Engagement in health care in young people living with perinatal HIV

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Statement of own work

I, Marthe Sophie Elise Le Prevost, 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.

Signed: Marthe Le Prevost Date: 3rd June 2021

Abstract

Evidence suggests that engagement in care (EIC) may be worse in young people with perinatal HIV (PHIV) than in adults or children living with HIV. However, there is no consensus on how best to measure EIC; and most studies use a simplistic definition based on number of clinic visits attended per year and examine limited predictors of EIC.

In this thesis, I took an existing EIC algorithm for adults living with HIV in England, and adapted it to young people with PHIV in the Adolescent and Adults Living with Perinatal HIV cohort (AALPHI), using data from 2013-2015. A wide range of potential predictors of EIC from the AALPHI dataset were explored in logistic regression models (allowing for clustered data). Predictors of EIC identified in the quantitative analysis were then explored in focus groups with young people with PHIV to help contextualise the findings and to explore if they resonated with the experiences of young people themselves.

Of 3,585 months of total follow-up in 306 young people, 3,126 (87%) person-months were classified as engaged in care. Multivariable predictors associated with poorer odds of being engaged in care were: baseline viral load >50c/mL vs. viral load ≤50c/mL; Asian/mixed ethnicity vs. black ethnicity; ever self-harmed vs. not; self-assessed adherence as bad/not so good/not on ART vs. good/excellent. Findings from the focus groups support and expand the quantitative results. Young people described actively choosing when to and when not to attend clinic depending on what they thought their viral load was or to hide non-adherence and self-harm.

My adapted algorithm provides a more sensitive method to measure EIC in young people with PHIV. Identifying which young people are less likely to engage in care may allow targeted interventions to support young people to attend clinic and optimise their health outcomes. Findings from the focus groups provide a much broader understanding of the social meaning of EIC.

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Table of contents

List of figures

List of tables

Frequently used abbreviations

AALPHI	Adolescents and Adults Living with Perinatal HIV cohort
Adolescents	10-19 years of age
AIDS	Acquired Immune Deficiency Syndrome
ALSPAC	Avon Longitudinal Study of Parents and Children
ART	Antiretroviral Therapy
AUDIT	Alcohol Use Disorders Identification Test
BHIV	Behaviourally acquired HIV
BHIVA	British HIV Association
CASI	Computer-assisted self-interviewing
cART	Combination Antiretroviral Therapy
CD4	Cluster of differentiation 4 (a glycoprotein found on the surface of immune cells)
CDC	Centers for Disease Control and Prevention
CHIPS	Collaborative HIV Paediatric Study
CRF	Case report form
EIC	Engagement in care
GEE	Generalized Estimating Equations
GUM	Genitourinary Medicine
HADS	Hospital anxiety and depression scale
HIV	Human Immunodeficiency Virus
HIV affected	HIV negative but born to a mother with HIV or living in a household with HIV
IDACI	Income Deprivation Affecting Children Index
IQR	Interquartile Range
LSHTM	London School of Hygiene and Tropical Medicine
LTFU	Loss to follow-up
MRC	Medical Research Council
NATSAL	National Survey of Sexual Attitudes and Lifestyles
NRTI	Nucleoside reverse transcriptase
NNRTI	Non-nucleoside reverse transcriptase
NPZ	Neuropsychological test composite z score
OR	Odds Ratio
PENTA	Paediatric European Network for Treatment of AIDS
Perinatal HIV	Perinatally acquired HIV
PHIV	Perinatal HIV
PI	Protease inhibitor
PR	Prevalence Ratio
SD	Standard Deviation
UCL	University College London
UNAIDS	Joint United Nations Programme on HIV/AIDS
UNICEF	United Nations International Children's Emergency Fund
USA	United States of America
WHO	World Health Organization
Young adults	19-24 years of age
Young people	Combination of adolescents and young adults (10-24 years old)

Chapter 1.Introduction

Engagement in care (EIC) is increasingly being recognised as a crucial step in improving the outcomes of patients with human immunodeficiency virus (HIV) (1–4) and lowering healthcare costs (4) and is therefore a desirable public health goal. Between 2000-2015, people living with HIV aged 10-19 years were the only age group whose mortality increased.(5,6) Therefore, improving engagement in care in this group, and health outcomes, is a priority.

This thesis describes my doctoral work on EIC in young people with perinatal HIV (PHIV), in which I took both quantitative and qualitative approaches. The quantitative data for this analysis was from the Adolescents and Adults Living with Perinatal HIV (AALPHI) cohort. AALPHI was a prospective cohort study of young people with PHIV, and HIV negative but HIV-affected young people, and it investigated the impact of life-long antiretroviral therapy (ART) on a range of health areas. The rich dataset available in AALPHI enabled me to investigate a wide range of exposures potentially affecting EIC. Given some of the unique difficulties many young people in this population subgroup face compared to other young people in the UK, it is crucial these factors are taken into consideration when examining EIC. Having access to data from the AALPHI study has therefore been a key strength of my approach.

I complemented these quantitative data by employing a qualitative approach, with the aim being to examine EIC in young people through qualitative understanding of the cohort themselves. Combining the quantitative results from the rich AALPHI dataset with qualitative research has ensured that the thesis is focused on the young people themselves and provides contextual analysis to the findings.

In this chapter, to set the scene for the focus of my PhD, I give overviews of:

- HIV clinical science and antiretroviral therapy
- the clinical epidemiology of HIV in children
- survival into adolescence and transition to adult care
- complexities of clinical management of young people with perinatal HIV
- engagement in care,

all with a focus on high and high middle income countries.

I then introduce:

- the data sources for my PhD
- the aim and objectives of my PhD

- the thesis overview and structure
- my role as the PhD candidate
- ethics and funding.

EIC in young people is not reviewed in detail here as it is the focus of the literature review.

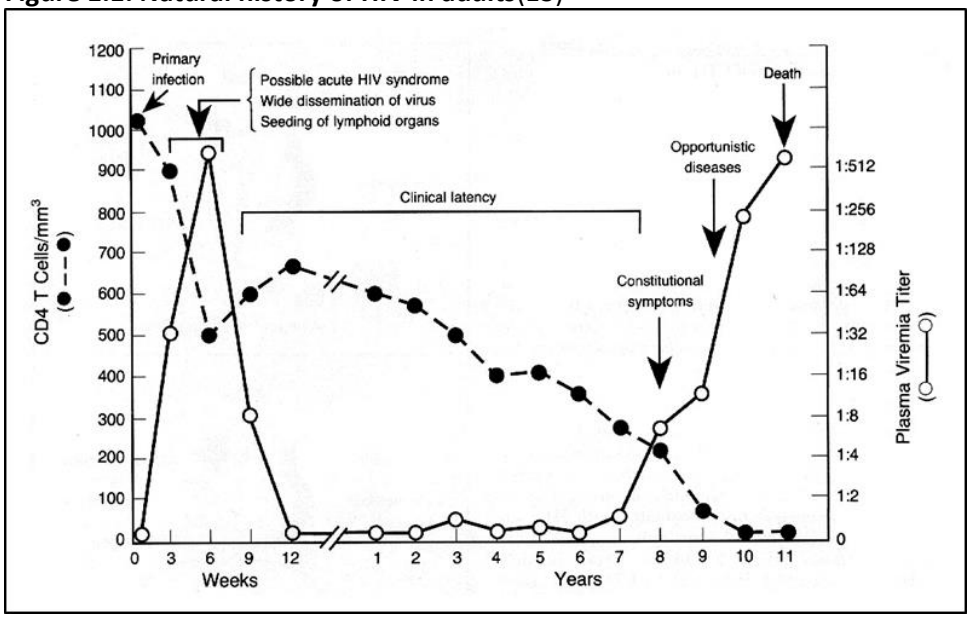
1.1. HIV clinical science and epidemiology

HIV was first identified it the early 1980s when small clusters of previously healthy men started presenting with rare infections such as *Pneumocystis carinii* pneumonia (now known as Pneumocystis jirovecii) and Karposi sarcoma in the USA.(7,8) These initial cases were noteworthy due to the rarity of the infections, that they only occurred in men who had sex with men, and because mortality was so high. In the following months, cases began to be reported in other population groups such as people who inject drugs,(9) blood product recipients (10) and children.(11)

HIV is a retrovirus that is transmissible through blood and other bodily fluids, and modes of acquisition include sexual contact, parenternally, perinatally or through breast milk. All retroviruses need a host cell in order to replicate, and in the case of HIV, these are primarily CD4 lymphocyte cells, also called CD4 cells. These CD4 cells are an essential part of the immune system coordinating the body's response to infection. Once HIV integrates itself into the host CD4 cell, the virus then uses the CD4 cell to replicate more copies of HIV and eventually causes the destruction of the host CD4 cell.(12)

The natural history of HIV in adults is shown in Figure 1.1. Not long after primary infection,

Figure 1.1: Natural history of HIV in adults(13)



there is a rapid rise in HIV plasma viremia during which individuals can have a seroconversion illness (acute HIV syndrome) with flu-like symptoms.(14) During this time, viral reservoirs are also established. This is when HIV infects cells that are more stable and inactive compared with the main replicating virus.(15) After the initial peak in which the viral load (the term used to describe the number of copies of HIV per millilitre of blood, copies/mL) can rise to over 1 million copies/mL, the viral load slowly declines to a steady set point probably after specific antibody has developed.(14) This period of 'clinical latency' can last for a number of years, and is generally characterised by asymptomatic disease. However, over time, there is a steady depletion of CD4 cells, weakening the individual's immune system and leaving them susceptible to infections.(16) Once the CD4 cell count drops to <200 cells/µL, opportunistic infections (such as Pneumocystis jirovecii pneumonia, cerebral toxoplasmosis, cryptosporidium/microsporidial diarrhoea, oesophageal candidiasis) or HIV malignancies (Kaposi sarcoma, aggressive B-cell non-Hodgkin lymphoma, and cervical cancer) can develop.(16,17)

For adults and children, CD4 cell counts and plasma viral load are used as markers of the effectiveness of ART. CD4 cell count is used as an indicator of the risk of developing acquired immune deficiency syndrome (AIDS) defining illnesses. (16,18,19) The amount of virus in the plasma is not only a contributing factor to CD4 cell decline,(16) but it is also an independent predictor of morbidity and mortality.(20) The goal of all antiretroviral therapy is to reduce the HIV viral load to a level at which it is 'undetectable' on an assay measurement. A viral load is commonly considered to be undetectable when it is ≤50 copies/mL (c/mL), despite recent developments that mean many current assays used are more sensitive and can detect virus below this cut-off.

This reduction in viral load and subsequent CD4 cell count improvement is achieved with combination ART (cART). ART is used to prevent the replication of HIV in the CD4 cell and reduce the amount of virus circulating in the blood. Although ART can reduce the virus in the blood, viral reservoirs are more persistent and so ART therapy cannot cure HIV.(15) However, the reduction in viral load to ≤50c/mL delays disease progression by preventing further damage to the immune system and allowing immune reconstitution. It also prevents transmission of the virus to other people.(21)

There are now 30 HIV treatments in six major drug classes. Different HIV drug classes prevent viral replication at different stages of the replication cycle. The first drug to be licensed by the US Food and Drug Administration (FDA) in 1987 was zidovudine, from the nucleoside reverse transcriptase inhibitors (NRTIs) class.(22) Zidovudine works by inhibiting the synthesis of viral RNA to DNA by blocking the reverse transcriptase enzyme. Zidovudine was initially given as monotherapy, and soon after other NRTIs were developed, enabling dual therapy, which was more effective at

suppressing virus. However, despite initial optimism it soon became apparent that monotherapy and dual therapy were insufficient. Due to high viral replication, HIV has a high rate of genetic error and subsequent high genetic heterogeneity. The virus responds to the host environment and selects the quasispecies that can dominate and survive. Therefore, a sufficiently potent drug combination is required to quickly stop replication so that the virus cannot mutate and select a strain that can survive in the presence of those drugs, thus causing drug resistance.(23)

The development of two new classes of drugs, protease inhibitors (PIs) and non-nucleotide reverse transcriptase inhibitors (NNRTIs) in the late 1990s meant that potent combinations of ART were available, now called "cART". Initial combinations included a backbone of two NRTI drugs with a choice of third agent from the PI or NNRTI drug classes. Three more classes of drugs have been developed in recent years: entry inhibitors (EIs); integrase inhibitors (IIs); and CCR5 inhibitors. More recent guidelines still recommend an NRTI backbone, and the preferred third agent is now either an II, boosted PI or NNRTI, for adults and children.(24–27)

The initiation of treatment was previously based on immunological and clinical criteria. Then in 2013 findings from the Children with HIV Early Antiretroviral Therapy (CHER) trial in South Africa (28) of infants with HIV changed HIV treatment guidelines, and now rapid initiation of cART is recommended for all infants and children at diagnosis. Following this, in 2015, treatment guidelines for adults worldwide were changed based on the results of the Strategic Timing of AntiRetroviral Treatment (START) and the Early Antiretroviral Treatment and/or Early Isoniazid Prophylaxis Against Tuberculosis in HIV-infected Adults (TEMPRANO ANRS 12136) trials. These established that there were substantial benefits to starting cART immediately after diagnosis rather than based on immune markers.(29,30) Due to these advances in the treatment of HIV, adults who start ART with a CD4 >350 cells/µL have a life expectancy similar to that of the general population.(31)

There are three main paediatric HIV guidelines used globally. The Paediatric European Network for Treatment of AIDS (PENTA) guidelines for treatment of paediatric HIV-1 infection are used in Europe;(27,32) the U.S. Department of Health and Human Services Guidelines for Use of Antiretroviral Agents in Pediatric HIV Infection are used in the USA;(26) and World Health Organization Consolidated Guidelines on the Use of Antiretroviral Drugs for Treating and Preventing HIV Infection,(33) are used in low and middle income countries.

Table 1.1: Licensed antiretroviral drugs in 2020

Drug class	Drug	Year of approval
Nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs)		
NRTIs inhibit the synthesis of viral RNA to DNA by blocking the reverse transcriptase enzyme	Zidovudine (AZT)	1987
	Didanosine (ddI)	1991
	Zalcitabine (ddC)	1992
	Stavudine (D4T)	1994
	Lamivudine (3TC)	1995
	Abacavir (ABC)	1998
	Tenofovir disoproxil fumarate (TDF)	2001
	Emtricitabine (FTC)	2003
	Tenofovir alafanamide fumerate (TAF)	2016
Non-nucleoside reverse transcriptase inhibitors (NNRTIs)		
NNRTIs inhibit the synthesis of viral RNA to DNA by binding to and altering the reverse transcriptase enzyme	Nevirapine (NVP)	1996
	Efavirenz (EFV)	1998
	Etravirine (ETR)	2008
	Rilpivirine	2011
	Doravirine (DOR)	2018
Protease inhibitors (PIs)		
PIs bind to the vial protease enzyme preventing the processing of viral proteins	Saquinavir hard gel (SQV)	1995
	Indinavir (IDV)	1996
	Ritonavir (RTV)	1996
	Saquinavir soft gel (SQV)	1997
	Nelfinavir (NFV)	1997
	Amprenavir	1999
	Lopinavir/ritonavir (LPV/r)	2000
	Atazanavir (ATZ)	2003
	Fosamprenavir	2003
	Tipranavir (TPV)	2005
	Darunavir (DRV)	2007
Entry inhibitors (EIs)		
Entry inhibitors block HIV from entering the CD4 cells of the immune system.	Enfuvirtide (T20)	2003
Integrase inhibitors (IIs)		
Integrase inhibitors bind to the viral enzyme integrase, interfering with the incorporation of reverse-transcribed HIV DNA into the host cell	Raltegravir (RAL)	2007
	Dolutegravir (DTG)	2013
CCR5 inhibitor s		
CCR5 inhibitors prevent the entry of HIV into the CD4 cell by blocking the CCR5 receptors	Maraviroc	2007

1.2. Clinical epidemiology of HIV in children

1.2.1. Clinical epidemiology of HIV in children in low and middle income countries

In 2019, the global total number of children living with HIV aged 0-14 years of age was estimated to be 1.8 million.(34) The vast majority of children and young people with HIV are living in low- and middle-income countries, with 88% in sub-Saharan Africa.

The predominant mode of HIV acquisition for most children is vertical transmission either in utero, intrapartum or through breastfeeding. Without ART, the risk of HIV vertical transmission is between 15-30%, with an additional risk of 10-25% from breastfeeding, depending on duration.(35) The roll out of ART to pregnant and breastfeeding women living with HIV has seen the global annual number of children with HIV halve since 2010.(36). However, there were still an estimated 150,000 new annual infections in children in 2019.(34)

Disease progression is much more rapid in children than adults. In sub-Saharan Africa around 50% of infants who acquire HIV perinatally and 25% of infants who acquire HIV during breastfeeding will die before the age of two years if they do not receive ART.(37) Mortality can be reduced by 75% if cART is started in the first three months of life, making early diagnosis and timely initiation of ART in infants crucial.(38,39)

Due to this very high mortality risk in infancy and childhood, prevention of vertical transmission of HIV has been a focus of many global health programmes. In 2011, the Global Plan Towards the Elimination of New HIV Infections was launched, and included the goals to eliminate new infections in children to <5% in countries where women breastfeed, and <2% in countries where women do not breastfeed, and focusing efforts on 22 countries that together accounted for 90% of new paediatric infections.(40) In the 2015 Progress Report on the Global Plan,(41) it was reported that there was a 48% decrease in the number of new HIV infections in children between 2009-2014, compared to a decrease of 13% between 2000-2008. However, although vertical transmission fell from 28% in 2009 to 15% in 2014, this was still much higher than the goal of <5%.

A recent Joint United Nations Programme on HIV/AIDS (UNAIDS) review of 56 countries, which together accounted for 87.5% of the global burden of HIV, and 87% of new infections, compared vertical transmission in higher prevalence (≥4.5%) and lower prevalence (<4.5%) countries.(42) Vertical transmission rates were higher in countries classified as low prevalence compared to high prevalence. Many high prevalence countries have been the focus of targeted support, which may account for their greater reductions.

In 2019, only 53% of the estimated 1.8 million infants and children aged 0-14 years of age living with HIV were diagnosed and on cART.(34) A major problem for children with HIV globally, and especially in low and middle income countries, is the research and development time lag for paediatric formulations compared to adults.(43,44) For infants under two years of age, only a quarter of the antiretroviral products approved by the FDA or European Medicines Agency (EMA) for adults are available for children.(44)

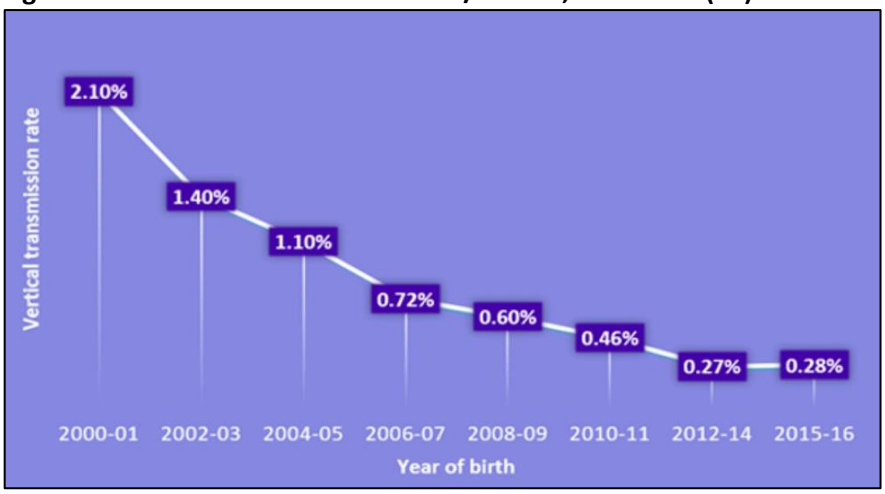
Treatment in children is more complicated than in adults because children are continually growing, and their metabolism changing, and therefore dosage needs regular revision. Children also need to take ART for longer than adults. Historically there were huge problems with the palatability of ART and practical issues for families who had to carry large quantities of liquids for long distances, if they lived far away from their HIV clinic.(36) Improvements in drug formulations have been made more recently, with some fixed dosed tablet and dispersible sprinkles formulations becoming more commonly, which facilitates transportation, storage and administration.(36)

Overall, annual HIV related deaths in children have fallen from 300,000 in 2000 to 95,000 in 2019, largely due to prevention of vertical transmission.(45) However the burden of HIV remains significant and globally HIV is the 14th cause of Disability Adjusted Life Years (DALY, the sum of years of potential life lost due to premature mortality and the years of productive life lost due to disability) in children aged 0-9 years.(46) Furthermore, estimates of both infant diagnosis and the number of infants and children on ART fall short of the UNAIDS 90-90-90 treatment targets for 2020 that aimed to achieve 90% of people living with HIV to be aware of their status, 90% of all diagnosed people to be on ART and 90% people on ART to be virally suppressed.(47) Although there have been many successes in the fight against HIV for infants and children, infant diagnosis and access to ART among infants and children remains a huge challenge in low and middle income countries.

1.2.2. Clinical epidemiology of HIV in children in high income countries

Prevention of vertical transmission of HIV has been a success story in Europe, and in 2018, less than 1% of new infections were due to vertical transmission.(48) In the UK, vertical transmission rates have continued to fall and by 2015-2016 had declined to 0.28% among a total of 20,111 live births (Figure 1.2).(49) In the USA, vertical transmission has declined from 2.6 per 100,000 in 2010 to 1.3 per 100,000 in 2015.(50) However, this varies by ethnicity, with 5.4 per 100,000 in black/African American women to 0.4 per 100,000 in white women.

Figure 1.2: Vertical transmission in UK/Ireland, 2000-2016(49)



Early studies from Europe and the USA described substantial health improvements following the introduction of cART regimens in children living with HIV. In 2001, the Pediatric AIDS Clinical Trials Group Protocol 219 (PACTG 219) cohort reported findings from 1,028 children and young people with perinatal HIV (PHIV) aged <20 years, of whom 73% were receiving cART. There was a 67% reduction in mortality irrespective of sociodemographic factors or CD4 cell count. Similarly, in 2003, an analysis from the CHIPS cohort in the UK reported on health outcomes of 944 children, with median age 5.7 (range 0.0-18.6) years. Since the introduction of cART mortality had fallen 80%, progression to AIDS 50%, and hospital admission 80%.(51)

Long-term trends in mortality and AIDS defining events have also been investigated in cohorts in high income countries. A pooled analysis of 3,526 children and young people from Europe and Thailand,(52) all of whom had initiated cART, reported outcomes a median of 5.6 (2.9, 8.7) years after cART start. Although mortality rates initially declined rapidly when cART was introduced in 1996, since 2006 mortality rates remained low but unchanged. Five year survival was 97.6%, however mortality rates for 0-14 year old PHIV living in Europe were 3-12 times higher than in the general European paediatric population. Half of the deaths (46%) occurred in the first 6 months of commencing cART, highlighting the importance of early diagnosis and timely cART initiation.(52)

1.2.3. Epidemiology of HIV in children in the UK

In the UK, children diagnosed with PHIV are followed throughout paediatric care in the Collaborative HIV Paediatric Study (CHIPS), a cohort with almost complete national coverage. To the end of March 2020, 2,210 children had been reported to CHIPS.(53) Of the 547 children and young people still alive and in active follow-up in 2020, half (57%) were female, 52% were born in the UK or Ireland, and 74% were black African.(54) In total, 124 children were known to have died

(104 prior to 2008) and 1,324 (60%) had left paediatric care and transitioned to adult care.(53) In the UK, almost all children and young people with perinatal HIV initially receive their HIV care in paediatric HIV services and then transition to adult HIV services (adolescent-specific or HIV in Genitourinary Medicine (GUM)) at a median age of 17 years.(55)

Of children with follow-up data available since January 2018 (n=514), 1% were ART naive, all of whom were ≥10 years of age, 97% were on a ≥3 drug regimen of whom 78% were on a fixed dose combination, and 47% were on an integrase-based regimen. Immunologically, 80% had a CD4% ≥25% and 81% had a viral load <50c/mL.(54)

1.3. Survival into adolescence and transition to adult care

The availability and extensive use of ART and success in the prevention of vertical transmission in high income countries has changed the epidemiology of paediatric HIV, with increasing numbers of children with perinatal HIV surviving in to adolescence and young adulthood.(56) This has resulted in an ageing paediatric cohort with more than half of the perinatal HIV population now in adolescence and transitioning to adult care.(54,57,58) However, transition to adult care is a vulnerable time for young people with HIV, who are not only transferring their healthcare but also becoming young adults. Rapid brain development that occurs during adolescence is characterised by considerable behavioural and psychosocial change.(59,60) This dynamic process is especially challenging due to the substantial social and economic transformations young people experience in the same period as they transition from childhood to adulthood.(60,61)

There is now considerable recognition at a global policy level of the importance of investment and support in young people in order for them to achieve their full potential in adulthood.(62–64) Ensuring that young people are appropriately supported during adolescence is crucial to encourage the establishment of good habits of self-management that underpin health and wellbeing in adulthood in general,(62,65) but even more so when they are growing up with a chronic condition such as HIV. Long-term follow up in this vulnerable group is crucial but hampered by a number of factors. Very few national surveillance studies exist and of the studies that do exist, they do not always span paediatric as well as adult care, or stratify data by age or mode of HIV acquisition.(5) These programmatic changes are essential steps to facilitate monitoring of outcomes for young people, so that appropriate interventions and support can then be put in place to help them thrive into adulthood.(5)

1.4. Complexities of clinical management of young people with PHIV

Increased survival of children with PHIV has changed the nature of problems faced by this group as they age. New and interrelated issues result from complications of long-term management of HIV, as well as psychosocial factors.

1.4.1. HIV-related clinical outcomes

Studies from the USA and Europe have found that as children with PHIV age into adulthood, they are at increased risk of unsuppressed viral load and immunosuppression,(66) with CD4 declining even before transition to adult care.(67) Associated with this, while the incidence of HIV-related opportunistic and bacterial infections has generally declined in the cART era, non-infectious conditions related to long-term HIV and cART have emerged in young people. Metabolic complications (dyslipidaemia and insulin resistance) and changes in fat distribution (lipoatrophy and lipohypertrophy) associated with ART toxicities have been reported in children and young people with PHIV on cART.(32,68)

There is increasing evidence that like adults, children with HIV experience ongoing immune activation even when fully suppressed on cART.(32) Although it is not clear what the consequences of this will be long-term, there are concerns that it may result in cardiovascular risk, neuroinflammation and increased risk of malignancy in adulthood.(32,69) Chronic bone disease is also an increased risk in children with PHIV, possibly resulting in premature osteoporosis and fractures. It is thought that this risk is from ART toxicities (in particular TDF) and low grade immune activation(69). Chronic renal disease risk is increased in children with PHIV even without traditional risks such as hypertension and type 2 diabetes.(68,69) Chronic renal disease has been associated with TDF use and some protease inhibitors but HIV-induced immune activation may also play a part. As children with PHIV transition to adolescence it is essential that they continue to be monitored for risks of non-communicable diseases, comorbidities and complications.(69)

There is growing awareness of the increasing number of deaths in young people with PHIV. Data from the PACTG 219C and International Maternal Pediatric Adolescent AIDS Clinical Trials Network (IMPAACT) P1074 cohorts in the USA were combined to assess the effect of long-term cART on young people with HIV (87% PHIV) between 2004 -2007.(70) In total 1,201 young people were included in the analysis with a mean age of 20.9 (SD 5.4) years at last interview. Although mortality in this time period was lower than in the pre-cART era, excess mortality remained at 31.5 times that of the USA general population, and similar findings have been reported in other studies from the USA and the UK.(66,71) While HIV associated opportunistic infections were uncommon, most deaths (86%) remained HIV related. Deaths were associated with poor HIV control and were more

likely to occur in older patients who were off cART with a lower CD4 cell count and higher viral load.(70)

1.4.2. Family

Growing up with PHIV is different to many other chronic conditions because of the multigenerational context, with a child with HIV usually having acquired it from their mother. This can pose problems around the stigma of both horizontal and vertical transmission within the family,(72) and it also means that children may grow up in a household with parents who have previously been unwell or are still suffering physical or mental health disabilities and/or ill-health related to HIV.(73,74) Furthermore, many young people have experienced the death of one or both parents, and subsequent multiple transitions between different carers.(75,76) In the USA, many children living with PHIV are born into families affected by parental psychiatric and substance abuse disorder, violence and neighbourhood disruption;(73,77,78) in contrast, children in Europe are commonly from ethnic minority migrant families, some with immigration concerns, and often residing in disadvantaged areas.(32)

1.4.3. HIV naming, stigma, secrecy, and onward disclosure

HIV naming to children (the first step in a process in which a child is told that they have HIV) is recognised as a process that occurs overtime. Recommendations on how this is carried out have also changed over time. When paediatric HIV was first discovered, children had very high morbidity and mortality, and parents/carers and healthcare staff were understandably concerned about talking to children about their HIV.(79) In addition, many children were too young to engage in discussion about HIV, so conversations were delayed until they were older. However, since prognosis in children living with HIV has improved, the importance of knowing their HIV status has changed, and the focus around HIV naming is now framed around a child's right to know their status.(80) In light of these developments, it is now advised that children are given accurate information about their health from an early age, and that this knowledge is incrementally built upon so that HIV is named when children are of school age (defined as between 6 and 12).(81)

In the past, many parents/carers had an understandable but misplaced concern that HIV disclosure would cause distress in their child.(81,82) Parents/carers also reported feeling ill-equipped for the consequences of naming HIV to their child, and in some instances also revealing their own HIV status, and this led to a desire to delay the disclosure process.(82–84) However, there is little evidence of harm from talking to children and naming HIV.(81) Furthermore, delayed disclosure has also been associated with negative psychological consequences for young people; when asked about HIV disclosure, some report that they were already aware that they had HIV

before it was named; others may construct their own narratives in the absence of open discussion.(80,85,86)

Unfortunately, the complexities of HIV disclosure and stigma often continue beyond the naming of HIV. Children and young people's experience of stigma within their family and the wider world is unique because it is experienced through silence.(87) Following disclosure of their HIV diagnosis, there is often very limited discussion of HIV within the family.(80) Attempts to ask questions about HIV can be closed down and conversations limited to medicalised talk around ART and previous illness stories, which are used to incentivise treatment adherence.(88,89) Children and young people therefore may experience HIV naming as a single event rather than an ongoing supportive process.

As young people move into adolescence and young adulthood, it can be very challenging for them to negotiate independent friendships and sexual relationships. Young people with PHIV may go to great lengths to keep their diagnosis secret.(90,91) Onward disclosure could have a number of potential benefits such as improved adherence, more frequent condom use, and improved wellbeing.(92) However, there are also barriers to onward disclosure. One of the concerns for young people when considering onward disclosure of HIV status is the risk of inadvertently revealing their mother's or the wider family's HIV status at the same time, and equally they may also face resistance about disclosing their status to others from their parents.(91) Young people also may choose to continue to keep their HIV status a secret for fear of isolation and rejection from peer groups and partners.(91)

In the AALPHI cohort in the UK, of 261 young people with PHIV with a median age of 16 [IQR 15, 18] years, 22% of the participants had told no one about their HIV and 31% had only told one or two people.(93) In a study from the USA examining sexual risk behaviour in young people with PHIV, of 67 active young people with information about their disclosure to sexual partners, 33% told their first partner their HIV status.(94)

1.4.4. Adherence to ART

Children face decades, if not a lifetime of taking cART. Adherence to these medications poses multiple challenges for young people. Adherence to cART may be complicated by young people's lack of autonomy and importance of the child-caregiver relationship for their medication adherence.(95) Suboptimal adherence in adolescence is not a unique problem to HIV and there are reports that adherence declines during adolescence across other chronic infections.(90,96,97) However, adherence in young people with PHIV is even more complex with research suggesting a

complicated interplay of individual,(93,98,99) familial,(73,74) structural (100) and ART (90,93,99) related factors.

Despite the discrepancy in adherence prevalence, a number of studies have consistently reported lower adherence in young people compared to adults and children (99,101–103) which is particularly concerning due to the extra years of treatment young people with PHIV face. A recent study analysed 1,190 self-reported adherence questionnaires completed by 379 young people aged 8-22 years, with a median of 3.3 years follow-up.(99) Prevalence of adherence declined with age with 69% adherence in 8-12 year olds and 50% in 18-22 year olds (p=<0.001).

An important aspect of adherence that emerges from qualitative studies is around patient experiences of managing long term ART and dialogue about adherence to ART in the clinic environment. In two large longitudinal qualitative studies, 147 children and young people with PHIV were interviewed as part of two large clinical trials. The interviews took place with children from Uganda, Zimbabwe, the UK and the USA.(104) Young people reported being frustrated about how little recognition there was from healthcare staff about the complexity of taking medication. When young people did report missed doses they were often scolded, and they felt that adherence was presented to them as a 'choice'. Consequently, young people described that they often withheld information about missed doses. This then results in lost opportunities for advice and support to be given to young people to help overcome adherence problems. An acknowledgment of how HIV disrupts adolescence is needed to provide young people with appropriate support.(104,105)

1.4.5. Mental health

Young people with PHIV may face an increased burden of mental health problems compared to other adolescents due to the complex mix of psychosocial issues and biomedical factors already described. Despite the reduction in severe cognitive complications since the advent of cART, many children may still experience mild cognitive deficits that can affect their quality of life, social relations and educational and employment outcomes.(106,107) Most of the earlier research examining mental health was from larger studies in the USA. There is a large range in prevalence of mental health issues reported across the studies, between 25-70%.(78,108–111) This broad range is likely to be due to between-study variation, with different ages at which young people were recruited, differences in scales used to measure different aspects of mental health problems, and differences in the person completing the assessment (young person or child vs caregiver). Studies predominantly found higher prevalence of mental health problems in young people with PHIV than the general population or other vulnerable populations, but similar levels to HIV

negative but HIV affected comparators.(73,109,111–113) Additionally, many studies' findings highlighted the important effect of contextual factors, such as age, gender, cognitive function, parent physical and mental health, and life stressors, on mental health, rather than HIV clinical factors such as viral load and CD4.(109,113–115)

However, it is important to note that many of these studies may include the first generation of survivors of PHIV who may be more likely have complex treatment histories. Furthermore, many of these studies have been carried out in the USA, where young people are exposed to different socioeconomic problems, such as parental drug use,(116) and with very different health and support provision compared to Europe and the UK.

1.5. Engagement in HIV care

1.5.1. Importance of engagement in care

As has been shown, cART has substantially improved mortality and morbidity in adults and children living with PHIV. However, for these benefits to be realised, people need to first be diagnosed with HIV, and secondly engaged in care. These steps form the first part of most HIV cascades of care. The cascade of care is a tool used for local, national and international benchmarking of treatment progress, tracking the sequential stages of healthcare that people with HIV need to go through between diagnosis of HIV and achievement of viral suppression.(117) Studies have found increased viral suppression and improved CD4 cell count in patients who have higher EIC.(118,119) Similarly missed visits have been associated with higher viral load.(120) In addition, studies have found that transmission of HIV is more frequent in people who are not engaged in care,(121) and higher EIC has been associated with lower healthcare costs.(4,122,123)

While younger children and older adults with HIV continue to see improved mortality on the cART era, young people are the only age group to be experiencing increasing HIV mortality.(5,119,124–132) A number of studies have found that young people have worse EIC when compared to adults and children.(118,133,134) A UK population study of 72,218 adults with HIV, including an undefined number of young people with PHIV, examined loss to follow-up in patients attending adult HIV services. Patients most likely to lost to follow-up, defined as no further follow-up or presence of a death certificate, were black African, aged 15-34 years, not on ART, and having acquired HIV outside the UK.(135) In a study of 87,146 people living with HIV from all age groups in New York, a u-shaped relationship between age and EIC was shown, with young people aged 20-29 years with the lowest EIC across the whole age spectrum.(133)

Thus, EIC results add to the evidence that young people living with HIV should be considered a vulnerable group. Findings point to the need for investment in research and interventions, to find sustainable ways of improving EIC in this group, to that they can fully benefit from HIV treatment programs.

1.5.2. Definition of engagement in care

Measuring EIC is complex, and there is no standard definition of this indicator, resulting in EIC being measured differently across different studies. The most common EIC measures are appointment adherence, gaps in care, visit constancy (visits at define intervals), and hybrids of these methods.(136–138) However, there is huge inconsistency in these definitions, in terms of the types of visits to be considered as either missed or attended (e.g. appointments with the doctor, nurse, psychologist or phlebotomist), the minimum amount of time considered between appointments (e.g. 1 visit in 6 months or 1 visit in 1 year).(136) There is also no consensus on what level of EIC is good enough, and further research is needed to understand the relationship between different EIC thresholds and clinical outcomes.(132) Ultimately, many methodological decisions when measuring EIC are pragmatic and based on the clinical and appointment information available to researchers. However, as this relatively new area of research continues to develop, greater consensus in definitions will help build a more robust evidence base. Further review of engagement in care definitions and papers is the focus of my literature review in Chapter 2.

1.6. Data sources for my PhD

In this section, I detail the quantitative data sources for this thesis. Data from two UK based HIV cohorts were used in this analysis:

- the Collaborative HIV Paediatric Study (CHIPS)
- the Adolescents and Adults Living with Perinatal HIV (AALPHI) cohort

The majority of the data used for this PhD thesis has come from the AALPHI study. However, I will first present an overview of paediatric surveillance in the UK (the CHIPS study) to better contextualise the AALPHI study. Both the AALPHI and CHIPS studies are coordinated at the Medical Research Council (MRC) Clinical Trials Unit at University College London (UCL).

1.6.1. Collaborative HIV Paediatric Study (CHIPS)

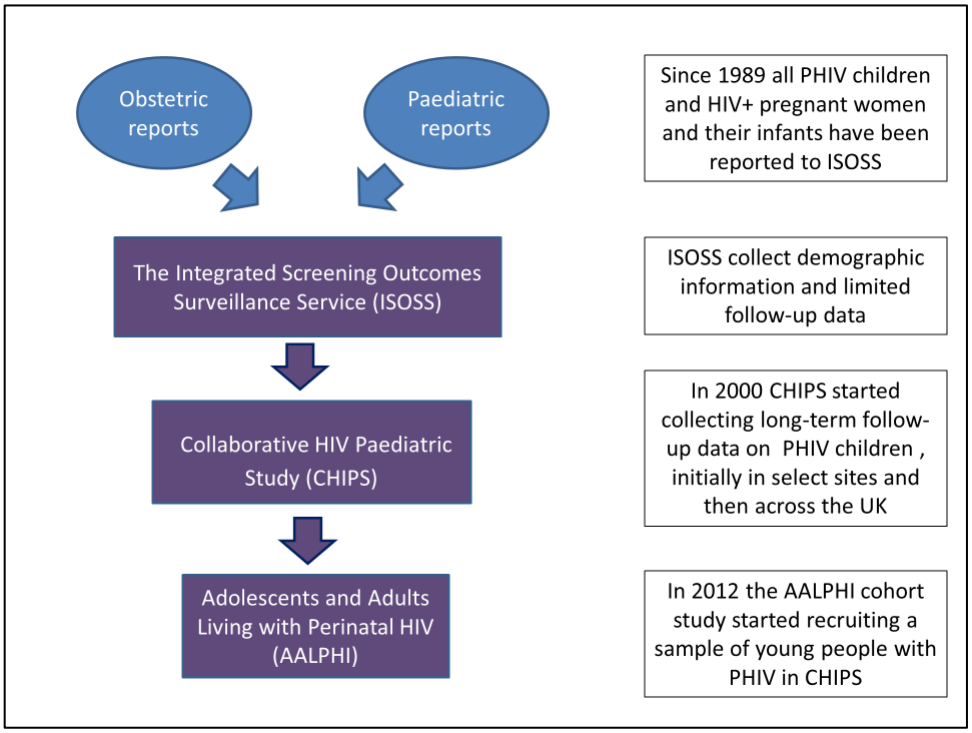
CHIPS, which started in April 2000, and is the national surveillance system for paediatric HIV in the UK and Ireland and includes all children diagnosed with HIV in the UK. There are very few national cohorts of children living with perinatal HIV globally.(5) Two important factors facilitated CHIPS

gaining complete national coverage. Firstly, when CHIPS was set up there were concerns that if consent were sought to collect data there could be serious ascertainment bias undermining the understanding of PHIV at a population level, particularly as it relates to vulnerable groups. Therefore, CHIPS was given ethics approval, and subsequently, PHE Regulation 3 approval[1] to collect and process patient identifiable information without consent.

Secondly, CHIPS is possible due to the existence of the UK's National Health Service that facilitates national surveillance in many disease areas. CHIPS is also unique because it benefits from a long duration of follow-up.

The main objectives of CHIPS are to describe clinical, laboratory and treatment outcomes for children with PHIV. All children diagnosed with HIV or born to women living with HIV in the UK are reported to the Integrated Screening Outcomes Surveillance Service (ISOSS) either via obstetric or paediatric reporting schemes. All PHIV children and young people are then followed through paediatric care in the CHIPS study (Figure 1.3).

Figure 1.3: Reporting and surveillance of infants born to women living with HIV and children with PHIV in the UK



[1] Patient data are collected under legal permissions granted to PHE under Regulation 3 of The Health Service (Control of Patient Information) Regulations 2002). The PHE Caldicott Advisory Panel has granted CHIPS permission to process patient identifiable information without consent (PHE reference CAP-EX-2019-04).

Following reporting of a new diagnosis of HIV in a child from ISOSS to CHIPS, baseline forms are sent to the reporting clinic and prospective follow-up forms are then sent on an annual basis until the patient leaves paediatric care. All data are abstracted from the medical notes onto a form by trained clinical staff. There are currently 37 study sites actively providing data to the study across England, Scotland, Wales, and Northern Ireland.

The inclusion criteria are as follows:

- Diagnosed with HIV
- Receiving care in England, Scotland, Wales, or Northern Ireland
- Receiving care in a paediatric HIV clinic aged <16 years

CHIPS forms include the data item shown in Table 1.2. All data are extracted from patient notes by clinic staff.

Table 1.2: CHIPS data items

Category	Data collected
Demographic	Sex, DOB, partial postcode
Clinical data	CDC B or C events, inpatient stays, hepatitis B and C co-infection tests, immune function (CD4 / total lymphocytes), HIV viral load, medication adverse events, clinician-reported lipodystrophy, lipids (cholesterol, triglycerides, HDL/LDL)
ART details	ART drug, doses, and frequency, start and stop dates, reasons for change in ART, and ART-associated serious adverse events (grade 2 or above)
Sexual health	Date of menarche and pregnancy details
Physical assessments	Blood pressure, height/weight
HIV resistance	Date of request for resistance testing
Clinic details	Clinic attended, name of paediatrician, hospital number, last date seen, shared care details

1.6.2. Adolescents and Adults Living with Perinatal HIV (AALPHI) cohort

AALPHI was a prospective cohort study which commenced in 2012. AALPHI was set up to answer a number of broader questions about the outcomes of young people living with PHIV, including the cognitive and psychosocial effects of having life-long HIV and long-term exposure to ART to improve the evidence base in this area. AALPHI recruited two groups of young people, PHIV, and an HIV negative but HIV-affected comparison group. Having an appropriate comparison group is important because young people growing up in families affected by HIV are likely have different

psychosocial and socioeconomic experiences compared to families from not affected by HIV. For AALPHI this was relevant as the study aimed to ascertain whether any additional ill health in the HIV positive group was due to having HIV, versus background factors.

A wide range of data were collected to describe the impact of life-long HIV and long-term ART on the following domains: cognitive function and psychosocial issues; cardiac function; metabolic function; sexual and reproductive health; and body composition. The aim was for findings to inform HIV treatment and care strategies for this group in the UK. At the time that AALPHI was set up, the only other large study including both PHIV young people and HIV negative young people was in the USA.(139)

The AALPHI inclusion criteria are listed in Table 1.3:

Table 1.3: AALPHI inclusion criteria

Young people living with PHIV	HIV negative young people
• Aged 13-21 years	• Aged 13-23 years
• Previously or currently receiving paediatric care in England • Aware of their HIV status for at least 6 months	• HIV negative on a point-of-care test at the interview and aware of HIV in the family for at least 6 months • Living in the same household as a PHIV participant or having an HIV positive parent, sibling, friend or partner
• In UK for > 6 months • Able to give informed consent/assent • Able to understand English • Willing to give a blood sample	• In UK for > 6 months • Able to give informed consent/assent • Able to understand English

AALPHI was coordinated by research nurses with a background in either paediatric or adult HIV. A psychologist trained the research nurses in cognitive testing techniques before carrying out interviews and recap sessions were held where any problems could be discussed at regular intervals throughout the study.

Participants were recruited from 16 NHS paediatric and adult HIV clinics and six voluntary sector organisations. Thirteen of the clinics and organisations were located in London and nine outside London. The NHS clinics were selected because they had the largest numbers of PHIV young

people attending from across England. Voluntary sector organisations were selected based on providing services for both PHIV young people and HIV negative young people affected by HIV.

Interviews took around two hours to complete and study participants were given vouchers to compensate for their time (£30). Interviews were conducted in a wide range of settings, including NHS clinics, voluntary sector organisations, participants' homes, and the study's offices, and at a variety of different times, including evenings and weekends.

Two interviews were conducted over 5 years. Details are only presented here for the first interview because data from the second interview were not used in this thesis.

The AALPHI interviews comprised of:

- face-to-face structured questions
- cognitive computer and paper tests
- computer-assisted self-interviewing (CASI) questions
- physical assessments
- rapid HIV diagnostic test for HIV negative participants
- blood samples.

Sensitive questions, including questions on sexual health, drug and alcohol use and mental health, were completed by the young people themselves using CASI, and other questions were completed face-to-face. One of the main components of the interview in both years was cognitive testing which was carried out using a combination of online and paper assessments. In addition to data collected in the interviews, clinical data were abstracted for all young people living with PHIV in AALPHI who had left paediatric care and thus were no longer in CHIPS. This data abstraction was carried out by clinic nurses and AALPHI research nurses. Table 1.4 describes the data collected and the method of data collection used.

Table 1.4: Data collected in interview 1

Category	Data collected	Data collection method
Demographic	Sex, age, country of birth, language spoken at home, ethnicity	Face-to-face structured questions
Social factors	Marital status, number of children, accommodation/living circumstances, parent/carers' employment, biological parents' country of residence and vital status, contact with social service/youth offenders/education system, education history, employment history, time off on sick leave	Face-to-face structured questions
Medical history	Prematurity, birth weight, medical history, non-ART medications, bone fracture history, family medical history, exercise	Face-to-face structured questions
Quality of life and mental health	Pediatric Quality of Life Inventory (PedsQL)™,(140) communication with family, Rosenberg Self-esteem Scale,(141) self-harm and suicidal ideation (adapted from the Avon Longitudinal Study of Parents and Children (ALSPAC), (142) Hospital Anxiety and Depression Scale (HADS),(143) psychology / mental health service contacts, major life events (adapted from ALSPAC)(144)	CASI
Alcohol and recreational drugs use	The Alcohol Use Disorders Identification Test (AUDIT),(145) smoking history, recreational drug use	CASI
Growth and sexual health	Body image satisfaction (from the Manchester Quality of Life Instrument),(146) referral for anorexia/obesity, tanner self-assessment, menstrual pattern/history, HPV and HBV vaccination history, sexual health history, contraception use, post-exposure prophylaxis (PEP) use, pregnancy and birth history	CASI
HIV disclosure (PHIV only)	Age told HIV status, how told and by whom, feelings about HIV, how often talk about HIV, how many friends have told about HIV	CASI
Adherence (PHIV only)	Frequency of medicines, missed doses, self-assessment of adherence, reasons for any missed doses	CASI
Cognition	Executive function (CogState(147) and Color Trails Test (148)), speed of information processing (CogState(147) and Color Trails Test(148)), attention/ working memory (CogState(147) and Wechsler Adult Intelligence Scale – Fourth Edition(149)), learning (CogState(147)), memory (CogState(147)), fine motor skills (Grooved Pegboard(150))	Cognitive computer and paper tests
Samples	EDTA plasma, SST serum, Lithium heparin plasma HIV negative only: HIV point of care test	Research nurse or clinic nurse[1]
Physical assessments	Blood pressure, height/weight measurements, hip/waist measurements, face changes	Research Nurse assessment
Clinical data (PHIV who were in adult care only)	CDC B or C events, inpatient stays, hepatitis B and C co-infection test results, immune function (CD4 / CD8 / total lymphocytes), HIV viral load results, medication adverse events, clinician-reported lipodystrophy, lipids (cholesterol, triglycerides, HDL/LDL)	Abstracted from medical notes

[1] The research nurse always carried out the HIV point of care test but blood tests where possible were carried out at the same time as routine clinic bloods

Data from paper case report forms (CRFs) were entered onto a secure database and 10% checks were conducted on all entered data. Data from the CASI and cognition tests were stored on separate secure databases and regular data downloads were accessed by the study statistician. The study statistician created data analysis files combing all the data on a regular basis. Further checks were carried out on these analysis files.

