Assessing outcomes of people living with HIV in the UK in relation to the continuum of care framework

THESIS

presented for the

DEGREE

of

DOCTOR OF PHILOSOPHY

(Field of Study –Epidemiology)

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Declaration

I, Sophie Louise Jose, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Abstract

HIV is now a chronic illness, requiring long-term care and adherence to treatment. The continuum of care depicts the stages of the HIV care pathway, including diagnosis, Antiretroviral Therapy (ART) uptake and viral suppression. It is a widely used framework that monitors the success of HIV care and potential for transmission in a population. However, it has limitations and does not capture information on important health indicators, particularly mortality.

The UK Collaborative HIV Cohort (CHIC) Study is an observational database of HIV-positive individuals accessing care. Linkage to HIV surveillance data is used to improve ascertainment of deaths, and, alongside additional data collected from participating centres, classify a principal cause of death.

Late diagnosis occurs in approximately 56% of those aged ≥50 years, but 42% of those ≤50, and is associated with an increased rate of death in the subsequent year. Late ART initiation is associated with lower CD4 counts over time on ART, leaving individuals at a higher risk of clinical progression for longer. Engagement in care (EIC) during the first 5 years on ART correlates with life expectancy, but is generally high (median 93% of months in care). Unsuppressed viral load is highly predictive of age at death in those on ART.

A longitudinal continuum of care provides information on person-time spent with unsuppressed viral load and incorporates additional outcomes of mortality and loss to follow-up. It has shown disparities in care across demographic subgroups in the UK, with younger HIV-positive individuals having lower levels of EIC and being slower to initiate ART than older individuals, who have higher mortality. Women and those of black ethnicity spend less time on ART with a suppressed viral load.

Targeted improvements in testing rates, adherence and engagement support are needed in those identified at high risk of sub-optimal care engagement, to reduce mortality and achieve a good continuum of care for all people with HIV in the UK.

Acknowledgements

I would like to thank my supervisors, Professor Caroline Sabin and Dr Colette Smith, for their help, guidance and support. Thank you for reading chapter drafts and for the very useful comments and advice you gave. This work was undertaken using data from the UK CHIC Study and would not be possible without the work and input of all those involved. I would like to thank Dr Frank Post, Dr Sarah Pett and Dr Alejandro Arenas-Pinto for all their time and valuable clinical input into classifying causes of death for use in these analyses. I would especially like to thank Teresa Hill, the study co-ordinator, for her tireless work in collecting and generating a new dataset each year, not to mention the many hours spent collating, preparing and electronically entering hundreds of CoDe forms.

Special thanks also go to current and ex-members of the HIV Epidemiology and Biostatistics Group for their support over the last 5 years. Thank you to Sarah Amele, Valentina Cambiano, Marina Daskolopolou and Kathryn Roberts for taking the time to read drafts of my chapters and provide comments. Thank you also to Alice Thornton and Anna Schultze for always being ready and willing to provide support and advice. I would also particularly like to thank Leah Shepherd for her moral support and encouragement over the last few months.

Finally I would like to thank my family, particularly my parents, without whom I would not have made it this far, and my sister, Siân, for proof-reading a chapter just a few weeks before her wedding.

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Frequently used abbreviations

AIDS	Acquired immunodeficiency syndrome
ART	Antiretroviral therapy
ART CC	Antiretroviral therapy cohort collaboration
BHIVA	British Human Immunodeficiency Virus Association
CI	Confidence interval
CoDe	Causes of Death
EIC	Engagement in Care
HANDD	HIV and AIDS New Diagnosis Database
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HR	(adjusted) Hazard ratio
IDU	Injecting drug use
IQR	Interquartile range
(a)IRR	(adjusted) Incidence rate ratio
LTC	Loss to care
LTCFU	Loss to cohort follow-up
LTFU	Loss to follow-up
MSM	Men who have sex with men
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NRTI	Nucleoside reverse transcriptase inhibitor
ONS	Office for National Statistics
(a)OR	(adjusted) Odds ratio
PHE	Public Health England
PI	Protease inhibitor
PLWH	People living with HIV
PWID	People who inject drugs
REACH	Retention and Engagement Across Care Services for HIV
(a)sHR	(adjusted) Subdistribution hazard ratio
SOPHID	Survey of Prevalent HIV Infections Diagnosed
UK CHIC	UK Collaborative HIV cohort
UNAIDS	Joint United Nations Programme on HIV/AIDS
US	United States
VL	Viral load

Chapter 1: Introduction

1.1 Human Immunodeficiency Virus (HIV)

1.1.1 The History of HIV

The first case reports of what is now known to be HIV/AIDS infection were made in 1981, with the appearance of cases of Pneumocystis Carinii pneumonia (PCP) and Kaposi's Sarcoma (KS) in clusters of previously healthy men in the United States (US) (1-3). These cases were notable at the time as mortality associated with these conditions was remarkably high and these conditions were previously rare. Also, in common with other infections found to be present in the majority of these individuals (e.g. cytomegalovirus and thrush), these illnesses were related to severe immunosuppression (4-7). These initial cases occurred exclusively in young, gay men, generating speculation that lifestyles of gay men were somehow responsible (4, 8). However, in the year following the initial case reports, new cases began to be reported outside the original clusters of only gay men, in recipients of blood products (9), injecting drug users (7) and children (10), pointing to the potential for multiple routes through which this disease could occur (11, 12).

Whilst the cause of this cluster of diseases was unknown, in 1982, the name Acquired Immunodeficiency Syndrome (AIDS) was given and a case definition, based on a set of clinical criteria and indicator diseases, was created by the US Centers for Disease Control (CDC), to define AIDS and enable surveillance (13-15). Whilst 1-2 new cases were being diagnosed daily in the US (14), numerous cases were also starting to be reported across Europe, pointing to unrelated epidemics (16-21). Soon after, a disease known as 'slim disease' in people living in Uganda came to be recognised as AIDS (22).

HIV, the virus now known to cause AIDS, was discovered in 1983. The virus was, in fact, discovered independently by two different laboratories. The Pasteur Institute was the first to publish in 1983 on a new virus they called the Lymphadenopathy Associated Virus (LAV), which they had isolated from an individual with lymphadenopathy syndrome (23). In 1984, Robert Gallo published on a virus called the Human T-cell Lymphotropic Virus 3 (HTLV-III) (24). After discovering that these were the same virus, it was renamed Human Immunodeficiency Virus. This discovery allowed the development of diagnostic antibody tests in 1984 (25-27), and since then, much has been learned about the virus.

1.1.2 The lifecycle of HIV

HIV is a retrovirus which, as with all viruses, invades and uses host cells in order to replicate. In the case of HIV this results in the destruction of the infected cell. HIV primarily infects CD4 T-cells (28), which are an integral part of the body's immune system, responsible for activating and coordinating the body's immune response to harmful pathogens. The virus genetic material is stored as single-stranded ribonucleic acid (RNA) which is converted to deoxyribose nucleic acid (DNA) in the host cell using the viral reverse transcriptase enzyme. This DNA is then inserted into the host cell genome. Once integrated into the cell genome, it is able to replicate and create new copies of HIV which are released from the cell into the body to go on and infect other cells (29, 30). Each infected cell can create up to 1,000-10,000 new HIV virions before it dies, with up to 10^{10} created each day in an untreated individual (31, 32).

The stages of the lifecycle of the HIV virion are shown in Figure 1.1.1. The first stage (*attachment*) occurs when the virus attaches to two CD4 receptors on the outside of the cell, known as CCR5 and CXCR4. The virus most commonly binds to the CCR5 receptor in the early stages of HIV infection, with a shift towards CXCR4 in the advanced stages of the disease. From here, its envelope fuses with the cell membrane, allowing the virus to enter the cell (*fusion*). Once inside the cell cytoplasm, the virus unpacks its cell content, and makes a copy of the viral RNA, before combining it into DNA via *reverse transcription*. This DNA, then integrates into the host cell's genome using the enzyme integrase (*integration*). The cell then rapidly produces copies of messenger-RNA (*transcription*). Messenger RNA is translated into viral proteins (*translation*), which together with RNA, assemble to form new immature virus that are released from the cell surface (*assembly/budding*). The final stage is *maturation*, in which viral proteins are cleaved by the protease enzyme. This stage is necessary in order for the virus to mature and be able to infect other cells (33-36).

Figure 1.1.1: The HIV lifecycle

From Sarah Laskey and Robert Siliciano, 2014, Nature Reviews Microbiology, A mechanistic theory to explain the efficacy of antiretroviral therapy.(35)

1.1.3 The course of HIV infection

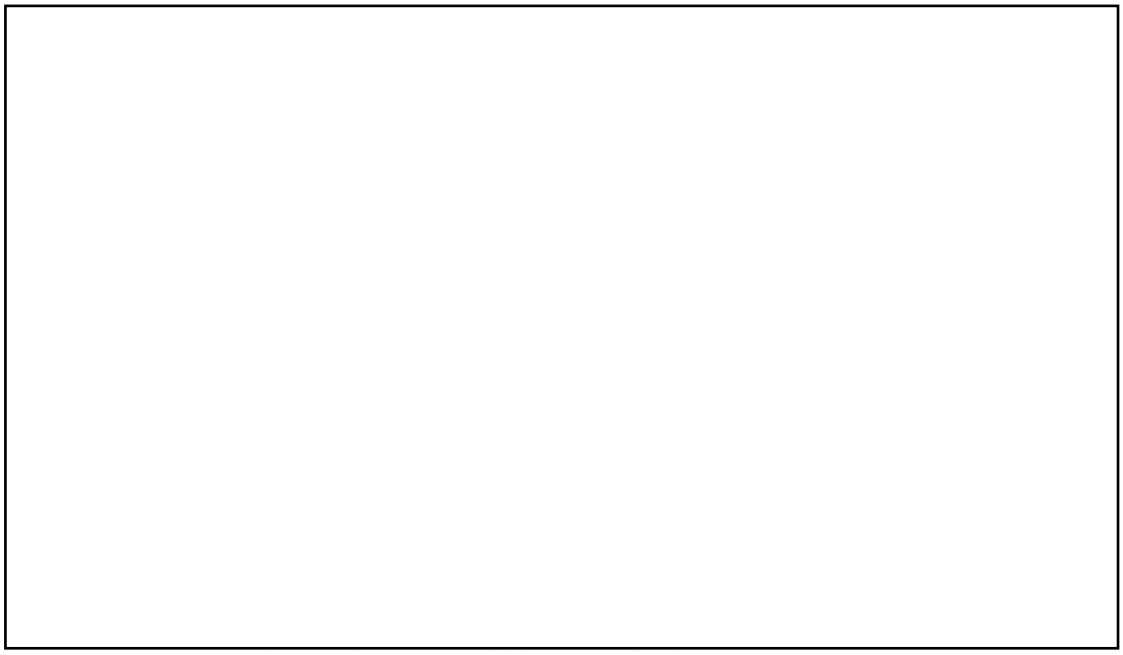
In the absence of treatment, HIV continues to replicate and infect more CD4 cells, resulting in reductions in the numbers of cells as they are destroyed. This in turn weakens the body's ability to mount an immune response against opportunistic infections and cancers (37, 38). This depletion of the immune system eventually results in the development of AIDS and death (39-41).

The initial weeks following HIV infection are referred to as primary or acute infection. During this initial period, HIV rapidly replicates and infects CD4 cells leading to extremely high levels of viraemia (>1 million copies of virus per millilitre (copies/ml)) in the plasma (42), which may first be detected between 4-11 days after infection (43, 44). This early phase of infection is characterised by rises in the amount of virus in the blood and rapid declines in CD4 count (Figure 1.1.2). However, the body does raise an initial immune response to the virus within the first few weeks of infection, producing antibodies to fight the virus (28, 45). This appearance of antibodies in the blood is known as seroconversion and occurs 2-3 months after infection, on average (46). During or prior to seroconversion, individuals may experience

mild symptoms similar to those experienced with other viruses such as influenza, and could include fever, rash, aches, diarrhoea and sore throat (28, 47, 48). Following this immune response there is a fall in the amount of virus in the blood, although it does not disappear completely (43), with some recovery of the number of CD4 cells in the blood (Figure 1.1.2) (49).

A period of asymptomatic infection follows, which is highly variable in length, but lasts for an average of 10 years (50, 51). This phase is characterised by a gradual increase in the amount of virus (52), and a decline in the number of CD4 cells (53). A healthy HIV-negative individual could be expected to have between 500-1500 CD4 cells present per mm3 of blood (54, 55). In an untreated individual with HIV, the CD4 count typically declines by an average 30-60 cells/mm3 per year (56). As the CD4 count falls and the immune system becomes compromised, individuals are at increased risk of developing opportunistic infections and malignancies (40, 57-59), the appearance of which constitute the final stage of infection known as AIDS. In 1993, the CDC developed a list of illnesses and opportunistic infections (indicator diseases) that are considered definitive of progression to AIDS (Table 1.1.1). However, in the US, AIDS will also be defined in the presence of a CD4 count <200 cells/mm3 or a CD4 percentage value <14%, irrespective of the development of indicator diseases (60, 61).

Figure 1.1.2: CD4 and viral load changes following HIV infection



From Giuseppe Pantaleo, Cecilia Graziosi, and Anthony S. Fauci, 1993, NEJM, The immunopathogenesis of Human Immunodeficiency Virus Infection (45)

1.1.4 Markers of disease progression

Due to the fact that HIV predominantly infects CD4 cells, the well described immunopathogenesis of HIV and prognostic ability of CD4 to predict AIDS (40, 57, 58) and mortality (41, 62), the CD4 count is a routinely used marker of HIV progression in the clinical care of people living with HIV (PLWH). Until recently, HIV monitoring guidelines have also used the CD4 count to guide decisions around when to start treatment for HIV (Section 1.3.4.1).

The amount of virus in the plasma, otherwise known as the HIV viral load, has been demonstrated as another highly predictive marker of outcomes in untreated individuals (52, 63), and is also a marker of treatment success. The goal of HIV treatment is to reduce the viral load to a level by which it is 'undetectable' by the assays used to measure it. A widely used definition of an undetectable viral load is to have ≤50 copies of virus per ml of plasma (copies/ml), however, some of the most sensitive assays used in clinical care in recent years can currently detect HIV virus down to levels of only 10 copies/ml.

Table 1.1.1: CDC list of AIDS-defining conditions

	Condition
1.	Bacterial infections, multiple or recurrent*
2.	Candidiasis of bronchi, trachea, or lungs
3.	Candidiasis of esophagus†
4.	Cervical cancer, invasive§
5.	Coccidioidomycosis, disseminated or extrapulmonary
6.	Cryptococcosis, extrapulmonary
7.	Cryptosporidiosis, chronic intestinal (>1 month's duration)
8.	Cytomegalovirus disease (other than liver, spleen, or nodes), onset at age >1 month
9.	Cytomegalovirus retinitis (with loss of vision)†
10.	Encephalopathy, HIV related
11.	Herpes simplex: chronic ulcers (>1 month's duration) or bronchitis, pneumonitis, or esophagitis (onset at age >1 month)
12.	Histoplasmosis, disseminated or extrapulmonary
13.	Isosporiasis, chronic intestinal (>1 month's duration)
14.	Kaposi sarcoma†
15.	Lymphoid interstitial pneumonia or pulmonary lymphoid hyperplasia complex*†
16.	Lymphoma, Burkitt (or equivalent term)
17.	Lymphoma, immunoblastic (or equivalent term)
18.	Lymphoma, primary, of brain
19.	Mycobacterium avium complex or Mycobacterium kansasii, disseminated or extrapulmonary†
20.	Mycobacterium tuberculosis of any site, pulmonary,†§ disseminated,† or extrapulmonary†
21.	Mycobacterium, other species or unidentified species, disseminated† or extrapulmonary†
22.	Pneumocystis jirovecii pneumonia (previously Pneumocystis Carinii)†
23.	Pneumonia, recurrent†§
24.	Progressive multifocal leukoencephalopathy
25.	Salmonella septicemia, recurrent
26.	Toxoplasmosis of brain, onset at age >1 month†
27.	Wasting syndrome attributed to HIV

* Only among children aged <13 years. † Condition that might be diagnosed presumptively. § Only among adults and adolescents aged ≥13 years.

1.1.5 HIV Transmission

HIV is present in most bodily fluids of an infected individual, although the quantities in sweat, tears and saliva are small, and the largest concentrations are found in the blood and in semen. Mucosal exposure to blood or bodily fluids from an infected person is required for the virus to be transmitted (64). The risk of transmission is highly dependent on the amount of virus present, with a higher viral load increasing the risk of transmission taking place (28, 65). The small concentration of virus in bodily fluids such as sweat and tears, as well as the fact that HIV cannot survive outside of the body, means that transmission through casual contacts including hand shaking or kissing is not possible (64, 66). Routes by which HIV can be transmitted between humans therefore include condomless sex, either between men or between men and women, through needle-stick injuries, sharing of injecting equipment and from mother-to-child during pregnancy, birth and breastfeeding (10, 64, 66). The predominant mode of transmission of HIV globally is through sexual intercourse (64, 66). Historically, some individuals acquired HIV through receipt of blood products (9, 66), although now all blood products are screened for HIV.

1.2 Epidemiology of HIV

1.2.1 The global HIV epidemic

According to the Joint United Nations Programme on HIV/AIDS (UNAIDS), 78 million people have been infected with HIV globally since the start of the epidemic and 35 million have died due to AIDS-related illness (67). By the end of 2016, 37 million (95% confidence interval (CI); 31 million – 43 million) people were known to be living with HIV (67). Globally the prevalence of HIV has remained stable since 2000 at 0.8% (68). Nearly 26 of these 37 million individuals living with HIV live in Sub-Saharan Africa, where prevalence of HIV markedly higher than the rest of the world; 7.1% in Central and Southern Africa, and 2.2% in West and Central Africa (67).

Following the start of the epidemic in the 1980's, the number of new infections continued to rise each year until its peak in 1996 when 3.5 million new infections were reported. This number has steadily declined each year, such that, in 2016, the estimated number of new infections globally was 1.8 million (69). This decline in new diagnoses has been observed in most areas of the world including Africa, Asia, Europe and North America. However, in Eastern Europe and Central Asia there have been substantial 57% increases in the number of new infections in 2015 compared to 2010 (69).

1.2.2 The HIV epidemic in the UK

Since the first reported cases of AIDS in 1981, the number of people infected with HIV in the UK has continued to rise, with around 101,200 people thought to be living with HIV at the end of 2015, 13% of whom were unaware of their positive status (Figure 1.2.1). Overall, the prevalence of HIV in the UK is estimated to be around 1.6 per 1,000 population. Whilst most regions have low prevalence <1 per 1,000 population there is a concentrated high prevalence of >5 per 1,000 persons in London, Manchester and Brighton (70). The prevalence is highest among men who have sex with men (MSM), with 1 in 17 thought to have HIV in 2015 (prevalence rate 59 per 1,000). Amongst heterosexual men and women the prevalence is considerably lower (1 per 1,000), with a concentrated prevalence amongst black African men and women (22 per 1,000 and 43 per 1,000 respectively). The majority of black African men and women are thought to have acquired HIV in their country of origin prior to migrating to the UK (71, 72). Amongst heterosexuals who were born abroad but received a diagnosis of HIV in the UK, 31% of black African individuals are believed to have acquired their HIV since moving to the UK, compared to 59% of black Caribbean and 36% of white ethnicity (73).

Figure 1.2.1: Estimated number of people living with HIV in the UK

From Kirwan et al., HIV in the UK: 2016 Report (70)

Transmission of HIV within the UK occurs largely through sexual contact, with a relatively small proportion of diagnoses (<3%) occurring amongst people who inject drugs (PWID) or

through mother-to-child transmission (MTCT) (70). Since the start of the epidemic, there has been a steady increase in the numbers of new diagnoses among MSM, reaching 3,360 new diagnoses in 2014 (74, 75). In 2015 and 2016, however, declines in the number of HIV diagnoses amongst MSM have been noted for the first time (76). Whereas new diagnoses amongst heterosexuals accounted for less than 1,000 new diagnoses in 1995, this rose steeply year on year to a peak of 4,840 diagnoses in 2005, overtaking the number of new diagnoses in MSM in 2000. Since this time, diagnoses amongst heterosexuals have declined just as rapidly as they increased and fell back below the number of newly diagnosed MSM in 2012 and were estimated to total 2,490 new diagnoses in 2014 (74, 75). This decline is thought to be a result of changing migration patterns, with fewer new diagnoses reported amongst individuals who were born and acquired HIV abroad (70).

Of 88,769 individuals who accessed HIV care in 2015, 61,097 (68.8%) were men and 27672 (31.2%) women. The majority of men (68.6%) accessing care were reported to have acquired HIV through sex with other men, such that MSM contributed 47.2% of all HIV-positive individuals accessing care. Most MSM (86%) accessing care are of white ethnicity. Heterosexual men and women totalled 42,710 (48.1%) individuals accessing care, of whom 61% were of black African ethnicity, 25% were white and 7% Caribbean or other black ethnicity (70). Only 2% of people who access HIV care are thought to have acquired HIV through MTCT and another 2% through injecting drug use (IDU) (75).

A major change in the HIV epidemic in the UK, as well as world-wide, has been the increasing age of the population. This has arisen as a result of both increased survival (Section 1.4.4) and increasing numbers of new HIV diagnoses amongst older individuals. In 2015, 34% of HIV-positive individuals accessing care in the UK were aged over 50, compared with only 14% in 2006 (70).

1.3 Treatment of HIV

1.3.1 History of ART development

All antiretrovirals act by interrupting the HIV life cycle and are separated into different classes according to which aspect of the HIV life cycle they act on (36). The first drug shown to have antiviral activity against HIV was approved by the US Food and Drug Administration (FDA) in 1987, 6 years after the first case reports of AIDS in New York and California. This antiretroviral drug, zidovudine (ZDV), was approved when its clinical trial was stopped early and those receiving placebo offered ZDV, due to reduced mortality rates in those in the treatment arm (77). However, subsequent trials and wider use in the HIV-positive population showed that

the benefits noted in the first 6 months of exposure, were not maintained after this time, and severe side effects were experienced by those taking the drug, particularly at high concentrations (78-82). Zidovudine was the first of a class of drugs called nucleoside reverse transcriptase inhibitors (NRTIs) and was followed by three other antiretrovirals; didanosine (ddI) in 1991, zalcitabine (ddC) in 1992 and stavudine (d4T) in 1994, all of which acted by inhibiting the same part of the HIV life cycle. These antiretrovirals were either taken singly (monotherapy) or in a combination of two drugs (dual therapy). However, the benefits on survival remained minimal, and were frequently accompanied by treatment-limiting toxicity (83). During this time, pharmaceutical companies had been developing a new type of antiretroviral drug, which acted on HIV by inhibiting a different aspect of the HIV life cycle; this class of drug was called the protease inhibitor (PI). The first of these PIs, saquinavir (SQV), was granted accelerated approval by the FDA in 1995 (84).

In 1996, at the XIth International AIDS Conference, results from the first trial of combination antiretroviral therapy (ART) were presented. These results showed that taking different types of antiretroviral drugs that acted on different parts of the HIV life cycle in combination resulted in more sustained benefits (85). These combination regimens were named highly active antiretroviral therapy (HAART) or combination antiretroviral therapy (cART or ART), and the definition was soon expanded to include any combinations of three or more antiretrovirals. In 1996, a drug from another class of antiretrovirals called non-nucleoside reverse transcriptase inhibitors (NNRTIs) was also approved by the FDA, providing further treatment options for people living with HIV (PLWH) (84). However, original ART regimens were associated with high levels of toxicity, and a very high pill burden, with regimens often containing up to 20 tablets that had to be taken in thrice-daily regimens with complicated food requirements (86, 87). For PIs, certain pharmacokinetic characteristics (low absorption and high hepatic metabolism) of early PIs meant that they had poor bioavailability (88). It was discovered that co-administration of PIs with low-doses of ritonavir, another PI which inhibits hepatic metabolism but was not often used due to high toxicity and low efficacy, boosted the bioavailability of this class of drugs (89). Boosted PI combinations (PI/r) are now commonly used in treating PLWH (90).

Since the early ART period, new drugs have continuously been developed, with improvements in efficacy and reductions in toxicity over time. Two more classes of drugs have been and there are currently over 20 licensed drugs from 5 classes (Table 1.3.1) (84). Pill burden has also improved over time, with longer dosing intervals and the introduction of co-formulated antiretrovirals, which combine multiple drugs into a single tablet (91, 92). In 2006 the first 'one tablet once a day' regimen called Atripla was approved (93). Currently there are 6 such single tablet regimens available (94).

1.3.2 Antiretroviral drug classes and their mechanism of action

The points of action in the HIV life cycle of the different antiretroviral drug classes are shown in Figure 1.1.1. NRTIs were the first class of drugs to be developed. They work by inhibiting reverse transcriptase, the process by which HIV turns its genetic material from single-stranded RNA to full DNA (35, 64). Two nucleotide reverse transcriptase inhibitors, tenofovir disoproxil fumerate (TDF) and tenofovir alafanamide fumerate (TAF) are also licensed, but are generally considered in the group of NRTIs. NNRTIs similarly inhibit reverse transcription, but achieve this through a different mechanism. NRTIs are nucleoside or nucleotide analogues that are similar enough to be incorporated into the generated DNA string causing errors and preventing complete transcription of RNA into DNA. NNRTIs instead bind to reverse transcriptase, blocking transcription (35, 95). PIs bind to protease, preventing maturation and resulting in the release of immature HIV virions that are unable to infect other cells (35, 64). Entry (Fusion) inhibitors prevent the HIV envelope from fusing with the CD4 cell membrane, allowing the virus to enter the cell (35, 96). CCR5 entry inhibitors block the CCR5 receptor on the cell surface, preventing HIV from attaching to the cell (97). The newest class of antiretrovirals are the integrase inhibitors (INSTIs). These drugs prevent HIV DNA from being integrated into the cell's genome (35).

Around 85-90% of individuals will achieve an undetectable viral load $\leq$50 copies/ml within 6 months of starting current ART regimens (64). However, HIV cannot be eliminated from the body entirely and so there is, as yet, no cure. One major reason for this is because certain cells, when infected with HIV may go into an inactive or latent state in which HIV is unable to replicate (35). These latent cells may be found in the brain, lymph nodes, and digestive tract and collectively are referred to as the HIV reservoir. Such latent cells may reactivate at any time. Once ART is stopped, some of these latent cells will reactivate and HIV will again become detectable (98, 99). One strategy for developing a HIV cure targets such latent cells, trying to force them to become active, as once they are reactivated they become a target for ART again (100-102).

Table 1.3.1: List of licensed antiretroviral drugs to date

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
	Emtricitabine (FTC)	2003
Nucleotide reverse-transcriptase inhibitors (NtRTIs/NRTIs)	Tenofovir disoproxil fumerate (TDF)	2001
	Tenofovir alafanamide fumerate (TAF)	2016
Protease Inhibitors (PIs)	Saquinavir hard gel (SQV)	1995
	Indinavir (IDV)	1996
	Ritonavir (/r)	1996
	Saquinavir soft gel	1997
	Nelfinavir (NFV)	1997
	Amprenavir (APV)	1999
	Lopinavir/ritonavir (LOP/r)	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 (TMC125)	2008
	Rilpivirine (RPV)	2011
Fusion/entry inhibitors	Enfuvirtide (T20)	2003
	Maraviroc (MVC)	2007
Integrase Inhibitors (INSTIs)	Raltegravir (RAL)	2007
	Dolutegravir (DTG)	2013
	Elvitegravir (ETG)	2012*/2014**
*As part of co-formulated single-tablet regimen stribild **As a single pill formulation to be administered with pharmacokinetic enhancer such as cobicistat or ritonavir.		

1.3.3 Side-effects of ART

As with most chemical agents, antiretroviral drugs may cause side-effects or toxicities in some individuals. If severe, such side-effects may cause illness, changes to physical appearance and cause long-term harms as well as affecting an individual's ability to adhere fully to ART (86, 103-105). It is therefore important to monitor for side-effects and select regimens to minimise toxicities and maximise the tolerability and adherence to these medications. Many side effects resolve if exposure to the responsible agent is removed. However, due to the life-long need for ART, an alternative medication will need to be used in place of the discontinued agent. Early antiretroviral drugs had severe side-effects to the extent that some early NRTIs, namely zalcitabine and stavudine, are no longer endorsed in clinical practice (106, 107). Over time, the toxicity profile of antiretrovirals has dramatically improved as newer drugs have been developed, but some side-effects still remain.

Severe effects of NRTIs include mitochondrial toxicity, manifesting as lactic acidosis, hepatic steatosis, peripheral neuropathy, and lipodystrophy (108, 109). The NRTI abacavir (ABC) can induce a hypersensitivity reaction presenting as a rash amongst people with the HLA B*5701 allele (36, 110). If very severe, this hypersensitivity may cause hepatitis or even result in death (111). For this reason, people undergo genetic testing for the presence of this allele before commencing ABC (112). Links have also been made between ABC and myocardial infarction in observational studies (113), whilst declining renal function, greater risk of chronic kidney disease and low BMD have all been associated with TDF exposure (103, 114-116).

Some of the earliest PIs (SQV, IDV, NFV) also carry a relatively high burden of toxicity. Severe effects of PIs include metabolic abnormalities such as dyslipidaemia, hyperglycaemia and lipodystrophy, and the earlier PIs were associated with severe gastrointestinal issues such as nausea, vomiting and diarrhoea (36, 106, 117). Some of the newer PIs have been linked to kidney dysfunction and decreased bone mineral density (104). ATV and LPV in particular have been identified as being associated with declining eGFR and increased incidence of chronic kidney disease (118).

NNRTIs are associated with hypersensitivity reactions, often presenting with a rash. Efavirenz, has been widely used and is still a recommended treatment option by the World Health Organisation (WHO), has been linked to CNS disorders, sleep disturbance and suicidal ideation (106, 119, 120). For this reason it is not recommended to be used in individuals with previous history of mental health illness. Nevirapine is associated with hepatotoxicity, with the life threatening Stevens-Johnson syndrome occurring in the most extreme cases (106, 121). The newest class of INSTIs are generally more tolerable and have limited uncommon side-effects reported to date. There is some indication that neuropsychiatric side effects may be occurring,

particularly with dolutegravir (122, 123). However as this is a new class of drug it may take time for side-effects to be recognised.

1.3.4 Resistance

During replication, the HIV virus uses single stranded RNA to create new genetic material (DNA). RNA is a sequence of amino acids that code the genetic material of the HIV virus. As HIV replicates extremely rapidly, with between 1 and 10 billion new virions created each day in untreated individuals, it regularly creates spontaneous errors in the amino acid sequence i.e mutations of the genetic material, and new variants or strains of the virus (32, 124). These mutations may be of advantage or disadvantage to the virus. One strain of the virus (known as the "wild type") is the fittest (i.e. has the highest replicative capacity) in the absence of treatment and so usually constitutes the majority virus in the absence of treatment. However, strains which contain mutations that confer resistance to a specific antiretroviral or antiretroviral drug class may become the fittest once drug pressure is added, meaning that this virus strain is able to replicate in the presence of ART (125). For some drugs, multiple resistance mutations must occur in order for the susceptibility of the virus to be reduced, whilst a single mutation may be sufficient to cause resistance to certain drugs (124). Further, certain mutations, alone or in combination, may cause resistance to multiple drugs, leading to class-wide resistance (125).

The development of resistance in the presence of sub-optimal ART concentrations (most often caused by poor adherence) will lead to treatment failure and require changes to be made to the treatment regimen. It is also possible for individuals who have never received ART to be resistant to ARVs, as drug resistant virus may be transmitted (126). It is recommended that resistance tests are performed once an individual is diagnosed with HIV and following a rebound of HIV viral load on ART to ensure individuals are treated with appropriate agents (127). ARVs that do not easily confer resistance are said to have a high genetic barrier and are more 'forgiving' of lower rates of adherence (128). Where there are concerns over adherence, drugs with a higher genetic barrier (usually PIs) may be prescribed so as to minimise the risk of resistance development. Drug resistance has traditionally been a problem as it reduces treatment options and can influence treatment response and outcomes (129, 130). However, in the UK, the prevalence of both developed and transmitted resistance has declined since 2002, with an estimated 33% of treatment experienced individuals resistant to any class of ARV in 2013, whilst 6.6% of ART-naïve individuals had transmitted resistance (131, 132).

1.3.4.1 When to start ART

For many years guidelines have recommend that treatment be initiated immediately amongst those with primary infection, those who have progressed to symptomatic HIV or AIDS, and amongst those with other comorbidities such as hepatitis B (HBV) or hepatitis C virus (HCV) co-infection. However, the optimal timing of ART initiation for asymptomatic, chronically infected individuals has been widely debated in recent years. Until relatively recently, CD4 count-guided treatment initiation was recommended. Prior to 2008, in the absence of good evidence as to the optimal timing of ART initiation and due to concerns over drug toxicity and resistance development, UK guidelines recommended the consideration of therapy initiation at CD4 counts of 200-350 cells/mm^3 with a strong recommendation for treatment with a CD4 count <200 cells/mm^3 (133-136).

In 2008, the threshold for ART initiation was increased to recommend ART initiation before the CD4 count fell below 350 cells/mm^3, and before it reached 200 cells/mm^3 (112). From this time a body of evidence started to grow around the potential benefits of earlier or immediate ART initiation. In 2009 the Swiss statement was released, which stated that an HIV positive person in receipt of ART with an undetectable viral load and without any concurrent sexually transmitted infections could not transmit HIV (137). This introduced the concept that HIV treatment could not only be used for the individual's own health but also as a means of preventing HIV transmission. This led to questions over the need for CD4 count-guided ART initiation as opposed to immediate treatment for all in order to reduce onward transmission (TasP).

In 2011 the HPTN 052 study demonstrated that earlier ART initiation reduced the risk of onward transmission between heterosexual couples by 96% (138). Subsequently, US guidelines changed in 2012 to recommend treatment with ART, regardless of an individual's CD4 count (139) with WHO guidelines changing in 2013 to recommend ART initiation at CD4 counts lower than 500 cells/mm^3. However, earlier ART initiation confers extra years of exposure to drugs with potential side-effects and the requirement for an individual to maintain high levels of adherence for a longer time to avoid resistance. As there was still no evidence as to the potential risk to benefit ratio for an individual's health of starting ART earlier, British HIV treatment guidelines remained unchanged (140) and European guidelines suggested that ART be considered irrespective of CD4 count but there was no strong recommendation for immediate ART. In 2015, the START study reported as to the benefits of immediate ART initiation amongst those with CD4 counts >500 cells/mm^3, in terms of both AIDS and non-AIDS morbidity and mortality (141). Subsequently UK guidelines were updated in 2015 and now recommend individuals initiate ART as soon as they are ready, irrespective of CD4 count (142).

1.3.4.2 What drugs to start

Treatment guidelines around the world differ somewhat as to the preferred choice of HIV treatment regimen for individuals newly starting ART. The first regimen started is referred to as first-line therapy. All guidelines recommend that first-line ART regimens should include a backbone of two NRTIs alongside a third agent from another class of ARVs (143-145). The choice of NRTI backbone and corresponding third agent differs by guidelines, according to setting, cost and availability of drugs in different regions. A summary of the recommended first-line ART regimen in various current guidelines is shown in Table 1.3.2. Guidelines in the UK currently recommend starting a NRTI backbone consisting of either TDF or TAF with FTC alongside an INSTI, boosted PI or RPV (142). In practice, however, the choice of initial ART regimen is also influenced by financial restraints, with EFV still used instead of INSTIs.

Table 1.3.2: Current recommended first-line regimens

Guideline body	NRTI	Third Agent
WHO (2016) (143) Low-income countries	TDF/FTC or TDF/3TC	EFV
IAS-USA (2016) (144) USA	ABC/3TC	DTG
	TAF/FTC	DTG RAL EVG/COBI
	TAF/FTC or TDF/FTC	RPV DRV/r or DRV/c
	TDF /FTC	EFV
EACS (2017) (145) Europe	ABC/3TC	DTG
	TDF/FTC or TAF/FTC	DTG RAL EVG/COBI RPV DRV/r or DRV/c
BHIVA (2016) (142) UK	TDF/FTC or TAF/FTC	RAL DTG ETG/c ATV/r DRV/r RPV

1.3.4.3 Treatment switches

In the event that someone is unable to achieve or maintain an undetectable viral load on treatment, it may be necessary to change some or all of the components of the ART regimen being taken. Transient and low level increases in viral load (blips) may occur, but treatment switches in this situation are currently not recommended. Virological failure is defined in UK guidelines if people are unable to suppress the virus to below detectable levels after 24 weeks of therapy, or if a confirmed rebound (≥2 results) of viral load to above 200 copies/ml occurs after the person achieves an undetectable viral load (146). In this instance it is important to try and achieve an undetectable load through alternative regimens. If a person experiences viral load rebound that would be defined as virological failure, resistance testing should be performed and the reasons for this rebound, including poor adherence, should be investigated. Treatment switches may also be made in the event of toxicities or if a patient requests a change due to side effects. The choice of new drug(s) should be made based on the results of resistance testing to ensure any new drugs are fully active against HIV, bearing in mind any concerns of adherence and tolerability (146). A regimen containing 2 NRTIs alongside a third agent from another class is recommended where possible. However if class-wide or multi-class resistance is present or the chance of new resistance development is high, the choice of active agents to choose from may be limited. Alternative combinations, such as combined third agents with no NRTI backbone, may need to be considered in consultation with a multi-disciplinary team (146).

1.4 Changing outcomes for people with HIV in the ART era

With effective and tolerable ART, individuals are able to achieve and then maintain long-term suppression of HIV (147). Long-term suppression is associated with favourable outcomes with regards to health and morbidity. This is because reducing the amount of virus in the blood allows the immune system to function better as CD4 cells aren't depleted. This dramatically slows or halts disease progression, reducing the risk of AIDS but also lowering immune activation and inflammation which is believed to play a role in the development of some non-AIDS illnesses (148-151). This has had large impacts on morbidity and mortality outcomes of PLWH. Another major benefit of viral suppression is the reduced potential for onward transmission of the virus (138, 152). This reduced infectiousness has important implications for reducing HIV incidence.

1.4.1 Declining AIDS incidence and mortality

The rate of AIDS-defining illness approximately halved amongst PLWH in the year following the introduction of combination ART (153-155). The initial very rapid decline in AIDS illness in the first 3-5 years after ART was introduced was followed by continuing moderate declines in the rate of AIDS (156, 157). Once ART has been started the risk of progression to AIDS may be as low as 5%, but this is highly dependent on someone's CD4 count at the time they start treatment. People who start ART with a low CD4 count will progress to AIDS more quickly (158, 159). With reductions in AIDS incidence on ART, the greatest burden of AIDS-related illness now occurs around the time of HIV diagnosis, in people who don't get diagnosed until HIV is already in an advanced stage (160).

Prior to the introduction of ART, median survival time following and AIDS diagnosis was just 18 months, with improvements observed even with ZDV monotherapy in the early ART era (161, 162). Throughout the ART era, survival following AIDS diagnosis has continued to improve (163, 164), with approximately 85% of individuals surviving 5 years after their diagnosis in recent years (165, 166). Combined with the declining AIDS incidence, this has dramatically reduced rates of deaths due to AIDS-defining illness in the ART era (167) by as much as 95% in some settings (168). From a high of greater than 10 AIDS deaths per 100 person years at the start of the ART era, this reduction was characterised by a rapid decline in the rate of AIDS deaths after the introduction of ART in 1996 (169, 170), followed by more moderate declines and eventual stabilisation of death rates since 2000 at <1 per 100 person years (168, 171-173).

1.4.2 Non-AIDS morbidity and mortality

Non-AIDS illnesses have become of increasing concern amongst PLWH in recent years as AIDS-free survival has increased. These non-AIDS conditions are traditionally related to aging in the general population e.g. malignancy, cardiovascular disease (CVD), liver disease, kidney disease, and osteoporosis (174-176). The prevalence and risk of co-morbidities among people living with HIV is significantly higher than in the general population (177). In fact, the comorbidity profile of PLWH is likened to that in the general population aged 10 years older, with a higher prevalence of multiple co-morbidities (174, 178). This has generated a hypothesis of premature or accelerated aging occurring in PLWH (174, 179). Whilst the aging of the population likely contributes to this increasing prevalence of non-AIDS illnesses in recent years, lifestyle factors, ART exposure and HIV itself may all contribute to the excess risk of non-AIDS co-morbidities in PLWH compared to the general population (176, 178, 180). For instance, smoking rates are significantly higher amongst PLWH than in the general population and smoking is a well-known risk factors for several conditions including stroke,

myocardial infarction and cancer (180, 181). The majority of liver-related morbidity and mortality amongst PLWH occurs in those who are co-infected with Hepatitis C Virus (HCV), which is more prevalent amongst PLWH than in the general population (182, 183). ART has also been linked to non-AIDS morbidity, with TDF and some PIs associated with renal impairment and bone mineral density loss (104, 118). Large observational studies also link ABC to myocardial infarction (113). These comorbidities present several challenges in the care and management of PLWH, of which polypharmacy and potential drug-drug interactions are one (184-186).

The rate of all non-AIDS mortality has declined in the ART era, but with more moderate declines than for AIDS-related deaths (172). Whilst the rates of death due to both liver and cardiovascular disease have steadily decreased, deaths due to non-AIDS malignancies have remained largely stable (168, 173, 187). There is an excess risk of some non-AIDS illnesses in PLWH compared to the general population (188). Compared to the general population, rates of death due to non-AIDS malignancies are 1.3-3 times higher in HIV-positive individuals (171, 189, 190). Rates of liver-related death are 3-69 times higher than the general population, depending on the prevalence of HCV in the population studied (171, 189-191). Rates of CVD death are 1.5-3 times higher (171, 189, 190). Rates of non-AIDS infection may be markedly higher at >10 times the rate in the general population (189).

1.4.3 Causes of death

As a result of the decreased incidence of AIDS and AIDS-related mortality rates following the wide-spread roll out of HAART, the distribution of deaths attributable to AIDS and non-AIDS defining causes has also changed over time. Whereas almost all deaths in the pre-ART era were AIDS-related, the proportion of deaths attributed to AIDS declined in the ART era, representing 20-30% of all deaths the modern ART era in high-income countries (173, 192-195).

Conversely, the portion of deaths attributed to non-AIDS causes has increased in the ART era, to represent the majority of deaths occurring in HIV-positive individuals (196). The most common non-AIDS cause of death is malignancy, which has markedly increased in the ART era, contributing approximately one-quarter of deaths since 2009 and overtaking AIDS as a cause of death (172, 173, 196). This is followed by liver disease, contributing approximately 7-15% of deaths (173, 196, 197). These deaths almost entirely occur in people with HCV co-infection (172, 198), leading to higher proportions of liver related deaths in settings with a higher prevalence of HCV. Between 7-11% of deaths are attributed to CVD (168, 173, 195-197, 199), and similar proportions were due to non-AIDs infections (196, 197). Approximately 5% of deaths in PLWH are due to suicide (172, 195, 196).

1.4.4 Improvements in life expectancy

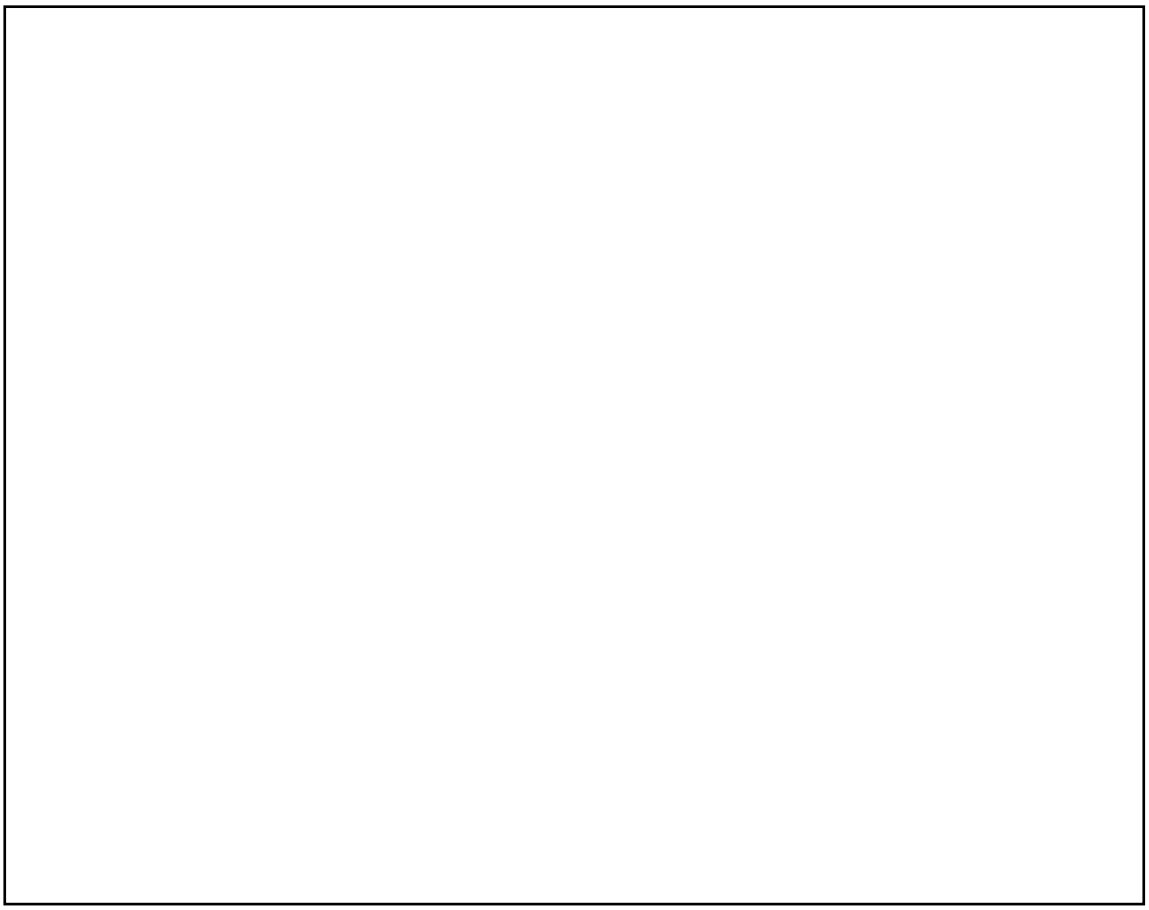
The introduction of ART has vastly reduced all-cause mortality rates and improved the survival of people living with HIV (153, 192, 193, 200, 201). In the pre-ART era, only 50% of people newly infected with HIV could be expected to survive for 10 years. Since 2000, 10 year survival rates from HIV seroconversion are estimated to be 94% (202). Consequently, the life expectancy of people living with HIV has increased over time, contributing to an aging HIV population (167, 203). At the time when combination ART became available, a 20 year old with HIV could be expected to live to approximately 39 years of age; a 44 year gap in comparison to the life-expectancy of the general population at the time (204). Studies now estimate that with timely diagnosis and ART initiation, a person with HIV who remains on treatment can achieve a life expectancy approaching that of the general population (205-208). However, a deficit does still exist (209) and it is unclear if this lower life expectancy in PLWH is attributable to HIV alone, a higher prevalence of high-risk lifestyle factors such as smoking (210, 211), or a combination of factors (212).

1.5 The continuum of HIV care

1.5.1 The spectrum of engagement with HIV care

In order for treatment to be successful, both in terms of individual outcomes and preventing onward transmission of the virus, it is important that HIV-positive individuals are promptly diagnosed, engaged with HIV care, started on ART and remain adherent to therapy to maintain viral load suppression. This process was first visualised in a bar chart, as shown in Figure 1.5.1, for PLWH in the United States of America (US) by Gardner et al. By describing these benchmark stages of care for a given HIV population, it is possible to assess both the potential for onward HIV transmission amongst those who are not virally suppressed, monitor the delivery of HIV care and understand the level of engagement with HIV care. This visualisation has since come to be known as the cascade or continuum of care. From the illustration by Gardner et al., it became evident that only 19% of PLWH in the USA were believed to be on ART with an undetectable viral load, demonstrating poor engagement with care and a high potential for ongoing HIV transmission.

Figure 1.5.1: Spectrum of engagement with HIV care in the USA

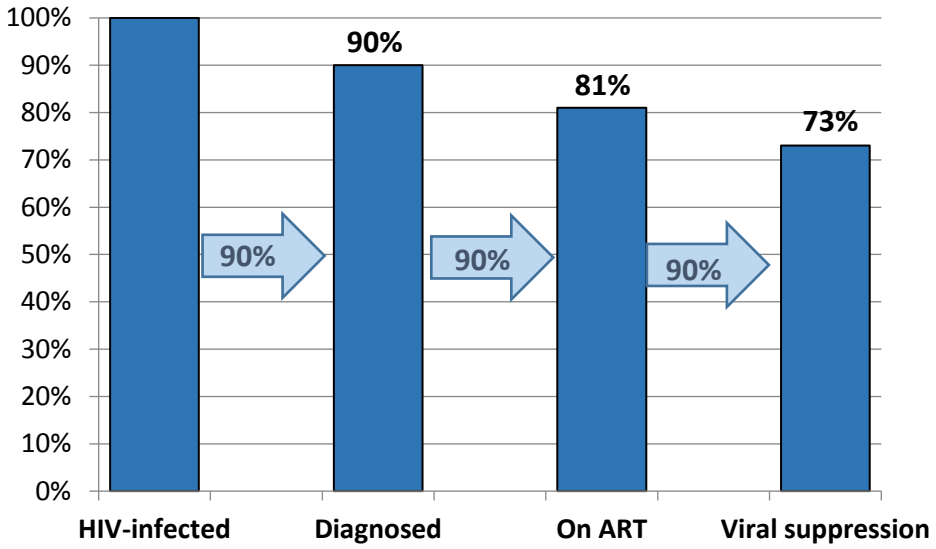


From Gardner et al, The spectrum of engagement in HIV care and its relevance to test-and-treat strategies for prevention of HIV infection 2011 (213)

1.5.2 UNAIDS 90-90-90 targets

In 2014, UNAIDS set a target to have 90% of the world's HIV-positive individuals diagnosed, 90% of those diagnosed on treatment and 90% of those treated with an undetectable viral load by 2020, in order to halt the HIV/AIDS epidemic (Figure 1.5.2) (214). Whilst the continuum of care had gained popularity and was already being reported in many different settings (215-217), these targets made this framework a key tool in monitoring HIV programme success world-wide. It has also generated a need to establish reliable and comparable estimates within countries, drawing focus to the stages of diagnosis, ART use and viral suppression.

Figure 1.5.2: Four-stage continuum of care illustrating the UNAIDS 90-90-90 targets



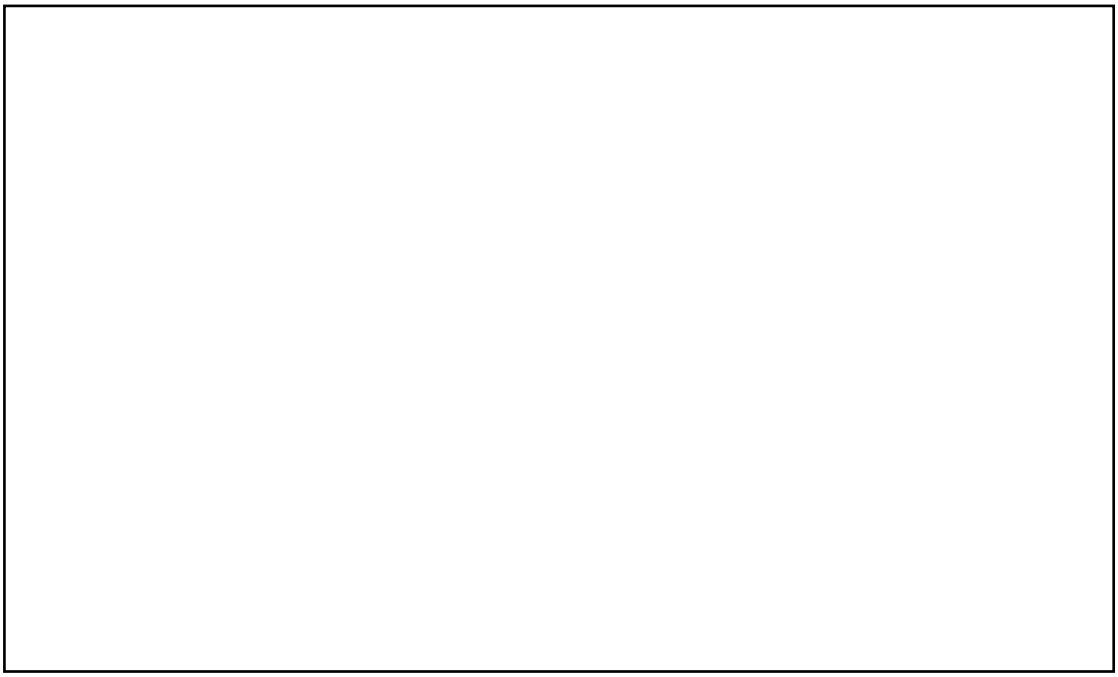
1.5.3 The HIV continuum of care in the UK

In 2011, the HIV continuum of care for the UK was estimated as follows: 77% of PLWH were aware of their status; 73% were retained in care; 64% were on treatment and 58% had a suppressed viral load (215). This demonstrated that the largest gap in the continuum of care for the UK was in achieving HIV diagnosis. This correlates with high prevalence (47%) of individuals diagnosed at an advanced stage of HIV, when their CD4 count had dropped below 350 cells/mm^3 (218). The continuum of care has improved in recent years such that in 2015, 87% of PLWH were aware of their status, 83% were receiving ART, and 78% had a suppressed viral load (Figure 1.5.3) (70). However, methods for defining the continuum of care also changed in this time. In 2015, the continuum of care surpassed two of the UNAIDS 90-90-90 targets, with 96% of those diagnosed on ART and 94% of those on ART with viral load suppression (Figure 1.5.3). However, the target of 90% diagnosed still has not been achieved. Few countries are able to report a continuum of care that achieves the 90% targets for diagnosis, ART use and viral suppression rates (219, 220).

Whilst the UK has a good continuum of care overall, this may not be the case within all subgroups of the population of PLWH. Observational studies of PLWH in the UK have found disparities across quality of care indicators and treatment responses according to certain demographic characteristics (221-224). In other settings, such disparities have also been

observed in the continuum of care (217, 225). However, in the UK, few data are available on the continuum of care in different populations (215). Further, whilst it is a useful public health monitoring tool, a cross-sectional continuum of care may have some limitations for assessing the success of HIV care, as mortality outcomes are not considered.

Figure 1.5.3: Continuum of HIV Care in the UK in 2015 according to public health surveillance



From Kirwan et al,. HIV in the UK: 2016 Report (2016) (70)

1.6 Focus of thesis

The aim of this thesis is to understand outcomes of people living with HIV in the established ART era, with particular reference to the quality of care indicators that compile the continuum of care. In particular I will consider how failure to achieve these care indicators impacts on mortality outcomes. A more detailed literature review of the current literature around the benchmarks of HIV care and how they impact on mortality follows this chapter. In subsequent chapters I present the methods of the UK CHIC Study (Chapter 3) and work undertaken to improve data on date and cause of death in UK CHIC analyses in order to enable analyses of mortality end-points (Chapter 4). In Chapter 5 I consider the impact of late diagnosis on both AIDS and non-AIDs mortality, particularly in relation to an aging HIV-positive population. Chapter 6 whether the disadvantages of late ART initiation remain over the long-term, if individuals are able to maintain viral suppression for a period following ART. I then investigate,

in Chapter 7, whether poor engagement in HIV care on ART correlates with lower life expectancy. My final analysis chapter presents a longitudinal HIV care continuum that I have devised, which incorporates the outcomes of death and loss to follow-up (LTFU). A final summary and discussion of the findings of my thesis is presented in Chapter 9.

Chapter 2: Literature Review

2.1 Introduction

In this section I summarise the literature to date regarding the stages of the HIV care pathway in the continuum of care, and how they relate to mortality outcomes among PLWH. This review will start by discussing the strengths and limitations of the HIV continuum of care as a tool for monitoring programme performance, before discussing each of the following stages of the HIV care pathway in detail: diagnosis, retention in care, ART initiation and viral suppression. For each stage of the continuum I consider methodological issues involved with defining each stage, factors associated with sub-optimal achievement of these stages and, finally, how such sub-optimal achievement affects mortality outcomes. In terms of factors associated with the continuum stages, I focus on disparities according to demographic characteristics (age, sex, ethnicity and mode of acquisition) in the UK or other high-income countries in order to identify findings most relevant to the HIV-positive population in the UK.

2.2 The continuum of HIV care as a measure of programmatic success

2.2.1 Strengths of the continuum of care framework

Since its first presentation as a 7-stage spectrum of engagement in care, the continuum of care has gained increasing visibility and is now a popular and widely used tool for monitoring programme performance. Drops between stages, or 'leakages,' along the continuum give valuable information as to the presence of gaps or disparities in HIV care in a population, and can direct interventions or health care resources. The continuum also creates the potential for easy comparisons in performance between countries and settings, although difficulties currently exist in generating comparable estimates (Section 2.2.2). For the stages of diagnosis onwards, it is not computationally intensive to generate, provided the data are available, as it only requires the calculation of proportions. As it is a cross-sectional measure it can be generated quickly and therefore gives real-time estimates of the current situation in a population. Finally, it is easily understood, giving comprehensive information on levels of engagement with HIV care services and a measure of the potential ongoing transmission within a given population at a particular point in time. Therefore, it is useful for conveying information to national and international health boards and health services providers who may

not be directly involved in providing HIV care but are involved in program evaluation or HIV care provision.

2.2.2 Methodological considerations in generating a continuum of care

2.2.2.1 Sources of data and a Population-based vs. a clinical cohort continuum

The first bar of the HIV continuum of care is the total number of people that have HIV infection. This number cannot truly be known, unless the entire population were to be tested for HIV, so instead must be estimated (Section 2.3.1). The subsequent stages (from diagnosis onwards) can be measured accurately if suitable surveillance data are available, which give the true number in the continuum with some degree of measurement error. Such population-based data are available in many countries, including the UK, for the purposes of public health surveillance, but not all countries have these systems in place. Further, in countries where some level of surveillance is in place, this may not cover all aspects of the continuum (e.g. laboratory test surveillance may give numbers diagnosed and numbers with viral suppression only), or the data itself may be limited or collected infrequently (e.g. a single annual report of viral load as in the UK). In settings where surveillance data are not sufficient to allow generation of all stages of the continuum, cohort data may be used instead of, or in combination with available surveillance data to generate estimates of the continuum of care (220).

In order to generate an unbiased estimate of the continuum of care, nationally representative population-based data are needed. However, cohort studies may not have national coverage, may recruit participants from particular settings (e.g. large teaching hospitals) and may further have specific inclusion criteria or require patient consent. They would therefore include a selected sample of the population and may produce biased estimates. Difficulties in estimating the total number of people with HIV infection for such a selected sample mean that the first stage of the continuum is often diagnosis rather than HIV infection.

In the UK, the continuum of care is estimated using a single national surveillance system, with modelled estimates of the total number of people who are HIV-infected (Section 2.3.1)(226). Different approaches are used in other settings according to the available data. The US continuum of care is generated using national surveillance datasets and the Medical Monitoring Project (MMP), which is a cross-sectional survey designed to obtain nationally representative estimates of people receiving care. National surveillance of name-based reporting of HIV diagnoses are used to generate estimates of undiagnosed infection; mandatory reporting of all CD4 counts and viral loads from 14 jurisdictions are used to estimate linkage to care the MMP is used to generate the stages of retention in care, ART use and viral suppression (217, 227, 228). In British Columbia (BC), Canada, data on testing and

diagnosis are acquired from the BC Centre for Disease Control, with data on HAART use and viral suppression from the BC Centre for Excellence in HIV/AIDS cohort, to generate a continuum of care from diagnosis onwards which has 100% coverage for the BC area (225). In Estonia, estimates of diagnosed HIV infection are generated using data from the Estonia Health Board and Cause of Death Registry, with linkage to and retention in care estimated from the Estonian Health Insurance Fund and ART use and viral suppression from the Estonian HIV cohort Study (229). Several studies report a cohort continuum of care, from diagnosis onwards, based on non-national clinical data (230-234).

2.2.2.2 Which stages to include

When originally suggested by Gardner et al., in 2011, the spectrum of engagement in care included 7 stages: HIV infection; diagnosis; linkage to care; retention in care; ART need; ART use; viral suppression (213). The UNAIDS targets focus on four of these stages, namely HIV infection, diagnosis, ART use and viral suppression. However, a continuum of care has been drawn using as few as 3 stages, omitting all stages prior to linkage to care (235). When constructing a continuum of care, the stages included will be determined by the data available, which varies from setting to setting. In a report produced by the European Centre for Disease Prevention and Control (ECDC), less than 70% of 40 countries in the EU and European Economic Area (EEA) were able to report data on viral suppression, with less than 50% of EEA countries able to do so (236).

Because of the dependence of the stages in the continuum, people counted as being in a given stage have to satisfy the requirement of all previous stages. Thus the decision whether or not to include a stage in a continuum can alter the estimates for later stages of the care pathway. For example, viral suppression or ART use might be higher in a continuum of care that doesn't include retention in care than for one that does, as in the former, people don't need to also satisfy the definition of retention in care to be defined as on ART or virologically suppressed. Some studies have suggested also presenting an independent continuum of care, which presents the number and proportion of individuals achieving each stage, with no requirement to have satisfied any of the previous stages. Using independent instead of dependent measures of viral suppression, estimates increased from 43% to 61% of diagnosed individuals in New York (237) and from 52% to 62% of HIV Infected veterans in Atlanta (231).

2.2.2.3 Defining the stages of the continuum of care

A lack of standardisation means that the definitions used for each stage of the continuum of care differ between settings, and makes comparability of the continuum of care difficult. Definitions utilised in the continuum of care are discussed in relevant sections of this chapter. A Europe-wide initiative, led by the ECDC, recently generated a standardised definition of the continuum of care to generate country-specific estimates that could be compared, as well as

a Europe-wide estimate (220). Using the developed standardised definitions of the four stage continuum of care, across 11 countries in Europe, 84% of all HIV-infected individuals were diagnosed, 71% had ever initiated ART, and 60% were virologically suppressed in 2013. Only two of these 11 countries, namely Denmark and Sweden, achieved the UNAIDS 90-90-90 targets. However, whilst these estimates are comparable between countries, they may not be the best estimates of the current situation in all countries.

2.2.3 Limitations of a cross-sectional care continuum as a measure of programmatic success

When assessing programmatic success, a traditional cross-sectional continuum may not always provide information that is sufficiently in-depth and detailed as required. For example, it may be useful to link the stages of care to clinically relevant patient outcomes such as disengagement from HIV care, mortality and AIDS-defining illness. In addition, the timing at which people enter into the stages of the care pathway is important in a model of optimal care (238), with late entry into the stages associated with poorer patient outcomes (Sections 2.3.5, 2.5.4). Many quality of care indicators are linked to the timing of events in care such as late diagnosis, late ART intiatiation, time to linkage to HIV services from diagnosis, and time to achieving virologic suppression (221). These timings are not represented in the continuum of care. Furthermore, although it depicts progressive sequential stages through HIV care, in practice individuals may move backward as well as forward through these stages of care, as levels of engagement in care (EIC), ART use and viral suppression can change over time. A traditional continuum of care only includes those who are alive in the calendar year of assessment, potentially giving a 'best-case' scenario. Further, it is not known what happens to individuals that drop out between stages; whether they are still engaged with care but have not progressed onto the next stage, or whether they have disengaged from care, left the country or have died.

2.2.4 Suggested alternatives to a cross-sectional care continuum

Some of the previously mentioned limitations of a cross-sectional continuum of care can be resolved using longitudinal data. Some such 'cohort' continuums follow a group of people forward in time from diagnosis, or entry into HIV care and are interpreted differently to a cross-sectional continuum of care, instead providing information on how a cohort progresses through the stages of HIV care after diagnosis (239). An approach used in two studies of the HIV-positive population in Sothern Alberta, Canada, between 2006 and 2013, classified individuals according to the latest stage of the continuum achieved during the follow-up period, prior to death or loss to follow-up. The stages of the continuum of care were measured

longitudinally and included linkage to care (attending initial visit at the Southern Alberta Clinic), retention in care (at least 2 regular visits within 12 months of HIV diagnosis) and viral suppression ($\geq$12 consecutive months with an undetectable viral load over follow-up) (230). One important use of this continuum design was to incorporate the burden of mortality at each stage along the continuum of care, finding that 55% of deaths occurring in this population occurred in individuals who linked to care, but were not retained in care in the year following diagnosis. A limitation of this approach is that it still assumes only forward movement through the stages of care occurs (240). A recent study of diagnosed HIV-positive individuals in Massachusetts constructed a continuum of care for the 2 years following HIV diagnosis, defining linkage to care if a visit occurred within 90 days of diagnosis, retention in care if a visit occurred in each 6 months interval over the 2 year period, and viral suppression amongst those retained if viral load at 24 months was ≤400 copies/ml. A strength of the approach in this study is that incorporates some measure of timely achievement of the stages of the care continuum, which could also be extended to include timely ART initiation in settings where these data are available. A disadvantage analysis is that it only considers the short-term period of care following diagnosis, by design, so is only relevant to this population and does not give information about longer-term care engagement or outcomes (241).

A methodology suggested by Lesko and others, utilising John's Hopkins University clinic data, calculated the cumulative incidence of 9 events relating to ART initiation, viral suppression, death (and its timing in relation to other events) and loss to follow-up (LTFU, and its timing in relation to other events). From these cumulative incidence curves, the proportion of time over 10 years spent in each of the 7 following defined stages of care were calculated and presented as a stacked area chart: (i) Died prior to ART initiation (ii) LTFU prior to ART initiation (iii) Died after ART initiation (iv) LTFU after ART initiation (v) on ART and suppressed (vi) On ART and not suppressed (vii) in care and not on ART (242). This methodology provides several benefits over a cross-sectional continuum of care for understanding programmatic success and patient outcomes in care, firstly as it incorporates the end-points of mortality and LTFU. Whilst still presenting a single comprehensive figure, more detailed information about the amount of time spent in each stage of HIV is provided; person-time spent unsuppressed will have important implications for ongoing transmission and is a useful metric. Whilst some movement in and out of the stages of care is allowed for, the fixed end-points required for the survival analyses approach taken means that it is not truly flexible to changing health status over time. Retention in care is not encapsulated except through LTFU, which is a different measure of disengagement. Another disadvantage of this method is that it is quite computationally intensive to derive, and as with other longitudinal continuums of care, only includes stages after linkage to care.

A 'states and transitions' framework was hypothesised by Powers et al., to describe a population-based continuum of care, including the stages of HIV infection, diagnosis, engagement in care, ART use and viral suppression, as well as rates of transition in both directions between each of these stages (243). Further, this could be theoretically be extended beyond the currently defined states to include mortality and LTFU. However, the authors highlight several challenges in the estimation of this framework using current HIV surveillance and monitoring data, as no country has sufficiently detailed and representative data at each stage of the continuum of care to generate the required estimated rates of transition between stages.

2.3 HIV Diagnosis

2.3.1 Estimating the burden of undiagnosed HIV

Estimates of the total number of people with HIV infection, and the proportion of those that remain unaware of their HIV-positive status can be achieved through a range of different methods. These include seroprevalence surveys, back-calculation and synthesis models (Table 2.3.1) (244-246). Briefly, unlinked anonymous seroprevalence surveys, estimate the numbers with undiagnosed and diagnosed HIV infection by testing a sample of the population for HIV and asking about their status. The prevalence of HIV amongst the samples (seroprevalence) can be used to estimate prevalence and therefore number of HIV-infected individuals in the population and responses to questions about status give the proportion diagnosed (247-249). Back calculation methods use information on the CD4 count or AIDS defining illness at diagnosis and work backwards from this to estimate when they were likely infected with HIV. From this an incidence rate and the cumulative number of individuals that have acquired HIV can then be estimated. HIV prevalence estimates are generated by subtracting the cumulative number of deaths (217). In the UK, a Bayesian Multi Parameter Evidence Synthesis model is used to estimate the number of individuals living with undiagnosed HIV in the UK (226).

2.3.2 The diagnosed HIV-positive population and definitions of late diagnosis

In a traditional continuum of care, the diagnosed population of PLWH is ideally defined as the cumulative number of individuals with a confirmed diagnosis by the time of assessment, minus the cumulative number of deaths and the number of individuals who have left the country or population studied. However, lack of data on out-migration and death mean that slight variations of this are used in different countries. In the UK, the diagnosed population for the national care continuum is given by the number of people seen for care in the year of

assessment (Zheng Yin, personal communication, February 6, 2015). This is done under the assumption that loss to care and migration out of the country is low. The proportion of individuals with HIV that are diagnosed is generated using the number of diagnosed individuals and the estimated total number of people with HIV infection, discussed in the previous section.

A consensus definition of late diagnosis was developed which defines it as diagnosis with a CD4 count ≤350 cells/mm^3 or an AIDS-defining illness, regardless of CD4 count. This definition was chosen due to the recommendation that ART should be initiated by these thresholds, and so failure to diagnose before this time would delay optimal initiation of treatment, resulting in poorer outcomes. Diagnosis with a CD4 count <200 cells/mm^3 would be considered diagnosis with advanced immunosuppression or very late diagnosis (250). This threshold has been shown as the best, of various immunological and clinical definitions, to predict short-term mortality (251). However, many different definitions of late diagnosis have been used in the literature. In the following sections I will refer to late diagnosis to indicate any marker of diagnosis at a stage that is not optimal, specifying definitions used where relevant. 'Advanced' diagnosis will reference advanced immunosuppression as defined above.

Table 2.3.1: Reported percentages of diagnosed HIV Infection according to continuum of care estimates

Paper	Region/population	Data source	Year	Method	%[1]
Gardner 2011(213)	US / General	Review of literature	2006	(252)	79%
Gourlay 2017(220)	Austria/ General	ECDC modelling tool[2,3]	2013	ECDC modelling tool[2]	88%
	Belgium/ General	ECDC modelling tool[2,3]		ECDC modelling tool[2]	84%
	Denmark/ General	Clinical cohort		ECDC modelling tool[2]	91%
	France/ General	Estimated numbers in/out of care		Other (country-specific) back-calculation tool	84%
	Germany/ General	Surveillance data		Other (country-specific) back-calculation tool	83%
	Greece/ General	Surveillance data		ECDC modelling tool[2]	78%
	Italy/ General	Clinic-based survey		Other (country-specific) back-calculation tool	90%
	The Netherlands/ General	Clinical cohort		ECDC modelling tool[2]	85%
	Spain/ General	Statistical modelling		Other (country-specific) back-calculation tool	82%
	Sweden/ General	Clinical cohort		Surveillance/survey estimates	90%
	UK/ General	Surveillance data		Multi-Parameter Evidence Synthesis Model	81%
	Europe/ General	-		-	84%
Hall 2013(217)	US / General	National surveillance data	2009	Back-calculation model	82%
Hsieh 2015(247)	Baltimore, US / General	-	2007	Seroprevalence survey	72%
Iroh 2015(253)	US / before incarceration	Literature review	-	-	78%
	US / incarcerated				79%
	US / after incarceration				79%
Kelen 2016(254)	US / General	-	2007	ED unlinked identity seroprevalence survey	73%
			2013		93%

Paper	Region/population	Data source	Year	Method	%[1]
Kirwan 2016(70)	UK / General	National surveillance data	2015	Multi-Parameter Evidence Synthesis Model	87%
Kohler 2015(255)	Switzerland / General	European MSM internet survey	2012	Back-calculation	81%
Krentz 2014(240)	Canada / General	Public Health Canada data	2006-2013	Diagnosed + estimated undiagnosed by public health agency Canada	80%
Laisaar 2016(229)	Estonia / General	Estonian health board, Estonian Insurance fund, Estonian HIV Cohort Study, Estonian Causes of death registry	2013	UNAIDS spectrum estimate + HIV diagnoses minus AIDS deaths 1988-2013	72%
Lippman 2016(256)	South Africa / Men South Africa / Women	-		Seroprevalence survey	48% 76%
Mangal 2014(231)	US / Veterans	Atlanta Veterans Affairs Medical Centre	2012	Mathematical model back-calculation	95%
Nosyk 2014(257)	Literature review	Public Health Agency Canada plus linked provincial datasets	1996 2011	Public Health Canada prevalence estimates minus diagnosed	51% 71%
Okeke 2016(258)	US / White MSM US / Black MSM	National HIV Behavioural Surveillance Survey	2004-2014 2004-2014	Previous awareness of HIV status at positive HIV test	88-100% 43-86%
Pokrovskya 2014(259)	Russia / General	-	2011-2013	-	45-49%
Raymond 2016(234)	Wellington, NZ / General	Clinic database	2015	Estimated undiagnosed fraction based on past research(260)	80%
Rosenberg 2014(261)	US / White MSM US / Black MSM	CDC surveillance data	2009	Diagnosed divided by black and white MSM proportion diagnosed	84% 75%

Paper	Region/population	Data source	Year	Method	%[1]
Santos 2014(248)	San Francisco, US / Transwomen	Respondent-driven sample study (262)	2010	Previous awareness of HIV status at positive HIV test, weighted population prevalence for RDS	95%
Supervie 2013(216)	France / General	HIV surveillance data	2010	Back-calculation model	81%
Wirtz 2016(249)	Moscow, Russia / MSM	Respondent-driven sample study	2010-2013	Previous awareness of HIV status at positive HIV test, weighted population prevalence for RDS	14%
Zanoni 2014(263)	US / Adolescents	Literature Review	-	(264)	40%

[1]If range is given, then estimates are given for each calendar year within the interval; first and last estimates are presented.
[2]This tool used back-calculation models to estimate both HIV incidence and the undiagnosed fraction from the number of diagnosed PLWH.
[3]Tool also used to generate number of diagnosed HIV-positive individuals
(E)CDC=(European) Centre for Disease Prevention and Control; ED=Emergency Department; MSM=Men who have sex with men; NZ=New Zealand.

2.3.3 Rate of late diagnosis

Most recent estimates of the proportion of HIV-infected individuals that are diagnosed and aware of their status range from 72-91% (Table 2.3.1), with extremely low rates of diagnosed HIV in Russia (249, 259), where HIV is highly stigmatised. In the UK, the proportion of all PLWH that have received a HIV diagnosis is estimated to have increased over time, from 76% in 2011 to 87% in 2015 (70, 218). To date, late diagnosis is defined using CD4 criteria in UK national surveillance estimates, which show a declining proportion of individuals being diagnosed with a CD4 count <350 cells/mm^3 over time; from 47% in 2011 to 39% in 2015 (70, 218). A single-centre UK cohort estimated that half of individuals have a CD4 count below this threshold at diagnosis (222). In a previous analysis of the UK Collaborative HIV Cohort (CHIC) Study, 46.4% of individuals had a CD4 count ≤350 cells/mm^3 at diagnosis (223).

As defined by a CD4 count $\leq$350 cells/mm^3 or an AIDS defining illness, studies outside the UK report between 45-55% of new diagnoses occurring late, with the lowest estimate of 25.3% found in a study of only MSM in Spain (265) and highest estimate of 62% found in a large European cohort collaboration (266). Interestingly this was higher than in another study performed using data from the same collaboration, which reported a 53.8% rate of late diagnosis (267). Estimates of advanced immunosuppression vary greatly depending on the underlying population studied; between 23-65% of those newly diagnosed with HIV. However estimates in the region of 35-40% are most commonly reported (266, 268-273).

2.3.4 Factors associated with late diagnosis

2.3.4.1 Age

Despite differing definitions and statistical adjustments, there is strong agreement amongst the published literature that older age at HIV diagnosis is associated with increased probability of being diagnosed late or with advanced immunosuppression (Table 2.3.2). Studies exclusively show an increasing proportion of individuals diagnosed late or with advanced disease with older age at diagnosis, with some studies showing over 70% of individuals diagnosed aged 50 or above having some form of late diagnosis (268, 274, 275). The largest study to show such an association was a study of HIV surveillance data in Florida on over 25,000 HIV diagnoses. Those diagnosed aged above 60 had more than 5 times the odds of being diagnosed once HIV had progressed to AIDS than those aged 13-19 at diagnosis (276). A similarly large Italian clinical cohort found that, amongst newly diagnosed individuals who attended for care, the odds of late diagnosis increased with age above 25 such that those aged above 55 at diagnosis had 7.5-fold increased odds of late diagnosis (consensus definition); an association that has been present since the start of the epidemic in 1985 (272).

In the UK, similar associations have been found, but of slightly smaller magnitude, with those aged above 50 at diagnosis between 3 and 4 times as likely to be diagnosed with a CD4 count <350 cells/mm^3 than those aged 15-24 (274, 277). Studies to consider both definitions of late diagnosis and advanced immunosuppression have found that the magnitude of association increases when considering advanced immunosuppression as opposed to late diagnosis (271, 273, 278). The association between late diagnosis and age has largely been shown to remain across demographic groups, although prevalence is often lower amongst MSM, who tend to test more frequently (218, 274, 275, 277, 279).

Table 2.3.2: Papers describing the association between age and late diagnosis, ordered by age grouping

Paper	Study/Population	N	Late diagnosis definition	Age	Late Diagnosis (%)	Adjusted Odds Ratio (95% CI)
Chadborn 2005(279)	UK HIV Surveillance - MSM 1993-2002	14158	CD4 <200	per 10 years	-	1.9 (1.8, 2.0)
Mugavero 2007(280)	US Single site clinical cohort 2002-2004	113	CD4 <200	per 10 years	-	1.72 (1.12, 2.64)
Shivaji 2014 [abstract](281)	Portugal HIV surveillance 2011-2013	3809	CD4 <350 or AIDS	per year	-	1.02 (heterosexuals) 1.04 (MSM)
Trepka 2014(276)	US, Florida CDC surveillance Diagnosed 2007-2011	25585	AIDS (includes CD4 <200 or CD4% <14) URBAN	13-19 20-39 40-59 >60	-	1.00 2.2 (1.8, 2.7) 4.3 (3.5, 5.2) 5.3 (4.2, 6.6)
			Rural	13-19 20-39 40-59 >60	-	1.0 2.7 (1.0, 7.2) 7.5 (2.8, 20.0) 5.2 (1.7, 15.9)
Desai 2015(277)	UK HIV surveillance - MSM 1999-2013	2602	CD4 <350	15-24 25-34 35-49 50+	24% 26% 33% 50%	1.00 1.2 (0.9, 1.6) 1.7 (1.3, 2.2) 3.2 (2.3, 4.4)
Rice 2014(274)	UK HIV surveillance - heterosexual 2002-2011	38228	CD4 <350	15-24 25-34 35-49 50+	45% 61% 70% 70%	1.00 1.7 (1.5, 1.9) 2.9 (2.5, 3.3) 3.8 (3.2, 4.5)

Paper	Study/Population	N	Late diagnosis definition	Age	Late Diagnosis (%)	Adjusted Odds Ratio (95% CI)
Raffetti 2016(272)	Italy Multi-centre clinical cohort (MASTER) Diagnosed 1985-2013	19391	CD4 <350 or AIDS	<25 25-34 35-44 45-54 >55	-	1.00 2.4 (2.2, 2.7) 4.1 (3.7, 4.6) 5.8 (5.0, 6.7) 7.5 (6.1, 9.2)
Dai 2015(282)	China Census/questionnaire 2009-2010	899	CD4 <200 or AIDS	18-27 28-37 38-47 48-57 58+	-	1.00 2.2 (1.2, 4.0) 2.4 (1.2, 4.5) 2.2 (1.1, 4.4) 2.8 (1.4, 5.6)
Camoni 2013(268)	Italy Mandatory reporting of HIV/AIDS 2010-2011	5545	CD4 <350 or AIDS	<29 30-34 35-39 40-49 50+	39% 51% 54% 61% 71%	1.00 1.7 (1.4, 2.1) 2.1 (1.7, 2.5) 2.9 (2.5, 3.4) 4.6 (3.8, 5.6)
Lee 2010(283)	South Korea CDC data 2000-2007	2299	CD4 <200	15-29 30-39 40-49 ≥50	21% 34% 49% 53%	1.00 1.7 (1.3, 2.3) 2.6 (1.9, 3.5) 2.7 (2.0, 3.7)
Nhac-Vu 2010(284)	Vietnam Single centre clinical cohort diagnosed 2004-2005	204	CD4 <200	18-30 31-54		1.00 1.0 (0.6, 1.9)
Kivela 2010(285)	Finland Single centre clinical cohort 1985-2005	934	CD4 <200 or AIDS	<30 30-39 ≥40	16% 21% 33%	1.00 1.5 (1.0, 2.3) 2.6 (1.6, 4.1)
Buetikofer 2014(286)	Switzerland Single centre (Zurich) chart review 2009-2011	281	CD4 <350 or AIDS	<30 30-39 40-49 50+		1.00 0.9 (0.5, 1.9) 1.5 (0.7, 3.1) 3.5 (1.2, 10.1)

Paper	Study/Population	N	Late diagnosis definition	Age	Late Diagnosis (%)	Adjusted Odds Ratio (95% CI)
Sobrino-Vegas 2016(278)	Spain Multi-centre clinical cohort 2004-2013	7165	CD4 <350 or AIDS	<30 31-40 41-50 >50	34.9 46.9 57.1 69	1.0 1.59 (1.39, 1.82) 2.18 (1.83, 2.60) 3.60 (2.92, 4.44)
			CD4 <200 or AIDS	<30 31-40 41-50 >50	16 28 41 49.9	1.0 1.96 (1.60, 2.40) 3.15 (2.52, 3.96) 4.35 (3.49, 5.43)
Delpierre 2006(270)	France Multi-centre clinical cohort 1996 – 2005	5702	CD4 <200 or AIDS	<30 30-39 40-49 50-59 ≥60	23 40 46 52 53	1.0 2.0 (1.6, 2.6) 2.7 (2.1, 3.6) 2.9 (2.0, 4.1) 4.1 (2.5, 6.72)
Wilson 2011 (275)	France Nationally representative survey 2003-2011	1096	CD4 <350 or AIDS - MSM	<30 30-40 40-50 50-60 >60	20 34 38 65 71	1.0 2.0 (0.9, 4.2) 2.5 (1.1, 5.5) 6.8 (2.4, 19.7) 7.3 (2.2, 24.0)
			CD4 <350 or AIDS - migrants	<30 30-40 >40	56 65 72	1.0 1.5 (0.7, 2.8) 2.1 (0.9, 4.8)
			CD4 <350 or AIDS – heterosexual	<30 30-40 40-50 >50	51 49 70 65	1.0 0.8 (0.3, 2.3) 2.0 (0.7, 5.8) 1.5 (0.4, 4.9)
			CD4 <350 or AIDS – French overseas departments	<30 30-39 40-49 >49	34 52 62 66	1.0 2.0 (0.9, 4.4) 2.4 (1.1, 5.4) 3.6 (1.5, 8.7)

Paper	Study/Population	N	Late diagnosis definition	Age	Late Diagnosis (%)	Adjusted Odds Ratio (95% CI)
			CD4 <200 or AIDS - MSM	<30 30-40 40-50 50-60 >60	5 15 25 40 60	1.0 3.1 (1.1, 9.0) 5.6 (1.9, 16.4) 11.9 (3.7, 38.2) 21.4 (5.9, 76.9)
			CD4 <200 or AIDS - migrants	<30 30-40 >40	34 46 42	1.0 1.7 (0.9, 3.4) 1.2 (0.5, 2.8)
			CD4 <200 or AIDS – heterosexual	<30 30-40 40-50 >50	15 31 53 45	1.0 2.1 (0.6, 7.3) 6.1 (1.9, 19.8) 3.1 (1.0, 10.0)
			CD4 <200 or AIDS – French overseas departments	<30 30-39 40-49 >49	21 34 43 53	1.0 1.9 (0.8, 4.1) 2.3 (1.0, 5.1) 3.4 (1.4, 8.2)
Yombi 2014(287)	Belgium Single centre clinical cohort Diagnosed 2007-2011	359	CD4 <350	<30 30-39 40-49 >50	33 39 43 62	1.0 1.3 (0.7, 2.4) 1.7 (0.8, 3.3) 2.8 (1.3, 6.4)
Castilla J 2002(288)	Spain HIV surveillance Diagnosis 1994-2000	7825	AIDS in month of/month following HIV diagnosis	15-24 25-34 35-44 >44	36 27 33 62	1.4 (0.9, 2.1) 1.0 1.2 (1.0, 1.4) 1.8 (1.5, 2.2)
Diaz A (265)	Spain Multiple STI and HIV testing centres 2003-2011	2499	CD4 <350 or AIDS	<25 25-34 35-44 ≥45	20 23 29 36	0.8 (0.6, 1.0) 1.0 1.3 (1.0, 1.7) 1.8 (1.3, 2. 5)

Paper	Study/Population	N	Late diagnosis definition	Age	Late Diagnosis (%)	Adjusted Odds Ratio (95% CI)
Crabtree-Ramirez 2012(289)	Brazil Single centre clinical cohort 2001-2008	429	CD4 <200 or AIDS	<34 34-45 ≥45	-	1.0 1.6 (0.9, 2.6) 2.4 (1.2, 4.7)
Buchacz 2012 (290)	US Multi-centre clinical cohort (HIV Outpatients Study) 2000-2009	936	CD4 <200	<35 ≥35	-	1.0 2.1 (1.6, 2.9)
Valentini 2015(273)	Brazil Single centre clinical cohort 2008-2009	520	CD4 <350 or AIDS	<35 >35	-	1.00 3.0 (2.1, 4.3)
			CD4 <200 or AIDS	<35 >35	-	1.00 4.3 (2.9, 6.3)
Yang 2010(291)	US, Texas HIV surveillance 2000-2007	9964	AIDS (includes CD4 <200)	13-19 20-29 30-39 40-49 50-59 ≥60	-	0.3 (0.3, 0.5) 0.6 (0.5, 0.7) 1.0 1.4 (1.3, 1.6) 1.6 (1.4, 1.9) 2.6 (2.0, 3.3)
Nacher 2005(292)	French Guinea (FHDH) Multi-centre clinical cohort 1992-2003	1952	CD4 <200, 200-350, 350-500, >500	<20 20-30 31-40 41-60 >60	-	0.4 (0.3, 0.7)* 0.5 (0.4, 0.7)* 1.00* 1.3 (1.1, 1.7)* 1.8 (1.1, 2.8)*
Dougan 2004(293)	UK HIV surveillance 1997-2001	16179	AIDS	<45 ≥45	13 26	-
Celesia 2013(269)	Italy Single centre clinical cohort 1985-2010	620	CD4 <350 or AIDS	<50 >50	-	1.00 2.1 (1. 1, 3.8)

Paper	Study/Population	N	Late diagnosis definition	Age	Late Diagnosis (%)	Adjusted Odds Ratio (95% CI)
Davis 2013(294)	UK HIV surveillance 2000-2009	48144	AIDS	<50 ≥50	9 19	-
Ellman 2014(295)	US, Manhattan Single centre cohort 2006-2011	287	CD4 <200 or AIDS	<50 ≥50	-	1.00 3.1 (1.6, 6.0)
Helleberg 2012(271)	Denmark National cohort Diagnosed 1995-2009	3027	CD4<350 or AIDS	<50 ≥50	-	1.00** 4.0 (3.5, 4.6)
			CD4 <200 or AIDS	<50 ≥50	-	1.00 4.6 (4.0, 5.4)
Iwuji 2013(222)	Brighton Single centre clinical cohort 1996-2010	1536	CD4 <350	<50 ≥50	48 64	1.00 2.2 (1.5, 3.1)
Smith 2010(296)	UK HIV surveillance 2000-2007	49795	CD4 <200	<50 ≥50	33 48	-
Yombi 2014(287)	Belgium Single centre clinical cohort Diagnosed 2007-2011	359	CD4 <350	<30 30-39 40-49 >50	33 39 43 62	1.0 1.3 (0.7, 2.4) 1.7 (0.8, 3.3) 2.8 (1.3, 6.4)

CDC=Centre for Disease Control; FHDH=French Hospitals Database; *Odds are of being in a lower CD4 count category; **Incidence Rate Ratio, not Odds Ratio.

2.3.4.2 Sex/Mode of Acquisition

Studies considering gender differences in late diagnosis either found that males had at least 30% higher odds of late diagnosis (272, 292, 297, 298) (maximum 2.4-fold increase (284)) or reported no difference (273, 280, 283, 289), with none showing females at higher risk. This may be explained by differences according to transmission risk groups, as the majority of men in HIV studies in high income stings are MSM, but was sometimes found to remain independently of this (276, 278). Those who acquired their HIV through sex between men and women are more likely to be diagnosed late than MSM (276), with estimated odds of late diagnosis between 1.4 and 2.2-fold higher (268, 272, 278, 287, 291, 299). This increased risk is predominantly driven by heterosexual men, who, in comparisons split by sex, are a group highlighted to be at particular risk of late diagnosis (222, 273, 300). In the UK, 67% of newly diagnosed heterosexual men are diagnosed late, compared to 36% of MSM, who are the risk group with the lowest proportion diagnosed late (221). This is likely due to better awareness of risk and higher testing amongst MSM (218).

2.3.4.3 Ethnicity

In the UK, a lower proportion of newly diagnosed white individuals were diagnosed late than individuals of either black or other non-white ethnicities. This has been evidenced by HIV surveillance data, with 66% of black African adults diagnosed with a CD4 <350 cells/mm^3 compared to just over 40% of white adults (221) and by a single centre study showing those of black, other and unknown ethnicities to have 2.6, 1.6 and 3.3-fold higher odds, respectively, of diagnosis with a CD4 <350 cells/mm^3 (222). However, amongst two studies of MSM using surveillance data in the UK, whilst one found any non-white ethnicity to be associated with a 72% increase in the odds of a CD4 <200 cells/mm^3 at diagnosis (279), the other found no association between ethnicity and late diagnosis, defined by a CD4 count <350 cells/mm^3 (277). Black, Hispanic and other non-white ethnicity are also a risk factor for late diagnosis in the US (276, 291), where non-white ethnicity is also associated with lower socio-economic status and poorer access to healthcare.

