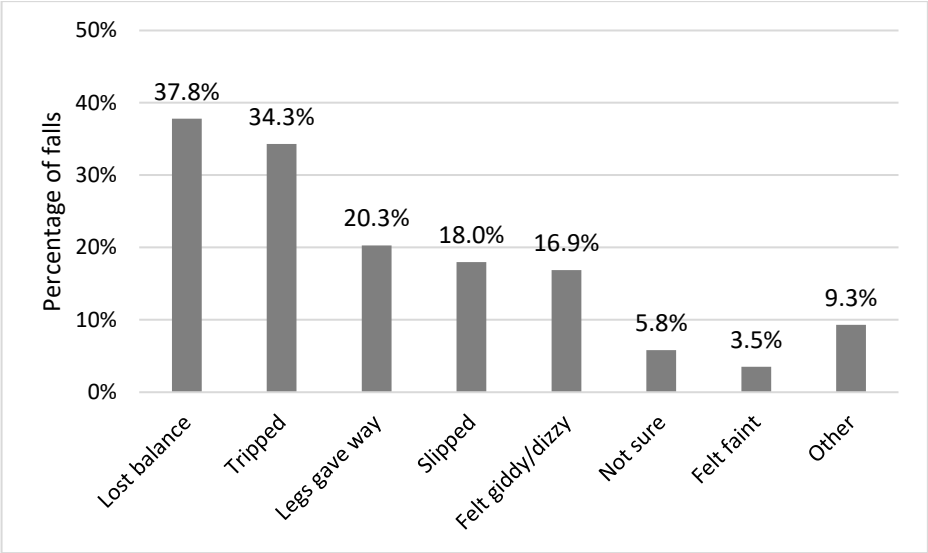


Figure 4.3: Reported cause of fall among the POPPY participants reporting a fall in the last 28 days, multiple causes reported by participants with more than 1 fall*

*percentages add more than 100% due to multiple causes reported

Table 4.10: Details of location of falls; multiple locations may be reported by participants with more than 1 fall

	n (%)*
Total number with a fall	172
Inside	138 (80.2)
Home entrance or in the garden	76 (44.2)
Away from home	125 (72.7)
Not stated	3 (1.7)
Inside*	
On the one level	47 (27.3)
Getting out of bed	25 (14.5)
Getting out of a chair	14 (8.1)
Using the shower/bath	33 (19.2)
Using the toilet	9 (5.2)
Walking up or down stairs	51 (29.7)
Other	40 (23.3)
Home entrance or in the garden*	
Walking up or down a step	35 (20.3)
On the one level (e.g. path)	21 (12.2)
In the garden	16 (9.3)
Other	24 (14.0)
Away from home*	
On the footpath	47 (27.3)
On a kerb/gutter	38 (22.1)
In a public building	24 (14.0)
Getting out of a vehicle	14 (8.1)
In another person's home	19 (11.0)
Other	40 (23.3)

*Study participants could report multiple falls locations and outcomes of injuries. Percentages add more than 100% due to multiple locations/injuries reported

Table 4.11: Details of injuries related to falls; multiple types of injuries may be reported by participants with more than 1 fall.

	n (%)
Total number with a fall	172
Were any injuries suffered?	
Yes	91 (43.6)
No	75 (52.9)
Not stated	6 (3.5)
Type of injury	
Bruises	69 (75.8)
Cuts/grazes	22 (24.2)
Broken wrist	3 (3.3)
Broken hip	0 (0.0)
Broken ribs	0 (0.0)
Back pain	16 (17.6)
Other	20 (22.0)

4.4.2.3 The prevalence of history of falls stratified by characteristics of the older POPPY participants

The prevalence of falls in the sub-group of older PLWH and HIV-negative controls was significantly higher among participants with unknown level of education, single, with a BMI≤22.8 kg/m^2, with past use of alcohol and a higher number of total co-medications. No difference in the prevalence of falls was observed for participants with different characteristics of age, gender, ethnicity, smoking and recreational drug use in the past 6 months, Table 4.12.

Table 4.12: Prevalence of falls among the older POPPY participants stratified by participant characteristics

			History of falls				
	Total N=973		No n=836		Yes n=137		
	n	(%)	n	(%)	n	(%)	p-value
Age							0.28
50-54	354	(100.0)	308	(87.0)	46	(13.0)	
55-59	261	(100.0)	224	(85.8)	37	(14.2)	
60-64	186	(100.0)	152	(81.7)	34	(18.3)	
65-69	109	(100.0)	94	(86.2)	15	(13.8)	
≥70	63	(100.0)	58	(92.1)	5	(7.9)	
Gender							0.91
Female	188	(100.0)	162	(86.2)	26	(13.8)	
Male	785	(100.0)	674	(85.9)	111	(14.1)	
Ethnicity							0.58

	Total N=973		History of falls				
			No n=836		Yes n=137		
	n	(%)	n	(%)	n	(%)	p-value
Black African	121	(100.0)	102	(84.3)	19	(15.7)	
White	852	(100.0)	734	(86.2)	118	(13.9)	
Education							<0.001
Finished education with no qualifications	96	(100.0)	82	(85.4)	14	(14.6)	
O levels/GCSEs (or equivalent)	159	(100.0)	132	(83.0)	27	(17.0)	
A levels (or equivalent)	133	(100.0)	119	(89.5)	14	(10.5)	
University degree or above	440	(100.0)	392	(89.1)	48	(10.9)	
Other	127	(100.0)	101	(79.5)	26	(20.5)	
Unknown	18	(100.0)	10	(55.6)	8	(44.4)	
Marital status							<0.001
Single	407	(100.0)	343	(84.3)	64	(15.7)	
Married/Civil Partnership/ Cohabiting	415	(100.0)	378	(91.1)	37	(8.9)	
Divorced/Living separately	117	(100.0)	86	(73.5)	31	(26.5)	
Widowed/Other	34	(100.0)	29	(85.3)	5	(14.7)	
BMI (kg/m^2)							0.02
≤22.8	181	(100.0)	147	(81.2)	34	(18.8)	
22.9-24.7	184	(100.0)	159	(86.4)	25	(13.6)	
24.8-26.7	194	(100.0)	178	(91.8)	16	(8.3)	
26.8-29.3	199	(100.0)	173	(86.9)	26	(13.1)	
≥29.4	202	(100.0)	166	(82.2)	36	(17.8)	
Unknown	13	(100.0)	13	(100.0)	0	(0.0)	
Current smoking							0.09
No	773	(100.0)	672	(86.9)	101	(13.1)	
Yes	194	(100.0)	158	(81.4)	36	(18.6)	
Unknown	6	(100.0)	6	(100.0)	0	(0.0)	
Current alcohol use							0.007
No	70	(100.0)	53	(75.7)	17	(24.3)	
Yes	793	(100.0)	694	(87.5)	99	(12.5)	
In the past	110	(100.0)	89	(80.9)	21	(19.1)	
Recreational drugs in the past 6 months							0.90
No	763	(100.0)	655	(85.9)	108	(14.2)	
Yes	210	(100.0)	181	(86.2)	29	(13.8)	
Number of total co-medications							<0.001
0	291	(100.0)	265	(91.1)	26	(8.9)	
1-4	441	(100.0)	378	(85.7)	63	(14.3)	
5-9	184	(100.0)	158	(85.9)	26	(14.1)	
≥10	57	(100.0)	35	(61.4)	22	(38.6)	

4.4.3 BMD

Among the POPPY participants, 93.8% (1292/1377) provided information for at least one of the LS, FN or TH BMD measurements at the baseline study visit. The characteristics that were significantly different between those with and without BMD data were the POPPY site and the history of use of recreational drugs, Table 4.13. In particular, the proportion of participants with complete data who were from SMH was significantly lower than the proportion of those with missing data who were from this site (18.2% (235/1292) vs. 2.4% (2/84), P<0.001). Among those with complete data, the proportion of those with a history of recreational drug use was significantly lower than the proportion among those with missing data (24.4% (315/1292) vs. 42.9% (36/84), P<0.001). Although the difference in marital status did not reach the standard threshold for significance, the proportion of those who provided data for BMD who were married was lower than that among those who did not provide BMD data (44.0% (569/1292) vs. 56.0% (47/84)). Furthermore, the proportions who were divorced also differed (6.9% (89/1292) vs. 3.6% (3/84), respectively, P=0.08). The differences observed between those with complete data and those with missing data with regards to POPPY group, gender, ethnicity, BMI, sexuality, current smoking status, current alcohol use and number of total co-medications were not statistically significant, Table 4.13.

Table 4.13: Characteristics of POPPY participants who did or did not provide data on BMD from at least one measured body site (LS, FN or TH)

			Provided data on BMD from at least one site (LS, FN or TH)				
	Total N=1377		No N=84		Yes N=1292		
	n	(%)	n	(%)	n	(%)	p-value
Study centre							<0.001
CWH	363	(26.4)	14	(16.7)	349	(27.0)	
DUH	81	(5.9)	2	(2.4)	79	(6.1)	
HUH	37	(2.7)	0	(0.0)	37	(2.9)	
KCH	129	(9.4)	6	(7.1)	123	(9.5)	
RFH	32	(2.3)	0	(0.0)	32	(2.5)	
RSH	263	(19.1)	10	(11.9)	253	(19.6)	
SMH	237	(17.2)	2	(2.4)	235	(18.2)	
UCL	234	(17.0)	50	(59.5)	184	(14.2)	
Group							0.20
Older PLWH	699	(50.8)	50	(59.5)	649	(50.2)	

	Total N=1377		Provided data on BMD from at least one site (LS, FN or TH)				
			No N=84		Yes N=1292		
	n	(%)	n	(%)	n	(%)	p-value
Younger PLWH	374	(27.2)	21	(25.0)	353	(27.3)	
HIV-negative	304	(22.1)	13	(15.5)	291	(22.5)	
Gender							0.22
Female	268	(19.5)	12	(14.3)	256	(19.8)	
Male	1109	(80.5)	72	(85.7)	1037	(80.2)	
Ethnicity							0.29
Black African	202	(14.7)	9	(10.7)	193	(14.9)	
White	1175	(85.3)	75	(89.3)	1100	(85.1)	
Marital status							0.08
Married	616	(44.7)	47	(56.0)	569	(44.0)	
Civil Partnership	210	(15.3)	11	(13.1)	199	(15.4)	
Cohabiting	176	(12.8)	8	(9.5)	168	(13.0)	
Single	184	(13.4)	15	(17.9)	169	(13.1)	
Divorced	92	(6.7)	3	(3.6)	89	(6.9)	
Living separately	56	(4.1)	0	(0.0)	56	(4.3)	
Widowed/Other	43	(3.1)	0	(0.0)	43	(3.3)	
BMI (kg/m^2)							0.14
≤22.8	278	(20.2)	24	(28.6)	254	(19.6)	
22.9-24.7	275	(20.0)	19	(22.6)	256	(19.8)	
24.8-26.7	266	(19.3)	15	(17.9)	251	(19.4)	
26.8-29.3	274	(19.9)	15	(17.9)	259	(20.0)	
≥29.4	268	(19.5)	9	(10.7)	259	(20.0)	
Unknown	16	(1.2)	2	(2.4)	14	(1.1)	
Sexuality/Route of HIV transmission							0.20
MSM	963	(69.9)	64	(76.2)	899	(69.5)	
Heterosexual	414	(30.1)	20	(23.8)	394	(30.5)	
Current smoking							0.13
No	1060	(77.0)	58	(69.1)	1002	(77.5)	
Yes	309	(22.4)	26	(31.0)	283	(21.9)	
Unknown	8	(0.6)	0	(0.0)	8	(0.6)	
Current alcohol use							0.57
No	108	(7.8)	6	(7.1)	102	(7.9)	
Yes	1120	(81.3)	66	(78.6)	1054	(81.5)	
In the past	149	(10.8)	12	(14.3)	137	(10.6)	
Recreational drug use in the past 6 months							<0.001
No	1026	(74.5)	48	(57.1)	978	(75.6)	
Yes	351	(25.5)	36	(42.9)	315	(24.4)	
Total number of co-medications							0.30
0	443	(32.2)	21	(25.0)	422	(32.6)	
1-4	633	(46.0)	43	(51.2)	590	(45.6)	
5-9	239	(17.4)	18	(21.4)	221	(17.1)	
≥10	62	(4.5)	2	(2.4)	60	(4.6)	

The BMD T-score was significantly lower at all three sites among older PLWH, compared to younger PLWH and HIV-negative controls: at LS (mean (SD), -0.7 (1.4) vs. -0.5 (1.3) and -0.1 (1.6), respectively, P<0.001); at FN (-0.9 (1.2) vs. -0.5 (1.2) and -0.5 (1.0), respectively, P<0.001); and at TH (-0.6 (1.1) vs. -0.4 (1.0) and -0.1 (1.0), respectively, P<0.001). Following the WHO cut-offs for the definition of osteopenia and osteoporosis (382), 30.5% (368/1207) had osteopenia at LS and 7.2% (87/1207) had osteoporosis. At FN the prevalence of osteopenia was 38.8% (494/1275) and osteoporosis 3.8% (49/1275). Finally, at TH, the prevalence of osteopenia was 26.9% (318/1183) and of osteoporosis 1.9% (22/1183). At all sites, the proportions of those with osteoporosis and osteopenia were significantly higher among older PLWH compared to younger PLWH and HIV-negative controls, Table 4.14.

Table 4.14: Mean (SD) BMD T-score among the study groups of POPPY participants

Lumbar spine

	BMD T-score			BMD level					
	N	Mean (SD)	p-value	Normal n (%)		Osteopenia n (%)		Osteoporosis n (%)	
Group			<0.001						
Older PLWH	610	-0.7 (1.4)		356	(58.3)	201	(33.0)	53	(8.7)
Younger PLWH	334	-0.5 (1.3)		209	(62.6)	105	(31.4)	20	(6.0)
HIV-negative	263	-0.1 (1.6)		187	(71.1)	62	(23.6)	14	(5.3)

Femoral neck

	BMD T-score			BMD level					
	N	Mean (SD)	p-value	Normal n (%)		Osteopenia n (%)		Osteoporosis n (%)	
Group			<0.001						
Older PLWH	642	-0.9 (1.2)		325	(50.6)	277	(43.2)	40	(6.2)
Younger PLWH	349	-0.5 (1.2)		223	(63.9)	120	(34.4)	6	(1.7)
HIV-negative	284	-0.5 (1.0)		184	(64.8)	97	(34.2)	3	(1.1)

Total hip

	BMD T-score			BMD level					
	N	Mean (SD)	p-value	Normal n (%)		Osteopenia n (%)		Osteoporosis n (%)	
Group			<0.001						
Older PLWH	595	-0.6 (1.1)		381	(64.0)	197	(33.1)	17	(2.9)
Younger PLWH	321	-0.4 (1.0)		241	(75.1)	77	(24.0)	3	(0.9)
HIV-negative	267	-0.1 (1.0)		221	(82.8)	44	(16.5)	2	(0.7)

4.4.3.1 The prevalence of osteopenia and osteoporosis stratified by characteristics of the older POPPY participants

The prevalence of osteoporosis at LS in the sub-group of older PLWH and HIV-negative controls was significantly higher among participants who finished education with no qualifications and BMI ≤22.8 kg/m^2. No difference in the prevalence of osteoporosis at LS was observed for participants with different characteristics of age, gender, ethnicity, marital status, smoking, alcohol, history of recreational drug use in the past 6 months and number of total co-medications, Table 4.15.

Table 4.15: Prevalence of osteopenia and osteoporosis at LS among the older POPPY participants stratified by participant characteristics

			BMD						
	Total N=873		Normal n=543		Osteopenia n=263		Osteoporosis n=67		
	n	(%)	n	(%)	n	(%)	n	(%)	p-value
Age									0.48
50-54	319	(100.0)	184	(57.7)	110	(34.5)	25	(7.8)	
55-59	228	(100.0)	146	(64.0)	67	(29.4)	15	(6.6)	
60-64	169	(100.0)	108	(63.9)	44	(26.0)	17	(10.1)	
65-69	97	(100.0)	64	(66.0)	27	(27.8)	6	(6.2)	
≥70	60	(100.0)	41	(68.3)	15	(25.0)	4	(6.7)	
Gender									0.94
Female	180	(100.0)	110	(61.1)	56	(31.1)	14	(7.8)	
Male	693	(100.0)	433	(62.5)	207	(29.9)	53	(7.7)	
Ethnicity									0.76
Black African	114	(100.0)	74	(64.9)	31	(27.2)	9	(7.9)	
White	759	(100.0)	469	(61.8)	232	(30.6)	58	(7.6)	
Education									0.007
Finished education with no qualifications	85	(100.0)	49	(57.7)	23	(27.1)	13	(15.3)	
O levels/GCSEs (or equivalent)	139	(100.0)	83	(59.7)	39	(28.1)	17	(12.2)	
A levels (or equivalent)	119	(100.0)	77	(64.7)	33	(27.7)	9	(7.6)	
University degree or above	383	(100.0)	250	(65.3)	116	(30.3)	17	(4.4)	
Other	111	(100.0)	68	(61.3)	34	(30.6)	9	(8.1)	
Unknown	36	(100.0)	16	(44.4)	18	(50.0)	2	(5.6)	
Marital status									0.21
Single	367	(100.0)	227	(61.9)	109	(29.7)	31	(8.5)	

	Total N=873		BMD Normal n=543		Osteopenia n=263		Osteoporosis n=67		
	n	(%)	n	(%)	n	(%)	n	(%)	p-value
Married/Civil Partnership/ Cohabiting	363	(100.0)	223	(61.4)	113	(31.1)	27	(7.4)	
Divorced/Living separately	106	(100.0)	70	(66.0)	33	(31.1)	3	(2.8)	
Widowed/Other	37	(100.0)	23	(62.2)	8	(21.6)	6	(16.2)	
BMI (kg/m^2)									<0.001
≤22.8	156	(100.0)	75	(48.1)	61	(39.1)	20	(12.8)	
22.9-24.7	163	(100.0)	87	(53.4)	60	(36.8)	16	(9.8)	
24.8-26.7	182	(100.0)	120	(65.9)	51	(28.0)	11	(6.0)	
26.8-29.3	177	(100.0)	119	(67.2)	47	(26.6)	11	(6.2)	
≥29.4	183	(100.0)	135	(73.8)	41	(22.4)	7	(3.8)	
Unknown	12	(100.0)	7	(58.3)	3	(25.0)	2	(16.7)	
Current smoking									0.23
No	698	(100.0)	445	(63.8)	200	(28.7)	53	(7.6)	
Yes	171	(100.0)	96	(56.1)	62	(36.3)	13	(7.6)	
Unknown	4	(100.0)	2	(50.0)	1	(25.0)	1	(25.0)	
Current alcohol use									0.69
No	66	(100.0)	37	(56.1)	25	(37.9)	4	(6.1)	
Yes	716	(100.0)	450	(62.9)	211	(29.5)	55	(7.7)	
In the past	91	(100.0)	56	(61.5)	27	(29.7)	8	(8.8)	
Recreational drugs in the past 6 months									0.75
No	694	(100.0)	436	(62.8)	206	(29.7)	52	(7.5)	
Yes	179	(100.0)	107	(59.8)	57	(31.8)	15	(8.4)	
Number of total co-medications									0.08
0	268	(100.0)	184	(68.7)	63	(23.5)	21	(7.8)	
1-4	392	(100.0)	235	(60.0)	131	(33.4)	26	(6.6)	
5-9	161	(100.0)	90	(55.9)	55	(34.2)	16	(9.9)	
≥10	52	(100.0)	34	(65.4)	14	(26.9)	4	(7.7)	

The prevalence of osteoporosis at FN in the sub-group of older PLWH and HIV-negative controls was significantly higher among participants who were older, male, white, finished education with no qualifications and BMI ≤22.8 kg/m^2. No difference in the prevalence of osteoporosis at FN was observed for participants with different characteristics of marital status, smoking, alcohol, history of recreational drug use in the past 6 months and number of total co-medications, Table 4.16

Table 4.16: Prevalence of osteopenia and osteoporosis at FN among the older POPPY participants stratified by participant characteristics

	Total N=926		BMD						
			Normal n=509		Osteopenia n=374		Osteoporosis n=43		
	n	(%)	n	(%)	n	(%)	n	(%)	p-value
Age									<0.001
50-54	334	(100.0)	214	(64.1)	112	(33.5)	8	(2.4)	
55-59	246	(100.0)	144	(58.5)	93	(37.8)	9	(3.7)	
60-64	180	(100.0)	77	(42.8)	93	(51.7)	10	(5.6)	
65-69	103	(100.0)	51	(49.5)	44	(42.7)	8	(7.8)	
≥70	63	(100.0)	23	(36.5)	32	(50.8)	8	(12.7)	
Gender									<0.001
Female	181	(100.0)	122	(67.4)	56	(30.9)	3	(1.6)	
Male	745	(100.0)	387	(52.0)	318	(42.7)	40	(5.4)	
Ethnicity									<0.001
Black African	117	(100.0)	90	(76.9)	26	(22.2)	1	(0.9)	
White	809	(100.0)	419	(51.8)	348	(43.0)	42	(5.2)	
Education									<0.001
Finished education with no qualifications	91	(100.0)	41	(45.1)	35	(38.5)	15	(16.5)	
O levels/GCSEs (or equivalent)	151	(100.0)	82	(54.3)	62	(41.1)	7	(4.6)	
A levels (or equivalent)	123	(100.0)	65	(52.9)	52	(42.3)	6	(4.9)	
University degree or above	407	(100.0)	235	(57.7)	161	(39.6)	11	(2.7)	
Other	118	(100.0)	65	(55.1)	49	(41.5)	4	(3.4)	
Unknown	36	(100.0)	21	(58.3)	15	(41.7)	0	(0.0)	
Marital status									0.88
Single	383	(100.0)	205	(53.5)	157	(41.0)	21	(5.5)	
Married/Civil Partnership/ Cohabiting	393	(100.0)	219	(55.7)	158	(40.2)	16	(4.1)	
Divorced/Living separately	114	(100.0)	62	(54.4)	47	(41.2)	5	(4.4)	
Widowed/Other	36	(100.0)	23	(63.9)	12	(33.3)	1	(2.8)	
BMI (kg/m^2)									<0.001
≤22.8	164	(100.0)	59	(36.0)	90	(54.9)	15	(9.2)	
22.9-24.7	174	(100.0)	79	(45.4)	82	(47.1)	13	(7.5)	
24.8-26.7	186	(100.0)	100	(53.8)	81	(43.6)	5	(2.7)	
26.8-29.3	192	(100.0)	121	(63.0)	63	(32.8)	8	(4.2)	
≥29.4	198	(100.0)	144	(72.7)	53	(26.8)	1	(0.5)	
Unknown	12	(100.0)	6	(50.0)	5	(41.7)	1	(8.3)	
Current smoking									0.65
No	742	(100.0)	416	(56.1)	291	(39.2)	35	(4.7)	
Yes	179	(100.0)	90	(50.3)	81	(45.3)	8	(4.5)	
Unknown	5	(100.0)	3	(60.0)	2	(40.0)	0	(0.0)	

	Total N=926		BMD Normal n=509		Osteopenia n=374		Osteoporosis n=43		
	n	(%)	n	(%)	n	(%)	n	(%)	p-value
Current alcohol use									0.35
No	69	(100.0)	42	(60.9)	25	(36.2)	2	(2.9)	
Yes	756	(100.0)	404	(53.4)	316	(41.8)	36	(4.8)	
In the past	101	(100.0)	63	(62.4)	33	(32.7)	5	(4.9)	
Recreational drugs in the past 6 months									0.14
No	733	(100.0)	415	(56.6)	285	(38.9)	33	(4.5)	
Yes	193	(100.0)	94	(48.7)	89	(46.1)	10	(5.2)	
Number of total co-medications									0.09
0	283	(100.0)	173	(61.1)	100	(35.3)	10	(3.5)	
1-4	418	(100.0)	229	(54.8)	168	(40.2)	21	(5.0)	
5-9	171	(100.0)	85	(49.7)	77	(45.0)	9	(5.3)	
≥10	54	(100.0)	22	(40.7)	29	(53.7)	3	(5.6)	

The prevalence of osteoporosis at TH in the sub-group of older PLWH and HIV-negative controls was significantly higher among participants who finished education with no qualifications and those with BMI ≤22.8 kg/m^2. No difference in the prevalence of osteoporosis at TH was observed for participants with different characteristics of age, gender, marital status, smoking, alcohol, history of recreational drug use in the past 6 months and number of total co-medications, Table 4.17.

Table 4.17: Prevalence of osteopenia and osteoporosis at TH among the older POPPY participants stratified by participant characteristics

	Total N=862		BMD Normal n=602		Osteopenia n=241		Osteoporosis n=19		
	n	(%)	n	(%)	n	(%)	n	(%)	p-value
Age									0.28
50-54	310	(100.0)	227	(73.2)	79	(25.5)	4	(1.3)	
55-59	226	(100.0)	163	(72.1)	58	(25.7)	5	(2.2)	
60-64	168	(100.0)	110	(65.5)	55	(32.7)	3	(1.8)	
65-69	97	(100.0)	63	(65.0)	30	(30.9)	4	(4.1)	
≥70	61	(100.0)	39	(63.9)	19	(31.2)	3	(4.9)	
Gender									0.05
Female	166	(100.0)	129	(77.7)	34	(20.5)	3	(1.8)	
Male	696	(100.0)	473	(68.0)	207	(29.7)	16	(2.3)	
Ethnicity									0.002

	Total N=862		BMD						
			Normal n=602		Osteopenia n=241		Osteoporosis n=19		
	n	(%)	n	(%)	n	(%)	n	(%)	p-value
Black African	98	(100.0)	83	(84.7)	15	(15.3)	0	(0.0)	
White	764	(100.0)	519	(67.9)	226	(29.6)	19	(2.5)	
Education									0.001
Finished education with no qualifications	88	(100.0)	53	(60.2)	27	(30.7)	8	(9.1)	
O levels/GCSEs (or equivalent)	142	(100.0)	92	(64.8)	47	(33.1)	3	(2.1)	
A levels (or equivalent)	120	(100.0)	86	(71.7)	32	(26.7)	2	(1.7)	
University degree or above	367	(100.0)	271	(73.8)	92	(25.1)	4	(1.1)	
Other	111	(100.0)	72	(64.9)	37	(33.3)	2	(1.8)	
Unknown	34	(100.0)	28	(82.4)	6	(17.7)	0	(0.0)	
Marital status									0.13
Single	355	(100.0)	248	(69.9)	94	(26.5)	13	(3.7)	
Married/Civil Partnership/ Cohabiting	363	(100.0)	250	(68.9)	111	(30.6)	2	(0.6)	
Divorced/Living separately	111	(100.0)	80	(72.1)	28	(25.2)	3	(2.7)	
Widowed/Other	33	(100.0)	24	(72.7)	8	(24.2)	1	(3.0)	
BMI (kg/m^2)									<0.001
≤22.8	153	(100.0)	69	(45.1)	75	(49.0)	9	(5.9)	
22.9-24.7	165	(100.0)	100	(60.6)	62	(37.6)	3	(1.8)	
24.8-26.7	175	(100.0)	126	(72.0)	46	(26.3)	3	(1.7)	
26.8-29.3	180	(100.0)	142	(78.9)	36	(20.0)	2	(1.1)	
≥29.4	180	(100.0)	161	(89.4)	18	(10.0)	1	(0.6)	
Unknown	9	(100.0)	4	(44.1)	4	(44.4)	1	(11.1)	
Current smoking									0.28
No	687	(100.0)	488	(71.0)	187	(27.2)	12	(1.8)	
Yes	170	(100.0)	111	(65.3)	52	(30.6)	7	(4.1)	
Unknown	5	(100.0)	3	(60.0)	2	(40.0)	0	(0.0)	
Current alcohol use									0.68
No	64	(100.0)	44	(68.8)	20	(31.3)	0	(0.0)	
Yes	705	(100.0)	495	(70.2)	194	(27.5)	16	(2.3)	
In the past	93	(100.0)	63	(67.7)	27	(29.0)	3	(3.2)	
Recreational drugs in the past 6 months									0.05
No	681	(100.0)	489	(71.8)	178	(26.1)	14	(2.1)	
Yes	181	(100.0)	113	(62.4)	63	(34.8)	5	(2.8)	
Number of total co-medications									0.16
0	261	(100.0)	197	(75.5)	59	(22.6)	5	(1.9)	

	Total N=862		BMD Normal n=602		Osteopenia n=241		Osteoporosis n=19		
	n	(%)	n	(%)	n	(%)	n	(%)	p-value
1-4	392	(100.0)	272	(69.4)	113	(28.8)	7	(1.8)	
5-9	158	(100.0)	99	(62.7)	54	(34.2)	5	(3.2)	
≥10	51	(100.0)	34	(66.7)	15	(29.4)	2	(3.9)	

4.4.4 Fractures

Among the 1377 POPPY participants, 527 reported a total of 847 fractures of which 495 (58.4%) occurred during adulthood, 248 (29.3%) during childhood and the remaining 104 (12.3%) at an unknown age. In total, 207 (24.4%) fractures occurred at an osteoporotic site and 640 (75.6%) at a non-osteoporotic site. Almost 40% of the fractures were caused by falling from a height more than the participant's length (323, 38.1%) while 205 (24.2%) were caused from falls from a height that was less than the participant's length and 34 (4.0%) were caused by falling from an unspecified height. Of the total fractures, 120 (14.2%) were due to traffic accidents and 155 (18.3%) due to other accidental causes (including sport and dropping heavy objects). Assaults, fights and attacks were the cause of 37 (4.4%) of the fractures and the cause of fracture was unknown or missing for the remaining 164 (19.4%) fractures.

The most common site for the fracture to occur was the other upper extremities (155, 18.3%), this was followed by fractures at the wrist (138, 16.3%) and fractures at other lower extremities (91, 10.7%). Fractures at ankles, fingers and toes accounted for 67, 63 and 60 of the fractures (7.9%, 7.4% and 7.1%, respectively). Fractures at the foot, upper arm, head, hand, vertebrae/back/neck, hip and pelvis all accounted separately for less than 6% of the total fractures. Finally, for 4 of the fractures (0.5%), the location of the fracture was unknown. Of the 847 fractures, 128 (15.1%) required open surgery, 638 (75.3%) did not require surgery and for 81 (9.6%) this information was unknown, Table 4.18.

Table 4.18: Characteristics of each fracture reported among POPPY participants

Total number of fractures	**N=847**	
	n	**(%)**
Age of participant when fracture occurred		
Adulthood fractures	495	(58.4)
Childhood fractures	248	(29.3)
Unknown	104	(12.3)
Cause of fracture		
Fall from height more than your own length	323	(38.1)
Fall from height less than your own length	205	(24.2)
Fall - height not specified	34	(4.0)
Traffic accident	120	(14.2)
Other accidental cause (including sport, dropping heavy objects)	155	(18.3)
Assault/Fight/Attack	37	(4.4)
Medical reason	14	(1.7)
Unknown/missing	164	(19.4)
Site of Fracture		
Head	42	(5.0)
Upper Arm	44	(5.2)
Wrist	138	(16.3)
Hand	34	(4.0)
Fingers	67	(7.9)
Other upper extremities (collar bone, elbow, forearm)	155	(18.3)
Vertebrae/back/neck	13	(1.5)
Ribs	60	(7.1)
Hip	12	(1.4)
Pelvis	8	(0.9)
Ankle	68	(8.0)
Foot	48	(5.7)
Toes	63	(7.4)
Other lower extremities (thigh, knee, lower leg)	91	(10.7)
Site unknown	4	(0.5)
Osteoporotic site		
Yes	207	(24.4)
No	640	(75.6)
Side of the body where fracture occurred		
Left	321	(37.9)
Right	328	(38.7)
Not applicable/head/torso	75	(8.9)
Unknown	123	(14.5)
Fractures requiring open surgery		
Yes	128	(15.1)
No	638	(75.3)
Unknown	81	(9.6)

Of the 847 fractures, 718 (84.8%) did not occur within the 5 years prior to study entry or had a missing date and so could not be classified; these were excluded from the analysis. In particular, 248 (29.3%) fractures occurred during childhood, 364 (43.0%) occurred during adulthood but more than 5 years before study entry and 106 (12.5%) were missing the date of fracture. The remaining 131 (15.5%) fractures were included in the calculation of the FIR. Among the older PLWH, 61 participants experienced a total of 78 fractures in the 5 years before study entry of which 22 were fragility fractures and 16 were osteoporotic; among the younger PLWH, 27 participants experienced a total of 32 fractures in the 5 years before study entry, of which 13 were fragility fracturs and 6 were osteoporotic. Finally, among the HIV-negative group, 19 participants experienced a total of 21 fractures in the 5 years before study entry of which 11 were fragility and 3 were osteoporotic, Figure 4.4.

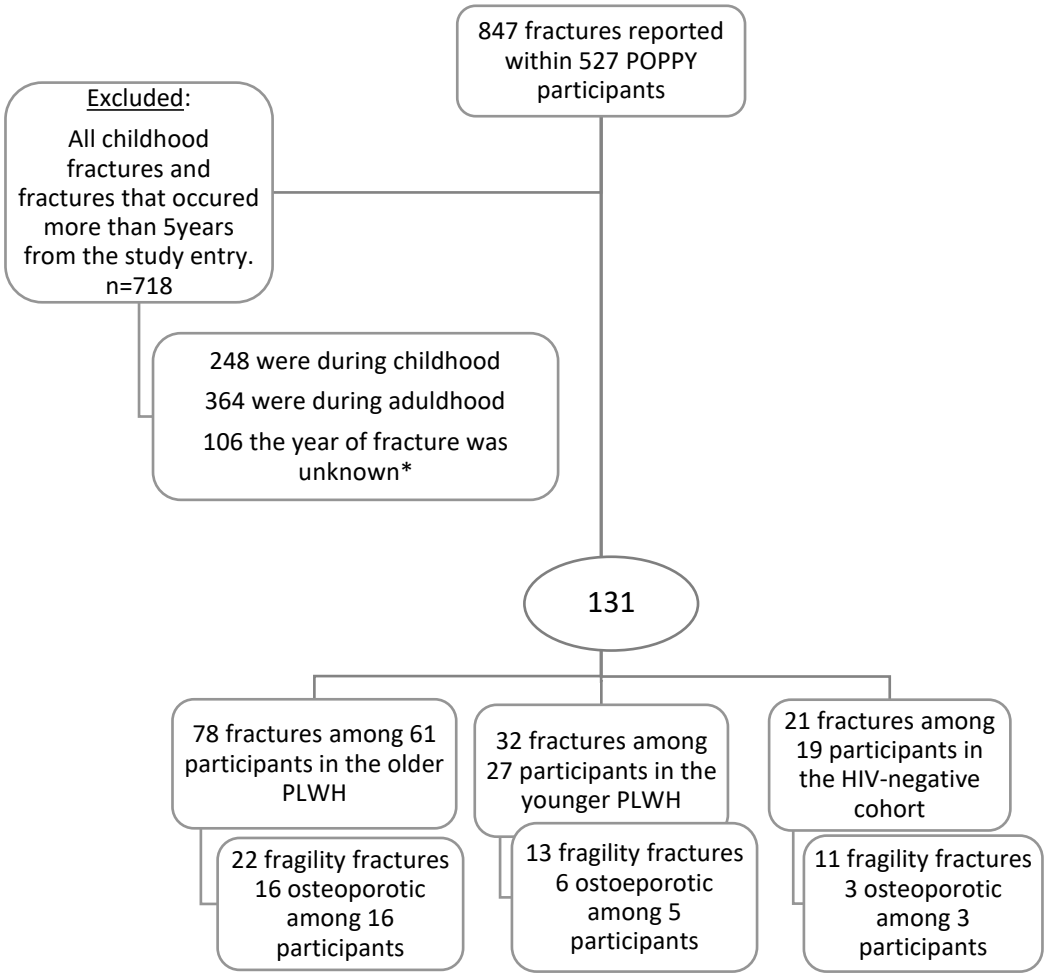


Figure 4.4: Flow chart of fractures reported in POPPY

*Assault/Fight/attack n=3, fall from unspecified height n=4, fall from height more or less than own height n=23, n=18 respectively, other accidental cause (including sports) n=20, traffic/vehicle accidents n=14 and unknown=22

4.4.4.1 Fracture rate amongst POPPY participants

Of the 78 fractures among the older PLWH, 12 were at the ribs, 11 at the wrist, 11 at either the collarbone, elbow or forearm, 11 at the toes and 8 or fewer at all other sites. Of the 32 fractures among younger PLWH 5 were at the ribs, 5 at the wrist and 4 or fewer in all other sites. Lastly, of the 21 fractures among HIV-negative controls, 3 were at either the collarbone, elbow or forearm, 3 at the thigh, knee, lower leg, 3 at the fingers and 2 or fewer at other sites, Figure 4.5.

The FIR (/100-years) was 2.23, 95% CI (1.74, 2.73), 1.71 (1.12, 2.30) and 1.38 (0.80, 1.97) among the older PLWH, the younger PLWH and the HIV-negative controls respectively (P=0.11).

4.4.4.2 Characteristics of the study participants with recent fractures

Compared to those without recent fractures, those with fractures were more likely to be male (88.8% (95/107) vs. 79.8% (1014/1270), P=0.03), of white ethnicity (97.2% (104/107) vs. 84.3% (1071/1270), P<0.001) and were more likely to have used recreational drugs in the past 6-months (35.5% (38/107) vs. 24.7% (313/1270), P=0.01). No significant differences were observed by POPPY group, BMI, current smoking status, current use of alcohol and total number of co-medications between those with and without recent fractures, Table 4.19.

Table 4.19: Characteristics of POPPY participants with and without recent fractures

	Total N=1377		Recent fractures: No n=1270		Recent fractures: Yes n=107		
	n	(%)	n	(%)	n	(%)	p-value
Group							0.36
Older PLWH	699	(50.8)	638	(50.2)	61	(57.0)	
Younger PLWH	374	(27.2)	347	(27.3)	27	(25.2)	
HIV-negative	304	(22.1)	285	(22.4)	19	(17.8)	
Gender							0.03
Female	268	(19.5)	256	(20.2)	12	(11.2)	
Male	1109	(80.5)	1014	(79.8)	95	(88.8)	
Ethnicity							<0.001
Black African	202	(14.7)	199	(15.7)	3	(2.8)	
White	1175	(85.3)	1071	(84.3)	104	(97.2)	
BMI (kg/m^2)							0.25
≤22.8	278	(20.2)	254	(20.0)	24	(22.4)	
22.9-24.7	275	(20.0)	246	(19.4)	29	(27.1)	
24.8-26.7	266	(19.3)	251	(19.8)	15	(14.0)	
26.8-29.3	274	(19.9)	255	(20.1)	19	(17.8)	
≥29.4	268	(19.5)	248	(19.5)	20	(18.7)	
Unknown	16	(1.2)	16	(1.3)	0	(0.0)	
Current smoking							0.12
No	1060	(77.0)	985	(77.6)	75	(70.1)	
Yes	309	(22.4)	277	(21.8)	32	(29.9)	
Unknown	8	(0.6)	8	(0.6)	0	(0.0)	
Current alcohol use							0.28
No	108	(7.8)	103	(8.1)	5	(4.7)	
Yes	1120	(81.3)	1027	(80.9)	93	(86.9)	
In the past	149	(10.8)	140	(11.0)	9	(8.4)	
Recreational drug use in the past 6 months							0.01
No	1026	(74.5)	957	(75.4)	69	(64.5)	
Yes	351	(25.5)	313	(24.7)	38	(35.5)	
Total number of co-medications							0.67
0	443	(32.2)	409	(32.2)	34	(31.8)	
1-4	633	(46.0)	588	(46.3)	45	(42.1)	
5-9	239	(17.4)	216	(17.0)	23	(21.5)	
≥10	62	(4.5)	57	(4.5)	5	(4.7)	

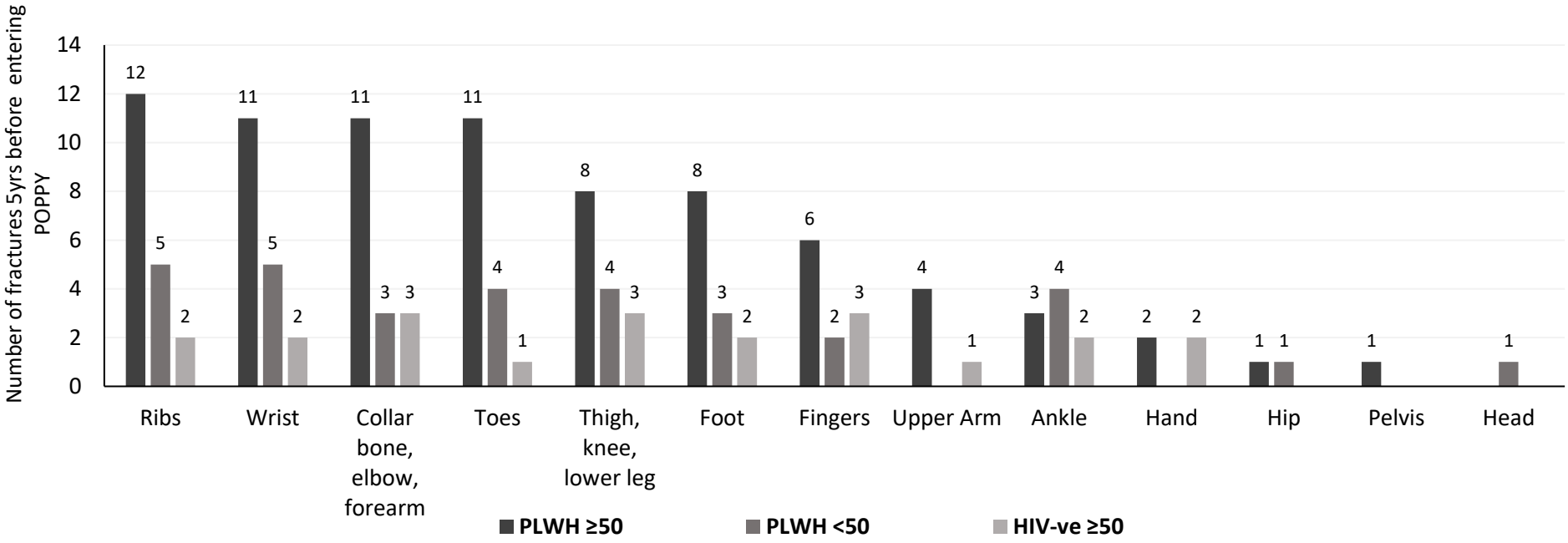


Figure 4.5: Number of fractures reported within the 5-year period before study entry stratified by site and POPPY group

4.4.4.3 The prevalence of recent fractures stratified by characteristics of the older POPPY participants

The prevalence of recent fractures in the sub-group of older PLWH and HIV-negative controls was significantly higher among participants who were white and those who used recreational drugs in the past 6 months. No difference in the prevalence of recent fractures was observed for participants with different characteristics of age, gender, education, marital status, BMI, smoking, alcohol and number of total co-medications, Table 4.20.

Table 4.20: Prevalence of fractures among the older POPPY participants stratified by participant characteristics

			History of recent fractures				
	Total N=1003		No n=923		Yes n=80		
	n	(%)	n	(%)	n	(%)	p-value
Age							0.42
50-54	368	(100.0)	344	(93.5)	24	(6.5)	
55-59	268	(100.0)	241	(89.9)	27	(10.1)	
60-64	190	(100.0)	173	(91.1)	17	(9.0)	
65-69	112	(100.0)	103	(92.0)	9	(8.0)	
≥70	65	(100.0)	62	(95.4)	3	(4.6)	
Gender							0.17
Female	196	(100.0)	185	(94.4)	11	(5.6)	
Male	807	(100.0)	738	(91.5)	69	(8.6)	
Ethnicity							0.001
Black African	127	(100.0)	126	(99.2)	1	(0.8)	
White	876	(100.0)	797	(91.0)	79	(9.0)	
Education							0.14
Finished education with no qualifications	97	(100.0)	93	(95.9)	4	(4.1)	
O levels/GCSEs (or equivalent)	160	(100.0)	150	(93.8)	10	(6.3)	
A levels (or equivalent)	134	(100.0)	124	(92.5)	10	(7.5)	
University degree or above	442	(100.0)	397	(89.8)	45	(10.2)	
Other	128	(100.0)	122	(95.3)	6	(4.7)	
Unknown	42	(100.0)	37	(88.1)	5	(11.9)	
Marital status							0.36
Single	423	(100.0)	383	(90.5)	40	(9.5)	
Married/Civil Partnership/ Cohabiting	422	(100.0)	392	(92.9)	30	(7.1)	
Divorced/Living separately	120	(100.0)	111	(92.5)	9	(7.5)	

	Total N=1003		History of recent fractures: No n=923		History of recent fractures: Yes n=80		
	n	**(%)**	**n**	**(%)**	**n**	**(%)**	**p-value**
Widowed/Other	38	(100.0)	37	(97.4)	1	(2.6)	
BMI (kg/m^2)							0.17
≤22.8	186	(100.0)	168	(90.3)	18	(9.7)	
22.9-24.7	190	(100.0)	168	(88.4)	22	(11.6)	
24.8-26.7	203	(100.0)	190	(93.6)	13	(6.4)	
26.8-29.3	202	(100.0)	191	(94.6)	11	(5.5)	
≥29.4	208	(100.0)	192	(92.3)	16	(7.7)	
Unknown	14	(100.0)	14	(100.0)	0	(0.0)	
Current smoking							0.40
No	797	(100.0)	737	(92.5)	60	(7.5)	
Yes	200	(100.0)	180	(90.0)	20	(10.0)	
Unknown	6	(100.0)	6	(100.0)	0	(0.0)	
Current alcohol use							0.38
No	75	(100.0)	72	(96.0)	3	(4.0)	
Yes	817	(100.0)	748	(91.6)	69	(8.5)	
In the past	111	(100.0)	103	(92.8)	8	(7.2)	
Education							0.46
High	704	(100.0)	643	(91.3)	61	(8.7)	
Low	286	(100.0)	268	(93.7)	18	(6.3)	
Unknown	13	(100.0)	12	(92.3)	1	(7.7)	
Recreational drugs in the past 6 months							0.04
No	782	(100.0)	727	(93.0)	55	(7.0)	
Yes	221	(100.0)	196	(88.7)	25	(11.3)	
Number of total co-medications							0.53
0	301	(100.0)	279	(92.7)	22	(7.3)	
1-4	454	(100.0)	421	(92.7)	33	(7.3)	
5-9	190	(100.0)	170	(89.5)	20	(10.5)	
≥10	58	(100.0)	53	(91.4)	5	(8.6)	

4.4.5 FRAX scores

In total 91.2% (1256/1377) of the POPPY participants were over the age of 40 years at study entry, of whom 90.3% (1134/1256) provided sufficient data for calculation of the FRAX scores. Of the 122 with insufficient data for the assessment of FRAX scores, 94 (77.0%) did not have their BMD T-score at FN assessed, for 13 (10.7%) their weight or height was unavailable, 10 (8.2%) had weight above 125 kg (the limit

allowed for the calculation of FRAX) and for 5 (4.1%) their smoking status was unknown.

Of those with sufficient data to permit FRAX score assessment, the proportion of participants with BMI ≥30.2 kg/m^2, of non-smokers and of participants with no history of recreational drug use was significantly higher (P<0.001) compared to those who did not have enough data to permit FRAX score assessment (19.9% (226/1134) vs. 18.0% (22/122), 78.8% (894/1134) vs. 72.9% (89/122) and 77.3% (876/1134) vs. 63.1% (77/122), respectively). No significant differences between those who had their FRAX scores assessed and those who did not were obtained with regards to POPPY group, age, gender, ethnicity, current use of alcohol and total number of co-medications, Table 4.21.

The overall median hip fracture score amongst POPPY participants was 0.7 IQR (0.2, 1.7) and ranged between 0.0 and 22.0 while the median major-osteoporotic score was 5.4 IQR (3.6, 8.0) and ranged between 1.1 and 33.0.

Table 4.21: Characteristics of POPPY participants with and without sufficient data to permit FRAX score assessment

			Sufficient data to permit FRAX scores assessment				
	Total N=1256		No N=122		Yes N=1134		
	n	(%)	n	(%)	n	(%)	p-value
Group							0.54
Older PLWH	699	(55.7)	72	(59.0)	627	(55.3)	
Younger PLWH	253	(20.4)	20	(16.4)	233	(20.6)	
HIV negative	304	(24.2)	30	(24.6)	274	(24.2)	
Age (years)							0.29
40-49	253	(20.1)	20	(16.4)	233	(20.6)	
50-54	368	(29.3)	44	(36.1)	324	(28.6)	
55-59	268	(21.3)	26	(21.3)	242	(21.3)	
60-64	190	(15.1)	14	(11.5)	176	(15.5)	
65-69	112	(8.9)	14	(11.5)	98	(8.6)	
≥70	65	(5.2)	4	(3.3)	61	(5.4)	
Gender							0.96
Female	245	(19.5)	24	(19.7)	221	(19.5)	
Male	1011	(80.5)	98	(80.3)	913	(80.5)	
Ethnicity							0.98
Black African	174	(13.9)	17	(13.9)	157	(13.8)	
White	1082	(86.2)	105	(86.1)	977	(86.2)	
BMI (kg/m^2)							<0.001

	Total N=1256		Sufficient data to permit FRAX scores assessment: No N=122		Sufficient data to permit FRAX scores assessment: Yes N=1134		
	n	(%)	n	(%)	n	(%)	p-value
≤23.2	249	(19.8)	26	(21.3)	223	(19.7)	
23.3-25.1	248	(19.8)	23	(18.9)	225	(19.8)	
25.2-27.0	248	(19.8)	18	(14.8)	230	(20.3)	
27.1-30.1	248	(19.8)	18	(14.8)	230	(20.3)	
≥30.2	248	(19.8)	22	(18.0)	226	(19.9)	
Unknown	15	(1.2)	15	(12.3)	0	(0.0)	
Current smoking							<0.001
No	983	(78.3)	89	(72.9)	894	(78.8)	
Yes	268	(21.3)	28	(23.0)	240	(21.2)	
Unknown	5	(0.4)	5	(4.1)	0	(0.0)	
Current alcohol use							0.73
No	94	(7.5)	8	(6.6)	86	(7.6)	
Yes	1022	(81.4)	98	(80.3)	924	(81.5)	
In the past	140	(11.2)	16	(13.1)	124	(10.9)	
Recreational drug use in the past 6 months							0.001
No	953	(75.9)	77	(63.1)	876	(77.3)	
Yes	303	(24.1)	45	(36.9)	258	(22.8)	
Total number of co-medications							0.95
0	391	(31.1)	37	(30.3)	354	(31.2)	
1-4	572	(45.5)	56	(45.9)	516	(45.5)	
5-9	231	(18.4)	24	(19.7)	207	(18.3)	
≥10	62	(4.9)	5	(4.1)	57	(5.0)	

The median of both of FRAX scores were significantly higher among the older PLWH compared to the younger PLWH and HIV-negative controls. Furthermore, participants in the older age groups compared to those in the younger groups, had significantly higher FRAX scores. Those of male gender, white ethnicity and those with lower BMIs had significantly higher FRAX scores. Furthermore, those currently drinking alcohol compared to previous and non-drinkers and those receiving a greater number of co-medications (≥10) had significantly higher scores. Finally, current smokers compared to non-smokers and those with a history of recreational drug use in the past 6-months compared to those without such a history had a significantly higher median of hip-score (with no significant differences in the major-osteoporotic score), Table 4.22.

Table 4.22: Median, IQR and range of FRAX scores stratified by characteristics of POPPY participants

	Hip fracture score				Major-osteoporotic score			
	n	Median (IQR)	(range)	p-value	n	Median (IQR)	(range)	p-value
Group								
Older PLWH	627	0.9 (0.3, 2.1)	(0.0, 22.0)	<0.001	627	5.9 (3.9, 8.7)	(1.1, 33.0)	<0.001
Younger PLWH	233	0.4 (0.1, 1.2)	(0.0, 12.0)		233	3.9 (2.8, 6.5)	(2.1, 18.0)	
HIV negative	274	0.5 (0.2, 1.1)	(0.0, 16.0)		274	5.6 (4.0, 7.5)	(2.2, 29.0)	
Age								
40-49	233	0.4 (0.1, 1.2)	(0.0, 12.0)	<0.001	233	3.9 (2.8, 6.5)	(2.1, 18.0)	<0.001
50-54	324	0.4 (0.1, 1.0)	(0.0, 14.0)		324	4.6 (3.2, 6.7)	(2.2, 24.0)	
55-59	242	0.7 (0.3, 1.5)	(0.0, 22.0)		242	5.8 (3.9, 8.3)	(1.1, 33.0)	
60-64	176	1.1 (0.5, 2.2)	(0.0, 13.0)		176	6.5 (5.0, 9.6)	(1.7, 27.0)	
65-69	98	1.5 (0.7, 2.9)	(0.1, 9.4)		98	7.6 (5.9, 9.8)	(3.1, 25.0)	
≥70	61	2.2 (1.1, 3.8)	(0.1, 22.0)		61	7.4 (5.1, 9.7)	(3.1, 29.0)	
Gender								
Female	221	0.2 (0.1, 0.7)	(0.0, 16.0)	<0.001	221	4.8 (3.3, 7.5)	(2.2, 29.0)	0.01
Male	913	0.8 (0.3, 2.0)	(0.0, 22.0)		913	5.6 (3.7, 8.1)	(1.1, 33.0)	
Ethnicity								
Black African	157	0.2 (0.0, 0.5)	(0.0, 5.1)	<0.001	157	3.8 (2.8, 5.6)	(1.1, 17.0)	<0.001
White	977	0.8 (0.3, 1.9)	(0.0, 22.0)		977	5.8 (3.8, 8.4)	(1.7, 33.0)	
BMI (kg/m^2)								
≤23.2	223	1.2 (0.5, 2.5)	(0.0, 22.0)	<0.001	223	5.8 (3.9, 9.0)	(2.2, 33.0)	<0.001
23.3-25.1	225	1.0 (0.4, 2.5)	(0.0, 22.0)		225	6.4 (4.2, 9.2)	(2.1, 28.0)	

	Hip fracture score				Major-osteoporotic score			
	n	Median (IQR)	(range)	p-value	n	Median (IQR)	(range)	p-value
25.2-27.0	230	0.6 (0.2, 1.3)	(0.0, 8.1)		230	5.2 (3.6, 7.6)	(2.3, 21.0)	
27.1-30.1	230	0.6 (0.2, 1.1)	(0.0, 13.0)		230	5.2 (3.7, 7.3)	(1.1, 27.0)	
≥30.2	226	0.3 (0.1, 0.9)	(0.0, 7.6)		226	4.6 (3.0, 7.0)	(1.7, 21.0)	
Current smoking								
No	894	0.6 (0.2, 1.5)	(0.0, 22.0)	<0.001	894	5.4 (3.6, 8.0)	(1.1, 33.0)	0.76
Yes	240	1.0 (0.4, 2.6)	(0.0, 14.0)		240	5.4 (3.6, 8.3)	(2.1, 25.0)	
Current alcohol use								
No	86	0.4 (0.1, 0.9)	(0.0, 8.3)	<0.001	86	4.2 (3.1, 6.5)	(2.3, 25.0)	0.002
Yes	924	0.7 (0.3, 1.8)	(0.0, 22.0)		924	5.6 (3.7, 8.1)	(1.1, 33.0)	
In the past	124	0.5 (0.2, 1.3)	(0.0, 13.0)		124	5.2 (3.4, 7.8)	(2.2, 22.0)	
Recreational drug use in the past 6 months								
No	876	0.6 (0.2, 1.6)	(0.0, 22.0)	<0.001	876	5.4 (3.5, 8.0)	(1.1, 33.0)	0.15
Yes	258	0.9 (0.3, 2.0)	(0.0, 22.0)		258	5.6 (3.8, 8.7)	(2.1, 28.0)	
Total number of co-medications								
0	119	0.5 (0.2, 0.9)	(0.0, 9.4)	<0.001	119	5.1 (3.5, 6.9)	(2.2, 18.0)	<0.001
1-4	450	0.6 (0.2, 1.3)	(0.0, 22.0)		450	5.1 (3.3, 7.5)	(1.1, 28.0)	
5-9	432	0.8 (0.3, 2.0)	(0.0, 22.0)		432	5.6 (3.7, 8.4)	(2.2, 33.0)	
≥10	133	1.1 (0.4, 2.7)	(0.0, 13.0)		133	7.2 (4.9, 10.0)	(1.7, 27.0)	

4.5 Confounding factors

Confounding factors are those that are associated with both the exposure and the outcome variables. To identify the factors that may confound the association between HIV and the outcomes I explored the prevalence of HIV (Section 4.3), frailty (Section 4.4.1.1), falls (Section 4.4.2.1), osteoporosis (Section 4.4.3.1) and fractures (Section 4.4.4.3) stratified by characteristics of the older POPPY participants. The factors that were significantly associated with both HIV and the outcomes of interest are summarised in Table 4.23.

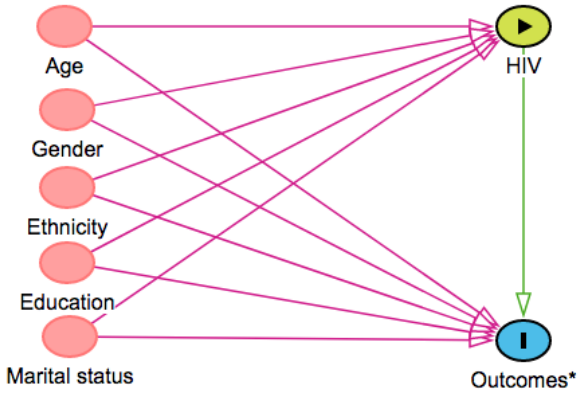
Table 4.23: Factors associated with HIV and the outcomes

	Frailty	History of falls	BMD T-score LS	BMD T-score FN	BMD T-score TH	Recent fractures
Gender	●	○	○	●	○	○
Marital status	●	●	○	○	○	○
BMI	○	●	●	●	●	
Alcohol use	○	●	○	○	○	○
Recreational drug use in the past 6 months	●	○	○	○	○	●
Number of total co-medications	●	●	●	○	○	○

● Associated with HIV (P<0.05)
○ Not associated with HIV (P≥0.05)

Some of the factors in Table 4.23 may not be considered confounders in the subsequent analyses due to an inability to deduce a causal relationship between both HIV and the outcomes. For example, current use of alcohol and history of recreational drug use in the past 6 months may be associated with HIV. Yet a cause-and-effect relationship cannot be determined because the majority of older PLWH had been diagnosed with HIV several years before entering the study (mean years since HIV diagnosis 15.9 years, SD (8.1)) and the route of HIV acquisition was via sexual route (study inclusion criterion). The factors of BMI and number of total co-medications may not have a causal association with HIV and may also be in the causal pathway between HIV and the outcomes. Therefore, bearing in mind the design of the POPPY study and findings from the literature I derived the factors confounding the

association of HIV with the outcomes, as illustrated in Figure 4.6. The factors considered to be associated with both HIV and the outcomes were age, gender, ethnicity, education and marital status. All will be considered for adjustment in the multivariable models and the reasons for considering them are described in the Sections 4.5.1 to 4.5.5 below.