1.7. Aim and objectives of my PhD

The aim of this doctoral project was to describe engagement in HIV care in young people with perinatal HIV in England and to assess whether psychosocial factors predicted engagement in care. Specific objectives were:

- To develop a sensitive measure of EIC in order to take into account changes over time in treatment and health status for young people with perinatal HIV in England
- To apply the measure to describe EIC in young people with perinatal HIV in England through quantitative analysis of the AALPHI cohort dataset
- To describe the characteristics of AALPHI participants
- To compare findings from analysis of AALPHI participants' data to the national HIV cohort or the wider general population where comparisons are available
- To investigate the relationship between a broad range of potential exposures and EIC in AALPHI participants, through quantitative analysis
- To take the results from the quantitative analyses, and explore them through focus group discussions with young people with PHIV
- To assess the whether the quantitative results of this study resonated with young peoples' own experiences and to enhance our understanding of them.

In this thesis, I hypothesised that psychosocial issues were more important in influencing EIC than clinical aspects of living with HIV. Therefore, gaining views of young people living with PHIV gathered via both the AALPHI study and the qualitative data collection methods are a pertinent component of understanding the psychosocial dimensions of EIC.

1.8. Thesis overview and structure

In this thesis, I used an epidemiological and sociological, mixed methods approach to answer my aim and objectives. This thesis has seven chapters. The first two chapters, the introduction and the literature review, follow the normal structure of a PhD. Chapters 3, 5 and 6 are structured so that each chapter has distinct introduction, methods, results and discussion sections. This structure was chosen due to the discrete nature of the sections of analysis, but also to aid

publishing post-submission. Chapter 4 is also a discrete chapter, however the format is slightly different. The introduction and methods are presented and then the results and discussion are presented together for eight specified domains of exposure variables. The overall discussion therefore pulls together the discussions from the preceding chapters. Below is an overview of the chapters in the thesis.

In Chapter 2, I review the literature to date on EIC in young people living with perinatal HIV in high and high middle income settings. In the identified papers, I describe how EIC is measured, summarise prevalence across the studies and describe any predictors, facilitators or barriers of EIC.

In Chapter 3, I present the quantitative methods used to adapt an existing algorithm by Howarth *et al* (151) that measured EIC in adults with HIV in the UK for use in young people with PHIV. The resultant flowcharts where then used to measure EIC using data on 306 young people with PHIV in the UK based Adolescents and Adults Living with Perinatal HIV (AALPHI) cohort study.

In Chapter 4, I present the quantitative methods by which the potential risk factors were derived. I then report analysis results of the potential risk factors using descriptive statistics and compare the findings to data from relevant studies and populations to contextualise the AALPHI cohort.

In Chapter 5, I take the exposure variables assembled and described in Chapter 4 and the EIC outcome variable detailed in Chapter 3 and put them together to investigate whether the exposure variables predict EIC in multivariable methods. I first describe the statistical methods outlining the multiple stages of variable investigation and the four stages of multivariable logistic regression modelling. Then in the results, I present descriptive results for each exposure variable within each of the domains and the four stages of multivariable logistic regression analyses examining the effect of the variables on the EIC outcome of EIC.

In Chapter 6, I present qualitative findings from focus groups discussions with young people with PHIV. There were two main topics. The first topic was use of clinical markers as a proxy for clinic visit attendance in the flowcharts. I explored with young people their reasons for clinic visits and regularity of tests and measurements to analyse the strengths and limitations of using clinical markers as proxies in the flowcharts. The second topic was the quantitative exposure variables found to be associated with EIC. I presented and discussed these with young people to elucidate if the predictors of EIC found in the quantitative analysis resonated with their experiences as patients.

In Chapter 7, I summarise the key findings from each of my results chapters. I then offer some concluding remarks, which encompass a description of my findings' relevance, the main strengths and limitations of my work and its generalisability. Finally, I explore future possible uses for the EIC flowcharts and for improvements to EIC.

In November 2020, I presented the findings from Chapter 5 in a poster at the International Workshop on HIV Pediatrics. After submission of the thesis, I plan to publish papers from Chapter 3, Chapter 5 and Chapter 6.

1.9. My role as the PhD candidate

I am a paediatric HIV nurse with over 20 years of clinical and research experience working with children, young people and families living with HIV. I am currently a Research Fellow at the MRC Clinical Trials Unit and the co-ordinator of the CHIPS cohort. I first joined the MRC Clinical Trials Unit in 2011 to work on the AALPHI cohort. My role on AALPHI was to coordinate the study, lead the development of the study interviews, organise the research nurse training and carry out participant interviews. I undertook an MSC in Medical Anthropology in 2002, however this PhD study is my first training in epidemiology.

For the purposes of this thesis, I was responsible for the overall design of the doctoral project, and for the methods and analysis of the quantitative data. I am also responsible for the methods, data collection and analysis of the qualitative data.

1.10. Ethics

This thesis was approved by the East Midlands – Leicester Central Health Research Authority as a sub study of AALPHI and has university ethics approval from the London School of Hygiene and Tropical Medicine.

1.11. Funding

I received a Medical Research Council studentship to carry out this part-time PhD. In addition, I received funding from the Parkes Foundation to support my qualitative research costs.

Chapter 2.Literature review

2.1. Introduction

In this chapter, I review the literature to date on EIC in young people living with PHIV in high and high middle income settings. In the identified papers, I describe how EIC is measured, summarise prevalence across the studies and describe any predictors, facilitators or barriers of EIC.

2.2. Methods

For the literature review, the following inclusion criteria were used:

- Written in English language
- Containing original research findings
- Published from 2000 onwards
- Originating from high and upper-middle income countries (based on the World Bank country classification by income level list (152))
- Describing measures of EIC (as opposed to loss to follow-up or missed appointments)
- >50% of study population including young people aged 13-24 years with PHIV, or, where young people were <50% of the study population, EIC estimates (proportion EIC or predictors of EIC) were stratified by mode of HIV acquisition.

Although review papers were excluded, their reference lists were scanned for additional relevant papers. Papers were only included from 2000 onwards because issues affecting EIC were likely to be very different in the pre-ART era. Papers were restricted to those describing high income and upper-middle income settings. This is because the model of healthcare and resources available are very different in many lower and lower-middle income countries. In those settings, young people with HIV often attend appointments in large primary care clinics, while in contrast in many upper-middle and high income countries (including young people in my study), the majority of young people attend specialist paediatric or adolescent clinics although some older young people do attend generic adult HIV clinics.(58) Papers that were measuring loss to follow-up or missed appointments were not included as these outcomes are different to my outcome which is engaged in care. Finally, ideally I would have only included papers where all participants had PHIV, however, there were only a small number of such papers so the definition was widened to include papers where PHIV constituted >50% of the study sample or EIC was stratified by mode of HIV acquisition.

In a few papers, the mode of HIV acquisition was not specified, most probably because the data were not available. In these instances, proxy markers for perinatal HIV status were used. Papers were included if age at diagnosis (or age at recruitment into a study) was <13 years,(153) or, as in one paper,(154) issues that are specific to PHIV, for example knowledge of HIV status, were discussed and included as variables in the analysis.

PubMed was the only search tool employed for the review of published papers, and search terms are listed in Table 2.1. Search terms were built by reviewing the titles of existing collated papers on EIC for relevant terms. Additionally, abstracts from relevant HIV conferences were searched using the terms "retention" and "engagement". Abstracts from the previous three years were searched for the following conferences: International Workshop on HIV Pediatrics (2017, 2018 and 2019) and the alternating International AIDS Conference (2018 only as 2020 abstracts were not yet available for when the literature review was conducted) and International AIDS Society Conference on HIV Science (2017 only as 2019 abstracts were not yet available).

The findings of the review were organised thematically into three key areas: methods to measure EIC; prevalence of EIC; and predictors, barriers and facilitators associated with EIC. In the third theme, variables included in the study analysis were grouped into domains to aid comparison. Domains and example variables were: Sociodemographic (age, ethnicity, rural/urban, socioeconomic status); risk behaviour practices (alcohol and substance abuse); mental health (internalisation); clinic (youth friendliness); HIV experience and management (discrimination, time to linkage); and HIV markers (HIV acquisition, viral load, CD4 count, calendar year of diagnosis, AIDS diagnosis and ART).

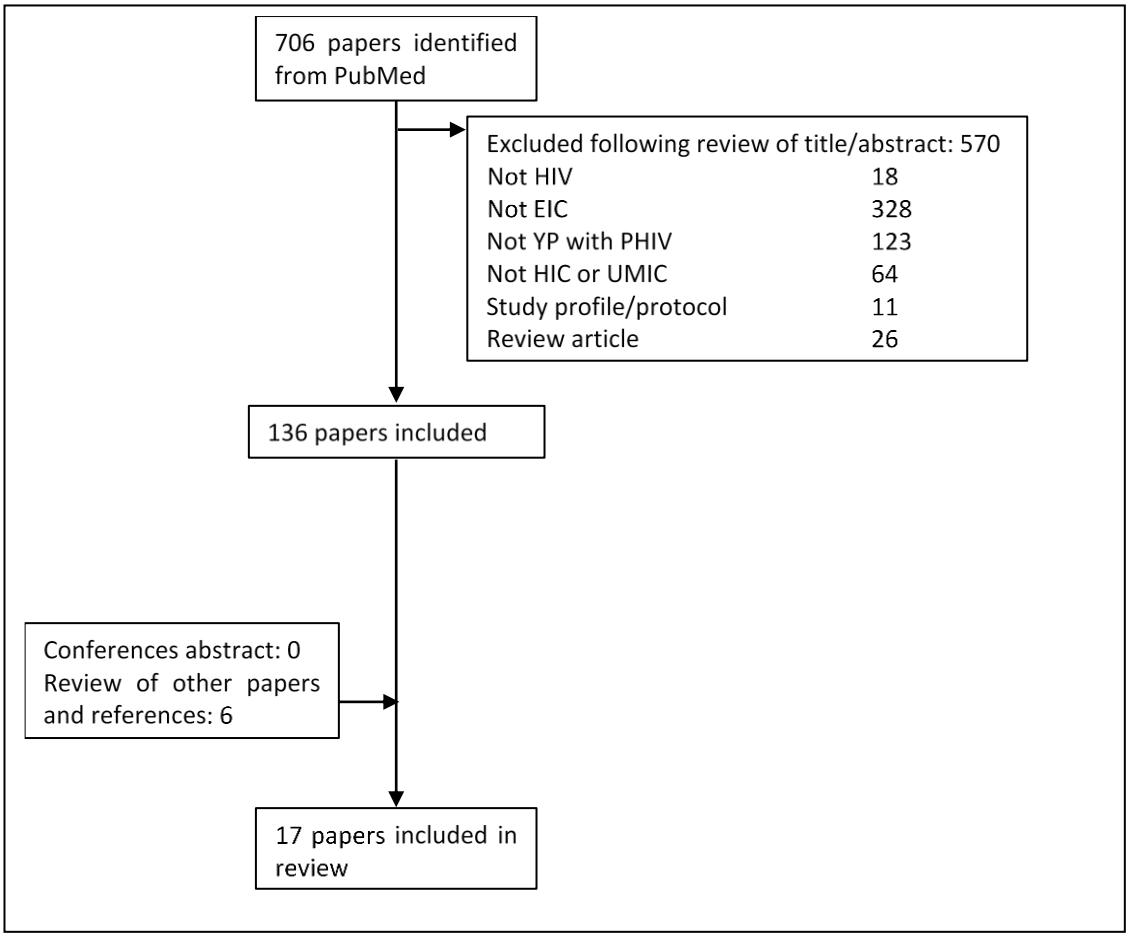
Table 2.1: PubMed search terms

Search terms
(HIV[TI] OR "Acquired immunodeficiency syndrome"[TI] OR AIDS[TI] OR "human immunodeficiency"[TI] OR hiv[MH] OR "acquired immunodeficiency syndrome"[MH]) AND ("lost to follow up"[MH] OR "retention in care"[MH] OR retain*[TI] OR retention[TI] OR engag*[TI] OR continuum[TI] OR cascade[TI] OR attend*[TI] OR "loss to follow up"[TI] OR "lost to follow up"[TI] OR "losses to follow up[TI]" OR attrition[TI] OR "patient engagement"[TI] OR "self-management"[TI] OR disengage*[TI]) AND (adolescent[MH] OR pediatrics[MH] OR child[MH] OR "young adult"[MH] OR paediatr*[TI] OR pediatr*[TI] OR adolescen*[TI] OR child*[TI] OR perinatal*[TI] OR vertical*[TI] OR young[TI] OR youth*[TI] OR teen*[TI] OR young adult[TI]) AND (2000:2020[dp]) NOT (Nigeria*[TI] OR Zimbabwe[TI] OR Rwanda[TI] OR India[TI] OR sub Sahara*[TI] OR Uganda*[TI] OR Kenya*[TI] OR Zambia[TI] OR Tanzania[TI] OR South Africa[TI] OR Southern Africa[TI] OR Mozambique[TI] OR Malawi[TI] OR Ethiopia[TI] OR Botswana[TI] OR Indonesia[TI] OR East Africa[TI] OR Cambodia[TI] OR Ghana[TI] OR MSM[TI] OR Transgender[TI] OR Bisexual[TI] OR 'men who have sex with men'[TI])

2.3. Results

Seven hundred and six papers were initially identified in the literature search (Figure 1). Following screening of the titles and abstracts, 136 papers remained for full paper review. Of the full papers reviewed, 103 were excluded because they did not contain participants who had PHIV, and 22 were excluded for other reasons, leaving a total of 11 papers for inclusion. A further six papers were identified from the references of included papers or from the references of excluded review papers, giving a final sample size of 17.

Figure 2.1: Flowchart of papers identified in the literature review



2.3.1. Summary of included papers

Table 2.2 summarises key characteristics of the 17 eligible papers. All of the papers were published in the last five years. Three papers were from Europe,(155–157) with one from each of the UK,(155) Italy (157) and Romania.(156) Five papers were from sub-Saharan Africa,(153,154,158–160) of which four were from South Africa (153,158–160) and one from Namibia.(154) Nine papers were from North America,(123,161–168) of which eight were from the USA.(123,161–166,168) Fifteen of the papers used quantitative methods (123,153–158,161–168) and two qualitative.(159,160) The number of patients in the papers ranged from 24 to 9,562. All of the papers included estimates of EIC of which 16 (123,153–162,164–168) were specifically for young people living with PHIV. Ten papers conducted modelling and presented predictors associated with EIC, or presented barriers and facilitators from qualitative analysis.(156,158–164,166,168) Seven were specifically for young people living with PHIV.(156,158–160,162,166,168)

Table 2.2: Summary of 17 papers included

First author, year published (reference)	Country	Quantitative or qualitative	Sample size (% perinatal HIV)	PHIV-specific estimates of EIC (Y/N)	PHIV-specific predictors/barriers or facilitators of EIC (Y/N)
Europe					
Chappell, 2019 (155)	UK	Quantitative	n=905 (100%)	Y	-[1]
Gingaras, 2019 (156)	Romania	Quantitative	n=545 (100%)	Y	Y
Izzo, 2018 (157)	Italy	Quantitative	n=24 (100%)	Y	-
Sub-Saharan Africa					
Davies, 2017 (153)	South Africa	Quantitative	n=460 (90%)	Y	-
Munyayi, 2020 (154)	Namibia	Quantitative	n=385 (100%)	Y	-
Pantelic 2020 (158)	South Africa	Quantitative	n=1,059 (79%)	Y	Y
Zanoni, 2018 (159)	South Africa	Qualitative	n=28 (100%)	Y	Y
Zanoni, 2020 (160)	South Africa	Qualitative	n=59 (100%)	y	Y
North America					
Gebrezgi, 2019 (161)	USA	Quantitative	n=2,872 (28%)	Y	N
Gray, 2019 (162)	USA	Quantitative	n=9,562 (100%)	Y	Y
Griffith, 2019 (168)	USA	Quantitative	n=89 (57%)	Y	Y
Hussen, 2017 (163)	USA	Quantitative	n=72 (15%)	N	N
Kakkar, 2016	Canada	Quantitative	n=25 (100%)	Y	-
Lee, 2016 (164)	USA	Quantitative	n=680 (35%)	Y	N
Ryscavage, 2016 (165)	USA	Quantitative	Pre transition n=50 (35%) Post transition n=43 (37%)	Y	-
Tassiopoulos, 2019 (166)	USA	Quantitative	n=124 (100%)	Y	Y
Xia, 2016 (123)	USA	Quantitative	n=1,535 (100%)	Y	-

[1] "-": no predictors/barriers or facilitators associated with EIC were presented in these papers

2.3.2. Measures of engagement in care

There was wide variability in the definitions of EIC used in the literature. Across 17 papers, there were eight different definitions used with one paper (157) stating no definition at all

(Table 2.3). Almost all of the studies used an EIC measure that combined appointment constancy and gap in care.(1) The three most commonly used definitions were ≥1 clinic visit within six months, which was used in four papers (159,160,166,167), ≥1 clinic visit within one year, which was also used in four papers (123,155,162) and ≥2 visits with ≥3 months apart within one year which was used in five papers.(123,162–164,168) Two studies, one from the USA and one from South Africa measured EIC using ≥2 clinic visits within one year, with ≥1 clinic visit in each six month.(153,165) In addition, two papers (123,162) from the USA used both ≥1 clinic visit within one year and ≥2 visits with ≥3 months apart within one year. One paper from Europe measured EIC longitudinally in person months.(156) Four of the eight definitions were used by only one paper each.(154,156,158,161) None of the papers considered different follow-up appointment times for patients based on their clinical status.

Of the eight different definitions of EIC used across the 16 papers, three definitions measured EIC with ≥1 clinic visit, four used multiple visits, one was a longitudinal measure and one measured self-reported appointment attendance combined with self-reported adherence. Three of the definitions were broadly comparable because they all measured two or more visits within one year (≥2 visits with ≥30 days apart within one year, ≥2 visits with ≥6 months apart within one year, and ≥2 visits within one year with ≥1 visit in each six months). However, apart from this example, the definitions were too variable to compare, such as ≥1 clinic visit in 24 months and ≥1 clinic visits in six months. It is important to note that despite the fact that all of the papers had longitudinal data, measuring visits over time, all but Gingaras *et al* (156), measured EIC as prevalence in a given period, usually a calendar year, following classical cascade of care approaches. Two thirds of the papers (6/9) from North America justified or referenced their choice of measure based on national guidelines or recommendations.(123,163–166,168) Four of these papers used the same measure (123,163,164,168) while the other two papers used easily comparable measures.(165,166) Outside of North America, the only paper to reference their choice of EIC definition across Europe and sub-Saharan Africa was Pantelic *et al* (158), who followed WHO recommendations for measuring EIC in pregnant and breastfeeding women.(169)

Table 2.3: Summary of engagement in care definitions and proportion of participants engaged in care

EIC definition	Author, Year (country)reference	Time period	No. of visits	Start point of EIC period	N (% PHIV)	EIC prevalence
≥1 clinic visit definition						
≥1 visit in 6 months	Tassiopoulos, 2019 (USA)(166)	6 months	≥1	6 months prior to participant interview	124 (100%)	80%
	Zanoni, 2018 (South Africa)(159)	6 months	≥1	6 months prior to participant interview	41 (100%)	98%
	Zanoni, 2020 (South Africa)(160)	6 months	≥1	6 months prior to participant interview	28 total (16 adolescent clinic, 12 paediatric) (100%)	94% adolescent clinic 83% paediatric clinic
	Kakkar, 2016 (Canada)(167)	6 months	≥1	6 months prior to participant interview	25 (100%)	76%
≥1 clinic visit within 1 year	Gray, 2019 (USA)(162)	1 year	≥1	Calendar year	9,562 (100%)	Overall 73% 13-17 80%, 18-25 73%
	Xia, 2016 (USA)(123)	1 year	≥1 & ≥2	Calendar year	1,596 (100%)	Overall 96% 99% aged 13-19 years 95% aged 20-29 years
	Chappell, 2019 (UK)(155)	1 year	≥1	Calendar year	905 (100%)	98%
≥1 clinic visit within 24 months	Munyayi, 2020 (Namibia)(154)	2 years	≥1	Within 2 year study period	385 (100%) (78 in intervention)	91% in intervention vs. 90% in SOC
Multiple visit definition						
≥2 clinic visits with ≥30 days apart within 1 year	Gebrezgi, 2019 (USA)(161)	1 year	≥2	Calendar year	2,872 (28%)	Overall 65% (73% perinatal) 85% in 13-17 years 82% in 18-20 years 61% in 21-24 years

EIC definition	Author, Year (country)reference	Time period	No. of visits	Start point of EIC period	N (% PHIV)	EIC prevalence
≥2 clinic visits with ≥3 months apart within 1 year	Gray, 2019 (USA)(162)	1 year	≥2	Calendar year	9,562 (100%)	Overall 61% 68% in 13-17 years 57% in 18-25 years
	Xia, 2016 (USA)(123)	1 year	≥1 & ≥2	Calendar year	1,535 (100%)	Overall 80% 89% in 13-19 years 76% in 20-29 years
	Lee, 2016 (USA)(164)	1 year	≥2	Calendar year	680 (35%)	85% of total (93% of perinatal) 94% in 15-19 years 82% in 20-24 years
	Griffith, 2019 (USA)(168)	1 year	≥2	1 year post transition	89 (57%)	89% of total
	Hussen, 2017 (USA)(163)	1 year	≥2	Pre transition, 1 and 2 years post transition	72 (15%)	93% last year of paediatrics Post transition to adult care: 89% 1st year, 56% 2nd year (p= <0.001)
≥2 clinic visits within 1 year, with ≥1 clinic visit in each 6 month	Davies, 2017 (South Africa)(153)	1 year	≥2	1, 2, and 3 years post transfer	460 (90%)	Post transfer: 90% 1st year, 88% 2nd year post, 84% 3rd year post 1st year: 93% 10-14, 81% 15-19 2nd year: 90% 10-14, 85% 15-19 3rd year: 85% 10-14, 85% 15-19
	Ryscavage, 2016 (USA)(165)	1 year	≥2	Year post linkage to adult care	50 pre transition (35%) 43 post transition (37%)	50% of total at 1st year post transition, 60% of perinatal

EIC definition	Author, Year (country)reference	Time period	No. of visits	Start point of EIC period	N (% PHIV)	EIC prevalence
Other definitions						
Attended all clinic visits within last year & >85% adherence	Pantelic, 2020 (South Africa)(158)	1 year	All visits	Calendar year (baseline and follow-up)	1,059 baseline (79%)	38% over 2 years
Total months engaged in care	Gingaras, 2019 (Romania)(156)	Longitudinal	≥1 visit previous year	Previous year at ages 15, 20, 25	545 (100%)	4,775 person-years, 92% aged 15 years 84% aged 20 years 74% aged 25 years
Not defined	Izzo, 2018 (Italy)(157)	n/a	n/a	n/a	24 (100%)	80%

A key aspect of measurement that complicates comparisons across papers is the starting point of the EIC period. A number of papers investigated EIC across a single calendar year (123,155,158,161,162,164) and one paper analysed data across two consecutive calendar years.(154) Other papers started the EIC period at a particular visit. This was either related to the point of transfer to another clinic (153) or from the first appointment (linkage) in adult care (163,165,167,168) or a time period prior to an interview date. Finally, one paper investigated EIC longitudinally focusing on three specific ages.(156)

Additionally, the timing of measuring EIC varied across the papers. A number of the papers compared EIC pre- or post-transition to adult care. There are additional challenges for young people transitioning to a new adult or adolescent clinic that are likely to pose different problems to maintaining EIC compared to young people in a stable clinic environment, for example leaving their long term paediatric health care provider (170) and issues around increased self-management expectations,(171,172). Further complicating comparison, young people transition much earlier in Europe, at around 18 years of age, compared to young people in the USA who transition by 25 years.(58) In the sub-Saharan African studies, many children were seen from diagnosis in a general primary care clinic spanning paediatric and adult care.(58,153) However, transfer did occur for some patients who were initiated on ART in a specialist paediatric clinic and were then transferred to their local primary care clinic, and this largely happened when patients were in their early teens.(153)

In terms of the way visits were measured, six (154,157,164,165,167,168) gave no information, presumably because actual visit dates were recorded in their datasets. Eight papers (123,153,155,156,159–162) used clinic visits or proxy markers (laboratory test, ART changes or record of a pharamcy refill). Of the remaining three, one paper (163) used scheduled appointments as opposed to attended appointments, because attendance was not documented. Two papers (158,166) used self-reported attendance, because documented attendance and proxy markers were not available, of which one (158) validated self-reports in a subset of patients who did have dates for viral load results.

2.3.3. Prevalence of engagement in care

Among the studies measuring EIC, a number measured EIC using a definition of at least one clinic visit. Four papers, two using quantitative methods (166,167) and two qualitative methods,(159,160) used ≥1 clinic visit within 6 months as their measure, all of which measured EIC around the time of transition to adult care (Table 2.3).(159,160,166,167) In the largest of these four papers, Tassiopoulos *et al* (166) investigated young people who were either about to transition or had already transitioned to adult care, within an existing longitudinal, multisite cohort study across the USA.(166) Of 455 participants, 27% (n=124) transitioned to adult care at a mean age of 22 (SD 2.9) years and 80% were engaged in care within the six months preceding the study interview (self-reported). Kakkar *et al* (167) approached all young people living with PHIV who had transferred from paediatric to adult care within one hospital in Montreal, Canada, between 1999 and 2012. Of 45 patients, 25 consented to the study. Young people had a mean age of 22 (range 19-25) years, and comparably to Tassiopoulos *et al* (166), 76% remained engaged in care post transition.

The two papers using qualitative methods were conducted in young people with PHIV in different hospitals in Kwa-Zulu Natal in South Africa. In the first paper, Zanoni *et al* (2018) (159) performed in-depth interviews with 12 young people in routine paediatric care and 16 young people in an adolescent-friendly clinic in a single hospital. In the paediatric clinic, 75% of the participants (n=9) were >15 years old and 83% were engaged in care, in the adolescent friendly clinic 94% of the participants (n=15) were >15 years old and 95% were engaged in care. In the second paper, Zanoni *et al* (2020) (159) undertook in-depth interviews with 41 young people living with PHIV prior to transition to adult services in a single centre in to explore aspects of care that could improve EIC. Paediatricians identified participants for the study based on them being ready to transition to adult care. Across the 41 participants with median age of 15 (range 14-16) years, EIC was 98%. Participants in the Tassiopoulos and Kakkar papers (166,167) were interviewed outside of the clinic setting which may account for the lower EIC than in these two South African papers (159,160) where participants were recruited in the clinic setting, so were likely to be a largely treated and engaged population. In addition, the two qualitative papers were design to explore why adolescent friendly

services had better EIC and what interventions could be put in place to improve EIC, and so did not set out to measure EIC as their main purpose.

All three papers using ≥1 clinic visit within a year as their measure, examined EIC in multiple clinics (5,12,17) two of which were national cohorts.(155,162) In the largest of the studies and the first of two from the USA, Gray *et al* (162) analysed data reported to the National HIV Surveillance System (NHSS) on all persons diagnosed with PHIV across the USA by the end of 2014 and still alive by the end of 2015. Overall, 9,562 young people were included in the analyses and the proportion engaged in care was 75%. Patients aged 13-17 years had higher EIC (80%) compared to 18-25 year olds (73%). In the second study from the USA, Xia *et al* (123) included 1,596 children and adults living with PHIV in New York City. Prevalence of EIC was 96% overall, 99% in 13-19 year olds, and 95% in 20-29 year olds. Chappell *et al* (155) described prevalence of EIC in children with PHIV in paediatric care across the UK. To be included patients had an appointment in the preceding year and were aged ≤21 years. Of 905 patients with a median age of 14 [IQR 11, 16] years, 98% were engaged in care in 2016.

Using this definition of at least one clinic visit within one year, two of the studies reported EIC to be high at 90% and above.(123,155) In addition, all three of the studies compared EIC stratified by age and reported that EIC was higher in young patients.(138,153,162)

One further paper used a measure with ≥1 clinic visit, but within 24 months as opposed to six or 12 months.(154) In this single centre study from Namibia, 385 PHIV young people who were aged 10-19 years between 2015 and 2017 were enrolled. Of these, 307 young people attended a paediatric clinic and 78 a 'Teen Club'. No difference was found in EIC between these groups (90% vs. 91% respectively, p=0.93), however the young people in the paediatric clinic were younger than those in the teen club (44% 15-19 years in the paediatric clinic vs. 67% in the Teen Club).

Eight papers measured EIC using multiple visit definitions, (123,153,161–165,168) two of which compared these multiple clinic visit measures to a measure of at least one clinic visit.(123,162) Unsurprisingly both of these papers reported that EIC was lower using a multiple clinic visit definition. Gray *et al* (162) reported, when using the multiple visit measure, 61% of young people living with PHIV were engaged in care, although younger

patients aged 13-17 years had higher engagement (68%) when compared to 18-25 year olds (57%). Using the less strict definition (≥1 clinic visit) in the same study EIC was 73% overall, and 80% in 13-17 year olds and 73% in 18-25 year olds. Likewise in Xia *et al's* (123) analysis, when using the multiple visit measure, overall EIC was 80% and did not vary by age (13-19 years old 89%, 20-29 years old 76%). Using the alternative definition of at least once clinic visit, EIC was 96% overall, and 99% in 13-19 year olds and 95% in 20-29 year olds.

Two further papers from the USA examined young people with PHIV alongside young people with BHIV and reported that young people with PHIV had higher prevalence of EIC.(161,164) Both were large studies, with around a third of patients with PHIV. Lee *et al* (164) assessed the effect of youth friendliness on 680 patients in 15 clinics who had a visit in 2011. Overall EIC was high at 85%, but with a potential decline with age (94% 15-19, 82% 20-24). Young people living with PHIV had the highest EIC (PHIV 93%, heterosexual 82%, MSM 80%, p=<0.001). Likewise, a large analysis by Gebrezgi *et al* (161) included all young people aged 13-24 diagnosed across Florida between 1993 and 2014 (n=2,872). EIC declined with age, from 85% in those aged 13-17 years, 82% in age 18-20 years and 61% in age 21-24 years.(161) Only 28% of the cohort had PHIV, but similarly to Lee *et al* (164), EIC was highest in this group compared to other HIV acquisition categories (PHIV 73%, MSM 66%, PWID 58%, heterosexual 58%).

Three of the 8 papers using a multiple visit measure, measured engagement in care in singe clinic studies during transition to adult care. Griffith *et al* (168) examined the electronic records of 89 patients (57% PHIV) who had transitioned from one paediatric clinic to two adult clinics in Maryland and New York, USA, between 2009 and 2015 (median age BHIV 25 years, PHIV 22 years). Overall 89% of young people were engaged in care at one year post transition. Hussen *et al* (163) evaluated EIC pre and post transition in 72 patients within a single hospital in Georgia, USA. In the year leading up to transition, 95% of young people were engaged in care (aged 24 years [IQR 22, 25]) which was slightly higher than 85% of young people who were engaged in care at one year post transition. EIC did significantly decline from the first to the second year post-transition, from 89% to 56% (p=<0.001). However, only 15% of the participants in this study had PHIV and results were not stratified by mode of HIV acquisition. The final study using multiple visits to measure EIC around the

time of transition was Ryscavage *et al* (165). In this study EIC in 50 young people (of whom 35% were PHIV) pre-transfer was compared to 43 different young people (37% PHIV) post transition. The study included young people who had attended a single paediatric clinic and followed them as they transitioned to three adult clinics in Maryland, USA from 2004 to 2012. The median age at transition was 21.8 (range 19.2, 26.9) years in the PHIV group compared to 25 (19.1, 28.2) years in the BHIV group. No statistical difference was found between the proportion in each of these groups who remained engaged in care (60% vs. 50% respectively).

Finally, Davies *et al* (153) used multiple visits to measure EIC in a retrospective study examining EIC at three time points following transfer of care across four cohort studies in Cape Town, South Africa. Transfer in this context is different to transition in Europe and North America and was defined as the movement of patients from a tertiary to primary care centre. However, in some cases this did coincide with a transition from a usually paediatric tertiary care service to an adult primary care service.(153) A total of 460 young people (90% PHIV) aged 10-19 years at transfer (72% 10-14 years), on ART, and with a Department of Health number, were included. EIC declined with increasing time from transfer, with 90% engaged in care one year after transfer, 88% at two years, and 84% after three years. EIC was higher at one and two years post-transfer in those aged 10-14 years at transfer, compared to 15-19 years olds (year 1: 93% vs. 81%,. year 2: 90% vs. 85%, respectively), but similar at three years (85% vs. 84%).

The stricter definitions of EIC employed in these eight papers (123,153,161–165,168) led to lower estimates of EIC prevalence when compared to studies using a measure of at least one visit.(123,154–156,159,160,162,166,167) In addition, the two studies that compared EIC between young people with PHIV and BHIV reported higher EIC in those with PHIV.(161,164) Furthermore, two studies measured EIC post transition to adult or primary services and both reported EIC declined with time post transfer.(153,163) Finally, all five papers that measured EIC by age,(123,153,161,162,164) report decreasing EIC with older age. Two of these studies had already show this pattern using an alternative EIC measure.(123,162)

Finally three of the 17 papers reviewed used alternative ways of measuring EIC, of which one was not defined. In a large study from sub-Saharan Africa, Pantelic *et al* (158) measured EIC in young people aged 10-19 years (79% PHIV) who had ever initiated ART treatment across 53 clinics (n=1,059). EIC was measured as a combination of self-reported attendance at all clinic visits within the last year as well as >85% ART adherence over the last week. Using this definition, 37% of young people over 2 years were engaged in care. In the second study, Gingaras *et al* (156) measured EIC longitudinally in 545 patients in a single clinic in Romania 92% of young people were EIC at 15 years, 84% at 20 years and 74% at 25 years using a definition of EIC of at least one visit in the previous year.(156)

Lastly, Izzo *et al* (157) describe the characteristics of 24 young people who had transferred to adult care at age ≈18 years in a single centre in Italy between 2004 and 2016. Of these, 80% were retained in care at the end of follow up, a median of 52 months later, though the definition of what constituted "retained in care" was not specified.

In summary, there was heterogeneity in the way EIC was measured across the 17 papers in my review. Eight different definitions were used to measure EIC. Three studies compared young people with PHIV and BHIV, (161,164,165) of which two reported that young people with PHIV had higher EIC.(161,165) Of five studies that stratified EIC by age, four reported that EIC declined with increasing age.(75,123,156,162) Finally, eight studies used a definition with at least one measurement over six months,(159,160,166,167) one year (123,155,162) or two years,(154) and EIC was generally higher in these studies than using stricter definitions incorporating multiple visits.(123,153,161–165,168)

2.3.3.1. Predictors, barriers and facilitators associated with engagement in care

Finally, eight quantitative (156,158,161–164,166,168) and two qualitative papers (159,160) identified predictors of, or facilitators and barriers to, EIC (Table 2.4). Across the ten papers, exposure variables included could be grouped into six domains: sociodemographic; risk behaviour practices; mental health; clinic; HIV experience and management; and HIV markers. Here I present study findings first by study and then by domain.

Only one European study, from Romania, and one Sub-Saharan African paper, from South Africa, reported predictors of EIC from quantitative analyses. In Gingaras *et al's* (156) analysis of EIC in 545 young people with PHIV in a paediatric HIV clinic, included predictors of EIC were from the sociodemographic and HIV marker domains. Only viral load and CD4 count were associated with disengagement in care. Young people with a viral load ≥400c/mL were more likely to be not engaged in care (15.1%) than young people with a viral load <400c/mL (10.5%, p=<0.001). In addition, severe immunosuppression was associated with having higher proportion of disengagement (not engaged in care: CD4 <200 cells/µL, 15.1%; CD4 200-349 cells/µL, 15.6%; CD4 350-499 cells/µL, 11.9%; CD4 ≥500 cells/µL, 11.6%, p=<0.001).

Pantelic *et al* (158) also reported an association between viral load from the HIV markers domain and EIC in their study of 979 young people (79% PHIV) aged 10-19 years of age in the Eastern Cape, South Africa. Viral load was not included in the main model, and was instead used to validate the self-reported EIC outcome variable in a subset of 514 young people who had available viral load data. After adjusting for sociodemographic factors and HIV acquisition (HIV marker domain), EIC was associated with lower odds of VL>1000c/mL (OR 0.37, 95%CI 0.22, 0.61). In the main model, Pantelic *et al* (158) examined the impact of four different types of discrimination (HIV experience and management and clinic domains) and internalised HIV stigma (mental health domain) on EIC in young people. These were discrimination due to the young person's HIV status (being teased/losing friends); discrimination due to a family members HIV status (being gossiped about or treated badly due to a family members HIV status); discrimination by clinic staff (frequency of being shouted at by clinic staff). In a multivariable logistic regression model adjusted for sociodemographic and HIV markers factors, discrimination in by clinic staff was associated

with reduced EIC (OR 0.54, 95%CI 0.37, 0.78) as was internalised stigma (OR 0.81, 95%CI 0.71, 0.94).

Six studies from the USA reported predictors of EIC. In the first study, Gebrezgi *et al* (161) investigated the effect of neighbourhood factors on EIC including socioeconomic status, non-Hispanic black density (a proxy for segregation) and rural/urban status in a population study of 2,872 young people in Florida (sociodemographic domain). After adjusting for individual and neighbourhood factors, a number of exposures were identified to be associated with EIC, from the sociodemographic and HIV markers domains. From the sociodemographic domain, males were less likely to be engaged in care than females (PR 0.86, 95%CI 0.79, 0.93). Those aged 13-17 years had better EIC than 18-20 year olds (PR 0.85, 95%CI 0.78, 0.92) and 21-24 year olds (PR 0.74, 95%CI 0.68, 0.80). Young people living in low socioeconomic areas had better EIC than young people in higher socioeconomic areas (PR 1.15, 95%CI 1.02, 1.20). Hispanics were less likely to be engaged in care than people of non-Hispanic white ethnicity (PR 0,88, 95%CI 0.81, 0.95) and areas with a high density of people of non-Hispanic black ethnicity were less likely to be engaged in care than areas of lower density (PR 0.90, 95%CI 0.83, 0.98). From the HIV markers domain, calendar year of diagnosis was associated with EIC, with young people diagnosed in 2005-2009 being less likely to be engaged in care (PR 0.88, 95%CI 0.81, 0.95) than people diagnosed between 2010-2014. Compared to young people with heterosexual acquisition of HIV, young people living with PHIV (PR 1.17, 95%CI 1.03, 1.33) and MSM (PR 1.26, 95%CI 1.15, 1.49) were more likely to be engaged in care. Finally, young people who had a previous diagnosis of AIDS (defined as AIDS <2016) were more likely to be engaged in care than young people who had not had a previous diagnosis of AIDS (PR 1.22, 95%CI 1.16, 1.30). However, young people living with PHIV only made up 28% of the participants in this study.

In the second study, Gray *et al* (162) analysed data from 9,562 young people living with PHIV across the USA. . Only variables from the sociodemographic domain were included in the analysis. In unadjusted analysis, female participants were more likely to be engaged in care than males (PR 1.1, 95%CI 1.1, 1.2). Young people aged 13-17 years had a higher prevalence of EIC that 18-25 year olds (prevalence ratio (PR) 1.2, 95%CI 1.1, 1.2). In addition, Hispanics/Latinos were more likely to be engaged in care than white participants (PR 1.1,

95%CI 1.1, 1.2). Finally, young people born outside the USA were more likely to be engaged in care than young people born in the USA (PR, 1.1, 95%CI 1.1, 1.2).

In their retrospective cohort study of 89 young people living with HIV (57% PHIV) in the USA, Griffith *et al* (168) investigated variables from the sociodemographic, risk behaviour practices, mental health and HIV markers domains in an adjusted analysis for EIC. The only variable found to be associated with EIC was HIV acquisition (HIV markers domain). Young people with PHIV were found to be more likely to be engaged in care post transition to adult care (OR 14.95, 95%CI 1.38, 161.68 p=0.03) compared to young MSM.

In the fourth study from the USA, Hussen e*t al* (163) measured EIC in 72 young people post transition to adult care. Variables from the sociodemographic, HIV experience and management domains and HIV markers were investigated in multivariable models for EIC. Increased time between final paediatric and first adult appointment (HIV management and experience domain) was reported to be associated with worse engagement in adult care after two years (Relative Risk (RR) 0.92, 95%CI 0.85, 0.99, p=0.03 per three month increase). Older age at transition from paediatric to adult care was associated with better EIC (Relative Risk (RR) 1.16 per year older, 95%CI 1.00, 1.35, p=0.047).

In Lee *et al's* (164) study including 680 15-25 year olds in the USA, clinics were assessed on five youth friendly structures (clinic domain) based on the WHO youth friendly framework. After adjusting for sociodemographic and HIV marker factors, three of the five youth friendly structures were reported to be associated with EIC: youth friendly space (aOR2.47, 95%CI 1.11, 5.52); evening clinic hours (OR 1.94, 1.13, 3.33); and providers with adolescent training (OR 1.98, 95%CI 1.01, 3.86). In addition, Lee *et al* (164), reported young people who had been prescribed ART were more likely to be engaged in care than young people who were not on ART (OR 4.96, 95%CI 3.08, 8.01). The model did not include viral load and it is possible that ART acted as a proxy for viral load to some extent.

In the final paper from USA, Tassiopoulos *et al* (166) compared sociodemographic, HIV markers and self-reported perceived social support (mental health domain) and self-management (HIV experience and management domain) by transition status in 455 young

people. Higher perceived social support was associated with higher EIC (OR 1.05, 95%CI 1.01, 1.10) as was increased ability to self-manage (OR 3.40, 95%CI 1.33, 9.12).

Two qualitative papers from South Africa reported facilitators and barriers to EIC. Following content analysis on data from interviews with 16 young people from the adolescent clinic and 12 from the paediatric clinic, Zanoni et al (2018) (159) reported a number of the barriers and facilitators to EIC that were related to clinic environment and clinic staff (clinic domain). Young people in the paediatric clinic identified appointments scheduled during the school day as a barrier to EIC because young people felt the need to balance their health and educational needs. Not only did this put their health at risk, but it also created tension with staff that then became an additional barrier to EIC. In addition, participants attending the paediatric clinic who reported difficulty disclosing their HIV status to others, felt subsequent increased internalised stigma and social isolation both of which were described as decreasing EIC. The importance of the timing of clinics was reiterated by young people attending the specialist adolescent clinic. They reported that there were several benefits to running after school clinics that acted as facilitators to EIC. Not only could young people access the support and health benefits of attending clinic more regularly but also it reduced the stigma of missing school and the negative impact on schoolwork. Improved EIC provided more regular contact with peers providing social support which further improved EIC. In addition, young people reported that more regular contact with clinic staff, meant that they developed a more positive relationships with the staff in the adolescent clinic compared to the relationship they had with the same staff in the paediatric clinic.

Finally, in the second qualitative paper from South Africa, Zanoni et al (2020) (160) conducted in-depth interviews with 41 young people and 18 of their caregivers to identify factors to improve EIC prior to transition to adult care. Young people who understood their HIV diagnosis at an earlier age (defined as before 12 years of age) described minimal internalized stigma and higher self-esteem with a subsequent improvement in EIC. Conversely, young people relayed negative consequences for their self-identity when their HIV was disclosed to them later, or when others had lied to them or they had a traumatic disclosure. All of these factors impacted on their relationships with clinic staff and subsequent EIC. The paper also describe a third group of young people who despite carers reporting a full disclosure process,

the young people remained in denial about their HIV which compromised their ability to fully engage in HIV care. Finally, young people who were orphaned and had frequent changes in carers, had reduced support to manage their HIV in general, but specifically in travelling to and attending to clinic.

2.3.3.2. Summary

Across the ten studies reporting predictors (156,158,161–164,166,168) or facilitators and barriers (159,160) to EIC, factors found to be associated with EIC came under five out of the six domains (sociodemographic, HIV markers, clinic, HIV experiences and management and mental health). Most variables found to be associated with EIC were in the sociodemographic and HIV markers domain. There was very little consistency across the 10 papers, with most of the variables found to be associated with EIC each being from a single study. Eight variables were found by more than one study. Two studies found female sex, younger age, and Hispanic/ Latino ethnicity (vs, white young people) from the sociodemographic domain to be associated with higher EIC.(161,162) In the mental health domain, reduced internalised stigma (158,159) and higher perceived social support.(159,166) In the clinic domain, two studies reported that evening clinic appointments helped improved EIC.(159,164) Finally, in the HIV markers domain, two studies reported that young people with PHIV were more likely to be engaged in care compared to young people with BHIV (161,168) and two studies found young people who had an undetectable viral load (<400c/mL) were more likely to be engaged in care.(156,158)

Table 2.4: Summary of predictors, barriers and facilitators of EIC

Author, year (ref)	Country	Sociodemographic		Risk behaviour practices		Mental health		Clinic		HIV experience and management		HIV markers	
Quantitative studies													
		Inc.[1]	Sig.[2]	Inc.	Sig.	Inc.	Sig.	Inc.	Sig.	Inc.	Sig.	Inc.	Sig.
Europe													
Gingaras, 2019(156)	Romania	Y	N	N	n/a	N	n/a	N	n/a	N	n/a	Y	Y
Sub-Saharan Africa													
Pantelic, 2020(158)	South Africa	Y	N	N	n/a	Y	Y	Y	Y	Y	N	Y	Y
USA													
Gebrezgi, 2019(161)	USA	Y	Y	N	n/a	N	n/a	N	n/a	N	n/a	Y	Y
Gray, 2019(162)	USA	Y	Y	N	n/a	N	n/a	N	n/a	N	n/a	N	n/a
Griffith, 2019(168)	USA	Y	N	Y	N	Y	N	Y	N	N	n/a	Y	Y
Hussen, 2017(163)	USA	Y	Y	N	n/a	N	n/a	N	n/a	Y	Y	Y	N
Lee, 2016(164)	USA	Y	N	N	n/a	N	n/a	Y	Y	N	n/a	Y	Y
Tassiopoulos, 2019(166)	USA	Y	N	N	n/a	Y	Y	Y	N	Y	Y	Y	N
Qualitative studies													
		Facilitates	Barrier	Facilitates	Barrier	Facilitates	Barrier	Facilitates	Barrier	Facilitates	Barrier	Facilitates	Barrier
Zanoni, 2018(159)	South Africa	N	Y	N	N	Y	Y	Y	Y	Y	Y	N	N
Zanoni, 2020(160)	South Africa	N	Y	N	N	Y	Y	Y	Y	Y	Y	N	N

[1] Variables from this group of predictors included in the analysis

[2] Variables from this group reported to be associated with EIC in the analysis

2.4. Discussion

In this literature review, I have summarised the methodology and presented the findings from 17 papers on EIC in young people with PHIV in high and high middle income countries. All papers were published in the last five years showing the recent recognition of the importance of EIC in HIV care.

There was high variation in estimates of prevalence of EIC across the included studies making comparison and generalisation difficult. There are likely to be a number of reasons for this. Firstly, high variation in estimates may be largely due to the different definitions used. Secondly, comparing young people in the process of transferring to adult care to either young people in stable paediatric or adult care is problematic due to the additional complexities of transitioning care. Finally, healthcare provision and geographical settings vary hugely across the papers.

The majority of the studies were from the USA, of which most were multicentre studies, although despite the studies being multicentre, five of the nine studies had a sample size of less than 150 participants each. Of the smaller number of studies from sub-Saharan Africa and Europe, most were single centre.

A wide range of predictors and barriers of EIC were identified, with little consensus between studies. The majority of predictors fell into the sociodemographic and HIV markers domains, and perhaps unsurprisingly variables from these domains were most commonly included in these analyses, as these variables are often available from routine healthcare records. Very few studies investigated factors within the risk behaviours, mental health domains and HIV experiences and management domains that may have great impact on young people's EIC.