2.3.5 The impact of late diagnosis on mortality

Individuals diagnosed late or with advanced disease (regardless of the definition used) are at a vastly increased risk of mortality (272, 292), with shorter estimated survival time (269, 301). Developing AIDS within 1 year of diagnosis has been shown to correlate strongly with AIDS-related mortality (Hazard ratio (HR)=4.3), but also with non-AIDS mortality (HR=2.3) (302). However, it is likely that any excess risk of mortality as a result of late diagnosis is only present in the short-term. In fact, the higher risk of mortality with either late or advanced HIV diagnosis has been shown to disappear after longer than 2-4 years with diagnosed HIV. In the national Danish cohort, a 3- and 6-fold increased rate of 1-year mortality due to late and

advanced diagnosis decreased to a mortality ratio of 1.1 in the third year following diagnosis (271). Similarly, in Spain, late presentation was no longer associated with mortality after 4 years diagnosed HIV, despite associations observed <1 and 1-4 years after diagnosis (278). Similar findings were made in by far the largest study of late diagnosis, which included data on over 84,000 individuals accessing care across Europe. Using first visit as a proxy for HIV diagnosis where none was available, the risk of progression to AIDS or death in those with late or advanced presentation was highest in the year following diagnosis (IRRs: 6.6-13.0 and 7.0-14.6 across regions of Europe) and no difference was seen compared to non-late or non-advanced presenters after 2 years (267).

A relatively large proportion of studies demonstrating an association between late diagnosis and mortality have been undertaken using UK HIV/AIDS surveillance data on all HIV diagnoses. An advantage of these studies is that they consider all diagnosed individuals, not just those linked to care. These studies, conducted over various time periods between 1999 and 2011, are also particularly relevant to this thesis as they consider a UK population. However, definition used depends only on CD4 count thresholds, without considering the occurrence of AIDS-defining events. From these combined studies we learn that: both MSM (279) and heterosexual men and women (300) diagnosed with CD4 counts below 200 cells/mm^3 experience higher rates of 1-year mortality than those with higher CD4 counts (14.1% vs. 1.1% MSM and 6.1% vs. 1.1% heterosexual); that low CD4 counts below 350 cells/mm^3 at diagnosis contribute a large burden of AIDS related mortality, with 98% of AIDS deaths within 1 year occurring amongst late presenters and a 10-fold increased risk of AIDS deaths in late presenters compared to non (303); and that older individuals also diagnosed with low CD4 counts have a particularly high risk of mortality compared to other groups (294). In a 2-year snap-shot of 2010-2011, the rate of 1-year mortality in those aged over 50 and diagnosed with a CD4 count <350 cells/mm^3 was 107 per 1000 population. This compared to a rate of 33/1000 for those aged 40-49 with the same CD4 count or 17/1000 for non-late diagnoses in those aged over 50 years (221). This high excess mortality might suggest that the impact of a late diagnosis on mortality outcomes are worse for older individuals. This could be due to faster CD4 count declines in this group in the absence of treatment meaning CD4 counts are lower at diagnosis, and/or subsequent poorer immunological recovery on ART (304-310). However, a single-centre study in Brighton with a largely white MSM population found that, despite an increased risk of mortality for both individuals with a low CD4 count and those of an older age, the interaction between the two covariates was not statistically significant, suggesting that the relative impact of late diagnosis is not greater for older PLWH (222).

In a simulation model, Nakagawa et al., modelled and compared the impact of two diagnosis rates on life expectancy in MSM. They found that in a scenario where 97% of HIV-infected

MSM were diagnosed within 10 years, the risk of death 10 years after diagnosis was only 5%, compared to 13% in a scenario where only 74% were diagnosed by 10 years, with a median CD4 count of 142 cells/mm^3 at diagnosis. This translated to a 4 year difference in life expectancy between the two diagnosis rates (207). This demonstrated, amongst MSM, that increased testing, leading to earlier diagnosis may have a beneficial impact on mortality.

2.4 Retention in care

2.4.1 Defining retention in care

2.4.1.1 Comparing different definitions of retention

There is no consensus definition for retention in care in the continuum, with a number of different definitions reported. The occurrence of a visit in a calendar may be a sufficient indication of retention. In the UK, retention in care is reported as the proportion of individuals seen for care in a given year that are also seen the following year (70, 311, 312). These are definitions likely driven by the availability of data. In the UK, the HIV/AIDS reporting system receives a single annual return for each attending individuals from HIV centres. However, as most individuals would be expected to attend for care on multiple occasions within a calendar year, this is generally not considered a sufficient measure of complete retention in care. Instead, measures that try to capture adherence to visit schedule are often used.

In the US, the CDC recommend the HRSA HAB measure of $\geq$2 visits at least 90 days apart within a 12 month period to define retention in care when estimating the continuum of care (217). This is therefore widely reported in literature from the US and elsewhere. Other widely used measures of retention in care in the literature include visit constancy (at least one visit in each 3 or 6 month interval in a given time-frame), gaps in care (no gaps of greater than 6 or 12 months between consecutive visits) and missed visits, where data on scheduled visits are available (Table 2.4.1). Previous studies have attempted to compare the predictive value of different measures of retention in care, often using viral suppression as the gold standard indicator of engagement. Mugavero et al., assessed the predictive value of 6 definitions of retention in care. The first 3 were based on missed visits and were: the number of missed visits, an indicator for any missed visits and the proportion of visits missed. The remaining 3 definitions were based on visits that actually took place: number of 4 month intervals with at least one visit; indicator for any gaps >6 months between consecutive visits; indicator for at least 2 visits separated by 90 days in the year of study. Rates of retention in care were very different according to the definition used. Only 33% had no missed visits, 51% had at least 1 visit in all 4-month intervals, 68% had no gaps between visits >6 months and 77% satisfied

the HRSA HAB definition of retention in care. The proportion of scheduled visits that were missed most strongly predicted viral load suppression, with 3.9 fold increased odds of viral load suppression per 50% higher percentage of visits missed and an area under the ROC Curve (AUROC) of 0.69. Of the three measures that did not involve missed visits, the HRSA HAB definition was the strongest predictor of viral suppression with those retained being nearly four times as likely to have viral suppression as those not retained in care, but had the smallest AUC of 0.59 with sensitivity of 91% and specificity of 27% (313).

Whereas a traditional continuum is cross-sectional, assessing retention in care over 1 year, cohort analyses consider longer-term retention. In this situation, retention in care in care will often only be defined if individuals satisfy annual retention definitions, as described previously, for a number of years. This results in lower estimates of retention in care. This was recently demonstrated in an Infectious Disease Program in Atlanta, US which defined retention in care over 3 years only if an individual made at least 2 visits at least 90 days apart in each of the 3 years of follow-up. Whereas 84% of individuals enrolling in the programme were defined as retained in care in the first year of follow-up, only 49% were able to be classified as continuously retained in care over 3 years (314). Within the Veterans Health Administration, retention in care over 2 years was approximately 40%, with smaller variations by definition. In this study again, the lowest estimate of retention in care was given by missed visits, with 35% of individuals having attended more than three-quarters of their scheduled visits over 2 years. Only 40% of veterans had at least 2 visits separated by 60 days in each year over both years and 44% had no gaps in care >6 months. Combining the definitions of missed visits or gaps in care to define retention in care gave much lower retention in care rates of 19% (315). When considered over an 8 year period, only 49% of PLWH who attended a HIV clinic in Kentucky between 2003 and 2011 were retention in care for all years for which they were considered to be in clinical follow up according to the HRSA HAB definition, despite 83% of all 12-month intervals meeting this criteria. Similarly, only 47% of people had a visit in every 6 month interval, but 81% of 6 month intervals had a visit. The predictive ability of different definitions of retention in care over a long period of time remained low and similar to that shown by Mugavero et al., for one-year measures. However, in this analysis, which didn't consider missed visits, visit constancy was best predictor of viral suppression. Having 100% of 6 month intervals over follow-up with at least one visit meant a 4.7-fold increased odds of suppression, with an AUROC of 0.62. Those retained in care according to the HRSA HAB definition were found to be 70% more likely to have viral suppression, but the AUC for this measure was low at 0.58, where an AUC of 0.5 indicates a test no better than chance for identifying those retained in care. Having no gaps in care of more than 12 months demonstrated 83% increased odds of viral suppression had a poor AUC of 0.57 (316).

A disadvantage of the above mentioned definitions is that they assume constant visit intervals (e.g. 3 or 6 months). In practice, an individual's scheduled visits will vary as their clinical or health status changes and as standards of care change overtime. For example, someone who has started ART but is experiencing viral rebound will be scheduled for more regular visits than someone who has remained stable and suppressed on treatment for a number of years. Further, for a definition such as the HRSA HAB, individuals are required to survive for at least a year for retention to be defined. As part of the Retention an Engagement Across Care Services for HIV (REACH) study in the UK, a novel time-updated measure of retention in care was developed using data from the UK CHIC Study (317). This method is utilised in this thesis (Chapter 7) and defines anticipated visit intervals according to clinical factors at each observed attendance and defines people as retained in care or not on a month by month basis depending on their observed attendances in relation to the anticipated visit schedule.

2.4.1.2 Laboratory measures as a proxy for attendance

As most outpatient visits include measurement of the CD4 count and/or viral load, and this data is almost always readily available, many studies use the presence of laboratory monitoring as a surrogate for clinic attendance. However, a recent study of public health surveillance data in Massachusetts found that the ability of laboratory tests to correctly identify individuals that are out of care was poor. This study contacted clinics of individuals thought to be out of care according to laboratory monitoring surveillance. They found that only 37% of individuals presumed out of care were in fact not receiving care at the clinic (318). This could reflect the less detailed nature of surveillance as opposed to clinical cohort data. Laboratory monitoring has also been shown to have high sensitivity but low specificity when compared to actual clinic attendance. This means that whilst a large proportion of those truly retained in care would be identified correctly using laboratory monitoring, large numbers of people who are not truly retained in care would also be incorrectly classified as retained in care, over-estimating levels of retention. For example, in a cross-sectional study by Firth et al., when compared to two or more face-to-face outpatient visits with a HIV care provider, presence of two or more laboratory measures gave 90% sensitivity, meaning that 90% of people truly retained in care were classified as such using laboratory measures. However, amongst 40 individuals who were not truly retained in care, the specificity was only 28%, meaning that 72% were classified as retained in care according to laboratory monitoring (319).

However, other studies have reported better performance of laboratory data as a surrogate for retention in care. One study focused on a population who attended at least once for care in the first 6 months of 2010. The laboratory measure of retention was defined as having at least two tests at least 90 days apart in 2011. 'True' retention in care was defined at least one visit in each of the three subsequent 6 month periods until the end of 2011. True non-retention

in care was only defined if a face-to-face visit occurred in the second half of 2010 but no visit occurred in 2011, with the remaining individuals excluded. These more specific definitions of true retention in care and the fact that laboratory-defined retention was assessed only in 2011, may be responsible for the higher specificity of 72% which was observed. Sensitivity was still high at 92%. The area under the ROC curve (AUC) was high at 0.96, where 1 would indicate perfect agreement between laboratory and visit data (320). In another US study, whilst both sensitivity and specificity were very high (100% and 94%) using the Health Resources and Services Administration HIV/AIDS Bureau (HRSA HAB) definition of two tests at least three months apart within a year, this laboratory measure gave higher estimates of retention in care compared to clinic visits at the same frequency. Whereas 36% of newly diagnosed individuals were considered truly retained in care, laboratory measures estimated retention in care to be 40% (321). The use of this HRSA HAB measure, which doesn't account for information on visit scheduling, may be problematic when comparing laboratory and clinic visits. In recent years, certainly for the UK, there has been a move towards less frequent face-to-face clinic visits in individuals who are stable and responding well on treatment. So individuals may only attend for annual clinic visits but still be considered to be adhering to their visit schedule and therefore retained in care. Current monitoring guidelines also recommend that CD4 counts can be performed less frequently, and in those with viral suppression and who have demonstrated a maintained CD4 above 350 cells/mm^3, may not be performed at all other than in the event of viral failure or HIV-related symptoms (322). There is therefore a changing landscape of visit scheduling, in which current measures of retention in care will need to be re-assessed.

2.4.2 Estimated rates of retention in care

In the UK, retention in care is thought to be high according to national HIV surveillance data; 95% of individuals seen for care in a given year will also return to care the following year. This is the basis for estimates of retention in care in the HIV continuum of care in the UK. However, two studies considering cumulative loss to follow-up in the UK estimate that as many as 20% may become lost to care over 5 years (323, 324).

Outside of the UK, estimated rates of retention in care are hugely variable. As well as reflecting true differences in retention, this may also be explained by the denominator populations used (325), the definition of retention in care used (313), whether CD4 and viral load are used as a proxy for clinic attendance (320) and whether retention is assessed longitudinally or for a single year (316). A meta-analysis by Marks et al., of 28 studies in the US reporting on retention in care rates using different definitions over different lengths of follow-up between 1996 and 2006 reported an aggregated estimate of 59% retention in care, with individual estimates ranging from 19-92%. Estimates were lowest in the studies with longest intervals,

with data collection after 2003 and where all persons in the database were sampled as opposed to random or convenience sampling (326). Table 2.4.1 summarises retention in care rates in the US and elsewhere in studies published since this date that have presented at least two of the care continuum stages.

Table 2.4.1: Estimates of retention in care in studies reporting at least 2 stages of a (A) cross-sectional or (B) longitudinal HIV care continuum

Paper	Country	Population	Calendar year	Definition of Retention	Denominator (stage)	Retained[1]
(A) Cross-sectional						
Gardner 2011(213)	US	General	-	Review of literature	HIV infected	50%
Hall 2013(217)	US	General	2009	≥1 visit Jan-Apr	HIV infected Diagnosed	37% 45%
Kohler 2015(255)	Switzerland	General	2012	≥1 visit in year (SHCS participants) Practitioner survey (non-SHCS) Extrapolation from ART use data	HIV infected	79%
Laisaar 2016(229)	Estonia	General	2013	HRSA HAB	HIV Infected	21%
Mangal 2014(231)	US	Veterans	2012	≥1 visit to clinic 8 months prior to end of 2012	HIV Infected	73%
Raymond 2016(234)	New Zealand	General	2015	Seen in clinic in last year or on ART and in communication with regional service	HIV Infected	80%
Rosenberg 2014(261)	US	White MSM Black MSM	2009	(327)	HIV Infected	43% 24%
Zanoni 2014(263)	US	Adolescents	-	Literature Review	HIV Infected	11%
Backus 2015(328)	US	Veterans	2013	≥2 visits in each 6 month interval, ≥60 days apart	Diagnosed	77%

Paper	Country	Population	Calendar year	Definition of Retention	Denominator (stage)	Retained[1]
Dombrowski 2012(325)	US	General	2009	HRSA HAB*	Diagnosed	72%
Helleberg 2013(329)	Denmark	General	2010	≥1 visit in last 13 months	Diagnosed	88%
Horberg 2015(232)	US	General	2010 - 2012	≥2 visits >60 days apart in year	Diagnosed	78-80%
Hu 2012(330)	US	General	2009	HRSA HAB	Diagnosed	52%
Mahle Gray 20147(331)	US	General	2010	HRSA HAB*	Diagnosed	51%
Singh 2014(227)	US	MSM	2010	HRSA HAB	Diagnosed	51%
Torian 2014(332)	US	General	2006 - 2010	HRSA HAB	Diagnosed	68%
Wester 2016(333)	US	General	2013	HRSA HAB	Diagnosed	55%
Whiteside 2014(228)	US	Black	2010	HRSA HAB	Diagnosed	48%
Wiewel 2015(237)	US	General	2011	HRSA HAB*	Diagnosed	70%
Burchell 2015(334)	Canada	General	2001-2011	HRSA HAB*	Linked to care	76-80%
Doshi 2015(335)	US	Ryan White	2011	HRSA HAB	Linked to care	82%

Paper	Country	Population	Calendar year	Definition of Retention	Denominator (stage)	Retained[1]
Lagasca 2015(233)	US	Veterans	2008 - 2013	≥1 visit or VL in years	Linked to care	75-91%
Lourenco 2014(225)	Canada	General	2011	HRSA HAB	Linked to care	87%
Paz-Bailey 2014(336)	US	MSM	2008	Self-report a visit in last 6 months	Study participants	88%
Supervie 2013(216)	France	General	2010	'In care'	HIV Infected	74%
van Beckhoven 2015(337)	Belgium	General	2011	CD4/VL in 2011, of those with CD4/VL in 2010	Linked/ In care 2010	92%
(B) Longitudinal/cohort continuum						
Krentz 2014(240)	Canada	Newly diagnosed	2006-2013	≥2 visits within 12 months diagnosis	HIV infected	60%
Rowan 2014(239)	US	Newly Diagnosed	2005-2009	≥1 visit in prior 12 months at 18 months post-diagnosis ≥1 visit in prior 12 months at 60 months post-diagnosis	HIV Infected	60% 51%
Krentz 2015(230)	Canada	Newly diagnosed	2006-2013	≥2 visits within 12 months diagnosis	Diagnosed	82%
Richey 2014(338)	US	Newly diagnosed	2008-2011	HRSA HAB (2 years)	Diagnosed	32%
Gardner 2013(339)	US	Newly diagnosed	2005-2007	No gap >6 months between visits	Linked to care	44%
Levison 2017(241)	US	Newly diagnosed	2000-2012	≥1 visit in each 6 month interval, >60 days apart over 24 months	Linked to care	69%

Paper	Country	Population	Calendar year	Definition of Retention	Denominator (stage)	Retained[1]
Rebeiro 2013(340)	US & Canada	General	2000-2008	HRSA HAB	Linked to care	75%
Ulett 2009(341)	US	Newly diagnosed	2000-2005	≥1 visit in each 6 month interval over 24 months	Linked to care	59%

HRSA HAB=Health Resources and Services Administration HIV/AIDS Bureau definition (≥2 visits within a year, >90 days apart); SHCS=Swiss HIV Cohort Study; MSM=Men who have sex with men; VL=Viral load.
[1]If range is given, then estimates are given for each calendar year within the interval; first and last estimates are presented.
*Visit=CD4/VL

2.4.3 Factors associated with retention in care

2.4.3.1 Age

Studies that have investigated retention in care by age have largely found that younger adults have lower rates of retention in care (336, 342, 343). There have been few studies to consider an association between retention in care and age outside of the US. In a previous UK CHIC analysis using the REACH measure of engagement in care, those aged below 25 were 33% less likely to be engaged in care in any given month than those aged above 45 (317). In two multi-centre Canadian Studies, those aged older than 50 had a 15% increased likelihood of achieving initial retention in care compared to those aged 30-39 (344) and 6% more likely to be retained in care in any calendar year than those aged <35 (334). In a small retrospective cohort study in China, those aged younger than 50 were approximately 45% less likely than those older than 50 to have been retained in care over the last year as defined by no missed clinic visits (345).

Five studies in the US considered HRSA HAB defined retention in care in a single calendar year, four of which utilised surveillance data. Doshi et al., investigated retention in care in 2011 in the Ryan White HIV/AIDS Program, with over 276,000 people included in their analysis. Decreasing odds of retention in care were observed in younger age groups compared to those aged $\geq$65 years, with those aged between 19-24 and 25-34 being 42% less likely to be retained in care (335). Amongst over 87,000 PLWH in New York in 2010, rates of retention in care were high, ranging from 75% in those aged 20-29 to 86% in those aged $\geq$60. They saw linearly increasing prevalence rates of retention in care with increasing 10 year age groups above age 20, after adjusting for other demographic factors. Those aged between 50-59 and those aged $\geq$60 had 1.22 and 1.26 times higher prevalence rates of retention than those aged 20-29 (332). Similarly in Tennessee, adults aged 45-54 and over 55 were more than 20% as likely to be retained in care as those aged 35-44 (333). In all the above studies, whilst the youngest adult age group was least likely to be retained, adolescents were found to have better rates of retention. Hall et al., who used this adolescent age group as the reference category, did not see such strong associations between retention and care and age. Compared to those aged between 13-24, a small 6% increased odds of retention in care was found for those aged between 45-64 only (346). According to Los Angeles surveillance data, those aged 13-44 were 8% less likely to be retained in care than those aged above 44 (330).

Longitudinal assessments have similarly noted poor retention amongst young adults. The NA-ACCORD followed over 61,000 individuals between 2000 and 2008 and used the HRSA HAB measure of retention in care in each calendar year in follow-up observing a 20% decreased likelihood of incomplete retention for each ten year increment in age (340). Another multi-centre US study found people age over 50 to be 50% more likely to be retained than those

aged below 50 by the same definition over a maximum 7 years of follow-up (347). Two studies by Crawford et al. investigated the effects of type and number of comorbidities on different measures of retention in care and found that older age was associated with higher odds of retention in care, independently of the burden of comorbidities (348, 349). Other measures including proportions of visits attended (350), annual laboratory measures (351) and intervals containing visits (341, 352, 353) have been assessed with similar conclusions drawn. Yehia et al., considered 3 separate definitions of retention in care in 17,425 people who had at least one outpatient visit between 2001 and 2009 in the HIV Research Network; one of 6 month gaps in care, one of 3 month intervals containing visits and the HRSA HAB measure. Only 35% of people aged 18-29 had complete retention over all follow-up years as defined by no gaps >6 months between visits. For all measures of retention in care considered, those aged above 50 were approximately twice as likely to be retained in care as those aged below 30 (354). Those aged above 40 had a 20% decreased risk of experiencing a gap in care >6 months in an analysis of over 6000 publically insured individuals accessing care (355), whilst those aged <25 had a 40% increased risk of experiencing a gap in care >6 months compared to those aged above 45 in a single centre US study (356).

Studies that have not reported an association between age and retention in care have generally not used the HRSA HAB definition of retention in care, with three studies considering retention in the year after initial diagnosis or linkage to HIV care (241, 357, 358). Patterns of engagement in care in a newly diagnosed group of individuals may differ from the wider population of people living with diagnosed HIV and could explain why no association was seen in these studies. One of the few studies to describe retention in care in a European setting also did not report an association between age and retention in care, but found that the overall retention rate was high at 92% (337, 359). Finally, a baseline analysis of a study aimed to understand and improve engagement in care in women of colour in the US also found no association. This measure of retention in care relied on self-reported HIV care engagement level (360).

2.4.3.2 Mode of acquisition/sex

In a UK setting women have poorer retention in care than men. In the UK CHIC analysis previously mentioned, women were less likely to be engaged in care in any given month (81% months in care compared to 85% in men), although this association was attenuated after adjusting for other demographic factors including route of acquisition (317). An analysis of HIV surveillance data from England, Wales and Northern Ireland, demonstrated that women were 50% more likely be lost to care than men (323). Studies in Canada and Australia, have also reported women to be approximately 30% less likely to be retained in care (225, 344, 361).

In the US, whilst no differences are observed in the crude proportions of men and women retained in care (330, 333, 335, 340, 347, 351, 353, 357), in regression models that adjust for mode of HIV acquisition, men have lower rates of retention (333, 335, 343, 351, 353, 355), being approximately 10% less likely to be retained in care than women (330, 332, 347, 354). MSM have better engagement in care than either heterosexuals or PWID, with PWID reporting very low rates of retention in care. This is evidenced in a study of over 22,000 American PLWH in which, heterosexuals were 15% less likely than MSM to be retained according to definitions of gaps in care, quarters with a clinic visit and the HRSA HAB criteria. PWID were between 24 and 33% less likely to be retained (354). Amongst over 15,000 PLWH in Tennessee and 32,000 in Los Angeles, PWID were 16% less likely to be retained than heterosexuals and 12% less likely than MSM. Differences between MSM and heterosexuals were smaller, with MSM approximately 5% more likely to be retained in care (330, 333). Combining both sex and mode of acquisition, in a large study of over 100,000 individuals, Hall et al., found that 50% of heterosexual females were retained in care according to the HRSA HAB definition, compared to 45% of heterosexual males. Amongst PWID, 37% of males and 43% of females were retained in 2009 (347). This would also suggest that disparities exist between men and women that are masked in populations where the majority of males report MSM route of acquisition.

In the UK, MSM have better retention in care than heterosexuals or PWID as measured through the time-updated measure of engagement in care and loss to care in HIV surveillance data. PWID are most likely to disengage from care, being half as likely to be in care as MSM in any given month of follow-up (317) and twice as likely to be lost to care (323).

2.4.3.3 Ethnicity

Black ethnicity is a risk factor for poor retention in care in both the UK and US (241, 332, 335, 340, 342, 347, 354). In the UK CHIC Study, whereas those of white ethnicity were engaged in care for 86% of months, those of black African ethnicity were engaged in care for 81% of months. Those of any other specified ethnicity, of whom the majority were black Caribbean or other black ethnicity, were also less likely to be engaged in care than those of white ethnicity (317). Across England, Wales and Northern Ireland, those of black African Ethnicity were twice as likely to be lost to care (323). In the US, those of black ethnicity are between 4 and 17% less likely to be retained in care than those of white ethnicity (333, 346) according analyses of surveillance data. In 2013, Adeyemi et al. drew attention to racial disparities in engagement in care in a clinical cohort in Chicago, including nearly 5000 individuals of whom 65% were black. They found that black patients were 40% more likely to not be engaged in care in 2010 than those of white ethnicity, demonstrating large disparities in care for these ethnic groups than seen in surveillance estimates (343). This association has been shown to remain amongst sub-groups of men (362) and veterans (352).

One study by Olatosi et al. did not find those of black ethnicity to have worse engagement, but they were 18% less likely to be not in care than white individuals. In this analysis undertaken in South Carolina, nearly three quarters of the population were black. The authors speculate that white people might experience the disadvantages of being in a minority status in this setting (351). This is supported by another study that had similarly high majority of black ethnicity; 80% of the population living with HIV were black. The authors did not find that those of black ethnicity were of increased risk of being not in care. However they were at higher risk of being in transient care (353).

2.4.4 The impact of poor engagement in care on mortality

Poorer retention in HIV care correlates with poorer mortality outcomes. Different measures of EIC have been shown to be associated with a greater risk of mortality including missed visits (363), visit constancy and gaps in care (364). Amongst individuals newly diagnosed or initiating care, both Tripathi et al., and Teixeira da Silva et al., have demonstrated that failure to attend for a visit in fewer than 3 of four quarters over 2 initial years of care results in a 3-4-fold higher risk of mortality (365, 366). Similarly, two US studies, in which approximately two-thirds of individuals had missed at least one visit in the year after linking to HIV care, linked missed visits to a higher risk of mortality. A single centre study of majority black ethnicity individuals found a 2.9-fold higher risk of mortality with any missed visits (367). The Kaiser Permanente Northern California cohort, which is a larger multi-centre clinical database, found a slightly smaller increased risk with any missed visits which was 1.7-fold higher than for no missed visits (368).

Retention in care has been shown to be better in people on ART than amongst ART naïve individuals (340, 357, 364). Several studies have still reported an association between retention in care and mortality amongst people starting treatment. One of the largest such studies was conducted in a national Free ART program in China. In this study, of over 27,000 individuals, missing 1-2 or 3-5 of 5 scheduled visits in the 6 months following ART initiation was associated with 30% and 70% increased risk of mortality. In a smaller single centre study in South Africa, 2 or more missed visits in the 6 months after ART initiation was associated with at least a 2-fold higher risk of mortality. In the US, Mugavero et al., found 3 separate measures of retention in care to be independently associated with mortality over the 2 years following ART initiation. Those not retained in care were more than 2 times as likely to die during follow up as those retained in care (367). Similarly the Department of Veterans Affairs found an increasing number of quarters with a clinic visit in the first year on ART was associated with reduced risk of mortality after adjusting for CD4 count, age, HCV co-infection and comorbidity score (369). One study that did not show a strong association between retention in care and mortality was a multicentre cohort in the US, which considered, over all

clinic follow-up, a gap of 12 months without a clinic visit to be not retained; once someone had experienced a gap they were classified as not retained for the remainder of follow-up. After adjusting for time-updated measures of CD4 count, viral load and AIDS, as well as baseline factors, having experienced such a gap in care was associated with a non-significant 20% increased risk of mortality over five years. (370). This was one of the only studies so far to adjust for changing measures of HIV markers and is a possible explanation for the attenuated effect after adjustment. However, a similar measure of loss to follow-up was not associated with mortality in a smaller study of the Australian HIV Observational Database (361).

Few studies linking retention in care to mortality have been conducted in the UK setting. In a recent analysis of the UK CHIC study a time-updated measure of retention in care was used which describes the proportion of time in care that is classified as adhering to a visit schedule (317). An advantage of a time-updated measure of retention in care to assess associations with mortality, is that individuals to not need to have survived for an initial period of time in order to be able to define retention in care, which may introduce bias. Whereas previous studies excluded individuals who did not survive for the 1 or 2 years necessary to define retention in care (367-369, 371), and so may be subject to a degree of survivorship bias, this study allowed all individuals with at least one attendance to be included. The findings of this study was that higher levels of engagement in care were associated with lower rates of mortality. However, this study also found that adjusting for the most recent CD4 count attenuated any association. This indicated that an association between engagement in care and mortality might be explained by the fact that people with better engagement in care also have higher CD4 counts and are more likely to be virologically suppressed if on ART (372).

2.4.5 Terminology in this thesis

In the continuum of care, and in much of the literature, the term retention in care is used to refer to many measures of frequency of attendance for care (Section 2.4.1.1). This is a different concept from LTFU, whereby individuals cease to attend for care, or are lost to the study cohort. Engagement in care in the context of the care continuum may be referred to in the literature to more generally encompass involvement with HIV services, i.e. optimal achievement of the stages of the care continuum, regular attendance of scheduled visits and adherence to treatment. In subsequent chapters in this thesis, I intend to use this terminology differently. I will refer to measures of attendance frequency as measures of EIC, as opposed to retention. The term retention in care will instead be used to indicate the absence of LTFU. Retention in care may occur, without individuals satisfying measures of visit frequency that constitute EIC. Engagement *with* care will be used to refer more generally to involvement with HIV services.

2.5 ART uptake and use

2.5.1 Definition

The ART stage of the continuum of care indicates some level of ART use, usually in the year considered, but sometimes ever use of ART up to or including the period of study is used. Information on ART uptake utilised in continuum estimates has been obtained from prescription data, medical note review, patient report or clinician reporting (Table 2.5.1).

Prior to recent guidelines changes, ART was not recommended in all individuals but would be initiated based on criteria that included CD4 count, pregnancy, co-morbidities, disease status and considerations of patient wishes and the potential for ongoing transmission. Leakage from the continuum prior to ART initiation therefore, may have indicated non-eligibility to initiate ART, and not merely been an indicator of sub-optimal progress along the care pathway. However, failure to initiate once eligible for therapy would indicate sub-optimal care. In order to be in a position to initiate ART once eligible, individuals need to be diagnosed and linked to care before they reach the eligibility criteria for ART initiation. Further they need to be retained in care and undergo regular CD4 monitoring in order to determine eligibility. A commonly used definition of late ART initiation in the literature is initiation with a CD4 count <200 cells/mm^3, as ART initiation has been recommended in asymptomatic individuals at higher CD4 counts than this since 2008, with a recommendation to initiate by this threshold prior to this. Presence of an AIDS-defining illness is also an indicator to initiate ART. Currently, following the results of the START trial and changes to recommend immediate ART regardless of CD4 count, what constitutes late ART is less clearly defined.

2.5.2 Prevalence of (late) ART uptake

Amongst individuals accessing care in high income countries, ART use is very high (373). In 2015 in the UK, 96% of people who attended for care were receiving antiretroviral therapy (70); 83% of all PLWH in the UK. This was an increase on 2011, where only 84% of people accessing care were on ART (218) and on 2004 when 66% were in receipt of treatment (74). In recent years, there have been declines in the proportion of individuals initiating ART with a CD4 ≤200 cells/mm^3, from just over one-third in 2009 to approximately a quarter in 2013 (311, 312). This decline in late ART initiation and higher CD4 counts at ART initiation over time has also been reported in other cohorts (374, 375) and reflects changes in treatment guidelines and increasing knowledge around the potential benefits of treatment as prevention for transmission. In the UK CHIC Study, of those to start ART with a CD4 count below 200

cells/mm^3, 75% had also presented with a CD4 count below this threshold, indicating that late diagnosis is the primary reason for late ART initiation (223).

Table 2.5.1: Proportion of PLWH in receipt of ART according to continuum of care estimates

Paper	Country /population	Data source	Year	Definition ART use	Denominator	%[1]
Backus 2015(328)	US / Veterans	Veterans Affairs Clinical Case Registry	2013	Prescription fills from ≥2 ART classes	Diagnosed Retained in care	73% 94%
Beer 2014(327)	US / White MSM US / Black MSM	Medical Monitoring Project	2009	Self-report ART use	Linked to care	91% 80%
Dombrowski 2012(325)	US / General	Medical monitoring Project and population-based chart review	2009	ART prescription	Linked to care Diagnosed	65% 53%
Doshi 2015(335)	US / Ryan White	Ryan White database	2011	ART prescription	In care Diagnosed	73% 64%
Gardner 2011(213)	US / General	Literature Review	-	-	HIV infected	24%
Gourlay 2017(220)	Austria/ General	Clinical cohort	2013	Ever on ART	HIV infected	90%
	Belgium/ General	Clinical cohort				96%
	Denmark/ General	Clinical cohort				94%
	France/ General	Clinical cohort				93%
	Germany/ General	Clinical cohort				87%
	Greece/ General	Clinical cohort				82%
	Italy/ General	Clinical cohort				80%
	The Netherlands	Clinical cohort				91%
	Spain/ General	Clinical cohort				76%
	Sweden/ General	Clinical cohort				92%
	UK/ General	Clinical cohort - UK CHIC Study				82%
	Europe/ General	-				71%

Paper	Country /population	Data source	Year	Definition ART use	Denominator	%[1]
Hall 2013(217)	US / General	Medical Monitoring Project	2009	Any ART prescription in past 12 months	HIV infected	33%
Helleberg 2013(329)	Denmark / General	Danish HIV Cohort	2010	Record of current ART	Diagnosed	73%
Horberg 2015(232)	US / General	Kaiser Permanente database	2010-2012	Filled at least 90 days of ART prescription	Diagnosed	66-71%
Hsieh 2015(247)	US / General	Sero-prevelance study and cross-sectional survey	2007	Self-report ART use	HIV Infected	27%
Kirwan 2016(70)	UK / General	HIV surveillance data	2015	Clinician reported ART use	HIV Infected	83%
Kohler 2015(255)	Switzerland / General	SHCS Survey of SHCS clinicians ART prescriptions	2012	Started ART before June 2012 Survey response ART sales data	HIV Infected	71%
Krentz 2015(230)	Canada / Newly Diagnosed	Linked Surveillance and Southern Alberta clinic database	2006-2013	Any ART use	Diagnosed	75%
Lagasca 2015(233)	US / Veterans	Clinical Case Registry for HIV – Dept. of Veterans Affairs	2008-2013	Pharmacy utilisation of any ART	Diagnosed	67-84%
Laisaar 2016(229)	Estonia / General	Estonia HIV Database (clinical cohort)	2013	On ART	HIV Infected Retained in care	18% 82%
Lourenco 2014(225)	Canada / General	Linked provincial datasets	2011	$\geq$2 drug dispensations, >3 months apart	Retained in care	91%
Mangal 2014(231)	US / General	Atlanta Veterans Affairs Medical Centre database	2012	ART prescribed – chart review	HIV Infected	63%

Paper	Country /population	Data source	Year	Definition ART use	Denominator	%[1]
Okeke 2016(258)	US / White MSM US / Black MSM	National HIV Behavioural Surveillance Surveys	2004-2014	Ever (in 2004) or in last 6 months of each year (2005-2014)	Diagnosed	70-95% 29–86%
Raimondo 2017(235)	Italy / General	Infectious Disease Clinic Databases	2013	Ever use	Linked to care	96%
Raymond 2016(234)	New Zealand / General	Regional service database, hospital laboratory database	2015	Self-report current use	HIV Infected	71%
Rosenberg 2014(261)	US / White MSM US / Black MSM	CDC surveillance	2009	(327)	HIV Infected	39% 20%
Rowan 2014(239)	US / General	Denver metropolitan area surveillance	2005-2009	Chart review. 2-log drop in viral load	HIV Infected	28% 36% 72% 30%
Santos 2014(248)	US / Transwomen	Respondent driven sample testing study	2010	Self-report current ART	HIV Infected	65%
Singh 2014(227)	US / MSM	CDC surveillance, Medical Monitoring Project	2010	ART prescription	Diagnosed	50%
Supervie 2013(216)	France / General	French Hospitals Database	2010	On ART >6 months	HIV Infected	60%
van Beckhoven 2015(337)	Belgium / General	AIDS reference centres database	2011	ART prescription	Diagnosed	83%
van Sighem 2014(376)	Netherlands / General	-	2014	-	HIV Infected	64%

Paper	Country /population	Data source	Year	Definition ART use	Denominator	%[1]
Whiteside 2014(228)	US / Black ethnicity	CDC surveillance, Medical Monitoring Project	2010	ART prescription	Diagnosed	46%
Wirtz 2016(249)	Russia / MSM	Respondent driven sample cross-sectional study	2010-2013	Self-report ART use	HIV Infected	5%

MSM=Men who have sex with men; SHCS=Swiss HIV Cohort Study; CDC=Centers for Disease Control
[1]If range is given, then estimates are given for each calendar year within the interval; first and last estimates are presented.

2.5.3 Disparities in ART uptake and use

2.5.3.1 Age

In the only study to consider ART initiation in people with known dates of HIV seroconversion across Europe, each additional year older at the time of HIV infection resulted in a 20% increase in the likelihood of ART initiation (377). This study has the benefit of being independent of stage of HIV at diagnosis, but points to faster initiation of ART in older individuals. This could be due to more rapid CD4 decline with older age (305), making older people eligible to initiate ART sooner. Amongst newly diagnosed individuals, older people have again been shown to be more likely to initiate ART in the UK. Between 2002 and 2011, a higher proportion of older individuals initiated ART within 1 year of HIV diagnosis, increasing from 40% in those aged 15-24 to 56% in those aged 50 and above. However, in the same age groups 45% and 70% of people were diagnosed late respectively, meaning that more people in the older groups were eligible and in need to receive treatment (274). When considering time from HIV diagnosis or entry into care to ART initiation, therefore, comparisons between age groups should somehow account for stage of HIV disease at diagnosis to remove its effect. Some studies that have done so have still found an association with older age and increased likelihood of ART initiation (222, 274, 378, 379). However, three US studies found disparate results: one found no association between age and ART initiation in the first year of care in a small single centre study that accounted for late diagnosis and engagement in care (341); another found no association between age and time from diagnosis to ART initiation (380); another, based on surveillance data, reported that increasing age was associated with a decreased likelihood of ART initiation using a baseline time point that was the latest of diagnosis or 1st January 2007 (381).

In comparisons only amongst those eligible for treatment, there is again evidence that older people are more likely to initiate ART. An increasing likelihood of ART initiation was seen up to age 59 in ART eligible individuals in North America, with a 23% increased likelihood in those aged 50-59 over those 18-29 years old. With small numbers of PLWH aged over 60 in this study, a non-significant 13% increased risk of ART initiation was found in this group (382). In the UK CHIC Study, the likelihood of starting ART after a first recorded CD4 count <350 cells/mm^3 between 2004 and 2008 increased by 15% for each 10 year increment in age, accounting for the value of the initial CD4 count and most recent CD4 count (383). CD4-level analyses have been performed to look at the probability of starting ART within 6 months of a given CD4 count in two analyses of UK CHIC with conflicting results. CD4- level analyses are a way of removing any influence of late diagnosis, where any CD4 counts below the eligible threshold should, in theory, be followed by ART initiation. The earliest study by Stohr et al., found no association between age and ART initiation (384). However, Sethi et al., performed

a similar analysis among a different population that included only MSM under follow up in later years and found 14% increased odds of initiating ART for each 10 year increment in age (385).

There is consensus that compared to younger PLWH, older PLWH starting ART do so at a more advanced stage of HIV with lower CD4 counts, higher viral loads and more frequently having experienced AIDS events. A large European collaboration of nearly 50,000 PLWH starting ART between 1998 and 2006 observed decreasing median CD4 count with increasing age at ART initiation, with a difference of 83 cells/mm^3 in the median CD4 count at starting ART between the oldest ($\geq$60 years) and youngest (18-29 years) adults. It was also observed that over 30% of adults in different age groups over 50 had an AIDS diagnosis prior to ART initiation, compared to only 18% of those aged 18-29 (306). Both single and multi-centre studies in France that compared the characteristics of PLWH over the age of 50 to those below the age of 50 at ART initiation found the older group to have a lower median CD4 count at ART initiation (in the region of 40-60 cells/mm^3), with approximately 10% higher prevalence of ART initiation with CD4 count <200 cells/mm^3 or a previous AIDS diagnosis (309, 386). In 502 PLWH who started ART in the Toronto Hospital Immunodeficiency Clinic, 40% of people aged over 50 started their first-line ART regimen with a CD4 count <100 cells/mm^3 compared to 29% of those younger than 50, and 32% and 27% respectively started ART having already had a prior AIDS diagnosis (387). In a much larger study of multiple provinces in the same country, those aged $\geq$50 years were approximately twice as likely to initiate ART late (defined as initiation with a CD4 count ≤200 cells/mm^3) compared to those aged 18-29 (374). This is likely entirely explained by late diagnosis, with another Canadian study demonstrating consistent results for those diagnosed with a CD4 count ≤200 cells/mm^3 and no association amongst those diagnosed with a CD4 count above 200 cells/mm^3 (375). This implies that late diagnosis is the reason for later ART initiation in this setting. In the UK setting, those starting ART aged 50 and above had a median CD4 count 50 cells/mm^3 lower than for those aged below 30 (388).

2.5.3.2 Sex/mode of acquisition

Several studies report no difference in time to treatment uptake between men and women independently of mode of HIV acquisition (377-379, 381, 389) or of late ART initiation (375, 390). In the French Hospital Database, within mode of acquisition groups, excluding MSM, there was no difference in the time to ART initiation from study enrolment between men and women (391). However, in two analyses of UK CHIC data, women were shown to be more likely to initiate ART after any CD4 count (384) and were more represented amongst individuals starting treatment late who had been diagnosed late, than those diagnosed in a timely manner who initiated late or as per guidelines (223). These differences likely reflect differences between heterosexual men and women with HIV in the UK, rather than women

and MSM, as evidenced in another UK CHIC analysis in which heterosexual women had shorter time to ART initiation following a first CD4 count below 350 cells/mm^3 than heterosexual men (383). Further, amongst only heterosexuals, women were more likely to initiate ART within 1 year of diagnosis than men, despite the fact that men were more likely to be diagnosed late (274).

PWID are less likely to initiate ART after diagnosis and more likely to start ART late (391, 392). This was observed in the European cohort of people with known dates of HIV infection, with PWID 21% less likely to initiate ART over the course of HIV infection than MSM (377). This has also been shown in other European cohorts of diagnosed individuals accessing care in Spain (378) and Switzerland (393). In the US, similarly, PWID newly enrolled in HIV care (379) and eligible to start ART (382) were between 15 and 36% less likely to initiate therapy than MSM, with a study of San Francisco surveillance data showing a similar trend for heterosexuals and MSM who also inject drugs (381). Two UK CHIC analyses have demonstrated PWID are less likely to initiate ART following a CD4 <350 cells/mm^3 (383) or at any given CD4 count threshold (384). Whilst these studies adjust for stage of disease and potentially higher rates of late diagnosis in PWID, it is possible that this delayed ART initiation could instead be due to levels of EIC, which have been shown to be lower. However, in a Canadian study of people accessing care in British Columbia, PWID who were classified as retained in care in 2011 were still 50% more likely not to use ART than similarly retained MSM, suggesting that other factors may also contribute to delayed ART initiation in PWID (225).

2.5.3.3 Ethnicity

In the UK, the role of ethnicity in late ART initiation is unclear. Black African individuals are over-represented amongst those starting ART with a CD4 count below 200 cells/mm^3 due to late presentation to care (45% as opposed to 13% of timely initiators), with white individuals under-represented (38% vs. 73% in timely initiators) (223). ART initiation in the 6 months following any CD4 count, adjusted for its value, was 17% less likely amongst black and minority ethnicity MSM compared to white in one UK CHIC analysis (385), but a non-significant 18% increased likelihood of ART initiation was found in those of black ethnicity compared to white in another analysis of CD4 counts in all acquisition risk groups (384). Neither black African or black Caribbean ethnicity was associated with ART uptake in the year following diagnosis amongst heterosexual men and women in the UK (274), or with ART uptake following a CD4 <350 cells/mm^3 in the UK CHIC Study (383). In contrast, studies conducted in the US almost exclusively find that those of black or other non-white ethnicities are less likely to initiate ART (379, 381, 382, 394), with the HIV Outpatient Study also reporting lower CD4 counts at ART initiation in those of non-white ethnicity (380). This would suggest delayed initiation of ART once in care amongst people of non-white ethnicity, as opposed to late

diagnosis as a reason for late ART initiation. In a study of US military personnel, there was no difference in ART initiation for those of black ethnicity compared to white in people eligible to initiate ART according to clinical criteria, however, elective ART was less likely to occur (389).

2.5.4 The impact of ART on mortality, according to timing of initiation

Initiation of ART reduces the rate of clinical progression in PLWH regardless of the stage of HIV at initiation (395, 396). However, from early in the epidemic, observational studies have found that lower CD4 counts at the time of ART initiation are a risk factor for higher mortality (397-405). In an analysis of over 20,000 individuals who initiated ART, those with a pre-ART CD4 count between 200 and 349 cells/mm^3 were less than half as likely to die over a median 3 years of follow-up than those <25 cells/mm^3. Mortality rates in those with a pre-ART CD4 count >350 cells/mm^3 were one-third of that in the lowest CD4 strata (406). This short term difference in mortality has been extended to the longer-term through the calculation of life expectancy in recent studies, one of which was an analysis of the UK CHIC cohort. In this study of people initiating ART between 2000 and 2008, the additional years of life expected to live at age 20 for those with a CD4 count between 200 and 350 cells/mm^3 was 53, resulting in an expected age at death approximately 5 and 7 years below men and women in the general population. In contrast, those initiating ART with a CD4 count below 100 cells/mm^3 were expected to live an additional 38 years from age 20; a difference in life expectancy of 15 years compared to the higher CD4 count group (205). Estimates based on observed mortality in a Canadian cohort found that at age 20, life expectancy for people initiating ART with a CD4 count below 50 cells/mm^3 was 22, 29, 49 and 53 years for pre-ART CD4 counts of <50, 50-199, 200-349 and >350 cells/mm^3, giving expected ages at death of 44, 49, 69 and 73, respectively (407). An earlier study of people starting ART in the US using lower CD4 count thresholds observed a 9 year difference in life expectancy at age 33 between those who started with a pre-ART CD4 count below 50 cells/mm^3 and those with a CD4 above 200 cells/mm^3 (408). Compared to the general population, the excess risk of mortality is much greater in those initiating ART with lower CD4 counts. Whereas mortality rates in people starting ART with CD4 count above 200 cells/mm^3 are approximately 2 to 3 times higher than in the general population, a CD4 count below 50 cells/mm3 is associated with 9-15 times higher rates of mortality (409, 410).

Three analyses of the ART-CC cohort have considered whether the impact of lower baseline CD4 counts on mortality may diminish in the long term. The first study, including people initiating ART between 1996 and 2004, found that compared to a CD4 count >350 cells/mm^3 at ART initiation, differences in mortality rates for those with CD4 counts <50 cells/mm^3 were somewhat attenuated after 2 years on ART, but a trend to higher mortality with lower CD4 counts remained out to 6 years (411). However, more recent analyses with longer follow-up

have looked at the association between baseline CD4 count and mortality after 10 years on therapy finding no association (412). In people who initiated ART between 1996 and 1999 and who survived at least 10 years on therapy, unadjusted analyses showed an association remained between the baseline CD4 count and mortality after 10 years, but adjusting for recent CD4 counts attenuated any association. This suggests that baseline CD4 may still impact mortality in the long term but that this is explained by subsequent sup-optimal responses to ART in people with lower baseline CD4 counts (195).

Few studies have looked at cause-specific mortality, but have found a CD4 <200 cells/mm^3 to be associated with a 2.8-fold increased risk of AIDS mortality compared to >350 cells/mm^3 and a one-log increase in CD4 count to be associated with a 40% decreased risk of HIV-related mortality. Whilst a log increase in the CD4 count was not strongly associated with non-HIV related deaths in a study of 3724 ART initiators in the Netherlands, a CD4 <200 was associated with a 2-fold higher risk of non-AIDS mortality in a group of women and MSM after age 35 in the US (413, 414); possibly a reflection of different classifications of non-AIDS or non-HIV related death or different methodologies. The combined analysis of MSM in the MACS Study and women in the Women's Interagency HIV Study (WIHS) was one of the few studies to account for lead-time bias, which may occur in comparisons of CD4 count at ART initiation, as those starting with lower CD4 counts have 'unobserved' follow-up time prior to the baseline of the analysis in which they have survived from a higher CD4 count to their current lower CD4 count (415). Studies that have accounted for lead-time bias have seen no difference in results (414).

The effect of delaying antiretroviral therapy at a given CD4 count is similarly associated with increased mortality in observational studies. However many of these studies were conducted with a goal to understanding whether ART should be initiated at higher CD4 counts than 350 cells/mm^3 and so compare relatively high CD4 count thresholds. In the Swiss HIV cohort Study, asymptomatic individuals initiating ART with a CD4 above 350 cells/mm^3 between 1996 and 1999 were matched to ART-naïve individuals with a visit within one year of ART initiation date who did not initiate ART with similar CD4 counts based on age, sex, viral load and mode of HIV acquisition. Those who initiated treatment had 80% lower risk of mortality compared to those who delayed therapy (416). Palella et al., looked within CD4 strata, at mortality rates for people initiating ART in this strata or delaying to a lower CD4 strata. Whilst there was no difference in mortality with delay of ART within CD4 strata 500-750 cells/mm^3 or 350-500 cells/mm^3, individuals with a CD4 between 200-350 cells/mm^3 who initiated ART had a 70% lower mortality rates than delaying ART (417). In similar analyses in a North American cohort collaboration, Amongst individuals with ART-naïve CD4 counts in the 351-500 cells/mm^3 range, deferral of therapy was associated with a 69% increased risk of mortality, even at this high CD4 values (418). Sterne et al., accounted for lead-time bias of deferring to lower CD4

count strata by imputing AIDS and mortality events in the deferral group prior to ART initiation. With this adjustment, they similarly noted a trend to higher mortality with deferral of therapy in all CD4 strata that had a lower limit below a lower limit of 350 cells/mm^3, with significantly raised mortality in all CD4 count thresholds with a lower limits below 225 cells/mm^3 that increased with each lower strata. Delaying to a CD4 count <100 cells/mm^3 from a CD4 count between 100-199 cells/mm^3 doubled the risk of mortality (415). The impact on mortality of initiating ART with 6 months of different CD4 count thresholds between 200 and 500 cells/mm^3 was assessed in the HIV CAUSAL collaboration, which includes UK CHIC data. Observational data were used to assess the mortality associated with different ART initiation thresholds, accounting for time-dependent confounding introduced by the fact that people at higher risk of mortality (i.e. those with lower CD4 counts) are more likely to initiate ART in clinical practice. Compared to initiating at a CD4 threshold of 500 cells/mm^3, initiating at a CD4 count of 200 cells/mm^3 demonstrated a non-significant 20% higher risk of mortality, with no other differences at intermediate CD4 count thresholds. The authors claim low mortality rates in the intervening time whilst CD4 count declines from 500 cells/mm^3 to 200 cells/mm^3 and the methods employed to account for bias may explain the different findings (419). Edwards et al., performed a similar analysis, estimating 5 and 10 year cumulative incidence of mortality for 3 initiation strategies at thresholds of 500, 350 and 200 cells/mm^3, this time using g-formula to account for time-depending confounding of ART initiation. However, this study agreed with previous findings, demonstrating increased 5 and 10 year mortality rates for both the 200 and 350 cells/mm^3 CD4 thresholds compared with 500 cells/mm^3. 10-year mortality was 25% higher with a treatment strategy for initiation below CD4 counts of 200 and 8% higher for a 350 cells/mm^3 threshold (420). Although not designed to assess this problem, a sub-study of the SMART RCT, demonstrated a mortality disadvantage to delaying ART below 350 cells/mm^3.

2.6 Virological response to antiretroviral therapy

2.6.1 Definition

Achievement of viral suppression is a commonly used indication of treatment success and the final stage of the HIV continuum of care. It is a marker for clinical benefit and potentially reduced risk of onward transmission of HIV. In a continuum of care, a cut-off of 200 copies/ml is most often used to indicate suppression, although this differs from setting to setting. This is to overcome heterogeneity of viral load assay lower detection limits over time and between settings (236). In clinical care, a viral load is considered suppressed when it is below 50 copies/ml. This is the threshold that is commonly used by most assays, although in recent

years more sensitive assays have become available, and the threshold under which HIV has been shown to not be transmitted (152). In a snap-shot continuum of care, the last viral load in the calendar year of assessment is commonly used. Methods to account for those without a viral load measure are not well defined. One approach would be to exclude these individuals from the denominator. Another would be to include them and impute the value of the viral load measure, for example, to assume that it is detectable.

Whilst a traditional continuum of care gives a cross-sectional measure of virological response to treatment, over many years on treatment an individual's viral load status may change. In the literature, as in clinical practice, virological response is measured in many ways. An initial successful response to ART requires suppression of the viral load to undetectable within 24-36 weeks of ART initiation. Individuals are considered to be experiencing virological failure if the viral load does not become undetectable in this time. Following initial suppression, people may experience a loss of virologic control. The extent of this virologic rebound may be characterised as transient 'blips' in which a single low (typically defined as below 400 copies/ml), but detectable, viral load is recorded, or low-level viraemia, in which a more prolonged period of time where the viral load is low but detectable is experienced. How virological failure is defined varies, but could include 2 consecutive viral load measures above a threshold of either 200 or 400 copies/ml or a single viral load above 1,000 copies/ml. A measure not used in clinical practice but that has emerged in the literature is viraemia copy years (VCY). This measure aims to capture the total burden of HIV replication that occurs in the presence of ART. It is calculated as the area under the curve of an individual's observed viral load measures over time, with undetectable viral loads contributing null values and is expressed in copies x years per ml or $\log_{10}$copies x years per ml (421).

2.6.2 Rate of virological success

In a HIV care continuum, a large number of populations, including the UK, report viral suppression levels of over 90% among people on ART. As a proportion of all PLWH, rates of viral suppression are hugely variable, ranging from 19% to 78%. Whilst differences may represent true disparities between different settings, they are also dependent on which earlier stages are included in the continuum, the denominator used and definition of viral suppression (Table 2.6.1).

In clinical practice, the time taken to achieve initial virological response is short with a median 3-5 months reported (387, 422-425); approximately 75-90% of people initiating ART will achieve virological suppression by 6 (426) or 12 months (424, 427-431). Following suppression, 15-45% can be expected to experience viral rebound or failure (428, 432-437), with the higher estimates generally reported in earlier studies when ART regimens were less

efficacious and less well tolerated. The rate of viral failure declines with longer time on ART, from 30 /100 pyrs in first 2 years to 2 /100 pyrs after 10 years (438).

Table 2.6.1: Rates of virological response to ART

Paper	Country/population	Data source	Year	Definition Suppression[1]	Denominator	%
Backus 2015(328)	US / Veterans	Veterans Affairs Clinical Case Registry	2013	Last VL ≤200	Linked/ in VA care	65%
Beer 2014(327)	US / White MSM US / Black MSM	Medical Monitoring Project	2009	Last VL ≤200	Linked/ in care	79% 64%
Dombrowski 2012(325)	US / General	HIV surveillance, Medical Monitoring Project and chart review	2009	Last VL ≤48	Linked/in care Diagnosed	65% 53%
Doshi 2015(335)	US / Ryan White	Ryan White database	2011	Last VL ≤200 (M=F)	Linked/ in care Diagnosed	73% 64%
Gardner 2011(213)	US / Review of literature	-	-	-	HIV infected	19%
Gourlay 2017(220)	Austria / General	Clinical cohort	2013	Last VL <200 or undetectable	HIV infected	66%
	Belgium / General	Clinical cohort				66%
	Denmark / General	Clinical cohort				80%
	France / General	Clinical cohort				72%
	Germany / General	Clinical cohort				58%
	Greece / General	Clinical cohort				52%
	Italy / General	Clinical cohort				59%
	The Netherlands	Clinical cohort				70%
	Spain / General	Clinical cohort				50%
	Sweden / General	Clinical cohort				77%
	UK / General	Clinical cohort (UK CHIC)				54%
	Europe / General	-				60%

Paper	Country/population	Data source	Year	Definition Suppression[1]	Denominator	%
Hall 2013(217)	US / General	Medical Monitoring Project	2009	Most recent VL ≤200	HIV infected	25%
Helleberg 2013(329)	Denmark / General	Danish HIV Cohort Study	2010	Most recent VL ≤500	Diagnosed	70%
Horberg 2015(232)	US / General	Kaiser Permanente	2010 2011 2012	Last VL each year ≤200	Diagnosed	61% 65% 66%
Kirwan 2016(70)	UK / General	HIV surveillance data	2015	Last VL in year ≤200	HIV infected	78%
Kohler 2015(255)	Switzerland / General	SHCS Survey of SHCS clinicians	2012	Closest VL to June 2012 <200 (SHCS) Survey results non-SHCS	On ART HIV infected	96% ~68%
Krentz 2014(230)	Canada / General	Southern Alberta Clinic database	2006-2013	VL undetectable for >12 months	HIV infected	46%
Laisaar 2016(229)	Estonia / General	Estonia HIV Study	2013	Most recent VL (last 12 months) <200	HIV infected On ART	12% 70%
Lourenco 2014(225)	Canada / General	BC Centre for Excellence in HIV/AIDS	2011	>3 months undetectable in year	On ART	85%
Mangal 2014(231)	US / General	Atlanta Veterans Affairs Clinic database	2012	Last VL in year ≤200	Infected	52%
Marks 2011(439)	US / General	Literature review	-	Last VL in year ≤200	Infected	29%
Rosenberg 2014(261)	US / MSM	CDC surveillance	2009	(327)	Black HIV Infected White HIV Infected	16% 34%

Paper	Country/population	Data source	Year	Definition Suppression[1]	Denominator	%
Rowan 2014(239)	US / General	Denver metropolitan area surveillance	2005-2009	Most recent VL in last 12 months <200 (M=F) @ 18 months post-diagnosis	HIV Infected On ART	28% 72%
Singh 2014(227)	US / MSM	CDC surveillance	2010	Last VL in year <200	Diagnosed	42%
Supervie 2010(216)	France / General	French Hospital Database	2010	VL <50	HIV Infected	52%
van Beckhoven 2015(337)	Belgium / General	Belgian HIV Cohort Study	2011	Last VL <50	Diagnosed Treated	70% 83%
van Sighem 2014(376)	The Netherlands / General	-	2014	-	HIV Infected	58%
Wester 2016(333)	US / General	Tennessee HIV surveillance	2013	Last VL in year <200	Diagnosed	56%
Whiteside 2014(228)	US / Black ethnicity	CDC surveillance	2010	Last VL in year <200	Diagnosed	35%
Wiewel 2015(237)	US / General	New York City HIV surveillance	2011	VL <200 within 6 months establishment in care	Diagnosed In care	43% 74%
Wirtz 2016(249)	Russia / MSM	Respondent driven sample survey	2010-2013	Patient report undetectable	HIV Infected	3%

VL=viral load; SHCS=Swiss HIV Cohort Study; CDC=Centers for Disease Control; MSM=Men who have sex with men; BC=British Columbia
[1]Viral load given in copies/ml

2.6.3 Disparities in virological response to ART

2.6.3.1 Age

There is strong evidence of improved virological response to ART in patients of older age (379, 440). Viral load decline following ART initiation is greater on average amongst older individuals (441-443). In a large Europe-wide study of initial virological responses conducted by Sabin et al., amongst nearly 50,000 people initiating ART, a 24%, 24% and 18% increased risk of achieving viral suppression in was found in those aged 50-54, 55-59 and >60 years when compared to those aged 30-39 years (306). Several other European studies (402, 444), as well as Canadian (424, 425, 445-447) and American studies (380, 448-451) have similarly shown better initial virological response to ART with older age, with a large Canadian and US cohort collaboration including over 9000 PLWH showing very similar results to the European findings. Those aged 50-59 were 24% more likely to achieve virological suppression than those aged 18-29, whilst those aged over 60 only had a 12% increased likelihood of suppression (382). This smaller increased risk amongst the oldest individuals could be due to smaller numbers of individuals in this group or could indicate an impact of co-morbidities and potential drug-drug interactions occurring in an aging population (452).

In a UK setting, a small single centre study of people initiating EFV-based regimens found each 10 year increment in age to be associated with a 30% decrease in the risk of viral failure (435) and in the UK CHIC study with a 30% decreased risk of extensive triple-class failure (453). Other studies from non-UK setting have similarly linked older age to a lower risk of virological failure or rebound (425, 432, 437, 445, 447, 454), including an analysis of clinical trials participants (455). When considering cross-sectional measures of virological response in a continuum of care context, again older age is associated with higher probability of VL suppression (314, 333, 335, 429). Using surveillance data from over 19 US jurisdictions, Cohen et al., found that 65% of 25-34 years olds compared to 82% of over 55's retained in care were virologically suppressed, giving a prevalence ratio of 0.85 (456). Further, in a consortium of 22 HIV clinics in the US, those aged over 50 were approximately 2.5 times as likely to be suppressed in a given calendar year, after adjustment for measures of retention in care (457)

This improved virological response has been attributed to poorer adherence in younger compared to older adults (458). Studies that have accounted for adherence have found little or no remaining association between older age and virological outcomes (459, 460). Silverberg et al found that accounting for adherence levels reduced the excess likelihood of achieving viral suppression in older adults from 15% in univariable analyses to only 3% after adjustment. This study also investigated sustained virological response by considering viral failure but found little difference in risk of failure after adjustment for adherence (308). Whilst a 1% increased risk of viral suppression and 2% decrease in the risk of viral rebound was observed

per year older in ART initiators in the HOMER cohort, adjusting for adherence differences attenuated this association (461). Amongst a cohort study of PWID in Canada, younger adults were found to have lower adherence than older adults (462), but in one of two studies in this cohort, adjusting for adherence did not alter the association between age and virological response. This study used a stricter definition of viral suppression and included fewer adults (463). Tumabarello et al. also adjusted for adherence and saw no effect of age on virological suppression in univariable or multivariable analyses (464). Analyses that have adjusted for measures of engagement in care, have similarly not seen an independent effect of age on virological response (436, 465).

Studies that have not observed an association with age, even without adjustment for adherence, have often studied short-term virological response (422, 423, 431, 466, 467), considered more adherent groups (468), or compared age within demographic sub-groups (469-471).

2.6.3.2 Sex/mode of acquisition

Evidence of an association between sex and virological response to ART in the literature is not conclusive (472, 473), with the majority of studies reporting no differences between men and women in initial response (378, 423, 431, 444, 451, 474-476), viral load rebound (433, 455, 459, 461, 477-480) or continuum of care measures (235, 314, 337, 457, 481). Whilst most have relatively small sample sizes, the largest study to find no difference in initial viral response was conducted amongst over 12,000 individuals in the NA-ACCORD. This study accounted for informative censoring due to loss to follow-up. But also combined Canadian and US cohorts (466). Amongst over 7,000 people accessing care in the Bronx, New York, there were no differences in the risk of suppression or rebound between men and women (429).

In the UK, a small single-centre study in London, in which gender was the exposure of interest in people starting EFV regimens, saw no difference in time to virological failure after 24 weeks of treatment (435). A subsequent analysis of attendees at this centre, which considered all people initiating ART, found no association with initial virological response, but did find women to be at higher risk of experiencing virological rebound (224) and another larger study of this centre combined with a single centre in Germany, amongst ART initiators who maintained suppression for a year, found women were more likely to experience virological rebound (468). Similar findings were made amongst heterosexual women in a UK CHIC analysis as well as a clinical cohort in Washington, DC (440) and another a multi-cohort collaboration in Canada (445). In the UK CHIC Study no difference was found in the time taken to achieve suppression between men and women, but women appeared to experience virological rebound sooner; a difference that was attenuated in adjusted analyses. Further, these univariate differences in rates of viral rebound appeared to be explained by the inclusion of pregnant women in the

study sample (482, 483). An earlier study of the Canadian cohort collaboration that included half the number of individuals, in fact found women to be less likely to achieve an initial virological response than men but did not assess rebound (424). Amongst one Canadian province included in this study, women were both more likely to achieve suppression but also more likely to experience subsequent viral rebound (425), but in another Canadian province, women retained in care in 2011, were less likely to be classified as having viral suppression in a continuum of care than retained men (225). Weak evidence of faster time to initial response in men has been observed in some studies (446, 484). Poorer virological responses amongst women have been found in large US continuum of care studies (335, 343). Amongst over 200,000 PLWH across 19 US jurisdictions, 69% of women and 75% of men retained in care in 2010 were suppressed; giving a prevalence ration of 0.93 (456). These studies combined point towards a trend for poorer virological suppression in women, but some conflicting findings and lack of information on the large confounding factor of ART use in pregnancy in many studies mean this evidence is not strong. In continuum of care estimates generated using surveillance data in New York City and Tennessee, men were less likely to have viral suppression than women, though effect sizes were small, with only a 5% relative difference (332, 333). These were not the only studies to report poorer virological response among men, with both US (379, 437) and European studies (427, 485) reporting similar findings.

People who acquired HIV through injecting drug use have poorer virological responses to ART (332, 333, 456, 457). In a European study of seroconverters, the rate of decline of viral load after ART initiation was significantly lower for PWID than MSM (443). The Danish HV cohort study demonstrated that, at 1 year after ART initiation, 55% of those reporting IDU as their main risk for HIV acquisition had a viral load below 500 copies/ml, compared to 77% of non-IDU. This difference remained 5 years after ART initiation, with 65% of PWID and 79% of non-IDU having viral suppression (486). Several studies have similarly shown acquisition of HIV through IDU to be associated with a 15-43% decreased risk of achieving initial viral suppression in the year following ART initiation compared to MSM (379, 382, 431, 466, 487) and non-IDU (424, 447). Failure to achieve initial suppression is 1.8-2.6 times more likely amongst PWID starting ART than MSM (485, 488), and amongst people retained in care in Canada, PWID were more likely not to be virologically suppressed (225). Viral rebound after achieving suppression is between 30 and 150% more likely amongst PWID than MSM (429, 445), with the largest increased risk observed amongst people also reporting MSM exposure risk in British Columbia (447). Few studies, however, can distinguish current from ever IDU. In British Columbia, a large 70% decreased risk of initial suppression was found for current IDU, and in the Swiss HIV cohort Study, a smaller 19% decrease was found of being currently undetectable for current use compared to never. Both studies found no difference between people who formerly injected drugs and never to have injected drugs (460, 489).

2.6.3.3 Ethnicity

There are relatively few data on disparities in virological response to ART for different ethnicities in the UK, In a UK CHIC analysis, amongst people initiating ART with a routine baseline resistance test available, black African ethnicity was associated with a 15% increased likelihood of suppression but was not associated with the risk of viral rebound adjusting for viral subtype, but no other associations with ethnicity were observed (428). And amongst MSM initiating ART in the cohort, no differences were observed in time to virological suppression or having an undetectable viral load 12 months after ART initiation in black and minority ethnicities, compared to those of white ethnicity (385).

Black ethnicity is a risk factor for poorer virological response to ART in other high income countries. Initial response to ART is between 9 and 40% less likely for those of black ethnicity (380, 431, 451, 466); viral rebound 30-100% more likely (436, 437, 440, 445, 455). Measuring viral suppression according to the last recorded viral load in a calendar year, 55% of black individuals with diagnosed HIV in New York City were suppressed in 2010, compared to 65% of white people translating to an 11% decreased odds of suppression (332). Similarly measured viral suppression using surveillance data in Tennessee, and across multiple US jurisdictions have shown 14% lower odds (333) and 15% lower prevalence (456) than those of white ethnicity. Amongst Ryan White beneficiaries in 2011, a 10% lower likelihood of suppression was found (335). The MMP in the US, which combines cross-sectional surveillance and patient interview data from sampled clinics and individuals, found differences in suppression between white men and black men and women were partially but not entirely explained by adjusting for poverty, homelessness and incarceration as well as demographic and clinical factors (490). Over periods of time longer than one year, stronger associations have been observed, showing those disparities in sustained viral suppression are greater between ethnic groups (314, 457). However not all studies have observed strong evidence of a difference between black and white ethnicity (343, 382, 429). Studies that have not found an association between black ethnicity and virological response on ART are generally smaller in size (448, 459, 476, 491), were conducted in a research study that only includes women (492, 493) and two studies consider rebound in a group of individuals shown to maintain suppression (468, 494), so restrict to a group who potentially have better adherence.

2.6.4 The impact of level of viral suppression on mortality

2.6.4.1 Initial response to therapy

Several different measures of viral non-suppression on ART are associated with increased risk of mortality in PLWH, and this association appears largely independent of corresponding changes in CD4 count. The initial viral load response within 6-12 months of ART initiation has been found to be predictive of mortality in cohorts contributing to the ART-CC, but the

protective threshold of viral load that is needed to be achieved is relatively high. In an analysis that included 9,323 individuals initiating therapy in the early ART era (1998-2001), any viral load below 100,000 copies/ml at 6 months after ART initiation more than halved the risk of mortality compared to a viral load above 100,000 copies/ml. The relative mortality decrease with a viral load between 10,000 to 99,999 copies/ml was 55%, with a similar 59% decrease in those with a viral load <500 copies/ml (495). In the only analysis to formally assess cause-specific mortality, unsuppressed viral load at 12 months after ART initiation was found to be strongly associated with AIDS related mortality (HR=3.61) as well as non-AIDS infections (HR=3.26). A trend to higher risk of all other causes of mortality except suicide was observed, with significant findings for liver-related and substance abuse related deaths (496). Interestingly these causes of death are more likely to occur in PWID, who also have poorer adherence and rates of suppression, but these analyses were mutually adjusted and still saw independent effects. Other studies have suggested that viral non-suppression on ART may play a greater role in HIV/AIDS-related mortality than for non-AIDS mortality, with poorer suppression noted amongst those dying of AIDS-related causes (497).

In the Netherlands HIV cohort, ATHENA, which contributes to ART CC, 24 week viral load amongst 3,678 individuals initiating ART between 1998 and 2003 was similarly associated with mortality. Compared to a viral load below 500 copies/ml, those with a viral load above 100,000 copies/ml had nearly 4 times the risk of mortality during the study period, whereas non-significant 80 and 90% increases were observed for viral loads 500-9,999 and 10,000-99,999 copies/ml (498). Amongst individuals with a suppressed viral load at 24 weeks in the ATHENA cohort, loss of virologic control to low (median 50-400 copies/ml over episode) or high (median >400 copies/ml over episode) level viraemia was associated with 22% and 157% increased risk of mortality over maintained suppression, but this was not significant. Interestingly, raising the threshold from 400 to 1,000 copies/ml in a sensitivity analysis, the relative increase in risk of mortality due to high level viraemia increased to 253% and was significant (499). This would again suggest that it is higher levels of non-suppression on treatment that are associated with mortality outcomes.

In a US study, 24 week viral load among ART initiators was associated with a 74% increased risk of mortality per $\log_{10}$ copies/ml increase, independently of the current CD4 count (421). One other small study, not contributing to the ART-CC, was conducted in ART initiators between 1996 and 1998 attending the Johns Hopkins University clinic. Amongst these 444 individuals, failure to achieve viral suppression below 500 copies/ml at any point in the 18 months following ART initiation was shown to be associated with a 3.5-fold increased risk of mortality compared to maintained VL below this threshold. This study also considered another group, who achieved suppression below this threshold but experienced a loss of virological control to over 1,000 copies/ml over the first 18 months on ART, finding a non-significant

80% higher mortality risk (500). Similarly, in the Danish HIV cohort, ART initiators prior to 2002 were grouped according to the proportion of time spent with a suppressed viral load between 6 and 18 months after ART was initiated. An increasing probability of mortality was observed with increasing proportion of time spent with a viral load above 400 copies/ml during this initial period; 93% of individuals with maintained suppression survived 7.5 years after ART initiation, compared to 76% of those who never achieved suppression (501).

2.6.4.2 Viral load status over time on ART

Different measures of non-suppression over time on ART have been linked to higher mortality risk, including time-updated viral load (502) and viraemia copy-years. Even after experiencing virological failure, presence of an undetectable viral load below 50 copies/ml at any time on ART may as much as half the risk of mortality compared to a detectable viral load (149). This association between viral response over time on ART and mortality translates into differences in the expected age at death, evidenced in a recent analysis of the UK CHIC Study. In this study of over 21,000 individuals, a viral load >400 copies/ml at 1, 2, 3, 4 and 5 years after initiating ART was associated with a 5-7 years lower life expectancy than for a suppressed viral load, within different CD4 strata (206).

Greater viraemia copy years, over a median 4.1 years of follow-up, was associated with a 50% increase in mortality risk in the Italian Master cohort of individuals starting ART between 1998 and 2012. Using an early (before 8 months) and late (after 8 months) measure of VCY, the authors further noted minimal effect of low-level VCY after 8 months, again suggesting that low levels of viraemia do not have a meaningful impact on outcomes (503). The prognostic value of VCY and other measures of viral suppression on ART, have been compared in multiple studies. Whilst different measures were found to be independently predictive of mortality, the best marker is still unclear. Mugavero et al., combined VCY, baseline VL, 24 week VL and most recent VL in a single multivariable model adjusted for baseline demographics, and current CD4, using inverse probability weights to allow for time-varying confounding. They found only VCY remained associated with mortality of all the VL measures considered (421). Conversely, in an earlier and smaller cohort in France, combining VCY, 8 month VL and latest VL in a single multivariable model saw the association between VCY and mortality attenuated, with latest viral load was strongly associated with mortality (504). Laut et al., compared 5 measures of viral suppression: current viral load; VCY; number of consecutive months with a detectable viral load; percentage of time on ART spent suppressed; being stable on ART. Whilst higher rates of mortality were observed for current VL >10,000 copes/ml (vs 0-50), >1128 copies x year/ml (vs 0), and lower rates for >95% time on ART suppressed, all measures had poor discriminative ability, with AUROC between 0.5 and 0.6 (505).

2.7 Summary

The HIV continuum of care is a useful and widely used framework for monitoring programme performance and the potential for ongoing transmission in a given population. However, it's cross-sectional design omits certain information on patient outcomes which makes it limited for understanding the success of HIV care programmes. Alternative longitudinal methods for describing patient engagement with the same stages of HIV care pathway, that may additionally include patient outcomes, are starting to be suggested in the literature, but equally have some disadvantages. Sub-optimal care, particularly late diagnosis, poor EIC, and late ART initiation may be prevalent in certain settings, with certain demographic groups identified as being at higher risk of sub-optimal care. However, fewer data on disparities are available in the UK compared to other settings, particularly the US. It has been shown that older individuals are more likely to be diagnosed late than younger individuals, who instead may have poorer EIC and viral suppression rates. Those of black ethnicity have been shown to be more likely to have sub-optimal diagnosis, EIC, ART uptake and viral suppression, but with data largely from a US setting, in which socioeconomic status may be an important contributing factor. Once diagnosed, PWID are more likely to have sub-optimal involvement with HIV care, having poorer EIC, being less likely to start ART and lower rates of viral suppression. The measures of sub-optimal care considered have all been found to be associated with mortality outcomes, but differences in the definitions used to define such sub-optimal care can make direct comparisons difficult. Understanding the gaps in care experienced by PLWH in the UK and the mortality burden associated with this is important to improve outcomes in this population.

Chapter 3: Study population, data collection and methods

3.1 Introduction

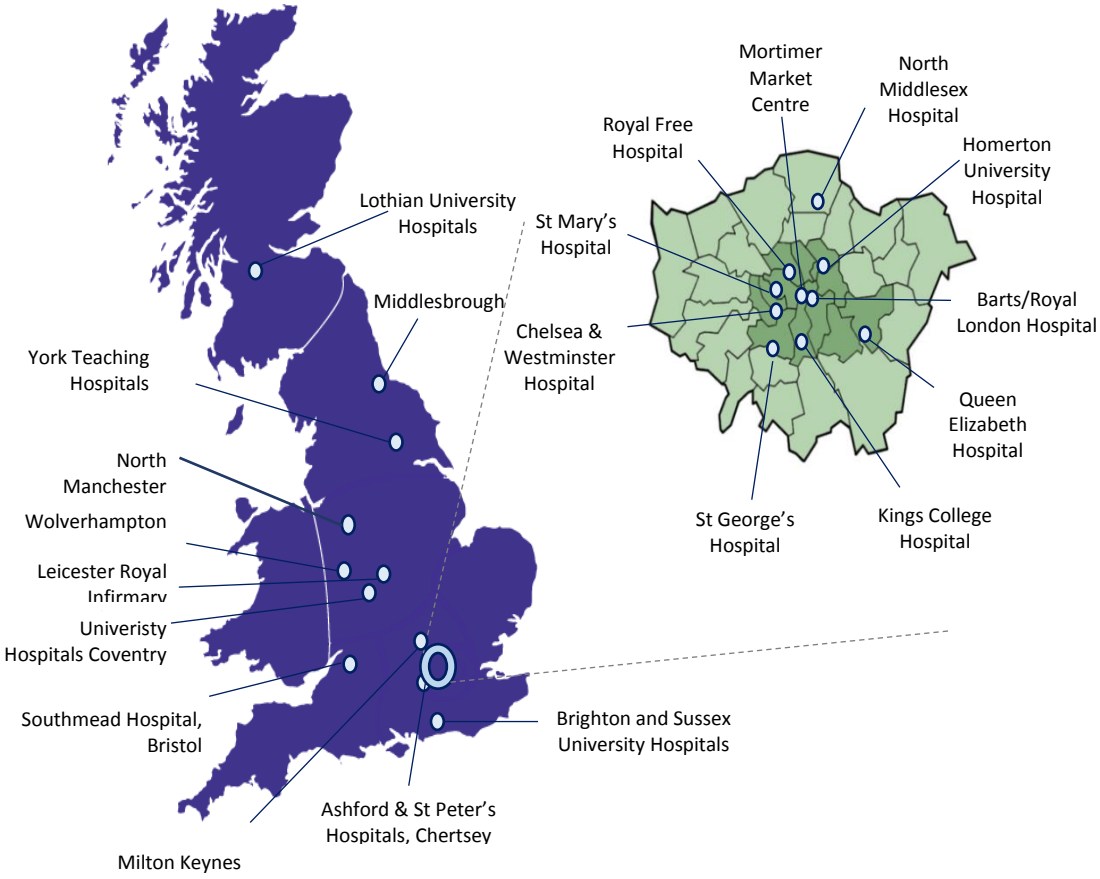
This thesis presents analyses that have been performed using data from the UK Collaborative HIV Cohort (CHIC) Study. This chapter gives a summary of the study, including methods of data collection, cleaning and preparation of datasets. Here I also describe some common statistical methods that have been used throughout the thesis.

3.2 The UK CHIC Study

The UK CHIC Study was initiated in 2001 to collate data that are routinely captured in HIV clinical care, with the initial objectives of describing the changing frequency of AIDS-defining illnesses, ART uptake and outcomes, and factors associated with virological and immunological responses to ART. Eligible participants are HIV-positive individuals aged 16 and above who have attended for care at any of the participating centres at least once since 1996. The study does not require informed consent and data from all eligible attendees at participating clinics are collected. The UK CHIC Study was approved by a multi-centre research ethics committee and local ethics committees (506).

Originally, 6 centres provided data on 13,833 individuals: Chelsea and Westminster Hospital; Kings College Hospital; Royal Free Hospital; Brighton and Sussex University Hospital; Mortimer Market Centre; and St Marys Hospital. Since then, additional HIV centres have joined the collaboration: Barts and the Royal London (2004); Edinburgh (2005); North Middlesex Hospital (2005); Homerton University Hospital (2005); Bristol (2006); Leicester (2008); Middlesbrough (2009); Woolwich (2010); St George's Hospital (2010); York (2011); Coventry (2012); Chertsey, Ashford and St Peter's (2012); Wolverhampton (2012); North Manchester (2014) and Milton Keynes (2014). The most recent dataset holds data on 59,427 HIV-positive individuals from 21 HIV centres throughout England and Scotland (Figure 3.2.1). This makes the study the largest cohort of PLWH accessing care in the country, excepting national HIV surveillance datasets, which collate minimal clinical data. The objectives of the study have also evolved over time, and now additionally include a focus on comorbidities such as HBV and HCV, pregnancy, resistance, toxicities and other adverse effects of ART (506, 507).

Figure 3.2.1: HIV clinics that participate in the UK CHIC Study



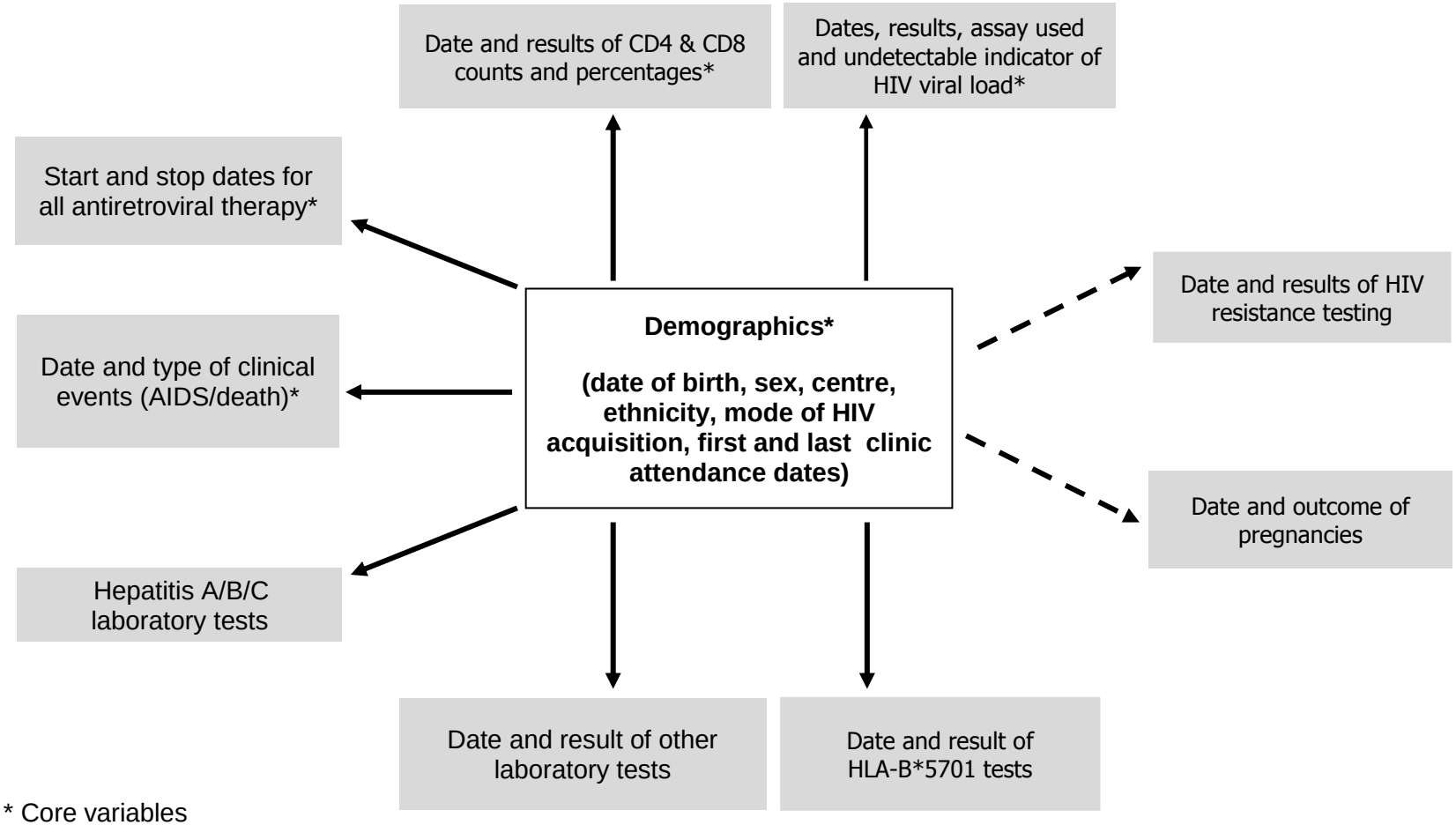
3.2.1 Data collection and checks

For each annual update, the UK CHIC Study coordinator (Teresa Hill, TH) sends out a request to all participating centres outlining the specifications for the data items requested and the required variable formats (Appendix I). As the priorities of HIV care, and therefore the UK CHIC Study objectives, have changed over time (508, 509), so the data items collected have increased. Figure 3.2.2 shows the data items available for use in analyses in the UK CHIC Study. In brief, these include: demographics; date and cause of death; ART data; CD4 and CD8 counts; viral loads; AIDS diagnoses; Hepatitis serology testing; laboratory markers of ART-related and other adverse events; HLA-B*5701 testing; attendance; and serious non-AIDS events. Although not all of the latter data items are consistently available, all participating centres are required to be able to provide at least the core data items that form the main analysis dataset, namely demographics, ART, CD4 and CD8, viral loads and clinical events. As such, certain data tables, namely serious non-AIDS events and clinic attendance, are not yet used for analysis as they are inconsistently reported. Patient identifying data

(initial, surname, soundex, clinic ID) are collected from centres for the purpose of tracking patient records through each annual upload and allowing de-duplication of records from individuals who appear more than once in the collated dataset. However, in-line with the study's data protection and ethics policies, data are pseudonymised meaning that these identifiers are removed from the dataset and each entry is allocated a unique study number (*patnum*) before the dataset is prepared and distributed to approved personnel for analysis.

The data request occurs in November of each year, with a submission deadline in December of that year. However, in recent years there have been delays of up to 9 months in data submission for some centres. Participating centres send all electronically available data at point of submission. For some centres there is a delay in making the routinely collected data available electronically, and so the information submitted does not cover the whole period of time up to the data request. Upon receipt of data from the participating centres, TH runs a set of queries to check for inconsistencies or errors in the formatting or quality of the data. Those found are returned to the appropriate centres for comment or correction. These checks ensure that all collected data items adhere to the specified formats, that dates are consistent and that all data items agreed to be submitted are received. At this stage changes are made to ART data so that co-formulated ARVs such as Atripla and Truvada are sub-divided into their component parts. For example, a record for an individual receiving Atripla becomes three separate records indicating receipt of the constituent components TDF, FTC and EFV. This is done as not all centres are able to provide information on whether drugs are taken as a co-formulation or separately. Where ART data are available only through prescription records, ARV stop dates are imputed from the date of issue. Records without at least basic demographic data (sex, ethnicity, mode of HIV acquisition) are excluded at this stage but their clinic ID, initial, soundex and allocated *patnum* is kept on record at the Medical Research Council Clinical Trials Unit (MRC CTU), where the main dataset is stored.

Figure 3.2.2: Data items available for use in analysis: the UK CHIC Study



* Core variables

– → Data obtained through record linkage with external datasets (as opposed to annual centre submissions)

3.2.2 De-duplication of records

PLWH will often attend more than one HIV clinic over the course of their HIV care. As such, a single individual may have different clinic IDs at different sites and subsequently hold multiple records. In addition, within a clinic an individual may be incorrectly allocated more than one clinic ID if they are not identified as having previously attended for care, for example, someone who has not attended for care for a long period of time might not be linked up to their old record when they re-attend, or a simple error in recording an individual's name might lead to a new record and clinic ID being created. Thus, when data from all participating centres is collated, some individuals will be represented by more than one patient record in the dataset. Therefore, it is important to identify duplicate entries and combine these patient records (510). Potential duplicate entries are initially identified by looking for matching initial, soundex and date of birth. A computerised algorithm, based on demographic and certain clinical factors is then used to decide whether these entries are a definite match, a definite non-match or an indeterminate match. Indeterminate matches are investigated further. Each indeterminate match is assessed by two independent investigators from the UK CHIC Study team. Each investigator must decide, based on the available demographic and clinical data (example Table 3.2.1), whether they believe each pair of records is, in fact, a match. Where a consensus is reached by the two investigators, the pair is linked or un-linked depending on the decision reached. Where there is no consensus, a third investigator will check the records in the same way, and if no majority decision is reached, the pair will remain as separate records in the dataset. For entries that have been highlighted as a match, meaning that separate records exist relating to a single individual, a single record is generated that combines the data from each entry.

A new study identifier is also generated for all patient records in the dataset and is referred to as the *duppatnum*. This identifier remains unchanged from the *patnum* where a record has not been linked to another. Where multiple records have been combined into a single record, *patnum* is changed to a distinguishable number that takes the form of the year that this number is generated, followed by a 5 digit unique study identifier e.g. 201100034, 2012004562.

Table 3.2.1: Hypothetical example of demographic data of duplicate records for manual review and final merged record

	Record 1	Record 2	Merged Record
Duppatnum	138	14845	201300024
Soundex:	J520	J520	J520
DOB:	01/01/1985	01/01/1985	01/01/1985
Sex	M	M	M
Ethnicity:	Black African	Unknown	Black African
Exposure:	Heterosexual	Unknown	Heterosexual
HIV-positive:	24/08/2009	-	24/08/2009
Death:	-	-	-

3.2.3 Generating the final dataset for analysis

The data collection and initial checks and de-duplication of the data take approximately one year to complete. Following the de-duplication process, clinic ID, soundex and initials removed leaving only the *duppatnum*. The data are sent to me in 14 separate text files (*patnum*, demographics, ART, CD4 and CD8, viral loads, AIDS, hepatitis serology, HLA-B*5701 tests, attendance and four sets of laboratory test results). I perform a series of checks on each data file before combining them into a final dataset for use in analyses using SAS. This dataset is named according to the year in which the *duppatnum* is generated; this will be the year following the data request. For example, the CHIC2013 dataset contains data requested at the end of 2012, with *duppatnums* indexed with the year 2013. The checks I perform are described in this sub-section

3.2.3.1 Generating the main dataset

All laboratory data, namely CD4 counts, CD8 counts, viral load measurements, HLA-B*5701 tests and hepatitis serology tests must first be de-duplicated. This process, performed in SAS, removes any test of the same date and result that have been repeated for a patient record. Similarly for AIDS diagnoses, if there is a repeat of the same diagnosis on the same date, any duplicated entries are removed. For CD4 and CD8 test results, further checks are performed for implausible and null values. Any CD4 or CD8 percentage tests with values over 100 are deleted as 100 is the maximum possible value. CD4 and CD8 tests performed on the same day with null values for all results are deleted as this indicates that the test has failed.