*(frailty, falls, BMD T-score, fractures and FRAX)

Figure 4.6: Directed acyclic graph of the association of HIV with the outcomes of interest

4.5.1 Age

Age is a factor that is well-known to be associated with all the outcomes of interest. The direction of the association is well-established and explained through the natural ageing process. The magnitude of the association of age with the outcome of interest has been described in Sections 2.2.7.1, 2.3.4.1 and 2.4.6.1.

Furthermore, age is a key factor for the acquisition of HIV via sexual route. Hormonal changes throughout the ageing process may have direct effects upon sexual activity and drastically change the sexual behaviour of younger and older people. Younger people may also be more likely to adopt risky behaviours during sex (e.g. condomless sex) due to poorer health literacy. However, over the last decade, the median age at HIV diagnosis among heterosexuals in the UK has increased (590), which may be explained by due to an increase in condomless sex in older people overall. Therefore, age was considered an important factor confounding the association between HIV and the outcome of interest.

4.5.2 Gender

Gender differences in the prevalence of the outcomes of interest have been reported among several researchers. Women have been reported to have a higher risk of bone demineralisation, fracture risk and a higher prevalence of frailty and loss of physical functioning compared to men. This may be attributed to hormonal changes occurring in women due to menopause as well as lower physical activity compared to men.

The reported prevalence of HIV differs between men and women across the world. In western Europe for example MSM face higher risk of HIV acquisition compared to women. Conversely in Eastern Europe women encounter a higher risk than men. The gender differences in HIV acquisition may mostly be explained by differences in health literacy, sexual activity and risky behaviours. For the above reasons gender plays an important factor confounding the association between HIV and the outcomes of interest.

4.5.3 Ethnicity

People from different ethnic backgrounds have been reported to exhibit differences in the prevalence of all outcomes of interest as seen in the literature review (Sections 2.2.7.1, 2.3.4.1 and 2.4.6.1). Furthermore, the prevalence and the incidence of HIV is known to vary among people of different ethnic backgrounds. While the UK has made progress in reducing HIV transmission since 2015, black African men and women still accounted for 44% of new HIV diagnoses among heterosexuals in 2018, and the proportion diagnosed late (CD4 cell count <350c/mm^3) remains high in this group (590). Therefore, ethnicity is one more factor that has been considered in the list of confounding factors in this thesis.

4.5.4 Education

Education is a key variable that may influence both HIV acquisition and all outcomes examined in this thesis.

Educational attainment has been used as an imperfect measure for socio-economic status and has been shown to be a good predictor for most chronic diseases (591-

593). Du *et al.* have confirmed the relationship between a lower educational attainment and a decreased BMD T-score (594). The underlying mechanism of this association involves some known modifiable behavioural traits and risks factors such as BMI, physical activity, smoking, calcium supplement intake and alcohol use (595-601). Educated people compared to those with lower education are more likely to have better health literacy with regards to nutrition, physical activity, general health and wellbeing and therefore be more likely to display better bone health (602). Other studies confirm the findings of POPPY highlighting the significant association of higher education with better general health and higher BMD (592, 603, 604).

The association of education and HIV acquisition is not straightforward. People with a higher educational attainment may have a higher health literacy compared to people with lower or no education, and be, in theory more likely to adopt healthier lifestyle behaviours and practices that may delay or prevent the onset of adverse outcomes such as frailty, falls, low BMD T-score, fractures, and fracture risk. Likewise, those with higher education may be more likely to understand the risks behaviours associated with HIV acquisition and therefore adopt sexual health practices that are protective of acquiring HIV. However, some research suggests that MSM who were more educated were significantly more likely to report condomless sex with HIV-serodifferent partners the past year compared to those less educated (605).

Therefore, it was essential to account for education as a confounder in the association between HIV and the outcomes of interest.

4.5.5 Marital status

Finally, marital status is a factor that may impact both HIV acquisition and the development of any of the outcomes of interest. People living alone, and especially those in the older groups, are more likely to find it more difficult to look after themselves. They may feel more socially isolated and lonely which can lead to physical inactivity and lack of motivation to go out, walk and perform activities of daily living such as shopping and cooking. In extreme cases this may lead to low physical functioning or malnutrition. All the above can lead to higher prevalence of frailty, falls, lower BMD T-score, higher fractures and higher FRAX scores.

Marital status may also play a key role in HIV acquisition due to differences between sexual practices among those with or without a regular partner. People without a regular sexual partner may be more likely to have several sexual partners which puts them at a higher risk for HIV acquisition. Therefore, marital status was considered as key parameter confounding the association between HIV and the outcomes of interest.

Chapter 5 Frailty in POPPY

5.1 Introduction

In the general population the prevalence of frailty is estimated to be 10.9%-20.3% among elderly adults (≥65 years of age) (127) while among those aged ≥70 it has between reported to range between 20.2%-25.0% (128, 606). Frailty appears to be more common among women and among those who are socially isolated (103). Compared to the general population, PLWH have been reported to experience frailty at earlier ages (24, 77, 145-150). HIV infection has been independently associated with increased frailty (144) while the effect of age on frailty has not been found to be modified by the effect of HIV (173).

Comorbidities such as anaemia, CVD, or metabolic abnormalities among PLWH have been linked with increased frailty (147, 148, 167, 168). Use of antidepressants and polypharmacy are also risk factors for frailty (187, 607, 608). A history of opportunistic illness, as well as of chronic illnesses resulting in lower serum albumin have been associated with increased prevalence of frailty while socio-demographic factors such as unemployment and lower education have also been associated with increased prevalence of frailty in this population (51, 145, 160, 172). Finally, some HIV-specific factors have been associated with an increased risk of frailty including a previous diagnosis of AIDS-defining illness, low current and nadir CD4 count, and a high (>50,000 copies/mL) VL (51, 77, 146, 155, 159, 163, 178, 181, 189).

5.2 Hypothesis

1. There is no difference in the prevalence of frailty between the older PLWH and the HIV-negative controls
2. The association of HIV with frailty is not modified by the association with age among the older POPPY participants
3. The association of HIV on frailty is not modified by the association with depressive symptoms among the older POPPY participants
4. There is no difference in the healthcare resource use between the frail and non-frail participants
5. HIV-specific factors, such as previous diagnosis of AIDS-defining illness, low current and nadir CD4 count, and a detectable VL, are associated with an increased prevalence of frailty among PLWH
6. The hypotheses 1-4 are valid when frailty is defined 1st by imputation of the missing criteria and 2nd by using the objective measures of weakness and slowness

5.3 Specific objectives

1. To investigate whether the prevalence of frailty is higher in the group of older PLWH than that in HIV-negative controls
2. In the group of older POPPY participants to explore whether the association of HIV with the prevalence of frailty is modified by the association with age
3. In the group of older POPPY participants to explore whether the association of HIV with the prevalence of frailty is modified by the association with depressive symptoms
4. To explore whether the healthcare resource use is higher among the frail participants compared to the non-frail group
5. In the subgroup of PLWH, to explore the association of HIV-related parameters with the prevalence of frailty. In particular, to assess the associations of time since HIV diagnosis, years on cART, current CD4 count and CD4 nadir, current VL, age and number of co-medications with the prevalence of frailty

6. To conduct sensitivity analyses to determine the robustness of findings to several factors, including: i) the use of a complete-case approach to the analysis; ii) the inclusion of objectively-defined components in the frailty definition.

5.4 Statistical analysis

For objective 1, the difference in the prevalence of frailty between the group of older PLWH and HIV-negative controls was compared using univariable and multivariable logistic regression models.

For objective 2, to explore whether the association of HIV with frailty is modified by the association with age I performed 2 multivariable analyses. In the first I adjusted for the confounders described in Section 4.5 and in the second I additionally adjusted for the interaction between HIV status and age group.

For objective 3, to explore whether the association of HIV with frailty is modified by the association with depressive symptoms I performed 2 multivariable analyses. In the first I adjusted for the confounders described in Section 4.5 and in the second I additionally adjusted for the interaction between HIV status and depressive symptoms. The fit of the multivariable regression models with and without the interaction of HIV with depressive symptoms were compared using the likelihood-ratio test to determine the model with the best fit.

For objective 4, the healthcare utilisation of the POPPY participants was explored stratified by the presence or absence of frailty at baseline. All information available on healthcare use as described in the Methods (Section 3.7.7), was explored. Differences in healthcare resource use between those who were deemed frail and those who were not were explored using Pearson's Chi-square test.

For objective 5, the subgroup of PLWH was selected (older and younger PLWH). Within this subgroup, the HIV-specific factors were examined; current CD4 count, CD4 nadir, years on cART and time since HIV diagnosis were each categorised into six groups, one for those with missing data and five groups, defined by the quintiles of the distribution of each factor. The total number and percentage of frail and non-frail individuals in each group was reported. Other HIV-specific factors with which I

considered the association with frailty were the HIV VL (detectable/undetectable) and previous diagnosis of AIDS-defining illness. The prevalence of frailty was also explored for the total number of co-medications. I considered two different variables - firstly, the total number of non-ART co-medications received, and secondly the cART regimen that the participant was receiving: NRTIs (categorised as either none, TFV/FTC, ABC/3TC or an 'other' combination); PIs (categorised as either boosted, unboosted PIs or no PI in the regimen); NNRTIs (categorised as either EFV, NVP, rilpivirine (RPV), etravirine (ETR) or none); and receipt of INSTIs (as a binary covariate [yes/no] due to the small numbers receiving specific INSTI drugs). The rationale behind the variable-split in the subgroup of PLWH, was to express separately the association of cART and the association of polypharmacy (total number of co-medications) and to investigate whether there were any associations between specific cART drugs/combinations separately from the other non-ART co-medications. The associations between the prevalence of frailty and these factors were explored using Pearson's Chi-square test and univariable logistic regression models. Factors that were significantly associated with frailty in these univariable models ($P<0.05$) were then considered in multivariable analysis, which included adjustment for BMI, gender, ethnicity, smoking, current alcohol use and recreational drug use in the past 6 months.

For objective 6, two sensitivity analyses were performed to test the robustness of the findings of this chapter. First, I explored whether similar findings for objectives 1-5 were obtained when frailty was assessed for all POPPY participants by imputing the components of the frailty score where data were missing. To achieve this, I assumed that the participants with missing information for any of the four components (slowness, weakness, exhaustion and low physical activity) did not meet the criteria for that component. This allowed me to include all participants in the analyses and to assess whether the imputed dataset and the dataset with missing information in the four frailty components yielded a similar association of HIV with frailty.

Second, I explored whether similar findings were obtained when frailty was assessed based on only one or two of the objective measures used to define frailty. To achieve this, the population that had information on the objective components (weakness, as

assessed by grip strength, and slowness, as assessed by the timed walk test) was used for the assessment of frailty. Compared to those who were deemed frail in the complete case analysis, in separate multivariable logistic regression models, I explored whether findings were similar when frailty was defined on the basis of weakness alone and slowness alone yielded similar findings with the dataset using the complete case analysis for the assessment of frailty.

5.5 Results

5.5.1 Frailty and HIV

The associations of frailty with HIV among the older POPPY groups (older PLWH and HIV-negative controls) were explored in this section. More specifically, I explored the prevalence of frailty among the older PLWH and the HIV-negative controls stratified by age group.

The group of older PLWH was more likely to be frail than the group of HIV-negative controls (13.0% vs. 3.2%) while the prevalence of pre-frailty was comparable in the two groups (72.3% vs. 73.0%), p<0.001. Within almost all age strata older PLWH were more likely to be frail than HIV-negative controls (Figure 5.1).

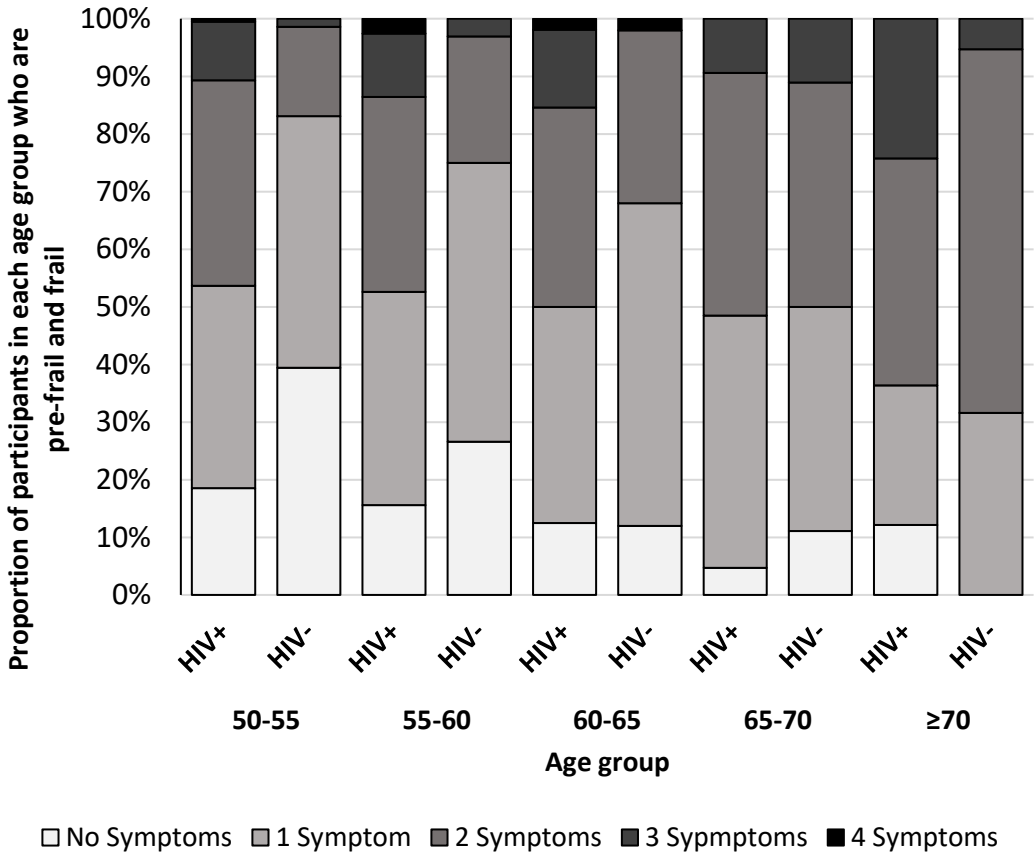


Figure 5.1: Proportion of older POPPY participants with zero, one, two, three or four symptoms present for defining frailty, stratified by age and HIV status

Univariable and multivariable logistic regression models explored the association of frailty with HIV among the older POPPY participants in Table 5.1. In the univariable

analysis, older PLWH had almost 5-fold higher odds of frailty compared to HIV-negative controls. After adjustment for confounding factors described in section 4.5, the group of older PLWH was found to have 4-fold higher odds of frailty compared to HIV-negative controls, aOR=4.06 (1.69, 9.75), Table 5.1.

Table 5.1: Univariable and multivariable association of frailty with HIV

	Univariable model	Multivariable model*
	OR (95% CI)	**aOR (95% CI)**
Group		
HIV-negative	Ref.	Ref.
Older PLWH	4.60 (2.09, 10.16)	4.06 (1.69, 9.75)

*Adjusted for age, gender, ethnicity, education and marital status

5.5.2 HIV ageing and frailty

To investigate whether the association of HIV with frailty is modified by the association with age I compared two regression models, the multivariable model of Section 5.5.1 with a model also adjusting for the interaction of HIV status with age. The model with the interaction had a poorer fit of the data compared to the model without the interaction term (Log likelihood -219.03 vs. -221.87, Likelihood ratio test Chi-square=5.68, P=0.06), suggesting that the association of HIV with frailty is not modified by any association with age, Table 5.2.

Table 5.2: Univariable and multivariable association of frailty and age with HIV

	Univariable model	Multivariable model*	Multivariable model**
	OR (95% CI)	**aOR (95% CI)**	**aOR (95% CI)**
Group			
HIV-negative	Ref.	Ref.	Ref.
Older PLWH	4.60 (2.09, 10.16)	4.06 (1.69, 9.75)	6.59 (0.85, 51.16)
Age			
50-54	Ref.	Ref.	Ref.
55-59	1.30 (0.71, 2.38)	1.28 (0.66, 2.46)	2.39 (0.21, 27.49)
60-64	1.36 (0.71, 2.64)	1.50 (0.74, 3.06)	1.61 (0.77, 3.33)
65-69	1.19 (0.51, 2.77)	1.26 (0.51, 3.08)	8.24 (0.67, 100.80)
≥70	2.30 (1.00, 5.31)	2.91 (1.11, 7.59)	4.34 (0.25, 75.55)

*Adjusted for gender, ethnicity, education and marital status
**Further adjusted for the interaction of age HIV with age

5.5.3 HIV depressive symptoms and frailty

POPPY participants above the age of 50 years who fulfilled the criteria of being frail had significantly higher depressive symptom scores according to both CES-D and

PHQ-9 than those who did not meet the frailty criteria. In particular, there was a significantly greater prevalence of frailty among those with severe depressive symptoms as assessed by CES-D (33.3% (44/132)) than among those with either moderate (13.1% (13/99)) or no to mild depressive symptoms (3.0% (15/504), P<0.001). Findings for PHQ-9 were similar with a higher prevalence of frailty in those with severe depressive symptoms (50.0% (12/24)) compared to those with moderately severe (22.4% (11/49)), moderate (32.5% (27/83)), mild (11.3% (16/141)) and minimal depressive symptoms (2.6% (12/459), P<0.001, Table 5.3).

Table 5.3: Prevalence of frailty among older POPPY participants stratified by level of depressive symptoms assessed using either the CES-D or PHQ-9 scores

	Total N=782		Frail				
			No N=702		Yes N=80		
	n	(%)	N	(%)	n	(%)	p-value
Levels of depressive symptoms (CES-D)							
No to mild (0-15)	504	(100.0)	489	(97.0)	15	(3.0)	<0.001
Moderate (16-23)	99	(100.0)	86	(86.9)	13	(13.1)	
Severe (24-60)	132	(100.0)	88	(66.7)	44	(33.3)	
Unknown	47	(100.0)	39	(83.0)	8	(17.0)	
Levels of depressive symptoms (PHQ-9)							
Minimal depression (1-4)	459	(100)	447	(97.4)	12	(2.6)	<0.001
Mild depression (5-9)	141	(100)	125	(88.7)	16	(11.3)	
Moderate depression (10-14)	83	(100)	56	(67.5)	27	(32.5)	
Moderately severe depression (15-19)	49	(100)	38	(77.6)	11	(22.4)	
Severe depression (20-30)	24	(100)	12	(50.0)	12	(50.0)	
Unknown	26	(100.0)	24	(92.3)	2	(7.7)	

The models adjusted for the standard confounders described in section 4.5 plus the depressive symptoms (middle section of Table 5.4 and Table 5.5, for CES-D and PHQ-9 respectively), suggested that at least some of the association of HIV with frailty appears to be explained by the higher prevalence of depressive symptoms in those with HIV.

I also explored whether the association of HIV with frailty was modified by the association with depressive symptoms (right section of Table 5.4 and Table 5.5). The models without the interaction terms were a better fit compared to the models with

the interaction term when depressive symptoms were assessed using the CES-D score (Log-likelihood=-170.85 vs. -170.21, Likelihood ratio test Chi-square=1.27, P=0.53) and when depressive symptoms were assessed using the PHQ-9 score (Log-likelihood=-173.40 vs. -171.98, Likelihood ratio test Chi-square=2.84, P=0.24). This suggested that the association of HIV with frailty was not modified by the association with depressive symptoms.

Table 5.4: Univariable and multivariable association of frailty and depressive symptoms with HIV

	Univariable model	Multivariable model*	Multivariable model**
	OR (95% CI)	**aOR (95% CI)**	**aOR (95% CI)**
Group			
HIV-negative	Ref.	Ref.	Ref.
Older PLWH	4.60 (2.09, 10.16)	2.09 (0.82, 5.36)	2.91 (0.64, 13.30)
Levels of depressive symptoms (CES-D)			
No to mild (0-15)	Ref.	Ref.	Ref.
Moderate (16-23)	4.93 (2.27, 10.72)	4.57 (2.00, 10.40)	3.92 (0.33, 46.88)
Severe (24-60)	16.30 (8.69, 30.56)	13.79 (6.83, 27.84)	35.76 (4.81, 265.90)

*Adjusted for age, gender, ethnicity, education and marital status

**further adjusted for the interaction of HIV with depressive symptoms (CES-D)

Table 5.5: Univariable and multivariable association of frailty and depressive symptoms with HIV

	Univariable model	Multivariable model*	Multivariable model**
	OR (95% CI)	**aOR (95% CI)**	**aOR (95% CI)**
Group			
HIV-negative	Ref.	Ref.	Ref.
Older PLWH	4.60 (2.09, 10.16)	2.35 (0.91, 6.07)	2.41 (0.51, 11.44)
Levels of depressive symptoms (PHQ-9)			
Minimal depression (1-4)	Ref.	Ref.	Ref.
Mild depression (5-9)	4.77 (2.20, 10.34)	4.09 (1.80, 9.30)	5.95 (0.76, 46.94)
Moderate depression (10-14)	17.96 (8.62, 37.44)	20.37 (8.70, 47.70)	9.32 (0.64, 136.57)
Moderately severe depression (15-19)	10.78 (4.46, 26.06)	14.31 (5.09, 40.22)	15.61 (5.29, 46.11)
Severe depression (20-30)	37.25 (13.92, 99.68)	49.04 (15.25, 157.66)	314.10 (9.29, 10625.60)

*Adjusted for gender, ethnicity, education and marital status

**further adjusted for the interaction of HIV with depressive symptoms (PHQ-9)

5.5.4 Frailty and healthcare resource use

Frail study participants over the past 12 months before entering the study made greater use of primary care (i.e. nurse visits) compared to non-frail, and made more use of secondary care, specifically hospital investigations and mental health-related visits. Furthermore, compared to non-frail participants, those deemed to be frail had a significantly greater acute care requirements, reporting significantly more A&E attendances and more frequent ambulance use, Table 5.6.

Table 5.6: Healthcare utilisation over the past 12 months among older POPPY participants stratified by frailty

	Total N=782		Non-frail N=702		Frail N=80		
	n	**(%)**	**n**	**(%)**	**n**	**(%)**	**p-value**
GP visit							0.21
No	159	(20.3)	147	(20.9)	12	(15.0)	
Yes	623	(79.7)	555	(79.1)	68	(85.0)	
Nurse visit							0.001
No	390	(49.9)	364	(51.9)	26	(32.5)	
Yes	392	(50.1)	338	(48.2)	54	(67.5)	
Hospital investigations							0.001
No	348	(44.5)	326	(46.4)	22	(27.5)	
Yes	434	(55.5)	376	(53.6)	58	(72.5)	
Physiotherapy visit							0.14
No	762	(97.4)	686	(97.7)	76	(95.0)	
Yes	20	(2.6)	16	(2.3)	4	(5.0)	
Hospital procedure							0.18
No	648	(82.9)	586	(83.5)	62	(77.5)	
Yes	134	(17.1)	116	(16.5)	18	(22.5)	
Mental health specialist							0.003
No	672	(85.9)	612	(87.2)	60	(75.0)	
Yes	110	(14.1)	90	(12.8)	20	(25.0)	
Other healthcare provider							0.83
No	546	(69.8)	491	(69.9)	55	(68.7)	
Yes	236	(30.2)	211	(30.1)	25	(31.3)	
A&E attendance							0.03
No	645	(82.5)	586	(83.5)	59	(73.7)	
Yes	137	(17.5)	116	(16.5)	21	(26.3)	
Ambulance use							0.01
No	747	(95.5)	675	(96.1)	72	(90.0)	
Yes	35	(4.5)	27	(3.9)	8	(10.0)	

5.5.5 Frailty in PLWH

In this section, the association of frailty with the HIV factors of current CD4 count, CD4 nadir, current VL, years since HIV-diagnosis, current cART and years since cART initiation is explored. In addition, the associations of age at baseline and the number of co-medications (excluding cART) with frailty is also explored.

Frail POPPY participants had also been diagnosed with HIV for a significantly longer time compared to non-frail participants (median (range) 18.0 (1.9, 30.5) vs. 12.7 (0.0, 34.0) years, P<0.001) and they had been on ART for a longer time (median (range) 12.8 (0.1, 24.1) vs. 8.8 (0.0, 26.3) years, P<0.001). Despite the differences observed in the prevalence of frailty among the older and the younger PLWH, the difference did not reach the threshold of statistical significance. More specifically, 10.5% (2/19) of PLWH ≤29 years of age were deemed to be frail, but this prevalence dropped to 5.2% (4/77) among those aged 30-39 years. The highest prevalence of frailty continued to be in those aged ≥70 years, 24.2% (8/33), therefore for the univariable analysis, a binary variable explored the association of age <70 and ≥70 years with frailty. The prevalence of frailty among those with a previous diagnosis of an AIDS-defining illness was significantly higher than that among those with no previous diagnosis of AIDS (15.5% (37/239) vs. 10.2% (63/615), P=0.03). No evidence of associations at the 5% level were detected between any of the other HIV factors. Those receiving 10 or more co-medications (excluding cART) had a significantly higher prevalence of frailty compared to those receiving 0, 1-4 and 5-9 co-medications (23.9% (11/46) vs. 17.4% (28/161), 11.1% (43/389) and 7.0% (18/258) respectively, P<0.001). With regards to antiretroviral treatment, no difference in the prevalence of frailty was observed between those receiving different ART combinations.

In particular, the prevalence of frailty among those not on any NRTIs was not significantly different to those on TDF/FTC, ABC/3TC and those on other NRTIs (14.2% (17/120), 10.1% (55/543), 11.2% (11/98) and 18.3% (17/93), respectively, P=0.12). The prevalence of frailty among those not on PIs was not significantly different to the prevalence among those on boosted or unboosted PIs (11.0% (55/500), 13.3% (38/285) and 10.1% (7/69), respectively, P=0.57). Similarly, the prevalence of frailty

among those not on NNRTIs did not differ significantly from that among those on EFV, NVP, RPV or ETR (12.7% (52/410), 9.9% (21/213), 8.1% (9/111), 13.3% (10/75) and 17.8% (8/45), respectively, P=0.37). No difference in the prevalence of frailty was observed among those on INSTIs and those not on INSTIs (11.1% (83/746) and 15.7% (17/108), respectively, P=0.16), Table 5.7.

Table 5.7: Prevalence of frailty among POPPY PLWH, stratified by age, history of AIDS, immune system markers and current antiretroviral medication characteristics

	Total N=854		Frail				
			No N=754		Yes N=100		
	n	(%)	n	(%)	n	(%)	p-value
Age group (years)							0.14
≤29	19	(100.0)	17	(89.5)	2	(10.5)	
30-39	77	(100.0)	73	(94.8)	4	(5.2)	
40-49	198	(100.0)	177	(89.4)	21	(10.6)	
50-54	205	(100.0)	183	(89.3)	22	(10.7)	
55-59	154	(100.0)	133	(86.4)	21	(13.6)	
60-64	104	(100.0)	88	(84.6)	16	(15.4)	
65-69	64	(100.0)	58	(90.6)	6	(9.4)	
≥70	33	(100.0)	25	(75.8)	8	(24.2)	
Previous diagnosis of AIDS-defining illness							0.03
No	615	(100.0)	552	(89.8)	63	(10.2)	
Yes	239	(100.0)	202	(84.5)	37	(15.5)	
CD4 count (cells/mm^3)							0.17
≤441	167	(100.0)	145	(86.8)	22	(13.2)	
442-564	167	(100.0)	153	(91.6)	14	(8.4)	
565-687	168	(100.0)	147	(87.5)	21	(12.5)	
688-858	166	(100.0)	152	(91.6)	14	(8.4)	
≥859	167	(100.0)	141	(84.4)	26	(15.6)	
CD4 nadir (cells/mm^3)							0.47
≤82	165	(100.0)	142	(86.1)	23	(13.9)	
83-170	170	(100.0)	148	(87.1)	22	(12.9)	
171-240	166	(100.0)	145	(87.4)	21	(12.7)	
241-340	161	(100.0)	146	(90.7)	15	(9.3)	
≥341	162	(100.0)	148	(91.4)	14	(8.6)	
VL							
Detectable	89	(100.0)	83	(93.3)	6	(6.7)	0.13
Undetectable	761	(100.0)	668	(87.8)	93	(12.2)	
Years on ART							0.009
≤3.9	168	(100.0)	159	(94.6)	9	(5.4)	
4.0-7.3	167	(100.0)	149	(89.2)	18	(10.8)	
7.4-12.4	168	(100.0)	149	(88.7)	19	(11.3)	
12.5-17.3	167	(100.0)	144	(86.2)	23	(13.8)	
≥17.4	167	(100.0)	137	(82.0)	30	(18.0)	
Time since HIV diagnosis (yrs)							0.004

	Total N=854		Frail				
			No N=754		Yes N=100		
	n	(%)	n	(%)	n	(%)	p-value
≤6.3	170	(100.0)	158	(92.9)	12	(7.1)	
6.4-10.9	170	(100.0)	157	(92.4)	13	(7.7)	
11.0-16.0	169	(100.0)	151	(89.4)	18	(10.7)	
16.1-22.0	170	(100.0)	140	(82.4)	30	(17.7)	
≥22.1	169	(100.0)	142	(84.0)	27	(16.0)	
Total number of co-medications (excluding cART)							0.001
0	258	(100.0)	240	(93.0)	18	(7.0)	
1-4	389	(100.0)	346	(89.0)	43	(11.1)	
5-9	161	(100.0)	133	(82.6)	28	(17.4)	
≥10	46	(100.0)	35	(76.1)	11	(23.9)	
NRTI backbone							0.12
None	120	(100.0)	103	(85.8)	17	(14.2)	
TFV/FTC	543	(100.0)	488	(89.9)	55	(10.1)	
ABC/3TC	98	(100.0)	87	(88.8)	11	(11.2)	
Other	93	(100.0)	76	(81.7)	17	(18.3)	
PIs							0.57
None	500	(100.0)	445	(89.0)	55	(11.0)	
Boosted PIs	285	(100.0)	247	(86.7)	38	(13.3)	
Unboosted PIs	69	(100.0)	62	(89.9)	7	(10.1)	
NNRTIs							0.37
None	410	(100.0)	358	(87.3)	52	(12.7)	
EFV	213	(100.0)	192	(90.1)	21	(9.9)	
NVP	111	(100.0)	102	(91.9)	9	(8.1)	
RPV	75	(100.0)	65	(86.7)	10	(13.3)	
ETR	45	(100.0)	37	(82.2)	8	(17.8)	
INSTIs							0.16
No	746	(100.0)	663	(88.9)	83	(11.1)	
Yes	108	(100.0)	91	(84.3)	17	(15.7)	

In the univariable analyses, PLWH aged 70 years or more had significantly higher risk of frailty compared to PLWH aged <70 years (OR=2.54, 95% CI (1.11, 5.79)). Among PLWH, those with previous diagnosis of AIDS had a significantly higher odds of frailty compared to those with no previous diagnosis of AIDS (OR=1.60, 95% CI (1.04, 2.48)). The results suggested an association of increased CD4 nadir with decreased odds of frailty. More specifically, those with a CD4 nadir of 83-170 cells/mm^3, 171-240 cells/mm^3, 241-340 cells/mm^3 or ≥341 cells/mm^3 had lower odds of being frail compared to whose with a CD4 nadir ≤82 cells/mm^3 (OR=0.92, 95% CI (0.49, 1.72), OR=0.89, 95% CI (0.47, 1.69), OR=0.63, 95% CI (0.32, 1.26) and OR=0.58, 95% CI (0.29, 1.18), respectively). Therefore, instead of expressing the CD4 nadir as a categorical

covariate, it was fitted as a continuous covariate. For every 50 cells/mm^3 increment in the CD4 nadir, the risk of frailty was reduced by 7% (OR=0.93, 95% CI (0.86, 1.00)). Similarly, the associations with the number of years on ART (initially expressed as a categorical covariate) suggested an association of longer time on ART with an increased prevalence of frailty. Compared to those on ART for ≤3.9 years, those with 4.0-7.3, 7.4-12.4, 12.5-17.3 and ≥17.4 years of ART use each had an increased odds of frailty (OR=2.13, 95% CI (0.93, 4.90), OR=2.25, 95% CI (0.99, 5.14), OR=2.82, 95% CI (1.26, 6.30) and OR=3.87, 95% CI (1.77, 8.43)). This covariate was therefore included as a continuous covariate in subsequent analyses, with the OR expressed per 5-year increment. After including the covariate in this way in univariable analysis, each 5-year additional exposure to ART was associated with a 30% increase in the odds of frailty (OR=1.30, 95% CI (1.12, 1.53)). Another HIV factor that was significantly associated with an increased odds of frailty was the time since HIV diagnosis. More specifically, those who had been diagnosed with HIV for 16.1-22.0 or ≥22.1 years (compared to ≤6.3 years) had an increased odds of frailty (OR=2.82, 95% CI (1.39, 5.72) and OR=2.50, 95% CI (1.22, 5.13)). Those receiving 5-9 and ≥10 co-medications had an increased odds of frailty compared to those not taking any co-medications (OR=2.81, 95% CI (1.50, 5.26) and OR=4.19, 95% CI (1.83, 9.61)). Finally, it is worth mentioning that despite not reaching the level of statistical significance, those with detectable VL had almost 2-fold higher odds of being frail (OR=1.93, 95% CI (0.82, 4.54)).

The factors that were significantly associated with frailty in the univariable analyses and the confounders of BMI, gender, ethnicity, smoking, current alcohol use, recreational drug use in the past 6 months and total number of co-medications (excluding cART), were included in the multivariable regression model. The association with the number of co-medications (excluding cART) received remained significant. In particular, there was a significant increase in the prevalence of frailty for participants receiving 5-9 co-medications and ≥10 vs. no co-medications (aOR=2.24, 95% CI (1.13, 4.47) and aOR=3.21, 95% CI (1.30, 7.94), respectively). The associations of age, CD4 nadir, years on ART and time since HIV diagnosis were generally reduced and became non-significant in the multivariable analysis.

Table 5.8: Association of frailty with age and HIV factors among PLWH in POPPY

	Univariable model	Multivariable model*
	OR (95% CI)	**aOR (95% CI)**
Age at baseline visit		
<70	Ref.	Ref.
≥70	2.54 (1.11, 5.79)	2.35 (0.96, 5.75)
Previous diagnosis of AIDS-defining illness		
No	Ref.	Ref.
Yes	1.60 (1.04, 2.48)	1.27 (0.77, 2.08)
CD4 count (cells/mm^3)		
≤441	Ref.	
442-564	0.60 (0.30, 1.22)	-
565-687	0.94 (0.50, 1.79)	-
688-858	0.61 (0.30, 1.23)	-
≥859	1.22 (0.66, 2.24)	-
CD4 nadir (cells/mm^3)		
≤82	Ref.	
83-170	0.92 (0.49, 1.72)	-
171-240	0.89 (0.47, 1.69)	-
241-340	0.63 (0.32, 1.26)	-
≥341	0.58 (0.29, 1.18)	-
CD4 nadir (50 cells/mm^3)	0.93 (0.86, 1.00)	0.98 (0.91, 1.07)
VL		
Undetectable	Ref.	
Detectable	1.93 (0.82, 4.54)	-
Years on ART		
≤3.9	Ref.	
4.0-7.3	2.13 (0.93, 4.90)	-
7.4-12.4	2.25 (0.99, 5.14)	-
12.5-17.3	2.82 (1.26, 6.30)	-
≥17.4	3.87 (1.77, 8.43)	-
Years on ART (per 5 years)	1.30 (1.12, 1.53)	1.06 (0.80, 1.41)
Time since HIV diagnosis (yrs)		
≤6.3	Ref.	Ref.
6.4-10.9	1.09 (0.48, 2.46)	0.82 (0.33, 2.08)
11.0-16.0	1.57 (0.73, 3.37)	1.36 (0.54, 3.43)
16.1-22.0	2.82 (1.39, 5.72)	2.06 (0.75, 5.67)
≥22.1	2.50 (1.22, 5.13)	1.70 (0.56, 5.15)
Number of total co-medications (excluding cART)		
0	Ref.	Ref.
1-4	1.66 (0.93, 2.94)	1.57 (0.85, 2.88)
5-9	2.81 (1.50, 5.26)	2.24 (1.13, 4.47)
≥10	4.19 (1.83, 9.61)	3.21 (1.30, 7.94)
NRTIs		
None	Ref.	

	Univariable model	Multivariable model*
	OR (95% CI)	**aOR (95% CI)**
TFV/FTC	0.68 (0.38, 1.22)	-
ABC/3TC	0.77 (0.34, 1.72)	-
Other	1.36 (0.65, 2.83)	-
PIs		
None	Ref.	
Boosted PIs	1.24 (0.80, 1.94)	-
Unboosted PIs	0.91 (0.40, 2.10)	-
NNRTIs		
None	Ref.	
EFV	0.75 (0.44, 1.29)	-
NVP	0.61 (0.29, 1.27)	-
RPV	1.06 (0.51, 2.19)	-
ETR	1.49 (0.66, 3.37)	-
INSTIs		
None	Ref.	
DTG/EVG/RAL	1.49 (0.85, 2.63)	-
Other/None	0.86 (0.30, 2.46)	-

*Adjusted for BMI, gender, ethnicity, smoking, current alcohol use and recreational drug use in the past 6 months

5.5.6 Sensitivity analysis

5.5.6.1 Comparison of the findings of the complete case analysis and the imputed analysis for the definition of frailty

In the first sensitivity analyses, a simple imputation strategy was explored. POPPY participants with missing information on each component of frailty were assumed to not meet the criteria for that component. This imputation enabled the assessment of frailty for all POPPY participants leading to an increase in the denominator for analysis. In total 8.5% (85/1003) of the POPPY participants were deemed to be frail with this approach. Of the additional 221 participants in whom frailty had previously not been assessed using the full case approach, 5 (2.3%) were deemed to be frail and 216 (97.7%) non-frail. In the group of older PLWH, 11.0% (77/699) were deemed to be frail, a significantly higher proportion compared to the HIV-negative control group 2.6% (8/304), respectively, P<0.001.

The results of both the univariable and the multivariable analyses using the imputed frailty definition were in line with the results of the complete case approach. In the univariable analysis, older PLWH had more than 4.5-fold higher odds of frailty

compared to HIV-negative controls using both the complete case analysis definition and the imputed frailty definition (OR=4.60, 95% CI (2.09, 10.16) and OR=4.58, 95% CI (2.18, 9.61), respectively), Table 5.9.

After adjustment for the standard confounders described in Section 4.5, using both the complete case analysis definition and the imputed frailty definition, the association of the older PLWH group with a higher odds of frailty remained significant. More specifically, older PLWH had more than 4-fold higher odds of frailty compared to HIV-negative controls using both the complete case analysis and imputed analysis (aOR=4.06, 95% CI (1.69, 9.75) and aOR=4.15, 95% CI (1.84, 9.38), respectively), Table 5.9.

In the multivariable analyses using both the complete case frailty definition and the imputed frailty definition, after adjusting for the standard confounders, the association of HIV with frailty was attenuated. The multivariable models exploring whether the association of HIV with frailty was modified by any association with depressive symptoms including the interaction of HIV with depressive symptoms had a poorer fit compared to the models without the interaction term suggesting that the association of HIV with frailty is not modified by the association with depressive symptoms, (Log-likelihood=-186.2 vs. -187.7, Likelihood ratio test Chi-square=2.96, P=0.23), Table 5.10.

Table 5.9: Association of HIV with frailty, as assessed in complete case analysis and imputed analysis among the older POPPY participants

	Complete case frailty definition		Imputed frailty definition	
	Univariable model	Multivariable model*	Univariable model	Multivariable model*
		N=769		N=960
Group	**OR (95% CI)**	**OR (95% CI)**	**aOR (95% CI)**	**OR (95% CI)**
HIV-negative	Ref.	Ref.	Ref.	Ref.
Older PLWH	4.60 (2.09, 10.16)	4.06 (1.69, 9.75)	4.58 (2.18, 9.61)	4.15 (1.84, 9.38)

*Adjusted for age, gender, ethnicity, education and marital status

Table 5.10: Association of frailty and imputed frailty with POPPY group and depressive symptoms as assessed by CES-D and PHQ-9 score

	Multivariable model* Complete case frailty definition	Multivariable model** Complete case frailty definition	Multivariable model* Imputed frailty definition	Multivariable model** Imputed frailty definition
Group	**aOR (95% CI)**	**aOR (95% CI)**	**aOR (95% CI)**	**aOR (95% CI)**
HIV-negative	Ref.	Ref.	Ref.	Ref.
Older PLWH	2.09 (0.82, 5.36)	2.91 (0.64, 13.30)	1.91 (0.80, 4.54)	3.28 (0.72, 14.90)
Levels of depressive symptoms (CES-D)				
No to mild (0-15)	Ref.	Ref.	Ref.	Ref.
Moderate (16-23)	4.57 (2.00, 10.40)	3.92 (0.33, 46.88)	4.42 (1.96, 9.96)	3.79 (0.32, 44.42)
Severe (24-60)	13.79 (6.83, 27.84)	35.76 (4.81, 265.90)	13.52 (6.77, 27.01)	51.11 (7.88, 331.32)
Group				
HIV-negative	Ref.	Ref.	Ref.	Ref.
Older PLWH	2.35 (0.91, 6.07)	2.41 (0.51, 11.44)	2.28 (0.95, 5.46)	2.93 (0.62, 13.75)
Levels of depressive symptoms (PHQ-9)				
Minimal depression (1-4)	Ref.	Ref.	Ref.	Ref.
Mild depression (5-9)	4.09 (1.80, 9.30)	5.95 (0.76, 46.94)	4.67 (2.09, 10.44)	7.23 (0.94, 55.63)
Moderate depression (10-14)	20.37 (8.70, 47.70)	9.32 (0.64, 136.57)	16.48 (7.32, 37.11)	8.36 (0.64, 110.09)
Moderately severe depression (15-19)	14.31 (5.09, 40.22)	15.61 (5.29, 46.11)	13.17 (4.89, 35.48)	13.56 (4.85, 37.90)
Severe depression (20-30)	49.04 (15.25, 157.66)	314.10 (9.29, 10625.60)	42.38 (14.52, 123.67)	581.23 (27.39, 12335.33)

*Adjusted for age, gender, ethnicity, education and marital status **Further adjusted for the association of HIV with depressive symptoms

5.5.6.2 Comparison of the four criteria-frailty definition with the single objective measures of weakness and slowness

In the second sensitivity analysis, I used the older POPPY groups that had information on the objective components for the assessment of frailty (weakness, as assessed by grip strength and slowness, as assessed by the timed walk test). In total, 41.8% (408/976) of those with information on grip strength were deemed to be weak and 16.0% (151/946) of those with information on the timed walk test were deemed to be slow.

The multivariable regression analyses for weakness and slowness provided results which were consistent with the results of the multivariable model of the complete case analysis for the definition of frailty suggesting that HIV is associated with higher weakness (aOR=1.48, 95% CI (1.07, 2.04)) and higher slowness (aOR=2.56, 95% CI (1.49, 4.39)) after adjusting for the standard confounders described in Section 4.5, Table 5.11.

The models that explored whether the association of HIV with weakness was modified by any association with depressive symptoms suggested that the models without the interaction terms were a better fit compared to the models with the interaction term when depressive symptoms were assessed using the CES-D score (Log-likelihood=-556.82 vs. -556.30, Likelihood ratio test Chi-square=1.03, P=0.60) and when depressive symptoms were assessed using the PHQ-9 score (Log-likelihood=-571.66 vs. -570.14, Likelihood ratio test Chi-square=3.04, P=0.22). This suggested that the association of HIV with weakness was not modified by the association with depressive symptoms.

The multivariable models that explored whether the association of HIV with slowness was modified by any association with depressive symptoms suggested a better fit in the models without the interaction term. In particular, using the CES-D score (Log-likelihood=-290.25 vs. -290.17, Likelihood ratio test Chi-square=0.16, P=0.92) and when depressive symptoms were assessed using the PHQ-9 score (Log-likelihood=-304.80 vs. -302.70, Likelihood ratio test Chi-square=4.20, P=0.12), Table 5.12.

Table 5.11: Association of frailty weakness, slowness and weakness/slowness with HIV among the older POPPY participants

	Frailty univariable	Frailty multivariable*	Weakness*	Slowness*
	OR (95% CI)	aOR (95% CI)	aOR (95% CI)	aOR (95% CI)
Group				
HIV-negative	Ref.	Ref.	Ref.	Ref.
Older PLWH	4.60 (2.09, 10.16)	4.06 (1.69, 9.75)	1.48 (1.07, 2.04)	2.56 (1.49, 4.39)

*Adjusted for age, gender, ethnicity, education and marital status

Table 5.12: Association of frailty and imputed frailty with POPPY group and depressive symptoms as assessed by CES-D and PHQ-9 score

	Multivariable model* Complete case frailty definition	Multivariable model** Complete case frailty definition	Multivariable model* Weakness	Multivariable model** Weakness	Multivariable model* Slowness	Multivariable model** Slowness
	aOR (95% CI)	aOR (95% CI)	aOR (95% CI)	aOR (95% CI)	aOR (95% CI)	aOR (95% CI)
Group						
HIV-negative	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Older PLWH	2.09 (0.82, 5.36)	2.91 (0.64, 13.30)	1.26 (0.89, 1.77)	1.36 (0.93, 1.99)	2.16 (1.21, 3.87)	2.07 (1.09, 3.92)
Levels of depressive symptoms (CES-D)						
No to mild (0-15)	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Moderate (16-23)	4.57 (2.00, 10.40)	3.92 (0.33, 46.88)	2.02 (1.32, 3.08)	2.68 (1.13, 6.37)	1.43 (0.76, 2.67)	1.06 (0.20, 5.52)
Severe (24-60)	13.79 (6.83, 27.84)	35.76 (4.81, 265.90)	1.86 (1.25, 2.76)	2.81 (0.84, 9.40)	1.74 (0.99, 3.04)	1.74 (0.20, 14.96)
Group						
HIV-negative	Ref.	Ref.	Ref.	Ref.	Ref.	Ref
Older PLWH	2.35 (0.91, 6.07)	2.41 (0.51, 11.44)	1.31 (0.93, 1.84)	1.45 (0.98, 2.14)	2.42 (1.36, 4.29)	2.13 (1.11, 4.09)
Levels of depressive symptoms (PHQ-9)						
Minimal depression (1-4)	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Mild depression (5-9)	4.09 (1.80, 9.30)	5.95 (0.76, 46.94)	1.18 (0.81, 1.72)	1.76 (0.81, 3.82)	1.64 (0.96, 2.80)	0.93 (0.19, 4.55)
Moderate depression (10-14)	20.37 (8.70, 47.70)	9.32 (0.64, 136.57)	2.30 (1.44, 3.69)	2.88 (0.85, 9.80)	1.85 (0.97, 3.53)	0.70 (0.07, 7.50)
Moderately severe depression (15-19)	14.31 (5.09, 40.22)	15.61 (5.29, 46.11)	1.40 (0.76, 2.59)	0.60 (0.06, 6.02)	1.14 (0.47, 2.75)	1.23 (0.50, 3.03)
Severe depression (20-30)	49.04 (15.25, 157.66)	314.10 (9.29, 10625.60)	1.78 (0.80, 3.95)	5.39 (0.45, 64.19)	2.30 (0.81, 6.51)	24.28 (1.27, 463.03)

*Adjusted for age, gender, ethnicity, education and marital status

**Further adjusted for the association of HIV with depressive symptoms

5.6 Discussion

In this chapter I demonstrated that the group of older PLWH are more likely to be frail than the group of similarly aged HIV-negative controls. The association of HIV with frailty was not modified by the association with age and the association with depressive symptoms. The frail study participants had a greater use of healthcare resources compared to non-frail. Among PLWH (younger and older), the multivariable analysis suggested that older age and the total number of co-medications were significant predictors of frailty; these associations were confirmed in a series of sensitivity analysis that assessed different definitions of frailty.

The finding that frailty prevalence was higher among the older PLWH (13%, 73/560) compared to HIV-negative controls (3%, 7/222) is consistent with findings from other studies conducted in high-income countries such as the USA and the Netherlands. In particular, Piggott *et al.* (149), Önen *et al.* (160) and Kooij *et al.* (173) investigated PLWH of similar age to that of the older POPPY participants and reported a similar prevalence of frailty (12.3%, 9% and 10.6% respectively). These authors also confirmed that the prevalence of frailty among PLWH is significantly higher than that among HIV-negative controls. Mechanisms known to raise the risk of frailty among PLWH include systemic inflammation, attenuated mitochondrial function and oxidative stress (144, 148, 169, 609-621); although these are factors that have not been measured within POPPY, they are likely to contribute to the higher prevalence of frailty seen among PLWH. Some authors postulate that prolonged ART exposure and advancing age may reduce mitochondria density in cells, and that this could explain the association with higher frailty (622-626). In POPPY the mitochondria density was not measured, however, the long exposure to cART (median 10.7 years in the group of older PLWH) may have resulted in reduced mitochondria density which can increase the frailty prevalence. Although new ART drugs are less toxic to mitochondria, ART use has been independently associated with high basal level energy requirements (627), higher oxidative stress and systemic inflammation (61) which, in turn, have been associated with compromised physical function and low

muscle mass in PLWH (148, 611), providing support for a direct association with frailty.

Other researchers investigating the population of PLWH or the elderly in the general population have also reported greater healthcare resource use among frail participants (186, 628) as I did among the POPPY participants. Piggott *et al.* (186) have found that frailty is associated with significantly higher all-cause, chronic and infectious disease hospitalization. Roe *et al.* (629), in a longitudinal study among the elderly in Ireland, found that frailty is associated with higher social care and medical care services (630). One of the key consequences of frailty is a reduced physical functioning which has been found to have an antagonistic effect on mental health (608, 631, 632), accidents and falls (131, 633) and wellbeing among (61, 634, 635) the elderly which, in turn, may increase both primary and the secondary healthcare utilization.

The relationship between higher depressive symptoms and increased frailty among the older POPPY participants is a finding that requires further investigation. Other researchers have suggested a positive association of depressive symptoms with frailty among PLWH. In particular, Ding *et al.* (187) in a study in China reported that HIV was associated with a higher prevalence of frailty independently of any association with depressive symptoms but the authors did not report any findings exploring whether the association of frailty with HIV was modified by the association with depressive symptoms and similarly to the data used in this thesis, they used cross-sectional data. With such data it is not possible to know whether depressive symptoms pre-existed the HIV infection or were an outcome of HIV and therefore a causal relationship between HIV infection, depressive symptoms and frailty cannot be determined. Furthermore, the number of participants with moderate and severe depressive symptoms was small and the analysis was underpowered.

Nevertheless, the association of depressive symptoms with frailty is a finding of great clinical relevance and highlights the need for multidisciplinary treatment of the older PLWH. Depressive symptoms may affect the physical and psychological health and reduce motivation. This could lead to physical inactivity, muscle weakness and

decreased gait speed (608, 636-638). Additionally, the link between depressive symptoms and frailty may be mediated by poor cART adherence (639) for which information was not available within POPPY. Poor cART adherence can lead to compromised virological response and thus weak immunity. In turn, immune deficiency may also present as symptoms of frailty, such as slow gait speed, increased weakness, exhaustion and low physical activity. Another mechanism that may explain the association of depressive symptoms with frailty may be prolonged inactivity, muscle weakness and deterioration of general health and wellbeing (640). The link between depression and loss of skeletal muscle mass, also referred to as sarcopenia, has been confirmed in a recent review by Chang *et al.* who highlighted the need for further investigation of the causal relationship between the two conditions (641).

5.6.1 Strengths and limitations

This chapter has several strengths and limitations. Frailty was assessed both among the older and the younger PLWH. Younger PLWH are often neglected when it comes to the assessment of frailty due to their younger age. However, the early identification of those in a frail/pre-frail state is very important. Earlier diagnosis and treatment may more effectively aid transition to a non-frail state. Another strength of this chapter is that the large sample size allowed me to explore whether the effect of age on the prevalence of frailty is modified by the effect of HIV.

There are five main limitations as follows. The first limitation was the use of a non-validated frailty definition. The modified frailty definition uses four criteria as opposed to five criteria as suggested by Fried *et al.* (95). This raises concerns for potential over estimation of the prevalence of frailty and pre-frailty. However, the use of the sensitivity analysis exploring the different definitions of frailty have ensured that the robustness of the results of the original analysis.

A second possible limitation is concerned with the reliance on participants' self-reported measures. Self-reported questions were used for two out of the four frailty criteria. This might have led to over/under estimation of frailty and pre-frailty prevalence. However, a sensitivity analysis that included only the objective measures,

confirmed the association of frailty among those in the older group of PLWH and those taking an increased number of co-medications.

A third limitation was the amount of missing data that was present when I undertook analyses of frailty. Some study centres had significantly more missing data from the variables used to construct the frailty index than others. This might have led to the exclusion of participants that would be deemed to be frail. However, a series of sensitivity analyses confirmed the findings of the original analysis regarding the strong association of increased number of co-medications and the higher depressive symptoms with increased frailty.

The fourth limitation was the lack of information on some key risk factors known to be associated with frailty, was an additional limitation. For instance, patterns and lifetime use of alcohol (642) and poor nutrition practices (643) have been associated with frailty in other studies among PLWH. Such data were not routinely collected in POPPY. However, further exploration of their association with frailty would inform policy makers in the design of more efficient interventions to prevent or delay signs of frailty among the ageing PLWH in England and Ireland. Further, whereas several studies (148, 173, 192, 211) have explored the association of inflammatory markers with frailty, this information was absent from POPPY.

Lastly and very importantly the limited statistical power is an important limitation of this chapter. In particular, the small number of participants who were frail and had depressive symptoms was very small which may explain why the model exploring the interaction between HIV and depressive symptoms suggested a poorer fit compared to the model without the interaction. Moreover, the small numbers of healthcare utilisation among the frail study participants has restricted the analysis to descriptive.

Chapter 6 Prevalence of falls among POPPY participants

6.1 Introduction

In the general population, falls are a common cause of injury that are associated with hospital admissions. People over the age of 65 are at increased risk of falling, with 30% of people aged 65 and over, and around half of people aged 80 or over, reporting at least one fall per year in the UK (644). The factors contributing to an increased number of falls are often overlooked (645). Impaired balance/gait ability, lack of coordination and poor posture control are considered to be the leading risk factors for an increased risk of falling among people over the age of 65 (226, 242, 251, 258, 259). Increased age is associated with compromised balance and poorer ability to avoid a fall (251-255). The risk of falling among PLWH has been reported to be higher than that among HIV-negative controls (194), with recurrent falls being more prevalent among frail PLWH (70).

Several risk factors for falls and recurrent falls among PLWH have been identified including female gender, current smoking status, weight loss, increased number of comorbidities (CVD, hypertension, dementia, neuropathy, arthritis, chronic pain, psychiatric disease, frailty), depressive symptoms, current use of antidepressants, sedatives and use of opiates (194, 244, 248, 257, 295).

In POPPY, overall cognitive performance has been reported to be significantly lower among PLWH compared to HIV-negative controls (646); this has been reported to be partly mediated by depressive symptoms and substance use such as recreational drugs and alcohol (647). Higher depressive symptoms have been associated with poorer social involvement and lower physical activity, which may further increase the risk for falling (648, 649)

6.2 Methods

Falls were recorded through a falls-specific questionnaire in POPPY. The question asked was “Over the past 28 days have you had any falls?”. Participants defined as having experienced recurrent falls were those reporting more than 1 fall in the past

28 days. More details of other falls-specific questions are described in the Methods chapter (Section 3.5.2).

The association of falls with fractures is investigated in Section 7.6.

6.3 Hypothesis

1. There is no difference in prevalence of falls between the older PLWH and HIV-negative controls
2. The association of HIV with the prevalence of falls is independent of any association with frailty
3. The association of HIV with the prevalence of falls is not modified by the association with depressive symptoms
4. HIV-specific factors, such as previous diagnosis of AIDS-defining illness, low current and nadir CD4 count, and a detectable VL, are associated with an increased risk for falls
5. The hypotheses 1-4 are valid for the outcome of recurrent falls

6.4 Specific objectives

1. To investigate whether older PLWH have a higher prevalence of falls in the past 28 days compared to HIV-negative controls
2. To investigate whether the association of HIV with the prevalence of falls is independent of the association with frailty
3. To investigate whether the association of HIV with the prevalence of falls is modified by the association with depressive symptoms
4. In the subgroup of PLWH, to explore the association of age, total number of co-medications and HIV-related parameters with the prevalence of falls. In particular, to assess the associations of previous diagnosis of AIDS-defining illness, CD4 count, CD4 nadir, VL, years since HIV-diagnosis, current cART and years since cART initiation
5. To explore objectives 2-5 for recurrent falls

6.5 Statistical analysis

For objective 1, using univariable and multivariable logistic regression models I explored the differences in the prevalence of falls between the group of older PLWH and the HIV-negative controls.

For objective 2, two multivariable logistic regression models I explored whether the association of HIV with the prevalence of falls was independent of frailty. In the first model I adjusted for the confounders described in Section 4.5 and in the second I additionally adjusted for frailty.

For objective 3, to explore whether the association of HIV with falls is modified by the association with depressive symptoms I performed 2 multivariable analyses. In the first I adjusted for the confounders described in Section 4.5 and in the second I additionally adjusted for the interaction between HIV status and depressive symptoms. The fit of the multivariable regression models with and without the interaction of HIV with depressive symptoms were compared using the likelihood-ratio test to determine the model with the best fit.

For objective 4, the subgroup of PLWH was selected and the association of HIV-specific factors with falls was explored. The HIV-specific factors considered were those associated with falls in the univariable analysis along with adjustment for current use of alcohol, medication for mental health and the physical functioning score from SF-36 questionnaire.

For objective 5, the same statistical analyses as described for objective 1-5 were followed for the outcome of recurrent falls (two or more falls during the last 28 days).

6.6 Results

6.6.1 Falls and HIV

In this section using univariable and multivariable logistic regression models I explored the association of HIV with history of falls.

The univariable model suggested that the prevalence of falls in the group of older PLWH was 4-fold higher compared to that of HIV-negative controls (OR=4.05, 95% CI (2.33, 7.06)). The association remained significant in the multivariable model after adjusting for the standard confounders described in Section 4.5, confirming the independent association of HIV with a higher prevalence for falls (aOR=4.44, 95% CI (2.36, 8.33), Table 6.1.

Table 6.1: Association of falls with HIV

	Univariable model	**Multivariable model***
	OR (95% CI)	**aOR (95% CI)**
Group		
HIV-negative	Ref.	Ref.
Older PLWH	4.05 (2.33, 7.06)	4.44 (2.36, 8.33)

*Adjusted for age, gender, ethnicity, education and marital status

6.6.2 HIV, frailty and history of falls

In this section, I investigated whether the association of HIV with falls was independent of any association with frailty. The univariable analysis suggested that frail study participants had almost 3-fold higher odds of having a fall compared to the non-frail participants (OR=2.63, 95% CI (1.52, 4.55)).

In the multivariable model adjusting for frailty and the standard confounders, the association of HIV with falls remained significant, suggesting that both HIV and frailty are independently associated with a higher prevalence of falls, (aOR=3.48, 95% CI (1.71, 7.09) for HIV and aOR=1.92, 95% CI (1.03, 3.57) for frailty), Table 6.2.