As national cohorts, Chappell *et al* (155) and Gray *et al* (162) are the two studies that are most likely to most accurately capture engagement in care across a population. This is because the risk from regional and especially single clinic studies is that patients could be erroneously classified as disengaged when they have actually decided to attend an alternative HIV clinics, transitioned to adult care or moved out of the area. National cohorts should have mechanisms to track these patients and identify such situations. Chappell *et al* (155) reported a much higher prevalence of EIC (98%) in the UK compared to Grey *et al* (75%) in the USA, but there were key methodological differences. To be included in the UK analyses, patients had to be in care in the previous year, whereas in the USA analyses, they included

all patients diagnosed and alive (through linkage with national mortality records) at the end of 2015. In addition, within the Gray *et al* (162) study, two definitions of EIC were compared, and lower prevalence of EIC (61%) was found with a stricter definition. It is therefore hard to know whether the differences between the estimates of EIC in the two national cohorts are real or not.

One of the major questions when investigating EIC in young people with PHIV is whether young people drop out of care because they have PHIV or because they are adolescents. From the literature reviewed in this chapter, it may be that both factors have a role. There was the suggestion of a trend of decreasing prevalence of EIC with increasing age across all of the studies that stratified EIC by age, including the studies that only included young people with PHIV as well as the studies that also included young people with BHIV. Furthermore, two studies found age was a predictor of EIC in multivariable analysis, similarly reporting that EIC reduced with increasing age. Additionally, of the four studies that compared EIC between young people with PHIV and BHIV, three reported that young people with BHIV had worse EIC, two of these in multivariable analyses. The most compelling evidence that both age and HIV acquisition are relevant is from Gebrezgi *et al*.(161) In their large study they measured EIC using a multiple visit definition of EIC (≥2 clinic visits with ≥30 days apart within 1 year), and in multivariable analysis, found that both younger age and PHIV acquisition of HIV were associated with better EIC. However, this is just one study and so needs corroboration from further research.

Another possible limitation of the studies included in this analysis, is that most of the studies defined the denominator (for example in care in last year or appointment pre transition), and then they followed up the cohort. In these studies, it means that the population at the beginning was in care. In addition, none of the studies looked at changes in EIC over time. Most studies defined their measure of EIC in response to the data available. Ideally, in a cohort of young people, maturing into adulthood and transitioning to adult/adolescent care, it would be useful to be able to track them over time to see their patterns of EIC, when they drop out and reconnect into care and what variables affect their EIC at what time points. However, this is more complicated to measure and few national datasets exist to enable this level of scrutiny.

Finally, all of the studies in this literature review used the same definition to measure EIC across all of the participants in their studies, irrespective of the young person's age or clinical status. Setting the same standard for how often a patient should be seen is inevitably not

going to be appropriate for a whole cohort of patients,(136) especially one as heterogeneous at young people living with PHIV. Some patients may have very well managed HIV and less need for very regular appointments, whilst others may have health issues which require regular visits. Arguably, these studies are therefore measuring EIC at a basic public health level,(138) but not providing enough detail to know whether patients are attending clinic as their individual health care needs necessitate.

In conclusion, there is an urgent need to both characterise engagement in HIV care during adolescence and young adulthood, and crucially, to understanding what factors support or prevent young people from attending HIV care. Studies in this literature review used a wide range of measures of EIC and there was little consistency in identified predictors. Importantly, studies were cross sectional and took no account of individual health care status in deciding when the next appointment should occur. Further investigation is needed to understand this important health care outcome.

Chapter 3. Defining the engagement in care outcome measure

3.1. Introduction

The first stage of this PhD project was to decide what was the most appropriate measure of EIC for use in young people with PHIV. Management of young people living with PHIV is complicated as they receive HIV care in adult as well as paediatric HIV services. Whilst many young people receiving HIV care in paediatric clinics routinely have clinic visits every three to four months,(173) older participants and those attending university quite regularly have clinic visits every 6 months, in accordance with adult HIV guidelines.(174) Basing this analysis on one of the commonly used EIC definitions from the literature with universal expected gaps between clinic visits would not pick up these nuances. In addition, neither scheduled nor attended visits are collected in the datasets used for this analysis which meant missed visits and appointment adherence could not be used for this analysis. At the outset of my PhD, I discussed potential definitions of EIC for this thesis with members of the AALPHI Steering Committee. Clinicians reported that they did not use a "standard" follow-up for young people with PHIV because their decisions about when next to see patients were more individualised, dependant on clinical and psychosocial characteristics. Based on these factors, I decided to use a sensitive visit constancy measure of EIC that could pick up changes in the health status and treatment of young people who received clinical care in paediatric and adult HIV care. The AALPHI Steering Committee recommended I adapt a novel EIC algorithm for adults developed by Howarth *et al* (151) due to its consideration of clinical factors in the decision on the timing of the next clinic appointment.

In this chapter, I detail the methods that I used to adapt the Howarth *et al*'s (151) EIC algorithm. Due to the increased number of considerations for managing young people with PHIV compared to adults with HIV, I developed three EIC flowcharts that classified clinical management (using a decision tree approach(175)) from the Howarth *et al* algorithm for use in young people. I describe how I assembled and prepared the dataset for this analysis, how the data were cleaned, and how I managed missing data. Finally, I describe how the flowcharts were used to classify EIC in young people with PHIV in the AALPHI cohort.

3.2. Objectives

- To develop a sensitive measure of EIC in order to take into account changes over time in treatment and health status for young people with perinatal HIV in England.
- To apply the measure to describe EIC in young people with perinatal HIV in England through quantitative analysis of the AALPHI cohort dataset.

3.3. Methods

3.3.1. Definitions

For clarity, a few of the main terms used through this chapter are defined in Table 3.1.

Table 3.1: Chapter definitions

Phrase	Definition
engagement in care (EIC)	The spectrum of engagement in care
in care	Engaged in care
time to next scheduled appointment	Time to participants next scheduled appointment as defined by the flowcharts (not an actual visit)
visit/visit date	Actual visit or visit date attended by participant

3.3.2. The Howarth et al algorithm

3.3.2.1. Clinical criteria for use in adults

Howarth *et al* (2016) developed the EIC algorithm for adults with HIV by carrying out semi-structured interviews with HIV clinicians.(151) Their rationale for developing this new algorithm was that standard EIC measures do not take into account how the frequency of clinic attendance is based on individual patients' health and treatment status and that this changes over time. Howarth *et al* interviewed eight adult HIV clinicians in 2013 and 2014 and the reasons for time to next appointment for 66 patients were discussed. Content analysis was conducted on interview transcripts identifying factors determining the scheduling of the next appointment, and time frames for the next scheduled appointment were identified to develop the algorithm. The clinicians reported that while they did follow guidelines for appointment scheduling, individual psychosocial and physical comorbidities and clinical factors made scheduling more individualised. However, although psychosocial comorbidities about mental health and social support needs were cited as a common reason for adjusting "standard" appointment scheduling, Howarth *et al* commented that these factors were

difficult to include in EIC analyses. This is because these factors are often not recorded electronically in hospitals or reported routinely in cohort studies, and likewise in my case they were not available in the CHIPS and AALPHI datasets. As a result, the Howarth *et al* EIC algorithm used clinical factors alone to predict when patients should next be seen in clinic (i.e. the expected next appointment date) and thus the algorithm developed for my analysis also only used clinical factors.

Table 3.2 presents the clinical factors and the corresponding scheduling of the next appointment according to the Howarth *et al* EIC algorithm. So for example, an adult patient who is not on ART, and has a CD4 cell count ≤350 cells/µL or any drop in CD4 cell count will be classified to be seen in 2 months. If more than one set of clinical factors applies at the time of the clinic visit the shortest time to the next scheduled appointment is taken.

Table 3.2: Clinical factors predicting the time to next scheduled appointment date in Howarth *et al*'s engagement in care algorithm (1)

Clinical factors at the current clinic visit	**Time to next scheduled appointment:**
Less than 1 month since HIV diagnosis	2 months
AIDS diagnosis	2 months
Started ART	2 months
Started new ART combination	2 months
Not on ART	
CD4 cell count ≤350 cells/μL or any drop in CD4 cell count	2 months
CD4 cell count ≤350 cells/μL and no drop in CD4 cell count	4 months
CD4 cell count 351-499 cells/μL	4 months
CD4 cell count ≥500 cells/μL and CD4 cell count drop ≥100 cells/μL	4 months
CD4 cell count ≥500 cells/μL and CD4 cell count drop <100 cells/μL and viral load ≥100,000c/mL	4 months
CD4 cell count ≥500 cells/μL and CD4 cell count drop <100 cells/μL and viral load <100,000c/mL	6 months
Already started ART	
Viral load >200c/mL	2 months
Viral load 51-200c/mL and does not appear to be a blip[1]	2 months
Viral load 51-200c/mL and appears to be a blip	4 months
Viral load ≤50c/mL and CD4 cell count ≤200 cells/μL	4 months
Viral load ≤50c/mL and CD4 cell count >200 cells/μL	6 months

[1]Blips are defined as a viral load 51-200c/mL following a previous viral load ≤50c/mL.

3.3.2.2. Management of multiple visits in the Howarth et al algorithm

Howarth *et al* (151) reported that patients often had multiple measures of different clinical factors (e.g. CD4, viral load) within very short time periods. On examination, these episodes were considered likely to be linked to the same clinic visit, and so clinic visits were grouped within month-long time periods.(151) For each month the lowest CD4 cell count and highest viral load were chosen, and, together with the other clinical factors detailed in Table 3.2, were used to calculate the date of the next scheduled clinic appointment.

3.3.2.3. Measuring 'in care'

For the Howarth *et al* (151) algorithm (and this analysis) the outcome is a binary classification of 'in care', coded as either 'yes' (i.e. engaged in care) or 'no' (i.e. not engaged in care) for each month of follow-up. The next scheduled appointment date was compared to the next observed visit date, and participants were classified as in care if their observed visit occurred on or before the scheduled appointment date. However if the observed visit occurred after the scheduled appointment date, the period of time between the previous visit and the scheduled next appointment was classified as in care, and the period of time following the scheduled appointment until the observed visit was classified as out of care. Table 3.3 presents an example of how a single patient's time following a clinic visit would be measured, using the Howarth *et al* algorithm. In this example a patient makes a clinic visit on 16 July 2008, and, based on their clinical characteristics (not shown), the time to their next scheduled appointment is two months later, on 16 September 2008. However, they do not attend until 16 October 2008. Therefore, months one and two would be classified as "in care", as the periods of follow-up time both precede the next scheduled appointment date of 16 September 2008. However, month three, the time following the next scheduled appointment date (16 September 2008) and preceding the next observed visit date (16 October 2008) would be classified as out of care. In this way, each person month of follow-up is ether in care of out of care. Once Howarth *et al* had developed the algorithm, they then applied It to data from the UK Collaborative HIV Cohort (UK CHIC) study.

Table 3.3: An example of a single participant classified in or out of care between two observed clinic visits, using the Howarth *et al* algorithm

Month	Observed visit date	Next scheduled appointment date	Month start date	Month end date	In care (Y / N)
1	16 Jul 2008	16 Sept 2008	16 Jul 2008	15 Aug 2008	Y
2			16 Aug 2008	15 Sept 2008	Y
3			16 Sept 2008	15 Oct 2008	N
4	16 Oct 2008				

3.3.3. Adapting the clinical criteria and developing the flowcharts for use in young people

Howarth *et al*'s EIC algorithm was originally developed for use in adults living with HIV and so required adaptation for use in PHIV young people. To assist in this process I met with two clinicians caring for young people living with PHIV in large London clinics and discussed the key aspects of the algorithm and how it should be adapted.

3.3.3.1. Clinical criteria for use in young people

The first step was to update Howarth *et al's* algorithm in line with the most recent British HIV Association (BHIVA) clinical monitoring guidelines, which had been published after Howarth *et al's* algorithm had been developed.(174) This provided a foundation to ensure that any later adaptations that I made to the Howarth *et al* algorithm were never more lenient than the follow-up recommendations made for adults living with HIV. The next step was for me to incorporate maximum appointment times for patients still in paediatric care based on the PENTA paediatric HIV guidelines,(173) which suggest more regular monitoring than for adults, due to some additional complexities of paediatric patients. For example, BHIVA monitoring guidelines for adults (174) recommend that if a participant is established on ART with two consecutive viral loads >50c/mL over one year apart, they do not require a subsequent CD4 measure (unless there is subsequent viral load failure or symptoms). The PENTA guidelines for children,(173) however, recommend that CD4 cell counts are measured every three to four months, regardless of viral load. Another example of an additional complexity in the paediatric population is weight. Young people who weigh <40kg may still be on weight-adjusted doses of ART (rather than fixed adult doses) and so require more regular appointments (minimum every three months) to ensure that they are still on the correct dose for their weight as they grow.

Initially, I categorised viral loads as in the Howarth *et al* algorithm (151) and BHIVA monitoring guidelines (174):

- ≤50c/mL
- 51-200 c/mL
- >200 c/mL

However, my discussions with the two clinicians revealed that they would react differently to a viral load >50c/mL for a patient on a NNRTI compared to those on a PI with greater urgency in following up a patient on NNRTIs. Therefore, the focus of scheduling the next appointment was the combination of ART regimen (PI vs NNRTI), rather than whether the amount of virus >50c/mL was considered a viral load blip or not. On this basis, I changed viral load categorisation to a binary ≤50 or >50c/mL variable.

For the purposes of this analysis, 'ART' means mono, dual or cART unless otherwise specified, and a cART regimen is defined as ≥3 ART drugs, including regimens containing a NNRTI, or a PI regimen with a booster.

3.3.3.2. Development of three flowcharts for young people

Through the conversations with clinicians, it also became evident to me that three main groupings of PHIV young people (based on ART status and viral load) were employed in clinical decision making to determine scheduled appointment dates.

1) Flowchart A: young people living with PHIV on ART with viral load ≤50c/mL
2) Flowchart B: young people living with PHIV on ART or starting/restarting ART with viral load >50c/mL
3) Flowchart C: young people living with PHIV off ART

Additionally within each of these groupings, there were a series of steps, in which different criteria were applied before the next scheduled appointment date could be estimated. Thus, I developed separate flowcharts for each of the three main groupings, based on a decision tree approach, in order to visually show each step. These were for the following groups of patients, at their "current" visit:

I presented the EIC flowcharts for young people living with PHIV to the CHIPS Steering Committee in September 2017. Many of the clinicians from the larger UK clinics treating children and young people living with PHIV were members of the Steering Committee and attended this meeting, and so it was an ideal opportunity to discuss the draft flowcharts with a wider group of clinicians as they were being developed. The draft versions presented are in Appendix A. The consensus from the Steering Committee was that the flowcharts were

clinically valid. However, some alterations were suggested, which I made (changes are summarised in Appendix B. Additionally I made final refinements during the statistical analysis programming stage, when minor inconsistencies were uncovered.

3.3.3.3. Engagement in care flowcharts for use in young people living with PHIV

The final three flowcharts developed after consultation with the clinicians are shown in the following figures: Figure 3.1 presents Flowchart A, Figure 3.2 Flowchart B, and Figure 3.3 Flowchart C. To note, the coloured boxes in my flowcharts are the terminal nodes and indicate the ends of decision making, with the colour itself indicating the timing of the next follow-up appointment.

Figure 3.1 shows how a patient on ART with a viral load ≤50c/mL at the current visit should be managed in relation to the scheduling of their next appointment. As an example, if a patient has had no CDC C event in the preceding three months, was not on a new ART regimen, was on cART, had a CD4 cell count >350 cells/μL, and was in adult care with a weight ≥40kg, their next scheduled appointment would be in six months' time.

Figure 3.1 : Flowchart A: Young people living with PHIV on ART with viral load ≤50c/mL

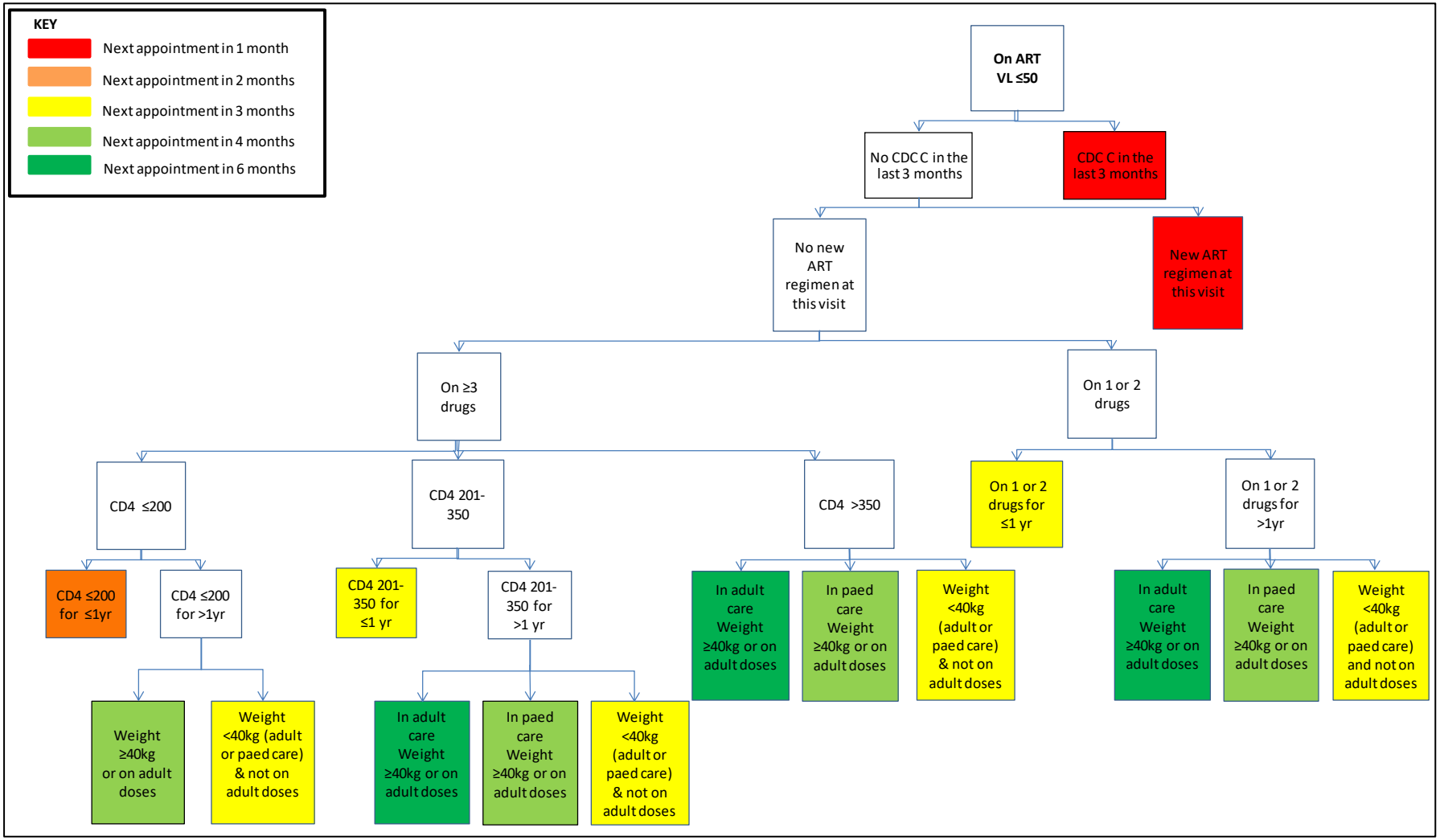


Figure 3.2 shows how a participant either already on ART, or starting or restarting ART, and with a VL >50c/mL, at the current visit should be managed in relation to the scheduling of their next appointment. As an example, if a participant had no CDC C events in the preceding three months, had been on an ART regimen for more than 6 months, was on a PI-based regimen, and this was their first VL >50c/mL, their next scheduled appointment would be in one month's time.

Figure 3.2: Flowchart B: Young people living with PHIV on ART or starting/restarting ART with viral load >50c/mL

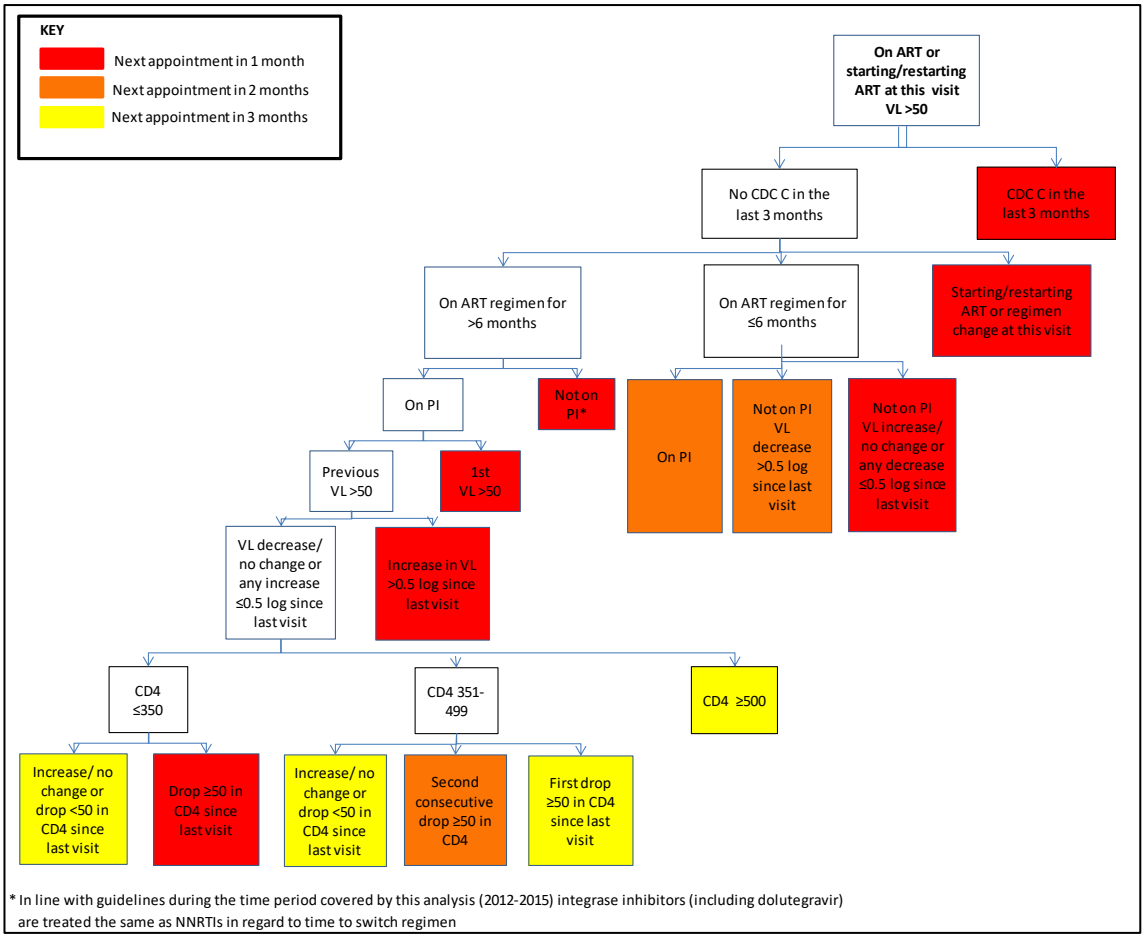
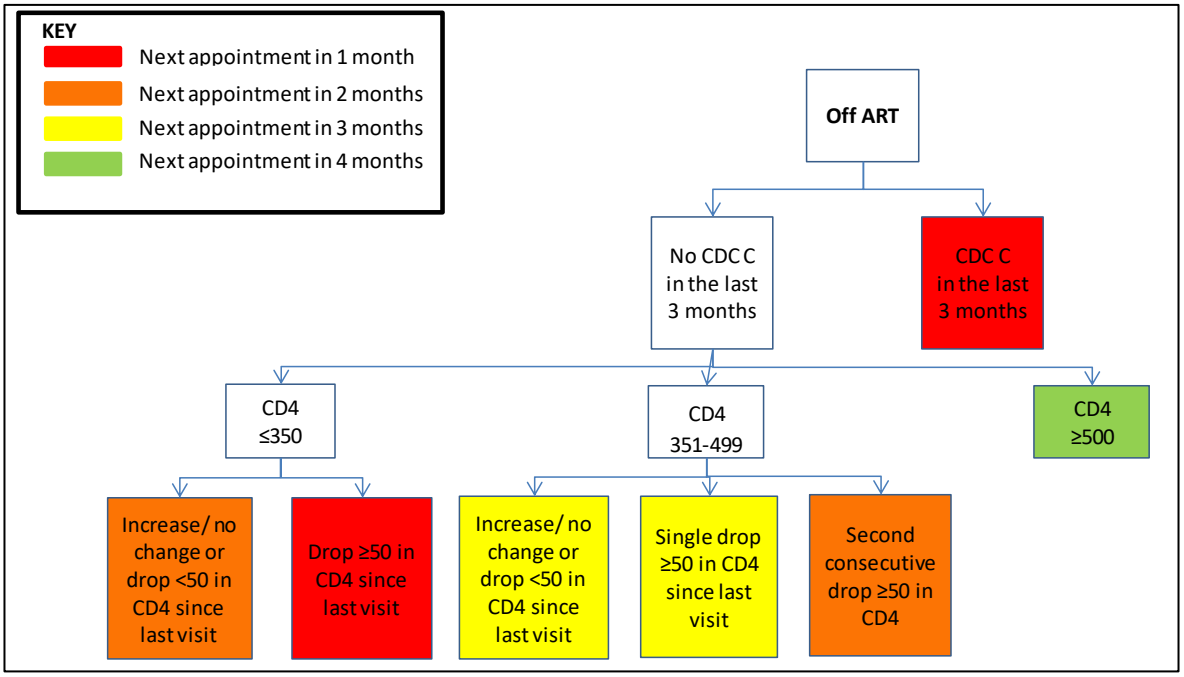


Figure 3.3 shows how a participant not taking ART at the current visit should be managed in relation to the scheduling of their next appointment. As an example, if a participant had no CDC C event in the preceding three months, and had a CD4 cell count ≥500 cells/μL, their next scheduled appointment would be in four months' time.

Figure 3.3: Flowchart C: Young people living with PHIV off ART



3.3.3.4. Comparison of engagement in care measures for adults and young people

My adaptation process of Howarth *et al's* algorithm changed the clinical factors and subsequent time to next scheduled appointment used in the adult criteria to this more complex picture for young people with HIV. Table 3.4 summarises the additional considerations and more conservative appointment scheduling in the flowcharts for young people living with PHIV compared to the criteria used for appointment scheduling for adults in the Howarth *et al* algorithm. This table is the same as Table 3.2 but has a new column with 'My amended criteria for young people living with PHIV' added to it.

Table 3.4: Adaptations to the Howarth et al algorithm for young people living with PHIV

Howarth *et al's* clinical factors at current visit	**Time to next scheduled appointment**	**My amended criteria for young people living with PHIV**
Less than 1 month since HIV diagnosis	2 months	Not applicable as have to be aware of HIV diagnosis for ≥6 months to be in AALPHI
AIDS diagnosis	2 months	1 month (and monthly for first 3 month)
Started ART	2 months	1 month
Started new ART combination	2 months	1 month
Not on ART		
CD4 cell count ≤350 cells/μL and any drop in CD4 cell count	2 months	Dependant on size of CD4 cell count change: - If increase, no change or drop of <50, next appt in 2 months - If CD4 cell count drop of ≥50, next appt in 1 month
CD4 cell count ≤350 cells/μL and no drop in CD4 cell count	4 months	2 months
CD4 cell count 351-499 cells/μL	4 months	Dependent on CD4 cell count change: - If increase, no change or drop of <50, next appt in 3 months - If single drop of ≥50, next appt in 3 months - If a consecutive drop ≥50, next appt in 2 months
CD4 cell count ≥500 cells/μL and CD4 cell count drop ≥100 cells/μL	4 months	No change – 4 months
CD4 cell count ≥500 cells/μL and CD4 cell count drop <100 cells/μL and viral load ≥100,000c/mL	4 months	No change – 4 months
CD4 cell count ≥500 cells/μL and CD4 cell count drop <100 cells/μL and viral load <100,000c/mL	6 months	4 months
Already started ART		
Viral load >200c/mL	2 months	Cut-off set at ≤50 or >50 (not ≤200). Management would depend on a number of factors: - how recently started cART - on PI or not - size of decrease or increase in VL

Howarth *et al's* clinical factors at current visit	**Time to next scheduled appointment**	**My amended criteria for young people living with PHIV**
		- if first VL >50 - CD4 cell count and CD4 cell count drop Management may be more lenient or more conservative
Viral load 51-200c/mL and does not appear to be a blip	2 months	Dependent on whether first VL is >50 or not: - If this is the first VL >50 would need appt irrespective of VL - If not first VL >50, would depend on the size of VL increase, CD4 cell count and CD4 cell count drop Management may be more lenient or more conservative
Viral load 51-200 c/mL and appears to be a blip	4 months	As above. Blip not treated differently
Viral load ≤50c/mL and CD4 cell count ≤200 cells/μL	4 months	Dependent on a number of combined factors: - Number and class of ART drugs - length of time CD4 cell count ≤200 - weight or ART dosing - whether in paediatric or adult care Management may be more lenient or more conservative
Viral load ≤50c/mL and CD4 cell count >200 cells/μL	6 months	Dependent on a number of combined factors: - number and class of ART drugs - CD4 cell count - weight or ART dosing - whether in paediatric or adult care Management may be more lenient or more conservative

Howarth *et al's* EIC algorithm grouped the possible clinical factors into 15 different pathways to determine the time to next scheduled appointment for adults (2, 4, or 6 months). In my EIC flowcharts for young people, the terminal nodes illustrate the 37 different pathways that result in the time to next scheduled appointment classification. Appendix C lists all of the clinical factors used in each stage of my flowcharts and the source/reference for each stage.

3.3.4. Assembling the dataset

I conducted data manipulation, cleaning and analysis in STATA version 15.(176)

3.3.4.1. Data linkage

Datasets from two UK-based HIV cohort studies were used in this analysis:

- the AALPHI cohort, and
- the CHIPS cohort.

All AALPHI participants were in the CHIPS cohort as this was one of the AALPHI eligibility criteria, and the CHIPS study number was common to both datasets. AALPHI data were linked to five CHIPS datasets (CD4 cell count dataset, viral load dataset, weight/height dataset, ART dataset and summary dataset (for date of last clinic visit)) which contained the clinical data required for this analysis, using the CHIPS study number. All of the CHIPS datasets, apart from the summary dataset, were in long format (multiple rows per patient) in contrast to the AALPHI datasets (and the CHIPS summary dataset) which were in wide format (one row per patient). Therefore, the relevant data from CHIPS datasets in long format were converted into wide format prior to the datasets being combined into one dataset.

3.3.4.2. Inclusion criteria

Clinical data (CD4 cell count, viral load etc.) were an essential component of this analysis. Therefore, participants who had no clinical data in the CHIPS dataset following their AALPHI interview date were excluded from the analysis.

3.3.4.3. Follow-up time

The in care outcome measure was defined using data on young people's attendance at their HIV clinic. For this analysis, follow-up for each AALPHI participant was for one year following their first AALPHI interview date.

3.3.4.4. Proxy visit dates

As actual clinic visit dates were not collected in the CHIPS or AALPHI studies, dates of clinical markers were used as proxy clinic visit dates. This is based on the assumption that participants would have to attend the clinic for these measurements to be taken. This is a common strategy used to estimate visit dates in many cohort study analyses.(151,177)

Creating proxy clinic visit dates

For the first stage of manipulation, I used multiple proxy markers to increase the chance of capturing true attendance in each clinic (CD4, viral load, weight, and height, ART start, switch or end). As an example of the sorts of data that I was manipulating, Table 3.5 presents how reported clinical data might have appeared for one participant during one week of follow-up.

Table 3.5: Example of clinical data for one participant over one week of follow-up

Date	15 Jan 2014	16 Jan 2014	17 Jan 2014	18 Jan 2014	19 Jan 2014	20 Jan 2014	21 Jan 2014
Proxy marker	Height	CD4		VL			
	Weight						

It is unlikely that the example participant depicted in Table 3.5 attended their clinic on three different days within the same week. It is much more likely that they attended the clinic on 15 January 2014 when they had their height and weight recorded, and a blood sample was taken on this date. The CD4 result came back to the clinic the next day, and the viral load two days after that, and these results were then recorded on the CHIPS CRF and entered into the database.

In order to manage these multiple proxy markers and not overestimate the number of actual clinic visits, I dropped all visit dates within 7 days of an earlier visit and collapsed the data to contain multiple markers in one row grouped by CHIPS study number and visit date. This is shown for a hypothetical participant in Table 3.6 and Table 3.7. Prior to collapsing the data, I first examined the data for any repeated clinical measures of the same type (so for example two different viral loads within the same week) which may indicate a true repeat visit.

Table 3.6: Proxy marker format before data collapsed for a hypothetical participant

CHIPS Study no.	Clinic	AALPHI interview date	DOB	Sex	Visit date	Measure type	CD4 count (cells/µL)	Weight	Viral load c/mL	ART date[1]
123456	Clinic A	01/01/2013	01/01/1997	Male	01/01/2013	CD4	41			
123456	Clinic A	01/01/2013	01/01/1997	Male	01/01/2013	Weight		25.2		
123456	Clinic A	01/01/2013	01/01/1997	Male	03/01/2013	VL			1435000	
123456	Clinic A	01/01/2013	01/01/1997	Male	15/02/2013	CD4	91			
123456	Clinic A	01/01/2013	01/01/1997	Male	15/02/2013	ART				15/02/2013
123456	Clinic A	01/01/2013	01/01/1997	Male	16/02/2013	VL			4033028	

[1] Date can be for ART start, switch or end

Table 3.7: Proxy marker format after data collapsed for a hypothetical participant

CHIPS Study no.	Clinic	AALPHI interview date	DOB	Sex	Visit date	Visit count	CD4 count (cells/µL)	Weight	Viral load c/mL	ART date
123456	Clinic A	01/01/2013	01/01/1997	Male	01/01/2013	1	41	25.2	1435000	
123456	Clinic A	01/01/2013	01/01/1997	Male	15/02/2013	2	91		4033028	15/02/2013

Handling duplicate CD4 cell counts, viral loads and weights

I individually examined all CD4 cell counts, viral loads and weights for which there was a subsequent measure within the next 7 days. For the majority of the subsequent measures, the same value of the clinical indicator had been reported, and so I dropped them, assuming the same value had erroneously been entered twice. Where any of the following criteria were met for the subsequent measure, I then checked the CHIPS paper CRF:

- CD4 cell count difference >100cells/μL
- Viral load difference >1 log
- Weight difference >3kg

In total, the CRFs of seven participants with repeated CD4 cell count or viral load measurements were checked. Three participants had CRF data entered incorrectly, so the data for these participants were corrected. For two participants the data reported on the CRF may have been completed incorrectly, for example in one case a total lymphocyte count was reported as a CD4 cell count. In these instances, the measurement that appeared most probable in relation to the previous trend was used. In the two remaining participants, there were no apparent data entry errors, but it was decided it was unlikely they were two genuine visits and so the worst result (lowest CD4 cell count or highest viral load) was entered. There were no repeat height or weight measurements that required checking.

In a small number of instances, the subsequent measure was not exactly the same value but was similar and did not meet the criteria outlined above, in which case the worst of the two measurements was taken.

3.3.5. Preparing the dataset to apply the engagement in care criteria

Once the dataset was prepared, a number of stages of manipulation were performed, and management of multiple visits, the outcome, start date and re-engaged in care classifications were defined.

3.3.5.1. Coding the data in accordance with the engagement in care criteria

For the first stage of data manipulation to apply the EIC flowcharts to the dataset, I coded the data so that time to next scheduled appointment could be classified correctly for each participant at each visit. For each visit, clinical data were used to predict the time to next scheduled appointment. This method assumes that all of the clinical variables were available to the clinician at the time of the current visit, and were used to predict the next appointment date.

In reality, however, and demonstrated in Table 3.5, blood tests may only be available after the current appointment has ended. In these cases clinicians would use previous results to determine the timing of the next appointment. However, subsequent test results available a few days later could prompt a rescheduling of the next appointment, if clinical measurements should change, and patients would be contacted by the clinic and the appointment rescheduled accordingly. Therefore, the approach I took here should approximate what actually happens in clinics.

I then derived individual variables for each of the decision tree questions set out in the boxes of the EIC flowcharts, so that I could calculate time (one, two, three, four or six months) to the next scheduled appointment. I coded each flowchart separately to ensure that every pathway ending in a terminal node was included, and that participants were only categorised within one pathway. For example, using Figure 3.3 for pathways requiring one or two months' follow-up time, participants were coded for the next appointment to be scheduled in one month if:

- They were off ART and had a CDC C event in the last three months

or

- They were off ART, had no CDC C event in the last three months, had a CD4 cell count ≤350 cells/μL and had a drop in CD4 cell count ≥50 cells/μL since the last visit

Similarly, participants were coded for the next appointment in two months if:

- They were off ART, had no CDC C event in the last three months, had a CD4 cell count ≤350 cells/μL and had an increase or no change or drop <50 cells/μL in CD4 count since the last visit

or

- They were off ART, had no CDC C event in the last 3 months, had a CD4 cell count 351-499 cells/μL and had a second consecutive drop of ≥50 cells/μL.

Once I had coded all the pathways in the three flowcharts, individual visit rows that had no time to next scheduled appointment date defined in this process were examined. A few minor inconsistencies were found in the coding at this stage, which I corrected. My management of rows with missing data are described in section 3.3.6.1 new patient. My checks indicated that no participants were categorised into two different pathways.

3.3.5.2. Splitting the data into month time frames

For this second stage of data manipulation, I recoded the data from representing one row per clinic visit date for each patient, to month time periods, so that I could then calculate the number of months in and out of care. This manipulation enabled me to calculate the time to next scheduled appointment. The date of the AALPHI interview was treated as the start date for the analysis. I created a new dataset with data organised so each row contained the month number and the date at the beginning of the month (the AALPHI interview date for month one) and the end of the month, so that visit dates (and the associated clinical data) could be merged into the corresponding rows. All months were retained even if there was no visit. If two visits occurred within a month, two rows were created for this month. A new variable was created for the date of next scheduled appointment, based on the current visit date and the time to next scheduled visit as determined by the flowcharts. Fifteen days were added to this variable to add some leniency into the analyses to make it more applicable in actual clinics, for two reasons. Firstly, it is plausible that there was no clinic availability at the exact time of the next scheduled clinic appointment date, so a slightly later appointment date may have been arranged. Secondly, a patient may be sent an appointment letter for their next visit, and subsequently rescheduled it slightly due to calendar conflicts.

3.3.5.3. Management of multiple visits

In the Howarth *et al* analysis, clinic visits were grouped into month episodes, and the lowest CD4 cell count and the highest viral load measurements were established for each visit. I manipulated my data slightly differently for my analysis of young people living with PHIV. Once proxy visits within seven days were collapsed, all visits were kept in the dataset (including multiple visits within a month). In the year of analysis, there were 81/3,873 (2%) instances in 59 participants of more than one visit in a month. Where multiple visits occurred, all visits were classified for time to next scheduled appointment, but the visit that occurred later in the month was prioritised over the previous visit(s) and so the earlier visit in the month was dropped. Table 3.8 presents a participant with two visits in one month. The second row (visit date 08/07/2013) is prioritised.

Table 3.8: Management of multiple visits in a month

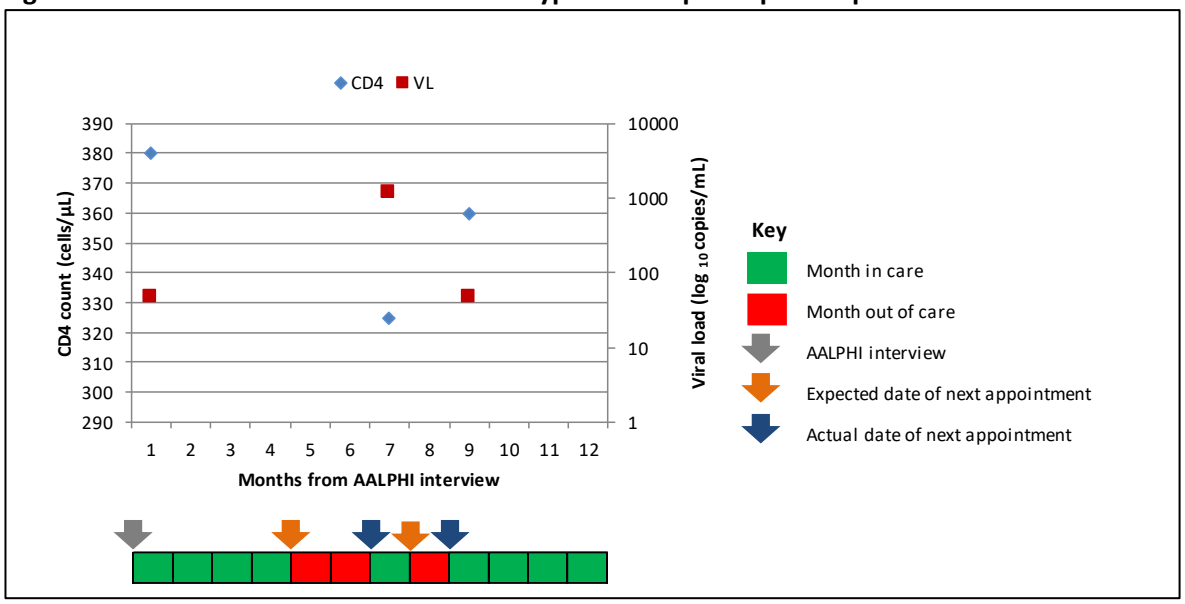
Month	Visit date	Time to next scheduled appt	Date of next scheduled appt[1]	Month start	Month end	In care
11	10/06/2013	1 month	25/07/2013	10/06/2013	09/07/2013	Yes
11	08/07/2013	3 months	23/10/2013	10/06/2013	09/07/2013	Yes

[1] Date of scheduled appointment is visit date plus time to next scheduled appointment, plus 15 days. 15 days is added to each month to make more applicable to what happens in clinic

3.3.5.4. Defining months as in or out of care

I then classified each month in the 12 months following the AALPHI interview date (start date) as in or out of care. For months where the next scheduled visits was due, participants were considered in care if (i) they attended clinic prior to the start of the month; or (ii) they attended clinic within the month. Those who attended after the month end were considered out of care for that month. For participants who attended their appointment early, the date of their next scheduled appointment was reset and based on their most recent appointment date. Figure 3.4 gives an example for a hypothetical participant in paediatric care.

Figure 3.4: Months in and out of care for a hypothetical participant in paediatric care

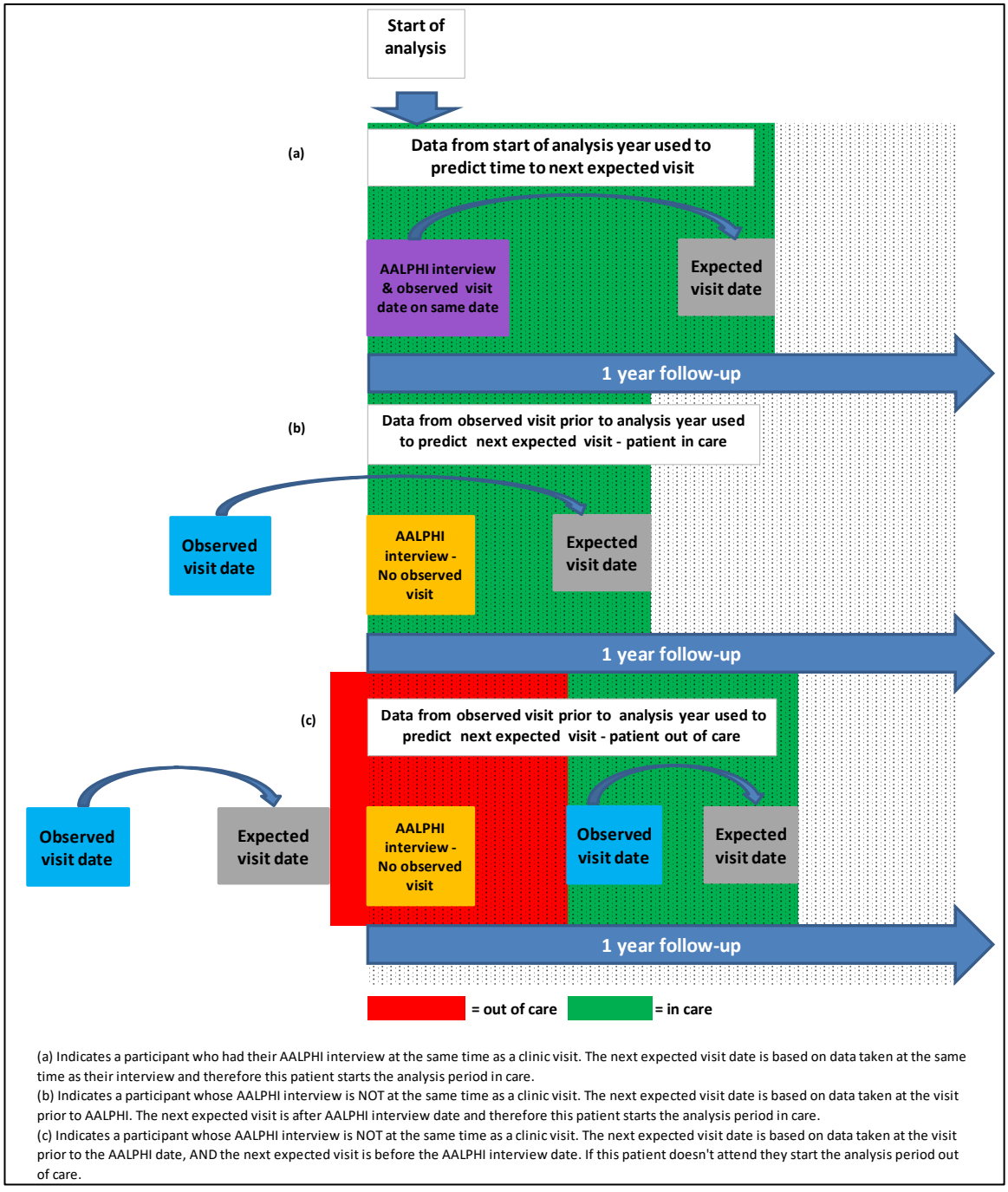


This participant had a clinic visit on the day of their AALPHI interview, with a viral load ≤50c/mL and CD4 cell count 380 cells/µL (Figure 3.4) and they are therefore classified in Flowchart A (Figure 3.1). The participant had no CDC C event in the last 3 months or ART changes, and was on three or more cART drugs, CD4 >350 cells/µL, they were in paediatric care and they were on adult cART doses, so their next scheduled appointment was four months later. They did not attend clinic until six months later, so were considered in care for the first four months and then out of care for the following two months past their scheduled appointment date. At the clinic visit in month seven, the participant had a viral load 1,200c/mL and their CD4 cell count decreased to 325 cells/µL (Figure 3.4) and they are therefore classified based on Flowchart B (Figure 3.2). The participant had no CDC C event, had been on their ART regimen for >6 months and was on a PI-based regimen. It was their first viral load >50c/mL, so the time to their next scheduled appointment was in one month. The participant attended clinic after two months so

was considered in care for the first month (month seven) and out of care the next month (month eight). The participant attended in month nine, and had a viral load ≤50c/mL again (and they are therefore classified in Flowchart A again, Figure 3.1) with no CDC, no new ART, on ≥3 drugs and their CD4 count increased to 360 cells/μL. The participant was still in paediatric care and was on adult doses and was therefore due to be seen in four months so was considered in care for the last four months (months 9-12). Overall, this participant had nine months in care and three months out of care.

For this analysis, I chose the AALPHI interview date as the start of the year's follow-up for all participants. Seven days leniency was allowed so that 18 participants (6% of total) who had a clinic visit within seven days after their AALPHI interview date were considered to have their interview at the same time as a clinic visit. I decided not to consider visits in the 7 days before the AALPHI interview as the same time as the AALPHI interview date because then the exposures measured during the AALPHI interview predicted the outcome measure, in care from the past. Participants with an interview date at the same time as their clinic visit had the time to their next scheduled clinic appointment based on clinical data taken at the same time as their AALPHI interview. However, only 43% of participants in AALPHI were interviewed in clinic in the same week as their clinic visit (including the 6% described above). For participants without a clinic visit in the same week as their AALPHI interview, I based time to next scheduled appointment on the visit prior to the AALPHI interview. Figure 3.5 shows how this effects different groups of participants. Participants with a clinic visit and AALPHI interview on the same day can only start the analysis year in care (Figure 3.5 example (a)). Conversely, participants with no observed visit on the day of their AALPHI interview whose scheduled appointment falls before the AALPHI interview date (Figure 3.5 examples (b) & (c)), may start the analysis year out of care (Figure 3.5 example (c)).