HIV viral load data are checked for consistency across the viral load value, lower level of detectability of the assay used and undetectable indicator value. For example, a viral load value below the known lower limit of detection of the assay used will be set to indicate an undetectable result in the undetectable indicator variable if it is missing or incorrect. Similarly, a result indicated to be undetectable with a specified assay will be given a value of the lower level of detection if this value is otherwise missing.

For ART history and all corresponding start and stop dates, the first check performed is to ensure that all stop dates occur after start dates. Where this is not the case, the start and stop dates are assumed to have been entered under the wrong headings and are swapped. This correction was decided upon since previous checking of errors of this kind with centres found that this was often the reason for such errors. I then remove any ART episodes of a given drug that are contained fully within another treatment episode of the same drug. Overlapping episodes of a given drug are also looked for and the intermediate start and stop dates removed to leave one episode spanning the whole period of the two overlapping episodes. If a drug is reportedly started and stopped on the same day, the stop date is changed to be a day later so that one day of follow-up is generated. Finally, gaps of less than 2 weeks between two successive episodes of a given drug are removed.

Birth dates, death dates, entry into the study and last seen dates are then checked for inconsistencies. Any dates of birth more than 100 years prior to the administrative censoring date of the dataset are assumed to be errors in data entry and are set as missing. A study entry date is created which takes the latest of 1st January 1996, earliest clinic attendance date in the dataset and the date at which someone turns 16. The records of those who won't turn 16 until after the administrative censoring date of the current dataset are deleted. Date of death is checked against last seen dates and the date of the last recorded CD4 count, viral load, AIDS events and drug start dates for consistency. If any of these occur after death, this list is manually checked by me and amended if there is an obvious error. Any queries that cannot be simply resolved are sent to TH, who checks against the main dataset. By this time the next data submission has taken place so TH is able to check any more recent data submitted on the individuals to confirm whether the date of death or the conflicting clinical data is correct.

Once each individual file has been cleaned, de-duplicated and a new SAS dataset created, these separate datasets are combined to create the main dataset. As a final step, if the sex, ethnicity or mode of HIV acquisition is missing for an individual, then these data points are completed using information from the previous year's dataset, where available.

3.2.3.2 Generating the toxicity dataset

In addition to the main dataset, data on laboratory testing of 29 markers of toxicity are collected. Due to differences in testing practices between centres, not all centres submit data on all of the laboratory markers requested. As UK CHIC is an observational database, tests are performed only as part of routine care and thus the frequency of testing is dependent on clinical status of the patient and the testing policies of centres. Furthermore, this information is not available from all centres. I perform the following checks. For each laboratory marker, the distribution of all test values is studied according to the unit of measurement used. Test results with implausible values for a given unit of measurement, are removed from the dataset. Where more than one unit of measurement may be used for a single laboratory marker, the most common unit of measurement is chosen and any test results not in this unit of measurement are converted wherever possible. For example, haemoglobin could be measured in g/L or g/dL. As g/dL is the chosen unit of measurement, any measures in g/L are multiplied by 10 to equal their equivalent in g/dL.

Table 3.2.2: Laboratory marker normal ranges

Laboratory marker	Normal range (511, 512)	Implausible value cut-off
ALT	5-40 U/L	>5000
AST	5-45 U/L	>5000
Albumin	34-48 g/L	>1000
Albumin (urine)	0-2.8 mg/mmol	>10000
Albumin/Creatinine ratio (ACR)	2.3 mg/mmol	-
Alkaline phosphatase	40-129 U/L (male) 35-104 U/L (female)	>5000
Amylase	28-100 U/L	>5000
Bilirubin	0-21 µmol/L	<0 or >1000
Calcium	2.1-2.6 mmol/L	>100
Cholesterol (total)	<5.0 mmol/L	>100
Cholesterol (HDL)	0.9-1.7 mmol/L	-
Cholesterol (LDL)	<4.0 mmol/L	-
Corrected calcium	2.2-2.7 mmol/L	-
Creatinine, serum	62-106 µmol/L (male) 44-80 µmol/L (female)	>3000
Creatinine phosphokinase	40-320 U/L (male) 25-200 U/L (female)	>10000
Glucose	3.0-6.0 mmol/L	>100
Gamma-glutamyl transpeptidase (GGT)	10-71 IU/L (male) 6-42 IU/L (female)	>5000
Haemoglobin	13-17 g/dL (male) 11-15 g/dL (female)	>1000
Lactate	0.7-2.1 mmol/L	-
Lactate dehydrogenase	135-255 U/L	>10000
Parathyroid hormone	1.6-6.9 pmol/L	
Phosphate	0.7-1.5 mmol/L	>100
Platelet count	150-400 $x10^9$ cells/L	>10000
Protein (Total)	60-80 g/L	-
Protein (24 hour)	<150 mg/day	>10000
Protein/Creatinine ratio (PCR)	0-45 mg/mmol	>5000
Triglycerides	<2.3 mmol/L	>100
Urea	1.7-8.3 mmol/L	>500
Vitamin D	>75 nmol/L	-

3.2.3.3 Date and cause of death

Date and cause of death are data items that are requested from participating UK CHIC sites in the annual data request, with cause of death collected as a single free-text field. However, the amount and quality of information on mortality has been believed to be incomplete in the past. As part of this thesis I have undertaken a project to improve the ascertainment of mortality data in the UK CHIC Study in recent years, which is outlined in Chapter 4.

3.2.4 HIV drug resistance data

The UK HIV Drug Resistance Database (UK HDRD) is a database containing information on routinely performed HIV drug resistance tests in the UK since 2001 (513). There are 14 participating virology laboratories who annually submit full genome sequences of all HIV resistance tests performed during the year. By the end of 2013, over 114,000 sequences were included in the database. These sequences are processed through the Stanford University Genotypic Resistance Interpretation Algorithm to generate lists of resistance mutations and drug susceptibility scores. Each year, once the pseudonomysed UK CHIC dataset has been generated for use in analyses, this dataset is linked with the UK HDRD. Records in the UK CHIC Study and UK HDRD that are believed to belong to the same individuals are identified and linked based on clinic ID. In the most recent dataset, resistance tests were available for 28,054 (51.8%) of 54,153 individuals in the UK CHIC Study.

3.2.5 National Study of HIV in Pregnancy and Childhood

In order to obtain information on pregnancies that have occurred in women in the UK CHIC Study, UK CHIC records are linked to those in the National Study of HIV in Pregnancy and Childhood (NSHPC) (514). The NSHPC receives mandatory quarterly reports from all maternity units in the UK detailing any HIV-positive pregnant women seen for care during that quarter. Information reported includes the dates of pregnancies, expected dates of delivery and the outcome, as well as information on ART, CD4 count and viral load at delivery. Details of all children born to HIV-positive mothers are also reported to the NSHPC, which includes information in the ascertained HIV status of these children. However, only data relating to HIV-positive mothers and their pregnancy are shared with the UK CHIC on an annual basis. These data are linked using an algorithm that matches patient records based on date of birth, ethnicity, CD4 count and ART.

3.3 The UK CHIC Study Population

3.3.1 Overview

In my thesis I have used the CHIC2013, CHIC2014 and CHIC2015 datasets for analyses, depending on the time at which analyses were undertaken. These datasets contain information that was requested from participating centres at the end of 2012, 2013 and 2014, respectively, with administrative censoring dates of 31st December of the corresponding year. Between the CHIC2014 and CHIC2015 datasets, two additional centres joined the study and contributed data, increasing the number of participating centres from 19 to 21. The centres attended by the largest number of patients were those primarily based in London, with over 12,000 of individuals having ever attended at the Chelsea & Westminster hospital for HIV care (Figure 3.2.2Figure 3.3.1). The demographic characteristics of the three versions of the dataset that were used are shown in Table 3.3.1 and were similar. Seventy-two percent were male, just over half were of white ethnicity, 28% were of black African ethnicity and 5% were of black Caribbean or other black ethnicity. The majority of people had acquired HIV through sex between men and 37% acquired HIV through heterosexual sex. Only 3% were reported to have acquired HIV through IDU.

Figure 3.3.1: Number of people to ever attend each centre in the CHIC2013, CHIC2014 and CHIC 2015 dataset

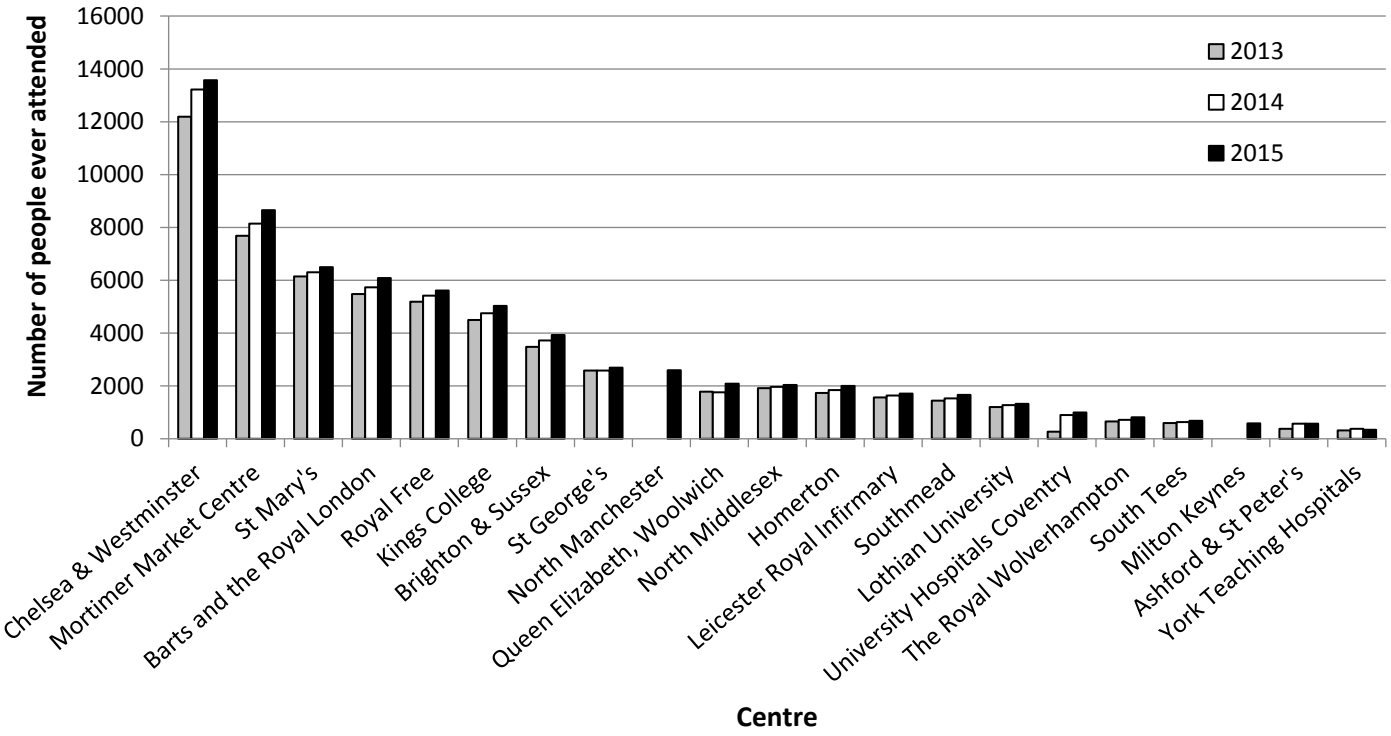


Table 3.3.1: Demographic characteristics of individuals in the CHIC2013, CHIC2014 and CHIC2015 datasets

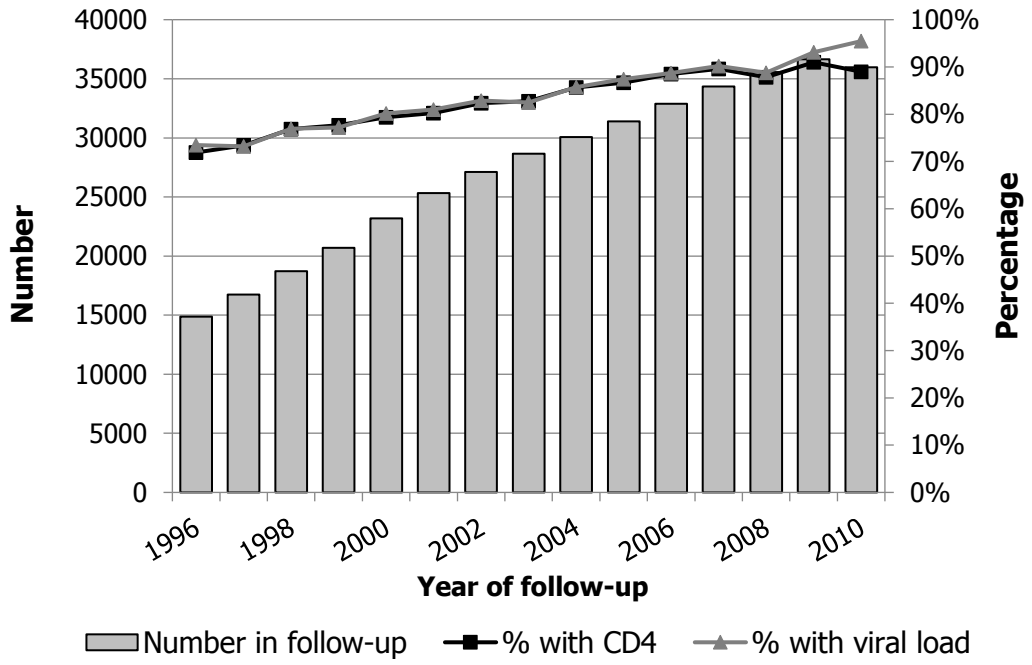
Characteristic		CHIC2013	CHIC2014	CHIC2015
N		50785	54153	59247
Age at entry	mean (SD)	36 (9.6)	36 (9.7)	35 (9.8)
Sex, n (%)	Male	36645 (72.2)	39180 (72.4)	42814 (72.3)
	Female	14134 (27.8)	14967 (27.6)	16400 (27.7)
Ethnicity, n (%)	White	26517 (52.2)	28266 (52.2)	31034 (52.4)
	Black Other	2686 (5.3)	2853 (5.3)	3208 (5.4)
	Black African	14107 (27.8)	15051 (27.8)	16502 (27.9)
	Other	4810 (9.5)	5125 (9.5)	5530 (9.3)
	Unknown	2665 (5.3)	2858 (5.3)	2973 (5.0)
Mode of HIV acquisition, n (%)	MSM	24799 (48.8)	27023 (49.9)	28778 (48.6)
	IDU	1710 (3.4)	1764 (3.3)	1874 (3.2)
	Heterosexual	18950 (37.3)	20422 (37.7)	22374 (37.8)
	Other	1861 (3.7)	850 (1.6)	1038 (1.8)
	Unknown	5326 (6.8)	4094 (7.6)	5183 (8.8)
Year of entry, n (%)	1996-1999	13670 (26.9)	13553 (25.0)	15622 (26.4)
	2000-2003	11225 (22.1)	11179 (20.6)	10682 (18.0)
	2004-2007	12437 (24.5)	12681 (23.4)	12696 (21.4)
	2008-2012	13361 (26.3)	14061 (26.0)	14398 (24.3)
	2013-2015	92 (0.2)	2679 (4.9)	5849 (9.9)

3.3.2 Follow-up and monitoring

For subsequent sections, the CHIC2015 dataset was used and individuals were classified as being in follow-up between study entry and the latest of: last clinic attendance as recorded by centres; last CD4 count; last viral load; last ART start date; death; 31st December 2014. The maximum length of follow-up was 19 years and the shortest 1 day; median (IQR) follow-up of individuals in the study was 5.6 (1.4, 11.4) years. The following results are presented from 2000 onwards, as future work in this thesis only utilises data

from this point. The number of individuals under follow-up in each calendar year increased from 14,883 in 2000 to a maximum of 35,961 in 2013. The number under follow-up decreased slightly in 2014, likely reflecting the reporting delay at some centres. The proportion under follow-up in each calendar year who had a CD4 count or viral load recorded in the corresponding year increased over time, from 71.9% and 73.5% in 2000 to 89.0% and 95.5% in 2014. As individuals receiving care in the calendar years considered should have CD4 counts or viral loads performed at least every 6 months, people classified as in follow-up but without a viral load or CD4 count in a given calendar year may have, in fact, disengaged from care but were still included as being under follow-up.

Figure 3.3.2: Number of individuals under follow-up, and proportion with recorded CD4 count and viral load result by calendar year in the CHIC2015 dataset



3.3.3 Changes over time in demographics of PLWH attending a UK CHIC participating centre for care

The demographic characteristics of the population under follow-up in each calendar year changed between 2000 and 2006, but remained relatively similar thereafter to 2014. In

2000, 79.7% of individuals under follow-up were male, declining to 72.4% in 2006 and then remaining constant, at 73.7% in 2014. Reflecting the close link between gender, mode of acquisition and ethnicity in characterising populations of PLWH in the UK, the proportion of MSM and individuals of white ethnicity similarly declined between 2000 and 2006, whereas the proportion of heterosexuals and those of black African ethnicity increased (72, 274). Corresponding proportions in 2000 and 2006 were; 60.5% and 51.9% for MSM, 66.2% and 56.2% white ethnicity, 27.5% and 38.8% heterosexual and 18.4% and 28.3% black African ethnicity (Figure 3.3.3). The proportion of IDU declined from 4.9% to 2.9% and was 2.1% in 2014.

An aging population has been observed in the UK CHIC Study as in the rest of the UK and other high-income countries (70, 376). The mean (standard deviation, SD) age, calculated at the end of each year, of individuals under follow-up increased from 37 years (8.7) in 2000 to 44 (10.8) in 2014. In 2000, only 1399 (9.4%) of individuals in follow-up were aged 50 and above, with 298 (2.0%) aged over 60. This compared to 11,364 (31.6%) individuals aged 50 and above in 2014, of whom 2985 (8.3%) were aged at least 60 (Figure 3.3.4).

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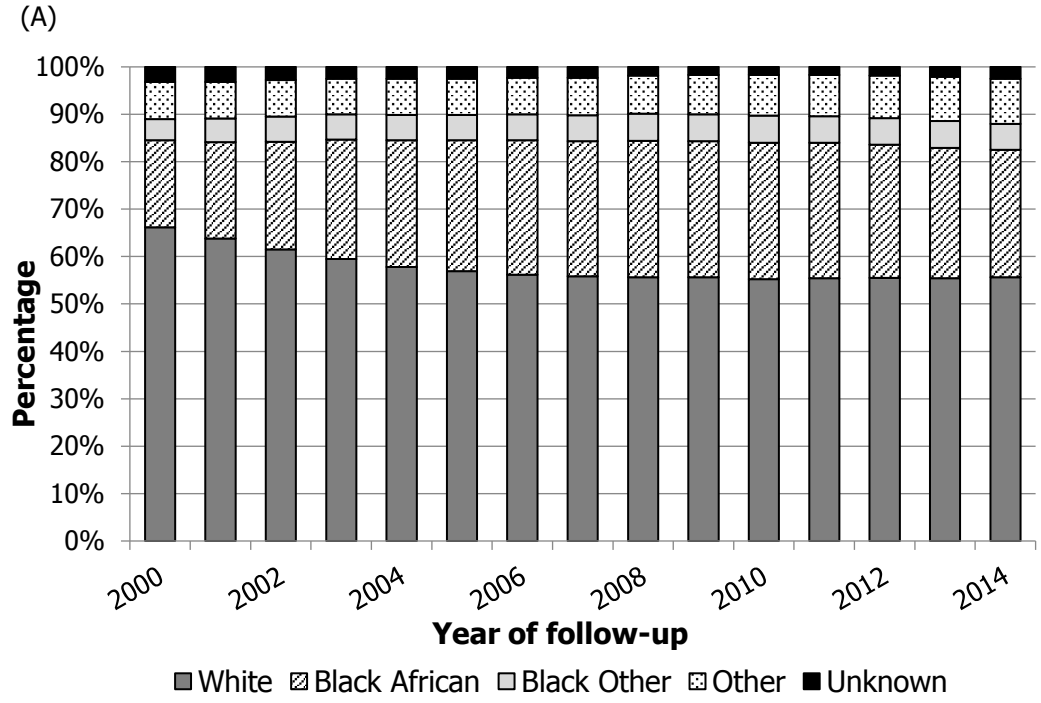
Figure 3.3.3: (A) Ethnicity and (B) Mode of acquisition of individuals under follow-up in each calendar year in the CHIC2015 dataset



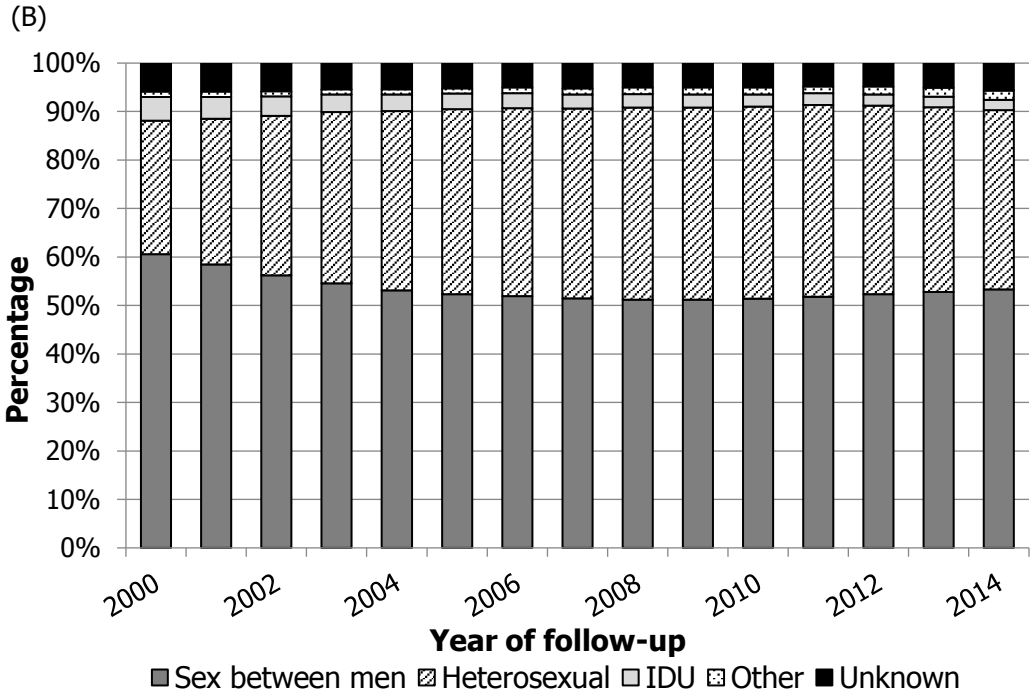
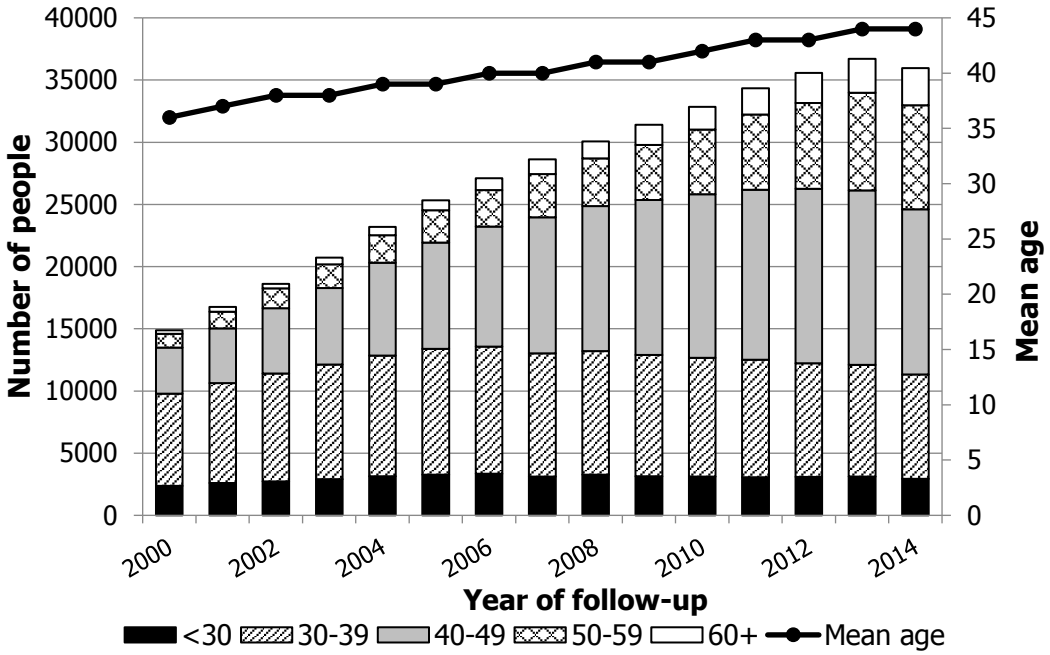


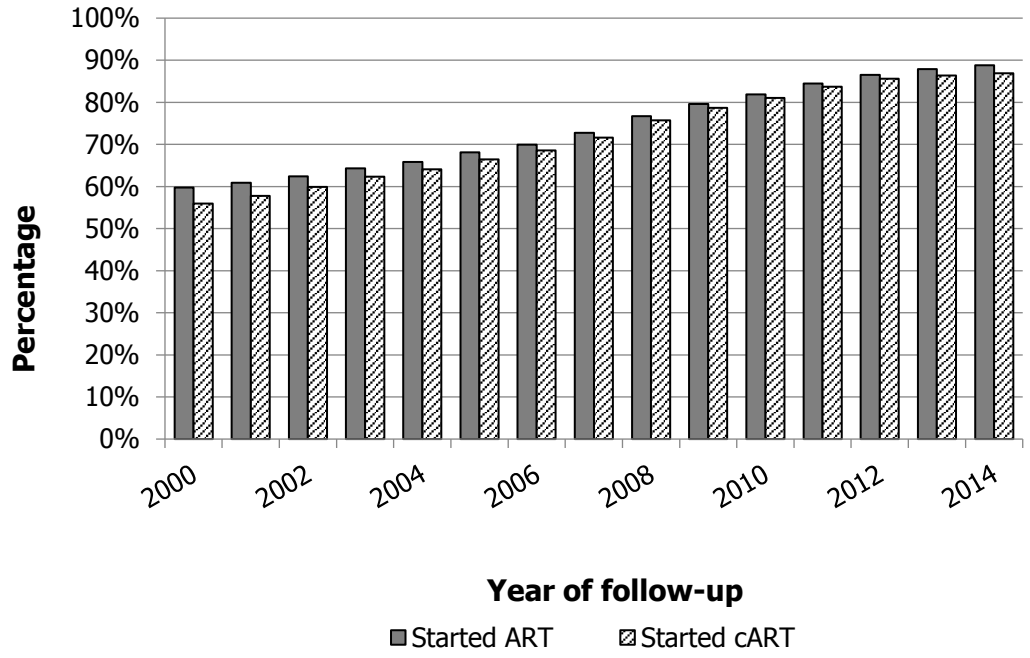
Figure 3.3.4: Age in years of individuals under follow-up in each calendar year in the CHIC2015 dataset



3.3.4 Changes over time in ART coverage

Coverage of ART increased amongst individuals in the CHIC2015 dataset after 2000. In 2000, 59.8% of individuals had started any ART and 55.9% had ever started combination ART consisting of at least 3 ARVs. By 2012, 88.8% had started ART; 86.9% had ever received a combination ART regimen.

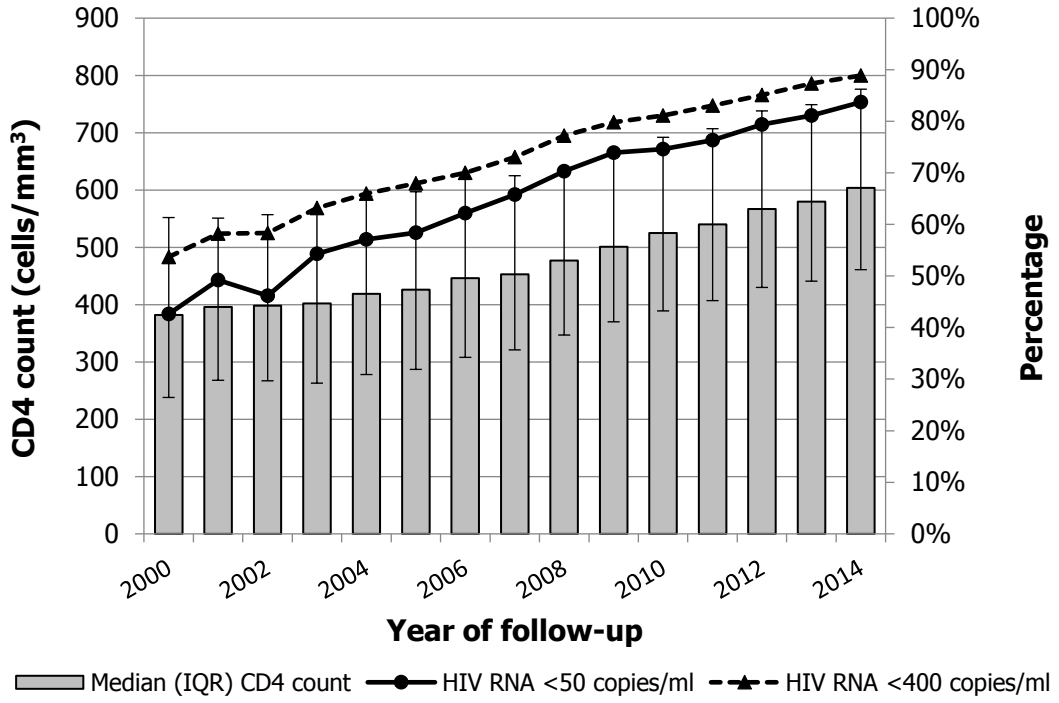
Figure 3.3.5: Percentage of individuals that had ever received any ART or combination ART by the end of each calendar year in the CHIC2015 dataset



3.3.5 CD4 count and viral load over time

Taking the latest recorded CD4 count or viral load result in a given calendar year, the median (interquartile range, IQR) CD4 count in each year increased over time, from 382 (241, 552) cells/mm^3 in 2000 to 604 (445, 791) cells/mm^3 in 2014 (Figure 3.3.6). The proportion of individuals with a viral load <50 copies/ml increased from just 42.6% in 2000 to 83.7% in 2012, reflecting greater ART coverage and more widespread use of viral load assays with a lower limit of detectability of 50 copies/ml.

Figure 3.3.6: Median (IQR) CD4 count and proportion with HIV RNA ≤50 and ≤400 copies/ml in each calendar year in the CHIC2015 dataset



3.4 Statistical Methods

Throughout my thesis, I have frequently used regression model analysis techniques to investigate the association between one or more factors (explanatory, or independent, variables) and a single outcome (dependent variable) of interest. Although the specific analyses undertaken in each chapter are outlined in detail in each chapter, in this section I describe the general concept of regression modelling. The choice of the most appropriate regression model to use for a particular analysis will depend on the statistical distribution of the outcome of interest and the data being considered.

Univariable regression is used to estimate the association of a single exposure variable with an outcome. Multivariable regression allows us to estimate, simultaneously, the effects of multiple explanatory variables on an outcome. Thus, each obtained parameter provides an estimate of the independent effect of a variable on the outcome, accounting for any potential confounding effects of other explanatory variables included in the regression model. A confounding variable is one that explains all or part of an observed association between an exposure and an outcome, and is associated with both the exposure and outcome of interest. For example, an observed association between HIV infection and lung cancer may be

explained by the fact that HIV-positive people are more likely to smoke than those without HIV (515). Here smoking is a confounding variable for the association between HIV and lung cancer. If data on the confounding variables are available, their effects can be accounted for in multivariable regression models. If information on confounding variables is not recorded, they are referred to as unmeasured confounders and cannot be adjusted for in analyses.

3.4.1 Linear Regression

Linear regression models are used when we wish to estimate the effect of one or more explanatory variables $(x_1, x_2, x_3, \ldots., x_n)$ on a single numerical outcome variable (y). Linear regression models take the form

$$\text{Mean of } y = \mu = \alpha + \beta_1 x_1 + \beta_2 x_2 + \ldots + \beta_n x_n$$

Where α is an intercept value, or the expected value of the outcome y, if the values of all explanatory variables are zero. For a quantitative explanatory variable, the corresponding regression coefficients $(\beta_1, \beta_2, \ldots \beta_n)$ represent the difference in the outcome variable as the explanatory variable increases by one unit, if all other variables remain constant. For qualitative (categorical) explanatory variables, the regression coefficient gives the mean difference in the outcome variable for each level of the categorical exposure, compared to a chosen reference group. Assumptions of linear regression models are that the outcome variable is normally distributed, has constant variance and that the relationship between explanatory variables and the outcome are linear. There is also included in the model an error term (ε_i), which represents spread of the observed values about the estimated mean. These error term values are commonly referred to as residuals, and for the main assumptions of linear regression models to be satisfied, these residuals should be independent, follow a normal distribution around a mean of zero with a constant variance, usually denoted by σ^2 (516).

The concept of linear regression can be extended to the more general family of regression models known as generalised linear models (GLMs). All GLMs take the same form, as shown in the equation below. The right hand side of the model is known as the systematic component, or linear component and describes the explanatory variables that are being considered in the model of interest. The left hand side of the model is known as the link function, and describes how the expected value (or mean) of the response μ relates to the linear combination of the covariates. In the linear regression example above, the link function was simply the identity function, and so $g(y)=\mu$. Finally there is also a random component specifying the probability distribution of the outcome variable and the form of the model's error terms (which is the Normal distribution in the case of linear regression).

$$g(y)= \alpha + \beta_1 x_1 + \beta_2 x_2 + \cdots + \beta_n x_n$$

Examples of generalised linear models include linear regression, logistic regression, log-linear models, and Poisson regression.

3.4.2 Logistic Regression

Logistic regression is typically performed in scenarios where the outcome of interest takes the form of a binary variable, for example, the presence or absence of a disease. For the binomially distributed probability (p) of the outcome event, it models the effect of a set of explanatory variables on the natural log $(\ln)$ of the odds, which are calculated as $\frac{p}{1-p}$. This is otherwise known as the logit transformation or link function. The equation of a logistic regression model is as follows:

$$\text{Log-odds } (y)= \ln\left(\frac{p}{1-p}\right) = \text{logit } (p)= \alpha + \beta_1 x_1 + \beta_2 x_2 + \ldots . \beta_n x_n$$

The logistic regression coefficients $(\beta_1,\beta_2,\ldots\beta_n)$ therefore provide an estimate of the (absolute) difference in the log-odds of the outcome associated with a one unit increase in the explanatory variable. As these coefficients are not easy to interpret, the exponential of the regression coefficients $(e^{\beta i})$ are usually presented instead as this provides an estimate of the relative change in the odds of the outcome associated with a one unit higher value in the corresponding explanatory variable, assuming all other variables remain constant. This is known as the odds ratio (OR).

3.4.3 Poisson Regression

Poisson regression models are traditionally used to model count data, with the outcome of the number of events occurring in a given interval following a Poisson distribution. However, these models may also be adapted to model the rate of an event (r). Considering the rate to be the number of events (n) that occur over a period of time (t), the Poisson regression model for rates can be expressed as:

$$\ln(r)= \ln\left(\frac{n}{t}\right)= \ln (n)-\ln (t) = \alpha + \beta_1 x_1 + \beta_2 x_2 + \ldots . . . . . + \beta_n x_n$$

and therefore

$$\ln (n)=\ln(t) + \alpha + \beta_1 x_1 + \beta_2 x_2 + \ldots . . . . . + \beta_n x_n$$

where $\ln(t)$ is the natural log of each individual's total follow-up time and is called the offset (517). As Poisson regression is performed on the natural log transformation of the rate, the regression coefficients are usually back-transformed in order to provide the impact of explanatory variables on the rate of the outcome of interest. The exponential of the regression coefficient β_i ($e^{\beta i}$) provides an estimate of the relative change in the rate of the outcome with a one unit increase in the explanatory variable, when all other variables remain constant. This is otherwise known as the relative rate or incidence rate ratio (IRR).

3.4.4 Survival Analyses

Survival analysis is a technique used to analyse censored binary outcomes in longitudinal studies. This occurs most commonly in studies with an outcome which is the time to an event occurring. It is often not possible to follow all individuals until they experience the event of interest. For example, the study might end or an individual may be lost to follow-up before the event occurs. Therefore, information about the time taken to experience the event of interest will be incomplete for some individuals; all that is known is that that they have not experienced the event by the time at which they were last under follow-up in the study. Such observations with incomplete information on time to event are referred to as censored, and statistical methods are needed which are able to take account of this censoring, as traditional methods such as linear regression cannot do so.

3.4.4.1 Survival probability and Kaplan Meier Estimates

The survival probability is the cumulative probability of remaining event-free at a given time. The Kaplan-Meier estimator is a nonparametric estimator of the survival function. For each time-point (t) at which an event occurs, the instantaneous risk of an event at that exact time is $\frac{d_t}{n_t}$ where n_t is the number of people still at risk of experiencing the event at time t (the risk-set) and d_t is the number of people that experience the event at time t. Individuals whose follow-up up is censored prior to time t are no longer considered be in the risk-set at time t. The survival probability at time t is then estimated as:

$$s_t = \frac{n_{t-} d_t}{n_t}$$

and is equal to 1 for all times where no event has occurred (517). The cumulative survival probability at a given time point is then the product of the current and all preceding survival probabilities.

$$\hat{S}(t) = \prod_{t_i<T} \frac{n_{i-} d_i}{n_i}$$

Often the inverse of the survival probability $(1 - \hat{S}(t))$ will be reported, denoting the probability of experiencing the event of interest by time t. As t increases, this probability will approach 1, as it is assumed that all individuals will experience the event if followed for long enough.

3.4.4.2 Cox Proportional Hazards models

Cox proportional hazards (CPH) models estimate the effect of one or more explanatory variables on the hazard of the outcome event of interest. This hazard at time t, denoted by $h(t)$, is the instantaneous rate of an event occurring at time t, given that it has not yet occurred by time t. The log of this hazard rate can be modelled in a regression model to explore its association with a set of n explanatory variables as follows.

$$\text{Log } [H(t)] = \log(h_o(t)) + \beta_1 x_1 + \beta_2 x_2 + \ldots \beta_n x_n$$

Similarly to the GLMs described above, $h_o(t)$ represents the baseline hazard, that is he hazard of the event at time t for the situation in which all explanatory variables take the value of zero (517). CPH models are semi-parametric models as no assumption is made as to a parametric form for the baseline hazard (518). The exponential of the regression coefficients $(e^{\beta i})$ are known as the hazard ratio (HR) for the corresponding explanatory variable x_i. For continuous explanatory variables, the hazard ratio is the relative change in hazard associated with a one unit increase in the explanatory variable when all other explanatory variables are fixed. For categorical variables it is the relative difference in hazard for a given level of the explanatory variable, compared to the reference level.

A main assumption of the CPH model is that of proportional hazards, which is to say that the hazard ratio remains constant over time. An assumption of censored data in standard survival methods is that of non-informative censoring. This means that censoring occurs independently of the outcome, and that censored individuals continue to have a similar risk of experiencing the outcome of interest after censoring to those who remain in the risk set.

3.4.4.3 Competing risks

Competing risks occur when it is possible for an individual to experience an event (or events) that will alter the likelihood of them experiencing the outcome of interest or even prevent it from happening altogether. An example of this is an outcome of interest that is a specific cause of death such as an AIDS-related death. Deaths that occur due to causes other than AIDS-defining illness are not the outcome of interest here. However, individuals may die from such non-AIDS causes, and if they do it will be impossible for them to experience an AIDS-related death, making death due to other causes a competing risk. This violates the

assumption of non-informative censoring described above, and therefore standard survival analysis techniques are no longer appropriate.

The cumulative incidence function can be used as an alternative to the Kaplan-Meier estimate in the presence of competing risks. This is the cumulative probability of experiencing the event of interest at or before time t and before the occurrence of the competing event(s) (519), and is sometimes referred to as the subdistribution incidence function. An alternative method to CPH models are Fine-Gray methods. These models are analogous to CPH regression models, but model the outcome of the subdistribution hazard, rather than the hazard, giving subdistribution hazard ratios (sHR) (520).

3.4.5 Methods for longitudinal or repeated measures data

When an outcome is measured on more than one occasion for some or all individuals, as is the case for longitudinal studies, observations are no longer independent. Two observations made in the same individual will have higher correlation than two observations made in two different individuals. This clustering must be accounted for in the methods used for analyses. The methods used in this thesis are described below.

3.4.5.1 Mixed-effects linear models

These models are an extension of linear regression models, with the outcome of interest being a continuous variable (e.g. CD4 count) that is measured on more than one occasion for each individual (521). In a mixed effects model, the effect of each explanatory variable for an individual is parameterised by fixed component, but can also include a random component. The fixed effect component gives the average effect of that explanatory variable on the outcome across individuals and may be interpreted similarly to estimates obtained from standard linear regression. The random component represents the individual variation about the fixed effect mean estimate and varies for each individual around a mean of zero. These random effects therefore are generally of less interest than fixed effects and are used only to capture the additional variability introduced through within-subject correlation.

In matrix notation, for $i = 1, 2, 3, \ldots N$ individuals with $j = 1, 2, 3, \ldots n_i$ observations per individual, a linear mixed effects model can be expressed by the following equation:

$$\mathbf{Y_i = X_i\beta + Z_iU_i + \varepsilon_i}$$

where $\mathbf{Y_i}$ is a $(n_i \times 1)$ vector of observed outcomes in individual i. The fixed element of the model is represented by the term $\mathbf{X_i\beta}$. The matrix $\mathbf{X_i}$ for person i is of size $(n_i \times p)$. It contains the values from the observed data of each of the p explanatory variables $(x_1, x_2, x_3, \ldots, x_p)$ for individual i at each $j = 1, 2, 3, \ldots n_i$ time-point. The $(p \times 1)$ vector, $\boldsymbol{\beta}$, represents regression

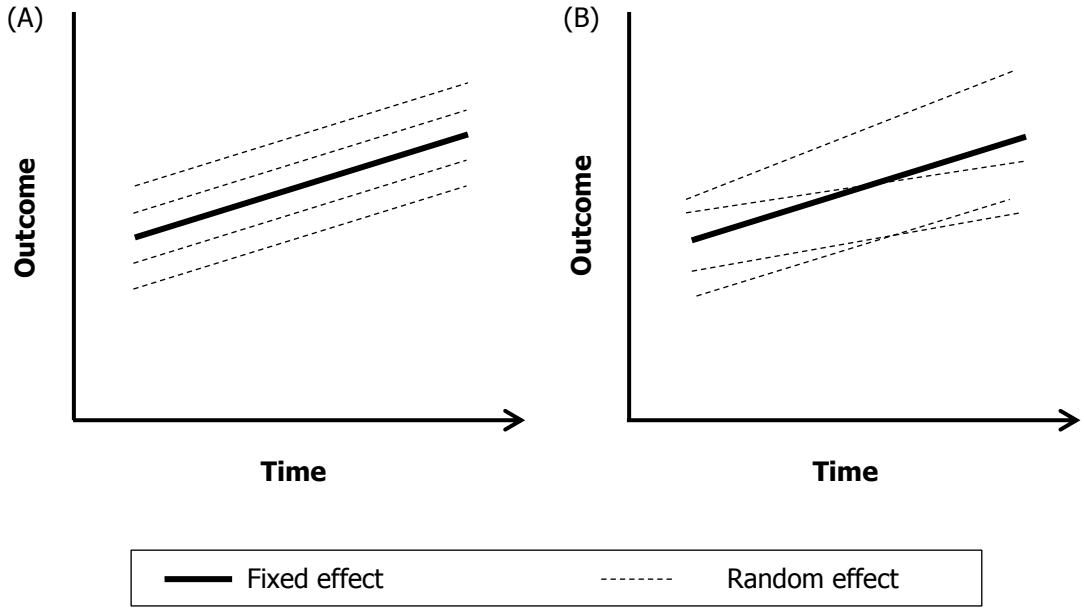
coefficients that are being estimated by the model (i.e. the $\beta_1, \beta_2, \beta_3, \ldots \beta_p$, estimates analogous with those obtained in the linear regression).

The random component of the model is represented by the two elements $\mathbf{Z_iU}$ and $\boldsymbol{\varepsilon_i}$ (522). Whilst $\boldsymbol{\varepsilon_i}$ is analogous to the error term in standard linear regression, following a normal distribution with a mean of zero and variance σ, $\mathbf{Z_iU}$ is an additional random component that represents variability, at the individual level, about the estimated fixed effect of a given variable x_k. The matrix $\mathbf{Z_i}$ is an $(n_i \times r)$ design matrix for the random effects and **U** the corresponding $(r \times 1)$ vector of unknown random effects to be estimated by the model, which follow a normal distribution with mean zero and standard deviation σ_c^2. $\boldsymbol{\varepsilon_i}$ is a $(n_i \times 1)$ vector of residual errors.

3.4.5.2 Random intercept and random slope models

A basic mixed effects model allows a random intercept term. This means that each individual is allowed to have their own intercept, which varies about the intercept of the overall mean. If we were to consider a random intercept model, we would get fixed and random effect regression lines as shown in Figure 3.4.1(A). We can see that each individual has their own regression line (dashed) with a different intercept, distributed about the fixed effect (bold). However, the effect of time is the same for all individuals, resulting in parallel regression lines. If we were to also include time as a random effect, allowing the effect of time, i.e. the slope, to vary between individuals, we would get random effect regression lines around the fixed effect regression estimate for each individual that were no longer parallel (Figure 3.4.1(B)). This is referred to as a random intercept and random slope model (523).

Figure 3.4.1: (A) Random intercept and (B) random slope mixed-effect linear models



Chapter 4: Ascertainment and classification of deaths amongst participants of the UK CHIC Study

4.1 Introduction

The study of mortality outcomes is central to understanding health outcomes within a population. Knowledge of the relative frequency of causes of death and how these may change over time can provide insight into which illnesses are of particular importance and thereby inform priorities of clinical care. By improving our understanding of the predictive factors of death, it is possible to identify the potential for interventions to improve outcomes and prevent future mortality. To reliably study mortality outcomes, it is important to have high ascertainment of accurate information on both date and cause of death.

4.1.1 Difficulties in ascertaining mortality outcomes

Ascertainment of information on date and cause of death is difficult in observational cohort studies and clinical databases. Reporting of date and cause of death in the UK CHIC Study is reliant on participating HIV outpatient clinics being aware of the death of a patient. Mortality outcomes for patients attending a particular HIV clinic for their care may be missed by that clinic for a number of reasons. Patients may be lost to follow up at a clinic, either through transferring to a different clinic for their HIV care, moving abroad, or ceasing to attend for HIV care at all. Also, place of death has changed in the ART era: in the pre- and early ART eras, PLWH were likely to die in hospital, probably on a HIV or Infectious Disease ward from illnesses related to AIDS. However, in the late ART era it is increasingly likely that people living with HIV will die in the community, either at home or in a nursing or palliative care home, for example (172, 192). Subsequently, even for patients retained in care, the care-giving clinic may not be notified of a patient's death unless the information is reported by friends or family. As a result, vital statistics received from participating centres within the UK CHIC Study are thought to be under-ascertained.

Accurate information on cause of death can similarly be difficult to obtain. A death certificate is issued for every death in the UK. This death certificate will state the conditions, illness or injuries that were believed to have been responsible for the death. They will be listed as direct, contributing or underlying causes of death depending on the role they were thought to play. There are some difficulties with using death certificates as a source of cause of death

information in observational research. Firstly, the death certificate is not always available to the HIV clinicians/clinic, or in hospital notes, particularly if the death occurred outside the hospital. If patients have moved abroad before they have died, a death certificate will not be available at all. This is thought to be fairly common in the HIV-positive population due to a relatively large proportion of the population having migrated to the UK from central and Southern Africa (324). In the absence of a death certificate, cause of death will be reported based on available information in medical records, physician reports, through information passed on by friends or family, or may not be reported at all. This information will be of varying detail and quality. Secondly, death certification itself may not be entirely accurate where an obvious cause of death is not seen. If multiple contributing illnesses are present at the time of death it may not be possible to determine which illness directly led to the death occurring. Autopsy to determine a true cause of death is only performed in certain instances, for example, where a death is unexpected and a medical cause of death is not known, or in cases where suicide is suspected. In the D:A:D study, 8% of all reported deaths had available autopsy findings (173). However, in the Swiss HIV Cohort Study, 19% of deaths occurring between 2005 and 2009 had an autopsy report; an increase from 7% in 1996. This increase likely reflected a decline in the proportion of deaths attributable to AIDS and an increase in non-AIDS deaths (172).

4.1.2 Methods to improve mortality ascertainment

At a clinic level, ascertainment of mortality can be improved through proactive tracing of individuals lost to-follow-up (524, 525). In some large HIV cohorts, linkage to national or regional mortality registries is used to obtain information on deaths (170, 171, 526, 527) as these registries contain information on all deaths occurring in a country/region. Thus, in such studies, ascertainment of deaths does not rely entirely on clinic reporting. In the UK, the Office of National Statistics (ONS) collects information on all deaths through mandatory reporting. However, linking to registries generally requires the use of patient identifying data such as date of birth, post code and/or a unique patient identity number. This can present difficulties to research studies, particularly in the field of HIV, as the sensitive nature of the data and the need to maintain confidentiality means that these personal identifiers are often not collected. In the UK, national HIV surveillance is performed by Public Health England (PHE) and collects information on date and cause of death through reporting to the HIV, AIDS and New Diagnoses Database (HANDD). Although reporting to this surveillance database is national, and is therefore not affected by patient movement between HIV clinics, it still relies largely on clinician report. Whilst HIV surveillance data can be requested for linkage to HIV clinical cohort studies, as no unique patient identifying information (such as an NHS number) is available, records can only be linked using the limited patient identifying information available.

In order to improve and standardise reporting of cause of death, the Copenhagen HIV Programme (CHIP) developed the Cause of Death (CoDe) protocol which includes a standardised case report form (CRF) and review process for reporting and establishing the date of death and immediate, contributing and underlying cause of death in HIV-positive individuals (528). This protocol has been adopted in several studies of PLWH (172, 173, 529-533), with other HIV cohorts using their own study specific death reporting forms (534, 535).

4.1.3 Classifying cause of death

It is often the goal in research to group or classify deaths as being due to a single disease or condition. A widely used coding system and algorithm for classifying all illnesses and causes of death is the International Classification of Diseases (ICD). This is a general coding system that can be used in any disease area and is frequently utilised in surveillance systems (164). However, particular issues in classifying deaths of HIV-positive individuals may make a HIV-specific system preferable. A difficulty within the field of HIV is classifying cause of death as either HIV or non-HIV related. Deaths are increasingly occurring that are not AIDS-defining, but that may still be considered to be the result of infection with HIV due to an infectious aetiology, an association with antiretroviral toxicity, or occurrence at much higher frequency and at younger ages in HIV-positive individuals than in the general population. However, it is possible that such non-AIDS deaths may not be attributed to HIV if HIV status is not known at the time of death. On the other hand, anecdotally, HIV may be reported as a cause of death in someone who has HIV, regardless of whether this was a contributing factor in the death. The CoDe protocol is a HIV-specific protocol for classifying cause of death using the HICDEP coding system which contains codes for over 30 different causes of death (528),

Different sources of data and different classification systems may have poor agreement with regards to chosen cause of death (172, 533). In 1999, the existing ICD codes (ICD-9) for selecting underlying cause of death were updated to the currently used ICD-10 coding system, which resulted in more deaths classified with HIV as an underlying cause (536). In the EuroSIDA study, which utilises the CoDe CRF, a range of algorithms based on the timing of any AIDS defining illness prior to death were developed to classify cause of death as AIDS-related or not. These classifications were then compared to the cause of death determined by a central review of data collected on the CoDe form with the best algorithm finding only moderate agreement with the CoDe cause of death (537). With a variety of different sources of cause of death information of varying quality and, in some instances, conflicting information available, classification of cause of death can be difficult and should involve a stage of independent review by multiple individuals with clinical knowledge (197, 528, 530).

4.1.4 Aims

Previous attempts to improve the ascertainment of death in the UK CHIC Study were made by contacting the lead clinician at participating centres and asking for information on new deaths not previously reported, as well as more detailed cause of death information for those that were. Unfortunately this was not successful, both due to poor response from centres and for the reasons discussed above, meaning that clinics had no other information to offer. Due to inconsistent and poor quality information on cause of death, this data has not previously been utilised in the study.

This aims of the work presented in this chapter were:

(i) To improve ascertainment of death in the UK CHIC Study through linkage with national HIV surveillance databases maintained by Public Health England (PHE).
(ii) To develop, for the first time in the UK CHIC Study, a method to classify cause of death in this and future versions of the dataset, consolidating information from four different sources.

Using the data resulting from this process, I undertook a descriptive analysis of cause-specific mortality rates in the UK CHIC population.

4.2 Data sources

For this chapter, I used data obtained from the four different data sources outlined below.

4.2.1 UK CHIC data collection

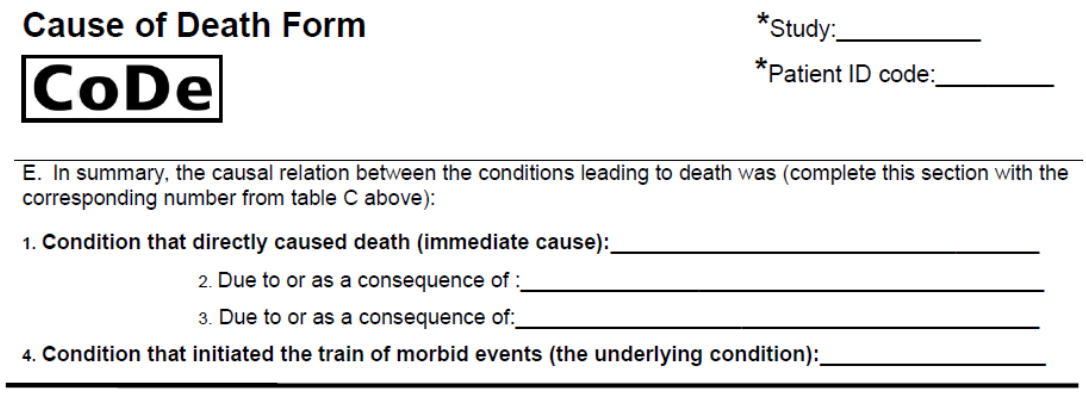
As discussed in Chapter 3, the date and cause of death are routinely collected from participating centres in the UK CHIC Study. Cause of death is collected as a single free text field, so the quality of the information provided is variable. The data included in the CHIC2013 dataset was requested from centres in November 2012. The administrative censoring date of this dataset is 31st December 2012, however, data may be available as late as August 2013 from certain centres, due to late submission of their data.

4.2.2 CoDe Forms

The use of CoDe forms was implemented as a means of collecting more detailed and standardised information in the UK CHIC Study in 2009. Participating centres were asked to

complete and return paper CoDe forms for any deaths from 2004 of which they were aware. These forms are generally sent in batches on an ad-hoc basis. In brief, the CoDe form is a case report form (CRF) consisting of 8 sections (Appendix II). As well as a section on cause of death, other information collected includes date of death and basic demographics, risk factors, comorbidities, ART status and HIV markers at time of death, autopsy findings (if applicable) and any potential role of medical treatment received. Information on cause of death is collected as direct, contributing and underlying causes (Figure 4.2.1).

Figure 4.2.1: Cause of death information collected on CoDe form



Cause of Death Form

CoDe

*Study:_____

*Patient ID code:_____

E. In summary, the causal relation between the conditions leading to death was (complete this section with the corresponding number from table C above):

1. **Condition that directly caused death (immediate cause):**_____
2. Due to or as a consequence of :_____
3. Due to or as a consequence of:_____
4. **Condition that initiated the train of morbid events (the underlying condition):**_____

Although these forms have been completed since 2006, they were not used in the dataset until the CHIC2013 dataset. When centres completed the forms and returned them to TH at the MRC CTU, their own clinic ID was used as a means of identifying individuals. To facilitate the CoDe forms being used in the finalised UK CHIC dataset, it was first necessary to identify the correct *patnum* for each recorded death and ensure it was noted on the form. Next, it was necessary for the information on the paper forms to be made available in electronic format. Date of death was recorded straight from the form into the main UK CHIC dataset stored at the MRC CTU. I created a Microsoft Access database on which the information on cause of death could be entered (Appendix III). As the database was to be held and maintained at UCL, clinic ID had to be removed from the CoDe forms before they could be released to me for data entry. This was done manually at the MRC CTU by myself and TH. The database was created to have a front form for data entry that resembled the sections and fields on the CoDe CRF form. TH and I then transcribed the information from the back-log of paper forms to the database over a series of months in 2013. From this point forwards,

the forms are entered onto the database on an ongoing basis, as and when they are received, by myself and TH.

4.2.3 Office of National Statistics mortality registry

In 2010, it was possible to perform a one-off linkage between UK CHIC records and ONS mortality data. At this time the MRC CTU had access to this ONS dataset, with permission to perform linkages with any other datasets held at MRC CTU. TH performed a linkage between UK CHIC and ONS mortality registry data to obtain information on date and cause of death for all deaths occurring between 2001 and 2008. Patient records in UK CHIC and the mortality registry were matched based upon date of birth, soundex, sex and clinic ID. In total, 424 patient records were matched using this method. Cause of death information from this source was available as up to 6 text fields and up to 6 corresponding ICD-9 codes.

4.2.4 HANDD database

HANDD is collated by PHE and contains data on all new HIV diagnoses, AIDS events and death in adults aged greater than 15 with HIV infection. Data on new HIV diagnoses are submitted from laboratories and genito-urinary medicine clinics across England, Wales and Northern Ireland. HIV clinicians supply data on new AIDS diagnoses and death as well as new HIV diagnoses. As well as surveillance reporting from clinicians and laboratories as outlined above, information on date and cause of death in HANDD is also supplemented through provision of mortality data collected by the ONS mortality registry for all deaths occurring under the age of 65 since 1999 and AIDS-related deaths occurring over the age of 65. Therefore, the information on deaths in HANDD is thought to be near-complete under the age of 65. Information on all deaths over the age of 65 are not provided due to the large number of deaths occurring above this age that would make linkage to this data inaccurate. The linkage to ONS data is performed by investigators at PHE based on pseudo-anonymised identifying data items (189). Cause of death information from ONS is provided in the form of up to 6 text fields and their corresponding ICD10 codes. The combined information on death in HANDD from both ONS and clinician report is referred to as HANDD data for the remainder of this chapter.

The Survey of Prevalent HIV Infections Diagnosed (SOPHID), initiated in 1995, contains data on all HIV-positive individuals aged 15 or older accessing care in in the UK. Every year a cross-sectional survey is completed and submitted to PHE by NHS HIV clinical centres across England, Wales and Northern Ireland. The survey is completed twice yearly by centres in London. Separate data on HIV-positive individuals accessing care in Scotland are obtained from Public Health Scotland (PHS). Data items collected are initial and soundex code, clinic

identification code, date of birth, Primary Care Trust of residence, postcode, site of care, route of probable HIV infection, clinical stage of HIV infection, date of most recent AIDS event, ethnicity, current ART use, first ART start date, most recent CD4 cell count, most recent viral load, date of most recent viral load, previous care at another site, first HIV positive test or date first seen at site, date last seen in survey year or date of death if in survey year. As this database includes all individuals accessing care, all participants in the UK CHIC Study should also be present in SOPHID.

Independent linkage of CHIC records to SOPHID and HANDD is performed, with records in SOPHID and HANDD also routinely linked internally by investigators at PHE. Whilst I will not be using information from SOPHID to supplement information on deaths in UK CHIC, the three-way linkage between UK CHIC, SOPHID and HANDD is used in certain instances to identify a match between a UK CHIC and HANDD record (Table 4.3.1).

4.2.5 Consolidating the data

Information on date, but not cause, of death from the one-off ONS linkage and upon receipt of CoDe forms is imported straight into the database held at MRC CTU, so that the final dataset for analysis includes date of death data from the annual data upload, ONS linkage and CoDe forms. The next sections of this chapter outline how this is further supplemented through linkage to HANDD. Prior to the CHIC2013 dataset, information on cause of death was not utilised at all in the UK CHIC Study.

4.3 Methods

4.3.1 Data Linkage

Whilst data linkage is performed between UK CHIC and both HANDD and SOPHID, it is the linkage to HANDD that is of focus in this chapter as this dataset collects information on death. In order to match all patient records from the two data sources with 100% accuracy, a common and unique patient identifier which is present in both datasets is required. A good example of such an identifier would be NHS number. However, no such unique and common identifier exists in both UK CHIC and HANDD, so it was necessary to link patient records using deterministic linkage, based on the identifiable information available in both datasets. The data fields available in both datasets on which the linkage was based were clinic ID, soundex, date of birth, sex and centre. Clinic ID is the patient identifier assigned to each patient record at the centre they attended. The benefit of using clinic ID to link records is that within each

centre an individual's clinic number will be unique. However, individuals who attend multiple centres will have a different clinic ID assigned by each centre, so linking records from different centres is not possible based on clinic ID alone. Soundex is a coding system that converts surnames into a string of letters and numbers. Soundex codes are not unique to a given surname and different surnames can generate the same soundex code if they are similarly spelled. However, when also combined with date of birth and sex, the potential uniqueness of this combination of information increases substantially.

The linkage was performed to try and match all patient records in UK CHIC to a record in HANDD, but only records for which there was a date of death in either database were of interest here. The linkage process to match UK CHIC patient records to SOPHID and HANDD patient records was performed by PHE, who also have internal processes in place that link patient records in SOPHID and HANDD. This means that after the independent linkages were run between UK CHIC and HANDD records and UK CHIC and SOPHID records, if a patient record in UK CHIC was linked only to a SOPHID record, the internal SOPHID-HANDD linkage table was used to complete gaps wherever possible. I provided the following data items from the UK CHIC dataset to PHE in order for the linkage to be performed; *duppatnum*, date of birth, sex, last date seen at a UK CHIC centre and all centre attendance dates. Clinic ID and soundex were provided by TH as these data items are not kept in the dataset held by me at UCL.

The agreement rules used in the deterministic linkage are shown in Table 4.3.1, along with the associated linkage score. These rules were defined by PHE, according to the linkage algorithm used. The agreement rule shows the minimum fields on which a record from HANDD and a record from UK CHIC must agree in order to be deemed a link. The strongest linkage showed an agreement on soundex, date of birth and sex between the two patient records and was allocated a matching score of 1. The weakest linkage was a link between a UK CHIC and a HANDD record that was based only upon the internal linkage available between SOPHID and HANDD, so was only linked via the SOPHID record.

The linkage was performed after I had completed the final checks on the CHIC2013 dataset, immediately prior to it being made available for use in analyses (Section 3.2.3.1). Once the linkage had been performed, a dataset was returned to me which contained the data items as listed in Table 4.3.2 for each linked pair of patient records.

Table 4.3.1: Linkage scores in linkage of UK CHIC to HANDD/SOPHID

Agreement Rule	Score
Soundex, date of birth, sex	1
Clinic number, site	2
First 3 characters of soundex, date of birth, site	3
From HANDD-SOPHID internal linkage	4

4.3.1.1 Initial linkage results

A total of 47,366 (93.2%) of 50,839 records in the CHIC2013 dataset were initially linked to a HANDD record, comprising 47,389 linked pairs, as 22 UK CHIC records linked to more than one HANDD record so appeared more than once. There were 1726 many-to-one links involving 1,726 UK CHIC records linked to only 850 HANDD records. Of the 47,389 linked pairs, 43,167 (91.1%) had a HANDD linkage score of 1, 1,467 (3.1%) had a linkage score of 2, 100 (0.2%) a linkage score of 3 and 2,655 (5.6%) a score of 4.

The 3,473 individuals who weren't linked to a HANDD record were more likely to be female (35.6% vs. 27.2%), of unknown ethnicity (18.8% vs. 4.3%) and unknown mode of HIV acquisition (30.0% vs. 5.2%) than those linked to a HANDD record (

Table 4.3.3). These individuals were also more likely to have entered the UK CHIC Study in an earlier calendar year than those who were linked to a HANDD patient record. The proportion of linked and unlinked patients who had a date of death in the UK CHIC dataset prior to linkage with HANDD was similar.

Table 4.3.2: Variables from PHE available from linkage

Variable	Description
SOPHID ID	SOPHID patient identifier
HANDD ID	HANDD patient identifier
Patnum	UK CHIC patient identifier
S_Match	Linkage score of SOPHID-CHIC linkage
H_Match	Linkage score of HANDD-CHIC linkage
DDeath	Date of death in HANDD
CD4Count	Earliest recorded CD4 count
CD4Date	Date of earliest recorded CD4 count
Viralload	Earliest recorded viral load measurement
Viral load date	Date of earliest recorded viral load measurement
Max DLSeen	Latest recorded date seen
H_Soundex	Soundex
H_Date of birth	Date of birth
H_Sex	Sex
H_Ethnicity	Ethnicity
H_Exposure	Exposure
cod1_text	Cause of death (text)
cod1	Cause of death (ICD10 code)
cod2_text	Cause of death (text)
cod2	Cause of death (ICD10 code)
cod3_text	Cause of death (text)
cod3	Cause of death (ICD10 code)
cod4_text	Cause of death (text)
cod4	Cause of death (ICD10 code)
cod5_text	Cause of death (text)
cod5	Cause of death (ICD10 code)
cod6_text	Cause of death (text)
cod6	Cause of death (ICD10 code)

Table 4.3.3: Characteristics of those in UK CHIC who were and were not linked to a HANDD record

Characteristics		Not linked N=3473	Linked N=47366
Sex, n (%)	Male	2233 (64.4)	34464 (72.8)
	Female	1236 (35.6)	12900 (27.2)
Ethnicity, n (%)	White	1473 (42.4)	25070 (52.9)
	Black African	868 (25.0)	13239 (28.0)
	Black Other	134 (3.9)	2552 (5.4)
	Other	346 (10.0)	4464 (9.4)
	Unknown	652 (18.8)	2041 (4.3)
Mode of HIV acquisition, n (%)	Sex between men	1020 (29.4)	23808 (50.3)
	Heterosexual	1059 (30.5)	17894 (37.8)
	IDU	186 (5.4)	1526 (3.2)
	Other	165 (4.8)	1699 (3.6)
	Unknown	1043 (30.0)	2439 (5.2)
Year of cohort entry	1996-1999	1450 (41.8)	12274 (25.9)
	2000-2004	1084 (31.2)	13554 (28.6)
	2005-2008	539 (15.5)	11329 (23.9)
	2009-2013	400 (11.5)	10209 (21.6)
Centre last attended	Brighton	129 (3.7)	2970 (6.3)
	St Mary's	342 (9.9)	4706 (9.9)
	Chelsea & Westminster	514 (14.8)	10271 (21.7)
	Mortimer Market Centre	355 (10.2)	6003 (12.7)
	King's College	140 (4.0)	3643 (7.7)
	Royal Free	149 (4.3)	4145 (8.8)
	Barts/ Royal London	867 (25.0)	3699 (7.8)
	Edinburgh	179 (5.2)	976 (2.1)
	North Middlesex	229 (6.6)	1436 (3.0)
	Homerton	70 (2.0)	1341 (2.8)
	Bristol	39 (1.1)	1317 (2.8)
	Leicester	66 (1.9)	1428 (3.0)
	Middlesbrough	36 (1.0)	521 (1.1)

Characteristics		Not linked N=3473	Linked N=47366
	Woolwich	24 (0.7)	1537 (3.3)
	St George's	239 (6.9)	1974 (4.2)
	York	7 (0.2)	282 (0.6)
	Coventry	15 (0.4)	243 (0.5)
	Chertsey	34 (1.0)	539 (1.1)
	Wolverhampton	38 (1.1)	333 (0.7)
Died, according to UK CHIC dataset, n (%)		284 (8.2)	3612 (7.6)

4.3.2 Multiple matches

Ideally, when linking records from two datasets, we would want a single record in UK CHIC to be linked to only one record in HANDD according to the agreement rules above, and vice versa. However, this is not always possible with a deterministic linkage in the absence of a common and unique identifier. This was indeed the case here and the linkage performed allowed for one-to-many and many-to-one linked pairs to occur. A one-to-many link refers to the instance where one patient record in the UK CHIC dataset was linked with more than one patient record in HANDD. A many-to-one link meant that multiple patient records in the UK CHIC dataset could be linked to a single patient record in HANDD. One-to-many and many-to-one linked pairs could be the result of incorrect linkage. However, it is possible that there are multiple records from the same individual within a dataset if the de-duplication methods employed by each study have not correctly internally linked records from the same individual. For UK CHIC records that had multiple associated clinic IDs through the deduplication process (Section 3.2.2), all of these numbers were used to match to the HANDD dataset. As the deterministic linkage is based on clinic ID, each clinic ID could link to a different HANDD patient record. Furthermore, whilst it is possible to determine where de-duplication has occurred in UK CHIC because of the distinguishing *duppatnums* used, this was not possible in HANDD. Many-to-one linkages could demonstrate a failure to correctly de-duplicate and link up multiple centre attendances as a single patient record within UK CHIC, or could be the result of incorrect linkage between independent records. As well as one-to-many and many-to-one linked pairs, it was also possible that a patient record in the UK CHIC dataset could not be linked to an individual in HANDD, based on the data available. However, all patients in the UK CHIC Study should also be present in HANDD as all will have had an HIV diagnosis (although the converse is not necessarily true).

Demographic variables as recorded in HANDD were provided in order to establish whether one-to-many and many-to-one linked pairs were, in fact, true or false matches. This was only investigated for multiple linked pairs where a date of death existed in either dataset. There were 4,658 linked pairs that had a date of death available in either the UK CHIC or HANDD record. Among linked record pairs with a death recorded in either dataset, 4,230 (90.8%), 54 (1.1%), 8 (0.2%) and 366 (7.9%) had linkage scores of 1, 2, 3 and 4 respectively.

Of these 4,658 linked pairs of records, 4,480 (96.2%) were a one-to-one link so were not investigated further at this stage. Of the remaining linked pairs, 167 (3.6%) were a many-to-one link, with 167 UK CHIC records linked to only 93 HANDD records. There were a total of 8 (1.0%) one-to-many linked pairs, where a date of death was recorded in either record, involving 5 UK CHIC records linked to 8 HANDD records. These 8 one-to-many linked pairs do not include the additional linked pairs for 2 of the 5 UK CHIC records, for which there was no date of death in either the UK CHIC or HANDD record (i.e. in the linkage overall these were 5 UK CHIC records linked to 10 HANDD records). The two linked pairs with no date of death in either UK CHIC or HANDD are not considered here. The process by which I decided on true matches is described below.

For linked pairs where a single patient record in UK CHIC linked to more than one record in HANDD (one-to-many link), I needed to determine which HANDD record was the best match to the UK CHIC patient record in question to avoid duplication of UK CHIC patient records. For all 5 UK CHIC records that were part of a one-to-many link, the *duppatnum* indicated that the original records received from participating centres had been de-duplicated (all 2013xxxxx numbers). For manual review, each linked UK CHIC-HANDD pair was assessed on the HANDD linkage score, and similarity between date of birth, sex, ethnicity, exposure group, CD4 count and viral load measures and last seen dates. However, the date of death was often itself most indicative of the best match between a UK CHIC record and all possible linked HANDD records. The linked records that were most similar according to these data fields were chosen as the best match. I was able to select a best match for 3 of the UK CHIC patient records reviewed, meaning 3 linked pairs were retained and 3 were unlinked. The remaining 2 pairs had no date of death in the UK CHIC dataset and the demographic data available matched fully for all records and had the same linkage score. As these two UK CHIC records were also linked to another HANDD record without a date of death, they were unlinked from the HANDD record with a death.

In the 167 instances where multiple UK CHIC records were linked to a single HANDD record (many-to-one links), upon review it was much more difficult to select a best match as outlined in the paragraph above. The links made between different UK CHIC records to a single HANDD record were often of similar quality. Therefore, a decision wasn't made at this stage as to

whether a given link was a true match, unless there was sufficient contradictory evidence to suggest that one of the links was a false match. This evidence was conflicting ethnicity, sex, CD4 count or viral load data. Death was not used to assess the quality of a match unless the HANDD date of death was implausible based on the UK CHIC data e.g. the death occurred prior to the time after which there was information available in UK CHIC for a patient record. In this instance, the linked pair without conflicting death data would be selected as a match. I was able to select 64 linked pairs as a match. I disregarded 71 linked pairs and 12 UK CHIC records linked to 8 HANDD records could not be decided on; 24 of these 83 UK CHIC records had a date of death in the UK CHIC dataset. For a further 20 linked pairs consisting of 20 UK CHIC records linked to 10 HANDD records, all linked pairs were retained as matches for the time-being. This was done as the UK CHIC records were so similar it was likely these 20 records were actually for 10 individuals that had not previously been identified as duplicates.

Three linked pairs were part of both many-to-one and one-to-many links, and upon manual review two of these linked pairs were retained and one unlinked.

4.3.3 Final linked pairs

Excluding 89 UK CHIC records that were part of multiple linked pairs for whom I could not be certain of a correct link, there were a final 4,569 linked pairs with a date of death in either the UK CHIC or HANDD record. Of these, 3,588 had a date of death according to the UK CHIC record and 3,988 had a date of death in the HANDD record; 3,007 had a date of death in both datasets. A further 284 deaths were identified from UK CHIC records that could not be linked to a HANDD record and 24 in UK CHIC records that were unlinked through manual checks.

4.3.4 Ascertainment of death (vital status) for individuals with conflicting information in UK CHIC and HANDD datasets

4.3.4.1 Developing a matching score

Once a final list of 4,569 linked pairs where at least one data source had a date of death was created, it was necessary to devise a set of rules to decide whether to change or update the data held in the UK CHIC dataset to the information held in HANDD, based on the information available for each match. As a general rule, my approach was to disregard HANDD data where there was conflicting data available in UK CHIC and to take the HANDD date of death where there was no conflicting data and I was confident that a correct match had been made. As PHE confirm their dates with ONS for all deaths under the age of 65, it is likely that, where a correct match is made, information from HANDD is more accurate than data from UK CHIC centres. Therefore, conflicting data could indicate an incorrect match. Disregarding HANDD data where there was conflicting information available in UK CHIC was fairly straightforward.

However, where there was no conflicting information available, I had to decide to include or disregard a date of death based on how certain I was of the strength of the match between UK CHIC and HANDD. I therefore investigated the HANDD linkage scores.

Just over 90% of the 4,658 originally linked pairs had the highest linkage score of 1, meaning that the UK CHIC and HANDD records linked had the same soundex, date of birth and sex. However, of those with a linkage score of 1,794 (17.0%) had at least one demographic inconsistency. From the manual checks performed on one-to-many and many-to one matches, I had observed that it was possible to have a good linkage score but to find inconsistencies in the demographic data, CD4 count, viral load, death dates and last seen dates that would point to two records not being a true match. I therefore wanted to incorporate extra data available to improve the certainty of a match over and above that provided by the linkage score. I devised my own matching score to be used when deciding whether to incorporate the HANDD date of death into the UK CHIC Study. This score incorporated the demographic, CD4 count and viral load data available in each dataset as well as the HANDD linkage score provided by PHE (Figure 4.3.1).

All linked pairs, regardless of previous checks for multiple matches, were given a score of zero. If inconsistencies were found in the demographic data between linked records or the linkage sore was greater than 1, a score was added. Therefore, a higher matching score would indicate a poorer match strength, as with the PHE linkage score. With regards to CD4 count and viral load data, an exact match in these data fields would be useful for ruling in correct matches, as the likelihood that two linked patient records with the same CD4 count occurring on the same date would belong to different individuals was low. However, a non-match in these fields would not be useful for ruling out matches as not all HANDD records had CD4 count or viral load data available. Also, failure to find a match where these data were available could easily arise if the CD4 count in HANDD came from a diagnosis or attendance at a non UK CHIC centre, as the UK CHIC record would not be expected to contain this information. Therefore, if a CD4 count or viral load match was found, a score was taken away from my matching score, but no score was added if a match was not found. A suitably high score was taken away from the matching score for exact CD4 count or viral load matches so that demographic inconsistencies or a poorer linkage score did not rule out a match where a CD4 count or viral load match was found. I also considered partial CD4 count and viral load matches where a CD4 count or viral load was present in both datasets that was within a 5 day interval and a given value range. For these partial matches, a smaller score was subtracted from the matching score. A partial match was defined as a CD4 count or viral load within 5 days and a value within 50 cells/mm^3 for CD4 count and 1 log copy for viral load.

Figure 4.3.1: HANDD matching score

Scenario	Score
All linked pairs	0
Sex inconsistent	+2
Ethnicity inconsistent	
white vs. black African/ black Caribbean/ Asian	+2
black African/ black Caribbean vs. Asian	+2
other differences in ethnicity	+1
Mode of Acquisition inconsistent	+1
HANDD linkage score >1	+1
CD4 count or viral load match	
Exact	-6
Partial (within 5 days and 50 cells/mm^3 or 1 log copy)	-3

The possible scenarios that could then result in each score are shown in Appendix IV. A score $\leq$1 was chosen as evidence of a suitably strong match as a score higher than this would have to indicate that no CD4 count or viral load match was found, that at least one demographic inconsistency existed and/or the HANDD linkage score was greater than 1. This cut-off was then applied, alongside other criteria, when resolving inconsistencies in the date of death information between UK CHIC and HANDD [Section 4.3.4.2]. Of the 4,658 linked records, 3,807 (81.7%) had a score of 0 or less including 936 (20.1%) who had a score of -6 indicating an exact CD4 count or viral load match, a HANDD linkage score of 1 and no differences in the sex, ethnicity and exposure of the linked patients in HANDD and UK CHIC. Including only one-to-one linked pairs and those one-to-many and many-to-one linked pairs decided to be a correct link after manual checking, the proportion with a score less than or equal to 0 was 82.3% (n=3,761) with 933 (20.4%) having a score of -6. The modal score was 0 with 2,224 (48.7%) of linked pairs having this matching score.

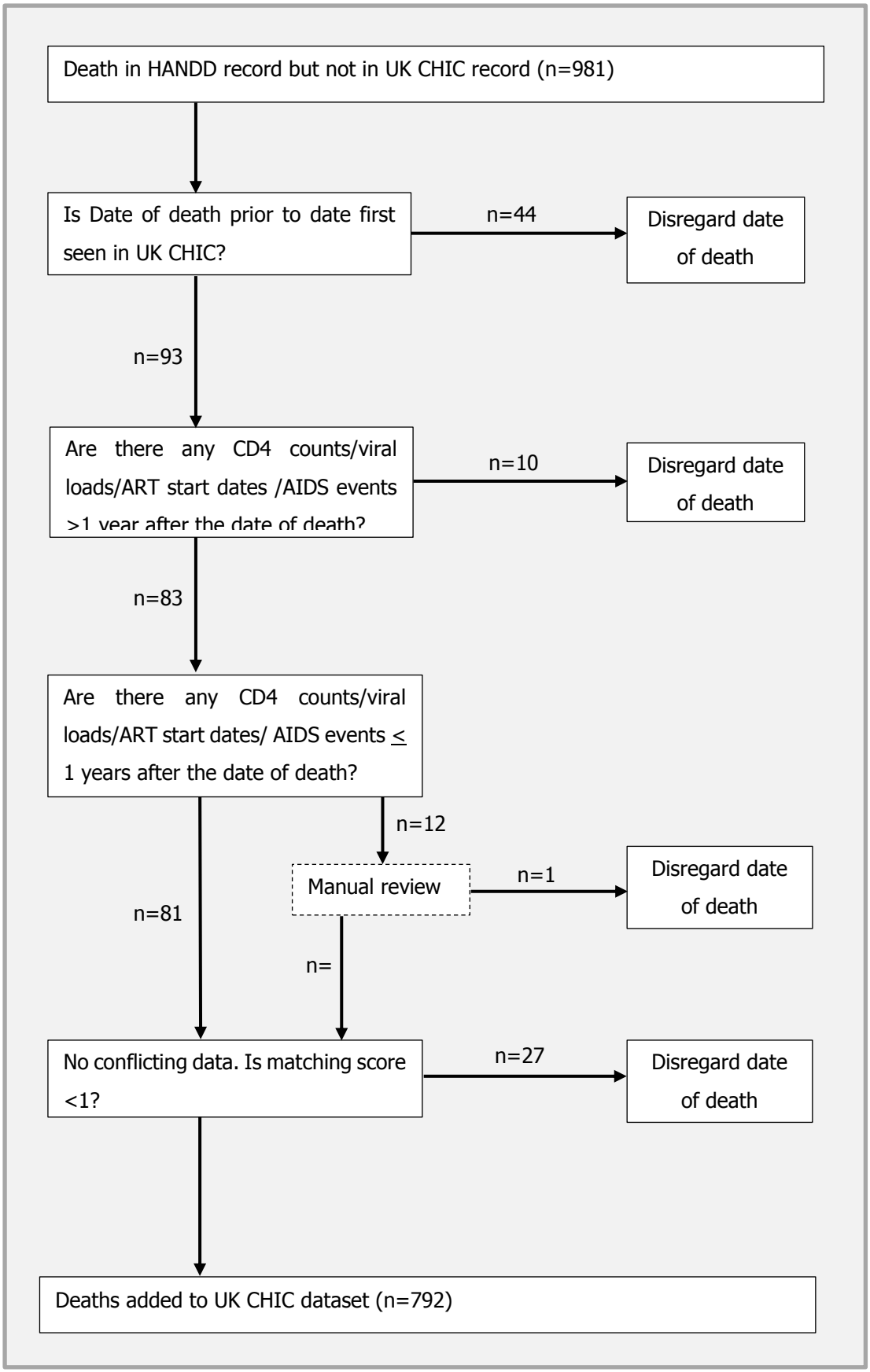
4.3.4.2 Selecting date of death

Of the 4,569 linked record pairs, 2,365 (51.8%) had dates of death in both the UK CHIC and HANDD records that agreed. Next I resolved 2,204 record pairs with inconsistencies in the date of death information in UK CHIC and HANDD for a linked pair of records. To decide on a final date of death, matched pairs were considered separately according to whether they had: a date of death recorded in the PHE datasets but not in the UK CHIC dataset (n=981; 44.5%);

a date of death recorded in both datasets that was not the same (n=642; 29.1%); a date of death recorded in the UK CHIC dataset but not in HANDD (n=581; 26.4%).

Firstly, I considered those linked records with a date of death recorded in HANDD but not in the UK CHIC dataset. For each individual, I needed to decide whether to add this new date of death to the UK CHIC dataset or to exclude it. The selection rules were as follows and are shown in Figure 4.3.2. I first rejected a date of death if it was prior to the date recorded as first being seen in the UK CHIC dataset (*fstseen*). I then considered those whose last recorded CD4 count, viral load, AIDS-defining event or drug start date (*lastdate*) in the UK CHIC dataset was later than the date of death for the linked HANDD record. I immediately excluded the date of death if the last recorded date of being seen in the UK CHIC Study was more than a year after the date of death. Where the *lastdate* was less than one year following the date of death, I reviewed the cases manually. I examined the data available for those with events in the year following the date of death by eye and decided to exclude anyone with any CD4 counts or viral load measures more than 3 days after this death date only. This left me with only those matches for which I had no conflicting data with the HANDD date of death in UK CHIC. Here I decided whether to add the date of death based on how confident I was in the matching. I therefore excluded any deaths where my matching score was greater than 1. The result of these steps was to add 792 new deaths to the dataset. The characteristics of those deaths are given in Table 4.4.2.

Figure 4.3.2: Rules for adding HANDD date of death to a UK CHIC record if no death is recorded in the UK CHIC Study



I next considered those with a death recorded in both datasets, but where the date was not the same (Figure 4.3.3). Here I had to decide whether to choose the date of death recorded in the PHE databases over the information we had already received from centres in the annual upload. My approach was to consider records separately according to whether:

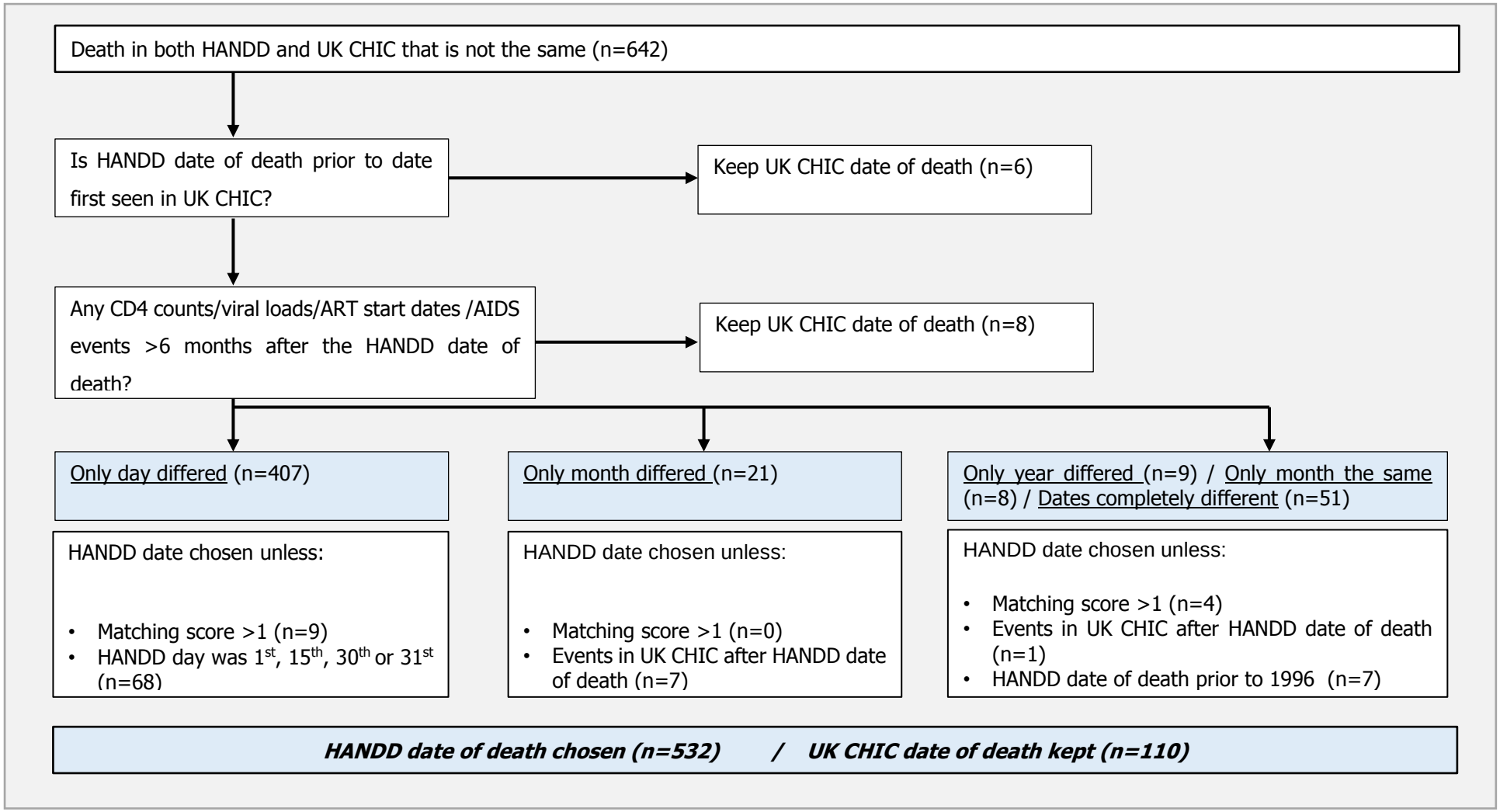
(i) only the day differed between the two dates
(ii) only the month differed between the two dates
(iii) only the year differed between the two dates
(iv) only the year was the same between the two dates
(v) only the month was the same between the two dates
(vi) the dates were completely different

In all of the above scenarios, I immediately excluded the PHE date of death for those who were first seen in the UK CHIC after this date and those whose *lastdate* was >6 months after this date. In scenario (i), as only very small differences existed between the two dates, I decided only to opt for the HANDD date of death where my matching score was $\leq$1 and the HANDD date wasn't the 1st, 15th, 30th or 31st of the month, which are dates that are often recorded when the true date is unknown. Otherwise, the date of death in the CHIC database was retained.

For scenarios (ii) and (iv) similar rules were applied. These differences in the date of death were likely to be small and could easily have arisen due to human error in data entry. The PHE date was only opted for where my matching score was $\leq$1 and there were no events in UK CHIC after the HANDD date of death.

In the remaining scenarios (iii), (v), (vi), the differences in date of death were larger so an added check was included. If the HANDD date of death was prior to 1st January 1996, the earliest possible date of entry into the UK CHIC Study, then the HANDD date was rejected for the alternative date given in the UK CHIC Study. I then applied the same rules as in (ii) and (iv).

Figure 4.3.3: Rules for choosing HANDD or UK CHIC death if there is a date of death in both datasets that is not the same



Finally, I considered the cases where a death was recorded in the UK CHIC dataset but not in the PHE datasets. This group consisted of 581 matched records but also a further 284 UK CHIC records that could not be linked to a HANDD record and 24 unlinked many-to-one links. For these records I retained the date of death recorded in the UK CHIC dataset. For the 20 *patnums* linked to 10 HANDD records, 12 remained the same and 8 changed their date of death.