Table 6.2: Association of HIV and frailty with falls

	Univariable model	Multivariable model*
	OR (95% CI)	**aOR* (95% CI)**
Group		
HIV-negative	Ref.	Ref.
Older PLWH	4.05 (2.33, 7.06)	3.48 (1.71, 7.09)
Frailty		
No	Ref.	Ref.
Yes	2.63 (1.52, 4.55)	1.92 (1.03, 3.57)

*Adjusted for age, gender, ethnicity, education and marital status

6.6.3 HIV depressive symptoms and history of falls

In this section I explored whether the association of HIV with falls is modified by any association with depressive symptoms.

The prevalence of falls was significantly higher among those with severe depressive symptoms (CES-D score of 20-27) compared to that of those with either moderate (1-4) or mild (5-9) depressive symptoms (36.5% (58/137) vs. 16.1% (19/118) and 6.4% (39/610), respectively, P<0.001, Table 6.3). Findings for PHQ-9 were similar with a higher prevalence of falls in those with severe depressive symptoms (58.1% (18/31)) compared to those with moderately severe (36.8% (21/57)), moderate (23.0% (23/100)), mild (13.8% (23/167)) and minimal depressive symptoms (6.2% (35/562), P<0.001, Table 6.3)

Table 6.3: Prevalence of falls among older POPPY participants stratified by the CES-D or PHQ-9 scores

			History of falls in the past 28 days				
	Total N=973		**No N=836**		**Yes N=137**		
	n	**(%)**	**n**	**(%)**	**n**	**(%)**	**p-value**
Level of depressive symptoms (CES-D)							<0.001
No to mild (0-15)	610	(100.0)	571	(93.6)	39	(6.4)	
Moderate (16-23)	118	(100.0)	99	(83.9)	19	(16.1)	
Severe (24-60)	159	(100.0)	101	(63.5)	58	(36.5)	
Unknown	86	(100.0)	65	(75.6)	21	(24.4)	
Level of depressive symptoms (PHQ-9)							<0.001
Minimal (1-4)	562	(100.0)	527	(93.8)	35	(6.2)	
Mild (5-9)	167	(100.0)	144	(86.2)	23	(13.8)	
Moderate (10-14)	100	(100.0)	77	(77.0)	23	(23.0)	

			History of falls in the past 28 days			
	Total N=973		No N=836		Yes N=137	
Moderately severe (15-19)	57	(100.0)	36	(63.2)	21	(36.8)
Severe (20-27)	31	(100.0)	13	(41.9)	18	(58.1)
Unknown	56	(100.0)	39	(69.6)	17	(30.4)

There was a strong linear trend such that those with a greater level of depressive symptoms as assessed using CES-D or PHQ-9 had a higher odds of experiencing a fall (left-hand section of Table 6.4 and Table 6.5). In particular, for CES-D, those with moderate and severe depressive symptoms compared to those with no to mild symptoms had almost 3-fold and 9-fold higher odds of having a fall (OR=2.85, 95% CI (1.67, 4.85), OR=8.89, 95% CI (5.93, 13.33), respectively). Similarly for PHQ-9, those with mild, moderate, moderately severe and severe depressive symptoms had increasingly higher odds of having a fall compared to those with minimal symptoms (OR=2.43, 95% CI (1.48, 4.00), OR=4.76, 95% CI (2.85, 7.95), OR=9.96, 95% CI (5.75, 17.26) and OR=22.23, 95% CI (11.25, 43.93), respectively).

After adjustment for the standard confounders described in section 4.5 plus the depressive symptoms, the models suggested that the association of HIV with higher odds of falls is independent of the depressive symptoms (middle section of Table 6.4 and Table 6.5). Further adjustment for the interaction of HIV and depressive symptoms explored whether the association of HIV with falls was modified by the association with depressive symptoms (right section of Table 6.4 and Table 6.5). The models without the interaction terms were a better fit compared to the models with the interaction term (Log-likelihood=-278.65 vs. -278.61, Likelihood ratio test Chi-squared test statistic 0.076, P=0.96 for CES-D score and Log-likelihood=-285.10 vs. -283.67, Likelihood ratio test Chi-squared test statistic 2.86, P=0.23 for PHQ-9 score). This suggested that the association of HIV with falls was not modified by the association with depressive symptoms.

Table 6.4: Association of falls with HIV and depressive symptoms as assessed by the CES-D score

	Univariable model	Multivariable model*	Multivariable model**
	OR (95% CI)	**aOR* (95% CI)**	**aOR* (95% CI)**
Group			
HIV-negative	Ref.	Ref.	Ref.
Older PLWH	4.05 (2.33, 7.06)	3.06 (1.52, 6.16)	2.97 (1.26, 6.96)
Level of depressive symptoms (CES-D)			
No to mild (0-15)	Ref.	Ref.	Ref.
Moderate (16-23)	1.03 (0.44, 1.62)	2.37 (1.27, 4.43)	2.49 (0.49, 12.75)
Severe (24-60)	2.13 (1.67, 2.59)	5.41 (3.22, 9.08)	4.38 (0.78, 24.72)

*Adjusted for age, gender, ethnicity, education and marital status

**further adjusted for the interaction of HIV and depressive symptoms

Table 6.5: Association of falls with POPPY group and depressive symptoms as assessed by the PHQ-9 score

	Univariable model	Multivariable model*	Multivariable model**
	OR (95% CI)	**aOR* (95% CI)**	**aOR* (95% CI)**
Group			
HIV-negative	Ref.	Ref.	Ref.
Older PLWH	4.05 (2.33, 7.06)	2.83 (1.44, 5.56)	2.03 (0.92, 4.50)
Levels of depressive symptoms (PHQ-9)			
Minimal (1-4)	Ref.	Ref.	Ref.
Mild (5-9)	0.88 (0.32, 1.43)	1.75 (0.96, 3.18)	0.73 (0.09, 5.96)
Moderate (10-14)	1.50 (0.93, 2.08)	3.37 (1.80, 6.33)	1.96 (0.22, 17.46)
Moderately severe (15-19)	2.17 (1.54, 2.81)	5.75 (2.75, 11.99)	6.68 (3.10, 14.40)
Severe (20-27)	3.04 (2.25, 3.83)	16.94 (7.03, 40.81)	7.92 (0.55, 113.33)

*Adjusted for age, gender, ethnicity, education and marital status

**further adjusted for the interaction of HIV and depressive symptoms

6.6.4 The association of HIV-specific factors with the prevalence of falls among PLWH

PLWH with a history of a fall in the past 28 days before the study entry were significantly older than those with no history of falls, although the difference in medians was only 3 years (median (range) 55 (26, 82) vs. 52 (20, 82) years, P=0.01). Those with a history of falls had been diagnosed with HIV for a significantly longer time compared to those with no history of falls (median (range) 15.4 (1.5, 34.0) vs. 12.9 (0.0, 33.7) years, P=0.003) and those with a history of falls had been on ART for a slightly longer time compared to those with no history of falls (median (range) 10.8 (0.1, 25.1) vs. 9.1 (0.0, 28.2) years, P=0.06). The prevalence of falls among older PLWH was significantly higher than that among younger PLWH (17.9% (122/680) vs. 9.7% (35/360), P<0.001). More specifically, a non-linear association between the prevalence of falls and age was found. With regards to age, the highest prevalence of falls was among those aged 60-64 years (24.4% (30/123)) while it was lower among those aged 65-69 and ≥70 years (15.4% (12/78) and 10.8% (4/37), respectively, P=0.007).

The prevalence of falls among those with a previous diagnosis of AIDS-defining illness was significantly higher compared to those with no previous diagnosis of AIDS-defining illness (19.5% (58/298) vs. 13.3% (99/742), P=0.01). No significant associations were detected between any of the other HIV factors and the prevalence of falls. Despite not reaching the significance level, there was some suggestion that those with a lower CD4 nadir, longer time since HIV diagnosis and longer time on ART, had a higher prevalence of falls. All three factors suggested a linear, dose-response relationship with higher risk of falls. Therefore, a linear term for those factors was considered in the univariable/multivariable models. In contrast, there was no evidence of an association with current CD4 count or VL.

The prevalence of falls was significantly higher among those taking a high number of co-medications (excluding cART) and significantly lower among those taking no co-medication. In particular, those receiving 10 or more co-medications had a

significantly higher prevalence of falls compared to those receiving 0, 1-4 and 5-9 co-medications (41.1% (23/56) vs. 8.2% (26/316), 16.4% (77/471) and 15.7% (31/197) respectively, P<0.001). With regards to antiretroviral treatment, no difference in the prevalence of falls was observed according to the specific NRTI and PIs received. However, the prevalence of falls among those receiving ETR was significantly higher (31.6%) compared to among those not receiving an NNRTI (14.3%) or to those receiving EFV (11.8%), NVP (16.7%) or RPV (16.5%). Finally, the prevalence of falls was significantly higher among those on INSTIs (22.2%) compared to those not on INSTIs (13.9%, P=0.01, Table 6.6).

Table 6.6: Prevalence of falls among POPPY PLWH, stratified by age, history of AIDS, immune system markers and current antiretroviral medication characteristics

			History of falls in the past 28 days				
	Total N=1040		No n=883		Yes n=157		
	n	(%)	n	(%)	n	(%)	p-value
Age group (years)							0.007
≤29	26	(100.0)	25	(96.2)	1	(3.9)	
30-39	86	(100.0)	78	(90.7)	8	(9.3)	
40-49	248	(100.0)	222	(89.5)	26	(10.5)	
50-54	257	(100.0)	214	(83.3)	43	(16.7)	
55-59	185	(100.0)	152	(82.2)	33	(17.8)	
60-64	123	(100.0)	93	(75.6)	30	(24.4)	
65-69	78	(100.0)	66	(84.6)	12	(15.4)	
≥70	37	(100.0)	33	(89.2)	4	(10.8)	
Previous diagnosis of AIDS-defining illness							0.01
No	742	(100.0)	643	(86.7)	99	(13.3)	
Yes	298	(100.0)	240	(80.5)	58	(19.5)	
CD4 count (cells/mm^3)							0.70
≤447	203	(100.0)	171	(84.2)	32	(15.8)	
448-567	203	(100.0)	170	(83.7)	33	(16.3)	
568-695	204	(100.0)	180	(88.2)	24	(11.8)	
696-865	202	(100.0)	170	(84.2)	32	(15.8)	
≥866	203	(100.0)	174	(85.7)	29	(14.3)	
CD4 nadir (cells/mm^3)							0.36
≤80	206	(100.0)	171	(83.0)	35	(17.0)	
81-169	194	(100.0)	163	(84.0)	31	(16.0)	
170-240	202	(100.0)	167	(82.7)	35	(17.3)	
241-341	197	(100.0)	170	(86.3)	27	(13.7)	
≥342	199	(100.0)	177	(88.9)	22	(11.1)	
VL							0.17

	Total N=1040		History of falls in the past 28 days: No n=883		Yes n=157		
	n	(%)	n	(%)	n	(%)	p-value
Detectable	104	(100.0)	93	(89.4)	11	(10.6)	
Undetectable	932	(100.0)	786	(84.3)	146	(15.7)	
Years on ART							0.40
≤3.9	204	(100.0)	179	(87.8)	25	(12.2)	
4.0-7.3	204	(100.0)	176	(86.3)	28	(13.7)	
7.4-12.3	203	(100.0)	166	(81.8)	37	(18.2)	
12.4-17.1	204	(100.0)	173	(84.8)	31	(15.2)	
≥17.2	203	(100.0)	167	(82.3)	36	(17.7)	
Time since HIV diagnosis (yrs)							0.07
≤6.4	206	(100.0)	181	(87.9)	25	(12.1)	
6.5-11.0	206	(100.0)	182	(88.4)	24	(11.7)	
11.1-16.0	206	(100.0)	173	(84.0)	33	(16.0)	
16.1-21.9	206	(100.0)	174	(84.5)	32	(15.5)	
≥22.0	206	(100.0)	163	(79.1)	43	(20.9)	
Total number of co-medications (excluding cART)							<0.001
0	316	(100.0)	290	(91.8)	26	(8.2)	
1-4	471	(100.0)	394	(83.7)	77	(16.4)	
5-9	197	(100.0)	166	(84.3)	31	(15.7)	
≥10	56	(100.0)	33	(58.9)	23	(41.1)	
NRTI in regimen							0.67
None	142	(100.0)	123	(86.6)	19	(13.4)	
TFV/FTC	650	(100.0)	546	(84.0)	104	(16.0)	
ABC/3TC	132	(100.0)	112	(84.9)	20	(15.2)	
Other	116	(100.0)	102	(87.9)	14	(12.1)	
PI in regimen							0.78
None	609	(100.0)	514	(84.4)	95	(15.6)	
Boosted PIs	338	(100.0)	288	(85.2)	50	(14.8)	
Unboosted PIs	93	(100.0)	81	(87.1)	12	(12.9)	
NNRTI in regimen							0.005
None	518	(100.0)	444	(85.7)	74	(14.3)	
EFV	254	(100.0)	224	(88.2)	30	(11.8)	
NVP	132	(100.0)	110	(83.3)	22	(16.7)	
RPV	79	(100.0)	66	(83.5)	13	(16.5)	
ETR	57	(100.0)	39	(68.4)	18	(31.6)	
INSTI in regimen							0.01
No	896	(100.0)	771	(86.1)	125	(13.9)	
Yes	144	(100.0)	112	(77.8)	32	(22.2)	

When considering the CD4 nadir, years on ART and time since HIV diagnosis as continuous variables in univariable analysis, only a longer time since HIV diagnosis was associated with an increased risk of falls (OR=1.18 per 5 years longer, 95% CI (1.06, 1.31), Table 6.7).

The multivariable analysis that also included the HIV factors that were associated with falls in univariable analysis found those taking 1-4 and ≥10 co-medications had significantly higher odds for falling compared to those not taking any co-medications (aOR=1.80, 95% CI (1.02, 3.17) and aOR=2.76, 95% CI (1.11, 6.88)). Finally, those on ETR and those on regimens including an INSTI, had 2.4-fold higher odds of falling (aOR=2.40 vs. not receiving an NNRTI, 95% CI (1.06, 5.43), P=0.12 and aOR=2.35 vs. not receiving an INSTI, 95% CI (1.29, 4.27), Table 6.7).

Table 6.7: Association of falls with age and HIV factors among PLWH in POPPY

	Univariable model	**Multivariable model***
	OR (95% CI)	**aOR (95% CI)**
Age at baseline visit		
≤29	Ref.	Ref.
30-39	2.56 (0.31, 21.51)	1.86 (0.20, 17.75)
40-49	2.93 (0.38, 22.51)	1.88 (0.22, 16.05)
50-54	5.02 (0.66, 38.07)	2.15 (0.25, 18.32)
55-59	5.43 (0.71, 41.49)	2.14 (0.24, 18.79)
60-64	8.06 (1.05, 62.06)	2.75 (0.31, 24.39)
65-69	4.55 (0.56, 36.80)	1.86 (0.20, 17.82)
≥70	3.03 (0.32, 28.81)	0.36 (0.02, 6.94)
Previous diagnosis of AIDS-defining illness		
No	Ref.	Ref.
Yes	1.57 (1.10, 2.24)	1.34 (0.85, 2.11)
CD4 count (cells/mm^3)		
≤447	Ref.	
448-567	1.04 (0.61, 1.76)	-
568-695	0.71 (0.40, 1.26)	-
696-865	1.01 (0.59, 1.72)	-
≥866	0.89 (0.52, 1.54)	-
CD4 nadir (/50 cells/mm^3)	0.96 (0.91, 1.01)	
VL		
Detectable	Ref.	
Undetectable	0.64 (0.33, 1.22)	
Years on ART (/5 years)	1.09 (0.95, 1.25)	

	Univariable model	Multivariable model*
	OR (95% CI)	**aOR (95% CI)**
Time since HIV diagnosis (/5 years)	1.18 (1.06, 1.31)	0.99 (0.85, 1.15)
Number of total co-medications (excluding cART)		
0	Ref.	Ref.
1-4	2.18 (1.36, 3.49)	1.80 (1.02, 3.19)
5-9	2.08 (1.20, 3.63)	0.96 (0.47, 1.97)
≥10	7.77 (3.99, 15.14)	2.98 (1.16, 7.65)
NRTI in regimen		
None	Ref.	
TFV/FTC	1.23 (0.73, 2.09)	-
ABC/3TC	1.16 (0.59, 2.28)	-
Other	0.89 (0.42, 1.86)	-
PI in regimen		
None	Ref.	
Boosted PIs	0.94 (0.65, 1.36)	-
Unboosted PIs	0.80 (0.42, 1.53)	-
NNRTI in regimen		
None	Ref.	Ref.
EFV	0.80 (0.51, 1.26)	1.15 (0.62, 2.11)
NVP	1.20 (0.71, 2.02)	1.57 (0.81, 3.04)
RPV	1.18 (0.62, 2.25)	2.08 (0.92, 4.72)
ETR	2.77 (1.50, 5.10)	2.40 (1.06, 5.43)
INSTI in regimen		
No	Ref.	Ref.
Yes	1.76 (1.14, 2.73)	2.35 (1.29, 4.27)

*also adjusted for current use of alcohol, medication for mental health and the physical functioning score from SF-36 questionnaire

6.6.5 Recurrent falls analyses

The majority of the participants with history of any fall had experienced recurrent falls (70.4% (121/172)). Therefore, the findings for any falls were similar for the outcome of recurrent falls. The group of older PLWH had higher odds of recurrent falls compared to HIV-negative controls. The analyses that explored whether the association of HIV with recurrent falls was independent of any association with frailty yielded similar results to that for the outcome of any falls. Similarly to the analysis for any falls, I found that the association of HIV with recurrent falls was not modified by

any association with depressive symptoms. Depressive symptoms were associated with increased odds of recurrent falls independently of HIV.

Among PLWH I found a difference compared to the analysis for any falls. The association of a higher risk of falls in those receiving a higher number of total co-medications was also seen for the outcome of recurrent falls, however, in the later analysis, this association was not statistically significant. Despite not reaching the level of significance the results of the multivariable model suggested that taking a higher number of total co-medications increases the odds of recurrent falls. The lack of a significant association may be a result of reduced power since the endpoint of recurrent falls has excluded all single falls; of which many may have been accidental and not due to an underlying clinical condition. The association of INSTIs with a higher odds for falls and recurrent falls was a consistent finding in both analyses, Appendix VI.

6.7 Discussion

In this chapter I demonstrated an increased prevalence of falls among the older PLWH compared to the HIV-negative controls. The association of HIV with higher prevalence of falls was independent of any association with frailty and was not modified by the association with depressive symptoms. Among PLWH I found that the increased number of total co-medications and the use of INSTIs were associated with increased fall risk. The sensitivity analysis for recurrent falls has yielded similar findings with the analysis for any falls in the past 28 days.

The prevalence of falls (14.1%) and recurrent falls (10.2%) among the older POPPY participants is comparable to the ACTG Study A5322, conducted in 32 clinical research sites in the U.S. including Puerto Rico, in which the prevalence for falls and recurrent falls was 18% and 7%, respectively (70), and in ANRS CO3 Aquitaine cohort study in south-western France where the prevalence of falls was 12% (238). The higher fall prevalence in the older PLWH as compared to the HIV-negative controls has been confirmed by other studies (157, 450, 566, 650) and potential explanations

may be the lower BMD among PLWH, as well as the neurocognitive impairment and neurotoxicity caused by ART (501). Despite the benefits of ART, it has been found to compromise balance (257) and increase the falls risk among PLWH (651). Several studies have suggested that HIV infection is linked to various movement disorders resulting in slowness, rigidity and/or balance and peripheral sensory function loss, such as chorea, ballism, dystonia, and myoclonus (236, 652, 653). All these conditions may increase fall risk.

In the analysis further adjusting for frailty I found a significant association of HIV with falls. This suggested that HIV is associated with an increased prevalence of falls, independently of any association with frailty. The estimate of frailty suggested that frail study participants have higher odds of falls. Whether frailty contributes to the occurrence of falls or if it is a result of falls is unclear in this dataset and the cross-sectional nature of the study prevents the establishment of temporality. Reverse causation cannot be ruled out since a fall may trigger frailty in an individual (654). A possible mechanism explaining the higher risk of falls among the frail participant is through depressive symptoms that may lead to physical inactivity, muscle weakness and decreased gait speed (608, 636-638).

The analyses that explored whether the association of HIV with falls was modified by the association with depressive symptoms suggested lack of evidence that the association of depressive symptoms with falls was intensified by HIV status. Furthermore, it was not possible to determine a causal relationship between HIV infection, depressive symptoms and falls due to the cross-sectional nature of the data.

As in several studies (248, 257, 295, 296), the results of the univariable analysis suggested a link between higher depressive symptoms and higher falls risk. Sedatives and antidepressant medications have been linked with an increased risk of falls by several researchers (248, 257, 295, 651). However, a recent review by Gebara *et al.* (655) debated whether selective serotonin reuptake inhibitors (SSRI), used to treat

depression, are a cause or an effect of falls and suggested that there is insufficient evidence to support changes to clinical guidelines which currently recommend that older adults at high risk for falls should avoid SSRIs. However, in the POPPY, among those on co-medications for mental health with a history of falls, 38% were on SSRIs and 62% on other classes of medication for mental health which may explain the retention of the association between depressive symptoms and the prevalence for falls independently of any association with HIV.

Finally in the analysis using the sub-population of PLWH that explored the association of HIV-specific factors with falls, I found that a history of diagnosis with an AIDS-defining illness, time since HIV diagnosis, and current use of NNRTI and INSTI regimens were associated with increased falls in the univariable analyses. In the multivariable analysis I found that only the increased number of total co-medications and the use of INSTIs remained significantly associated with increased fall risk. This may be explained by the fact that use of INSTIs may result in side effects such as neuropsychiatric symptoms, sleep disturbances and dizziness (304-308) that could subsequently result in a higher risk for falls. Polypharmacy (expressed as number of total co-medications excluding cART) is more common among PLWH (656) and has been associated with an increased risk for falls that require medical attention (295, 298, 655). This association may be better explained by the fact that an increased number of co-medications among PLWH is an indication of poor clinical condition and increased number of co-occurring comorbidities. Furthermore, an increased number of co-medications in combination with cART has been reported to induce serious drug-drug interactions (657, 658). More specifically Nachega *et al.* (657), have shown that cART, cardiovascular medications, alpha-antagonist and nervous system co-medications interact causing side effects such as dizziness and loss of balance, which both lead to increased risk for falls among PLWH. Furthermore, a recent study by Siefried *et al.* (659) has shown that polypharmacy among PLWH was associated with higher odds of fatigue and peripheral neuropathy, adverse events that also may increase the risk for falls. Although the above may explain the association between

polypharmacy and falls, the causal pathway of this association cannot be definitive since the increased prevalence of falls among PLWH may be responsible for increasing the number of total co-medications.

The lack of association of the other HIV-specific factors with falls may be explained by the fact that the POPPY PLWH are not very old (median age=52, IQR (47, 59)) and therefore still maintain a good physical functioning. Furthermore, the majority have been treated for a prolonged period of time and have achieved immune status reconstitution. More specifically the median time since HIV diagnosis was 13.2 years, the median time since cART initiation was 9.5 years and 90% have achieved an undetectable VL at the time of assessment. Therefore, their current HIV-specific factors may not have a significant effect on the prevalence of falls and recurrent falls. Similar results have been reported by Erlandson *et al.* who also found no association of falls with current or nadir CD4 count or VL among well-treated PLWH (257). The lack of an independent association of HIV-serostatus with falls, contrasts the results seen in other studies (660, 661). This may be due to the increased burden of fall risk factors such as comorbidities and a greater number of medications reported in other studies assessing the general population.

The analysis or recurrent falls yielded similar results with the analyses of any fall, which was what I anticipated considering the 72.3% overlap between the prevalence of any falls and recurrent falls in the older POPPY groups. Furthermore, the outcome of recurrent falls has removed a lot of the random variation by excluding those with a single fall which could have been a random/accidental fall which has resulted in revealing a stronger association with HIV.

6.7.1 Limitations

A limitation relating to the Chapter 6, is the self-reported nature of data collection that may introduce recall bias. This bias is introduced from the ability or inability of study participants to accurately recall a past event which can lead to inaccurate reporting of fall prevalence. Under-reporting is expected to be greater among older

participants considering the deterioration of memory with ageing (662). Whilst it is difficult to quantify the degree to which the recall bias has affected the data accuracy, it is important to note that the recall window for falls in POPPY was 28 days. This may be a short time frame to capture recurrent falls however it reduces the chances of forgetting a fall. Furthermore, having a short recall time frame may have assisted in reducing random/accidental falls which may have happened over a wider time frame.

An additional limitation of Chapter 6 is the lack of environmental, weather and season data that may play an important role in the prevalence of falls. These data were not routinely collected among the POPPY participants. The cause of the falls was the only information that could sometimes provide environmental data to a certain extent (e.g. fell due to ice on road). Studies have shown that winter months are associated with higher risk for falls among the elderly due to higher risk of slipping on icy pavements and roads, heavy clothing, lack of vitamin D (663-665). Yet I do not expect that this could bias the results, considering that the baseline study visit was conducted over a period that covered all seasons/months between the spring of 2013 (April) and the winter of 2016 (February).

Finally, another important limitation of this chapter was the limited statistical power. The small number of participants with a history of falls who had more severe depressive symptoms was very small which may explain why the model exploring the interaction between HIV and depressive symptoms suggested a poorer fit compared to the model without the interaction.

Chapter 7 BMD amongst POPPY participants

7.1 Introduction

In the general population, bone health may be compromised in older people (356, 357). Bone demineralization is a natural process resulting from a decrease of the minerals in bone tissue that is experienced by all humans after reaching their peak bone density at the age of 20 to 25 years. In the general population, reduced BMD has been identified as a risk factor for fractures (359) and individuals with a history of hip fracture have been reported to have an increased functional disability, a longer functional healing, high depressive symptoms following a fracture and high risk of institutionalization and mortality (666, 667). More specifically, for each standard deviation decrease in BMD, the risk of an osteoporotic fracture has been reported to increase by 1.5 to 3-fold (361, 362) and the risk of mortality by 3-fold (668). Factors such as smoking, inactivity, vitamin D hypovitaminosis and immune and endocrine mechanisms of depression as expressed by lower levels of serotonin, are suggested to induce bone loss and osteoporotic fractures (491, 492).

A higher prevalence of bone disease has been reported in PLWH compared to age-, ethnicity- and sex-matched HIV-negative individuals and there is evidence that the loss of bone mass is 2- to 6-fold higher in PLWH (449). A longitudinal study among PLWH found that the prevalence of osteopenia was 47.5% and the prevalence of osteoporosis 23.0% while progression to bone demineralization was observed in 28% of the PLWH over a median of 2.5 years (543). The prevalence of osteopenia among PLWH has been reported to vary from 22.0% to 67.5% (71, 367, 434), and of osteoporosis from 1.0% to 26.8% (71, 433, 436, 457, 505).

Several studies have confirmed that initiation of cART is associated with a decrease in BMD irrespective of regimen. In a longitudinal study of 96 weeks, TDF exposure during the first 24 weeks of therapy has been associated with a reduced hip BMD up to the 48th week of therapy. From 49 to 96 weeks, BMD either reached a plateau or

improved modestly (669). Compared to other NRTIs, TDF has been associated with 1–3% greater loss of BMD during the first year of cART (500). Several studies have reported that TDF-containing regimens cause an abnormal calcium deposition in both cART-naïve and chronically treated PLWH, which suggests that the effect of TDF on BMD may be independent of the immunological or viral status of the individual (67, 71, 401, 451, 499, 500, 506, 510, 532, 670). Other researchers have suggested that use of PIs (71, 543) and use of TDF boosted with RTV or Cobicistat (COBI) are associated with adverse effects on bone and renal function (671) while others have reported that the use of EFV or TDF/FTC regimens is associated with a lower risk of adverse bone outcomes compared to use of other TDF-containing regimens (672). Switching from TDF to ABC has been reported to have a positive effect on bone tissue, since bone turnover markers appear to decrease (552).

As in the general population, BMD among PLWH is also affected by genetic and lifestyle characteristics such as smoking and alcohol use, weight loss and physical inactivity (365, 543). In addition to recent cART initiation or long-term cART use, increased depressive symptoms, HIV-stigma and alcohol use have been associated with poor adherence to cART, lower BMD and increased fracture risk among PLWH (71, 488, 543, 639, 673-675). Other risk factors for decreased BMD among PLWH include increased age, low BMI, low CD4 count (<350 cells/mm^3), endocrine-related diseases such as androgen/oestrogen deficiency, low testosterone and hypogonadism (461, 470, 485, 487, 518, 565) and renal dysfunction (489).

7.2 Hypotheses

1. There is no difference in BMD T-score between older PLWH and HIV-negative controls
2. The association of HIV with BMD T-score is independent of any associations with frailty and history of falls
3. The association of HIV with BMD T-score is not modified by the association with depressive symptoms
4. HIV-specific factors, such as previous diagnosis of AIDS-defining illness, low current CD4 count, low CD4 nadir and use and duration of specific cART drugs, are associated with a lower BMD T-score
5. There is no difference in BMD T-score between those with low or high plasma concentration of TDF, FTC, ABC and 3TC PK parameters

7.3 Specific objectives

1. To explore whether older PLWH have a lower BMD T-score compared to HIV-negative controls
2. To explore whether the association of HIV with BMD T-score is independent of the association with frailty and history of falls
3. To explore whether the association of HIV with BMD T-score is modified by the association with depressive symptoms
4. In the subgroup of PLWH, to explore the associations of HIV-related parameters (previous diagnosis of AIDS-defining illness, current CD4 count, CD4 nadir, current VL, years since HIV diagnosis, current cART and years since cART initiation) with BMD T-score
5. In the subgroup of PLWH, to investigate whether the concentration of TDF, FTC, ABC and 3TC PK parameters is associated with lower BMD T-scores

7.4 Statistical analysis

For objective 1, the mean and the range of BMD T-scores at LS, FN and TH are reported separately in groups defined by HIV status among the group of older POPPY participants and tested using independent samples T-test. The association of BMD T-scores at LS, FN and TH with HIV was tested using univariable and multivariable linear regression models. The multivariable models were adjusted for the confounders described in Section 4.5.

For objective 2, the mean and the range of BMD T-scores at LS, FN and TH are reported separately in groups defined by frailty and history of falls over the past 28 days. The differences in the distribution of T-scores between the groups is tested for significance using independent samples T-tests. Univariable and multivariable linear regression models were used to assess the whether the association of BMD T-scores at LS, FN and TH with HIV is independent of the association with frailty and history of falls.

For objective 3, similarly to the objective 1 and 2, the mean and the range of BMD T-scores at LS, FN and TH are reported separately in groups defined by depressive symptoms. The differences in the distribution of T-scores between the groups were tested for significance using independent samples T-tests. Univariable and multivariable linear regression models were used to assess the whether the association of BMD T-scores at LS, FN and TH with HIV is modified by the association with depressive symptoms. The fit of the multivariable regression models with and without the interaction of HIV with depressive symptoms adjusted for the standard confounders described in Section 4.5 were compared using the Bayesian Information Criterion (BIC) to determine the model with the best fit.

For objectives 4, the subgroup of PLWH was selected and the association of HIV-specific factors with BMD was explored. The mean and SD of BMD T-scores at each site were reported in the different groups of HIV-specific factors and any differences in their distributions were tested for significance using ANOVA and

independent samples T-tests. The linearity of the association of the ordinal variables with BMD T-score was tested using a trend test. Factors that were significantly associated with BMD T-score at each site in the univariable analysis were then considered in multivariable analysis.

For objective 5, the subgroup of PLWH was used and the PK parameters $AUC_{0\text{-}24}$, C_{max}, C_{min} and CL_{24} of TDF, FTC, ABC and 3TC were categorised into five groups using the quintiles of their distributions. First, a contingency table was used to describe some baseline characteristics of the study participants that were taking the investigated drug stratified by whether PK data were available or not. Subsequently, the mean and SD of BMD T-scores at LS, FN and TH were reported for each group and the distribution of their values across the groups were compared using ANOVA. Univariable and multivariable linear regression models further explored the associations of the PK parameters with BMD T-score at each site after controlling for the confounders: POPPY group, ethnicity, gender, BMI, current smoking, current use of alcohol, history of recreational drugs use in the past 6 months and total number of co-medications.

7.5 Results

7.5.1 The associations of BMD with HIV

In this section I explored the association of HIV with BMD T-score. Both the univariable models and the models adjusted for the standard confounders suggested that the group of older PLWH had a lower BMD T-scores at LS, FN and TH, compared to HIV-negative controls, Table 7.1.

Table 7.1: Univariable and multivariable associations of LS, FN and TH BMD T-score with HIV

				Univariable models	Multivariable models*
	N	**Mean (SD)**	**p-value**	**β-coeff. (95% CI)**	**β-coeff. (95% CI)**
				LS BMD	
Group			<0.001		
HIV-negative	263	-0.1 (1.6)		Ref.	Ref.
Older PLWH	610	-0.7 (1.4)		-0.59 (-0.80, -0.38)	-0.71 (-0.95, -0.47)
				FN BMD	
Group			<0.001		
HIV-negative	284	-0.5 (1.0)		Ref.	Ref.
Older PLWH	642	-0.9 (1.2)		-0.40 (-0.56, -0.24)	-0.45 (-0.62, -0.28)
				TH BMD	
Group			<0.001		
HIV-negative	267	-0.1 (1.0)		Ref.	Ref.
Older PLWH	595	-0.1 (1.6)		-0.47 (-0.63, -0.31)	-0.57 (-0.74, -0.40)

*Adjusted for age, gender, ethnicity, education and marital status

7.5.2 The associations of BMD with frailty and falls

In section exploring the association of frailty and history of falls in the past 28 days with the BMD T-scores I found that the the mean BMD T-score at LS did not differ significantly between those who were frail and those who were not frail (mean (SD) -0.6 (1.6) vs. -0.5 (1.4), P=0.24) nor between those with and without a history of falls in the past 28 days (-0.6 (1.4) vs. -0.5 (1.5), P=0.18, Table 7.2). Therefore, the association of BMD T-score at LS with frailty and falls was not further tested. However, both at FN and at TH the mean BMD T-score was significantly lower among frail study participants compared to non-frail participants (-1.3 (1.0) vs. -0.8 (1.2), P<0.001 at FN and -0.8 (1.0) vs. -0.4 (1.1), P=0.01 at TH). The mean BMD T-score at FN and TH was significantly lower among those with a history of falls in the past 28

days compared to those without (-1.1 (1.3) vs. -0.8 (1.1), P=0.004 at FN and -0.7 (1.1) vs. -0.4 (1.1), P=0.004 at TH, Table 7.2).

The multivariable analyses suggested that HIV was significantly associated with a lower BMD T-score at FN and TH independently of the association with frailty (Table 7.3) and history of falls (Table 7.4).

Table 7.2: Mean (SD) of BMD at LS, FN and TH among POPPY participants stratified by frailty and history of falls

	Lumbar spine			Femoral neck			Total hip		
	n	**Mean (SD)**	**p-value**	**n**	**Mean (SD)**	**p-value**	**n**	**Mean (SD)**	**p-value**
Frailty			0.24			<0.001			0.01
No	623	-0.5 (1.4)		654	-0.8 (1.2)		609	-0.4 (1.1)	
Yes	74	-0.6 (1.6)		75	-1.3 (1.0)		73	-0.8 (1.0)	
Unknown	176	-0.5 (1.5)		197	-0.8 (1.0)		180	-0.5 (1.0)	
History of falls in the past 28 days			0.18			0.004			0.004
No	729	-0.5 (1.5)		775	-0.8 (1.1)		717	-0.4 (1.1)	
Yes	120	-0.6 (1.4)		125	-1.1 (1.3)		121	-0.7 (1.1)	
Unknown	24	-1.1 (1.3)		26	-1.0 (1.0)		24	-0.7 (1.0)	

Table 7.3: Univariable and multivariable associations of FN and TH BMD T-score with frailty

	FN		TH	
	Univariable models	**Multivariable model***	**Univariable models**	**Multivariable model***
	β-coeff. (95% CI)	**β-coeff. (95% CI)**	**β-coeff. (95% CI)**	**β-coeff. (95% CI)**
Group				
HIV-negative	Ref.	Ref.	Ref.	Ref.
Older PLWH	-0.40 (-0.56, -0.24)	-0.37 (-0.57, -0.16)	-0.47 (-0.63, -0.31)	-0.52 (-0.72, -0.32)
Frailty				
No	Ref.	Ref.	Ref.	Ref.
Yes	-0.50 (-0.79, -0.22)	-0.40 (-0.69, -0.11)	-0.35 (-0.63, -0.08)	-0.27 (-0.54, 0.01)

*Adjusted for age, gender, ethnicity, education and marital status

Table 7.4: Univariable and multivariable associations of FN and TH BMD T-score with history of falls in the past 28 days

	FN		TH	
	Univariable models	**Multivariable model***	**Univariable models**	**Multivariable model***
	β-coeff. (95% CI)	**β-coeff. (95% CI)**	**β-coeff. (95% CI)**	**β-coeff. (95% CI)**
Group				
HIV-negative	Ref.		Ref.	
Older PLWH	-0.40 (-0.56, -0.24)	-0.42 (-0.60, -0.25)	-0.47 (-0.63, -0.31)	-0.54 (-0.71, -0.37)
History of falls in the past 28 days				
No	Ref.	Ref.	Ref.	Ref.
Yes	-0.32 (-0.54, -0.11)	-0.25 (-0.47, -0.03)	-0.31 (-0.52, -0.10)	-0.22 (-0.44, -0.01)

*Adjusted for age, gender, ethnicity, education and marital status

7.5.3 HIV depressive symptoms and BMD

In this section, I explored whether the association of HIV with BMD T-scores was modified by the association with depressive symptoms as assessed by CES-D and PHQ-9 scores. In the univariable analysis, the BMD T-score at all sites was significantly lower among those with severe depressive symptoms compared to those with moderate or none-mild depressive symptoms suggesting a dose-response relationship of BMD T-scores with CES-D (Table 7.6, Table 7.7, Table 7.8). A similar dose-response relationship was obtained for the association of BMD T-scores with PHQ-9 without reaching the level of significance. The estimates though still suggested a linear association between the severity of symptoms and BMD T-scores, with lower T-scores in those with greater depressive symptoms.

In the multivariable models, the association of HIV with a lower BMD T-score was consistent for all sites. However, the associations of CES-D and PHQ-9 with BMD T-score at all sites were attenuated after adjusting for the risk factors described in Section 4.5. In particular, compared to those with none/mild symptoms, those with moderate or severe symptoms did not have a significantly lower BMD T-score at either site (Table 7.6, Table 7.7, Table 7.8).

The models without the interaction terms were a better fit compared to the models with the interaction term at all sites. This was confirmed using the Bayesian Information Criterion (BIC) which was consistently lower in all models without the interaction term compared to the models with the interaction term, Table 7.5.

Table 7.5: Model selection among multivariable models with and without the interaction of HIV with depressive symptoms as assessed by CES-D and PHQ-9 scores

		Model without the interaction	Model with interaction
		BIC*	BIC*
LS	CES-D	2865.0	2877.4
	PHQ-9	2939.9	2963.4
FN	CES-D	2531.8	2544.8
	PHQ-9	2649.2	2673.4
TH	CES-D	2343.9	2356.7
	PHQ-9	2403.0	2427.2

* Bayesian Information Criterion

Table 7.6: Mean (SD) of BMD T-score at LS and univariable and multivariable associations with depressive symptoms as assessed by CES-D and PHQ-9 scores

	BMD T-score			Univariable models	Multivariable model*	Multivariable model**
	n	Mean (SD)	p-value	β-coeff. (95% CI)	β-coeff. (95% CI)	β-coeff. (95% CI)
Group			<0.001			
HIV-negative	263	-0.1 (1.6)		Ref.	Ref.	Ref.
Older PLWH	610	-0.7 (1.4)		-0.59 (-0.80, -0.38)	-0.69 (-0.95, -0.43)	-0.64 (-0.92, -0.36)
Levels of depressive symptoms (CES-D)			0.01			
No to mild (0-15)	535	-0.4 (1.5)		Ref.	Ref.	Ref.
Moderate (16-23)	100	-0.6 (1.4)		-0.18 (-0.50, 0.14)	-0.07 (-0.39, 0.26)	0.20 (-0.45, 0.85)
Severe (24-60)	143	-0.8 (1.4)		-0.40 (-0.68, -0.13)	-0.23 (-0.53, 0.07)	-0.12 (-1.07, 0.83)
Unknown	95	-0.6 (1.4)		-	-	
Group			<0.001			
HIV-negative	263	-0.1 (1.6)		Ref.	Ref.	Ref.
Older PLWH	610	-0.7 (1.4)		-0.59 (-0.80, -0.38)	-0.73 (-0.98, -0.48)	-0.71 (-0.99, -0.43)
Levels of depressive symptoms (PHQ-9)			0.26			
Minimal (1-4)	490	-0.4 (1.5)		Ref.	Ref.	Ref.
Mild (5-9)	149	-0.5 (1.5)		-0.08 (-0.35, 0.19)	0.03 (-0.24, 0.31)	0.15 (-0.42, 0.71)
Moderate (10-14)	89	-0.7 (1.3)		-0.23 (-0.57, 0.10)	-0.01 (-0.36, 0.33)	-0.37 (-1.26, 0.52)
Moderately severe (15-19)	49	-0.8 (1.2)		-0.39 (-0.82, 0.05)	-0.15 (-0.61, 0.30)	0.35 (-1.33, 2.02)
Severe (20-27)	26	-0.8 (1.6)		-0.34 (-0.93, 0.24)	-0.14 (-0.74, 0.46)	1.22 (-0.84, 3.28)
Unknown	70	-0.8 (1.5)		-	-	

*Adjusted for age, gender, ethnicity, education and marital status

**further adjusted for the interaction of HIV and depressive symptoms

Table 7.7: Mean (SD) of BMD T-score at FN and univariable and multivariable associations with depressive symptoms as assessed by CES-D and PHQ-9 scores

	BMD T-score			Univariable models	Multivariable model*	Multivariable model**
	n	Mean (SD)	p-value	β-coeff. (95% CI)	β-coeff. (95% CI)	β-coeff. (95% CI)
Group			<0.001			
HIV-negative	284	-0.5 (1.0)		Ref.	Ref.	Ref.
Older PLWH	642	-0.9 (1.2)		-0.40 (-0.56, -0.24)	-0.40 (-0.58, -0.23)	-0.38 (-0.58, -0.19)
Levels of depressive symptoms (CES-D)			0.007			
No to mild (0-15)	575	-0.7 (1.2)		Ref.	Ref.	Ref.
Moderate (16-23)	106	-0.9 (1.0)		-0.19 (-0.42, 0.05)	-0.13 (-0.36, 0.10)	0.00 (-0.44, 0.45)
Severe (24-60)	149	-1.0 (1.1)		-0.31 (-0.52, -0.11)	-0.27 (-0.48, -0.05)	-0.25 (-0.91, 0.40)
Unknown	96	-0.7 (1.3)		-	-	
Group			<0.001			
HIV-negative	284	-0.5 (1.0)		Ref.	Ref.	Ref.
Older PLWH	642	-0.9 (1.2)		-0.40 (-0.56, -0.24)	-0.42 (-0.60, -0.24)	-0.37 (-0.57, -0.17)
Levels of depressive symptoms (PHQ-9)			0.16			
Minimal (1-4)	527	-0.7 (1.2)		Ref.	Ref.	Ref.
Mild (5-9)	153	-0.8 (1.2)		-0.04 (-0.25, 0.17)	0.03 (-0.17, 0.23)	0.31 (-0.10, 0.72)
Moderate (10-14)	92	-1.1 (1.1)		-0.32 (-0.58, -0.07)	-0.23 (-0.49, 0.02)	-0.32 (-0.97, 0.32)
Moderately severe (15-19)	53	-0.8 (1.0)		-0.03 (-0.36, 0.29)	-0.11 (-0.45, 0.22)	0.01 (-1.08, 1.10)
Severe (20-27)	29	-0.9 (1.1)		-0.18 (-0.61, 0.25)	-0.25 (-0.67, 0.18)	-0.50 (-2.05, 1.05)
Unknown	72	-0.9 (1.1)		-	-	

*Adjusted for age, gender, ethnicity, education and marital status

**further adjusted for the interaction of HIV and depressive symptoms

Table 7.8: Mean (SD) of BMD T-score at TH and univariable and multivariable associations with depressive symptoms as assessed by CES-D and PHQ-9 scores

	Total hip			Univariable models	Multivariable model*	Multivariable model**
	n	Mean (SD)	p-value	β-coeff. (95% CI)	β-coeff. (95% CI)	β-coeff. (95% CI)
Group			<0.001			
HIV-negative	267	-0.1 (1.0)		Ref.	Ref.	Ref.
Older PLWH	595	-0.1 (1.6)		-0.47 (-0.63, -0.31)	-0.54 (-0.73, -0.36)	-0.53 (-0.73, -0.33)
Levels of depressive symptoms (CES-D)			0.05			
No to mild (0-15)	528	-0.4 (1.1)		Ref.	Ref.	Ref.
Moderate (16-23)	98	-0.5 (1.0)		-0.10 (-0.34, 0.14)	-0.01 (-0.25, 0.22)	0.12 (-0.34, 0.58)
Severe (24-60)	143	-0.7 (1.2)		-0.26 (-0.46, -0.05)	-0.15 (-0.37, 0.06)	-0.23 (-0.88, 0.42)
Unknown	93	-0.5 (0.9)		-	-	
Group			<0.001			
HIV-negative	267	-0.1 (1.0)		Ref.	Ref.	Ref.
Older PLWH	595	-0.1 (1.6)		-0.47 (-0.63, -0.31)	-0.57 (-0.75, -0.39)	-0.53 (-0.73, -0.33)
Levels of depressive symptoms (PHQ-9)			0.55			
Minimal (1-4)	487	-0.4 (1.1)		Ref.	Ref.	Ref.
Mild (5-9)	141	-0.4 (1.1)		0.01 (-0.20, 0.21)	0.07 (-0.13, 0.28)	0.32 (-0.08, 0.73)
Moderate (10-14)	89	-0.6 (1.1)		-0.14 (-0.39, 0.11)	-0.01 (-0.26, 0.24)	-0.17 (-0.82, 0.47)
Moderately severe (15-19)	49	-0.4 (1.1)		-0.01 (-0.33, 0.32)	0.02 (-0.31, 0.35)	0.05 (-0.99, 1.10)
Severe (20-27)	28	-0.7 (1.2)		-0.30 (-0.72, 0.12)	-0.28 (-0.70, 0.14)	-0.21 (-1.70, 1.28)
Unknown	68	-0.6 (1.1)		-	-	

*Adjusted for age, gender, ethnicity, education and marital status

**further adjusted for the interaction of HIV and depressive symptoms

7.5.4 The association of HIV-specific factors with BMD among PLWH

In this section, I explore the association of HIV-specific parameters with BMD T-score at LS, FN and TH. The mean and SD of BMD T-score at each site stratified by HIV-specific characteristics is presented in Table 7.9. I found no differences in the mean BMD T-score at LS among different levels of HIV-specific factors. However, the mean BMD T-score was significantly lower among study participants on ETR (mean (SD), -1.1 (1.2)), followed by those on EFV (-0.7 (1.3)) and those on RPV (-0.6 (1.5)), while those on NVP had the highest BMD T-score among those on NNRTIs (-0.2 (1.4), P<0.001).

The BMD T-score at FN was significantly lower among those with previous diagnosis of an AIDS-defining illness compared to those without (-0.9 (1.3) vs. -0.7 (1.2), P=0.02). Among those with an undetectable VL, the BMD T-score at FN was significantly lower compared to those with detectable VL (-0.8 (1.2) vs. -0.4 (1.2), P=0.002). The mean BMD T-score at FN was increasingly lower for increased time since HIV diagnosis, longer time on ART and increased number of total co-medications (P<0.001, P<0.001 and P=0.002, respectively). Amongst PLWH, those who were on an ABC/3TC NRTI regimen had significantly higher BMD T-score, compared to those not on NRTIs and those on TDF/FTC or other NRTIs (-0.6 (1.1) vs. -0.8 (1.3), -0.8 (1.2) and -1.0 (1.1), P=0.05). Finally, those taking an INSTI-containing regimen had a significantly lower BMD T-score at FN, compared to those not on INSTIs (-1.0 (1.1) vs. -0.7 (1.2), P=0.02).

At TH, the BMD T-score was increasingly lower for increasing length of time since HIV diagnosis (P=0.02). Furthermore, the BMD T-score at TH was significantly lower among those with an undetectable VL compared to those with detectable VL (-0.6 (1.1) vs. -0.3 (1.1), P=0.02) and among those taking boosted PIs compared to those taking unboosted PIs (-0.7 (1.0) vs. -0.5 (1.2), P=0.05). The study participants that were on an ETR-containing regimen had significantly lower BMD T-score at TH (-0.7 (1.1)), compared to those not on NNRTIs (-0.6 (1.0)), those on EFV (-0.5 (1.2)), RPV (-0.4 (1.1)) and NVP (-0.3 (1.1), P=0.03). Despite no evidence of associations at the

5% level, those with more years on ART and those not taking any NRTIs had a lower BMD T-score (P=0.08 and P=0.08, respectively).

Finally, after inspecting the summary statistics reported in the Table 7.9, I performed a test for trend and I confirmed that the relationship of years on ART and years since HIV-diagnosis with BMD T-score at FN was linear (P_{trend}<0.001). Therefore, for the univariable and multivariable linear regression models both years on ART and years since HIV-diagnosis are expressed as continuous variables, with estimates scaled to reflect a five-year increment in each value. All other factors that were significantly associated with BMD T-score at each site in the univariable models, were included in the multivariable analysis.

Table 7.9: Mean (SD) of BMD at LS, FN and TH, stratified by HIV-specific characteristics of the PLWH in POPPY participants

	LS n=1262			FN n=1264			TH n=1189		
	n	**Mean (SD)**	**p-value**	**N**	**Mean (SD)**	**p-value**	**N**	**Mean (SD)**	**p-value**
Previous diagnosis of AIDS-defining illness			0.19			0.02			0.20
No	664	-0.6 (1.4)		700	-0.7 (1.2)		644	-0.5 (1.0)	
Yes	280	-0.7 (1.4)		291	-0.9 (1.3)		272	-0.6 (1.2)	
CD4 count (cells/mm^3)			0.27			0.17			0.43
≤448	179	-0.5 (1.6)		194	-0.7 (1.3)		176	-0.5 (1.2)	
449-570	188	-0.6 (1.4)		196	-0.7 (1.1)		175	-0.6 (1.0)	
571-698	184	-0.7 (1.2)		192	-0.9 (1.0)		178	-0.6 (1.0)	
699-874	186	-0.6 (1.4)		192	-0.7 (1.5)		184	-0.5 (1.2)	
≥875	184	-0.8 (1.2)		194	-0.9 (1.1)		183	-0.6 (1.0)	
Unknown	23	-0.8 (1.1)		23	-0.8 (1.1)		20	-0.6 (1.0)	
CD4 nadir (cells/mm^3)			0.74			0.11			0.32
≤80	182	-0.7 (1.5)		196	-0.9 (1.2)		178	-0.6 (1.1)	
81-168	180	-0.7 (1.4)		184	-0.9 (1.4)		175	-0.6 (1.2)	
169-243	188	-0.6 (1.4)		193	-0.7 (1.3)		177	-0.5 (1.1)	
244-347	178	-0.7 (1.3)		187	-0.7 (1.1)		167	-0.6 (1.0)	
≥348	180	-0.6 (1.3)		190	-0.7 (1.1)		180	-0.4 (1.0)	
Unknown	36	-0.5 (1.2)		41	-0.7 (0.9)		39	-0.3 (1.1)	
VL			0.23			0.002			0.02
Detectable	90	-0.5 (1.4)		96	-0.4 (1.2)		88	-0.3 (1.1)	
Undetectable	849	-0.7 (1.4)		891	-0.8 (1.2)		823	-0.6 (1.1)	
Unknown	5	-1.0 (1.3)		4	-0.4 (0.8)		5	0.2 (1.3)	
Time since HIV diagnosis (yrs)			0.42			<0.001			0.02
≤6.4	184	-0.5 (1.4)		196	-0.5 (1.1)		187	-0.4 (1.1)	
6.5-11.1	188	-0.6 (1.3)		197	-0.6 (1.1)		170	-0.5 (1.0)	
11.2-15.8	188	-0.6 (1.4)		196	-0.7 (1.4)		176	-0.5 (1.2)	

	LS n=1262			FN n=1264			TH n=1189		
	n	**Mean (SD)**	**p-value**	**N**	**Mean (SD)**	**p-value**	**N**	**Mean (SD)**	**p-value**
15.9-21.9	189	-0.6 (1.5)		197	-1.0 (1.2)		188	-0.6 (1.2)	
≥22.0	187	-0.8 (1.3)		197	-1.1 (1.1)		189	-0.7 (1.0)	
Unknown	8	-1.1 (1.1)		8	-0.5 (0.8)		6	0.1 (1.1)	
Years on ART			0.72			<0.001			0.08
≤3.9	184	-0.7 (1.3)		195	-0.6 (1.0)		188	-0.5 (1.0)	
4.0-7.3	183	-0.7 (1.3)		192	-0.7 (1.2)		174	-0.5 (1.1)	
7.4-12.2	187	-0.5 (1.4)		194	-0.6 (1.5)		175	-0.4 (1.2)	
12.3-17.1	187	-0.7 (1.5)		194	-0.9 (1.2)		176	-0.6 (1.1)	
≥17.2	184	-0.6 (1.4)		195	-1.1 (1.0)		186	-0.7 (1.0)	
Unknown	19	-0.1 (1.3)		21	-0.4 (0.9)		17	-0.3 (1.0)	
Total number of co-medications (excluding cART)			0.23			0.002			0.15
0	289	-0.5 (1.4)		301	-0.6 (1.3)		277	-0.4 (1.1)	
1-4	433	-0.7 (1.3)		452	-0.8 (1.1)		420	-0.6 (1.0)	
5-9	172	-0.8 (1.5)		183	-0.9 (1.2)		168	-0.6 (1.2)	
≥10	50	-0.6 (1.4)		55	-1.1 (1.4)		51	-0.7 (1.0)	
NRTI backbone			0.23			0.05			0.08
None	127	-0.5 (1.4)		136	-0.8 (1.3)		126	-0.6 (1.0)	
TDF/FTC	588	-0.7 (1.4)		617	-0.8 (1.2)		564	-0.5 (1.1)	
ABC/3TC	123	-0.5 (1.4)		128	-0.6 (1.1)		123	-0.3 (1.1)	
Other	106	-0.7 (1.4)		110	-1.0 (1.1)		103	-0.7 (1.1)	
PIs			0.24			0.14			0.05
None	555	-0.6 (1.4)		584	-0.8 (1.2)		540	-0.5 (1.1)	
Boosted PIs	302	-0.8 (1.3)		312	-0.9 (1.2)		293	-0.7 (1.0)	
Unboosted PIs	87	-0.6 (1.4)		95	-0.6 (1.4)		83	-0.5 (1.2)	
NNRTIs			<0.001			0.21			0.03
None	466	-0.7 (1.3)		489	-0.8 (1.1)		447	-0.6 (1.0)	

	LS n=1262			FN n=1264			TH n=1189		
	n	**Mean (SD)**	**p-value**	**N**	**Mean (SD)**	**p-value**	**N**	**Mean (SD)**	**p-value**
EFV	235	-0.7 (1.3)		242	-0.8 (1.3)		221	-0.5 (1.2)	
NVP	121	-0.2 (1.4)		126	-0.6 (1.1)		118	-0.3 (1.1)	
RPV	73	-0.6 (1.5)		78	-0.7 (1.2)		75	-0.4 (1.1)	
ETR	49	-1.1 (1.2)		56	-1.0 (1.6)		55	-0.7 (1.1)	
INSTIs			0.55			0.02			0.14
No	813	-0.6 (1.4)		852	-0.7 (1.2)		785	-0.5 (1.1)	
Yes	131	-0.7 (1.4)		139	-1.0 (1.1)		131	-0.7 (1.1)	

The only HIV-specific factor associated with BMD at LS was the use of NNRTIs, therefore this was the only factor that was tested further in multivariable linear regression models. The associations remained significant in the multivariable analysis after adjustment for age, BMI and smoking, suggesting that those on NVP compared to those not on NNRTIs had significantly higher BMD T-score at LS (β-coeff.=0.50, 95% CI (0.23, 0.77), Table 7.10.

Table 7.10: Univariable and multivariable associations of LS BMD T-score with HIV-specific confounders

	Univariable models	Multivariable model*
	β-coeff. (95% CI)	**β-coeff. (95% CI)**
NNRTIs in regimen		
None	Ref.	Ref.
EFV	0.04 (-0.18, 0.25)	0.01 (-0.20, 0.22)
NVP	0.55 (0.28, 0.82)	0.50 (0.23, 0.77)
RPV	0.14 (-0.20, 0.47)	0.07 (-0.26, 0.41)
ETR	-0.38 (-0.79, 0.02)	-0.33 (-0.73, 0.06)

*Multivariable model adjusted for age, BMI and smoking

In the multivariable analysis of the FN BMD T-score, all associations that were significant in univariable analysis were attenuated and became non-significant in the multivariable model. However, despite not reaching the level of significance, previous diagnosis of AIDS-defining illness suggested an association with lower BMD T-score (β-coeff.=-0.18, 95% CI (-0.36, 0.00), Table 7.11).

Table 7.11: Univariable and multivariable associations of FN BMD T-score with HIV-specific confounders

	Univariable models	Multivariable model*
	β-coeff. (95% CI)	**β-coeff. (95% CI)**
Previous diagnosis of AIDS-defining illness		
No	Ref.	Ref.
Yes	-0.19 (-0.35, -0.03)	-0.18 (-0.36, 0.00)
VL		
Undetectable	Ref.	Ref.
Detectable	-0.40 (-0.65, -0.15)	-0.15 (-0.43, 0.12)
Years on ART (per 5 years)	-0.16 (-0.22, -0.10)	-0.06 (-0.15, 0.04)
Time since HIV diagnosis (/5 years)	-0.13 (-0.18, -0.09)	0.01 (-0.06, 0.09)
Total number of co-medications (excluding cART)		
0	Ref.	Ref.
1-4	-0.25 (-0.42, -0.08)	-0.13 (-0.32, 0.06)
5-9	-0.31 (-0.53, -0.10)	-0.17 (-0.41, 0.06)
≥10	-0.54 (-0.88, -0.19)	-0.13 (-0.51, 0.24)
INSTI in regimen		

	Univariable models	Multivariable model*
	β-coeff. (95% CI)	β-coeff. (95% CI)
No	Ref.	Ref.
Yes	-0.25 (-0.47, -0.04)	-0.12 (-0.35, 0.12)

*Adjusted for age, ethnicity, BMI, frailty and falls in the past 28 days

The multivariable analyses of BMD T-score at TH suggested that the only HIV-specific factor that remained significantly associated with BMD T-score at TH was the use of NNRTI. In particular those on NVP compared to those not on any NNRTIs had a significantly higher BMD T-score at TH (β-coeff.=0.30, 95% CI (0.07, 0.54), Table 7.12).