Figure 3.5: AALPHI analysis start date scenarios



(a) Indicates a participant who had their AALPHI interview at the same time as a clinic visit. The next expected visit date is based on data taken at the same time as their interview and therefore this patient starts the analysis period in care.
(b) Indicates a participant whose AALPHI interview is NOT at the same time as a clinic visit. The next expected visit date is based on data taken at the visit prior to AALPHI. The next expected visit is after AALPHI interview date and therefore this patient starts the analysis period in care.
(c) Indicates a participant whose AALPHI interview is NOT at the same time as a clinic visit. The next expected visit date is based on data taken at the visit prior to the AALPHI date, AND the next expected visit is before the AALPHI interview date. If this patient doesn't attend they start the analysis period out of care.

To assess the effect of this choice of start date on exposure variables, I conducted a sensitivity analysis, to examine using an alternative start date to the AALPHI interview date. This sensitivity analysis is detailed in Chapter 5 because it was performed on the final logistic regression model presented in that chapter.

3.3.5.5. Classifying participants in or out of care: issues resulting from moving from continuous to discrete time

Moving from continuous time to monthly intervals introduced some assumptions. Since 15 days was added to the calculated scheduled appointment date, a participant for whom a scheduled appointment fell towards the end of a month, still had time allowed to attend (minimum 15 days), before being classified as out of care in that month.

Classifying a participant as in care in any month they attended a visit was adopted. Other options were considered around classification of the visit month as in or out of care based on time since scheduled appointment or days into the month (late/early in the month). Using a strict cut off based on the end of the 15 days leeway was problematic, as if for example, a participant on monthly follow-ups was classified as out of care when they attended a visit on the third day into the month as they were due (including the 15 day leeway) on the first day of the month and then they did not return in the following month, they would be classified as out of care for two months despite having attended clinic. Carrying forward 'in care' was also problematic due to covariates being updated at the beginning of each month and the impact on the subsequent appointment schedule. Splitting the month by days into the month seemed arbitrary and also led to similar problems if 'in care' were carried forward.

However, classifying a participant in care for a visit month did mean participants for whom a scheduled appointment fell towards the beginning of the month were allowed more leeway in addition to the 15 days added to the initial calculated scheduled appointment date, as they were classified as in care, irrespective of how late they attended in the month. This may have led to some patients being classified as in care when they had in fact missed a scheduled appointment. To explore this, I considered all the visits that were attended late where the participant was in care in the preceding month; 103/183 (58%) visits were attended within the intended 15 days leeway and the median (Interquartile Range (IQR)) time from calculated visit to attended visit was 11 days [5, 25].

3.3.6. Missing data and data cleaning/checking

3.3.6.1. Missing data

For missing data, I had three primary considerations. The first was to manage missing clinical data when creating the proxy clinic visit dates. The second was to manage missing data so that time to next scheduled appointment could be classified correctly at each visit. The third was to apply data cleaning and consistency checks. Missing AALPHI data are discussed in Chapter 5. Any

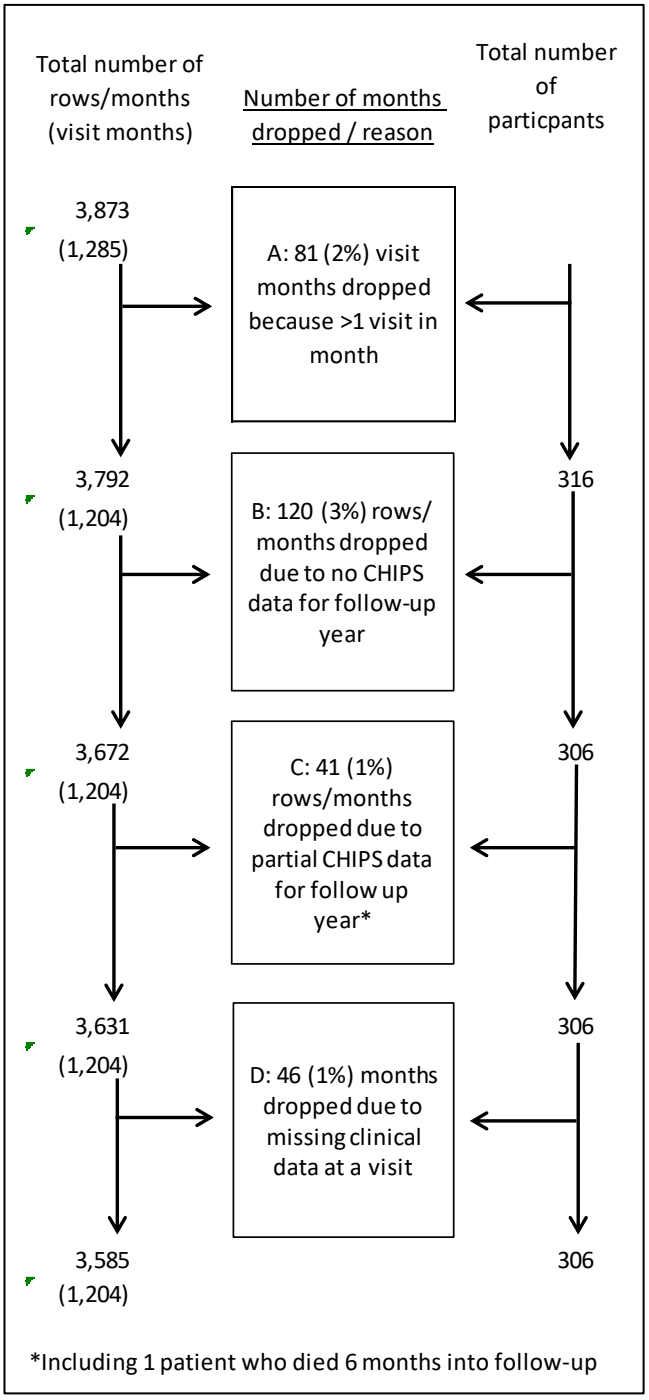
errors identified or additional data obtained were reported to the CHIPS or AALPHI statisticians so that changes could be made to the relevant source dataset.

In my analysis dataset, each row represented a month of follow-up and was classified as either in or out of care. Figure 3.6 presents all of the rows/months (I will use these terms interchangeably) with and without a visit that were dropped from the analysis due to missing data and the total number of participants at each stage.

Rows were dropped for four reasons:

- A: Multiple visits in one month (section 3.3.5.3)
- B: Participants with missing proxy clinic dates
- C: Participants with partially missing proxy clinic dates
- D: Participants with proxy visits dates for whom next scheduled appointment date cannot be estimated

Figure 3.6: Number of rows dropped from the analysis



When the data were initially split into 12 rows (one per month of follow-up) for each participant there were 3,873 rows included in the analysis. Once the 81 visit months were dropped due to multiple visits in a month, there were 3,792 rows remaining, of which 1,204 (32%) had a clinic visit, across 316 participants.

Participants with missing proxy clinic dates (B)

Some participants had missing proxy clinic dates for the whole year covered in my analysis because they did not have clinical data submitted by clinics in the CHIPS study for this period.

Identifying these participants was important to make sure that they were not categorised as out of care in error when in fact there was simply no CHIPS form. All participants whose last clinic visit (as recorded on the CHIPS form) was before the end of the follow-up year were examined. The last clinic visit date was compared to the date of form completion and follow-up status as recorded on the CHIPS database to ensure correct identification of participants with missing CHIPS forms.

The CHIPS Data Manager assisted me in trying to obtain missing data from clinics. Participants whose clinical data remained missing were included in my analysis of descriptive characteristics. However, for the subsequent analysis of predictors of EIC (Chapter 5) participants with no clinical data for the whole year were dropped completely. In total, I dropped 10 participants completely (accounting together for 120 months/ rows) which left 3,672 rows, of which 1,204 were visit months, in 306 participants.

Participants with partially missing proxy dates (C)

In addition, a number of participants had missing proxy clinic date for part of the follow-up year because clinical data were not collected for the entire year of analysis. The affected months where I had no clinical data were dropped. In total, I dropped 41 rows in eight participants (one of whom died halfway through follow-up). This left 3,631 rows with 1,204 clinic visits in 306 participants.

Participants with proxy visits dates for whom next scheduled appointment date cannot be estimated (D)

Where proxy visit dates existed but clinical data (viral loads and CD4 cell counts) were not complete enough to estimate the time to next scheduled appointment, the last count (VL or CD4) was carried forward for a maximum of six months to correspond to the longest time between appointments in the flowcharts. Once I had calculated the time to next scheduled appointment for every appointment, I examined all rows where the time to next scheduled appointment remained unclassified (i.e. did not have the necessary data to fit into a terminal node). I then checked the CHIPS database and paper CRFs for all participants with missing data (or an 'unclassified row') in the analysis year to check if any data were available and had not been entered into the database in error. Where data were found to be actually missing, the CHIPS Data Manager tried to contact clinics to ask them to report it.

This process revealed that time to next scheduled visit remained unclassified for 84 of the 1,204 visit months (7%), due to viral load and CD4 data being missing for more than six months. In

some instances, CD4 cell count and viral load measurements were present for a particular visit, but a missing CD4 cell count or viral load from the previous visit resulted in variables requiring consecutive measures, such as 'consecutive drop in CD4 cell count' or 'VL compared to last VL', being incalculable. I then reviewed all participants who still had gaps in their data, and defined imputation criteria to carry data forward for longer than 6 months in stable participants (Table 3.9). The imputation criteria detailed are only in relation to the data in this analysis rather than all possible situations that could occur using a different dataset.

Table 3.9: Missing data imputation rules

Rule no.	Missing value	Imputation criteria	Imputed value based on imputation criteria	Number of visits affected
1	CD4 cell count	VL ≤50c/mL >1 year and CD4 351-499 cells/μL within last year	CD4 351-499 cells/μL	3
2	CD4 cell count	VL ≤50c/mL >1 year and CD4 ≥500 cells/μL within last 2 years	CD4 cell count ≥500 cells/μL	26
3	CD4 cell count	VL ≤50c/mL <1 year and CD4 ≥500 cells/μL within last year	CD4 cell count ≥500 cells/μL	5
4	CD4 cell count	VL ≤50c/mL <1 year, 351-499 cells/μL within last 9 months	CD4 351-499 cells/μL	1
5	CD4 cell count	ART naïve and previous CD4 ≥500 cells/μL within the last 6 months	CD4 cell count ≥500 cells/μL	1
6	Consecutive CD4 cell count drop (caused by previous missing CD4 cell count)	Previous CD4 >350 cells/μL and within 6 months	No	3
7	VL change (caused by previous missing VL)	On ART >12 months, VL>50c/mL, and last viral load (irrespective of date) < than current viral load	Higher than previous	3
8	VL	VL ≤50c/mL >1 year and last VL is within 1 year & CD4≥500 cells/μL	≤50c/mL	2
9	VL	VL ≤50c/mL <1 year and last VL is within 9 months & CD4≥500 cells/μL	≤50c/mL	2
			Total	46

Time to next scheduled visit was classified in 46/84 clinic visits after I had applied the nine imputation rules, leaving 38 visits still unclassified (Table 3.9). The remaining 38 unclassified visit

months were coded as in care for one month (the minimum time to next scheduled appointment). If the participant did not attend again by the time of the next scheduled appointment, based on this month, then subsequent months (or rows) without a visit were dropped until the participant attended again. Forty-six months without a visit in 17 participants were subsequently dropped until the next visit occurred. In all of these cases, unclassified visits were due to missing data (e.g. CD4 cell count or viral load) rather than an omission in the flowchart coding. This resulted in a total of 3,585 months, where 1,204 were visit months across 306 participants.

3.3.6.2. Data cleaning/checking

The AALPHI and CHIPS datasets that I used for my analysis had already been cleaned by the respective studies' statisticians prior to this analysis, to check for inconsistencies and errors. In addition, I conducted the following checks for my analysis.

ART data

For a few patients the ART start date fell between two visit dates, probably due to a drug being prescribed on the visit date, followed by a short delay in starting or switching to the drug, or a data error. In these cases, I recoded the ART start date so that it was the same as the preceding visit date. When examined, the difference between the ART start date and the visit date was no larger than 14 days and therefore no further investigations were considered necessary.

Mono/dual therapy

Participants with evidence of multi-drug resistance may be prescribed mono or dual therapy due to a lack of other viable options, but cART is the recommended standard treatment approach for HIV.(178,179) During my data cleaning process I identified a small number of participants who appeared to be prescribed mono or dual therapy in the CHIPS database. As this is contrary to the recommended treatment approach, I checked the CHIPS paper CRFs for these participants to make sure that their ART data had been entered correctly. Errors were found in a small number of participants which were corrected in my analysis dataset.

Shared care visits

A possible source of missing data was from participants who are in "shared care". All paediatric HIV patients should have access to and review by a multidisciplinary team. Due to the small number of children with HIV, a formal paediatric clinical care network was established across the UK to allow patients in more remote areas to attend their local clinic for most appointments, as well as to have regular review from, and possibly occasionally attend, a multidisciplinary

specialist paediatric HIV clinic.(180) Due to a range of different established so called “shared care” pathways, reporting to CHIPS is sometimes by both “shared care” clinics, while in other instances only one or other clinic reports to CHIPS. Subsequently, one clinic may not be fully aware of the visits at the other clinic and so reporting omissions might happen. There is also potentially an increased chance of this cohort being in shared care due to their age. Young people at University may receive local care while at University and attend their routine clinic when home in the holidays. Therefore, the number of participants in shared care was examined and the median number of visits over the year follow-up for this analysis compared in participants in shared care vs. participants not in shared care.

Newly diagnosed patients

Howarth *et al* (151) categorised patients in the adult algorithm to be followed-up sooner if they had been diagnosed with HIV in the last month. This was not relevant for this analysis because to be eligible for AALPHI, patients had to be aware of their HIV diagnosis for at least 6 months. However, follow-up in the first year of diagnosis may be more regular, especially if the patient is off ART. The different requirements for new patients were not taken into account when classifying time to next scheduled appointment for these flowcharts, therefore, the number of AALPHI participants diagnosed in the last year was examined.

Early attendance for appointments

My analysis categorised patients who attended their visits as either on time, or early (both of which would be considered in care) or late (out of care). However if too many participants were classified as attending visits early, this could indicate that parts of the flowcharts are not representative of clinical practice. To check how frequently this occurred I created a variable describing the actual number of months between visits, and compared this to the scheduled next appointment time frame. The last appointment for all participants within the 12 month period was dropped because it was not possible to assess if participants attended early or not for this appointment because this visit could have occurred after the follow-up period.

I then classified all participants as being ‘not early’ (which included both participants who attended on time and those who attended late) or ‘early’. Participants cannot come early to a scheduled appointment classified as one month, so scheduled appointments of one month were not examined here. To allow for the reality of booking appointments in busy NHS clinics, some leniency was added into the time frames, so that any participant attending one month early for a visit was considered ‘not early’. For this reason, time to next scheduled appointments of two months were also not examined any further here.

Two analyses were undertaken to investigate the potential effect of early attenders for 6, 4 or 3 month appointments on the results of my analyses. Firstly, I wanted to be assured that early attenders were no different in characteristics to those who attended on time or late. If early attenders were different in some way, this might point to my flowchart criteria being wrong and the need for additional decision boxes to incorporate the characteristic which was different. Therefore, I compared key characteristics (e.g. age group, sex, ethnicity, clinic type, on adult doses) of participants who attended early to those who were not early. I also changed definitions of flowchart classifications (e.g. CD4 groupings, consecutive CD4 drop to single CD4 change, viral load log increase from 0.5 log to 1.0 and 0.25 log changes) in the flowchart to see if this highlighted a difference between participants who attended early vs. not early to their visit. Secondly, to understand the effect of early attenders in more detail, the actual time to the next visit was then cross tabulated with all the possible terminal nodes for each of the three EIC flowcharts. If the proportion of early visits out of the total visits in each terminal node was a gross departure (e.g. more than half of the participants came early) it might indicate that the scheduling for the next appointment for that terminal node was not reflective of actual clinical practice, and might need to be shortened.

3.3.7. Summary across the three flowcharts

The flowcharts were summarised in three ways. Firstly, total time 'in care' for this analysis was examined by calculating the total number of months in the analysis classified as in care. Secondly, to understand overall frequency of time to next scheduled appointment over the three flowcharts, I examined distribution within the three flowcharts and across the whole cohort. Finally, I looked at the frequency of time to next scheduled appointment across all participants (as opposed to frequency across flowcharts). The median (and IQR) number of attended visits per participant was calculated. Then, I examined the number of participants with at least one visit within each scheduled next appointment time (1, 2, 3, 4, 6 months) across the follow-up year. Finally, I looked at all patients in month 7 (selected arbitrarily) and checked what appointment schedule they were predicted to be on at that time (either based on the month 7 attended visit or the most recent attended visit prior to month 7) for all participants in care'. This was to look at the distribution of predicted appointment intervals, which could not be done across all months, as for example a patient scheduled to be on one-monthly appointments would contribute 12 observations in a year, while a patient on 6-monthly visit would contribute two observations in the same time period. Month 1 was not selected because participants could start the year out of care.

3.4. Results

In the year starting on the date of the AALPHI interview for each participant, there were 3,585 months of follow-up across 306 participants. Across these 3,585 months, there were 1,204 (34%) months with a clinic visit. Of the 1,204 visit months, 38 were not classified due to missing data. Of the remaining 1,166 visit months, the number and proportion of visit months were distributed across the three flowcharts as follows:

- Flowchart A (young people living with PHIV on ART with viral load ≤50c/mL): 734/1,204 (61%)
- Flowchart B (young people living with PHIV on ART or starting/restarting ART with viral load >50c/mL): 320/1,204 (27%)
- Flowchart C (young people living with PHIV off ART): 112/1,204 (9%)

3.4.1. Flowchart A: Young people living with PHIV on ART with viral load ≤50c/mL

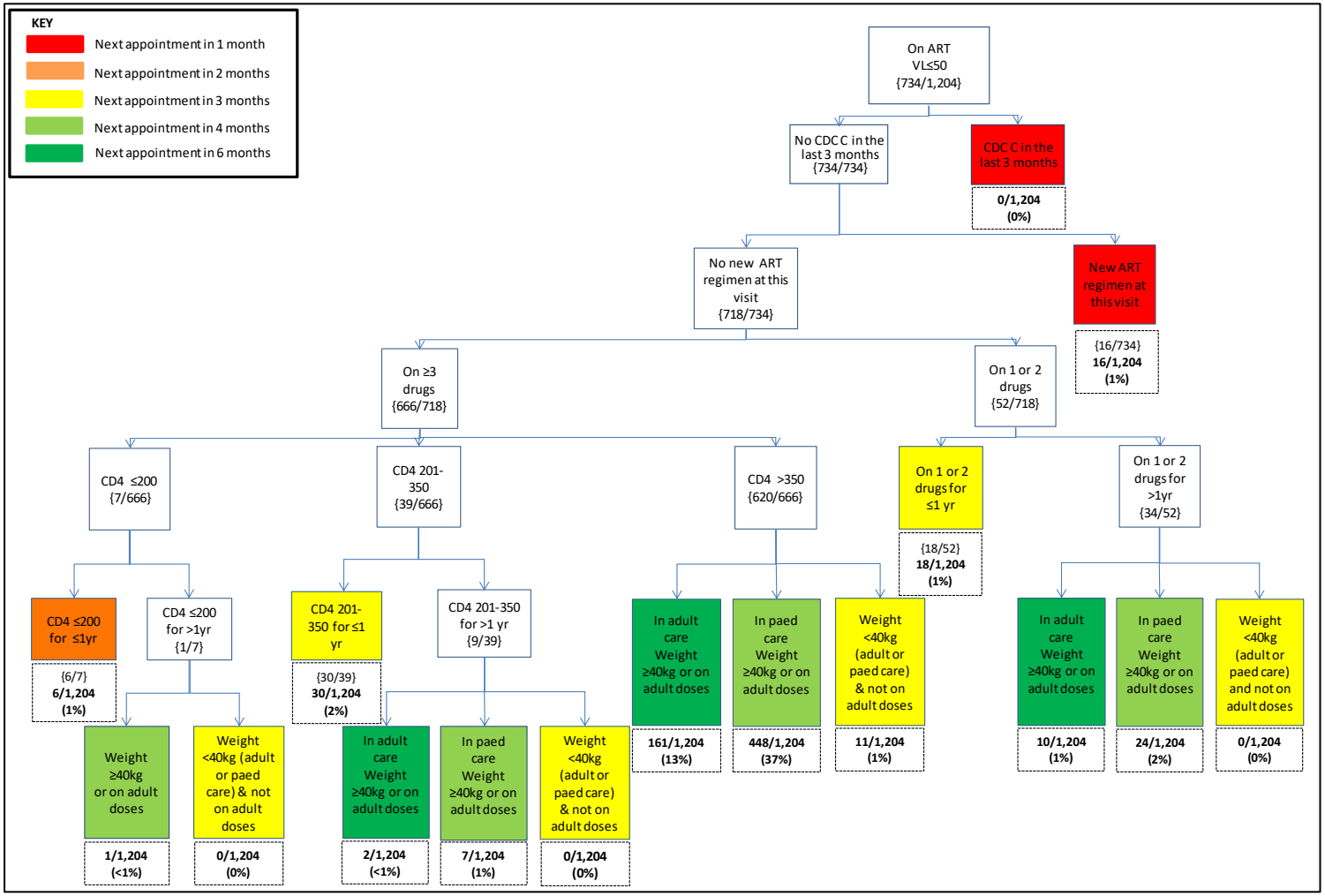
For all of the 734 visit months in 235 participants on ART with a viral load ≤50c/mL (Figure 3.7) there were no CDC C event in the last 3 months (734/734), and the majority (718/734) had no new ART regimen at this visit.

Of the 718 visit months where no new ART regimen was started, 666 were in participants on three or more drugs, of whom 620 had a CD4 cell count >350 cells/µL. Of these 620 visit months: 161 were in participants who weighed ≥40kg or were on adult doses and who had already transferred to adult care; 448 were in participants who weighed ≥40kg or were on adult doses but were in paediatric care; and the remaining 11 visit months were in participants weighing <40kg and not on adult doses, who were in either paediatric or adult care.

Only seven of 666 visit months in participants with a viral load ≤50c/mL on three or more drugs were in those with a CD4 cell count ≤200 cells/µL. In six of these visit months, participants had a CD4 count ≤200 cells/µL for less than a year, and in one visit month a participant had a CD4 cell count ≤200 cells/µL for over a year.

Of the 718 with no new ART regimen at the visit, 52 were on mono or dual therapy, and most of these (34) had been on this regimen for at least a year.

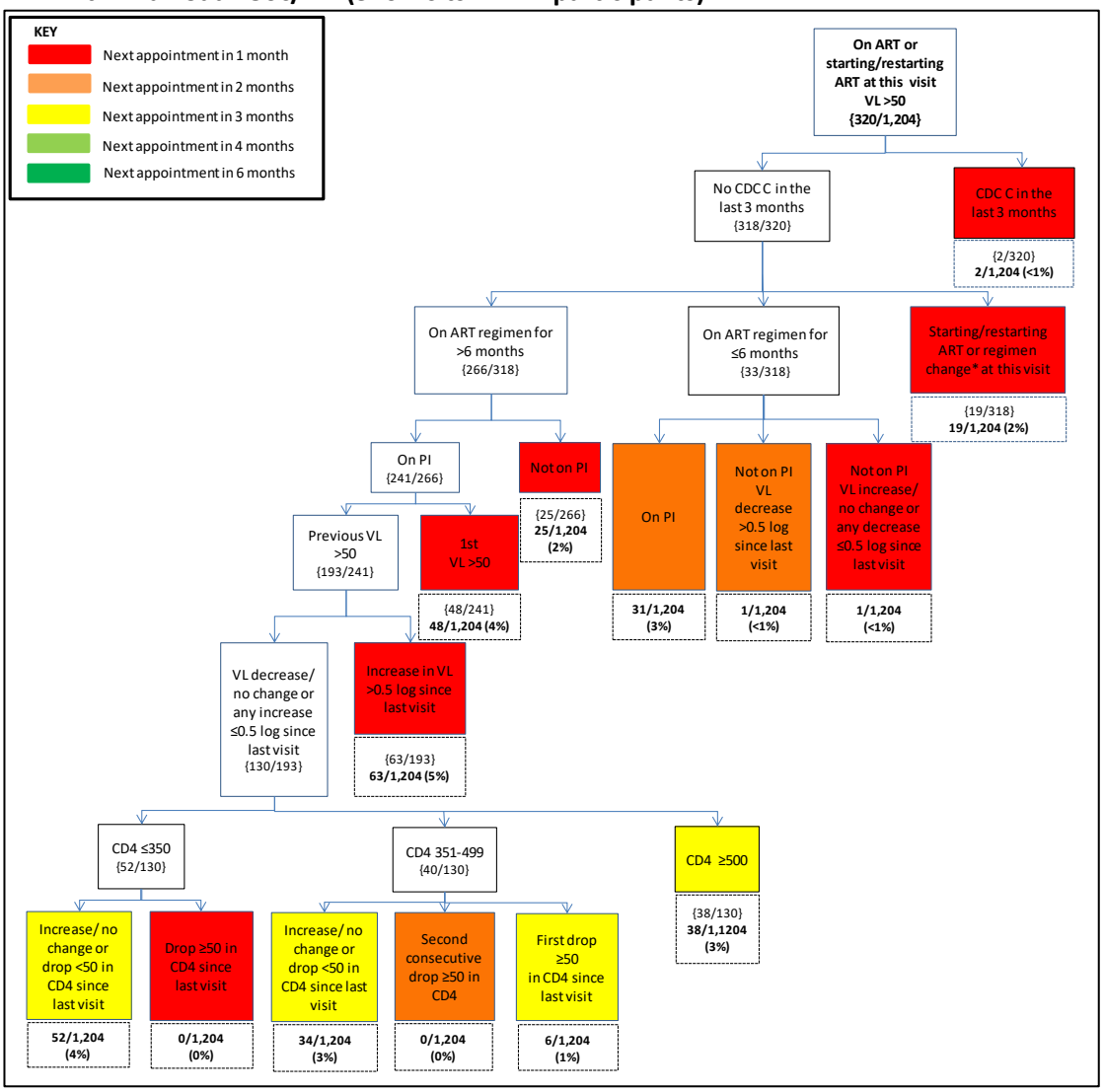
Figure 3.7: Results for Flowchart A: Visits in young people living with PHIV on ART with viral load ≤50c/mL (734 visits in 235 participants)



3.4.2. Flowchart B: Young people living with PHIV on ART or starting/restarting ART with viral load >50c/mL

Three hundred and twenty visit months were in 112 participants who were on ART with a detectable viral load (>50cmL) (Figure 3.8). Almost all of these visit months (318/320) were in participants with no CDC C event in the last three months. Of these 318, 266 were in participants who had been on the same ART regimen for >6 months, and the regimens were mainly PI-based (241/266). In half (130/266) of these visit months, participants had a previous viral load >50c/mL but their viral load had not substantially increased (either had decreased, not changed or increased <0.5 log) since last visit. Of these 130 visit months: 52/130 visit months were in participants with a CD4 cell count ≤350 cells/μL and an increase or no change in CD4 cell count since their last visit; 40/130 of these visit months were in participants who had a CD4 cell count between 351-499 cells/μL and again either an increase or no change in CD4 cell count since their last visits (34/40) or it was their first drop in CD4 cell count (6/40); in 38/130 visit months, participants had a CD4 cell count ≥500 c/mL.

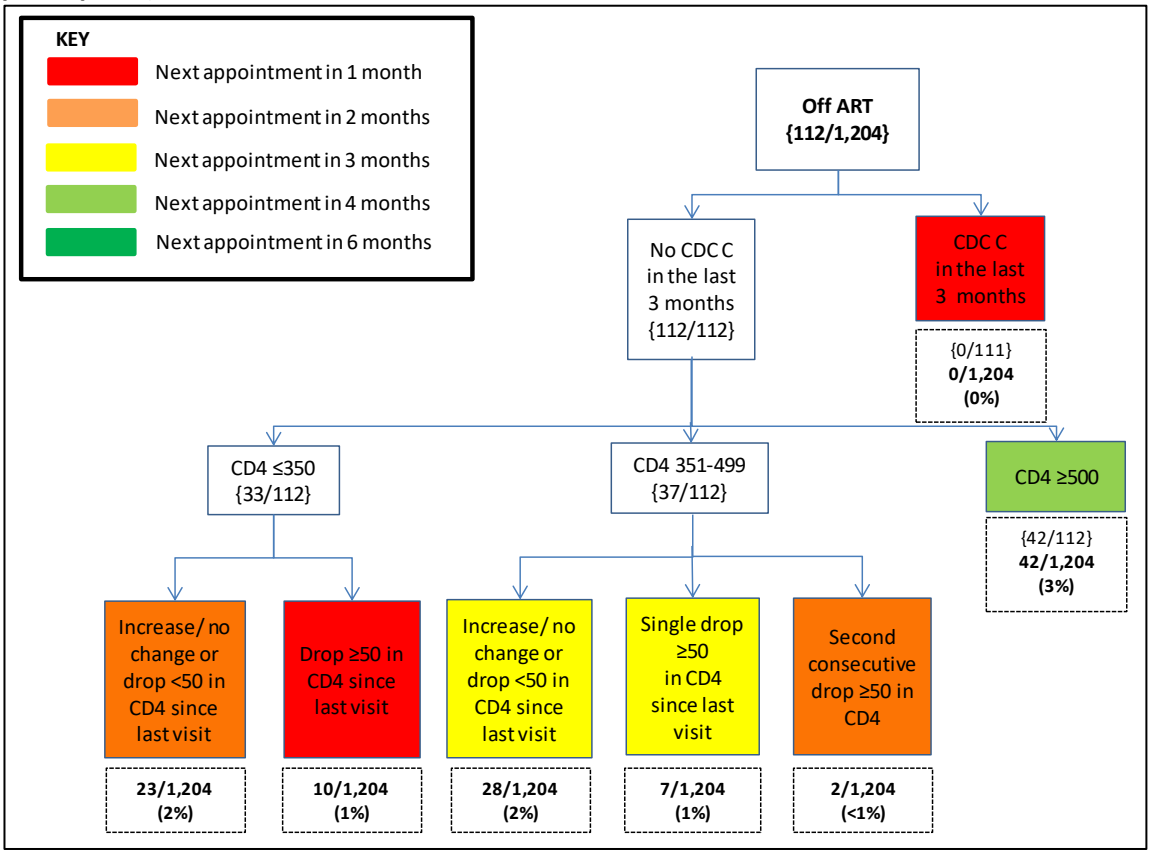
Figure 3.8: Results for Flowchart B: Young people living with PHIV on ART or starting/restarting ART with viral load >50c/mL (320 visits in 112 participants)



3.4.3. Flowchart C: Young people living with PHIV off ART

A total of 112 visit months were in 35 participants who were off ART (Figure 3.9). Reassuringly, none of the visit months were in participants who had a CDC C diagnosis in the last three months. In a third (33/112) of the visit months, participants had a CD4 count ≤350 cells/µL of which 23/33 of the visit months were in participants where their CD4 count had increased/ not changed or dropped <50 cells/µL and 10/33 of the visit months were in participants who had a drop in CD4 count ≥50 cells/µL. A further third (37/112) of visit months were in participants with a CD4 cell count 351-499 cells/µL. Of these 37 visit months: 28/37 visit months were in participants with an increase/no change or drop of <50 cells/µL; 7/37 visit months were in participants who had a single drop ≥50 cells/µL; and 2/37 visit months were in participants who had a second consecutive drop in CD4 cell count ≥50 cells/µL. The final third of visit months (42/112) were in participants with a CD4 cell count ≥500 cells/µL.

Figure 3.9: Results for Flowchart C: Young people living with PHIV off ART (112 visits in 35 participants)



In summary across the 1,204 visits represented in Flowcharts A, B and C, the largest number of visit months fell into the following categories:

- 609 (51%) for participants on ART with a viral load ≤50c/mL, who were stable on cART with a CD4 cell count >350c/µL (Flowchart A);
- 241 (20%) for participants on ART with a viral load >50c/mL, who had been on a PI-based regimen for >6 months (Flowchart B);
- and 112 (9%) for participants off ART (Flowchart C).

3.4.4. Shared care visits

In total, 41 (13%) of the 306 participants in the AALPHI cohort were in shared care at the time of their AALPHI interview. The medium number of visits over the follow-up year for my analysis was four, for both participants who were in shared care [interquartile range (IQR) 3, 4] and participants who were not in shared care [IQR 3, 5] suggesting that "shared care" visits were reasonably well captured.

3.4.5. Newly diagnosed patients

Four (1%) of the 306 participants in the AALPHI cohort were diagnosed with HIV in the UK in the last year, and together accounted for 14 visit months. All four of these participants were previously diagnosed abroad. Three of the four spent the entire year of follow-up with a viral load ≤50c/mL, and one participant had a VL ≤50c/mL at baseline and then rebounded and supressed again over the 1 year follow-up. None of the ART naive participants classified in flowchart C were diagnosed in the UK in the last year.

3.4.6. Early attendance for appointments

The number of visits that participants attended earlier than their next scheduled appointment date as well as a summary of months attended early or not early are shown in Table 3.10, stratified by the time frame of the next scheduled appointment. A total of 262 (39%) visit months were earlier than originally scheduled, and 416 (61%) not early. For participants whose next scheduled appointment was at 3 months' time or 4 months' time, around a third of visits were early. However, for participants whose time to next scheduled appointment was in 6 months' time, 77% (85/110) visits were early, with most participants attending 2 (23%) or 3 (30%) months early.

Table 3.10: Number of visits attended early by time frame of next scheduled appointments

	Time to next scheduled appointment: 3 months (n=185)			**Time to next scheduled appointment: 4 months (n=383)**				**Time to next scheduled appointment: 6 months (n=110)**						**Total (n=678)**					
	n (%)																		
# of early or not early visits	Not early		Early	Not early		Early		Not early		Early				Not early		Early			
	120 (65%)		65 (35%)	271 (71%)		112 (29%)		25 (23%)		85 (77%)				416 (61%)		262 (39%)			
Timing of early visits	Not early	1m early	2m early	Not early	1m early	2m early	3 m early	Not early	1m early	2m early	3m early	4m early	5m early	Not early	1m early	2m early	3m early	4m early	5m early
	77 (42%)	43 (23%)	65 (35%)	131 (34%)	140 (36%)	60 (16%)	52 (14%)	8 (7%)	17 (15%)	25 (23%)	32 (30%)	11 (10%)	17 (15%)	216 (32%)	200 (29%)	150 (22%)	84 (12%)	11 (2%)	17 (3%)

m=month/s

The comparisons across appointment schedules should be viewed with caution because there was greater opportunity for participants to be early for a six month appointment than a three or four month appointment. To see if there was a difference in the characteristics of those who attended on time or late, key characteristics and slightly altered definitions of flowchart classifications were compared for participants who attended on time at 3, 4, and 6 month appointments, and participants attending before the scheduled appointment dates. Results are presented in Table 3.11, Table 3.12, Table 3.13 and no major differences were found.

Table 3.11: Comparison of key characteristics of participants who were early for their 3 month appointment compared to those who were not early

	Not early for 3 month appointment n=120 (%)		Early for 3 month appointment n=65 (%)		p value
Participant characteristic					
Age group					
≤15 years of age	47	(39%)	24	(37%)	0.93
16-18 years of age	52	(43%)	30	(46%)	
19-21 years of age	21	(18%)	11	(17%)	
Sex					
Male	48	(40%)	35	(54%)	0.07
Female	72	(60%)	30	(46%)	
Ethnicity					
Black	105	(87%)	59	(91%)	
Asian/mixed/prefer not to say	13	(11%)	6	(9%)	0.54
White	2	(2%)	0	(0%)	
On all adult ART doses					
Yes	146	(54%)	50	(45%)	0.08
No	114	(42%)	58	(52%)	
Missing	10	(4%)	4	(3%)	
Re-categorised flowchart definitions					
CD4 category[1]					
≥600 cells/μL	24	(20%)	11	(17%)	0.25
500-599 cells/μL	13	(11%)	5	(8%)	
400-499 cells/μL	19	(24%)	10	(15%)	
<400 cells/μL	54	(45%)	39	(60%)	
CD4 change					
≥50 cells/μL lower than previous	37	(31%)	12	(19%)	0.10
Same as previous	69	(59%)	47	(75%)	
≥50 cells/μL higher than previous	12	(10%)	4	(6%)	
VL change					
>1.0 log lower than previous	41	(35%)	22	(65%)	0.31
Same as previous	74	(42%)	41	(35%)	
>1.0 log higher than previous	4	(3%)	0	(0%)	
VL change					
>0.25 log lower than previous	55	(46%)	30	(48%)	0.95
Same as previous	55	(46%)	29	(46%)	
>0.25 log higher than previous	9	(8%)	4	(6%)	

[1] CD4 cell count is categorised into a greater number of categories than in the main analyses

Table 3.12: Comparison of key characteristics of participants who were early for their 4 month appointment compared to those who were not early

	Not early for 4 month appointment n=271 (%)	Early for 4 month appointment n=112 (%)	p value
Participant characteristic			
Age group			
≤15 years of age	163 (60%)	70 (62%)	0.42
16-18 years of age	92 (34%)	39 (35%)	
19-21 years of age	16 (6%)	3 (3%)	
Sex			
Male	111 (41%)	48 (43%)	0.73
Female	160 (59%)	64 (57%)	
Ethnicity			
Black	232 (86%)	99 (88%)	
Asian/mixed/prefer not to say	28 (10%)	9 (8%)	0.76
White	11 (4%)	4 (4%)	
On all adult ART doses			
Yes	146 (54%)	50 (45%)	0.08
No	114 (42%)	58 (52%)	
Missing	10 (4%)	4 (3%)	
Re-categorised flowchart definitions			
CD4 category[1]			
≥600 cells/μL	175 (64%)	74 (66%)	
500-599 cells/μL	51 (19%)	17 (15%)	0.84
400-499 cells/μL	34 (13%)	15 (14%)	
<400 cells/μL	12 (4%)	6 (5%)	
CD4 change			
≥50 cells/μL lower than previous	75 (29%)	26 (24%)	
Same as previous	112 (43%)	59 (54%)	0.15
≥50 cells/μL higher than previous	73 (28%)	24 (22%)	
VL change			
>1 log lower than previous	15 (6%)	11 (10%)	
Same as previous	243 (93%)	98 (88%)	0.31
>1 log higher than previous	3 (1%)	2 (2%)	
VL change			
>0.25 log lower than previous	31 (16%)	18 (16%)	
Same as previous	218 (79%)	88 (79%)	0.53
>0.25 log higher than previous	12 (5%)	5 (5%)	

[1] CD4 cell count is categorised into a greater number of categories than in the main analyses

Table 3.13: Comparison of key characteristics of participants who were early for their 6 month appointment compared to those who were not early

	Not early for 6 month appointment n=25 (%)	Early for 6 month appointment n=85 (%)	p value
Participant characteristic			
Age group			
≤15 years of age	1 (4%)	1 (1%)	0.50
16-18 years of age	8 (32%)	35 (41%)	
19-21 years of age	16 (64%)	49 (58%)	
Sex			
Male	12 (48%)	33 (39%)	0.41
Female	13 (52%)	52 (61%)	
Ethnicity			
Black	24 (96%)	73 (86%)	
Asian/mixed/prefer not to say	0 (0%)	8 (9%)	0.27
White	1 (4%)	4 (5%)	
Clinic type			
Adolescent	17 (68%)	60 (71%)	0.18
Adult/GUM	6 (26%)	24 (28%)	
On all adult ART doses			
Yes	13 (52%)	39 (46%)	0.59
No	12 (48%)	46 (54%)	
Re-categorised flowchart definitions			
CD4 category[1]			
≥600 cells/μL	14 (56%)	60 (71%)	
500-599 cells/μL	7 (28%)	9 (11%)	0.14
400-499 cells/μL	3 (12%)	8 (9%)	
<400 cells/μL	1 (4%)	8 (9%)	

[1] CD4 cell count is categorised into a greater number of categories than in the main analyses

To understand whether participants who attended early fell into any particular terminals in the flowcharts, the 262 appointments attended two to five months early were then cross tabulated with all the possible terminal nodes separately in the three flowcharts, and results are presented for Flowcharts A, B and C in Table 3.14, Table 3.15, and Table 3.16 respectively.

In total, 38% (n=195) of terminal nodes where participants attended early fell in Flowchart A (Table 3.14). The terminal node where appointments were most frequently attended early was for young people with a CD4 count >350 in adult care. This raised a question about whether it was common practice outside of the clinicians interviewed for this analysis to schedule clinic appointments for young people for 6 months. Unfortunately, there was not time to interview a wider range of clinicians; instead a sensitivity analysis was conducted in the modelling stages (Chapter 5) to examine the effect of 6 month scheduled appointments on the predictors of EIC. For this sensitivity analysis, the maximum time to next scheduled appointment was set at 4

months and the results of the model compared to results including time to next scheduled appointments at 6 months as detailed here.

Forty-seven per cent of early visits were in flowchart B (Table 3.15). These early visits were spread across four terminal nodes. Early attenders fell most commonly in the terminal node where participants had a CD4 count ≤250 cells/μL, with an increase, no change or drop of <50 in CD4 since last visit. Although the proportion is just over 50%, the numbers are quite small and it is perhaps not that surprising as this is one of the three terminal nodes with most visits in Flowchart B.

Finally, 26% (n= 15) of the early visits fell in Flowchart C (Table 3.16). These early visits were spread across three terminal nodes and the numbers of visits were relatively small.

Table 3.14: Summary of appointments attended early by terminal node in Flowchart A: AALPHI participants on ART with a viral load ≤50c/mL

Flowchart classification details[1]	On cART							On 1 or 2 drugs			All terminal nodes
	CD4 ≤200 for	CD4 201-350			CD4 >350			≤1 year	>1 year		
	>1 year	≤1 year	>1 year								
Terminal node details[2]	Weight ≥40kg or on adult doses		In adult care, Weight ≥40kg or on adult doses	In paed care, Weight ≥40kg or on adult doses	In adult care, Weight ≥40kg or on adult doses	In paed care, Weight ≥40kg or on adult doses	Weight <40kg (in adult or paed care) & not on adult doses		In adult care, Weight ≥40kg or on adult doses	In paed care, Weight ≥40kg or on adult doses	
Visit frequency[3]	4 months	3 months	6 months	4 months	6 months	4 months	3 months	3 months	6 months	4 months	
Number of early visits/ total visits (%)	1/1[4] (100%)	7/23 (30%)	1/1 (100%)	2/5 (40%)	78/103 (76%)	93/330 (28%)	0/7 (0%)	2/17 (12%)	6/6 (100%)	5/18 (28%)	195/511 (38%)

[1] None of the participants in this table had new ART at that clinic visit

[2] Terminal nodes in which no participants attended the clinic appointment early are not shown in the table

[3] As above due to a month's leniency being added to early appointments, participants cannot be classified as early for visits with a 1 or 2 month follow-up time frame. Therefore, only visits with scheduled appointment time for 3, 4 or 6 months are included in this summary table.

[4] Total months differ from those in Figures 3.8-3.10 due to last visit being dropped for each participant

Table 3.15: Summary of appointments attended early by terminal node in Flowchart B: AALPHI participants on ART with a detectable viral load (>50c/mL)

Flowchart classification details	On ART> 6 months, on PI, previous VL>50, VL decrease or no change				All terminal nodes
	CD4 ≤350,	CD4 351-499		CD4 ≥500	
Terminal node details	Increase/ no change or drop <50 in CD4 since last visit	Increase/ no change or drop <50 in CD4 since last visit	First drop ≥50 in CD4 since last visit		
Visit frequency[1]	3 months	3 months	3 months	3 months	
Number of early visits / total visits (%)	26/46 (57%)	11/28 (39%)	1 / 4 (25%)	14/32 (44%)	52/110 (47%)

[1] Due to a month's leniency being added to early appointments, participants cannot be classified as early for visits with a 1 or 2 month follow-up time frame. Therefore, visits with scheduled appointment time for 3, 4 or 6 months are included in this summary table.

Table 3.16: Summary of appointments attended early by terminal node in Flowchart C: AALPHI participants not on ART

Flowchart classification details	No CDC C in last 3 months			All terminal nodes
	CD4 351-499		CD4 ≥500	
Terminal node details	Increase/ no change or drop <50 in CD4 since last visit	Single drop ≥50 in CD4 since last visit		
Visit frequency1	3 months	3 months	4 months	
Number of early visits / total visits (%)1	3/23 (13%)	1/5 (20%)	11/29 (38%)	15/57 (26%)

[1] Due to a month's leniency being added to early appointments, participants cannot be classified as early for visits with a 1 or 2 month follow-up time frame. Therefore, visits with scheduled appointment time for 3, 4 or 6 months are included in this summary table.

3.4.7. Summary results across the three flowcharts

In the previous sections, I described the number and proportion of visit months which fell into each terminal for each of the flowcharts. In this section, I will summarise the findings overall for the three flowcharts by presenting the:

- Overall EIC across all participants
- Timing of next visit scheduling for each flowchart
- Number of visits per participant

3.4.7.1. Overall engagement in care

Of the 3,585 months of follow-up in this analysis, 3,126 (87%) months were classified as in care.

3.4.7.2. Next scheduled appointment timing overall for the three flowcharts

The majority of visit months (653/734) were in participants with a viral load ≤50c/mL (Flowchart A) who were categorised to have scheduled appointments in four to six months' time. In participants on ART with a detectable viral load (Flowchart B), at half of visit months (158/320) participant had their next scheduled appointments categorised as in one month and over a third at three months. Where visit months were in participants off ART (Flowchart C), over two thirds were categorised to have their next scheduled visit at three or four months.

Overall, nearly half of coded appointment months (522/1,166) were categorised as requiring the time to next scheduled appointment in four months, with around a fifth categorised with a time to next scheduled appointment at each of one (184/1,116), three (224/1166) or six months (173/1,166).

Table 3.17: Distribution of time to next scheduled appointment by flowchart

Scheduled appointment frequency	Flowchart A: participants with PHIV on ART with a viral load ≤50c/mL	Flowchart B: participants with PHIV on ART or starting/restarting ART with a viral load >50c/mL	Flowchart C: participants with PHIV off ART	Total number appointment months
	Number and % of visit months			
1 month	16 (2%)	158 (49%)	10 (9%)	184 (16%)
2 months	6 (1%)	32 (10%)	25 (22%)	63 (5%)
3 months	59 (8%)	130 (41%)	35 (31%)	224 (19%)
4 months	480 (65%)	-	42 (38%)	522 (45%)
6 months	173 (24%)	-	-	173 (15%)
Total	734 (63%)	320 (27%)	112 (10%)	1,166

3.4.7.3. Next scheduled appointment timing per participant

Overall, 306 participants had 1,166 visits, equating to a median of 4 [IQR 3, 5] visits per patient. Table 3.18 presents for each time to next appointment scheduled (1, 2, 3, 4, 6 months' time) the number of participants that were predicted to be seen at this time at least once over follow-up. Over follow-up, 186 participants (61%) had at least one appointment scheduled for 4 months' time. Over a third of participants (112, 37%) also had at least one appointment scheduled in one month's time. Under a third of participants had at least one appointment scheduled for 3 months (94, 31%) or 6 months (n=73, 24%). Two months was the least common appointment timing (28, 9%).

Table 3.18: Number of participants with at least 1 visit at each scheduled next appointment time

Next appointment scheduled in…	Number of appointments	Number of participants[1]	% of participants n=306
1 month	184	112	(37%)
2 months	63	28	(9%)
3 months	224	94	(31%)
4 months	522	186	(61%)
6 months	173	73	(24%)
Not coded	38		

[1] Total participants not shown as each participant could have multiple next schedule appointment timings

When the timing of participants' next scheduled appointment was examined for a single exemplar month (in participants classified in care), month 7 (Table 3.19), 4 months remained the most frequent time to next scheduled appointment (n=137, 46%). Around twenty per

cent of participants had appointments scheduled for 3 (n=60, 20%) and 4 months (n=54, 18%), and as before the least common appointment timing was two months (n=8, 3%).