In summary, 792 deaths were added to the 3,896 deaths originally in the CHIC2013 dataset and 532 dates of death were changed to the HANDD date of death. Of the new deaths added, 54 occurred prior to 1996. Upon review of these patient records, no data was available after 1996 so these individuals were removed from the dataset, giving a final 4,634 deaths in 50,785 individuals.

4.3.5 Methods for selecting principal cause of death in UK CHIC

4.3.5.1 Compiling data on cause of death

As previously mentioned, information on cause of death was available from four sources: annual data submission by participating centres; the one-off linkage to ONS mortality registry data; CoDe forms completed by participating centres; and the linkage of UK CHIC records to HANDD and SOPHID. The format in which cause of death was collected in each of these sources differed, with between 1 and 6 text fields used to describe cause of death (Table 4.3.4, Table 4.3.5). A single dataset was created which contained all causes of death available from each of the different sources of information for each patient who had died. Of 4634 deaths in the CHIC2013 dataset, 3,053 had any text information available on cause of death. There were a total 4,221 causes of death available for the 3,053 individuals. 2,108 (69.0%) had cause of death information from 1 data source only, 746 (24.4%) had information from 2 data sources, 175 (5.7%) had information from 3 data sources and 24 (0.8%) had information from all 4 data sources. Most of the cause of death information (n=2,515) was provided was from the linkage to PHE data. Only 947 causes of death were available from the UK CHIC electronic upload provided by centres and 309 were available from linkage to ONS. 440 causes of death were available from CoDe forms but for only 430 individuals; 10 people had two CoDe forms completed by different centres. The dataset was arranged as one line per source of data, and the below strategy was applied to each cause separately. When a principal cause of death had been determined and coded for each cause, these principal causes were compared within individuals and inconsistencies in principal cause consolidated.

Table 4.3.4: Different sources of cause of death information in the UK CHIC Study

Source	Updated	Time period	Format
UK CHIC data collection	Annual Since 2001	1996 - present	Single text field
Linkage to ONS data	One-off 2010	2001-2008	Up to 6 text fields Up to 6 ICD9 codes
CoDe forms	Ongoing Since 2009	2004 - present	Direct Contributing (x2) Underlying
Linkage to PHE surveillance data	Annual Since 2013	1996 - present	Up to 6 text fields Up to 6 ICD10 codes

4.3.5.2 Mortality Review Sub-group

As clinical input would be important in interpreting and understanding the available text information on cause of death, a mortality review sub-group of the UK CHIC Study was convened including 3 clinical members as well as me and the UK CHIC Principal Investigator (CS). The clinical members of this subgroup were Dr Frank Post (FP), Dr Sarah Pett (SLP) and Dr Alejandro Arenas-Pinto (AAP). The first meeting of this sub-group was held in December 2014, after the CHIC2013 dataset had been generated. In this meeting, FP, SLP and AAP were acquainted with the UK CHIC dataset and different data sources and our objectives were outlined: to determine a principal cause of death where information was available. This principal cause of death would be the end-organ disease or condition thought to ultimately be responsible for death. The decision to select only a single principal cause was based on pragmatic reasoning. It was not felt that there was enough consistently detailed and high-quality information available for most deaths to allow selection of direct, contributing and underlying causes of death. It was, however, decided to retain and code information on other mentioned contributing conditions.

As a first attempt to select a principal cause of death, two of the clinical members of the group and I were given a sample of data on 2,087 causes of death. We each selected a principal cause of death, based on the information available. Upon review of the group's independent decisions it was found that there was only 22.5% agreement between the 2 clinical members and 6.0% agreement between all 3 of us in the choice of principal cause of death. In the second meeting of the mortality review group, the available data and decisions made were

discussed. It had been observed that certain causes appeared repeatedly, and that a principal cause of death could be assigned easily, whereas some cases were more complicated and would require detailed clinical review (Table 4.3.5). For example, a cause of death mentioning only one AIDS-defining illness would be a straightforward case, whereas a cause mentioning multiple non-AIDS conditions would require more detailed clinical input to decide which condition was ultimately responsible for death. Therefore it was decided to develop a set of guidelines for assigning and coding a principal cause of death that could be applied consistently and systematically for more straightforward cases and to then conduct a further review of those causes not covered in such a strategy, rather than attempting independent review for all 3053 deaths with available information on cause of death.

Table 4.3.5: Examples of (A) simple cause of death (B) complex cause of death

(A) Examples of simple cause of death						
Source	**Cause text 1**	**Cause text 2**	**Cause text 3**	**Cause text 4**	**Cause text 5**	**Cause text 6**
CHIC	Lung Cancer					
CoDe	Multiple injuries from fall					
PHE	Kaposi's sarcoma	HIV				
PHE	End stage Liver Disease	Hepatitis C	HIV			

(B) Examples of complex cause of death						
Source	**Cause text 1**	**Cause text 2**	**Cause text 3**	**Cause text 4**	**Cause text 5**	**Cause text 6**
CoDe	Congestive cardiac failure	Enterococcus Septicaemia		HIV		
ONS	Bronchopneumoni unspecified	Varicella without complications	Zoster without complication	Encephalitis myelitis and encephalomyelitis unspecified	Bronchiectasis	Pulmonary mycobacterial infection
PHE	Ischaemic hepatitis & acute kidney injury	Severe right heart failure & severe pulmonary hypertension	HIV			
PHE	Multiorgan failure	Faecal peritonitis	Necrosis and perforation of large bowel	HIV, diabetes mellitus, coronary artery	Bypass grafting on 23/01/07	

4.3.5.3 Adapted HICDEP coding

The HICDEP coding system is widely used in HIV cohorts and collaborations, including the UK CHIC Study and collaborations in which UK CHIC participates. The HICDEP coding for cause of death is a coding system of over 30 codes, with further sub-categories, and is the coding system used in the CoDe protocol (Table 4.3.6). It was chosen as the most appropriate coding system for use in UK CHIC, to remain consistent with other studies and for ease of submitting data to cohort collaborations. Whilst this is a flexible coding system with a large number of possible codes, it was felt that some adaptions were needed in order to fulfil the needs of our study.

The first and largest adaptation was to expand the coding system for death due to AIDS-defining illness (ADI). The HICDEP coding system allows for deaths from ADI to be coded as AIDS infection, AIDS malignancy or non-specific AIDS (Table 4.3.6). We wanted to expand this coding system in order to allow for analyses of specific AIDS-defining conditions in future. We also wanted to have a code for HIV virus, as many conditions in the post-HAART era may be considered attributable or related to HIV without being classified as AIDS-defining according to the 1993 CDC list. The adapted coding is given in Table 4.3.7. By expanding the coding system, within the pre-existing HICDEP code categories, we allow for the original HICDEP codes to be easily re-applied when submitting data elsewhere.

A further adaptation was to create a new code for pneumonias. In the UK CHIC adaptation, any bronchopneumonia, aspiration pneumonias, lobar or bacterial pneumonias were all coded under a single code since the underlying organism causing the pneumonia was, in most cases, unknown. However, these were still coded as distinct from deaths caused by infection. Slight adaptations were made to codes 14 (liver failure) and 15 (kidney failure). These codes were used to describe any severe disease of the liver or kidney respectively, as well as organ failure. The HICDEP code for unknown infection with sepsis (code 2.3.1) was used to indicate sepsis and sepsis-like syndromes, including multi-organ failure.

Table 4.3.6: HICDEP coding (version 1.8)

HICDEP Code		Cause of Death
1		AIDS (ongoing active disease)
	1.1	Infection
	1.2	Malignancy
2		Infection (other than 01.1)
	2.1	Bacterial
	02.1.1	Bacterial with sepsis
	2.2	Others
	02.2.1	Others with sepsis
	2.3	Unknown aetiology
	02.3.1	Unknown with sepsis
3		Chronic viral hepatitis (progression of/complication to)
	3.1	HCV
	3.1.1	HCV with cirrhosis
	3.1.2	HCV with liver failure
	3.2	HBV
	3.2.1	HBV with cirrhosis
	3.2.2	HBV with liver failure
4		Malignancy (other than 01.2 and 03, 03.1, 03.2)
	4.03	ANUS - Anal cancer
	4.04	BLAD - Bladder cancer
	4.05	BONE - Bone cancer
	4.06	BRAC - Brain cancer
	4.07	BRCA - Breast cancer
	4.10.1	ALL - Leukaemia: Acute lymphoid
	4.10.2	AML - Leukaemia: Acute myeloid
	4.10.3	CLL - Leukaemia: Chronic lymphoid
	4.10.4	CML - Leukaemia: Chronic myeloid
	4.10.9	LEUK - Leukaemia: unspecified
	4.18	COLO - Colon cancer
	4.11	COTC - Connective tissue cancer
	4.12	ESOP - Esophagus cancer
	4.13	GALL - Gallbladder cancer
	4.14	GYCA - Gynaecologic cancer
	4.15	HDL - Hodgkin lymphoma
	4.16	HENE - Head and neck (incl. face) cancers
	4.17	KIDN - Kidney cancer
	4.19	LIPC - Lip cancer
	4.2	LIVR - Liver cancer

HICDEP Code	Cause of Death
4.21	LUNG - Lung cancer
4.22	MALM - Malignant melanoma
4.27	MULM - Multiple myeloma
4.29	PANC - Pancreas cancer
4.31	PENC - Penile cancer
4.32	PROS - Prostate cancer
4.33	RECT - Rectum cancer
4.34	STOM - Stomach cancer
4.35	TESE - Testicular seminoma
4.36	UTER - Uterus cancer
4.40.1	MEAC - Metastasis: of adenocarcinoma
4.40.2	MEOC - Metastasis: of other cancer type
4.40.3	MESC - Metastasis: of squamuos cell carcinoma
4.40.9	META - Metastasis: unspecified
4.9	OTH - Other Malignancy Type
4.99	UNKP - Unknown Malignancy Type
5	Diabetes Mellitus (complication to)
6	Pancreatitis
7	Lactic acidosis
8	MI or other ischemic heart disease
8.1	AMI
8.1.1	Definitive AMI (Dundee 1)
8.1.2	Possible AMI (Dundee 2/9)
8.2	Other ischemic heart disease
9	Stroke
10	Gastro-intestinal haemorrhage (if chosen, specify underlying cause)
11	Primary pulmonary hypertension
12	Lung embolus
13	Chronic obstructive lung disease
14	Liver failure (other than 03, 03.1, 03.2)
15	Renal failure
16	Accident or other violent death (not suicide)
17	Suicide
18	Euthenasia
19	Substrance abuse (active)
19.1	Chronic Alcohol abuse
19.2	Chronic intravenous drug-use
19.3	Acute intoxication
20	Haematological disease (other causes)

HICDEP Code		Cause of Death
21		Endocrine disease (other causes)
22		Psychiatric disease (other causes)
	22.1	Mental and behavioural disorders due to use of psychoactive substances (other than alcohol and intravenous opioids)
	22.2	Schizophrenia schizotypal and delusional Disorders
	22.3	Mood /Affective disorders (Major depressive disorder Bipolar disorder and other mood disorders)
	22.4	Neurotic stress-related and somatoform disorders (including anxiety disorders phobias OCD stress reaction dissociative disorders somatoform disorders)
	22.5	Behavioral syndromes associated with physiological disturbances and physical factors (including eating disorders sleep disorders sexual disorders)
	22.9	Other psychiatric disorders
23		CNS disease (other causes)
	23.1	Movement disorders (Parkinsons disease; dystonias and Parkinson-like syndromes)
	23.2	Degenerative disorders of the central nervous system (Alzheimer's disease; Creutzfeldt-Jakob disease and other degenerative diseases of nervous system)
	23.3	Demyelinating diseases of the central nervous system (Multiple sclerosis other demyelinating diseases)
	23.4	Epilepsy (including localised and generalized epilepsy and epileptic syndromes)
	23.5	Polyneuropathies (GuillainBarr syndrome and other polyneuropathies/disorders of the peripheral nervous system)
	23.6	Diseases of myoneural junction and muscle (Miastenia gravis and other myoneural disorders)
	23.9	Other disorders of the nervous system
24		Heart or vascular (other causes)
25		Respiratory disease (other causes)
26		Digestive system disease (other causes)
27		Skin and motor system disease (other causes)
28		Urogential disease (other causes)
29		Obstetric complications
30		Congenital disorders
31		Symptoms caused by mitochondrial toxicity (other than 06, 07)
32		Bleeding (haemophilia)
33		Sudden infant death
	33.1	Child abuse
90		Other causes
91		Unclassifiable causes
92		Unknown
	92.1	Unknown, Competing risks

Table 4.3.7: Adapted HICDEP coding for AIDS-defining illness

Code	AIDS-defining event
1.1.01	Candidiasis
1.1.02	Coccidioidomycosis, disseminated or extrapulmonary
1.1.03	Cryptococcosis, extrapulmonary
1.1.04	Cryptosporidiosis, chronic intestinal for longer than 1 month
1.1.05	Cytomegalovirus disease (other than liver, spleen or lymph nodes)
1.1.06	Cytomegalovirus retinitis (with loss of vision)
1.1.07	Encephalopathy (HIV-related)
1.1.08	Herpes simplex: chronic ulcer(s) (for more than 1 month); or bronchitis, pneumonitis, or esophagitis
1.1.09	Histoplasmosis, disseminated or extrapulmonary
1.1.10	Isosporiasis, chronic intestinal (for more than 1 month)
1.1.11	Mycobacterium avium complex or Mycobacterium kansasii, disseminated or extrapulmonary
1.1.12	Mycobacterium, other species, disseminated or extrapulmonary
1.1.13	Mycobacterium tuberculosis, any site
1.1.14	Pneumocystis jirovecii pneumonia (formerly Pneumocystis carinii)
1.1.15	Pneumonia (recurrent)
1.1.16	Progressive multifocal leukoencephalopathy
1.1.17	Salmonella septicemia (recurrent)
1.1.18	Toxoplasmosis of the brain
1.2.01	Kaposi's sarcoma
1.2.02	Lymphoma, any
1.2.03	Cervical cancer
1.3	Wasting syndrome due to HIV
1.9	Multiple AIDS-defining events
0.1	HIV

4.3.5.4 Guidelines for selecting a principal cause of death

AIDS-defining illness

If a specific AIDS-defining illness (Table 4.3.7) was mentioned, this would be listed as the principal cause of death, irrespective of any other information that might be available. If other non-AIDS causes were also listed, these would be retained as contributing causes. If "AIDS", "Acquired Immunodeficiency Syndrome", "end stage HIV" or similar was listed as a cause of death, the principal cause was chosen to be AIDS (unspecified). If multiple AIDS-defining illnesses were listed, the principal cause of death chosen would be multiple AIDS-defining events, with the specific AIDS-defining illnesses each listed as a contributing cause of death. Where AIDS was chosen as the principal cause of death, an underlying cause of HIV was entered.

Non-AIDS illnesses

If information on only one non-AIDS illness was available, this was listed as the principal cause of death. If multiple non-AIDS conditions were listed, a hierarchical approach was followed. Multi-organ failure and sepsis are often reported as a cause of death but could be the result of any number of underlying causes or sequence of illness or events in the run up to death. Any sepsis, sepsis-like syndromes or multi-organ failure would be listed as a principal cause of death only if no other specifically named non-AIDS conditions were listed. Pneumonias were also treated as such, as these were believed to be a consequence of other underlying disease. Similarly general terms to describe death such as "cardiac failure" and "cardio-respiratory arrest" were treated as secondary to other specifically named non-AIDS causes as these are vague terms and do not necessarily reflect cardiovascular disease. If only one such specific non-AIDS condition was mentioned, this would be the principal cause of death with infection, sepsis, pneumonia or cardiac failure listed as a contributing cause of death. If multiple specific non-AIDS causes of death were listed, these cases were further reviewed by the clinical team.

For the choice of HICDEP code for some specific non-AIDS conditions, certain rules were applied. For example, hepatocellular carcinoma was always given a principal cause of death, with hepatitis virus entered as the underlying cause of death where it was also specified. All malignancies were coded according to the principal site (e.g. lung, liver, skin), regardless of whether the malignancy was known to be disseminated or metastasised. All end-organ liver disease was given a code relating to liver failure, regardless of the aetiology (e.g. hepatitis, alcohol), which was then listed as an underlying cause. For drug overdose and violent or

traumatic deaths, if suicidal intent was mentioned, suicide was entered as the principal cause of death, with other information entered as contributing causes as appropriate. An accidental or violent death or drug overdose with no mention of suicide was coded as such.

Review of cases not assigned a principal cause of death

Any cases that I couldn't code using the above guidelines were sent for independent review by the 3 clinical members of the mortality review group, alongside 514 records where both AIDS and non-AIDS conditions had been listed, to confirm agreement with the selected strategy for these deaths. Each clinician chose a principal cause of death for each case, referring to the guidelines where possible. These decisions were made without consultation with each other and were returned to me for comparison. If a majority agreement existed upon comparison, this principal cause was chosen and other listed illnesses were entered as contributing causes. For 372 cases of complete disagreement, a further review of the cause of death was conducted in a meeting of the clinical team and me.

Consolidating different sources of information

Once a principal cause of death was chosen and coded for each case, principal causes for people with information from more than one data source were compared. This constituted 2,113 causes of death in 945 individuals. Initially, cases were broadly grouped by cause of death: AIDS, infection, pneumonia, malignancy, heart/CVD, lung disease, kidney disease, liver disease, external causes (including suicide, drug overdose, accidental and other violent deaths), other causes and no code assigned. For 534 (56.5%) people, the principal cause of death chosen agreed exactly for different sources of information. For a further 131 (13.9%) people with different principal causes of death but the same broad classification, it was a straightforward task to assign a single cause of death upon manual review of all the data available. This left 280 (29.6%) people with assigned principal causes of death (640 cause of death records) that belonged to different broad groupings. A quarter of the 680 causes of death were classified as AIDS deaths, 14% were pneumonia, 11% unknown, 10% infection, 8% other non-AIDS causes, 7% non-AIDS malignancy and 6% each for CVD and liver. In the majority of cases, information was not conflicting between the different sources of data, but the differences in assigned principal cause of death had arisen because one data source contained additional information over another. I was therefore able to select a principal cause of death for such cases using the guidelines above. For cases where a choice of the principal cause of death was not clear (n=55), a clinical member of the team reviewed the information available to select a principal cause of death.

4.3.6 Statistical Analysis

Section 0 summarises the results of the processes outlined in Section 4.3. The changes made to the death data in the UK CHIC Study after linkage to supplement information on date of death are described. Differences in ascertainment of deaths in UK CHIC and HANDD are also considered by describing the demographic characteristics of deaths that were only recorded in one of the two datasets. Overall ascertainment of deaths following the linkage was assessed using capture-recapture methods. Capture-recapture is a method originally developed in the biological sciences for estimating the population size of a species within a given region. The basic concept is to sample a population within the region and mark those that are sampled (the capture stage). Then at a later point in time a second sample is taken and the number of this sample that were previously 'captured' is recorded. The total population size can be extrapolated from the numbers in the first and second sample and the number re-captured. These methods have been applied to the study of disease within a population and can be used to estimate the total number of cases within a population when cases are ascertained from two or more samples. The number of disease cases ascertained in each sample and the number common to both can be used to estimate the number of cases missed by both samples and therefore total number of cases in the population (538). If N_1 is the number of cases in sample 1 but not in sample 2, N_2 is the number of cases in sample 2 but not in sample 1 and N_3 is the number of cases in both samples, then the number of cases missed by both samples (x) can be defined as

$$x = (N_1 \times N_2) \div N_3$$

and the total number of cases (N) is

$$N = N_1 + N_2 + N_3 + [(N_1 \times N_2) \div N_3]$$

In order to estimate ascertainment of all deaths using combined UK CHIC and HANDD data, this approach was performed for all linked records in UK CHIC that matched with a HANDD record. This included all records where the date of death was the same, or where the date of death was not the same and the matching score was ≤ 1 and there was no conflicting data between records to indicate a linked pair were not a correct match, in line with the rules used to select a date of death previously mentioned (Figure 4.3.2 and Figure 4.3.3).

The assigned principal causes of death in the UK CHIC Study are described. Differences in the proportion assigned a principal cause of death according to demographic characteristics are compared using chi-square tests. Deaths were broadly categorised as being AIDS-related, non-AIDS related or of unknown cause according to the chosen HICDEP code for the principal

cause of death. AIDS deaths were further categorised as being due to AIDS infection, AIDS malignancy and multiple or unspecified AIDS illness. Non-AIDS deaths were further categorised as: infection; sepsis (including sepsis-like syndromes and multiorgan failure); pneumonia; lung disease; malignancy; heart disease (including ischaemic heart disease, other cardiovascular disease and stroke); liver disease; kidney disease; external causes; other (specified); other (not specified but not AIDS-related); unascertained and unknown. The proportion of deaths attributable to each cause and rates of AIDS and non-AIDS deaths are described overall and by calendar time. Differences in the cause of death according to demographic characteristics are compared using chi-square tests for categorical and Analysis of Variance (ANOVA) or Kruskal-Wallis tests for normally distributed and non-normal numeric variables, respectively. Rates of cause-specific mortality in two-year intervals between 1996 and 2012 were estimated.

4.4 Results

4.4.1 Changes to date of death in the UK CHIC Study as a result of linkage to surveillance datasets

In 50,839 individuals initially included in the CHIC2013 dataset, 3,896 (7.7%) deaths were recorded prior to linkage with the HANDD database. The characteristics of these individuals with a recorded date of death are shown in Table 4.4.1. The majority of deaths occurred in the earliest calendar period between 1996 and 2000. Median (IQR) age at death was 41 (35, 49) years. Almost 80% of people who had a recorded date of death in the UK CHIC Study had a CD4 count available within one year of death. The median (IQR) CD4 count prior to death was low at 120 (25, 302) cells/mm^3. Fewer people had a viral load available within one year of death (68.7%) and the median (IQR) viral load at death was 2.7 (1.7, 4.9) $\log_{10}$copies/ml

The demographic characteristics of those with a recorded date of death differed slightly to those of the wider UK CHIC population. A higher proportion of those that died were male (80.3% of those who died vs. 72.2% in the CHIC2013 dataset) and were reported as having an IDU route of HIV transmission (12.0% of those who died vs. 3.4% of the CHIC2013 dataset).

The characteristics of the final 4,688 deaths after incorporating information from HANDD are shown in Table 4.4.1. The changes made to the date of death did not alter the characteristics of those who had died in the UK CHIC dataset. The majority of those who had died were white men who acquired HIV through sex between men. The majority of those who had died had entered UK CHIC follow up in earlier calendar years. Median age at death was similar at 41

years prior to linkage and 42 years after. The median CD4 count and viral load at death remained unchanged with a small decrease in the proportion with an available CD4 count or viral load within one year of death. The proportion of deaths recorded in the latest calendar period increased after the linkage to HANDD was performed, reflecting a likely reporting delay in the original UK CHIC data that was improved by the deaths added to the dataset from HANDD.

Excluding 54 people believed to have died prior to 1996 similarly did not change the characteristics of people who had died. These 54 people were of white (48.1%) or unknown (51.9%) ethnicity, and the majority acquired HIV through sex between men (53.7%) or had an unknown transmission route (31.5%).

Table 4.4.1: Patient characteristics at death before and after linkage to HANDD

Characteristics		Deaths in original dataset	Deaths after linkage	Deaths in final dataset
N		3896	4688	4634
Age [years], n (%)	≤25	68 (1.7)	84 (1.8)	83 (1.8)
	26-35	956 (24.5)	1120 (23.9)	1102 (23.8)
	36-45	1528 (39.2)	1802 (38.4)	1779 (38.4)
	46-55	848 (21.8)	1045 (22.3)	1033 (22.3)
	56-55	341 (8.8)	434 (9.3)	434 (9.4)
	65+	155 (4.0)	203 (4.3)	203 (4.4)
Sex, n (%)	Male	3128 (80.3)	3775 (80.5)	3723 (80.3)
	Female	768 (19.7)	913 (19.5)	911 (19.7)
Ethnicity, n (%)	White	2372 (60.9)	2846 (60.7)	2820 (60.9)
	Black African	700 (18.0)	819 (17.5)	819 (17.7)
	Black Other	146 (3.8)	174 (3.8)	174 (3.8)
	Other	307 (7.9)	347 (7.4)	347 (7.5)
	Unknown	371 (9.5)	502 (10.7)	474 (10.2)
Mode of HIV acquisition, n (%)	Sex between men	1911 (49.1)	2284 (48.7)	2255 (48.7)
	Heterosexual	1064 (27.3)	1251 (26.7)	1248 (26.9)
	IDU	469 (12.0)	533 (11.4)	531 (11.5)
	Other	119 (3.1)	146 (3.1)	143 (3.1)
	Unknown	333 (8.6)	474 (10.1)	457 (9.9)

Characteristics		Deaths in original dataset	Deaths after linkage	Deaths in final dataset
Year of cohort entry	1996-1999	2518 (64.6)	3009 (64.2)	2955 (63.8)
	2000-2004	868 (22.3)	1019 (21.7)	1019 (22.0)
	2005-2008	399 (10.2)	501 (10.7)	501 (10.8)
	2009-2012	111 (2.8)	159 (3.4)	159 (3.4)
Centre last attended	Brighton	271 (7.0)	391 (8.3)	371 (8.0)
	St Mary's	373 (9.6)	430 (9.2)	427 (9.2)
	Chelsea & Westminster	828 (21.3)	1013 (21.6)	992 (21.4)
	Mortimer Market Centre	425 (10.9)	505 (10.8)	497 (10.7)
	King's College	339 (8.7)	363 (7.7)	362 (7.8)
	Royal Free	428 (11.0)	484 (10.3)	484 (10.4)
	Barts/ Royal London	290 (7.4)	382 (8.2)	381 (8.2)
	Edinburgh	305 (7.8)	305 (6.5)	306 (6.6)
	North Middlesex	173 (4.4)	192 (4.1)	191 (4.1)
	Homerton	60 (1.5)	74 (1.6)	74 (1.6)
	Bristol	94 (2.4)	104 (2.2)	104 (2.2)
	Leicester	51 (1.3)	67 (1.4)	67 (1.5)
	Middlesbrough	25 (0.6)	30 (0.6)	30 (0.7)
	Woolwich	125 (3.2)	146 (3.1)	146 (3.2)
	St George's	71 (1.8)	151 (3.2)	151 (3.3)
	York	6 (0.2)	10 (0.2)	10 (0.2)
	Coventry	0 (0.0)	6 (0.1)	6 (0.1)

Characteristics		Deaths in original dataset	Deaths after linkage	Deaths in final dataset
	Ashford & St Peter's	29 (0.7)	31 (0.7)	31 (0.7)
	Wolverhampton	3 (0.1)	4 (0.1)	4 (0.1)
Calendar year of death	<1996	-	54 (1.2)	-
	1996-1999	1231 (31.6)	1437 (30.7)	1437 (31.0)
	2000-2004	1085 (27.8)	1180 (25.2)	1180 (25.5)
	2005-2008	934 (24.0)	1021 (21.8)	1021 (22.0)
	2009-2013	646 (16.6)	996 (21.2)	996 (21.5)
CD4 count recorded in the year prior to death, n (%)		3092 (79.4)	3514 (75.0)	3484 (75.2)
CD4 count prior to death, median (IQR)	Cells/mm^3	120 (25, 302)	121 (25, 313)	121 (25, 313)
Viral load recorded in the year prior to death, n (%)		2677 (68.7)	2995 (63.9)	2984 (64.4)
Viral load prior to death, median (IQR)	Log_{10}copies/ml	2.7 (1.7, 4.9)	2.7 (1.7, 4.9)	2.7 (1.7, 4.9)

4.4.2 Differences between UK CHIC and HANDD ascertainment

Among linked records there were 581 individuals with a date of death recorded in UK CHIC but no date of death in the HANDD record. There were 792 linked patient records with a date of death in the HANDD record but not in the UK CHIC record. The majority of these individuals were white men who had acquired HIV through sex between men, as was seen for all deaths occurring in the UK CHIC dataset (Table 4.4.2). However, a higher proportion of people with a date of death reported in HANDD but not in UK CHIC had unknown ethnicity or mode of acquisition than of those with a date of death in UK CHIC only. Individuals who were known to have died in UK CHIC but who could not be linked to a HANDD record were much more likely to have acquired HIV through injecting drug use.

The highest proportion of deaths reported in UK CHIC but not in HANDD occurred between 2000 and 2004 (32.0% vs. 26.5% 2005-2008 and 22.2% 2009-2013). In contrast, deaths reported in HANDD but not in UK CHIC were most likely to have occurred between 2009 and 2012, and were more likely to have occurred in the most recent calendar period than deaths found in the UK CHIC dataset only (43.7% vs 22.2% in linked records with a CHIC death only and 3.9% in records that were not linked). This again would be consistent with a reporting delay in the death data submitted to the UK CHIC Study from participating centres.

A higher proportion of deaths reported in HANDD but not in UK CHIC occurred in individuals who had most recently attended clinics in Brighton and St George's Hospital prior to the date of death. This would suggest poorer reporting of deaths to the UK CHIC Study from these centres, possibly due to higher rates of loss-to-follow-up prior to death as median time between last clinic contact and death were longer for these two centres. None of the deaths reported in HANDD but not in UK CHIC occurred in people who had recently attended the HIV clinic in Edinburgh, reflecting the fact that PHE HIV surveillance covers Wales and England only, with Scottish surveillance data collected by PHS. Further evidence of this is that 37.7% of individuals in UK CHIC who had died but could not be linked to a HANDD record were most recently known to be attending for HIV care in Edinburgh.

Approximately three-quarters of deaths reported in UK CHIC but not HANDD had a CD4 count or viral load recorded within 1 year of the date of death in UK CHIC. The individuals in the group with a date of death in HANDD but not UK CHIC were less likely to have a CD4 count or viral load recorded in UK CHIC within one year of the date of death, with 47.6% vs. 76.9% having a CD4 count and 37.6% vs. 73.5% having a viral load. For those where a CD4 count was available, the median CD4 count was higher in those with a date of death in HANDD but not in UK CHIC. Correspondingly, the viral loads at death in this group were lower than in those with a date of death in UK CHIC but not in HANDD.

Table 4.4.2: Characteristics of deaths in either HANDD or UK CHIC

Characteristics		Deaths in HANDD but not UK CHIC	Deaths in UK CHIC but not HANDD (linked)	Deaths in UK CHIC but not HANDD (not linked)
N		792	581	284
Age [years], n (%)	≤25	17 (2.2)	15 (2.6)	3 (1.1)
	26-35	159 (20.1)	124 (21.3)	101 (35.7)
	36-45	276 (34.9)	210 (36.1)	98 (34.6)
	46-55	199 (25.1)	113 (19.5)	56 (19.8)
	56-55	93 (11.7)	76 (13.1)	19 (6.7)
	65+	48 (6.1)	43 (7.4)	6 (2.1)
Sex, n (%)	Male	647 (81.7)	478 (82.3)	206 (72.5)
	Female	145 (18.3)	103 (17.7)	78 (27.5)
Ethnicity, n (%)	White	474 (59.9)	340 (58.5)	183 (64.4)
	Black African	119 (15.0)	108 (18.6)	52 (18.3)
	Black Other	28 (3.5)	30 (5.2)	4 (1.4)
	Other	40 (5.1)	58 (10.0)	18 (6.3)
	Unknown	131 (16.5)	45 (7.8)	27 (9.5)
Mode of HIV acquisition, n (%)	Sex between men	373 (47.1)	306 (52.7)	80 (28.2)
	Heterosexual	187 (23.6)	167 (28.7)	83 (29.2)
	IDU	64 (8.1)	52 (9.0)	70 (24.7)
	Other	27 (3.4)	22 (3.8)	16 (5.6)

Characteristics		Deaths in HANDD but not UK CHIC	Deaths in UK CHIC but not HANDD (linked)	Deaths in UK CHIC but not HANDD (not linked)
	Unknown	141 (17.8)	34 (5.9)	35 (12.3)
Year of cohort entry	1996-1999	491 (62.0)	323 (55.6)	209 (73.6)
	2000-2004	151 (19.1)	180 (31.0)	55 (19.4)
	2005-2008	102 (12.9)	62 (10.7)	17 (6.0)
	2009-2012	48 (6.1)	16 (2.8)	3 (1.1)
Centre last attended	Brighton	120 (15.2)	16 (2.8)	2 (0.7)
	St Mary's	57 (7.2)	57 (9.8)	17 (6.0)
	Chelsea & Westminster	185 (23.4)	164 (28.2)	57 (20.1)
	Mortimer Market Centre	80 (10.1)	80 (13.8)	16 (5.6)
	King's College	24 (3.0)	50 (8.6)	8 (2.8)
	Royal Free	56 (7.1)	61 (10.5)	9 (3.2)
	Barts/ Royal London	92 (11.6)	60 (10.3)	28 (9.9)
	Edinburgh	0 (-)	19 (3.3)	107 (37.7)
	North Middlesex	19 (2.4)	17 (2.9)	20 (7.0)
	Homerton	14 (1.8)	10 (1.7)	2 (0.7)
	Bristol	10 (1.3)	22 (3.8)	1 (0.4)
	Leicester	16 (2.0)	9 (1.6)	4 (1.4)
	Middlesbrough	5 (0.6)	4 (0.7)	4 (1.4)
	Woolwich	21 (2.7)	5 (0.9)	2 (0.7)
	St George's	80 (10.1)	5 (0.9)	6 (2.1)

Characteristics		Deaths in HANDD but not UK CHIC	Deaths in UK CHIC but not HANDD (linked)	Deaths in UK CHIC but not HANDD (not linked)
Centre last attended	York	4 (0.5)	0 (-)	0 (-)
	Coventry	6 (0.8)	0 (-)	0 (-)
	Ashford & St Peters	2 (0.3)	2 (0.3)	1 (0.4)
	Wolverhampton	1 (0.1)	0 (-)	0 (-)
Calendar year of death	<1996	54 (6.8)	-	-
	1996-1999	199 (25.1)	112 (19.3)	144 (50.7)
	2000-2004	100 (12.6)	186 (32.0)	87 (30.6)
	2005-2008	93 (11.7)	154 (26.5)	42 (14.8)
	2009-2013	346 (43.7)	129 (22.2)	11 (3.9)
Days between last recorded clinic contact[1] and death, median (IQR)		217 (78, 844)	73 (28, 201)	47 (22, 138)
CD4 count recorded in the year prior to death, n (%)		377 (47.6)	447 (76.9)	206 (72.5)
CD4 count prior to death, median (IQR)	cells/mm^3	190 (35, 446)	147 (30, 348)	72 (16, 219)
Viral load recorded in the year prior to death, n (%)		298 (37.6)	427 (73.5)	148 (52.1)
Viral load prior to death, median (IQR)	log_{10}copies/ml	2.2 (1.7, 4.7)	2.9 (1.7, 4.9)	3.6 (1.9, 5.1)

[1]Last recorded contact is last CD4, viral load, ART start date or AIDs, if available, and study entry otherwise

4.4.2.1 Capture-recapture estimate of death ascertainment

In 4,328 linked record pairs, 3,536 deaths were recorded in the UK CHIC Study, 3,747 deaths were recorded in HANDD; and 2,955 (68.3%) deaths were recorded in both the UK CHIC and HANDD lists. Thus a 2x2 table can be drawn as in Table 4.4.3. The estimated number of deaths missed (x) by both UK CHIC and HANDD can then be calculated to be 156 as shown in Table 4.4.3. This gives a total number of deaths (N) amongst this group of 4,484 and an estimate of overall ascertainment amongst matched records of 96.5% (95% CI (95.9%, 97.0%)).

Table 4.4.3: Capture-recapture approach for ascertainment of deaths through linkage

		HANDD death		
		Yes	No	
UK CHIC death	Yes	2955	581	3536
	No	792	x = (581x792)/2955 =156	-
Total		3747	-	N = 581 + 792 + 2955 + 156

Assuming a total 4,484 deaths amongst matched records, we could estimate that HANDD alone captures 83.6% of all deaths and that UK CHIC alone captures 78.9%. Applying this rate to the 360 un-matched records in UK CHIC with a death (that were not previously considered above) would mean an additional 97 deaths were missed amongst all UK CHIC Study participants. With 4,688 deaths observed and an estimated total of 253 missed deaths, the ascertainment of all deaths in the UK CHIC Study after linkage to HANDD would be 94.9% (95% CI (94.2%, 95.5%)).

4.4.3 Assigned principal cause of death

Despite the efforts to improve ascertainment on cause of death, using multiple sources of data, 34% of all deaths still could not be attributed a cause of death due to the fact that no information on cause of death was available from any of the four sources for these individuals. Of 4,634 deaths in the CHIC2013 dataset, some information on cause of death was available for 3,053 (65.9%) deaths. As seen in Table 4.4.4, information on cause of death was more likely to be available for those aged between 40 and 60 ($p<0.0001$), for women ($p=0.037$),

those of black ethnicity (p<0.0001) and those with a heterosexual route of HIV infection (p<0.0001). Those with unknown ethnicity or mode of HIV acquisition also had a lower probability of having available information on cause of death; only 48.1% of those with unknown ethnicity and 59.3% with unknown transmission route had any information on cause of death. There was much more information on cause of death available for deaths occurring in later calendar years, with only 43.3% of deaths between 1996-1999 but 83.4% of deaths occurring since 2008 having information on cause of death (p<0.0001),

Where information on cause of death was available, 2,938 (96.2%) of deaths were assigned a principal cause of death. Amongst those where information on cause of death was available, there was little difference in the proportions assigned a principal cause of death according to demographic characteristics (Table 4.4.4).

Table 4.4.4: Ascertainment of principal cause of death, according to patient characteristics

Characteristics		Cause of death information available N (%)	Assigned cause of death N (%)	Assigned cause of death, where data available (%)
Sex	Male	2426 (65.2)	2322 (62.4)	95.7%
	Female	627 (68.8)	616 (67.6)	98.3%
Ethnicity	White	1865 (66.1)	1776 (63.0)	95.2%
	Black African	615 (75.1)	608 (74.2)	98.9%
	Black other	123 (70.7)	120 (69.0)	97.6%
	Other	222 (64.0)	211 (60.8)	95.1%
	Unknown	228 (48.1)	223 (47.1)	97.8%
Mode of Acquisition	MSM	1459 (64.7)	1405 (62.3)	96.3%
	Heterosexual	921 (73.8)	907 (72.7)	98.5%
	IDU	310 (58.4)	302 (56.9)	97.4%
	Other	92 (64.3)	88 (61.4)	95.7%
	Unknown	271 (59.3)	236 (51.6)	87.1%
Age at death	≤30	238 (57.5)	226 (54.6)	95.0%
	31-40	1058 (63.1)	1024 (61.0)	96.8%
	41-50	1065 (70.2)	1020 (67.2)	95.8%
	51-60	460 (70.0)	448 (68.2)	97.4%
	>60	231 (63.3)	219 (60.0)	94.8%

Characteristics		Cause of death information available N (%)	Assigned cause of death N (%)	Assigned cause of death, where data available (%)
Year HIV diagnosed	<1996	1454 (57.7)	1383 (54.8)	95.1%
	1996-1999	564 (66.7)	538 (63.6)	95.4%
	2000-2003	472 (77.1)	462 (75.5)	97.9%
	2004-2007	394 (86.4)	388 (85.1)	98.5%
	≥2008	169 (85.4)	167 (84.3)	98.8%
Year of death	1996-1999	622 (43.3)	570 (39.7)	91.6%
	2000-2003	593 (62.0)	551 (57.6)	92.9%
	2004-2007	799 (80.3)	790 (79.4)	98.9%
	≥2008	1039 (83.4)	1027 (82.4)	98.9%

4.4.4 Cause of death in the UK CHIC Study

Of 4,634 deaths, 1,032 (22.3%) were classified as being due to AIDS-defining illness (ADI) and 1862 (40.2%) as being due to non-AIDS illness. A further 1,740 (37.6%) could not be classified as either AIDS or non-AIDS related deaths, of which 1,696 had an unknown cause of death; the remaining were unascertained/unclassifiable. The overall rate of AIDS and non-AIDS deaths were 2.5 per 1,000 person years and 4.4 per 1,000 person years respectively. The rate of deaths with an unknown or unascertained cause was 4.1 per 1,000 person years.

Amongst the 3,053 deaths that had information on cause of death, 33.8% were classified as AIDS deaths: 458 (44.4%) of these were AIDS infection, 386 (37.4%) were AIDS malignancy, 99 (9.6%) were multiple AIDS events and 89 (8.6%) were unknown or unspecified AIDS events. Non-AIDS deaths accounted for 61.0% of deaths where information on cause of death had been available. Non-AIDS malignancy was the most common non-AIDS cause of death, accounting for 7.7% of all deaths and 11.7% of deaths with information on cause. Heart disease, including ischaemic heart disease, other cardiovascular disease and stroke, was the next most common cause of death accounting for 9.4% of deaths, followed by pneumonias (9.3%), deaths due to external causes including suicide, drug overdose and accidental death (8.7%) and liver disease (7.0%) (Table 4.4.5).

4.4.4.1 Mortality rates by cause in the UK CHIC Study over time

Between 1996 and 2012 there was a decrease in the rate of AIDS deaths over time in the UK CHIC Study, with the most rapid decreases in the early-ART period. The rate of AIDS deaths in 1996/1997 was 10.7 per 1,000 person years, and decreased to 2.6 per 1,000 person years in 2000/2001. During subsequent years there was a more moderate decline, with a rate of 1.1 AIDS-related deaths per 1,000 person years in 2010/11 (Figure 4.4.1). Whereas between 1996-1999, the highest rates of AIDS-related deaths were deaths due to AIDS infections (5.7 per 1,000 person years vs. 3.8 per 1,000 person years for AIDS malignancy and 1.5 per 1,000 person years for multiple AIDS illnesses or AIDS unspecified), in 2010/2011 rates of death due to all three types of AIDS illness were similar (0.2, 0.4 and 0.2 per 1,000 person years for AIDS infection, AIDS malignancy and AIDS other respectively) (Figure 4.4.2).

The rate of non-AIDS deaths similarly declined in the early HAART period, from 11.4 per 1,000 person years in 1996/1997 to 5.4 per 1,000 person years in 2000/2001. Between 2000/2001 to 2010/11 a slower decline in the rate of all non-AIDS deaths was observed, with a rate of 3.5 per 1000 person years in 2010/2011 (Figure 4.4.1). Considering specific non-AIDS causes of death, I observed a rapid and large decline in the rate of deaths due to pneumonia in the early-HAART period, from 6.8 per 1,000 person years in 1996/1997 to 1.3 per 1000 person years in 2000/2001. Rates of other non-AIDS causes remained relatively stable between 1996-2012 (Figure 4.4.3).

Rates of all non-AIDS deaths remained higher than the rate of AIDS deaths over the entire period studied. Deaths with an unknown cause occurred at a much higher rate in the early HAART period than either AIDS or non-AIDS deaths, due to the large amount of unavailable data on cause of death in earlier years; only 43% of deaths had available information on cause between 1996-1999. However, as the amount of available data increased in later years, the rate of unknown deaths markedly decreased, and was lower than the rate of AIDS and non-AIDS deaths in 2010/2011 (0.6 per 1,000 person years).

Figure 4.4.1: Rates of AIDS, non-AIDS and unknown causes of death over time in the UK CHIC Study; 1996-2012

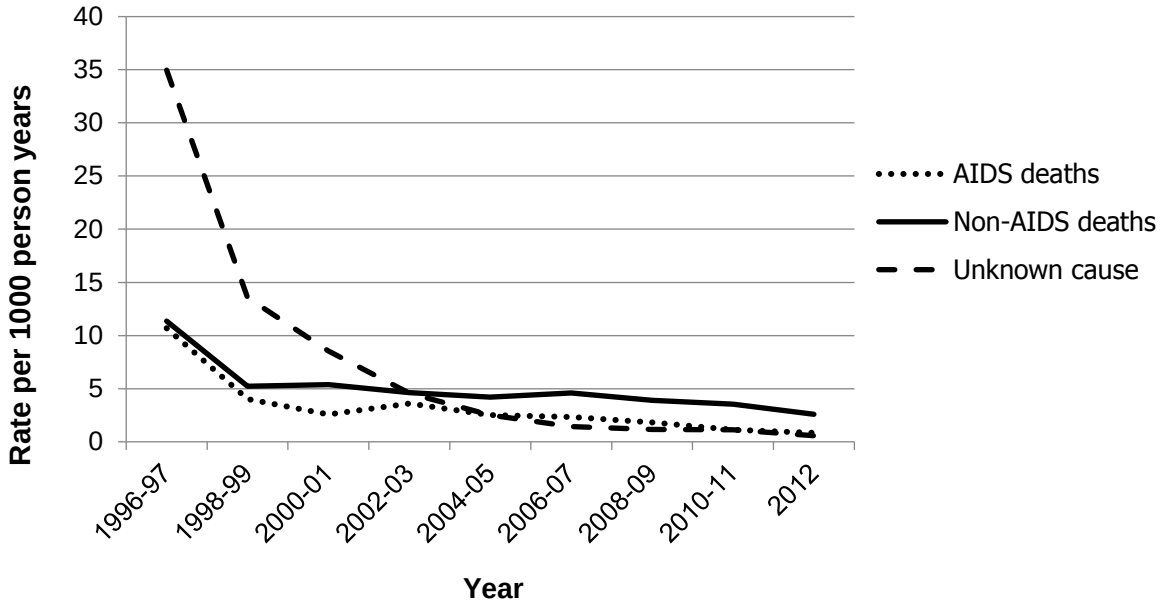


Figure 4.4.2: Rates of AIDS deaths over time in the UK CHIC Study stratified by AIDS cause; 1996-2012

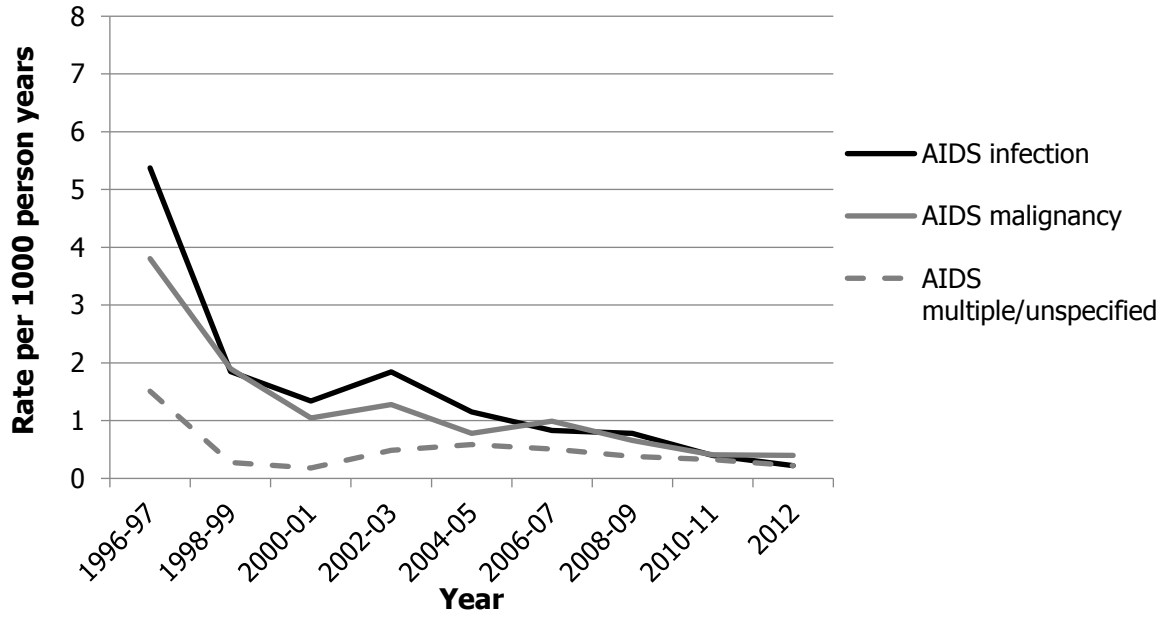
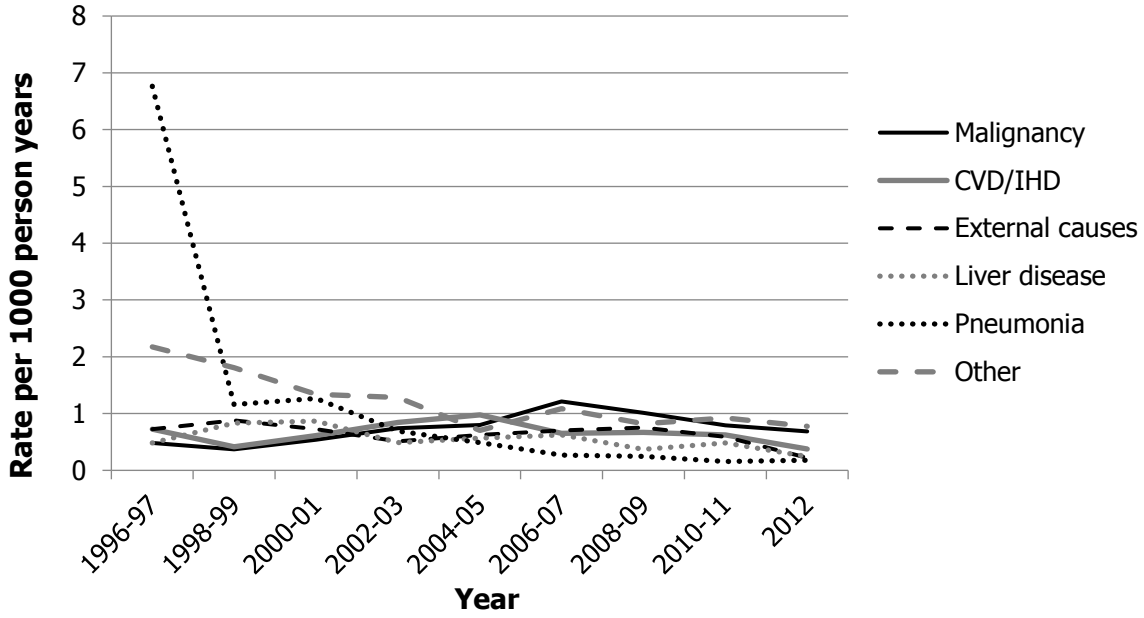


Figure 4.4.3: Rates of specific non-AIDS deaths over time in the UK CHIC Study; 1996-2012



Considering deaths for which there was available information on cause, the proportion of deaths attributable to ADI decreased over time (Table 4.4.5). Of deaths occurring between 1996 and 1999, 42.4% were due to AIDS. However, between 2008 and 2012 only 27.1% of deaths were classified as AIDS-related. The proportion of deaths attributed to AIDS infections halved, from 20.7% in 1996-1999 to 10.5% in 2008-2012. The proportion of deaths due to AIDS malignancy also decreased from 16.7% to 9.7%, however other, unknown or multiple AIDS events remained fairly stable as a proportion of deaths. Conversely, the proportion of deaths that were attributed to non-AIDS causes increased over time. This was largely driven by increases in the proportion of deaths due to non-AIDS malignancy, cardiovascular disease, external causes and liver disease. Pneumonias markedly decreased as a proportion of deaths in the HAART era. Other non-AIDS causes remained fairly stable over time but the proportion of deaths with unknown or unascertained causes decreased after the early HAART period.

Table 4.4.5: Principal cause of death after mortality review in the UK CHIC Study, 1996-2012

Cause	All deaths		Deaths with any information on cause				
	N	(%)	Total (%)	1996-99, n (%)	2000-03, n (%)	2004-07, n (%)	2008-13, n (%)
N	4634		3503	622	593	799	1039
AIDS infection	458	9.9	15.0	129 (20.7)	109 (18.4)	111 (13.9)	109 (10.5)
AIDS malignancy	386	8.3	12.6	104 (16.7)	79 (13.3)	102 (12.8)	101 (9.7)
AIDS other (incl. wasting, multiple and unknown)	188	4.1	6.2	31 (5.0)	24 (4.1)	62 (7.8)	71 (6.8)
Infection	21	0.5	0.7	4 (0.6)	2 (0.3)	6 (0.8)	9 (0.9)
Sepsis/sepsis-like syndrome (incl. multi-organ failure)	117	2.5	3.8	23 (3.7)	25 (4.2)	28 (3.5)	41 (4.0)
Pneumonias	284	6.1	9.3	137 (22.0)	62 (10.5)	42 (5.3)	43 (4.1)
Lung disease (incl. COPD and respiratory failure)	75	1.6	2.5	8 (1.3)	12 (2.0)	16 (2.0)	39 (3.8)
Non-AIDS malignancy	357	7.7	11.7	16 (2.6)	44 (7.4)	117 (14.6)	180 (17.3)
Cardiovascular disease/stroke/ischaemic heart disease	286	6.2	9.4	21 (3.4)	50 (8.4)	91 (11.4)	124 (11.9)
Severe liver disease/failure	215	4.6	7.0	26 (4.2)	43 (7.3)	68 (8.5)	78 (7.5)
Severe kidney disease/failure	59	1.3	1.9	10 (1.6)	15 (2.5)	11 (1.4)	23 (2.2)
External causes*	264	5.7	8.7	31 (5.0)	40 (6.8)	76 (9.5)	117 (11.3)

Cause	All deaths		Deaths with any information on cause				
	N	(%)	Total (%)	1996-99, n (%)	2000-03, n (%)	2004-07, n (%)	2008-13, n (%)
CNS disease	61	1.3	2.0	7 (1.1)	14 (2.4)	17 (2.1)	23 (2.2)
Other (specified)	118	2.6	3.8	17 (2.7)	22 (3.7)	29 (3.6)	50 (4.8)
Other (unclassified)	4	0.1	0.1	1 (0.2)	1 (0.2)	1 (0.1)	2 (0.2)
Unascertained	45	1.0	1.5	5 (0.8)	9 (1.5)	13 (1.6)	17 (1.6)
Unknown	1696/115[†]	36.6	3.8	52 (8.4)	42 (7.0)	9 (1.1)	12 (1.0)
Total AIDS	1032	22.3	33.8	264 (42.4)	212 (35.8)	275 (34.4)	281 (27.1)
Total non-AIDS	1862	40.2	61.0	301 (48.4)	330 (55.7)	502 (62.8)	729 (70.2)
Unascertained/unknown	1741/160[†]	37.6	4.6	57 (9.2)	51 (8.6)	22 (2.8)	29 (2.8)

*Including suicide, accidental or violent deaths, drug overdose and poisoning
[†] Number out of those with information on cause of death

4.4.5 Patient characteristics at time of death, according to cause of death

Age at death was significantly lower for those who died from AIDS-related or unknown causes compared to those who died from non-AIDS causes ($p<0.001$) (Table 4.4.6). Approximately three quarters (74.2%) of those who died from AIDS-related causes were male. This was lower than observed for deaths with non-AIDS and unknown causes where 81.6% and 82.6% were male, respectively. A higher proportion of those who died from AIDS-related illness were of black African ethnicity than those who died due to non-AIDS and unknown causes: 28.8% vs 16.3% and 12.6% respectively. Those with an unknown cause of death were also more likely to have unknown ethnicity. Differences were also observed in the mode of acquisition of people who died from AIDS, non-AIDS and unknown causes, with a higher proportion of people who died from AIDS-related illness having acquired HIV through heterosexual sex: 38.6% vs. 26.9% and 20.1% respectively. Those whose cause of death was unknown were more likely to have died in the early HAART period, as was shown previously, and were therefore also more likely to have entered the UK CHIC cohort between 1996-1999 compared to those with a known cause of death ($p<0.001$). Approximately 78% of individuals with unknown cause of death entered the cohort between 1996 and 1999 compared with 51.4% and 57.5% of those who died due to AIDS and non-AIDS causes respectively.

Considering HIV-related characteristics, deaths of unknown cause most closely resembled AIDS-related deaths as opposed to non-AIDS deaths. The majority of deaths occurred in follow-up i.e. within 6 months of the date last seen in UK CHIC. However, a slightly lower proportion of deaths due to non-AIDS causes occurred during follow-up than of deaths related to AIDS (77.4% and 83.0% respectively). Amongst 3,699 deaths that occurred in follow-up, less than half of those dying from AIDS and unknown causes were thought to be on ART at the time of last visit prior to death. Conversely, approximately 60% of deaths attributed to non-AIDs causes occurred in people who were on ART at their last visit. Whilst more likely to be in follow-up prior to death, those who died from AIDS and unknown causes were less likely to have a CD4 count or viral load available in the year prior to death than those who died from non-AIDS causes ($p<0.001$). The median (IQR) CD4 count in the year prior to death was very low for those dying from AIDS-related illness (49 (11, 141)) cells/mm^3. This was significantly lower than the median CD4 count amongst those who died of non-AIDS illnesses (230 (79, 430)). Only 32% and 32.9% of those dying from AIDS-related and unknown causes had an undetectable viral load in the year prior to death compared to 49.8% of those who died of non-AIDS causes.

Table 4.4.6: Characteristics at death according to cause of death

Characteristics		Cause of death			
		AIDS n=1032	Non-AIDS n=1862	Unknown n=1741	P-value
Age, median (IQR)	years	40 (35, 47)	44 (37, 51)	41 (34, 49)	<0.001
Sex, n (%)	Male	766 (74.2)	1519 (81.6)	1438 (82.6)	<0.001
	Female	266 (25.8)	343 (18.4)	302 (17.4)	
Ethnicity, n (%)	White	522 (50.6)	1227 (65.9)	1071 (61.6)	<0.001
	Black African	297 (28.8)	303 (16.3)	219 (12.6)	
	Black Other	39 (3.8)	80 (4.3)	55 (3.2)	
	Other	82 (8.0)	127 (6.8)	138 (7.9)	
	Unknown	92 (8.9)	125 (6.7)	257 (14.8)	
Mode of HIV acquisition, n (%)	Sex between men	438 (42.4)	944 (50.7)	873 (50.2)	<0.001
	Heterosexual	398 (38.6)	500 (26.9)	350 (20.1)	
	IDU	54 (5.2)	239 (12.8)	238 (13.7)	
	Other	26 (2.5)	60 (3.2)	57 (3.3)	
	Unknown	116 (11.2)	119 (6.4)	222 (12.8)	
Year of cohort entry, n (%)	1996-1999	530 (51.4)	1071 (57.5)	1354 (77.8)	<0.001
	2000-2004	209 (20.3)	393 (21.1)	241 (13.9)	
	2005-2008	196 (19.0)	284 (15.3)	102 (5.9)	
	$\geq$2008	97 (9.4)	114 (6.1)	43 (2.5)	

Characteristics		Cause of death			P-value
		AIDS n=1032	Non-AIDS n=1862	Unknown n=1741	
Centre last attended, n (%)	Brighton	76 (7.4)	149 (8.0)	146 (8.4)	-
	St Mary's	55 (5.3)	184 (9.9)	188 (10.8)	
	Chel & West	185 (17.9)	337 (18.1)	470 (27.0)	
	Mortimer Market Centre	82 (8.0)	226 (12.1)	189 (10.9)	
	King's College	97 (9.4)	195 (10.5)	70 (4.0)	
	Royal Free	186 (18.0)	213 (11.4)	85 (4.9)	
	Barts/ Royal London	75 (7.3)	154 (8.3)	152 (8.7)	
	Edinburgh	23 (2.2)	71 (3.8)	212 (12.2)	
	North Middlesex	70 (6.8)	79 (4.2)	42 (2.4)	
	Homerton	17 (1.7)	39 (2.1)	18 (1.0)	
	Bristol	33 (3.2)	47 (2.5)	24 (1.4)	
	Leicester	22 (2.1)	32 (1.7)	13 (0.8)	
	Middlesbrough	10 (1.0)	17 (0.9)	3 (0.2)	
	Woolwich	43 (4.2)	35 (1.9)	68 (3.9)	
	St George's	39 (3.8)	60 (3.2)	52 (3.0)	
	York	4 (0.4)	5 (0.3)	1 (0.1)	
	Coventry	5 (0.5)	1 (0.1)	0 (0.0)	
	Ashford & St Peters	8 (0.8)	17 (0.9)	6 (0.3)	
	Wolverhampton	2 (0.2)	1 (0.1)	1 (0.1)	

Characteristics		Cause of death			
		AIDS n=1032	Non-AIDS n=1862	Unknown n=1741	P-value
Calendar year of death, n (%)	1996-1999	264 (25.6)	301 (16.2)	872 (50.1)	<0.001
	2000-2004	212 (20.5)	330 (17.7)	414 (23.8)	
	2005-2008	275 (26.7)	502 (27.0)	218 (12.5)	
	2009-2013	281 (27.2)	729 (39.2)	236 (13.6)	
In follow up at time of death[1], n (%)		857 (83.0)	1441 (77.4)	1401 (80.5)	<0.001
On ART[2], n (%)		415 (48.4)	851 (59.1)	544 (38.8)	<0.001
CD4 count recorded in the year prior to death, n (%)		735 (85.8)	1300 (90.2)	1148 (81.9)	<0.001
CD4 count prior to death[2], median (IQR)	cells/mm^3	49 (11, 141)	230 (79, 430)	88 (17, 264)	<0.001
Viral load recorded in the year prior to death, n (%)		640 (74.7)	1225 (85.0)	872 (62.2)	<0.001
Undetectable viral load (≤50) prior to death[2], n (%)		205 (32.0)	610 (49.8)	287 (32.9)	<0.001

[1] Defined where death occurred within 6 months of last follow-up date in UK CHIC i.e. last recorded CD4 count, viral load or ART start date
[2] Amongst those in follow-up at death

4.5 Discussion

4.5.1 Summary and Interpretation

In this chapter I have demonstrated and applied a method for improving mortality ascertainment within an observational cohort study through linkage to HIV surveillance datasets, and through that, a national mortality registry. Further, I have described work undertaken to consolidate information on cause of death from a variety of different data sources in order to assign a principal cause to deaths occurring in the UK CHIC Study. This work has resulted in improved ascertainment of deaths in the UK CHIC Study, with 792 deaths added, and provided useable data on cause of death for the first time. Through this data we are able to observe a decline in rate of AIDS related mortality and an increasing proportion of deaths due to non-AIDS causes. However, a relatively large number of deaths have an unknown cause of death, particularly in earlier years.

4.5.1.1 Ascertaining deaths through the linkage process

As a result of linking to HANDD, I was able to add information on a further 792 deaths to the UK CHIC Study, including deaths in 54 patients that occurred prior to 1996, who were subsequently excluded from the dataset. This is a reasonably large number, given the 3,896 deaths reported in the UK CHIC Study prior to the linkage. The proportion of deaths occurring in years since 2009 increased from 16.6% prior to linkage to 21.5% after the linkage process. In fact, of the 792 new deaths added to the UK CHIC Study dataset, 43.7% had occurred since 2009, with only 12.6% and 11.7% having occurred between 2000-2004 and 2005-2008 respectively. This would suggest that there is a long delay in reporting recent deaths to the UK CHIC Study, so that deaths occurring in more recent years were more likely to be missed prior to linkage. This reporting delay would cause a bias for any time-trend analyses undertaken, underestimating mortality rates in more recent years. Of the deaths added, a higher proportion were amongst those with unknown ethnicity and route of acquisition than was seen in all deaths or for deaths only recorded in UK CHIC. I also observed that patients for whom a HANDD date of death was added were less likely to have a CD4 count or viral load available in UK CHIC in the year prior to death than for all deaths or deaths only ascertained in the UK CHIC Study. These findings suggest that prior to the linkage, the different processes of recording deaths in the UK CHIC Study, relying predominantly on clinician reporting, meant that deaths were more likely to be missing for people who have fewer interactions with participating centres and who are lost to follow-up or transfer care prior to the time of death. This would have important implications for any future analyses of mortality outcomes using UK CHIC data, resulting in an ascertainment (or detection) bias and under-estimating mortality rates for those individuals who have less frequent visits and are lost to study follow-up (539); likely those with poorer engagement in HIV care (540). Further,

those who are lost to follow-up may in fact have higher rates of mortality than those who remain in care (364, 366, 369). By performing this linkage and incorporating information on deaths from both national HIV surveillance and mandatory reporting of deaths, ascertainment of events is no longer reliant on clinician report only, and any ascertainment bias that may have been present previously has been minimised. This linkage has therefore proved to be a worthwhile process.

My estimate of death ascertainment after combining the information in both datasets was high at 95%, using a capture-recapture approach. This was an increase from an estimated 79% prior to the linkage process. Whilst only a relatively small number of deaths were therefore estimated to have been missed, the deaths not ascertained through either UK CHIC or HANDD will not be missing completely at random (541). As HANDD death data is only supplemented with data from ONS for deaths under the age of 65, deaths are more likely to be missing amongst individuals over 65. Any future assessments of age trends in mortality may therefore underestimate associations between mortality older age above this threshold.

I observed that 581 linked records had a date of death recorded in UK CHIC that had not been ascertained in HANDD. The demographic characteristics of these individuals were largely similar to the characteristics seen for all deaths, with approximately 80% male and just over half being of white ethnicity and having acquired HIV through sex between men. However, a slightly higher proportion were amongst those of other non-white or non-African black ethnicity. Compared to all deaths originally available in the UK CHIC dataset, these deaths were less likely to occur in earlier calendar years. Compared to deaths occurring in HANDD only, they were also less likely to occur in the more recent calendar period, again indicating the reporting delay in the UK CHIC Study. Scenarios in which UK CHIC would have a record of a death that would not be recorded in HANDD, either through clinician report or ONS reporting are unclear. Deaths occurring abroad will not be captured on the ONS mortality registry but may reported to the HIV clinic by family or friends, this may explain why deaths are captured in the UK CHIC Study but not be present in ONS data. However, once reported to the HIV clinic, the death should also be reported to HANDD. It is possible that the method of clinician report may influence whether deaths are reported; clinician reporting to HANDD occurs through bi-annual survey completion (542), whereas UK CHIC data collection involves submission of all electronically available data in the patient record. Deaths occurring in individuals who attended for care in Scotland may not be reported to HANDD through clinician report as this surveillance system only covers England, Wales and Northern Ireland, but this only appeared to explain a small number of these deaths (Table 4.4.2). It is possible that incorrect linkage may explain some of these differences, however the majority (86%) of these matches had a linkage score of 1, meaning that a link to HANDD was made based on soundex, sex and date of birth. Also, 428 (73.7%) had a matching score $\leq$0, suggesting no demographic

inconsistencies between linked records. The availability of deaths in UK CHIC not reported to HANDD would imply that this is a mutually beneficial process for both the UK CHIC Study and HIV surveillance, and this information was fed back to investigators at PHE.

4.5.1.2 Assigning a principal cause of death

Of the final 4,634 deaths in the CHIC2013 dataset, only 3,053 (65.9%) had any information available on cause of death, despite consolidating information on cause of death from four different sources of data. A principal cause of death was assigned to 2,938 deaths; 63.4% of all deaths and 96.2% of deaths where there was any information available on cause. Amongst deaths where there was information on cause of death, the majority (61.0%) of deaths in the UK CHIC Study were classified as being due to non-AIDS illnesses according to the chosen HICDEP code for the principal cause of death, with only 33.8% due to AIDS-related illnesses.

Where there was available information on cause of death, a principal cause of death was assigned in 96.2% of cases. However, for a large proportion (34.1%) of deaths, there was no information on cause of death available in any of the four data sources utilised. These deaths predominantly occurred in earlier calendar years and again were more likely in those with other missing data items i.e. those with unknown ethnicity and exposure. A higher proportion of those younger than 30 were also missing cause of death information when compared to the older age groups. Due to the early calendar period and young age at death, it is likely that a high proportion of these deaths were in fact due to AIDS-defining illness and that the true number of AIDS-related deaths is in fact under-estimated. This is also supported by the apparent lower rates of deaths due to AIDS-related compared to non-AIDS deaths observed prior to 2000. With combination ART only introduced in 1996, we would expect to see a high rate of AIDS-related deaths at this time, that is higher than the rate of non-AIDS events and that declines rapidly in the early HAART era, as has been reported in other studies (171, 193). In our study, this is the pattern observed for deaths of unknown cause. Further, the low CD4 counts at time of death and low proportion on ART with an undetectable viral load would suggest that AIDS is a likely cause of death in those with currently unknown cause of death.

The proportion of deaths with information on cause only reached high levels (approximately 80%) for deaths from 2004 onwards, when rates of deaths of unknown cause are lower than for either AIDS or non-AIDS deaths for the first time also. It is unlikely that we will be able to improve the information on cause of deaths occurring in the early ART era (i.e. pre 2000) if it has not been possible to do so using the combination of data sources used here. This will need to be carefully considered in further analyses of cause of death in the UK CHIC Study. Any time-trend analyses should not include this early ART-era as cause-specific mortality rates will be incorrect, with a likely underestimate of AIDS deaths in the early era obscuring evidence of a decline over time. Further, factors associated with cause-specific mortality in earlier years

could be incorrectly estimated. Approaches used in future to account for this will depend on the analysis being undertaken but could involve restricting analyses to later calendar years when information on cause of death is more frequently available. Although this approach is not ideal as it excludes events, any events excluded may be less relevant to current mortality trends so should not reduce generalisability of findings to people currently living with HIV. Alternatively, if we are only interested in classifying deaths as related to AIDS or non-AIDS causes, an approach similar to that utilised by Kowalska et al., in the EuroSIDA study could be employed, which used clinical factors around the time of death to classify deaths as being AIDS related or not. However, this approach was shown to have only moderate agreement with cause of death when classified using the CoDe protocol and relies on data on CD4 count and AIDS-defining illness to be available prior to death (537). In the UK CHIC Study, this will not be the case for a large number of individuals who are LTFU or who transfer their care to a centre that does not participate in the study.

4.5.1.3 Repetition of this process in future

Due to the addition of new centres and patients to the UK CHIC Study and different results of the de-duplication process each year, the linkage to HANDD will need to be repeated when generating each new update of the UK CHIC Study dataset. Having established the steps required to select a best match from one-to-many and many-to-one record links, developed a matching score and algorithm to select a date of death in linked individuals, the process to improve ascertainment of mortality outcomes can now be undertaken quickly. Therefore it is possible to repeat this process each year to improve ascertainment of deaths as part of the annual process of updating the UK CHIC dataset for analysis. As this was the first time that a principal cause of death has been assigned in the UK CHIC Study, and information provided in hand-written CoDe forms needed to be made electronically available, this process took approximately one year to complete and required several face-to-face meetings with clinical members of the mortality review sub-group. It is aimed to streamline this process in future so that subsequent updates can be undertaken more rapidly. Firstly, now that the back-log of CoDe forms has been entered electronically, only smaller numbers new forms will need to be entered going forward. This can be conducted as and when forms are received throughout the year. For the majority of deaths where a principal cause of death is already assigned, it is likely that this information will not change. Exceptions to this situation may be where, in repeating the linkage each year, UK CHIC records link to different HANDD records. New CoDe forms or new information in the annual electronic upload, submitted by centres, will also need to be incorporated in future. This will involve review of information for substantially fewer deaths than were considered in this initial process. Further, as a strategy has now been decided to assign a principal cause of death in simple cases, this can be undertaken by me wherever possible. This will mean that cause of death can be assigned rapidly in some cases, with smaller numbers also requiring review by clinical members of the team. The frequency

of review by the clinical team will ideally be performed annually also, but this will rely on the support and availability of clinicians.

4.5.2 Comparison to the literature

I have used linkage to national surveillance data, which is in turn supplemented with national vital registry data, to improve ascertainment of death in the UK CHIC Study. I report on 4,634 (9.1%) deaths occurring in 50,785 individuals accessing care in England and Scotland, with potential for approximately 253 extra missed deaths in these individuals. Recent reports from HANDD estimate 5,302 (6%) deaths to have occurred in 88,994 individuals diagnosed in England and Wales between 1997 and 2012 (189). The apparent higher risk of mortality in the UK CHIC Study participants could be due to the inclusion of deaths occurring in 1996, when ART was only just beginning to become widely available and mortality rates were still high, and the inclusion of patients attending for care in Scotland. I also observed 581 deaths in UK CHIC participants linked to HANDD records that were not recorded in HANDD.

The majority of HIV cohorts obtain information on deaths through the care-giving hospital or clinic, either through direct extraction from medical records (193), prospective real-time reporting of deaths (173) or the use of CoDe or other similar study-specific data collection forms (172, 534). Additionally, cohorts may employ other methods such as linkage to national vital registries (171, 187) or other local registries (199, 543) alongside standard data collection methods to maximise ascertainment of mortality outcomes. Cohort collaborations such as the ART-CC and CASCADE rely on cohort-specific methods of data collection which may vary (197, 544). Few studies have attempted to estimate the extent to which they are able to ascertain deaths. In the ART-CC, participating cohorts in Europe and North America were asked to report their estimated mortality ascertainment, none of which reported rates below 75%; 9 of the 17 cohorts reported ascertainment rates between 90-95%, which is comparable to the UK CHIC Study, and 4 reported ascertainment above 95%. Ten of the cohorts linked to death registries to get information on deaths, alongside data from hospitals and family or friends. Where death registry data was not used, 4 studies reported receiving information through local registries also. However, the method by which ascertainment was estimated in each study was unknown. Importantly, ascertainment was associated with differences in the mortality rates between cohorts in the 2 years following ART initiation; studies with higher ascertainment reported higher mortality rates, highlighting the importance of linking to registries if possible (545). In France, ascertainment of mortality in HIV-positive adults has been assessed across three data sources; the Mortalité 2000 survey, the French Hospitals Database (FHDH) and a national registry of death certificates. The cross-sectional Mortalité 2000 study, which surveyed HIV clinicians at 185 HIV wards across France, has assessed completeness of death ascertainment through further review of patients LTFU in a sample of

wards, and through a capture-recapture approach, matching to the remaining two data sources. With respect to patients LTFU, relatively small numbers of deaths appeared to be missed, giving an estimated ascertainment of 91% (535). However, a capture-recapture analysis found that only 55% of deaths were ascertained. The FHDH, correctly ascertained only 38% of all deaths in the capture-recapture analysis (546). Further, amongst individuals LTFU in the cohort study, 30% were reported to have died in either the Mortalité 2000 survey or the registry of death certificates, and accounting for this loss-to follow-up impacted survival estimates in the cohort (539).

Our ability to classify cause of death in the UK CHIC Study is somewhat worse than other studies for deaths occurring in the early HAART period due to large amounts of missing data. Cause of death rates in the region of 80-98% have been reported in various cohorts (192, 496, 534). However, few of these cohorts use linkage to external mortality registries to ascertain deaths (171, 547) so most rely on clinician report. If a reporting clinician is aware that a death has taken place they may also be more likely to have information on cause of death, so this could contribute to these high rates of deaths with known cause.

In the UK CHIC Study we report a lower proportion of deaths attributable to AIDS compared to some other studies (193, 201, 534, 547). Data from HANDD and ONS for deaths in England and Wales between 1997 and 2012, classify 58% of deaths as AIDS-related. The proportion of deaths attributed to non-AIDS malignancy, CVD, liver disease and external causes including suicide were similar, however. This higher proportion of AIDS-related deaths is not entirely surprising, as investigators at PHE were able to assign a cause of death for 91% of all deaths in this period (likely through extra data provided only to HANDD) and further steps were taken by PHE investigators to classify AIDS or non-AIDS infections from clinical data if it was not otherwise clear (189). As the majority of deaths with missing information in UK CHIC occurred in the early ART era and were likely to be AIDS related. This may also explain differences observed in other cohorts. In the ART CC, classification rules such as those used in the UK CHIC Study were used to classify cause of death according to the same HICDEP coding system. They were able to assign a cause of death for 85% of cases, similar to the rate in UK CHIC in more recent years. For the period 1996-2006 the ART-CC reported higher proportions of deaths attributable to AIDS, in the region of 10% higher (197). This difference could reflect the periods of study. However, where we were able to assign a cause of death, we observed similar results to those reported in the D:A:D Study over a similar time-period, with 34% of deaths attributed to AIDS in the UK CHIC Study and 29% in the D:A:D Study. The proportion of deaths attributable to CVD and malignancy were also similar in both studies; 12% and 15% malignancy in UK CHIC and D:AD respectively and 9% and 11% attributed to CVD (173, 548). We also found similar causes of death to those seen in France in the Mortalite 2000, 2005 and 2010 surveys (196, 549).

4.5.3 Strengths and Limitations

A large proportion of patient records within the UK CHIC Study were succesfully linked to HIV surveillance data, and through this it was possible to incorporate national registry data on deaths in PLWH. Thus we now have a viable method for improving ascertainment of mortality outcomes that does not rely solely on reporting from HIV clinics. However, it was not possible to link all individuals to a HANDD record, based on the data fields available. Females, those of unknown ethnicity and acquisition risk and those who entered the UK CHIC cohort in earlier calendar years were less likely to be linked to a HANDD record. A high proportion (24.7%) of unlinked individuals for whom there was a date of death in the UK CHIC Study reported IDU transmission risk, a group shown to have high mortality rates (189, 550) and in whom it may be more difficult to capture complete information on deaths due to high rates of LTFU (539, 551, 552). Unlinked individuals who were known to have died in the UK CHIC Study were also younger, more likely to be female, of white ethnicity, to have died in an earlier calendar year and to have most recently attended for HIV care at Edinburgh prior to death than individuals with a death in HANDD only or amongst all individuals who had died in the dataset. Edinburgh is a centre that is known to have a large proportion of IDU clients and it is unsurprising that these records were less likely to be linked and their deaths less likely to be recorded in HANDD, as this dataset provides surveillance of England, Wales and Northern Ireland only. It is likely that amongst those whose records were not linked, mortality may still be under-ascertained, which could result in the attenuation of mortality differences in future analyses or even the appearance of a mortality benefit (553). Further, my estimate of 95% ascertainment after the linkage process, assumes that death ascertainment prior to the linkage is the same for those who are and are not subsequently linked to HANDD, as I applied the ascertainment rate amongst matched individuals to those not linked to get an overall estimate of missing deaths. This may not be a valid assumption, and the overall proportion of deaths ascertained may actually be lower than 95%. However, due to the large number of records successfully linked, any impact should be small.

Another limitation is the large amount of missing data on cause of death, particularly in the early HAART period. This missing data may affect our estimates of cause-specific death rates and proportions, and future analyses of cause of death may need to be restricted to later calendar years. The majority of analyses undertaken in the UK CHIC Study use 2000 as the earliest calendar year for analysis, as this is when viral load monitoring became more routinely available (Figure 3.3.2). From this point on, 76% of deaths had any information on cause of death and 74% were assigned a principal cause of death. The variable quality of cause of death reporting is a difficulty faced by all cohort studies and was an issue when classifying cause of death in the UK CHIC Study. We opted to classify cause of death as best we could according to the information available, regardless of how detailed that information was. This

resulted in probable misclassification in some instances and variable confidence in the selected principal cause of death. Despite these difficulties we found that causes of death in the UK CHIC Study were similar to estimates in another large HIV cohort in high income settings, and for non-AIDS deaths was similar to other reports from the UK. Further, cause of death classification did improve over time.

4.5.4 Conclusion

By linking UK CHIC patient records to HIV surveillance data, the ascertainment of deaths within UK CHIC participants has been improved, and is estimated to have increased from 79% to 95% of all deaths. For the first time in the UK CHIC Study, we have been able to classify cause of death and are now able to study these outcomes amongst PLWH in the UK. In subsequent chapters I shall utilise this newly available data to assess the impacts of late diagnosis on cause-specific mortality and associations between poor engagement in care and late ART initiation on all-cause mortality.

Chapter 5: The role of late diagnosis on mortality in an aging HIV-positive population

5.1 Introduction

HIV diagnosis is the first step towards entering HIV care and initiating ART. Diagnosis once HIV has progressed to an advanced stage of disease, referred to as late diagnosis, is associated with high rates of morbidity and mortality (272, 292), particularly in the short-term following HIV diagnosis (251, 267, 271, 294). In the UK, as many as 95% of deaths in the year following HIV diagnosis occur amongst those diagnosed late (274). It is associated with high rates of AIDS-related morbidity, due to ongoing destruction of the immune system as HIV replicates in the absence of treatment, which leads to the occurrence of opportunistic infections and cancers (40, 58). In approximately 15% of instances, HIV will be diagnosed in concurrence with an AIDS-defining illness (288, 293, 294). Therefore, a large proportion of deaths occurring following late diagnosis are related to AIDS-defining illness (303).

Recent studies have clearly demonstrated both the individual (141) and public health benefits (138, 152) of initiating ART early in the course of HIV infection. Therefore, timely diagnosis is a key element of achieving good outcomes in PLWH and reducing HIV incidence. However, for many countries, including the UK, undiagnosed HIV represents the largest gap along the care pathway depicted in the continuum of care (216, 229, 240, 376). In the UK it is estimated that 13% of PLWH in 2015 were undiagnosed and 39% of new diagnoses occurred after the individual's CD4 count had dropped below 350 cells/mm^3 (70).

HIV-positive individuals that are diagnosed at an older age are more likely to be diagnosed with advanced HIV disease than younger HIV-positive individuals (265, 271, 272, 274, 275, 277). This could be because older adults are less likely to test and test less frequently for HIV than younger adults (554, 555), although data on HIV testing patterns amongst older individuals in the UK are lacking. The apparent faster progression of HIV in older individuals may also be a contributing factor (304, 305, 556, 557). This higher rate of progression could also contribute to notably high rates of mortality that are observed amongst older newly diagnosed PLWH with advanced HIV disease, compared to older individuals who are not diagnosed late and to younger individuals also diagnosed late (296). However, it is not understood if the impact of late diagnosis on mortality is greater for older individuals than younger PLWH. One single-centre UK study to investigate the effect of late presentation to care and age on mortality did not find an interaction effect between these two factors (222). Furthermore, whilst it has been shown that approximately half of deaths occurring shortly

following HIV diagnosis may be attributed to AIDS-related illness, few studies have formally estimated the effect of late diagnosis on mortality according to cause of death (302).

In this chapter I investigate the relationships between age, late diagnosis and mortality outcomes. As well as examining the association between older age and late diagnosis, I investigate the role of each of these factors in both AIDS and non-AIDS related mortality, further, considering whether the impact of late diagnosis on mortality is greater for older newly diagnosed PLWH than younger.

5.2 Methods

5.2.1 Patients

Included individuals were those who were diagnosed with HIV between 2000 and 2012 aged $\geq$16 years and entered the UK CHIC Study within 6 months of this diagnosis date. The CHIC2013 dataset was used for this analysis, using the causes of death as derived in Chapter 4.

5.2.2 Definitions

5.2.2.1 Date of HIV diagnosis

Date of first ever HIV positive test result is requested as part of the annual data submission received from centres. However, this information is not known for all individuals in the dataset and further, centres may often re-test patients who newly present for care at their clinic, meaning that the HIV-positive test date received is not the date of initial HIV diagnosis. In the past, date of diagnosis has been estimated by taking the earliest of: this HIV positive test date; the first available CD4 count; first recorded AIDS event; first drug start date; first date seen at a participating clinic. From the CHIC2013 dataset onwards, a date of HIV diagnosis is also available through the linkage to HANDD. Therefore, for the purposes of this analysis, date of diagnosis was selected using information on the recorded HIV positive test date, the earliest event date in UK CHIC and the HANDD date of diagnosis as follows. For UK CHIC records not linked to a HANDD record or those not considered to be a true match, the earliest of HIV positive test date and earliest event in the UK CHIC dataset was taken to be the date of diagnosis. For records linked to HANDD that were considered to be a true match, the earliest of HANDD date of diagnosis, UK CHIC HIV positive test date and earliest event date was chosen as the date of diagnosis, except in the circumstances outlined in Table 5.2.1.

Table 5.2.1: Scenarios when the earliest date NOT chosen as date of diagnosis for matched patient records

Date order	Scenario	Date updated to:
-	(i) CD4 count, viral load, ART start date or AIDS event prior to HDD	(i) Earliest of CHP / CEE (ii) CEE if CHP is 1st January
HDD < CHP < CEE	(i) HDD is 1st January (ii) All dates occur in same calendar year and month and HDD is 1st of month	CHP
HDD < CEE < CHP		CEE
HDD < CEE = CHP	(i) HDD is 1st January / 1st June / 15th June / 1st July (ii) All dates occur in same calendar year and month and HDD is 1st of month	CEE / CHP
CHP < CEE (HDD missing)	(i) CHP is 1st January	CEE
CHP < HDD < CEE	(i) CHP is 1st January (ii) CHP is 1st of month with HDD and CEE <6 months apart	HDD
CHP < CEE < HDD		CEE
CHP < CEE = HDD	(i) CHP is 1st January / 1st June / 15th June / 1st July (ii) All dates occur in same calendar year and month and CHP is 1st of month	CEE / HDD
CEE < HDD < CHP	(i) Only the first seen date is before HDD and any CD4, viral load, drug start or study entry date is still after HDD	Diagnosis date
	(ii) As (i) with CHP before any CD4, viral load, drug start or entry date and HDD is 1st January in same year as CHP	CHP
CEE < CHP < HDD	(i) Only the first seen date is before CHP and any CD4, viral load, drug start or study entry date is still after CHP	CHP
	(ii) As (i) with HDD before any CD4, viral load, drug start or	HDD

Date order	Scenario	Date updated to:
	entry date and CHP is 1st January in same year as HDD	
CEE < CHP=HDD	(i) Only the first seen date is before CHP/HDD and any CD4, viral load, drug start or study entry date is still after CHP/HDD	CHP / HDD
HDD=HANDD date of diagnosis; CHP=CHIC HIV-positive test date; CEE=CHIC earliest event date		

5.2.2.2 Late diagnosis

Individuals were defined as being diagnosed late if they had a CD4 count ≤350 cells/mm^3 or diagnosis of an AIDS-defining illness up to 90 days after entry into the UK CHIC Study. This cut-off has been widely used to define late diagnosis as it has been shown to be predictive of poor outcomes and prior treatment guidelines have recommended this as the threshold for ART initiation (112, 250, 251). Individuals without a CD4 count result within this time period were included in the analysis and were classified as having a late diagnosis if an AIDS-defining event occurred within 90 days or non-late diagnosis otherwise. As defined in previous studies, advanced immunosuppression was defined as the presence of a CD4 count <200 cells/mm^3 or AIDS-defining illness within 90 days of entry into the UK CHIC Study (250, 251).

5.2.2.3 Other definitions

Older age was defined as those aged at least 50 years at presentation for care. Deaths were classified as AIDS-related, non-AIDS related or of unknown cause according to the principal cause of death HICDEP code (Chapter 4). Those without a selected principal cause of death and those with codes for unknown or unclassifiable causes of death were classified as unknown causes.

5.2.3 Statistical Analysis

Differences in characteristics between those who were older and younger at diagnosis were assessed using Chi-square and Mann Whitney U tests. The proportion of people with late diagnosis and advanced immunosuppression was compared by age group using chi-squared tests. The association between age and late diagnosis was further assessed using univariable and multivariable logistic regression with late diagnosis as the dependent variable. In the multivariable model, potential confounders that were considered were sex (male/female), ethnicity (white, black African, black other, other, unknown), mode of HIV acquisition (sex between men, heterosexual, other, unknown), location of HIV clinic (London, other UK), HBV

co-infection and HCV co-infection at diagnosis (no, yes, not tested). Interaction effects between age and all other independent variables were tested in the main model and stratified analysis were performed to determine what factors were associated with late diagnosis amongst those aged below 50 and those aged 50 and above. Factors that remained significant at 5% level in univariable analysis were included in the multivariable model.

Follow-up was considered from date of entry into the UK CHIC Study until the earliest of: 6 months after the date last seen at a UK CHIC participating centre, 31st December 2012 or death. Crude mortality rates were calculated according to time since diagnosis (0-0.5, 0.5-1, 1-3, 3-5, 5-7 and >7 years) and cause of death (AIDS, non-AIDS, unknown). Mortality rates were then stratified by age and late diagnosis. The population attributable risk fraction (PAR%) was calculated for late diagnosis amongst those aged 50 and above and below 50, to determine the proportion of deaths that could be avoided if no-one were to be diagnosed late in either age group. The PAR% is estimated using the following equation:

$$PAR\% = \frac{p \times (RR - 1)}{1 + (p \times (RR - 1))} \times 100$$

where p is the prevalence of late diagnosis and RR is the crude relative risk of mortality for those with late diagnosis.

To assess formally the associations between age, late diagnosis and mortality, only mortality in the year following diagnosis was considered, and follow-up was censored after 1 year. This was done to generate 'cleaner' estimates of the association between late diagnosis and mortality. Previous studies have shown that the majority of mortality associated with late diagnosis occurs soon after diagnosis (267, 271). In the longer term, this association becomes mixed with ART effects as people start treatment, and with an individual's ability to adhere to treatment and remain in care over time. It is hypothesised that, whilst some individuals once diagnosed late will engage well with care, for others, late diagnosis is a consequence of more chaotic lifestyles which would also affect adherence and engagement with care services that would not be adequately captured in UK CHIC data to allow this to be accounted for in analyses (558). The long-term effects of late ART initiation are studied in Chapter 6.

Kaplan-Meier methods were used to estimate the probability of all-cause mortality over 1 year according to (i) age, (ii) late diagnosis and (iii) late diagnosis separately for those aged $<$ or $\geq$ 50 years. Cox Proportional Hazards models assessed the independent effects of age and late diagnosis on all-cause mortality in the year following diagnosis, adjusting for other factors. Factors considered in adjusted models were sex, ethnicity, mode of HIV acquisition, year of diagnosis, HIV viral load ($\log_{10}$copies/ml), HBV and HCV co-infection, with factors significant at the 5% level retained in the model, unless there was evidence of colinearity. In order to

determine whether the association between late diagnosis and 1 year mortality differed in older and younger individuals, an interaction effect between age and late diagnosis was tested for significance in the adjusted model.