Table 7.12: Univariable and multivariable associations of TH BMD T-score with HIV-specific confounders

	Univariable models	Multivariable model*
	β-coeff. (95% CI)	β-coeff. (95% CI)
VL		
Undetectable	Ref.	Ref.
Detectable	-0.30 (-0.54, -0.05)	-0.24 (-0.48, 0.01)
Time since HIV diagnosis (/5 years)	-0.08 (-0.12, -0.03)	0.00 (-0.06, 0.05)
NNRTI in regimen		
None	Ref.	Ref.
EFV	0.12 (-0.06, 0.29)	0.05 (-0.13, 0.24)
NVP	0.32 (0.10, 0.55)	0.30 (0.07, 0.54)
RPV	0.21 (-0.06, 0.48)	0.23 (-0.04, 0.50)
ETR	-0.11 (-0.42, 0.20)	-0.08 (-0.40, 0.25)

*Adjusted for age, ethnicity, BMI, education, frailty and history of falls in the past 28 days

7.5.5 The association of BMD with PK parameters

7.5.5.1 TDF and PK parameters

In the subgroup of PLWH who were receiving FTC (N=746), 554 (74.3%) provided samples for the assessment of TDF PK parameters. Of those who did provide PK samples, there was a higher proportion of males and those of white ethnicity compared to among those who did not provide PK samples (88.6% (491/554) vs. 78.7% (151/192), P=0.001, and 89.5% (496/554) vs. 68.8% (132/192), P<0.001, respectively). There was a significant difference between those who did and did not provide samples for TDF PK parameters concerning BMI. More specifically, of those who provided PK samples, there was a significantly lower proportion of participants with BMI ≥29.3 kg/m^2 compared to among those who did not provide PK samples (17.5% (97/554) vs. 24.5% (47/192)). Conversely, of those who provided PK samples,

there was a higher proportion of participants with a BMI ≤22.5 kg/m^2 compared to those who did not provide PK samples (21.1% (117/554) vs. 17.2% (33/192), P=0.01). Lastly, among those who did provide PK samples, there was a lower proportion of participants taking 1-4 co-medications and a higher proportion of those taking more than 10 co-medications, compared to those without PK samples (36.1% (200/554) vs. 43.2% (91/192) and 13.2% (73/554) vs. 9.4% (18/192), P=0.02, Table 7.13). Finally, there was no significant difference between those who provided PK samples and those who did not concerning POPPY group, current smoking, current alcohol use and history of recreational drugs.

Table 7.13: Characteristics of POPPY participants on TDF whom samples for PK testing were and were not available

			Samples available for PK testing				
	Total on TDF N=746		No n=192		Yes n=554		
	n	(%)	n	(%)	n	(%)	p-value
Group							0.49
Older PLWH	470	(63.0)	117	(60.9)	353	(63.7)	
Younger PLWH	276	(37.0)	75	(39.1)	201	(36.3)	
Gender							0.001
Female	104	(13.9)	41	(21.4)	63	(11.4)	
Male	642	(86.1)	151	(78.7)	491	(88.6)	
Ethnicity							<0.001
Black African	118	(15.8)	60	(31.3)	58	(10.5)	
White	628	(84.2)	132	(68.8)	496	(89.5)	
BMI (kg/m^2)							0.01
≤22.5	150	(20.1)	33	(17.2)	117	(21.1)	
22.6-24.8	150	(20.1)	36	(18.8)	114	(20.6)	
24.9-26.4	145	(19.4)	31	(16.2)	114	(20.6)	
26.5-29.2	152	(20.4)	41	(21.4)	111	(20.0)	
≥29.3	144	(19.3)	47	(24.5)	97	(17.5)	
Unknown	5	(0.7)	4	(2.1)	1	(0.2)	
Current smoking							0.33
No	546	(73.2)	146	(76.0)	400	(72.2)	
Yes	196	(26.3)	46	(24.0)	150	(27.1)	
Unknown	4	(0.5)	0	(0.0)	4	(0.7)	
Current alcohol use							0.22
No	57	(7.6)	20	(10.4)	37	(6.7)	
Yes	608	(81.5)	150	(78.1)	458	(82.7)	
In the past	81	(10.9)	22	(11.5)	59	(10.7)	
History of recreational drugs use							0.24
No	519	(69.6)	140	(72.9)	379	(68.4)	
Yes	227	(30.4)	52	(27.1)	175	(31.6)	

	Total on TDF N=746		Samples available for PK testing				
			No n=192		Yes n=554		
	n	(%)	n	(%)	n	(%)	p-value
Total number of co-medications							0.02
1-4	291	(39.0)	91	(47.4)	200	(36.1)	
5-9	364	(48.8)	83	(43.2)	281	(50.7)	
≥10	91	(12.2)	18	(9.4)	73	(13.2)	

The mean BMD T-score at all sites was significantly lower in those with higher TDF $AUC_{0\text{-}24h}$, C_{max} and C_{min}, while it was significantly higher among those with lower CL_{24h} values (Table 7.14, Table 7.15, Table 7.16). Results from univariable analysis suggested that higher TDF levels of $AUC_{0\text{-}24h}$, C_{max} and C_{min} were associated with increasingly lower BMD T-scores at LS (Table 7.14), FN (Table 7.15) and TH (Table 7.16). The associations remained significant in multivariable models. Whilst results for C_{max} were similar, for C_{min} the associations were attenuated and became non-significant in multivariable models.

In the univariable analysis higher CL_{24h} levels were associated with higher BMD T-scores at LS (Table 7.14), FN (Table 7.15) and TH (Table 7.16). In the multivariable analyses, the associations at FN and TH remained significant in the multivariable models.

Table 7.14: Mean (SD) BMD T-score at LS and univariable and multivariable associations with TDF PK parameters

				Univariable model	Multivariable model*
	n	Mean (SD)	p-value	β-coef. (95% CI)	β-coef. (95% CI)
$AUC_{0\text{-}24h}$ (mg.h/L)					
≤2.355	95	-0.3 (1.4)	<0.001	Ref.	Ref.
2.356-2.616	98	-0.5 (1.4)		-0.19 (-0.57, 0.19)	-0.14 (-0.53, 0.24)
2.617-2.941	99	-0.8 (1.4)		-0.56 (-0.94, -0.18)	-0.41 (-0.81, -0.02)
2.942-3.410	96	-1.0 (1.2)		-0.75 (-1.13, -0.37)	-0.50 (-0.93, -0.08)
≥3.411	97	-1.0 (1.3)		-0.73 (-1.11, -0.35)	-0.47 (-0.90, -0.03)
C_{max} (mg/L)					
≤0.219	97	-0.2 (1.4)	<0.001	Ref.	Ref.
0.220-0.241	101	-0.5 (1.2)		-0.34 (-0.71, 0.03)	-0.29 (-0.68, 0.11)
0.242-0.263	98	-0.7 (1.5)		-0.53 (-0.90, -0.15)	-0.43 (-0.86, 0.00)
0.264-0.289	92	-1.0 (1.2)		-0.85 (-1.23, -0.47)	-0.67 (-1.13, -0.21)
≥0.290	97	-1.2 (1.2)		-1.04 (-1.42, -0.67)	-0.74 (-1.24, -0.25)
C_{min} (mg/L)					
≤0.042	101	-0.5 (1.4)	0.05	Ref.	Ref.
0.043-0.050	105	-0.6 (1.5)		-0.11 (-0.48, 0.27)	-0.07 (-0.45, 0.30)
0.051-0.058	88	-0.9 (1.3)		-0.42 (-0.81, -0.03)	-0.34 (-0.74, 0.06)
0.059-0.072	96	-0.9 (1.4)		-0.39 (-0.78, -0.01)	-0.22 (-0.63, 0.19)
≥0.073	95	-0.9 (1.2)		-0.48 (-0.87, -0.10)	-0.33 (-0.74, 0.09)
CL_{24h} (L/h)					
≤40.462	97	-1.1 (1.2)	<0.001	Ref.	Ref.
40.463-46.793	94	-1.1 (1.2)		0.05 (-0.33, 0.43)	-0.01 (-0.40, 0.38)
46.794-52.448	100	-0.7 (1.4)		0.37 (0.00, 0.75)	0.20 (-0.20, 0.59)
52.449-58.096	99	-0.5 (1.4)		0.63 (0.26, 1.01)	0.40 (-0.03, 0.83)
≥58.097	95	-0.3 (1.5)		0.85 (0.47, 1.23)	0.57 (0.13, 1.02)

*Adjusted for POPPY group, ethnicity, gender, BMI, current smoking, current use of alcohol, history of recreational drug use in the past 6 months and total number of co-medications

Table 7.15: Mean (SD) BMD T-score at FN and univariable and multivariable associations with TDF PK parameters

	n	Mean (SD)	p-value	Univariable model β-coef. (95% CI)	Multivariable model* β-coef. (95% CI)
$AUC_{0\text{-}24h}$ (mg.h/L)					
≤2.355	102	-0.2 (1.6)	<0.001	Ref.	Ref.
2.356-2.616	101	-0.6 (1.1)		-0.37 (-0.68, -0.06)	-0.23 (-0.53, 0.08)
2.617-2.941	102	-0.8 (0.9)		-0.59 (-0.90, -0.27)	-0.26 (-0.57, 0.05)
2.942-3.410	99	-1.3 (0.9)		-1.05 (-1.36, -0.74)	-0.54 (-0.87, -0.20)
≥3.411	102	-1.2 (1.0)		-0.98 (-1.29, -0.67)	-0.48 (-0.82, -0.14)
C_{max} (mg/L)					
≤0.219	102	-0.3 (1.1)	<0.001	Ref.	Ref.
0.220-0.241	104	-0.6 (1.6)		-0.24 (-0.56, 0.07)	0.01 (-0.31, 0.32)
0.242-0.263	100	-0.8 (1.1)		-0.49 (-0.80, -0.17)	-0.16 (-0.50, 0.18)
0.264-0.289	99	-1.2 (0.8)		-0.83 (-1.15, -0.51)	-0.42 (-0.78, -0.05)
≥0.290	101	-1.3 (1.0)		-0.97 (-1.28, -0.65)	-0.42 (-0.82, -0.03)
C_{min} (mg/L)					
≤0.042	106	-0.3 (1.6)	<0.001	Ref.	Ref.
0.043-0.050	112	-0.7 (1.0)		-0.40 (-0.70, -0.09)	-0.23 (-0.53, 0.06)
0.051-0.058	89	-0.9 (1.1)		-0.54 (-0.87, -0.22)	-0.24 (-0.55, 0.08)
0.059-0.072	99	-1.1 (1.0)		-0.77 (-1.09, -0.45)	-0.33 (-0.66, -0.01)
≥0.073	100	-1.2 (0.9)		-0.86 (-1.18, -0.54)	-0.40 (-0.72, -0.07)
CL_{24h} (L/h)					
≤40.462	102	-1.4 (0.9)	<0.001	Ref.	Ref.
40.463-46.793	98	-1.3 (0.9)		0.06 (-0.25, 0.38)	-0.02 (-0.33, 0.28)
46.794-52.448	103	-0.7 (0.9)		0.63 (0.33, 0.94)	0.38 (0.06, 0.69)
52.449-58.096	101	-0.5 (1.6)		0.88 (0.57, 1.19)	0.50 (0.16, 0.83)
≥58.097	102	-0.3 (1.1)		1.07 (0.76, 1.38)	0.57 (0.22, 0.91)

*Adjusted for POPPY group, ethnicity, gender, BMI, current smoking, current use of alcohol, history of recreational drug use in the past 6 months and total number of co-medications

Table 7.16: Mean (SD) BMD T-score at TH and univariable and multivariable associations with TDF PK parameters

				Univariable model	Multivariable model*
	n	Mean (SD)	p-value	β-coef. (95% CI)	β-coef. (95% CI)
$AUC_{0\text{-}24h}$ (mg.h/L)					
≤2.355	94	0.0 (1.3)	<0.001	Ref.	Ref.
2.356-2.616	96	-0.4 (1.1)		-0.38 (-0.68, -0.08)	-0.21 (-0.50, 0.08)
2.617-2.941	98	-0.5 (0.9)		-0.46 (-0.76, -0.16)	-0.12 (-0.42, 0.18)
2.942-3.410	92	-1.0 (0.9)		-0.97 (-1.28, -0.67)	-0.47 (-0.79, -0.15)
≥3.411	96	-1.0 (1.0)		-0.98 (-1.28, -0.68)	-0.49 (-0.82, -0.16)
C_{max} (mg/L)					
≤0.219	96	0.0 (1.1)	<0.001	Ref.	Ref.
0.220-0.241	100	-0.3 (1.2)		-0.29 (-0.58, 0.00)	-0.01 (-0.31, 0.29)
0.242-0.263	91	-0.6 (1.0)		-0.59 (-0.89, -0.29)	-0.14 (-0.47, 0.18)
0.264-0.289	94	-0.9 (0.8)		-0.87 (-1.17, -0.57)	-0.35 (-0.69, 0.00)
≥0.290	95	-1.1 (1.1)		-1.14 (-1.43, -0.84)	-0.51 (-0.88, -0.13)
C_{min} (mg/L)					
≤0.042	100	-0.2 (1.3)	<0.001	Ref.	Ref.
0.043-0.050	104	-0.4 (1.1)		-0.26 (-0.56, 0.05)	-0.12 (-0.41, 0.16)
0.051-0.058	84	-0.6 (1.0)		-0.45 (-0.77, -0.14)	-0.21 (-0.51, 0.10)
0.059-0.072	93	-0.7 (1.1)		-0.51 (-0.82, -0.20)	-0.18 (-0.49, 0.13)
≥0.073	95	-0.9 (0.9)		-0.75 (-1.06, -0.44)	-0.39 (-0.70, -0.07)
CL_{24h} (L/h)					
≤40.462	96	-1.1 (0.9)	<0.001	Ref.	Ref.
40.463-46.793	93	-1.0 (0.9)		0.18 (-0.12, 0.48)	0.11 (-0.18, 0.40)
46.794-52.448	95	-0.4 (0.9)		0.73 (0.44, 1.03)	0.53 (0.23, 0.83)
52.449-58.096	98	-0.3 (1.3)		0.82 (0.53, 1.12)	0.45 (0.13, 0.78)
≥58.097	94	-0.1 (1.1)		1.07 (0.77, 1.37)	0.56 (0.23, 0.90)

*Adjusted for POPPY group, ethnicity, gender, BMI, current smoking, current use of alcohol, history of recreational drug use in the past 6 months and total number of co-medications

7.5.5.2 FTC and PK parameters

In the subgroup of PLWH that were on FTC (N=691), 516/691 (74.7%) provided samples for the assessment of the FTC PK parameters and 175/691 (25.3%) did not.

Among those who did provide PK samples, there was a higher proportion of males and participants of white ethnicity, compared to among those who did not provide PK samples (89.4% (463/516) vs. 79.2% (137/175), P=0.001 and 90.0% (466/516) vs. 69.9% (121/175), P<0.001, respectively). Furthermore, among those who provided PK samples for FTC, there was a lower proportion of participants with BMI ≥29.2 kg/m^2 compared to those without PK samples (17.6% (91/516) vs. 25.4% (44/175), P<0.001). Finally, among those who provided a PK sample, the proportion of those who were taking ≥10 co-medications was significantly higher compared to that among those without FTC PK samples (12.0% (62/516) vs. 8.7% (15/175), P=0.03). There were no significant differences between those who did and did not provide samples for PK analysis in relation to POPPY group, current smoking and alcohol use and history of recreational drugs in the past 6 months (Table 7.17).

Table 7.17: Characteristics of POPPY participants on FTC whom samples for PK testing were and were not available

			Samples available for PK testing				
	Total on FTC N=691		**No** N=175		**Yes** N=516		
	n	(%)	n	(%)	n	(%)	**p-value**
Group							0.40
Older PLWH	430	(62.2)	103	(59.5)	327	(63.1)	
Younger PLWH	261	(37.8)	70	(40.5)	191	(36.9)	
Gender							0.001
Female	91	(13.2)	36	(20.8)	55	(10.6)	
Male	600	(86.8)	137	(79.2)	463	(89.4)	
Ethnicity							<0.001
Black African	104	(15.1)	52	(30.1)	52	(10.0)	
White	587	(85.0)	121	(69.9)	466	(90.0)	
BMI (kg/m^2)							0.001
≤22.6	138	(20.0)	29	(16.8)	109	(21.0)	
22.7-24.9	144	(20.8)	38	(22.0)	106	(20.5)	
25.0-26.5	130	(18.8)	20	(11.6)	110	(21.2)	
26.6-29.1	139	(20.1)	38	(22.0)	101	(19.5)	
≥29.2	135	(19.5)	44	(25.4)	91	(17.6)	
Unknown	5	(0.7)	4	(2.3)	1	(0.2)	
Current smoking							0.6

	Total on FTC N=691		Samples available for PK testing: No N=175		Samples available for PK testing: Yes N=516		
No	502	(72.7)	129	(74.6)	373	(72.0)	
Yes	187	(27.1)	44	(25.4)	143	(27.6)	
Unknown	2	(0.3)	0	(0.0)	2	(0.4)	
Current alcohol use							0.28
No	53	(7.7)	18	(10.4)	35	(6.8)	
Yes	565	(81.8)	136	(78.6)	429	(82.8)	
In the past	73	(10.6)	19	(11.0)	54	(10.4)	
Recreational drug use in the past 6 months							0.50
No	481	(69.6)	124	(71.7)	357	(68.9)	
Yes	210	(30.4)	49	(28.3)	161	(31.1)	
Total number of co-medications							0.03
1-4	278	(40.2)	84	(48.6)	194	(37.5)	
5-9	336	(48.6)	74	(42.8)	262	(50.6)	
≥10	77	(11.1)	15	(8.7)	62	(12.0)	

The mean BMD T-score at LS was not significantly different at different levels of the FTC PK parameters $AUC_{0\text{-}24h}$, C_{max}, C_{min} and CL_{24h} (P=0.43, P=0.42, P=0.41 and P=0.48, respectively, Table 7.18), therefore this outcome was not explored further in either univariable or multivariable analysis. However, both at FN and TH, the BMD T-score was significantly lower among those with higher FTC $AUC_{0\text{-}24h}$, C_{max} and C_{min} values, while it was significantly higher among those with lower FTC CL_{24h} values ($AUC_{0\text{-}24h}$: P≤0.003, C_{max}: P≤0.004, C_{min}: P≤0.005, CL_{24h}: P≤0.003, Table 7.19 and Table 7.20).

The associations were attenuated and became non-significant in the multivariable models after adjusting for BMI, gender, ethnicity, smoking, current alcohol use, recreational drug use in the past 6 months and total number of co-medications (excluding cART). However, a trend of lower BMD T-score at FN and TH was found for higher $AUC_{0\text{-}24h}$, C_{max} and C_{min} (Table 7.19 and Table 7.20). Higher CL_{24h} levels were associated with higher BMD T-score at all sites.

Table 7.18: Mean (SD) BMD T-score at LS stratified by FTC PK parameters

	BMD T-score		
	n	**Mean (SD)**	**p-value**
$AUC_{0\text{-}24h}$ (mg.h/L)			
≤9.017	91	-0.6 (1.4)	0.43
9.018-9.897	88	-0.8 (1.3)	
9.898-10.800	87	-0.5 (1.6)	
10.801-12.352	93	-0.8 (1.2)	
≥12.353	92	-0.8 (1.4)	
C_{max} (mg/L)			
≤1.051	92	-0.6 (1.4)	0.42
1.052-1.105	88	-0.8 (1.3)	
1.106-1.164	88	-0.5 (1.6)	
1.165-1.268	91	-0.9 (1.2)	
≥1.269	92	-0.7 (1.4)	
C_{min} (mg/L)			
≤0.057	96	-0.7 (1.4)	0.41
0.058-0.068	86	-0.7 (1.3)	
0.069-0.081	86	-0.5 (1.6)	
0.082-0.106	95	-0.9 (1.3)	
≥0.107	88	-0.7 (1.4)	
CL_{24h} (L/h)			
≤16.263	94	-0.8 (1.4)	0.48
16.264-18.542	91	-0.8 (1.3)	
18.543-20.228	87	-0.5 (1.5)	
20.229-22.228	88	-0.8 (1.3)	
≥22.229	91	-0.6 (1.4)	

Table 7.19: Mean (SD) BMD T-score at FN and univariable and multivariable associations with FTC PK parameters

	n	Mean (SD)	p-value	Univariable model β-coef. (95% CI)	Multivariable model* β-coef. (95% CI)
$AUC_{0\text{-}24h}$ (mg.h/L)					
≤9.017	97	-0.4 (1.6)	<0.001	Ref.	Ref.
9.018-9.897	94	-0.6 (1.2)		-0.21 (-0.54, 0.13)	-0.18 (-0.50, 0.14)
9.898-10.800	91	-0.9 (0.9)		-0.47 (-0.80, -0.13)	-0.23 (-0.55, 0.10)
10.801-12.352	95	-0.9 (1.0)		-0.55 (-0.89, -0.22)	-0.37 (-0.71, -0.03)
≥12.353	96	-1.1 (1.0)		-0.75 (-1.08, -0.41)	-0.45 (-0.79, -0.11)
C_{max} (mg/L)					
≤1.051	97	-0.4 (1.6)	<0.001	Ref.	Ref.
1.052-1.105	96	-0.6 (1.2)		-0.21 (-0.54, 0.13)	-0.20 (-0.52, 0.12)
1.106-1.164	90	-0.9 (0.9)		-0.47 (-0.81, -0.13)	-0.24 (-0.57, 0.09)
1.165-1.268	96	-1.0 (1.0)		-0.56 (-0.90, -0.23)	-0.40 (-0.73, -0.06)
≥1.269	96	-1.1 (1.0)		-0.75 (-1.08, -0.42)	-0.45 (-0.79, -0.11)
C_{min} (mg/L)					
≤0.057	102	-0.4 (1.6)	<0.001	Ref.	Ref.
0.058-0.068	92	-0.6 (1.2)		-0.17 (-0.50, 0.16)	-0.11 (-0.43, 0.21)
0.069-0.081	90	-0.8 (0.9)		-0.39 (-0.73, -0.05)	-0.15 (-0.47, 0.18)
0.082-0.106	97	-1.0 (1.0)		-0.54 (-0.87, -0.21)	-0.32 (-0.65, 0.01)
≥0.107	92	-1.1 (1.0)		-0.71 (-1.04, -0.37)	-0.40 (-0.74, -0.06)
CL_{24h} (L/h)					
≤16.263	98	-1.2 (1.0)	<0.001	Ref.	Ref.
16.264-18.542	93	-0.9 (1.0)		0.21 (-0.12, 0.55)	0.10 (-0.21, 0.42)
18.543-20.228	91	-0.9 (0.9)		0.29 (-0.04, 0.63)	0.24 (-0.08, 0.56)
20.229-22.228	94	-0.6 (1.2)		0.55 (0.22, 0.89)	0.29 (-0.03, 0.61)
≥22.229	97	-0.4 (1.6)		0.79 (0.46, 1.12)	0.48 (0.14, 0.83)

*Adjusted for POPPY group, ethnicity, gender, BMI, current smoking, current use of alcohol, history of recreational drugs use in the past 6 months and total number of co-medications

Table 7.20: Mean (SD) BMD T-score at TH and univariable and multivariable associations with FTC PK parameters

				Univariable model	Multivariable model*
	n	Mean (SD)	p-value	β-coef. (95% CI)	β-coef. (95% CI)
$AUC_{0\text{-}24h}$ (mg.h/L)					
≤9.017	89	-0.3 (1.4)	0.003	Ref.	Ref.
9.018-9.897	92	-0.4 (1.1)		-0.38 (-0.68, -0.08)	-0.15 (-0.45, 0.15)
9.898-10.800	88	-0.5 (0.9)		-0.46 (-0.76, -0.16)	-0.10 (-0.40, 0.21)
10.801-12.352	88	-0.6 (1.0)		-0.97 (-1.28, -0.67)	-0.30 (-0.62, 0.02)
≥12.353	91	-0.9 (1.0)		-0.98 (-1.28, -0.68)	-0.42 (-0.73, -0.10)
C_{max} (mg/L)					
≤1.051	89	-0.3 (1.4)	0.004	Ref.	Ref.
1.052-1.105	92	-0.4 (1.1)		-0.29 (-0.58, 0.00)	-0.15 (-0.45, 0.14)
1.106-1.164	87	-0.5 (0.9)		-0.59 (-0.89, -0.29)	-0.10 (-0.40, 0.21)
1.165-1.268	89	-0.6 (1.0)		-0.87 (-1.17, -0.57)	-0.31 (-0.63, 0.00)
≥1.269	91	-0.9 (1.0)		-1.14 (-1.43, -0.84)	-0.42 (-0.74, -0.10)
C_{min} (mg/L)					
≤0.057	94	-0.3 (1.4)	0.005	Ref.	Ref.
0.058-0.068	89	-0.4 (1.1)		-0.26 (-0.56, 0.05)	-0.08 (-0.38, 0.21)
0.069-0.081	86	-0.5 (0.9)		-0.45 (-0.77, -0.14)	-0.03 (-0.34, 0.27)
0.082-0.106	90	-0.6 (1.0)		-0.51 (-0.82, -0.20)	-0.24 (-0.55, 0.07)
≥0.107	87	-0.9 (1.0)		-0.75 (-1.06, -0.44)	-0.39 (-0.70, -0.07)
CL_{24h} (L/h)					
≤16.263	93	-0.9 (1.0)	0.003	Ref.	Ref.
16.264-18.542	86	-0.6 (1.0)		0.18 (-0.12, 0.48)	0.16 (-0.13, 0.45)
18.543-20.228	88	-0.5 (0.9)		0.73 (0.44, 1.03)	0.33 (0.04, 0.63)
20.229-22.228	91	-0.4 (1.2)		0.82 (0.53, 1.12)	0.27 (-0.02, 0.57)
≥22.229	88	-0.3 (1.4)		1.07 (0.77, 1.37)	0.46 (0.15, 0.78)

*Adjusted for POPPY group, ethnicity, gender, BMI, current smoking, current use of alcohol, history of recreational drugs use in the past 6 months and total number of co-medications

7.5.5.3 ABC and PK-parameters

In the subgroup of PLWH, 158 were taking ABC at the baseline visit. Of those, 68.4% (108/158) provided samples for the assessment of the ABC PK parameters and 31.6% (50/158) did not.

Among those who provided PK samples, there was a higher proportion of participants of white ethnicity compared to those who did not provide PK samples (83.3% (90/108) vs. 58.0% (29/50), P<0.001). There were no significant differences between those who provided samples for PK analysis and those who did not concerning POPPY group, gender, BMI, current smoking, current alcohol use, history of recreational drugs use and total number of co-medications, Table 7.21.

Table 7.21: Characteristics of POPPY participants on ABC whom samples for PK testing were and were not available

			Samples available for PK testing				
	Total on ABC N=158		No N=50		Yes N=108		
	n	(%)	n	(%)	n	(%)	p-value
Group							0.83
Older PLWH	103	(65.2)	32	(64.0)	71	(65.7)	
Younger PLWH	55	(34.8)	18	(36.0)	37	(34.3)	
Gender							0.35
Female	39	(24.7)	10	(20.0)	29	(26.9)	
Male	119	(75.3)	40	(80.0)	79	(73.2)	
Ethnicity							<0.001
Black African	39	(24.7)	21	(42.0)	18	(16.7)	
White	119	(75.3)	29	(58.0)	90	(83.3)	
BMI (kg/m^2)							0.39
≤22.8	32	(20.3)	9	(18.0)	23	(21.3)	
22.9-24.8	33	(20.9)	11	(22.0)	22	(20.4)	
24.9-26.9	27	(17.1)	9	(18.0)	18	(16.7)	
27.0-29.9	31	(19.6)	6	(12.0)	25	(23.2)	
≥30.0	30	(19.0)	12	(24.0)	18	(16.7)	
Unknown	5	(3.2)	3	(6.0)	2	(1.9)	
Current smoking							0.63
No	126	(79.8)	41	(82.0)	85	(78.7)	
Yes	32	(20.3)	9	(18.0)	23	(21.3)	
Unknown	-						
Current alcohol use							0.23
No	22	(13.9)	7	(14.0)	15	(13.9)	
Yes	115	(72.8)	33	(66.0)	82	(75.9)	
In the past	21	(13.3)	10	(20.0)	11	(10.2)	
Recreational drug use in the past 6 months							0.23

	Total on ABC N=158		Samples available for PK testing				
			No N=50		Yes N=108		
	n	(%)	n	(%)	n	(%)	p-value
No	120	(76.0)	41	(82.0)	79	(73.2)	
Yes	38	(24.0)	9	(18.0)	29	(26.9)	
Total number of co-medications							0.55
1-4	57	(36.1)	17	(34.0)	40	(37.0)	
5-9	71	(44.9)	21	(42.0)	50	(46.3)	
≥10	30	(19.0)	12	(24.0)	18	(16.7)	

The mean BMD T-scores at LS, FN and TH were not significantly different for the different levels of ABC PK parameters (Table 7.22). Therefore, these associations were not explored further using multivariable analysis.

7.5.5.4 3TC and PK parameters

Among the older and the younger PLWH, 199 were on 3TC, of which 70.9% (141/199) provided samples for the assessment of the 3TC PK parameters and 29.1% (58/199) did not.

Among those who did provide PK samples for 3TC, there was a higher proportion of those of white ethnicity compared to among those who did not provide PK samples (86.5% (122/141) vs. 58.6% (34/58), P<0.001). There were no significant differences between those who provided samples for PK analysis and those who did not concerning POPPY group, gender, BMI, current smoking, current alcohol use, recreational drug use and total number of co-medications, Table 7.23.

Table 7.22: Mean (SD) BMD T-score at LS, FN and TH stratified by ABC PK parameters

	BMD T-score								
	LS			FN			TH		
	n	Mean (SD)	p-value	N	Mean (SD)	p-value	N	Mean (SD)	p-value
$AUC_{0\text{-}24h}$ (mg.h/L)			0.48			0.86			0.92
≤10.333	17	-0.9 (1.0)		18	-0.8 (1.1)		17	-0.5 (1.2)	
10.334-11.686	21	-0.1 (1.1)		22	-0.5 (0.9)		22	-0.3 (0.9)	
11.687-12.941	21	-0.8 (1.7)		20	-0.9 (1.3)		21	-0.5 (1.1)	
12.942-14.679	19	-0.6 (1.3)		19	-0.7 (0.9)		17	-0.3 (0.9)	
≥14.680	17	-0.6 (1.4)		19	-0.7 (1.2)		16	-0.6 (1.3)	
C_{max} (mg/L)			0.93			0.98			0.85
≤3.846	17	-0.6 (1.2)		18	-0.6 (1.5)		17	-0.3 (1.4)	
3.847-4.052	22	-0.4 (1.1)		22	-0.8 (0.8)		22	-0.6 (0.9)	
4.053-4.255	20	-0.7 (1.8)		20	-0.7 (1.4)		21	-0.3 (1.2)	
4.256-4.447	19	-0.7 (1.2)		19	-0.8 (0.6)		17	-0.5 (0.6)	
≥4.448	17	-0.6 (1.4)		19	-0.7 (1.2)		16	-0.6 (1.3)	
C_{min} (mg/L)			0.42			0.54			0.73
≤0.0013	17	-0.4 (1.3)		18	-0.6 (1.1)		17	-0.4 (1.0)	
0.0014-0.0020	21	-0.3 (1.6)		22	-0.5 (1.2)		22	-0.3 (1.2)	
0.0021-0.0028	23	-1.0 (1.1)		22	-1.0 (1.0)		21	-0.6 (0.9)	
0.0029-0.0052	17	-0.8 (1.3)		17	-0.9 (0.8)		17	-0.7 (0.8)	
≥0.0053	17	-0.4 (1.5)		19	-0.6 (1.4)		16	-0.3 (1.4)	
CL_{24h} (L/h)			0.28			0.32			0.51
≤39.245	18	-0.4 (1.4)		20	-0.6 (1.4)		17	-0.3 (1.4)	
39.246-45.993	21	-0.9 (1.2)		21	-0.9 (1.0)		19	-0.6 (1.0)	
45.994-50.050	19	-1.0 (1.0)		18	-1.1 (0.9)		19	-0.8 (0.6)	
50.051-55.326	21	-0.2 (1.6)		22	-0.5 (1.2)		22	-0.3 (1.3)	
≥55.327	16	-0.5 (1.3)		17	-0.5 (1.1)		16	-0.2 (1.0)	

Table 7.23: Characteristics of POPPY participants on 3TC whom samples for PK testing were and were not available

	Total on 3TC N=199		Samples available for PK testing: No n=58		Samples available for PK testing: Yes n=141		
	n	(%)	n	(%)	n	(%)	p-value
Group							0.11
Older PLWH	133	(66.8)	34	(58.6)	99	(70.2)	
Younger PLWH	66	(33.2)	24	(41.4)	42	(29.8)	
Gender							0.48
Female	45	(22.6)	15	(25.9)	30	(21.3)	
Male	154	(77.4)	43	(74.1)	111	(78.7)	
Ethnicity							<0.001
Black African	43	(21.6)	24	(41.4)	19	(13.5)	
White	156	(78.4)	34	(58.6)	122	(86.5)	
BMI (kg/m^2)							0.32
≤23.2	41	(20.6)	11	(19.0)	30	(21.3)	
23.3-25.1	36	(18.1)	8	(13.8)	28	(19.9)	
25.2-27.0	39	(19.6)	11	(19.0)	28	(19.9)	
27.1-30.1	39	(19.6)	9	(15.5)	30	(21.3)	
≥30.2	37	(18.6)	16	(27.6)	21	(14.9)	
Unknown	7	(3.5)	3	(5.2)	4	(2.8)	
Current smoking							0.19
No	160	(80.4)	50	(86.2)	110	(78.0)	
Yes	39	(19.6)	8	(13.8)	31	(22.0)	
Current alcohol use							0.003
No	25	(12.6)	10	(17.2)	15	(10.6)	
Yes	153	(76.9)	36	(62.1)	117	(83.0)	
In the past	21	(10.6)	12	(20.7)	9	(6.4)	
Recreational drug use in the past 6 months							0.05
No	153	(76.9)	50	(86.2)	103	(73.1)	
Yes	46	(23.1)	8	(13.8)	38	(27.0)	
Total number of co-medications							0.47
1-4	76	(38.2)	26	(44.8)	50	(35.5)	
5-9	89	(44.7)	23	(39.7)	66	(46.8)	
≥10	34	(17.1)	9	(15.5)	25	(17.7)	

The mean BMD T-scores at LS, FN and TH were not significantly different for the different levels of 3TC PK parameters (Table 7.24) and therefore these associations were not explored further using univariable or multivariable analysis.

Table 7.24: Mean (SD) BMD T-score at lumbar spine, femoral neck and total hip stratified by 3TC PK parameters

	BMD T-score								
	LS			FN			TH		
	N	Mean (SD)	p-value	N	Mean (SD)	p-value	N	Mean (SD)	p-value
$AUC_{0\text{-}24h}$ (mg.h/L)			0.93			0.99			0.95
≤6.957	28	-0.6 (1.3)		27	-0.9 (1.1)		26	-0.5 (1.2)	
6.958-9.031	25	-0.7 (1.2)		25	-0.8 (0.7)		24	-0.4 (0.5)	
9.032-11.641	25	-0.9 (1.2)		25	-0.8 (0.9)		24	-0.6 (0.9)	
11.642-17.600	26	-0.6 (1.8)		28	-0.9 (1.1)		28	-0.4 (1.3)	
≥17.601	24	-0.7 (1.6)		26	-0.9 (1.3)		25	-0.5 (1.3)	
C_{max} (mg/L)			0.18			0.12			0.21
≤2.304	28	-0.8 (1.7)		29	-1.1 (1.5)		29	-0.7 (1.2)	
2.305-2.341	26	-1.1 (1.5)		26	-1.0 (1.1)		25	-0.7 (1.0)	
2.342-2.389	24	-0.8 (1.4)		25	-0.9 (0.7)		24	-0.6 (0.7)	
2.390-2.513	24	-0.5 (1.0)		25	-0.7 (0.8)		24	-0.3 (0.8)	
≥2.514	26	-0.2 (1.2)		26	-0.4 (1.2)		25	-0.1 (1.3)	
C_{min} (mg/L)			0.81			0.78			0.53
≤0.0014	28	-0.6 (1.3)		27	-0.9 (1.1)		26	-0.5 (1.2)	
0.0015-0.0075	24	-0.8 (1.2)		25	-0.7 (0.7)		25	-0.3 (0.6)	
0.0076-0.0268	25	-0.9 (1.2)		25	-0.8 (0.9)		23	-0.6 (0.9)	
0.0269-0.1372	27	-0.8 (1.7)		28	-1.1 (1.1)		28	-0.7 (1.2)	
≥0.1373	24	-0.5 (1.6)		26	-0.8 (1.2)		25	-0.3 (1.2)	
CL_{24h} (L/h)			0.94			0.96			0.91
≤16.879	25	-0.6 (1.6)		27	-0.9 (1.3)		26	-0.4 (1.3)	
16.880-25.939	27	-0.8 (1.7)		28	-1.0 (1.0)		28	-0.6 (1.1)	
25.940-33.384	25	-0.9 (1.2)		25	-0.8 (0.9)		23	-0.5 (0.9)	
33.385-44.602	25	-0.7 (1.2)		25	-0.8 (0.7)		25	-0.4 (0.5)	
≥44.603	26	-0.6 (1.3)		26	-0.8 (1.2)		25	-0.5 (1.3)	

7.6 Discussion

In this chapter I explored the association of HIV status with BMD T-score. I further explored whether this association was independent of any association with frailty, falls and whether it was modified by any association with depressive symptoms. Among the group of PLWH I investigated whether HIV-specific factors were linked to BMD T-score. Finally, within the study participants who provided samples for the assessment of PK parameters, I explored the association between NRTI PK parameters and BMD T-score.

7.6.1 The association of BMD with HIV

According to the guidelines suggested by WHO for the definition of osteopenia and osteoporosis, in POPPY the overall prevalence of osteopenia in the older groups ranged from 28% to 40% and osteoporosis from 2% to 8% depending on the site examined (LS, FN and TH). The proportion of those with osteopenia and osteoporosis was significantly higher among older PLWH compared to HIV-negative controls. The prevalence of osteopenia and osteoporosis in POPPY were comparable to that among other studies of similarly aged PLWH (449, 508, 559). Duvivier *et al.* (559) reported that among PLWH with a median age of 40 years, 31% had osteopenia and 3% had osteoporosis. Yin *et al.* (508) reported that 42% of PLWH had osteoporosis and Brown *et al.* (449) 15%. A rise in prevalence of osteopenia from 13% to 22% over a period of 1.8 years has been reported by Mallon *et al.* (676) in a longitudinal study among newly treated PLWH.

The analysis using the BMD T-score as a continuous measure suggested that BMD T-score is lower among group of older PLWH compared to HIV negative controls at all sites and this is in line with other studies (470, 484, 501, 539, 677) and the findings of a systematic review (449) using data of similarly aged PLWH in the USA (374, 438, 507, 508), Argentina (376), Ireland (472), Germany (371), France (375, 435), Spain (436) and Italy (441).

The prevalence of osteoporosis among PLWH may be higher among other reasons due to the effect of HIV viral proteins on osteoblast and osteoclast function which in

turn this results in reduced BMD (678) and higher levels of inflammation (464, 521). Another mechanism that may explain the negative association of HIV with BMD T-score is the reported effect of ART initiation on bone metabolism and the effect of immune system reconstruction in bone resorption (512, 532). This dictates a progressive slowdown in bone-building which subsequently is overtaken by bone resorbing resulting in the reduction of BMD (72, 679). Other factors that may explain the low BMD among PLWH may be the low vitamin D levels. In the general population in the UK 30%-40% people have low vitamin D levels (680) while among PLWH it is 47% according to Rodriguez *et al.* (681). In POPPY the levels of vitamin D were not available for the study participants and therefore it was not possible to explore this association. Finally, BMI may be another factor that may explain the negative association of HIV with BMD T-score. Several researchers have reported a negative association of lower BMI with reduced BMD and osteoporosis among PLWH (433, 453, 501, 539, 682) and in the general population (679, 683-686). This is explained by the presence of factors such as chronic illness, poor nutrition and inadequate calcium intake. Furthermore, systemic inflammation due to comorbidities and advancing of HIV infection may influence insulin resistance (687, 688) and along with hormonal changes (501) due to ageing may have a significant effect on reducing BMI and BMD.

In separate models' further adjustment for frailty and for history of falls I found an independent association of HIV with a lower BMD T-score both at FN and TH. Frailty and history of falls were also independently associated with lower BMD T-score at FN while at TH only the association with history of falls was independent of any association with HIV. Relevant literature suggests that both frailty and a history of falls are associated with reduced BMD, osteopenia and osteoporosis (165, 215, 474, 486). However, their lack of association with LS BMD T-score may be due to the higher BMD T-score among the frail and those with history of falls possibly induced by underlying conditions such as ankylosing spondylitis and osteoarthritis that are known to activate new bone formations among the elderly (689). Nevertheless, it is important to note that the cross-sectional data used in this chapter restrict any assumptions for causality or directionality of the associations. Therefore, I cannot

determine whether low BMD T-score increased the prevalence of falls and the prevalence of frailty or whether falls and frailty preceded any low BMD T-score.

I found a lack of association between depressive symptoms and BMD T-scores in the multivariable models adjusting for HIV and the standard confounders and the models with the interaction of HIV with depressive symptoms suggested that the association of HIV with BMD T-scores was not modified by the association with depressive symptoms. Several researches have suggested a positive association of depressive symptoms with low BMD T-scores in the general population (491, 690-695) however sparce remains the literature among PLWH. To the best of my knowledge the analysis of this chapter is the first attempt to explore whether the association of HIV with BMD T-scores is modified by any association with depressive symptoms.

The literature suggests an inconclusive relationship between BMD and HIV-specific factors. Some researchers have reported a lack of association between BMD, CD4 count and VL among cART-naïve PLWH (512) while others have found a significant link between CD4 and BMD (401, 510, 511). Emerging research suggests that greater HIV severity defined by CD4 count and chronic inflammation, is associated with reduced BMD among treated PLWH (447, 451, 532) and findings from this study confirm that a detectable VL and a previous diagnosis of AIDS-defining illnesses are associated with reduced BMD.

Several studies have shown that use of PIs reduces BMD (401, 449, 531, 534, 559) while others did not find an association (375, 376, 445, 560). In POPPY, the lack of association between use of PIs and BMD may be, among other reasons, due to the compliance of the clinical practices with the safe and effective national guidelines. The British HIV association (BHIVA) recommends all PLWH over the age of 50 to have their FRAX score assessed and those at increased risk of fracture to have their BMD measured (696). Compliance to these recommendations suggests that those at risk for fractures may have already been identified and switched to cART regimens that are less bone-toxic before recruitment into the study, thus limiting my ability to find an association between use of PIs and low BMD. However, I found that those on NVP NNRTIs had a significantly higher BMD T-score at LS and TH compared to those not

on NNRTIs. This relationship has been previously confirmed among other researchers (697-699) and the pathogenesis of this association is not fully understood and has not been investigated ex-vivo.

7.6.2 BMD and PK parameters

In the second part of Chapter 7 I explored the association of TDF, FTC, ABC and 3TC PK parameters with the BMD T-score. $AUC_{0\text{-}24h}$ and C_{max} and C_{min} determine exposure and maximum and minimum concentration of the drug and CL_{24h} determines the rate of elimination of the drug from the body.

Higher TDF and FTC $AUC_{0\text{-}24h}$ were associated with a lower BMD T-scores at FN and TH while higher TDF $AUC_{0\text{-}24h}$ was also associated with a lower BMF T-score at LS. Higher TDF and FTC C_{max} were associated with a lower BMD T-scores at FN while higher TDF C_{max} was also associated with a lower BMD T-score at LS and higher FTC C_{max} with a lower BMD T-score at TH. Higher FTC C_{min} was associated with lower BMD T-score at FN and TH. Finally, higher TDF CL_{24h} was associated with higher BMD T-score at all sites while higher FTC CL_{24h} was associated with a higher BMD T-score at FN and TH.

Gupta *et al.* (669) have also explored the association of TDF PK parameters with BMD and also found a significant negative association between TDF $AUC_{0\text{-}24h}$ and BMD T-score at TH, however, they found no association with BMD at LS. A well-established positive association of TDF intake with bone metabolism has been suggested among several other studies (544, 547, 669).

Other studies that did have TDF PK parameters available confirmed the association of current TDF with lower BMD measured at arm or hip (500, 544, 700). The mechanism behind the TDF-induced BMD loss is explained by the osteoclast activation, which has a significant effect on the bone microstructure. The activation of bone-metabolism markers by TDF has been confirmed among several other studies (500, 544, 549, 672). It is important to note that the association seen between TDF concentration and BMD T-scores was not present when I looked the association of current TDF use with BMD. This highlights the importance of how the drug is handled

(dosage/frequency) and the importance of monitoring the effect of the drug concentration on bone health rather than looking at the risk of including or excluding a medication from the treatment regime.

In the analysis that explored the association of the FTC PK parameters with BMD T-score, I found no association of the FTC PK parameters with BMD T-scores at LS, but at FN and TH. There is no literature concerning the association of FTC alone with BMD due to the common co-administration of FTC with TDF. Studies that have explored the effect of the TDF/FTC compared to other treatment have found a significant association with lower BMD (534, 546).

Finally, I found no association between any of the ABC or 3TC PK parameters and BMD T-scores at any of the three sites explored. A similar finding has been reported by other researchers who reported that bone turnover among those treated with ABC-3TC was significantly lower compared to those treated with TDF-FTC (501, 546, 700, 701).

7.6.3 Strengths and limitations

Out of the total older POPPY participants, 93.7% (940/1003) had their BMD T-score assessed at any three sites of LS, FN and TH. Assessing the BMD in more than one body sites presents as one of the major strengths of this study.

Chapter 7 has also some limitations that should be considered. First, low BMD may be underestimated, and this is because the proportion of smokers and those with history of recreational drugs was significantly higher among those who had not their BMD assessed compared to those who had. Second, I cannot exclude the possibility of measurement bias. The different DEXA scanners used across the study sites may have produced data with varying accuracy due to differences between machines. It was not possible to check the results validity by performing additional DEXA scans per study participant. This would have doubled radiation exposure and dramatically increased BMD assessment time required. This type of bias was minimized by utilizing experienced and well-trained healthcare-providers for the scan assessment.

An additional limitation of this chapter was the lack of information on the duration of treatment with previous cART. Therefore, I cannot rule out that associations seen with current cART may be due to the legacy of previous treatments considering that time on previous treatment and the time to switching was not available for the current participant's cART. However, the use of PK data assisted to overcome this challenge and provided more reliable data regarding the association between use of NRTIs and BMD.

Concluding, another limitation of this chapter is the limited statistical power. In particular, the small number of participants with more severe depressive symptoms was small which may explain why the model exploring the interaction between HIV and depressive symptoms suggested a poorer fit compared to the model without the interaction.

Chapter 8 Fractures and FRAX scores in POPPY

8.1 Introduction

Fall-related fractures are the most prevalent serious injury in older people (702). In the UK, hip fracture is the commonest reason for older people to need emergency anaesthesia and surgery, and the commonest cause of accidental death. Quality of life among those undergoing surgery for a hip fracture is significantly compromised with a quarter of these individuals suffering with post-surgery confusion and delirium (703). Greater resource use, longer institutionalization, long-term disability, loss of independence, increased morbidity and mortality are challenges among the elderly with a history of fractures (702-705). Fragility fractures are more prevalent among women, are commonly caused by low-energy falls and are associated with older age (702). Other characteristics that have been linked with increased fracture risk include lifestyle factors such as smoking, caffeine and alcohol intake and clinical factors such as type 2 diabetes, rheumatoid arthritis, CVD, liver disease, asthma, anxiety, use of tricyclic antidepressants, poor visual acuity, low BMD, high FRAX scores, history of falls and a history of prior fractures (354, 386, 481, 490, 706).

PLWH have been found to have a greater risk of fractures compared to HIV-negative controls (24, 50, 367-369, 371, 373-377, 398, 401, 403, 432-443, 447, 450-469) with the rate of fragility fractures reported to be 2-fold higher among men with HIV aged 50–59 years compared to HIV-negative controls (448). A recent review has also reported that the risk of fractures among PLWH is double that of HIV-negative controls (444) and other researchers suggest that the fracture rate starts to increase a decade earlier among PLWH compared to age-, ethnicity- and sex-matched HIV-negative individuals (446). Several risk factors for increased fracture risk and bone turnover are shared between PLWH and HIV-negative controls (444) including demographic factors (white ethnicity (460, 482), ageing (453, 470, 707), history of fractures (65, 707), low BMI (453, 542, 556, 682), smoking (707, 708) and alcohol abuse (432)) and clinical factors (frailty (467), falls (65), depressive symptoms (460, 488, 709), sarcopenia (707) and renal disease (65)). Among PLWH, cumulative exposure to TDF has been associated with an increased risk of osteoporotic

fractures while no significant association has been found between ABC and fracture risk (482). Additional risk factors for fracture risk are chronic inflammation and immune reconstitution inflammatory syndrome (532), ART use (50, 366, 460, 482, 540) and in particular use of TDF (544, 546, 553, 669, 672, 710, 711) and PIs (436, 554, 557, 559), HBV co-infection (712), HCV co-infection (442, 456, 713), low CD4 count (453, 509, 707, 713) and a history of an AIDS-defining illness (713).

One of the most commonly used measures for bone health is the FRAX score, a validated tool that assesses the 10-year probability of hip and major-osteoporotic fractures among people aged 40–90 years. Major-osteoporotic fractures are considered to be those that occur at the spine, forearm or shoulder. Female gender, lower BMI (<25 kg/m^2), use of alcohol and glucocorticoids, use of PIs and disease duration have been identified as risk factors for increased FRAX scores among PLWH (714).

8.2 Methods

In the general population and among PLWH the amount of literature that explores the association of basic demographic characteristics with FRAX score is limited; one reason for this may be that many of these basic demographic characteristics, such as ethnicity, age, gender, height, weight, smoking, and a history of fractures, are used for the calculation of the scores. However, due to the diverse population of the POPPY Study further exploration of their association with FRAX was deemed crucial.

The calculation of FRAX scores in POPPY has been described in detail in Section 3.5.5. FRAX scores were calculated with the use of all 12 parameters required through the FRAX® web page for objectives 5-8 (Figure 3.3). However, since results of DEXA scanning might not be available in all studies, the FRAX® web page allows the calculation of the scores without the use of the use of the FN BMD T-score. Due to the positively skewed distribution of both FRAX scores, the median (IQR) and range are reported for the different characteristics of the POPPY participants. In the sensitivity analysis of this chapter, I explored whether the FRAX scores calculated without the use of the 12th parameter (FN BMD T-score) among POPPY participants

yielded similar results to those when the FN BMD T-score was included in the calculation of the scores.

8.3 Hypotheses

1. There is no difference in fracture rate between older PLWH and HIV-negative controls
2. The association of HIV on fracture rate is independent of any associations with frailty, history of falls and/or recurrent falls and BMD T-score
3. The association of HIV with fracture rate is not modified by the association with depressive symptoms
4. HIV-specific factors such as AIDS history, low CD4 count, low CD4 nadir and use and duration of exposure to specific cART drugs are associated with a higher fracture rate; these associations are independent of any associations with frailty and/or falls
5. There is no difference in FRAX scores (hip and major-osteoporotic) between older PLWH and HIV-negative controls
6. The association of HIV with FRAX scores is independent of any associations with frailty, history of falls
7. The association of HIV with FRAX scores is not modified by the association with depressive symptoms
8. HIV-specific factors, such as AIDS diagnosis, low current and nadir CD4 count, and a high VL, are associated with increased FRAX scores among PLWH
9. There is no difference in FRAX scores for higher or lower plasma concentration of PK parameters of TDF, FTC, ABC and 3TC
10. FRAX scores calculated without the use of BMD yield similar results to those when BMD is included for the hypothesis 5-9

8.4 Specific objectives

1. To explore whether the fracture incident rate (FIR) over a 5-year period prior to enrolment is higher in the group of older PLWH compared to HIV-negative controls

2. To investigate whether the association of HIV with FIR is independent of any association with frail, history of falls/recurrent falls and low BMD T-score
3. To investigate whether the association of HIV with FIR is modified by the association with depressive symptoms
4. In the subgroup of PLWH, to explore the association between HIV-related parameters (AIDS history, CD4 count, CD4 nadir, VL, time since HIV diagnosis, current cART and years since cART initiation) with the FIR after adjusting for the confounders described in Section 4.5
5. To explore whether FRAX scores are higher among older PLWH compared to HIV-negative controls after controlling for the confounders described in Section 4.5
6. To explore whether the association of HIV with FRAX scores is independent of any association with frailty, history of falls
7. To explore whether the association of HIV with FRAX scores is modified by the association with depressive symptoms as assessed by CES-D and PHQ-9 scores
8. To explore whether HIV-specific factors, such as AIDS diagnosis, low current and nadir CD4 count, and a high VL, are associated with the FRAX scores
9. In the subgroup of PLWH, to explore whether higher PK parameters of TDF, FTC, ABC and 3TC are associated with the FRAX scores
10. In a sensitivity analysis to explore whether assessing the FRAX scores without the use of BMD leads to the same conclusions for objectives 5-9

8.5 Statistical analysis

To address objective 1, I calculated the FIR, defined as the number of any fractures occurring in the five years before study entry, divided by the total number of participants in the group times five (for the five years considered for the fracture rate).

The formula was:

$$FIR = \frac{Total\ number\ of\ fractures\ over\ 5\ years\ before\ entering\ POPPY}{Total\ number\ of\ participants\ in\ the\ group * 5}$$

Next, I explored whether the FIR was significantly different between the group of older PLWH compared to HIV-negative controls using univariable and multivariable Poisson regression models with robust standard errors adjusting for the standard confounders described in Section 4.5.

For objective 2, using univariable and multivariable models, I explored whether the association of HIV with FIR was independent of any association with frailty, history of falls and history of recurrent falls in the past 28 days. The multivariable model of objective 1 was compared to multivariable models further adjusting for frailty, history of falls and history of recurrent falls when the association of frailty, history of falls and history of recurrent falls with FIR was significant in univariable models.

For objective 3, using univariable and multivariable, I explored whether the association of HIV with FIR was modified by the association with depressive symptoms as assessed by the CES-D and PHQ-9 scores. The fit of the multivariable regression models with and without the interaction of HIV with depressive symptoms adjusted for the standard confounders described in Section 4.5 were compared using the likelihood-ratio test to determine the model with the best fit.

For objective 4, the subgroup of PLWH was selected (older and younger PLWH). Within this subgroup, the associations between FIR and the HIV-specific factors, CD4 count, CD4 nadir, current cART, years on cART and time since HIV diagnosis were explored. The continuous factors were expressed in 6 groups, one unknown and five groups defined by the quintiles of the distribution of each factor. Current cART was explored through four separate covariates following the categorization used in the Chapter 4. Univariable and multivariable Poisson regression models with robust standard errors were used to assess the association between FIR and the HIV factors after adjusting for gender, ethnicity, BMI, current smoking, current alcohol use, recreational drug use in the past 6 months, frailty and history of falls in the past 28 days.

For objective 5, the FRAX scores between the older PLWH and the HIV-negative controls were compared using the Kruskal-Wallis test. Univariable and multivariable linear regression models with cubic root transformation of FRAX scores were used to

explore the association of HIV with FRAX scores after adjusting for the standard confounders described in Section 4.5. The cubic root transformation allowed a better approximation of the normal distribution and the errors of the models suggested a close to normal symmetrical distribution hence this transformation was performed for all the models of the FRAX scores.

For objective 6, the association between HIV and FRAX scores was tested for independence of the association with frailty and history of falls. The association of HIV with FRAX score from the multivariable models of objective 5 was compared to multivariable models additionally adjusting for frailty and history of falls.

For objective 7, I explored whether the association between HIV and FRAX scores was modified by the association with depressive symptoms as assessed by CES-D and PHQ-9 scores. The fit of the multivariable regression models with and without the interaction of HIV with depressive symptoms adjusted for the standard confounders described in Section 4.5 were compared using the likelihood-ratio test to determine the model with the best fit.

For objective 8, the subgroup of PLWH was selected (older and younger PLWH). The associations between FRAX scores and the HIV-specific factors (CD4 count, CD4 nadir, years on cART and time since HIV diagnosis) were explored using univariable linear regression models with cubic root transformation of the scores. The HIV-specific factors that were significantly associated with FRAX and major-osteoporotic scores in univariable models were then considered in multivariable analysis along with gender, ethnicity, BMI, current smoking, current alcohol use, recreational drug use in the past 6 months, frailty and history of falls in the past 28 days.

For objective 9, the subgroup of PLWH was selected (older and younger PLWH). Within this subgroup, univariable and multivariable linear regression models with cubic root transformation of FRAX scores were used to explore the association with the PK parameters of TDF, FTC, ABC and 3TC. The separate multivariable linear regression models for each of the four PK parameters $AUC_{0\text{-}24}$, C_{max}, C_{min} and CL_{24h} for TDF, FTC, ABC and 3TC were adjusted for age at baseline, gender, ethnicity, current

smoking, current use of alcohol, recreational drug use in the past 6 months and total number of co-medications.

For objective 10, the FRAX scores without the use of BMD were used to explore the objectives 5-9. The purpose of this objective is to explore whether the calculation of the FRAX scores without the use of BMD yielded similar results to those when BMD was included. Assessment of BMD is not always possible in settings around the world and I wanted to allow the comparability of my results with the results of studies that were unable to assess BMD.

8.6 Results

8.6.1 The association of FIR with HIV

The univariable models suggested that the group of older PLWH had more than 1.5-fold higher FIR compared to HIV-negative controls (IRR=1.61, 95% CI (1.00, 2.62)). The multivariable analysis adjusting for the standard confounders described in Section 4.5 suggested that HIV was independently associated with a higher FIR. In particular, the group of older PLWH had 70% higher risk for fractures compared to HIV-negative controls, (aIRR=1.70, 95% CI (1.00, 2.92)), Table 8.1.

Table 8.1: Association of fracture risk with HIV infection

	Univariable model	**Multivariable model***
	IRR (95% CI)	**aIRR (95% CI)**
Group		
HIV-negative	Ref.	Ref.
Older PLWH	1.61 (1.00, 2.62)	1.70 (1.00, 2.92)

IRR: incidence risk ratio, CI: confidence interval
*Adjusted for age, gender, ethnicity, education and marital status

8.6.2 HIV, frailty, falls and the association with recent fractures in the group of older POPPY participants

In this section I explored whether the association of HIV with FIR was independent of any association with frailty and falls. The descriptive analysis suggested that there was a significantly higher prevalence of recent fractures among those with a history of falls and recurrent falls compared to those without (14.6% (20/137) vs. 6.5%

(54/836), P=0.001 and 15.2% (15/99) vs. 6.8% (59/874), P=0.001, respectively, Table 8.2). No differences were observed in the in the prevalence of recent fractures between those with and without frailty. Therefore, this association was not explored in the multivariable analysis.

In two multivariable models, I explored the association of HIV with FIR adjusting for the standard confounders described in Section 4.5 and further adjusting for history of falls in one model and recurrent falls in another model. In both models, the association of HIV with fractures was attenuated suggesting that the variability in FIR after adjusting for the standard confounders is better explained by the association with history of falls and recurrent falls in the past 28 days. In particular, in the first model, the study participants with a history of falls in the past 28 days had more than 2.6-fold higher rate of fractures compared to those with no history of falls (aIRR=2.61, 95% CI (1.61, 4.21)). Similarly, in the second multivariable model, those with a history of recurrent falls had almost 3-fold higher rate of fractures compared to those without recurrent falls (aIRR=2.91 (1.74, 4.86), Table 8.2).