Table 3.19: Number of participants with each next scheduled appointment timing in month 7

Next appointment scheduled in….	n with ≥1 appointment	
	n	(%)
1 month	28	(9%)
2 months	8	(3%)
3 months	60	(20%)
4 months	137	(46%)
6 months	54	(18%)
Not coded[1]	9	(3%)
No visit before month 7	4	(1%)
Total	300[2]	((0.0)%)

[1] "Not coded" rows are where participants were given one month in care when missing data prevented classification
[2] Total is less than the total number of participants because some participants have rows/months dropped due to missing data or are 'out of care'

Table 3.20 shows visit timings for two patients to explain why the findings in Table 3.18 and Table 3.19 differ. Patient A has nine 1 month scheduled appointments and Patient B only two 1 month scheduled appointments over the 12 months follow-up. On this basis, both patients have a visit in 1 month over the year. In a cross sectional time point (month 7 in my example), Patient B is less likely to be captured as having a 1 month follow-up than Patient A, which is appropriate because Patient B only has two 1 month scheduled appointments over the 12 month follow-up. This variation shows the changing clinic needs in these patients over the course of the year.

Table 3.20: Visit timings in two sample patients

Month	1	2	3	4	5	6	7	8	9	10	11	12
Month until next scheduled appointment	1	1	1	1		1	1	1	3		1	
Patient A: Clinical characteristics (no CDC C event, in paediatric care, on adult doses)	**VL ≥200** (↔ prev) **Not on PI CD4 ≥500** (↔prev)	**VL ≥200** (↔prev) **Not on PI CD4 351-499** (↓prev)	**VL ≥200** (↑prev) **Not on PI CD4 351-499** (↔prev)	**VL ≥200** (↔prev) **Not on PI CD4 200-350** (↓prev)		**VL ≥200** (↑prev) **Not on PI CD4 200-350** (↔prev)	**VL ≥200** (↓prev) **On a PI CD4 200-350** (↔prev)	**VL ≥200** (↓prev) **On a PI CD4 200-350** (↔prev)	**VL ≥200** (↓prev) **On a PI CD4 351-499** (↑prev)		**VL ≥200** (↑prev) **On a PI CD4 200-350** (↓prev)	
Month of next scheduled appointment		1	4				4				1	1
Patient B: Clinical characteristics (no CDC C event, no new ART, in paediatric care, not on adult doses)		**VL >50** (↑prev) **1st VL>50 On a PI CD4 ≥500** (↓prev)	**VL ≤50** (↔prev) **On ≥3 drugs CD4 ≥500** (↓prev)				**VL ≤50** (↔prev) **On ≥3 drugs CD4 ≥500** (↔prev)				**VL >50** (↑prev) **1st VL>50 On a PI CD4 ≥500** (↓prev)	**VL >50** (↑ >0.5) **Prev VL>50 On a PI CD4 351-499** (↓prev)

↔=same
↓ lower
↑ higher
prev=previous

3.5. Discussion

3.5.1. Summary of main findings

In this chapter, I detail the methods that I used to adapt the Howarth *et al*'s (151) EIC algorithm for young people living with PHIV in the AALPHI cohort. PENTA and BHIVA guidelines were used alongside clinician experience to modify and develop the flowcharts for this population. Due to the complexity in caring for young people living with HIV, the flowcharts developed in this thesis are more detailed and have more criteria to determine time to next appointment compared to the Howarth *et al* algorithm for adults.

Patients were included in the analysis if they were in AALPHI and had clinical data in the follow-up period. The AALPHI interview date was classified as the start of the follow-up period and clinical data were used as proxy visit markers in the absence of records of attended appointments. Clinical data were aligned to fit the defined EIC criteria so that at each visit, the time to the next scheduled appointment could be defined.

Across 3,585 months of follow-up for the participants, 34% were months with a visit. At those visits, 61% of participants had an undetectable viral load (Flowchart A), 27% were on ART with a detectable viral load (Flowchart B) and reassuringly only 9% were off ART (Flowchart C). Three per cent were unclassified due to missing data. Overall, nearly 90% of follow-up months were classified as 'in care'. Participants had a median of 4 [IQR 3, 5] visits, and most frequently had time to next scheduled appointment at 4 months. However, 37% of participants had at least one of their appointments over the year scheduled in a month's time, suggesting the changing clinical needs in these patients over the course of their year. Based on my model, participants attended 39% of visits early, most commonly when the time to their next scheduled appointment was at 6 months.

3.5.2. Findings in comparison to the wider literature

The methods that I used to measure EIC in this analysis are very different to the methods used in published EIC literature. The fundamental difference between the two is the purpose of the measurement. My measurement attempts to take into account clinical monitoring decisions, recognising that some patients will need to be seen more frequently than others, and is thus relatively complex to construct. However most other analyses in the literature have more simplistic measures, for example, one or more visits in a given year, which give a population estimate useful for public health monitoring and the cascade of care.

In my analysis, I found that 87% of patient months of follow-up were in care. Noting the limitations above, as shown in Chapter 2, European studies of young people living with PHIV have reported engagement ranging from 80% to 98%, (155,156) and sub-Saharan African studies 83% to 98%.(153,154,158–160) Only one study estimated EIC in young people living with PHIV in the UK. Chappell *et al* (155) measured the proportion of children attending paediatric clinics in the CHIPS study. Patients were included if they had at least one visit in the year, and found 98% engagement. In that study the median age was 14.4 years [IQR 11.2, 16.4], so younger than in my study, and crucially all children had to be in care at baseline to be included in the analysis. Both of these factors may explain why engagement was so high. It should be noted that as my study sample is a subset of those ever in the national HIV paediatric study (CHIPS), some of the younger patients in my analysis may also be in the Chappell *et al* analyses.

The proportion of participants in care in studies from the USA vary more than studies from Europe and sub-Saharan Africa, ranging from 56% to 99%.(138,161–168) This is despite relative consistency in their use of EIC definitions, favouring either ≥1 visit within 1 year (138,156,162), or the CDC recommended Health Resource & Services HIV/AIDS Bureau (HRSA HAB) measure of ≥2 visits with ≥3 months apart within 1 year.(138,153,162–164,168) The study with the lowest EIC prevalence used a stricter multiple visit marker (≥2 visits with ≥3 months apart within 1 year), and measured EIC post-transition to adult care. In the second year post-transition, they reported 56% were engaged in care in a cohort of 72 participants in which only 15% of the participants had PHIV.(163) In contrast, the study that found the highest prevalence of young people in care used a single visit measure (≥1 visit within 1 year) in exclusively young people living with PHIV (n=1,535). Data were stratified by age and 99% of 13-19 year olds were classified to be in care.(162)

Besides the lack of consistency in EIC definitions used in the different regions, there are many other sociodemographic and health care factors that limit comparability between young people living with PHIV in the USA, UK and Africa. Sub-Saharan Africa has the highest burden of HIV with 85% of all adolescents with PHIV living in this region (181) Healthcare provision in sub-Saharan Africa is largely decentralised with most care provided in large primary care clinics (153) and few specialist adolescent clinics exist.(154) In Europe and North America, numbers of patients are much smaller and care is provided in specialist HIV clinics often specifically adolescent clinics.(162,182) The sub-Saharan African birth cohort is younger than European and North American cohorts, patients have less ART exposure and HIV-related mortality is higher.(183) Differences also exist between European and North American cohorts of children and young

people born with PHIV. In the UK, most young people with HIV were born in sub-Saharan Africa and migrated to the UK, or were born in the UK but have parents from sub-Saharan Africa (32). In contrast, in the USA, many parents of children living with PHIV have a history of psychiatric illness and substance use (73,184). All of these differences could account for disparity in EIC across these populations.

The use of such a complex measure in my analysis is inevitably much more time consuming to calculate than other simpler measures, demonstrating a trade-off between the detail and potential accuracy of the measure versus the simplicity and comparability of the definition used. However, the use of such a complex measure in this population of young people living with PHIV is perhaps justifiable. All groups of HIV patients have vulnerable sub-populations, but arguably, young people with PHIV are perhaps uniquely complex due to them having life-long HIV and long-term ART exposure.(185) There is of course variability within young people with PHIV. Young people born with PHIV more recently are more likely to have started effective cART regimens very young prior to experiencing AIDS defining illnesses, had higher CD4 counts at ART start and have been managed in a much more clinically optimistic era.(185) For young people born prior to the era of effective cART, there was huge uncertainty about their life expectancy when they were diagnosed with HIV. They are more likely to have started ART later in life with lower CD4 nadirs which reduces the likelihood of immune reconstitution.(55,67,186) Early ART regimens were less efficacious and may have contributed to comorbidities and resistance.(67,162,186)

3.5.3. Limitations

The methods by which I adapted Howarth *et al*'s (151) algorithm to young people living with PHIV potentially introduced a number of biases, which need careful consideration when interpreting the flowcharts' findings. The full list of biases considered, are shown in Table 3.21, I describe and the main ones below.

Firstly, when developing the flowcharts for use in young people, I tried to categorise in detail something that might otherwise be considered by a clinician to be a "feeling" or "clinical suspicion" about how the patient will be over the next few months (Table 3.21, bias 1). In addition, the clinician is very likely to take the patient's history into account, and not judge solely how they present at this one visit. The strict criteria and requirement for each patient to fit into a terminal box discounts all of this clinical "skill" and much of the patient history, which could result in a misclassification of the time to next scheduled appointment. This could result in an over- or underestimate of EIC.

When classifying patients in the flowcharts, it was only possible to use criteria that were measured in CHIPS (CD4, VL, weight etc.) (Table 3.21, bias 2). There are other criteria that I was not able to take into consideration, such as reported adherence to medication, which may influence the time to next scheduled appointment. This misclassification could result in either an over- or underestimation of EIC.

It is also possible that the clinicians involved in the development and review of the flowcharts were not representative of clinicians across England, as they were all from large tertiary clinics (Table 3.21, bias 3). Therefore, the criteria of time to next scheduled appointment, as set out in the flowcharts, may not always reflect national practice. A possible example is the issue of a high proportion of patients apparently attending 6 month appointments early. A number of the clinicians reported they scheduled appointments with stable, older patients, and those away at university, every 6 months. However, participants classified for 6 months follow-up were more likely to come back earlier than those classified for 3 or 4 months. If clinicians were recalling patients more frequently than reported, I may have overestimated EIC. If time had allowed I would have further clarified scheduling with clinicians. Instead, to examine the possible effect of early attendance to 6 month appointments on the predictors of EIC, a sensitivity analysis was performed on the final logistic regression model, with results reported in Chapter 5.

Howarth *et al* (151) classified newly diagnosed patients for an earlier follow-up visit because these patients need a number of baseline investigations, additional support and clinical input around their diagnosis and to start ART.(187) For my analysis, it was decided not to include new patients as a separate group because one of the inclusion criteria for the AALPHI study was that participants had to be aware of their diagnosis for at least 6 months (Table 3.21, bias 4). However, even after 6 months it is likely that young people with a new HIV diagnosis may need additional support and more careful management. Any new patients who attended more regularly would have been categorised in these flowcharts as an early attender, which would not bias the EIC estimate. However, any young people who did not attend these more frequent appointments would have been classified by these flowcharts as in care when in fact they were not. This differential bias could result in an overestimation of EIC. To investigate the extent of this possible bias, the number of patient diagnosed within the last year was examined. As there were only four participants who fell into this category, the effect of this is likely to be very small.

When assembling the data sets, the methodological decision to use clinical markers to assemble proxy clinic appointments may also have led to possible bias. Firstly, in the assembling of the visit date, it was assumed that clinical markers occurring within a week of each other were a

cluster related to the same visit (Table 3.21, bias 5). Within this cohort there are a number of very complex patients with HIV sequelea, poor immune function, mental health problems and increased risk of mortality.(182) These patients may have periods attending clinic very frequently, and so it is plausible that in some instances the multiple clinical markers are actually related to separate visits. In these cases, grouping these visits would be a misclassification and EIC will have been underestimated.

Howarth *et al* (151) highlight that one of the major weaknesses of their algorithm is that patients may visit HIV clinics for psychosocial issues which may not be captured in the clinical dataset (Table 3.21, bias 6). A fully comprehensive measure of EIC would capture this activity. However, visits for psychosocial reasons are not collected in the CHIPS dataset. Missing these additional appointments would be a measurement error and could result in an underestimation of EIC.

Another potential problem with the use of clinical markers as proxy clinic visits is that there is an assumption that all of these measurements happen in conjunction with a clinic appointment (Table 3.21, bias 7). The EIC outcome measured in this analysis is of an interaction with a clinician. However, there is potential that some of the clinical markers could occur in the absence of an actual clinic visit, for example if a patient attends clinic for bloods with a phlebotomist and not a clinician. Therefore, this bias could have resulted in a misclassification and an overestimation of EIC.

The final potential source of bias related to the use of proxy markers pertains to the frequency of HIV marker measurement (Table 3.21, bias 8). Xia *et al* (138) noted that due to guidelines recommending less frequent CD4 and viral load measurements, participants could be mistakenly classified as out of care because despite attending clinic where no blood test was taken. UK guidelines similarly recommend less frequent testing in adults.(187) Therefore, a young person who is stable on adult ART doses and has reached adult height may not have any anthropometric measurements taken (height or weight), a change in ART medication or any blood tests. Consequently, such visits may not be identified in this dataset. However, guidelines for patients in a paediatric clinic still recommend monitoring viral load every 3 to 4 months and CD4 every 6-12 months.(173,188) Therefore, young people attending paediatric clinic, may be more likely to be classified as EIC than young people in adult clinic, resulting in differential misclassification and a possible underestimation of EIC in young people seen in adult clinic.

As this was a retrospective analysis, all the blood results were assumed to be available at each 'visit' during the categorisation of time to next scheduled appointment in the flowcharts (Table

3.21, bias 9). In the clinic setting, follow-up appointments are based on patient's report of their health and adherence to ART and the findings during a clinical examination. Blood test results are not available to the clinician when scheduling the next appointment. If the blood test reveals an unexpected result, it is likely the patient may be contacted to have their appointment changed; this is especially likely if an earlier appointment is required. However, in a busy clinic this may not happen in all cases. This possible bias would cause a misclassification of time to next scheduled appointment and could either over- or underestimate EIC.

Another potential bias of the flowcharts was introduced when the data were changed moving from continuous time to month intervals and how this then affected classification of in or out of care (Table 3.21, bias 10). To make the model more like actual clinic visits, participants were given an extra 15 days beyond the time to their scheduled appointment date before they were expected to be back in care. It was also decided to classify participants as 'in care' if they attended a visit in a month irrespective of when in the month their visit was due that they attended. The risk of not doing this was that one month intervals would be classified as 'out of care' when actually the participant, or clinic, had just deferred the visit by mutual agreement. However, this introduces potential bias because participants were classified as in care despite being a possible maximum of 6 weeks late for their appointment. This may have caused misclassification and underestimated the periods and length of time participants had out of care. Reassuringly, when this was investigated, of 183 visits that were late but classified as 'in care', 58% (n=103) were within the intended 15 days leeway and across the 183 visits median time from scheduled appointment to attended visit was 11 days [IQR 5, 25].

Missing data are inescapable in epidemiological studies but they do have the potential to undermine the validity of results so it important to consider them carefully.(189) At the beginning of this analysis, efforts were made to reduce the impact of missing data by collecting as much missing data as possible. Thereafter, imputation was performed where appropriate. Despite this, there remained a number of ways in which missing data may have impacted on the accuracy of the estimation of EIC for this analysis. The important issue when considering missing data is whether the data are missing at random or systematically (when there is a relationship between the risk of a value to be missing and its value).(189)

There were a small number of patients who did not have any clinical data for the follow-up period and so they were excluded from the analysis (Table 3.21, bias 11). Other patients had partial missing clinical data resulting in months/rows being dropped (Table 3.21, bias 12). It is most likely that data were missing at random, as the missing data were due to clinic staff not

returning annual follow-up forms which affected the whole or part of the follow-up period. The instances where this occurred were small (<5% of months), but if this is selection bias, it could result in either an over- or underestimate of EIC.

In addition to patients and rows being dropped, there were missing values that prevented time to next scheduled appointment being classified (Table 3.21, bias 14). These missing values could have been caused by values not being entered on the form, missing values at the clinic end (lost samples) or an incomplete range of blood tests being taken. These errors are most likely to be missing at random and could have caused either an over- or underestimate of EIC.

Finally, participants could have proxy markers or serious event such as CDC C events not reported on their CHIPS forms (Table 3.21, bias 16). It is likely these were missing at random and could have over- or underestimated EIC.

Overall, the bias caused by missing data is unlikely to have too great an impact on the outcome of EIC because the amount of missing data was relatively small. In total, 8% of all rows, 6% of rows with a visit and 3% of patients were dropped. Thirteen per cent of patients were in shared care but they had a similar number of median visits to patients not in shared are.

Table 3.21: Summary of potential biases in defining the EIC outcome, and their potential impact on the EIC estimate

Method	Issue, [bias number]	Type of error	Over-or under-estimation of EIC	Adjustments made
Adapting the clinical criteria and developing the flowcharts for use in young people:				
Classification of clinical criteria for use in YP	Strict categorisation of patient clinical data does not capture the clinical "skill" and historical context used when assessing patients and scheduling the timing of the next appointment. [1]	Misclassification	Either	
	When classifying patients in the flowcharts, only criteria that were measured in CHIPS were taken into consideration. Additional factors, e.g. adherence, might have been useful. [2]	Misclassification	Either	
Time to next scheduled appointment classification	The time to next scheduled appointment classification used may not be reflective of wider clinical care practice in England, especially when criteria used deviated from Penta consensus guidelines. Therefore, actual times to next appointment might have been earlier or later than my classifications if my flowcharts did not represent actual practice. [3]	Misclassification	Either	Patient characteristics and alternate clinical cut offs were assessed for participants who were but early vs. not early (all 'in care'), and no substantial differences were found. Sensitivity analyses are conducted and presented in Chapter 5
New patients	Flowcharts did not allow for more careful monitoring of newly diagnosed patients, who in reality may have been assigned more frequent appointments (e.g. recurring monthly appointments), and were incorrectly assigned longer gaps between appointments in my flowcharts. New patients who attended these frequent appointments would have been categorised in my flowcharts as "early" attenders, and this does not affect their outcomes. However, new patients who did not attend these more frequent appointments would have been classified as EIC when in fact they were not. [4]	Differential misclassification	Overestimation	The number of new patients was reviewed and was very small
Assembling the dataset:				
Proxy markers	When proxy visits were created using clinical data, the assumption was that clusters of 'proxy markers' in the same week were for the same visit, but this may not have been the case. [5]	Misclassification	Underestimation	

Method	Issue, [bias number]	Type of error	Over-or under-estimation of EIC	Adjustments made
	Patients could be attending additional appointments for psychosocial reasons not captured in clinical measurements used as proxy markers. [6]	Measurement error	Underestimation	
	My EIC outcome was a measure of interaction with a clinician. Some of the tests may have been taken outside of a clinic visit (for example bloods with a phlebotomist) and therefore my algorithm may be incorrectly assuming a clinic appointment when patients attended hospital just for a blood test and did not see a clinician. [7]	Misclassification	Overestimation	
	Adult HIV guidelines recommend less frequent monitoring of viral load and CD4 markers. Therefore, an older young person, who has reached their full height, is on stable ART and attends an adult clinic, may not have a CD4 count, viral load, or height or weight measurement recorded at every clinic visit, and visits may therefore be missed. However, paediatric HIV guidelines do recommend frequent monitoring of these markers, and so my methods are more likely to completely capture paediatric clinic visits than adult clinic visits. [8]	Differential misclassification	Underestimation	
Real time delay in blood results	In real life clinical practice, the next appointment is often scheduled at the current visit, before all the blood results are available. Although appointments may be rescheduled if there are unexpected bloods results, in a busy clinic, this may not always happen. Therefore, the assumption that all of the results were available when then next appointment was scheduled may not be representative of real life scenarios.[9]	Misclassification	Either	
Classifying patients as in or out of care	By adding 15 days and allowing participants to be considered in care whenever they attend a visit in the month following their schedule appointment may introduce too much leniency in the model underestimating the periods and length of time participants had out of care. [10]	Misclassification	Underestimation	Late visits for participants in care were examined. 103/183 (58%) were with I 15 days. Overall median time to visits from scheduled appointment date was 11 days [IQR 5. 25]

Method	Issue, [bias number]	Type of error	Over-or under-estimation of EIC	Adjustments made
Missing data/data cleaning:				
Exclusion of patients	A small number of patients had no clinical (CHIPS) data for the follow-up year and were excluded. [11]	Selection bias	Either	
Partial missing data	Some patients had partial missing clinical (CHIPS) data, for which person months were dropped. [12]	Selection bias	Either	
Dropping rows	If there were two visits within a single month, the first visit was dropped so that scheduling for next appointment was based on the most recent results. However, these two visits could have been true separate visits. [13]	Misclassification	Underestimation	
Data errors	There may have been inaccurately recorded or missing clinical data on CHIPS forms, and data entry errors. These may lead to patients' time to next scheduled appointment being classified incorrectly. [14]	Misclassification	Either	Data checks and imputation were performed
	HIV guidelines recommend that patients should be on cART, so those on 1 or 2 drugs could be indicative of errors in data entry. [15]	Misclassification	Underestimation	Data checks were conducted on all patients on 1 or 2 drugs
Unreported proxy markers – shared care	Proxy markers or serious events such as a CDC C event may be erroneously omitted from CHIPS forms, due to them being completed elsewhere. [16]	Missing data	Underestimation	

Many of the biases mentioned may account for the 39% of clinic visits that were attended early. For example, patients may be coming back for mental health visits or they could be coming back for a repeat viral load following a viral load blip. However, the classification of the 6 month appointments are likely to account for a substantial proportion of early visits which is why it is examined in the predictors chapter.

In addition to the methodological limitations, there are a number of practical considerations and limitations of the flowcharts. Due to the number of criteria used in the classification of the follow-up of young people living with HIV, the flowcharts were complex and time consuming to set up and they require regular updates in accordance with changing guidelines, practice and treatment options. For example, these flowcharts focus on the treatment choice between the use of PIs and NNRTIs as third agents. Integrase inhibitors were new when the flowcharts were developed but now are recommended as possible first line third agents alongside PIs and NNRTIs.

Finally, application of a "simpler" definition of EIC to my population of young people living with PHIV in addition to the flowcharts I have developed may have added value as it would have allowed a more direct comparison of different definitions of EIC. However, such "simpler" definitions still require relatively complex programming, and it was beyond the scope of my PhD to carry this out.

3.5.4. Concluding remarks

Despite the limitations and possible biases discussed, there are a number of benefits of the flowcharts that I developed that lend them to possible future use. The flowcharts are easy to understand and provide a flexible way to measure EIC taking into account changes in patients' health status and ART treatment over time. Moreover, only routinely collected data were required to classify participants so the flowcharts can be adapted to other cohorts or datasets.

Future possible application includes examining EIC over a much longer period of time and allowing comparison across different time periods. The flowcharts can also be used for commissioning purposes to examine the complexity of this cohort's clinical care needs within clinics, regionally or nationally. Children and young people living with HIV have very different clinical needs compared to adults in the UK. Therefore, the existence of flowcharts that have been developed specifically to measure engagement in clinical care for young people living

with PHIV is a useful tool to highlight the clinical management needs of this group to HIV commissioners.

3.5.5. Key messages from this chapter

- Development of a flexible new approach to measuring EIC that takes into account changing health status
- Classifications are based on both clinical guidelines and clinician's experience
- 87% of 3,585 person months of follow-up across 306 participants were engaged in care
- Two thirds of clinic visits were in participants with on ART with a viral load ≤50c/mL
- Participants off ART accounted for less than 10% of months with a visit
- Nearly half of appointments were categorised as requiring the next schedule appointment after 4 months.
- Participants were most likely to attend their appointment early if their time to next scheduled appointment was at 6 months

Chapter 4.Characteristics of participants enrolled in AALPHI contributing follow-up to the analysis

4.1. Introduction

In this chapter, I describe the methods by which I complied the exposures considered as potential predictors for EIC in the models described in Chapter 6. I then present these exposure variables using descriptive statistics and compare to data from other relevant studies and populations to contextualise the AALPHI cohort for the reader. The exposures are grouped in "domains" of related factors. In this chapter, the characteristics are presented and then discussed within each domain, so this chapter does not follow the usual format of results then discussion.

4.2. Objectives

- To describe the characteristics of AALPHI participants
- To compare findings from analysis of AALPHI participants' data to the national HIV cohort or the wider general population where comparisons are available

4.3. Methods

4.3.1. Exposure variable inclusion

Potential exposure variables considered for inclusion in the models in Chapter 5 were from the AALPHI and CHIPS studies. Due to the large number of data items collected in the AALPHI study, inclusion of exposure variables in this analysis were based on prior published reports of factors with a known to be associated with EIC in young people living with PHIV or expert opinion. In addition, exposure variables that may affect recognised factors were also included. For example, mental health has been found to be associated with poorer EIC,(190) therefore variables that are associated with mental health problems (such as exclusion from school and death of parents) have also been included in this analysis.

Table 4.1 shows all the variables considered for inclusion in the predictive models analysis, grouped by domain, as well as the rationale for their inclusion. *A priori* variables were those included in all multivariable models while variable selection methods (described in the next chapter) were applied to potential exposure variables in other domains. Variables in the *a prio*ri domain were selected based on the rationale that they were key potential confounders

for the analysis and as such, they needed to be included in all the multivariable models. A confounder is a variable that causes the distortion of the association between an exposure and health outcome.(191) In the *a priori* domain, sex, ethnicity and age are acknowledged as fundamental factors that may affect health and illness research. Time from AALPHI interview and born outside of the UK, are more specific to this analysis. Time from interview was included as an *a priori* variable as it was recognised that EIC might change over time since AALPHI interview (baseline) and to explore whether any potential associations between exposure variables (measured at baseline) and EIC changed over the one year follow up period. Whether patients were born abroad or in the UK was included specifically for this population because a high proportion of the cohort are born abroad, largely in Sub-Saharan Africa (192) and place of birth might be associated with EIC and a number of the other variables included in this analysis.

Other exposure variables considered for inclusion in the predictive models were classified into six domains: sociodemographic; risk behaviour practices; mental health; cognition; clinic and HIV markers. Examples of variables that were considered based on evidence from the literature are alcohol use, which has been associated with lower EIC, and adolescent services (clinic type) which has been associated with better EIC. Examples of variables that were considered based on expert opinion were smoking (ever smoke cigarettes) and condom use, which were due to the association between other risk behaviour factors and lower EIC and mental health problems. Clinic location was included due to work by an MSc student being conducted at the time which suggested a possible cluster of complex patients in the North of England (unpublished).

Table 4.1: Exposure variables considered for inclusion in the multivariable models, and the rationale for inclusion, by domain

Domain, exposure variables	Exposure – outcome rationale for inclusion in this analysis (references)
A priori (included in all multivariable models)	
Time from AALPHI interview (months)	To understand the effect of time since AALPHI variables were collected
Sex	Males associated with lower EIC (161,162)
Age at entry	Older child age associated with lower EIC (161,162,193,194) Adolescents have lower EIC compared to adults (2,118,127,190,195)
Ethnicity	Ethnicity associated with EIC but varying trends across studies (127,161,162,190,195–198)
Born outside of the UK/Ireland	Being born outside USA associated with higher EIC in USA (162)
Sociodemographic	
Education/employment status	Unemployment associated with lower EIC (199) Employment associated with lower EIC (200) HIV and socioeconomic disadvantage associated with underachievement and mental health problems (201–203)
Ever excluded from school	Exclusion from school associated with mental health problems and social exclusion (204,205)
Death of parents	Death of parents associated with mental health problems and reduced social support (114,115,206)
Fostered/adopted	People who were orphaned and have frequent carers had lower EIC (160)
Number of main carers	
Live with parents/carers	Living in a household with another person living with HIV associated with increased EIC (199)
Parent/carer in work	Employment associated with lower EIC (200)
Main language spoken at home	Speaking a language other than English at home associated with mental health problems (114)
Income deprivation affecting children index (IDACI) deprivation score	Low socioeconomic areas associated with increased EIC (161)
Risk behaviour practices	
Ever smoked cigarettes	Based on expert opinion
Had alcohol in the last year	Alcohol misuse associated with lower EIC (190)
Alcohol amount	Alcohol misuse associated with lower EIC (190)
Ever used recreational drugs	Use of recreational drugs (ever) associated with mental health problems (207) and lower EIC (1,11,24,25,26)
Ever had sex (vaginal or anal)	Sexual activity in young people associated with mental health problems (210)
Age at first sex	Pre-adult sexual activity associated with mental health problems (207)
Condom use	Based on expert opinion

Domain, exposure variables	Exposure – outcome rationale for inclusion in this analysis (references)
Mental health	
Feelings about HIV	Acceptance of HIV associated with increased EIC (193)
Ever self-harmed	Self-harm associated with other mental health problems (211)
Ever felt life was not worth living	Ever felt life was not worth living is associated with other mental health problems (114)
Major life events	Negative life events cause other mental health problems (212,213)
Pediatric Quality of Life Inventory (PedsQL™)	Lower social functioning associated with other mental health problems (204)
Rosenberg Self-Esteem Scale	Self-esteem associated with other mental health problems (204,211)
Hospital anxiety and depression Scale (HADS) anxiety score	Anxiety associated with other mental health and behavioural problems (77)
HADS depression score	Depression associated with lower EIC (190)
Cognition domain	
Neuropsychological test composite z score-6 (NPZ-6) score[1]	Cognitive impairment associated with worse EIC (190) Poorer cognition associated with depression (107)
Clinic	
Clinic location	Based on expert opinion
Clinic type	Adolescent friendly services associated with better EIC (164,214–217)
Distance from home to clinic (km)	Further distance from home to clinic associated with worse EIC (218)
Travel time from home to clinic (min)	Longer travel time from home to clinic associated with worse EIC (218)
HIV experience and management	
Age told HIV diagnosis	Had experience of disclosure associated with lower EIC (160)
Number of people told about HIV	Difficulty disclosing to others associated with increased internalised stigma and social isolation and decreased EIC (159)
Doses of missed in last 3 days	Missed doses associated with mental health problems (207)
Self-assessment of adherence	Associated with mental health problems (207)
HIV markers	
HIV severity:	
Previous CDC C event	Previous AIDS diagnosis associated with higher EIC (156) Lower EIC associated with CDC C events (119)
Nadir CD4 cell count (cells/µL)	Higher CD4 nadir associated higher EIC (151)
CD4 cell count (cells/µL)	Lower CD4 count associated with lower EIC (156,190,219)
Viral load (c/mL)	Treatment failure before disengagement associated with lower EIC (118,119,156,158,216,219,220)
ART:	
Age at ART start	Younger age at ART start associated with lower EIC (220)

Domain, exposure variables	Exposure – outcome rationale for inclusion in this analysis (references)
On efavirenz Treatment interruption ≥30 days	Efavirenz associated with depression (221) Taking ART associated with better EIC (219,222)

[1] Summary score of six cognition domains

4.3.1.1. Data collection tools

A number of tools were used to collect the data included in this analysis. All the tools and scoring information related to each tool are described in Table 4.2. Nine tools were used predominantly in the mental health domain, but also in the sociodemographic, risk behaviour practices and cognition domains. All of the tools described are published tools apart from the 'Feelings about HIV' tool. Using published tools is beneficial because these tools have been validated and comparative data are available. An example is the Pediatric Quality of Life Inventory which has been utilised in many paediatric and adolescent cohorts. The 'Feelings about HIV' tool was developed by the AALPHI team in the absence of an identified tool asking young people how they felt about living with HIV.

Table 4.2: Data collection tools used in AALPHI

Domain, variable	Name of tool/source	Details of tool	Scoring information
Sociodemographic			
Deprivation	IDACI (223)	A residential deprivation score (based on postcode). Small areas of relatively equal size (Lower Super Output Areas) are scored based on multiple deprivation measures Timeframe: Current (from the last updated postcode)	Participant postcode can be used to measure deprivation. Scored from 0-1 on a continuous scale with 0 being the most deprived
Risk behaviour practices			
Alcohol amount	Alcohol Use Disorders Identification Test (AUDIT)(145)	Self-report questionnaire to identify hazardous drinking and harmful patterns of alcohol consumption Timeframe: Current	Each response was given a score ranging from 0-4 and the scores summed over 10 questions. A total score of more than eight indicates hazardous and harmful alcohol use
Mental health			
Feelings about HIV	AALPHI feelings about HIV questions (not validated)	Five response scales displayed as a visual analogue scale. Q: How do you feel about having HIV now? • Very upset-Not upset at all; • Think about it all the time–Don't think about it at all; • Really sad–Not sad at all; • Feel really alone–Feel really supported • Really worry about my future health–Feel positive about my future health Timeframe: Current	Scores ranged from 0-10 for each question. A summary score was created for analysis ranging from 0-50 where a higher score represents a better perception about living with HIV
Quality of life	Pediatric Quality of Life Inventory (140)	Self-report questionnaire. Two versions: Teenage report (13-18) and the Young adult (18-25)	Responses to all 23 questions were on a five- point Likert scale scored from 0-4. Scores were then transformed as follows: 0=100, 1=75, 2=50, 3=25,

Domain, variable	Name of tool/source	Details of tool	Scoring information
		Timeframe: Past month	4=0. Then the mean score of all responses was calculated (Total scale score). Higher scores indicate better health related quality of life
Major life events	Avon Longitudinal Study of Parents and Children (ALSPAC) questionnaire	Questionnaire from ALSPAC 'Life of a 16+ Teenager' questionnaire. Questionnaire includes a list of major life events. Participant answered yes or no to experiencing the event. If they had experienced the event they ranked the effect of the event Timeframe: Last year	Responses to all 21 questions were on a five point Likert scale scored from -2 to 2. The summary of scores from the 21 questions were then categorised into quartiles from most unpleasant to most pleasant
Self-esteem	Rosenberg Self-Esteem Scale (141)	Self-report questionnaire Timeframe: Current	Responses to all questions were on a four point Likert scale scored from 0-3 (10 questions in total of which five are reverse scored). The total for the 10 responses was calculated. Scores ranged from 0-30. The higher the score the higher the self-esteem
Anxiety	HADS (143)	Self-report questionnaire. One questionnaire measures both anxiety and depression Timeframe: Past week	Responses to all questions were four point Likert scale scored from 0-3 (14 questions in total of which six were reverse scored). Two scores were calculated, one for anxiety and one for depression (seven questions each). Scores ranged from 0-21. Higher score indicated higher anxiety or depression. Scores were categorised using standard definitions: normal <8, mild 8-10, moderate 11-15, severe >15 (224)
Depression			
Cognition			
NPZ-6	Summary score across six cognitive domains(107)	Details of the manufacturers' reference data for the AALPHI cognitive NPZ-6 scores have previously been described.(107)	Using the manufacturers' reference data, z scores were calculated to measure how many standard

Domain, variable	Name of tool/source	Details of tool	Scoring information
		Manufacturers' reference data were from Australian and UK adults.	deviations AALPHI participants were below or above the normative population mean

4.3.2. Data cleaning and consistency checks

4.3.2.1. Data cleaning/checking

The study statisticians cleaned both the AALPHI and CHIPS datasets prior to this analysis to check for inconsistencies and errors. In addition, I carried out several checks for this analysis described below.

4.3.2.2. Consistency

Consistency was checked throughout the coding process, for example, using cross tabulations of derived variables with original variables. In addition, I made checks between the CHIPS and AALPHI data where variables were collected in both studies (sex, date of birth (DOB), ethnicity, born outside the UK Ireland). Inconsistencies were found for two participants who had their ethnicity documented in the CHIPS study but ticked the 'Prefer not to answer' option in AALPHI. I decided to classify these two as 'Prefer not to answer', as they had requested, in my analysis dataset.

4.3.3. Description of variables, comparison to normative data and tests for difference

The distributions of variables were described, presenting the number of participants in each category including those with missing data. Additionally, the proportion of participants by category is presented, excluding the missing data. To improve comparability between exposure variables, all scores were coded so that they went in the same directions, so higher scores were better and lower scores worse.

For the majority of the domains (sociodemographic, risk behaviour practices, mental health, cognition, clinic and HIV experience and management domains) distributions were compared to normative data from the wider population of young people in the UK. However, for the *a priori* and HIV markers domains and the clinic type variable in the clinic domain, comparison to the CHIPS UK and Ireland dataset was possible.

4.3.3.1. Comparison to UK normative data

Where possible normative data from the time of the AALPHI interview (2013-2015) were selected. Normative data from the UK and Ireland were used; one exception was the manufacturer reference data which for the Cognition Neuropsychological test composite z score-6 (NPZ-6) score was based on adult Australians.(107) Where population data were

available, the AALPHI sample proportion was compared to the population proportion (i.e. under a null hypothesis that the probability of "success" in the AALPHI data was the same as the population proportion, where a low p-value suggests the proportion in the AALPHI data was different to the population); the *bitesti* command in Stata was used. Similarly, the AALPHI sample mean was compared to the population mean using the *ttest* command. The *prtesti* command for a test of two proportions was used to compare proportions in the AALPHI sample to another study sample (not population). When analysing proportions "don't know", "prefer not to answer" and missing data categories were excluded from the denominator.

As detailed in Table 4.2, a number of the mental health tools were used for which normative data were available (Pediatric Quality of Life Inventory, Rosenberg Self-Esteem, Hospital anxiety and depression Scale (HADS) anxiety score, HADS depression score). For each of these variables, *z* scores were calculated from the normative data using this equation:

$$\frac{\text{AALPHI mental health } var\text{-comparative study mean score}}{\text{comparative study standard deviation}}$$

For the Pediatric Quality of Life Inventory there were two normative samples one to compare to healthy young people and the second to compare to young people with diabetes. Therefore, two *z* scores were calculated. For the Rosenberg Self-Esteem Scale, age/sex-appropriate means and standard deviations were used, and for the HADS anxiety and depression scores, data were adjusted for sex. HADS anxiety and depression scores were the opposite direction to the rest of the scores (a score above zero means worse anxiety or depression). Therefore, scores were reversed for HADS anxiety and HADS depression so all the scores could be viewed in one direction (a minus value means worse anxiety or depression than population mean). Mean *z* scores were tested for difference from zero using the *ttest* command in stata.

4.3.3.2. Comparison to the UK and Ireland CHIPS cohort

For the *a priori* and HIV markers domains and the clinic type variable in the clinic domain, normative data were available from the UK and Ireland CHIPS dataset. CHIPS participants from across the UK and Ireland were included in the comparison group if:

- they were not in AALPHI
- they were aged 15-18 years (the IQR for participants in AALPHI) at the midpoint of the AALPHI interview period which was 01.01.14

The midpoint of the AALPHI interview period (2013-2015) was also chosen as a proxy date for selection of clinical data for CHIPS participants for comparison to AALPHI participants.

Fifty-seven otherwise eligible CHIPS participants were excluded because they had died (n=26), moved aboard (n=26) or were lost to follow-up (n=5) prior to the proxy date. For participants in CHIPS who had transferred to adult care before 01.01.14, their clinical data at transfer was used for this comparison as adult data were not routinely recorded in CHIPS.

For most categorical variables, the number and proportion in each category were described and compared between the AALPHI and CHIPS groups using the chi-squared test. When the expected numbers in the categories were <5, a Fisher's exact test was used. For continuous variables, which were not normally distributed, data were summarised as medians (interquartile range) and compared between AALPHI and CHIPS participants using the Wilcoxon rank sum test.

In the HIV markers domain, the closest CD4 cell count (cells/μL) and viral load (c/mL) measurements prior to the first interview date were used if they were taken within a window of 6 months before and 7 days after the first interview for AALPHI participants or proxy interview date for CHIPS comparisons[2]. Treatment interruption was defined as a gap in ART treatment for ≥30 days within the last 2 years before the interview date.

4.3.4. Missing data

Individual variable missing data were described within each domain. Forty seven participants (15%) were found to have at least one missing AALPHI CRF out of a possible 12.

4.4. Characteristics

4.4.1. A priori domain

Table 4.3 compares *a priori* characteristics of young people in AALPHI to young people living with PHIV aged 15-18 years in the UK and Ireland national CHIPS cohort and not in AALPHI. Of the 316 AALPHI participants, 129 (41%) were male and the median age was 17 [IQR 15, 18]. Most (258, 82%) were black African, and 184 (58%) were born outside of the UK or Ireland.

[2] The 7 days after the date of the AALPHI interview was given to match the leniency allowed to classify whether the AALPHI interview was at the same time as a clinic appointment.

Table 4.3: *A priori* characteristics of young people living with PHIV in AALPHI and a CHIPS comparison group

Variable and categories	AALPHI cohort (n=316)		CHIPS cohort (n=247)		p value
	n (%)or median [interquartile range (IQR)]				
Male sex	129	(41%)	130	(53%)	0.005
Age[1]	17	[15, 18]	17	[16, 17]	
Ethnicity:					
Black African	258	(82%)	203	(84%)	0.06
Black other	13	(4%)	2	(1%)	
Mixed	30	(10%)	20	(8%)	
White	9	(3%)	12	(5%)	
Asian	4	(1%)	6	(2%)	
Born outside UK/Ireland	184	(58%)	151	(62%)	0.42

[1]Age not compared due to it being a selection criterion.

4.4.1.1. Comment

A lower proportion of AALPHI participants were male compared to the remainder of the national cohort (41% vs. 53%, p=0.005). The characteristics of young people who refused to participate in AALPHI were not collected, so it is not possible to say whether this finding is because fewer males were approached or more males declined. Apart from sex however, the other *a priori* characteristics were similar between AALPHI and the wider CHIPS cohort, suggesting that participants in AALPHI are broadly similar to the rest of the UK and Ireland population of young people living with PHIV, and therefore representative of the complete population.

4.4.2. Sociodemographic domain

Table 4.4 presents sociodemographic characteristics of AALPHI participants compared to normative data from a variety of studies in the UK. Two hundred and ninety-two (93%) AALPHI participants were in education, 8 (3%) were employed and 13 (4%) were not in education or employment at AALPHI interview. The majority (259, 82%) had never been excluded from school, while 47 (15%) had ever had a fixed period exclusion, and 8 (3%) had been permanently excluded. For 94 (30%) of the young people, one parent had died and for 14 (4%) both parents had died. Fifteen (11%) of the participants were fostered or adopted. One in five (64, 20%) young people had ever had a change in main carer (e.g. mother and/or father and then grandparent/s) and 47 (15%) had more than two changes in main carer. The majority (286, 91%) lived with their parents or carers, and the majority (224, 73%) of parents and carers were in work. Half (164, 52%) of participants only spoke English at home and 143 (45%) spoke English and another language. Two hundred and six (75%) lived in "more deprived" or the "most deprived" neighbourhoods in England.

Table 4.4: Sociodemographic characteristics of AALPHI participants (n=316) compared to normative data

Variable	AALPHI n (%)		Normative data	p-value
Education/employment status				
In full-time education	292	(93%)	7% of 16-18 year olds in England were not in education or employment in Jan-March 2014 (225)	0.05
Employed	8	(3%)		
Not in education or employment	13	(4%)		
Missing	3			
Ever excluded from school			Of pupils enrolled in England in the academic year 2013/2014, there were 0.1% permanent exclusions and 7% fixed exclusions (226) Permanent exclusion in black Africans in England was 0.1% (for 2016/2017) (227)	Data not comparable
No	259	(82%)		
Fixed exclusion	47	(15%)		
Permanent exclusion	8	(3%)		
Missing	2			
Death of parents			By the age of 16, the death of a mother or father occurred in 5% of 11,000 participants in the 1970 British Cohort Study (228)	<0.001
None	187	(60%)		
One parent died	94	(30%)		
Both parents died	14	(4%)		
Don't know	19	(6%)		
Missing	2			
Fostered/adopted[1]			0.6% of children <18 years in the UK were fostered or adopted by the end of March 2014 (229)	0.02
No	116	(89%)		
Yes	15	(11%)		
Missing	185			
Number of main carers				
1 carer	203	(65%)	No comparative data	-
2 carers	64	(20%)		
3 or more carers	47	(15%)		
Missing	2			
Live with parents/carers			93% of 10-19 year olds lived in households with a parent or carer in the UK in 2017 (230)	0.18
Yes	286	(91%)		
No	28	(9%)		
Missing	2			
Parent/carer in work			73% of people in the UK aged 16-64 were employed in Apr-June 2014 (231) Of 781 adults living with HIV, 64% were employed (Data from Positive Voices Survey cited in HIV in the UK report, PHE (232)	1.00 0.005
Yes	224	(73%)		
No	83	(27%)		
Don't know	7			
Missing	2			
Main language spoken at home			92% of residents in England aged >3 years spoke English as the main language at home (233)	Data not comparable
English only	164	(52%)		
English & another language	143	(45%)		
A language other than English	8	(3%)		
Missing	1			

Variable	AALPHI n (%)		Normative data	p-value
IDACI deprivation score			IDACI measures childhood deprivation in small areas and categories represent population quartiles allowing comparison across England (223)	<0.001
Least deprived	8	(3%)		
Less deprived	63	(22%)		
More deprived	140	(51%)		
Most deprived	66	(24%)		
Missing	39			

[1]Added halfway through interview process thus 50% missing data

4.4.2.1. Comment

A slightly lower proportion of AALPHI participants (4%) were not in education compared to national data (7%) for 16-18 year olds in a similar calendar period (p=0.05).(225)

School exclusions reported by Department of Education figures for England (226) show that of pupils enrolled in secondary schools in the academic year 2013/2014, 0.1% were given permanent exclusions, and 7% fixed exclusions, with no difference for black African children (227). However, the national data are only for one academic year while AALPHI examined lifetime history of exclusion over a young person's whole school career. After multiplying the national figure by 6 to approximate to the whole of secondary school, the proportion of young people ever reporting permanent exclusions in AALPHI was ~5 times higher than that for England (3% vs. 0.6%). It was not possible to compare the proportion of young people with fixed exclusions, but 15% is unlikely to be lower than the 7% for England.

There was very strong evidence to suggest a higher proportion of participants in the AALPHI cohort experienced the death of a parent (one or both) compared to the UK population. Overall, for a third of AALPHI participants (108, 34%) one or both parents had died, in contrast to 5% of 11,000 participants by 16 years of age who were in the 1970 British Cohort Study (p<0.001).(228)

A higher proportion of AALPHI participants (11%) had been fostered or adopted compared to children less than 18 years of age in the UK (0.6%, p=0.02).(229) No UK comparative data could be found for the change in number of main carers that young people in AALPHI experienced in their childhood. It seems likely, however, that young people in AALPHI would have had more changes than the general population due to the relatively high levels of parental death and adoption and fostering in the cohort. The majority of young people in

AALPHI (91%) still lived with their parents/carers, similar to data for 10-19 (93%, p=0.18) year olds in the UK (230) although the AALPHI group are older

There was no difference in the proportion of working parents/carers (73%) as reported by the AALPHI participants when compared to adults in the general population in 2014 (73%, p=1.0) (234). This was significantly higher, however, than reported in a survey of 781 adults living with HIV from clinics across the UK (AALPHI: 73% vs. Positive Voices: 64%, p=0.005).(235) However, respondents to the survey were predominantly white men (68%) who had sex with men (78%) making comparison difficult.(236) It is also important to bear in mind that the percentage of parents/carers of participants in the AALPHI cohort who were living with HIV is not known.

Census data from 2011 (233) reported that 92% of residents in England aged over three years spoke English at home. A greater proportion of people in the AALPHI cohort spoke some English in their home (97%=52% English only and 45% English and another language) but data were not collected in AALPHI about whether English was the main language spoken.

Using the Income deprivation affecting children index (IDACI) measure of deprivation, three quarters (75%) of AALPHI participants were classified as living in areas in the lowest five out of 10 IDACI deprivation deciles (bottom 50%). There was strong evidence (75% vs. 50%, <0.001) therefore that AALPHI participants were living in disproportionately disadvantaged areas compared to other children and young people in England.

4.4.3. Risk behaviours practices domain

Risk behaviour practice characteristics in the AALPHI cohort are compared to normative data from various parts of the UK in Table 4.5. The majority of AALPHI participants did not smoke cigarettes (242, 83%) and had not drunk alcohol in the last year (174, 59%). Of the young people who did drink, 30 (25%) were classified in the Alcohol Use Disorders Identification Test (AUDIT) Tool as drinking to hazardous levels.(145) Forty-three (25%) young people had ever used recreational drugs.