Competing-risks survival analyses were used to assess the impact of age and late diagnosis on AIDS and non-AIDS related mortality in the year after diagnosis, with follow-up censored at this point. For the outcome of AIDS mortality, deaths from non-AIDS or unknown causes were considered to be competing risk events. Similarly for non-AIDS mortality, AIDS deaths and deaths from unknown causes were considered competing risks. The cumulative incidence of both AIDS and non-AIDS mortality was estimated according to (i) age, (ii) late diagnosis and (iii) late diagnosis separately for those aged $<$ or $\geq$ 50. The SAS macro %CUMINCID was used to estimate cumulative incidence. Fine-Gray methods investigated relationships between age, late diagnosis and cause-specific mortality, adjusting for other factors that were significant at the 5% level. Again an interaction effect between age and late diagnosis was tested for significance in adjusted models. These analyses were performed using the SAS macro %PSHREG.

5.2.4 Sensitivity Analyses

A sensitivity analysis was performed in which individuals who did not have a CD4 count available at entry into the UK CHIC Study and who did not have an AIDS defining illness were assumed to be diagnosed late. Further, the factors associated with having a CD4 count at entry into the UK CHIC Study were investigated in a logistic regression analysis.

5.3 Results

5.3.1 Characteristics at entry into the UK CHIC Study

Of 50,785 individuals in the UK CHIC Study, 32,283 had a date of HIV diagnosis between 2000 and 2012. Of these, 24,691 entered the UK CHIC Study within 6 months of this diagnosis date and 24,675 were aged at least 16 at diagnosis.

The median (IQR) age of study participants was 34 (28, 41) with a maximum recorded age of 84. Of 24,675 included individuals, 2203 (8.9%) were aged at least 50 at the time of diagnosis; 612 (2.5%) were aged at least 60. The majority of study participants were aged between 30 and 40 (9858 (40.0%)).

Those diagnosed with HIV aged at least 50 were more likely to be male (73.5% vs. 67.3%), white (54.0% vs. 44.4%) and have a heterosexual (49.0% vs. 44.0%) or unknown (11.9% vs. 6.9%) mode of HIV acquisition than those diagnosed aged below 50 (all $p<0.001$; Table 5.3.1). Older age was also associated with being diagnosed in a more recent calendar year. A higher proportion of older newly diagnosed individuals presented to a UK CHIC centre that was located outside of London compared to the younger group (24.2% vs 19.2%). Whilst statistically significant differences were found in the HBV and HCV co-infection status by 10 year age groups, the proportion of individuals that had either HBV or HCV co-infection was largely similar in each age category and no difference were found when comparing those aged at least 50 to those aged below 50.

Median (IQR) time to entry in the UK CHIC Study after diagnosis was short in all age groups, but shortest in those aged below 30 at 1 (0, 23) days. The median CD4 count at study entry was lower amongst those diagnosed aged $\geq$50 and the proportion who experienced an AIDS-defining illness increased with older age. CD4:CD8 ratio was low in both groups, but was lowest in those aged $\geq$60; median (IQR)=0.2 (0.1, 0.5). The median (IQR) viral load was 4.8 (3.8, 5.4) $\log_{10}$copies/ml in those aged 50 and above compared to 4.5 (3.7, 5.1) $\log_{10}$copies/ml in those aged below 50.

Table 5.3.1: Characteristics at entry into UK CHIC Study according to age at diagnosis

	N	Age[1]					Age[2]		p-value[1]	p-value[2]
		<30	30-39	40-49	50-59	≥60	<50	≥50		
N	24675	7492	9858	5122	1591	612	22472	2203	-	-
Follow-up [years],									<0.001	<0.001
median (IQR)	24675	3.9 (1.2, 7.7)	4.4 (1.5, 8.0)	3.8 (1.3, 7.1)	3.2 (1.1, 6.5)	2.9 (1.0, 6.0)	4.1 (1.4, 7.7)	3.1 (1.1, 6.4)		
Time to entry [days],									<0.001	<0.001
median (IQR)	24675	1 (0, 23)	5 (0, 25)	6 (0, 26)	7 (0, 28)	7 (0, 27)	4 (0, 24)	7 (0, 27)		
Age [years],										
median (IQR)	24675	26 (23, 28)	34 (32, 37)	43 (41, 46)	53 (51, 56)	64 (61, 67)	33 (28, 39)	55 (52, 60)	-	-
Sex									<0.001	<0.001
Male	16745	4682 (62.5)	6663 (67.6)	3782 (73.9)	1153 (72.5)	465 (76.0)	15127 (67.3)	1618 (73.5)		
Female	7927	2809 (37.5	3194 (32.4)	1339 (26.2)	438 (27.5)	147 (24.0)	7342 (32.7)	535 (26.6)		
Ethnicity									<0.001	<0.001
White	11162	3315 (44.3)	4226 (42.9)	2432 (47.5)	855 (53.7)	334 (54.6)	9973 (44.4)	1189 (54.0)		
Black African	8264	2394 (32.0)	3640 (36.9)	1665 (32.5)	427 (26.8)	138 (22.6)	7699 (34.3)	565 (25.7)		
Black Other	1562	525 (7.0)	559 (5.7)	321 (6.3)	112 (7.0)	45 (7.4)	1405 (6.3)	157 (7.1)		
Other	2602	936 (12.5)	1036 (10.5)	473 (9.2)	113 (7.1)	44 (7.2)	2445 (10.9)	157 (7.1)		
Unknown	1085	322 (4.3)	397 (4.0)	231 (4.5)	84 (5.3)	51 (8.3)	950 (4.2)	135 (6.1)		
HIV acquisition									<0.001	<0.001
Sex between men	10576	3538 (47.2)	4158 (42.2)	2110 (41.2)	571 (35.9)	199 (32.5)	9806 (43.6)	770 (35.0)		
Heterosexual	10968	3098 (41.4)	4507 (45.7)	2283 (44.6)	771 (48.5)	309 (50.5)	9888 (44.0)	1080 (49.0)		

	N	Age[1]					Age[2]		p-value[1]	p-value[2]
		<30	30-39	40-49	50-59	≥60	<50	≥50		
Other	1308	355 (4.7)	544 (5.5)	319 (6.2)	71 (4.5)	19 (3.1)	1218 (5.4)	90 (4.1)		
Unknown	1823	501 (6.7)	649 (6.6)	410 (8.0)	178 (11.2)	85 (13.9)	1560 (6.9)	263 (11.9)		
Year of diagnosis									<0.001	<0.001
2000-2003	6947	2300 (30.7)	3042 (30.9)	1145 (22.4)	332 (20.9)	128 (20.9)	6487 (28.9)	460 (20.9)		
2004-2007	8563	2602 (34.7)	3478 (35.3)	1766 (34.5)	511 (32.1)	206 (33.7)	7846 (34.9)	717 (32.6)		
2008-2012	9165	2590 (34.6)	3338 (33.9)	2211 (43.2)	748 (47.0)	278 (45.4)	8139 (36.2)	1026 (46.6)		
Centre									<0.001	<0.001
London	19819	6059 (80.9)	7996 (81.1)	4095 (80.0)	1186 (74.5)	483 (78.9)	4322 (19.2)	534 (24.2)		
Outside London	4856	1433 (19.1)	1862 (18.9)	1027 (20.0)	405 (25.5)	129 (21.1)	18150 (80.8)	1669 (75.8)		
HBV co-infection									0.023	0.637
No	6958	2138 (28.5)	2732 (27.7)	1480 (28.9)	449 (28.2)	159 (26.0)	6350 (28.3)	608 (27.6)		
Yes	359	83 (1.1)	149 (1.5)	91 (1.8)	30 (1.9)	6 (1.0)	323 (1.4)	36 (1.6)		
Not tested	17358	5271 (70.4)	6977 (70.8)	3551 (69.3)	112 (69.9)	447 (73.0)	15799 (70.3)	1559 (70.8)		
HCV co-infection									<0.001	0.449
No	7021	2133 (28.5)	2705 (27.4)	1531 (29.9)	479 (30.1)	173 (28.3)	6369 (28.3)	652 (29.6)		
Yes	306	60 (0.8)	131 (1.3)	87 (1.7)	20 (1.3)	8 (1.3)	278 (1.2)	28 (1.3)		
Not tested	17348	5299 (70.7)	7022 (71.2)	3504 (68.4)	1092 (68.6)	431 (70.4)	15825 (70.4)	1523 (69.1)		
CD4 count [cells/mm^3]										
median (IQR)	19193	386 (242, 557)	317 (153, 506)	271 (107, 469)	248 (89, 430)	198 (84, 402)	332 (166, 516)	230 (88, 421)	<0.001	<0.001
<200	6012	1072 (14.3)	2524 (25.6)	1614 (31.5)	559 (35.1)	243 (39.7)	5210 (23.2)	802 (36.4)	<0.001	<0.001
201-350	4282	1274 (17.0)	1770 (18.0)	875 (17.1)	271 (17.0)	92 (15.0)	3919 (17.4)	363 (16.5)		

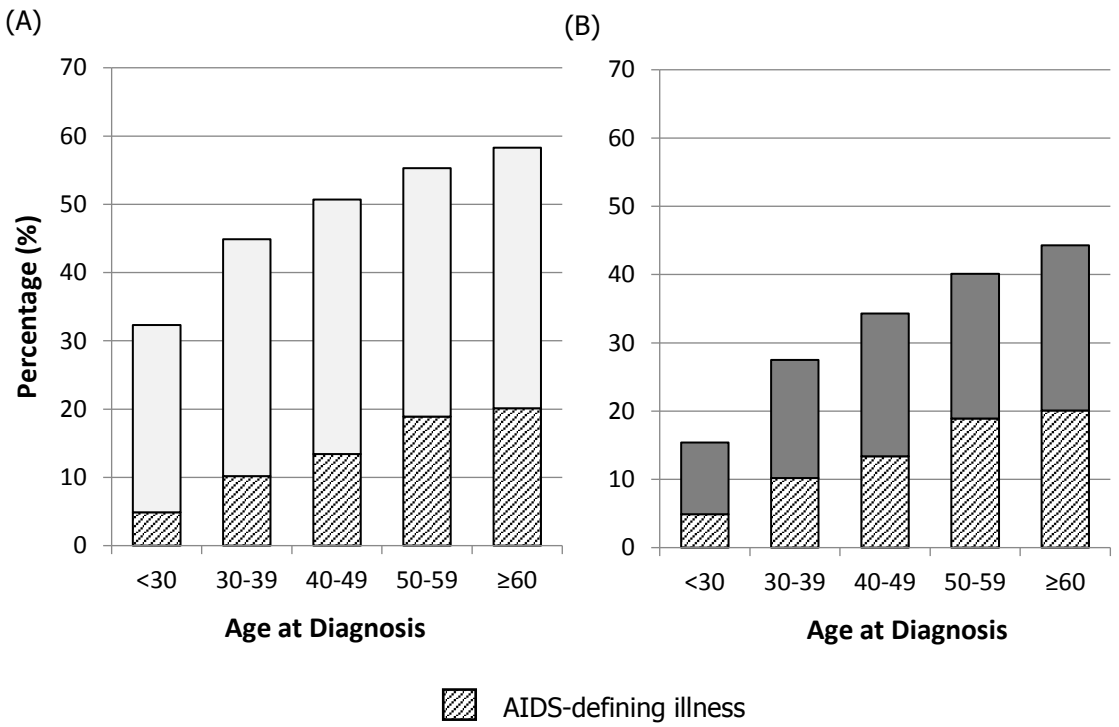
	N	Age[1]					Age[2]		p-value[1]	p-value[2]
		<30	30-39	40-49	50-59	≥60	<50	≥50		
351-499	3880	1348 (18.0)	1535 (15.6)	718 (14.0)	223 (14.0)	56 (9.2)	3601 (16.0)	279 (12.7)		
>500	5019	1774 (23.7)	2024 (20.5)	902 (17.6)	231 (14.5)	88 (14.4)	4700 (20.9)	319 (14.5)		
missing	5482	2024 (27.0)	2005 (20.3)	1013 (19.8)	307 (19.3)	133 (21.7)	5042 (22.4)	440 (20.0)		
AIDS diagnosis									<0.001	<0.001
No	22196	7126 (95.1)	8854 (89.8)	4436 (86.6)	1291 (81.1)	489 (79.9)	20416 (90.9)	1780 (80.8)		
Yes	2479	366 (4.9)	1004 (10.2)	686 (13.4)	300 (18.9)	123 (20.1)	2056 (9.2)	423 (19.2)		
CD4:CD8 ratio									<0.001	<0.001
median (IQR)	15414	0.4 (0.3, 0.7)	0.4 (0.2, 0.6)	0.3 (0.1, 0.5)	0.3 (0.1, 0.5)	0.2 (0.1, 0.5)	0.4 (0.2, 0.6)	0.2 (0.1, 0.5)		
Viral load [log_{10}copies/ml]										
median (IQR)	19247	4.3 (3.6, 5.0)	4.5 (3.7, 5.2)	4.7 (3.7, 5.3)	4.7 (3.8, 5.4)	4.9 (3.9, 5.5)	4.5 (3.7, 5.1)	4.8 (3.8, 5.4)	<0.001	<0.001
<10,000	6333	2045 (27.3)	2559 (26.0)	1226 (23.9)	376 (23.6)	127 (20.8)	5830 (25.9)	503 (22.8)	<0.001	<0.001
10,000-100,000	6979	2107 (28.1)	2929 (29.7)	1402 (27.4)	402 (25.3)	139 (22.7)	6438 (28.7)	541 (24.6)		
>100,000	5935	1349 (18.0)	2384 (24.2)	1475 (28.8)	508 (31.9)	219 (35.8)	5208 (23.2)	727 (33.0)		
missing	5428	1991 (26.6)	1986 (20.2)	1019 (19.9)	305 (19.2)	127 (20.8)	4996 (22.2)	432 (19.6)		

[1]Comparison between all age groups (<30, 30-39, 40-49, 50-59, >60)
[2] Comparison between older (>50) and younger (<50)

5.3.2 Late diagnosis

Of 24,675 included individuals, 10,680 (43.3%) were diagnosed late (95% CI (42.7%, 43.9%)). Among those diagnosed late, 2,479 (23.2%) had experienced an AIDS-defining illness of whom 235 (9.5%) did not have a CD4 count. Amongst those aged <30, 30-40, 40-49, 50-59 and ≥60, 2,420 (32.3%), 4,427 (44.9%), 2,596 (50.7%), 880 (55.3%) and 357 (58.3%) were diagnosed late respectively (Figure 5.3.1(A)). 6,533 (26.5%) newly diagnosed individuals had advanced immunosuppression (95% CI (25.9%, 27.0%)). As with late diagnosis, the proportion of people with advanced immunosuppression increased with older age such that 271 (44.3%) of those aged 60 and above had advanced immunosuppression compared to 1156 (15.4%) of those aged below 30 (p<0.001; Figure 5.3.1(B))

Figure 5.3.1: Proportion of individuals with (A) late diagnosis and (B) advanced immunosuppression, according to age at diagnosis



5.3.2.1 Factors associated with late diagnosis

The odds of late diagnosis increased with older age (Table 5.3.2). After adjusting for potential confounders including sex, ethnicity, mode of HIV acquisition and calendar year, older age was more strongly associated with late diagnosis. Compared to those aged <30 at diagnosis, those aged 50-59 had 186% higher odds of late diagnosis (adjusted OR (95% Confidence Interval; CI)=2.86 (2.55, 3.21)), whilst those aged 60 and above had a 242% increase in the odds of late diagnosis (aOR (95% CI)=3.42 (2.86, 4.08)).

Late diagnosis was more prevalent amongst females (49.9%), those of black African ethnicity (57.7%), those who acquired HIV through heterosexual sex (55.7%) and those with HBV co-infection (57.1%). Sex, ethnicity, mode of HIV acquisition, calendar year of diagnosis, HBV and HCV co-infection were found to be independently associated with late diagnosis (Table 5.3.2). In adjusted analyses, compared to those of white ethnicity, those of black African and black other ethnicity were 99% (95% CI=1.82, 2.16) and 20% (95% CI=1.06, 1.35) more likely to be diagnosed late than those of white ethnicity. Those of any other known ethnicity were also more likely to be diagnosed late (aOR (95% CI)=1.43 (1.30, 1.56)). Heterosexuals and those with other known modes of HIV acquisition had higher odds of late diagnosis than MSM; aOR (95% CI)= 1.86 (1.70, 2.03) and 1.55 (1.37, 1.75) respectively. Those of unknown ethnicity or unknown mode of HIV acquisition had the lowest odds of late diagnosis compared to those of white ethnicity and MSM, respectively (aOR (95% CI)=0.72 (0.62, 0.84) and 0.66 (0.58, 0.75)), likely due to the definition of late diagnosis used that classifies those without a CD4 count as non-late diagnosis. After adjusting for other demographic factors, females were 17% less likely to be diagnosed late than males (95% CI=0.77, 0.89). The odds of being diagnosed late decreased by 3% each year (95% CI=0.97, 0.98). HIV/HBV co-infected individuals were 25% more likely to be diagnosed late (95% CI=1.00, 1.57) than HIV mono-infected individuals. In both unadjusted and adjusted analyses those with an unknown HCV co-infection status were less likely to be diagnosed late that HIV mono-infected individuals. There was weak evidence that those presenting for care at a centre in London were less likely to be diagnosed late than those presenting outside London (aOR (95% CI)=0.94 (0.88, 1.00)).

Table 5.3.2: Factors associated with late diagnosis amongst those presenting for care at a UK CHIC centre

		% late diagnosis	Unadjusted estimates		Adjusted estimates	
			OR (95% CI)	P-value	OR (95% CI)	P-value
Age	<30	32.3	1.00	<0.001	1.00	<0.001
	30-39	44.9	1.71 (1.61, 1.82)		1.66 (1.55, 1.77)	
	40-49	50.7	2.15 (2.00, 2.32)		2.23 (2.06, 2.41)	
	50-59	55.3	2.59 (2.32, 2.90)		2.86 (2.55, 3.21)	
	≥60	58.3	2.93 (2.48, 3.47)		3.42 (2.86, 4.08)	
Sex	Male	40.1	1.00	<0.001	1.00	<0.001
	Female	49.9	1.49 (1.41, 1.57)		0.83 (0.77, 0.89)	
Ethnicity	White	34.8	1.00	<0.001	1.00	<0.001
	Black African	57.7	2.56 (2.41, 2.71)		1.99 (1.82, 2.16)	
	Black Caribbean	42.6	1.39 (1.25, 1.55)		1.20 (1.06, 1.35)	
	Other	42.5	1.39 (1.27, 1.51)		1.43 (1.30, 1.56)	
	Unknown	24.0	0.59 (0.51, 0.68)		0.72 (0.62, 0.84)	
Mode of acquisition	Sex between men	33.3	1.00	<0.001	1.00	<0.001
	Heterosexual	55.7	2.52 (2.38, 2.66)		1.86 (1.70, 2.03)	
	Other	45.1	1.64 (1.46, 1.85)		1.55 (1.37, 1.75)	
	Unknown	25.1	0.67 (0.60, 0.75)		0.66 (0.58, 0.75)	
Year of diagnosis	Per year	-	0.98 (0.97, 0.98)	<0.001	0.97 (0.97, 0.98)	<0.001
Centre	Outside London	45.4	1.00	0.001	1.00	0.065
	London	42.8	0.90 (0.84, 0.96)		0.94 (0.88, 1.00)	

		% late diagnosis	Unadjusted estimates		Adjusted estimates	
			OR (95% CI)	P-value	OR (95% CI)	P-value
HBV co-infection	No	45.0	1.00	<0.001	1.00	0.047
	Yes	57.1	1.63 (1.31, 2.01)		1.25 (1.00, 1.57)	
	Not tested	42.3	0.90 (0.85, 0.95)		0.95 (0.88, 1.03)	
HCV co-infection	No	46.3	1.00	<0.001	1.00	<0.001
	Yes	43.5	0.89 (0.71, 1.12)		0.86 (0.68, 1.10)	
	Not tested	42.1	0.84 (0.80, 0.89)		0.73 (0.67, 0.79)	

OR=Odds ratio; CI=Confidence interval

5.3.2.2 Factors associated with late diagnosis amongst those aged 50 and above

Amongst those aged 50 and above, there was strong evidence that ethnicity, mode of HIV acquisition and calendar year were associated with late diagnosis (Table 5.3.3). Those of black African and other known ethnicity were 45% (95% CI=1.13, 1.87) and 60% (95% CI= 1.12, 2.30) more likely to be diagnosed late compared to those of white ethnicity. Those who acquired HIV through heterosexual sex were 29% more likely than MSM to be diagnosed late (95% CI=1.02, 1.62). Those of unknown ethnicity or unknown mode of HIV acquisition again had the lowest odds of late diagnosis when compared to those of white ethnicity and MSM (aOR (95% CI)=0.51 (0.33, 0.79) and 0.46 (0.33, 0.65), respectively). Late diagnosis was again less likely for older diagnosed individuals in more recent calendar years (aOR (95% CI) =0.96 (0.93, 0.98)). There was some evidence of increased odds of late diagnosis with older age amongst people aged 50 and above. Those aged 60 and above had 21% higher odds of late diagnosis than those aged 50-59 (95% CI=0.99, 1.47). As was seen in the main analysis, HCV co-infection status was found to be significantly associated with late diagnosis overall, with those without a HCV serology test being 36% less likely to be diagnosed late than those who were not co-infected with HCV (95% CI=0.52, 0.79). However, those who were co-infected with HCV showed no statistically significant difference in the likelihood of late diagnosis when compared to those who were not co-infected with HCV (aOR (95% CI)=0.55 (0.26, 1.19)).

Table 5.3.3: Factors associated with late diagnosis amongst those aged ≥50 years

		% late diagnosis	Unadjusted		Adjusted	
			OR (95% CI)	P-value	OR (95% CI)	P-value
Age	50-59	55.3	1.00	0.201	1.00	0.063
	≥60	58.3	1.13 (0.94, 1.37)		1.21 (0.99, 1.47)	
Sex	Male	55.9	1.00	0.661	-	-
	Female	56.9	1.04 (0.86, 1.26)			
Ethnicity	White	53.7	1.00	<0.001	1.00	<0.001
	Black African	65.5	1.63 (1.33, 2.01)		1.45 (1.13, 1.87)	
	Black Caribbean	58.0	1.19 (0.85, 1.66)		1.06 (0.73, 1.52)	
	Other	63.7	1.51 (1.07, 2.13)		1.60 (1.12, 2.30)	
	Unknown	27.4	0.33 (0.22, 0.48)		0.51 (0.33, 0.79)	
Mode of acquisition	Sex between men	54.4	1.00	<0.001	1.00	<0.001
	Heterosexual	63.8	1.48 (1.22, 1.78)		1.29 (1.02, 1.62)	
	Other	54.4	1.00 (0.65, 1.55)		0.95 (0.60, 1.48)	
	Unknown	30.4	0.37 (0.27, 0.49)		0.46 (0.33, 0.65)	
Year of diagnosis	per year	-	0.97 (0.95, 1.00)	0.023	0.96 (0.93, 0.98)	0.002
Centre	Outside London	57.1	1.00	0.606	-	-
	London	55.8	0.95 (0.78, 1.16)			
HBV co-infection	No	63.2	1.00	<0.001	-	-
	Yes	61.1	0.92 (0.46, 1.83)			
	Not tested	53.3	0.67 (0.55, 0.81)			

		% late diagnosis	Unadjusted		Adjusted	
			OR (95% CI)	P-value	OR (95% CI)	P-value
HCV co-infection	No	63.2	1.00	<0.001	1.00	<0.001
	Yes	50.0	0.58 (0.27, 1.24)		0.55 (0.26, 1.19)	
	Not tested	53.3	0.66 (0.55, 0.80)		0.64 (0.52, 0.79)	
OR=Odds ratio; CI=Confidence interval						

5.3.2.3 Factors associated with late diagnosis amongst those aged below 50

Whilst neither sex nor HBV co-infection were associated with late diagnosis amongst those aged 50 and above in adjusted analyses, these factors were found to be predictive of late diagnosis in those aged below 50 (Table 5.3.4). In younger diagnosed individuals, women were less likely to be diagnosed late than men (aOR (95% CI)=0.81 (0.75, 0.88)). Those with HIV/HBV co-infection were 30% (95% CI=1.02, 1.64) more likely to have a late diagnosis than HIV mono-infected individuals. As was seen in those aged 50 and above at diagnosis, ethnicity, mode of HIV acquisition and calendar year were also associated with late diagnosis amongst those younger than 50. In the younger group, a stronger effect of black African ethnicity was found than in over 50's, with those of black African ethnicity being more than twice as likely to be diagnosed late than those of white ethnicity (aOR (95% CI)=2.02 (1.85, 2.12)). Those of other black ethnicity were 20% (95% CI=1.06, 1.36) more likely to be diagnosed late. Compared to MSM, heterosexuals were 95% (95% CI=1.77, 2.14) more likely to be diagnosed late; again a greater relative difference than was seen in those aged 50 and above. In the younger group those with other known mode of acquisition were also more likely to be diagnosed late than MSM (aOR (95% CI)=1.61 (1.41, 1.82)), although such a difference was not observed in those aged 50 and above. As with the older age group, the odds of late diagnosis decreased over time in the younger age group, with a 2% decreased odds of late diagnosis per calendar year (95% CI=0.97, 0.99).

Upon testing for interactions between age and other factors in the main model, significant interaction effects were found between age and mode of HIV acquisition (p=0.038) and age and calendar year (p=0.016) only.

Table 5.3.4: Factors associated with late diagnosis amongst those aged <50 years

		% late diagnosis	Unadjusted		Adjusted	
			OR (95% CI)	P-value	OR (95% CI)	P-value
Age	<30	32.3	1.00	<0.001	1.00	<0.001
	30-39	44.9	1.71 (1.61, 1.82)		1.65 (2.22, 1.65)	
	40-49	50.7	2.15 (2.00, 2.32)		2.22 (2.05, 2.40)	
Sex	Male	38.5	1.00	<0.001	1.00	<0.001
	Female	49.4	1.56 (1.47, 1.65)		0.81 (0.75, 0.88)	
Ethnicity	White	32.5	1.00	<0.001	1.00	<0.001
	Black African	57.1	2.77 (2.60, 2.94)		2.02 (1.85, 2.21)	
	Black Caribbean	40.9	1.43 (1.28, 1.61)		1.20 (1.06, 1.36)	
	Other	41.1	1.45 (1.32, 1.59)		1.42 (1.29, 1.56)	
	Unknown	23.5	0.64 (0.55, 0.74)		0.75 (0.64, 0.89)	
Mode of acquisition	MSM	31.7	1.00	<0.001	1.00	<0.001
	Heterosexual	54.8	2.62 (2.47, 2.77)		1.95 (1.77, 2.14)	
	Other	44.4	1.73 (1.53, 1.95)		1.61 (1.41, 1.82)	
	Unknown	24.2	0.69 (0.61, 0.78)		0.70 (0.61, 0.81)	
Year of diagnosis	Per year	-	0.97 (0.97, 0.98)	<0.001	0.98 (0.97, 0.99)	<0.001
Centre	Outside London	44.0	1.00	0.004	-	-
	London	41.6	0.91 (0.85, 0.97)			
HBV co-infection	No	43.3	1.00	<0.001	1.00	0.042
	Yes	56.7	1.71 (1.37, 2.15)		1.30 (1.02, 1.64)	

		% late diagnosis	Unadjusted		Adjusted	
			OR (95% CI)	P-value	OR (95% CI)	P-value
	Not tested	41.2	0.92 (0.87, 0.97)		0.96 (0.88, 1.04)	
HCV co-infection	No	44.5	1.00	<0.001	1.00	<0.001
	Yes	42.8	0.93 (0.73, 1.19)		0.89 (0.69, 1.15)	
	Not tested	41.0	0.87 (0.82, 0.92)		0.73 (0.67, 0.80)	
OR=Odds ratio; CI=Confidence interval						

5.3.3 Mortality

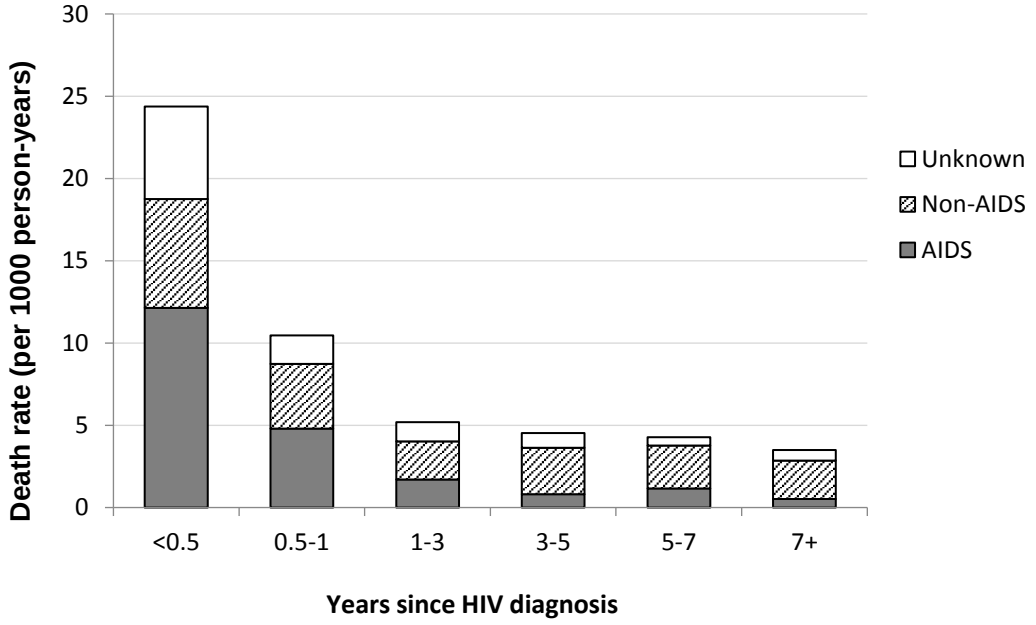
5.3.3.1 Mortality rates over time since HIV diagnosis

A total of 823 (3.3%) individuals died over 115,068 person-years of follow-up (median follow-up 3.9 years), giving a mortality rate (95% CI) of 7.2 (6.7, 7.6) per 1,000 person years in this study population. Mortality rates (95% CI) were markedly higher in the year following HIV diagnosis, with a mortality rate of 24.4 (21.6, 27.2) per 1,000 person years from 0-0.5 years and 10.5 (8.5, 12.4) per 1,000 person years from 0.5-1 years since HIV diagnosis (Figure 5.3.2). Comparatively, between 1-3, 3-5, 5-7 and over 7 years since diagnosis, mortality rates were 5.2 (4.4, 6.0), 4.5 (3.7, 5.4), 4.3 (3.3, 5.3) and 3.5 (2.6, 4.4) per 1,000 person years, respectively.

There was an initial rapid decline in the rate of AIDS-related deaths following diagnosis, but AIDS mortality rates remained relatively stable after 1 year: 12.1 (10.2, 14.1) per 1,000 person-years 0-0.5 years following diagnosis; 1.7 (1.3, 2.2) per 1,000 person-years between 1-3 years; 0.5 (0.2, 0.9) per 1,000 person-years after 7 years. The rate of non-AIDS mortality showed a less marked decline with time from HIV diagnosis, from 6.6 (5.2, 8.1) per 1,000 person-years between 0-0.5 years to 2.3 (1.6, 3.1) per 1,000 person-years after 7 years.

The proportion of deaths attributable to AIDS was highest in the first 6 months following diagnosis and declined with longer time since diagnosis; 50%, 46%, 33%, 18%, 27%, 15% between 0-0.5, 0.5-1, 1-3, 3-5, 5-7 >7 years respectively. Conversely, the proportion of deaths attributable to non-AIDS causes increased with longer time since diagnosis; 27%, 38%, 45%, 62%, 61% and 67% between 0-0.5, 0.5-1, 1-3, 3-5, 5-7 and >7 years respectively ($p<0.001$).

Figure 5.3.2: Mortality rates by cause, according to time since HIV diagnosis

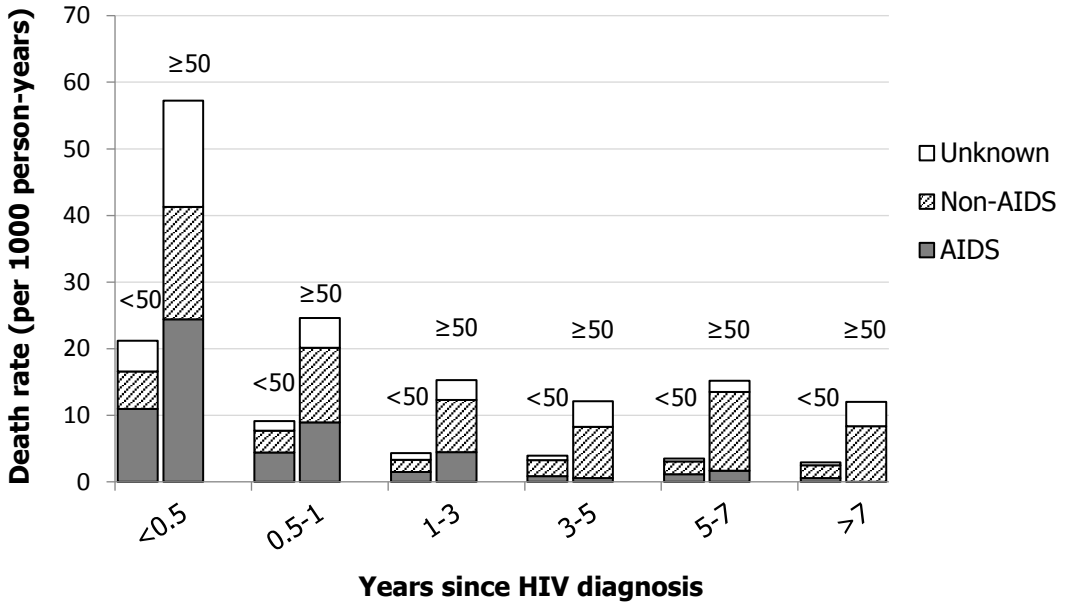


Stratifying by age at diagnosis, there were 177 (8.0%) deaths amongst those aged 50 and above and 779 (2.9%) deaths among those aged below 50. Mortality rates (95% CI) were significantly higher in those aged 50 and above compared to those aged below 50 (20.3 (17.3, 23.3) vs. 6.1 (5.6, 6.5) per 1,000 person-years; Figure 5.3.3). Considering mortality rates according to time since diagnosis, the rate remained higher in the older age group at all times. Mortality rates were extremely high in those aged 50 and above in the first 6 months following diagnosis at 57.2 (42.9, 71.7) per 1,000 person-years, an excess mortality rate of 37.3 per 1,000 person years over those aged below 50.

Amongst those aged 50 and above there was a steep decline in the rate (95% CI) of AIDS-related deaths with longer time since diagnosis; from 25.2 (15.0, 33.8) per 1,000 person-years 0-0.5 years to 1.7 (0.8, 6.1) per 1,000 person-years 5-7 years after diagnosis. No deaths occurring >7 years since HIV diagnosis in those aged 50 and above were attributed to AIDS-related illness. Similar patterns were observed amongst those aged below 50 at diagnosis. The rate (95% CI) of AIDS-related mortality declined steeply within the first year of diagnosis, from 11.0 (9.0, 12.9) per 1,000 person-years between 0-0.5 years to 0.6 (0.2, 0.9) per 1,000 person years after 7 years. The rate (95% CI) of non-AIDS deaths did not decrease as rapidly as for AIDS-related deaths with time since diagnosis in either those aged below 50 (5.6 (4.9, 7.2) 0-0.5 years to 2.0 (1.3, 2.6) >7 years) or those aged 50 and above (16.9 (9.1, 24.7) 0-0.5 years to 8.3 (2.9, 13.8) >7 years).

The proportion of deaths attributable to AIDS-related illness decreased with longer time since diagnosis in both age groups, with subsequent increases in the proportion of deaths attributable to non-AIDS causes. In the first six months of diagnosis, 42.6% and 51.7% of deaths were due to AIDS-related illness in those aged above and below 50 respectively, with 29.5% and 26.5% due to non-AIDS causes. However, after this time point, deaths occurring amongst those aged 50 and above were more likely to be due to non-AIDS causes. Whereas no deaths occurring more than 7 years after diagnosis in the older age group were attributed to AIDS-related illness, 18.8% of deaths amongst those below 50 were AIDS-related.

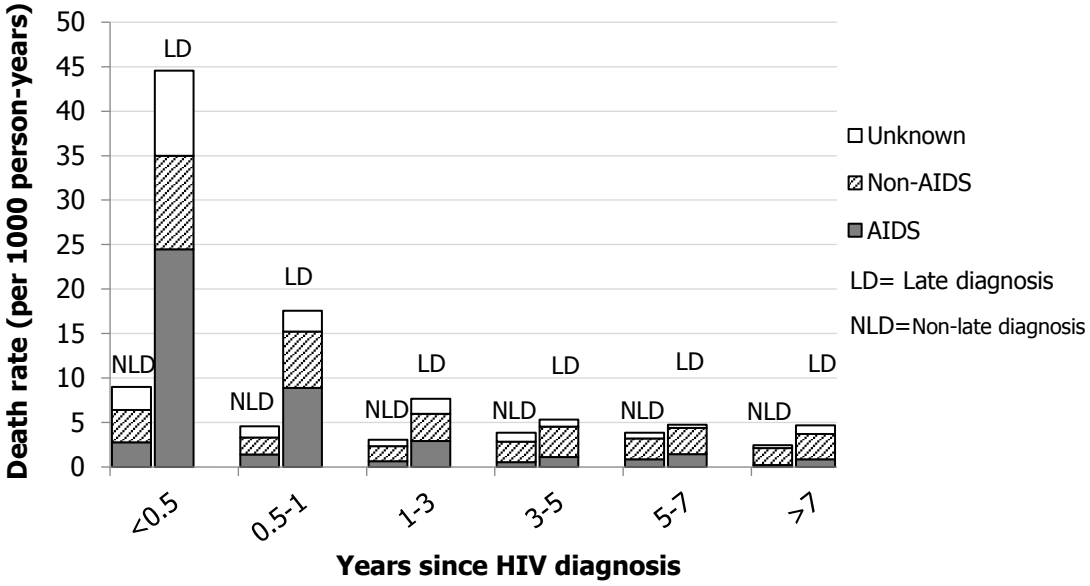
Figure 5.3.3: Cause-specific mortality rates with time from HIV diagnosis, according to age (</≥50 years)



Mortality rates amongst those with a late diagnosis were markedly higher than those who were not diagnosed late in the year following HIV diagnosis, but became similar after 3 years since HIV diagnosis (Figure 5.3.4). Between 0-0.5 and 0.5-1 years following HIV diagnosis, mortality rates (95% CI) in those diagnosed late were 44.6 (38.8, 50.3) and 17.6 (13.8, 21.4) per 1,000 person-years. This compared to 9.0 (6.8, 11.3) and 5.0 (2.8, 6.3) per 1,000 person-years, respectively, in those who were not diagnosed late.

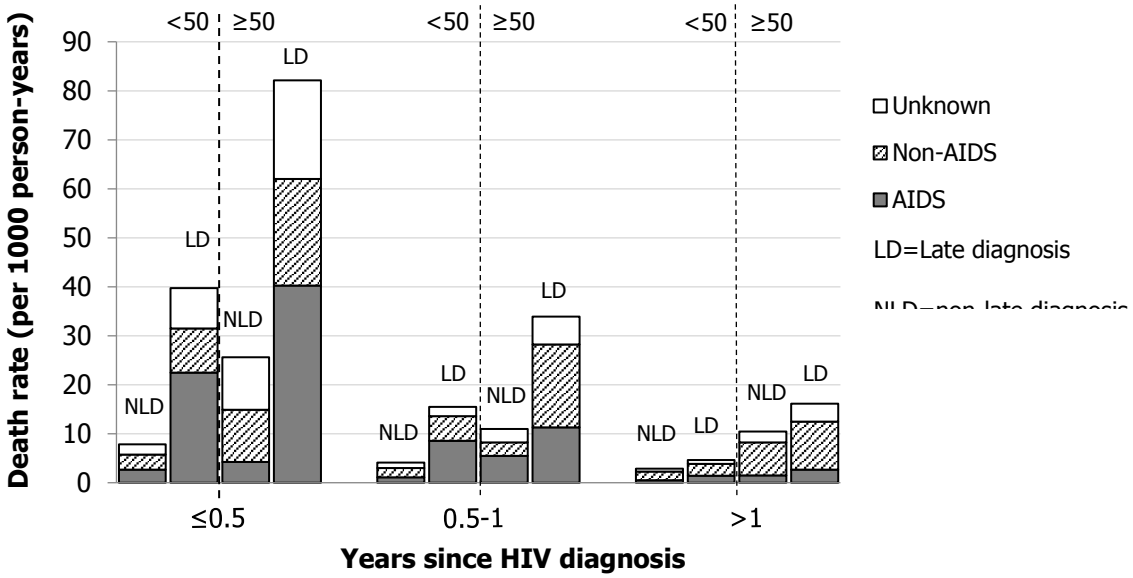
Of deaths occurring between 0-0.5 and 0.5 to 1 years since HIV diagnosis, 54.9% and 50.6% were attributable to AIDS amongst those diagnosed late but only 30.6% and 30.8% were AIDS-related amongst those with a timely diagnosis. Of all deaths occurring more than 7 years after HIV diagnosis, the proportion of AIDS-related deaths had decreased in both the late and timely diagnosis, but remained higher in the late diagnosis group (18.4% vs. 8.7%). A lower proportion of deaths in those diagnosed late were due to non-AIDs causes; 60.5% and 78.3%, respectively.

Figure 5.3.4: Cause-specific mortality rates with time from HIV diagnosis, according to late diagnosis



In the year following HIV diagnosis, older individuals with late diagnosis had the highest mortality rates; 82.1 (59.2, 105.2) per 1,000 person years <0.5 years, 33.9 (18.2, 49.6) per 1,000 person years between 0.5-1 years (Figure 5.3.5). Older individuals who were diagnosed late had an absolute excess mortality rate of 31.2 per 1,000 person years compared to younger individuals with late diagnosis, and 40.2 per 1,000 person years compared to older individuals who were not diagnosed late in the year following diagnosis. The lowest mortality rates were found in younger adults who had a timely diagnosis. After one year since diagnosis, older individuals had a higher mortality rate than younger individuals, regardless of the timing of diagnosis.

Figure 5.3.5: Mortality rates according to age and late diagnosis with time since HIV diagnosis



5.3.3.2 Population Attributable Risk fraction for late diagnosis

Over all follow-up the PAR% of late diagnosis was 46.2%; 44.7% amongst those <50 and 43.3% amongst those aged ≥50. This would indicate that approximately 45% of all deaths over follow-up could be avoided if late diagnosis were removed from the population. Of deaths within the first year of HIV diagnosis, 61.6% could be avoided if late diagnosis was no longer present. Amongst those aged below 50 years, the PAR% was 61.3%, whereas for those aged 50 and above 56.0% of deaths would be avoided if no-one were diagnosed late.

5.3.3.3 One year mortality

A total of 404 (1.6%) people died within one year of HIV diagnosis. Amongst those aged above and below 50 at diagnosis 83 (3.8%) and 321 (1.4%) died within 1 year of HIV diagnosis, respectively. These deaths accounted for 46.9% of all deaths amongst those aged 50 and above and 49.7% of deaths amongst those aged below 50. Amongst those who were and were not diagnosed late, 316 (3.0%) and 88 (0.6%) died within the first year of HIV diagnosis. Deaths within the first year accounted for 55.2% of all deaths amongst those diagnosed late, compared to 35.1% amongst those not diagnosed late.

In a Kaplan-Meier analysis, the probability of all-cause mortality by 1 year after diagnosis was 4.0% in those aged 50 and above and 1.5% in those below 50 ($p<0.001$; Figure 5.3.6(A)). In a competing risks analysis, the cumulative incidence of AIDS-related and non-AIDS causes

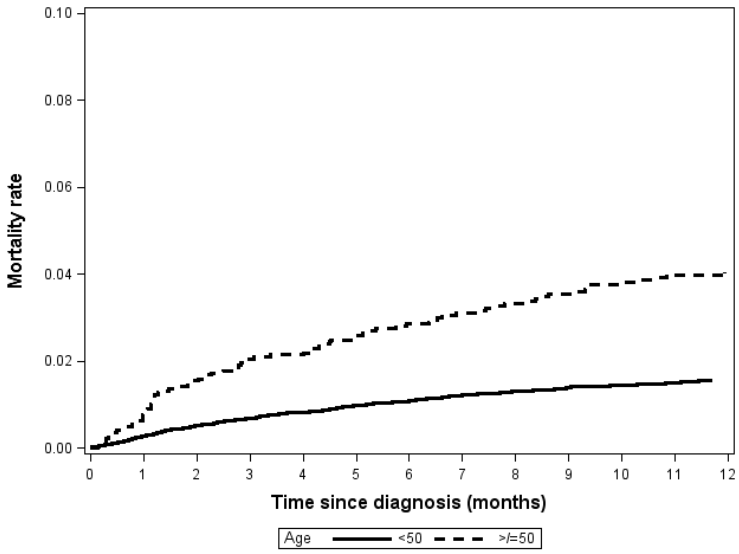
of death as the first event was also higher in the older age group compared to the younger group; 1.6% vs 0.8%, 1.4% vs 0.4% respectively by 1 year (Figure 5.3.7(A); Figure 5.3.8(A)).

The probability of all-cause mortality was higher for those diagnosed late, than for those with a timely diagnosis (3.0% vs 0.7%) (Figure 5.3.6(B)). This was largely driven by AIDS-related mortality, which was higher for those diagnosed late than those not diagnosed late (1.6% vs 0.2%) (Figure 5.3.7(B)). There were much smaller differences in the cumulative incidence of non-AIDS causes of death between those who were and were not diagnosed late (0.8% vs. 0.3%) (Figure 5.3.8(B)).

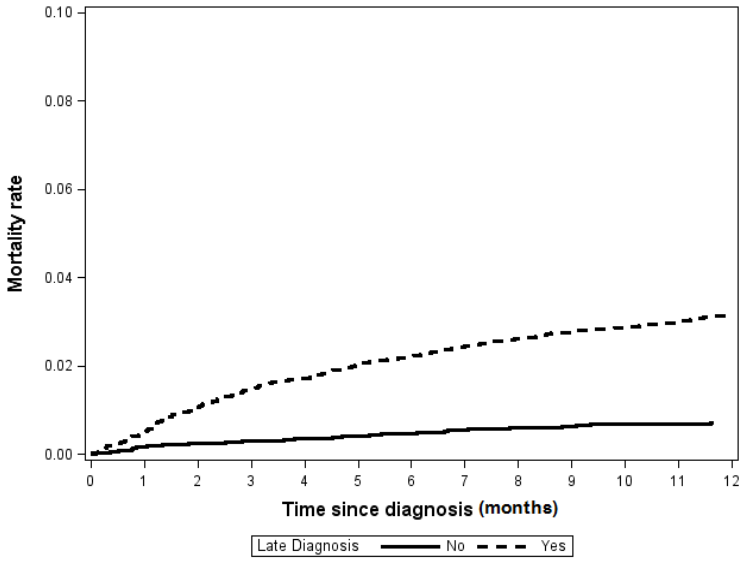
Older individuals diagnosed late showed the highest probability of death within 1 year of diagnosis due to all causes (5.6%), AIDS (2.5%) and non-AIDS (1.9%) mortality. This compared to 0.6%, 0.2% and 0.3% respectively in those aged less than 50 who were diagnosed with a CD4 count >350 cells/mm^3 (Figure 5.3.6(C); Figure 5.3.7(C); Figure 5.3.8(C)).

Figure 5.3.6: Cumulative incidence of all-cause mortality according to (A) age at diagnosis (</≥50), (B) late diagnosis (C) age and late diagnosis

(A)



(B)



(C)

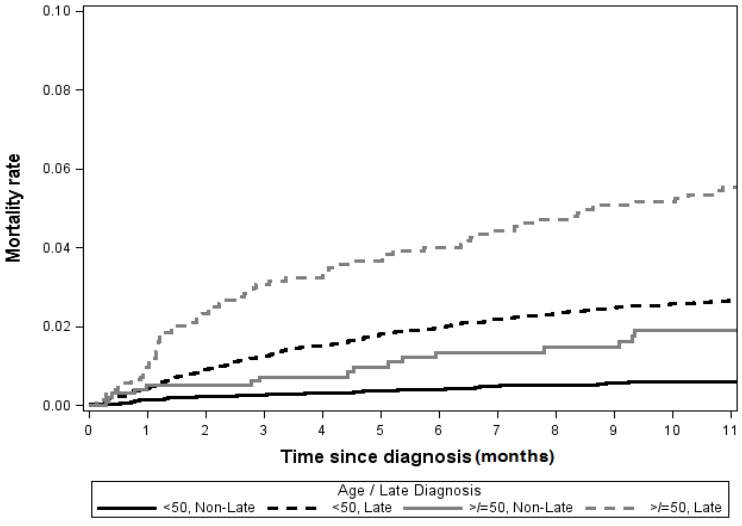
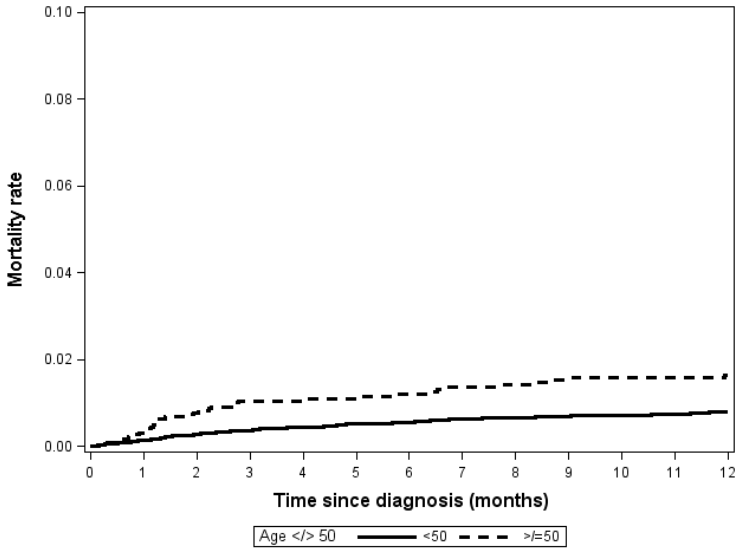
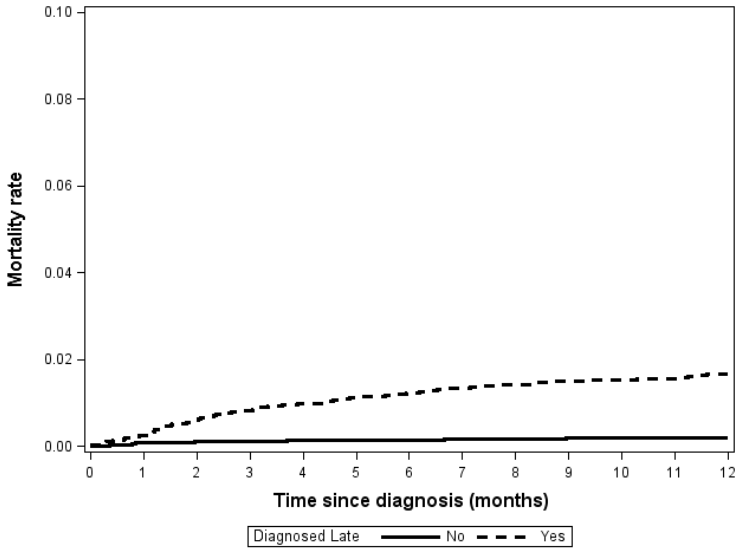


Figure 5.3.7: Cumulative incidence of AIDS-related mortality according to (A) age at diagnosis (</≥50), (B) late diagnosis (C) age and late diagnosis

(A)



(B)



(C)

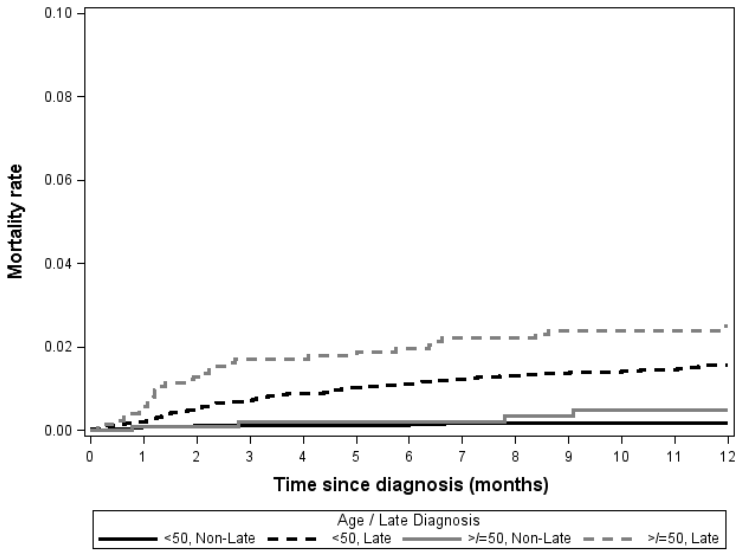
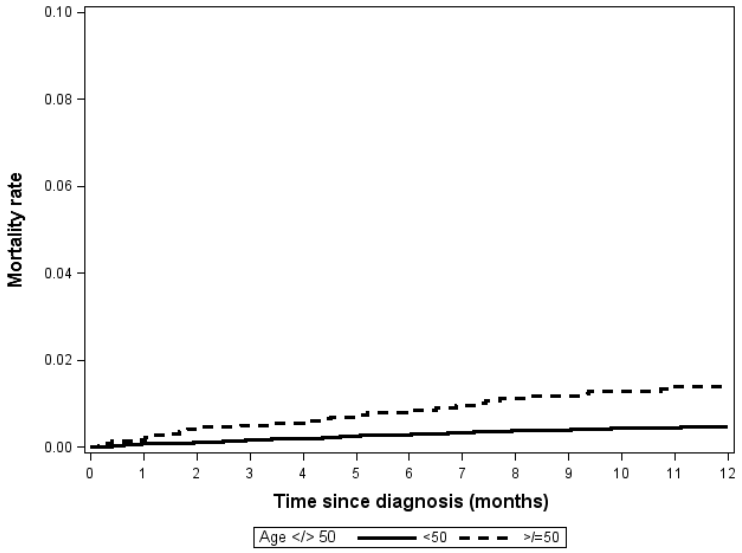
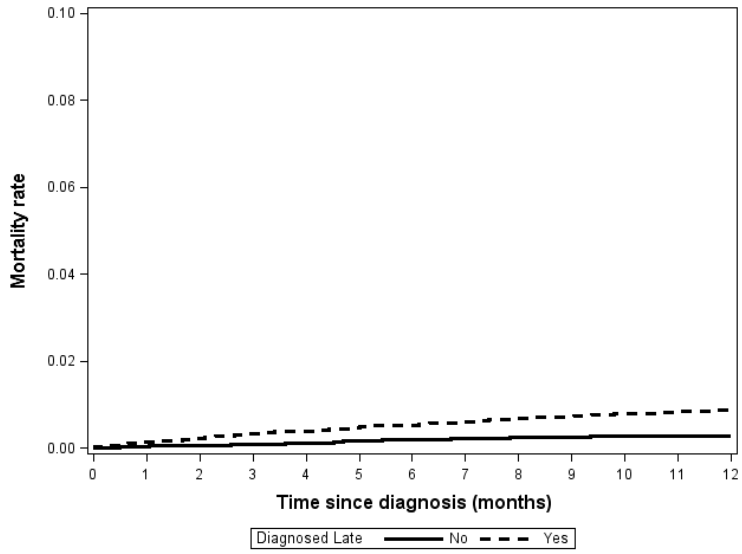


Figure 5.3.8: Cumulative incidence of non-AIDS mortality according to (A) age at diagnosis (</≥50), (B) late diagnosis (C) age and late diagnosis

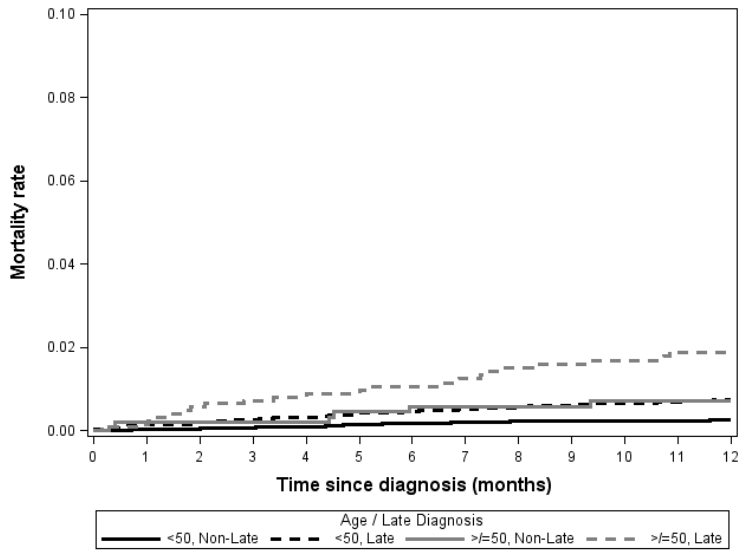
(A)



(B)



(C)



5.3.3.4 Factors associated with all-cause mortality in the year following diagnosis

In a Cox Proportional Hazards model, both older age and late diagnosis were independently associated with one year all-cause mortality. Those aged over 50 had 2.34 (95% CI=(1.78, 3.07)) times the rate of death as those aged below 50 (Table 5.3.5). Late diagnosis was associated with a 4.4-fold (95% CI=(3.06, 6.23)) higher rate of death compared to timely diagnosis. The association between late diagnosis and all-cause mortality was similar in analyses stratified by age at diagnosis (Table 5.3.8) and there was no evidence of an interaction between age and late diagnosis on all-cause mortality when tested in the full model (aHR (95% CI)=1.11 (0.41, 2.96), p=0.84).

Calendar year, mode of HIV acquisition, co-infection with HBV and HIV viral load were also independently associated with all-cause mortality (Table 5.3.5). For each year later an individual was diagnosed, the hazard of death from any cause decreased by 7% (95% CI=(0.90, 0.96)). MSM showed the lowest rate of mortality when compared those who acquired HIV through sex between men and women, other and unknown acquisition routes. Those not tested for HBV had 1.77 (1.25, 1.22) times the hazard of death over the year following diagnosis than those who were HBV negative. For each $\log_{10}$ copies/ml higher viral load at entry into the UK CHIC Study, the rate of mortality increased by 35% (95% CI=(1.21, 1.51)), independently of the effect of late diagnosis.

Table 5.3.5: The effect of age and late diagnosis on all-cause mortality in the year following HIV diagnosis; results from Cox Proportional Hazards models

		Unadjusted		Adjusted	
		HR (95% CI)	**P-value**	**HR (95% CI)**	**P-value**
Age	<50	1.00	<0.001	1.00	<0.001
	≥50	2.69 (2.12, 3.43)		2.34 (1.78, 3.07)	
Late diagnosis	No	1.00	<0.001	1.00	<0.001
	Yes	4.62 (3.65, 5.85)		4.37 (3.06, 6.23)	
Sex	Male	1.00	0.064	-	-
	Female	1.21 (0.99, 1.48)			
Ethnicity	White	1.00	<0.001	-	-
	Black African	1.83 (1.46, 2.29)			
	Black Other	1.14 (0.72, 1.80)			
	Other	1.62 (1.17, 2.25)			
	Unknown	2.09 (1.35, 3.23)			
Mode of acquisition	MSM	1.00	<0.001	1.00	<0.001
	Heterosexual	2.59 (2.00, 3.36)		1.78 (1.33, 2.39)	
	Other	3.40 (2.26, 5.10)		3.75 (2.42, 5.80)	
	Unknown	6.83 (5.00, 9.33)		7.98 (5.47, 11.64)	
Year of diagnosis	per year	0.92 (0.89, 0.94)	<0.001	0.93 (0.90, 0.96)	<0.001
HBV co-infection	No	1.00	<0.001	1.00	0.001
	Yes	2.36 (1.08, 5.16)		1.95 (0.89, 4.28)	
	Not tested	2.40 (1.82, 3.17)		1.77 (1.31, 2.38)	
HCV co-infection	No	1.00	<0.001	-	-
	Yes	0.90 (0.29, 2.87)			
	Not tested	1.72 (1.34, 2.20)			
Viral load	log_{10}copies/ml	1.52 (1.37, 1.70)	<0.001	1.35 (1.21, 1.51)	<0.001

HR=Hazard ratio; CI=Confidence interval; MSM=Men who have sex with men

5.3.3.5 Factors associated with AIDS-related mortality in the year following HIV diagnosis

Older age and late diagnosis were also associated with AIDS-related mortality (Table 5.3.6). There was a 78% (95% CI=(1.20, 2.65)) increase in the subdistribution hazard of AIDS-related mortality amongst those aged $\geq$50 compared to those <50. A very strong association was observed between late diagnosis and AIDS-related mortality in the year following diagnosis, with an 11.8-fold (95% CI=(5.27, 26.23)) higher subdistribution hazard for those diagnosed late. Amongst those aged below 50, being diagnosed late was found to increase the subdistribution hazard by greater than 10-fold (adjusted sHR=12.48; 95% CI=(5.24, 29.76)) (Table 5.3.8). Amongst those aged $\geq$50, late diagnosis was associated with 9.29 (95% CI=(1.12, 76.91)) times the sub-distribution hazard of AIDS-related mortality. However, a test for an interaction effect between age and late diagnosis was not statistically significant (asHR (95% CI)=0.86 (0.10, 7.36), p=0.91).

Mode of HIV acquisition, co-infection with HBV, and HIV viral load were also associated with one year AIDS-related mortality. Having acquired HIV through sex between men was protective against AIDS-related mortality, compared to other modes of acquisition. Those with HBV co-infection were more likely to die from AIDS-related causes than those without HBV co-infection (asHR (95% CI)=2.79 (1.07, 7.26)), as were those who were not tested for HBV (asHR (95% CI)=1.80 (1.18, 2.74)). Each $\log_{10}$ copies/ml higher viral load at entry into the UK CHIC Study, increased the subdistribution hazard of AIDS-related death by 49% (95% CI=(1.23, 1.81)), independently of the effect of late diagnosis. Unlike for all-cause mortality, no association was found between calendar year and AIDS-related mortality.

Table 5.3.6: The effect of age and late diagnosis on AIDS-related mortality in the year following HIV diagnosis; results from Fine-Gray models

		Unadjusted		Adjusted	
		sHR (95% CI)	**P-value**	**sHR (95% CI)**	**P-value**
Age	<50	1.00	<0.001	1.00	0.004
	≥50	2.15 (1.49, 3.12)		1.78 (1.20, 2.65)	
Late diagnosis	No	1.00	<0.001	1.00	<0.001
	Yes	8.08 (5.38, 12.13)		11.76 (5.27, 26.23)	
Sex	Male	1.00	0.052	-	-
	Female	1.33 (1.00, 1.77)			
Ethnicity	White	1.00	<0.001	-	-
	Black African	2.42 (1.75, 3.34)			
	Black Other	0.87 (0.40, 1.90)			
	Other	1.66 (1.02, 2.71)			
	Unknown	2.14 (1.09, 4.20)			
Mode of acquisition	MSM	1.00	<0.001	1.00	<0.001
	Heterosexual	3.27 (2.24, 4.77)		2.07 (1.33, 3.22)	
	Other	2.11 (1.01, 4.38)		2.35 (1.10, 4.99)	
	Unknown	7.93 (4.98, 12.61)		9.05 (5.31, 15.41)	
Year of diagnosis	per year	0.96 (0.93, 1.00)	0.035	-	
HBV co-infection	No	1.00	<0.001	1.00	0.012
	Yes	3.27 (1.27, 8.43)		2.79 (1.07, 7.26)	
	Not tested	2.26 (1.53, 3.34)		1.80 (1.18, 2.74)	
HCV co-infection	No	1.00	0.026	-	-
	Yes	0.56 (0.08, 4.05)			
	Not tested	1.56 (1.11, 2.20)			
Viral load	$\log_{10}$ copies/ml	1.79 (1.48, 2.17)	<0.001	1.49 (1.23, 1.81)	<0.001

sHR=Subdistribution hazard ratio; CI=Confidence interval; MSM=Men who have sex with men

5.3.3.6 Factors associated with non-AIDS mortality in the year following HIV diagnosis

A weaker association between late diagnosis and non-AIDS mortality was observed than was seen for AIDS-related mortality. Late diagnosis was associated with an estimated 93% (95% CI=(1.19, 3.12)) increase in the sub-distribution hazard of non-AIDS mortality. Those aged over 50 had approximately 2.4 (95% CI=(1.51, 3.87)) times the subdistribution hazard of non-AIDS death of those aged below 50 years. There was no statistically significant interaction between age and late diagnosis in an adjusted model (asHR (95% CI)=1.52 (0.41, 5.65), p=0.53). In stratified models (Table 5.3.8), late diagnosis was associated with an increased rate of non-AIDS death amongst those aged over 50 years, but the evidence for this effect was weak (asHR (95%CI)=2.82 (0.81, 9.76)). Amongst those younger than 50, a 76% (95% CI=(1.03, 3.01)) increase in the subdistribution hazard of non-AIDS mortality was observed for ate diagnosis.

Mode of HIV acquisition, co-infection with HBV and HIV viral load were associated with non-AIDS mortality. Again, having acquired HIV through sex between men was protective against non-AIDS mortality, compared to other modes of acquisition (Table 5.3.7). Those who were not tested for HBV were more likely to die from non-AIDS causes than those without HBV co-infection (asHR (95% CI)=1.67 (1.04, 2.67)). Each $\log_{10}$ copies/ml higher viral load at entry into the UK CHIC Study, increased the subdistribution hazard of non-AIDS mortality by 24% (95% CI=(1.00, 1.53)), a weaker association than was seen for AIDS-related mortality. Unlike for all-cause mortality, no association was found between calendar year and death due to non-AIDS causes.

Table 5.3.7: The effect of age and late diagnosis on non-AIDS mortality in the year following HIV diagnosis; results from Fine-Gray models

		Unadjusted		Adjusted	
		sHR (95% CI)	P-value	sHR (95% CI)	P-value
Age	<50	1.00	<0.001	1.00	<0.001
	≥50	3.11 (2.04, 4.75)		2.48 (1.55, 3.96)	
Late diagnosis	No	1.00	<0.001	1.00	0.007
	Yes	2.99 (2.03, 4.41)		1.94 (1.20, 3.15)	
Sex	Male	1.00	0.963	-	-
	Female	0.99 (0.67, 1.45)			
Ethnicity	White	1.00	0.370	-	-
	Black African	1.50 (1.01, 2.24)			
	Black Other	1.42 (0.69, 2.89)			
	Other	1.34 (0.74, 2.43)			
	Unknown	1.45 (0.58, 3.63)			
Mode of acquisition	MSM	1.00	<0.001	1.00	<0.001
	Heterosexual	1.96 (1.27, 3.02)		1.61 (1.00, 2.64)	
	Other	3.99 (2.15, 7.39)		4.34 (2.26, 8.32)	
	Unknown	4.05 (2.21, 7.44)		3.77 (1.79, 7.94)	
Year of diagnosis	per year	0.96 (0.91, 1.02)	0.159	-	-
HBV co-infection	No	1.00	<0.001	1.00	<0.001
	Yes	0.00 (0.00,0.00)		-	
	Not tested	1.83 (1.17, 2.88)		1.64 (1.03, 2.64)	
HCV co-infection	No	1.00	0.321	-	-
	Yes	1.65 (0.39, 6.92)			
	Not tested	1.37 (0.90, 2.09)			
Viral load	$\log_{10}$copies/ml	1.30 (1.06, 1.59)	0.013	1.22 (1.00, 1.50)	0.046

sHR=Subdistribution hazard ratio; CI=Confidence Interval; MSM=Men who have sex with men

Table 5.3.8: Stratified analyses of the impact of late diagnosis on all-cause, AIDS-related and non-AIDS mortality in the year following HIV diagnosis for those aged < or ≥50 years

		Age <50				Age ≥50			
		Unadjusted		Adjusted		Unadjusted		Adjusted	
		s/HR (95% CI)	P-value	s/HR (95% CI)	P-value	s/HR (95% CI)	P-value	s/HR (95% CI)	P-value
All-cause	Non-late	1.00	<0.001	1.00	<0.001	1.00	<0.001	1.00	0.001
	Late diagnosis	4.69 (3.61, 6.09)		4.36 (2.96, 6.42)		3.18 (1.84, 5.48)		4.70 (1.86, 11.86)	
AIDS-related	Non-late	1.00	<0.001	1.00	<0.001	1.00	0.001	1.00	0.039
	Late diagnosis	8.23 (5.29, 12.78)		12.48 (5.24, 29.76)		5.69 (2.00, 16.24)		9.29 (1.12, 76.91)	
Non-AIDS	Non-late	1.00	<0.001	1.00	0.034	1.00	0.030	1.00	0.10
	Late diagnosis	2.81 (1.82, 4.33)		1.79 (1.05, 3.06)		2.70 (1.10, 6.64)		2.80 (0.81, 9.70)	

s/HR=Hazard ratio for all-cause mortality; Subdistribution hazard ratio for AIDS related and non-AIDS mortality

5.3.4 Sensitivity analyses

5.3.4.1 Late Diagnosis

A total of 5,428 (21.9%) individuals did not have a CD4 count result within 90 days of entry into the study. The likelihood of having a CD4 count at entry increased with older age, later year of HIV diagnosis and attending a London-based centre (Table 5.3.9). Unsurprisingly those with missing information with respect to other factors were less likely to have a CD4 count at entry into the study. Having an unknown mode of HIV acquisition (aOR (95% CI)=0.23 (0.20, 0.26)) or unknown ethnicity (aOR (95% CI)=0.44, (0.38, 0.51)), no test for HBV (aOR (95% CI)=0.69 (0.62, 0.78)) or no test for HCV (aOR (95% CI)=0.22 (0.19, 0.25)) was associated with a significantly reduced likelihood of also having a CD4 count.

Redefining late diagnosis to include individuals with a missing CD4 count (regardless of whether they also had an AIDS diagnosis), 15,927 (64.6%) individuals were classified as being diagnosed late; 74.3% amongst older individuals and 63.6% amongst younger. This indicates that the true prevalence of late diagnosis in this cohort lies between 43.3% and 64.6%. Factors associated with late diagnosis remained largely similar, however, missing or unknown data at diagnosis was now associated with an increased likelihood of being diagnosed late (Table 5.3.10).

The associations between late diagnosis and mortality remained similar. Late diagnosis was associated with an increased likelihood of all-cause (aHR (95% CI= 5.39 (3.57, 8.14)) and non-AIDS (asHR (95% CI=2.64 (1.57, 4.45)) mortality. An extremely strong association was observed between late diagnosis and AIDS-related mortality (asHR (95% CI=23.13 (7.29, 73.41)). Still there was no evidence that the effect of late diagnosis differed according to age at diagnosis for mortality due to any cause (p=0.69 all-cause mortality; p=0.59 AIDS-related mortality; p=0.83 non-AIDS mortality).

Table 5.3.9: Factors associated with presence of a CD4 count within 90 days of entry into the UK CHIC Study

		Unadjusted		Adjusted	
		OR (95% CI)	**P-value**	**OR (95% CI)**	**P-value**
Age	<30	1.00	<0.001	1.00	<0.001
	30-39	1.45 (1.35, 1.56)		1.51 (1.40, 1.63)	
	40-49	1.50 (1.38, 1.64)		1.52 (1.38, 1.67)	
	50-59	1.55 (1.35, 1.77)		1.76 (1.51, 2.04)	
	≥60	1.33 (1.09, 1.63)		1.65 (1.32, 2.06)	
Sex	Male	1.00	<0.001	1.00	0.669
	Female	0.88 (0.82, 0.93)		0.98 (0.90, 1.07)	
Ethnicity	White	1.00	<0.001	1.00	<0.001
	Black African	1.05 (0.98, 1.13)		1.28 (1.15, 1.42)	
	Black Caribbean	0.76 (0.67, 0.86)		0.87 (0.75, 0.99)	
	Other	0.95 (0.85, 1.05)		1.06 (0.94, 1.18)	
	Unknown	0.21 (0.19, 0.24)		0.44 (0.38, 0.51)	
Mode of acquisition	MSM	1.00	<0.001	1.00	<0.001
	Heterosexual	1.00 (0.94, 1.07)		1.14 (1.02, 1.27)	
	Other	1.18 (1.01, 1.37)		1.08 (0.92, 1.27)	
	Unknown	0.17 (0.15, 0.19)		0.23 (0.20, 0.26)	
Year of diagnosis	Per year	1.11 (1.10, 1.12)	<0.001	1.07 (1.06, 1.08)	<0.001
Centre	Outside London	1.00	<0.001	1.00	<0.001
	London	1.19 (1.11, 1.28)		1.26 (1.16, 1.36)	
HBV co-infection	No	1.00	<0.001	1.00	<0.001
	Yes	1.01 (0.69, 1.48)		1.08 (0.73, 1.61)	
	Not tested	0.25 (0.23, 0.27)		0.69 (0.62, 0.78)	
HCV co-infection	No	1.00	<0.001	1.00	<0.001
	Yes	0.72 (0.46, 1.11)		0.76 (0.49, 1.19)	
	Not tested	0.14 (0.13, 0.16)		0.22 (0.19, 0.25)	

OR=Odds ratio; CI=Confidence interval; MSM=Men who have sex with men

Table 5.3.10: Factors associated with late diagnosis amongst those presenting for care at a UK CHIC centre: results from sensitivity analysis

		Unadjusted		Adjusted	
		OR (95% CI)	**P-value**	**OR (95% CI)**	**P-value**
Age	<30	1.00	<0.001	1.00	<0.001
	30-39	1.27 (1.20, 1.35)		1.23 (1.15, 1.31)	
	40-49	1.58 (1.46, 1.70)		1.67 (1.54, 1.81)	
	50-59	1.92 (1.70, 2.16)		2.05 (1.81, 2.33)	
	≥60	2.93 (1.97, 2.91)		2.47 (2.02, 3.03)	
Sex	Male	1.00	<0.001	1.00	<0.001
	Female	1.69 (1.59, 1.79)		0.81 (0.75, 0.88)	
Ethnicity	White	1.00	<0.001	1.00	<0.001
	Black African	2.62 (2.46, 2.79)		1.80 (1.65, 1.98)	
	Black Caribbean	1.70 (1.52, 1.91)		1.34 (1.18, 1.51)	
	Other	1.41 (1.30, 1.54)		1.37 (1.25, 1.51)	
	Unknown	3.01 (2.59, 3.50)		1.84 (1.56, 2.17)	
Mode of acquisition	MSM	1.00	<0.001	1.00	<0.001
	Heterosexual	2.54 (2.40, 2.69)		1.71 (1.55, 1.87)	
	Other	1.46 (1.29, 1.64)		1.47 (1.30, 1.67)	
	Unknown	4.35 (3.83, 4.94)		3.24 (2.81, 3.73)	
Year of diagnosis	Per year	0.91 (0.90, 0.91)	<0.001	0.93 (0.92, 0.93)	<0.001
Centre	Outside London	1.00	<0.001	1.00	<0.001
	London	0.83 (0.78, 0.89)		0.86 (0.80, 0.93)	
HBV co-infection	No	1.00	<0.001	1.00	0.002
	Yes	1.60 (1.29, 2.00)		1.20 (0.95, 1.51)	
	Not tested	1.93 (1.82, 2.04)		1.15 (1.06, 1.25)	
HCV co-infection	No	1.00	<0.001	1.00	<0.001
	Yes	0.95 (0.76, 1.20)		0.88 (0.69, 1.12)	
	Not tested	2.19 (2.07, 2.32)		1.45 (1.34, 1.58)	

OR=Odds ratio; CI=Confidence interval; MSM=Men who have sex with men

5.4 Discussion

5.4.1 Summary and interpretation

Amongst adults newly presenting for HIV-outpatient care in the UK following diagnosis, older age was associated with much higher odds of late diagnosis. Amongst people aged 50 and above, the majority (56.2%) were diagnosed late and 41.3% had advanced immunosuppression. Whilst significantly lower, a large proportion (42.0%) of individuals aged below 50 were also diagnosed late. This high percentage of late diagnosis points to poor HIV testing rates in the UK, particularly amongst older individuals. This may be because older individuals do not perceive themselves to be at risk of HIV so do not seek a HIV test, and are less likely to attend sexual health clinics, where the majority of HIV tests in the UK are performed (559, 560). Further, healthcare providers may similarly not perceive older individuals to be at risk for HIV and so opportunities to provide a HIV test when these at risk individuals have interactions with health care services may be missed (560, 561). Strategies to improve HIV testing rates may involve education to improve perceptions of risk in older individuals for both those at-risk and healthcare providers (555). Better access to testing, including more routine testing at locations outside of sexual health services may also help to improve testing rates, for example, GPs, Accident and Emergency departments and at home, through self–sampling or self-test (560). Whilst universal and routine testing at GP surgeries or A&E departments would be an effective way of reaching a large number of individuals, this has been found to not be cost-effective in areas with HIV prevalence below 2 per 1,000 and still requires people to have contacts with healthcare services in order to be effective (562). Therefore targeted testing and promotion may be more appropriate in some settings, and identifying specific groups in need of testing interventions is important. Heterosexuals and those of black ethnicity were identified as having high rates of late diagnosis amongst both older and younger individuals in this study, as has been shown previously (221, 222, 563).

Mortality rates were markedly high in the six months following diagnosis, with a rate of AIDS mortality that was double that for non-AIDS deaths. Whilst half of all deaths during this time were AIDS-related, a further 23% were of unknown cause and may also be AIDS-related (Chapter 4), meaning the true proportion could be as high as 73%. More than 1 year after diagnosis, the rate of AIDS-related mortality and proportion of deaths attributed to AIDS had declined and were, in fact, lower than the rate and proportion of deaths attributed to non-AIDS causes. This shift in mortality is likely a consequence of people initiating ART following diagnosis, which protects against AIDS morbidity and mortality. Further, those with the most advanced disease at diagnosis are perhaps more likely to die from AIDS-related illness early on, such that those that survive this initial period are those with a lower risk of AIDS death. Amongst those who survive more than one year after diagnosis, non-AIDS morbidity and

mortality should become a focus of HIV care. Prior to this, AIDS-related mortality is of primary concern and the initiation of ART a priority to prevent this.

Late diagnosis was found to increase the risk of mortality within one year of diagnosis. The attributable risk fraction for late diagnosis on one-year mortality was 62%, indicating that the majority of short-term mortality could be avoided if all PLWH were diagnosed in a timely manner. An extremely strong association was found with AIDS-related mortality, which is not unsurprising given the predictive value of low CD4 counts on AIDS morbidity and mortality (58, 557). However, although weaker, a strong association between late diagnosed and non-AIDS mortality was also observed, independently of other factors. This association may arise through the effect of ongoing HIV replication on immunosuppression and inflammation, which have been identified as etiologic risk factors for certain non-AIDS illness such as cancer (150, 564). Improvements in testing rates and earlier diagnosis, enabling earlier ART initiation, may therefore impact non-AIDS as well as AIDS-related mortality. However, according to the findings of this study, any reductions in rates of non-AIDS mortality would likely be smaller than for AIDS-related mortality.

Those aged 50 and above at diagnosis were also at a higher risk of all-cause, AIDS-related and non-AIDS mortality within one year of HIV diagnosis, when compared to those aged below 50. To some extent this higher mortality rate in older individuals might be expected due to natural aging. But it is also hypothesised that the impact of HIV is worse in older individuals, leading to faster clinical progression or so-called 'premature aging', which could contribute to shorter survival. However, in this study there was no strong evidence that late diagnosis carried a higher risk of short-term mortality for older individuals compared to younger. Despite this, a notably large absolute difference in the rate of mortality was observed in older individuals with late diagnosis. Considering the increasing number of new diagnoses amongst older individuals and large proportion of older individuals that are diagnosed late (296, 312), this excess mortality could contribute a disproportionate and increasingly large burden of mortality in the HIV-positive population in years to come. Reducing late diagnosis amongst older PLWH through improved testing strategies should therefore be a focus of future efforts to improve mortality outcomes.

5.4.2 Comparison to the literature

The association between older age and late diagnosis has been reported in much of the literature (Table 2.3.2)(265, 271, 272, 274, 275, 277). I observed that 56.2% of older and 42.0% of younger were diagnosed late. Use of different definitions of 'late' diagnosis makes direct comparisons with some studies difficult. However, my estimates appear somewhat lower than UK surveillance data, which reported 68% and 57% of older and younger

individuals with CD4 counts <350 cells/mm^3 at diagnosis between 2000 and 2007 (296). However, these rates were estimated excluding 25% of newly diagnosed individuals without a CD4 count. In our analysis, individuals without a CD4 count at study entry and no AIDS-defining illness were assumed to have a timely diagnosis i.e. CD4 count >350 cells/mm^3. With 22.2% of individuals missing a CD4 count at entry into the study, the true proportion of late diagnoses in this cohort lies between 43% and 65%; 56-74% amongst older adults and 41-59% amongst younger adults. Other European studies to similarly use a CD4 cut-off of <350 cells/mm^3 or AIDS to define late diagnosis have found overall estimates of late diagnosis between 42% and 56% (268, 269, 286), which are broadly in-keeping with my findings.

In this study, 1.6% of newly diagnosed individuals died within a year of diagnosis; 3.8% of those aged 50 and above and 1.5% of those aged below 50. This is lower than the 10% of over 50s and 3% of newly diagnosed adults under 50 in the UK who died within a year of diagnosis according to surveillance data (294, 296). This likely reflects the fact that surveillance data will capture all newly diagnosed individuals, not only those who have linked to HIV care. Undiagnosed individuals who have extremely advanced HIV disease before becoming aware of their HIV status, are likely to be diagnosed in an emergency or in-patient care setting (293, 295) and have a high risk of mortality so may therefore die before linking to HIV outpatient care. In extreme cases these individuals may not be diagnosed with HIV until after they have died. This very high risk of mortality in those with the most advanced disease who do not link to care may partly explain the higher rate of mortality reported by HIV surveillance systems.

I found increasing odds of late diagnosis with increasing age above 30, with an approximate 3-fold increase in the odds of late diagnosis amongst those aged over 50. This is in agreement with several previous studies that have found similarly higher odds of diagnosis with advanced HIV with older age after adjusting for other factors, in the region of 2 to 4-fold higher (268, 282, 283, 285, 289, 291). A multicentre study in France demonstrated individuals diagnosed with HIV between 50-59 and >60 to be 2.9 and 4.0 times as likely to present for care with advanced immunosuppression as those aged <30 (270). Reassuringly this is also consistent with data from UK HIV surveillance data, which reported 3.8 times higher odds of late diagnosis in those ≥50 compared to those aged 25-34 years (274).

The fact that no statistically significant interaction was noted between age and late diagnosis supports the few studies to have assessed this previously (222). Whilst this current study includes a larger number of individuals, we may still be under-powered to detect an interaction effect, as evidenced by the large confidence intervals around these estimates. Larger studies with data on a larger number of events may be warranted to detect such an interaction, particularly bearing in mind the few studies to formally assess this question to date.

5.4.3 Strengths and limitations

In this study we were able to formally assess whether there is a differential impact of late diagnosis on mortality for older and younger newly diagnosed HIV-positive individuals who entered into HIV care. Due to good ascertainment of mortality and collected information on cause of death, were able to do this not only for all-cause mortality but according to whether deaths were AIDS or non-AIDS related. A limitation of this study, as previously mentioned, is that we consider a group of individuals who have been able to link to HIV care. The highest burden of mortality amongst PLWH is following HIV diagnosis and prior to linkage to care (240); the sickest individuals with most advanced HIV disease at or prior to diagnosis are more likely to die before linking to HIV care and are therefore are not considered here. These results therefore may under-estimate the effect of late diagnosis on mortality. In the UK, approximately 92% of diagnosed individuals link to HIV care so only a small proportion of the diagnosed population are excluded and any impact to these analyses will hopefully be small (294). However, if older diagnosed individuals represent a sicker group with more advanced HIV disease and are less likely to link to care, it is possible that an interaction between age and late diagnosis exists that we are unable to capture. There may also be an under-ascertainment of deaths in individuals over the age of 65, as ONS data is unavailable for deaths at ages above this cut-off (Section 4.2.4). This could attenuate any associations between older age and mortality. However in the whole dataset I estimated that only 156 deaths have been missed, so the number of deaths missing in this analysis, which only considers one-year mortality, is likely small.

It is possible that in using a CD4 count cut-off to define late diagnosis, individuals experiencing transient drops in CD4 count in acute HIV infection may be incorrectly classified as being diagnosed late. In the Swiss HIV Cohort Study, it was found that of all individuals considered to be diagnosed late according to the same criteria, 14% were actually experiencing acute infection (286). Further, by relying on CD4 count at diagnosis, we were unable to accurately define late diagnosis in individuals where the CD4 count was missing, unless an AIDS-defining illness was present. However, whilst making different assumptions about missing CD4 counts led to a difference in estimates of the proportion of late diagnoses, the factors found to be associated with late diagnosis and their magnitude remained unchanged, as did associations between late diagnosis and mortality.

I calculated the PAR% as a measure of the amount of mortality that could be attributed to late diagnosis. However, a main assumption of this measure is that the association between late diagnosis and mortality is directly causal. This may not be a valid assumption and so these estimates should be interpreted with some caution.

5.4.4 Conclusions

Amongst a group of newly diagnosed PLWH that have linked to care, late diagnosis greatly increases the risk of short-term mortality, particularly from an AIDS-defining illness, regardless of the age at which HIV is diagnosed. With increasing numbers of new diagnoses amongst older individuals, of whom an increasing majority will be diagnosed late, we have and will continue to observe an extremely high excess mortality in this group. This excess mortality could potentially be avoided with earlier diagnosis which enables earlier uptake of ART and is possibly the biggest current obstacle in achieving optimal outcomes along the continuum of care.

Chapter 6: Do the disadvantages of late ART persist over time in patients who maintain viral suppression during the first year?

6.1 Introduction

Whilst CD4 counts at ART initiation have increased over time (374, 384), late ART initiation is still prevalent, and is increasingly due to late diagnosis (375). In a previous UK CHIC Study, nearly half of ART initiators started ART with a CD4 count <200 cells/mm^3, and of those, approximately three-quarters did so due to late diagnosis (223).

Initiating ART only when HIV has progressed to an advanced stage of disease with severe immunosuppression has been associated with poorer outcomes for people living with HIV (406, 417, 565-568). Recently the START trial reported on the further morbidity and mortality benefits of immediate ART initiation in people with CD4 counts above 500 cells/mm^3, compared to deferring to the previous standard threshold for initiation of 350 cells/mm^3 (141). However, these studies generally only consider outcomes over the relatively short-term (median follow-up <5 years), despite the fact that combination ART has now been accessible for over 20 years in high income countries such as the UK. Further, previous studies have shown that initial responses in the first few months of ART to be better predictors of outcomes than baseline values, with those achieving suppression and immunological response having better outcomes (406, 569, 570). In this study it is hypothesised that amongst those able to achieve and maintain a virological response on ART, differences in outcomes will reduce over the long-term on ART, with those starting ART with advanced immunosuppression having similar outcomes to those with higher CD4 counts.

In this chapter I investigate the long-term clinical, immunological and virological outcomes of individuals who initiate ART with low CD4 counts who achieve and maintain viral suppression on ART during the first year. In particular, I consider whether differences in outcomes according to baseline CD4 count attenuate with longer time on ART. I then investigate whether any differences in outcome for those with low CD4 counts at ART initiation might be explained by differences in EIC.

6.2 Methods

6.2.1 Patients and inclusion

Individuals in the UK CHIC Study were eligible to be included in this analysis if they initiated a first-line PI- or NNRTI-based regimen (at least 1 NRTI with either a NNRTI or PI) between 2000 and 2014 with a CD4 count <350 cells/mm^3 in the 6 months prior to or up to two weeks following ART initiation, and at least one viral load measurement and one day of follow-up on ART. Individuals who died or were lost to follow-up from the study within a year of initiating ART were excluded, as were those who did not achieve an undetectable viral load (≤50 copies/ml) within 6 months of ART initiation or who did not maintain viral suppression for the remainder of the first year. This was done as we aimed to study the effects of late ART initiation amongst a group of people who were able to achieve and maintain viral suppression for an initial period.

6.2.2 Definitions and outcomes

For all analyses, individuals were grouped according to the CD4 count at ART initiation: ≤100, 101-200, 201-350 cells/mm^3. The reference group for these analyses is those starting ART with a CD4 count between 201-350 cells/mm^3, reflecting timely initiation of ART in line with UK HIV treatment guidelines during the period of analysis. Outcomes assessed were (i) changes in the CD4 count on ART, (ii) rate of viral rebound (2 consecutive viral loads >200 copies/ml) after 1 year on ART and (iii) rate of AIDS event or death after 1 year on ART. A combined end-point of AIDS or death was used, with follow-up censored after the first event.

EIC was defined using the REACH algorithm. This algorithm uses clinical factors including whether an individual is on ART, CD4 count, viral load and AIDS-defining illness within a calendar month to predict when an individual would next be expected to return for a clinic visit (Table 6.2.1). The predicted time-frames, as shown in Table 6.2.1, were derived from interviews with HIV clinicians who were asked, for their last 10 patients, what factors determined when the next clinic visit was scheduled to occur. For example, an individual who is stable on ART, with an undetectable viral load and CD4 count above 200 cells/mm^3, would only be expected to be seen every six months. However, individuals newly diagnosed or those who have newly started ART would be scheduled to be seen more frequently, within two months. The presence of either a CD4 count, viral load, haemoglobin measure or ART start date was used as a proxy for a clinic visit, as data on actual clinic attendance are not reliably collected across all centres. If multiple visit events occurred within a single calendar month, these events were grouped into a single index visit. For each visit in the dataset, the next predicted visit is calculated, based on the algorithm in Table 6.2.1. For subsequent months of follow-up until the next observed visit, an individual will be classified as 'in care' providing they are not yet scheduled for a visit or they have attended within the predicted time-frame.