8.6.3 Fractures HIV and depressive symptoms

In this section, I explored whether the association of HIV with fracture rate was modified by the association with depressive symptoms as assessed by CES-D and PHQ-9 scores. The prevalence of recent fractures was significantly higher among those with severe depressive symptoms compared to those with moderate or non-mild depressive symptoms as assessed by CES-D score (13.0% (21/162) vs. 8.5% (10/118) and 6.4% (39/613), respectively). Although a similar pattern was observed when depressive symptoms were assessed using the PHQ-9 score, the level of significance was not achieved and therefore multivariable associations were not explored for PHQ-9 score. The estimates though still suggested a linear association between the severity of symptoms and recent fractures, with higher risk for fractures in those with greater depressive symptoms, Table 8.3.

In the multivariable analysis the association of HIV with higher fracture risk was attenuated. However, the association with severe CES-D remained significant after adjusting for the risk factors described in Section 4.5. Compared to those with

none/mild symptoms, those with severe symptoms had more than 2-fold higher risk for fractures (aIRR=2.32, 95% CI (1.34, 4.01), Table 8.3).

Whether the association of HIV with fracture risk was modified by the association with depressive symptoms was only tested for the CES-D score due to the significant association with recent fractures and the lack of any association with PHQ-9 score. The multivariable model suggested that the model without the interaction term was a better fit compared to the models with the interaction term (Likelihood=-260.8 vs. -258.8, Likelihood ratio test Chi-square=3.95, P=0.14) which suggests that the association of HIV with fracture risk was not modified by any association with depressive symptoms, Table 8.3.

Table 8.2: Frailty and history of falls and recurrent falls among older POPPY participants with and without recent fractures and univariable and multivariable association of FIR with HIV frailty and history of falls

	Total N=1003		Recent fractures				p-value	Univariable model	Multivariable models*
			No N=923		Yes N=80			IRR (95% CI)	aIRR (95% CI)
	n	(%)	n	(%)	n	(%)			
Frailty							0.51		
No	702	(100.0)	649	(92.5)	53	(7.5)		Ref.	Ref.
Yes	80	(100.0)	71	(88.8)	9	(11.3)		1.61 (0.85, 3.06)	n/a
Unknown	221	(100.0)	203	(91.9)	18	(8.1)			
Group							0.18		
HIV-negative	699	(100.0)	638	(91.3)	61	(8.7)		Ref.	Ref.
Older PLWH	304	(100.0)	285	(93.8)	19	(6.3)		1.61 (1.00, 2.62)	1.47 (0.84, 2.59)
History of falls in the past 28 days							0.001		
No	836	(100.0)	782	(93.5)	54	(6.5)		Ref.	Ref.
Yes	137	(100.0)	117	(85.4)	20	(14.6)		2.63 (1.69, 4.09)	2.61 (1.61, 4.21)
Unknown	30	(100.0)	24	(80.0)	6	(20.0)			
Group							0.18		
HIV-negative	699	(100.0)	638	(91.3)	61	(8.7)		Ref.	Ref.
Older PLWH	304	(100.0)	285	(93.8)	19	(6.3)		1.61 (1.00, 2.62)	1.52 (0.86, 2.69)
History of recurrent falls in the past 28 days							0.001		
No	874	(100.0)	815	(93.3)	59	(6.8)		Ref.	Ref.
Yes	99	(100.0)	84	(84.9)	15	(15.2)		2.90 (1.81, 4.65)	2.91 (1.74, 4.86)
Unknown	30	(100.0)	24	(80.0)	6	(20.0)			

IRR: incidence risk ratio, CI: confidence interval

*Model adjusted for age, gender, ethnicity, education and marital status

Table 8.3: Depressive symptoms as assessed by CES-D and PHQ-9 among the older POPPY participants with and without recent fractures

	Total		Recent fractures						
			No		Yes				
	N=1003		n=1270		n=107				
	n	(%)	n	(%)	n	(%)	p-value	Univariable model IRR (95% CI)	Multivariable model* aIRR (95% CI)	Multivariable model** aIRR (95% CI)
Group							0.18			
HIV-negative	699	(100.0)	638	(91.3)	61	(8.7)		Ref.	Ref.	Ref.
Older PLWH	304	(100.0)	285	(93.8)	19	(6.3)		1.61 (1.00, 2.62)	1.38 (0.77, 2.47)	1.25 (0.65, 2.42)
Levels of depressive symptoms (CES-D)							0.05			
No to mild (0-15)	613	(100.0)	574	(93.6)	39	(6.4)		Ref.	Ref.	Ref.
Moderate (16-23)	118	(100.0)	108	(91.5)	10	(8.5)		1.36 (0.72, 2.56)	1.41 (0.72, 2.75)	1.82 (0.52, 6.32)
Severe (24-60)	162	(100.0)	141	(87.0)	21	(13.0)		1.97 (1.21, 3.23)	2.32 (1.34, 4.01)	2.56 (0.11, 5.08)
Unknown	110	(100.0)	100	(90.9)	10	(9.1)		-	-	-
Levels of depressive symptoms (PHQ-9)							0.56			
Minimal (1-4)	565	(100.0)	525	(92.9)	40	(7.1)		Ref.		
Mild (5-9)	167	(100.0)	154	(92.2)	13	(7.8)		0.99 (0.54, 1.79)	-	-
Moderate (10-14)	102	(100.0)	93	(91.2)	9	(8.8)		1.15 (0.58, 2.28)	-	-
Moderately severe (15-19)	57	(100.0)	53	(93.0)	4	(7.0)		1.03 (0.41, 2.59)	-	-
Severe (20-27)	31	(100.0)	27	(87.1)	4	(12.9)		1.90 (0.76, 4.77)	-	-
Unknown	81	(100.0)	71	(87.7)	10	(12.4)		-		

IRR: incidence risk ratio, CI: confidence interval

*Adjusted for age, gender, ethnicity, education and marital status

** Further adjusted for the interaction of HIV with depressive symptoms

8.6.4 Fractures among PLWH

Despite not reaching significance, lower CD4 nadir, increased time since HIV diagnosis and longer time on ART appeared to be associated with a higher FIR. More specifically, those who had a positive HIV diagnosis 16.0-22.0 and ≥22.1 years before entering the study, had a higher FIR (IRR=1.57, 95% CI (0.91, 2.72) and IRR=1.10, 95% CI (0.61, 1.99), respectively, P=0.07, Table 8.4) compared to those diagnosed ≤6.4 years before study entry. Overall, the univariable analysis suggested that the HIV-specific factors were not significantly associated with fracture rate; thus, further adjusted analyses were not performed.

Table 8.4: Characteristics of PLWH with and without recent fractures and the association of FIR with age and HIV factors in POPPY

	Total N=1073		No N=985		Yes N=88			Univariable model
	n	(%)	n	(%)	n	(%)	p-value	IRR (95% CI)
Age at baseline visit (years)							0.08	
≤29	29	(2.7)	28	(2.9)	1	(1.1)		Ref.
30-39	92	(8.6)	87	(8.8)	5	(5.7)		2.21 (0.27, 17.93)
40-49	253	(23.6)	232	(23.6)	21	(23.9)		2.75 (0.37, 20.33)
50-54	266	(24.8)	251	(25.5)	15	(17.1)		2.73 (0.37, 20.11)
55-59	188	(17.5)	162	(16.5)	26	(29.6)		4.78 (0.65, 35.03)
60-64	125	(11.7)	114	(11.6)	11	(12.5)		3.02 (0.39, 23.05)
65-69	81	(7.6)	74	(7.5)	7	(8.0)		2.51 (0.31, 20.37)
≥70	38	(3.5)	36	(3.7)	2	(2.3)		1.53 (0.14, 16.83)
Group							0.39	
Older PLWH	699	(65.1)	638	(64.8)	61	(69.3)		
Younger PLWH	374	(34.9)	347	(35.2)	27	(30.7)		
AIDS history							0.11	
No	762	(71.0)	693	(70.4)	69	(78.4)		Ref.
Yes	311	(29.0)	292	(29.6)	19	(21.6)		0.88 (0.57, 1.34)
CD4 count (cells/mm^3)							0.57	
≤444	210	(20.1)	194	(20.1)	16	(19.8)		Ref.
445-567	209	(20.0)	194	(20.1)	15	(18.5)		1.00 (0.52, 1.93)
568-695	210	(20.1)	198	(20.5)	12	(14.8)		1.17 (0.62, 2.19)
696-873	209	(19.7)	192	(19.9)	17	(21.0)		1.06 (0.56, 2.02)
≥874	209	(19.7)	188	(19.5)	21	(25.9)		1.45 (0.80, 2.65)
CD4 nadir (cells/mm^3)							0.87	
≤80	213	(20.7)	197	(20.8)	16	(19.1)		Ref.
81-166	202	(19.6)	182	(19.2)	20	(23.8)		1.42 (0.76, 2.62)
167-240	211	(20.5)	193	(20.4)	18	(21.4)		1.55 (0.84, 2.86)
241-340	199	(19.3)	184	(19.5)	15	(17.9)		1.09 (0.56, 2.09)

	Total N=1073		No N=985		Yes N=88			Univariable model
	n	(%)	n	(%)	n	(%)	p-value	IRR (95% CI)
≥341	205	(19.9)	190	(20.1)	15	(17.9)		1.09 (0.56, 2.12)
VL							0.20	
Detectable	104	(9.7)	92	(9.4)	12	(13.6)		Ref.
Undetectable	964	(90.3)	888	(90.6)	76	(86.4)		0.68 (0.40, 1.18)
Time since HIV diagnosis (yrs)							0.19	
≤6.4	213	(20.0)	195	(20.0)	18	(20.7)		Ref.
6.5-11.1	213	(20.0)	201	(20.6)	12	(13.8)		0.76 (0.40, 1.46)
11.2-15.9	212	(19.9)	199	(20.4)	13	(14.9)		0.77 (0.40, 1.47)
16.0-22.0	213	(20.0)	189	(19.4)	24	(27.6)		1.57 (0.91, 2.72)
≥22.1	212	(19.9)	192	(19.7)	20	(23.0)		1.10 (0.61, 1.99)
Years on ART							0.52	
≤3.9	211	(20.1)	196	(20.3)	15	(17.4)		Ref.
4.0-7.3	210	(20.0)	194	(20.1)	16	(18.6)		1.00 (0.53, 1.90)
7.4-12.3	210	(20.0)	196	(20.3)	14	(16.3)		0.85 (0.44, 1.65)
12.4-17.1	210	(20.0)	192	(19.9)	18	(20.9)		1.16 (0.63, 2.15)
≥17.2	210	(20.0)	187	(19.4)	23	(26.7)		1.69 (0.96, 2.99)
Number of total co-medications (excluding cART)							0.92	
0	321	(29.9)	296	(30.1)	25	(28.4)		Ref.
1-4	491	(45.8)	451	(45.8)	40	(45.5)		1.10 (0.71, 1.71)
5-9	204	(19.0)	185	(18.8)	19	(21.6)		0.98 (0.56, 1.72)
≥10	57	(5.3)	53	(5.4)	4	(4.6)		0.70 (0.25, 1.99)
NRTIs							0.14	
None	144	(13.4)	126	(12.8)	18	(20.5)		Ref.
TDV/FTC	670	(62.4)	618	(62.7)	52	(59.1)		0.71 (0.43, 1.15)
ABC/3TC	138	(12.9)	126	(12.8)	12	(13.6)		0.70 (0.35, 1.37)
Other	121	(11.3)	115	(11.7)	6	(6.8)		0.34 (0.14, 0.84)

	Total N=1073		No N=985		Yes N=88			Univariable model
	n	(%)	n	(%)	n	(%)	p-value	IRR (95% CI)
PIs							0.58	
None	629	(58.6)	578	(58.7)	51	(58.0)		Ref.
Boosted PIs	342	(31.9)	311	(31.6)	31	(35.2)		1.30 (0.88, 1.92)
Unboosted PIs	102	(9.5)	96	(9.8)	6	(6.8)		0.61 (0.26, 1.40)
NNRTIs							0.89	
None	534	(49.8)	486	(49.3)	48	(54.6)		Ref.
EFV	263	(24.5)	243	(24.7)	20	(22.7)		0.76 (0.48, 1.22)
NVP	137	(12.8)	126	(12.8)	11	(12.5)		0.73 (0.39, 1.35)
RPV	81	(7.6)	76	(7.7)	5	(5.7)		0.62 (0.27, 1.43)
ETR	58	(5.4)	54	(5.5)	4	(4.6)		0.58 (0.21, 1.58)
INSTIs							0.22	
None	924	(86.1)	852	(86.5)	72	(81.8)		Ref.
DTG/EVG/RAL	149	(13.9)	133	(13.5)	16	(18.2)		1.46 (0.91, 2.35)

8.6.5 The association of FRAX scores with HIV

Although the calculations of the FRAX scores incorporate age and gender, it was felt to be important to adjust for these factors in multivariable analysis to account for potential residual confounding. The univariable and multivariable analyses suggested the group of older PLWH had a higher hip fracture and major-osteoporotic score compared to HIV-negative controls. In particular, the hip-fracture score was 0.71 units higher and the major-osteoporotic 1.20 units higher in the group of older PLWH compared to HIV-negative controls (aβ-coeff.=0.71, 95% CI (0.40, 1.02) and aβ-coeff.=1.20, 95% CI (0.58, 1.82), respectively, Table 8.5).

Table 8.5: Univariable and multivariable association of HIV with the FRAX scores

				Hip fracture score	
				Univariable model	**Multivariable model***
	n	**Median (IQR)**	**p-value**	**β-coeff. (95% CI)**	**aβ-coeff. (95% CI)**
HIV status			<0.001		
HIV-negative	274	0.5 (0.2, 1.1)		Ref.	Ref.
Older PLWH	627	0.9 (0.3, 2.1)		0.70 (0.41, 0.99)	0.71 (0.40, 1.02)
				Major-osteoporotic score	
Group			0.05		
HIV-negative	274	5.6 (4.0, 7.5)		Ref.	Ref.
Older PLWH	627	5.9 (3.9, 8.7)		0.68 (0.09, 1.26)	1.20 (0.58, 1.82)

*Adjusted for age, gender, ethnicity, education and marital status

8.6.6 The association between FRAX scores and frailty, falls among older POPPY participants

In this section I explored whether the association of HIV with FRAX scores is independent of any associations with frailty, history of falls. The univariable analysis suggested that the median hip and major-osteoporotic scores among the frail study participants (median (range) 1.3 (0.0, 13.0) and 6.7 (2.2, 27.0)) were significantly higher than those among the non-frail participants (0.6 (0.0, 22.0) and 5.3 (1.1, 33.0), P<0.001 and P=0.004, respectively). Furthermore, the FRAX scores were significantly higher among those with a history of falls in the past 28 days (1.0 (0.0, 22.0) for hip and 6.5 (1.7, 33.0) for major-osteoporotic fractures) than among those with no

history of falls (0.6 (0.0, 16.0) and 5.2 (1.1, 29.0), P<0.001 and P<0.001, respectively, Table 8.6).

The multivariable linear regression models suggested that the association of HIV with FRAX scores was independent of any association with frailty and history of falls, Table 8.6.

Table 8.6: Median, IQR and range of FRAX scores and univariable and multivariable associations with frailty and a history of falls in the past 28 days

			Hip fracture score		
	n	**Median (IQR)**	**p-value**	**Univariable model β-coeff. (95% CI)**	**Multivariable model aβ-coeff. (95% CI)**
HIV status			<0.001		
HIV-negative	627	0.9 (0.3, 2.1)		Ref.	
Older PLWH	274	0.5 (0.2, 1.1)		0.70 (0.41, 0.99)	0.64 (0.30, 0.99)
Frailty			<0.001		
No	645	0.7 (0.3, 1.7)		Ref.	Ref.
Yes	74	1.8 (0.7, 2.8)		0.82 (0.33, 1.30)	0.57 (0.09, 1.05)
Unknown	182	0.7 (0.3, 1.7)		-	-
HIV status			<0.001		
HIV-negative	627	0.9 (0.3, 2.1)		Ref.	Ref.
Older PLWH	274	0.5 (0.2, 1.1)		0.70 (0.41, 0.99)	0.62 (0.32, 0.91)
History of falls in the past 28 days			<0.001		
No	751	0.7 (0.3, 1.6)		Ref.	Ref.
Yes	124	1.2 (0.4, 2.5)		0.76 (0.39, 1.13)	0.62 (0.25, 0.98)
Unknown	26	1.0 (0.4, 2.0)		-	-
			Major-osteoporotic score		
HIV status			0.05		
HIV-negative	627	5.9 (3.9, 8.7)		Ref.	Ref.
Older PLWH	274	5.6 (4.0, 7.5)		0.68 (0.09, 1.26)	1.12 (0.43, 1.81)
Frailty					
No	645	5.6 (3.9, 8.2)	<0.001	Ref.	Ref.
Yes	74	7.9 (5.2, 9.4)		1.44 (0.47, 2.40)	1.23 (0.26, 2.20)
Unknown	182	6.0 (4.1, 8.2)		-	-
HIV status			0.05		
HIV-negative	627	5.9 (3.9, 8.7)		Ref.	Ref.
Older PLWH	274	5.6 (4.0, 7.5)		1.44 (0.47, 2.40)	1.04 (0.43, 1.66)
History of falls in the past 28 days					
No	751	5.6 (3.8, 8.1)	<0.001	Ref.	Ref.
Yes	124	6.7 (5.1, 9.3)		1.56 (0.79, 2.34)	1.24 (0.47, 2.01)
Unknown	26	7.3 (4.9, 8.6)		-	-

*Adjusted for age, gender, ethnicity, education and marital status

8.6.7 HIV depressive symptoms and FRAX scores

In the descriptive analysis, no differences in the distribution of FRAX scores was seen according to the different levels of depressive symptoms as assessed using the CES-D questionnaire (P=0.05 for hip fracture score and P=0.14 for major-osteoporotic fracture score) and the PHQ-9 questionnaire (P=0.06 for hip fracture score and P=0.15 for major-osteoporotic fracture score). Additionally, a dose-response relationship was not apparent between severity of depressive symptom (as assessed using the PHQ-9 score) and the FRAX scores, therefore no further analyses were performed to explore whether the association of HIV with FRAX scores is modified by the association with depressive symptoms.

Table 8.7: Median, IQR and range of FRAX scores stratified by depressive symptoms as assessed by CES-D and PHQ-9 scores

		Hip fracture score	
	n	**Median (IQR)**	**p-value**
Levels of depressive symptoms (CES-D)			
No to mild (0-15)	555	0.7 (0.3, 1.6)	0.05
Moderate (16-23)	103	0.9 (0.4, 1.9)	
Severe (24-60)	148	0.9 (0.3, 2.3)	
Unknown	95	0.7 (0.2, 1.6)	
Levels of depressive symptoms (PHQ-9)			
Minimal (1-4)	509	0.6 (0.2, 1.5)	0.06
Mild (5-9)	149	0.8 (0.4, 2.0)	
Moderate (10-14)	91	1.1 (0.3, 3.0)	
Moderately severe (15-19)	53	0.4 (0.2, 1.3)	
Severe (20-27)	29	0.8 (0.3, 1.8)	
Unknown	84	1.0 (0.3, 2.5)	
	Major-osteoporotic score		
Levels of depressive symptoms (CES-D)			
No to mild (0-15)	555	5.6 (3.9, 8.2)	0.14
Moderate (16-23)	103	6.2 (4.2, 8.3)	
Severe (24-60)	148	6.3 (4.1, 9.1)	
Unknown	95	5.5 (3.8, 8.0)	
Levels of depressive symptoms (PHQ-9)			
Minimal (1-4)	509	5.6 (3.9, 8.2)	0.15
Mild (5-9)	149	6.1 (4.2, 8.3)	
Moderate (10-14)	91	6.2 (4.8, 9.1)	
Moderately severe (15-19)	53	4.9 (3.4, 8.1)	
Severe (20-27)	29	6.4 (4.3, 8.6)	
Unknown	70	6.8 (4.7, 9.1)	

8.6.8 The association between FRAX scores and HIV-specific factors

Older age amongst POPPY PLWH was associated with higher FRAX scores (P<0.001 for both hip and major-osteoporotic fracture scores). The hip fracture score was significantly higher among those with undetectable VL compared to those with detectable or unknown VL (median (range) 0.8 (0.0, 22.0) vs. 0.4 (0.0, 8.6) and 0.4 (0.0, 0.8), P=0.01). Furthermore, those with a longer time since HIV diagnosis, longer time on ART and increased number of total co-medications had significantly higher hip fracture and major-osteoporotic score. Study participants whose current cART did not contain any NRTI had a significantly higher hip fracture score (P<0.001) and major-osteoporotic score (P=0.002) compared to those taking TDF/FTC, ABC/3TC or other NRTIs. Those on a boosted PI-containing regimen had a significantly higher hip fracture score compared to those on unboosted PIs or no PIs (0.9 (0.0, 14.0) vs. 0.6 (0.0, 8.5) and 0.7 (0.0, 22.0), P=0.04). Finally, those on INSTI-containing regimens had a higher hip fracture score (P=0.08) and major-osteoporotic score (P=0.03) compared to those not on INSTIs (Table 8.8).

The multivariable analysis for FRAX scores included the parameters that were significantly associated (P<0.05) in the univariable models with hip fracture score (age, VL, time since HIV diagnosis, years on ART, number of total co-medications (excluding ART) and NRTIs) and major-osteoporotic score (age, time since HIV diagnosis, years on ART, number of total co-medications (excluding ART) and use of NRTIs). Older age and number of total co-medications (excluding ART) were the only factors that remained significantly associated with the FRAX scores in the multivariable model. However, the associations between the other HIV-specific factors with the FRAX scores were attenuated in the multivariable model and became non-significant, suggesting that they were not independently associated with the FRAX scores (Table 8.9).

Table 8.8: Median, IQR and range of FRAX scores stratified by HIV-specific factors

	Hip fracture score				Major-osteoporotic score			
	n	Median (IQR)	(range)	p-value	n	Median (IQR)	(range)	p-value
Age at baseline visit (years)								
40-49	233	0.4 (0.1, 1.2)	(0.0, 12.0)	<0.001	233	3.9 (2.8, 6.5)	(2.1, 18.0)	<0.001
50-54	236	0.4 (0.2, 1.3)	(0.0, 14.0)		236	4.9 (3.2, 7.2)	(2.2, 24.0)	
55-59	170	0.8 (0.4, 1.9)	(0.0, 22.0)		170	6.1 (4.0, 8.6)	(1.1, 33.0)	
60-64	115	1.3 (0.6, 2.7)	(0.0, 13.0)		115	6.4 (4.9, 11.0)	(1.7, 27.0)	
65-69	69	1.5 (0.9, 3.0)	(0.2, 8.6)		69	8.3 (6.2, 9.9)	(3.3, 25.0)	
≥70	37	3.0 (1.4, 4.6)	(0.4, 22.0)		37	7.9 (5.3, 12.0)	(3.1, 28.0)	
AIDS history								
No	585	0.7 (0.2, 1.8)	(0.0, 22.0)	0.09	585	5.3 (3.5, 8.1)	(1.7, 33.0)	0.30
Yes	275	0.9 (0.3, 2.1)	(0.0, 14.0)		275	5.6 (3.5, 8.4)	(1.1, 25.0)	
CD4 count (cells/mm^3)								
≤437	164	0.6 (0.3, 1.6)	(0.0, 14.0)	0.40	164	5.1 (3.4, 8.1)	(2.2, 27.0)	0.34
438-566	164	0.7 (0.2, 1.5)	(0.0, 7.1)		164	5.2 (3.5, 7.7)	(2.3, 25.0)	
567-695	169	0.8 (0.3, 2.4)	(0.0, 22.0)		169	5.8 (3.6, 8.6)	(2.1, 33.0)	
696-874	169	0.7 (0.2, 1.9)	(0.0, 13.0)		169	5.3 (3.2, 7.6)	(1.1, 25.0)	
≥875	172	0.8 (0.3, 2.1)	(0.0, 22.0)		172	6.0 (3.9, 8.1)	(2.3, 28.0)	
Unknown	22	0.4 (0.2, 2.6)	(0.0, 8.5)		22	5.8 (3.2, 9.9)	(2.8, 24.0)	
CD4 nadir (cells/mm^3)								
≤70	165	0.7 (0.3, 1.7)	(0.0, 14.0)	0.18	165	5.2 (3.6, 8.1)	(2.2, 27.0)	0.58
71-153	160	1.0 (0.4, 2.2)	(0.0, 8.6)		160	5.9 (3.6, 8.8)	(1.1, 25.0)	
154-225	163	0.6 (0.2, 2.0)	(0.0, 22.0)		163	5.2 (3.4, 7.9)	(1.7, 28.0)	
226-319	165	0.7 (0.3, 1.8)	(0.0, 22.0)		165	5.3 (3.5, 8.2)	(2.3, 33.0)	
≥320	174	0.8 (0.2, 1.9)	(0.0, 12.0)		174	5.3 (3.1, 8.4)	(2.1, 18.0)	

	Hip fracture score				Major-osteoporotic score			
	n	Median (IQR)	(range)	p-value	n	Median (IQR)	(range)	p-value
Unknown	33	0.7 (0.3, 1.6)	(0.0, 7.1)		33	5.5 (3.8, 8.5)	(2.4, 25.0)	
VL								
Undetectable	782	0.8 (0.3, 2.0)	(0.0, 22.0)	0.01	782	5.4 (3.5, 8.3)	(1.1, 33.0)	0.32
Detectable	75	0.4 (0.2, 1.4)	(0.0, 8.6)		75	5.3 (3.0, 7.7)	(2.2, 24.0)	
Unknown	3	0.4 (0.0, 0.8)	(0.0, 0.8)		3	4.6 (3.4, 5.2)	(3.4, 5.2)	
Time since HIV diagnosis (yrs)								
≤7.7	166	0.6 (0.2, 1.5)	(0.0, 22.0)	<0.001	166	5.1 (3.1, 8.4)	(2.2, 33.0)	<0.001
7.8-12.4	172	0.5 (0.2, 1.3)	(0.0, 7.6)		172	4.5 (3.2, 7.2)	(1.1, 24.0)	
12.5-17.1	169	0.7 (0.3, 1.8)	(0.0, 11.0)		169	5.3 (3.7, 7.6)	(2.1, 21.0)	
17.2-22.8	174	1.0 (0.4, 2.4)	(0.0, 14.0)		174	5.7 (3.7, 9.0)	(2.2, 27.0)	
≥22.9	171	1.1 (0.4, 2.4)	(0.0, 22.0)		171	6.1 (4.1, 9.3)	(1.7, 28.0)	
Unknown	8	0.7 (0.1, 1.3)	(0.1, 1.7)		8	6.1 (4.2, 7.1)	(3.3, 7.3)	
Years on ART								
≤4.7	170	0.6 (0.2, 1.5)	(0.0, 7.8)	<0.001	170	5.3 (3.2, 8.1)	(2.2, 17.0)	0.005
4.8-8.1	169	0.6 (0.2, 1.8)	(0.0, 22.0)		169	4.7 (3.2, 7.5)	(2.2, 33.0)	
8.2-13.1	168	0.7 (0.2, 1.8)	(0.0, 7.1)		168	5.5 (3.3, 8.3)	(1.1, 25.0)	
13.2-17.5	168	0.7 (0.3, 2.0)	(0.0, 22.0)		168	5.3 (3.6, 7.9)	(2.1, 28.0)	
≥17.6	173	1.0 (0.4, 2.7)	(0.0, 14.0)		173	6.1 (4.2, 9.2)	(2.2, 27.0)	
Unknown	12	0.4 (0.2, 1.1)	(0.0, 8.6)		12	5.3 (3.0, 11.3)	(2.5, 16.0)	
Number of total co-medications (excluding cART)								
0	241	0.5 (0.2, 1.4)	(0.0, 22.0)	<0.001	241	4.4 (3.0, 7.0)	(1.1, 28.0)	<0.001
1-4	390	0.8 (0.3, 1.9)	(0.0, 22.0)		390	5.6 (3.7, 8.3)	(2.1, 33.0)	
5-9	174	1.0 (0.3, 2.6)	(0.0, 13.0)		174	6.0 (3.7, 8.8)	(2.3, 27.0)	

	Hip fracture score				Major-osteoporotic score			
	n	Median (IQR)	(range)	p-value	n	Median (IQR)	(range)	p-value
≥10	55	1.1 (0.4, 3.1)	(0.0, 13.0)		55	7.8 (5.0, 11.0)	(1.7, 25.0)	
NRTI in regimen								
None	115	1.0 (0.3, 2.2)	(0.0, 8.6)	<0.001	115	6.6 (3.9, 9.7)	(1.7, 25.0)	0.002
TFV/FTC	541	0.7 (0.2, 1.8)	(0.0, 22.0)		541	5.3 (3.4, 7.9)	(1.1, 33.0)	
ABC/3TC	103	0.4 (0.2, 1.1)	(0.0, 8.3)		103	4.8 (3.2, 7.2)	(2.2, 25.0)	
Other	101	0.9 (0.4, 2.8)	(0.0, 14.0)		101	5.7 (3.9, 9.6)	(2.4, 22.0)	
PI in regimen								
None	498	0.7 (0.2, 1.9)	(0.0, 22.0)	0.04	498	5.3 (3.5, 8.3)	(1.1, 33.0)	0.82
Boosted PIs	283	0.9 (0.3, 2.0)	(0.0, 14.0)		283	5.5 (3.6, 8.0)	(1.7, 27.0)	
Unboosted PIs	79	0.6 (0.1, 2.0)	(0.0, 8.5)		79	5.1 (3.2, 8.4)	(2.2, 15.0)	
NNRTI in regimen								
None	423	0.8 (0.2, 1.9)	(0.0, 14.0)	0.24	423	5.4 (3.5, 8.2)	(2.1, 27.0)	0.46
EFV	216	0.7 (0.3, 1.8)	(0.0, 22.0)		216	5.4 (3.4, 7.9)	(1.1, 33.0)	
NVP	114	0.5 (0.2, 2.1)	(0.0, 22.0)		114	5.4 (3.4, 8.7)	(2.2, 28.0)	
RPV	55	0.7 (0.3, 1.5)	(0.0, 8.6)		55	5.1 (3.5, 7.5)	(2.2, 25.0)	
ETR	52	1.1 (0.4, 2.3)	(0.0, 6.6)		52	6.1 (4.2, 8.8)	(1.7, 22.0)	
INSTI in regimen								
No	737	0.7 (0.2, 1.9)	(0.0, 22.0)	0.08	737	5.3 (3.5, 8.1)	(1.1, 33.0)	0.03
Yes	123	1.0 (0.3, 2.5)	(0.0, 13.0)		123	6.2 (3.9, 8.7)	(2.5, 25.0)	

Table 8.9: Univariable and multivariable association of FRAX scores with age and HIV factors among PLWH in POPPY

	Hip fracture score		Major-osteoporotic score	
	Univariable model	**Multivariable model***	**Univariable model**	**Multivariable model***
	β-coeff. (95% CI)	**aβ-coeff. (95% CI)**	**β-coeff. (95% CI)**	**aβ-coeff. (95% CI)**
Age at baseline visit				
40-49	Ref.	Ref.	Ref.	Ref.
50-54	0.03 (-0.06, 0.11)	0.07 (-0.02, 0.15)	0.06 (0.00, 0.11)	0.08 (0.01, 0.14)
55-59	0.15 (0.06, 0.24)	0.11 (0.02, 0.20)	0.18 (0.12, 0.25)	0.16 (0.09, 0.23)
60-64	0.31 (0.21, 0.41)	0.25 (0.14, 0.35)	0.27 (0.20, 0.35)	0.24 (0.16, 0.32)
65-69	0.42 (0.29, 0.54)	0.39 (0.27, 0.52)	0.38 (0.29, 0.47)	0.34 (0.25, 0.44)
≥70	0.59 (0.44, 0.75)	0.52 (0.37, 0.68)	0.33 (0.22, 0.45)	0.28 (0.17, 0.40)
AIDS history				
No	Ref.	Ref.	Ref.	Ref.
Yes	0.06 (-0.01, 0.13)	-	0.03 (-0.02, 0.08)	-
CD4 count (cells/mm^3)				
≤437	Ref.	Ref.	Ref.	Ref.
438-566	-0.01 (-0.12, 0.09)	-	0.01 (-0.07, 0.08)	-
567-695	0.06 (-0.04, 0.16)	-	0.03 (-0.04, 0.11)	-
696-874	0.02 (-0.09, 0.12)	-	-0.02 (-0.09, 0.06)	-
≥875	0.09 (-0.02, 0.19)	-	0.05 (-0.03, 0.12)	-
CD4 nadir (cells/mm^3)				
≤70	Ref.	Ref.	Ref.	Ref.
71-153	0.05 (-0.05, 0.16)	-	0.03 (-0.04, 0.11)	-
154-225	-0.05 (-0.15, 0.06)	-	-0.03 (-0.10, 0.05)	-
226-319	-0.02 (-0.12, 0.09)	-	0.01 (-0.06, 0.09)	-
≥320	-0.03 (-0.13, 0.07)	-	-0.02 (-0.09, 0.06)	-
VL				
Undetectable	Ref.	Ref.	Ref.	Ref.
Detectable	-0.13 (-0.25, -0.02)	-0.07 (-0.18, 0.04)	-0.04 (-0.12, 0.04)	-

	Hip fracture score		Major-osteoporotic score	
	Univariable model	Multivariable model*	Univariable model	Multivariable model*
	β-coeff. (95% CI)	aβ-coeff. (95% CI)	β-coeff. (95% CI)	aβ-coeff. (95% CI)
Time since HIV diagnosis (yrs)				
≤7.7	Ref.	Ref.	Ref.	Ref.
7.8-12.4	-0.07 (-0.17, 0.03)	-0.03 (-0.15, 0.08)	-0.04 (-0.11, 0.03)	-0.01 (-0.09, 0.08)
12.5-17.1	0.03 (-0.07, 0.13)	0.07 (-0.05, 0.19)	0.01 (-0.06, 0.08)	0.04 (-0.06, 0.13)
17.2-22.8	0.13 (0.03, 0.23)	0.04 (-0.09, 0.18)	0.07 (0.00, 0.15)	0.04 (-0.06, 0.14)
≥22.9	0.16 (0.06, 0.27)	0.01 (-0.12, 0.14)	0.11 (0.03, 0.18)	0.01 (-0.09, 0.11)
Years on ART				
≤4.7	Ref.	Ref.	Ref.	Ref.
4.8-8.1	0.03 (-0.07, 0.13)	0.00 (-0.10, 0.11)	-0.01 (-0.08, 0.07)	-0.03 (-0.11, 0.05)
8.2-13.1	0.02 (-0.09, 0.12)	0.01 (-0.11, 0.13)	0.02 (-0.06, 0.09)	-0.02 (-0.11, 0.07)
13.2-17.5	0.06 (-0.04, 0.16)	-0.08 (-0.21, 0.05)	0.02 (-0.05, 0.10)	-0.10 (-0.20, 0.00)
≥17.6	0.21 (0.11, 0.31)	0.01 (-0.13, 0.14)	0.11 (0.04, 0.18)	-0.03 (-0.14, 0.07)
Number of total co-medications (excluding cART)				
0	Ref.	Ref.	Ref.	Ref.
1-4	0.11 (0.03, 0.19)	0.07 (0.00, 0.14)	0.11 (0.05, 0.16)	0.06 (0.01, 0.12)
5-9	0.15 (0.06, 0.24)	0.12 (0.03, 0.21)	0.13 (0.07, 0.20)	0.09 (0.02, 0.16)
≥10	0.29 (0.15, 0.43)	0.14 (0.00, 0.28)	0.27 (0.17, 0.37)	0.13 (0.03, 0.24)
NRTI in regimen				
None	Ref.	Ref.	Ref.	Ref.
TFV/FTC	-0.09 (-0.19, 0.00)	-0.02 (-0.12, 0.08)	-0.10 (-0.17, -0.03)	-0.04 (-0.12, 0.04)
ABC/3TC	-0.21 (-0.33, -0.08)	-0.07 (-0.20, 0.06)	-0.14 (-0.23, -0.05)	-0.05 (-0.15, 0.05)
Other	0.02 (-0.11, 0.15)	0.01 (-0.11, 0.13)	-0.03 (-0.12, 0.07)	-0.02 (-0.12, 0.07)
PI in regimen				

	Hip fracture score		Major-osteoporotic score	
	Univariable model	**Multivariable model***	**Univariable model**	**Multivariable model***
	β-coeff. (95% CI)	**aβ-coeff. (95% CI)**	**β-coeff. (95% CI)**	**aβ-coeff. (95% CI)**
None	Ref.	Ref.	Ref.	Ref.
Boosted PIs	0.06 (-0.01, 0.13)	-	0.00 (-0.05, 0.05)	-
Unboosted PIs	-0.08 (-0.19, 0.04)	-	-0.02 (-0.11, 0.06)	-
NNRTI in regimen				
None	Ref.	Ref.	Ref.	Ref.
EFV	-0.02 (-0.09, 0.06)	-	-0.01 (-0.07, 0.05)	-
NVP	-0.06 (-0.16, 0.04)	-	0.02 (-0.06, 0.09)	-
RPV	-0.03 (-0.17, 0.10)	-	-0.02 (-0.12, 0.08)	-
ETR	0.07 (-0.06, 0.21)	-	0.07 (-0.03, 0.17)	-
INSTI in regimen				
No	Ref.	Ref.	Ref.	Ref.
Yes	0.08 (-0.01, 0.17)	-	0.07 (0.00, 0.13)	-

*Adjusted for gender, ethnicity, BMI, current smoking, current alcohol use, recreational drug use in the past 6 months, frailty and history of falls in the past 28 days

8.6.9 Association between PK parameters and FRAX scores among POPPY PLWH

The descriptive analysis suggested that higher TDF and FTC $AUC_{0\text{-}24h}$, C_{max} and C_{min} and lower CL_{24h} were associated with higher FRAX scores. In contrast, no associations were seen between the PK parameters for ABC and either score. While the higher $AUC_{0\text{-}24h}$ for 3TC was associated with higher major-osteoporotic scores, no other associations were apparent between the PK parameters for 3TC and either of the FRAX scores (Table 8.10, Table 8.11).

Table 8.10: Median (range) of hip fracture score in subgroups defined by PK parameters for TDF, FTC, ABC and 3TC

	Hip fracture score											
	TDF			FTC			ABC			3TC		
	n	Median (range)	p-value	N	Median (range)	p-value	N	Median (range)	p-value	N	Median (range)	p-value
$AUC_{0\text{-}24h}$ (mg.h/L)			<0.001			<0.001			0.57			0.40
<1nd quintile	75	0.3 (0.0, 8.0)		69	0.5 (0.0, 9.0)		16	0.9 (0.0, 6.6)		22	1.0 (0.0, 6.6)	
1st -2nd quintile	82	0.5 (0.0, 11.0)		84	0.6 (0.0, 7.1)		19	0.4 (0.1, 4.3)		21	0.3 (0.1, 4.9)	
2nd -3rd quintile	96	0.6 (0.0, 9.0)		84	0.7 (0.0, 7.6)		18	0.7 (0.0, 6.5)		23	0.7 (0.1, 5.0)	
4th -5th quintile	96	1.6 (0.0, 14.0)		92	1.0 (0.0, 11.0)		14	0.4 (0.0, 7.5)		26	0.7 (0.0, 14.0)	
≥5th quintile	99	1.2 (0.0, 22.0)		90	1.3 (0.0, 22.0)		18	0.8 (0.0, 5.9)		25	1.1 (0.0, 5.9)	
C_{max} (mg/L)			<0.001			<0.001			0.95			0.59
<1nd quintile	85	0.4 (0.0, 11.0)		69	0.5 (0.0, 9.0)		16	0.7 (0.0, 6.6)		27	1.0 (0.0, 14.0)	
1st -2nd quintile	86	0.6 (0.0, 8.0)		84	0.6 (0.0, 7.1)		20	0.5 (0.1, 5.0)		25	0.9 (0.0, 5.9)	
2nd -3rd quintile	89	0.9 (0.0, 7.6)		85	0.6 (0.0, 7.6)		17	0.6 (0.0, 6.5)		22	0.6 (0.1, 4.7)	
4th -5th quintile	91	1.2 (0.1, 7.8)		90	1.0 (0.0, 11.0)		14	0.4 (0.1, 7.5)		21	0.9 (0.0, 6.6)	
≥5th quintile	97	1.2 (0.0, 22.0)		91	1.3 (0.0, 22.0)		18	0.8 (0.0, 5.9)		22	0.6 (0.0, 6.5)	
C_{min} (mg/L)			<0.001			<0.001			0.86			0.49
<1nd quintile	74	0.4 (0.0, 9.0)		73	0.5 (0.0, 9.0)		16	0.6 (0.1, 5.0)		22	1.0 (0.0, 6.6)	
1st -2nd quintile	99	0.6 (0.0, 11.0)		82	0.6 (0.0, 7.1)		18	0.6 (0.0, 4.3)		21	0.4 (0.1, 4.9)	
2nd -3rd quintile	81	0.9 (0.0, 7.8)		84	0.6 (0.0, 7.6)		20	0.6 (0.0, 7.5)		23	0.6 (0.1, 5.0)	
4th -5th quintile	96	1.4 (0.0, 14.0)		94	1.0 (0.0, 11.0)		12	0.6 (0.2, 5.9)		27	1.0 (0.0, 14.0)	
≥5th quintile	98	1.0 (0.0, 22.0)		86	1.4 (0.0, 22.0)		19	0.6 (0.0, 5.1)		24	1.1 (0.0, 5.1)	
CL_{24h} (L/h)			<0.001			<0.001			0.67			0.64
<1nd quintile	100	1.3 (0.0, 22.0)		93	1.3 (0.0, 22.0)		20	0.6 (0.0, 5.1)		26	1.1 (0.0, 5.9)	
1st -2nd quintile	92	1.6 (0.0, 14.0)		89	0.9 (0.0, 11.0)		16	0.6 (0.0, 7.5)		26	0.9 (0.0, 14.0)	
2nd -3rd quintile	97	0.6 (0.0, 9.0)		85	0.6 (0.0, 7.6)		16	0.7 (0.1, 6.5)		23	0.5 (0.1, 5.0)	
4th -5th quintile	84	0.5 (0.0, 11.0)		84	0.6 (0.0, 9.0)		18	0.6 (0.0, 4.3)		20	0.4 (0.1, 4.9)	
≥5th quintile	75	0.3 (0.0, 6.1)		68	0.4 (0.0, 8.0)		15	0.4 (0.1, 5.0)		22	0.8 (0.0, 6.6)	

Table 8.11: Median (range) of major-osteoporotic score in subgroups defined PK parameters for TDF, FTC, ABC and 3TC

	Major-osteoporotic FRAX score											
	TDF			FTC			ABC			3TC		
	n	Median (range)	p-value	N	Median (range)	p-value	N	Median (range)	p-value	N	Median (range)	p-value
$AUC_{0\text{-}24h}$ (mg.h/L)			<0.001			<0.001			0.51			0.04
<1nd quintile	75	4.2 (1.1, 15.0)		69	3.8 (1.1, 15.0)		16	6.8 (2.8, 14.0)		22	5.8 (2.5, 25.0)	
1st -2nd quintile	82	4.5 (2.2, 17.0)		84	5.1 (2.3, 18.0)		19	4.8 (2.4, 16.0)		21	4.2 (2.7, 11.0)	
2nd -3rd quintile	96	5.5 (2.4, 17.0)		84	5.3 (2.4, 24.0)		18	5.6 (2.2, 25.0)		23	5.7 (2.8, 16.0)	
4th -5th quintile	96	6.5 (2.4, 24.0)		92	5.6 (2.3, 17.0)		14	4.0 (2.3, 16.0)		26	5.2 (2.2, 21.0)	
≥5th quintile	99	6.1 (2.3, 28.0)		90	6.2 (2.2, 28.0)		18	5.8 (2.8, 21.0)		25	7.9 (2.3, 21.0)	
C_{max} (mg/L)			<0.001			<0.001			0.82			0.42
<1nd quintile	85	4.5 (2.2, 17.0)		69	3.8 (1.1, 15.0)		16	5.7 (2.3, 12.0)		27	6.0 (2.2, 21.0)	
1st -2nd quintile	86	5.1 (1.1, 17.0)		84	5.1 (2.3, 18.0)		20	5.3 (2.4, 16.0)		25	6.0 (2.2, 21.0)	
2nd -3rd quintile	89	5.6 (2.1, 24.0)		85	5.2 (2.4, 24.0)		17	5.3 (2.2, 25.0)		22	5.3 (2.7, 12.0)	
4th -5th quintile	91	5.9 (2.5, 20.0)		90	5.6 (2.3, 17.0)		14	4.0 (2.5, 16.0)		21	5.9 (2.8, 22.0)	
≥5th quintile	97	6.1 (2.2, 28.0)		91	6.3 (2.2, 28.0)		18	5.8 (2.8, 21.0)		22	5.4 (2.3, 25.0)	
C_{min} (mg/L)			<0.001			<0.001			0.89			0.17
<1nd quintile	74	4.2 (1.1, 15.0)		73	3.9 (1.1, 17.0)		16	4.5 (2.8, 14.0)		22	5.8 (2.5, 25.0)	
1st -2nd quintile	99	4.6 (2.2, 17.0)		82	5.1 (2.3, 18.0)		18	5.3 (2.2, 16.0)		21	5.0 (2.7, 11.0)	
2nd -3rd quintile	81	5.4 (2.3, 17.0)		84	5.1 (2.4, 24.0)		20	5.6 (2.2, 25.0)		23	5.3 (2.8, 16.0)	
4th -5th quintile	96	6.5 (2.3, 24.0)		94	5.6 (2.3, 17.0)		12	5.4 (2.7, 21.0)		27	5.2 (2.2, 21.0)	
≥5th quintile	98	6.0 (2.4, 28.0)		86	6.4 (2.2, 28.0)		19	5.4 (2.3, 21.0)		24	7.0 (2.3, 21.0)	
CL_{24h} (L/h)			<0.001			<0.001			0.59			0.09
<1nd quintile	100	6.5 (2.6, 28.0)		93	6.3 (2.2, 28.0)		20	5.1 (2.3, 21.0)		26	7.7 (2.3, 21.0)	
1st -2nd quintile	92	6.1 (2.4, 24.0)		89	5.5 (2.3, 17.0)		16	5.4 (2.7, 21.0)		26	5.2 (2.2, 21.0)	
2nd -3rd quintile	97	5.6 (2.4, 17.0)		85	5.2 (2.4, 24.0)		16	5.9 (2.5, 25.0)		23	5.3 (2.8, 16.0)	
4th -5th quintile	84	4.5 (1.1, 17.0)		84	5.1 (2.3, 17.0)		18	5.2 (2.2, 16.0)		20	5.0 (2.7, 11.0)	
≥5th quintile	75	3.8 (2.2, 14.0)		68	3.8 (1.1, 15.0)		15	4.1 (2.8, 14.0)		22	5.8 (2.5, 25.0)	

8.6.9.1 TDF

The univariable analysis suggested that all TDF PK parameters (higher $AUC_{0\text{-}24}$, higher C_{max}, higher C_{min} and lower CL_{24h}) were significantly associated with higher FRAX scores (Figure 8.1, Figure 8.2 and Table 8.12). The associations of higher $AUC_{0\text{-}24h}$ and lower CL_{24h} with higher FRAX scores remained significant in the multivariable models after adjusting for BMI, gender, ethnicity, smoking, current alcohol use, recreational drug use in the past 6 months and total number of co-medications (excluding cART). The association of higher C_{max} with higher hip fracture score remained in the multivariable analysis however, for major-osteoporotic score this association was attenuated and became non-significant after adjustment (Table 8.12).

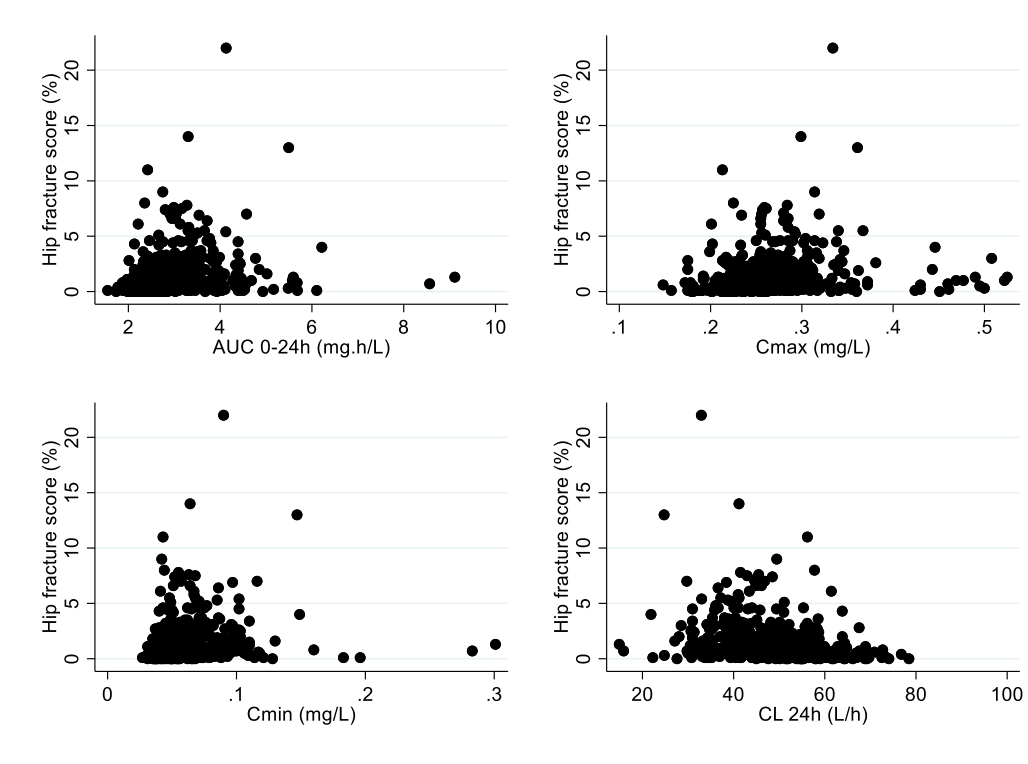


Figure 8.1: Association of TDF PK parameters with hip fracture score

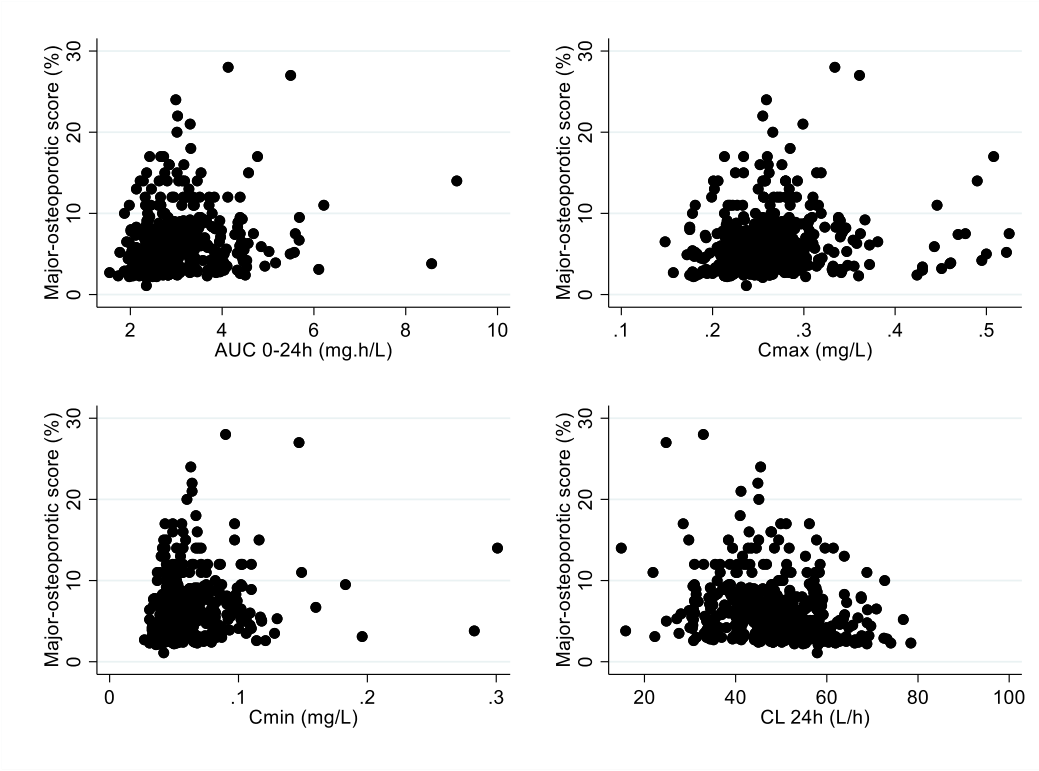


Figure 8.2: Association of TDF PK parameters with major-osteoporotic score

Table 8.12: Univariable and multivariable association between FRAX scores and TDF PK parameters

	Hip fracture score		Major-osteoporotic FRAX score	
	Univariable model	Multivariable model*	Univariable model	Multivariable model*
	β-coeff. (95% CI)	aβ-coeff. (95% CI)	β-coeff. (95% CI)	aβ-coeff. (95% CI)
$AUC_{0\text{-}24h}$ (mg.h/L)				
≤2.355	Ref.	Ref.	Ref.	Ref.
2.356-2.616	0.11 (-0.03, 0.24)	0.07 (-0.06, 0.20)	0.04 (-0.07, 0.14)	0.03 (-0.07, 0.13)
2.617-2.941	0.20 (0.07, 0.33)	0.09 (-0.04, 0.21)	0.15 (0.05, 0.24)	0.09 (-0.01, 0.19)
2.942-3.410	0.43 (0.30, 0.56)	0.26 (0.12, 0.40)	0.25 (0.15, 0.34)	0.16 (0.05, 0.26)
≥3.411	0.36 (0.23, 0.49)	0.21 (0.07, 0.35)	0.20 (0.11, 0.30)	0.11 (0.00, 0.22)
C_{max} (mg/L)				
≤0.219	Ref.	Ref.	Ref.	Ref.
0.220-0.241	0.11 (-0.03, 0.24)	0.04 (-0.08, 0.17)	0.04 (-0.06, 0.14)	0.02 (-0.08, 0.12)
0.242-0.263	0.18 (0.05, 0.31)	0.12 (-0.02, 0.26)	0.12 (0.02, 0.22)	0.08 (-0.02, 0.19)
0.264-0.289	0.31 (0.18, 0.44)	0.21 (0.07, 0.36)	0.18 (0.08, 0.28)	0.14 (0.03, 0.25)
≥0.290	0.36 (0.23, 0.49)	0.23 (0.07, 0.38)	0.18 (0.08, 0.27)	0.09 (-0.02, 0.21)
C_{min} (mg/L)				
≤0.042	Ref.	Ref.	Ref.	Ref.
0.043-0.050	0.14 (0.01, 0.28)	0.07 (-0.06, 0.19)	0.08 (-0.01, 0.18)	0.04 (-0.06, 0.13)
0.051-0.058	0.19 (0.05, 0.33)	0.06 (-0.07, 0.19)	0.12 (0.01, 0.22)	0.05 (-0.05, 0.15)
0.059-0.072	0.33 (0.20, 0.47)	0.15 (0.02, 0.28)	0.23 (0.13, 0.33)	0.10 (0.00, 0.20)
≥0.073	0.31 (0.17, 0.44)	0.15 (0.01, 0.28)	0.18 (0.09, 0.28)	0.06 (-0.04, 0.17)
CL_{24h} (L/h)				
≤40.462	Ref.	Ref.	Ref.	Ref.
40.463-46.793	0.02 (-0.11, 0.14)	0.02 (-0.10, 0.13)	0.00 (-0.09, 0.09)	0.02 (-0.07, 0.11)
46.794-52.448	-0.25 (-0.37, -0.13)	-0.19 (-0.31, -0.07)	-0.09 (-0.18, 0.00)	-0.04 (-0.14, 0.05)
52.449-58.096	-0.32 (-0.44, -0.20)	-0.21 (-0.34, -0.08)	-0.20 (-0.29, -0.11)	-0.11 (-0.21, -0.01)
≥58.097	-0.44 (-0.57, -0.32)	-0.31 (-0.45, -0.17)	-0.25 (-0.35, -0.15)	-0.17 (-0.28, -0.06)

*Adjusted for age, gender, ethnicity, current smoking, current use of alcohol, recreational drug use in the past 6 months and total number of co-medications

8.6.9.2 FTC

The univariable analysis suggested that higher levels $AUC_{0\text{-}24}$, C_{max} and C_{min} and lower CL_{24h} were associated with higher FRAX scores (Figure 8.3, Figure 8.4 and Table 8.13). The univariable associations of hip fracture score remained significant in the multivariable model after adjusting for BMI, gender, ethnicity, smoking, current alcohol use, recreational drug use in the past 6 months and total number of co-medications (excluding cART). More specifically, higher $AUC_{0\text{-}24h}$, C_{max}, C_{min} and lower CL_{24h} were associated with higher hip fracture score. However, the univariable associations with major-osteoporotic scores were attenuated and became non-significant (Table 8.13).