Ninety-three (32%) young people were sexually active, of whom 70 (77%) were aged 15-17 years when they first had sex. Thirty young people (10%) reported ever having sex without a condom. Table 4.5: Risk behaviour practices of participants in AALPHI (n=316) compared to normative data

Variable	AALPHI n (%)	Normative data	p value
Ever smoked cigarettes		23% of 16-24 year olds were current smokers in 2014 in Great Britain (237)	0.05
No	242 (83%)		
Yes	54 (18%)		
Missing	20		
Had alcohol in the last year		48% of 16-24 year olds in 2014 drank in the last week in Great Britain (238)	Data not comparable
No	174 (59%)		
Yes	123 (41%)		
Missing	19		
Alcohol amount (n=123)		17% of 16-24 year olds who drank, consumed more than their weekly allowance in a single day in Great Britain (238)	Data not comparable
Drink but not hazardous	92 (75%)		
Hazardous drinking	30 (25%)		
Missing hazardous drinking score	1		
Ever used recreational drugs		19% of 16-19 year olds and 19% of 20-24 year olds had used recreational drugs in the last year in England and Wales from 2013/14 (239)	0.07
No	248 (75%)		
Yes	43 (25%)		
Missing	25		
Ever had sex (vaginal or anal)		31% of all 16-34 year olds had sex before 16 years old in Britain (National Surveys of Sexual Attitudes and Lifestyles (NATSAL)) in 2010-2012 (240)	Data not comparable
No	195 (68%)		
Yes	93 (32%)		
Prefer not to answer	8		
Missing	20		
Age at first sex (n=93)			
≤14	18 (20%)		
15-19	70 (77%)		
20+	3 (3%)		
Missing	2		
Condom Use		14% of 16-24 year olds had at least 2 sexual partners with whom no condom was used in the last year (NATSAL) in 2010-2012 (240)	0.09
Not sexually active	195 (68%)		
Always use a condom	63 (22%)		
Do not always use a condom	30 (10%)		
Missing	28		

4.4.3.1. Comment

The fifth (18%) of young people in AALPHI who ever smoked cigarettes was marginally lower than the proportion of 16-24 years olds in Britain who reported currently smoking in 2014 (23%, p=0.05).(237) It seems likely that this difference would have been even bigger if current smoking had been measured in the AALPHI cohort. There are no UK normative data for the AUDIT tool for young people, although Office for National Statistics data suggest that 48% of 16-24 year olds in Great Britain drank in the last week. Notwithstanding the different reporting window used by the Office for National Statistics, these results suggest that AALPHI participants' alcohol consumption was either less than or similar to other young people in Great Britain.(238) Of the 48% of 16-24 year olds who drank in the last week in the Office for National Statistics study, 17% drank more than the recommended weekly alcohol limit on their heaviest day, which compares to 25% of AALPHI participants who were classified as hazardous drinkers based on alcohol consumption in the last year. Although the two studies were using different reporting windows to measure hazardous drinking, the findings are not inconsistent with each other. Similar proportions of participants in AALPHI (25%) and 16-24 year olds (19%) in England and Wales had used recreational drugs (p=0.07), although the reporting windows were lifetime in AALPHI and in the last year in the national dataset.(239)

In the National Survey of Sexual Attitudes and Lifestyle (NATSAL) in 2010-2012, a third of 16-34 year olds reported having sex before the age of 16.(240) In the AALPHI cohort, a third of the cohort also reported being sexually active, but the cohort was older (aged 13-21 years of age) suggesting that young people in AALPHI may be delaying their first sexual encounters. Comparable proportions of young people in NATSAL reported inconsistent condom use as in AALPHI (14% vs. 10%), but the definitions were dissimilar ("do not always use a condom" vs. "had at least 2 sexual partners with whom no condom was used in the last year") to consider testing formally.

4.4.4. Mental health domain

The mental health characteristics of the AALPHI cohort, and comparative data from studies in the UK and Ireland, are presented in Table 4.6. The median score for feelings about HIV was 35 out of 50 (maximum score) [IQR 22,43] where a higher score represents a better perception about living with HIV, and as this measure was not a standard tool, no comparative data were available. Thirty-seven (12%) young people had ever self-harmed and 117 (39%) had ever felt that life was not worth living. Three-fifths reported experiencing life events in the last year which were pleasant (106, 35%) or very pleasant (82, 27%).

Table 4.6: Mental health characteristics of participants in AALPHI (n=316) and normative data

Variable	AALPHI n(%) or mean {standard deviation (SD)} median [interquartile range (IQR)]		Normative data	p value
Feelings about HIV (summary score)			No normative data	-
Median score	35	[22, 43]		
Ever self-harmed			19% of 4,810 16-17 year olds ever self-harming in England (ALSPAC) 2007-2008 (142)	0.002
No	265	(88%)		
Yes	37	(12%)		
Missing	14			
Ever felt life was not worth living			16% of 4,810 16-17 year olds ever felt life was not worth living in England (ALSPAC) 2007-2008 (142)	<0.001
No	182	(61%)		
Yes	117	(39%)		
Missing	17			
Major life events in the last year (quartiles)			No normative data	-
Most unpleasant events	49	(16%)		
Some unpleasant events	63	(21%)		
Some pleasant events	106	(35%)		
Most pleasant events	82	(27%)		
Missing	16			

The mean Pediatric Quality of Life Inventory summary score was 75 out of 100 (maximum score) (SD=14) and the mean Rosenberg Self-Esteem Scale was 21 out of 30 (maximum score) (SD=5). There were 172 (61%) participants who scored within the normal range on the HADS anxiety tool, and 112 (40%) who scored above the normal range. Only 8 (3%) of AALPHI participants scored within the severe range for anxiety. The majority of young people had a normal score for the HADS depression measure (240, 85%), while 32 (11%) participants scored within the mild range, 12 (4%) within the moderate range, and none within the severe range for depression (Table 4.7).

Table 4.7: Mental health variables compared to normative compared to mean and *z* scores

Variable	AALPHI n (%) or mean {standard deviation(SD)}		Normative data		p value (*z* score)
			mean {standard deviation(SD)}	95% CI (z score)	
Pediatric Quality of Life Inventory					
Mean total score	75	{14}	Mean total score from 8-18 year olds in UK: Healthy 84 {12} Diabetes[1] 82 {13} (241)	-0.90, -0.63 -0.73, -0.48	<0.001 (healthy) <0.001 (diabetes)
Mean *z* score healthy	-0.77	{1.2}			
Mean *z* score diabetes	-0.59	{1.1}			
Missing	14				
Rosenberg Self-Esteem					
Mean score	21	{5}	Mean score for 13-17 year olds -27 {4.0} in Ireland (242)	-2.11, -1.72	<0.001
Mean z score	-1.91	{1.6}			
Missing	14				
HADS anxiety score[2]					
Mean score	6	{4}	Mean scores for 25-29 year olds in England: females 7{4} and males 6 {4} (243)	-0.08, 0.12	0.66
Mean *z* score	0.2	{0.8}			
Normal	172	(61%)			
Mild	64	(23%)			
Moderate	40	(14%)			
Severe	8	(3%)			
Missing	32				
HADS depression score[2]					
Mean score	4	{3}	Mean score for 25-29 year olds in England: females 4{4} and males 3{4} (243)	-0.20, -0.01	0.04
Mean *z* score	-0.10	{0.8}			
Normal	240	(85%)			
Mild	32	(11%)			
Moderate	12	(4%)			
Severe	0	(0%)			
Missing	32				

[1]Mean quality of life score from children with diabetes

[2] HADS anxiety and depression scores are reversed to allow comparability to other mental health scores (so a minus score indicates worse anxiety or depression

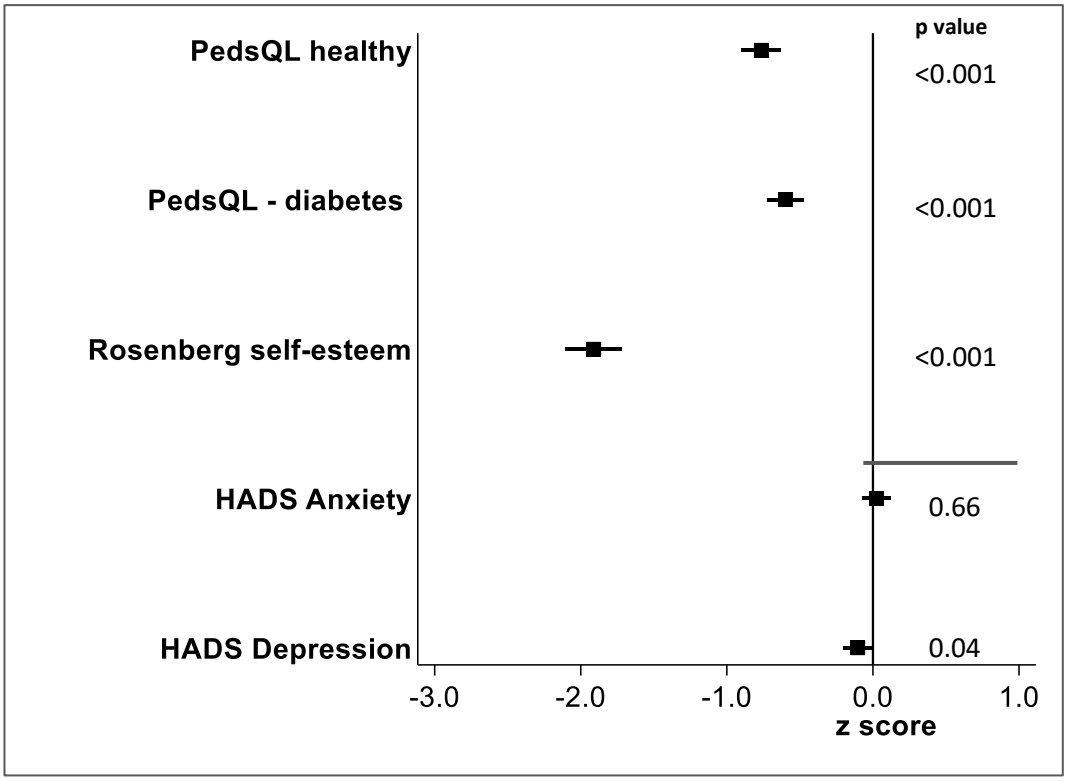
4.4.4.1. Comment

No normative data exist for the feelings about HIV score because this was a set of questions developed by the AALPHI team in the absence of any available measure specific to young people living with PHIV. Reassuringly there was strong evidence to suggest that the proportion of young people who self-harmed was lower in the AALPHI cohort (37, 12%) than in 16-17 year olds in the Avon Longitudinal Study of Parents and Children study (ALSPAC) (19%, p=0.002).(142) However, there was very strong evidence that a higher proportion of young people in AALPHI had felt life was not worth living compared to 16-17 year olds in the ALSPAC study (39% vs. 16%, p=<0.001)

Z scores were calculated for Pediatric Quality of Life Inventory, Rosenberg Self-Esteem and the Hospital Anxiety and Depression Score (HADS). For the Pediatric Quality of Life Inventory normative data were from a sample of 8-18 year olds in the UK (mean scores available from healthy young people and young people with diabetes). For Rosenberg Self-Esteem, normative data were from 13-17 year olds in Ireland. For the HADS anxiety and depression score, data were from 25-29 year olds in England.

Z scores from Table 4.6 are displayed in a forest plot in . The *z*-scores were significantly below 0 in four out of the five mental health variables suggesting that AALPHI participants had on average worse mental health scores than the reference population used to derive the scores. The AALPHI participants Pediatric Quality of Life Inventory mean *z* scores were significantly below 0 when compared to healthy young people, (p<0.001) and young people with diabetes (p<0.001). Most noticeably, the AALPHI participant's Rosenberg Self-Esteem mean scores (-1.91, 95% CI -2.11, -1.72, p<0.001), were close to two standard deviations below 0 when compared to the reference population. There was no difference between AALPHI participants' mean HADS anxiety *z* scores and reference population (0.2, 95% CI -0.08, 0.12, p=0.66) and weak evidence of worse mean HADS depression scores compared to the reference population, with the upper limit of the confidence interval for the mean very close to 0 (*z* score -0.10, 95%CI -0.20, -0.01, p=0.04). However, it was not possible to find age-appropriate normative date for the HADS anxiety and depression tool and therefore the normative data are based on older participants.

Figure 4.1:Forest plot of mean (95%CI) mental health scores for young people in AALPHI



4.4.5. Cognition domain

Table 4.8 presents the NPZ-6 *z* score mean and the NPZ-6 category for AALPHI participants. The mean *z* score was -0.54 and 215 participants (75%) scored below the reference mean, with 74 (26%) of young people scoring more than one standard deviation below the reference mean.

Table 4.8: Cognition characteristics of participants in AALPHI (n=316) and normative data

Variable	n (%)or mean {standard deviation (SD)}		Normative data	95% CI	p value[1] (*z* score)
NPZ-6 *z* score	-0.54	{0.86}	Manufacturer normative data used for 11 tests in 6 cognitive domains (107)	-0.57, -0.52	<0.001
NPZ-6 category					
<-1	74	(26%)			
≥ -1 to <0	141	(49%)			
≥0	75	(26%)			
Missing	27	(24%)			

[1]The p value represents a test of the null hypothesis that the mean *z* score = 0

4.4.5.1. Comment

When summary NPZ-6 scores were compared to reference population, there was strong evidence that young people in the AALPHI study had poorer cognitive performance ($p<0.001$).

4.4.6. Clinic domain

Table 4.9 presents the clinic characteristics for the clinics from which the AALPHI cohort were recruited or where participants received their HIV care (if recruited in the voluntary sector), as well as the available UK and Ireland normative data for comparison. Two hundred and thirty (73%) AALPHI participants were recruited from London clinics and 234 (77%) from paediatric care. The median distance from home to clinic was 10km ([IQR 5, 21], min 1, max 405) and the median travel time to clinic was 31 minutes ([IQR 19, 46], min 5, max 327). In paediatric HIV, a number of patients do travel long distances (and therefore have a long travel time) usually to tertiary clinics because paediatric HIV is a rare disease and is managed in a small number of clinics across the UK.

Table 4.9: Clinic characteristics of participants in AALPHI (n=316) and normative data

Variable	AALPHI n (%) or median [interquartile range (IQR)]		Normative data	P value
Clinic location				
Enrolled in London	230	(73%)	No UK data	-
Enrolled outside London	86	(27%)		
Missing	0			
Clinic type[1]			Of 247 15-18 year old participants in CHIPS but not in AALPHI, 201 (81%) were still in paediatric care, 14 (6%) had transitioned to adolescent clinic, 32 (13%) to an adult/GUM clinic	-
Paediatric care	234	(77%)		
Adolescent clinic	51	(17%)		
Adult/GUM clinic	17	(6%)		
Missing	4			
Distance from home to clinic (km)				
Median distance	10	[5, 21]	No UK data	-
0-59	245	(90%)		
≥60	28	(10%)		
Missing	43			
Travel time from home to clinic (min)				
Median travel time	31	[19, 46]	No UK data	-
0-59	231	(85%)		
≥60	42	(15%)		
Missing	43			

4.4.6.1. Comment

Clinics were purposively selected for the AALPHI study based on having large numbers of eligible participants for the study, which meant that research nurses recruited in all of the largest adolescent clinics in the country. Therefore, although a higher proportion of young people in AALPHI had transferred to adolescent clinics than in the comparative CHIPS group (17% vs. 6%) the clinics attended by the AALPHI cohort are not representative of clinics attended by adolescents living with HIV in the UK. In addition, clinic type was classified by AALPHI research nurses for the AALPHI clinics and by clinic staff in the CHIPS study, which may cause further disparity. There were no comparative data in the UK for clinic location, travel time to clinic or distance to clinic.

4.4.7. HIV experience and management domain

Table 4.10 presents the HIV experience and management characteristics of AALPHI participants. The median age when AALPHI participants were told their HIV diagnosis was 12 years [IQR 11, 13]. Fifty young people (17%) were told about their HIV diagnosis when they were 13 years or older. More than half of the AALPHI participants (161, 55%) had never independently told anyone about their HIV status and only a small proportion had told 5 or more people (4% had told 5-9 people and 4% had told ≥10 people). One hundred and ninety (73%) AALPHI participants reported that they had not missed doses of ART in the three days preceding the AALPHI interview.

Table 4.10: HIV experience and management characteristics of participants in AALPHI (n=316) and normative data

Variable	n (%) or median [interquartile range (IQR)]		Normative data	p value
Age told HIV diagnosis:				
Median age at naming of HIV	12	[11, 13]		-
Age at naming of HIV			UK audit of clinics providing HIV services for PHIV in UK & Ireland. Median age of naming 12 year olds (age range 10-15) Cited in (79)	-
<11 years	88	(30%)		
11 years	43	(15%)		
12 years	38	(13%)		
≥13 years	50	(17%)		
Don't know	75	(26%)		
Missing	22			
Number of people told about HIV				
0	161	(55%)	No UK normative data	-
1-2	75	(26%)		
3-4	32	(11%)		
5-9	12	(4%)		
10+	12	(4%)		
Missing	24			
Adherence:				
Doses missed in last 3 days			In 502 adults living with HIV (on treatment) in London based adults (aged >18 year olds) 79% did not miss a dose in last week (244)	0.06[1]
No	190	(73%)		
Yes	70	(27%)		
Not on ART	35			
Missing	21			
Self-assessment of adherence				
Excellent	104	(35%)	No UK normative data	-
Good	121	(41%)		
Not so good	24	(8%)		
Bad	10	(4%)		
Not on ART	35	(12%)		
Missing	22			

[1] Proportion of AALPHI participants on ART (260) who had not missed a dose (190, 73%) were compared to 79% of adults in London

4.4.7.1. Comment

The age at which participants in AALPHI were told their HIV diagnosis (median age 12, [IQR 11,13]) was the same as data from an audit of clinics seeing children and young people living with PHIV in the UK in 2007.(79) Of note, a quarter of participants in AALPHI (75, 26%) could not remember how old they were when they were told their HIV diagnosis. No comparative data were available for the number of people, young people had themselves, told about their HIV status. Of those on ART (260), a similar proportion of AALPHI participants (190, 73%) did not miss a dose of their medication in the last three days as adults living with HIV (79%,

p=0.06), although the time frame for missing a dose in AALPHI was only 3 days compared to 7 in the adult study.

4.4.8. HIV markers domain

Variables from the HIV markers domains, comparing all young people in AALPHI to young people living with PHIV not in AALPHI in the UK and Ireland national CHIPS cohort are shown in Table 4.11. A total of 84 (27%) AALPHI participants had had a previous CDC C event, the median CD4 nadir was 221 [IQR 121, 352], the median CD4 cell count was 597 cells/µL [IQR 427, 791] and 202 (69%) had a viral load ≤50c/mL. The majority of participants (88%) were on ART and the median age at ART start was 7 years [IQR 3, 12]. Nearly a third of AALPHI participants on ART (85, 30%) were taking efavirenz as part of a cART regimen. Of the 37 (12%) participants who were off ART, 14 were on an ART interruption of more than 30 days.

Table 4.11: HIV markers of participants in AALPHI at time of interview, and a CHIPS comparison group

Variable	AALPHI cohort (n=316)		CHIPS cohort (n=247)		p value
	n (%) or median [interquartile range (IQR)]				
HIV severity:					
Previous CDC C event	84	(27%)	48	(19%)	0.05
Nadir CD4 cell count (cells/μL)	221	[121, 352]	276	[180, 362]	0.005
CD4 cell count (cells/μL)[1]	597	[427, 791]	592	[446, 752]	0.97
Viral load ≤50c/mL[2]	202	(69%)	152	(70)	0.82
ART:					
On ART	279	(88%)	207	(84%)	0.12
On efavirenz[3]	85	(30%)	9	(4%)	0.64
Off ART	37	(12%)			
On an ART interruption (≥30 days)[4]	14	(38%)			
Age of ART start	7	[3, 12]	8	[3, 12]	0.84

[1] Data only available on 492 patients (279 in AALPHI and 213 in CHIPS) at the time of the AALPHI interview
[2] Data only available on 507 patients (291 in AALPHI and 216 in CHIPS) at the time of the AALPHI interview
[3] Proportion of participants on ART (279/316)
[4] Proportion of participants off ART (14/37)

4.4.8.1. Comment

A slightly lower proportion of young people in CHIPS (19%) had had a previous CDC C event than in AALPHI (27%, p=0.05) and, consistent with this, there was strong evidence to suggest young people in CHIPS had a higher median CD4 nadir (276 [IQR 180, 362] vs. 221 [IQR 121, 352], p=0.005). Otherwise, there was little difference between the HIV markers of the two groups suggesting that they were similar.

4.5. Discussion

4.5.1. Summary of main findings

In this chapter, I defined the variables included in my quantitative analysis and outlined the rationale for their use. In addition, all the tools used to collect data that were then used in the analysis were described. I also outlined the methods for cleaning the data and comparing the variables between young people living with PHIV in AALPHI and HIV- youth in the general UK population. Summary statistics for the domains (*a priori*, sociodemographics, risk behaviour practices, mental health, cognition, clinic, HIV experience and management and HIV markers) were presented with comparative data, where it existed, to contextualise AALPHI participants. In summary for each domain:

- *A priori* domain: participants in AALPHI were broadly similar to participants in CHIPS except AALPHI participants were more likely to be female than CHIPS participants.
- Sociodemographic domain: similar proportions of young people were in education and employment as well as living at home when compared to other young people in the UK population. However, young people in AALPHI were much more likely to have had a parent die and or to be fostered or adopted.
- Risk behaviour practices domain: AALPHI participants were not taking more risks than other young people and were perhaps drinking less and having sex later, although it is difficult to compare the data due to different definitions employed.
- Mental health domain: AALPHI participants differed noticeably from other young people in the UK general population in regard to their mental health. AALPHI participants had on average worse scores or higher prevalence for self-harm, feeling life was not worth living, quality of life, self-esteem and depression.
- Cognition domain: AALPHI participants had lower cognition scores than normative data.
- Clinic domain: There were no comparative data in the UK for clinic variables.
- HIV markers domain: When AALPHI participants were compared to CHIPS participants, HIV markers were similar across the two groups except for CD4 nadir count, which was on average lower in AALPHI participants and there was marginal evidence that participants in AALPHI had experienced had more CDC C events.

4.5.2. Limitations

My results need to be considered alongside some limitations of AALPHI, many of which are common to cohort studies. Firstly, there was a risk of selection bias because young people who regularly attended their HIV appointments were more likely to have been recruited into the study, as much recruitment took place in the clinic setting. To try and limit this bias, recruitment also took place in the voluntary sector, where young people who drop out of care may also attend. Reassuringly, AALPHI participants' characteristics were broadly representative of young people with HIV in the UK and Ireland. However, the cohorts were only compared in terms of demographics and clinical markers. It is much harder to compare issues such as cognitive function and so possible differences may have been be missed.

Another possible selection bias was that young people with severe cognitive delay may not have been referred by clinical staff to the study, despite clinic staff being encouraged to make such referrals. The final possible source of selection bais, is that to be included in the AALPHI study, young people had to have been aware of their diagnosis for at least six months, therefore no newly diagnosed young people are included in this analysis. The reason newly diagnosed young people were not recurited, was because there was concern this goup may be especially vulnerable. However, the number of children and young people newly diagnosed in paediatric care in the UK has been stable at 30-50 per year since 2012 and the average age at diagnosis is below four years old.(245) Therefore the effect of this is likely to be very small.

The use of questionnaires can also introduced a number of possible measurment errors into the analysis. Self-completed questionnaires may introduce social desirability bias by respondants completing the questionniare in a way that they think will please the administrator.(246) For example, respondants may rate their adherence higher than it actually is or report more or less sexual partners than they have actually had. In an attempt to reduce this, AALPHI interviews were carefully constructed so that all of the more sensative questionnaires asking about topcis such as drugs, sex and mental health measures were completed using Computer Assissted Interview (CASI) techniques.(114) Young people completed these parts of the interview without help from the research nurse, with the screen turned away so the research nurses could not see their responses. Young people were also reassured that the research nurse would not see their answers and these were analyses by a statistician who could only see their study number.

Another possible source of measurement error was that respondents were sometimes asked to recall events from the past. In these instances, recall bias may have occurred when young people remember events incorectly.(246,247) Examples of interview questions where young people sometimes seemed more hesitant were in response to questions about their past medical history or the reasons and dates of their parents deaths. Measurement error can also occur when questionnaires are poorly phrased and misleading.(247) To try and reduce this risk, where possible, standardised tools were utilised in AALPHI. In addition, a working manual was produced and updated on a regular basis. Training sessions were also carried out with all the research nurses throughout the study to try and standardise responses to commonly asked questions or to update the patient guidance text where possible. Measurment error can also occur when participants do not read the instructions properly. The main way this error was reduced was by tyring to make sure the instructions were clear and by spending time explaining all the sections to the participants.

Other sources of possible measurement error are related to poor execution of the study protocol.(247) Multiple nurses were involved in the study and there may have been a failure to carry out the protocol properly by all of the nurses througout the whole of the study. Regular training was carried out to try and reduce this. Errors can also occur at any point of the data collection and data entry process or when the variables were being programmed for the analysis.(246,247) Attempts were made to mitigate this risk by carrying out data entry checks (10% overall) throughout the study by a data manager and the proportion of errors by each resrearch nurse reported to the study coordinator so that specific training could be implemented if needed. Research nurses may have also influenced participants responses due to their own sociodemographic characteristics or nursing background. Finally, the statistician carried out best practice and included appropriate checks when creating variables and programming the data.

Variables were chosen for inclsuion in this analysis based on the literature and expert opinion, however, important exposures for EIC may have been missed using this methods. In addition, factors identified in the literature that were not included in the AALPHI iterview will be missed. For example, issues to do with youth friendliness of the clinic and relationships with clinic staff have been found to be associated with EIC in a number of analyses, as has stigma.(158,159,248)

4.5.3. Concluding remarks

There are a number of strengths of the AALPHI study. Few such cohorts exist worldwide making AALPHI an important addition to the evidence base. Young people recruited into AALPHI are some of the first generation of young people surviving perinatal HIV and reaching adulthood globally. Understanding these young people's needs can help health workers in the UK and further afield provide appropriate services. AALPHI asked questions on a broad range of themes providing information on many aspects of the participants' lives which could then be used to interigate topcs such as EIC in a way that many other stuides cannot.

A combination of data collection methods were used in AALPHI (face to face, self-administered, use of medical records) to maximise the benefits of the different data collection methods. Employment of research nurses allowed the collection of more complex, detailed questions. To try to improve the acceptability of the study questions, the AALPHI interview was piloted extensively with young people who were HIV negative and not exposed, HIV negative but exposed and young people who were living with HIV.

In this chapter, I summarised the variables used in this analysis and compared them to literature from the UK. Young people in AALPHI are broadly similar to the UK population in many ways. However, they are much more likely to have experienced the death of a parent and subsequent multiple alternative carers creating a much more unstable environment growing up. In addition, young people in AALPHI scored worse in almost all of the mental health assessments when compared to young people in the general UK population.

4.6. Key points from this chapter

- Due to the breadth of the data collected in the AALPHI study, a large number of variables were available for consideration for inclusion in this analysis
- Variables were justified for inclusion based on evidence from the literature or expert opinion
- Participants in AALPHI were broadly similar to participants in CHIPS except AALPHI participants were more likely to be female than CHIPS participants, and have lower CD4 nadir on average
- AALPHI participants were also broadly similar to the UK population in many ways. Where they differed was that more young people in AALPHI had lost a parent and were in foster care or adopted. In addition, AALPHI participants had on average

lower cognitive scores and worse mental health than young people in the general population.

Chapter 5.Predictors of engagement in care

5.1. Introduction

In this chapter, I take the exposure variables assembled and described in Chapter 5 and the EIC outcome variable detailed in Chapter 4 and put them together to investigate whether the exposure variables predict EIC in multivariable methods. I first describe the statistical methods outlining the multiple stages of variable investigation, the four stages of multivariable logistic regression modelling, and the methods and rationale for the sensitivity analyses. Then I present descriptive results for each exposure variable within each domain (*a priori*, sociodemographic, risk behaviour practices, mental health, cognition, clinic, HIV experience and management, HIV markers), including the person months and proportion in care. Finally, I present results from the four stages of multivariable logistic regression analyses examining the effect of the variables on the EIC outcome, as well as the results from the sensitivity analyses.

5.2. Objective

- To investigate the relationship between a broad range of potential exposures and EIC in AALPHI participants, through quantitative analysis

5.3. Statistical methods

5.3.1. Missing data

A variable comparing participants with at least one missing AALPHI CRF vs. participants with no missing CRFs was created to help describe missing data. To assess if there was evidence for CRFs being missing at random or not, the missing CRF variable was fitted in a model as a predictor of EIC adjusted for time from AALPHI interview (month of follow-up). Missing data from the CHIPS study are described in detail in Chapter 4. Methods for examining missing data for individual variables are described in section 5.3.2.1.

5.3.2. Exposure variable investigation

As described in Chapter 5, a wide variety of exposures potentially related to engagement in HIV care were considered for this analysis. Therefore, all exposure variables were examined for between-covariate associations prior to the modelling stages to avoid introducing co-

linearity and to improve model stability. The investigation process is shown in Figure 5.1. Six stages of investigation (a-f) were performed and thresholds were set at each stage for when variables would be dropped. Investigations were conducted separately for each domain (*a priori*, sociodemographic, risk behaviour practices, mental health, cognition, clinic, HIV experience and management, HIV markers) as individual domains were most likely to include interrelated variables. Variables that remained at the end of the investigations were considered for inclusion in the modelling stages. Of note, there were situations where the decision process occasionally differed and this is described in the results section.

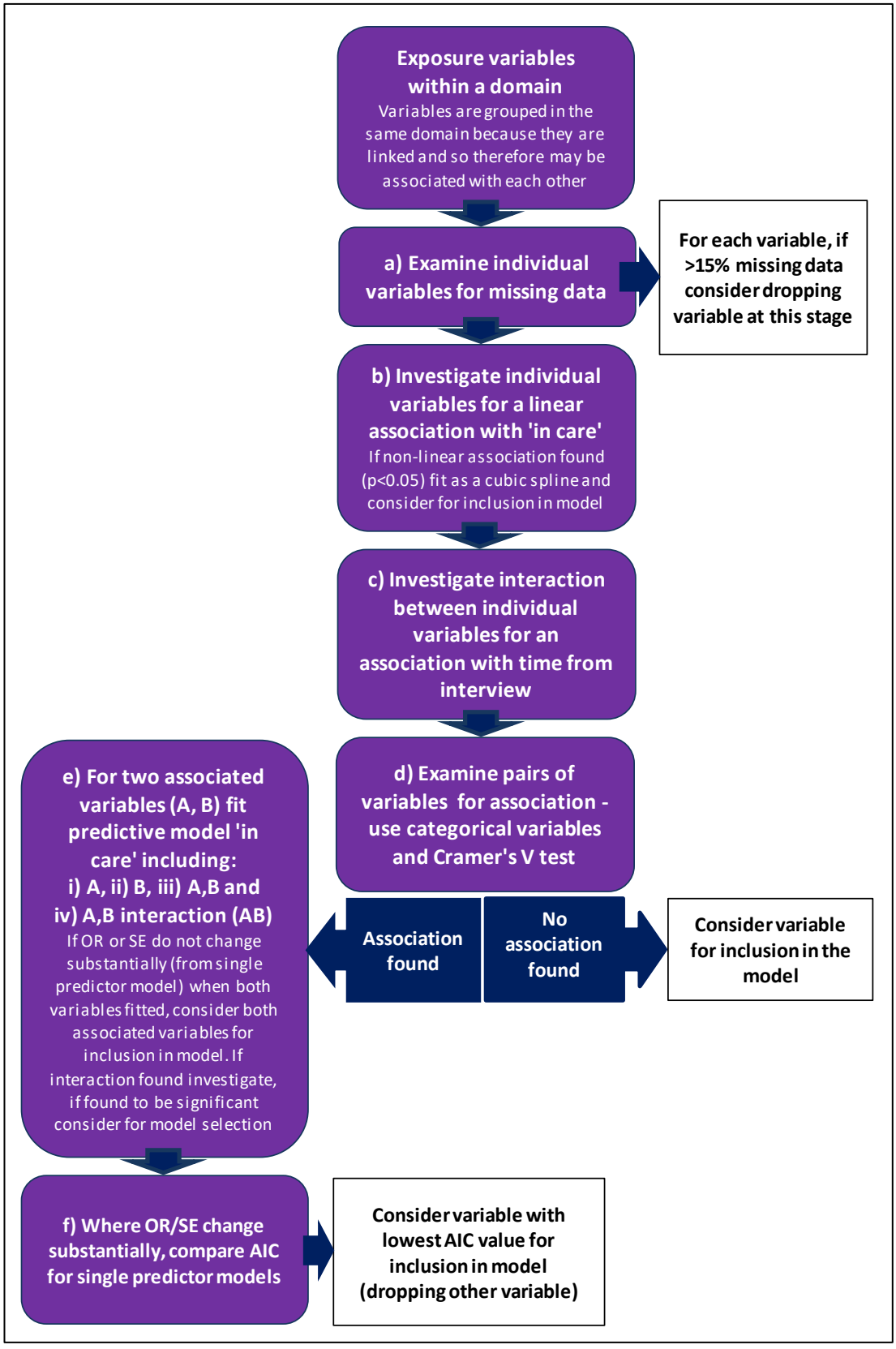
During the variable investigation described in the following sections, logistic regression models were used to examine associations between exposure variables and the binary outcome of 'in care'. Patient months were treated as separate observations in this analysis; therefore, models were fitted with a generalized estimating equation (GEE) using 'xtgee' in STATA, to take into account the clustered nature of the data, whereby each patient contributes multiple months:

```
noi xtgee incare var, link(logit) corr(indep) family(binomial)
i(subjectid) eform robust
```

where 'in care' is a binary variable (0=out of care, 1=in care).

Prior to exposure variables being fitted into any models in the exploratory stage, categorical variables with small numbers of observations in a single category were recoded (e.g. in "language spoke at home" exposure variable, a "language other than English" (n=3) was combined with "English and another language" (n=143)).

Figure 5.1: Flowchart describing exposure variable investigation



5.3.2.1. Examine individual exposure variables for missing data – stage (a)

Firstly, the missing data for all the variables in the domain were examined. If any variable had a substantial amount of missing data (>15%) it dropped from the analysis due to the effect on the sample size during modelling and the risk of introducing bias.

5.3.2.2. Investigate individual exposure variables for a non-linear association with engagement in care – stage (b)

All continuous variables were investigated for evidence of a non-linear association with EIC using scatter graphs and by fitting spline functions. Restricted cubic splines were fitted using the stata 'mkspline' function with three knots. Stata chooses knots based on Harrell's recommended percentiles locations.(249)

```
mkspline newvar=oldvar, cubic nknots (3)
```

Logistic regression models were fitted to explore the association between the spline and the outcome in care, adjusted for time since AALPHI interview. Where evidence for non-linearity was found ($p<0.05$), variables were fitted using a spline function in subsequent models.

5.3.2.3. Investigate interactions between individual exposure variables and time since AALPHI interview – stage (c)

Interactions were investigated between each individual exposure variable and time since AALPHI interview (months 1 to 12 following AALPHI interview) in a model including the respective variable, time and interaction terms for each level of the covariate with time and the outcome EIC. Where an interaction was found ($p<0.05$), the corresponding variable was considered for inclusion with the interaction term, if it would otherwise be dropped.

5.3.2.4. Examine pairs of exposure variables for association – stage (d)

Including collinear exposure variables in the same statistical model can cause instability by increasing the variance, which can result in difficulty identifying correct predictors as it can appear that neither variable is associated with the outcome (250). When two variables are strongly collinear, large increases are present in standard errors, therefore, careful examination of exposure variables that may be associated is important (251).

Where exposure variables contained the same or largely overlapping groups, the variable with the least information was dropped. For example, the variable, "Had alcohol in the last

year" has two levels, "no drinking" and "drinking", while the variable "Current alcohol amount" has three levels, "no drinking", "drinking but not hazardously", and "hazardous drinking". Both variables have a group of non-drinkers which completely overlaps. Therefore, "Alcohol amount" was kept as it splits the group of participants who do drink, and thus provides more information.

Continuous exposure variables were categorised using quartiles for this stage. The relationships between all pairs of exposure variables within domains were then examined using cross-tabulations (shown in the results where evidence for a strong association was found) and a Cramer's V test. The advantage of the Cramer's V over a standard Chi-squared test is that it provides a measure of the association between two categorical variables (where 0 is no association and 1 is perfect association) rather than just a significance test. A Cramer's V of ≥0.5 was considered to indicate strong association between two two-level categorical variables, and ≥0.35 for cross tabulations with more dimensions, and suggested further investigation of the effect of including both exposure variables in the same model was required.(252)

Exposure variables with no pairwise associations were considered directly for inclusion in the modelling process. Pairs of variables that were strongly associated (as above) were examined in more detail (stages (e) and (f)).

5.3.2.5. For two associated exposure variables (A, B) fit predictive model for engagement in care – stage (e)

Where two exposure variables were strongly associated with each other, a series of logistic regression models were built (all adjusted for the *a priori* variables). Firstly, each exposure variable was fitted as a predictor of EIC, then both exposure variables were fitted simultaneously as predictors, and finally where indicated, both exposure variables were fitted simultaneously with an interaction term included between the two. Models were compared between those with the two variables fitted individually (A or B) and the joint model (including A and B). If the inclusion of both variables did not change the odds ratios or standard errors substantially when compared to the individual models (A or B), or cause a qualitative change in the odds ratio which would change the interpretation, then both variables were considered for inclusion in model fitting.

Where the inclusion of both exposure variables in the same model changed the interpretation of the effects of either/both individual variables, these variables were examined for evidence of an interaction. Where an interaction was found between two categorical variables ($p<0.05$) a new variable was created combining information from the two variables (e.g. for two two-level factors (A(0), A(1) and B(0), B(1)), a four-level variable was created as A(0) B(0), A(0) B(1), A(1) B(0) and A(1) B(1). The new combined exposure variable was then fitted in a logistic regression model with the EIC outcome (adjusted for the *a priori* variables) to help interpretation. Variables where an interaction was found were still considered for inclusion in the modelling stages separately and interactions were further examined when both variables were retained. Where inclusion of both variables caused a substantial changes in odds ratio or standard error but no interaction was found (suggesting collinearity and that only one variable should be included), further investigation was required (see (f)).

5.3.2.6. Comparing models using an Akaike Information Criteria (AIC) value– stage (f)

When the inclusion of both exposure variables changed the odds ratios and standard errors in the models but no interaction was found (e.g. the two associated variables were providing very similar information) further investigation was carried out. Models including the associated individual exposure variables (A in first model and B in the second), and adjusted for *a priori* variables and the other variables in the domain, were compared using the Akaike Information Criteria (AIC) value. AIC is a formula to determine the best fitting model using the likelihood function but including a penalty for increasing numbers of parameters. When comparing models, a lower AIC value is the best fit as it signifies the model that minimises the amount of information lost. Therefore, the variable with the lowest AIC value was included in the modelling stage.

For this stage, models were fitted ignoring the clustered nature of the data, as the GEE does not use the likelihood function.(253) While this is not ideal, more complex methods for comparisons of GEEs were outside the scope of this thesis.

5.3.3. Logistic regression modelling

The multivariable logistic regression model was constructed in four stages. The outcome for all models was in care. For all four stages, the models were fitted with GEE using 'xtgee' in STATA, to take into account the clustered nature (multiple months per participant) of the

data. For categorical exposure variables with more than two categories, a Wald test was carried out using the 'testparm' function in Stata to obtain an overall p value for the variable. Continuous exposure variables that were converted into categorical variables during the investigation of pairwise associations between variables were included in the modelling stages as continuous variables.

5.3.3.1. Stage 1 - Adjusting for time since AALPHI interview

In this first stage, exposure variables were fitted individually as predictors of EIC adjusting for time from interview (month of follow-up). Variables with a p value <0.15 were considered associated with EIC.

5.3.3.2. Stage 2 - Adjusting for a priori exposure variables

In this second stage, exposure variables were fitted individually in multivariable models for EIC, adjusting for the *a priori* factors (time from interview, sex, age at entry and ethnicity and born abroad) and effect estimates and p values compared to the stage 1 outputs. Where the OR for an exposure variable changed considerably between stage 1 and stage 2 or where the effect changed direction (from being more likely to be in care (OR >1.0) to less likely (OR <1.0) or vice versa,), *a priori* exposure variables were taken out of the model one by one to understand what was causing the change. Exposure variables with a p value <0.15 were considered associated with EIC.

5.3.3.3. Stage 3 – Domain-specific multivariable model including a priori and domain exposure variables

In this third stage, all exposure variables in a domain were included in a multivariable model for EIC, adjusting for *a priori* variables. Manual backwards selection was used to build a domain specific model. Exposure variables with a p value ≥0.15 were removed one by one (starting with the variable with the highest p value and fitting an updated model each time a variable was removed) until only the exposure variables with a p value <0.15 and the *a priori* variables remained in the model. At this stage, all removed variables were added back into the model individually to see if the p value for each remained ≥0.15. If any p value was lower than this cut off, this variable was added back in and the same process was performed again. If a variable was removed where an interaction with time since AALPHI interview had previously been identified, the inclusion of the variable and its interaction was also tested.

As described in stage 2, where effect estimates changed considerably, these changes were examined.

At the end of this stage, any pairs of exposure variables with a plausible rationale for an interaction were investigated.

5.3.3.4. Stage 4 - Full multivariable model

In this fourth stage, all exposure variables from the domain specific models with a p value <0.15 were fitted in a combined multivariable model for EIC adjusting for the *a priori* factors. Manual backwards selection was used to identify independent predictors of EIC. Variables with a p value ≥0.05 were removed one by one (the highest first, fitting a new model each time a variable was dropped) until only exposure variables with p<0.05 remained in the model with the *a priori* variables. All variables previously dropped in this stage were then added back into the model one at a time to see if they became significant. If any of the variables became significant, the variable was included in the primary stage 4 model and the same procedure was conducted again.

5.3.4. Checks to the final model (stage 4 model) and sensitivity analyses

A number of steps were conducted to improve the model stability including stages (a) to (f) in the variable investigation and the four stages of the model building process (Stage 1 to Stage 4). Once the final stage 4 model was completed, a number of additional checks and sensitivity analysis were conducted to further check the stability and thus confidence in the model and to test some key methodological decisions.

5.3.4.1. Alternate final model exposure variables

Due to the large number of variables included in this analysis, checks to the final model were made by replacing exposure variables found to be associated with EIC with similar exposure variables within the same domain (other than those in the *a priori* domain). For example, self-harm was replaced with all of the other mental health variables one by one (feelings about HIV, ever felt life was not worth living, major life events, Pediatric Quality of Life Inventory, Rosenberg Self-Esteem Scale, HADS anxiety score, HADS depression score). In addition, for any exposure variable that was investigated with AIC values in stage (f) and remained in the final model, the other exposure variable was replaced in the model (for example replacing “adherence self-assessment” with “doses missed in the last three days”).

5.3.4.2. Alternate p value cut off (<0.1 compared to <0.05)

The first sensitivity analysis tested the impact of changing the p value cut off at which variables were retained in the final stage 4 model. Statistical significance in medical research is commonly considered as a p value <0.05 (251) and was therefore used for this analysis. However, other p value cut offs are used for identifying predictors, particularly where sample sizes are not large, so a sensitivity analysis was performed using p<0.1 in the final stage4 model.

5.3.4.3. Alternate start date

In the second sensitivity analysis, an alternate start date was used to address possible bias introduced by using the AALPHI interview date as the start date. The AALPHI interview date was selected as the beginning of the one year follow up for two reasons. Firstly, the variables used in the analysis were collected at this time point. Secondly, many participants were recruited in their clinic at the time of a clinic appointment which meant there were also clinical data available from this date. However, 57% (n=175) of the AALPHI cohort were interviewed in the community (home, study offices or voluntary sector) or in clinic but not on the day of a clinic visit and therefore did not have clinical data available on this day. As a result, participants who were not interviewed on the same day as a clinic visit could potentially start the one year of follow up classified as 'out of care' (or be lost from care quickly) whereas this could not happen for the group with a clinic visit on the same day (who remained in care until their next predicted visit date). Therefore, a start date three months after the AALPHI start date for all participants was used for the stage 4 model to assess this potential bias.

5.3.4.4. Early attenders

To assess the issue of participants attending early for their appointments (described in the EIC Flowcharts, Chapter 3) a sensitivity analysis was performed to see if changing the maximum predicted appointment time from 6 months to 4 months altered the final multivariable results. This sensitivity analysis was conducted for all four stages of the modelling process.

5.4. Results

5.4.1. Missing data

No association was found between having a missing AALPHI CRF and the EIC outcome (p=0.78).

5.4.2. Exposure variable investigation

Descriptive results for the exposure variables within each domain are presented below. A summary of results of all of the within domain variable investigations is shown in Appendix D.

5.4.2.1. Investigation of a priori exposure variables

Table 5.1 shows the exposure variables in the *a priori* domain, along with each category's total person months and proportion of months in care. The number of person months for some of the ethnicity categories was relatively small and thus combined. The proportion in care was similar across categories for time since AALPHI interview, sex and born outside of the UK/Ireland. However, EIC appeared to decline with increasing age group, and was perhaps lower in the Asian ethnicity category (though numbers were small).

Table 5.1: *A priori* exposure variables included in the analysis

A priori variable	Category	Person months	% in care	Further details
Time since AALPHI interview	0-3 months	909	88%	Time from AALPHI interview (months 1-12). Modelled as continuous
	4-6 months	900	86%	
	7-9 months	892	88%	
	10-12 months	884	87%	
Sex	Male	1,487	87%	
	Female	2,098	87%	
Age at entry	13-15 years	1, 414	90%	Inclusion criteria 13-21 years of age. Modelled as continuous
	16-18 years	1, 472	86%	
	19-21 years	699	83%	
Ethnicity	Black African	2,923	88%	Categories used in modelling: (1) Black (black African/black other) (2) Asian/mixed (Asian/mixed/ prefer not to say) (3) White
	Black other	156	89%	
	Mixed	356	80%	
	White	108	88%	
	Asian	42	74%	
	Prefer not to answer	22	91%	
Born outside of the UK/Ireland	Yes	1,480	87%	
	No	2,105	87%	

Examination of missing data – stage (a)

There were no missing data in *a priori* variables.

Investigation of a non-linear association with engagement in care- stage (b)

There was no evidence for a non-linear association between either time since AALPHI interview (p=0.42) or age at entry (p=0.45) and the EIC outcome.

Investigation of an association with time since AALPHI interview – stage (c)

No interactions were found between time since AALPHI interview and any of the *a priori* variables as predictors of EIC (p≥0.05 for all interaction tests).

Examination of paired exposure variables for association – stage (d)

Cramer's V between pairs of exposure variables are shown in Table 5.2.There was evidence for an association between ethnicity and born abroad (p=0.002) however, the strength of this association was weak (Cramer's V = 0.20). No other significant pairwise associations between exposure variables were found in the *a priori* domain.

Table 5.2: Stage (d) test for association of paired exposure variables in the *a priori* domain

A priori variable	Sex	Age group at entry	Ethnicity	Born abroad
Sex		a) 0.11 b) 0.13	a) 0.09 b) 0.30	a) 0.10 b) 0.09
Age group			a) 0.09 b) 0.33	a) 0.10 b) 0.21
Ethnicity				a) 0.20 b) 0.002
Born abroad				

a = Cramer's V
b = P value for Cramer's V
Strong association on V test (Cramer's V ≥0.5 between two two-level categorical variables and ≥0.35 for tables with more dimensions)

5.4.2.2. Investigation of sociodemographic exposure variable

Table 5.3 shows the exposure variables in the sociodemographic domain, along with each category's total person months and proportion of person months in care. A number of the subgroups in the sociodemographic categories were small and therefore combined with other subgroups (education/employment status, death of parents and main language spoken at home). The proportion in care was similar across categories for death of parents, fostered/adopted, number of main carers and IDACI deprivation score. However, EIC appeared lower in participants who were employed and perhaps in participants who had

fixed or permanent exclusions from school, who lived with others, did not know if their parent/carer was employed, and spoke another language at home, although numbers were small in most of the subgroups.