If an individual does not attend for another visit within the predicted time-frame, they will be classified as being out of care for those months between the predicted visit and their next observed visit.

All months from the start of ART initiation to the last known visit at a UK CHIC centre classified as in care or not in care. The proportion of months classified as in care at any given time point gave the EICR.

Table 6.2.1: Next scheduled visit according to clinical factors: REACH algorithm

Conditions at time of care episode*	Next care episode expected within
Within 1 month of HIV diagnosis	2 months
AIDS diagnosis	2 months
Started ART	2 months
Started new combination	2 months
Not on ART	
CD4≤350 cells/mm^3, any drop in CD4 since last visit	2 months
CD4≤350 cells/mm^3, no drop in CD4	4 months
CD4=351-499 cells/mm^3	4 months
CD4≥500 cells/mm^3, CD4 drop≥100 cells/mm^3	4 months
CD4≥500 cells/mm^3, CD4 drop<100 cells/mm^3, viral load≥100,000 copies/ml	4 months
CD4≥500 cells/mm^3, CD4 drop<100 cells/mm^3, viral load<100,000 copies/ml	6 months
Already started ART	
Viral load>200 copies/ml	2 months
Viral load=51-200 copies/ml, does not appear to be blip §	2 months
Viral load=51-200 copies/ml, appears to be blip	4 months
Viral load≤50 copies/ml, CD4≤200 cells/mm^3	4 months
Viral load≤50 copies/ml, CD4>200 cells/mm^3	6 months

*If more than one condition applies at time of care episode, next care episode is expected within least number of months associated with those conditions
§ Blips are defined as having a viral load of between 50 and 200 following a previous viral load of less than 50

Table from: Howarth et al., Development and application of a new measure of engagement in out-patient HIV care (2016) (571)

6.2.3 Statistical Analyses

Baseline characteristics were compared according to CD4 count at ART initiation using the Chi-squared test for categorical factors, Kruskal-Wallis and ANOVA for continuous factors, as appropriate. EICR over time on ART was described and compared according to baseline CD4 count. Both the median (IQR) proportion of months engaged in care and percentage of individuals that were EIC for less than 80% of follow-up months were described.

Both the rates of viral rebound and clinical progression to AIDS or death were compared according to baseline CD4 count using time-updated Poisson regression models. Time since ART initiation was fitted as a categorical covariate (1-3, 3-5, 5-7, 7+ years). Baseline covariates adjusted for included sex, ethnicity (white, black African, black other, other/unknown), mode of HIV acquisition (sex between men, heterosexual, other/unknown), baseline age, calendar year of ART initiation (2000-04, 2005-09, 2010-14), baseline viral load and initial regimen class (PI or NNRTI). Those covariates with $p<0.1$ in univariable analyses were included in multivariable models. To determine whether any effect of a lower CD4 count on these outcomes was attenuated with longer time on ART, an interaction between time and baseline CD4 count was then investigated. Finally, in order to assess whether any observed associations between baseline CD4 count and either virological rebound or clinical progression might be explained by differences in EIC, the full model including the interaction term was further adjusted for current EICR (per 10% decrease). In sensitivity analyses, EICR was lagged by 6 months.

CD4 count changes were assessed as follows: Median (IQR) CD4 count, median (IQR) CD4 count change from baseline and the proportion of individuals achieving CD4 counts ≤350, 351-500 and >500 cells/mm^3 at 1, 3, 5, 7 and 9 years after ART initiation were described and compared according to baseline CD4 count using univariate tests previously mentioned. The rate of change in CD4 count from 0-1, 1-7, 7+ years following ART initiation was then further compared according to baseline CD4 count in a piecewise linear mixed effects model. The effect of time was allowed to change and assessed separately during each time interval (0-1, 1-7, 7+ years). These intervals were chosen based on descriptive changes in CD4 count on ART (Figure 6.3.4). An interaction effect between baseline CD4 count and time in each segment of the piecewise regression was tested to determine whether the rate of change in CD4 count in each time period was different for the different baseline CD4 categories. In order to assess whether EIC might play a role in any observed difference in changes in CD4 count, analyses were then restricted to those with high EICR ($\geq$80% of months in care) over the follow-up period.

6.3 Results

There were 14,236 individuals in the UK CHIC Study who had initiated a PI- or NNRTI-based regimen since 2000 with a CD4 count below 350 cells/mm^3. Of these, 1,420 individuals died, were lost to study follow-up or administratively censored within 1 year of ART initiation. A further 3,341 failed to achieve a viral load $\leq$50 copies/ml within 6 months and 1,793 had a subsequent viral load >50 copies/ml during the first year on ART. The proportion of individuals with at least one year of follow-up who achieved viral load suppression by six months increased with higher baseline CD4 count (69.7% ≤100 cells/mm^3, 72.4% 101-200 cells/mm^3 and 77.0% 201-350 cells/mm^3). The proportion that experienced viral rebound within 1 year was lower with higher baseline CD4 count (14.3% ≤100 cells/mm^3, 12.4% 101-200 cells/mm^3 and 9.6% 201-350 cells/mm^3). There were a total of 7,682 individuals included in the present analysis. Those excluded were less likely to be male, white and to have acquired HIV through sex between men ($p<0.001$). They were more likely to have started between 2005 and 2009 and to have started a PI-based regimen than those included ($p <0.001$).

The characteristics of the 7,682 individuals included in the analysis are shown in Table 6.3.1, stratified by baseline CD4 count. Overall, 1,726 (22.5%), 1,991 (25.9%) and 3,965 (51.6%) initiated ART with CD4 counts ≤100, 101-200 and 201-350 cells/mm^3, respectively. Those with a lower CD4 count at ART start were more likely to be female, heterosexual and of black ethnicity (all $p<0.001$). Those with a lower CD4 count were also more likely to have started ART prior to 2005 with a PI-based regimen and to have a higher baseline viral load. The median (IQR) years of follow-up in the dataset for those with CD4 count 201-350, 101-200 and ≤100 cells/mm^3 was 5.6 (3.4, 7.6), 7.2 (4.5, 9.8) and 7.3 (4.4, 10.3) years, with median (IQR) year of ART initiation 2008 (2006, 2011), 2007 (2004, 2009) and 2006 (2003, 2009), respectively.

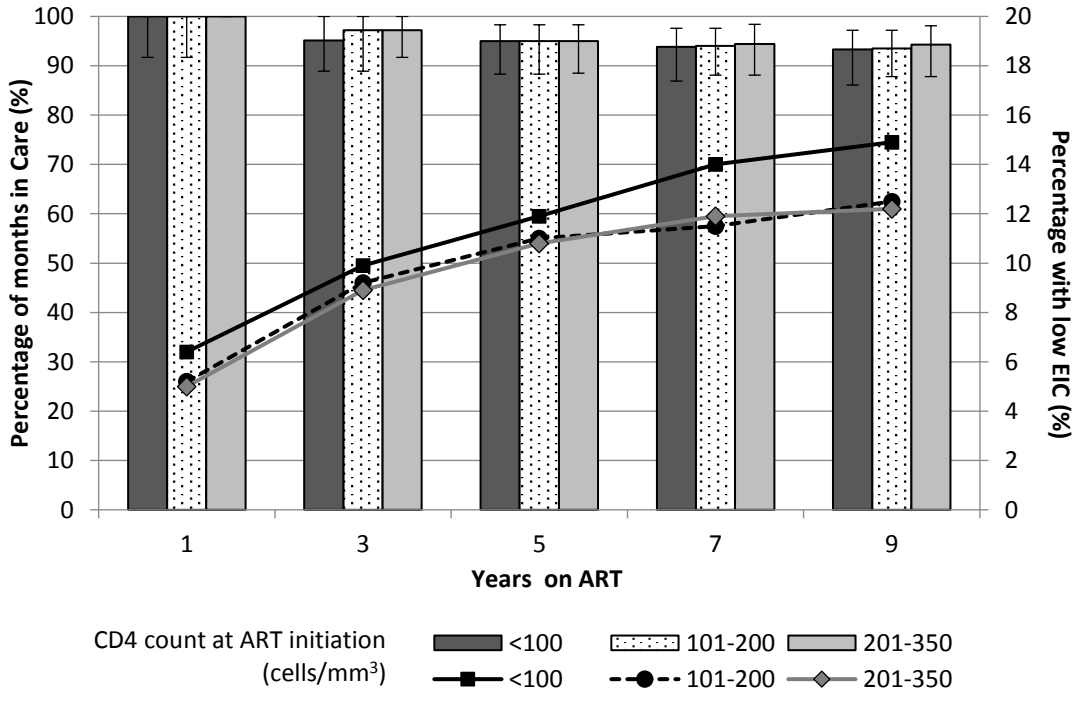
Table 6.3.1: Characteristics at ART initiation according to baseline CD4 count

		Total	Pre-ART CD4 count (cells/mm^3)			P-value
			≤100	101-200	201-350	
Number (%) of individuals		7682	1726 (22.5)	1991 (25.9)	3965 (51.6)	
Sex, n (%)	Male	5876 (76.5)	1203 (69.7)	1492 (74.9)	3181 (80.3)	<0.001
	Female	1804 (23.5)	523 (30.3)	499 (25.1)	782 (19.7)	
Age, median (IQR)	Years	38 (32, 44)	38 (33, 45)	38 (32, 44)	37 (31, 43)	<0.001
Ethnicity, n (%)	White	4256 (55.4)	712 (41.3)	1080 (53.5)	2464 (61.7)	<0.001
	Black African	2145 (27.9)	696 (40.3)	621 (31.9)	828 (21.4)	
	Black other	459 (6.0)	143 (8.3)	92 (5.0)	224 (5.6)	
	Other/unknown	822 (10.7)	175 (10.1)	198 (9.7)	449 (11.3)	
Mode of acquisition, n (%)	Sex between men	4195 (54.6)	657 (38.1)	1042 (52.3)	2496 (63.0)	<0.001
	Heterosexual	3021 (39.3)	960 (55.6)	832 (41.8)	1229 (31.0)	
	Other/unknown	466 (6.1)	109 (6.3)	117 (5.9)	240 (6.1)	
Year of ART, n (%)	2000-2004	1713 (22.3)	598 (34.7)	572 (28.7)	543 (13.7)	<0.001
	2005-2009	3703 (48.2)	748 (43.3)	1009 (50.7)	1946 (49.1)	
	2010-2014	2226 (29.5)	380 (22.0)	410 (20.6)	1476 (37.2)	
Pre-ART VL, median (IQR)	log_{10}copies/ml	4.8 (4.3, 5.3)	5.2 (4.8, 5.6)	4.9 (4.4, 5.3)	4.6 (4.1, 5.1)	<0.001
Regimen, n (%)	NNRTI	5815 (75.7)	1223 (70.9)	1540 (77.4)	3052 (77.0)	<0.001
	PI(/r)	1867 (24.3)	503 (29.1)	451 (22.7)	913 (23.0)	
Years of follow-up, median (IQR)		6.2 (3.8, 8.9)	7.3 (4.4, 10.3)	7.2 (4.5, 9.7)	5.6 (3.4, 7.6)	<0.001

6.3.1 Engagement in Care

EIC was high over the first 9 years on ART, but decreased over time, from 100% of months in care (IQR (100, 100)) after 1 year on ART, to 93.7% (87.5%, 97.7%) of months in care over 9 years on ART (Figure 6.3.1). The distribution of EIC differed significantly according to baseline CD4 count at each time point on ART, however the median proportion of months in care at each time point was not greatly different (Figure 6.3.1). The proportion of individuals with low EIC (<80%) increased with longer time on ART, from 5.4% after 1 year on ART, to 12.9% after 9 years on ART. A small but significantly higher proportion of individuals with a CD4 count ≤100 cells/mm^3 at baseline had low EIC at 7 and 9 years on ART (14.0% vs 11.5% 101-200 and 11.9% 201-350 cells/mm^3 after 7 years, p=0.041; 14.9% vs 12.5% and 12.2% after 9 years cells/mm^3, p=0.017).

Figure 6.3.1: Engagement in care of those still under follow-up over time on ART, according to CD4 count at ART initiation



6.3.2 Virological rebound

Overall, 245 (14.2%), 255 (12.8%) and 335 (8.5%) of those with a baseline CD4 count ≤100, 101-200 and 201-350 cells/mm^3 experienced virological rebound respectively. Over a total 9,503, 10,756 and 16,810 person years of follow-up, the rate (95% CI) of virological rebound was 2.6 (2.3, 2.9), 2.4 (2.1, 2.7) and 2.0 (1.8, 2.2) per 100 person-years. The rate of virological rebound was highest in the 1-3 years after ART initiation and declined with time on ART in both unadjusted and adjusted analyses. The rate of rebound after 7 years on ART was one third of the rate 1-3 years after ART initiation (Table 6.3.2). Whilst a lower baseline CD4 count was associated with a higher rate of virological rebound in unadjusted analyses, there was only a non-significant 13-14% increased rate of rebound for those with a CD4 count ≤200 cells/mm^3 compared to those with a CD4 count 201-350 cells/mm^3 at baseline after adjusting for other factors.

Other factors associated with virological rebound were age, ethnicity, mode of HIV acquisition, baseline viral load, regimen class and year of starting ART. The rate of rebound decreased with older age (aIRR (95% CI)=0.72 (0.66, 0.78) per 10 years older), whilst those of black ethnicity and heterosexual or other/unknown mode of acquisition were more likely to experience rebound. Starting a PI-based regimen (aIRR (95% CI)=1.72 (1.48, 1.99)) was associated with an increased rate of rebound. The rate of virological rebound decreased if ART was initiated in a later calendar year (aIRR (95% CI)=0.66 (0.57, 0.78) 2005-2009 and 0.52 (0.41, 0.67) 2010-2014 vs. 2000-2004).

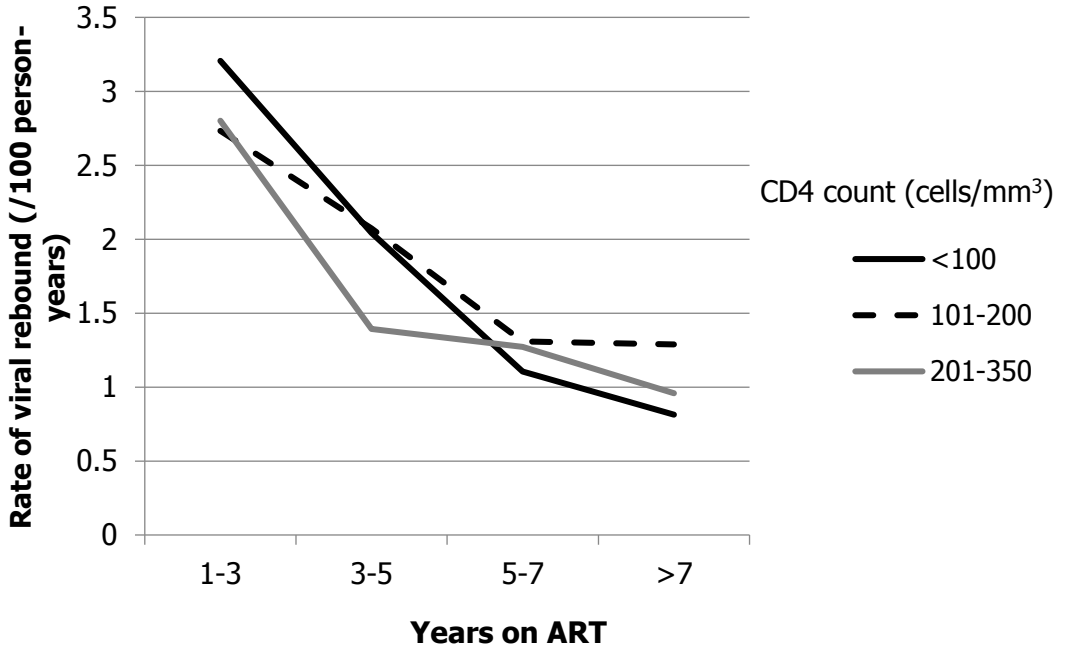
There was no strong evidence of an interaction between baseline CD4 count and time on ART (p=0.12, Figure 6.3.2(A)). However, the rate of viral rebound declined fastest on ART in those with a baseline CD4 count ≤100 cells/mm^3; from 3.2 (2.6, 4.1) by 1-3 years on ART to 0.8 (0.6, 1.2) after 7 years on ART. Further, whilst EIC was associated with the rate of viral rebound in univariable (aIRR (95% CI)=1.31 (1.25, 1.36) per 10% decrease) and multivariable analyses (aIRR (95% CI)=1.30 (1.25, 1.35)), adjusting for current EICR did not alter the conclusions (Figure 6.3.2(B)). Similarly, adjusting for lagged EICR did not alter the results.

Table 6.3.2: Results of Poisson Regression models showing the association between CD4 count at ART initiation and time on ART with the rate of viral rebound

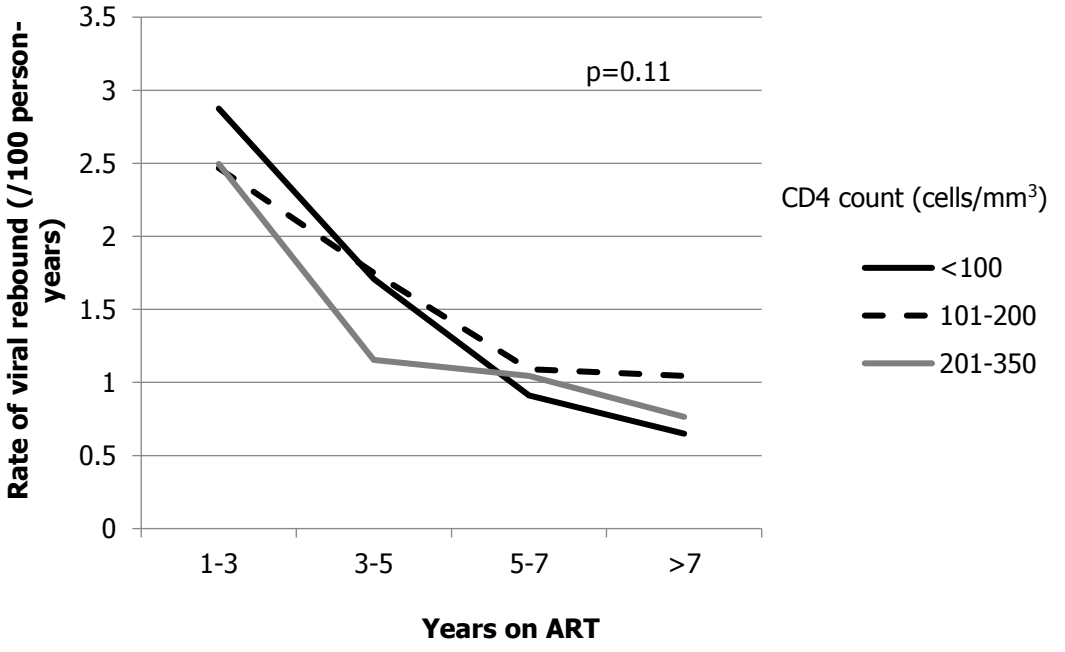
	Unadjusted		Adjusted	
	IRR (95% CI)	**P-value**	**IRR (95% CI)**	**P-value**
CD4 count (cells/mm^3)				
≤100	1.29 (1.10, 1.53)	0.006	1.13 (0.95, 1.34)	0.24
101-200	1.19 (1.01, 1.40)		1.14 (0.96, 1.35)	
201-350	1.00		1.00	
Time on ART				
1-3 years	1.00	<0.001	1.00	<0.001
3-5 years	0.63 (0.54, 0.75)		0.61 (0.52, 0.72)	
5-7 years	0.47 (0.38, 0.58)		0.42 (0.34, 0.53)	
>7 years	0.43 (0.35, 0.54)		0.34 (0.27, 0.43)	
Age				
Per 10 years	0.71 (0.65, 0.77)	<0.001	0.72 (0.66, 0.78)	<0.001
Sex				
Male	1.00	<0.001	1.00	0.92
Female	1.53 (1.32, 1.77)		0.99 (0.81, 1.20)	
Ethnicity				
White	1.00	<0.001	1.00	0.071
Black African	1.64 (1.42, 1.91)		1.26 (1.01, 1.57)	
Black Other	1.52 (1.16, 2.00)		1.31 (0.98, 1.75)	
Other/unknown	1.02 (0.79, 1.33)		0.93 (0.72, 1.21)	
Mode of acquisition				
Sex between men	1.00	<0.001	1.00	0.010
Heterosexual	1.59 (1.38, 1.83)		1.27 (1.01, 1.59)	
Other/unknown	1.69 (1.29, 2.22)		1.52 (1.15, 2.01)	
Viral load at ART initiation				
Log_{10}copies/ml	1.05 (0.95, 1.16)	0.33	-	
ART regimen class				
NNRTI	1.00	<0.001	1.00	<0.001
PI	1.73 (1.49, 2.00)		1.72 (1.48, 1.99)	
Year				
2000-2004	1.00	0.029	1.00	<0.001
2005-2009	0.82 (0.71, 0.95)		0.66 (0.57, 0.77)	
2010-2014	0.86 (0.69, 1.09)		0.52 (0.41, 0.67)	

IRR=Incidence rate ratio; CI=Confidence interval

Figure 6.3.2(A): Estimated rate of viral rebound over time on ART according to baseline CD4 count: Results from Poisson regression model test for interaction



(B): Estimated rate of viral rebound over time according to baseline CD4 count, adjusted for EICR: Results from Poisson regression model test for interaction



6.3.3 Clinical Progression

Of those with a baseline CD4 count ≤100, 101-200, 201-350 cells/mm^3, 130 (7.5%), 103 (5.2%) and 144 (3.6%) progressed to AIDS or death. Of those who progressed, 240 (63.7%) experienced an AIDS-defining illness and 137 (36.3%) died. Over a total 10,844, 12,117 and 18,693 person years of follow-up in the ≤100, 101-200 and 201-350 cells/mm^3 baseline CD4 count groups, the corresponding incidence rates (95% CI) of clinical progression were 1.2 (1.0, 1.4), 0.9 (0.7, 1.0) and 0.8 (0.6, 0.9) per 100 person-years of follow-up.

Baseline CD4 count was associated with the rate of clinical progression on ART, with those with a baseline CD4 count $\underline{\leq}$100 cells/mm^3 having 1.60 (95% CI=1.24, 2.03) times the rate of progression as those with a baseline CD4 count 201-350 cells/mm^3 after adjusting for other factors. The rate of clinical progression was highest in the 1-3 years following ART initiation, with a 16-35% lower rate of clinical progression after 3 years on ART (Table 6.3.3). The only other factor found to be associated with clinical progression was older age at ART initiation. For each 10 year increment in age at the start of ART, the rate (95% CI) of clinical progression was estimated to be 26% (1.12, 1.39) higher.

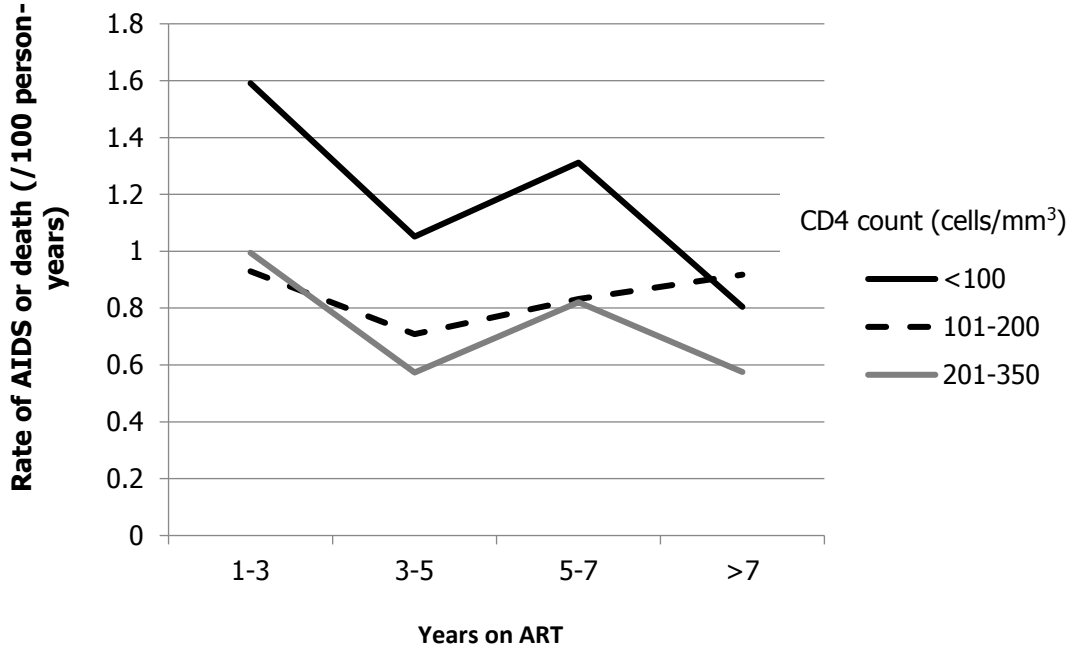
There was no strong evidence of a significant interaction between baseline CD4 count and time on ART (p=0.63, Figure 6.3.3). The estimated rate of clinical progression declined over time on ART in all 3 baseline CD4 count groups. However, whilst the estimated rate (95% CI) of clinical progression was highest for the $\underline{\leq}$100 cells/mm^3 CD4 group after 1 year on ART (1.6 (1.2, 2.1) vs 0.9 (0.7, 1.3) and 1.0 (0.8, 1.3) per 100 person years) and up to 7 years, the rates (95% CI) of AIDS or death were similar amongst the three CD4 groups after 7 years on ART (0.8 (0.5, 1.2), 0.9 (0.6, 1.4) and 0.6 (0.4, 0.9) per 100 person years respectively, Figure 6.3.3). Adjusting for current EICR did not alter the associations observed between baseline CD4 count, time on ART and clinical progression (Figure 6.3.3(B)). However, lower EICR was associated with a 17% higher rate of clinical progression when included in the model (aIRR (95% CI)=1.17 (1.08, 1.26)). Using EICR lagged by 6 months did not alter these conclusions.

Table 6.3.3: Results of Poisson Regression models showing the association between CD4 count at ART initiation and time on ART with the rate of clinical progression

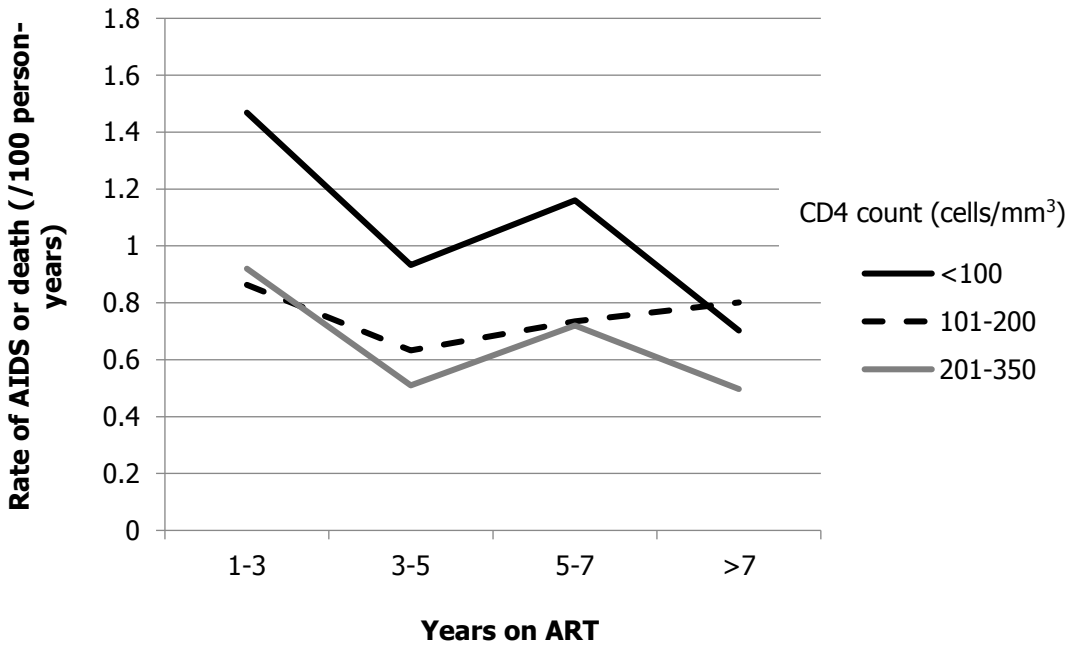
	Unadjusted		Adjusted	
	IRR (95% CI)	**P-value**	**IRR (95% CI)**	**P-value**
CD4 count (cells/mm^3)				
≤100	1.56 (1.23, 1.97)	0.001	1.59 (1.24, 2.03)	0.001
101-200	1.10 (0.86, 1.42)		1.12 (0.87, 1.45)	
201-350	1.00		1.00	
Time on ART				
1-3 years	1.00	0.004	1.00	0.003
3-5 years	0.65 (0.50, 0.85)		0.65 (0.49, 0.85)	
5-7 years	0.85 (0.64, 1.12)		0.84 (0.64, 1.11)	
>7 years	0.68 (0.51, 0.90)		0.65 (0.48, 0.87)	
Age				
Per 10 years	1.26 (1.13, 1.40)	<0.001	1.25 (1.12, 1.39)	<0.001
Sex				
Male	1.00		-	
Female	0.93 (0.73, 1.19)	0.56		
Ethnicity				
White	1.00	0.82	-	
Black African	0.97 (0.76, 1.22)			
Black Other	1.05 (0.68, 1.61)			
Other/unknown	0.85 (0.58, 1.23)			
Mode of acquisition				
Sex between men	1.00	0.08	1.00	0.09
Heterosexual	1.06 (0.86, 1.31)		0.97 (0.78, 1.20)	
Other/unknown	1.58 (1.09, 2.31)		1.50 (1.03, 2.20)	
Viral load at ART initiation				
Log_{10}copies/ml	1.06 (0.91, 1.22)	0.45	-	
ART regimen class				
NNRTI	1.00	0.57	-	
PI	1.07 (0.85, 1.36)			
Year				
2000-2004	1.00	0.50	-	
2005-2009	0.94 (0.76, 1.17)			
2010-2014	0.81 (0.57, 1.16)			

IRR=Incidence Rate Ratio; CI=Confidence interval

Figure 6.3.3(A): Estimated rate of AIDS or death over time on ART according to baseline CD4 count: Results from Poisson regression model test for interaction



(B): Estimated rate of AIDS or death over time on ART according to baseline CD4 count, adjusted for current EICR: Results from Poisson regression model test for interaction



6.3.4 CD4 count changes

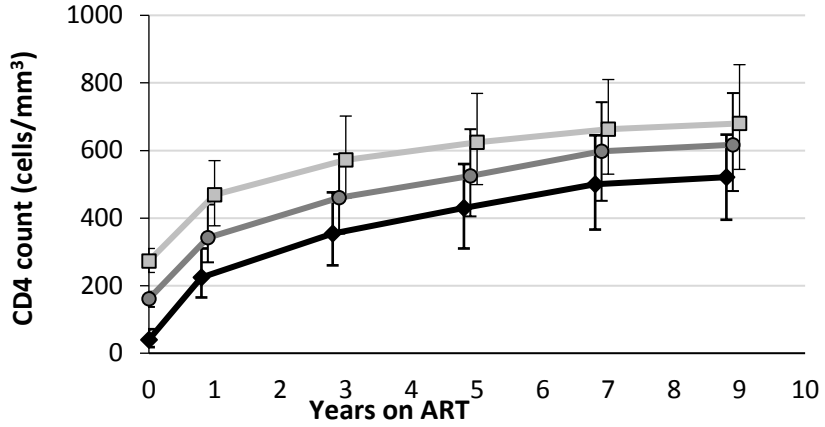
As expected, an increase in CD4 count on ART was seen across all baseline CD4 count groups. The median CD4 count at 1, 3, 5, 7, and 9 years after starting ART was consistently lowest amongst those with a baseline CD4 count ≤100 cells/mm^3, and highest amongst those with a baseline CD4 count 201-350 cells/mm^3 (Figure 6.3.4(A)). The median (IQR) change in CD4 count up to 3 years on ART was similar across CD4 groups: 307 (218, 433) CD4 ≤100 cells/mm^3, 300 (200, 426) CD4 101-200 cells/mm^3 and 305 (191, 430) CD4 201-350 cells/mm^3, respectively. There were differences in the median change in CD4 count after this point, with those with the highest baseline CD4 count showing the smallest changes in CD4 count from baseline on average; 468 (350, 638) CD4 ≤100 cells/mm^3, 466 (330, 610) CD4 101-200 cells/mm^3 and 437 (281, 602) cells/mm^3 by 9 years, respectively (Figure 6.3.4(B), p=0.001). The proportion of individuals achieving a CD4 count above 500 cells/mm^3 on ART increased over time on ART and was highest in those with a baseline CD4 count between 201-350 cells/mm^3. Amongst this group, 40.6% and 80.1% of those in follow-up at years 1 and 9 had achieved a CD4 count above 500 cells/mm^3. Conversely, amongst those with a baseline CD4 count ≤100 cells/mm^3, only 4.3% and 53.5% had achieved a CD4 count above 500 cells/mm^3 by the same time-points (Figure 6.3.4(C), p<0.001).

Results of piecewise mixed effects models are summarised in Figure 6.3.5. As before, CD4 count was significantly lower on ART in those who commenced ART with a lower baseline CD4 count (p<0.001). In the year after ART initiation, the rate of increase in CD4 count was significantly higher in those with baseline CD4 count ≤100 cells/mm^3 compared to those with a CD4 201-350 cells/mm^3 (14.3 (13.8, 14.9) cells/mm^3 per month vs 13.0 (12.6, 13.4) cells/mm^3 per month, p<0.001). Those with baseline CD4 count between 101-200 cells/mm^3 had a significantly lower increase in CD4 in the first year (12.1 (11.6, 12.7)) cells/mm^3 increase per month. Compared to those with a baseline CD4 count 201-350 cells/mm^3, the rate of CD4 increase from 1-7 years after ART initiation was significantly higher in those with baseline CD4 ≤100 cells/mm^3 (3.7 (3.6, 3.9) vs 4.1 (4.0, 4.2) cells/mm^3 per month vs 3.3 (3.2, 3.5) cells/mm^3 per month, p<0.001), but there was no evidence of a difference in CD4 increase for those with baseline CD4 101-200 (3.4 (3.2, 3.5) cells/mm^3 per month, p=0.67). After 7 years on ART, there was no significant difference in the rate of CD4 count increase according to baseline CD4 count: 1.3 (0.9, 1.6), 1.4 (1.0, 1.7) and 1.0 (0.7, 1.4) cells/mm^3 per month respectively for baseline CD4 count <100, 101-200 and 201-350 cells/mm^3.

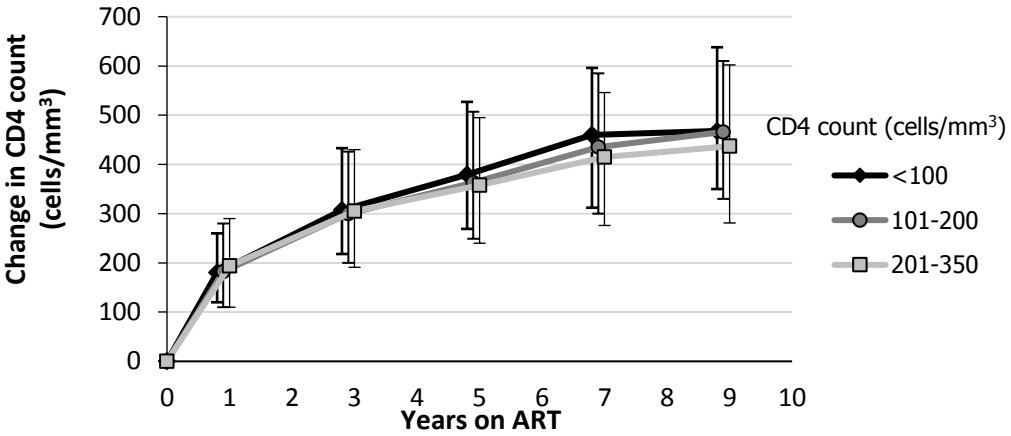
Restricting to those with high EIC, we saw similar results to the main analysis, with those with baseline CD4 count $\underline{\leq}$100 cells/mm^3 having lowest CD4 counts at all time-points on ART but with significantly faster increases in CD4 count between 0-1 and 1-7 years compared with the highest CD4 count group. There was no significant difference in CD4 change for those with

baseline CD4 count 101-200 cells/mm^3 compared to the highest CD4 count group during these periods. After 7 years on ART, there was no significant difference in the rate of CD4 increase according to baseline CD4 count.

Figure 6.3.4 (A): Median (IQR) CD4 count over time since ART initiation, according to baseline CD4 count



(B) Median (IQR) CD4 count and CD4 count change over time since ART initiation, according to baseline CD4 count



(C) Proportion of individuals achieving CD4 count thresholds by year since ART initiation and baseline CD4 count

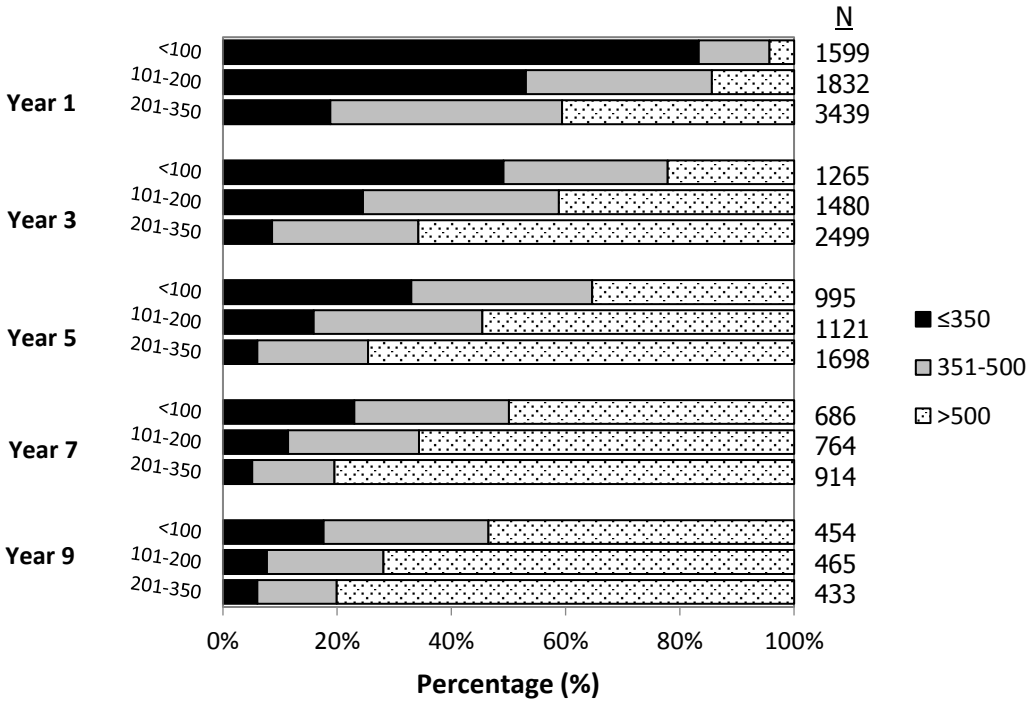
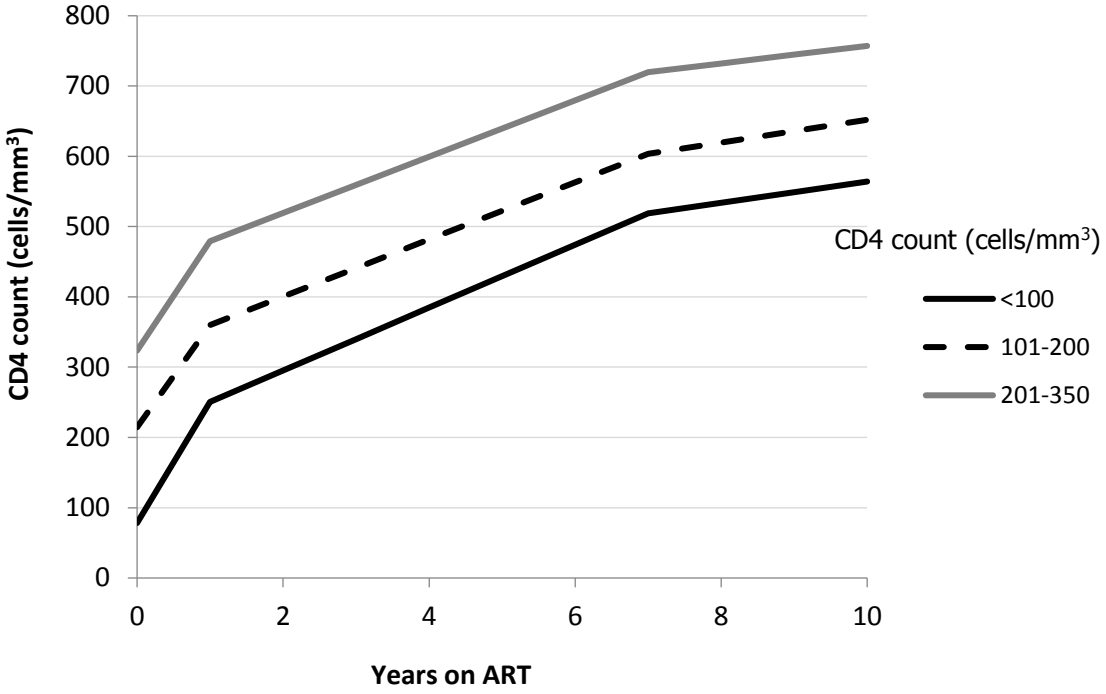


Figure 6.3.5: Estimated mean CD4 count over time on ART, according to baseline CD4 count: Results from piecewise linear mixed effects model including interaction term



	Baseline CD4 count (cells/mm^3)			P-value	P-value
	≤100	101-200	201-350	(<100 vs. 201-350)	(101-200 vs. 201-350)
Mean (95% CI) change in CD4 count per month amongst whole cohort					
0-1 years	14.3 (13.8, 14.9)	12.1 (11.6, 12.7)	13.0 (12.6, 13.4)	<0.001	0.011
1-7 years	3.7 (3.6, 3.9)	3.4 (3.2, 3.5)	3.3 (3.2, 3.5)	<0.001	0.67
>7 years	1.3 (0.9, 1.6)	1.4 (1.0, 1.7)	1.0 (0.7, 1.4)	0.41	0.23
Mean (95% CI) change in CD4 count per month amongst those with high EIC					
0-1 years	14.2 (13.6, 14.8)	12.3 (11.8, 12.9)	13.1 (12.7, 13.5)	0.002	0.029
1-7 years	3.8 (3.7, 4.0)	3.5 (3.4, 3.7)	3.5 (3.4, 3.6)	0.001	0.77
>7 years	1.4 (1.0, 1.8)	1.4 (1.1, 1.8)	1.0 (0.7, 1.4)	0.15	0.14

6.4 Discussion

6.4.1 Summary and interpretation

Over a maximum 14 years of follow-up on ART, amongst individuals who achieved and maintained viral suppression during the first year of ART experience, virological, immunological and clinical outcomes improved for all groups, re-enforcing the benefits of ART for patient outcomes, regardless of the CD4 count at ART initiation. Virological and immunological improvement continued to be seen after seven years on ART, showing that ART continues to have benefits for PLWH in the long-term.

The CD4 count at ART initiation was not strongly associated with virologic rebound after adjustment for other factors, and the rate of viral load rebound declined similarly over time for all CD4 count groups. This suggests that the CD4 count itself is not associated with the rate of viral rebound but that poor adherence is the primary driver of a loss of virologic control in those on treatment. Adjusting for ethnicity and mode of acquisition attenuated the association between CD4 count and viral rebound that was observed in unadjusted analyses, with those of black African or other black ethnicity and those who acquired HIV through routes other than sex between men having higher rates of rebound. This could point to lower rates of adherence in these groups, who were also more likely to also have a lower CD4 count at ART initiation. In a previous chapter, I similarly observed that these groups were more likely to be diagnosed late (Table 5.3.2). Further, this analysis is restricted to individuals who achieved and maintained viral suppression during the first year of treatment, in whom it is possible to assume relatively high levels of adherence overall.

There was evidence that those with a lower CD4 count at ART initiation did not experience CD4 recovery to the same level as those starting with a CD4 count between 201 and 350 cells/mm^3 and were less likely to achieve CD4 counts approaching that in healthy HIV-negative individuals. Only half of those starting ART with a CD4 count ≤100 cells/mm^3 had achieved a CD4 count above 500 cells/mm^3 by 9 years on ART, whereas by only 3 years on ART, two-thirds of those starting ART with a CD4 count 201-350 cells/mm^3 had a CD4 count above 500 cells/mm^3. With CD4 counts in healthy HIV-negative individuals ranging from 500-1600 cells/mm^3 (54, 55), this shows that whilst the CD4 count can recover to normal levels in those who initiate ART late, it is less likely to occur in those starting ART with low CD4 counts and when it does occur takes considerably longer. In mixed effects regression models, small but significantly faster increases in CD4 count were observed from 0-1 and 1-7 years in those with a baseline CD4 count ≤100 cells/mm^3. Despite this, the mean CD4 count did not recover to the same level as for those with baseline CD4 count 201-350 cells/mm^3, remaining at least 200 cells/mm^3 lower. Similarly for those initiating ART with a CD4 count 101-200 cells/mm^3,

CD4 counts remained at least 100 cells/mm^3 lower. After seven years of ART, the rate of CD4 count increase did not differ according to baseline CD4 count. Further follow-up is needed to definitively know whether CD4 counts in a similar range can be obtained for all individuals starting ART with CD4 ≤200 cells/mm^3, however, my results suggest it is more likely that this group will always have a median CD4 count that does not fully recover to the level of those with higher baseline CD4 counts. This means that individuals who start ART in a state of immunosuppression are at higher risk of progression to AIDS for longer. Further, prolonged immunosuppression may also have consequences for non-AIDS morbidity (572, 573). These findings highlight the importance of prompt diagnosis and initiation of ART before severe immunosuppression can occur, in order to achieve optimal immune recovery.

Whether this sub-optimal immunological response in those who start ART with immunosuppression will continue to have implications for clinical progression in the long-term on ART is unclear. Lower CD4 counts on ART are associated with a higher risk of clinical progression (557, 574), and, as discussed above, CD4 counts remained lower in those with immunosuppression at baseline, with many not recovering to levels of those in healthy HIV negative individuals. However, when modelling an interaction between baseline CD4 count and time on ART, the overall higher rate of clinical progression observed in those with a CD4 ≤100 cells/mm^3 appeared to attenuate over time, with similar rates of progression after 7 years on ART to those with a baseline CD4 count 201-350 cells/mm^3. This was not a statistically significant interaction, but this apparent attenuation of differences after 7 years on ART corresponded with the time taken for the mean CD4 count in this group to reach levels above 500 cells/mm^3 in mixed effects models. This could suggest that, although CD4 counts in those with immunosuppression are unlikely to reach similar levels to those with higher CD4 counts at ART initiation, achieving CD4 counts that approach the normal range (i.e. 500 cells/mm^3) will be sufficient to remove any differences in the rate of clinical progression introduced by late ART initiation. In other words, it is perhaps unreasonable to expect CD4 counts to recover to the same level as those initiating ART at a less advanced stage of disease. However, further follow-up including a larger number of individuals with long-term follow-up on ART is needed to support this hypothesis. Recently, a large European cohort collaboration published data on CD4 reference curves. This work followed a similar idea, identifying average CD4 growth trajectories after ART initiation according to baseline characteristics as a better indication of what constitutes a good CD4 count response than whether individuals achieve a pre-defined level of immune recovery such as a 100 cells/mm^3 increase or CD4 count >500 cells/mm^3 (575).

It was hypothesised that differential levels of adherence and EIC, might explain poorer responses to ART in those with a lower CD4 count, if observed. However, in this study there was no evidence that differences in EIC might explain those differences that were seen in

outcomes on ART. EIC was high on average in all CD4 count groups over time on ART. The proportion of individuals with low EIC was only significantly higher for those with a low baseline CD4 count (≤100 cells/mm^3) after 7 years on ART. As this analysis considers a group who were able to achieve and maintain viral load suppression for at least 1 year on ART, we may have minimised any role of poor EIC by restricting to a group who have demonstrated an ability to remain engaged and adherent to medication.

6.4.2 Comparison to the literature

My finding that late ART initiation was not associated with viral rebound after 1 year on ART is consistent with previous analyses of UK CHIC data (576). Studies to report on an association between the CD4 count at which ART is initiated and virological rebound have found somewhat conflicting results with studies from Europe and Canada finding both evidence for (445, 447) and against (478, 577) an association. These studies did not have the same criteria for early and maintained viral suppression as in this study, and compared different thresholds of baseline CD4 count, which may explain the different findings. In a study of 2 outpatient clinics in the UK and Germany, Geretti et al., found no association between baseline CD4 count and virological rebound after 1 year on ART in patients who achieved and maintained viral load suppression during the first year (468). However, in an earlier analysis of the same two outpatient clinics, Phillips et al. found each 100 cells/mm^3 increase in CD4 at ART initiation to be associated with a 17% decreased hazard of rebound, accounting for baseline viral load, ART drugs and demographic factors (578). The close correlation of baseline CD4 count with baseline viral load also makes ascertaining a true causal association difficult. At least one study found no association between CD4 count and rebound in univariable analyses that became significant after adjusting for other factors including baseline viral load (445).

As was observed here, previous studies to consider CD4 changes on ART have almost exclusively found that those starting ART with a lower baseline CD4 count have poorer likelihood of CD4 count recovery (579-582) and consistently lower CD4 counts over time on ART (580, 583-585). Reports from the Swiss HIV cohort Study in the early ART era estimated that each 100 cells/mm^3 increase at ART initiation doubled the odds of achieving a CD4 >500 cells/mm^3 and reduced the odds of a CD4 count <200 cells/mm^3 by nearly 75%. However, changes from baseline over 4 years were similar according to baseline CD4 count and did not observe or explicitly model initial rapid increases in CD4 count in the first one to three months on ART that have been demonstrated elsewhere (565). A more recent study by Lifson et al., looking at CD4 responses in nearly 2000 military personnel in the US, similarly found rapid initial increases in CD4 count that plateaued after 4 years (586). Those with a baseline CD4 count <200 cells/mm^3 had CD4 counts on ART that were approximately 150-200 cells/mm^3 lower than for those with baseline CD4 count 201-350 cells/mm^3, which is consistent with this

study's findings. However, the average CD4 counts for those with a baseline CD4 count <200 cells/mm^3 remained below 400 cells/mm^3 after 10 years on ART, whereas in our study they reached this point by 3-5 years on ART. This may have significant implications for clinical progression as a poor CD4 response on ART has been linked to higher rates of progression to AIDS and death (587). The PISCIS cohort demonstrated that achieving a CD4 count above 200 cells/mm^3 on ART was the most protective factor against clinical progression over a maximum 13 years of follow-up (588) and two other large cohorts demonstrated that 6 month CD4 response to ART predicted clinical regression, mediating any association with baseline CD4 count (589, 590).

Several studies have found lower baseline CD4 count to be associated with clinical progression to AIDS and/or death on ART, either in comparison to a CD4 count above 350 (566, 567, 580, 591) or in the very short-term (592). In this study, I similarly found baseline CD4 count to be associated with clinical progression when we did not consider the impact of time on ART, and found that differences in the rate of progression were greatest in the short-term. Over time on ART, the rate of clinical progression declined for all baseline CD4 count groups, with slightly (but not significantly) faster decline in the lowest CD4 count group, meaning the rate of clinical progression after 7 years on ART became similar. This is consistent with findings from the ART-CC, which found no significant difference in the rate of AIDS-defining illness according to baseline CD4 count between 4-6 years on ART, where one had been present prior to this point. However, there was still evidence of an association with all-cause mortality up to 6 years (411).

6.4.3 Strengths and limitations

A strength of this study is that we were able to study nearly 8,000 individuals with a maximum follow-up of 14 years on ART, which is longer than all but a few other studies of this kind (585, 586). Despite the large number of individuals and long follow-up in this study, we may be underpowered to detect statistical interactions, particularly for clinical progression where there were a small number of events.

Relatively few individuals were followed for more than 10 years in this cohort, meaning that estimates of very long-term effects are less reliable. Particularly for analysis CD4 count changes, LTFU or death may result in biased estimates of CD4 count responses. This is because those who are LTFU no longer contribute data after they leave the study, but may be more likely to have poorer CD4 count changes on ART than those who remain in follow-up. This means that estimates generated amongst those remaining alive and in care may present a 'best-case' scenario of CD4 count response. In this study, LTFU was relatively low,

with 10% of individuals LTFU at least one year prior to the administrative censoring data of 31st December 2014.

Through the REACH algorithm we are able to consider the impact of EIC, but a lack of information on adherence is a limitation, as this is likely an important confounding factor, particularly for virologic outcomes. I excluded individuals who failed to achieve and maintain virologic suppression in the first year on ART so as to restrict to those with successful initial response to ART who likely adhered well. However this will probably over-estimate benefits of ART as compared to all starters. The reference group for these analyses is those starting ART with a CD4 count between 201-350 cells/mm^3. For the period under study this would reflect timely initiation of ART in line with UK HIV treatment guidelines. Individuals starting ART at CD4 counts above 350 cells/mm^3 in the study at this time would likely do so for reasons such as pregnancy, HBV co-infection or, in more recent years, for treatment as prevention, as opposed to for their own heath. However, following recent changes to guidelines world-wide as a result of evidence for treatment as prevention and the benefits of early ART for health, this CD4 threshold would now be considered late ART initiation.

6.4.4 Conclusions

In this chapter I have shown that immunological, clinical and virological outcomes improve over time on ART, regardless of how late ART is initiated. Individuals initiating ART with immunosuppression who are able to suppress their viral load and keep it suppressed during the first year on ART are less likely to recover their CD4 count to normal levels and are unlikely to have CD4 counts approaching that in those starting ART with higher CD4 counts. However, it is possible that clinical outcomes will become comparable to those with more timely ART initiation after approximately 7 years. Nevertheless, timely diagnosis and ART initiation are imperative to reduce the amount of time individuals spend with immunosuppression and increased risk of clinical progression.

Chapter 7: The association between engagement in care and life expectancy

7.1 Introduction

Life expectancy is a main measure of health within a population. As HIV has shifted from a disease with extremely high mortality to a chronic disease that can be successfully managed with ART, so the life expectancy of the HIV-positive population has increased, contributing to an aging epidemic. Several studies have now shown life expectancies in the HIV population that are approaching that of the general population (208, 593). However, gaps between the HIV-positive and general population remain, particularly amongst those diagnosed late (205, 207), those who have sub-optimal responses on ART (206) and smokers (210, 211).

Measures of missed visits, visit frequency and visit constancy have been shown to be associated with higher rates of viral suppression and lower rates of mortality, independently of other clinical factors such as CD4 count (366, 367, 369, 371, 436, 456, 477). Whilst associations between such measures of EIC and mortality have previously been investigated, to my knowledge, its association with life expectancy has not been studied.

In the HIV care continuum, as in the literature, frequently used measures of EIC based on missed visits, measures of visit frequency and time between visits are typically assessed over a short-term fixed period (e.g. 1 year) (215, 229, 257, 329, 335, 337, 341, 346, 367, 369). However, these short-term measures may over-estimate levels of EIC compared to when measured over the long-term (314, 316). Furthermore, they use definitions of visit frequency that do not allow for the fact that the frequency at which HIV care appointments are scheduled may change over time, as an individual's health and clinical status changes (127). Further, individuals' EIC may change over time and this may not be captured through cross-sectional or short-term measures.

In this chapter I investigate differences in life expectancy in the UK CHIC Study according to levels of time-updated EIC during the first 5 years of ART, as measured using the REACH algorithm (317). In order to determine if there was any impact of EIC on life expectancy independently of ongoing adherence to ART, I also estimated life expectancy according to different levels of EIC and viral suppression at 1, 2, 3, 4 and 5 years after ART initiation.

7.2 Methods

7.2.1 Patients

The CHIC2014 dataset was used for this analysis, with data requested from participating centres at the end of 2013. Individuals who initiated ART (≥1 drug) between 2000 and 2012, with at least 1 year of follow-up in the UK CHIC Study were initially included. Women who were pregnant at the time of starting ART were excluded from these analyses as they may have only initiated ART for short periods to prevent MTCT. PWID were also excluded from the analyses, as this was likely to be a major confounding factor, with these individuals likely to have both poorer engagement and higher rates of mortality.

7.2.2 Defining Engagement in Care

EIC was established using the previously described REACH algorithm (Section 6.2.2) (571). All months between ART initiation and the earliest of: 6 months after the date last seen in a UK CHIC centre, death or 31st December 2013 were classified as EIC or not in care. At 1, 2, 3, 4 and 5 years after ART initiation, the engagement in care rate (EICR) was calculated as the proportion of months since starting ART for which an individual was classified as being in care. Any prolonged periods of non-engagement in care (i.e. >12 months) during the first 5 years on ART were incorporated in the measure of EICR, as opposed to being separately treated as LTFU. EICR was treated as both a continuous variable and using an arbitrarily chosen cut-off of 80% to define high (≥80%) and low (<80%) EICR. EICR was compared according to current viral load at each time-point on ART (1, 2, 3, 4, 5 years after ART initiation) using Mann-Whitney U and Chi-squared tests, as appropriate.

7.2.3 Estimating Life expectancy

Abridged life-tables were used for the estimation of life expectancy. Methods for constructing such tables were first introduced by Chiang (594). In brief, these tables apply the cohort-observed age-specific mortality rates to a hypothetical cohort in order to estimate the expected number of additional years an individual can expect to live at a given age, otherwise known as the life expectancy at that age. Each row of the life-table refers to one of the specified age groupings, in this case: 20-24, 25-29, 30-34, 35-39, 40-44, 45-49, 50-54, 55-59, 60-64, 65+. Those aged over 65 are grouped into a single age band to allow meaningful estimates of mortality rates, owing to small numbers of individuals above this age in the cohort. In the methods for constructing abridged life-tables, special consideration is made for the oldest age group (65+), as this is an open-ended interval, in which the probability of death is assumed to be equal to 100%. Due to under-estimation of the mortality rate in the final open-ended age group in the cohort, the age-specific mortality rate in this age group is adjusted, as outlined in Table 7.2.1. This is done such that the mortality rate in this age group

is equal to the mortality rate in the general population (595), multiplied by an average of the rate ratio of mortality in the UK CHIC Study compared to the general population, for the 55-59 and 60-64 age groups. Sensitivity analyses were performed in which the adjusted mortality rate in the 65+ age group was increased and decreased by 20%. The columns of the abridged life-table, their meaning and calculation are shown in Table 7.2.1.

Traditionally the unadjusted age-specific mortality rate (um_x) is calculated using observed deaths and person-years of follow-up in the cohort. To estimate life expectancy according to a factor of interest (e.g. gender), age-specific mortality rates would need to be calculated for men and women in the cohort separately, with separate abridged life-tables constructed for each sex. To estimate life expectancy according to more than one factor, mortality rates and abridged life tables would need to be generated for each possible combination of levels of all factors, thereby, splitting the cohort down into smaller sub-groups resulting in smaller numbers of events. This can prove problematic in practice, with estimates influenced by small numbers of events within each sub-group. Therefore, it is not possible to consider many factors at the same time when estimating life expectancy. Further, this does not allow for estimation of life expectancy according to continuous variables. An alternative approach is to use Poisson regression to estimate the age-specific mortality rates for different levels of a small number of independent variables that, in turn, construct the abridged life-tables. This approach has several advantages. Firstly, it provides smoother estimates of mortality rates across categories (e.g. age groups), but also allows estimation of mortality rates at any level of a continuous variable. Chiang also suggested methods for calculating the standard error of the estimated life expectancies, based on either the observed number of deaths in the cohort or the mortality rate in each age interval (594, 596). However, these methods are not appropriate when using Poisson regression to estimate mortality rates and so bootstrapping was used instead to generate standard errors. In order to generate bootstrapped standard errors, I first randomly sampled with replacement from the available dataset 1,000 times. Age-specific mortality rates and life expectancies were calculated for each of the 1,000 samples. The standard deviation of the 1,000 generated life expectancies was used as an estimate of the standard error (597).

Table 7.2.1: Definitions of the elements involved in constructing an abridged life-table

Column name	Meaning	Method
n_i	width of age band for row i	Fixed: n_i=5
a_i	Trend of mortality in age interval x to x+n	Fixed: a_i=0.5 This assumes equal distribution of deaths throughout the interval
um_x	unadjusted rate of death in age interval x to x+n	Estimated by Poisson regression
am_x	adjusted rate of death in age interval x to x+n	Mortality rate in over 65 group assumed to be at least as high as mortality rate in UK population for that age band (www.mortality.org.uk) multiplied by the average rate ratio in 55-60 and 60-65 age groups (595).
q_x	probability of death within age interval, x to x+n	$q_x = \frac{n_i\ am_x}{1 + (1 - a_i)n_i\ am_x}$ or $q_x = 1$, for open-ended interval
l_x	survivors of hypothetical cohort to exact age x	$l_{x+n} = l_x - d_x$ or $l_x = 1000$, for x=20
d_x	deaths experienced by hypothetical cohort in age interval x to x+n	$d_x = l_x q_x$ or $d_x = l_{x+n} - l_x$
L_x	person-years lived by hypothetical cohort in age interval x	$L_x = n_i(l_x - d_x) + a_i n_i d_x$ or $L_x = \frac{l_x}{am_x}$, for open-ended interval
T_x	Summation of Lx column up to age x	$T_x = L_x + T_{x+n}$ or $T_x = L_x$, for open-ended interval
e_x^0	expected years of life remaining for individuals achieving exact age x	$e_x^0 = \frac{T_x}{l_x}$

For these analyses, age-specific mortality rates were estimated from 1, 2, 3, 4 and 5 years after ART initiation, in those still known to be attending a UK CHIC centre at these time-points, using Poisson regression models. Separate regression models were fitted as outlined in Table 7.2.2 for each time-point on ART, to generate age-specific mortality rates in five-year age

bands for different EICR and viral load criteria. An undetectable viral load was defined as a viral load ≤50 copies/ml and was based on the nearest viral in the 6 months prior to, or up to 2 weeks after each time point of interest (1, 2, 3, 4 or 5 years). For calculation of mortality rates, follow-up was considered from each time-point of interest on ART until the earliest of last date seen in a UK CHIC centre plus 6 months, 31st December 2013 or death. Abridged life-tables were constructed for each of the EICR/viral load categories outlined in Table 7.2.2. For each abridged life-table I will focus on the exact ages 35 and 50 for illustration of the findings, and instead of life expectancy, I present expected age at death, which is calculated by adding the respective estimated life expectancy to each exact age.

Table 7.2.2: Poisson Regression models fitted and levels of EIC and viral load considered in analyses

Model	Variables included in model, alongside age	Levels at which life expectancy will be estimated
1	(i) EICR (High (≥80%), low (<80%))	a) High EICR b) Low EICR
2	(i) EICR (High (≥80%), low (<80%)) (ii) Current viral load (≤50 copies/ml, >50 copies/ml)	a) High EICR / Viral load ≤50 copies/ml b) High EICR / Viral load >50 copies/ml c) Low EICR / Viral load ≤50 copies/ml d) Low EICR / Viral load >50 copies/ml
3	(i) EICR (continuous)	a) EICR 100% b) EICR 75% c) EICR 50% d) EICR 25%
4	(i) EICR (continuous) (ii) Current viral load (≤50 copies/ml, >50 copies/ml)	a) EICR 100% / Viral load ≤50 copies/ml b) EICR 100% / Viral load >50 copies/ml c) EICR 75% / Viral load ≤50 copies/ml d) EICR 75% / Viral load >50 copies/ml e) EICR 50% / Viral load ≤50 copies/ml f) EICR 50% / Viral load >50 copies/ml g) EICR 25% / Viral load ≤50 copies/ml h) EICR 25% / Viral load >50 copies/ml

7.3 Results

7.3.1 Baseline Characteristics

There were 24,816 individuals who initiated ART between 2000 and 2012 in the UK CHIC Study. Of these, 1,032 (4%) pregnant women and 531 (2%) IDU were excluded from the analysis. After excluding those with <1 year of follow-up, a final 20,325 individuals were included in analyses.

Given the exclusion criteria indicated, excluded individuals were more likely to be female, heterosexual or to have another non-MSM exposure, of black African ethnicity and to have HCV-coinfection than included individuals. Excluded individuals had a higher CD4 count and lower viral load at ART start and were less likely to have experienced an AIDS-defining illness than those included in the analysis. Excluded individuals were also more likely to have started ART in a more recent calendar year (all $p<0.001$, Table 7.3.1).

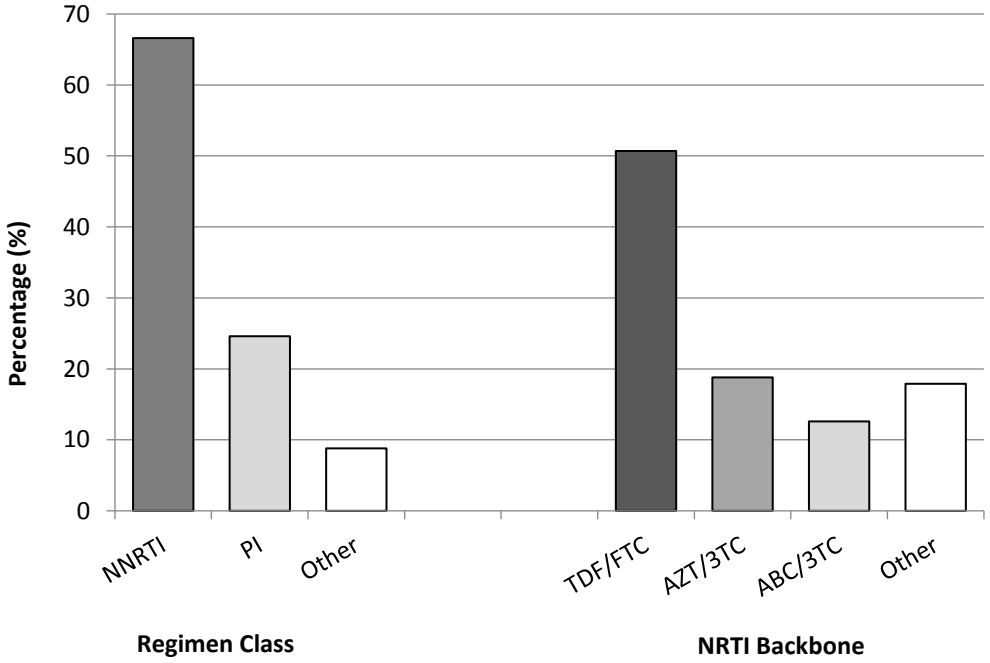
Of those included in the analysis, the majority were male (74.3%), of white ethnicity (54.1%) and acquired HIV through sex between men (53.6%). Approximately 3% had either HBV or HCV co-infection. The median (IQR) CD4 count at starting ART was low at 240 (141, 349) cells/mm^3, and 16.9% had experienced an AIDS event at the time of starting ART. Median (IQR) viral load was 4.6 (3.4, 5.2) log copies/ml. Two-thirds of individuals started an NNRTI-based regimen; 56.7% of individuals received EFV. A quarter started treatment with a PI-based regimens; 11.1% LPV/r, 8.1% ATV(/r) and 5.3% DRV(/r). TDF/FTC was the most common NRTI backbone, with half of the cohort starting this combination (Figure 7.3.1).

Of 20,325 individuals included with at least 1 year of follow-up on ART, the median (IQR) year of ART initiation was 2007 (2004, 2010) and 17,463 (85.9%), 15,025 (73.9%), 12,812 (63.0%) and 10,624 (52.3%) were still alive and retained in a UK CHIC centre by 2, 3, 4 and 5 years after ART initiation, respectively.

Table 7.3.1: Characteristics of included and excluded individuals

		Excluded N=4491	Included N=20325	P-value
Age, median (IQR)	years	35 (30, 41)	38 (32, 44)	<0.001
Sex, n (%)	Male	2283 (50.8)	15097 (74.3)	<0.001
	Female	2208 (49.2)	5228 (25.7)	
Ethnicity, n (%)	White	1806 (40.2)	10996 (54.1)	<0.001
	Black African	1877 (41.8)	6077 (29.9)	
	Black other	245 (5.5)	1134 (5.6)	
	Other	406 (9.0)	1806 (8.9)	
	Unknown	157 (3.5)	312 (1.5)	
Year of starting ART, n (%)	2000-2003	905 (20.2)	4422 (21.8)	<0.001
	2004-2007	1304 (29.0)	6561 (32.3)	
	2008-2012	2282 (50.8)	9342 (46.0)	
Mode of HIV acquisition, n (%)	Sex between men	1147 (25.5)	10885 (53.6)	<0.001
	Heterosexual	2438 (54.3)	8501 (41.8)	
	Other	672 (15.0)	161 (0.8)	
	Unknown	234 (5.2)	778 (3.8)	
HBV co-infection, n (%)	No	1969 (43.8)	10743 (52.9)	<0.001
	Yes	120 (2.7)	559 (2.8)	
	Not tested	2402 (53.5)	9023 (44.4)	
HCV co-infection, n (%)	No	2127 (47.4)	11858 (58.3)	<0.001
	Yes	334 (7.4)	594 (2.9)	
	Not tested	2030 (45.2)	7873 (38.7)	
CD4 count, median (IQR)	cells/mm^3	275 (150, 415)	240 (141, 349)	<0.001
CD4 count, n (%)	<200	1299 (34.3)	6974 (38.0)	<0.001
	200-349	1178 (31.1)	6808 (37.1)	
	350-499	690 (18.2)	2768 (15.1)	
	≥500	623 (16.4)	1794 (9.8)	
AIDS, n (%)	No	3883 (86.5)	16882 (83.1)	<0.001
	Yes	608 (13.5)	3443 (16.9)	
Viral load, median (IQR)	log_{10} copies/ml	4.2 (2.7, 5.0)	4.6 (3.4, 5.2)	<0.001

Figure 7.3.1: ART regimens started in individuals with at least 1 year of follow-up in the UK CHIC Study (n=20,325)

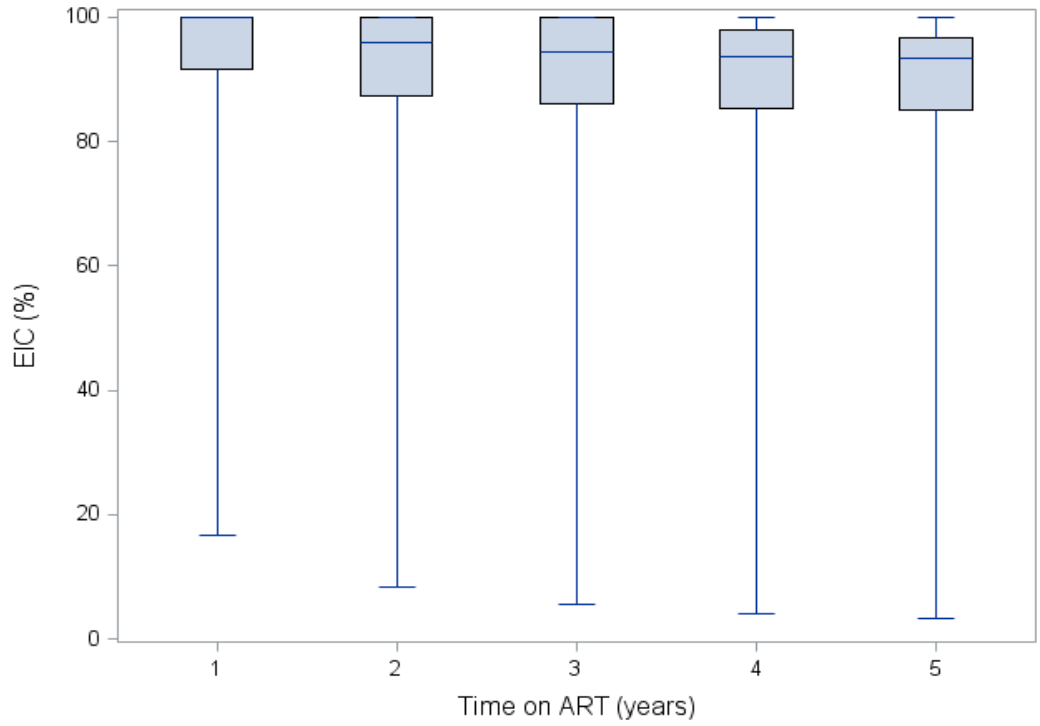


7.3.2 Engagement in Care

EICR was high in the first 5 years on ART, with the median proportion of months for which individuals were engaged in care remaining above 90% at all time-points (Figure 7.3.2). However, there was evidence that EICR declined with longer time on ART, with median (IQR) EICR of 100% (91.7, 100) at 1 year on ART and 93.3% (85.0, 96.7) at 5 years on ART ($p<0.001$). The proportion of individuals with EICR $\geq$80% was 83.4% after 1 year on ART, compared to 81.5% over all 5 years.

Conversely, the proportion of individuals with an undetectable viral load increased with longer time on ART; 84.8%, 86.2%, 87.2%, 88.1% and 89.1% at 1, 2, 3, 4 and 5 years after ART initiation respectively ($p<0.001$). Median (IQR) CD4 count also increased with longer time on ART; 400 (270, 543), 450 (320, 600), 487 (350, 645), 510 (371, 673) and 530 (387, 700) cells/mm^3 by 1, 2, 3, 4 and 5 years on ART ($p<0.001$).

Figure 7.3.2: EICR at 1, 2, 3, 4 and 5 years after ART initiation



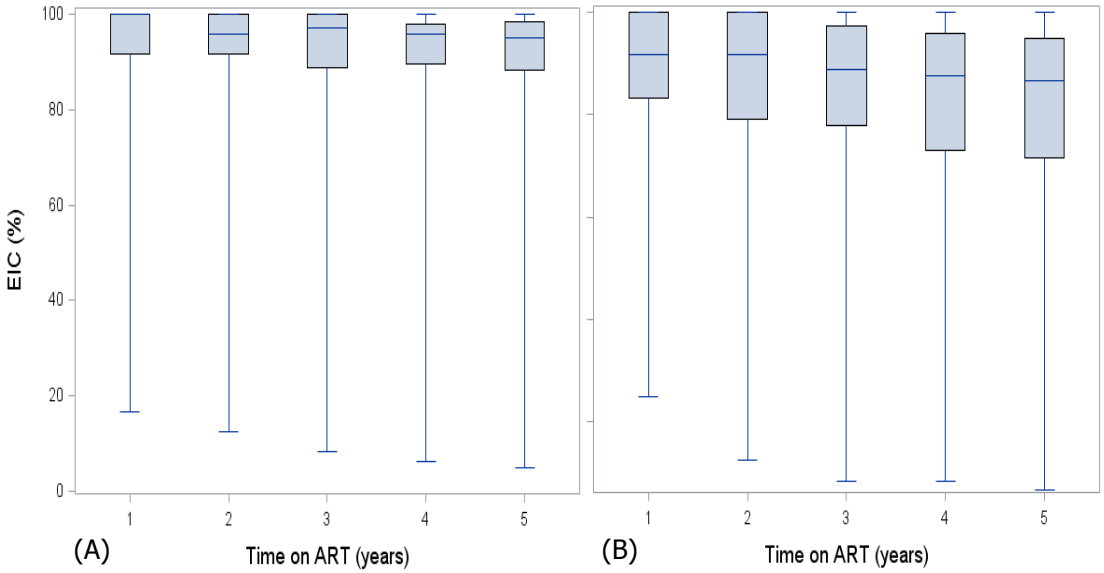
	1 year	2 years	3 years	4 years	5 years
N	20325	17463	15025	12812	10624
EICR, median (IQR)	100 (91.7, 100)	95.8 (87.5, 100)	94.4 (86.1, 100)	93.8 (85.4, 97.9)	93.3 (85.0, 96.7)
EICR ≥80%	83.7%	80.9%	82.3%	80.9%	81.7%

7.3.2.1 Engagement in care according to viral load at each time-point on ART

At each time-point following ART initiation, EICR was significantly lower in individuals whose viral load was >50 copies/ml compared to those with an undetectable viral load (Figure 7.3.3). There were declines in EICR with longer duration on ART for both those with undetectable and detectable viral load at each time point. Of those with an undetectable viral load (≤50 copies/ml) at 1 year after ART initiation, 92% were engaged in care at least 80% of months (i.e. 10 out of 12 months), compared to only 80% of those with a detectable viral load ($p<0.001$). After 5 years on ART, 88.8% and 64.2% of individuals with undetectable and detectable viral load, respectively, had been engaged in care for at least 80% of follow-up months ($p<0.001$).

EICR was lower in individuals who did not have a viral load available at each time point on ART, compared to those with either detectable or undetectable viral load. However, this is partly due to the way that EIC is defined using the REACH algorithm, with presence of a viral load measure used as a proxy for a visit, alongside CD4 counts and ART start dates. With longer duration on ART, median (IQR) EICR in those with a missing viral load increased from 50.0% (25.0, 75.0) after 1 year on ART to 75.0% (38.3, 88.3) by 5 years.

Figure 7.3.3: EICR at 1, 2, 3, 4 and 5 years after ART initiation in those with latest viral load (A) ≤50 copies/ml and (B) >50 copies/ml



		1 year	2 years	3 years	4 years	5 years
Median (IQR) EICR	≤50 c/ml	100.0 (91.7, 100)	95.8 (91.7, 100)	97.2 (88.9, 100)	95.8 (89.6, 97.9)	95.0 (88.3, 98.3)
	>50 c/ml	91.7 (83.3, 1.0)	91.7 (79.2, 100)	88.9 (77.8, 97.2)	87.5 (72.9, 95.8)	86.7 (71.7, 95.0)
	Missing	50.0 (25.0, 75.0)	58.3 (25.0, 83.3)	63.9 (27.8, 86.1)	70.8 (33.3, 89.6)	75.0 (38.3, 88.3)
P-value		<0.001	<0.001	<0.001	<0.001	<0.001
≥80% EICR	≤50 c/ml	92.0%	89.5%	90.4%	88.4%	88.8%
	>50 c/ml	79.5%	71.0%	71.6%	65.3%	64.2%
	missing	19.0%	27.4%	33.6%	38.8%	42.3%
P-value		<0.001	<0.001	<0.001	<0.001	<0.001
At 1, 2, 3, 4 and 5 years, n=1934, 1817, 1648, 1331 and 1120 were missing a viral load.						

7.3.3 Engagement in care and mortality

Amongst individuals still known to a UK CHIC centre by 1, 2, 3, 4 and 5 years after ART initiation, there were 534 (2.6%), 410 (2.3%), 334 (2.2%), 271 (2.1%) and 216 (2.0%) deaths that occurred within 6 months of the last recorded visit date. Crude mortality rates (95% CI) amongst individuals alive and in follow-up at 1, 2, 3, 4 and 5 years after ART

initiation were therefore 5.2 (4.7, 5.6), 4.9 (4.4, 5.4), 5.0 (4.5, 5.6), 5.2 (4.6, 5.8) and 5.5 (4.7, 6.2) per 1,000 person-years, respectively.

In Poisson regression models that included age and EICR as a categorical variable (model 1), EICR <80% at all years after ART initiation was associated with an increased rate of mortality, compared to EICR ≥80% (Table 7.3.2). Whereas there was a 32% increase in the rate of mortality with low EICR after 1 year on ART (95% CI=1.06, 1.63), low EICR after 5 years on ART was associated with a 75% increased rate of mortality (95% CI=1.28, 2.37). After including viral load in the model (model 2), it was observed that an undetectable viral load at each time-point on ART was associated with a decreased rate of mortality (Table 7.3.2). The inclusion of viral load in the model attenuated the association between EICR and mortality somewhat, particularly the associations seen at 4 and 5 years after ART initiation in model 1. Low EICR after 4 and 5 years on ART respectively, was now only associated with a 24% (95% CI=0.88, 1.75) and 36% (95% CI=0.94, 1.97) increased rate of mortality after adjusting for viral load. There was only strong evidence of an association between EICR and mortality at 1 and 3 years after ART initiation.

Considering models that included age and EICR as a continuous variable (model 3), lower EICR was associated with an increased rate of mortality, although effect sizes were moderate (Table 7.3.2). As was seen in model 1, lower EICR was more strongly associated with increased mortality after a longer duration on ART: Incidence rate ratio IRR (95% CI)=1.04 (0.99, 1.08) per 10% decrease in EICR by 1 year on ART and IRR (95% CI)=1.08 (1.01, 1.15) per 10% decrease in EICR by 5 years on ART. Including viral load in the models with continuous EICR (model 4), an undetectable viral load at each time-point on ART was independently associated with a lower rate of mortality. Contrary to what was found for categorical EIC, when adjusting for viral load, each 10% decrease in EICR by 1, 2, and 3 years on ART was associated with a greater relative increase in the mortality rate: 8% (95% CI=1.01, 1.16), 6% (95% CI=0.99, 1.14) and 9% (95% CI=1.01, 1.18) increase in mortality rate at 1, 2 and 3 years after ART initiation, respectively. The association between EICR at 4 and 5 years and mortality was, however, attenuated by inclusion of viral load in the model: IRR (95% CI) of 1.02 (0.93, 1.12) per 10% decrease in EICR at 4 years and 1.06 (0.96, 1.17) at 5 years on ART.

Table 7.3.2: Associations between EIC, viral load and mortality; results from Poisson regression models to estimate mortality rates

	Incidence rate ratio of mortality (95% Confidence Interval)				
	Year 1	**Year 2**	**Year 3**	**Year 4**	**Year 5**
Models 1					
EICR <80% (vs. ≥80%)	1.32 (1.06, 1.63)	1.32 (1.05, 1.67)	1.54 (1.19, 1.99)	1.64 (1.25, 2.16)	1.75 (1.28, 2.37)
Models 2					
EICR <80% (vs. ≥80%)	1.31 (1.00, 1.70)	1.23 (0.94, 1.62)	1.47 (1.08, 2.01)	1.24 (0.88, 1.75)	1.36 (0.94, 1.97)
Viral load <50 c/ml (vs. >50 c/ml)	0.43 (0.35, 0.52)	0.40 (0.32, 0.51)	0.46 (0.35, 0.60)	0.38 (0.28, 0.52)	0.35 (0.25, 0.49)
Models 3					
EICR (per 10% decrease)	1.04 (0.99, 1.08)	1.03 (0.99, 1.08)	1.05 (1.00, 1.11)	1.06 (1.00, 1.13)	1.08 (1.01, 1.15)
Models 4					
EICR (per 10% decrease)	1.08 (1.01, 1.16)	1.06 (0.99, 1.14)	1.09 (1.01, 1.18)	1.02 (0.93, 1.12)	1.06 (0.96, 1.17)
Viral load <50 c/ml (vs. >50 c/ml)	0.43 (0.35, 0.52)	0.41 (0.33, 0.51)	0.46 (0.35, 0.60)	0.37 (0.27, 0.50)	0.34 (0.25, 0.48)

All models also included categorical current age (20-24, 25-29, 30-34, 35-39, 40-44, 45-49, 50-54, 55-59, 60-64, 65+);
c/ml=copies/ml

7.3.4 Life expectancy

Considering life expectancy according to level of EIC, it was found that the expected age at death was higher for those with higher levels of engagement at all time-points on ART (Figure 7.3.4; Table 7.3.3). There was an approximate 5 year difference in life expectancy for those with >80% EICR over the first 5 years on ART, compared with <80% EIC. Similar findings were made for life expectancy at the exact age of 50 (Figure 7.3.4b, Table 7.3.3). The expected age at death at age 50 for someone with >80% EICR at all times on ART was 77, and for someone with EICR <80% was approximately 72 (ranging between 71.2 and 73.3).

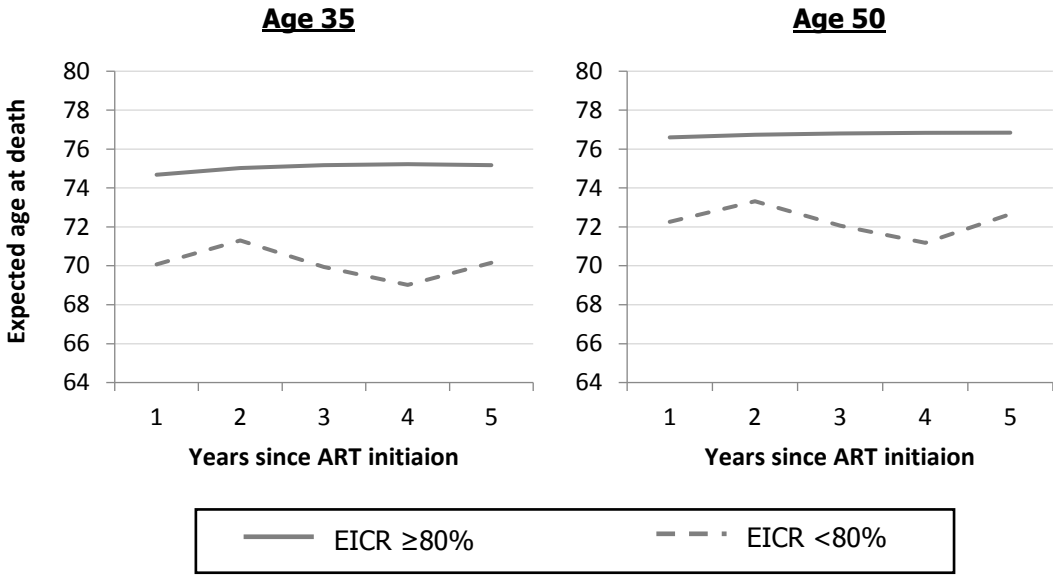
When EICR was considered as a continuous variable, the expected age at death remained stable over 5 years in those with 100% EIC, but declined in those with lower EICR over periods of more than 2 years on ART. Whereas the expected age at death at age 35 remained at 75 for those with 100% EIC, the expected age at death (standard error; se) for those with 25% EICR at 1, 2 and 5 years on ART was 70.0 (0.7), 71.4 (0.7) and 67.9 (1.0), respectively. This meant a 7 year difference in life expectancy for those with 25% EICR over 5 years, compared to those with 100% EICR over the same period. Similarly, at exact age of 50, life expectancy was nearly 5 years lower in those with 25% EICR at 1 year compared to 100% EICR (expected age at death 72.2 vs. 76.6). Comparing levels of EICR over 5 years, life expectancy was nearly 7 years lower with only 25% EICR as opposed to 100% EICR (expected age at death 70.4 vs. 76.8).

For both those with and without an undetectable viral load at each time point in ART, higher EICR still appeared to confer higher life expectancy and therefore older expected age at death compared to lower EICR (Figure 7.3.4; Table 7.3.3). Amongst those with an undetectable viral load at each time-point on ART, at exact ages of 35 and 50, the expected age at death (se) for someone with 100% EICR remained stable at 77 and 79, respectively. With 25% EIC, the expected age at death at age 35 was 69.0 (1.0), 71.3 (1.2), 69.0 (1.1), 74.2 (1.1) and 70.5 (1.2) at 1, 2, 3, 4 and 5 years on ART; between 3 and 8 years lower than for 100% EIC. At exact age of 50, the expected age at death was 71.1 (0.9), 73.3 (0.8), 71.1 (0.8), 75.7 (0.8) and 72.2 (0.9) at 1, 2, 3, 4 and 5 years on ART, giving differences of between 4 and 8 years compared to 100% EIC.

The expected age at death was considerably lower for those with a detectable (as opposed to undetectable) viral load at each time-point on ART (Figure 7.3.5, Table 7.3.3). For individuals with a detectable viral load but high levels of EICR (>80% or 100%), the expected age at death at age 35 was between 64 and 66. This was approximately 10 years lower than for those with an undetectable viral load and 100% EICR at all time-points on ART, and between 1-10 years lower than those with an undetectable viral load and only 25% EICR. At

exact age 35, the expected age at death (se) for someone with a detectable viral load but 25% EICR at 1, 2, 3, 4 and 5 years on ART was very low at 61.0 (1.1), 62.3 (1.1), 61.6 (1.0), 63.9 (1.1) and 60.7 (1.4). At exact age 50, findings were similar, with an approximate 2 year increase in the expected age at death than for exact age 35 (Figure 7.3.4; Table 7.3.3).