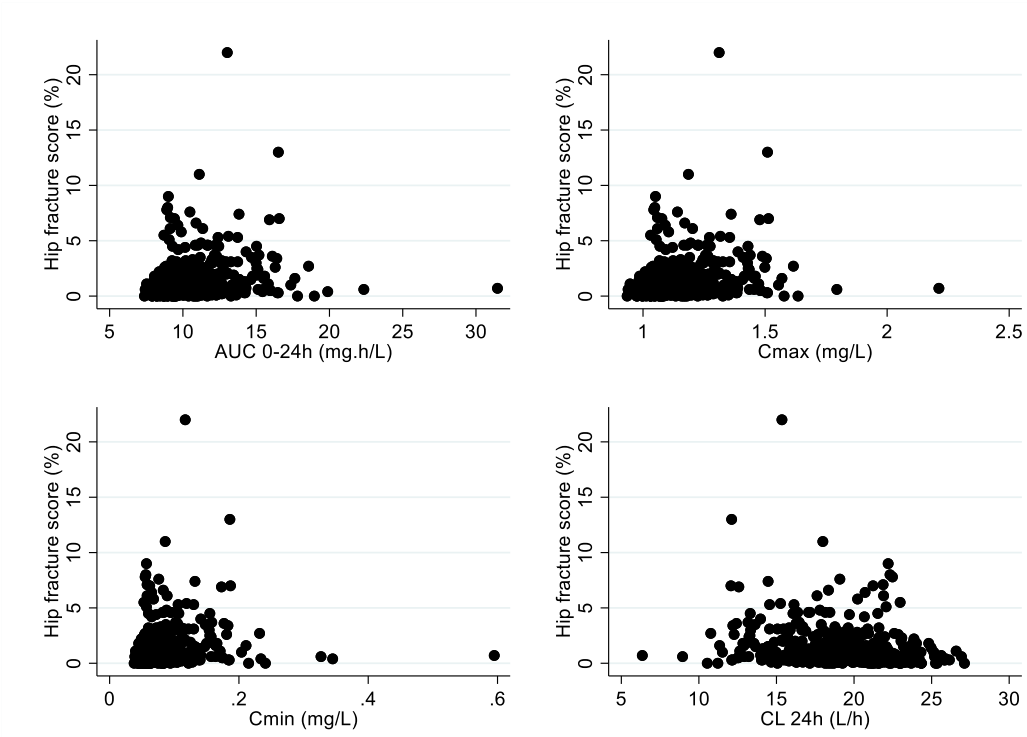


Figure 8.3: Association of FTC PK parameters with hip fracture score

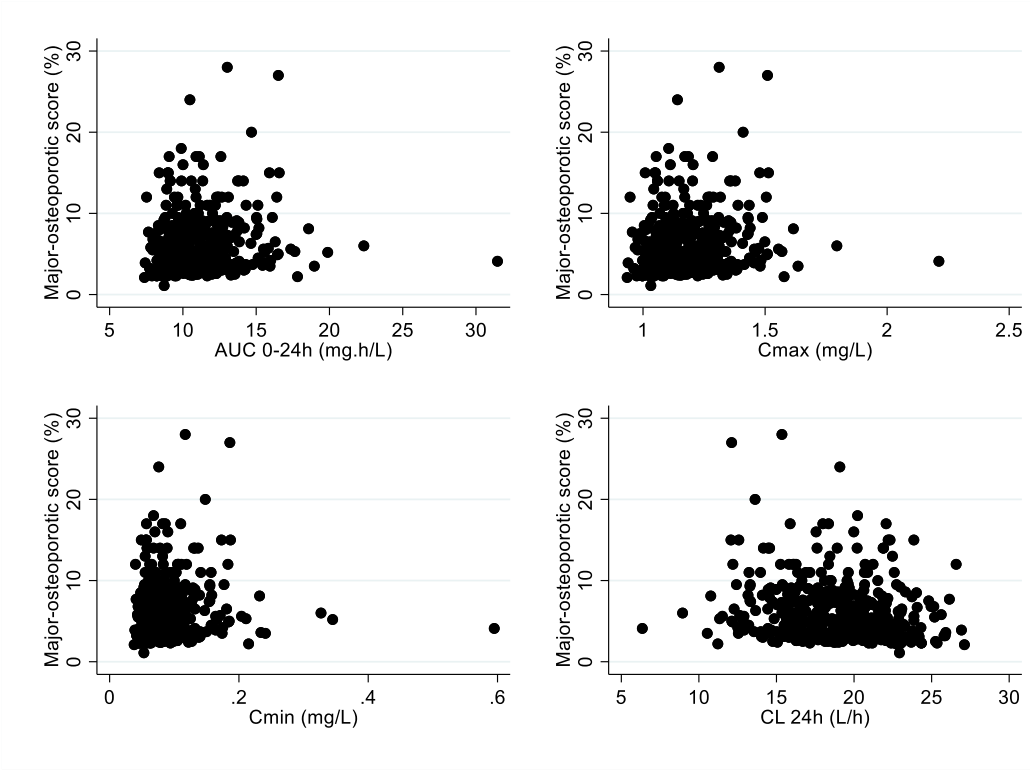


Figure 8.4: Association of FTC PK parameters with major-osteoporotic score

Table 8.13: Univariable and multivariable association between FRAX scores and FTC PK parameters

	Hip fracture score		Major-osteoporotic FRAX score	
	Univariable model	Multivariable model*	Univariable model	Multivariable model*
	β-coeff. (95% CI)	aβ-coeff. (95% CI)	β-coeff. (95% CI)	aβ-coeff. (95% CI)
$AUC_{0\text{-}24h}$ (mg.h/L)				
≤9.017	Ref.	Ref.	Ref.	Ref.
9.018-9.897	0.11 (-0.03, 0.25)	0.07 (-0.07, 0.20)	0.10 (0.00, 0.20)	0.04 (-0.05, 0.14)
9.898-10.800	0.16 (0.02, 0.30)	0.06 (-0.07, 0.19)	0.10 (0.00, 0.21)	0.04 (-0.06, 0.14)
10.801-12.352	0.19 (0.05, 0.33)	0.12 (-0.02, 0.25)	0.14 (0.04, 0.24)	0.06 (-0.05, 0.16)
≥12.353	0.33 (0.19, 0.47)	0.20 (0.07, 0.34)	0.22 (0.12, 0.33)	0.10 (0.00, 0.21)
C_{max} (mg/L)				
≤1.051	Ref.	Ref.	Ref.	Ref.
1.052-1.105	0.11 (-0.03, 0.25)	0.07 (-0.06, 0.20)	0.10 (0.00, 0.20)	0.05 (-0.05, 0.14)
1.106-1.164	0.16 (0.02, 0.30)	0.06 (-0.08, 0.19)	0.10 (0.00, 0.20)	0.04 (-0.06, 0.14)
1.165-1.268	0.19 (0.05, 0.33)	0.12 (-0.01, 0.26)	0.14 (0.04, 0.24)	0.06 (-0.05, 0.16)
≥1.269	0.33 (0.19, 0.47)	0.20 (0.06, 0.33)	0.23 (0.13, 0.33)	0.10 (0.00, 0.21)
C_{min} (mg/L)				
≤0.057	Ref.	Ref.	Ref.	Ref.
0.058-0.068	0.09 (-0.05, 0.23)	0.03 (-0.10, 0.16)	0.09 (-0.01, 0.19)	0.03 (-0.07, 0.12)
0.069-0.081	0.12 (-0.02, 0.26)	0.01 (-0.12, 0.14)	0.07 (-0.03, 0.17)	0.00 (-0.09, 0.10)
0.082-0.106	0.19 (0.05, 0.32)	0.10 (-0.03, 0.23)	0.14 (0.04, 0.24)	0.04 (-0.06, 0.14)
≥0.107	0.31 (0.17, 0.45)	0.18 (0.05, 0.31)	0.21 (0.11, 0.31)	0.09 (-0.01, 0.19)
CL_{24h} (L/h)				
≤16.263	Ref.	Ref.	Ref.	Ref.
16.264-18.542	-0.14 (-0.27, -0.01)	-0.09 (-0.20, 0.03)	-0.08 (-0.17, 0.01)	-0.05 (-0.14, 0.04)
18.543-20.228	-0.17 (-0.30, -0.04)	-0.14 (-0.26, -0.02)	-0.12 (-0.21, -0.02)	-0.06 (-0.15, 0.03)
20.229-22.228	-0.21 (-0.34, -0.08)	-0.14 (-0.26, -0.01)	-0.12 (-0.22, -0.03)	-0.06 (-0.15, 0.04)
≥22.229	-0.36 (-0.49, -0.22)	-0.22 (-0.36, -0.09)	-0.24 (-0.34, -0.14)	-0.12 (-0.22, -0.01)

*Adjusted for age, gender, ethnicity, current smoking, current use of alcohol, recreational drug use in the past 6 months and total number of co-medications

8.6.9.3 ABC and 3TC

The univariable and the multivariable analysis suggested that the ABC PK parameters were not associated with either of the FRAX scores (Figure 8.5, Figure 8.6 and Table 8.14). Similarly, the univariable models for hip fracture score suggested lack of association with the 3TC PK parameters.

The univariable and the multivariable analysis suggested that the 3TC PK parameters were not associated with hip fracture score (Figure 8.7 and Table 8.15). Whilst for major-osteoporotic score, the univariably significant association with $AUC_{0\text{-}24h}$ was attenuated in the multivariable model and became non-significant (Figure 8.8 and Table 8.15).

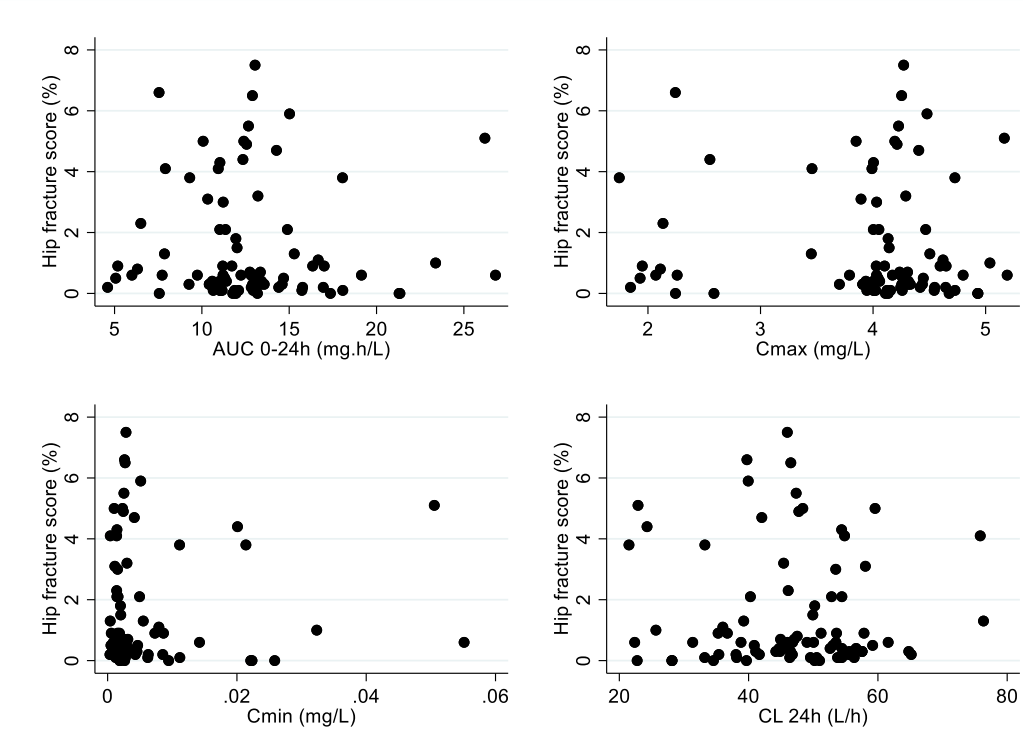


Figure 8.5: Association of ABC PK parameters with hip fracture score

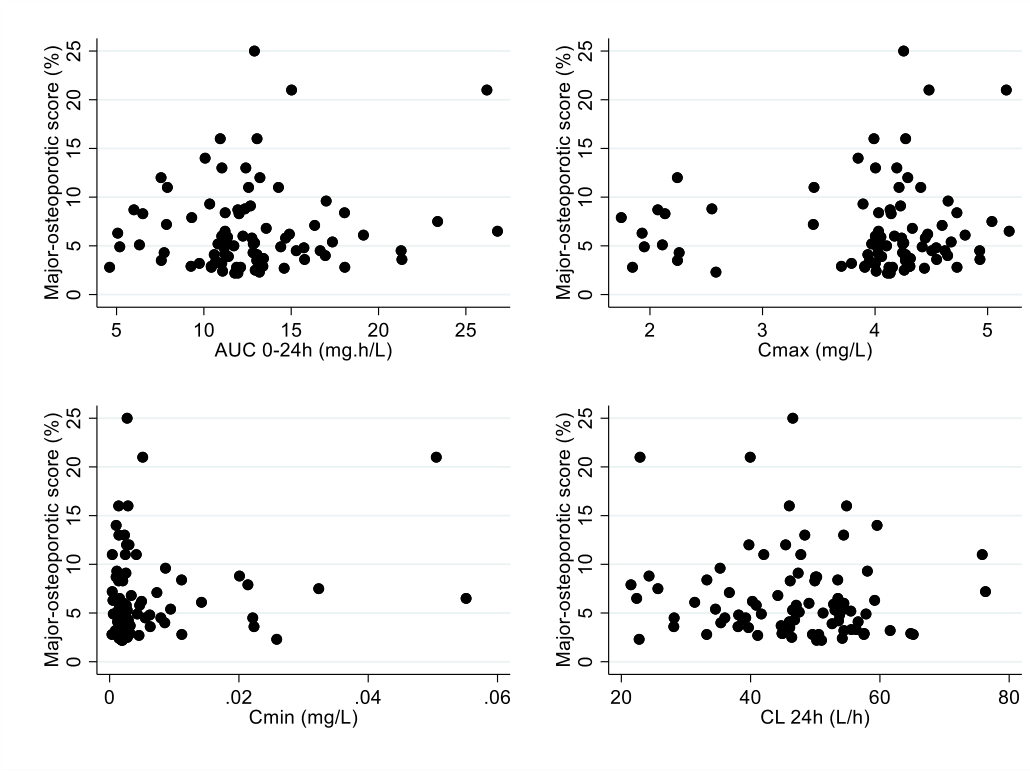


Figure 8.6: Association of ABC PK parameters with major-osteoporotic score

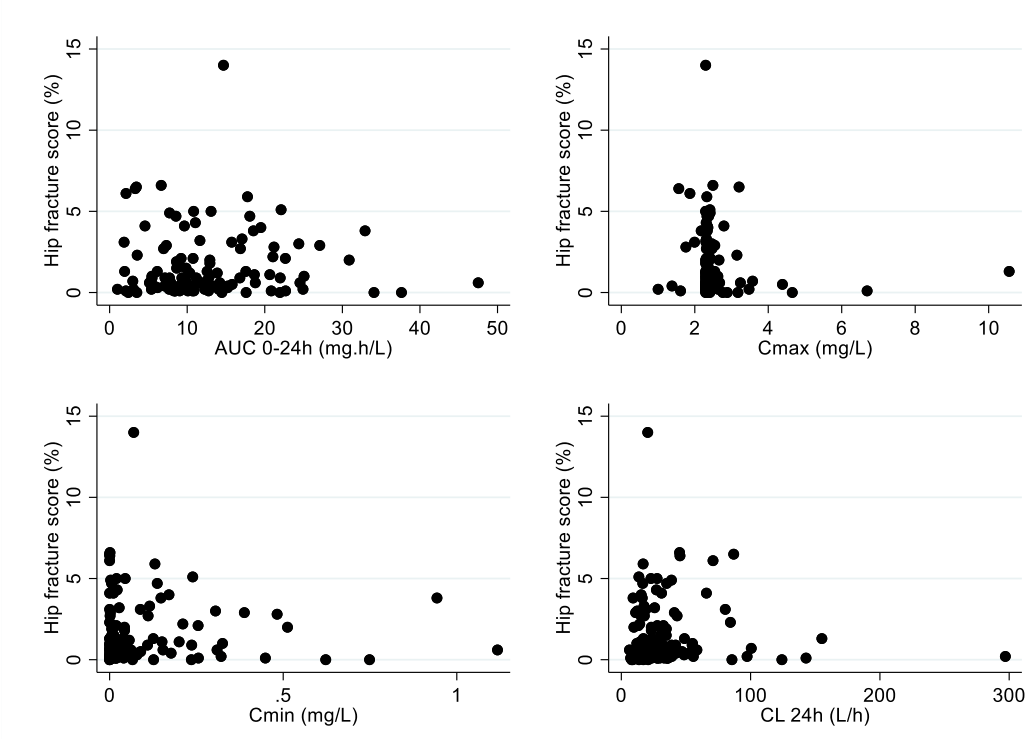


Figure 8.7: Association of 3TC PK parameters with hip fracture score

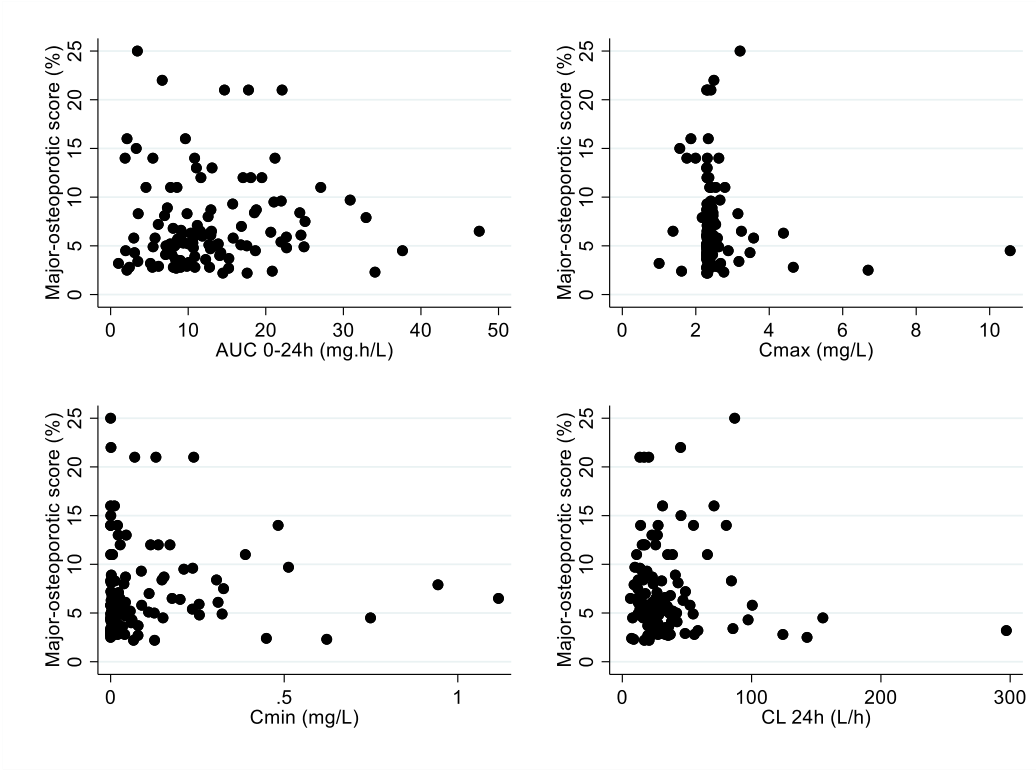


Figure 8.8: Association of 3TC PK parameters with major-osteoporotic score

Table 8.14: Univariable and multivariable association between FRAX scores and ABC PK parameters

	Hip fracture score		Major-osteoporotic FRAX score	
	Univariable model	Multivariable model*	Univariable model	Multivariable model*
	β-coeff. (95% CI)	aβ-coeff. (95% CI)	β-coeff. (95% CI)	aβ-coeff. (95% CI)
$AUC_{0\text{-}24h}$ (mg.h/L)				
≤10.333	Ref.	Ref.	Ref.	Ref.
10.334-11.686	-0.20 (-0.54, 0.14)	-0.02 (-0.34, 0.29)	-0.14 (-0.38, 0.11)	-0.01 (-0.26, 0.23)
11.687-12.941	-0.11 (-0.46, 0.24)	-0.08 (-0.45, 0.29)	-0.03 (-0.28, 0.22)	0.03 (-0.26, 0.32)
12.942-14.679	-0.18 (-0.55, 0.19)	0.04 (-0.33, 0.40)	-0.13 (-0.39, 0.13)	0.01 (-0.27, 0.29)
≥14.680	-0.22 (-0.57, 0.12)	0.00 (-0.36, 0.37)	0.00 (-0.24, 0.25)	0.06 (-0.23, 0.34)
C_{max} (mg/L)				
≤3.846	Ref.	Ref.	Ref.	Ref.
3.847-4.052	-0.03 (-0.37, 0.32)	0.09 (-0.22, 0.40)	-0.01 (-0.25, 0.24)	0.07 (-0.17, 0.31)
4.053-4.255	-0.04 (-0.39, 0.32)	-0.01 (-0.35, 0.34)	0.04 (-0.21, 0.29)	0.08 (-0.19, 0.35)
4.256-4.447	-0.05 (-0.42, 0.32)	0.16 (-0.19, 0.51)	-0.06 (-0.32, 0.21)	0.07 (-0.21, 0.35)
≥4.448	-0.13 (-0.48, 0.22)	0.09 (-0.27, 0.45)	0.07 (-0.17, 0.32)	0.11 (-0.17, 0.39)
C_{min} (mg/L)				
≤0.0013	Ref.	Ref.	Ref.	Ref.
0.0014-0.0020	-0.03 (-0.37, 0.32)	0.03 (-0.28, 0.35)	0.03 (-0.22, 0.28)	0.09 (-0.15, 0.34)
0.0021-0.0028	0.10 (-0.24, 0.44)	0.14 (-0.18, 0.46)	0.14 (-0.10, 0.38)	0.20 (-0.05, 0.45)
0.0029-0.0052	0.09 (-0.30, 0.47)	0.30 (-0.06, 0.66)	0.09 (-0.18, 0.37)	0.19 (-0.09, 0.48)
≥0.0053	-0.11 (-0.45, 0.23)	0.06 (-0.27, 0.40)	0.07 (-0.17, 0.32)	0.11 (-0.16, 0.37)
CL_{24h} (L/h)				
≤39.245	Ref.	Ref.	Ref.	Ref.
39.246-45.993	0.23 (-0.10, 0.57)	0.19 (-0.11, 0.49)	0.06 (-0.18, 0.31)	0.10 (-0.14, 0.33)
45.994-50.050	0.24 (-0.10, 0.58)	0.12 (-0.21, 0.44)	0.10 (-0.14, 0.34)	0.12 (-0.13, 0.37)
50.051-55.326	0.04 (-0.28, 0.37)	-0.11 (-0.44, 0.22)	-0.06 (-0.29, 0.18)	-0.05 (-0.31, 0.21)
≥55.327	0.09 (-0.25, 0.43)	-0.07 (-0.40, 0.27)	-0.09 (-0.33, 0.16)	-0.12 (-0.38, 0.14)

*Adjusted for age, gender, ethnicity, current smoking, current use of alcohol, recreational drug use in the past 6 months and total number of co-medications

Table 8.15: Univariable and multivariable association between FRAX scores and 3TC PK parameters

	Hip fracture score		Major-osteoporotic FRAX score	
	Univariable model	Multivariable model*	Univariable model	Multivariable model*
	β-coeff. (95% CI)	aβ-coeff. (95% CI)	β-coeff. (95% CI)	aβ-coeff. (95% CI)
$AUC_{0\text{-}24h}$ (mg.h/L)				
≤6.957	Ref.	Ref.	Ref.	Ref.
6.958-9.031	-0.18 (-0.47, 0.11)	-0.05 (-0.32, 0.23)	-0.24 (-0.46, -0.03)	-0.16 (-0.38, 0.06)
9.032-11.641	-0.06 (-0.35, 0.22)	0.02 (-0.24, 0.29)	-0.10 (-0.31, 0.11)	-0.08 (-0.29, 0.13)
11.642-17.600	-0.08 (-0.35, 0.20)	-0.13 (-0.38, 0.13)	-0.13 (-0.34, 0.07)	-0.18 (-0.38, 0.02)
≥17.601	0.01 (-0.27, 0.29)	0.03 (-0.23, 0.29)	0.06 (-0.15, 0.27)	0.02 (-0.18, 0.23)
C_{max} (mg/L)				
≤2.304	Ref.	Ref.	Ref.	Ref.
2.305-2.341	-0.03 (-0.30, 0.23)	0.02 (-0.21, 0.26)	0.01 (-0.19, 0.21)	0.03 (-0.16, 0.22)
2.342-2.389	-0.16 (-0.43, 0.12)	-0.14 (-0.40, 0.12)	-0.17 (-0.37, 0.04)	-0.16 (-0.37, 0.05)
2.390-2.513	-0.09 (-0.37, 0.18)	-0.03 (-0.29, 0.23)	0.02 (-0.19, 0.23)	0.07 (-0.14, 0.28)
≥2.514	-0.25 (-0.53, 0.02)	-0.24 (-0.49, 0.01)	-0.08 (-0.29, 0.13)	-0.06 (-0.26, 0.14)
C_{min} (mg/L)				
≤0.0014	Ref.	Ref.	Ref.	Ref.
0.0015-0.0075	-0.16 (-0.46, 0.13)	-0.08 (-0.36, 0.20)	-0.22 (-0.44, -0.01)	-0.17 (-0.39, 0.05)
0.0076-0.0268	-0.11 (-0.40, 0.18)	0.01 (-0.26, 0.27)	-0.14 (-0.35, 0.08)	-0.10 (-0.31, 0.11)
0.0269-0.1372	0.02 (-0.26, 0.29)	-0.02 (-0.27, 0.23)	-0.06 (-0.27, 0.14)	-0.11 (-0.31, 0.10)
≥0.1373	-0.06 (-0.34, 0.23)	-0.05 (-0.32, 0.22)	0.01 (-0.20, 0.22)	-0.03 (-0.24, 0.19)
CL_{24h} (L/h)				
≤16.879	Ref.	Ref.	Ref.	Ref.
16.880-25.939	-0.05 (-0.31, 0.22)	-0.05 (-0.31, 0.20)	-0.17 (-0.37, 0.03)	-0.16 (-0.36, 0.05)
25.940-33.384	-0.11 (-0.39, 0.16)	-0.03 (-0.28, 0.22)	-0.21 (-0.41, 0.00)	-0.15 (-0.35, 0.05)
33.385-44.602	-0.13 (-0.42, 0.16)	-0.02 (-0.30, 0.27)	-0.26 (-0.47, -0.05)	-0.14 (-0.37, 0.08)
≥44.603	-0.03 (-0.31, 0.25)	-0.04 (-0.30, 0.22)	-0.06 (-0.27, 0.14)	-0.04 (-0.25, 0.17)

*Adjusted for age, gender, ethnicity, current smoking, current use of alcohol, recreational drug use in the past 6 months and total number of co-medications

8.6.10 Comparison of the results of FRAX scores calculated with and without BMD

8.6.10.1 FRAX scores without BMD among older POPPY participants

The median hip fracture score without BMD among the older POPPY participants was 0.7 (IQR 0.3, 1.4) with a range of 0.1 to 26.0; the median major-osteoporotic score was 5.4 (IQR 3.5, 7.7, range 1.8 to 39.0). The National Osteoporosis Foundation Guide suggests that those with a hip fracture score ≥3% and those with major-osteoporotic score ≥20% should be treated for osteoporosis. When hip fracture score was calculated with and without BMD the proportion of those that require treatment according to those guidelines was 120/1003 (12.0%) and 73/1003 (7.3%) respectively. For major-osteoporotic score the corresponding proportions were 19/1003 (1.9%) with BMD and 11/1003 (1.1%) without BMD.

The results of the univariable and multivariable analyses exploring the association of HIV with the FRAX scores when calculated without BMD were not in line with the results of the Section 8.6.5. In particular, when the FRAX scores were calculated without BMD I found lack of association between HIV and hip fracture score and major-osteoporotic score, Table 8.16.

Table 8.16: Univariable and multivariable association between HIV and the FRAX scores (calculated without BMD)

	Hip fracture score	
	Univariable	**Multivariable***
	β-coeff. (95% CI)	**aβ-coeff. (95% CI)**
Group		
HIV negative	Ref.	Ref.
Older PLWH	-0.18 (-0.39, 0.03)	0.12 (-0.07, 0.30)
	Major-osteoporotic score	
Group		
HIV negative	Ref.	Ref.
Older PLWH	-0.69 (-1.20, -0.17)	0.25 (-0.24, 0.75)

*Adjusted for age, gender, ethnicity, education and marital status

8.6.10.2 The association between FRAX scores without BMD and frailty, falls among POPPY participants

The univariably significant associations of frailty and history of falls with the FRAX scores seen when the scores were calculated using the BMD data (Section 8.6.6),

were not present when the FRAX scores were calculated without BMD and therefore no multivariable models further explored the association, Table 8.17.

Table 8.17: Univariable association of FRAX scores (calculated without BMD) with frailty and history of falls in the past 28 days

	Hip fracture score Univariable model β-coeff. (95% CI)
Frailty	
No	Ref.
Yes	0.26 (-0.09, 0.62)
History of falls in the past 28 days	
No	Ref.
Yes	0.16 (-0.11, 0.43)
	Major-osteoporotic score
Frailty	
No	Ref.
Yes	0.42 (-0.41, 1.26)
History of falls in the past 28 days	
No	Ref.
Yes	0.66 (-0.01, 1.33)

8.6.10.3 The association between FRAX scores without BMD and depressive symptoms

The descriptive analysis suggested that there was no clear dose-response association between FRAX scores when calculated without BMD with depressive symptoms, therefore univariable and multivariable regression models were not used to explore the association further, Table 8.18. I yielded similar results when the FRAX scores were calculated using the BMD T-score in Section 8.6.7.

Table 8.18: Median (IQR) and range of FRAX scores calculated without BMD stratified by depressive symptoms as assessed by CES-D and PHQ-9 score

		Hip fracture score		
	n	**Median (IQR)**	**(range)**	**p-value**
Levels of depressive symptoms (CES-D)				
No to mild (0-15)	599	0.7 (0.3, 1.3)	(0.1, 26.0)	0.71
Moderate (16-23)	115	0.7 (0.4, 1.3)	(0.1, 6.6)	
Severe (24-60)	161	0.7 (0.3, 1.4)	(0.1, 8.6)	
Unknown	109	0.7 (0.3, 1.7)	(0.1, 15.0)	
Levels of depressive symptoms (PHQ-9)				
Minimal (1-4)	551	0.7 (0.3, 1.4)	(0.1, 26.0)	0.01
Mild (5-9)	165	0.8 (0.4, 1.4)	(0.1, 7.7)	
Moderate (10-14)	101	0.7 (0.4, 1.5)	(0.1, 7.3)	
Moderately severe (15-19)	57	0.4 (0.2, 1.1)	(0.1, 8.6)	
Severe (20-27)	31	0.5 (0.3, 1.0)	(0.1, 8.0)	
Unknown	79	0.9 (0.3, 1.7)	(0.1, 15.0)	
		Major-osteoporotic score		
Levels of depressive symptoms (CES-D)				
No to mild (0-15)	599	5.3 (3.6, 7.7)	(1.8, 39.0)	0.98
Moderate (16-23)	115	5.5 (3.6, 7.2)	(2.1, 17.0)	
Severe (24-60)	161	5.5 (3.5, 7.7)	(2.0, 26.0)	
Unknown	109	5.8 (3.4, 8.0)	(2.4, 21.0)	
Levels of depressive symptoms (PHQ-9)				
Minimal (1-4)	551	5.3 (3.6, 7.7)	(1.8, 39.0)	0.29
Mild (5-9)	165	5.5 (3.6, 7.4)	(2.1, 27.0)	
Moderate (10-14)	101	5.8 (3.8, 7.8)	(2.0, 21.0)	
Moderately severe (15-19)	57	4.1 (3.3, 6.6)	(2.4, 26.0)	
Severe (20-27)	31	5.6 (3.2, 7.4)	(2.4, 21.0)	
Unknown	76	6.4 (3.4, 9.0)	(2.4, 21.0)	

8.6.10.4 The association between FRAX scores without BMD and HIV-specific factors

Among PLWH, the results of the multivariable analysis using the FRAX scores with and without the use of BMD T-score were consistent, suggesting that increased age and increased number of co-medications were significantly associated with increased FRAX scores without BMD (Table 8.19).

8.6.11 Association between PK parameters and FRAX scores (calculated without BMD) among POPPY PLWH

For TDF, I found that only the association of lower CL_{24h} with increased FRAX scores remained consistently significant with both methods of calculating the scores. Conversely, the association of $AUC_{0\text{-}24h}$ and $C_{max,}$ with hip fracture score obtained in Section 8.6.9 was attenuated and became non-significant when the score was calculated without BMD (Table 8.20).

The associations of the FTC PK parameters with FRAX scores calculated using the BMD T-score were consistent to those not using the BMD T-score. More specifically, higher $AUC_{0\text{-}24h,}$ C_{max} and C_{min} and lower CL_{24h} were associated with higher hip fracture score. Similarly, the results of major-osteoporotic score were consistent regardless of the method of calculation, suggesting a lack of association between major-osteoporotic score and FTC PK parameters (Table 8.21). Finally, the lack of association between the ABC and 3TC PK parameters and FRAX scores with or without BMD was consistent (Table 8.22, Table 8.23). The only disparity was that the multivariable model for the association of 3TC C_{max} with the major-osteoporotic score calculated without BMD was significant (Table 8.23) while when it was calculated with BMD it was not (Table 8.15). However, in both analyses there was not a clear dose-response relationship of the 3TC C_{max} with the major-osteoporotic score. Furthermore, the association of 3TC C_{max} with the major-osteoporotic score when BMD was not used for the calculation, was not significant at the univariable analysis, therefore this finding may be an artefact of the data or a result of adjustment for confounders. This discrepancy cannot be used as an evidence of difference between the two methods for calculating the scores.

Table 8.19: Univariable and multivariable association of FRAX scores (calculated without BMD) with age and HIV factors among PLWH in POPPY

	Hip fracture score		Major-osteoporotic score	
	Univariable model	Multivariable model[1]	Univariable model	Multivariable model[2]
	β-coeff. (95% CI)	aβ-coeff. (95% CI)	β-coeff. (95% CI)	aβ-coeff. (95% CI)
Age at baseline visit				
40-49	Ref.	Ref.	Ref.	Ref.
50-54	0.08 (0.04, 0.12)	0.09 (0.05, 0.13)	0.08 (0.03, 0.12)	0.09 (0.05, 0.13)
55-59	0.26 (0.22, 0.30)	0.26 (0.22, 0.30)	0.24 (0.19, 0.29)	0.23 (0.18, 0.28)
60-64	0.38 (0.33, 0.42)	0.39 (0.34, 0.43)	0.30 (0.24, 0.36)	0.30 (0.24, 0.36)
65-69	0.55 (0.49, 0.61)	0.57 (0.51, 0.62)	0.45 (0.39, 0.52)	0.44 (0.38, 0.51)
≥70	0.79 (0.71, 0.87)	0.83 (0.76, 0.90)	0.45 (0.36, 0.54)	0.44 (0.35, 0.53)
AIDS history				
No	Ref.	Ref.	Ref.	Ref.
Yes	0.00 (-0.04, 0.04)	-	-0.01 (-0.05, 0.03)	-
CD4 count (cells/mm^3)				
≤437	Ref.	Ref.	Ref.	Ref.
438-566	-0.02 (-0.08, 0.04)	-	0.02 (-0.04, 0.08)	-
567-695	0.02 (-0.05, 0.08)	-	0.02 (-0.05, 0.08)	-
696-874	-0.05 (-0.11, 0.01)	-	-0.04 (-0.10, 0.02)	-
≥875	-0.01 (-0.07, 0.05)	-	0.01 (-0.05, 0.07)	-
CD4 nadir (cells/mm^3)				
≤70	Ref.	Ref.	Ref.	Ref.
71-153	0.04 (-0.02, 0.10)	-	0.03 (-0.03, 0.09)	-
154-225	0.01 (-0.05, 0.07)	-	0.01 (-0.06, 0.07)	-
226-319	0.01 (-0.06, 0.07)	-	0.02 (-0.04, 0.08)	-
≥320	-0.04 (-0.10, 0.02)	-	-0.02 (-0.08, 0.04)	-
VL				

	Hip fracture score		Major-osteoporotic score	
	Univariable model	Multivariable model[1]	Univariable model	Multivariable model[2]
	β-coeff. (95% CI)	aβ-coeff. (95% CI)	β-coeff. (95% CI)	aβ-coeff. (95% CI)
Undetectable	Ref.	Ref.	Ref.	Ref.
Detectable	0.00 (-0.07, 0.07)	-	0.03 (-0.04, 0.10)	-
Time since HIV diagnosis (yrs)				
≤7.7	Ref.	Ref.	Ref.	Ref.
7.8-12.4	-0.06 (-0.12, 0.01)	-0.04 (-0.09, 0.01)	-0.05 (-0.11, 0.01)	-0.05 (-0.10, 0.00)
12.5-17.1	0.00 (-0.07, 0.06)	-0.02 (-0.07, 0.03)	-0.03 (-0.09, 0.04)	-0.06 (-0.11, 0.00)
17.2-22.8	0.04 (-0.02, 0.10)	-0.01 (-0.06, 0.05)	0.03 (-0.03, 0.09)	-0.04 (-0.09, 0.01)
≥22.9	0.10 (0.04, 0.16)	0.00 (-0.06, 0.06)	0.07 (0.01, 0.13)	-0.06 (-0.12, -0.01)
Years on ART				
≤4.7	Ref.	Ref.	Ref.	Ref.
4.8-8.1	0.00 (-0.06, 0.06)	0.00 (-0.05, 0.04)	-0.02 (-0.08, 0.04)	-
8.2-13.1	0.00 (-0.06, 0.06)	-0.02 (-0.06, 0.03)	-0.01 (-0.07, 0.05)	-
13.2-17.5	0.06 (0.00, 0.12)	-0.04 (-0.09, 0.01)	0.01 (-0.05, 0.08)	-
≥17.6	0.11 (0.05, 0.17)	-0.04 (-0.10, 0.02)	0.06 (0.00, 0.12)	-
Number of total co-medications (excluding cART)				
0	Ref.	Ref.	Ref.	Ref.
1-4	0.11 (0.06, 0.15)	0.04 (0.01, 0.07)	0.09 (0.05, 0.14)	0.04 (0.00, 0.08)
5-9	0.15 (0.09, 0.21)	0.05 (0.02, 0.09)	0.13 (0.07, 0.18)	0.05 (0.00, 0.10)
≥10	0.30 (0.21, 0.38)	0.13 (0.07, 0.19)	0.27 (0.18, 0.35)	0.14 (0.07, 0.22)
NRTI in regimen				
None	Ref.	Ref.	Ref.	Ref.
TFV/FTC	-0.09 (-0.15, -0.03)	0.00 (-0.04, 0.04)	-0.09 (-0.15, -0.03)	-0.03 (-0.08, 0.02)
ABC/3TC	-0.09 (-0.17, -0.01)	0.00 (-0.05, 0.06)	-0.09 (-0.16, -0.01)	-0.02 (-0.09, 0.04)
Other	0.00 (-0.08, 0.08)	-0.02 (-0.07, 0.04)	-0.04 (-0.12, 0.03)	-0.05 (-0.11, 0.02)
PI in regimen				
None	Ref.	Ref.	Ref.	Ref.

	Hip fracture score		Major-osteoporotic score	
	Univariable model	Multivariable model[1]	Univariable model	Multivariable model[2]
	β-coeff. (95% CI)	aβ-coeff. (95% CI)	β-coeff. (95% CI)	aβ-coeff. (95% CI)
Boosted PIs	0.03 (-0.02, 0.07)	-	-0.01 (-0.05, 0.03)	-
Unboosted PIs	-0.06 (-0.13, 0.01)	-	-0.03 (-0.10, 0.04)	-
NNRTI in regimen				
None	Ref.	Ref.	Ref.	Ref.
EFV	0.02 (-0.03, 0.07)	-	0.02 (-0.03, 0.06)	-
NVP	0.05 (-0.01, 0.11)	-	0.07 (0.01, 0.13)	-
RPV	-0.04 (-0.12, 0.05)	-	-0.01 (-0.09, 0.07)	-
ETR	0.00 (-0.08, 0.09)	-	0.02 (-0.06, 0.11)	-
INSTI in regimen				
No	Ref.	Ref.	Ref.	Ref.
Yes	0.03 (-0.03, 0.09)	-	0.04 (-0.02, 0.09)	-

[1]Adjusted for gender, ethnicity, BMI, current smoking, current alcohol use and recreational drug use in the past 6 months

[2]Adjusted for gender, ethnicity, BMI, current smoking, current alcohol use, recreational drug use in the past 6 months and history of falls in the past 28 days

Table 8.20: Univariable and multivariable association between FRAX scores (calculated without BMD) and TDF PK parameters

	Hip fracture score		Major-osteoporotic FRAX score	
	Univariable model	Multivariable model*	Univariable model	Multivariable model*
	β-coeff. (95% CI)	aβ-coeff. (95% CI)	β-coeff. (95% CI)	aβ-coeff. (95% CI)
$AUC_{0\text{-}24h}$ (mg.h/L)				
≤2.355	Ref.	Ref.	Ref.	Ref.
2.356-2.616	0.05 (-0.04, 0.13)	0.04 (-0.04, 0.11)	0.04 (-0.05, 0.12)	0.02 (-0.06, 0.10)
2.617-2.941	0.14 (0.06, 0.22)	0.06 (-0.01, 0.14)	0.14 (0.06, 0.22)	0.08 (0.00, 0.16)
2.942-3.410	0.23 (0.15, 0.31)	0.09 (0.01, 0.17)	0.17 (0.09, 0.25)	0.06 (-0.02, 0.15)
≥3.411	0.27 (0.19, 0.35)	0.11 (0.03, 0.20)	0.18 (0.10, 0.26)	0.05 (-0.03, 0.14)
C_{max} (mg/L)				
≤0.219	Ref.	Ref.	Ref.	Ref.
0.220-0.241	0.05 (-0.03, 0.13)	0.02 (-0.06, 0.10)	0.05 (-0.03, 0.13)	0.02 (-0.06, 0.10)
0.242-0.263	0.09 (0.01, 0.17)	0.05 (-0.04, 0.13)	0.10 (0.02, 0.18)	0.03 (-0.05, 0.12)
0.264-0.289	0.16 (0.08, 0.24)	0.07 (-0.01, 0.16)	0.14 (0.06, 0.22)	0.06 (-0.03, 0.15)
≥0.290	0.29 (0.21, 0.37)	0.13 (0.04, 0.23)	0.18 (0.10, 0.26)	0.05 (-0.05, 0.14)
C_{min} (mg/L)				
≤0.042	Ref.	Ref.	Ref.	Ref.
0.043-0.050	0.09 (0.01, 0.17)	0.04 (-0.03, 0.12)	0.07 (-0.01, 0.15)	0.03 (-0.04, 0.11)
0.051-0.058	0.11 (0.02, 0.20)	0.03 (-0.05, 0.11)	0.09 (0.01, 0.18)	0.03 (-0.05, 0.11)
0.059-0.072	0.23 (0.15, 0.31)	0.08 (0.00, 0.16)	0.18 (0.10, 0.26)	0.06 (-0.02, 0.14)
≥0.073	0.25 (0.16, 0.33)	0.09 (0.01, 0.17)	0.17 (0.08, 0.25)	0.04 (-0.04, 0.13)
CL_{24h} (L/h)				
≤40.462	Ref.	Ref.	Ref.	Ref.
40.463-46.793	-0.10 (-0.17, -0.02)	-0.05 (-0.12, 0.03)	-0.05 (-0.12, 0.03)	-0.01 (-0.08, 0.06)
46.794-52.448	-0.15 (-0.23, -0.07)	-0.05 (-0.12, 0.02)	-0.04 (-0.11, 0.04)	0.03 (-0.04, 0.11)
52.449-58.096	-0.24 (-0.32, -0.16)	-0.09 (-0.17, 0.00)	-0.14 (-0.22, -0.07)	-0.03 (-0.11, 0.06)
≥58.097	-0.31 (-0.39, -0.23)	-0.15 (-0.23, -0.06)	-0.20 (-0.28, -0.12)	-0.08 (-0.17, 0.00)

*Adjusted for age, gender, ethnicity, current smoking, current use of alcohol, recreational drug use in the past 6 months and total number of co-medications

Table 8.21: Univariable and multivariable association between FRAX scores (calculated without BMD) FTC PK parameters

	Hip fracture score		Major-osteoporotic FRAX score	
	Univariable model	Multivariable model*	Univariable model	Multivariable model*
	β-coeff. (95% CI)	aβ-coeff. (95% CI)	β-coeff. (95% CI)	aβ-coeff. (95% CI)
$AUC_{0\text{-}24h}$ (mg.h/L)				
≤9.017	Ref.	Ref.	Ref.	Ref.
9.018-9.897	0.09 (0.00, 0.18)	0.03 (-0.05, 0.11)	0.10 (0.01, 0.18)	0.04 (-0.04, 0.12)
9.898-10.800	0.14 (0.05, 0.23)	0.06 (-0.02, 0.14)	0.13 (0.04, 0.22)	0.07 (-0.01, 0.15)
10.801-12.352	0.18 (0.09, 0.27)	0.08 (0.00, 0.17)	0.14 (0.05, 0.22)	0.05 (-0.03, 0.13)
≥12.353	0.30 (0.21, 0.39)	0.16 (0.07, 0.24)	0.22 (0.13, 0.30)	0.10 (0.01, 0.18)
C_{max} (mg/L)				
≤1.051	Ref.	Ref.	Ref.	Ref.
1.052-1.105	0.09 (0.00, 0.18)	0.03 (-0.05, 0.11)	0.10 (0.01, 0.18)	0.04 (-0.04, 0.12)
1.106-1.164	0.14 (0.05, 0.23)	0.06 (-0.02, 0.14)	0.13 (0.04, 0.21)	0.07 (-0.01, 0.15)
1.165-1.268	0.17 (0.08, 0.26)	0.08 (-0.01, 0.16)	0.13 (0.05, 0.22)	0.04 (-0.04, 0.13)
≥1.269	0.31 (0.22, 0.40)	0.16 (0.08, 0.25)	0.23 (0.14, 0.31)	0.10 (0.02, 0.19)
C_{min} (mg/L)				
≤0.057	Ref.	Ref.	Ref.	Ref.
0.058-0.068	0.08 (-0.01, 0.17)	0.01 (-0.07, 0.09)	0.09 (0.00, 0.18)	0.02 (-0.06, 0.11)
0.069-0.081	0.13 (0.04, 0.21)	0.04 (-0.04, 0.12)	0.11 (0.03, 0.20)	0.05 (-0.03, 0.13)
0.082-0.106	0.17 (0.08, 0.26)	0.07 (-0.01, 0.15)	0.13 (0.05, 0.22)	0.04 (-0.04, 0.12)
≥0.107	0.30 (0.21, 0.39)	0.16 (0.07, 0.24)	0.21 (0.13, 0.30)	0.09 (0.01, 0.17)
CL_{24h} (L/h)				
≤16.263	Ref.	Ref.	Ref.	Ref.
16.264-18.542	-0.12 (-0.21, -0.04)	-0.09 (-0.16, -0.01)	-0.08 (-0.16, 0.00)	-0.05 (-0.12, 0.02)
18.543-20.228	-0.16 (-0.25, -0.08)	-0.10 (-0.17, -0.02)	-0.09 (-0.17, -0.01)	-0.03 (-0.10, 0.05)
20.229-22.228	-0.21 (-0.30, -0.13)	-0.14 (-0.21, -0.06)	-0.13 (-0.21, -0.05)	-0.06 (-0.14, 0.02)
≥22.229	-0.32 (-0.41, -0.23)	-0.17 (-0.26, -0.09)	-0.24 (-0.32, -0.15)	-0.11 (-0.20, -0.02)

*Adjusted for age, gender, ethnicity, current smoking, current use of alcohol, recreational drug use in the past 6 months and total number of co-medications

Table 8.22: Univariable and multivariable association between FRAX scores (calculated without BMD) and ABC PK parameters

	Hip fracture score		Major-osteoporotic FRAX score	
	Univariable model	Multivariable model*	Univariable model	Multivariable model*
	β-coeff. (95% CI)	aβ-coeff. (95% CI)	β-coeff. (95% CI)	aβ-coeff. (95% CI)
$AUC_{0\text{-}24h}$ (mg.h/L)				
≤10.333	Ref.	Ref.	Ref.	Ref.
10.334-11.686	-0.12 (-0.33, 0.10)	0.07 (-0.13, 0.26)	-0.11 (-0.32, 0.10)	0.04 (-0.17, 0.25)
11.687-12.941	-0.09 (-0.31, 0.12)	0.05 (-0.18, 0.28)	-0.07 (-0.29, 0.14)	0.07 (-0.17, 0.31)
12.942-14.679	-0.18 (-0.40, 0.04)	-0.08 (-0.29, 0.13)	-0.16 (-0.38, 0.05)	-0.08 (-0.30, 0.14)
≥14.680	-0.01 (-0.22, 0.20)	0.05 (-0.16, 0.25)	0.03 (-0.17, 0.24)	0.05 (-0.17, 0.27)
C_{max} (mg/L)				
≤3.846	Ref.	Ref.	Ref.	Ref.
3.847-4.052	-0.02 (-0.23, 0.19)	0.15 (-0.04, 0.33)	-0.01 (-0.21, 0.20)	0.13 (-0.07, 0.33)
4.053-4.255	0.01 (-0.21, 0.23)	0.13 (-0.08, 0.34)	0.03 (-0.19, 0.25)	0.14 (-0.08, 0.36)
4.256-4.447	-0.13 (-0.35, 0.08)	-0.02 (-0.23, 0.18)	-0.11 (-0.33, 0.11)	-0.03 (-0.24, 0.19)
≥4.448	0.05 (-0.16, 0.26)	0.10 (-0.11, 0.30)	0.10 (-0.11, 0.30)	0.10 (-0.12, 0.31)
C_{min} (mg/L)				
≤0.0013	Ref.	Ref.	Ref.	Ref.
0.0014-0.0020	0.02 (-0.20, 0.24)	0.15 (-0.05, 0.36)	-0.01 (-0.22, 0.21)	0.14 (-0.07, 0.35)
0.0021-0.0028	0.04 (-0.17, 0.25)	0.15 (-0.04, 0.35)	0.03 (-0.18, 0.24)	0.16 (-0.05, 0.37)
0.0029-0.0052	-0.06 (-0.30, 0.17)	0.02 (-0.20, 0.24)	-0.04 (-0.27, 0.19)	0.02 (-0.21, 0.25)
≥0.0053	0.08 (-0.13, 0.29)	0.13 (-0.07, 0.32)	0.06 (-0.15, 0.27)	0.08 (-0.13, 0.29)
CL_{24h} (L/h)				
≤39.245	Ref.	Ref.	Ref.	Ref.
39.246-45.993	-0.09 (-0.30, 0.12)	-0.08 (-0.27, 0.11)	-0.07 (-0.28, 0.14)	-0.03 (-0.23, 0.17)
45.994-50.050	-0.02 (-0.24, 0.20)	0.02 (-0.19, 0.23)	0.02 (-0.20, 0.24)	0.11 (-0.11, 0.33)
50.051-55.326	-0.08 (-0.29, 0.13)	0.00 (-0.21, 0.22)	-0.08 (-0.29, 0.13)	0.04 (-0.18, 0.26)
≥55.327	-0.06 (-0.27, 0.15)	-0.10 (-0.30, 0.10)	-0.05 (-0.26, 0.16)	-0.07 (-0.28, 0.14)

*Adjusted for age, gender, ethnicity, current smoking, current use of alcohol, recreational drug use in the past 6 months and total number of co-medications

Table 8.23: Univariable and multivariable association between FRAX scores (calculated without BMD) and 3TC PK parameters

	3TC PK parameters			
	Hip fracture score		Major-osteoporotic FRAX score	
	Univariable model	Multivariable model*	Univariable model	Multivariable model*
	β-coeff. (95% CI)	aβ-coeff. (95% CI)	β-coeff. (95% CI)	aβ-coeff. (95% CI)
$AUC_{0\text{-}24h}$ (mg.h/L)				
≤6.957	Ref.	Ref.	Ref.	Ref.
6.958-9.031	-0.22 (-0.39, -0.04)	-0.12 (-0.29, 0.05)	-0.24 (-0.42, -0.07)	-0.17 (-0.35, 0.01)
9.032-11.641	0.00 (-0.18, 0.17)	0.01 (-0.15, 0.17)	-0.06 (-0.23, 0.12)	-0.06 (-0.23, 0.11)
11.642-17.600	0.00 (-0.18, 0.17)	-0.04 (-0.20, 0.12)	-0.08 (-0.26, 0.09)	-0.12 (-0.29, 0.05)
≥17.601	0.17 (0.00, 0.34)	0.10 (-0.06, 0.27)	0.13 (-0.05, 0.30)	0.05 (-0.12, 0.22)
C_{max} (mg/L)				
≤2.304	Ref.	Ref.	Ref.	Ref.
2.305-2.341	-0.04 (-0.22, 0.13)	-0.02 (-0.17, 0.13)	0.01 (-0.17, 0.18)	0.01 (-0.14, 0.17)
2.342-2.389	-0.19 (-0.36, -0.01)	-0.21 (-0.37, -0.06)	-0.16 (-0.34, 0.02)	-0.18 (-0.35, -0.02)
2.390-2.513	-0.01 (-0.19, 0.16)	0.04 (-0.12, 0.20)	0.06 (-0.12, 0.23)	0.09 (-0.07, 0.26)
≥2.514	-0.06 (-0.24, 0.12)	-0.04 (-0.19, 0.12)	0.02 (-0.17, 0.20)	0.03 (-0.13, 0.20)
C_{min} (mg/L)				
≤0.0014	Ref.	Ref.	Ref.	Ref.
0.0015-0.0075	-0.18 (-0.36, 0.00)	-0.10 (-0.27, 0.07)	-0.21 (-0.39, -0.03)	-0.15 (-0.33, 0.03)
0.0076-0.0268	-0.04 (-0.21, 0.14)	-0.01 (-0.17, 0.15)	-0.09 (-0.27, 0.09)	-0.08 (-0.25, 0.09)
0.0269-0.1372	0.02 (-0.16, 0.19)	-0.02 (-0.18, 0.14)	-0.06 (-0.23, 0.12)	-0.09 (-0.26, 0.08)
≥0.1373	0.16 (-0.02, 0.33)	0.09 (-0.07, 0.26)	0.11 (-0.07, 0.28)	0.03 (-0.14, 0.21)
CL_{24h} (L/h)				
≤16.879	Ref.	Ref.	Ref.	Ref.
16.880-25.939	-0.20 (-0.37, -0.04)	-0.15 (-0.31, 0.01)	-0.23 (-0.39, -0.06)	-0.17 (-0.34, 0.00)
25.940-33.384	-0.23 (-0.39, -0.07)	-0.15 (-0.31, 0.00)	-0.24 (-0.40, -0.07)	-0.17 (-0.33, -0.01)
33.385-44.602	-0.38 (-0.55, -0.21)	-0.21 (-0.38, -0.03)	-0.35 (-0.52, -0.18)	-0.20 (-0.38, -0.02)
≥44.603	-0.16 (-0.33, 0.01)	-0.10 (-0.27, 0.06)	-0.12 (-0.29, 0.05)	-0.05 (-0.22, 0.11)

*Adjusted for age, gender, ethnicity, current smoking, current use of alcohol, recreational drug use in the past 6 months and total number of co-medications

8.7 Discussion

8.7.1 FIR in POPPY

The results of Chapter 8 have suggested a higher risk for fractures in the group of older PLWH compared to HIV-negative controls. The mechanisms of the association between HIV infection and fracture risk remain unclear. The relevant literature is inconclusive with some studies confirming the association but others refuting these findings (432). In three multivariable analyses adjusting for the standard confounders and additionally adjusting for history of falls, recurrent falls and for depressive symptoms as assessed using the CES-D score, I found that the association of HIV with FIR was attenuated and became non-significant. However, history of falls, history of recurrent falls and severe depressive symptoms were all factors independently associated with an increased FIR. Among PLWH I found longer time since HIV-diagnosis to be the only HIV-specific factor associated with a higher FIR.

Unlike Womack *et al.* (467), who suggested that frailty is an important predictor for fractures among HIV-positive male veterans in the VACS study, I found no association between frailty and FIR in the analysis that attempted to explore whether HIV was associated with FIR independently of any association with frailty. The association reported by Womack *et al.* may be due to the poorer immune system reconstitution among the VACS participants compared to the older PLWH participants of POPPY, CD4 count mean (range) 280 cells/mm^3 (114, 472) in VACS vs. 657 cells/mm^3 (58, 2460) in POPPY and the significantly higher proportion of current smokers, 75.0% in VACS compared to 21.2% in POPPY. Both smoking and immune reconstruction result in higher inflammation markers that may trigger components of frailty such as slowness, weakness, low physical activity and exhaustion.

Nevertheless, in the analyses that explored whether the association of HIV with FIR was independent from any association with history of falls and whether the association of HIV with FIR was modified by the association with depressive symptoms, I found that the association of HIV with FIR was attenuated in both analyses. The findings of these analyses suggested that those with any fall history had an increased FIR as did those with depressive symptoms.

The association of falls with fractures has been supported by several bone health researchers. A review from Ambrose *et al.* in 2015 has suggested that 87% of fractures among the elderly are due to falls (715). The association of higher depressive symptoms with a higher risk for fractures has been reported among other researchers (481, 490, 716). Wu *et al.* confirmed the presence of a dose-response relationship between the duration of depressive symptoms and the risk of fractures in a meta-analysis (490), however, the duration of depressive symptoms in POPPY was not available. Nevertheless, the FIR was elevated among those with moderate depressive symptoms and significantly higher among those with severe depressive symptoms, confirming a clear dose-response relationship. Therefore, this association should alert the need for interventions and management plans to manage depression and fracture risk among the ageing cohort of PLWH and the general population.

Longer time since HIV-diagnosis was associated with an increased risk for fractures in POPPY. This is in line with findings from other researchers who reported that longer treatment for HIV increases inflammation which in turn activates osteoclasts, increases bone turnover (717) and increases the risk for fractures (346, 353).

Immune system reconstruction has been linked with bone demineralization and increased fracture risk (532). Therefore, the lack of association of other HIV-specific parameters in this study may be explained due to the already achieved immune system reconstruction among the POPPY participants. Results from other studies among PLWH with achieved immune reconstruction have also confirmed the lack of association between fractures and CD4 count (469, 474, 718) or VL (509).

8.7.2 FRAX scores in POPPY

I found that the median the FRAX scores were significantly higher among older PLWH compared to HIV-negative controls. Using the cut-offs of ≥3% for the hip-fracture score and ≥20% for the major-osteoporotic score as suggested by the National Osteoporosis Foundation Guide, the proportion among the older POPPY participants in need for treatment for osteoporosis was 12.0% and 1.9%, according to the hip-fracture and the major-osteoporotic score respectively.

Results from the multivariable analyses suggested that HIV was associated with higher FRAX scores among the older POPPY participants.

The higher FRAX scores among the older PLWH compared to HIV-negative controls was unsurprising. The mechanism behind this association is that parameters used to calculate the FRAX scores (rheumatoid arthritis, secondary osteoporosis, smoking, alcohol use, low BMD T-score at FN) have been systematically reported to be at high prevalence among PLWH (444, 446, 453, 719, 720) and this is among other reasons due to systemic inflammation, attenuation of mitochondrial function and oxidative stress (144, 148, 169, 609-621). Yin *et al*. (403) have reported that FRAX scores are significantly higher among PLWH compared to HIV-negative controls. Furthermore, univariable analyses among other researchers have found that PLWH compared to HIV-negative controls have a 35% higher risk for fragility fractures (50, 453) and this increases with older age (460).

The association of HIV with higher FRAX score was independent of any association with frailty and history of falls. The association of FRAX scores with frailty and falls has been reported by several researchers (400, 721) regardless of whether the scores were calculated with or without the FN BMD (722). Therefore, the association of higher FRAX scores among those deemed frail is consistent with the literature considering that the frail with history of falls are more susceptible to hip and major-osteoporotic fractures. Furthermore, the multivariable model that considers adjustment for history of falls takes into consideration concerns for possible underestimation of fracture risk raised by Yin *et al.* (398).

Although Whitson *et al.* (723) reported that depressive symptoms were not associated with clinical fracture risk, other researchers have demonstrated an independent association of higher depressive symptoms with higher FRAX scores (724, 725). Conversely Bolton *et al.* (726) have suggested that when adjusting for medication for mental health the association of depressive symptoms with FRAX was attenuated and became non-significant. In POPPY the association of depressive symptoms with FRAX scores did not suggest a dose-response relationship and a clear direction of the association could not be confirmed. Therefore, no further analysis

was performed to explore whether the association of HIV with FRAX scores was modified by the association with depressive symptoms.

Among PLWH, I did not find an association between cART and the FRAX scores. This is in contrast to Bedimo *et al.* (482) who reported that exposure to specific ART drugs, and in particular TDF, boosted PI and among the PIs LPV/RTV, is associated with a higher risk for osteoporotic fractures. Older age was the only factor that was associated with higher hip-fracture risk score. Older age and an increased number of co-medications (excluding ART drugs) were the factors that were associated with a higher score for major-osteoporotic fractures. Both factors may be considered part of the natural ageing process considering that the increased number of co-medications is a result of co-occurring comorbidities. The increased pill burden may make disease management more difficult due to side effects, drug-drug interactions and treatment adherence challenges (196, 659, 727).