Table 5.3: Sociodemographic exposure variables included in the analysis

Sociodemographic variable	Category	Person-months	% in care	Further details
Education/employment status	Education	3,302	88%	Categories used in modelling: (1) in full time education (2) employed OR not in education, employment or training
	Employed	94	70%	
	Not in education/employment	153	81%	
Ever excluded from school	No	2,937	88%	Categories used in modelling: (1) no exclusion (2) fixed term OR permanent exclusion (i.e. any exclusion)
	Yes - fixed term exclusion	528	82%	
	Yes – permanent exclusion	96	85%	
Death of parents	None	2,118	88%	Categories used in modelling: (1) none OR unknown (2) death of one/both parents
	Death of one parent	1,076	85%	
	Death of both parents	154	90%	
	Unknown	213	88%	
Fostered/adopted	No	1,321	86%	
	Yes	167	84%	
Number of main carers	1 carer	2,333	87%	Categories used in modelling: (1) 1 carer (2) 2 carers (3) ≥ 3 carers. (Participants had up to 10 carers but small numbers so grouped ≥3)
	2 carers	691	87%	
	3 or more carers	537	86%	
Live with parents/carers	Live with parents	3,273	88%	
	Live with other	288	78%	
Parent/carer in work	Yes	2,595	88%	
	No	882	86%	
	Don't know	84	79%	
Main language spoken at home	English only	1,838	87%	Categories used in modelling: (1) English only OR English and another language (2) A language other than English
	English and another language	1,645	88%	
	Another language	90	78%	
IDACI deprivation score	Least deprived	831	87%	Based on postcode. Higher number=worse deprivation. Modelled as continuous (0-1)
	Less deprived	776	89%	
	More deprived	741	89%	
	Most deprived	828	83%	

Examination of missing data – stage (a)

The proportion of each exposure variable in the sociodemographic domain which was missing in shown in Table 5.4. The fostered/adopted variable had 58% missing data and was dropped from the analysis. Missing data were below the threshold (15%) in all the other variables which were therefore retained to the next stage.

Table 5.4: Stage (a) missing data in the sociodemographic exposure variables

Sociodemographic variable	Participants with missing data	
	n	%
Education/employment status	3	1%
Ever excluded from school	2	1%
Death of parents	2	1%
Fostered or adopted	179	58%
Number of main carers	2	1%
Live with parent/carer	2	1%
Parent/carer in work	2	1%
Main language spoken at home	1	<1%
IDACI deprivation score	36	12%

Investigation of a non-linear association with engagement in care- stage (b)

There was no evidence for a non-linear association between the IDACI deprivation score exposure variable and the EIC outcome ($p \geq 0.05$).

Investigation of association with time since AALPHI interview – stage (c)

No interactions were found between time since AALPHI interview and any of the sociodemographic exposure variables as predictors of EIC ($p \geq 0.05$).

Examination of paired exposure variables for association – stage (d)

For this stage of the analysis, IDACI was treated as a categorical variable with four levels. Table 5.5 shows the results of the tests for pairwise associations in the sociodemographic domain. For seven pairs of variables there was evidence of an association, however for each pair the strength of association (measured by Cramer's V) was less than the pre-specified level, therefore all variables were carried forward to the modelling stages.

Table 5.5: Stage (d) test for association of paired exposure variables in the sociodemographic domain

Sociodemographic variable	Education/ employment status	Ever excluded from school	Death of parents	Number of main carers	Live with parent/carer	Parent/carer in work	Main language spoken at home	IDACI deprivation score
Education/employment status		a) 0.01 b) 0.85	a) 0.08 b) 0.17	a) 0.15 b) 0.04	a) 0.11 b) 0.05	a) 0.13 b) 0.07	a) 0.04 b) 0.43	a) 0.10 b) 0.45
Ever excluded from school			a) 0.06 b) 0.32	a) 0.07 b) 0.47	a) 0.15 b) 0.007	a) 0.08 b) 0.42	a) 0.09 b) 0.13	a) 0.14 b) 0.15
Death of parents				a) 0.23 b) <0.001	a) 0.17 b) 0.002	a) 0.07 b) 0.45	a) 0.10 b) 0.09	a) 0.07 b) 0.77
Number of main carers					a) 0.16 b) 0.02	a) 0.10 b) 0.24	a) 0.06 b) 0.62	a) 0.09 b) 0.68
Live with parent/carer						a) 0.29 b)<0.001	a) 0.03 b) 0.62	a) 0.09 b) 0.51
Parent/carer in work							a) 0.10 b) 0.21	a) 0.16 b) 0.03
Main language spoken at home								a) 0.13 b) 0.22

a = Cramer's V
b = P value for Cramer's V
Strong association on V test (Cramer's V ≥0.5 between two two-level categorical variables and ≥0.35 for tables with more dimensions)

5.4.2.3. Investigation of risk behaviour practices exposure variables

Table 5.6 shows the exposure variables in the risk behaviour practices domain, along with each category's total person months and proportion of person months in care. The number of person months for some of the age at first sex categories were relatively small and so were combined. The proportion EIC was similar across the recreational drug categories. However, EIC appeared to decrease with increasing amount of current alcohol use, and was lower if participants smoked, if age of first sex was ≥20 years (though numbers were small) and if participants did not always use a condom.

Table 5.6: Risk behaviour practices exposure variables included in the analysis

Risk behaviour practices variable	Category	Person-months	% in care	Further details
Ever smoked	No	2,740	89%	
	Yes	620	81%	
Current alcohol amount	No drinking	1,980	90%	Drink but not hazardous score = <8, Drink hazardously score= ≥8
	Drink but not hazardously	1,051	84%	
	Drink hazardously	329	81%	
Ever taken recreational drugs	No	2,806	88%	Categorised as per literature to show hierarchical effect of cannabis vs. harder drugs
	Yes cannabis	376	86%	
	Yes other drugs	118	86%	
Age of first sex	Not sexually active	2,214	88%	Categories used in modelling: (1) Not sexually active (2) ≤14 years (3) ≥15 years (15-19 and ≥20 years due to small numbers in ≥20 group)
	≤14 years	216	90%	
	15-19 years	766	86%	
	≥20 years	36	81%	
Condom use	Not sexually active	2,214	88%	
	Always use a condom	725	89%	
	Do not always use a condom	317	80%	

Examination of missing data – stage (a)

Missing data were below the threshold (15%) and so no variables were dropped at this stage (Table 5.7).

Table 5.7: Stage (a) missing data in the risk behaviour practices exposure variables

Risk behaviour practices variable	Participants with missing data	
	n	%
Ever smoked	19	6%
Current alcohol amount	19	6%
Ever taken recreational drugs	24	8%
Age of first sex	30	10%
Condom use	28	9%

Investigation of a non-linear association with engagement in care- stage (b)

None of the variables were continuous therefore investigation for non-linearity was not required.

Investigation of an association with time since AALPHI interview – stage (c)

No interaction was found between time since AALPHI interview and ever smoked, current alcohol amount, ever taken recreational drugs or condom use (all p≥0.05) models with EIC as the outcome. However, an interaction between time since interview and age of first sex was found (p=0.04). There was no effect of time since AALPHI interview on EIC for young people who had sex for the first time aged 15 years or older (OR 0.98 per month, 95%CI 0.90, 1.07, p=0.64). However, participants who had sex for the first time aged less than 15 years of age were less likely to be in care over time (OR 0.80 per month, 95% CI 0.67, 0.95, p=0.01).

Examination of paired exposure variables for association – stage (d)

All pairwise combinations of variables were significantly associated with each other (Table 5.8). The association was strong for four pairs: ever smoked and current alcohol amount (Cramer's V=0.42); ever smoked and ever taken recreational drugs (Cramer's V=0.49); current alcohol amount and ever taken recreational drugs (Cramer's V=0.47) and age at first sex and condom use (Cramer's V=0.71). These variables were therefore investigated further.

Table 5.8: Stage (d) tests for association of paired exposure variables in the risk behaviour practices domain

Risk behaviour practices variable	Ever smoked	Current alcohol amount	Ever taken recreational drugs	Age of first sex	Condom use
Ever smoked		a) <u>0.42</u> b) <0.001	a) <u>0.49</u> b) <0.001	a) 0.25 b) <0.001	a) 0.24 b) <0.001
Current alcohol amount			a) <u>0.47</u> b) <0.001	a) 0.34 b) <0.001	a) 0.32 b) <0.001
Ever taken recreational drugs				a) 0.26 b) <0.001	a) 0.28 b) <0.001
Age at first sex					a) <u>0.71</u> b) <0.001

a = Cramer's V
b = P value for Cramer's V
Values meeting the threshold for strong association on V test (Cramer's V ≥0.5 between two two-level categorical variables and ≥0.35 for tables with more dimensions) are underlined

Findings from predictive models for associated exposure variables (A, B) and engagement in care – stage (e)

For the four associated exposure pairs found in stage (d), variables were investigated in a series of logistic regression models (all adjusted for the *a priori* variables) for EIC (tables of model

results are shown in Appendix E). For ever smoked and current alcohol amount there was little change in the odds ratios when both variables were included in the same model, compared to models with the two variables included individually, and no evidence for an interaction between the two variables (p=0.18) (Table 5.9).

Table 5.9: Stage (e) predictive model for effect of ever smoked and current alcohol amount on EIC in the risk behaviour practices domain

Risk behaviour practices variable	Ever smoked adjusted for *a priori*			Current alcohol amount adjusted for *a priori*			Ever smoked and current alcohol amount adjusted for *a priori*			Ever smoked and current alcohol amount fitted with an interaction		
	OR (95% CI)	SE	P value	OR (95% CI)	SE	P value	OR (95% CI)	SE	P value	OR (95% CI)	SE	P value
Ever smoked												
No	1	-	-				1	-	-	1	-	-
Yes	0.68 (0.40, 1.13)	0.18	0.14				0.77 (0.45, 1.33)	0.21	0.36	1.50 (0.66, 3.44)	0.64	0.34
Current alcohol amount												
No drinking				1	-	-	1	-	-	1	-	-
Drink but not hazardous				0.68 (0.44, 1.04)	0.15	0.16	0.71 (0.47, 1.08)	0.15	0.26	0.86 (0.53, 1.40)	0.21	0.59
Hazardous drinking				0.64 (0.32, 1.27)	0.22		0.72 (0.35, 1.48)	0.26		0.65 (0.27, 1.56)	0.29	
Ever smoked# current alcohol amount												
Yes smoke# not hazardous drinking										0.36 (0.12, 1.06)	0.24	0.18
Yes smoke# hazardous drinking										0.70 (0.17, 2.95)	0.51	

For ever smoked cigarettes and ever taken recreational drugs, the effect of ever smoked remained stable and showed a similar association with EIC when fitted separately or in combination with ever taken recreational drugs (Table 5.10). The ORs and SEs for the effects of drug use did change when fitted in the model with ever smoked but the confidence intervals were very wide and the direction of the effects were the same. No interaction was found between the variables (p=0.67), and therefore, both variables were considered for inclusion in the model, although it was expected that use of recreational drugs would be dropped (for lack of significance).

Table 5.10: Stage (e) predictive model for effect of ever smoked cigarettes and ever taken recreational drugs on EIC in the risk behaviour practices domain

Risk behaviour practices variable	Ever smoked adjusted for a priori			Ever taken recreational drugs adjusted for *a priori*			Ever smoked and ever taken recreational drugs adjusted for *a priori*			Ever smoked and ever taken recreational drugs fitted with an interaction		
	OR (95% CI)	SE	P value	OR (95% CI)	SE	P value	OR (95% CI)	SE	P value	OR (95% CI)	SE	P value
Ever smoked												
No	1	-	-				1	-	-	1	-	-
Yes	0.68 (0.40, 1.13)	0.18	0.14				0.53 (0.30, 0.94)	0.15	0.03	0.51 (0.27, 0.97)	0.17	0.04
Ever taken recreational drugs												
No				1	-	-	1	-	-	1	-	-
Cannabis ever				1.07 (0.64, 1.79)	0.81	0.63	1.35 (0.76, 2.40)	1.02	0.22	1.19 (0.60, 2.37)	0.42	0.22
Other drugs ever				1.73 (0.56, 5.33)	0.99		2.80 (0.83, 9.38)	1.66		2.90 (0.83, 10.10)	1.85	
Ever smoked# ever recreational drugs												
No smoke# Other drug ever										1	empty	
Yes smoke# Cannabis ever										1.28 (0.42, 0.39)	0.73	0.67
Yes smoke# Other drug ever										1	empty	

The effects of current alcohol amount were similar when fitted separately or in combination with recreational drug use and was associated with EIC (Table 5.11). The ORs and SEs for the effects of drug use did change when fitted in the model with current alcohol amount, but the confidence intervals were wide and the direction of the effect was in the same direction. No interaction was found between the two variables (p=0.11) however, there was a change in the direction of the relationship between recreational drug use and EIC. It was therefore decided to drop recreational drug use as there was a consistent association between current alcohol and EIC but no consistent association between recreational drug use and EIC.

Table 5.11: Stage (e) predictive model for effect of current alcohol amount and ever taken recreational drugs in EIC in the risk behaviour practices domain

Risk behaviour practices variable	Current alcohol amount adjusted for *a priori*			Ever recreational drugs adjusted for *a priori*			Current alcohol amount and ever recreational drugs adjusted for *a priori*			Current alcohol amount and ever recreational drugs fitted with an interaction		
	OR (95% CI)	SE	P value	OR (95% CI)	SE	P value	OR (95% CI)	SE	P value	OR (95% CI)	SE	P value
Current alcohol amount												
No drinking	1	-	-				1	-	-	1	-	-
Drink but not hazardous	0.68 (0.44, 1.04)	0.15	0.16				0.63 (0.40, 0.98)	0.14	0.06	0.63 (0.39, 1.01)	0.15	0.02
Hazardous drinking	0.64 (0.32, 1.27)	0.22					0.44 (0.18, 1.06)	0.20		0.30 (0.10, 0.87)	0.16	
Ever recreational drugs												
No				1	-	-	1	-	-	1	-	-
Cannabis ever				1.07 (0.64, 1.79)	0.81	0.63	1.42 (0.75, 2.69)	0.46	0.31	0.58 (0.21, 1.65)	0.31	0.11
Other drug other				1.73 (0.56, 5.33)	0.99		2.65 (0.70, 10.07)	1.80		4.23 (0.87, 20.51)	3.41	
Current alcohol amount# ever recreational drugs												
No drinking# Other drug ever										1	empty	0.11
Drink not hazardous# Cannabis ever										2.18 (0.61, 7.73)	1.41	
Drink not hazardous# Other drug ever										0.19 (0.04, 1.05)	0.17	
Hazardous drinking# Cannabis ever										4.85 (0.95, 24.86)	4.04	
Hazardous drinking# Other drug ever										1	empty	

Age at first sex and condom use were not fitted in a joint model because the category "not sexually active" was the baseline level for both variables (Table 5.12).

Table 5.12: Stage (e) predictive model for effect of age of first sex and condom use and EIC in the risk behaviour practices domain

Risk behaviour practices variable	Age at first sex adjusted for *a priori*			Condom use adjusted for *a priori*		
	OR (95% CI)	SE	P value	OR (95% CI)	SE	P value
Age of first sex						
Not sexually active	1	-	-			
≤14 years	1.56 (0.86, 2.83)	0.47	0.35			
≥15 years	1.12 (0.65, 1.93)	0.31				
Condom use						
Not sexually active				1	-	-
Always use a condom				1.55 (0.87, 2.75)	0.45	0.11
Do not always use a condom				0.73 (0.39, 1.38)	0.24	

Therefore, a combined variable was created with five subgroups (Table 5.13). When the new combined variable was fitted in a logistic regression model (adjusted for the *a priori* variables) there was no evidence of an association with EIC (p=0.17).

Table 5.13: Combined sex age and condom use exposure variable in the risk behaviour practices domain

Risk behaviour practices variable/ category	Frequency n	Per cent %	% in care	Combined age of first sex and condom use variable adjusted for *a priori*		
				OR (95% CI)	SE	P value
Combined age at first sex/condom use variable						
Not sexually active	190	69%	88%	1	-	-
≤14 years, always use condom	12	4%	94%	2.26 (0.90, 5.69)	1.06	0.17
≤14 years, do not always use a condom	6	2%	83%	1.01 (0.54, 1.88)	0.32	
≥15 years, always use condom	48	18%	88%	1.47 (0.77, 2.81)	0.49	
≥15 years, do not always use a condom	20	7%	79%	0.65 (0.31, 1.38)	0.25	

Comparing models using Akaike Information Criteria (AIC) value – stage (f)

Two logistic regression models (with no adjustment for clustering) were fitted to estimate the AIC, the first including condom use and the second age at first sex, both adjusted for *a priori* variables and the other variables in the domain. The AIC was lower for the model including condom use compared to age at first sex (2294.771 vs 2305.752). The condom use variable was therefore taken forward to the modelling stages instead of the age at first sex variable or the combined variable. As age at first sex was dropped prior to the modelling stage, there was no need to investigate the interaction with time since AALPHI interview any further.

5.4.2.4. Investigation of mental health exposure variables

Table 5.14 shows the exposure variables in the mental health domain, along with each category's total person months and proportion of person months in care. No categories were very small and so none were combined. The proportion of person months in care was similar across all of the categories in the domain, except for ever self-harmed, where EIC was perhaps lower in young people who reported ever having self-harmed.

Table 5.14: Mental health exposure variables included in the analysis

Mental health variable	Category	Person-months	% in care	Further details
Feelings about HIV	Worst feelings about HIV	813	87%	Higher score is better (0-60)
	Bad feelings about HIV	797	88%	
	Good feelings about HIV	807	89%	Modelled as continuous
	Best feelings about HIV	914	86%	
Ever self-harmed	No	3,011	88%	
	Yes	424	83%	
Ever felt life was not worth living	No	2,073	88%	
	Yes	1,326	87%	
Major life events	Most unpleasant events	566	85%	Higher score is better (-10-10)
	Some unpleasant events	714	89%	
	Some pleasant events	1206	87%	Modelled as continuous
	Most pleasant events	910	89%	
Pediatric Quality of Life Inventory	Worst quality of life	842	86%	Higher score is better (0-100)
	Low quality of life	871	89%	
	Good quality of life	826	88%	Modelled as continuous
	Best quality of life	896	86%	
Rosenberg Self-Esteem Scale	Worst self-esteem	751	87%	Higher score is better(0-31)
	Low self-esteem	672	93%	
	Good self-esteem	1,087	85%	Modelled as continuous
	Best self-esteem	925	86%	
HADS anxiety score	Normal	1,959	87%	Higher score is better (0-21, scores reversed for consistency with other variables)
	Mild	724	87%	
	Moderate	444	88%	
	Severe	83	84%	Modelled as continuous
HADS depression Score	Normal	2,700	87%	Higher score is better (0-21, scores reversed for consistency with other variables)
	Mild	366	85%	
	Moderate	143	85%	Modelled as continuous

Examination of missing data – stage (a)

Missing data were below the threshold (15%) therefore no variables were dropped at this stage (Table 5.15).

Table 5.15: Stage (a) missing data in the mental health exposure variables

Mental health variable	Participants with missing data	
	n	%
Feelings about HIV	22	7%
Ever self-harmed	14	5%
Ever felt life was not worth living	17	6%
Major life events	16	5%
Pediatric Quality of life Inventory	14	5%
Rosenberg Self-Esteem Scale	14	5%
HADS anxiety score	32	10%
HADS depression Score	32	10%

Investigation for a non-linear association with engagement in care- stage (b)

There was no evidence for a non-linear association between feelings about HIV (p=0.13), major life events (p=0.84), Pediatric Quality of Life Inventory (p=0.90), Rosenberg Self-Esteem Scale (p=0.31), HADS anxiety score (p=0.72) or HADS depression score (p=0.32) and EIC.

Investigation for association with time since AALPHI interview – stage (c)

No interactions were found between time since AALPHI interview and any of the mental health exposure variables as predictors of EIC (all p≥0.05).

Examination of paired exposure variables for association – stage (d)

A number of exposure pairs showed a significant association with each other, based on the p value for Cramer's V (Table 5.16). However, there were only three pairs where the association was strong, namely ever thought life was not living with each of: Pediatric Quality of Life Inventory (Cramer's V=0.44); Rosenberg Self-Esteem Scale (Cramer's V=0.46); and HADS anxiety score (Cramer's V=0.41). The associations between these variables were therefore investigated further.

Table 5.16: Stage (d) tests for association of paired exposure variables in the mental health domain

Mental health variable	Feelings about HIV	Ever self-harmed	Ever felt life was not worth living	Major life events	Pediatric Quality of Life	Rosenberg Self-Esteem Scale	HADS anxiety score	HADS depression score
Feelings about HIV		a) 0.09 b) 0.51	a) 0.29 b) <0.001	a) 0.15 b) 0.02	a) 0.25 b) <0.001	a) 0.22 b) <0.001	a) 0.17 b) 0.005	a) 0.10 b) 0.45
Ever self-harmed			a) 0.36 b) <0.001	a) 1.7 b) 0.05	a) 0.20 b) 0.008	a) 0.26 b) <0.001	a) 0.12 b) 0.25	a) 0.13 b) 0.10
Ever felt life was not worth living				a) 0.30 b) <0.001	a) <u>0.44</u> b) <0.001	a) <u>0.46</u> b) <0.001	a) <u>0.41</u> b) 0.001	a) 0.14 b) 0.09
Major life events					a) 0.18 b) 0.001	a) 0.20 b)<0.001	a) 0.19 b) 0.001	a) 0.14 b) 0.13
Pediatric Quality of Life						a) 0.29 b) <0.001	a) 0.29 b) <0.001	a) 0.15 b) 0.05
Rosenberg Self-Esteem Scale							a) 0.34 b) <0.001	a) 0.23 b) <0.001
HADS anxiety score								a) 0.23 b) <0.001

a = Cramer's V

b = P value for Cramer's V

Values meeting the threshold for strong association on V test (Cramer's V ≥0.5 between two two-level categorical variables and ≥0.35 for tables with more dimensions) are underlined

Findings from predictive models for associated exposure variables (A, B) and engagement in care – stage (e)

The three paired exposure variables found in stage (d) were investigated in a series of logistic regression models (all adjusted for the *a priori* variables) with EIC as the outcome (Table 5.17, Table 5.18 and Table 5.19). In all three models, there was little change in the odds ratios when both variables were included in the same model, compared to the models with the two variables included individually, and no interactions were found (all $p \geq 0.05$). Therefore, all variables were considered in the analysis.

Table 5.17: Stage (e) predictive model for effect of ever felt life was not worth living and quality of life on EIC in the mental health domain

Mental health variable	Ever felt life was not worth living adjusted for *a priori*			Quality of life (total score) adjusted for *a priori*			Ever felt life was not worth living and quality of life adjusted for *a priori*			Ever felt life was not worth living and quality of life fitted with an interaction		
	OR (95% CI)	SE	P value	OR (95% CI)	SE	P value	OR (95% CI)	SE	P value	OR (95% CI)	SE	P value
Ever felt life was not worth living												
No	1	-	-				1	-	-	1	-	-
Yes	0.98 (0.64, 1.52)	0.22	0.94				0.90 (0.56, 1.45)	0.22	0.66	0.97 (0.08, 11.25)	1.21	0.98
Quality of life (total score) (Higher score is better)				0.99 (0.98, 1.01)	0.01	0.46	0.99 (0.97, 1.01)	0.01	0.40	1.00 (0.97, 1.03)	0.01	0.48
Ever felt life was not worth living # quality of life												
Yes										1.00 (0.97, 1.03)	0.02	0.95

Table 5.18: Stage (e) predictive model for effect of ever felt life was not worth living and Rosenberg Self-Esteem Scale on EIC in the mental health domain

Mental health variable	Ever felt life was not worth living adjusted for *a priori*			Rosenberg Self-Esteem Scale adjusted for *a priori*			Ever felt life was not worth living and Rosenberg Self-Esteem Scale adjusted for *a priori*			Ever felt life was not worth living and Rosenberg Self-Esteem Scale fitted with an interaction		
	OR (95% CI)	SE	P value	OR (95% CI)	SE	P value	OR (95% CI)	SE	P value	OR (95% CI)	SE	P value
Ever felt life was not worth living												
No	1	-	-				1	-	-	1	-	-
Yes	0.98 (0.64, 1.52)	0.22	0.94				0.87 (0.57, 1.40)	0.21	0.57	0.67 (0.12, 3.62)	0.57	0.64
Rosenberg Self-Esteem Scale (higher score is better)				0.98 (0.94, 1.01)	0.02	0.22	0.97 (0.93, 1.01)	0.02	0.16	0.96 (0.91, 1.02)	0.03	0.20
Ever felt life was not worth living # Rosenberg Self-Esteem Scale												
Yes										1.01 (0.93, 1.01)	0.04	0.76

Table 5.19: Stage (e) predictive model for effect of ever felt life was not worth living and HADS anxiety score on EIC in the mental health domain

Mental health variable	Ever felt life was not worth living adjusted for *a priori*			HADS anxiety score adjusted for *a priori*			Ever felt life was not worth living and HADS anxiety score adjusted for *a priori*			Ever felt life was not worth living and HADS anxiety score fitted with an interaction		
	OR (95% CI)	SE	P value	OR (95% CI)	SE	P value	OR (95% CI)	SE	P value	OR (95% CI)	SE	P value
Ever felt life was not worth living												
No	1	-	-				1	-	-	1	-	-
Yes	0.98 (0.64, 1.52)	0.22	0.94				1.17 (0.76, 1.81)	0.26	0.48	2.02 (0.75, 5.50)	1.03	0.17
HADS anxiety score												
(Higher score is better)				1.00 (0.95, 1.05)	0.03	0.92	1.00 (0.95, 1.06)	0.03	0.91	0.97 (0.89, 1.04)	0.04	0.36
Ever felt life was not worth living # HADS anxiety score												
Yes										1.08 (0.97, 1.21)	0.06	0.17

5.4.2.5. Investigation of cognition exposure variables

NPZ-6 was the only variable in the cognition domain, therefore it was only necessary to investigate it for missing data (stage (a)), a linear association with EIC (stage (b)) and an association with time since AALPHI interview (stage (c)). Table 5.20 shows the total person months and proportion in care for NPZ-6. The proportion of person months in care appeared to decline with increasing NPZ-6 score.

Table 5.20: Cognition exposure variables included in the analysis

Cognition variable	Category	Person-months	% in care	Further details
NPZ-6	<-1	818	90%	Modelled as continuous
	≥-1 to <0	1,600	88%	
	≥0	848	86%	

Examination of missing data – stage (a)

Twenty-seven (9%) participants had missing NPZ-6 scores, which was below the threshold (15%), so NPZ-6 was not dropped at this stage.

Investigation of a non-linear association with engagement in care- stage (b)

There was no evidence for a non-linear association between NPZ-6 scores and EIC (p=0.56).

Investigation for association with time since AALPHI interview – stage (c)

No interaction was found between time since AALPHI interview and the NPZ-6 score as exposure predictors of EIC (p≥0.05).

5.4.2.6. Investigation of Clinic exposure variables

Table 5.21 shows the exposure variables in the Clinic domain, along with each category's total person months and proportion of months in care. No categories were very small and so none were combined. For all four variables, there was an indication of better or worse EIC in specific categories. The proportion in care appeared lower if young people attended a clinic in London compared to outside London, if they attended an adolescent clinic and if they travelled more than 60km to clinic or their travel time was more than 60 minutes.

Table 5.21: Clinic exposure variables included in the analysis

Clinic variables	Category	Person-months	% in care	Further details
Clinic location	Enrolled in London/	2,642	86%	
	Enrolled outside London	943	90%	
Clinic type	Paediatric HIV clinic	2,736	88%	
	Adolescent HIV clinic	600	84%	
	Adult HIV/GUM clinic	201	94%	
Distance to clinic	0-4 km	706	89%	
	5-9km	784	88%	Range 1-405 km
	10-19km	809	87%	Modelled as
	20-59km	510	88%	continuous
	≥60 km	312	80%	
Travel time to clinic	0-29 min	1,499	89%	Range 5-327 min
	30-59 min	1,137	88%	Modelled as
	≥60 min	485	81%	continuous

Examination of missing data – stage (a)

Missing data were below the threshold (15%), therefore no variables were dropped at this stage (Table 5.22).

Table 5.22: Stage (a) missing data in the Clinic exposure variables

Clinic variable	Participants with missing data	
	n	%
Clinic location	0	0%
Clinic type	4	1%
Distance to clinic (km)	40	13%
Travel time to clinic (min)	40	13%

Investigation of a non-linear association with engagement in care - stage (b)

There was no evidence for a non-linear association between distance to clinic (p=0.43) or travel time to clinic (p=0.53) and EIC.

Investigation of association with time since AALPHI interview – stage (c)

No interactions were found between time since AALPHI interview and any of the Clinic variables as predictors of EIC (p≥0.05).

Examination of paired exposure variables for association – stage (d)

Continuous variables (distance to clinic and travel time to clinic) were categorised for this stage. A number of exposure pairs showed a significant association with each other based on the P value for Cramer's V (Table 5.23). However, there was only evidence for a strong

association between distance to clinic and travel time to clinic (Cramer's V=0.74). Therefore, these variables were investigated further.

Table 5.23: Stage (d) tests for association of paired exposure variables in the Clinic domain

Clinic variable	Clinic location	Clinic type	Distance to clinic (km)	Travel time to clinic (min)
Clinic location		a) 0.22 b) 0.001	a) 016 b) 0.008	a) 0.19 b) 0.001
Clinic type			a) 0.15 b) 0.06	a) 0.12 b) 0.13
Distance to clinic (km)				a) <u>0.74</u>[1] b)<0.001

a = Cramer's V

b = P value for Cramer's V

Values meeting the threshold for strong association on V test (Cramer's V ≥0.5 between two two-level categorical variables and ≥0.35 for tables with more dimensions) are underlined

Findings from predictive models for associated exposure variables (A, B) and engagement in care – stage (e)

Distance to clinic and travel time to clinic were investigated for association in a series of logistic regression models (all adjusted for the *a priori* variables) with EIC as the outcome (Table 5.24). The ORs and SEs for the effect of both distance to clinic and travel time to clinic did change when the two variables were fitted together compared to when the variables were fitted individually. There was also a change in the OR for distance when fitted in a model with travel time. The close association of the two variables is shown in the scatter plot in Figure 5.2. No interaction was found between the two variables (p=0.16). Therefore, these two variables were compared further in stage f using AIC.

Figure 5.2: Scatter plot showing association between travel time to clinic and distance to clinic

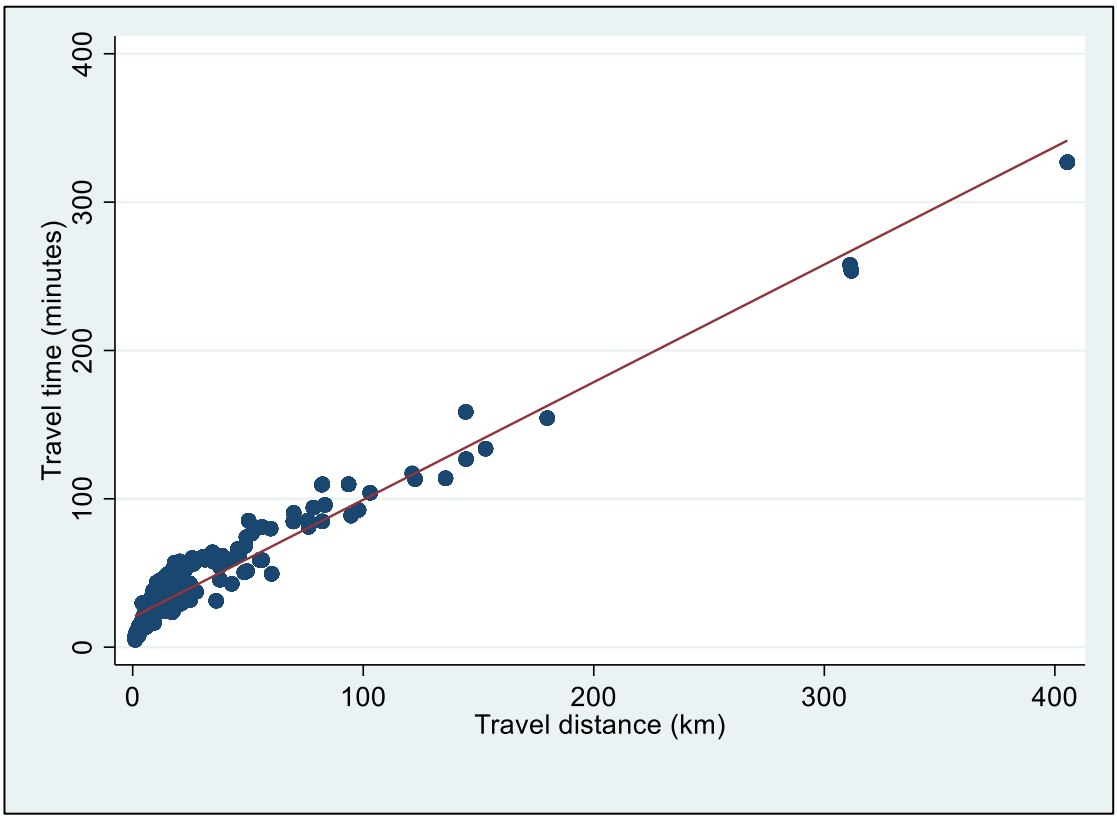


Table 5.24: Stage (e) predictive model for effect of distance to clinic and travel time to clinic on EIC in the Clinic domain

Clinic variable	Distance adjusted for *a priori*			Travel time adjusted for *a priori*			Distance and travel time adjusted for *a priori*			Distance and travel time fitted with an interaction		
	OR (95% CI)	SE	P value	OR (95% CI)	SE	P value	OR (95% CI)	SE	P value	OR (95% CI)	SE	P value
Distance/10 km	0.90 (0.80, 1.02)	0.06	0.10				1.99 (0.96, 4.12)	0.74	0.06	1.27 (0.48, 3.32)	0.62	0.63
Travel time/10 min				0.84 (0.71, 1.00)	0.07	0.05	0.36 (0.14, 0.94)	0.18	0.04	0.44 (0.17, 1.15)	0.22	0.09
Distance/10 km # travel time/10 min										1.06 (0.98, 1.15)	0.05	0.16

Comparing models using Akaike Information Criteria (AIC) value – stage (f)

Logistic regression models were fitted to estimate the AIC for EIC including travel time (per 10 min increase) or distance to clinic (per 10 km increase) adjusted for *a priori* variables and the other variables in the domain. The two models had very similar AIC scores, suggesting that they were measuring the same thing. However, the model including travel time with *a priori* variables and the other variables in the domain had a lower AIC when compared to a model including distance to clinic (2289.509 vs. 2291.224), and so distance to clinic was dropped.

5.4.2.7. Investigation of HIV experience and management exposure variables

The exposure variables in the HIV experience and management domain, along with each category's total person months and proportion of months in care are shown in Table 5.25. The numbers of person months for some categories in the age told HIV diagnosis, number of people told about HIV, and self-assessment of HIV exposure variables were relatively small and so these were combined. The proportion of person months in care was similar across categories of the age told HIV diagnosis variable. However, EIC appeared lower for participants who had told ≥10 people their HIV diagnosis, were not on ART (in both the doses missed in the last three days and self-assessment of adherence variables), and who reported in the self-assessment of adherence that they were not so good or were bad at taking their ART.

Table 5.25: HIV experience and management exposure variables included in the analysis

HIV experience and management variable	Category	Person-months	% in care	Further details
Age told HIV diagnosis	≤10 years	960	85%	Categories used in modelling: (1) ≤11 years (2) ≥ 12 years (3) Don't remember
	11 years	503	87%	
	12 years	432	90%	
	≥13 years	573	88%	
	Don't remember	863	88%	
Number of people told about HIV	0	1,820	89%	Categories used in modelling: (1) 0-2 (2) 3-4 (3) 5-9 (4) ≥10
	1-2	850	87%	
	3-4	364	84%	
	5-9	141	91%	
	≥10	132	75%	
Doses missed in last 3 days	No	2,146	89%	
	Yes	795	87%	
	Not on ART	414	77%	
Self-assessment of adherence	Excellent	1,167	91%	Categories used in modelling: (1) excellent/ good (2) not so good/ bad
	Good	1,393	90%	
	Not so good	273	78%	
	Bad	96	78%	
	Not on ART	414	77%	

Examination of missing data – stage (a)

Missing data were below the threshold (<15%) therefore all of the variables were carried forward (Table 5.26).

Table 5.26: Stage (a) missing data in the HIV experience exposure variables

HIV experience and management variable	Participants with missing data	
	n	%
Age told HIV diagnosis	22	7%
Number of people told about HIV	24	8%
Doses missed in last 3 days	20	7%
Self-assessment of adherence	21	7%

Investigation of a non-linear association with engagement in care- stage (b)

There were no continuous variables in the HIV experience and management domain and so this stage was not relevant.

Investigation of an association with time since AALPHI interview – stage (c)

No interactions were found between time since AALPHI interview and any of the HIV experience and management variables as predictors of EIC (all p≥0.05).

Examination of paired exposure variables for association – stage (d)

Cramer's V between pairs of exposure variables are shown in Table 5.27. There was evidence for an association between doses missed in last three days and self-assessment of adherence,

and the strength of association was strong (Cramer's V=0.78). Therefore, doses missed in the last three days and self-assessment of adherence were investigated further.

Table 5.27: Stage (d) tests for association of paired exposure variables in the HIV experience and management domain

HIV experience and management variable	Age told diagnosis	Number of people told about HIV	Doses missed in last 3 days	Self-assessment of adherence
Age told diagnosis		a) 0.15 b) 0.11	a) 0.07 b) 0.65	a) 0.10 b) 0.67
Number of people told about HIV			a) 0.13 b) 0.28	a) 0.15 b) 0.05
Doses missed in last 3 days				a) <u>0.78</u> b) <0.001
Self-assessment of adherence				

a = Cramer's V
b = P value for Cramer's V
Values meeting the threshold for strong association on V test (Cramer's V ≥0.5 between two two-level categorical variables and ≥0.35 for tables with more dimensions) are underlined

Findings from predictive models for associated exposure variables (A, B) and engagement in care – stage (e)

When fitted individually in logistic regression models (adjusted for *a priori* variables) strong evidence for an association with EIC was found for doses missed in the last three days (p=0.002) and self-assessment of adherence (p<0.001) (Table 5.28). However, it was clear from a cross tabulation of these two variables that they were measuring the same thing i.e. adherence. In addition, both variables included a group who were not on ART (Table 5.28). Therefore, the variables were not fitted in the same model. Instead, the variables were compared in stage (f) to see which of the two variables should be taken forward to the modelling stages.

Table 5.28: Stage (e) predictive model for effect of doses missed in the last 3 days and self-assessment of adherence on EIC in the HIV experience and management domain

HIV experience and management variable	Doses missed in the last 3 days adjusted for *a priori*			Self-assessment of adherence adjusted for *a priori*		
	OR (95% CI)	SE	P value	OR (95% CI)	SE	P value
Doses missed in the last 3 days						
No	1	-	-			
Yes	0.76 (0.48, 1.22)	0.18	0.002			
Not on ART	0.39 (0.23, 0.65)	0.10				
Self-assessment of adherence						
Excellent				1	-	-
Good				0.86 (0.55, 1.35)	0.20	
Not so good				0.38 (0.21, 0.69)	0.12	<0.001
Bad				0.28 (0.08, 0.95)	0.18	
Not on ART				0.32 (0.18, 0.58)	0.10	

Table 5.29: Cross-tabulation of missed any doses in the last three days and self-assessment of adherence

Missed doses in last 3 days	Self-assessment of adherence					Total
	Excellent	Good	Not so good	Bad	Not on ART	
	n (% row)					
No	94 (51)	79 (43)	9 (5)	1 (1)	0 (0)	183 (100)
Yes	6 (9)	40 (60)	14 (21)	7 (10)	0 (0)	67 (100)
Not on ART	0 (0)	0 (0)	0 (0)	0 (0)	35 (100)	35 (100)
Total	100 (35)	119 (42)	23 (8)	8 (3)	35 (12)	285 (100)

Comparing models using Akaike Information Criteria (AIC) value – stage (f)

Logistic regression models (with no adjustment for clustering) were fitted to estimate AIC including doses missed in the last three days or self-assessment of adherence and adjusted for *a priori* variables and the other variables in the domain. The model including self-assessment of adherence had a lower AIC when compared to a model with doses in the last three days (2367.317 vs. 2396.45), and so doses missed in the last three days was dropped.

5.4.2.8. Investigation of HIV marker exposure variables

Table 5.30 shows the exposure variables in the HIV marker domain, along with each category's total person months and proportion of person months in care. No categories were very small and so none were combined. The proportion in care was similar across categories for previous CDC C event, nadir CD4 cell count, time on ART, and on efavirenz exposure variables. However, EIC appeared lower in participants with a lower CD4 count, a detectable viral load and in participants who had a treatment interruption in the last 2 years. Of note, all of the HIV marker exposures represent status at AALPHI interview date (baseline).

Table 5.30: HIV markers exposure variables included in the analysis

HIV marker	Category	Person months	% in care	Further details
HIV severity:				
Previous CDC C event	No CDC C event	2,624	88%	Measured at baseline
	CDC C event	961	86%	
Nadir CD4 cell count (cells/µL)	<200	1,482	86%	Baseline nadir CD4 count. Modelled as continuous
	200-350	1,233	87%	
	351-499	460	88%	
	≥500	410	90%	
CD4 cell count (cells/µL)	<200	201	78%	Baseline CD4. Value included if collected within 6 months prior to baseline. Modelled as continuous
	200-350	292	80%	
	351-499	734	88%	
	≥500	2,118	91%	
Viral load (c/mL)	≤50	2,361	92%	Baseline viral load. Value included if collected within 6 months prior to baseline
	>50	1,044	79%	
ART:				
Time on ART (cumulative)	0 to ≤1 year	80	90%	Cumulative time on ART at baseline
	>1 to ≤5 years	609	89%	
	>5 to ≤10 years	1,120	88%	
	>10 years	1,593	86%	
	ART naive	183	87%	
On efavirenz	No	3,067	88%	Measured at baseline
	Yes	991	92%	
Treatment interruption in last 2 years	No	3,067	88%	Gap in ART treatment for ≥30 days in last 2 years as measured at baseline
	Yes	518	81%	

Examination of missing data – stage (a)

Only viral load and CD4 count had any missing data and the proportion missing was below the cut off for this analysis (15%) for both variables, therefore all of the variables were carried forward (Table 5.31).

Table 5.31: Stage (a) missing data in the HIV markers domain

HIV markers variable	Participants with missing data	
	n	%
Previous CDC C event	0	0%
Nadir CD4 cell count (cells/µL)	0	0%
CD4 cell count (cells/µL)	21	7%
Viral load (c/mL)	17	6%
Time on ART (cumulative)	0	0%
On efavirenz during follow-up	0	0%
Treatment interruption in last 2 years	0	0%

Investigation of a non-linear association with engagement in care - stage (b)

There was no evidence for a non-linear association between nadir CD4 cell count (p=0.87) or CD4 cell count (p=0.35) and EIC.

Investigation of an association with time since AALPHI interview – stage (c)

No interactions were found between time since AALPHI interview and any of the HIV marker domain variables as predictors of EIC (all p≥0.05).

Examination of paired exposure variables for association – stage (d)

Tests for association were carried out on all paired variables in the HIV markers domain. A number of exposure pairs showed a significant association with each other based on p value for Cramer's V (Table 5.32). However, the association was only strong for two pairs, previous CDC C event and time on ART (Cramer's V=0.37), and CD4 cell count and viral load (Cramer's V=0.45). Therefore, these two pairs of variables were investigated further.

Table 5.32: Stage (d) tests for association of paired exposure variables in the HIV markers domain

HIV markers variable	Previous CDC C event	Nadir CD4 cell count	CD4 cell count	Viral load	Time on ART	On efavirenz	Treatment interruption in last 2 yrs
Previous CDC C event		a) 0.16 b) 0.06	a) 0.04 b) 0.90	a) 0.05 b) 0.40	a) <u>0.37</u>[1] b) <0.001	a) 0.11 b) 0.05	a) 0.04 b) 0.48
Nadir CD4 cell count			a) 0.28 b) <0.001	a) 0.12 b) 0.22	a) 0.18 b) 0.005	a) 0.15 b) 0.07	a) 0.13 b) 0.17
CD4 cell count				a) <u>0.45</u> b) <0.001	a) 0.12 b) 0.44	a) 0.21 b) 0.005	a) 0.28 b) <0.001
Viral load					a) 0.33 b) <0.001	a) 0.34 b) <0.001	a) 0.34 b) <0.001
Time on ART						a) 0.29 b) <0.001	a) 0.17 b) 0.06
On efavirenz							a) 0.24 b)<0.001

a = Cramer's V
b = P value for Cramer's V
Values meeting the threshold for strong association on V test (Cramer's V ≥0.5 between two two-level categorical variables and ≥0.35 for tables with more dimensions) are underlined

Findings from predictive models for associated exposure variables (A, B) and engagement in care – stage (e)

The two associated pairs found in stage (d) were investigated in a series of logistic regression models, adjusted for *a priori* variables, for EIC. There was little change in the odds ratio when both previous CDC C event and time on ART were included in the same model, compared to models with variables included individually, and no interaction between the variables were found (p=0.76) (Table 5.33). Therefore, both variables were considered for inclusion in the modelling stages.

Table 5.33: Stage (e) predictive model for effect of previous CDC C event and time on ART on EIC in the HIV markers domain

HIV markers variable	Previous CDC C event adjusted for *a priori*			Time on ART adjusted for *a priori*			Previous CDC C event and Time on ART adjusted for *a priori*			Previous CDC C event and Time on ART fitted with an interaction		
	OR (95% CI)	SE	P value	OR (95% CI)	SE	P value	OR (95% CI)	SE	P value	OR (95% CI)	SE	P value
Previous CDC C event												
No	1	-	-				1	-	-	1	-	-
Yes	0.86 (0.57, 1.31)	0.18	0.49				0.90 (0.58, 1.40)	0.20	0.64	0.81 (0.46, 1.41)	0.23	0.45
Time on ART												
>10 years				1	-	-	1	-	-	1	-	-
>5 to ≤10 yrs				1.32 (0.79, 2.20)	0.34		1.29 (0.76, 2.17)	0.34		1.20 (0.68, 2.13)	0.62	
>1to ≤5 yrs				1.17 (0.68, 1.87)	0.29	0.83	1.09 (0.64, 1.84)	0.29	0.86	0.99 (0.56, 1.76)	0.29	0.92
0 to ≤1 yr				0.92 (0.38, 2.20)	0.41		0,88 (0.36, 2.15)	0.40		0.83 (0.33, 2.07)	0.39	
ART naive				1.14 (0.62, 2.09)	0.35		1.01 (0.57, 2.06)	0.35		1.03 (0.54, 1.98)	0.34	
Previous CDC C event # Time on ART												
CDC C event#On ART for >5 to ≤10 yrs										1.27 (0.35, 4.63)	0.84	
CDC C event#On ART for >1 to ≤5 yrs										1.62 (0.42, 6.23)	1.11	0.76
CDC C event#On ART for 0 to ≤1 yr										1	empty	
CDC C event#ART naïve										1	empty	

When CD4 cell count was fitted with viral load in a logistic model for EIC, odds ratios for both variables remained stable and similar to the individual models, but baseline CD4 cell count changed from having evidence for an association with EIC (p=0.001) when fitted without viral load, to no association (p=0.23) when fitted without. There was very strong evidence for an association with viral load and EIC when viral load was in the model individually (p=<0.001) and when it was fitted with CD4 cell count (p=<0.001) (Table 5.34). This suggested that viral load explained the effect of CD4 on EIC, so CD4 cell count was dropped and viral load considered for the modelling stages.

Table 5.34: Stage (e) predictive model for effect of CD4 cell count (cells/µL) and viral load (c/mL) on EIC in the HIV markers domain

HIV markers variable	CD4 cell count (cells/µL) adjusted for *a priori*			Viral load (c/mL) adjusted for *a priori*			CD4 cell count (cells/µL) and viral load (c/mL) adjusted for *a priori*		
	OR (95% CI)	SE	P value	OR (95% CI)	SE	P value	OR (95% CI)	SE	P value
CD4 cell count (per 50 cells/µL)	1.06 (1.03, 1.10)	0.02	0.001				1.02 (0.99, 1.06)	0.02	0.23
Viral load (c/mL) ≤50c/mL >50c/mL				1 0.33 (0.23, 0.48)	0.06	<0.001	1 0.35 (0.23, 0.53)	0.07	<0.001

5.4.3. Logistic regression modelling

In this section, I present the results of the four stages of modelling. Stage 1-3 models are presented by domain.