Figure 7.3.4: Expected age at death for exact ages 35 and 50, according to EICR as a (A) categorical and (B) continuous variable at 1, 2, 3, 4 and 5 years after starting ART



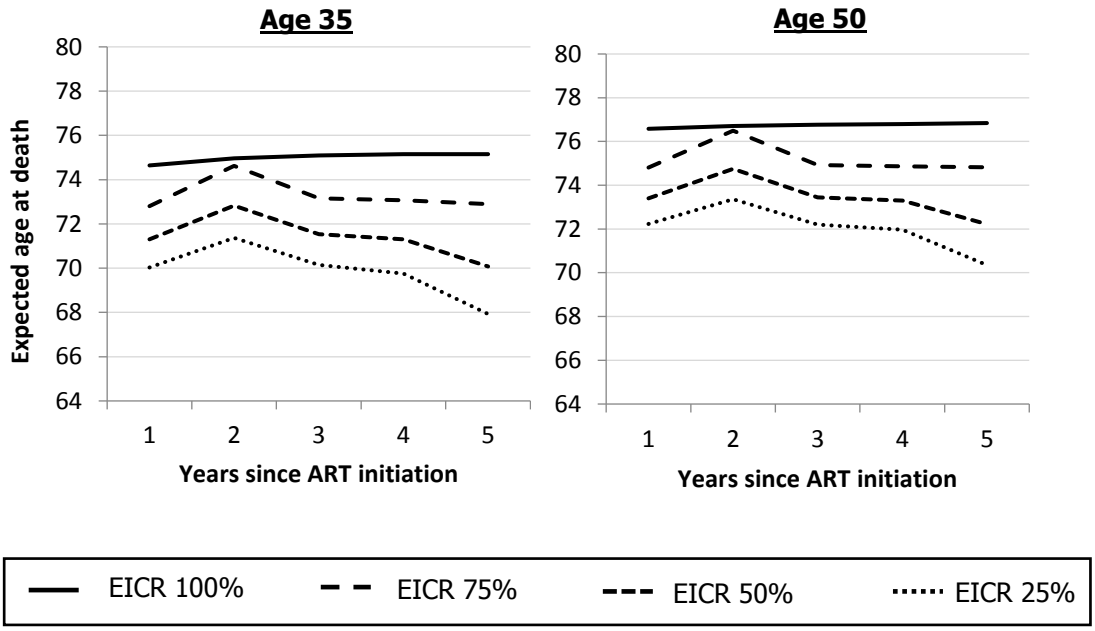
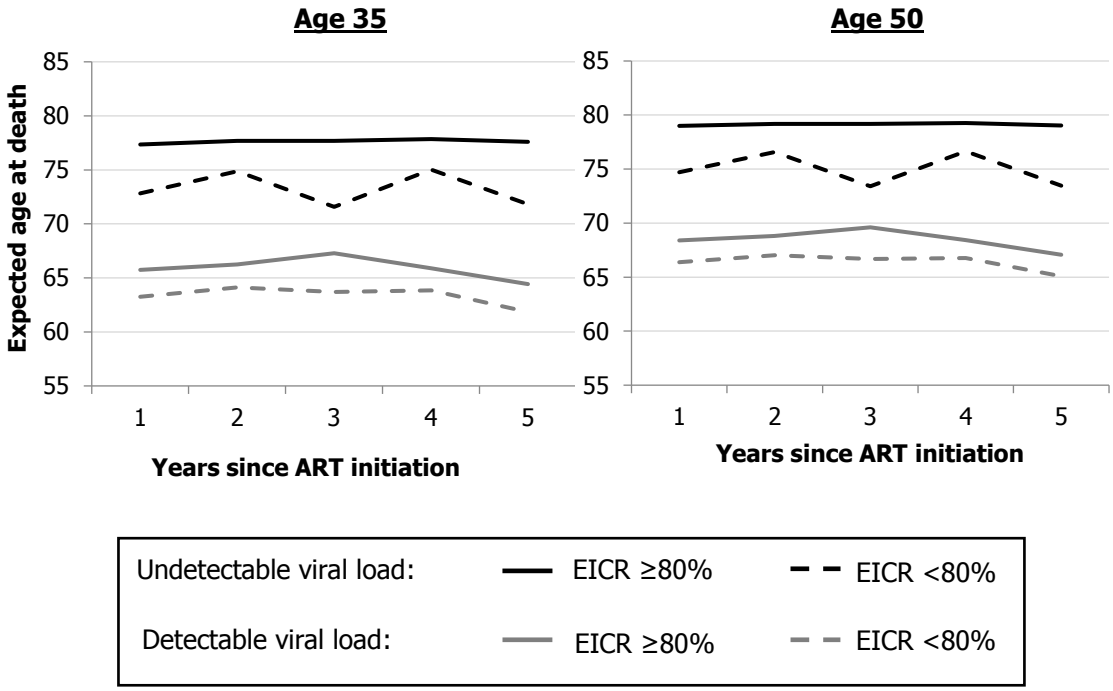


Figure 7.3.5: Expected age at death for exact ages 35 and 50, according to latest viral load and EICR as a (A) categorical and (B) continuous variable at 1, 2, 3, 4 and 5 years after starting ART



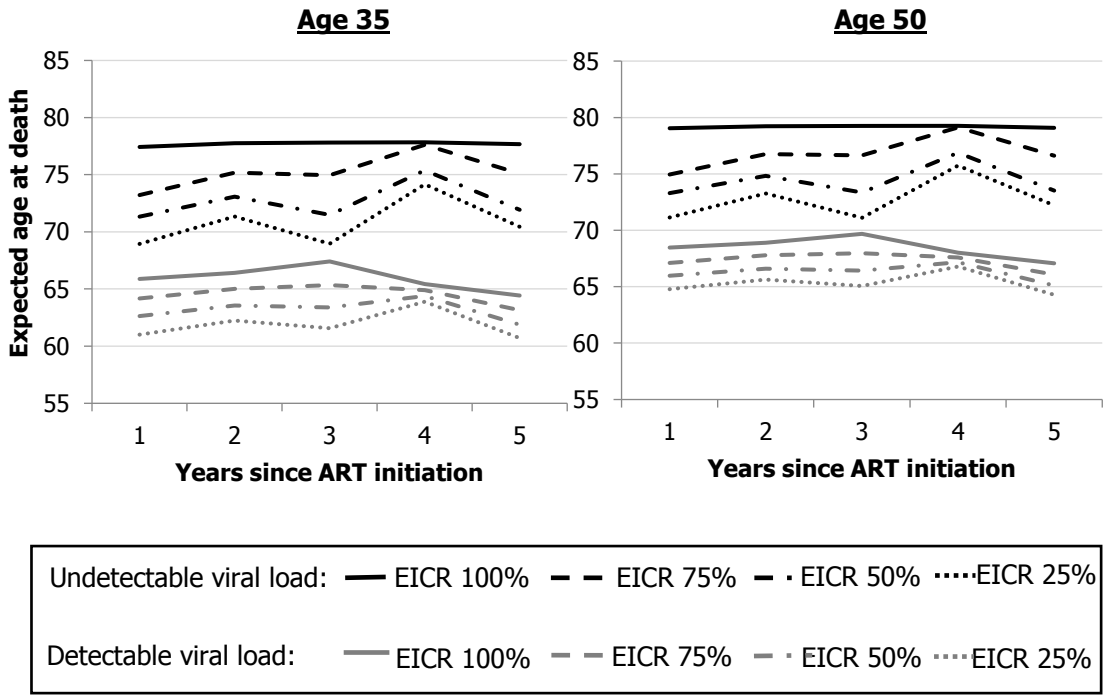


Table 7.3.3: Expected age at death at exact ages 35 and 50, according to EICR and viral load criteria

		Expected age at death (Standard error)				
		Year 1	**Year 2**	**Year 3**	**Year 4**	**Year 5**
Model1						
EICR ≥80%	At age 35	74.7 (0.2)	75.0 (0.3)	75.2 (0.3)	75.2 (0.3)	75.2 (0.3)
	At age 50	76.6 (0.2)	76.7 (0.2)	76.8 (0.2)	76.8 (0.3)	76.8 (0.3)
EICR <80%	At age 35	70.1 (0.5)	71.3 (0.5)	69.9 (0.7)	69.0 (0.7)	70.2 (0.9)
	At age 50	72.3 (0.4)	73.3 (0.4)	72.1 (0.5)	71.2 (0.5)	72.7 (0.6)
Model 2						
EICR ≥80% / VL <50 c/ml	At age 35	77.4 (0.2)	77.7 (0.3)	77.7 (0.3)	77.9 (0.3)	77.6 (0.4)
	At age 50	79.0 (0.2)	79.2 (0.2)	79.2 (0.2)	79.3 (0.3)	79.0 (0.3)
EICR ≥80% / VL >50 c/ml	At age 35	65.8 (0.6)	66.3 (0.7)	67.3 (0.7)	65.7 (0.8)	64.4 (0.9)
	At age 50	68.4 (0.5)	68.8 (0.6)	69.6 (0.6)	68.4 (0.5)	67.1 (0.5)
EICR <80% / VL <50 c/ml	At age 35	72.8 (0.6)	74.9 (0.6)	71.6 (0.8)	75.0 (0.7)	71.8 (0.9)
	At age 50	74.7 (0.4)	76.6 (0.4)	73.4 (0.5)	76.6 (0.5)	73.5 (0.6)
EICR <80% / VL >50 c/ml	At age 35	63.3 (0.9)	64.1 (0.9)	63.7 (1.1)	63.9 (1.0)	61.8 (1.2)
	At age 50	66.4 (0.5)	67.0 (0.5)	66.7 (0.6)	66.8 (0.5)	65.1 (0.7)
Model 3						
EICR 100%	At age 35	74.6 (0.2)	75.0 (0.3)	75.1 (0.3)	75.2 (0.3)	75.2 (0.4)
	At age 50	76.6 (0.2)	76.7 (0.2)	76.8 (0.2)	76.8 (0.3)	76.8 (0.3)
EICR 75%	At age 35	72.8 (0.2)	74.6 (0.3)	73.2 (0.3)	73.1 (0.3)	72.9 (0.4)
	At age 50	74.8 (0.2)	76.5 (0.3)	74.9 (0.3)	74.9 (0.3)	74.8 (0.3)
EICR 50%	At age 35	71.3 (0.4)	72.8 (0.5)	71.5 (0.5)	71.3 (0.6)	70.1 (0.7)

		Expected age at death (Standard error)				
		Year 1	**Year 2**	**Year 3**	**Year 4**	**Year 5**
	At age 50	73.4 (0.3)	74.8 (0.3)	73.4 (0.4)	73.3 (0.4)	72.2 (0.5)
EICR 25%	At age 35	70.0 (0.7)	71.4 (0.7)	70.2 (0.8)	69.8 (0.9)	67.9 (1.0)
	At age 50	72.2 (0.4)	73.4 (0.5)	72.2 (0.5)	72.0 (0.6)	70.4 (0.5)
Model 4						
EICR 100% / VL <50 c/ml	At age 35	77.4 (0.2)	77.7 (0.3)	77.8 (0.3)	77.8 (0.3)	77.7 (0.4)
	At age 50	79.1 (0.2)	79.2 (0.2)	79.3 (0.2)	79.3 (0.3)	79.1 (0.3)
EICR 100% / VL >50 c/ml	At age 35	65.9 (0.6)	66.4 (0.7)	67.4 (0.8)	65.5 (0.8)	64.4 (0.9)
	At age 50	68.5 (0.5)	68.9 (0.6)	69.7 (0.6)	68.0 (0.6)	67.1 (0.7)
EICR 75% / VL <50 c/ml	At age 35	73.2 (0.4)	75.2 (0.4)	75.0 (0.4)	77.6 (0.4)	75.1 (0.5)
	At age 50	74.9 (0.3)	76.8 (0.3)	76.6 (0.3)	79.1 (0.3)	76.6 (0.4)
EICR 75% / VL >50 c/ml	At age 35	64.2 (0.8)	65.0 (0.8)	65.3 (1.0)	64.9 (1.3)	63.2 (0.8)
	At age 50	67.1 (0.6)	67.8 (0.6)	68.0 (0.8)	67.6 (1.2)	66.1 (1.4)
EICR 50% / VL <50 c/ml	At age 35	71.3 (0.8)	73.1 (0.7)	71.5 (0.8)	75.4 (0.7)	71.9 (0.9)
	At age 50	73.3 (0.5)	74.8 (0.5)	73.4 (0.6)	76.9 (0.5)	73.5 (0.7)
EICR 50% / VL >50 c/ml	At age 35	62.6 (0.9)	63.6 (1.6)	63.4 (1.9)	64.4 (1.9)	61.9 (1.0)
	At age 50	66.0 (0.5)	66.6 (1.3)	66.4 (1.6)	67.2 (1.6)	65.1 (1.1)
EICR 25% / VL <50 c/ml	At age 35	69.0 (1.0)	71.3 (1.2)	69.0 (1.1)	74.2 (1.1)	70.5 (1.2)
	At age 50	71.1 (0.9)	73.3 (0.8)	71.1 (0.8)	75.7 (0.8)	72.2 (0.9)
EICR 25% / VL >50 c/ml	At age 35	61.0 (1.1)	62.3 (1.1)	61.6 (1.1)	63.9 (1.0)	60.7 (1.4)
	At age 50	64.8 (0.9)	65.6 (0.9)	65.1 (1.0)	66.8 (1.0)	64.3 (1.1)
VL=viral load; c/ml=copies/ml						

7.3.5 Sensitivity analysis

In a sensitivity analysis that changed the adjusted mortality rate in the over 65 age group in abridged life-tables, the same overall patterns were observed, with higher EICR and an undetectable viral load at each time point on ART associated with higher expected age at death (Table 7.3.4; Table 7.3.5). Varying the mortality rate in the over 65 age group resulted in differences in the expected age at death of approximately 5 years for those with an undetectable viral load. For those with a detectable viral load, in whom mortality rates were already higher, varying the mortality rate changed my estimates of life expectancy by approximately 2 years.

Table 7.3.4: Expected age at death at exact age 35, changing mortality rate in over 65's by 20%

		Expected age at death (Standard error)				
		Year 1	**Year 2**	**Year 3**	**Year 4**	**Year 5**
Model 1						
EICR ≥80%	20% lower	77.6 (0.3)	78.0 (0.3)	78.2 (0.3)	78.2 (0.3)	78.2 (0.4)
	20% higher	72.7 (0.2)	73.1 (0.2)	73.2 (0.2)	73.2 (0.3)	73.2 (0.3)
EICR <80%	20% lower	72.0 (0.5)	73.5 (0.5)	71.8 (0.7)	70.7 (0.6)	72.2 (0.8)
	20% higher	68.8 (0.4)	69.9 (0.4)	68.7 (0.5)	67.9 (0.5)	68.8 (0.7)
Model 2						
EICR ≥80% / VL <50 c/ml	20% lower	80.9 (0.3)	81.3 (0.3)	81.2 (0.3)	81.4 (0.4)	81.1 (0.5)
	20% higher	75.0 (0.2)	75.3 (0.2)	75.3 (0.2)	75.5 (0.3)	75.2 (0.4)
EICR ≥80% / VL >50 c/ml	20% lower	66.9 (0.5)	67.5 (0.7)	68.7 (0.8)	67.0 (0.7)	65.3 (0.9)
	20% higher	65.0 (0.4)	65.5 (0.5)	66.4 (0.6)	65.1 (0.6)	63.9 (0.8)
EICR <80% / VL <50 c/ml	20% lower	75.3 (0.7)	77.8 (0.6)	73.8 (0.8)	78.0 (0.4)	74.0 (0.8)
	20% higher	71.2 (0.5)	72.9 (0.4)	70.1 (0.5)	73.1 (0.6)	70.3 (0.7)
EICR <80% / VL >50 c/ml	20% lower	64.0 (0.8)	65.0 (0.9)	64.5 (0.8)	34.7 (0.9)	62.4 (1.1)
	20% higher	62.8 (0.7)	63.6 (0.8)	63.2 (0.7)	63.3 (0.8)	61.5 (1.0)
Model 3						
EICR 100%	20% lower	77.6 (0.3)	77.9 (0.3)	78.1 (0.3)	78.1 (0.3)	78.1 (0.4)
	20% higher	72.7 (0.2)	73.0 (0.2)	73.1 (0.2)	73.2 (0.3)	73.2 (0.3)
EICR 75%	20% lower	75.3 (0.3)	77.5 (0.3)	75.7 (0.3)	75.6 (0.3)	75.4 (0.4)
	20% higher	71.1 (0.2)	72.7 (0.3)	71.5 (0.3)	71.4 (0.3)	71.2 (0.3)
EICR 50%	20% lower	73.5 (0.5)	75.3 (0.5)	73.7 (0.5)	73.5 (0.6)	72.0 (0.6)

		Expected age at death (Standard error)				
		Year 1	**Year 2**	**Year 3**	**Year 4**	**Year 5**
	20% higher	69.9 (0.4)	71.2 (0.3)	70.1 (0.4)	69.9 (0.4)	68.8 (0.5)
EICR 25%	20% lower	72.0 (0.7)	73.6 (0.7)	72.1 (0.8)	71.6 (0.9)	69.4 (1.0)
	20% higher	68.8 (0.6)	69.9 (0.5)	68.9 (0.5)	68.5 (0.6)	66.9 (0.8)
Model 4						
EICR 100% / VL <50 c/ml	20% lower	81.0 (0.3)	81.3 (0.3)	81.4 (0.3)	81.4 (0.3)	81.2 (0.5)
	20% higher	75.1 (0.2)	75.4 (0.2)	75.4 (0.2)	75.5 (0.3)	75.3 (0.4)
EICR 100% / VL >50 c/ml	20% lower	67.0 (0.5)	67.6 (0.7)	68.8 (0.8)	66.5 (1.4)	65.3 (0.9)
	20% higher	65.1 (0.4)	65.6 (0.6)	66.5 (0.6)	64.8 (1.2)	63.9 (0.8)
EICR 75% / VL <50 c/ml	20% lower	75.8 (0.4)	78.2 (0.4)	77.9 (0.4)	78.6 (0.4)	78.1 (0.5)
	20% higher	71.5 (0.3)	73.2 (0.3)	73.0 (0.3)	75.3 (0.3)	73.1 (0.4)
EICR 75% / VL >50 c/ml	20% lower	65.0 (0.6)	66.0 (0.8)	66.4 (1.0)	65.9 (1.3)	63.8 (0.9)
	20% higher	63.6 (0.5)	64.3 (0.6)	64.7 (0.8)	64.3 (1.2)	62.7 (0.8)
EICR 50% / VL <50 c/ml	20% lower	73.5 (0.8)	75.6 (0.7)	73.7 (0.8)	78.4 (0.7)	74.2 (0.9)
	20% higher	69.9 (0.7)	71.4 (0.5)	70.0 (0.6)	73.4 (0.5)	70.4 (0.7)
EICR 50% / VL >50 c/ml	20% lower	63.3 (1.0)	64.3 (1.0)	64.1 (1.1)	65.3 (1.2)	62.4 (1.2)
	20% higher	62.2 (0.9)	63.0 (0.9)	62.9 (1.0)	63.8 (1.1)	61.5 (1.1)
EICR 25% / VL <50 c/ml	20% lower	70.6 (1.3)	73.5 (1.2)	70.7 (1.5)	77.1 (1.1)	72.4 (1.4)
	20% higher	67.8 (1.0)	69.9 (1.0)	67.8 (1.3)	73.2 (0.9)	69.2 (1.1)
EICR 25% / VL >50 c/ml	20% lower	61.5 (1.6)	62.9 (1.6)	62.1 (1.7)	64.7 (1.6)	61.1 (1.8)
	20% higher	60.7 (1.4)	61.8 (1.4)	61.2 (1.6)	63.4 (1.5)	60.4 (1.6)
VL=viral load; c/ml=copies/ml						

Table 7.3.5: Expected age at death at exact age 50, changing mortality rate in over 65's by 20%

		Expected age at death (Standard error)				
		Year 1	**Year 2**	**Year 3**	**Year 4**	**Year 5**
Model 1						
EICR ≥80%	20% lower	79.7 (0.3)	79.9 (0.3)	79.9 (0.3)	80.0 (0.3)	80.0 (0.3)
	20% higher	74.5 (0.2)	74.7 (0.2)	74.7 (0.2)	74.7 (0.2)	74.8 (0.3)
EICR <80%	20% lower	74.3 (0.3)	75.6 (0.3)	74.1 (0.4)	73.0 (0.4)	74.9 (0.6)
	20% higher	70.9 (0.3)	71.8 (0.2)	70.7 (0.3)	70.0 (0.3)	71.2 (0.5)
Model 2						
EICR ≥80% VL <50 c/ml	20% lower	82.7 (0.3)	82.9 (0.3)	82.9 (0.3)	83.0 (0.3)	82.7 (0.4)
	20% higher	76.5 (0.2)	76.7 (0.2)	76.7 (0.2)	76.8 (0.2)	76.6 (0.3)
EICR ≥80% VL >50 c/ml	20% lower	69.6 (0.4)	70.2 (0.3)	71.7 (0.4)	69.7 (0.3)	68.0 (0.6)
	20% higher	67.6 (0.3)	67.9 (0.2)	68.6 (0.3)	67.6 (0.4)	66.4 (0.5)
EICR <80% VL <50 c/ml	20% lower	77.4 (0.5)	79.7 (0.6)	75.8 (0.7)	79.7 (0.5)	75.8 (0.6)
	20% higher	72.9 (0.3)	74.5 (0.4)	71.8 (0.5)	74.6 (0.4)	71.9 (0.5)
EICR <80% VL >50 c/ml	20% lower	67.3 (0.5)	68.0 (0.5)	67.6 (0.6)	67.7 (0.6)	65.7 (0.7)
	20% higher	65.8 (0.4)	66.4 (0.4)	66.1 (0.5)	66.2 (0.5)	64.7 (0.6)
Model 3						
EICR 100%	20% lower	79.7 (0.3)	79.8 (0.3)	79.9 (0.3)	79.9 (0.3)	80.0 (0.3)
	20% higher	74.5 (0.2)	74.6 (0.2)	74.7 (0.2)	74.7 (0.3)	74.8 (0.3)
EICR 75%	20% lower	77.5 (0.3)	79.6 (0.3)	77.6 (0.3)	77.6 (0.3)	77.5 (0.3)
	20% higher	73.0 (0.2)	74.4 (0.3)	73.1 (0.3)	73.1 (0.3)	73.0 (0.2)
EICR 50%	20% lower	75.7 (0.3)	77.4 (0.5)	75.8 (0.5)	75.6 (0.6)	74.3 (0.5)

		Expected age at death (Standard error)				
		Year 1	**Year 2**	**Year 3**	**Year 4**	**Year 5**
	20% higher	71.8 (0.3)	73.0 (0.3)	71.9 (0.4)	71.8 (0.4)	70.5 (0.3)
EICR 25%	20% lower	74.3 (0.4)	75.7 (0.7)	74.3 (0.8)	74.0 (0.9)	72.0 (0.6)
	20% higher	70.9 (0.3)	71.8 (0.5)	70.8 (0.5)	70.6 (0.6)	69.3 (0.5)
Model 4						
EICR 100% VL <50 c/ml	20% lower	82.7 (0.3)	83.0 (0.3)	83.0 (0.3)	83. (0.3)	82.8 (0.4)
	20% higher	74.0 (0.2)	74.9 (0.2)	74.9 (0.2)	75.0 (0.3)	74.6 (0.3)
EICR 100% VL >50 c/ml	20% lower	69.7 (0.4)	70.3 (0.7)	77.4 (0.8)	75.5 (1.4)	74.9 (0.6)
	20% higher	67.6 (0.3)	68.0 (0.6)	68.7 (0.6)	67.3 (1.2)	66.4 (0.5)
EICR 75% VL <50 c/ml	20% lower	77.6 (0.3)	79.9 (0.4)	79.7 (0.4)	82.8 (0.4)	79.7 (0.5)
	20% higher	73.6 (0.2)	74.7 (0.3)	74.6 (0.3)	76.7 (0.3)	74.6 (0.3)
EICR 75% VL >50 c/ml	20% lower	68.1 (0.4)	68.9 (0.8)	69.1 (1.0)	68.6 (1.3)	66.9 (0.6)
	20% higher	66.5 (0.3)	67.0 (0.6)	67.2 (0.8)	66.9 (1.2)	65.6 (0.5)
EICR 50% VL <50 c/ml	20% lower	75.6 (0.5)	77.5 (0.7)	75.7 (0.8)	80.0 (0.7)	75.9 (0.6)
	20% higher	71.7 (0.4)	73.1 (0.5)	71.8 (0.6)	74.8 (0.5)	72.0 (0.5)
EICR 50% VL >50 c/ml	20% lower	66.8 (0.6)	67.5 (1.6)	67.3 (1.9)	68.2 (1.9)	65.7 (0.8)
	20% higher	65.5 (0.5)	66.0 (1.3)	65.9 (1.6)	66.5 (1.6)	64.7 (0.6)
EICR 25% VL <50 c/ml	20% lower	73.0 (0.8)	75.6 (1.2)	72.9 (1.5)	78.9 (1.1)	74.3 (0.9)
	20% higher	69.9 (0.6)	71.7 (0.8)	69.9 (1.0)	74.7 (0.7)	70.8 (0.7)
EICR 25% VL >50 c/ml	20% lower	65.4 (0.9)	66.4 (1.0)	65.7 (1.3)	67.7 (1.1)	64.8 (1.1)
	20% higher	64.4 (0.8)	65.1 (0.8)	64.7 (1.1)	66.2 (1.0)	64.0 (0.9)
VL=viral load; c/ml=copies/ml						

7.4 Discussion

7.4.1 Summary and interpretation

In this chapter, I have shown that EIC is generally high amongst individuals who have initiated ART since 2000 in the UK CHIC Study, with at least one year of follow-up. The median proportion of months that individuals spent in care over five years on ART was 93.3%, corresponding to only 4 months of non-engagement in care over the five year period. Lower EIC was found to be significantly associated with higher rates of mortality in unadjusted analyses. The association between EIC and mortality became stronger at later time-points on ART. For EIC measured at years 1 and 5 on ART, respectively, there was a 30% and 75% increase in mortality rates for EICR <80%, and a 4% and 8% increase with each 10% decrease in EICR. The association between EIC and mortality was reflected in analyses of life expectancy, in which higher EIC was associated with greater life expectancy and therefore older expected age at death. Low EIC over a longer period of time resulted in lower expected age at death. This shows that this time-updated measure of EIC, which allows for differing frequency of scheduled visits, is a marker of long-term mortality outcomes. Further, interventions to improve EIC may result in increases in life expectancy for people on ART.

Considering life expectancy according to both EIC and viral suppression, I observed a very clear difference in the expected age at death for those with and without viral suppression at all time-points on ART. Those individuals with 100% EICR but detectable virus still had substantially lower life expectancy than those with an undetectable viral load but only 25% EICR over the first 5 years on ART. Although these analyses were not adjusted for some important confounders, for example the CD4 count, this demonstrates the value of viral load as a highly predictive marker of long-term mortality. Further, this is a more important marker than EIC. This re-enforces the importance of good adherence and maintaining viral suppression on ART in order to achieve good outcomes. Interventions to improve rates of viral suppression, possibly through adherence support could result in the greatest improvements in mortality outcomes of PLWH who are receiving ART.

However, amongst both those with and without an undetectable viral load, there still appeared to be an association between high EIC and greater life expectancy. For those who managed to achieve an undetectable viral load and who therefore could be assumed to have good adherence to ART, those with 100% EICR 5 years after ART initiation were estimated to be approximately 5 years older at death than those with only 25% EIC. This suggests that even amongst those who adhere well to ART and maintain good treatment responses, that there is a benefit to maintaining regular contact with HIV care providers. These benefits could arise through closer monitoring resulting in earlier detection and treatment for adverse events that

can influence mortality, such as viral rebound, treatment toxicity, AIDS-defining illnesses or other comorbidities unrelated to HIV. Another reason could be better access to other non-HIV care specialities for the treatment and management of co-morbid illnesses. However, as this is an observational study it is not possible to rule out the role of unmeasured confounding.

Adjusting for the effect of viral suppression mostly attenuated the associations between EIC and mortality in Poisson regression models at later time-points on ART. This likely reflects greater differences in EIC according to viral suppression with longer time on ART, suggesting the association between EIC and viral suppression becomes stronger with longer time on ART. Amongst those with and without viral suppression at 5 years on ART, 88.8% and 64.2% respectively had high EICR; an absolute difference of 24.6% (vs. 12.5% at year 1). Due to the observational nature of this analysis, the direction of the association between EIC and viral suppression is not known. It is very likely that poor EIC may lead to lower levels of viral suppression, as if people are less likely to attend they may be less likely to receive prescriptions of ART. Conversely, both poor EIC and viral suppression may be consequences of other factors, including social, economic and lifestyle factors. Ongoing drug use (341, 352, 360, 362, 460, 486), unstable housing (440, 598), care-giving responsibilities (598), low income (342, 348, 362) and poor mental, including depression and psychiatric illness (341, 342, 355, 440, 492), have all previously been associated with both EIC and viral suppression, but are not collected in UK CHIC. The association between EIC and viral suppression suggests that interventions to improve either EIC or viral suppression may be better delivered in combination or designed such that they are able to improve both. In this cohort at each year after ART initiation, approximately 12% of the cohort under follow-up had a detectable viral load; 3% had a detectable viral load and low EIC. Therefore, it is potentially a small group of individuals who are in need of interventions to improve both adherence and EIC. The reasons for poor EIC and adherence, therefore, need to be understood and interventions tailored accordingly, with peer and social support likely to be important aspects of such interventions (599). However, the benefits of both EIC and adherence should be continuously promoted to all PLWH receiving ART, especially in light of the differences in life expectancy according to EICR for those with viral load suppression on ART in this study.

7.4.2 Comparison to the literature

EIC was extremely high in this group and remained so over 5 years on ART. This is consistent with HIV surveillance data which reports 95% retention in care from one year to the next in the UK (600). Other studies, mostly reporting from the United States, suggest rates of retention in care amongst HIV-positive individuals that are often considerably lower than in the current study, with estimates as low as 55% retained in care 5 years after diagnosis (239) and EIC of 85% in one year being considered high (335).

In Poisson regression analyses, the associations observed between EIC and mortality in this study were moderate after adjusting for current viral load in comparison to some US studies. Amongst newly diagnosed individuals in the Ryan White HIV/AIDS programme, missed visits in the year following diagnosis were associated with a 71% increase in mortality after adjusting for demographic factors, CD4 count and AIDS status at diagnosis (368). Failure to be retained in care in the 2 years following ART initiation was associated with a greater than 2-fold increased risk of mortality adjusting for demographics and baseline HIV status in the CNICS cohort (371). Differences in EIC and its stronger association with mortality may, to some extent, be driven by the US Healthcare system, where access to care and treatment is not free, thus creating barriers and greater disparities in access to care and patient outcomes amongst those with lower socio-economic status. Substance abuse, mental health illness, black or other minority ethnicity and public or no health insurance are factors frequently shown to be predictive of poor engagement in HIV care in the US (335, 357, 367). However, the different measures of retention in care used also makes direct comparisons with these studies difficult. These different measures include measures of visit constancy, gaps between visits and missed visits. It has previously been shown that estimated rates of retention in care were dependent on the definition used. Mugavero et al., demonstrated retention in care rates that varied between 51% and 77% depending on the measure of retention in care that was used (313).

For those with an undetectable viral load and 100% EIC, expected age at death was approximately 75 at exact age 35 and 77 at exact age 50. This is approaching, but still lower than, the expected age at death in the general population in the UK over the same period; which is estimated to be 82 at exact age 35 and 83 at exact age 50, using mortality statistics from the human mortality database (595). This is also slightly lower than was observed for individuals with viral suppression and good CD4 count responses on ART in previous UK CHIC analyses. In this analysis, men and women with viral suppression and CD4 count >350 cells/mm^3 at each time-point on ART had expected age of death of approximately 81 and 83 at exact age 35 and 83 and 85 at exact age 50. This lower life expectancy is likely to be due to the fact that we have not conditioned on CD4 count in these analyses, or could reflect differences in the adjusted mortality rate in the abridged life tables, which can influence estimates of life expectancy. In this analysis I have assumed that the mortality rate in the over 65 age group in the HIV-positive cohort is higher than in the general population, by at least as much as for the 55-60 and 60-65 age groups. This means that the life expectancy in the UK CHIC cohort will always be lower than in the general population. In sensitivity analyses in which the mortality rate in the over 65 age group was lowered by 20%, the expected age at death increased by approximately 3 years.

7.4.3 Strengths and limitations

Whilst several studies have investigated a link between retention in care and mortality, this is the first to my knowledge to relay this association in the context of life expectancy. Further, these previous studies have investigated retention as a fixed measure over a finite period of time. By using the REACH algorithm I was able to use a measure of EIC which is adaptive to changing health status of patients and more reflective of real-life changes in engagement with care services over time. A limitation of the REACH algorithm, as it has been developed to be used within the UK CHIC Study, is that it does not currently take account of co-morbidities, mental health, behavioural or social factors. It is likely that such factors will influence the decision as to timing of an individual's next clinic visit, with more complex patients being scheduled for more frequent visits. As we are unable to factor these into the algorithm due to lack of data on these factors in the UK CHIC Study, we may over-estimate levels of EIC. Further, the use of CD4, viral load and ART start as proxy measures for clinic attendance may over-estimate engagement in care compared to actual clinic attendance (321). As this algorithm has not yet been validated outside of the UK CHIC Study, it is not clear to what extent the algorithm may over-estimate EIC.

A large limitation of this study is that EIC was measured in a group of individuals who are known to still be in contact with a UK CHIC HIV clinic at each time point on ART. This, therefore, excludes individuals once they are LTFU from the study without re-engaging in care at a participating UK CHIC centre before the administrative censoring date, and leaves a group who are retained in care in some capacity in the analysis. Therefore these estimates of EIC may be higher than might be expected for all individuals starting ART, affecting the external generalisability of this analysis. Further, mortality rates in those retained in care may be somewhat lower than in those LTFU (364), resulting in an under-estimate of the association between EIC and mortality. Conversely, it is possible that individuals do not attend at a participating centre for long periods of time but are not be classified as LTFU as they were known to re-attend before the administrative censoring date. In this analysis, these months were classified as not in care and incorporated in the EICR. However, as will be discussed in Chapter 8, 30% of this follow-up time may be explained by individuals attending for HIV care elsewhere, who could be EIC. This could result in an underestimate of the true EICR in this group and could contribute to the small drop in EICR with longer time on ART, as there is more opportunity to dis-engage or transfer care with longer time on ART. However, only 0.5% of individuals were not in care for >9 consecutive months in the first 5 years on ART (as LTFU was defined in Chapter 5), meaning this is unlikely to affect my estimate of EICR.

Some caution is needed when interpreting these results, as it cannot be assumed that the association between EIC and mortality/life expectancy is causal. This is the case in most cohort

studies, as high levels of EIC may reflect more general positive health seeking behaviours that result in good outcomes, but that are difficult to measure and therefore account for in analyses. EIC may not impact mortality directly but may be mediated through its impact on the CD4 count and viral load. Using the REACH algorithm to measure EIC in the CHIC cohort, it has been shown that the effect of EIC on mortality, lagged by 12 months, was mediated through the higher CD4 counts achieved by those individuals with higher EIC (372). Nevertheless, EIC may be a predictive marker of long-term mortality, and non-attendance for scheduled visits in clinical practice should be monitored and followed-up. In those with ongoing non-attendance, interventions are needed to re-engage individuals and promote good adherence. In these analyses particularly, by using life expectancy as a measure of patient outcomes we were not able to adjust for many confounding factors. We did however exclude IDU, who represent only a small proportion of the cohort, so as to exclude this as a potential source of confounding.

The number of individuals aged above 60 in this cohort was low (<3%), which necessitated the grouping of those aged over 65, and may result in imprecise estimates of mortality rates, and therefore life expectancy, for older ages. By using Poisson regression models to estimate mortality rates I have ensured that the estimated mortality rates were smoother across age groups than if I were to have used crude rates. Also, by using Poisson regression, I was able to treat EIC as a continuous variable and estimate mortality rates at hypothetical and low levels of EIC. However, as previously mentioned, EIC was high in this group, and so estimates of mortality rates at low levels of EIC may be imprecise due to small numbers.

Finally, I have only considered EIC over the first five years on ART. In the context of HIV as a life-long chronic condition, this is a relatively short period of time. It is possible for PLWH in this analysis to have been taking combination ART regimens for up to 14 years. EIC is likely to be highest after initial ART initiation, but may vary over time with changing life circumstances and this could influence future mortality. A possible limitation of life expectancy estimates is that they use current mortality rates in a population to predict future mortality. If mortality rates were to change significantly in future years, these estimates may not reflect the mortality actually experienced by this cohort as it ages.

7.4.4 Conclusions

Whilst adherence to ART and maintaining viral suppression is vital in order to achieve a normal life expectancy amongst PLWH, maintaining good engagement with HIV care services may also play a role in achieving good life expectancy. Interventions to improve EIC are likely to have the greatest impact amongst those with poor adherence to ART, who are a relatively small group of people. As levels of adherence and EIC are likely linked, it is important to

understand what factors influence both poor adherence and EIC, and target behavioural interventions that use a holistic approach to improving both.

Chapter 8: A longitudinal continuum of care

8.1 Introduction

The HIV care continuum is traditionally depicted as a bar chart, displaying a 'snap-shot' of the proportion of all HIV-positive individuals at each stage of the HIV care pathway at a particular time-point (213). It is a useful monitoring tool to display up-to-date information on the potential for ongoing transmission and success of HIV care programs within a given population and has gained much popularity in recent years, particularly in light of UNAIDS targets to reduce HIV incidence (214). However, as previously mentioned in Chapter 2, this framework has some limitations for understanding programme success as measured by patient outcomes. Firstly, a traditional care continuum only includes those who are known to be alive and therefore does not consider mortality, which is a key measure of patient health. Those who are lost from the continuum at each stage, and potentially most in need of intervention are not well described and their outcomes are unknown. Further, the later stages of the continuum are assessed as fixed outcomes in a cross-sectional framework with assumed sequential progression through each level of the cascade. However, in practice, individuals' EIC, ART use and viral suppression status may change over time.

As a result, new methods of measuring the HIV care continuum have been utilised in cohort studies that combat some of these limitations. Powers et al., conceptualise a "states and transitions" framework that describes the numbers of individuals in each stage of the care continuum as well as the rate of transition both forward and backward between stages (243). Both Haber et al., and Lesko et al., consider time-to-event analyses of each of the stages of the cascade, with Lesko et al., also including the outcomes of death and loss to care relative to ART initiation with time from enrolment (242, 601). In contrast, Krentz et al., more simply, depict the proportion of deaths occurring at each stage of the continuum as a way of incorporating mortality and showing where the greatest burden of mortality lies along the HIV care pathway (240). Whilst the latter incorporate mortality and/or loss-to follow-up along the continuum of care, the outcomes along the continuum are still treated as fixed and are not allowed to vary with time.

It is important to identify gaps in the HIV care continuum to understand what interventions should be targeted in which individuals to make the biggest improvements in outcomes. The biggest gaps in the care continuum may not be the same for all populations. Several cohort-driven estimates of the care continuum have reported disparities in retention in care, ART use and viral suppression according to ethnicity (227, 232, 314, 328, 333, 335, 379), mode of HIV

acquisition (225, 235, 242, 333, 379), age (225, 227, 228, 232, 235, 237, 328, 335, 379, 602, 603) and sometimes sex (225, 228, 256), with PWID, those of black ethnicity and young adults often doing worse. However, UK national surveillance estimates of the HIV care cascade for 2015 report little or no disparity in the proportions of HIV-infected individuals retained in care, in receipt of ART or virologically suppressed, with all except the undiagnosed proportion reaching the UNAIDS 90-90-90 targets. Extrapolating from the most recent estimates of the care continuum in the UK, 96% of those diagnosed and seen for care in 2015 were on ART and 90% had viral suppression (70).

In this chapter, I present a method I devised to generate a longitudinal care continuum. This longitudinal continuum of care illustrates the passage through the HIV care continuum, after linkage to care, for a cohort of HV-positive individuals over a 10 year period, incorporating LTFU and mortality. I further estimate this according to demographic factors and CD4 count at diagnosis in order to describe potential disparities in HIV care experience and outcomes.

8.2 Methods

8.2.1 Inclusion criteria

This analysis used data from the CHIC2015 dataset, for which data was requested at the end of 2014. The entry criteria for this analysis were broad and initially only restricted to individuals with a cohort entry date between 2000-2004, to allow for a maximum of 10 years' follow-up. In a sub-set analysis that assessed transfer of care after loss to follow-up from the UK CHIC Study (LTCFU), only individuals whose UK CHIC record could be linked to a record in SOPHID were included. For analyses of CD4 count at diagnosis, I restricted to those with a diagnosis date no more than 6 months prior to entry. Individuals were required to have a CD4 count available within 3 months of entry to be included in analyses stratified by CD4 count at diagnosis.

8.2.2 Generating the longitudinal continuum of care

For the purposes of this analysis, individuals were followed from the date of entry into the UK CHIC Study. All individuals were given an artificial follow-up end date that was 10 years after entry into the cohort, regardless of death or loss to follow-up from UK CHIC (LTCFU). For each month during this 10 year period, individuals were classified into categories as defined in Table 8.2.1. These categories related to current EIC, ART and viral load status as well as

the occurrence of LTCFU and death. EIC was defined on a month by month basis according to the REACH algorithm (Table 6.2.1)(317).

In order to assess transfer of care when individuals are LTCFU, the previously established linkage to SOPHID was used (Section 4.2.4). For records that had been identified as a match with a SOPHID record, data was provided which indicated whether an individual had been seen for care in a given calendar year at a HIV clinic that did not participate in UK CHIC.

There were 10 stages defined in the longitudinal continuum of care. These are outlined in Table 8.2.1. Current viral load suppression was defined as a most recent viral load $\leq$200 copies/ml, recorded in the previous 9 months. A cut-off of 200 copies/ml was used to be consistent with the cut-off used in a typical HIV continuum of care (70). If no viral load was recorded in the previous 9 months, then the individual was assumed to have a detectable viral load. Once an individual was reported to have died, they were categorised as dead for all remaining months, to the end of their 10 year follow-up period. LTCFU was considered to have started once an individual had been "not in care" (NIC), using the REACH algorithm, for at least 9 months consecutively. Thus, an individual who was next expected to return for care within 6 months would be classified as LTCFU once they had not attended for care for at least 15 months. Similarly, an individual expected to next attend for care within 4 months would be considered LTCFU once they had not attended for at least 13 months. In the analysis that restricted to those linked to a SOPHID record, those LTCFU were further divided as either a transfer or true loss to care (LTC) as follows. Months in which individuals had been classified as LTCFU were defined as transfer providing there was a SOPHID record of attendance at a non-CHIC centre for that calendar year. If a month was classified as LTCFU and had not been classified as transfer then it was considered true loss to care (LTC).

Table 8.2.1: Stages of the time-updated Continuum of care

Stage	Definition			Notation
1	Engaged in Care Not on ART with CD4 >350 cells/mm^3 Not undetectable			EIC / ART- (CD4 >350)
2	Engaged in Care Not on ART with CD4 $\leq$350 cells/mm^3 or CD4 unavailable Not undetectable			EIC / ART- (CD4 <350)
3	Not in care Not on ART Not undetectable			NIC / ART-
4	Engaged in care Started ART Not undetectable			EIC / ART+ /VL>200
5	Not in care Started ART Not undetectable			NIC / ART+ / VL>200
6	Engaged in care Started ART Undetectable			EIC / ART+ / VL $\leq$200
7	Not in care Started ART Undetectable			NIC / ART + / VL $\leq$200
8	Dead			Dead
9	Lost from CHIC follow-up (LTCFU)	**9***	True loss to care	True LTFU
		10*	Transfer	Transfer
*Only defined for individuals linked to a SOPHID record.				

8.2.3 Statistical methods

Each month of follow-up over the 10 years was represented on a stacked area chart to illustrate how people move between stages of the continuum over time. Changes over calendar time in the longitudinal continuum of care were next investigated by plotting the stacked area chart stratified by year of cohort entry. For this analysis, the period of follow-up was reduced to only 5 years and individuals who entered the cohort between 2004-2009 were additionally included. The longitudinal continuum of care was then drawn according to year

of entry; 2000-2003, 2004-2007, 2008-2009. These periods were chosen due to changes in HIV treatment guidelines over when to initiate ART in 2008.

For this reason also, comparisons of the longitudinal continuum stratified by demographic factors (age (<30, 30-39, 40-49, 50+); sex (male, female); ethnicity (white, black, other/unknown); mode of acquisition (sex between men, heterosexual, other/unknown)) and CD4 count at diagnosis (≤200, 201-350, >350 cells/mm^3) were also plotted, restricting analyses to the contemporaneous cohort with cohort entry dates of 2008-2009.

8.2.4 Sensitivity Analyses

Firstly we tested the definition of ART use by considering treatment interruptions. As ART should be life-long when initiated, the main analysis treats individuals who have initiated ART as 'on ART' thereafter. However, it is possible that individuals will interrupt treatment. Therefore, in a sensitivity analysis, any person-month after ART initiation for which an individual did not appear to be taking ART according to drug start and stop dates was classified as a treatment interruption. This approach was not taken for the main analysis due to a relatively low level of confidence in some drug stop dates, particularly as these are imputed for centres where UK CHIC receives only prescription ART data which only gives the date a new prescription is issued. Further, not all treatment interruptions will be captured through ART data as some individuals may stop taking their ART without their doctor's knowledge.

Analyses were also conducted that tested the definition of LTCFU by changing the number of cumulative months required to be not in care to either 6 or 12 months. Finally, the 10 year longitudinal continuum was re-estimated only including individuals who had at least 2 visit dates in the UK CHIC cohort. This is more consistent with previous analyses of the REACH algorithm (372, 571) and excludes attenders who have only one record of contact with a clinic. Such individuals would become almost immediately LTCFU and are less likely to have information available on demographic or clinical characteristics and outcomes.

8.3 Results

A total of 13,762 individuals entered the UK CHIC Study between 2000 and 2004. The characteristics of these individuals are displayed in Table 8.3.1. The majority were male (65.2%), with 6107 (44.4%) aged 30-39 at entry and 952 (6.9%) aged 50 years or above. Similar proportions were of white (43.5%) and black (43.6%) ethnicity. Approximately half of individuals reported heterosexual mode of HIV acquisition (49.0%) and 39.3% reported sex between men as their mode of HIV acquisition. A total of 10,611 (77.1%) had been diagnosed

less than 6 months prior to entry and just over a quarter of those newly diagnosed had a CD4 count $\leq$200 cells/mm^3 at diagnosis. In total, 12,811 UK CHIC records were linked to a SOPHID record; a 93.1% linkage rate. Characteristics of those linked to a SOPHID record were similar to that of the whole cohort (Table 8.3.1).

Table 8.3.1: Characteristics of included individuals

		All	Linked to SOPHID		
		2000-04 N=13762	2000-03 N=9954	2004-07 N=11259	2008-09 N=5318
Age	<30	4287 (31.2)	3182 (32.0)	3344 (29.7)	1414 (26.6)
	30-39	6107 (44.4)	4458 (44.8)	4669 (41.5)	2030 (38.2)
	40-49	2404 (17.5)	1650 (16.6)	2379 (21.1)	1324 (24.9)
	≥50	952 (6.9)	664 (6.7)	867 (7.7)	550 (10.3)
Sex	Male	8963 (65.2)	6565 (66.0)	7416 (65.9)	3686 (69.3)
	Female	4788 (34.8)	3389 (34.1)	3843 (34.1)	1632 (30.7)
Ethnicity	White	5990 (43.5)	4399 (44.2)	5106 (45.4)	2543 (47.8)
	Black	6001 (43.6)	4334 (43.5)	4914 (43.6)	2087 (39.2)
	Other/unknown	1771 (12.9)	1221 (12.3)	1239 (11.0)	688 (12.9)
Mode of acquisition	Sex between men	5414 (39.3)	4054 (40.7)	4617 (41.0)	2205 (41.5)
	Heterosexual	6739 (49.0)	4873 (49.0)	5477 (48.9)	2355 (44.3)
	Other/unknown	1609 (11.7)	1027 (10.3)	1165 (10.3)	758 (14.3)
Newly diagnosed at entry		10611 (77.1)	7948 (79.9)	8110 (72.0)	3737 (70.3)
CD4 at diagnosis	<200	2957 (21.5)	2112 (21.2)	2599 (23.1)	1062 (20.0)
	201-350	1844 (13.4)	1310 (13.2)	1787 (15.9)	896 (16.8)
	>350	3112 (22.6)	2204 (22.1)	3223 (28.6)	1664 (31.3)
	Missing	5849 (42.5)	4328 (43.5)	3650 (32.4)	1696 (31.9)

8.3.1 A 10 year longitudinal continuum of care

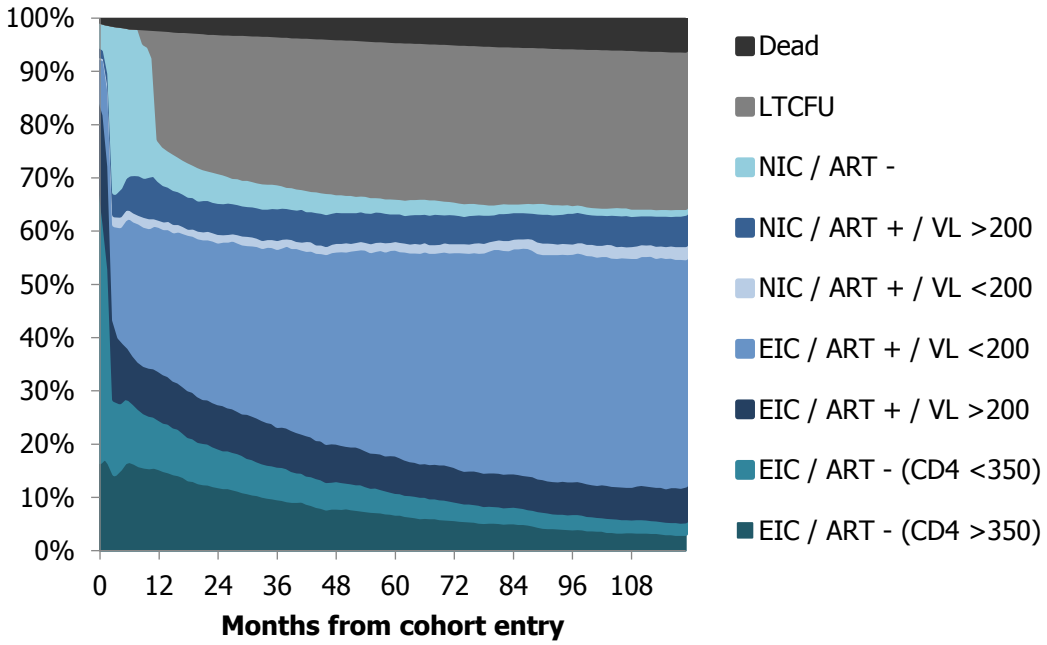
Figure 8.3.1 shows a time-updated 10 year continuum of care for the 13,762 individuals who entered the UK CHIC cohort between 2000 and 2004. Over 10 years, a total of 627,867 (38.0%) person-months were spent on ART with a viral load $\leq$200 copies/ml. Of 317,320 (29.2%) person-months spent ART-naive, 167,361 (44.7%) were classified as not in care, and 85,967 (22.9%) were spent EIC but with a CD4 count $\leq$350 cells/mm^3. A total of 670 (6.3%) individuals died within 10 years of cohort entry, meaning a total of 53,210 (4.2%) person-months were lost. Just over a quarter of individuals who entered the cohort were LTCFU by 10 years after cohort entry.

The proportion of individuals not to have initiated ART decreased with time from entry (85.0% at entry to 6.7% at 10 years), and the proportion of time spent ART experienced increased (from 25.2% at entry to 57.8% at 10 years). Whilst 31.3% of individuals who had started ART at entry had a viral load $\leq$200 copies/ml (7.9% of all individuals), this increased to 78.0% after 10 years. Overall, 45.1% of individuals in the cohort had a viral load ≤200 copies/ml 10 years after entry into care. As a proportion of all person-months spent ART naive, 25.8% of months were spent not engaged in care (NIC). However, of all person-months post-ART initiation, engagement in care was higher with 14.4% of months classified as NIC.

Restricting to 12,811 individuals linked to a SOPHID record (Figure 8.3.2) showed similar results. The proportion of individuals that were LTCFU increased from 5.0% (n=637) at 12 months after entry, to 28.2% (n=3612) at 120 months after entry. When further categorised as true LTC and transfer, true LTC remained constant at approximately 21% of person-months from 2 years onwards, whereas transfer increased from 4.3% of all person-months at 2 years to 7.4% of person months at 10 years. As a proportion of person-months LTCFU, transfer increased from 17.2% at 2 years to 26.4% at 10 years.

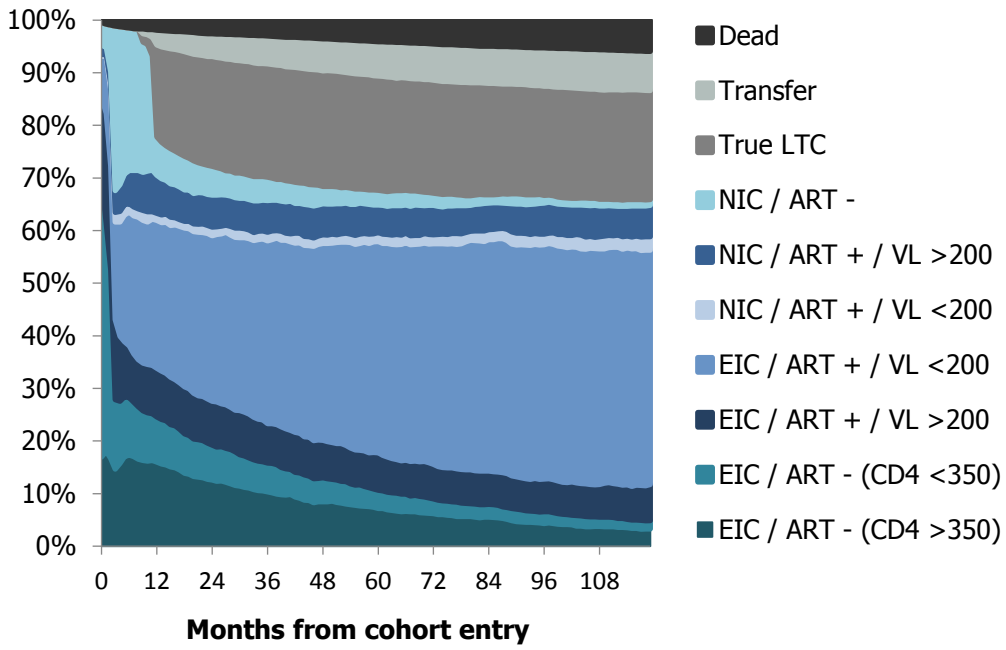
In order to see how our longitudinal continuum of care was comparable to a national cross-sectional continuum, we considered the proportion of individuals that have started ART and are suppressed, of all those still alive and in follow-up. By 2, 5 and 10 years after cohort entry, 72.4%, 68.4% and 65.9% of all individuals in the cohort were still alive and not lost to UK CHIC follow-up. Of those still accessing care at a UK CHIC centre at 2, 5 and 10 years after cohort entry, 65.3%, 78.8% and 90.9% had started ART. Of those to have started ART, 69.8%, 77.1% and 78.5% had a suppressed viral load; 45.6%, 60.8% and 71.4% of those still alive and in care at 2, 5 and 10 years respectively.

Figure 8.3.1: Longitudinal Continuum of care over 10 years



% in each stage of continuum	Months from cohort entry					
	1	**24**	**48**	**72**	**96**	**120**
EIC / ART – (CD4 >350)	16.8	12.4	8.2	6.1	4.4	3.3
EIC / ART – (CD4 <350)	52.7	7.4	5.1	3.6	2.8	2.3
EIC / ART + / VL >200	15.5	8.3	7.2	6.5	6.2	6.8
EIC / ART + / VL ≤200	7.6	30.4	35.9	40.0	42.7	42.6
NIC / ART + / VL ≤200	0.3	1.6	1.5	1.8	2.0	2.5
NIC / ART + / VL >200	1.8	5.7	5.8	5.4	5.7	5.9
NIC / ART –	4.7	5.6	3.7	2.5	1.6	1.1
LTCFU	0.0	25.9	29.0	29.5	29.3	29.5
Dead	0.5	2.7	3.6	4.6	5.3	6.0

Figure 8.3.2: Longitudinal continuum of care over 10 years considering transfer amongst 12,811 individuals linked to a SOPHID record



% in each stage of continuum	Months from cohort entry					
	1	**24**	**48**	**72**	**96**	**120**
EIC / ART – (CD4 >350)	17.0	12.7	8.5	6.3	4.4	3.3
EIC / ART – (CD4 <350)	52.5	6.9	4.4	2.9	2.1	1.6
EIC / ART + / VL >200	16.0	8.4	7.3	6.7	6.2	6.9
EIC / ART + / VL ≤200	7.8	31.5	37.2	41.6	44.5	44.5
NIC / ART + / VL ≤200	0.3	1.5	1.6	1.8	2.1	2.5
NIC / ART + / VL >200	1.7	5.9	5.9	5.5	5.8	6.0
NIC / ART –	4.3	5.6	3.8	2.4	1.7	1.1
True LTC	0	20.7	21.9	21.5	20.7	20.7
Transfer	0	4.3	5.9	6.8	7.2	7.4
Dead	0.5	2.6	3.5	4.5	5.2	5.9

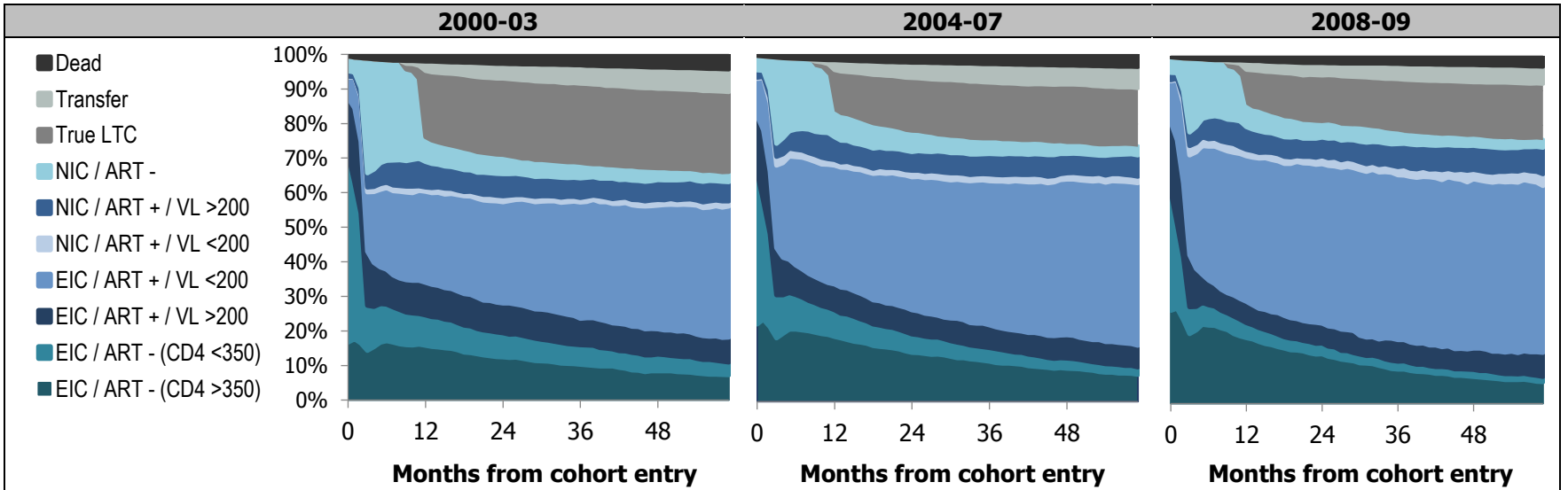
8.3.2 Changes to the care continuum over time

Restricting to only 5 years of follow-up we observed changes in the longitudinal care continuum over time (Figure 8.3.3). True LTC was lower in the cohort that entered the study in 2008-2009 than between 2000-2003. At 2 and 5 years after entry, 13.8% and 16.3% of person months were classified as true LTC amongst those who entered between 2008 and 2009. In comparison, 22.0% and 23.1% were classified as true LTC at 2 and 5 years after entry between 2000 and 2003. The proportion of person-months classified as not in care prior to ART initiation was also lower in the year following cohort entry; 13.0% amongst the 2008-2009 cohort and 23.2% in the 2000-2003 cohort.

ART initiation appeared more rapid in the recent cohort compared to the earliest cohort; 57.1% of individuals were classified as having initiated ART one year after entry in the 2008-2009 cohort, compared to 44.9% and 50.3% between 2000-2003 and 2004-2007 respectively. Further, of person-months pre-ART, a lower proportion were considered engaged with a CD4 count below 350 cells/mm^3 in the 2008-2009 cohort. Whereas only 23.4% of all pre-ART months classified as engaged in care were with a CD4 ≤350 cells/mm^3 in this group, 42.2% and 32.2% were categorised as such between 2000-2003 and 2004-2007. This would align with changes over time in treatment guidelines regarding the optimal CD4 count at which to initiate ART.

Viral suppression also improved over time, with 68.1%, 75.5% and 77.9% of all person-months on ART over 5 years classified as virologically suppressed in the 2000-2003, 2004-2007 and 2008-2009 cohorts respectively. Finally, mortality very moderately improved in the most recent cohort compared to the earliest, with 3.0% classified as dead compared to 4.2%.

Figure 8.3.3: Longitudinal continuum of care over 5 years according to calendar year of entry



	2000-03					2004-07					2008-09				
	12	**24**	**36**	**48**	**60**	**12**	**24**	**36**	**48**	**60**	**12**	**24**	**36**	**48**	**60**
EIC / ART – (CD4 >350)	16.1	12.5	10.4	8.4	7.3	19.3	14.6	11.8	9.7	7.8	19.4	14.2	10.0	7.9	6.3
EIC / ART – (CD4 <350)	8.9	7.1	5.7	4.6	3.7	7.9	5.6	4.0	2.8	2.1	4.8	3.1	2.4	2.0	1.5
EIC / ART + / VL >200	9.6	8.6	8.3	7.6	7.2	7.1	7.0	6.8	6.5	6.2	6.0	6.0	6.4	5.8	6.9
EIC / ART + / VL <200	26.0	29.3	33.0	35.6	37.9	34.1	38.1	41.3	44.8	46.9	41.6	45.5	47.7	48.1	48.0
NIC / ART + / VL <200	1.3	1.7	1.4	1.6	1.5	1.7	1.6	1.7	1.8	1.8	2.0	2.1	2.0	3.3	3.4
NIC / ART + / VL >200	8.0	6.3	5.5	5.6	5.5	7.4	5.5	5.7	5.8	6.1	7.5	5.5	6.2	7.1	7.6
NIC / ART –	23.2	5.6	4.6	3.9	3.0	16.5	5.5	4.0	3.0	2.4	13.0	4.5	3.7	2.6	2.2
True LTC	3.7	22.0	22.8	23.0	23.1	3.3	15.7	16.8	17.0	17.0	3.6	13.8	15.1	15.9	16.3
Transfer	1.3	4.3	5.2	6.0	6.6	1.2	4.4	5.3	5.5	6.1	0.9	3.5	4.3	4.9	4.9
Dead	1.9	2.6	3.0	3.7	4.2	1.5	2.2	2.6	3.0	3.5	1.2	1.9	2.2	2.5	3.0

8.3.3 Continuum of care according to demographic characteristics

When split by age at entry into the cohort, ART initiation was more rapid with older age at entry (Figure 8.3.4). At 12 months after entry 40.8%, 57.9%, 67.5% and 70.8% of those aged 30, 30-39, 40-49 and ≥50 were on ART and a larger overall proportion of person-months over 5 years were spent on ART in the oldest group (68.4% vs. 47.3% amongst those aged <30). Higher levels of viral suppression were similarly seen amongst the older age group, with 71.5%, 77.6%, 81.0% and 83.2% of person-months on ART amongst those aged 30, 30-39, 40-49 and ≥50 spent with a viral load ≤200 copies/ml. The youngest age group spent the largest proportion of person months off ART and not engaged in care in the year following entry, and true loss to follow-up was highest over 5 years in this group (15.3% of person-months vs. 9.0% for those aged 50 and above). However, the proportion of person-months lost due to death over 5 years increased with older age at entry. The proportion (n) of person-months lost for those aged <30, 30-39, 40-49 and ≥50 was 1.1% (887), 1.6% (1895), 2.6% (2026) and 4.3% (1398), respectively.

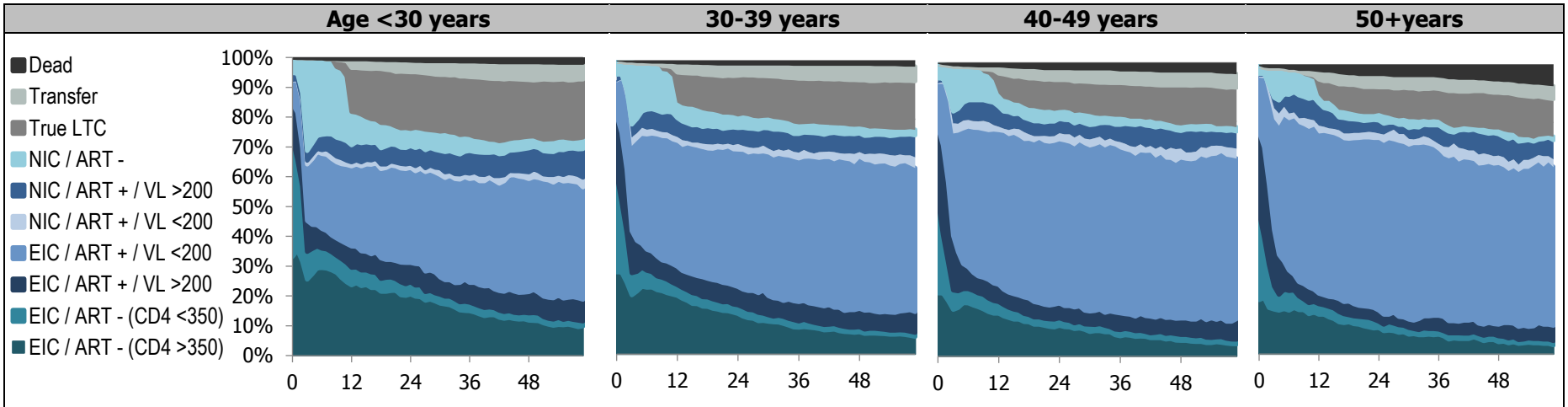
Differences in the 5 year continuum in men and women were less marked (Figure 8.3.5). Following cohort entry, ART initiation was more rapid amongst women, as 66.0% of women and only 53.2% of men had initiated ART by 12 months. Over the 5 year period, 57.6% person-months in men were spent on ART and 64.3% of person-months in women. Of those months spent on ART in men and women, 19.8% and 26.6% respectively were spent with a viral load >200 copies/ml, showing that viral suppression was poorer amongst women.

Compared to those of white ethnicity, ART initiation was initially more rapid amongst those of black ethnicity, with 66.5% and 50.1% having initiated ART 12 months after cohort entry (Figure 8.3.6). However, those of black ethnicity spent a larger percentage of time on ART with a viral load >200 copies/ml (16.4% of person-months vs. 11.0%). This was also the case as a proportion of all person-time on ART (25.5% person-months on ART vs. 19.3%). Loss to follow-up was also somewhat higher for those of black ethnicity compared to white, with 17.4% truly LTC at 5 years after entry. However, LTFU was highest amongst those of other or unknown ethnicity with 19.9% true LTC at 5 years, accounting for 14.3% of all person-months in this group (10.7% amongst those of white ethnicity). Mortality was also slightly higher amongst those of other or unknown ethnicity, and only 48.8% were on ART with a viral load ≤200 copies/ml 5 years after entry, compared to 54.0% amongst those of white ethnicity.

LTCFU and mortality were also higher amongst those of other or unknown mode of HIV acquisition compared to MSM or heterosexual acquisition. By 5 years after cohort entry, 5.1% of individuals of other or unknown mode of acquisition had died, compared to 1.5% of MSM

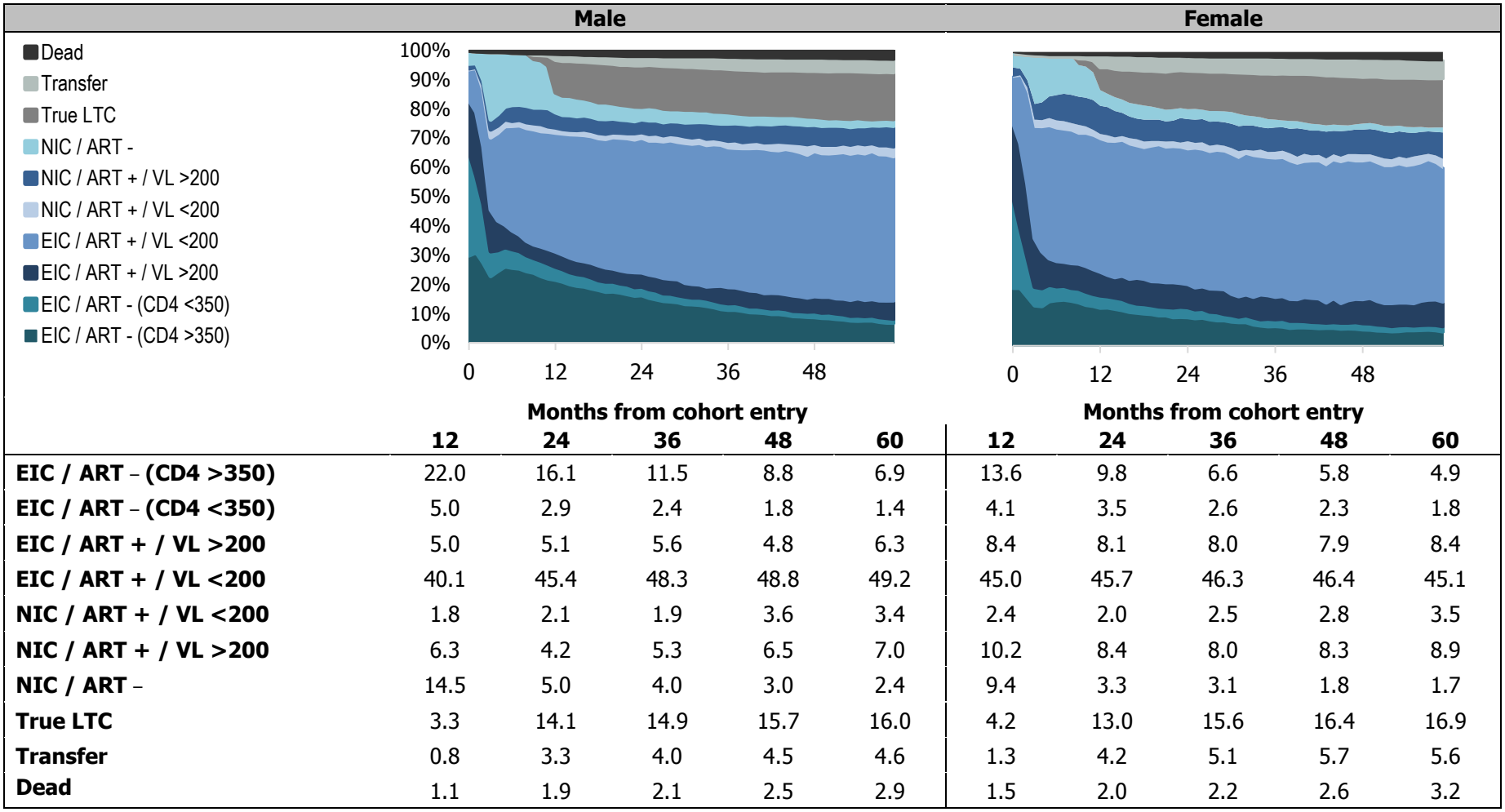
and 3.7% of heterosexual men and women. 14.7% of all person-months were classified as true LTC and a further 4.3% as transfer of care; these respective proportions were 10.9% and 2.7% amongst MSM. Over 5 years, 56.6%, 64.9% and 55.0% of all person-months were spent on ART amongst those of other/unknown, heterosexual and MSM respectively. Of person-months on ART in each respective group, 74.2%, 75.5% and 82.4% were spent with a viral load ≤200 copies/ml.

Figure 8.3.4: Longitudinal continuum of care over 5 years according to age



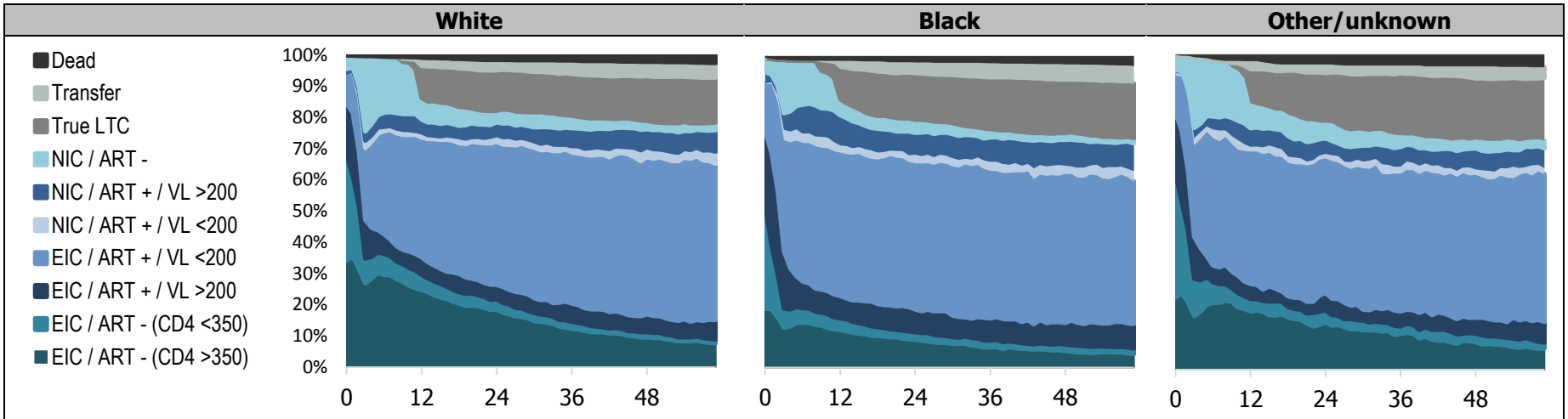
	Age <30 years					30-39 years					40-49 years					50+years				
	Months from cohort entry					Months from cohort entry					Months from cohort entry					Months from cohort entry				
	12	24	36	48	60	12	24	36	48	60	12	24	36	48	60	12	24	36	48	60
EIC / ART – (CD4 >350)	24.6	20.2	15.1	12.2	9.9	20.4	14.2	9.2	7.3	6.0	14.6	9.9	7.3	5.4	4.2	14.4	8.9	6.5	4.9	3.1
EIC / ART – (CD4 <350)	6.6	3.9	3.0	2.2	1.6	4.0	2.8	2.4	1.7	1.4	4.4	2.7	1.9	2.2	1.6	3.6	3.1	2.2	1.8	1.5
EIC / ART + / VL >200	6.3	7.1	7.4	6.8	7.3	6.3	6.5	6.5	6.0	7.0	6.0	5.0	5.8	5.2	7.0	4.4	4.0	4.5	3.6	5.3
EIC / ART + / VL <200	26.5	31.5	34.4	38.6	37.7	41.7	45.6	48.3	49.7	49.0	51.6	55.1	56.5	53.0	54.5	56.2	58.0	58.2	54.7	54.7
NIC / ART + / VL <200	1.4	1.6	1.5	1.9	3.3	2.1	2.1	2.5	3.4	3.6	2.2	2.3	1.9	4.7	3.5	2.2	2.5	2.2	3.3	2.7
NIC / ART + / VL >200	6.6	5.4	7.1	7.6	9.5	7.8	6.0	6.1	6.8	7.5	7.7	5.1	5.6	6.5	5.9	8.0	4.4	5.5	8.0	6.7
NIC / ART –	21.8	6.7	5.7	4.0	3.9	12.2	4.1	3.5	2.5	1.8	7.6	3.5	2.6	1.8	1.4	6.2	2.0	2.0	1.3	1.1
True LTC	5.1	18.9	19.5	19.2	19.5	3.2	13.4	15.5	16.0	16.6	3.5	10.6	11.6	13.4	13.6	1.5	9.5	10.7	12.7	13.1
Transfer	0.6	3.8	5.0	5.9	5.6	1.1	3.4	4.2	4.8	4.9	0.9	3.3	4.1	4.4	4.5	1.3	3.6	3.8	3.8	4.4
Dead	0.5	0.9	1.3	1.6	1.7	1.2	1.7	1.8	1.8	2.1	1.6	2.5	2.8	3.3	3.9	2.4	4.0	4.4	5.8	7.5

Figure 8.3.5: Longitudinal continuum of care over 5 years according to sex



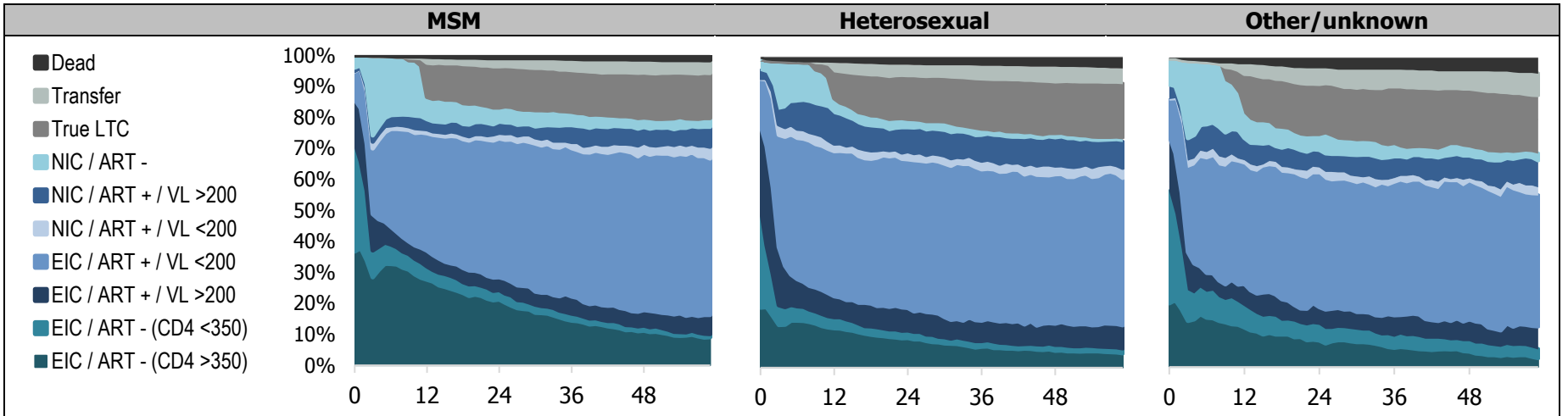
	Male					Female				
	12	**24**	**36**	**48**	**60**	**12**	**24**	**36**	**48**	**60**
EIC / ART – (CD4 >350)	22.0	16.1	11.5	8.8	6.9	13.6	9.8	6.6	5.8	4.9
EIC / ART – (CD4 <350)	5.0	2.9	2.4	1.8	1.4	4.1	3.5	2.6	2.3	1.8
EIC / ART + / VL >200	5.0	5.1	5.6	4.8	6.3	8.4	8.1	8.0	7.9	8.4
EIC / ART + / VL <200	40.1	45.4	48.3	48.8	49.2	45.0	45.7	46.3	46.4	45.1
NIC / ART + / VL <200	1.8	2.1	1.9	3.6	3.4	2.4	2.0	2.5	2.8	3.5
NIC / ART + / VL >200	6.3	4.2	5.3	6.5	7.0	10.2	8.4	8.0	8.3	8.9
NIC / ART –	14.5	5.0	4.0	3.0	2.4	9.4	3.3	3.1	1.8	1.7
True LTC	3.3	14.1	14.9	15.7	16.0	4.2	13.0	15.6	16.4	16.9
Transfer	0.8	3.3	4.0	4.5	4.6	1.3	4.2	5.1	5.7	5.6
Dead	1.1	1.9	2.1	2.5	2.9	1.5	2.0	2.2	2.6	3.2

Figure 8.3.6: Longitudinal continuum of care over 5 years according to ethnicity



	White					Black					Other/unknown				
	12	**24**	**36**	**48**	**60**	**12**	**24**	**36**	**48**	**60**	**12**	**24**	**36**	**48**	**60**
EIC / ART – (CD4 >350)	25.3	18.3	12.7	9.5	7.7	12.4	9.1	6.4	5.6	4.4	19.3	14.2	11.0	9.0	6.7
EIC / ART – (CD4 <350)	5.7	3.3	2.4	1.7	1.2	3.8	2.5	2.3	2.1	1.7	4.1	4.2	2.9	2.6	1.9
EIC / ART + / VL >200	5.3	4.8	6.0	5.1	6.2	7.4	7.8	7.3	6.9	7.9	4.7	5.1	4.8	4.8	6.5
EIC / ART + / VL <200	38.2	45.2	48.7	49.7	50.1	46.0	46.6	47.8	47.0	45.7	41.3	43.0	43.5	45.2	46.9
NIC / ART + / VL <200	1.2	2.2	1.5	3.5	3.9	2.8	2.1	2.6	3.4	3.3	2.2	1.3	2.2	2.5	1.9
NIC / ART + / VL >200	5.4	3.7	5.4	6.5	6.8	10.3	7.7	7.1	8.1	8.9	6.7	5.2	6.0	6.0	6.3
NIC / ART –	14.6	4.4	4.1	3.0	2.5	10.5	4.2	3.2	2.1	1.7	14.2	5.2	4.2	2.6	2.5
True LTFU	2.8	13.0	13.4	14.2	14.4	4.4	14.0	15.9	16.6	17.4	4.1	16.0	19.2	20.1	19.9
Transfer	0.8	3.5	4.1	4.7	4.7	1.0	4.0	5.1	5.6	5.7	1.3	2.5	2.8	3.5	3.3
Dead	0.7	1.5	1.7	2.1	2.5	1.5	2.0	2.3	2.6	3.2	2.2	3.2	3.5	3.8	4.1

Figure 8.3.7: Longitudinal continuum of care over 5 years according to mode of HIV acquisition



	MSM					Heterosexual					Other/unknown				
	12	**24**	**36**	**48**	**60**	**12**	**24**	**36**	**48**	**60**	**12**	**24**	**36**	**48**	**60**
EIC / ART – (CD4 >350)	28.3	21.0	14.9	11.0	9.1	13.0	9.5	6.5	5.9	4.7	13.7	8.8	6.5	5.1	2.9
EIC / ART – (CD4 <350)	5.1	3.1	2.4	1.6	1.0	3.7	2.5	2.0	2.0	1.6	7.3	5.0	3.8	3.2	2.8
EIC / ART + / VL >200	4.6	4.3	5.7	4.7	6.1	7.4	7.4	6.8	6.5	7.5	5.7	6.9	6.9	6.5	7.5
EIC / ART + / VL <200	37.2	44.2	48.1	50.1	50.5	46.5	47.9	49.3	47.6	47.4	39.4	41.6	41.3	43.7	42.2
NIC / ART + / VL <200	1.2	2.0	1.4	3.5	3.8	2.9	2.0	2.6	3.6	3.3	1.3	2.5	2.1	2.1	2.6
NIC / ART + / VL >200	4.1	3.3	5.0	5.5	6.4	10.1	7.4	6.9	8.3	8.2	9.4	5.7	7.3	7.9	8.8
NIC / ART –	16.3	5.4	4.4	3.4	2.8	10.2	3.7	3.1	1.8	1.6	11.7	4.2	3.6	2.8	2.1
True LTC	2.3	13.3	13.5	14.6	14.5	3.5	13.2	15.2	16.1	17.0	7.7	17.0	19.4	18.9	19.0
Transfer	0.6	2.6	3.5	4.3	4.1	1.0	3.9	4.8	5.3	5.1	1.7	4.9	5.4	5.5	6.9
Dead	0.3	0.9	1.0	1.3	1.5	1.8	2.5	2.7	3.1	3.7	2.1	3.4	3.8	4.4	5.1

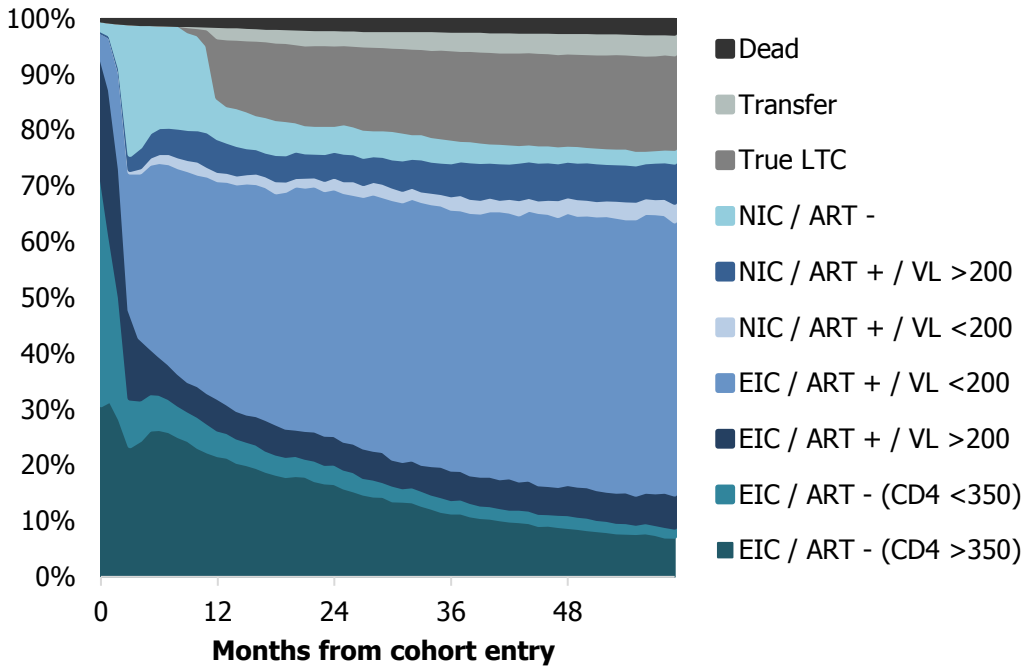
8.3.4 Continuum of care according to CD4 count at diagnosis

Results did not differ largely from the main analysis when considering 3,737 individuals who were newly diagnosed at entry into the UK CHIC Study between 2008 and 2009, results did not differ largely from the main analysis for this period (Figure 8.3.8). Over 5 years, 26.8% of person-months were spent off ART. During the first month of follow-up, 42.1% of individuals were EIC but off ART with a CD4 count $\leq$350 cells/mm^3 or unavailable. This decreased to only 5.1% at 1 year and represented only 1.6% of individuals 5 years after cohort entry. Approximately half of newly diagnosed individuals who entered the study between 2008 and 2009 had started ART and were virologically suppressed 5 years after entry, as was seen amongst all entrants to the cohort at this time.

Marked differences were seen in the longitudinal continuum of care according to CD4 count at diagnosis (Figure 8.3.9). ART initiation was much more rapid in those with a diagnosis CD4 count $\leq$200 cells/mm^3, in line with treatment guidelines to initiate ART. One year after cohort entry, 83.9%, 53.0% and 23.5% had initiated ART in those with diagnosis CD4 count ≤200, 201-350 and >350 cells/mm^3 respectively. Of all pre-ART person-months amongst those with a CD4 count >350 cells/mm^3 at diagnosis, 66.9% were spent with a CD4 count >350 cells/mm^3 so would not necessarily indicate that treatment be initiated. However, 20.3% of these pre-ART person months were classified as not in care (6.6% of all person-months). The corresponding proportion of pre-ART months not in care amongst those with a diagnosis CD4 count 201-350 cells/mm^3 was 23.9%, however, overall only 3.2% of all person-months in this group were classified as not in care prior to ART initiation. A similar proportion (approximately 14%) of all person-months were spent with a viral load >200 for each CD4 group. However, as a proportion of time on ART, 20.6%, 22.4% and 28.7% of person months were spent unsuppressed amongst those with a diagnosis CD4 count ≤200, 201-350 and >350 cells/mm^3 respectively.

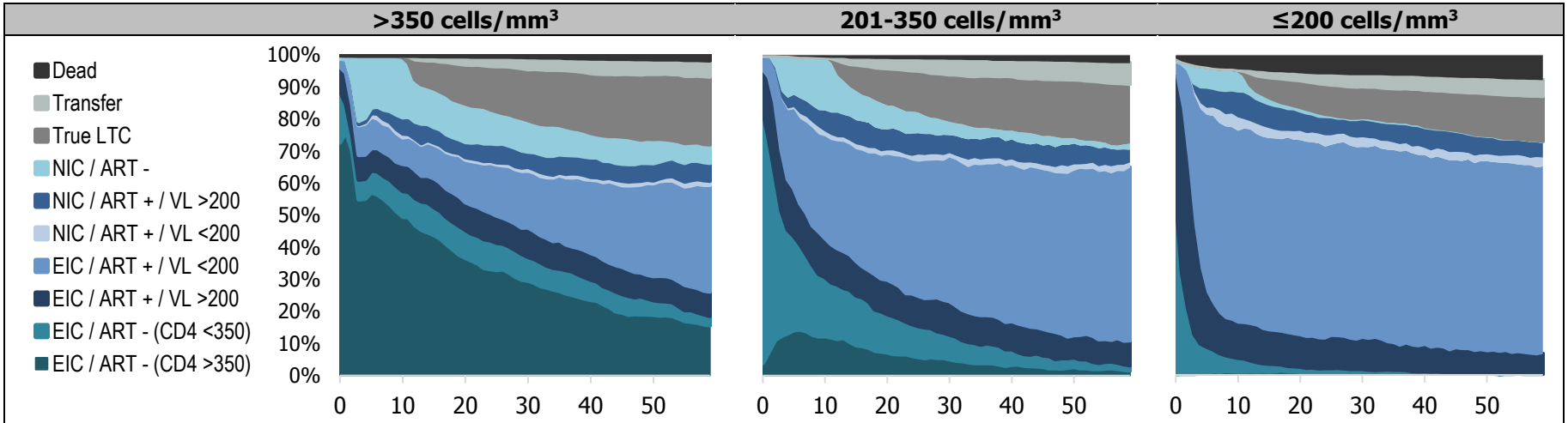
A larger proportion of person-months were lost due to death amongst those with a diagnosis CD4 count $\leq$200 cells/mm^3 (7.5% vs 2.3% for 201-350 cells/mm^3 and 1.7% >350 cells/mm^3). Conversely, a smaller proportion of those with a diagnosis CD4 count $\leq$200 cells/mm^3 were LTC; 14.0% at 5 years compared to 21.1% of those with diagnosis CD4 >350 cells/mm^3.