When I explored the association of TDF, FTC, ABC and 3TC PK parameters with FRAX scores, I found that among those on TDF, higher $AUC_{0\text{-}24}$, C_{max} and lower CL_{24h} were associated with higher hip-fracture scores. Similarly, higher $AUC_{0\text{-}24h}$ and lower CL_{24h} were associated with increased major-osteoporotic scores. Consistent with the widely reported association of TDF with bone-turnover (500, 549, 672, 728) the results of POPPY confirmed that higher exposure to TDF and a lower drug elimination were associated with increased FRAX scores.

For those on FTC, despite not reaching the level of significance, higher $AUC_{0\text{-}24h}$, C_{max} and C_{min} and lower CL_{24h} suggested higher FRAX scores. The fact that those associations were close to reaching the level of significance may be a carry-over effect of the association of TDF with the PK parameters, considering that FTC is frequently co-administered with TDF. In POPPY, 97.0% (500/516) of the study participants who provided samples for the calculation of the FTC PK parameters were also on TDF and in analyses simultaneously adjusting for TDF and FTC PK parameters, only the association of TDF CL_{24h} was associated with increased hip-fracture score (data not shown).

Among the participants who provided samples for the assessment of ABC and 3TC PK parameters, I found no association between the PK parameters and either of the FRAX scores. This may be explained by, among other reasons, the lack of adverse effects of ABC and 3TC on bone metabolism. This finding is in line with Rasmussen *et al.* and Tebas *et al.* who suggested that TDF/FTC-containing therapy compared to ABC/3TC-containing and EFV/FTC/TDF compared to dolutegravir (DTG) plus ABC/3TC was associated with greater decreases in BMD while it increases markers of bone turnover (728, 729).

The sensitivity analysis excluding the FN BMD T-score from the FRAX scores calculation suggested that the 10-year hip fracture risk was 7.3% and the major-osteoporotic fracture risk 1.1%. These estimates are significantly lower compared to the FRAX scores calculated using the FN BMD T-score measurements (12.0% and 1.9%, respectively). This finding is in line with Tsai *et al.* (406) who suggested that when BMD is included in score calculation, more candidates are considered for treatment. The amendment in the calculation of the FRAX scores resulted in scores that were less sensitive to identify patients in need for treatment. Thus, people at risk for fractures may not receive timely treatment for osteoporosis which may lead to irreversible bone damage among the elderly.

In the sensitivity analysis the prevalence of those in need of treatment is lower when the FRAX scores are calculated without the FN BMD T-score and the result of the univariable and multivariable regression analyses suggested lack of association between HIV and the FRAX scores.

Furthermore, the association of frailty and history of falls with FRAX scores was not present in the sensitivity analysis. This may be explained, among other reasons, by the lack of power and the fact that the scores marked lower in comparison to the original analysis deeming the difference between frail and non-frail non-significant. Therefore, the results of the original analysis should be more reliable, considering that the FRAX developers recommend the inclusion all the 12 components (when possible) for score calculation (Figure 3.3).

8.7.3 Strengths and limitations

Instead of restricting the study participants to only report the specific fracture type (e.g. recent/osteoporotic/requiring surgery), they were also asked to provide detailed fracture history. This enabled several descriptive layers of categorization of the fractures (e.g. osteoporotic/non-osteoporotic, etc.). The BMD T-score was available for the majority of the study participants over the age of 40. This allowed more detailed analysis of the FRAX score assessments and uncovered those study participants requiring osteopenia and osteoporosis treatment.

One of the main drawbacks was the use of a five-year window-period for the FIR calculation. The study participants reported fractures from childhood through to adulthood, and those occurring up to five years before study entry were used for the FIR assessment. This carries a risk of inaccurate reporting, considering that some participants may have forgotten or mistakenly reported the time of fracture. However, the five-year window-period was deemed appropriate for identifying fractures that could be associated with HIV and/or HIV treatment, as the median time since diagnosis was 13.2 years.

Another limitation is the lack of information on the intensity of the recreational drug use and its association with higher FIR. A dose-response relationship suggested among other researchers may have been present among the POPPY participants. However, it was not possible to replicate this finding.

The FRAX scores were calculated using the UK-specific FRAX score calculator since all POPPY participants were residing in the UK or Ireland. Both countries exhibit similar lifestyle, socioeconomic conditions, and life expectancy prescribing this approach over country-of-birth-specific calculators. This approach may have led to lower accuracy and reliability of the FRAX scores. This concern has been acknowledged among other researchers (730). However, the calculation of country-of-birth-specific FRAX scores was not feasible considering the time constraints of completing my thesis, therefore, the use of the UK-specific FRAX calculator for all POPPY participants was deemed appropriate. This method has been adopted by other researchers (731). I am confident that the calculation of country-of-birth-specific FRAX scores would

yield similar findings as those presented here. In fact, only one third (487/1377) of the study participants were born outside of the UK and Ireland of which 157 were born in Europe and North America.

The limited statistical power is another limitation of this chapter. The small number of participants with recent fractures who had depressive symptoms was small thereby the model exploring the interaction between HIV and depressive symptoms suggested a poorer fit compared to the model without the interaction.

Chapter 9 Discussion

9.1 Overview

In 2014 the UNAIDS set ambitious targets to help end the AIDS epidemic. The 90-90-90 targets suggested that by 2020 90% of all PLWH will know their HIV status, 90% of all diagnosed HIV positive people will receive ART and 90% of all people receiving ART will achieve viral suppression. These numbers were exceeded by the UK in 2018 (590) (93%, 97% and 97%, respectively) while they were close to being achieved by Ireland (732) (90%, 80% and 76% respectively). Effective ART and wider availability of pre-exposure prophylaxis (PrEP) has led to a significant reduction in new infections and longer life expectancy (37, 140, 733). However, as a result, ageing PLWH, their caregivers and healthcare providers have already started to face several new age-related challenges such as frailty, falls, low BMD and increased fracture risk. In many developed countries, including the USA, South Africa and several European countries, new studies are exploring the particular challenges faced by older PLWH. The research conducted in POPPY will inform clinical practice regarding the specific needs of ageing PLWH.

To date this is the largest study that has collectively assessed the endpoints of frailty, falls, low BMD and fractures among PLWH in western Europe. This thesis aimed to deepen our knowledge around the challenges of frailty, falls, low BMD, fractures and fracture risk among groups of older and younger PLWH and a group of HIV-negative controls. The rich data on objective measures, including the walk and strength tests, DEXA scans and the PK analysis along with the available data on confounding factors measured in POPPY enabled the exploration of several hypotheses. Although other studies in the USA (70, 149, 155, 172, 174, 178), South Africa (161), Italy (181) and the Netherlands (173) have explored a similar range of outcomes to those considered in this thesis, few have included a group of HIV-negative controls or a group of demographically and lifestyle matched controls and none has collectively reviewed these outcomes.

This chapter summarises the main common and novel findings of my thesis followed by the general study strengths and limitations and concluding with recommendations for future studies and final remarks.

9.2 My involvement in this thesis

I was the lead statistician for all analyses presented in this thesis and I played a central role in all steps from literature review to data cleaning and the hypotheses and objective development for each of the results chapters. I performed the statistical analysis, interpreted the results and wrote the thesis. All the hypotheses, objective as well as other outputs (i.e. manuscripts and conference abstracts) have been discussed with my supervisors and the wider POPPY team.

9.3 Thesis key findings

9.3.1 Common findings

- The frail POPPY participants had a greater use of healthcare resources compared to the non-frail participants
    - Primary care (nurse visits)
    - Secondary care (specifically hospital investigations and mental health-related visits)
    - Acute care requirements (A&E and ambulance use)
- Older PLWH compared to similarly aged HIV-negative controls had:
    - 4-fold higher odds of frailty
    - 4-fold higher odds of falls and 5-fold higher odds of recurrent falls
    - Lower BMD T-score at LS, FN and TH
    - Higher FIR
    - Higher FRAX scores
- Among PLWH
    - Those on NVP NNRTIs had a significantly higher BMD T-score at LS and TH compared to those not on NNRTIs
    - Those with a detectable VL appeared to have low BMD T-score at TH
    - Those with a previous diagnosis of AIDS-defining illness appeared to have a lower BMD T-score at FN

    - Participants with a higher concentration and lower elimination of TDF and FTC PK parameters had a lower BMD T-scores at FN
    - Longer time since HIV-diagnosis was associated with higher FIR
    - Older age was associated with a higher hip fracture score
    - Increased number of co-medications taken (excluding ART) was associated with a higher score for major-osteoporotic fractures
    - Higher TDF $AUC_{0\text{-}24h}$, was associated with lower BMD T-score at FN,
    - Higher TDF $AUC_{0\text{-}24h}$ and C_{max} were associated with lower BMD T-score at FN
    - Higher TDF CL_{24h} was associated with significantly higher BMD T-scores at FN and at TH
- FIR appeared to be elevated among those with moderate and severe depressive symptoms as assessed by the CES-D, no clear dose-response relationship could be confirmed
- History of falls and recurrent falls was associated with increased FIR
- FIR appeared to be elevated among those with moderate and severe depressive symptoms (as assessed by the CES-D score) but not a clear dose-response relationship could be determined for the PHQ-9 score
- Severe depressive symptoms (as assessed by CES-D) were associated with a higher FIR independently of HIV
- Frailty and history of falls were associated with increased FRAX scores
- When FRAX scores were calculated without the use of FN BMD measurements the number of people in need for treatment was lower
- FRAX scores appeared to be elevated among those with moderate and severe depressive symptoms (as assessed by either the CES-D score or the PHQ-9 score) but not a clear dose-response relationship could be determined

9.3.2 Novel findings

- The association of HIV with frailty was not modified by any association with age in the older POPPY groups
- The association of HIV with frailty, fall, low BMD T-score, fractures and fracture risk was not modified by any association with depressive symptoms in the older POPPY groups

- HIV was associated with higher odds for falls independently of any association with frailty
- HIV was associated with higher FRAX scores independently of any association with frailty and history of falls
- HIV was associated with lower BMD T-score at FN and TH independently of any association with frailty and history of falls
- The association of HIV with FRAX scores was independent of any association with frailty and history of falls
- Among PLWH:
    - Lack of association between TDF and FTC PK parameters and BMD T-score at LS
    - Higher FTC concentration and lower elimination were associated with significantly lower BMD T-scores at FN and TH
    - The concentration and the elimination of the ABC and 3TC PK parameters were not associated with BMD T-scores at any of the three sites examined
    - Higher TDF concentration and lower elimination were associated with increased FRAX scores
    - Higher FTC concentration and lower elimination suggested elevated FRAX scores
    - The concentration and the elimination of the ABC and 3TC PK parameters were not associated with the FRAX scores

9.4 General strengths and the chapter-specific limitations of my work, barriers, bias, data gaps

9.4.1 General strengths

POPPY has been one of the largest studies conducted in Western Europe exploring the effect of ageing among PLWH. The richness of the data allowed the correction of the estimates by adjusting for potential confounders including demographic, lifestyle, clinical and HIV-specific factors. The inclusion of the demographically and lifestyle-similar HIV-negative group allowed me to investigate an association of HIV with frailty, falls, BMD and fractures and understand the different healthcare needs of those with and without HIV. Furthermore, the assessment of BMD by DEXA scan for the majority of the POPPY participants and the availability of biological samples

for the assessment of PK parameters are key strengths of POPPY that allowed the investigation of complex hypotheses and objectives within this thesis.

The entirety of this thesis is based on data from the POPPY observational cohort study. Despite observational studies being a very useful study design by reflecting a real-world clinical condition, they have several limitations.

9.4.2 General limitations

A general limitation that applies to all results chapters is the limited statistical power. This limitation may reduce the likelihood that findings that in the statistical analysis were deemed significant actually reflect a true effect. However, to the best of my knowledge I accounted for confounding factors and I examined the relevant literature in a critical way to draw conclusion. All four results chapters face the following general limitations: use of cross-sectional data, missing data, selection bias and unmeasured confounding.

9.4.2.1 Cross-sectional data

The first general limitation concerns the use of cross-sectional data. Such data restrict causality assumptions or directionality of the presented associations between variables such as HIV, frailty, falls, BMD, depressive symptoms, number of co-medications. It cannot be determined whether one event caused the other or whether one preceded the other. Although POPPY is a prospective cohort study, the data used to explore the hypotheses of my thesis are cross-sectional data derived from the baseline visit. Despite this limitation, I have presented data trends, I explored the biological pathways and the relevant literature to illustrate and support the direction of potentially bidirectional associations.

An additional study design limitation is that the inclusion/exclusion criteria for the ageing PLWH were set to be as broad as possible. This resulted in the inclusion of individuals with a wide spectrum of comorbidities such as neurological diseases (e.g. Bell's Palsy, epilepsy, Alzheimer's disease etc.). Although the prevalence of those with neurological conditions was less than one third of the study participants (26%), I

cannot rule out the fact that the manifestation of the outcomes studied in this thesis may be driven by specific comorbidities and their treatment practices.

9.4.2.2 Missing data

In observational cohort studies, finding complete data among all variables is highly unlikely. In POPPY, data on the fractures outcomes (Chapter 8) were complete and this was due to the way the 5yr-FIR was defined, while for falls (0) and BMD (Chapter 7) the missing data were 14.1% and 3.2% respectively. The highest proportion of missing data occurred for the frailty outcome (Chapter 5). More specifically, missing data among the four variables used to assess frailty resulted in missing frailty for 21.8% of the study participants. The proportion of missing values for the other variables used in the statistical analysis never exceeded 3% of the total number of POPPY participants. Throughout the results chapters of this thesis, for the descriptive analyses I used a missing indicator approach by creating an "unknown" category for all missing data variables. However, in univariable and multivariable regression analyses a complete case analysis approach was adopted. The inclusion of an unknown category in the data analysis has been linked with introduction of bias (734, 735).

The aetiology of the missingness is hard to be determined and the type of missingness is most likely to be missing at random (MAR). Missingness may be induced by loss of data, errors in data entry, wrong or missed reporting on the electronic or hardcopy forms or refusal or inability of the study participant to respond. For example, 14.1% of the older POPPY participants did not have their BMD T-score assessed at TH, 13.0% at LS and 7.7% at FN (Chapter 7). The variation of the missing data of the BMD T-score is likely to be due to the differences in assessing BMD T-score among the study sites. Additionally, it may be due to the length of time required to complete the BMD assessment which may have led to interruption or assessment error that needs resolving.

The FN BMD T-score, was one of the 12 assessment parameters for the FRAX scores (Chapter 8). The proportion of missing on FN BMD T-score together with missing data on smoking (0.4%) resulted in 9.7% missing data on the FRAX scores. However, when

I assessed the FRAX scores without the use of FN BMD T-score, I managed to reduce the proportion of missingness to 1.6%.

All regression analyses used a complete case analysis. This means that the study participants having missing data in any of the variables involved in the regression models were excluded (listwise exclusion). When data are missing completely at random (MCAR), in other words when the cause of missingness is not induced by any systematic factor, the listwise exclusion does not introduce any bias (736). In cases where missingness is induced by an underlying systematic reason, bias may be introduced. For example, failure to complete the grip strength test for the assessment of weakness may suggest, among other things, very low grip strength or a general low physical functioning condition. However, the proportion of missing data was very low (2.4%) and similar across the three POPPY groups, therefore unlikely to have affected the results. The missing data for weakness along with the missingness in slowness, low physical activity and exhaustion combined contributed to the 21.8% of missing frailty data which may be explained by variable clinical practice across the study sites. This missingness was acknowledged as a limitation and the actions taken are explained in the following Section **Error! Reference source not found.**.

9.4.2.3 Selection bias

The comparison between those enrolled in the study and those not suggested that in POPPY the proportion of white, MSM and those who have achieved immunosuppression (median HIV RNA<50 copies/ml) was significantly higher and the nadir CD4 count among the POPPY participants was also significantly higher compared to the eligible non-POPPY participants (580).

At the beginning of each of the results chapters I compared the study participants who did and did not provide data for each of the outcomes of interest and identified differences with regards to study site and participants characteristics.

Nevertheless, the recruitment process cannot be deemed random as this would have required a recruitment strategy from a wider range of communities beyond just sexual health/HIV clinics. This could have introduced selection bias. The study

participants were recruited from clinics for infectious diseases or sexual health, which suggests that they would be in a state of physical functionality that allowed them to access healthcare services. Those who did not participate in the study may have not required HIV treatment or were not physically able to attend such services due to restricted mobility caused by chronic or acute clinical conditions. This suggests a potential underestimation of all the outcomes examined in this thesis. The sampling bias has been minimised by the almost 3-year recruitment period that allowed information gathering from a wider group of eligible participants. Yet those with functionality restrictions may have preferentially opted to join POPPY if they had health concerns. This may have led to an overestimation of frailty, history of falls and fractures and may limit the generalisability of results.

Another limitation relevant to selection bias is that the recruitment sites were university affiliated and based in big cities which means that PLWH in rural areas with limited access to infectious diseases and sexual health clinics are underrepresented. Furthermore, the targets were not achieved resulting in a study population that was 31% smaller than the initial target. The resulting cohort of study participants in POPPY is predominantly represented by white, male MSM participants, representative of individuals attending infectious diseases and sexual health services in England and Ireland. This restricts the generalisability of the findings for HIV positive women as well as the wider population of PLWH in England and Ireland or indeed communities with limited resources and lower cART uptake.

9.4.2.4 Unmeasured and residual confounding

All observational studies are subject to unmeasured confounding. Randomised control trials can control for confounding since the participants are allocated randomly to exposure groups. The random allocation of study participants in the three POPPY groups was not possible since it would require grouping based on HIV status and age.

Multivariable statistical analysis accounts for bias introduced by measured confounding, however, it is impossible to adjust for confounders that are unmeasured hence bias by unmeasured confounding may be introduced. In POPPY

potential residual confounding may have resulted from errors or inaccuracies in the measurement of certain variables, even after adjustment. For example, the total number of co-medications, a confounding factor that has been considered across all chapters, may have collection method inaccuracies leading to underreporting due to participant difficulties in recalling the co-medications taken over the past 12 months. Other confounding factors that may be inaccurately self-reported and most likely under-reported due to self-denial, stigma and fear of confrontation include smoking, use of alcohol and use of recreational drug use over the past 6 months.

Since it is impossible to completely account for unmeasured or residual confounding, I could only measure what was available and what was known about and there may be confounding mechanisms that I could not know about. The strengths and limitations relating to each chapter are presented in the following section.

9.5 Clinical significance

The association of HIV with all the adverse outcomes examined in this thesis highlight the need for a better understanding of the implications of HIV and HIV treatment in the ageing cohort of PLWH. A polymodal view of communication among healthcare specialists is required when treating older PLWH to achieve a healthy ageing with a good quality of life.

These association of HIV with frailty, falls, low BMD T-score, fractures and fracture risk highlight the need for disentangling the complex mechanism for those adverse outcomes. Treatment of PLWH with medication that are less bone-toxic but still effective for treating HIV is essential to achieve a better bone health. The findings of my thesis regarding the association of the TDF and FTC concentration with lower BMD T-score and higher FRAX scores call attention to HIV-specialists to closely monitor the difference in the drug metabolism in older PLWH. Both the concentration in the plasma and the clearance of those drugs should be closely monitored when treating older PLWH at risk for adverse bone diseases.

These association of HIV with depressive symptoms may confirm previously known pathophysiological mechanisms but can also reveal unknown mechanism of the

association and help to generate new hypotheses to further elucidate possible pathophysiological pathways. The association of depressive symptoms with frailty and falls is a finding of great clinical relevance and highlights the need for multidisciplinary treatment of the older PLWH.

Depressive symptoms negatively impact the self-care practices and quality of life of PLWH. Therefore, the levels of depressive symptoms amongst older PLWH need to be closely monitored to ensure care retention and adherence to ART. This will also help evaluate the success of outreach strategies. Addressing the needs of depression in HIV research is very important (737). Healthcare specialists treating PLWH need to understand the complex mechanisms of the association of HIV and depressive symptoms and be cognizant of referral services and social support networks which could provide individuals with social and emotional support and advice to cope with depressive symptoms.

Furthermore, strategies to actively engage stakeholders in mental health management and polypharmacy reduction in relation to comorbidities and deficit accumulation are essential to reduce frailty (213). It is essential to assess the unique configuration of social and behavioural traits such as engagement with social support, treatment adherence and proactive self-care. This will provide more insight into health outcomes not only among PLWH but also among the ageing cohort of the general population (738, 739).

9.6 Future work and recommendations for other studies

Over the last few years, research in the field of HIV has shown that the life expectancy amongst PLWH is similar to that of the general population. Although this is a great milestone achievement in the course of the HIV epidemic, the emergent needs of ageing PLWH requires adaptation of healthcare services and restructure of resource allocation. A better understanding of the needs among the ageing group is required while several questions remain to be answered, including for example the quantification of the rate of progression to more severe stages of frailty, falls, low BMD and fractures which would be of major importance for achieving a healthy ageing among PLWH.

Future work would benefit from extending the analyses in Chapter 4 to investigate temporal patterns and fluctuations of frailty amongst PLWH. Frailty has been reported to be highly fluctuant in the MACS longitudinal study (145). Modelling studies suggest a trend of a drop in the prevalence of frailty from 26% to 7% amongst those aged 50 years for the period 2015-2030, whereas an increase from 43% to 52% is expected for those aged 75 years or over (740). Our knowledge about the trajectories of frailty patterns both in the general population and among PLWH need to deepen in order to identify the age groups at higher risk and to understand the mechanisms and behaviours that are associated with higher frailty. An adaptation of the frailty definition to allow its assessment across a broader range of settings would benefit the development of universal strategies to tackle frailty and extend the functional ageing window. These endeavours would also facilitate the identification of the core risk factors and biological mechanisms associated with frailty across different settings. As the follow-up of POPPY participants is still ongoing, the enriched data could be used to elucidate the changes over time in the components of frailty and will identify those risk factors responsible for frailty progression.

In POPPY, I found that frail participants had significantly greater use of healthcare resources which is consistent with the findings of other studies confirming that the total healthcare costs increase due to frailty (741). This highlights the need for the adoption of health promotion policies among the elderly who show early signs of frailty (742). Further work is needed to explore the burden of polypharmacy on frailty, falls, low BMD and fractures. The combination of ART with polypharmacy significantly increases the chance of potentially serious drug–drug interactions (DDIs) and it is critical to develop strategies to reduce pill burden among older PLWH (657, 743). However, the recent orientation of the primary care landscape is not addressing this gap and this is becoming increasingly recognised as growing concern amongst treated PLWH (744-746).

Exploration of risk factors for falls, other than those presented in Chapter 5, would be essential for future research. In POPPY 70% of those with history at least one fall had recurrent falls, 80% of the falls occurred at home and 41% of those with a history of fall had a low physical functioning score and higher depressive symptoms.

Strategies and interventions to tackle deterioration of physical functioning and frank depression are crucial to promote risk reduction among the elderly. Exploration of the effect of the environment and the effect of the season on falls among the elderly would be an advancement in achieving falls reduction. Depressive symptoms have been reported to progress with ageing. Therefore, decoding the biological mechanisms of this association and identifying the risk factors for frailty and falls is crucial for both PLWH and the general population. The ageing PLWH have been reported to experience higher levels of social isolation and loneliness (747, 748) and higher levels of physical inactivity (749). The effectiveness of therapies for reduction of depressive symptoms, social isolation and engagement with physical activities should be evaluated. Qualitative work involving groups with higher depressive symptoms, at higher risk of social isolation and loneliness and increased co-occurring comorbidities could inform the design of services to address these emergent needs.

Future studies exploring the risk factors for the key endpoints of this thesis would also benefit from assessing the effects of nutrition and social deprivation. Several recent studies in the general population have shown the link between poor nutrition, social deprivation and increased frailty, falls, low BMD and fractures (750-755), while among PLWH the relevant literature is sparse.

Extending the results of Chapter 6 and Chapter 7 regarding the association of NRTI PK parameters with low BMD and fracture risk, future studies should try to disentangle the biological mechanisms behind the association of ART with low BMD and fracture risk. The ongoing development of less bone-toxic medication for treating PLWH should continue.

Further work is also needed to refine the FRAX score (Chapter 7) or to spearhead the development of a new tool to accommodate settings where DEXA scans are not available. Not having a value of BMD to support the calculation of the FRAX scores, is a major limitation. This results in identification of less people at risk for hip and major-osteoporotic fractures who are in need for treatment compared to the FRAX scores including BMD (Chapter 7). Therefore, appropriate adjustments should be considered for improving the accuracy and safety of the prediction of FRAX scores

when BMD data are not available. In resource-limited settings the assessment of BMD may not be feasible and future studies should be able to use a reliable tool for the assessment of the fracture risk that would appropriately identify the people at high risk.

Finally, future research among the older PLWH should consider the establishment of studies using mixed methods research approaches to support the collection of both qualitative and quantitative or contextual data. This can help to better understand the challenges and the needs of older PLWH and would allow tailoring of the interventions to fit the needs of this population by adopting the right policy prescriptions to support vitality in ageing among the older PLWH.

9.7 Concluding remarks

The current literature has recognised the importance of being prepared for the demographic shift of ageing in the epidemic of HIV (756). The aims of this thesis have considered the challenges of ageing with HIV and my findings have helped to improve and increase our knowledge concerning the effect of HIV on ageing. My primary objective was to assess frailty, falls, low BMD, fracture rate and fracture risk among PLWH and assess the differences with HIV-negative controls. A second objective was to identify whether the differences obtained between PLWH and HIV-negative controls remained after controlling for confounding factors identified through the literature. The third objective was to identify the HIV-specific factors among the PLWH that are associated with changes in frailty, falls, BMD, fracture rate and fracture risk and the fourth objective was to assess the effect of cART-specific PK parameters on BMD and fracture risk.

This thesis provides several major contributions in the field of HIV and ageing and the findings suggest that HIV is associated with greater frailty, a higher prevalence of falls and recurrent falls, low BMD, higher fracture and higher FRAX scores. The findings of this thesis confirmed the association between TDF and FTC PK parameters with BMD T-score and hip fracture score. Another important contribution of this thesis was the quantification of the effect of HIV and other risk factors in bone health among PLWH.

Furthermore, this thesis highlighted the importance of close monitoring and early onset of bone health screening among the older PLWH.

The results of this thesis can be used to quantify the need for effective interventions among the vulnerable group of ageing PLWH and also to inform HIV-specialists to adapt treatment practices accordingly to the needs of this group and motivate the group of ageing PLWH to pursue lifestyle changes that may have an impact on reducing the rate of bone loss. The results are also very important among HIV-specialists treating older PLWH and geriatricians treating elderly people of the general population. It is crucial to confirm the known risk factors and identify new ones and also to understand the mechanisms leading to elevated risk for hip and major-osteoporotic fractures among PLWH. The group of PLWH would also improve their knowledge on the challenges of ageing with HIV from using the findings of my thesis. I highlighted the association of potentially modifiable risk factors such as physical functioning, depressive symptoms and polypharmacy with frailty, falls, low BMD, fractures and fracture risk. The follow up of the ageing PLWH in POPPY and similar other cohorts will further elucidate the trajectory of the effect of HIV on frailty falls, low BMD, fractures and fracture risk, thus enriching our knowledge of the mechanisms of ageing in PLWH as well as extending the research agenda in the field of HIV and ageing.

Appendix I

POPPY

Study Number

A prospective, observational study to examine the effects of ageing on the clinical outcomes of people living with HIV in England and Ireland.

POPPY – 'Pharmacokinetic and Clinical Observations in People over Fifty'

POPPY

Pharmacokinetic and clinical observations in people over 50

PATIENT STUDY FILE

Name	
First Name	
DOB	
Site	

This file should be kept with the POPPY Site Investigator file and retained for monitoring purposes.

If you find this folder please return to the POPPY team or contact the POPPY Trial Manager ……

Contents

POPPY

Study Number

1. Inclusion Criteria (summary) tick yes

Older HIV-positive cohort (n=1000):

- documented HIV infection
- age ≥50 years at study entry
- self defined white or black African ethnicity
- likely route of HIV acquisition via sexual exposure
- able to comprehend study patient information leaflet

Subjects with primary HIV infection are eligible and investigators are encouraged to recruit such subjects.

Our target population (those of white or black African ethnicity and those infected with HIV via sexual routes) has been chosen as these groups represent the vast majority of older HIV-positive individuals attending for care in the UK; analyses of other groups (e.g. injection drug users, those infected through blood/blood products), who may have very different needs and outcomes, would likely be under-powered.

Younger HIV-positive cohort (n=500):

- documented HIV infection
- age <50 at study entry*
- self defined white or black African ethnicity
- likely route of HIV acquisition via sexual exposure
- able to comprehend study patient information leaflet

* this group will comprise of at least 150 subjects in each of the following age groups: 20-29, 30-39, 40-49 years. Recruitment will be monitored by the Study Monitoring Team

HIV-negative cohort (n=500):

- documented negative HIV test at screening
- age ≥50 years at study entry
- self defined white or black African ethnicity
- registered with a General Practitioner

POPPY

Study Number

2. Exclusion Criteria (summary)

- in the opinion of the investigator, those unable or unwilling to comply with the requirements of the study
- life expectancy in the opinion of the investigator - less than 6 months.
- Subjects of black African ethnicity who have acquired HIV infection by M2M contact.

3. Screening visit: *date:*

❑ INFORMED CONSENT (3 copies)
(copy to be filed in patient file)

Each subject must sign an Informed Consent Form prior to the conduct of any screening procedures.

The purpose of the screening visit is to evaluate that the subject meets study inclusion/exclusion criteria. HIV antibody testing will be undertaken for subjects undergoing screening for the HIV-negative cohort.

Screening questions:

1. **Likely route of HIV acquisition: code; sex between men / sex between men and women / other (if other, then exit interview).**

2. **Self-defined ethnicity: code; white / black African / other (if other, then exit interview)**

3. **If black African if +ve and acquired by M2M contact exclude**
4. **Date of birth: dd/mm/yyyy**

5. **Age group: ≥50 years / <50 years**

POPPY

Study Number

6. HIV status: code: positive / confirmed negative

Inclusion criteria	
Exclusion criteria	
CONSENT date	
GROUP	

Signature
Name
Position

4. Visit 1: BASELINE: *date:*

The baseline visit will perform evaluations as per schedule of visits (2.0).

The baseline visit is expected to take 1-2 hours; if possible the subject should attend fasted. The following information will be collected:

SOCIAL HISTORY

- ❑ Gender: code; Male/ Female
- ❑ Marital status: code; Single / Married / civil partnership / Cohabiting / Divorced / Living separately / Widow / Widower **(tick all that apply)**
- ❑ How many persons (including yourself) does your household comprise? Code; number adults, number children:.....
- ❑ Number of children to whom subject is a parent (adult and younger children); number:.....

POPPY

Study Number

- ❑ Number of children under 16 subject cares for; number: ……
- ❑ Country of birth; ……
- ❑ Mother's country of birth; ……
- ❑ Father's country of birth; ……
- ❑ Since what year living in UK (if applicable) / Ireland; code number years:……

EXAMINATION

- Anthropometrics:
  height:……cm weight:……kg waist circumference:…… body mass index

- Blood pressure will be estimated using an automated device. Three readings to be taken after a period of rest and a minimum of 3 minutes between each reading. INFORM will calculate the average of readings 2 and 3

time	systolic	diastolic

Antiretroviral Regimen

- ❑ Date of HIV+ve diagnosis……and
- ❑ date of HIV-seroconversion if known. (mm/yy)……
- ❑ Is patient currently receiving ART? yes / no
- ❑ Current antiretroviral regimen

If yes above, list drugs in current regimen (drop-down list), dose and frequency

- ❑ In past 12 months type of antiretroviral; start/stop dates; dose; frequency of dosing; side effects; reasons for prior changes/discontinuations

Drug	Dose	Frequency	Start date	Stop date

POPPY

Study Number

Intoxications

1. History of smoking (ever); code yes/no
2. If yes:
    a. At what age did they start, age:……
    b. Does patient still smoke; yes/no
    c. If yes, how many per day; number……
    d. If no, age of stopping smoking; ……
3. Has subject ever consumed alcoholic beverage, yes/no
4. If yes:
    a. Age started to drink alcoholic beverages, age:……
    b. Does subject consume alcoholic beverages at the moment, yes/no
    c. If no:
        i. age stopped drinking, age…….
        ii. when consuming alcohol, how often; code less than monthly, monthly, weekly, daily or nearly daily
    d. If yes
        i. Number of units per week; code units (and nurses will have a chart to work out units):……..
        ii. How frequent; code less than monthly, monthly, weekly, daily or nearly daily
        iii. How often in the last 6 months has subjects consumed 6 or more alcoholic beverages in one day; code less than monthly, monthly, 2-3 weeks, weekly, daily or nearly daily
5. History of recreational drugs in past 6 months; code yes/no
6. If yes complete below table with nurse:
7. Has patient ever injected drugs; code yes/no
8. If yes:
    a. At what age did subjects inject for first time; code age
    b. Does subject still inject drugs, code yes/no.

Marijuana	Blunt, dope, ganja, grass, herb, joint, bud, Mary Jane, pot, reefer, green, trees, smoke, sinsemilla, skunk, weed	Smoked, swallowed
Hashish	Boom, gangster, hash, hash oil, hemp	Smoked, swallowed
Opium	*Laudanum, paregoric*: big O, black stuff, block, gum, hop	Swallowed, smoked
Heroin	Smack, Ska,H, Brown, junk	Injected, snorted, smoked
Methadone	Symoron, Dolophine, Amidone, Methadose, Physeptone, Heptadon, Phy Dollies, Dolls, Done, Meth, Phy, Junk, Metho, Jungle Juice, Fizzies, Chocolate Chip Cookies, Maria, Pastora, Salvia, Wafer, Juice.	Swallowed injected
Mephedrone	Miaow, miaow. Meph, Snow, Blow	Snorted, swallowed
Cocaine	*Cocaine hydrochloride*: blow, bump, C, candy, Charlie, coke, crack, flake, rock, snow, toot	Snorted, smoked, injected
Amphetamine	*Biphetamine, Dexedrine*: bennies, black beauties, crosses, hearts, LA turnaround, speed, truck drivers, uppers	Swallowed, snorted, smoked, injected
Methamphetamine/ crystal meth	*Desoxyn*: meth, ice, crank, chalk, crystal, fire, glass, go fast, speed, Tina	Swallowed, snorted, smoked, injected
MDMA (methylenedioxy-methamphetamine)	Ecstasy, Adam, clarity, Eve, lover's speed, peace, uppers	Swallowed, snorted, injected
Benzodiazepines	*Valium, Rohypnol*: forget-me pill, Mexican Valium, R2, roach, Roche, roofies, roofinol, rope, rophies	Swallowed, snorted
GBL/GHB	G, Gina, Georgia home boy, grievous bodily harm, liquid ecstasy, soap, scoop, goop, liquid X	Swallowed
Ketamine	*Ketalar SV:* cat Valium, K, Special K, vitamin K	Injected, snorted, smoked
PCP and analogs	*Phencyclidine:* angel dust, boat, hog, love boat, peace pill	Swallowed, smoked, injected
Salvia divinorum	Salvia, Shepherdess's Herb, Maria	Chewed, swallowed, smoked

	Pastora, magic mint, Sally-D	
Dextromethorphan (DXM)	Found in some cough and cold medications: Robotripping, Robo, Triple C	Swallowed
LSD	*Lysergic acid diethylamide:* acid, blotter, cubes, microdot yellow sunshine, blue heaven	Swallowed, absorbed through mouth tissues
Mescaline	Buttons, cactus, mesc, peyote	Swallowed, smoked
Psilocybin	Magic mushrooms, purple passion, shrooms, little smoke	Swallowed
Anabolic steroids	*Anadrol, Oxandrin, Durabolin, Depo-Testosterone, Equipoise*: roids, juice, gym candy, pumpers	Injected, swallowed, applied to skin
Inhalants	*Solvents (paint thinners, gasoline, glues); gases (butane, propane, aerosol propellants, nitrous oxide); nitrites (isoamyl, isobutyl, cyclohexyl)*: laughing gas, poppers, snappers, whippets	Inhaled through nose or mouth
OTHER		

POPPY

Study Number

Healthcare utilisation EXPAND FOR VISITS 2& 3

1. Details of all healthcare providers subject has seen over past year specifically asking regarding the following:
   a. GP – number of times attended and for what conditions

   b. GP investigations

   c. GP nurse or other health care provider at GP or community site

   d. Attendance at A & E department

   e. Hospital specialists – number of times attended and for what conditions

f. Hospital procedures eg operation, PCTA, blood transfusion

g. Hospital investigations eg Xray, ECG, SCANS, blood tests (do not include trial blood tests)

h. Attended psychiatrist / counsellor / psychologist – number of times attended and details of reasons

i. Other community healthcare providers – number of times attended and details

j. Use of ambulance or hospital transport

k. OTHER

POPPY

Study Number

Participation in population screening:

For female

1. Ever had a mammogram; code yes/no
2. If yes:
    a. Number of mammograms; code number:……
    b. For each mammogram, was this part of population screening; code yes/no
    c. For each mammogram, were there any abnormalities; code yes/no
    d. If known, details of abnormality; code free text?
3. Ever had a cervical smear; code yes/no
4. If yes:
    a. Year of last smear; code year……
    b. History of any abnormalities on smear; code yes/no
    c. If yes, details of all abnormalities ever detected on smear tests if known; code **free** text?:……
    d. Has colposcopy been performed y/n date result……
    e. Date of next planned smear:……
5. Participated in any other screening? y/n
6. If yes above, provide details (free text)……

For male participants

1. Have you been examined for anal cancer in the past; code yes/no
2. If yes:
    a. When was the last time; code year:……
    b. Have abnormalities ever been found; code yes no
    c. If yes, details of all abnormalities ever detected (if known); code **free text?:**……
3. Participated in any other screening (e.g. PSA)? Y/n
4. If yes above, provide details (free text)……

POPPY

Study Number

Medical History: Include medication where relevant & link to con meds

Family medical history Reminder to update at each visit (ALLOW MULTIPLE FAMILY MEMBERS)

1. Has a first degree family member (father, mother, brother, sister, son, daughter) experienced a heart attack (myocardial infarction)? Code yes/no, if yes details of family member and age at onset

2. Does hypertension (high blood pressure) occur in the family (parents, brothers, sisters or children)? Code yes/no, if yes details of family member and age at onset

3. Does high cholesterol occur in the family (parents, brothers, sisters or children)? Code yes/no, if yes details of family member and age at onset

4. Does diabetes occur in the family (parents, brothers, sisters or children)? Code yes/no, if yes details of family member and age at onset

5. Is there a family history of dementia; code yes/no, if yes details of family member and age at onset

6. Have either parents had a hip fracture; code yes/no, if yes details of family member and age at onset

7. Apart from these, is there a family history of other diseases code yes/no

8. If yes:
   a. List of diseases; code open text
   b. Family members affected;

9. Unknown family history

Medical History - AIDS Defining Events

SYSTEMS LIST (ICD10)

In all sections if treatment is on-going a prompt should say is the treatment on the con meds list

- ***Infections***
  - History of TB: code; yes / no

  If yes above, year and month of each episode of TB; code year, month
  - History of other AIDS events: code; yes / no

  If yes above, type of diagnosis **(drop-down menu of AIDS-defining conditions),** year and month of each diagnosis
  - **OTHER**

Medical History - Infections and Paracytic

- History of Sexually Transmitted Disease Yes/No
- History of STD Details
- Infected with Hepatitis B yes/no

  If yes above, year and month of first diagnosed; code year, month
- Infected with Hepatitis C yes/no

  If yes above, year and month of first diagnosed; code year, month
- History of any other Infections yes/no
- Other Infections:

POPPY

Study Number

Medical History - Endocrine disease

- ***Endocrine disease nutritional and metabolic including diabetes***
  - Type 1 diabetes, code yes/ no

If yes above, year and month of first diagnosed; code year, month
If yes above, year and month of first diagnosed; code year, month

  - Type 2 diabetes; code yes/ no

If yes above, year and month of first diagnosed; code year, month

  - Thyroid disease

If yes, diagnosis and year and month first diagnosed; code year and month.

  - Underactive Details
  - Overactive Details

- **Endocrine Diseases**
  - History of any other endocrine diseases yes/no

- **OTHER Endocrine Diseases**

Medical History - Blood Diseases

- ***Blood and blood forming organs*** yes/ no
  - **Other blood or blood forming organs - provide details for each event**

Medical History - Mental Health

- ***Mental disorders***
  - History of depression; code; yes/ no
  - Medically diagnosed depression (treated by a doctor) yes/no

If yes above, year and month of first diagnosed; code year, month

- **Other mental disorders**

POPPY

Study Number

Medical History - Nervous System

- ***Nervous system***
  - Does patient have Parkinson's disease or other movement disorder, code; yes/no and diagnosis
    If yes above, year and month of first diagnosed; code year, month
  - Does patient experience dizziness or vertigo which causes them to fall, code yes/no
    If yes above, year and month of first diagnosed; code year, month
  - Any condition associated with loss of consciousness for 30 minutes or more; code yes/no and if yes reason for each episode and month/year
    If yes above, year of diagnosis and year of last seizure.
  - Any history of brain surgery; code yes/no and if yes reason for each episode and month/year
  - History of encephalitis, code yes/no and if yes reason for each episode and month/year
  - History of epilepsy; code yes / no
  - History of peripheral neuropathy; code yes / no
  - Other Nervous System

Medical History - Cardiovascular disease

- ***Cardiovascular disease***
  - History of MI: code; yes/ no

  If yes above, year and month of each MI; code year, month
  - History of heart failure; code; yes/ no

  If yes above, year and month of first diagnosed; code year, month
  - History of angina pectoris; code yes/ no

  If yes above, year and month of first diagnosed; code year, month
  - History of narrowed blood vessels in legs or abdomen; code yes, no

  If yes above, year and month of first diagnosed; code year, month
  - History of CVA or TIA, code yes, no

  If yes above, year and month of each TIA; code year, month
  - History of CABG or PTCA: code; yes / no

  If yes above, type of each intervention (CABG / PTCA), year and month
  - **OTHER**

- ***Chest disease***
  - History of asthma, bronchitis chronic or acute, pulmonary emphysema or COPD; code yes/ no

  If yes above, year and month of first diagnosed; code diagnoses, year, month
  - **OTHER**

POPPY

Study Number

Medical History - Heart Failure

- History of heart failure yes/no

Medical history - Angina Pectoris

- History of angina pectoris yes/no

Blood vessels in legs or abdomen

- History of narrowed blood vessels in legs or abdomen yes/no

Medical History - Chest disease

- History of asthma, bronchitis (chronic or acute), pulmonary emphysema or COPD
- **Chest disease details - provide details of each disease**
- **Chest Disease**

  History of any other Chest disease
- **Other Chest Diseases**

Medical History - Gastro Intestinal

- ***Gastro-intestinal***
  - Persistent bowel disorder over last 3 months; code yes/no

  If yes above, year and month of first diagnosed; code year, month
  - History any other liver disease, code; yes/no

  If yes above, cause of liver disease (drop-down list), year and month of first diagnosed; code year, month
  - Any complications of liver disease yes/no

    If yes above, year and month of first diagnosed; code year, month
  - OTHER

Medical History - Renal/Urinary/Reproductive

- ***Genitourinary***
  - History of end stage renal disease (receipt of dialysis or renal transplant): code; yes/ no

  If yes above, year and month of first diagnosed; code year, month
  - Urinary incontinence requiring treatment; code; yes/ no
  - **OTHER**

POPPY

Study Number

Medical History - Related to Childbirth

- ***Related to child birth***
  - For women, age stopped menstruating; code; age and include a tick box if woman is still menstruating

For women, number of pregnancies and number of birth children; code

Medical History - Skin

- History of any skin disorders yes/ no

OTHER

Medical History - Joint, Bone and connective tissue

- ***Joint, bone and connective tissue***
  - History of joint inflammation or rheumatoid or osteo arthritis; code yes/ no

If yes above, year and month of first diagnosed; code year, month

  - History of arthritis of knee or hips; code yes, no

If yes above, year and month of first diagnosed; code diagnoses, year, month

  - History of any joint replacements; code: yes/ no

If yes above, code joint replaced and year, month

  - How many fractures has the patient experienced; code number (including 0)

If yes, complete following:

a. Year of each fracture; code year
b. Location of each fracture; code; Wrist, Upper arm, Hand, fingers, Other upper extremities (collar bone, elbow, forearm), Ribs, Pelvis, Ankle, Foot, toes, Hip, Other lower extremities (thigh, knee, lower leg), Head (skull, nose, jaw), Vertebrae (back, neck), Unknown
c. Side of body of fracture; code: left/ right
d. Cause of fracture; code; Fall from height more than your own length, Fall from height less than your own length, Traffic accident, Other (open text)
e. Did fracture require open surgery: code; yes / no

  - History of congenital bone disease (osteogenesis imperfecta); code yes/no
  - **OTHER**

POPPY

Study Number

Medical History - Congenital

- History of any Congenital disorders yes, no

Medical History - Injury and Poisoning

- History of any Injury or Poisoning

Medical History - Cancer

- ***Cancer (not recorded elsewhere)***
  History of any form of cancer; code yes, no
  If yes above, year and month diagnosed for each cancer (**drop down list**), code year, month

Medical History - Chronic Disease

- ***Chronic disease***
  How many chronic diseases does the patient think they have; code number (this question a prompt to capture other diagnoses so far missed)
  If yes above, for each disease complete the following:
  f. **Name of disease or condition:**
  g. **Year/month diagnosed; code year/month**

Fasting Lipids (Please see the eCRF for test request)

- Date of sample
- Was the patient fasting

Haematology(Please see the eCRF for test request)

- Sample collected /Recent results accessed
- Date of sample

Immunology CD4 count(Please see the eCRF for test request)

- Date of First ever result (Year only)
- Date of recent sample

Biochemistry and Urinalysis(Please see the eCRF for test request)

- Sample taken/Recent results accessed
- Date of sample

POPPY

Study Number

Hepatitis B and C serology

- Date of sample for Hepatitis B
- Hepatitis B Surface Antigen(Anti-Hbs
- Date of sample for Hepatitis C
- Hepatitis C Antibodies

Sexual Health Results

- **History of sexually transmitted disease: yes/no Separate form on INFORM**
  Diagnosis and year and month of each diagnosis
  Syphilis
  Gonorrhoea
  Chlamydia
  LGV
  Other STI:

Sample storage

- Study Blood Sample taken? **yes/no**
- Study Urine Sample taken? **yes/no**

PK Study

- PK Sample taken?
- Date and time of last food intake

DXA Results

- Date of test

Hand Grip strength

- Hand used
- Strength 1
- Strength 2
- Strength 3

Walk Test

- Did subject complete walk test Yes/No
- *Time taken to walk 15 feet (457 cm) (in seconds*
- Were there any problems

POPPY

Study Number

Physical Examination

Physical examination completed as indicated by symptoms Yes/No
List any abnormalities

Reading

- Reading test completed Yes/No
- Score
- Language

Lawton Instrumental Activities of Daily Living Scale Yes/No

Visit AE CM

- Have there been any Adverse events? Yes/No
- Have there been any Concomitant medications? Yes/No

QUESTIONAIRES & TESTS TO BE COMPLETED BY PARTICIPANT

- ❑ Adherence assessment for HIV+ve on treatment. (*confidential*)
- ❑ COGSTATE TESTS
- ❑ General self-completed and *confidential* questionnaires to include:
  Neurocognitive function: specific memory and cognitive testing assessing cortical and sub-cortical function.
  Pain assessment: regional and widespread pain collected using a validated mannequin; nature of onset; duration; intensity; resulting disability (see study questionnaire in appendix 1)
  Falls risk (see study questionnaire in appendix 1)
  Fracture risk (see study questionnaire in appendix 1)
  Frailty assessment (see study questionnaire in appendix 1)

POPPY

Study Number

HAVE THERE BEEN ANY SAEs over the past year
YES/No
If YES

Complete SAE FORM:

1.
2.
3.
4.

INVESTIGATIONS

- ❑ Most recent laboratory tests will be recorded (assessed in the HIV-negative cohort): renal, liver, lipid and bone profiles, glucose, full blood count, sexual health screen, hepatitis B & C serology
- ❑ Blood (serum, plasma) and urine samples: stored for subsequent projects of the potential pathogenic mechanisms underlying age-related diseases. This will include assessment of vitamin-D and PTH
- ❑ Blood (plasma) will be collected for pharmacokinetic analysis (including but not limited to antiretroviral drug exposure)

Efforts will allow for blood sample collection at least 5 hours after the drug dose is administered in order to ensure the sample is post-absorption and to enable the modeling of sparse data.

- ❑ DXA scan for bone mineral density (full body DXA where available)

POPPY

Study Number

Other Medication

1. How many OTHER different regular medications is the patient taking at this moment including over the counter, dietary and vitamin supplements and homeopathic agents, painkillers (ask each category individually); code; number
2. For each medication complete:
    a. Name of medication;
    b. Start date dd/mm/yy (dd may be UK- unknown)
    c. Dosage;
    d. Frequency;
    e. Stop date

Drug	Dose	Frequency	Start date	Stop date

Appendix II

Study Number:

POPPY
Pharmacokinetic and clinical observations in people over 50

STUDY NUMBER:

PATIENT INITIALS:

DATE:

VISIT:

POPPY

Pharmacokinetic and clinical observations in people over 50

Questionnaire

Thank you for taking the time to fill in this questionnaire.
If you would like help with filling in the questionnaire, one of the study team will be happy to help you.

All information that you give will be treated as strictly confidential.

The nursing team will not assess your answers, they will we entered anonymously at Imperial College.

Take your time – it is not a competition.

Your answers are very important to the POPPY study.

They will give us a good idea how we may treat people as they get older.

The questions will take about 30 minutes to answer.

Study Number:

INSTRUCTIONS

Fill out your answers with a black pen provided – put a cross in the box which most fits your response. The boxes vary in size.

X

COGNITIVE COMPLAINTS		Never	Hardly ever	Yes, definitely
Q1	Do you experience frequent memory loss (for example, do you forget the occurrence of special events even the more recent ones, appointments etc.)?			
Q2	Do you feel that you are slower when reasoning, planning activities, or solving problems?			
Q3	Do you have difficulties paying attention (for example to a conversation, a book, or a movie)?			

IN GENERAL:

Q4	In general, would you say your health is:	Excellent	Very good	Good	Fair	Poor

Q5	Compared to one year ago, how would you rate your health in general now?	Much better now than one year ago	Somewhat better now than one year ago	About the same as one year ago	Somewhat worse now than one year ago	Much worse now than one year ago

SPECIFICALLY:

Study Number:

The following items are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?				
		Yes, limited a lot	Yes, limited a little	No, limited not at all
Q6	Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports			
Q7	Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf			
Q8	Lifting or carrying groceries			
Q9	Climbing several flights of stairs			
Q10	Climbing one flight of stairs			
Q11	Bending, kneeling or stooping			
Q12	Walking more than a mile			
Q13	Walking several blocks (say 150 yards)			
Q14	Walking one block (say 50 yards)			
Q15	Bathing or dressing yourself			

IN THE PAST 4 WEEKS:

During the past 4 weeks, have you had any of the following problems with your work or regular daily activities as a result of your physical health?		Yes	No
Q16	Cut down the amount of time you spent on work or other activities		
Q17	Accomplished less than you would like		
Q18	Were limited in the kind of work or other activities		
Q19	Had difficulty performing the work or other activities (for example, it took extra effort)		

FEELINGS OF ANXIETY OR DEPRESSION:

Study Number:

During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?		Yes	No
Q20	Cut down the amount of time you spent on work or other activities		
Q21	Accomplished less than you would like		
Q22	Didn't do work or other activities as carefully as usual		

Q23	During the past 4 weeks, to what extent have your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours, or groups?	Not at all	Slightly	Moderately	Quite a bit	Extremely

PAINS:

Q24	How much bodily pain have you had during the past 4 weeks?	None	Very Mild	Mild	Mode rate	Severe	Very severe
Q25	During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?	Not at all	slightly	moderate	Quite a bit	Extremely	

You have completed a third of the questions.

Well done!

HOW ARE YOU FEELING?

Study Number:

These questions are about how you feel and how things have been with you during the past 4 weeks. For each question please give the one answer that comes closest to the way you have been feeling:							
		All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
Q26	Did you feel full of pep (energy)?						
Q27	Have you been a very nervous person?						
Q28	Have you felt down in the dumps that nothing could cheer you up?						
Q29	Have you felt calm and peaceful?						
Q30	Did you have a lot of energy?						
Q31	Have you felt downhearted and blue?						
Q32	Did you feel worn out?						
Q33	Have you been a happy person?						
Q34	Did you feel tired?						

Q35. During the past 4 weeks, how much of the time have your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives etc)?						
		All of the time	Most of the time	Some of the time	A little of the time	None of the time

GENERAL HEALTH:

How TRUE or FALSE is each of the following statements to you?						
		Definitely true	Mostly true	Don't know	Mostly false	Definitely false
Q36	I seem to get sick a little easier than other people?					
Q37	I am as healthy as anybody I know					
Q38	I expect my health to get worse					

Q39	My health is excellent					

DEPRESSION:

During the past week

		Rarely or none of the time (less than 1 day	Some or a little of the time (1-2 days)	Occasionally or a moderate amount of time (3-4 days)	Most or all of the time (5-7 days)
Q40	I was bothered by things that usually don't bother me				
Q41	I did not feel like eating: my appetite was poor				
Q 42	I felt that I could not shake off the blues even with help from my family or friends				
Q43	I felt I was just as good as other people				
Q44	I had trouble keeping my mind on what I was doing				
Q45	I felt depressed				
Q46	I felt that everything I did was an effort				
Q47	I felt hopeful about the future				
Q48	I thought my life had been a failure				
Q49	I felt fearful				
Q50	My sleep was restless				
Q51	I was happy				
Q52	I talked less than usual				
Q53	I felt lonely				
Q54	People were unfriendly				
Q55	I enjoyed life				
Q56	I had crying spells				
Q56a	I felt sad				

Study Number:

Q57	I felt that people dislike me				
Q58	I could not get "going"				

Over the last 2 weeks, how often have you been bothered by

		Not at all	Several days	More than half the days	Nearly every day
Q59	Little interest or pleasure in doing things				
Q60	Feeling down, depressed or hopeless				
Q61	Trouble falling asleep, staying asleep, or sleeping too much				
Q62	Feeling tired or having little energy				
Q63	Poor appetite or overeating				
Q64	Feeling bad about yourself – or that you're a failure or have let yourself or your family down				
Q65	Trouble concentrating on things, such as reading the newspaper or watching television				
Q66	Moving or speaking so slowly that other people could have noticed. Or the opposite – being so fidgety or restless that you have been moving around a lot more than usual				
Q67	Thoughts that you would be better off dead, or of hurting yourself.				

RISK OF FALLING:

Q68	Over the past 28 days have you had any falls?	I have not fallen	Once	Twice	Three or more times

Study Number:

If you have had no falls please do not answer the next few questions and proceed to question 73, otherwise please answer the next question.

Where have you fallen?

Q69	Inside You may tick more than one	On the one level	
		Getting out of bed	
		Getting out of a chair	
		Using the shower/bath	
		Using the toilet	
		Walking up or down stairs	
		Other	
	Home entrance or in the garden You may tick more than one	Walking up or down a step	
		On the one level (e.g path)	
		In the garden	
		Other	
	Away from home: You may tick more than one	On the footpath	
		On a kerb/gutter	
		In a public building	
		Getting out of a vehicle	
		In another person's home	
		Other	

Q70	How did you fall? Tick more than one if necessary						
I tripped	I slipped	I lost my balance	My legs gave way	I felt faint	I felt giddy/dizzy	I am not sure	Other

Q71	As a result of this fall or falls did you suffer any injuries?	Yes	No

Q72	If yes, what type of injuries did you suffer?					
Bruises	Cuts/grazes	Broken wrist	Broken hip	Broken ribs	Back pain	Other

Study Number:

POPPY
Pharmacokinetic and clinical observations in people over 50

ACHES AND PAINS

Q73	During the past month have you had any aches or pains which have lasted for one day or longer?	Yes	No

if YES, please continue with question 74, otherwise go to question 78

		Yes	No
Q74	Do you have any such aches or pains today?		
Q75	If you work - did you miss any days in the past month from work because of aches or pains? *LEAVE BLANK IF YOU DO NOT WORK*		
Q 76	Have you previously consulted your family doctor because of these aches or pains?		

Study Number:

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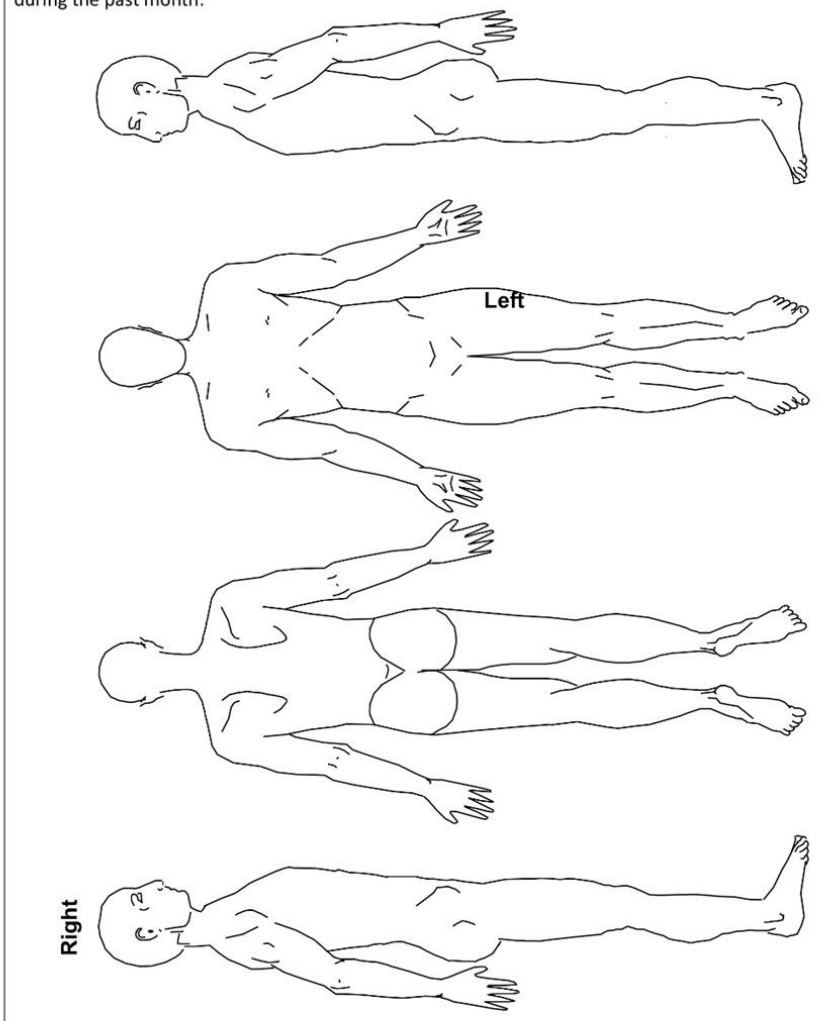
Q77 Please shade any area on the diagrams below where you feel, or have felt, aches and pains during the past month:



EMPLOYMENT, EDUCATION AND HOUSING

Study Number:

Q78	What is your current work situation?	*cross one square only*
Employed or self-employed FULL-TIME (at least 30 hours per week)		
Employed or self-employed PART-TIME (less than 30 hours per week)		
Full time student / education / training		
Unemployed and registered for benefits		
Unemployed, NOT registered for benefits		
Permanently sick / disabled (for 3 months or more)		
Temporarily sick / disabled (for less than 3 months)		
Looking after home / family / dependants full-time		
Retired		
Other (please specify)		
		Enter number below
If you work, or are a full time student, or you have been temporarily sick or disabled (for less than 3 months), how many days have you been off sick in the last year?		

Q79	What is your current housing situation?	*cross one square only*
Own my own home (including with mortgage / loan / shared ownership)		
Renting from the council or housing association		
Renting from private landlord		
Temporary accommodation (hostel, shelter, bed & breakfast, squat)		
Staying with partner / friend(s) / family		
Homeless		
Other (please specify)		

Study Number:

Q80	Do you have enough money to cover your basic needs? (e.g. food, heating)	*cross one square only*
Yes, all of the time		
Yes, most of the time		
Yes, some of the time		
No		

Q81	At what level did you COMPLETE your education? (Please tick ONE ONLY)	*cross one square only*
Finished education with no qualifications		
O levels / GCSEs (or equivalent qualifications at age 16)		
A levels (or equivalent qualifications at age 18)		
University degree or above		
Other qualifications (please specify)		

SEXUAL FUNCTION

Q82	Regarding your sexuality: which of the following options best describes how you think of yourself?	*cross one square only*
Gay or homosexual		
Bisexual		
Straight or heterosexual		
Any other term (please state)		
I don't usually use a term		

Q83	How often have you felt unsatisfied with your own sex life during the last 4 weeks?	*cross one square only*
Never		

Rarely	
Now and then	
Often	
Always	

Q84	How often have you worried about minimal sexual desire during the last 4 weeks?	*cross one square only*
Never		
Rarely		
Now and then		
Often		
Always		

IF YOU ARE MALE PLEASE ANSWER THE FOLLOWING QUESTION. **MALES ONLY PLEASE**.

Q85	How often could you develop an erection while being sexually active during the last 4 weeks?	*cross one square only*
I haven't been sexually active / not applicable		
Nearly always or always		
Most of the times (much more than half of the times)		
Sometimes (approximately half of the times)		
A few times (much less than half of the times)		
Almost never or never		

IF YOU ARE FEMALE PLEASE ANSWER THE FOLLOWING QUESTIONS. **FEMALES ONLY PLEASE.**

Q86	How often have you been satisfied about your sexual arousal during sexual activities or sexual intercourse during the last 4 weeks?	*cross one square only*
I haven't been sexually active / not applicable		

Study Number:

Nearly always or always	
Most of the times (much more than half of the times)	
Sometimes (approximately half of the times)	
A few times (much less than half of the times)	
Almost never or never	

Q87. Relating to women's periods.			
Usually women's periods stop in their 40s or 50s. This is known as the **menopause** or **'the change'**. Some women experience physical and emotional symptoms as their periods begin to stop and for some time after. We want to ask a few questions to find out how this may affect you.			
Section A: **Factors affecting cycle.**	**(please tick the appropriate box)**		
1. In the past 6 months have you used	Yes	No	Don't Know
The contraceptive implant (Nexplanon).			
The contraceptive injection (Depo or Depo-provera),			
The hormone coil (Mirena),			
The contraceptive pill?			
2. In the past 12 months have you been pregnant or breastfed?			
3. Are you currently having treatment for any type of cancer?			
If yes please give details of the cancer and any treatment.			
4. Have you had your ovaries and/or uterus (womb) removed?			
Section B: **Menstrual pattern.**			
1. When was your last period?	Month (if known)……/Year……		
2. Thinking about your periods, which of the following best applies to you (tick one):			

a. I have had regular periods in the past 3 months.	a
b. I have had periods in the past 3 months but they are irregular.	b
c. My last period was more than 3 months ago but less than 12 months ago.	c
d. I have not had a period for between one to two years.	d
e. I have not had a period for over two years.	e
f. Not relevant to me.	f

Section C:	
1	

Study Number:

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Which of the following symptoms apply to you at this time? Please, mark the appropriate box for each symptom. For symptoms that do not apply, please mark 'none'.

Symptoms:	none	mild	moderate	severe	very severe
Score =	0	1	2	3	4
1. Hot flushes, sweating (episodes of sweating)	☐	☐	☐	☐	☐
2. Heart discomfort (unusual awareness of heart beat, heart skipping, heart racing, tightness)	☐	☐	☐	☐	☐
3. Sleep problems (difficulty in falling asleep, difficulty in sleeping through, waking up early)	☐	☐	☐	☐	☐
4. Depressive mood (feeling down, sad, on the verge of tears, lack of drive, mood swings)	☐	☐	☐	☐	☐
5. Irritability (feeling nervous, inner tension, feeling aggressive)	☐	☐	☐	☐	☐
6. Anxiety (inner restlessness, feeling panicky)	☐	☐	☐	☐	☐
7. Physical and mental exhaustion (general decrease in performance, impaired memory, decrease in concentration, forgetfulness)	☐	☐	☐	☐	☐
8. Sexual problems (change in sexual desire, in sexual activity and satisfaction)	☐	☐	☐	☐	☐
9. Bladder problems (difficulty in urinating, increased need to urinate, bladder incontinence)	☐	☐	☐	☐	☐
10. Dryness of vagina (sensation of dryness or burning in the vagina, difficulty with sexual intercourse)	☐	☐	☐	☐	☐
11. Joint and muscular discomfort (pain in the joints, rheumatoid complaints)	☐	☐	☐	☐	☐

Have you ever used hormone replacement therapy (HRT)? (tick one below)

a. Yes I am using it currently.	a
b. Yes I have used it in the past but not at the moment.	b
c. No.	c

Study Number:

d. I don't know what hormone replacement therapy (HRT) is.	d

2 If you have ever had any of the symptoms above, and thought that these might be due to the menopause, is there anything else you did to relieve your symptoms?

Please write below:

Finished!

Well done

Thank you for answering all these questions.

You answers are very important to the study

Appendix III

Table 0.1: Patterns of the missing data on components required for the assessment of frailty stratified by POPPY centre

	Not missing frailty components		Components of frailty score that were missing								Number of total POPPY participants	
			Slowness		Weakness		Exhaustion		Low physical activity			
Site	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
SMH	218	(92.0)	2	(0.8)	0	(0.0)	13	(5.5)	11	(4.6)	237	(100.0)
RSH	226	(85.9)	4	(1.5)	1	(0.4)	28	(10.7)	31	(11.8)	263	(100.0)
UCL	184	(78.6)	27	(11.5)	15	(6.4)	20	(8.6)	17	(17.3)	234	(100.0)
CWH	285	(78.5)	27	(7.4)	7	(1.9)	49	(13.5)	46	(12.7)	363	(100.0)
HUH	25	(67.6)	1	(2.7)	1	(2.7)	11	(29.7)	8	(21.6)	37	(100.0)
KCH	81	(62.3)	12	(9.2)	5	(3.9)	40	(30.8)	36	(27.7)	130	(100.0)
DUH	50	(61.7)	1	(1.2)	0	(0.0)	29	(35.8)	31	(38.3)	81	(100.0)
RFH	7	(21.9)	3	(9.4)	4	(12.5)	23	(71.9)	23	(71.9)	32	(100.0)
Total	**1076**	**(78.1)**	**77**	**(5.6)**	**33**	**(2.4)**	**213**	**(15.5)**	**203**	**(14.7)**	**1377**	**(100.0)**

Appendix IV

Questions/Variables	Method of data capture	Quality control
Demographic characteristics		
Date of birth	Nurse-led interview	Dates correspond to an age within the inclusion criteria
Gender		Checked for missing
Marital status		Corrected the status of those who reported more than one
Ethnic group		Corrected to unique codes per country
Sexual orientation for the HIV-negative and route of HIV transmission for the PLWH		Checked for missing
Maternal country of birth		Corrected to unique codes per country
Paternal country of birth		Corrected to unique codes per country
Anthropometric characteristics		
Height	Measured by research nurse	Checked the extreme vales ≤5th and ≥95th centile
Weight		Checked the extreme vales ≤5th and ≥95th centile
Body mass index		Checked the extreme vales ≤5th and ≥95th centile

Questions/Variables	Method of data capture	Quality control
Waist circumference		Checked the extreme vales ≤5th and ≥95th centile
Systolic blood pressure	Estimated using the average of 3 subsequent measurements from an automated device lead by research nurse	Checked the extreme vales ≤5th and ≥95th centile
Diastolic blood pressure		Checked the extreme vales ≤5th and ≥95th centile
Grip strength	Assessed by nurse using a dynamometer	Checked the extreme values <1Kg and >80Kg
Time to walk 15 feet	Assessed by the nurse using the average of 2 subsequent measurements	Checked the extreme values ≤2 sec and ≥25 sec
Lifestyle characteristics		
Smoking and cigarette/day	Nurse-led interview	Checked the extreme values ≥60 cigarettes
Alcohol use and units of alcohol/week	Nurse-led interview	Checked the extreme values ≥50 units/week and unified the units among those drinking only at special orations
History injecting drug	Nurse-led interview	Checked for missing
Use of recreational drugs	A detailed list of the recreational drugs was listed	Checked for missing
Laboratory measurements		
Total cholesterol (mmol/L)	Extracted from clinical notes for PLWH and sample taken for HIV-negative	Checked the extreme vales ≤5th and ≥95th centile
HDL cholesterol (mmol/L)		
LDL cholesterol (mmol/L)		
Triglycerides (mmol/L)		
Hemoglobin (g/dl)		

Questions/Variables	Method of data capture	Quality control
WBC (x109/l)		
RBC (x1012/l)		
Neutrophils (x109/l)		
Monocytes (x109/l)		
Platelets (x109/l)		
Eosinophils (x109/l)		
MCV (fl)		
Albumin (g/L)		
Bilirubin (µmol/L)		
Urea (mmol/L)		
Creatinine (µmol/L)		
Glucose (mmol/L)		
Total protein (g/L)		
Calcium (mmol/L)		
Sodium (mmol/L)		
Phosphate (mmol/L)		
Potassium (mmol/L)		
AST (U/L)		
ALT (U/L)		
Gamma-GT (U/L)		
Alkaline Phosphatase (U/L)		
Albumin:creatinine ratio (mg/mmol)		
Albumin concentration (mg/l)		
Protein:creatinine ratio (mg/mmol)		
CD4 (cells/mm3)	Extracted from clinical notes	Existing data were cross-checked with UK CHIC and
CD4%		

Questions/Variables	Method of data capture	Quality control
Viral load (IU/mL)		Dublin ID cohorts and missing data were replaced by UK CHIC or Dublin ID data that were in the range from 6 months before or up to 1 month after the baseline POPPY visit
eGFR MDRD (mL/min/1.73m2)	Calculated using the appropriate laboratory and demographic data (757)	Checked the extreme vales ≤5th and ≥95th centile
eGFR CKD-EPI (mL/min/1.73m2)	Calculated using the appropriate laboratory and demographic data (758)	
Creatinine clearance Cockroft-Gault (mL/min)	Calculated using the appropriate laboratory and demographic data (759)	
HBV positive test (%)	Extracted from clinical notes	Checked for missing
HCV positive test (%)		Checked for missing
Current antiretroviral medication		
Name of drug	Extracted from clinical notes	Cross-checked with UK-CHIC and the Dublin ID cohort
Start date		
Stop date		
Co-medications		
Drug name	Nurse-led interview	
Indication		
Start date		
Stop date		
Dose		
Frequency		

Questions/Variables	Method of data capture	Quality control
Side effects		
Healthcare utilisation		
GP visit	Nurse-led interview	
HIV-specialist		
Nurse visit		
Hospital specialist visit		
A&E visit		
Hospital procedure		
Hospital Investigations		
Community healthcare provider		
Hospital investigation		
Attended psychiatrist/ counsellor/psychologist		
Use of ambulance or hospital transport		
Reported family history of medical events		
Myocardial infarction (MI)	Nurse-led interview	Made the assumption that those who had missing data in any of the events had no family history of that event
Hypertension		
High cholesterol		
Dementia		
Diabetes		
Hip fracture		
Cardiovascular disease		
Transient ischaemic attack/Stroke/CVA		
Angina		
Arrythmia		
Atrial fibrillation		

Questions/Variables	Method of data capture	Quality control
Heart failure		
Emphysema		
Brain haemorrhage		
TB		
Knee replacement		
Heart bypass		
Aneurysm		
Osteoporosis		
Arthritis		
Knee problems		
Spondylitis		
Alzheimer's disease		
Parkinsons disease		
Kidney failure		
Asthma		
Autism		
Thyroid disease		
Glaucoma		
Depression		
Colitis/Cron's disease		
HIV		
Any cancer		
Screening men		
Examined for anal cancer in the past	Nurse-led interview	Made the assumption that those who had missing data in any of the screening
Year tested		
Abnormalities found		

Questions/Variables	Method of data capture	Quality control
Abnormalities details		questions had have an examination
Any other screening		
Other screening details		
Screening women		
Ever had a mammogram		
Number of mammograms	Nurse-led interview	Made the assumption that those who had missing data in any of the screening questions had have an examination
For each mammogram, was this part of population screening		
For each mammogram, were there any abnormalities		
Details of abnormality		
Cervical smear		
Year of last smear		
History of any abnormalities on smear		
Details of all abnormalities ever detected on smear tests		
Has colposcopy been performed		
Date of next planned smear		
Participated in any other screening		
Other screening details		
Personal medical history		
AIDS-defining events		
History of TB	Nurse-led interview	Updated the data from three sources, 1st the healthcare utilisation, 2nd the co-
History of other AIDS events		
History of infections and paracytic events		
History of sexually transmitted disease	Nurse-led interview	

Questions/Variables	Method of data capture	Quality control
Infected with Hepatitis B		medications, 3rd from the list of adverse events
Infected with Hepatitis C		
History of any other Infections		
Endocrine disease		
Type 1 Diabetes	Nurse-led interview	
Type 2 Diabetes		
History of Thyroid disease		
History of any other endocrine diseases		
History of blood diseases		
Blood and blood forming organ events	Nurse-led interview	
History of mental health		
History of depression	Nurse-led interview	
Medically diagnosed depression (treated by a doctor)		
History of any other mental disorders		
Medical history of nervous system		
Does the patient have Parkinson's disease or any other movement disorder? (dosage, units, frequency, non-drug intervention, medication ongoing)	Nurse-led interview	
Does patient experience dizziness or vertigo which causes them to fall?		
Any condition associated with loss of consciousness for 30 minutes or more		
Any history of brain surgery?		
History of Encephilitis		

Questions/Variables	Method of data capture	Quality control
History of epilepsy		
History of peripheral neuropathy		
History of any other nervous system disorders		
Medical history of chest disease		
History of heart failure	Nurse-led interview	
History of angina pectoris		
History of narrowed blood vessels in legs or abdomen		
History of asthma, bronchitis (chronic or acute), pulmonary emphysema or COPD		
History of any other chest disease		
Medical history of gastro Intestinal		
Persistent bowel disorder over last 3 months	Nurse-led interview	
Medical history of liver disease		
History of any other liver disease	Nurse-led interview	
Medical history of gastro-intestinal disorders		
Other Gastro-Intestinal disorders	Nurse-led interview	
Medical history of genitourinary disorders		
Urinary incontinence requiring treatment	Nurse-led interview	
Other Genitourinary disorders		
Medical history related to childbirth		
Is patient still menstruating?	Nurse-led interview	
Has patient had any pregnancies?		
Medical history of skin disorders		

Questions/Variables	Method of data capture	Quality control
History of any skin disorders	Nurse-led interview	
Medical history of joint, bone and connective tissue		
History of any joint inflammation or rhumatoid or osteoarthritis	Nurse-led interview	
History of arthritis of knee or hip		
History of any joint replacement		
Medical history of joint, bone or connective tissue disorders		
Has the subject suffered any fractures	Nurse-led interview	
History of congenital bone disease (osteogenesis imperfecta)		
Other joint, bone or connective tissue disorders		
Medical history of congenital disorders		
History of any Congenital disorders	Nurse-led interview	
Medical history of injury and poisoning		
History of any Injury or Poisoning	Nurse-led interview	
Medical history of cancer		
History of any form of Cancer (if not covered elsewhere)	Nurse-led interview	
Medical history of chronic disease		
Does the patient think that they have any chronic diseases not recorded elsewhere?	Nurse-led interview	
Dual-energy X-ray absorptiometry (DEXA) scan		

Questions/Variables	Method of data capture	Quality control
Arm fat (kg)	Clinical examination (lead by nurse)	Checked the extreme vales ≤5th and ≥95th centile
Leg fat (kg)		
Limb fat (kg)		
Trunk fat (kg)		
Body fat (kg)		
Arm muscle (kg)		
Leg muscle (kg)		
Limb muscle (kg)		
Trunk muscle (kg)		
Body muscle (kg)		
Arm tissue (kg)		
Leg tissue (kg)		
Limb tissue (kg)		
Trunk tissue (kg)		
Body tissue (kg)		
Spine BMD, T and Z score		
Femoral neck BMD, T and Z score		
Ward s triangle BMD, T and Z score		
Trochanter BMD, T and Z score		
Femoral shaft BMD, T and Z score		
Total hip BMD, T and Z score		

Appendix V

Table 1-Appendix IV: Reported personal medical history of POPPY participants, stratified by group

	Cohort					
	Older PLWH		Younger PLWH		HIV negative	
N	699		374		304	
AIDS event	241	(34.5)	70	(18.7)	-	-
TB	53	(7.6)	30	(8.0)	-	-
CMV	25	(3.6)	3	(0.8)	-	-
PCP	78	(11.2)	16	(4.3)	-	-
K.Sarcoma	56	(8.0)	14	(3.7)	-	-
Other AIDS events	105	(15.0)	19	(5.1)	-	-
AIDS Dementia – Definitive/Presumptive	4	(0.6)	0	(0.0)	-	-
Bacterial pneumonia – Definitive/Presumptive	5	(0.7)	2	(0.5)	-	-
Candidiasis (oesophageal) – Definitive/Presumptive	38	(5.4)	2	(0.5)	-	-
Candidiasis (tracheal) – Definitive/Presumptive	2	(0.3)	0	(0.0)	-	-
Cryptococcosis – Definitive/autopsy	6	(0.9)	1	(0.3)	-	-
Cryptosporidiosis – Definitive/autopsy	13	(1.9)	2	(0.5)	-	-
HIV wasting syndrome-Definitive	8	(1.1)	0	(0.0)	-	-
Herpes simplex ulcers (duration > 1month) – Definitive/autopsy	10	(1.4)	2	(0.5)	-	-
Lymphoma – Definitive/autopsy	14	(2.0)	2	(0.5)	-	-
Mycobacterium (Pulmonary and/or extrapulmonary) – Definitive/Presumptive	15	(2.1)	1	(0.3)	-	-
Pneumonia Oesophagitis – Definitive/autops	10	(1.4)	3	(0.8)	-	-
Salmonella (non-typhoid) Bacteriaemia (>=2 episodes)	1	(0.1)	0	(0.0)	-	-
Toxoplasmosis – Definitive/autops/Presumptive	4	(0.6)	5	(1.3)	-	-
Recurrent pneumonia	0	(0.0)	1	(0.3)	-	-
Infections, Non-AIDS	196	(28.0)	89	(23.8)	49	(16.1)
TB (non-AIDS)	-	-	-	-	8	(2.6)
Fungal	40	(5.7)	14	(3.7)	8	(2.6)
Glandular fever/EBV	0	(0.0)	2	(0.5)	1	(0.3)
Giardiasis	3	(0.4)	1	(0.3)	2	(0.7)

	Cohort					
	Older PLWH		Younger PLWH		HIV negative	
Malaria	3	(0.4)	2	(0.5)	2	(0.7)
MRSA	5	(0.7)	3	(0.8)	1	(0.3)
VZV/HZV	114	(16.3)	41	(11.0)	9	(3.0)
Leukoplakia	1	(0.1)	0	(0.0)	0	(0.0)
Klebsiella	3	(0.4)	0	(0.0)	0	(0.0)
Other non-AIDS infections	59	(8.4)	31	(8.3)	21	(6.9)
Endocrine disease	146	(20.9)	34	(9.1)	35	(11.5)
Type 1 diabetes	2	(0.3)	0	(0.0)	3	(1.0)
Type 2 diabetes	40	(5.7)	6	(1.6)	13	(4.3)
Non-specified diabetes	15	(2.1)	2	(0.5)	3	(1.0)
Erectile dysfunction	61	(8.7)	14	(3.7)	8	(2.6)
Low testosterone	30	(4.3)	4	(1.1)	3	(1.0)
Hypogonadism	3	(0.4)	1	(0.3)	0	(0.0)
Pancreatitis	13	(1.9)	3	(0.8)	1	(0.3)
History of any other endocrine diseases	13	(1.9)	5	(1.3)	5	(1.6)
Thyroid disease	31	(4.4)	7	(1.9)	18	(5.9)
Hypothyroidism	18	(2.6)	4	(1.1)	6	(2.0)
Hyperthyroidism	5	(0.7)	2	(0.5)	5	(1.6)
Grave's disease	1	(0.1)	1	(0.3)	2	(0.7)
Other/Unknown thyroid disease	7	(1.0)	1	(0.3)	6	(2.0)
Blood and blood forming organ events	144	(20.6)	40	(10.7)	42	(13.8)
Anaemia	12	(1.7)	11	(2.9)	8	(2.6)
Sickle cell anaemia	4	(0.6)	1	(0.3)	1	(0.3)
Antiphospholipid syndrome	1	(0.1)	1	(0.3)	0	(0.0)
Haemochromatosis	3	(0.4)	2	(0.5)	0	(0.0)
Thalassaemia	2	(0.3)	3	(0.8)	1	(0.3)
Platelet deficiency	3	(0.4)	0	(0.0)	1	(0.3)
Reynaud's syndrome	1	(0.1)	0	(0.0)	1	(0.3)
Blood clotting disorder	3	(0.4)	1	(0.3)	1	(0.3)
Thrombocytopenia	8	(1.1)	2	(0.5)	0	(0.0)
Spleen disorder	2	(0.3)	1	(0.3)	1	(0.3)
Polycythaemia	3	(0.4)	1	(0.3)	0	(0.0)
Varicose veins	5	(0.7)	1	(0.3)	2	(0.7)
Deep vein thrombosis	8	(1.1)	1	(0.3)	0	(0.0)
Other blood disorder	10	(1.4)	4	(1.1)	9	(3.0)
Mental disorders	303	(43.3)	153	(40.9)	73	(24.0)
History of depressive symptoms	29	(4.1)	15	(4.0)	5	(1.6)
Medically diagnosed depression	243	(34.8)	124	(33.2)	57	(18.8)
Panic attacks	10	(1.4)	10	(2.7)	3	(1.0)
Anxiety	42	(6.0)	25	(6.7)	11	(3.6)
Insomnia	34	(4.9)	13	(3.5)	1	(0.3)

	Cohort					
	Older PLWH		Younger PLWH		HIV negative	
Bipolar disorder	6	(0.9)	3	(0.8)	0	(0.0)
Sleeping problems	12	(1.7)	9	(2.4)	4	(1.3)
Low mood	0	(0.0)	1	(0.3)	0	(0.0)
Schizophrenia	1	(0.1)	1	(0.3)	0	(0.0)
Suicidal ideation	3	(0.4)	1	(0.3)	1	(0.3)
Unspecified psychosis	3	(0.4)	4	(1.1)	0	(0.0)
Other mental disorder	16	(2.3)	7	(1.9)	3	(1.0)
Nervous system	214	(30.6)	82	(21.9)	58	(19.1)
Parkinson's or other movement disorder	6	(0.9)	2	(0.5)	1	(0.3)
Dizziness or vertigo	85	(12.2)	31	(8.3)	25	(8.2)
Loss of consciousness	21	(3.0)	10	(2.7)	6	(2.0)
Brain surgery	4	(0.6)	1	(0.3)	2	(0.7)
Encephalitis	8	(1.1)	8	(2.1)	2	(0.7)
Epilepsy	31	(4.4)	14	(3.7)	5	(1.6)
Peripheral neuropathy	34	(4.9)	9	(2.4)	3	(1.0)
Migraines/Headaches	19	(2.7)	14	(3.7)	4	(1.3)
Carpel tunnel syndrome	13	(1.9)	3	(0.8)	2	(0.7)
Sciatica	12	(1.7)	3	(0.8)	2	(0.7)
Attention deficit hyperactivity disorder (ADHD)	1	(0.1)	0	(0.0)	1	(0.3)
Other nervous system disorders	48	(6.9)	9	(2.4)	15	(4.9)
Cardiovascular	384	(54.9)	90	(24.1)	121	(39.8)
Myocardial infarction (MI)	37	(5.3)	4	(1.1)	4	(1.3)
Angina	30	(4.3)	4	(1.1)	5	(1.6)
Narrowed blood vessels	14	(2.0)	5	(1.3)	8	(2.6)
Heart failure	19	(2.7)	6	(1.6)	4	(1.3)
Ischaemic heart disease (IHD)	8	(1.1)	0	(0.0)	0	(0.0)
Hypertension	200	(28.6)	31	(8.3)	66	(21.7)
Transient ischaemic attack/Stroke/CVA	27	(3.9)	4	(1.1)	3	(1.0)
Coronary artery bypass graft CABG	24	(3.4)	0	(0.0)	6	(2.0)
Dyslipidaemia	244	(34.9)	49	(13.1)	61	(20.1)
Arrhythmia	2	(0.3)	1	(0.3)	1	(0.3)
Atrial fibrillation	10	(1.4)	3	(0.8)	5	(1.6)
Other Cardiovascular disease	48	(6.9)	10	(2.7)	14	(4.6)
Chest disease	289	(41.3)	136	(36.4)	70	(20.4)
History of asthma bronchitis chronic or acute pulmonary emphysema or COPD	187	(26.8)	77	(20.6)	52	(17.1)
Pneumonia	38	(5.4)	6	(1.6)	8	(2.6)
Aortic valve disease	1	(0.1)	0	(0.0)	0	(0.0)
Acquired Bronchiectasis	1	(0.1)	0	(0.0)	1	(0.3)
Chest infection	82	(11.7)	32	(8.6)	11	(3.6)

	Cohort					
	Older PLWH		Younger PLWH		HIV negative	
Hay fever/allergies	46	(6.6)	31	(8.3)	8	(1.3)
Respiratory Tract Infection (upper/lower)	7	(1.0)	4	(1.1)	0	(0.0)
Pulmonary embolism	5	(0.7)	3	(0.8)	1	(0.3)
Chronic/Persistent cough	2	(0.3)	1	(0.3)	0	(0.0)
Pleurisy	1	(0.1)	1	(0.3)	3	(1.0)
Sleep apnoea	7	(1.0)	1	(0.3)	1	(0.3)
Pneumothorax	2	(0.3)	1	(0.3)	1	(0.3)
Other chest infection	24	(3.4)	6	(1.6)	2	(0.7)
Gastrointestinal diseases	397	(56.8)	174	(46.5)	97	(31.9)
Persistent bowel disorder	157	(22.5)	71	(19.0)	25	(8.2)
Hepatitis A virus	31	(4.4)	13	(3.5)	10	(3.3)
Hepatitis B virus	98	(14.0)	49	(13.1)	8	(2.6)
Hepatitis C virus	48	(6.9)	27	(7.2)	2	(0.7)
Irritable bowel syndrome (IBS)/Crohn's Disease/Ulcerative Colitis	23	(3.3)	7	(1.9)	12	(4.0)
Hernia	23	(3.3)	4	(1.1)	7	(2.3)
Gastrointestinal reflux	55	(7.9)	15	(4.0)	21	(6.9)
Pancreatic insufficiency	8	(1.1)	1	(0.3)	0	(0.0)
Other liver disease	66	(9.4)	18	(4.8)	6	(2.0)
Other gastrointestinal disorders	120	(17.2)	45	(12.0)	32	(10.5)
Genitourinary diseases	209	(29.9)	48	(12.8)	78	(25.7)
Urinary incontinence requiring treatment	34	(4.9)	7	(1.9)	7	(2.3)
Non-specific urethritis	43	(6.2)	15	(4.0)	15	(4.9)
Renal problems	24	(3.4)	4	(1.1)	7	(2.3)
Prostate problems	30	(4.3)	1	(0.3)	13	(4.3)
Urinary incontinence/other urine problems not requiring treatment	17	(2.4)	4	(1.1)	9	(3.0)
Kidney stones	24	(3.4)	4	(1.1)	6	(2.0)
Urinary tract infections (UTIs)	29	(4.1)	2	(0.5)	12	(4.0)
Haemorrhoids	4	(0.6)	4	(1.1)	4	(1.3)
Other genitourinary disorders	59	(8.4)	15	(4.0)	22	(7.2)
Joint, bone and connective tissue	371	(53.1)	108	(28.9)	150	(49.3)
History of any joint inflammation or rheumatoid or osteoarthritis	144	(20.6)	32	(8.6)	49	(16.1)
History of any joint replacement	23	(3.3)	1	(0.3)	10	(3.3)
History of Arthritis of knee or hip	99	(14.2)	22	(5.9)	45	(14.8)
Other arthritis	8	(1.1)	1	(0.3)	2	(0.7)

	Cohort					
	Older PLWH		Younger PLWH		HIV negative	
Osteopenia/osteoporosis/low BMD	62	(8.9)	7	(1.9)	7	(2.3)
Aches and pains	42	(6.0)	19	(5.1)	22	(7.2)
Back pain	46	(6.6)	19	(5.1)	20	(6.6)
Duputreyn's	2	(0.3)	0	(0.0)	4	(1.3)
Gout	21	(3.0)	2	(0.5)	6	(2.0)
Plantar fasciitis	5	(0.7)	1	(0.3)	1	(0.3)
Congenital bone disease	27	(3.9)	7	(1.9)	17	(5.6)
Other joint bone or connective tissue disorder	66	(9.4)	26	(7.0)	27	(8.9)
Fractures	274	(39.2)	141	(37.7)	111	(36.5)
Fractured Ankle	35	(5.0)	15	(4.0)	12	(4.0)
Fractured Fingers	30	(4.3)	18	(4.8)	17	(5.6)
Fractured Foot	26	(3.7)	12	(3.2)	6	(2.0)
Fractured Hand	16	(2.3)	7	(1.9)	9	(3.0)
Fractured Head	16	(2.3)	19	(5.1)	3	(1.0)
Fractured Hip	8	(1.1)	2	(0.5)	2	(0.7)
Fractured Upper extremities (collar bone, elbow, forearm)	65	(9.3)	34	(9.1)	32	(10.5)
Fractured Lower extremities (thigh, knee, lower leg)	47	(6.7)	26	(7.0)	11	(3.6)
Fractured Pelvis	5	(0.7)	2	(0.5)	1	(0.3)
Fractured Ribs	36	(5.2)	11	(2.9)	6	(2.0)
Fractured Toes	26	(3.7)	16	(4.3)	11	(3.6)
Fractured Upper Arm	22	(3.1)	9	(2.4)	6	(2.0)
Fractured Vertebrae back neck	6	(0.9)	4	(1.1)	2	(0.7)
Fractured Wrist	66	(9.4)	27	(7.2)	24	(7.9)
Fracture Unknown	2	(0.3)	1	(0.3)	1	(0.3)
Injury or Poisoning	103	(14.7)	60	(16.0)	37	(12.2)
Cancer	103	(14.7)	23	(6.1)	36	(11.8)
Anal	6	(0.9)	4	(1.1)	2	(0.7)
Rectal	2	(0.3)	0	(0.0)	0	(0.0)
Colon	5	(0.7)	0	(0.0)	2	(0.7)
Bladder	29	(4.1)	2	(0.5)	7	(2.3)
Breast	2	(0.3)	2	(0.5)	5	(1.6)
Gynaecological	0	(0.0)	0	(0.0)	1	(0.3)
Lymphoma	17	(2.4)	5	(1.3)	1	(0.3)
Myeloma / Myelodysplasia	1	(0.1)	0	(0.0)	1	(0.3)
Head & Neck	1	(0.1)	0	(0.0)	2	(0.7)
Kidney	2	(0.3)	0	(0.0)	1	(0.3)
Lung	2	(0.3)	0	(0.0)	0	(0.0)
Oral	2	(0.3)	0	(0.0)	0	(0.0)
Oesophageal	28	(4.0)	2	(0.5)	7	(2.3)
Bowel	3	(0.4)	0	(0.0)	0	(0.0)

	Cohort					
	Older PLWH		Younger PLWH		HIV negative	
Appendix	2	(0.3)	0	(0.0)	0	(0.0)
Pseudomyxoma peritonei	1	(0.1)	0	(0.0)	0	(0.0)
Penile	1	(0.1)	0	(0.0)	0	(0.0)
Prostate	12	(1.7)	0	(0.0)	6	(2.0)
Stomach	0	(0.0)	1	(0.3)	0	(0.0)
Testicular	1	(0.1)	4	(1.1)	1	(0.3)
Thyroid	2	(0.3)	0	(0.0)	0	(0.0)
Uterus	0	(0.0)	0	(0.0)	2	(0.7)
Unknown	6	(0.9)	0	(0.0)	0	(0.0)
Skin cancer	53	(7.6)	14	(3.7)	13	(4.3)
Melanoma	11	(1.6)	3	(0.8)	5	(1.6)
Squamous cell	5	(0.7)	0	(0.0)	1	(0.3)
BCC	13	(1.9)	2	(0.5)	4	(1.3)
Lesion	13	(1.9)	4	(1.1)	3	(1.0)
Sexually transmitted disease	433	(61.9)	237	(63.4)	97	(31.9)
Syphilis	229	(32.8)	97	(25.9)	30	(9.9)
Gonorrhoea	289	(41.3)	168	(44.9)	61	(20.1)
Chlamydia	131	(18.7)	114	(30.5)	32	(10.5)
LGV	27	(3.9)	19	(5.1)	2	(0.7)
HPV	61	(8.7)	38	(10.2)	15	(4.9)
HSV	86	(12.3)	36	(9.6)	8	(2.6)
Pubic Lice	16	(2.3)	8	(2.1)	2	(0.7)
Other STD (can't recall)	7	(1.0)	1	(0.3)	0	(0.0)
Skin disorders	226	(32.3)	122	(32.6)	74	(24.3)
Acne	6	(0.9)	8	(2.1)	4	(1.3)
Actinic keratosis	10	(1.4)	3	(0.8)	1	(0.3)
Allergic reaction	4	(0.6)	6	(1.6)	5	(1.6)
Athlete's foot	1	(0.1)	2	(0.5)	0	(0.0)
Candidiasis	0	(0.0)	2	(0.5)	0	(0.0)
Cellulitis	2	(0.3)	2	(0.5)	2	(0.7)
Cracked/ Dry skin	32	(4.6)	14	(3.7)	4	(1.3)
Dermatitis	28	(4.0)	14	(3.7)	5	(1.6)
Eczema	48	(6.9)	22	(5.9)	18	(5.9)
Folliculitis	9	(1.3)	1	(0.3)	0	(0.0)
Itching	13	(1.9)	10	(2.7)	3	(1.0)
Lichen Sclerosis	1	(0.1)	2	(0.5)	2	(0.7)
Moles	10	(1.4)	4	(1.1)	8	(2.6)
Pruritus	2	(0.3)	0	(0.0)	1	(0.3)
Psoriasis	33	(4.7)	14	(3.7)	8	(2.6)
Rashes	40	(5.7)	24	(6.4)	7	(2.3)
Skin tags	2	(0.3)	1	(0.3)	3	(1.0)
Thrush	1	(0.1)	3	(0.8)	0	(0.0)
Warts	10	(1.4)	6	(1.6)	4	(1.3)
Urticaria	6	(0.9)	3	(0.8)	1	(0.3)
Other skin	22	(3.1)	12	(3.2)	13	(4.3)

	Cohort					
	Older PLWH		Younger PLWH		HIV negative	
Eye problems	73	(10.4)	8	(2.1)	24	(7.9)
Ear dysfunction	24	(3.4)	6	(1.6)	6	(2.0)
Vitamin deficiencies	14	(2.0)	8	(2.1)	2	(0.7)
Vitamin D deficiency	13	(1.9)	5	(1.3)	2	(0.7)
Vitamin B deficiency	1	(0.1)	3	(0.8)	0	(0.0)
Other						
Chronic fatigue	0	(0.0)	0	(0.0)	2	(0.7)
Gynaecomastia	0	(0.0)	3	(0.8)	0	(0.0)
Lipodystrophy	19	(2.7)	1	(0.3)	0	(0.0)
Lipoatrophy	3	(0.4)	1	(0.3)	0	(0.0)
Tinnitus	10	(1.4)	4	(1.1)	6	(2.0)
Any chronic diseases not recorded elsewhere	20	(2.9)	5	(1.3)	9	(3.0)

Appendix VI

Table 0.1: Prevalence of recurrent falls among older POPPY participants stratified by individual demographic and lifestyle characteristics

			History of recurrent falls in the past 28 days				
	Total N=973		No N=874		Yes N=99		
	n	(%)	n	(%)	n	(%)	p-value
Group							<0.001
Older PLWH	680	(100.0)	589	(86.6)	91	(13.4)	
HIV-negative	293	(100.0)	285	(97.3)	8	(2.7)	
Gender							0.40
Female	188	(100.0)	172	(91.5)	16	(8.5)	
Male	785	(100.0)	702	(89.4)	83	(10.6)	
Age group (years)							0.83
50-54	354	(100.0)	316	(89.3)	38	(10.7)	
55-59	261	(100.0)	236	(90.4)	25	(9.6)	
60-64	186	(100.0)	165	(88.7)	21	(11.3)	
65-69	109	(100.0)	98	(89.9)	11	(10.1)	
≥70	63	(100.0)	59	(93.7)	4	(6.4)	
Ethnicity							0.39
Black African	121	(100.0)	106	(87.6)	15	(12.4)	
White	852	(100.0)	768	(90.1)	84	(9.9)	
BMI (kg/m^2)							0.20
≤22.9	180	(100.0)	158	(87.8)	22	(12.2)	
23.0-24.9	184	(100.0)	170	(92.4)	14	(7.6)	
25.0-26.8	195	(100.0)	180	(92.3)	15	(7.7)	
26.9-29.4	200	(100.0)	179	(89.5)	21	(10.5)	
≥29.5	201	(100.0)	174	(86.6)	27	(13.4)	
Unknown	13	(100.0)	13	(100.0)	0	(0.0)	
Marital status							<0.001
Single	407	(100.0)	356	(87.5)	51	(12.5)	
Married	165	(100.0)	155	(93.9)	10	(6.1)	
Civil Partnership	143	(100.0)	137	(95.8)	6	(4.2)	
Cohabiting	107	(100.0)	102	(95.3)	5	(4.7)	
Divorced	82	(100.0)	65	(79.3)	17	(20.7)	
Living separately	35	(100.0)	28	(80.0)	7	(20.0)	
Widowed/Other	34	(100.0)	31	(91.2)	3	(8.8)	
Current smoking							0.01
No	774	(100.0)	706	(91.2)	68	(8.8)	
Yes	194	(100.0)	163	(84.0)	31	(16.0)	
Unknown	5	(100.0)	5	(100.0)	0	(0.0)	
Current alcohol use							<0.001
No	70	(100.0)	54	(77.1)	16	(22.9)	
Yes	793	(100.0)	728	(91.8)	65	(8.2)	
In the past	110	(100.0)	92	(83.6)	18	(16.4)	
Recreational drug use in the past 6 months							0.67
No	763	(100.0)	687	(90.0)	76	(10.0)	

	Total N=973		History of recurrent falls in the past 28 days				
			No N=874		Yes N=99		
	n	(%)	n	(%)	n	(%)	p-value
Yes	210	(100.0)	187	(89.1)	23	(11.0)	

Table 0.2: Association of recurrent falls with HIV

	Univariable model	Multivariable model*
	OR (95% CI)	aOR (95% CI) n=1122
Group		
HIV-negative	Ref.	Ref.
Older PLWH	5.50 (2.64, 11.50)	5.35 (2.34, 12.2)

*Adjusted for age, gender, ethnicity, education and marital status

Table 0.3: Prevalence of recurrent falls among older POPPY participants stratified by frailty

	Total N=973		History of recurrent falls in the past 28 days				
			No N=874		Yes N=99		
	n	(%)	n	(%)	n	(%)	p-value
Meets frailty criteria							<0.001
No	699	(100.0)	644	(92.1)	55	(7.9)	
Yes	78	(100.0)	60	(76.9)	18	(23.1)	
Unknown	196	(100.0)	170	(86.7)	26	(13.3)	

Table 0.4: Association of frailty with recurrent falls

	Univariable model	Multivariable model*
	OR (95% CI)	aOR (95% CI)
Group		
HIV-negative	Ref.	Ref.
Older PLWH	5.50 (2.64, 11.50)	4.45 (1.64, 12.03)
Frailty		
No	Ref.	Ref.
Yes	3.51 (1.94, 6.36)	2.27 (1.16, 4.43)

*Adjusted for age, gender, ethnicity, education and marital status

Table 0.5: Prevalence of recurrent falls among older POPPY participants stratified by level of depressive symptoms assessed using either the CES-D or PHQ-9 scores

			History of recurrent falls in the past 28 days				
	Total N=973		No N=874		Yes N=99		
	n	(%)	n	(%)	n	(%)	p-value
Levels of depressive symptoms (CES-D)							<0.001
No to mild (0-15)	610	(100.0)	592	(97.1)	18	(2.9)	
Moderate (16-23)	118	(100.0)	102	(86.4)	16	(13.6)	
Severe (24-60)	159	(100.0)	110	(69.2)	49	(30.8)	
Unknown	86	(100.0)	70	(81.4)	16	(18.6)	
Levels of depressive symptoms (PHQ-9)							<0.001
Minimal depression (1-4)	744	(100.0)	544	(96.8)	18	(3.2)	
Mild depression (5-9)	247	(100.0)	151	(90.4)	16	(9.6)	
Moderate depression (10-14)	141	(100.0)	83	(83.0)	17	(17.0)	
Moderately severe depression (15-19)	83	(100.0)	37	(64.9)	20	(35.1)	
Severe depression (20-27)	43	(100.0)	16	(51.6)	15	(48.4)	
Unknown	75	(100.0)	43	(76.8)	13	(23.2)	

Table 0.6: Association of recurrent falls with POPPY group and depressive symptoms as assessed by the CES-D score

	Univariable models	Multivariable model*	Multivariable model**
	OR (95% CI)	**aOR* (95% CI)**	**aOR* (95% CI)**
Group			
HIV-negative	Ref.	Ref.	Ref.
Older PLWH	5.50 (2.64, 11.50)	3.13 (1.25, 7.82)	4.98 (1.10, 22.51)
Levels of depressive symptoms (CES-D)			
No to mild (0-15)	Ref.	Ref.	Ref.
Moderate (16-23)	1.64 (0.94, 2.35)	4.12 (1.96, 8.66)	9.88 (1.30, 74.89)
Severe (24-60)	2.68 (2.11, 3.26)	8.91 (4.73, 16.80)	15.34 (1.89, 124.72)

* Adjusted for age, gender, ethnicity, education and marital status

**Further adjusted for the interaction of HIV with depressive symptoms

Table 0.7: Association of recurrent falls with POPPY group and depressive symptoms as assessed by the PHQ-9 score

	Univariable models	Multivariable model*	Multivariable model**
	OR (95% CI)	**aOR* (95% CI)**	**aOR* (95% CI)**
Group			
HIV-negative	Ref.	Ref.	Ref.
Older PLWH.	5.50 (2.64, 11.50)	3.28 (1.31, 8.22)	2.35 (0.74, 7.43)
Levels of depressive symptoms (PHQ-9)			
Minimal (1-4)	Ref.	Ref.	Ref.
Mild (5-9)	1.16 (0.47, 1.86)	2.16 (1.04, 4.52)	1.91 (0.20, 17.87)
Moderate (10-14)	1.82 (1.12, 2.52)	4.08 (1.92, 8.68)	3.71 (0.37, 37.53)
Moderately severe (15-19)	2.79 (2.07, 3.51)	9.42 (4.13, 21.50)	10.37 (4.39, 24.50)
Severe (20-27)	3.34 (2.50, 4.19)	19.35 (7.59, 49.31)	23.58 (8.74, 63.60)

* Adjusted for age, gender, ethnicity, education and marital status

**Further adjusted for the interaction of HIV with depressive symptoms

Table 0.8: Prevalence of recurrent falls among POPPY PLWH, stratified by age, history of AIDS, immune system markers and current antiretroviral medication characteristics

	Total N=1040		History of recurrent falls in the past 28 days				
			No n=927		Yes n=113		
	n	(%)	n	(%)	n	(%)	p-value
Age group (years)							0.02
≤29	26	(100.0)	26	(100.0)	0	(0.0)	
30-39	86	(100.0)	82	(95.4)	4	(4.7)	
40-49	248	(100.0)	230	(92.7)	18	(7.3)	
50-54	257	(100.0)	221	(86.0)	36	(14.0)	
55-59	185	(100.0)	160	(86.5)	25	(13.5)	
60-64	123	(100.0)	104	(84.6)	19	(15.5)	
65-69	78	(100.0)	70	(89.7)	8	(10.3)	
≥70	37	(100.0)	34	(91.9)	3	(8.1)	
Previous diagnosis of AIDS-defining illness							0.03
No	742	(100.0)	671	(90.4)	71	(9.6)	
Yes	298	(100.0)	256	(85.9)	42	(14.1)	
CD4 count (cells/mm^3)							0.94
≤447	203	(100.0)	179	(88.2)	24	(11.7)	
448-567	203	(100.0)	183	(90.2)	20	(9.9)	
568-695	204	(100.0)	185	(90.7)	19	(9.3)	
696-865	202	(100.0)	180	(89.1)	22	(10.9)	
≥866	203	(100.0)	181	(89.2)	22	(10.8)	
CD4 nadir (cells/mm^3)							0.19
≤80	206	(100.0)	181	(87.9)	25	(12.1)	
81-169	194	(100.0)	171	(88.1)	23	(11.9)	

	Total N=1040		History of recurrent falls in the past 28 days				
			No n=927		Yes n=113		
	n	(%)	n	(%)	n	(%)	p-value
170-240	202	(100.0)	174	(86.1)	28	(13.9)	
241-341	197	(100.0)	176	(89.3)	21	(10.7)	
≥342	199	(100.0)	186	(93.5)	13	(6.5)	
VL							0.15
Detectable	104	(100.0)	97	(93.3)	7	(6.7)	
Undetectable	932	(100.0)	826	(88.6)	106	(11.4)	
Years on ART							0.17
≤3.9	204	(100.0)	189	(92.7)	15	(74)	
4.0-7.3	204	(100.0)	184	(90.2)	20	(9.8)	
7.4-12.3	203	(100.0)	176	(86.7)	27	(13.3)	
12.4-17.1	204	(100.0)	182	(89.2)	22	(10.8)	
≥17.2	203	(100.0)	174	(85.7)	29	(14.3)	
Time since HIV diagnosis (yrs)							0.06
≤6.4	206	(100.0)	189	(91.8)	17	(8.3)	
6.5-11.0	206	(100.0)	191	(92.7)	15	(7.3)	
11.1-16.0	206	(100.0)	182	(88.4)	24	(11.7)	
16.1-21.9	206	(100.0)	181	(87.9)	25	(12.1)	
≥22.0	206	(100.0)	174	(84.5)	32	(15.5)	
Total number of co-medications (excluding cART)							<0.001
0	316	(100.0)	300	(94.9)	16	(5.1)	
1-4	471	(100.0)	414	(87.9)	57	(12.1)	
5-9	197	(100.0)	175	(88.8)	22	(11.2)	

	Total N=1040		History of recurrent falls in the past 28 days: No n=927		Yes n=113		
	n	(%)	n	(%)	n	(%)	p-value
≥10	56	(100.0)	38	(67.9)	18	(32.1)	
NRTI backbone							0.31
None	142	(100.0)	130	(91.6)	12	(8.5)	
TFV/FTC	650	(100.0)	573	(88.2)	77	(11.9)	
ABC/3TC	132	(100.0)	116	(87.9)	16	(12.1)	
Other	116	(100.0)	108	(93.1)	8	(6.9)	
PIs							0.83
None	609	(100.0)	540	(88.7)	69	(11.3)	
Boosted PIs	338	(100.0)	303	(89.6)	35	(10.4)	
Unboosted PIs	93	(100.0)	84	(90.3)	9	(9.7)	
NNRTIs							0.009
None	518	(100.0)	466	(90.0)	52	(10.0)	
EFV	254	(100.0)	235	(92.5)	19	(7.5)	
NVP	132	(100.0)	114	(86.4)	18	(13.6)	
RPV	79	(100.0)	68	(86.1)	11	(13.9)	
ETR	57	(100.0)	44	(77.2)	13	(22.8)	
INSTIs							0.03
No	896	(100.0)	806	(90.0)	90	(10.0)	
Yes	114	(100.0)	121	(84.0)	23	(16.0)	

Table 0.9: Association of recurrent falls with age and HIV factors among PLWH in POPPY

	Univariable model	Multivariable model*
	OR (95% CI)	**aOR (95% CI)**
Age group (years)		
≤39	Ref.	
40-49	2.11 (0.70, 6.39)	2.39 (0.57, 10.01)
50-54	4.40 (1.53, 12.67)	2.74 (0.66, 11.44)
55-59	4.22 (1.43, 12.46)	2.47 (0.57, 10.72)
60-64	4.93 (1.62, 14.99)	2.32 (0.51, 10.52)
65-69	3.09 (0.90, 10.63)	2.27 (0.41, 12.41)
≥70	2.38 (0.51, 11.18)	0.81 (0.07, 9.95)
Previous diagnosis of AIDS-defining illness		
No	Ref.	Ref.
Yes	1.55 (1.03, 2.33)	1.16 (0.67, 2.01)
CD4 count (cells/mm^3)		
≤447	Ref.	
448-567	0.82 (0.43, 1.53)	-
568-695	0.77 (0.41, 1.45)	-
696-865	0.91 (0.49, 1.69)	-
≥866	0.91 (0.49, 1.68)	-
CD4 nadir (/50 cells/mm^3)	0.94 (0.88, 1.00)	-
VL		
Detectable	Ref.	
Undetectable	0.56 (0.25, 1.24)	-
Years on ART (/5 years)	1.15 (0.98, 1.34)	-
Time since HIV diagnosis (/5 years)	1.21 (1.07, 1.36)	0.96 (0.80, 1.15)
Number of total co-medications (excluding cART)		
0	Ref.	Ref.

	Univariable model	Multivariable model*
	OR (95% CI)	aOR (95% CI)
1-4	2.58 (1.45, 4.58)	1.71 (0.84, 3.52)
5-9	2.36 (1.21, 4.61)	0.83 (0.34, 2.00)
≥10	8.88 (4.18, 18.86)	1.70 (0.53, 5.45)
NRTI in regimen		
None	Ref.	Ref.
TFV/FTC	1.46 (0.77, 2.75)	-
ABC/3TC	1.49 (0.68, 3.29)	-
Other	0.80 (0.32, 2.03)	-
PI in regimen		
None	Ref.	Ref.
Boosted PIs	0.90 (0.59, 1.39)	-
Unboosted PIs	0.84 (0.40, 1.74)	-
NNRTI in regimen		
None	Ref.	Ref.
EFV	0.72 (0.42, 1.25)	1.09 (0.50, 2.37)
NVP	1.41 (0.80, 2.51)	2.08 (0.95, 4.52)
RPV	1.45 (0.72, 2.91)	3.24 (1.22, 8.56)
ETR	2.65 (1.34, 5.24)	1.66 (0.59, 4.63)
INSTI in regimen		
No	Ref.	Ref.
Yes	1.70 (1.04, 2.80)	2.74 (1.35, 5.59)

*Adjusted for current alcohol use, co-medications for mental health physical functioning and general health score

Appendix VII

Author, Year	Country	Cohort	Setting	Lower age limit or specified range	Prevalence (95% CI)	Mean/median age	Number (%) female
Aguilar-Navarro 2019 (760)	Mexico	Recruited from memory clinic	outpatient	≥60	22.2% (16.4, 29.0)	73 (6.6)	NA
Al Snih 2009 (761)	USA	H-EPESE study	community	≥67	4.3% (3.4, 5.4)	75 (6)	NA
Avila-Flunes 2008 (762)	France	Three-City study	community	≥65	7.0% (6.4, 7.7)	74.1 (5.2)	3726 (61.3%)
BelloChavolla 2017 (763)	Mexico	Coyoacán Cohort Study	community	≥70	14.1% (8.7, 21.1)	77.7 (5.8)	NA
Cakmur 2015 (764)			community	≥65	7.1% (3.7, 12.1)	72.7 (7.7)	90 (53.6%)
Calado 2016 (765)	FIBRA study		community	≥65	9.1% (6.4, 12.4)	73.9 (6.5)	249 (64.7%)
Castrejon Perez 2012 (766)	Mexico	Mexican Study of Nutritional and Psychosocial Markers of Frailty (the Coyoacan cohort)	community	≥70	15.0% (12.4, 17.9)	77.9 (6.3)	NA
Cesari 2006 (767)	Italy	In Chianti study	community	≥65	8.8% (7.0, 10.8)	74.8 (6.8)	NA
Chang 2010 (768)	USA	WHAS I and II	community	70-79	10.8% (8.5, 13.5)	74.15 (2.8)	NA
Chang 2012 (634)	Taiwan		outpatient	≥65	5.9% (3.7, 8.8)	74.6 (6.3)	NA
Chaves 2005 (769)	USA	WHAS I and II	community	70-80	14% (11.5, 16.9)	74.3 (2.9)	NA
Chen 2010 (770)	Taiwan	Survey of Health and Living Status of the Elderly in Taiwan	community	≥65	4.9% (4.1, 5.9)	73.3 (1.5)	NA

Author, Year	Country	Cohort	Setting	Lower age limit or specified range	Prevalence (95% CI)	Mean/median age	Number (%) female
Chen 2014 (771)	Taiwan	The Coming of the Aging Society: An Integrative Study on Social Planning in Taiwan in 2025	community	≥65	8.3% (6.0, 11.1)	73.4	239 (48.3%)
Cigolle 2009 (127)	Usa	HRS		≥65	7.0% (6.3, 7.7)	75	NA
Crow 2018 (772)	USA	National Health and Nutrition Examination Survey		≥60	9.2% (8.4, 10.0)	71.1 (0.19)	NA
Danon-Hersch 2012 (773)	Switzerland	Lc65+	community	65-70	2.5% (1.7, 3.5)	67 (65-70)	NA
Fried 2001 (95)	USA	CHS	community	≥65	6.9% (6.2, 7.6)	73.6	3079 (57.9%)
Hanlon 2018 (774)	UK	UK Biobank	community	40-70	3.3% (3.3, 3.4)	62	NA
Khanderwal 2012 (775)	India		inpatient	≥60	33.2% (27.4, 39.4)	66.4 (6.3)	NA
Kitamura 2019 (776)	Japan	National Center for Geriatrics and Gerontology – Study of Geriatric Syndromes.		≥65	11.9% (10.2, 13.8)	71. (5.6)	730 (57.2%)
Lahousse 2014 (777)	Netherlands	Rotterdam Study		≥55	5.8% (4.9, 6.7)	74 (9)	NA
Lee 2017 (778)	Japan			≥65	9.2% (8.7, 9.8)	73.6 (5.5)	5037 (52.4%)

Author, Year	Country	Cohort	Setting	Lower age limit or specified range	Prevalence (95% CI)	Mean/median age	Number (%) female
Lin 2015 (779)	Taiwan	Taichung Community Health Study for Elders	community	≥65	13.8% (11.8, 16.1)	74 (7)	497 (48%)
Mohr 2007 (780)	USA	MMAS	community	≥50	7% (5.8, 10.1)	67.9 (6)	0 (0%)
Moreira 2017 (781)	Brazil		community	≥65	8.0% (7.1, 8.9)	74 (6)	2951 (66.3%)
Moreira 2016 (782)	Brazil	FIBRA study	community	≥65	9.1% (7.2, 11.2)	72	99 (100%)
Nadruz 2017 (783)	USA	ARIC	community	≥68	5.3% (4.6, 6.0)	75.6 (5)	2355 (59%)
Ng 2014 (784)	Singapore	Singapore Longitudinal Aging Study	community	≥55	5.3% (4.3, 6.5)	66.7 (7.7)	1084 (64.3%)
Nguyen 2019 (785)	Vietnam		community	≥60	48.1% (42.6, 53.7)	72.8 (8.2)	358 (68.5%)
Nguyen 2019b (786)	New Zealand		outpatient	≥60	21.7% (18.2, 25.4)	69.5 (6.8)	98 (62%)
Orkaby 2019	USA	Framingham Heart study	community	≥60	31.9% (31.8, 32.0)	69.7 (7)	1194 (55%)
Ottenbacher 2009 (787)	USA	H-EPESE study	community	≥65	7.6% (6.5, 8.8)	74.3 (6.4)	1195 (58.3%)
Pollack 2017 (788)	USA		community	≥65	85.6% (78.2, 91.2)	73.4 (6.4)	0 (0%)
Ricci 2014 (789)	Brazil	FIBRA study	community	≥65	9.7% (7.7, 12.1)	71.9 (5.9)	489 (64.3%)
Tamura 2018 (790)	Japan		outpatient		24.1% (19.6, 29.2)	78 (75-82)	201 (62.2%)
Tepper 2018 (791)	Israel		outpatient	≥60	3.4% (0.9, 8.5)	70.6 (6.5)	46 (39.3%)
Thein 2018 (792)	Singapore	Singapore Longitudinal Ageing Study	community	≥55	19.8% (18.3, 21.4)	66 (7.6)	1693 (62.8%)

Author, Year	Country	Cohort	Setting	Lower age limit or specified range	Prevalence (95% CI)	Mean/median age	Number (%) female
Vaingankar 2017 (793)	Singapore	Well-being of the Singapore Elderly study	community	≥60	5.7% (4.8, 6.8)	69	1134 (53.9%)
Vaz Fragozo 2009 (794)	USA		community	≥78	41.1% (36.1, 46.4)	84.3 (4.5)	252 (67.4%)
Veronese 2017 (795)	Iceland	Age, Gene/Environment Susceptibility (AGES)—Reykjavik Study	community	≥65	7.9 (7.0, 8.7)	76.2 (5.6)	2444 (64%)
Watanabe 2017 (796)	Japan	Obu Study of Health Promotion for the Elderly		≥60	11.3% (10.4, 12.2)	72.1 (5.6)	2446 (51.8%)
Weinstein 2018 (797)	Israel		community	45-74	28.1% (23.3, 33.3)	77.2 (6.4)	0 (0%)
Wong 2010 (798)	Canada	Montreal Unmet Needs Study	community	≥75	7.4% (5.6, 9.6)	79.6 (4)	502 (67.8%)
Wu 2009 (799)	United States		inpatient	≥60	23.3% (15.1, 33.4)	74.7 (7.7)	NA
Wu 2018 (800)	China		inpatient	≥65	92.7% (92.1, 93.3)	78.5 (9)	NA
Xue 2019 (801)	China		inpatient	≥60	7.0% (6.3, 7.7)	78.5 (9)	NA
Wu 2018 (800)	China		inpatient	≥65	95.3% (94.6, 95.9)	78.5 (9)	NA

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