Figure 8.3.8: Longitudinal continuum of care over 5 years amongst those newly diagnosed



% in each stage of continuum	Months from cohort entry					
	1	**12**	**24**	**36**	**48**	**60**
EIC / ART – (CD4 >350)	30.8	22.5	17.0	11.9	9.2	7.3
EIC / ART – (CD4 <350)	42.1	5.1	3.3	2.6	2.2	1.6
EIC / ART + / VL >200	20.6	5.5	5.2	5.4	5.0	5.9
EIC / ART + / VL <200	4.1	38.8	43.8	46.8	48.4	48.9
NIC / ART + / VL <200	0.0	1.7	1.8	2.1	3.0	3.3
NIC / ART + / VL >200	0.3	6.2	4.8	5.6	6.6	7.2
NIC / ART –	1.8	15.4	5.0	4.4	3.0	2.5
True LTC	0	3.1	14.5	15.9	16.6	16.9
Transfer	0	0.6	2.7	3.3	3.8	3.7
Dead	0.2	1.1	1.8	2.0	2.3	2.6

Figure 8.3.9: Longitudinal continuum of care over 5 years according to CD4 count at diagnosis



	>350 cells/mm³					201-350 cells/mm³					≤200 cells/mm³				
	Months from cohort entry					Months from cohort entry					Months from cohort entry				
	12	24	36	48	60	12	24	36	48	60	12	24	36	48	60
EIC / ART – (CD4 >350)	49.3	33.5	26.4	19.1	15.7	11.9	6.7	3.9	2.3	1.6	1.0	0.8	0.9	0.6	0.4
EIC / ART – (CD4 <350)	8.0	9.0	6.9	5.3	3.0	17.2	10.2	5.8	2.9	1.6	4.2	1.2	0.7	0.1	0.04
EIC / ART + / VL >200	8.4	9.1	8.9	7.9	7.6	11.9	8.9	9.2	8.5	7.8	10.8	9.0	8.0	7.1	6.1
EIC / ART + / VL <200	8.9	14.5	20.2	27.1	33.3	32.5	42.1	46.7	49.5	53.8	61.2	61.4	60.7	59.6	58.7
NIC / ART + / VL <200	0.8	0.8	0.9	1.3	1.2	1.6	1.1	1.8	1.9	1.6	2.9	3.0	2.3	2.0	2.7
NIC / ART + / VL >200	5.4	5.5	5.6	5.3	5.6	7.0	6.4	6.3	6.3	4.0	9.0	5.7	6.3	6.2	5.2
NIC / ART –	16.7	11.4	9.2	8.0	5.8	15.6	7.1	3.6	3.1	1.9	5.2	1.0	0.5	0.2	0.1
True LTC	2.0	13.0	17.2	20.0	21.1	1.5	13.0	16.3	18.1	18.7	1.0	9.1	10.2	12.6	14.0
Transfer	0.2	2.7	3.9	4.7	5.0	0.0	3.2	4.8	5.4	6.4	0.4	2.8	3.8	4.5	4.9
Dead	0.3	0.5	0.8	1.3	1.7	0.8	1.3	1.6	2.0	2.5	4.5	6.0	6.4	7.1	7.8

8.3.5 Sensitivity Analyses

8.3.5.1 Treatment interruptions

Thus far, I have referred to people who have initiated ART as 'on ART'. However it is possible that people will discontinue ART for short periods and so having started ART may not be equivalent to currently being on ART. Considering treatment interruption as a separate end-point, we saw that this accounted for a relatively low percentage of person-months over 10 years (4.7%; Figure 8.3.10). Discounting those undergoing a treatment interruption from the denominator of those on ART, I observed that of all person-months on ART over 10 years, 80.1% of person months on ART were spent virologically suppressed. This figure was 74.9% in the main analysis.

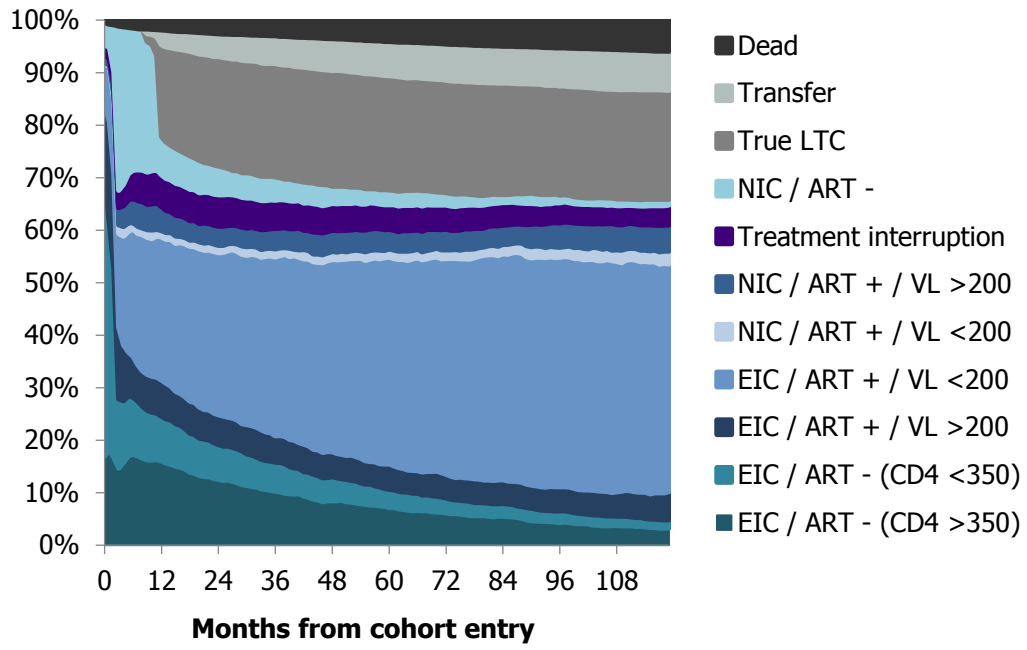
8.3.5.2 Loss to follow-up

Changing to 6 or 12 months not in care to define LTCFU we saw very little change in the longitudinal continuum (Figure 8.3.11). Using 6 cumulative months not in care to define LTCFU saw that 20.9% of all person-months over 10 years were classified as true LTC and 6.0% as transfer of care. Using 12 months we observed that 17.6% and 5.3% were classified as true LTC and transfer, respectively.

8.3.5.3 Excluding one-off attenders

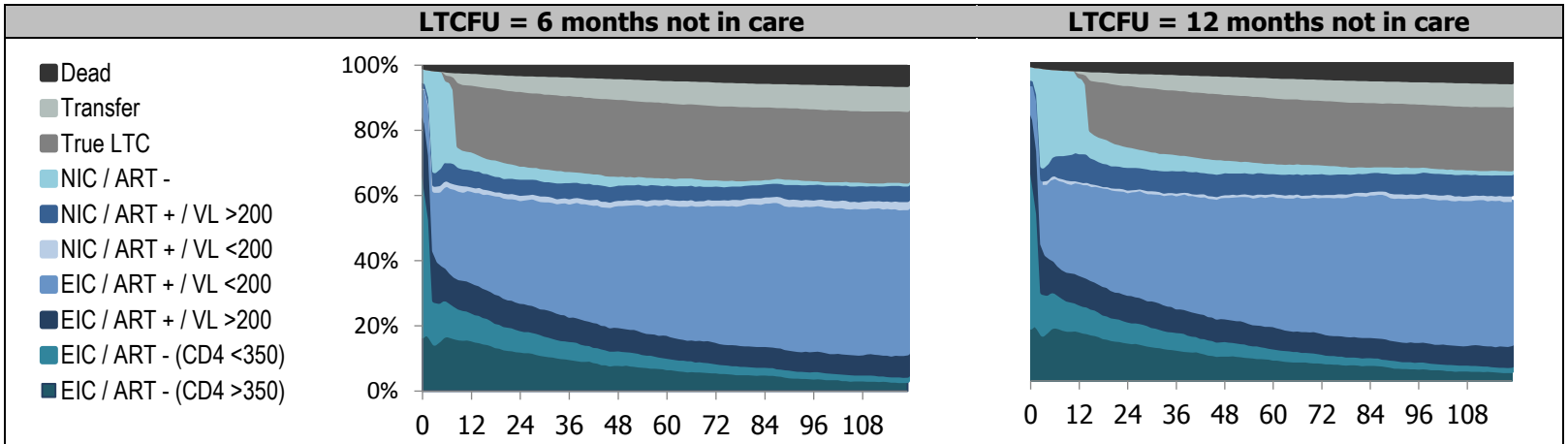
Restricting to those individuals who had at least two separate visits in the UK CHIC study (n=11,272), lower rates of true LTC were observed than in the main analysis; 16.2% at 10 years compared to 20.7%. The proportion to transfer care did not change greatly and the percentage who had died by 10 years after cohort entry was also quite similar at 5.0%. A larger proportion of person-months in this sensitivity analysis were spent with viral suppression; 44.9% overall, compared to 39.5% in the main analysis (Figure 8.3.12).

Figure 8.3.10: Longitudinal continuum of care over 10 years including treatment interruptions



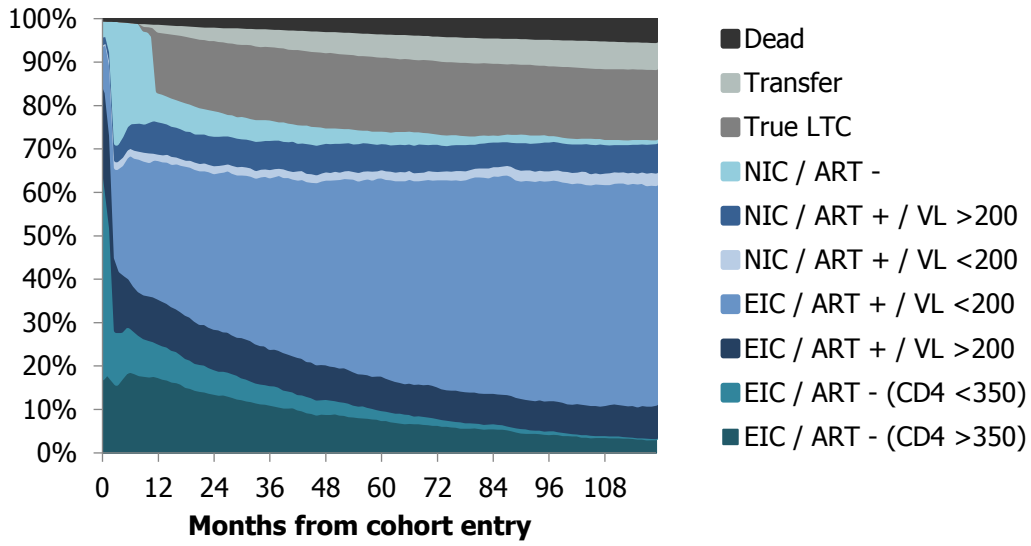
% in each stage of continuum	Months from cohort entry					
	1	**24**	**48**	**72**	**96**	**120**
EIC / ART – (CD4 >350)	17.0	12.7	8.5	6.3	4.4	3.3
EIC / ART – (CD4 <350)	52.5	6.9	4.4	2.9	2.1	1.6
EIC / ART + / VL >200	14.6	5.6	4.9	4.7	4.6	5.3
EIC / ART + / VL <200	7.5	30.8	36.4	40.7	43.7	43.4
NIC / ART + / VL <200	0.3	1.4	1.4	1.7	2.0	2.4
NIC / ART + / VL >200	1.5	3.6	4.1	3.8	4.6	5.0
Treatment interruption	1.8	5.9	5.2	4.7	3.8	3.8
NIC / ART –	4.3	5.6	3.8	2.4	1.7	1.1
True LTFU	0	20.7	21.9	21.5	20.7	20.7
Transfer	0	4.3	5.9	6.8	7.2	7.4
Dead	0.5	2.6	3.5	4.5	5.2	5.9

Figure 8.3.11: Time-updated continuum of care over 10 years using different definitions of LTCFU



	Months from cohort entry					Months from cohort entry				
	24	**48**	**72**	**96**	**120**	**24**	**48**	**72**	**96**	**120**
EIC / ART – (CD4 >350)	12.7	8.5	6.3	4.4	3.3	12.7	8.5	6.3	4.4	3.3
EIC / ART – (CD4 <350)	6.9	4.4	2.9	2.1	1.6	6.9	4.4	2.9	2.1	1.6
EIC / ART + / VL >200	8.4	7.3	6.7	6.2	6.9	8.4	7.3	6.7	6.2	6.9
EIC / ART + / VL <200	31.5	37.2	41.6	44.5	44.5	31.5	37.2	41.6	44.5	44.5
NIC / ART + / VL <200	1.5	1.6	1.8	2.1	2.5	1.6	1.6	1.8	2.1	2.5
NIC / ART + / VL >200	4.7	4.6	4.2	4.7	4.8	6.9	6.9	6.5	6.5	6.7
NIC / ART –	4.3	3.0	1.9	1.2	0.9	6.6	4.3	2.9	1.9	1.3
True LTC	22.6	23.7	22.9	22.0	22.0	19.0	20.7	20.3	20.0	20.1
Transfer	4.9	6.3	7.2	7.5	7.7	3.9	5.6	6.6	7.0	7.3
Dead	2.6	3.5	4.5	5.2	5.9	2.6	3.5	4.5	5.2	5.9

Figure 8.3.12: Longitudinal continuum of care over 10 years amongst those with at least 2 visits



% in each stage of continuum	Months from cohort entry					
	1	**24**	**48**	**72**	**96**	**120**
EIC / ART – (CD4 >350)	17.3	14.2	9.4	6.9	4.8	3.5
EIC / ART – (CD4 <350)	51.6	5.9	3.3	1.7	0.7	0.3
EIC / ART + / VL >200	16.9	9.3	8.1	7.5	6.9	7.7
EIC / ART + / VL <200	8.3	35.8	42.3	47.2	50.6	50.6
NIC / ART + / VL <200	0.4	1.8	1.8	2.1	2.4	2.9
NIC / ART + / VL >200	1.8	6.6	6.7	6.2	6.6	6.8
NIC / ART –	3.8	6.0	4.0	2.5	1.7	0.9
True LTC	0.0	16.0	17.2	16.8	16.0	16.2
Transfer	0.0	3.1	4.8	5.6	5.9	6.2
Dead	0.0	1.5	2.4	3.5	4.3	5.0

8.4 Discussion

8.4.1 Summary and Interpretation

In this chapter I devised and presented a longitudinal continuum of care composed of time-updated measures of the stages of the HIV care pathway. This longitudinal continuum depicts the progress of a cohort of PLWH through the stages of the HIV continuum of care, giving population-level data as to the amount of person-time spent in each state over 10 years. This method has certain advantages over a traditional cross-sectional continuum of care for monitoring levels of engagement with HIV care and patient outcomes. By creating classifications that include sub-optimal responses along the HIV care pathway, gaps in HIV care are better described. By considering a closed cohort and not censoring follow-up when people drop out of the study this method allows estimation of rates of LTC and can ascertain the amount of person-time lost due to mortality.

Using this method, I observed increasing ART uptake and viral suppression after entry into HIV care, as would be expected. Over 10 years of follow-up 39.5% of person-months were classified as virologically suppressed; 74.9% of all person-months spent ART experienced. Therefore, individuals had the potential to transmit HIV for the majority of person-time in this study. The potential for ongoing transmission is a primary output of a traditional continuum of care. The amount of person-time unsuppressed presented in this longitudinal continuum of care provides better understanding as to the potential for ongoing transmission than a cross-sectional measure of the proportion of people unsuppressed. This demonstrates an advantage of this longitudinal continuum of care over a cross-sectional one. The context in which this person time occurs may also be an important factor. Transmission may be more likely to occur during periods of unsuppressed viraemia that are a consequence of poor adherence or that occur whilst individuals are poorly EIC, as this may also be associated with more risk-taking behaviour (604, 605). Further, unsuppressed viraemia whilst in receipt of ART is associated with poorer mortality outcomes. Conversely, viraemia occurring prior to ART initiation, with treatment guidelines during the period of study is of less concern for patient outcomes.

LTCFU in this cohort was high, with 28.1% of individuals lost to the study 10 years after entry. Only around a quarter of LTCFU time was explained by individual's transferring to a centre that does not participate in the UK CHIC Study for care. The remainder of this LTCFU was unaccounted for. It is possible, therefore, that those individuals who are LTCFU but did not transfer care are completely disengaged from HIV care. Individuals who are disengaged from care are more likely to transmit HIV (604, 605) and have poorer mortality outcomes (364, 540). In light of the potentially high LTC shown in this study, reducing disengagement and encouraging those who are disengaged to re-engage with care should be a focus of efforts to

improve patient outcomes and reduce transmission. In a traditional continuum of care, those lost to cohort follow-up are not accounted for. Particularly, in the UK, the diagnosed population in a given calendar year is defined as those seen for care that year (Zheng Yin, personal communication, February 6, 2015), thereby excluding anyone already disengaged from care prior to this point, which, from estimates in this study, could be a considerable number. This cross-sectional continuum, therefore, may be biased as it represents those individuals who are accessing care and who are more likely to be on ART and virologically suppressed. However, it is possible that some of the LTC observed in this study could be explained by migration out of the country, as HIV-positive individuals born abroad may return to their country of origin. Data on levels of out-migration of HIV-positive individuals in the UK are unavailable, but in a single centre London study, over half of individuals lost to clinic follow-up (of whom two-thirds were black African or black Caribbean ethnicity) had evidence of intent to leave the country in their medical notes, with 20% at risk of deportation (324). High levels of migration would mean that levels of true disengagement in care, and therefore the potential for ongoing transmission in the country, is not as high as the longitudinal continuum of care estimates.

In this study, the longitudinal continuum changed over time, with increasing time spent ART experienced and virologically suppressed. Whilst this might suggest an improvement in the HIV continuum of care over time, it more likely reflects changes to treatment guidelines and developing knowledge as to the benefits of ART initiation at higher CD4 counts over this period (112). Therefore, whilst an earlier continuum of care might appear worse, it may in fact reflect optimum care under the guidelines that existed at that time. It is therefore important to consider the context when comparing either a longitudinal or cross-sectional continuum of care over time. However, LTCFU rates decreased in more recent periods showing that there were some improvements in retention in care over time. Improved retention in care may be an indirect consequence of earlier ART initiations, as previous studies have shown engagement in care to be better amongst ART experienced individuals, but may also be a consequence of better care and efforts to reduce disengagement.

ART initiation was much more rapid amongst those with a CD4 count $\leq$200 cells/mm^3 at diagnosis. This is as we would expect in relation to treatment guidelines in the UK. Despite this rapid ART uptake, mortality was by far higher amongst those diagnosed late, consistent with findings in Chapter 5 of this thesis. This re-enforces the need for better testing strategies to prevent late diagnosis in order to improve mortality outcomes in PLWH. Of time spent ART experienced, a much larger proportion of person-months were spent with detectable viral load in people with a CD4 count $\leq$200 cells/mm^3. This could indicate poorer adherence amongst those initiating ART with low CD4 counts, highlighting those diagnosed late as a group who may be in need of adherence support. No difference in the rate of viral rebound was found

amongst those initiating ART late in Chapter 6. However, in that analysis, I restricted to those who initially maintained virological suppression, and so may have excluded those with lower levels of adherence.

I observed differences in progression through stages of HIV care according to demographic factors. Despite more rapid ART initiation in those aged 50 and above, mortality was strikingly high in comparison to younger ages. To what extent this mortality is expected due to natural aging and how much is potentially preventable through earlier engagement in the HIV care cascade is unknown. As shown in Chapter 5, older individuals were significantly more likely to be diagnosed late and therefore be in need of immediate ART, with subsequently high rates of mortality. As a traditional continuum of care only includes those that are alive during the year of assessment, this mortality would not be considered, giving a more favourable impression of the success of HIV care for older individuals. It is important to consider this higher mortality when making inferences from a care continuum that may otherwise suggest better patient outcomes in older individuals. As discussed in Chapter 5, efforts to improve HIV testing rates amongst older individuals are needed to enable earlier initiation of ART and reduce rates of mortality, particularly AIDS-related mortality. In the younger age group, mortality was low but the continuum of care appeared worse than for older adults. A large proportion of person-time was spent ART naïve and disengaged from care. It would seem, therefore, that poorer EIC amongst younger individuals is leading to slower uptake of ART (341) and less time spent with suppressed viral load. This is of concern as delayed ART initiation can have negative impacts on morbidity and mortality outcomes (141, 417, 419), and unsuppressed viraemia in this group, who are likely more sexually active, could result in high HIV incidence. These low levels of EIC, do not appear to be explained by perinatally infected adolescents transitioning into adult care (who number only a few in this age group), in whom barriers to EIC have been identified (606). The reasons for poor EIC amongst younger PLWH who are not perinatally infected likely differ somewhat from those infected from birth, and may include fears of stigma, difficulties in accepting their diagnosis, disclosing to friends and family and managing a life-long chronic condition (607). Youth-focused services and additional peer and social support are needed when these young PLWH enter into adult care to help them effectively manage their HIV and reduce disengagement from care to improve the number of years lived in good health (608).

Despite more rapid ART initiation in women and those of black ethnicity, a larger proportion of ART-experienced person-months were spent with a detectable viral load compared to men and those of white and other ethnicities. Sex and ethnicity are closely correlated amongst PLWH, as the majority of men are white MSM, whilst women are largely represented by those of black African ethnicity. In the UK, black African individuals, particularly women, are disproportionately affected by HIV, with a prevalence of around 56 per 1,000 population (312),

and contributing 61% of heterosexuals accessing care (70). But despite this, my findings suggest that they may have difficulties in successfully managing their illness compared to other groups and are a group need of adherence support.

Those who acquired HIV through non- sexual or unknown transmission routes had poor longitudinal progression through the continuum of care. LTFU and mortality were high, with a smaller proportion of time on ART spent with viral suppression. Of time spent off ART, a higher proportion of months were spent not engaged in care or with a CD4 count below 350 cells/mm^3. This group is largely made up of those with an unknown mode of acquisition (67.4%) or people who inject drugs (PWID 21.4%), with perinatally infected individuals and blood products recipients only a small number of this group. PWID are known to have poorer engagement and high mortality rates. Missing data on mode of HIV acquisitions could arise through non-disclosure or an individual being unaware of HIV acquisition risk. This, in turn, may be indicative of multiple high-risk behaviours and would appear to align with poor engagement with HIV services and individuals having lower ability to manage their HIV, as demonstrated by a poor continuum of care in this analysis. Identifying and supporting these individuals to engage and adhere with care early on may be key for improving the long-term success of their HIV care. In order to achieve this, in-depth qualitative data on why these individuals have sub-optimal engagement and treatment responses will be useful.

8.4.2 Comparison to the literature

LTC was considerably higher in this longitudinal continuum than the estimated 5% annual LTFU nationally, despite linkage to national surveillance data to ascertain when care was transferred to a non-CHIC centre. Previous studies have shown that longitudinal measures of retention in care rates are worse than when assessed cross-sectionally (314). Further, my estimate of LTC is more consistent with 5-year cumulative LTFU rates of 20% found in previous studies in the UK (323, 324).

Of all individuals still alive 10 years after cohort entry, less than half were virologically suppressed in this longitudinal continuum of care. This is considerably lower than reported in the cross-sectional continuum of care in the UK, which estimates 78% of all PLWH to be virologically suppressed (70). Reasons for this difference may be the fact that I have studied a historic cohort that entered care in the relatively early ART era, who have long-term ART exposure and experience of less effective and less tolerable agents. A cross-sectional continuum of care, on the other hand, provides more up-to-date information of all PLWH at that time. This group will include those more recently diagnosed and initiated on ART. The use of all recorded viral loads in the longitudinal continuum of care may also mean that I am

more likely to capture short-term periods of non-suppression that would be missed in a cross-sectional continuum that uses only the latest available measure in the calendar year.

This is not the first study to report a poorer continuum of care amongst younger individuals (217, 225, 231, 237, 328). Studies have also separately shown poorer EIC (333, 335, 336, 343), decreased likelihood of ART uptake (235, 379, 602) and lower rates of viral suppression (306, 424, 448) amongst younger adults with HIV, which are consistent with the findings of this longitudinal continuum of care. UK HIV surveillance data also report lower ART coverage amongst younger individuals, with 88% of 15-24 year olds on ART in 2015 compared to 98% of over 50's. However, in contrast to my findings, retention in care (defined by attendance for care in two consecutive years) is reportedly similar according to demographic subgroups, but estimates are not provided making any comparison difficult (70).

My finding that a larger proportion of person-months were spent with unsuppressed viral load in women and those of black ethnicity is consistent with findings from the US. In a traditional continuum, black ethnicity has been shown to be associated with lower rates of viral suppression in comparison to white ethnicity (232, 237, 314, 328, 333). In US national estimates, 30% of all white PLWH are suppressed compared to 21% amongst black PLWH. This translates to 86% and 72% of people prescribed ART amongst white and black people, respectively (217). Evidence of lower viral suppression rates amongst those of black ethnicity in the UK is not as strong. Cross-sectional surveillance data estimates 90% viral suppression across ethnic groups and for both men and women (312). Whilst a single centre study found women and heterosexual men to have similar initial virological responses to MSM (224), other cross-sectional assessments from the ASTRA study showed that those of non-white ethnicity had lower rates of viral suppression explained by lower adherence (609). Previous data from the UK CHIC study have shown differing results in regards to ethnicity differences, possibly due to the different inclusion criteria of each study and different virological end-points assessed (385, 428). This study therefore adds to the limited UK data on differences in virologic responses according to ethnicity.

8.4.3 Strengths and limitations

This chapter presents a novel way of describing passage through HIV care. By defining an individual's status in HIV care on a month-by month basis it is possible to capture the movement between stages of the continuum of care, which have previously been treated as fixed end-points. It is also able to give an overview of progress through HIV care on a population level and incorporates LTC and mortality. Because of the rich clinical data available in the UK CHIC study, and the ability to classify engagement on a month-by-month basis using the REACH algorithm, it is possible to get a more detailed picture of the care continuum.

Further, as with a traditional care continuum, this information is still displayed in a single figure that easily conveys this information. The detailed clinical data required to construct this longitudinal continuum of care might not be available in many settings, which means that is not suggested as an alternative to the traditional continuum of care, which is a useful public health monitoring tool. Instead this is better used as a research tool to complement the traditional continuum of care, investigate disparities in care and relate the stages of the care pathway to patient outcomes. The fact that it is a descriptive measure is a limitation as it is not possible to adjust for potential confounding in a formal way.

A limitation in using a 10 year time-frame is that it is a historic cohort that is considered, with individuals required to have the potential for 10 years follow-up in order to be included. This historic cohort may not be entirely reflective of individuals entering care in more recent periods when guidance for treating and monitoring patients have changed and ART agents have become more effective and better tolerated than in the relatively early ART era. Further, the UK CHIC study is not a national cohort, so may not be representative of all PLWH that enter care in the UK. However, no restrictions besides year of entry were made to the inclusion criteria. Further, these methods can be applied to shorter time frame, enabling the study of more recent cohorts, and when we considered a 5 year continuum, similar patterns were seen, with small changes over time which reflected changes to treatment guidelines.

Although some individuals LTCFU were identified as having transferred care to a centre that does not participate in UK CHIC, it was not possible to classify these individuals further according to EIC, ART use or viral suppression. This is because SOPHID contains only a single annual record of ART use and viral suppression and EIC could not be classified according to the REACH algorithm. Therefore these estimates of ART use and viral suppression may not be accurate for all individuals in care in the UK. Including those who transferred care into the denominator of those alive and accessing care in the UK, the true proportion of individuals on ART with virological suppression at 10 years after cohort entry would range from 64% if none who transferred were suppressed to 74% if all who transferred were suppressed.

It should be noted that these graphs represent the care continuum in a group diagnosed and linked to care and need to be interpreted in context. For example, amongst those aged over 50 and with a CD4 count $\leq$200 cells/mm^3 we observed very rapid ART initiation and a large proportion of person-months on ART. Whilst ART uptake is considered a favourable outcome along the continuum of care we must remember that immediate ART initiation is necessary for this group because they are diagnosed with such advanced stage of HIV infection. Whilst these methods can be applied to a population of PLWH from HIV diagnosis onwards, they could not easily be adapted to incorporate all HIV-infected individuals. A baseline time point such as seroconversion would need to be known to calculate the person-time contributed as

undiagnosed. This information is rarely known, with few notable symptoms at the time of seroconversion, and is difficult to estimate due to different progression rates (610-612). This is a limitation as compared to a traditional continuum of care.

Finally, whilst it is possible to account for changing viral load and EIC status over time by categorising on a month-by-moth basis (and ART status if including treatment interruptions), the relative timing of events is not known in this longitudinal continuum of care. But this was shown in other studies (242, 243). For example, it is not known whether death occurred before or after ART initiation, or achievement of viral suppression. This could be achieved by creating further categories, however, to improve readability due to the sometimes small number of person months and a wish not to generate too many categories, this was not done here.

8.4.4 Conclusions

Using a time-updated continuum of care it is possible to describe the progress of a cohort of HIV-positive individuals through the HIV care continuum over time, including the additional outcomes of mortality and loss to follow-up. My findings suggest that engagement with HIV care and patient outcomes may not be optimal for all groups, and for all individuals was lower than would be suggested in a traditional continuum of care. Further, different groups may require interventions in different aspects of HIV care to improve outcomes. Those in whom ethnicity and mode of HIV acquisition remain unknown had the poorest progress through the HIV care continuum and highest mortality and loss-to-follow-up rates. More in-depth qualitative research to improve understanding of barriers to these individuals successfully engaging with care and managing their HIV is needed in order to inform potential intervention designs. Whereas women and those of black ethnicity had poorer suppression on ART and would benefit from interventions to improve adherence, younger adults may benefit most from interventions to improve EIC, particularly whilst ART naïve, to increase ART uptake. For older adults, improved testing rates to prevent late diagnosis are key to reducing a large burden of mortality amongst PLWH.

Chapter 9: Concluding remarks

9.1 Summary and relevance of main findings

The introduction of ART has drastically changed outcomes for PLWH, with reduced morbidity and mortality, increasing life expectancy and a shift from AIDS to non-AIDS causes of death. ART also has important public health implications as it reduces the risk of onward transmission which will, in turn, impact on HIV incidence. HIV is now a chronic condition requiring ongoing care and adherence to treatment regimens. The key elements of the pathway through HIV care, including diagnosis, ART uptake and viral suppression, are summarised in the continuum of care, aligning with global targets to reduce HIV incidence. In this context, the continuum of care is now a popular framework for monitoring programme success and the potential for ongoing transmission within a population. It has also been used to assess the successful engagement of PLWH with care and as an indicator of disparities in care on a population level. However, it's cross-sectional design has some limitations. One important limitation being that it does not incorporate mortality outcomes, which are a key indicator of health in a population. Whilst the continuum of care is estimated to be good in the UK, meeting 2 of the 3 UNAIDS 90% targets (214), it has been estimated for few subgroups of the population, in whom, observational studies have previously shown sub-optimal treatment responses and engagement with HIV care. As a result, the aims of this thesis were to investigate sub-optimal achievement of the stages of the continuum of care in the UK and, in particular, how these are associated with mortality outcomes.

I undertook this research using data from the UK CHIC Study, which is the largest clinical cohort of HIV-positive individuals accessing care in the UK. Prior to the commencement of this work, information on mortality outcomes in the study relied almost entirely on clinician report, and data on cause of death was limited so was not used in analyses. In Chapter 4, I presented work undertaken to improve the ascertainment of mortality outcomes and to classify a principal cause of death based on a variety of data sources, including linkage to HIV surveillance datasets, which are supplemented by ONS national death registry data. This work was vital in order to be able to estimate the impact of sub-optimal care on mortality outcomes, as prior to this work estimates would have been biased. This is because deaths were under-ascertained and were more likely to be missing in more recent calendar years, for those with missing information on demographic characteristics and those LTCFU. This also enabled analyses that considered end-points of cause-specific mortality. The result of this work was to add 792 deaths to the dataset and classify a principal cause for 2,938 deaths. With this data I was able to describe declining AIDS-related mortality and a shift towards non-AIDS

causes of death throughout the advancing ART era, as has been reported in other countries. However, a large amount of missing data on cause of death for deaths occurring in the early ART era is a limitation of this data. Any future analyses of mortality will likely need to be restricted to later years when the proportion of deaths with a classified cause improves.

In Chapter 5 I studied associations between late diagnosis and both all-cause and cause specific mortality in the year following HIV diagnosis. In particular, I assessed whether the association between late diagnosis and mortality was stronger amongst older individuals, who are much more likely to be diagnosed late, than younger individuals. This was only formally assessed in one previous single centre study in the UK, which did not detect an interaction, but was likely under-powered to do so (222). The main finding of this chapter was that there was no interaction between age at diagnosis and late diagnosis observed, indicating that older individuals diagnosed late do not have a relatively poorer prognosis than younger individuals diagnosed late. Another important finding was that whilst the relative impact of late diagnosis on mortality in older individuals was not higher, an extremely high absolute excess risk of death, particularly for AIDS-related mortality, was observed amongst older individuals diagnosed late. Already higher rates of mortality amongst older individuals expected through aging, high rates of late diagnosis in this age group, and the strong association between late diagnosis and mortality are the likely causes of this excess mortality. Much of this mortality burden could potentially be prevented through more timely diagnosis, enabling earlier initiation of ART. Older individuals are therefore a group very much in need of interventions to improve HIV testing rates to reduce levels of late diagnosis.

Late ART initiation is a consequence of late diagnosis and has previously shown to be associated with poor treatment responses and outcomes. In Chapter 7 I looked at whether those starting ART with immunosuppression (≤200 cells/mm^3) who achieved and maintain a virological response, could eventually have similar outcomes to those starting in a less advanced stage of HIV disease. In those who maintained suppression during the first year, the rate of viral rebound continued to decline with longer time on ART and was not different for those with immunosuppression at ART initiation after accounting for demographic factors that may have represented differences in adherence. CD4 counts did not recover to the level of those without immunosuppression and it looked likely that even with further follow-up this would not be achieved. It took longer for the CD4 to recover to levels approaching that in HIV-negative individuals, during which time those with baseline immunosuppression were at higher risk of clinical progression. However, there was an indication that rate of clinical progression might become similar in the long-term on ART, as CD4 counts in those with immunosuppression approached normal levels. If supported by other studies, this is an important clinical message for those in care who have already, or may in future initiate ART with immunosuppression, as well as for HIV clinicians. However, despite the large numbers

included in this study, a small number of clinical events meant that a statistical test for interaction was not significant, meaning that these findings would need to be confirmed in a bigger study with more events in the long-term. Even if the risk of clinical progression does decrease in the long term, it is better to minimise the time spent at high risk of clinical progression. To this end, it is important to avoid late ART initiation by ensuring PLWH are diagnosed in a timely manner and are prepared and in a position to start ART before they become immunosuppressed.

EIC has previously been shown to be associated with mortality. However, the studies which addressed this question were largely conducted in the US, where access to healthcare is not free, and used short term measures of visit attendance that did not account for the changing frequency of scheduled visits as individuals health status changes. The association between EIC and life expectancy was investigated in Chapter 6 using the REACH study time-updated measure of EIC. EIC over the first 5 years after ART initiation was found to correlate with life expectancy, with an approximate 5 year difference in age at death between those with low and high EIC. Maintained low EIC over each of the first 5 years on ART was associated with declines in life expectancy. This highlights the importance of achieving and then maintaining high EIC over time. In order to assess whether this correlation was partly explained by better viral suppression in those with higher EIC, life expectancy was also estimated according to both viral load and level of EIC. This analysis showed that viral suppression was the more important predictor of life expectancy, as those with a detectable viral load and 100% EIC had lower life expectancy than those with only 25% EIC but an undetectable viral load. However, in both those with and without viral suppression, higher EIC was associated with older age at death. Those with low EIC and non-suppressed viral load have particularly poor mortality outcomes, but are only a relatively small number of all ART experienced individuals. The benefits of higher EIC in those with suppressed viral load may arise through closer monitoring, which enables earlier detection and management of illness and better access to other health and support services such as mental health services. These findings highlight that adherence support interventions should be a key focus of efforts to improve mortality in those on ART. However, due to the apparent benefits of higher EIC in those with and without viral suppression and the close link between EIC and suppression, interventions to improve both EIC and adherence may have the largest benefits.

My final results chapter presented a longitudinal continuum of care that I have devised. This longitudinal continuum characterises ART use, EIC and viral suppression on a month-by-month basis to give a population-level picture of achievement of the stages of HIV care over time in care. This method additionally incorporated mortality and LTFU and described sub-optimal care categories. This has certain advantages over a cross-sectional continuum of care for measuring disparities in care and success of HIV care. Quantifying LTFU and mortality is

not possible using a cross-sectional continuum, and this longitudinal analysis demonstrated higher levels of LTC than had previously been assumed in the UK. If true, these high levels of LTC need to be tackled as they have potential implications for individuals' health and ongoing transmission in the UK. However, a lack of data on migration means this could be an overestimate of the number of HIV-positive individuals living in the UK and not receiving care. Person-time spent with unsuppressed viral load was also shown to be lower than previous cross-sectional estimates would suggest, and is a useful care indicator to monitor as it gives a better understanding of the potential for ongoing transmission than a cross-sectional measure. Further, cumulative measures of viraemia have been shown to be predictive of mortality outcomes. I therefore think this chapter has particular relevance, as this devised longitudinal continuum can be used to generate findings that have implications for both public health and clinical care. This longitudinal continuum of care also has disadvantages. In order to characterise long-term outcomes, a historic cohort is studied who likely have different experiences of care to individuals entering care currently. Further, it currently studies a group of individuals linked to care, as this is the population included the UK CHIC Study. Though it could similarly be applied to a population of newly diagnosed individuals, it could not incorporate measures of undiagnosed HIV infection, which is an important element of the continuum of care, and the global target least often achieved in many settings, including the UK. Due to the in-depth clinical data needed to generate the month-by-month classifications of care, it would not be useful as a country-wide programme monitoring tool, but is instead more useful for research.

Generating a longitudinal continuum of care for different age, sex, ethnic and HIV acquisition risk groups highlighted certain differences in the care continuum. I observed that older people initiated ART more quickly but had higher mortality. This is supported by findings from Chapter 5, in which older individuals were more likely to be diagnosed late, and therefore in need of immediate ART, and had markedly higher rates of mortality. The continuum of care in younger adults showed that those aged <30 years at cohort entry spent a larger amount of time disengaged from care, particularly whilst ART naïve, and uptake of ART was therefore slower. Women, and those of black ethnicity were found to spend more time with unsuppressed viral load whilst ART experience. These findings highlight that sub-optimal achievement of the key stages of HIV care is more likely amongst those other than middle-aged, white, men who acquired HIV through sex between men. Also, they show that the gaps in care that are likely to be experienced by these groups differs. This is important as, although such disparities in the continuum of care have been shown in other countries, it has not been shown in the UK where access to healthcare is free. Targeted support interventions focused on improving the biggest gaps in the populations at highest risk will be needed to achieve an equally good continuum of care for all PLWH in the UK.

9.2 Limitations

Though a randomised controlled trial is the gold-standard for evidence-based medicine, this thesis is interested in outcomes of care in a real-life clinical setting. Further, many of the research questions addressed investigate exposures to which it is not possible to randomise individuals (for example, EIC). Therefore, a cohort study provides the best quality evidence to answer these research questions. The specific limitations of each analysis are discussed in the relevant chapters, but there are some general limitations of cohort studies, and the UK CHIC Study particularly, that should be considered when interpreting these findings.

Firstly, the majority of clinics that contribute data to the UK CHIC Study are large London-based clinics whose attendees may have different demographic characteristics to attendees at centres outside London. Therefore, the UK CHIC population may not be a representative sample of all PLWH in the UK. The possibility of unmeasured confounding that cannot be accounted for in these analyses cannot be ruled out. A limitation of using data from the UK CHIC Study to answer the questions posed in this thesis is that it collates data from HIV clinics and only those data that are routinely collected as part of HIV care. This limits the potential confounding factors that I was able to account for in analyses to factors directly relating to HIV care. Adherence and socioeconomic status are two potentially important confounders for many of these analyses that are not captured in the UK CHIC Study and so cannot be accounted for in these analyses. The study also does not collate information on wider health outside of HIV, for example, mental health, which would be important to consider in relation to engagement in care. Reliable capture of non-AIDS illnesses would be an important outcome to consider in the context of an aging HIV-positive population, particularly in light of findings in Chapter 5, demonstrating an association between late diagnosis, older age and non-AIDS mortality. Whilst some information is collected on non-AIDS illness in the study, reporting is dependent on the HIV clinic being aware of a diagnosis and has been found not to be consistent or reliable, so is not used for analysis.

Cohorts, particularly observational databases that utilise routine clinical data, may be subject to attrition bias as people become LTFU, with certain groups more likely to be LTFU than others. Further, those disengaged from care may be more likely to have poorer outcomes than those remaining in care and this can result in an under or over-estimate of the true effect as these outcome events are not included in the analysis. Those with poorer engagement in care are also more likely to have missing information on other variables, as there are fewer opportunities to gather information in the HIV clinic, and it may be harder to get individuals to participate fully in care when they do attend. As a consequence, it was not possible to

understand characteristics or investigate predictors of those lost to study follow-up and lost to care, which were an important outcome of interest in this thesis.

Missing data are unavoidable in most studies and are present in this thesis. Mechanisms of missing data include data missing completely at random (MCAR), in which missingness is unlikely to introduce bias. This assumption is unlikely in most epidemiological studies. Data missing at random (MAR) are a more likely assumption and are missing in a systematic way that can be explained by the observed data. This missingness may introduce bias if not dealt with using appropriate methods, such as multiple imputation. Data missing not at random (MNAR) are missing in a way that is associated with unobserved data. This may also be a valid assumption for this study. Few analysis techniques currently eliminate bias in the presence of MNAR data (541, 613). Throughout this thesis I have dealt with missing information on demographic variables by creating an unknown category where data are missing. As previously mentioned, these unknown categories therefore likely represent a group of individuals with poorer engagement in care, who may have more difficult or chaotic lifestyles and who are more likely to experience poor outcomes. In Chapter 5 it was seen that those of unknown mode of acquisition had significantly higher rates of mortality than for any other exposure group. In regression analyses, particularly confounder-adjusted multivariable models such as those in chapters 5 and 6, the inclusion of an additional unknown category has the potential to introduce bias (541, 614). Whilst such individuals account for only a small proportion of the included population, the mechanisms behind the occurrence of this missing data may still cause biased estimates in regression models (541).

A deterministic linkage to HARS data was used to supplement information on date and cause of death. As no unique identifier was available that was common to both datasets, it is possible that matches were made through this linkage that were incorrect. In order to avoid accepting information from incorrect matches, I generated my own matching score based on agreement between certain mutually available data items and only accepted information if this score was below a threshold of 1. I used a score so that these decisions were objectively and consistently made across all linked records. However, the matching score I used was derived only on my own feeling of what was sensible, in agreement with my supervisor. If this score does not perform well, I may still be accepting some incorrect matches whilst also disregarding information from correct matches. A more in-depth assessment of the validity and precision of the initial linkage may have been useful to assess the extent to which incorrect linkage may have occurred (615).

Throughout this thesis I have used the REACH algorithm to generate measures of engagement in care. This was done to incorporate and allow for varying visit schedules between individuals according to current health status and to create a time-updated measure of engagement in

care. However, the performance of this algorithm for measuring true engagement in care has not been assessed and it has not been externally validated in another cohort. The visit intervals defined in the algorithm are estimates based on clinician experiences and a small set of available variables within the UK CHIC dataset. Due to the previously mentioned limitations of the UK CHIC Study in the scope of the data it collects, the set of variables on which the REACH algorithm is based relate solely to HIV care. It does not incorporate factors not related to HIV, such as mental health and non-AIDS comorbidities that could influence the frequency at which HIV visits are scheduled. It also currently reflects visit scheduling practices at the time that the REACH Study was conducted and will need to be updated over time as recommended intervals for visits in stable treated HIV-positive individuals become longer (322). Finally, by relying on laboratory tests and ART prescription data to measure attendance, we may not capture all visits to the HIV clinic that an individual makes. This is likely to be of increasing importance in future years as CD4 count monitoring is reduced (322). These factors have most likely lead to an underestimate of engagement in care in the presented analyses.

For certain analyses I have created categories from continuous variables. In chapter 5, I grouped age into <50 or ≥50 years. This was done to be consistent with other HIV literature, where age ≥50 has widely been adopted as a threshold for older age in PLWH (222, 294, 296). In Chapter 7, I grouped EIC as high (≥80%) or low (<80%), as it may be useful to have a definition of 'engaged' and 'not engaged' in care, but also analysed EIC as a continuous variable. Such dichotomisation of numeric data results in a loss of information, which could reduce the power to detect an association between the categorised variable and outcome of interest (616, 617). Categorisation assumes that the size of an association between an independent variable and the outcome variable is the same across all underlying values within a group, but is different as you cross the dichotomy (616, 617). This is to say, using EICR as the example, that an EICR of 25% has the same association with mortality as an EICR of 79%, but the association between and EICR of 79% and mortality is different to an EICR of 81%. This underestimates the variability in outcome responses within each group and is not a valid assumption. The choice of cut-off may also impact observed associations resulting in biased estimates (616, 617). As was seen in Chapter 7, the 'low' EIC group had a life expectancy similar to that of people with 25% EICR in analysis using continuous EICR, ignoring increases in life expectancy seen for those with 50% and 75% EICR in the continuous analysis. Therefore, the analysis using continuous EICR is a more valid analysis.

9.3 Future work

This thesis has highlighted issues of loss to HIV care in the UK, which has previously not been well recognised (70). This is an important finding as those lost to care are more likely to have poor outcomes and could contribute to the ongoing epidemic if not on treatment with a

suppressed viral load. Further work should focus on generating reliable estimates of the number of PLWH in the UK who aren't receiving care, as well as understanding drivers of disengagement from care and barriers to re-engaging in care. Key to this would be to identify where individuals lost to follow-up have migrated out of the country and where they have remained but do not receive care. It would not be possible to investigate this in any detail using only the clinical HIV data collected in the UK CHIC Study. Mixed methods research that utilises surveillance data, data linkage and qualitative elements would ideally be needed to fully investigate loss to care. A quantitative element to reliably estimate rates and understand predictors of loss to care would require the ability to actively trace outcomes of those lost-to-follow-up from clinics; in particular to establish whether individuals have migrated out of the UK. Previous attempts to actively contact and ascertain outcomes of individuals lost to care in a single centre were not able to trace the majority (324). However, this would likely be the best approach, as linking data on HIV status to migration data poses ethical concerns due to the stigma still surrounding HIV and fears over identifying, on a patient-level, those with unconfirmed immigration status or those remaining in the country illegally. The national HARS dataset could be used to determine whether individuals remain in HIV care in the UK. Alternatively, electronic patient records may provide a unique opportunity to establish whether individuals are accessing care in any health setting (for example, through their GP) in the UK, not only HIV care. However, this would require linking of the HIV record to NHS number. Currently, HIV clinic records are still often treated as a special case and are not linked to NHS number and an individual's wider health record. If it were possible to utilise electronic patient records, it may also present an opportunity to access additional data on individuals lost to care such as mental health, socioeconomic status and psychosocial factors that would be of benefit to understand predictors of disengagement. However, as many barriers to engagement in care may be related to individuals' circumstances, a qualitative element to understand drivers of this loss to care would be useful inform potential targeted interventions to prevent disengagement and encourage re-engagement. Such a study would need to purposively sample and recruit those individuals identified as lost to care, so may be small in size, as it may be difficult to access and recruit individuals who are not engaged in care to a research study.

Recent changes to HIV treatment guidelines as to when to start ART may affect the relevance of some of these findings to newly diagnosed PLWH now and in future. If people newly diagnosed with HIV start ART as soon as they are ready to do so as part of routine care, whilst the continuum of care will likely improve in those who are diagnosed early, disparities in outcomes between those with late as opposed to timely diagnosis and ART initiation could increase. Immediate ART could contribute to reductions in HIV transmission in combination with pre-exposure prophylaxis in HIV–negative individuals, meaning that the largest burden of HIV in future years will remain amongst those who have poorer engagement with care and

are slower to be diagnosed and initiate ART. These individuals, will become increasingly important to the epidemic in the UK. For these reasons further follow-up in the era of immediate ART is needed to assess the impact of these changes on the continuum of care and whether disparities will continue or even worsen across different populations of PLWH in the UK. In the coming years, the longitudinal continuum of care will need to be re-assessed to determine the impacts of immediate ART in different age, ethnic and HIV risk groups.

9.4 Concluding remarks

The aims of this thesis were to investigate the occurrence of sub-optimal achievement of some of the key elements that make up the HIV continuum of care, and the impact of such factors on mortality outcomes. I have shown that late diagnosis is common and associated with a high mortality burden soon after diagnosis. I have also seen that whilst viral suppression is a hugely predictive marker of mortality, better EIC independently correlates with life expectancy amongst both those with and without a virological response to ART. Whilst those who initiate ART with immunosuppression have poorer CD4 recovery, the risk of clinical progression may reach similar levels to that in those who start ART earlier in the long-term, if viral suppression is achieved. Finally, a longitudinal continuum of care has demonstrated disparities in care and treatment response amongst demographic groups.

Interventions to improve testing rates, and adherence and engagement support are needed for those populations identified as being at high risk of sub-optimal engagement with HIV care. Above all, these findings highlight the importance of achieving a truly optimal continuum of care across all demographic groups to reduce the burden of mortality in PLWH in the UK. It is hoped that this thesis will provide needed data for a UK setting that can inform discussions and interventions towards achieving this goal.

Appendix I: UK CHIC Study data request form sent to participating centres annually

UK CHIC Data Submission Guidelines: Tables 1-12, November 2014

We are now requesting the next data download from centres. It is appreciated that some centres may not be able to provide all of this data electronically for all files. If certain data items are not available at present, could you let me know if they may be available in future?

If you have any queries, please contact Teresa Hill (020 7670 4730 or 020 7794 0500 ext 36762)

or email teresa.hill@ucl.ac.uk

Thank you.

Deadline

We ask that you submit all data **by Friday 19th December 2014.**

Format

- Please provide data on all HIV positive patients seen for care at any time at your HIV clinic
- All data can be submitted as Access tables, Excel spreadsheets, or text files with the variables comma or tab delimited
- All dates should be provided in dd/mm/yyyy format, including leading zeros, and without time after dates
- All files should include the clinic ID and date of birth for each patient so that the files can be easily merged
- DO NOT send patient names, addresses or postcodes

Coding

- Codes for the variables in the data tables (Files 1 – 12) are listed on page 5 onwards. Data must be coded using UK CHIC codes otherwise it will not be accepted. If you need help with coding or mapping your data please contact us

How to submit data securely (Encryption plus secure transfer)

- **Data encryption:** please encrypt data using either 7-Zip or Winzip (select 256-bit AES encryption).
  Please DO NOT USE AXCRYPT as this is no longer an approved encryption software.
  The encryption password (minimum 10 characters long, include upper/lowercase, numbers and special characters, do not use 'ukchic', or the clinic name), to be communicated by telephone or separate email
- **Secure Data transfer/submission:** submit the encrypted files by the FTP secure transfer system.

Email teresa.hill@ucl.ac.uk or telephone if you need FTP details

Feedback on data quality

Following data submission and some general format checks, we will contact you if there are issues that need to be resolved. At a later date, we may send you more detailed data queries for resolution where possible

Anything new this time?

As a result of Steering Committee discussions, we may collect new data some years. These items will be highlighted in blue here and in the data specifications. NO NEW DATA ITEMS THIS YEAR.

No longer collected - File 8 PCP prop – please do not send this table

File 1 – PATIENTCENTRE table

Field Name	Description	Type
ClinicNo	HIV Clinic's unique patient identifier	text (12)
DOB	Date of birth	dd/mm/yyyy
Soundex	Soundex code	text (4)
Initial	Patient initial/s	text (2)
SexID	Patient sex code	integer
HIVPos	Date of first known positive HIV antibody test	dd/mm/yyyy
HIVNeg	Date of last negative HIV antibody test	dd/mm/yyyy
Firstseen	Date of first HIV attendance at centre	dd/mm/yyyy
Lastseen	Date when last seen by a clinician at the centre	dd/mm/yyyy
ExposureID	HIV exposure category	integer
EthnicityID	Ethnicity code	integer
CountryID	Country of birth code	text (30)
DiedID	Is patient known to have died code	integer
DDeath	Date of death	dd/mm/yyyy
Cause	Cause of death (where known)	text (100)
TransferFr	Transfer in from which previous centre	text (100)
TransferFrDate	Transfer in from previous centre date	dd/mm/yyyy
TransferTo	Transfer out to which other centre	text(100)
TransferToDate	Transfer out to other centre date	dd/mm/yyyy

File 2 – AIDSEVENT table

Field Name	Description	Type
ClinicNo	HIV Clinic's unique patient identifier	text (12)
DOB	Date of birth	dd/mm/yyyy
DAIDS	Date of AIDS event	dd/mm/yyyy
AIDSID	AIDS event code	integer

File 3 – ANTIRETRO table

Field Name	Description	Type
ClinicNo	HIV Clinic's unique patient identifier	text (12)
DOB	Date of birth	dd/mm/yyyy
DStart	Date started taking drug	dd/mm/yyyy
DStop	Date stopped taking drug	dd/mm/yyyy
DrugID	Drug code	integer (15)
ReasonStopID1	Reason for stopping drug	integer
ReasonStopID2	Reason for stopping drug (if multiple codes)	integer
ReasonstopID3	Reason for stopping drug (if multiple codes)	integer

File 4 – CD4 table

Field Name	Description	Type
ClinicNo	HIV Clinic's unique patient identifier	text (12)
DOB	Date of birth	dd/mm/yyyy
Dlab	Date of lab measurement	dd/mm/yyyy
CD4A	Absolute CD4 count in cells/mm^3	integer
CD4P	CD4 percentage	number (1dp)
CD8A	Absolute CD8 count in cells/mm^3	integer

CD8P	CD8 percentage	number (1dp)

File 5 – RNA/HIV Viral Load table

Field Name	Description	Type
ClinicNo	HIV Clinic's unique patient identifier	text (12)
DOB	Date of birth	dd/mm/yyyy
Dlab	Date of lab measurement	dd/mm/yyyy
RNA	HIV Viral Load level in copies/ml	long integer
UndetID	Result status: below/within/above assay limit	integer
AssayID	HIV RNA assay code	integer

File 6 – HEPATITIS table

Field Name	Description	Type
ClinicNo	HIV Clinic's unique patient identifier	text (12)
DOB	Date of birth	dd/mm/yyyy
DHeptest	Date of hepatitis test	dd/mm/yyyy
HepTestID	Hep test code	integer
HepResultID	test result (-/+/indet)	integer
Hepvalue	test result value, e.g. RNA copies	long integer
UndetID	Result status: below/within/above assay limit	integer
HepUnitID	test result units	integer
HepAssayID	please ignore this	integer

File 7 – ADHERENCE table

Field Name	Description	Type
ClinicNo	HIV Clinic's unique patient identifier	text (12)
DOB	Date of birth	dd/mm/yyyy
DAdherence	Date of clinic visit	dd/mm/yyyy
AdherPeriodID	Adherence period codes	integer
AdherPerOther	Adherence period other	text (50)
DosesMiss	Number of doses missed (approximately)	integer/text
ReasonMissID	Reason for missing treatment code	integer
AdhComment	Text description relating to adherence	text (50)

File 8 – PCPPROP table (PCP prophylaxis data are no longer required - PLEASE DO NOT SEND)

File 9 – TOXICITY table

Field Name	Description	Type
ClinicNo	HIV Clinic's unique patient identifier	text (12)
DOB	Date of birth	dd/mm/yyyy
DToxtest	Date of toxicity test	dd/mm/yyyy
ToxTestID	Tox test code	integer
ToxResult	Test result value	integer/number,single (if dec places in result)
ToxUnitID	Test result units, coded	integer

File 10 – HLA-B57 table

Field Name	Description	Type
ClinicNo	HIV Clinic's unique patient identifier	text (12)

DOB	Date of birth	dd/mm/yyyy
DHLAB57	Date of HLA-B*5701 test	dd/mm/yyyy
HLAB57ResultID	test result (-/+/indet)	integer

File 11- Attendance table

Field Name	Description	Type
ClinicNo	HIV Clinic's unique patient identifier	text (12)
DOB	Date of birth	dd/mm/yyyy
DAttend	Date of attendance	dd/mm/yyyy
AttSeenBy	Who patient is seen by eg doc, nurse, virtual, dietician, psycologist, other etc	integer
AttType	Attendance: scheduled, walk-in, virtual, in-patient, other	integer
Ddischarge	Date of discharge if in-patient	dd/mm/yyyy

File 12 - SeriousNonAIDS

Field Name	Description	Type
ClinicNo	HIV Clinic's unique patient identifier	text (12)
DOB	Date of birth	dd/mm/yyyy
DSerNA	Date of serious Non-AIDS event	dd/mm/yyyy
SNAID	Serious Non-AIDS event code	integer
SNAConf	Serious Non-AIDS event status, whether Confirmed/Probable/Status unknown	integer
ICDcode	ICD code if used	text
SNOMEDcode	SNOWMED code if used	text

Coding/Mapping Tables – see below

CODING / MAPPING TABLES

Coding	Description
AdherPeriodID	**AdherPeriod**
1	Last 3 days
2	Last 14 days/2 weeks
3	Last 30 days/1 month
4	Last 90 days/3 months
98	Other adherence period
99	Not known
AIDSID	**AIDS**
1	Bacterial infections (multiple or recurrent) at age < 13 years
2	Candidiasis, oesophageal
3	Candidiasis, trachea/bronchi/lungs
4	Candidiasis, site unknown
5	Cervical cancer, invasive
6	Coccidioidomycosis, extrapulmonary
7	Cryptococcosis, extrapulmonary
8	Cryptosporidiosis, duration > 1 month
9	Cytomegalovirus retinitis
10	Cytomegalovirus disease, other
11	Cytomegalovirus, site unknown
12	Herpes simplex disease, duration > 1 month
13	Histoplasmosis, extrapulmonary and/or disseminated
14	HIV Encephalopathy
15	Isosporiasis, duration > 1 month
16	Kasposi's sarcoma
17	Lymphoid interstitial pneumonia or pulmonary lymphoid hyperplasia at age <13 years
18	Lymphoma, Burkitt's, immunoblastic or equivalent
19	Lymphoma, primary in brain
20	Mycobacterium avium, extrapulmonary (MAI/MAC)
21	Mycobacterium tuberculosis, pulmonary
22	Mycobacterium tuberculosis, extrapulmonary
23	Mycobacterium, other (disseminated)
24	Pneumoncystis carinii pneumonia (P. jiroveci)
25	Pneumonia, recurrent in a 12-month period
26	Progressive multifocal leukoencephalopathy
27	Salmonella Septicaemia, recurrent
28	Toxoplasmosis, cerebral
29	HIV wasting syndrome
31	Lymphoma Site Unknown
51	Mycobacterium tuberculosis, Site Unknown
98	AIDS disease, not specified
99	Not Known
AssayID	**Assay**
1	Roche Amplicor HIV-1 Monitor v1.0 (<400)
2	Roche non-B (<400)
3	Roche Amplicor HIV-1 Monitor v1.5 (<400)
4	Roche Amplicor HIV-1 Monitor v1.5 US (<50)

5	Roche – version unknown
6	Cobas v1.5 (<400)
7	Cobas v1.5 US (<50)
9	Cobas – version unknown
10	NASBA (<400)
11	NASBA US
12	NASBA – version unknown
13	Chiron b-DNA v1.0
14	Chiron b-DNA v2.0 (<500)
15	Chiron b-DNA v3.0 US (<50)
16	Chiron – version unknown
17	Nuclisens (<400)
18	Nuclisens US (<50?)
19	Nuclisens – version unknown
21	Cobas<10 copy assay
22	Abbott RealTime HIV-1 (ultra-sensitive)
23	Abbott LCx HIV RNA
29	Roche Cobas TaqMan v1.0 (<40)
30	Roche Cobas TaqMan v2.0 (<20)
31	Abbott RealTime HIV-1 (<40)
98	Other
99	Not known
AttSeenBy	**Attendance**
1	Clinician
2	Nurse
3	Health advisor
4	Pharmacy/Pharmacist
5	Dietician
6	Psychologist / Counsellor
98	Other
99	Not known
AttType	**Type of attendance**
1	Scheduled or booked
2	Walk-In
3	Virtual – telephone or email contact
4	In-patient
98	Other
99	Not known
DiedID	**Died**
0	No
1	Yes
99	Not known
DrugID	**Drug**
1	Zidovudine (AZT)
2	Zalcitabine (ddC)
3	Didanosine (ddI)
4	Stavudine (d4T)
5	Lamivudine (3TC)

6	Abacavir
7	Combivir (AZT+3TC)
8	Lodenosine
9	Trizivir (AZT + 3TC + abacavir)
10	Tenofovir (TDF)
11	Emtricitabine (FTC)
12	Kivexa (3TC + abacavir)
13	Truvada (tenofovir/TDF + emtricitabine /FTC)
14	Tenofovir alafenamide fumarate (TAF)
19	Other NRTI
20	Nevirapine
21	Efavirenz
22	Loviride
23	Delavirdine
24	Etravirine / TMC125
25	Rilpivirine (RPV)
26	Eviplera (rilpivirine + tenofovir/TDF + emtricitabine/FTC)
39	Other NNRTI
40	Saquinavir hard gel (invirase)
41	Indinavir
42	Ritonavir – any dose
43	Nelfinavir
44	Saquinavir soft gel (fortovase)
45	Amprenavir
46	Lopinavir (ABT 378) (kaletra)
47	Saquinavir (form unknown)
48	Atazanavir
49	Other PI
50	Hydroxyurea / hydroxycarbamide
51	IL-2
60	Acyclovir
61	Fos amprenavir
62	Tipranavir
63	Darunavir / TMC114
70	Enfuvirtide / T20
80	Adefovir
90	Blinded treatment in clinical trial
95	Maraviroc
96	Vicriviroc
97	Other Entry (CCR5) Inhibitor
98	Other ART drug (ART drug is known, but not on this list)
99	Not known (ART, but not known which drug)
110	Raltegravir / MK-0518
111	elvitegravir
112	dolutegravir
119	Other Integrase Inhibitor
120	Atripla (Efavirenz/Tenofovir/Emtricitabine)

121	STRIBILD™ (QUAD) ((elvitegravir + cobicistat + emtricitabine + tenofovir disoproxil fumarate)
122	(dolutegravir/lamivudine/abacavir)
130	cobicistat
131	cobicistat/atazanavir
132	cobicistat/darunavir
133	cobicistat/elvitegravir
EthnicityID	**Ethnicity**
1	White
2	Black-Caribbean
3	Black-African
4	Black – unspecified/black-other
5	Indian/Pakistani/Bangladeshi
6	Other Asian/Oriental
7	Other/mixed
98	Other
99	Not known
ExposureID	**Exposure**
1	Homosexual/bisexual (including homo / bi sex who **also** injected drugs)
2	Injecting drug use
3	Heterosexual
4	Blood/blood products recipient
5	Mother-to-child transmission
98	Other
99	Not Known
HepResultID	**HepResult**
0	Negative
1	Positive
2	Indeterminate /weakly reactive/equivocal
HepTestID	**HepTest**
1	Hep A antibody (total IgG+IgM)
2	Hep B surface antigen (HbsAg)
3	Hep B surface antibody (anti-HBs)
4	Hep B core antibody (anti-HBc)
5	Hep B e antigen
6	Hep B e antibody
7	Hep C antibody
8	Hep C virus PCR/bDNA
9	Hep B core antibody (IgM)
10	Hep A antibody (IgM)
11	Hep B DNA (Genotype unknown)
12	Hep D antibody (total)
13	Hep B surface antigen (titre)
14	Hep D antibody (IgM)
98	Other
99	Not known
HepUnitID	**HepUnit**
1	IU/mL

2	copies/mL
3	mIU/ml
98	Other
99	Not known
HLAB57ResultID	**HLAB57Result**
0	Negative
1	Positive
2	Indeterminate /weakly reactive/equivocal
PCPpDrugID	**PCPpDrug** (PCPp Drug data no longer collected - please do not send)
1	Co-trimoxazole/septrin
2	Dapsone
3	Pentamidine
4	Atovaquone
5	Azithromycin
6	Clarithromycin
7	Clindamycin
8	Fansidar (=pyrimethamine + sulphadoxine)
9	Primaquine
10	Pyrimethamine
11	Sulphadiazine
12	Sulphadimidine
13	Sulfametopyrazine
14	Trimetrexate
15	Trimethoprim
16	Sulfadoxine
17	Maloprim (pyrimethamine + dapsone)
18	Eflornithine
98	Other
99	Not known
ReasonMissID	**ReasonMiss**
1	Forgot
2	Ran out of medicaiton
3	Wanted a short break
4	Side effects
5	Away from home/supply
6	In company
7	Treatment holiday
98	Other
99	Not known
ReasonStopID	**ReasonStop**
10	Failure-cause unknown
11	Virological
12	Immunological
13	Clinical
14	VL / CD4
20	Toxicity-type unknown
30	Skin
31	Hypersensisity – Abacavir

32	Rash
40	GI
41	Nausea/Vomiting
42	Diarrhoea
43	Pancreatitis
44	Abnormal LFT
50	Neuro
51	CNS Disturbance
52	Peripheral Neuropathy
53	Headache
60	Metabolic
61	Lipids
62	Glucose Intolerance
63	Hyperlactataemia
64	Osteopaenia
70	Lipodystrophy
80	Myelotoxicity
81	Anaemia
82	Neutropenia
83	Thrombocytopenia
91	Myotoxicity
92	Nephrolithiasis/Renal Dysfunction
100	Patient Choice
110	Clinician decision
120	Interaction
130	Simplification
140	Poor Adherence
150	Joined clinical trial
160	Study/Trial End
170	New drug available
180	Known treatment interruption
190	Protocol amendment
200	Pregnancy
201	At start/during pregnancy
202	End of short-course ART
210	Intercurrent illness, not HIV/ drug related
220	VL sufficiently low
230	CD4 sufficiently high
240	Regimen change
250	Transfer of care
260	Drug Experience / Resistance
998	Other
999	Not Known
SNAConf	**Serious Non-AIDS event Confirmed**
1	Confirmed
2	Probable
99	Status Unknown (not known whether Confirmed or Probable)
SNAID	**Serious Non-AIDS**

10	Acute Myocardial Infarction (AMI)
11	Congestive Heart Failure (CHF)
12	Coronary Artery Disease Requiring Drug Treatment
13	Coronary Revascularization (coronary angioplasty, artery by-pass grafting, stent, carotic endarterectomy
50	Decompensated Liver Disease (DLD)
51	Alcoholic liver disease
52	Liver Cirrhosis
53	Liver Fibrosis
56	HAART associated liver disease (including non-alcoholic steatohepatosis, nodular regenerative hyperplasia, hepatoportal sclerosis
58	Liver disease, other
59	Liver disease, chronic, unspecified
70	Diabetes Mellitus (DM)
75	Lactic acidosis, symptomatic
80	End Stage Renal Disease (ESRD)
81	HIV nephropathy
82	HAART associated renal failure (including Fanconi syndrome)
89	Renal disease, other
100	Anal cancer
101	Bowel cancer
102	Breast cancer
103	Castleman's disease
104	Cervical cancer
105	Hodgkins Lymphoma (HL)
106	Liver cancer
107	Lung cancer
108	Stomach cancer
109	Prostate cancer
110	Other Non-AIDS-Defining cancer (NADC), unspecified
120	Peripheral Arterial Disease (PAD)
121	Pulmonary Embolism (PE)
122	Deep Vein Thrombosis (DVT)
123	Stroke
129	Other vascular / thromboembolic disease
130	Osteopenia
131	Osteoporosis
132	Fracture, fragility
133	Fracture, traumatic
134	Fracture, mixed (traumatic+fragility)
135	Fracture, unspecified
138	Other bone disease
139	Bone disease, unspecified
140	Sepsis (or Sepsis Syndrome)
141	Multi-organ failure
142	Haemophagocytic Syndrome
143	Bacterial infection, severe (non-sepsis)
144	Fungal infection, severe

145	Viral infection, severe
149	Infection, severe, unspecified (non-AIDS), other
998	Serious Non-AIDS event, other
999	Serious Non-AIDS event, not specified
SexID	**Sex**
1	Male
2	Female
99	Not known
ToxTestID	**ToxTest**
1	ALT
2	Albumin
3	Alkaline phosphatase
4	Amylase
5	AST
6	Bilirubin
7	Cholesterol total (non fasting or unknown)
8	CPK (creatine phosphokinase)
9	Creatinine (serum)
10	Glucose
11	GGT(g-glutamyl transferase)
12	Haemoglobin
13	HDL
14	Lactate
15	LDL
16	Triglycerides
17	Urea
18	Lactate dehydrogenase
19	Cholesterol (fasting)
20	Protein Total (urine)
21	Creatinine (urine)
22	Protein/Creatinine Ratio (PCR) (urine)
23	Albumin (urine)
24	Albumin/Creatinine Ratio (ACR) (urine)
25	Protein 24hr (urine)
26	Platelet count
27	Vitamin D
28	Phosphate (serum)
29	Calcium (serum)
30	Parathyroid hormone (PTH)
31	Calcium (serum, corrected)
98	Other
99	Not known
ToxUnitID	**ToxUnit**
1	IU/L
2	g/L
3	U/L
4	μmol/L
5	μmol/L (plasma)

6	mmol/L
7	mmol/L (urine)
8	g/dL
9	mg/L
10	mg/mmol
11	g/day
12	mg/day
13	μg/L
14	ng/L
15	10^9/L
16	mg/dL
17	pg/ml
18	nmol/L
19	pmol/L
98	Other
99	Not known
UndetID	**Undet**
-1	< Below lower limit of detectability
0	Any value that is detectable but below the upper limit of quantification
1	> Above upper limit of quantification

Appendix II: CoDe Case Report Form

Cause of Death Form (CRF)

CoDe

*Study:_____

*Patient ID code: _____

*Date of death : ___–___ –___
(dd/mmm/yy eg 01-FEB-08)

If the patient experienced any D:A:D event(s), please report such event(s) on a designated D:A:D event form in addition to the completion of the CoDe form

Section 1♦ Background demographics

- * A. Year of birth (yyyy) ____ B. Gender : ☐male ☐female
- C. Height (cm):___ D. Weight (kg) : ___ E. Date :___–___–___
  (most recent before death) (dd-mmm-yy; weight measured)

Section 2♦ What data sources were available for the completion of this form? (please mark all that apply)

- A. Hospital files ☐Yes, complete ☐Yes, incomplete ☐No
- B. Outpatient clinic chart ☐Yes, complete ☐Yes, incomplete ☐No
- C. Autopsy report ☐Yes, complete ☐Yes, incomplete ☐No
- If other, specify:
- D. Registry ☐ • G. Patient's medical provider ☐
- E. Obituary ☐ • H. Nursing home ☐
- F. Patient's relatives or partner ☐ • I. Other:_____

Section 3♦ Risk factors:

A. Ongoing risk factors in the year prior to death:

1. Cigarette smoking ☐ Yes ☐ No ☐ Unknown
2. Excessive alcohol consumption ☐ Yes ☐ No ☐ Unknown
3. Active illicit injecting drug use ☐ Yes ☐ No ☐ Unknown
4. Active illicit non-injecting drug use ☐ Yes ☐ No ☐ Unknown
5. Opiate substitution (methadone) ☐ Yes ☐ No ☐ Unknown

Section 4♦ Co-morbidities:

A. Ongoing chronic conditions:

1. Hypertension ☐ Yes ☐ No ☐ Unknown
2. Diabetes mellitus ☐ Yes ☐ No ☐ Unknown
3. Dyslipidemia ☐ Yes ☐ No ☐ Unknown

B. Prior cardiovascular disease ☐ Yes ☐ No ☐ Unknown
(myocardial infarction, stroke or invasive cardiovascular procedure)

C. History of depression ☐ Yes ☐ No ☐ Unknown

D. History of psychosis ☐ Yes ☐ No ☐ Unknown

E. Liver disease:

1. Chronic elevation of liver transaminases ☐ Yes ☐ No ☐ Unknown
2. Chronic HBV infection ☐ Yes ☐ No ☐ Unknown
3. Chronic HCV infection ☐ Yes ☐ No ☐ Unknown
4. HDV infection ☐ Yes ☐ No ☐ Unknown
5. History of previous liver decompensation ☐ Yes ☐ No ☐ Unknown
6. Clinical signs of liver failure in the 4 weeks before death ☐ Yes ☐ No ☐ Unknown
7. Liver histology available (ever) ☐ Yes ☐ No ☐ Unknown

*Please note that if any mandatory fields remain empty the CRF will not be registered

Cause of Death Form

CoDe

*Study:_____

*Patient ID code:_____

If Yes, please indicate:

the date of most recent biopsy __ - ___ -__ the stage of fibrosis (0-4): |__|

(dd-mmm-yy eg 01-FEB-08)

Section 5♦ Cause of death

A. Was the death sudden? ☐ Yes ☐ No ☐ Unknown

B. Was the death unexpected? ☐ Yes ☐ No ☐ Unknown

C. Please complete the table below by recording all illnesses and conditions (acute and chronic) or injuries that the patient had at the time of death.

	Illness / Condition / Injury (text)	Date of onset dd/mmm/yy (eg 01-FEB-08)	Certainty of diagnosis*		
			Definite	Likely	Possible
1.		____-_____-____	☐	☐	☐
2.		____-_____-____	☐	☐	☐
3.		____-_____-____	☐	☐	☐
4.		____-_____-____	☐	☐	☐
5.		____-_____-____	☐	☐	☐
6.		____-_____-____	☐	☐	☐
7.		____-_____-____	☐	☐	☐
8.		____-_____-____	☐	☐	☐
9.		____-_____-____	☐	☐	☐

*Certainty of Diagnosis: Definite=95-100% certainty, Likely=80-95% certainty, Possible=50-80% certainty

*D. Brief narrative of the sequence of events leading to death (please include means of diagnosis of illnesses):

_____

_____

_____

_____

_____

_____

*Please note that if any mandatory fields remain empty the CRF will not be registered

Cause of Death Form

CoDe

*Study:_____

*Patient ID code:_____

E. In summary, the causal relation between the conditions leading to death was (complete this section with the corresponding number from table C above):

1. **Condition that directly caused death (immediate cause):**_____

2. Due to or as a consequence of :_____

3. Due to or as a consequence of:_____

4. **Condition that initiated the train of morbid events (the underlying condition):**_____

Section 6♦ Post-mortem / Autopsy:

A. Has autopsy been performed: ☐ Yes ☐ No ☐ Unknown

B. Did the autopsy reveal any evidence of intoxication?

☐ Yes, with the agent:_____ ☐ No ☐ Unknown

Please provide a brief summary of the findings from the autopsy report (please also include a copy of the full report):

Section 7 ♦ ART and laboratory values prior to death

A. Has the patient EVER received ART: ☐ Yes ☐ No ☐ Unknown

If YES, when was ART started (in months before death):

☐ ≤ 1 month before ☐ ≤ 3 months before ☐ ≤ 6 months before ☐ More than 6 months before

B. Did the patient receive ART at the time of death? ☐ Yes ☐ No ☐ Unknown

- *If No*, Date of stopping __ __ - __ __ __ - __ __ **(dd/mmm/yy eg 01-FEB-05)**

C. Laboratory values (please complete all fields where data is available)

Laboratory values	Time	Value	Unit	Date dd/mmm/yy (eg 01-FEB-05)
CD4+ cell count	1. Most recent prior to last stopping ART		Cells/mm^3	__ __ - __ __ __ - __ __
	2. Most recent prior to death		Cells/mm^3	__ __ - __ __ __ - __ __
HIV RNA	1. Most recent at time of stopping ART		Copies/mL	__ __ - __ __ __ - __ __
	2. Most recent prior to death		Copies/mL	__ __ - __ __ __ - __ __
Haemoglobin	Most recent prior to death		/	__ __ - __ __ __ - __ __

*Please note that if any mandatory fields remain empty the CRF will not be registered

Cause of Death Form (CRF)

CoDe

*Study:_____

*Patient ID code: _____

Section 8 ♦ Adverse effects to any type of medical treatment

A. Was the death considered to be related to a medical treatment? ☐ Yes ☐ No ☐ Possibly

B. The suspected relation was to: ☐ Antiretroviral treatment ☐ Other medical treatment

Please provide a brief narrative of the suspected association including the name of the medication and the date of starting:

_____

_____

_____

_____

Please refer to the 'CoDe instructions' for definitions and guidelines for the completion of this form

---

Completed by: Name (in print) _____

Position : ☐ Physician ☐ Nurse ☐ Other, describe _____

Directly involved in the medical care of the patient around the time of death? ☐Yes ☐ No

Date (dd/mmm/yy): __ __ - __ __ __ - __ __ **Signature:** _____

*Please note that if any mandatory fields remain empty the CRF will not be registered

Appendix III: Microsoft Access database for CoDe form data entry

Figure s1: Data entry form, page 1

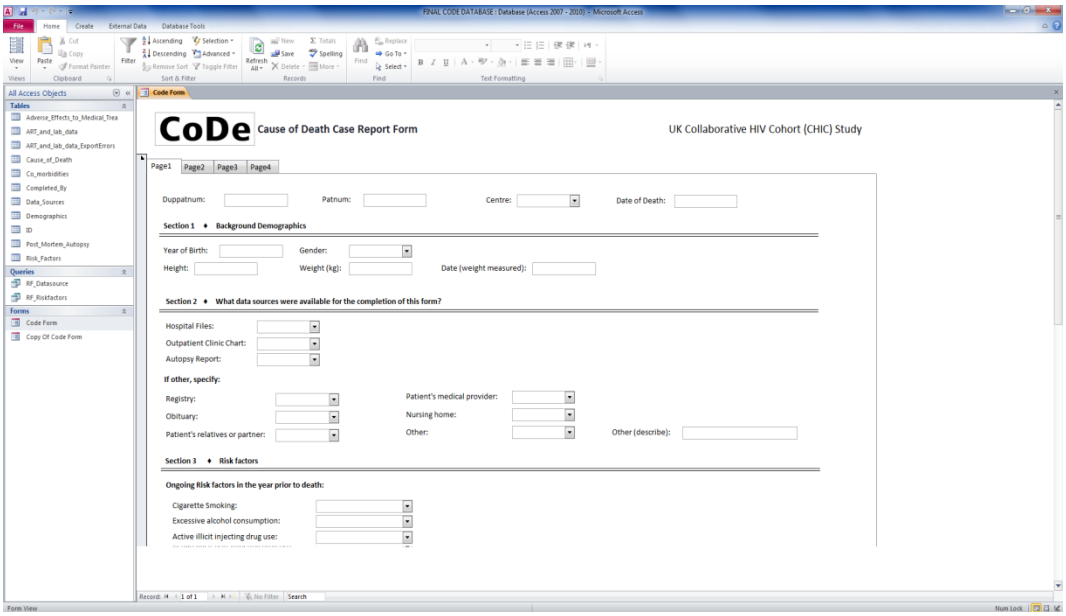


Figure s2: Data entry form, page 2

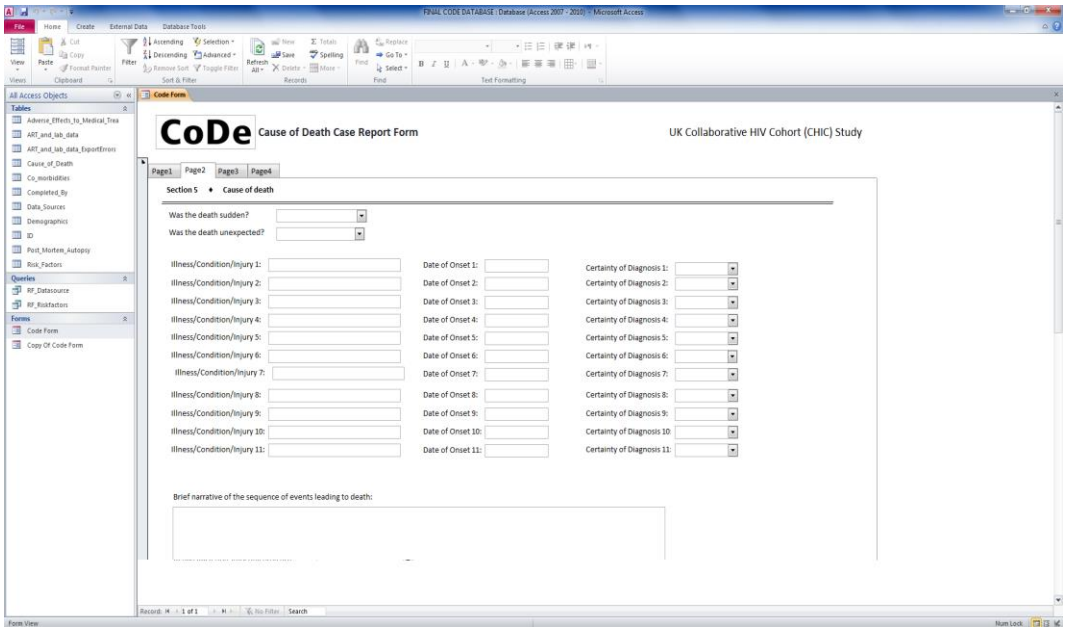


Figure s3: Data entry form, page 3

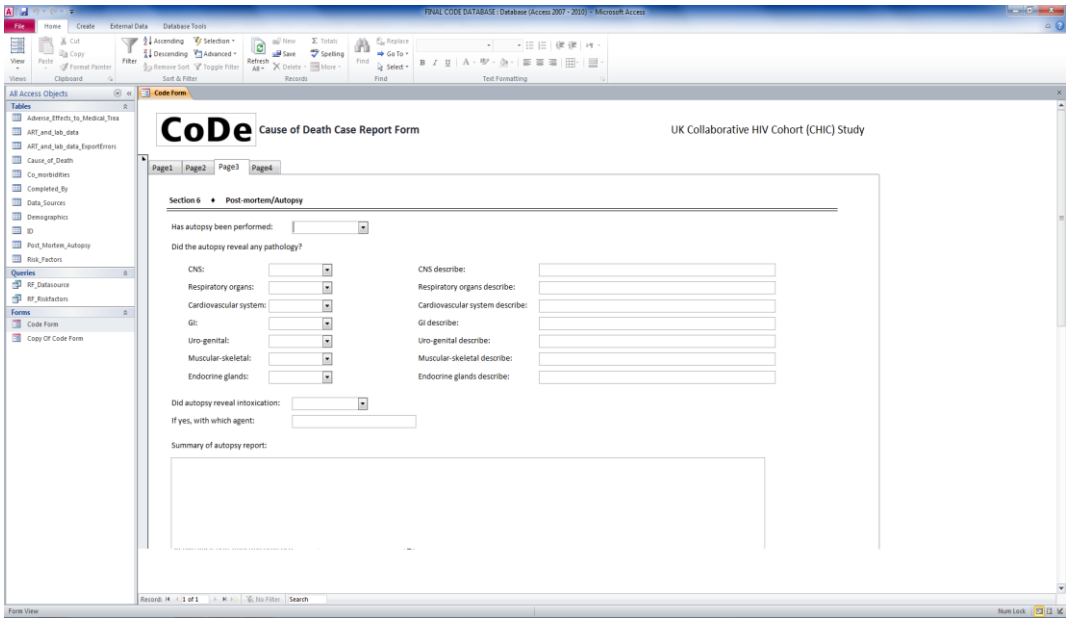
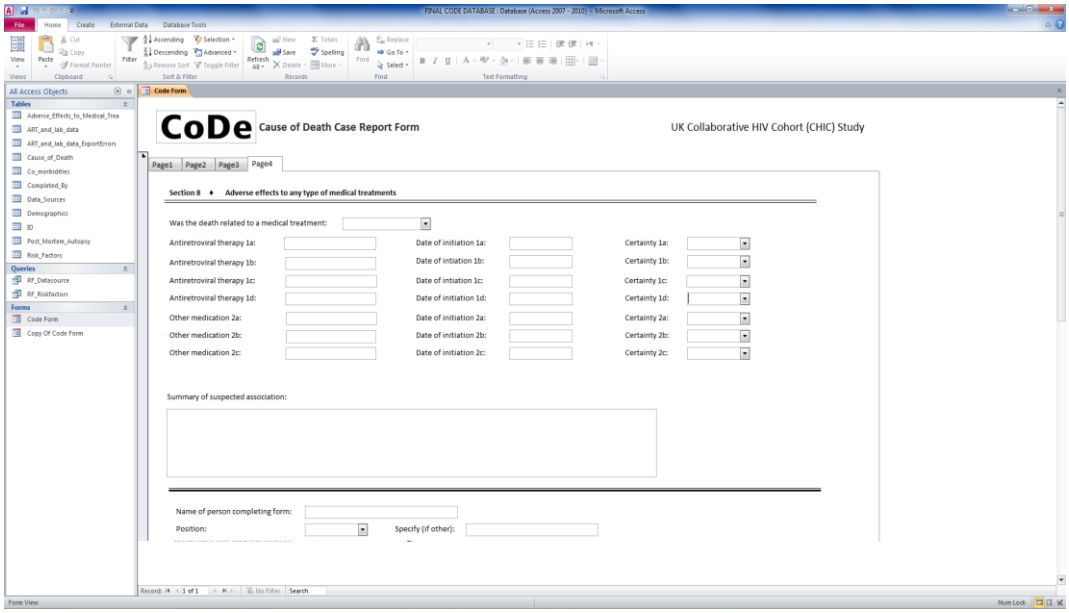


Figure s4: Data entry form, page 4



Appendix IV: Matching score scenarios

Table s1: Possible matching scores and the corresponding combinations of CD4 or viral load match, HANDD linkage score and demographic inconsistencies that could result in each

Score	CD4/VL match	HANDD Linkage score[1]	Demographics
-6	CD4 count OR VL exact match	1	No demographic inconsistencies
-5	CD4 count OR VL exact match	1	Exposure inconsistency
	CD4 count OR VL exact match	1	"Partial" ethnicity inconsistency
	CD4 count OR VL exact match	2,3,4	No demographic inconsistencies
-4	CD4 count OR VL exact match	1	Sex inconsistency
	CD4 count OR VL exact match	1	Ethnicity inconsistency
	CD4 count OR VL exact match	1	Exposure inconsistency and 'partial' ethnicity inconsistency
	CD4 count OR VL exact match	2,3,4	Exposure inconsistency
	CD4 count OR VL exact match	2,3,4	"Partial" ethnicity inconsistency
-3	CD4 count OR VL exact match	1	Sex inconsistency and exposure inconsistency
	CD4 count OR VL exact match	1	Sex inconsistency and 'partial' ethnicity inconsistency
	CD4 count OR VL exact match	1	Ethnicity inconsistency and exposure inconsistency
	CD4 count OR VL exact match	2,3,4	Sex inconsistency
	CD4 count OR VL exact match	2,3,4	Ethnicity inconsistency
	CD4 count OR VL part match	1	No demographic inconsistencies
-2	CD4 count OR VL exact match	1	Sex inconsistency and ethnicity inconsistency
	CD4 count OR VL exact match	1	Sex inconsistency and exposure inconsistency and 'partial' ethnicity inconsistency
	CD4 count OR VL exact match	2,3,4	Sex inconsistency and exposure inconsistency
	CD4 count OR VL exact match	2,3,4	Sex inconsistency and partial ethnicity inconsistency
	CD4 count OR VL part match	1	Exposure inconsistency
	CD4 count OR VL part match	1	"Partial" ethnicity inconsistency
	CD4 count OR VL part match	2,3,4	No demographic inconsistencies

Score	CD4/VL match	HANDD Linkage score[1]	Demographics
-1	CD4 count OR VL exact match	2,3,4	Sex inconsistency and ethnicity inconsistency
	CD4 count OR VL part match	1	Sex inconsistency
	CD4 count OR VL part match	1	Ethnicity inconsistency
	CD4 count OR VL part match	2,3,4	Exposure inconsistency
	CD4 count OR VL part match	2,3,4	"Partial" ethnicity inconsistency
0	CD4 count OR VL part match	1	Sex inconsistency and exposure inconsistency
	CD4 count OR VL part match	1	Sex inconsistency and "partial" ethnicity inconsistency
	CD4 count OR VL part match	1	Ethnicity inconsistency and exposure inconsistency
	CD4 count OR VL part match	2,3,4	Sex inconsistency
	CD4 count OR VL part match	2,3,4	Ethnicity inconsistency
	CD4 count OR VL part match	2,3,4	Exposure inconsistency and 'partial' ethnicity inconsistency
	No CD4 count or VL match	1	No demographic inconsistencies
1	No CD4 count or VL match	1	Exposure inconsistency
	No CD4 count or VL match	1	"Partial" ethnicity inconsistency
	No CD4 count or VL match	2,3,4	No demographic inconsistencies
2	No CD4 count or VL match	1	Sex inconsistency
	No CD4 count or VL match	1	Ethnicity inconsistency
	No CD4 count or VL match	1	"Partial" ethnicity inconsistency and exposure inconsistency
	No CD4 count or VL match	2,3,4	Exposure inconsistency
	No CD4 count or VL match	2,3,4	"Partial" ethnicity inconsistency
3	No CD4 count or VL match	1	Sex inconsistency and exposure inconsistency
	No CD4 count or VL match	1	Sex inconsistency and "partial" ethnicity inconsistency
	No CD4 count or VL match	2,3,4	Sex inconsistency
	No CD4 count or VL match	2,3,4	Ethnicity inconsistency
	No CD4 count or VL match	2,3,4	Exposure inconsistency and 'partial' ethnicity inconsistency
4	No CD4 count or VL match	1	Sex inconsistency and ethnicity inconsistency

Score	CD4/VL match	HANDD Linkage score[1]	Demographics
	No CD4 count or VL match	2,3,4	Sex inconsistency and exposure inconsistency
	No CD4 count or VL match	2,3,4	Sex inconsistency and "partial" ethnicity inconsistency
5	No CD4 count or VL match	2,3,4	Sex inconsistency and ethnicity inconsistency
	No CD4 count or VL match	2,3,4	Sex inconsistency and exposure inconsistency and 'partial' ethnicity inconsistency
6	No CD4 count or VL match	2,3,4	Sex inconsistency and ethnicity inconsistency and exposure inconsistency

[1]Linkage score proved by PHE based on fields matched in linkage process

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