5.4.3.1. A priori domain logistic regression modelling

All *a priori* variables were investigated in the modelling process (models 1 and 2), and were:

- Sex
- Age at entry
- Ethnicity
- Born outside the UK

Stage 1 models - Adjusting for time since AALPHI interview

As might be expected based on the results from Table 5.1, when *a priori* variables were fitted individually, along with time since AALPHI interview, in multivariable models to explore the association with EIC, age at entry was the only variable that was associated with the outcome. There was strong evidence of an association between age at entry and EIC, with older participants having worse EIC (OR 0.90 per 1 year increase, 95% CI 0.83, 0.97, p=0.009). There was also weak evidence of an association between ethnicity and EIC (p=0.06) with young people from Asian/ mixed ethnicity being less likely to be in care than black young people, while white young people were similar to black young people ((Asian/mixed OR 0.53, 95% CI 0.31, 0.89, white OR 0.98, 95%CI 0.34, 2.81, reference black ethnicity). Results are shown in Table 5.37.

Stage 2 models - Adjusting for a priori exposure variables

In models including time since AALPHI interview and all the *a priori* variables, findings were very similar to stage 1 models. Age at entry and ethnicity remained associated with EIC, with older participants, and those from Asian/ mixed ethnicity, being less likely to be in care (Table 5.37).

Stage 3 of the modelling process was not carried out for the a priori domain.

5.4.3.2. Sociodemographic domain logistic regression modelling

The following variables from the sociodemographic domain were investigated in the modelling process:

- Education/employment status
- Ever excluded from school
- Death of parents
- Number of main carers
- Live with parent/carer
- Parent/carer in work
- Main language spoken at home
- IDACI Deprivation Score

Stage 1 models - Adjusting for time since AALPHI interview

In multivariable models in which sociodemographic variables were fitted individually, along with time since AALPHI interview, four variables were associated with EIC. As might be expected based on results from Table 5.3, these variables were education/employment status, ever excluded from school, living with parent/carer, and main language spoken at home. Young people were less likely to be in care if they were: employed or not in education, employment or training (OR 0.46, 95% CI 0.21, 0.97, p=0.04) compared to young people in full-time education; had ever been excluded from school (OR 0.61, 95% CI 0.39, 0.95, p=0.03) versus had not; if they did not live with their parents (OR 0.50, 95% CI 0.25, 0.97, p=0.04) compared to young people living with their parents; or if they spoke a language other than English at home (OR 0.50, 95% CI 0.22, 1.14, p=0.10) compared with English only/ English and another language (Table 5.37).

Stage 2 models - Adjusting for a priori exposure variables

When the domain-specific variables were fitted individually in models including the *a priori* variables, only ever excluded from school and main language spoken at home continued to show evidence of an association with the outcome (Table 5.37) and ORs for these two variables in the stage 2 models were similar to the stage 1 models.

Stage 3 model – Domain-specific multivariable model including a priori and sociodemographic domain exposure variables

After backwards selection was conducted, both ever excluded from school (OR 0.61, 95% CI 0.38, 0.99, p=0.04) versus not, and speaking a language other than English at home (OR 0.52, 95% CI 0.24, 1.16, p=0.11) compared with English only/ English and another language remained associated with EIC. Therefore, both of these variables were considered in the primary stage 4 model (Table 5.37), full stage 3 model results are shown in see Appendix E, Table s4).

5.4.3.3. Risk behaviour practices domain logistic regression modelling

The following variables from the risk behaviour practices domain were investigated in the modelling process:

- Ever smoked cigarettes
- Amount of alcohol
- Condom use

Stage 1 models - Adjusting for time since AALPHI interview

In multivariable models in which risk behaviour practice variables were fitted individually, along with time since AALPHI interview, as might be expected based on results from Table 5.6, all three variables showed an association with EIC. Young people were less likely to be in care if they had ever smoked (OR 0.55, 95% CI 0.35, 0.89, p=0.01) compared with never smokers, or if they reported drinking but not hazardously or hazardous drinking compared to young people who did not drink (OR for drink but not hazardously, 0.58, 95% CI 0.39, 0.87; OR for hazardous drinking OR 0.46, 95% CI 0.24, 0.87, reference do not drink, p=0.006). Young people who did not always use a condom during sex were less likely to be in care, and young people who always used a condom were more likely to be in care, than young people who were not sexually active (did not use a condom OR 0.57, 95% CI 0.31, 1.04, always use a condom OR 1.17, 95% CI 0.73, 1.87, reference not sexually active, p=0.11) (Table 5.37).

Stage 2 models - Adjusting for a priori exposure variables

When the domain-specific variables were fitted individually in models including the *a priori* variables, only ever smoked and condom use continued to show evidence of an association with the outcome (Table 5.37) and the ORs for these two variables in the stage 2 models were similar to the stage 1 models.

Stage 3 model – Domain-specific multivariable model including a priori and risk behaviour practice domain exposure variables

After backwards selection was carried out, both current alcohol amount (drinking but not hazardously OR 0.64, 95% CI 0.40, 1.01; hazardous drinking OR 0.57, 95% CI 0.28, 1.19, reference do not drink, p=0.12) and condom use (always use a condom OR 0.1.76 95% CI 0.95, 3.26; do not always use a condom OR 0.80, 95% CI 0.42, 1.54, reference not sexually active, p=0.07) remained associated with EIC (Table 5.38). Therefore, both of these variables were considered in the primary stage 4 model (Table 5.37.), full stage 3 model results are shown in Appendix E, Table s5).

5.4.3.4. Mental health domain logistic regression modelling

The following variables from the mental health domain were investigated in the modelling process:

- Feelings about HIV
- Ever self-harmed
- Ever felt life was not worth living
- Major life events
- Paediatric Quality of Life (PedsQL)
- Rosenberg Self-Esteem Scale
- HADS anxiety score
- HADS depression score

Stage 1 models - Adjusting for time since AALPHI interview

In multivariable models in which mental health variables were fitted individually, along with time since AALPHI interview, as might be expected based on results in Table 5.14, only self-harm showed an association with EIC. Young people who had ever self-harmed (OR 0.67, 95% CI= 0.40, 1.11, p=0.12) were less likely to be in care than those who had never self-harmed (Table 5.37).

Stage 2 models - Adjusting for a priori variables

When the mental health variables were fitted individually in models including the *a priori* variables, self-harm continued to be the only variable to show evidence of an association with the outcome (Table 5.37). ORs in the stage 2 models were similar to the stage 1 models.

Stage 3 model – Domain-specific multivariable model including a priori and mental health domain exposure variables

After backwards selection was conducted, ever self-harmed (OR 0.66, 95% CI 0.38, 1.14, reference no self-harm, p=0.14) remained the only variable associated with EIC. Therefore this variable was considered in the primary stage 4 model (Table 5.37), full stage 3 model results shown in Appendix E, Table s6).

5.4.3.5. Cognition domain logistic regression modelling

The NPZ-6 variable was the only variable in this domain.

Stage 1 model - Adjusting for time since AALPHI interview

In a multivariable model in which NPZ-6 was fitted with time since AALPHI interview, there was no evidence of an association of NPZ-6 with EIC (OR 0.88 per one unit increase in Z score, 95% CI 0.68, 1.15, p=0.37) (Table 5.37).

Stage 2 model - Adjusting for a priori variables

When NPZ6 was fitted in a model including the *a priori* variables, there remained no evidence of an association with EIC (Table 5.37). ORs in the stage 2 model were similar to those in the stage 1 model.

Stage 3 model – Domain-specific multivariable model including a priori and cognition domain variables

The stage 3 model was not carried out because NPZ-6 was the only variable in this domain and it was not considered in the final model because there was no evidence of an association between it and the outcome.

5.4.3.6. Clinic domain logistic regression modelling

The following variables from the clinic domain were investigated in the modelling process:

- Clinic location
- Clinic type
- Travel time to clinic

Stage 1 models - Adjusting for time since AALPHI interview

In multivariable models in which clinic variables were fitted individually, along with time since AALPHI interview, as might be expected based on results in Table 5.21, clinic location and travel time to clinic were associated with EIC. Young people were more likely to be in care if they attended clinic outside London (OR 1.43, 95% CI 0.93, 2.19, p=0.10) compared to if they attended clinic inside London, or if their travel time to clinic was longer (OR 0.97 per 10 minute increase, 95% CI 0.94, 1.01, p=0.14) (Table 5.37).

Stage 2 models - Adjusting for a priori variables

When the domain-specific variables were fitted individually in models including *a priori* variables, clinic location and travel time to clinic continued to show evidence of an association with EIC. ORs for these two variables in the stage 2 models were similar to the stage 1 models. In addition, clinic type showed evidence of an association with EIC, with young people attending either an adolescent or adult/GUM clinic being more likely to be in

care compared to young people still in paediatric care (adolescent clinic OR 1.28, 95% CI 0.64, 2.58, adult/GUM clinic OR 4.13, 95% CI 1.23, 13.89, reference paediatric clinic, p=0.07) although confidence intervals were quite wide for young people attending adult/GUM clinic (Table 5.37).

When the clinic type variable was adjusted for a priori variables, there was a change in direction of the OR for the adolescent clinic (stage 2 and 3 models) compared to when adjusted for time since AALPHI interview only (stage 1 model) (stage 1 model: adolescent clinic OR 0.75, 95% CI 0.45, 1.25; stage 2 model adolescent clinic OR 1.28. 95% CI 0.64, 2.58; stage 3 model adolescent clinic OR 1.42, 95% CI 0.67, 3.00). Therefore, clinic type was investigated further. A series of multivariable models were fitted with clinic type and a priori variables to explore this association with EIC, dropping one a priori variable in each model. The change in direction of the OR remained when sex and ethnic group were dropped, however when age at entry was dropped, young people in adolescent clinics were less likely to be in care when compared to young people in paediatric clinic as in stage 1 model. This suggests that young people's EIC may not change in the same way by age for each clinic type category. A new variable was created, combining age group and clinic type (Table 5.35). The combined variable suggested that young people aged 16 and older had worse EIC in paediatric care than those of the same age range in adolescent or adult care.

Table 5.35: Proportion of person-months engaged in care for new combined clinic type and age variable

Combined clinic type and age variable	Person-months	% in care
In paediatric care aged 13-15 years	1,414	90
In paediatric care aged 16-18 year	1,202	85
In paediatric care aged 19-21 years	120	76
In adolescent care aged 16-18 years	174	84
In adolescent care aged 19-21 years	426	84
In adult care aged 18-19 years	84	99
In adult care aged 19-21 years	117	90

In addition, as shown in Table 5.36, all young people aged 13-15 years were in paediatric care and the majority of young people aged 16-18 years were also in paediatric clinics, rather than adolescent or adult clinics.

Table 5.36: Number of person-months by clinic type and age group

Age group	Person-months by clinic type			Total
	Paediatric clinic	Adolescent clinic	Adult clinic	
13-15 years	1,414	0	0	1,414
16-18 years	1,202	174	84	1,460
19-21 years	120	426	117	663
Total	2,736	600	201	3,537

An interaction was fitted between clinic type and age at entry and no interaction was found (p=0.67), therefore, clinic type remained in the model at this stage

Stage 3 model – Domain-specific multivariable model including a priori and clinic domain variables

After backwards selection was conducted, both clinic type (adolescent clinic OR 1.42, 95% CI 0.67, 3.00; adult/GUM clinic OR 3.88, 95% CI 1.00, 15.10, reference paediatric clinic, p=0.14) and travel time to clinic (OR 0.97 per 10 minute increase, 95% CI 0.94, 1.00, p=0.08) remained associated with EIC (Table 5.37), full stage 3 model results are shown in Appendix E, Table s7).

5.4.3.7. HIV experience and management domain logistic regression modelling

The following variables from the HIV markers domain were investigated in the modelling process:

- Age at naming of HIV
- Number of people told about HIV
- Adherence self-assessment

Stage 1 models - Adjusting for time since AALPHI interview

In multivariable models in which HIV experience and management variables were fitted individually, along with time since AALPHI interview, two variables showed an association with EIC. As might be expected based on results from Table 5.25, these variables were number of people told about HIV, and adherence self-assessment. The direction of the association varied between the categories in the number of people told about HIV variable. Compared to young people who had told 0-2 people about their HIV status, young people were less likely to be in care if they had told 3-4 other people (OR 0.70, 95% CI 0.38, 1.29) or ≥10 people (OR 0.40, 96% CI 0.17, 0.93), and they were more likely to be in care if they had told 5-9 people (OR 1.43, 95% CI 0.41, 5.00)(p=0.11). Young people were also less likely to be

in care if their adherence self-assessment was not so good or bad (OR 0.38, 95% CI 0.22, 0.66) or if they were not on ART (OR 0.37, 95% CI 0.22, 0.63) compared to those on ART who rated their adherence as excellent or good (p=<0.001) (Table 5.37).

Stage 2 models - Adjusting for a priori variables

When the HIV experience and management variables were fitted individually in models including *a priori* variables, number of people told about HIV and adherence self-assessment continued to show evidence of an association with EIC (Table 5.37). ORs for these two variables in the stage 2 models were similar to variables in the stage 1 models.

Stage 3 model – Domain-specific multivariable model including a priori and HIV experience and management domain variables

After backwards selection was carried out only adherence self-assessment (not so good or bad OR 0.39, 95% CI 0.23, 0.64, p=<0.001; not on ART OR 0.35, 95%CI 0.21, 0.59, reference excellent or good adherence, p=<0.001) remained associated with EIC. Therefore, adherence self-assessment was considered in the primary stage 4 model (Table 5.37, full stage 3 model results shown in Appendix E, Table s8).

5.4.3.8. HIV markers domain logistic regression modelling

The following baseline variables from the HIV markers domain were investigated in the modelling process:

- Previous CDC C event
- Nadir CD4 cell count (cells/µL)
- Viral load (c/mL)
- Time on ART (cumulative)
- On efavirenz
- Treatment interruption in last 2 years

Stage 1 models - Adjusting for time since AALPHI interview

In multivariable models in which HIV marker variables were fitted individually, along with time since AALPHI interview, three variables showed an association with EIC. As might be expected based on results from Table 5.30, these variables were viral load, on efavirenz, and having had a treatment interruption in the 2 years. Young people were less likely to be in care if they had a viral load >50c/mL (OR 0.34, 95% CI 0.23, 0.49, p=<0.001) compared with those who were suppressed, or if they had had a treatment interruption in the last two years

(OR 0.56, 96% CI 0.35, 0.91, p=0.02) compared with those who had not. Young people were also more likely to be in care if they were on efavirenz at baseline (OR 2.01, 95% CI 1.24, 3.28, p=0.005) compared to those who were not (Table 5.37).

Stage 2 models - Adjusting for a priori variables

When the domain-specific variables were fitted individually models including *a priori* variables, viral load, on efavirenz, and treatment interruption in the 2 years continued to be associated with EIC (Table 5.37). ORs for these three variables in the stage 2 models were similar to the stage 1 models.

Stage 3 model – Domain-specific multivariable model including a priori and HIV markers domain variables

After backwards selection was conducted, only viral load (>50c/mL OR 0.33, 95% CI 0.23, 0. 48, reference ≤50c/mL, p=<0.001) continued to have evidence of an association with EIC (Table 5.37). Therefore, viral load was considered in the primary stage 4 model (full stage 3 model results are shown in Appendix E, Table s9).

Table 5.37:Logistic regression results for stage 1-3 models across all domains

Domain, variable and category	Stage 1 models: Adjusted for time since AALPHI interview		Stage 2 models: Adjusted for *a priori* variables		Stage 3 models: Domain-specific multi-variable model including *a priori* and domain variables[1]	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
A priori domain						
Month of follow-up (1-12), per month later			0.99 (0.95, 1.03)	0.49		
Sex						
Male	1	-	1	-		
Female	1.05 (0.72, 1.52)	0.81	1.05 (0.73, 1.53)	0.79		
Entry age, per year increase	0.90 (0.83, 0.97)	0.009	0.89 (0.82, 0.96)	0.004		
Ethnicity						
Black	1	-	1	-		
Asian/mixed	0.53 (0.31, 0.89)	0.06	0.49 (0.28, 0.85)	0.04		
White	0.98 (0.34, 2.81)		0.98 (0.35, 2.77)			
Born outside of UK						
No	1	-	1	-		
Yes	1.03 (0.70, 1.51)	0.90	0.94 (0.63, 1.42)	0.78		
Sociodemographic domain						
Education/employment status						

Domain, variable and category	Stage 1 models: Adjusted for time since AALPHI interview		Stage 2 models: Adjusted for *a priori* variables		Stage 3 models: Domain-specific multi-variable model including *a priori* and domain variables[1]	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
In full time education	1	-	1	-		
Employed or not in education, employment or training	0.46 (0.21, 0.97)	0.04	0.57 (0.24, 1.38)	0.21		
Ever excluded from school						
No	1	-	1	-	1	-
Yes	0.61 (0.39, 0.95)	0.03	0.59 (0.37, 0.95)	0.03	0.61 (0.38, 0.99)	0.04
Death of parents						
None or unknown	1	-	1	-		
One or both parent died	0.81 (0.55, 1.19)	0.29	0.85 (0.58, 1.25)	0.41		
Number of main carers						
1 carer	1	-	1	-		
2 carers	0.99 (0.63, 1.57)	0.92	0.89 (0.56, 1.42)	0.76		
≥3 carers	0.88 (0.49, 1.60)		0.82 (0.45, 1.49)			
Live with parents/carers						
Yes	1	-	1	-		
No	0.50 (0.25, 0.97)	0.04	0.68 (0.29, 1.58)	0.37		
Parent/carer in work						
Yes	1	-	1	-		
No	0.82 (0.54, 1.25)	0.42	0.93 (0.60, 1.45)	0.65		
Don't know	0.50 (0.13, 1.90)		0.54 (0.14, 2.07)			
Main language spoken at home						
English/English and another language	1	-	1	-	1	-
A language other than English	0.50 (0.22, 1.14)	0.10	0.47 (0.21, 1.06)	0.07	0.52 (0.24, 1.16)	0.11
IDACI deprivation score[2], per decile increase (0-1, higher worst)	2.11 (0.65, 6.85)	0.22	1.91 (0.60, 6.12)	0.28		
Risk behaviour practice domain						
Ever smoked						
No	1	-	1	-		
Yes	0.55 (0.35, 0.89)	0.01	0.68 (0.40, 1.13)	0.14		
Current alcohol amount						
No drinking	1	-	1	-	1	-
Light drinking	0.58 (0.39, 0.87)	0.006	0.68 (0.44, 1.04)	0.16	0.64 (0.40, 1.01)	0.12
Hazardous drinking	0.46 (0.24, 0.87)		0.64 (0.32, 1.27)		0.57 (0.28, 1.19)	

Domain, variable and category	Stage 1 models: Adjusted for time since AALPHI interview		Stage 2 models: Adjusted for *a priori* variables		Stage 3 models: Domain-specific multi-variable model including *a priori* and domain variables[1]	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Condom use						
Not sexually active	1	-	1	-	1	-
Always use a condom	1.17 (0.73, 1.87)	0.11	1.55 (0.87, 2.75)	0.11	1.76 (0.95, 3.26)	0.07
Do not always use a condom	0.57 (0.31, 1.04)		0.73 (0.39, 1.38)		0.80 (0.42, 1.54)	
Mental health domain						
Feelings about HIV, per 1 point increase (higher score better)	1.00 (0.99, 1.01)	0.86	1.00 (0.60, 1.35)	0.49		
Ever self-harmed						
No	1	-	1	-	1	-
Yes	0.67 (0.40, 1.11)	0.12	0.66 (0.38, 1.14)	0.14	0.66 (0.38, 1.14)	0.14
Ever felt life not worth living						
No	1	-	1	-		
Yes	0.90 (0.61, 1.34)	0.60	0.98 (0.64, 1.52)	0.94		
Major Life events, per 1 point increase (higher score better)	1.02 (0.96, 1.09)	0.47	1.03 (0.96, 1.10)	0.42		
Pediatric Quality of Life, per 1 point increase (higher score better)	1.00 (0.98, 1.01)	0.61	0.96 (0.98, 1.01)	0.46		
Rosenberg Self-Esteem Scale, per 1 point increase (higher score better)	0.98 (0.95, 1.02)	0.34	0.98 (0.94, 1.01)	0.22		
HADS anxiety score, per point 1 increase (higher score better)	1.01 (0.96, 1.06)	0.76	1.00 (0.95, 1.05)	0.92		
HADS depression score, per 1 point increase (higher score better)	1.01 (0.94, 1.08)	0.81	1.01 (0.94, 1.07)	0.83		
Cognition domain						
NPZ-6 score, per unit increase in *z* score (higher score better)	0.88 (0.68, 1.15)	0.37	0.98 (0.75, 1.27)	0.87		
Clinic domain						
Clinic location						
In London	1	-	1	-		
Outside London	1.43 (0.93, 2.19)	0.10	1.46 (0.93, 2.28)	0.10		
Clinic type						
Paediatric	1	-	1	-	1	
Adolescent	0.75 (0.45, 1.25)	0.20	1.28 (0.64, 2.58)	0.07	1.42 (0.67, 3.00)	0.14
Adult/GUM clinic	2.06 (0.70, 6.09)		4.13 (1.23, 13.89)		3.88 (1.00, 15.10)	

Domain, variable and category	Stage 1 models: Adjusted for time since AALPHI interview		Stage 2 models: Adjusted for *a priori* variables		Stage 3 models: Domain-specific multi-variable model including *a priori* and domain variables[1]	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Travel time to clinic, per 10 minute increase[4]	0.97 (0.94, 1.01)	0.14	0.97 (0.93, 1.00)	0.05	0.97 (0.94, 1.00)	0.08
HIV experience and management domain						
Age at naming of HIV						
Aged ≤11 years	1	-	1	-		
Aged ≥12 years	1.31 (0.83, 2.01)	0.44	1.26 (0.80, 1.99)	0.59		
Don't remember	1.26 (0.80, 1.98)		1.15 (0.73, 1.80)			
How many people told about HIV						
0-2	1	-	1	-		
3-4	0.70 (0.38, 1.29)	0.11	0.76 (0.41, 1,41)	0.12		
5-9	1.43 (0.41, 5.00)		1.63 (0.45, 5.96)			
≥10	0.40 (0.17, 0.93)		0.43 (0.20, 0.93)			
Adherence self-assessment						
Excellent or good	1	-	1	-	1	-
Not so good or bad	0.38 (0.22, 0.66)	<0.001	0.39 (0.23, 0.64)	<0.001	0.39 (0.23, 0.64)	<0.001
Not on ART	0.37 (0.22, 0.63)		0.35 (0.21, 0.59)		0.35 (0.21, 0.59)	
HIV markers domain						
HIV severity						
Previous CDC C event						
No CDC C	1	-	1	-		
CDC C ever	0.90 (0.59, 1.39)	0.65	0.86 (0.57, 1.31)	0.49		
Viral load						
≤50c/mL	1	-	1	-	1	-
>50c/mL	0.34 (0.23, 0.49)	<0.001	0.33 (0.23, 0.48)	<0.001	0.33 (0.23, 0.48)	<0.001
ART						
Time on ART						
>10 years	1	-	1	-		
>5 to ≤10 years	1.39 (0.87, 2.23)	0.69	1.32 (0.80, 2.20)	0.83		
>1 to ≤5 years	1.22 (0.74, 1.99)		1.13 (0.68, 1.87)			
0 to ≤1 years	0.93 (0.34, 2.52)		0.92 (0.38, 2.20)			
ART naive	1.24 (0.69, 2.24)		1.14 (0.62, 2.09)			
On efavirenz at baseline						
No	1	-	1	-		
Yes	2.01 (1.24, 3.28)	0.005	1.85 (1.14, 2.99)	0.01		

Domain, variable and category	Stage 1 models: Adjusted for time since AALPHI interview		Stage 2 models: Adjusted for *a priori* variables		Stage 3 models: Domain-specific multi-variable model including *a priori* and domain variables[1]	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Treatment interruption in last 2 yrs						
No	1	-	1	-		
Yes	0.56 (0.35, 0.91)	0.02	0.59 (0.35, 0.98)	0.04		

[1] Modelling carried out using backwards selection

5.4.4. Stage 4 model

When all the exposure variables showing an association with in care from the stage 3 domain-specific models were combined in a multivariable model across domains, following backwards selection, four variables continued to show evidence of an association with EIC in this primary stage 4 model. These were ethnicity, ever self-harmed, adherence self-assessment, and baseline viral load. Young people were less likely to be in care if they were Asian/ mixed ethnicity compared to black ethnicity, with the white ethnic group similarly likely to be in care to the black ethnic group (Asian/mixed ethnicity OR 0.44, 95% CI 0.25, 0.78, white OR 1.05, 95%CI 0.29, 3.81, reference black ethnicity, p=0.02). Young people were also less likely to be in care if they had ever self-harmed (OR 0.55, 95% CI 0.32, 0.95, p=0.03) compared to those who had not, and if they had assessed their adherence to ART as not so good or bad (OR 0.46, 95% CI 0.25, 0.84) or were not on ART (OR 0.64, 95% CI 0.34, 1.21) compared to those on ART who assessed their adherence as excellent or good (p=0.04). Finally participants were less likely to be in care if they had a baseline viral load >50c/mL (OR 0.47, 95% CI 0.30, 0.75, p=0.002) compared to ≤50c/mL (Table 5.38).

Table 5.38: Primary stage 4 model

Domain, variable and category	OR (95% CI)	P value
A-priori domain		
Month of follow-up (1-12), per month later	0.97 (0.93, 1.02)	0.24
Sex		
Male	1	-
Female	1.29 (0.86, 1.94)	0.22
Entry age, per year increase	0.94 (0.87, 1.02)	0.15
Ethnicity		
Black	1	-
Asian/mixed	0.44 (0.25, 0.78)	0.02
White	1.05 (0.29, 3.81)	
Born outside the UK		
No	1	-
Yes	0.86 (0.57, 1.30)	0.47
Other domains		
Self-harm ever		
No	1	
Yes	0.55 (0.32, 0.95)	0.03
Adherence self-assessment		
Good / excellent	1	
Not so good/ bad	0.46 (0.25, 0.84)	0.04
Not on ART	0.64 (0.34, 1.21)	
Viral load		
≤50c/mL	1	-
>50c/mL	0.47 (0.30, 0.75)	0.002

5.4.5. Results of checks to the final model and sensitivity analyses

The results of a number of checks and sensitivity analyses that were performed on the primary stage 4 model are described below.

5.4.5.1. Alternate stage 4 model exposure variables

The primary stage 4 model was rerun, replacing self-harm with all of the other mental health variables one by one (feelings about HIV, ever felt life was not worth living, major life events, Pediatric Quality of Life Inventory, Rosenberg Self-Esteem Scale, HADS anxiety score, HADS

depression score) and none were found to be associated with EIC (p≥0.05) (results not shown). Self-assessment of adherence was replaced in the model with missed doses in last three days but was not found to be associated with EIC (p≥0.05) (results not shown). Finally, viral load was replaced in the model by CD4 cell count but this was not found to be associated with EIC (p≥0.05) (results not shown).

5.4.5.2. Sensitivity analysis – using an alternate p value cut off (<0.1 compared to <0.05)

The primary stage 4 model was rerun, including all the exposure variables with a p value <0.15 from the stage 3 model but using an alternative <0.1 p value for inclusion in the final model (instead of <0.05). The stage 4 model for this sensitivity analysis was very similar to the primary stage 4 model with all the exposure variables from the primary stage 4 model remaining. However, two additional exposure variables were found to be associated with EIC: language spoken at home; and type of clinic attended. Participants who spoke a language other than English at home were less likely to be in care (OR 0.39, 95% CI 0.14, 1.08 p=0.07) than participants who spoke English or English and another language. In addition, participants who attended adolescent or adult clinics (adolescent clinic OR 1.66, 95% CI 0.83, 3.32; adult clinic OR 4.08, 95% CI 1.28, 12.99, p=0.04) were more likely to be in care compared to participants attending paediatric clinics (Table 5.39).

Table 5.39: Stage 4 model sensitivity analysis with p value <0.1 cut off

Domain, variable and category	OR (95% CI)	P value
A-priori domain		
Month of follow-up (1-12), per month later	0.97 (0.93, 1.02)	0.23
Sex		
Male	1	-
Female	1.20 (0.80, 1.81)	0.22
Entry age, per year increase	0.86 (0.77, 0.95)	0.004
Ethnicity		
Black	1	-
Asian/mixed	0.42 (0.24, 0.71)	0.005
White	1.07 (0.28, 4.06)	
Born outside the UK		
No	1	-
Yes	0.90 (0.60, 1.36)	0.63
Other domains		
Main language spoken at home		
English/English and another language	1	-
Another language only	0.39 (0.14, 1.08)	0.07
Type of clinic attended		
Paediatric clinic	1	-
Adolescent clinic	1.66 (0.83, 3.32)	0.04
Adult/GUM clinic	4.08 (1.28, 12.99)	
Self-harm ever		
No	1	-
Yes	0.53 (0.31, 0.92)	0.02
Adherence self-assessment	1	-
Good / Excellent	0.47 (0.26, 0.84)	0.03
Not so good/bad	0.62 (0.33, 1.17)	
Viral load		
≤50c/mL	1	-
>50c/mL	0.48 (0.30, 0.76)	0.002

When these two additional exposure variables were included in the model, the *a priori* age at entry variable became associated with EIC, when it was not previously. The relationship

between age at entry and language spoken at home and type of clinic was therefore investigated. Stage 4 models (using a cut off of <0.1) were run removing clinic type and language individually. Age at entry was only associated with EIC when clinic type was in the model. As shown previously (Table 5.35) young people aged 16 years and older had worse EIC in paediatric care than those of the same age range in adolescent or adult care. As shown in Table 5.40, all young people aged 13-15 years were in paediatric care and the majority of young people aged 16-18 years were also in paediatric clinics, rather than adolescent or adult clinics. There was no evidence for an interaction between clinic type and age at entry was fitted (p=0.67).

Table 5.40: Number of person-months by clinic type and age group

	Person-months by clinic type			Total
Age group	Paediatric clinic	Adolescent clinic	Adult clinic	
13-15 years	1,414	0	0	1,414
16-18 years	1,202	174	84	1,460
19-21 years	120	426	117	663
Total	2,736	600	201	3,537

5.4.5.3. Sensitivity analysis using an alternate start date

In a sensitivity analysis, the primary stage 4 model was fitted using an alternate start date for the follow-up year, which was three months later than the AALPHI interview date (baseline) used for the main analysis. The model using the alternate start date was very similar to the primary stage 4 final model (Table 5.41). The retained variables were the same apart from the addition of travel time to clinic, and the odds ratios, confidence intervals and p values were all similar. Travel time was kept in the final model for this sensitivity analyse despite having a p value of ≥0.05. After the initial backwards elimination process, only adherence remained in the model. However, when travel time was added to this model, it was found to be significant. Self-harm and viral load were also found to be significant when adherence and travel time were included in the model; however, travel time became just non-significant. As the p value (p=0.06) was just above the cut off, it was decided to keep it in.

Table 5.41: Stage 4 model sensitivity analysis using an alternate start date

Domain, variable and category	OR (95% CI)	P value
A-priori domain		
Month of follow-up (1-12), per month later	1.00 (0.95, 1.04)	0.84
Sex		
Male	1	-
Female	1.33 (0.87, 2.02)	0.19
Entry age, per year increase	0.92 (0.86, 1.00)	0.05
Ethnicity		
Black	1	-
Asian/ mixed	0.46 (0.25, 0.87)	0.04
White	0.56 (0.17, 1.90)	
Born outside the UK		
No	1	-
Yes	0.86 (0.56, 1.33)	0.51
Other domains		
Self-harm ever		
No	1	-
Yes	0.52 (0.28, 0.96)	0.04
Adherence self-assessment		
Good / excellent	1	-
Not so good/bad	0.43 (0.24, 0.80)	0.03
Not on ART	0.64 (0.33, 1.24)	
Viral load		
≤50c/mL	1	-
>50c/mL	0.60 (0.37, 0.98)	0.04
Travel time to clinic (per 10 min increase)	0.96 (0.92, 1.00)	0.06

5.4.5.4. Sensitivity analysis using a four month maximum time to next appointment

In a sensitivity analysis including all of the stages of modelling, the maximum time to next scheduled appointment was reduced to 4 months instead of 6 months. Results from all four stages of modelling are presented in Appendix F and stage 4 model results are shown in Table 5.42.

The stage 4 model for this sensitivity analysis was similar to the primary stage 4 model. Thus young people were less likely to be in care if they: self-harmed (OR 0.56, 95% CI 0.34, 0.93,

p=0.03); had not so good/bad adherence (OR 0.44, 95% CI 0.25, 0.75) or were not on ART (OR 0.64, 95%CI 0.35, 1.18)(p=0.01); or had a viral load >50c/mL (OR 0.62, 95% CI 0.41, 0.96, p=0.03). Similarly to the primary stage 4 model, young people who were of Asian / mixed ethnicity were also less likely to be in care compared to black young people, with white young people similar to black young people (Asian/mixed OR 0.52, 95% CI 0.30, 0.91, white OR 1.05, 95% CI 0.36, 3.07) although only a weak association with ethnicity was found (p=0.07). In contrast to the main model, young people were less likely to be in care with increasing month through the 12 month follow up period (time per month from baseline OR 0.95, 95% CI 0.91, 0.99, p=0.02), and if they were older (age per year increase OR 0.89, 95% CI 0.83, 0.95, p=0.001).

Table 5.42: Stage 4 model sensitivity analysis using 4 month maximum time to next appointment

Domain, variable and category	OR (95% CI)	P value
A-priori category		
Month of follow-up (1-12), per month later	0.95 (0.91, 0.99)	0.02
Sex		
Male	1	-
Female	1.27 (0.88, 1.82)	0.20
Entry age, per year increase	0.89 (0.83, 0.95)	0.001
Ethnicity		
Black	1	-
Asian/mixed	0.52 (0.30, 0.91)	0.07
White	1.05 (0.36, 3.07)	
Born outside the UK		
No	1	-
Yes	0.91 (0.63, 1.31)	0.61
Other domains		
Self-harm ever		
No	1	-
Yes	0.56 (0.34, 0.93)	0.03
Adherence self-assessment		
Good / excellent	1	-
Not so good/ bad	0.44 (0.25, 0.75)	0.01
Not on ART	0.64 (0.35, 1.18)	
Viral load		
≤50c/mL	1	-
>50c/mL	0.62 (0.41, 0.96)	0.03

5.5. Discussion

5.5.1. Summary of the main findings

In this chapter, I detailed the methods used to identify predictors of EIC in young people living with PHIV in the AALPHI cohort. Due to the large number of exposure variables which may be related with EIC, extensive investigations as part of stages (a) to (f) were carried out to detect any between-covariate associations, to avoid introducing co-linearity and to improve model stability. Once the variables for inclusion were established, four stages of multivariable logistic regression modelling for EIC were employed. Stage 1 to 3 models were fitted within domains, and the stage 4 model brought together variables from across the domains.

In the primary stage 4 model, four factors were found to be associated with EIC, each from a different domain. From the *a priori* domain, young people were less likely to be in care if they were of Asian/mixed ethnicity compared to being of black or white ethnicity. From the mental health domain, participants had worse EIC if they reported having ever self-harmed compared to not. From the HIV experience and management domain participants were less likely to be in care if they reported having not so good/bad adherence to ART or if they were not on ART compared to excellent/good adherence to ART. Finally from the clinical markers domain, participants had poorer EIC if they had a viral load >50c/mL compared to ≤50c/mL. The sensitivity analysis models were reassuringly similar to the primary stage 4 model, suggesting that the role of identified potential biases in affecting the findings might be small. Self-harm, adherence and viral load remained associated to in care in all three sensitivity analyses. Ethnicity remained associated with in care in the models using a higher p-value cut off (<0.1) and an alternate start time (3 months after AALPHI interview date) although it was only weakly associated to in care when the maximum time to next appointment was changed to 4 months (p=0.07). Of note, entry age was found to be associated to in care in both the sensitivity analyses using a higher cut off (p=0.004) and when the maximum time to next appointment was 4 months (p=0.001). In addition, it was only very marginally above the significance cut off in the alternate start time model (p=0.05). Investigations showed that young people age 16 and older had worse EIC in paediatric care than young people of the same age in adult or adolescent care. However, the majority of young people aged age 16-18 (1,202/1,460) and about a fifth of 19-21 years olds were still seen in paediatric care.

5.5.2. Findings in comparison to the wider literature

My analysis of exposure variables and their association with EIC was largely exploratory, and I included a large number of potential exposures. In order to facilitate a structured and thorough approach to model building, I grouped these variables into eight different domains. This allowed me to better identify the complex interplay between variables which may be associated with each other, and to prevent issues of collinearity and model instability. Two examples are described below. On initial investigation of the risk practices domain variables, the proportion of young people in care who smoked was lower than young people who did not smoke (81% vs. 89%) suggesting a possible association with EIC. A strong association was then found between ever smoked and alcohol amount (Cramer's V=0.42), with no evidence of an interaction between the two variables and when both variables were fitted in the same logistic regression model for EIC, there were very few changes to the ORs or confidence intervals for either variable. Although when fitted in a model with *a priori* variables as well as with *a priori* variables and alcohol amount, ever smoked was no longer associated with EIC. Nevertheless, ever smoked was taken ahead to the modelling stages. When adjusted for only time in a logistic regression model for EIC, ever smoked was associated with EIC (p=0.01), as expected based on previous results, this association however disappeared when the *a priori* and other risk behaviour variables were included in the model (p=0.14) and therefore ever smoked was dropped.

Based on the proportion of months in care, there was also the suggestion of a trend for CD4 count and EIC in the HIV markers domain (<200=78%, 200-350=80%, 351-499=88%, ≥500=91%). When tests for association were carried out, a strong association was found between CD4 count and viral load (Cramer's V=0.45). When CD4 count was fitted in a logistic regression model adjusted for *a priori* variables, an association with EIC was found (p=0.001), however, when viral load was also included in the model, the association between CD4 and EIC disappeared (p=0.23) suggesting that viral load explained the effect of CD4 on EIC. CD4 count was therefore not carried forward to the modelling stages.

My approach was similar to a "conceptual framework" approach used in other analyses of young people with HIV,(93,254) and proposed by Haberer and Mellins.(72) Their conceptual framework comprised of four categories: the child, caregiver(s) and family, the ART regimen, and society and culture. Harberer and Mellins (72) recommend that due to the complex challenges of long-term adherence to ART, factors within these four categories need to be taken into consideration when measuring adherence or planning adherence interventions. I

benefited from a wide range of potential exposures measured in AALPHI, far beyond the more common and rather limited range of clinical HIV factors included in many analyses. This approach is supported by my findings, in which predictors found to be associated with EIC, were from four different domains (*a priori*, mental health, HIV experience and management, and HIV markers). This suggests that similarly to adherence, a complex array of factors influence young people's EIC and therefore need to be taken into consideration both when measuring EIC and when suggesting possible ways of improving EIC.

As detailed in Chapter 3, flowcharts used in this analysis were derived from an algorithm developed by Howarth *et al* (151), in their analyses of adults with HIV in the UK. Consequently, the results from their analyses are perhaps the most directly comparable to findings from this analysis. I will therefore first compare the findings to the Howarth et al findings and then to the wider literature.

Howarth *et al* (151) applied their EIC algorithm to 44,432 patients aged 16 years or older from the UK CHIC study in the UK. In their multivariable analysis, they reported that age was associated with EIC, with lower EIC in adults aged 25-45 years (OR 0.74, 95% CI 0.59, 0.93, p=0.008) compared to adults aged >45 years. In addition, the proportion of patients EIC was lowest in the <25 age group (<25 years in care 77%, 25-45 years in care 83%, >45 years in care 87%) however, when compared to >45 year olds in multivariable analysis, only a weak association with EIC was found (<25 years OR 0.67, 95% CI 0.42, 1.06, p=0.09). Although age was not found to be associated with EIC in my primary model 4 results, an association with increasing age and worsening EIC was found in the two sensitivity analyses in which the p value for inclusion in the model was increased to <0.1 (instead of <0.05) and when the maximum time to next appointment was capped at 4 months. In addition, there was a weak association between age and EIC in the third sensitivity analysis, when an alternate start date was used (p=0.05). This is consistent with the rest of the literature.

Howarth *et al* (151), also described that while people of black African or 'unknown' ethnicity were found to have similar EIC to people of white ethnicity (black African OR 0.96, 95% CI 0.83, 1.11, p=0.55, unknown OR 0.87, 95% CI 0.73, 1.03, p=0.11, reference white ethnicity) people of 'Other ethnicity' were less likely to be in care (OR 0.79, 95% CI 0.68, 0.92, p=0.002) compared to people of white ethnicity. Patients in Howarth *et al's* 'other ethnicity' group and in my Asian/mixed ethnicity group are minorities in HIV clinics in the UK, which may create a barrier to engaging in care. People of white ethnicity are also a minority in paediatric

HIV clinics, however, white patients are not a minority in many adolescent and adult clinics, which may be why there is no association with worse EIC in this group.

Similarly to my analysis, Howarth *et al* (151) reported that ART status was associated with EIC. People who were on ART were more likely to be in care than people who were off ART (OR 1.44, 95% CI 1.15, 1.81, p=0.022). Howarth *et al* also found that patients with lower nadir CD4 counts were less likely to be in care (nadir CD4 count <200c/µL: OR 0.55, 95% CI 0.41, 0.74 , 200-349 c/µL: OR 0.37, 95% CI 0.28, 0.50, reference ≥350 c/µL, p=0.0001).(151) In my analysis, nadir CD4 was not associated with EIC, and CD4 count was dropped in the early modelling stages as there was evidence that viral load explained the effect of CD4 on EIC. However, Howarth *et al* did not include viral load in their model. Howarth *et al* also described an association between three additional variables and EIC that were not included in my analysis because they are either not relevant to young people with PHIV, (route of HIV acquisition and time since entry in the UK CHIC study) or to this analysis (calendar time which was not relevant as this analysis included one year follow-up which only spanned two calendar years).

In addition to my and the Howarth *et al* analysis, other studies have also found an association between ethnicity and EIC, although there were varying trends across the studies. In Gray et al's (162) population-based analysis of young people with PHIV across the USA (n=11,747), Hispanics/Latinos were more likely to be in care than people of white ethnicity (unadjusted, prevalence ratio (PR) 1.1, 95% CI 1.1, 1.2). In contrast, in a population-based cohort analysis of young people aged 13-24 years with HIV in Florida (n=2,872), Gebrezgi *et al* (161) reported that after adjusting for sociodemographic and neighbourhood factors, Hispanics were less likely to be in care than people of non-Hispanic white ethnicity (PR 0.88, 95% CI 0.81, 0.95). However, only 28% of the young people in Gebrezgi *et al*'s analysis had perinatal HIV as their mode of HIV acquisition. Additionally the differences between the social and cultural contexts of young people of Latino/Hispanic ethnicity in the USA and Asian/mixed ethnicity in the UK may limit comparability.

Another of the variables which was associated with EIC in my analysis was self-harm. Young people who reported ever having self-harmed were less likely to be in care than young people who did not report a history of self-harm. None of the other EIC papers included self-harm in their analyses so it is not possible to compare my finding to other studies. In my analysis, 12% of participants reported a history of self-harm, using computer assisted self interviewing to encourage honest reporting. This prevalence is similar to a large (n=6,477)

analysis of responses to the Adult Psychiatric Morbidity Survey of adults ages 16-74 in the UK general population from 2014.(255) In that Survey, the prevalence of self-harm was highest at 13.7% in persons aged 16-24 compared to all the other age groups. However, using self-harm in a clinical setting to identify young people at risk of disengagement may be problematic because of the secrecy around self-harm. In Copelyn *et al*'s (211) analysis of self-harm from the AALPHI cohort, only 14% of young people reported seeking help following an incident of self-harm. Although young people in AALPHI were not asked whether they discussed their self-harm with clinical staff, hiding self-harm from health care professionals is consistent with the literature.(142,211,255)

Based on the relatively high prevalence of self-harm found in AALPHI population, all clinics seeing young people could consider routinely discussing self-harm with their patients. However, due to the hidden nature of self-harm, clinics routinely assessing young people for self-esteem or depression could perhaps use these as a proxy for risk of disengagement in care or introduce simple assessment tools in clinics to measure them. Although none of the other mental health variables were found to be associated with EIC in my analysis even when self-harm was not in the model, studies have described associations between other mental health exposures and self-harm as an outcome variable. In Copelyn *et al* (211) , in analysis from the AALPHI cohort, self-esteem was strongly associated with self-harm, with each one point increase in the Rosenberg Self-Esteem Scale (higher score=better self-esteem) being associated with a 10% reduction in the odds of self-harm (95% CI 0.8, 0.9, p<0.001). In the Avon Longitudinal Study of Parents and Children (ALSPAC) ongoing population based study, investigators reported that concurrent depression was associated with a much increased risk of self-harm (OR 5.43, 95% CI 4.60, 6.40, p=<0.001).(142)

Also found to be associated with EIC in my analysis was self-assessed adherence. Young people with not so good/bad adherence or who were off ART were less likely to be engaged in care than people with excellent/good adherence. Most other studies of EIC only included routinely collected sociodemographic and clinical factors in their analysis and therefore no analysis of the effect of adherence on EIC was conducted. Adherence self-assessment may be useful in the clinical setting as it is ostensibly very easy to assess and so offers a simple way of identifying those at risk of disengaging from care. However, it is important that discussions about adherence are not limited to just simply authoritatively reinforcing message about the importance of taking ART.(104,256,257) Conversations around ART

adherence need to be pre-emptive rather than reactive and it's essential that both the social and structural complexities of taking long-term ART are acknowledged.(104,258)

Young people in my analysis with an unsuppressed viral load were less likely to be in care than young people with suppressed viral load. Other studies have similarly described an association between EIC and viral load. Pantelic *et al* (158) in their study of 979 young people (79% PHIV) in the Eastern Cape, South Africa reported that EIC was associated with lower odds of viral failure (VL>1000c/mL) (OR 0.37, 95%CI 0.22, 0.61). What it is not possible to tell from either the Pantelic *et al* study, or my analysis, is whether EIC improves viral load or whether having a viral load ≤50c/mL leads to improved EIC. It does mean however, that people who have a viral load >50c/mL may be more likely to disengage in the future; so these young people would be a good group for which additional support could be offered.

In addition to Howarth *et al*,(151) two other studies identified age as a predictor of EIC. Gray *et al* (162) in the USA, reported that young people living with PHIV aged 13-17 years had a higher EIC that 18-25 year olds (PR 1.2, 95% CI 1.1, 1.2) although this finding was from a univariable model. Similarly, Gebrezgi *et al* (161) reported that 13-17 year olds had better EIC than 18-20 year olds (PR 0.85, 95% CI 0.78, 0.92) and 21-24 year olds (PR 0.74, 95% CI 0.68, 0.80) in a multivariable model. This is similar to the trend shown in this analysis with EIC declining as young people got older.

In this analysis, young people who attended adolescent and GUM or adult clinics were more likely to be in care than young people who attended paediatric clinics. Clinic structures such as having appointments outside school hours (159,164) and adolescent friendly clinic environments (164) have been reported to be associated with improved EIC in other studies. Lee *et al* (164) assessed the impact of youth friendliness on 680 young people (35% PHIV, 65% BHIV) aged 15-24 years attending 15 clinics across the USA. After adjusting for demographic and clinical factors, they reported that three youth friendly structures were found to be associated with EIC: youth friendly space (OR 2.47, 95% CI 1.11, 5.52); evening clinic hours (OR 1.94, 95% CI 1.13, 3.33); and providers with adolescent training (OR 1.98, 95%CI 1.01, 3.86).

Travel time to clinic was also found to be associated to EIC with young people who had to travel further having worse EIC. Similarly, a study 771 adults aged ≥18 years receiving HIV care in Chicago, USA, reported that median travel time to care was 15.9 [IQR 10, 23] versus. 17 [IQR 12, 25] minutes for those not retained in care compared to those who were

(p=0.04).(218) The final variable found to be associated to EIC in the analysis was language spoken at home. Young people who lived in homes where only another language apart from English was spoken were less likely to be in care than young people who lived in a household that spoke English, or English and another language. No other studies reported this finding.

It is important to note that relatively few studies have looked at EIC in young people living with PHIV. Additionally the method of measuring EIC varies widely in the literature, limiting direct comparisons. In general, the other analyses included most variables from the *a priori* and HIV markers domains while variables from the sociodemographic, mental health, cognition, clinic, and HIV experience and management domains were largely absent.

5.5.3. Limitations

My analysis has several limitations and possible sources of biases that could affect the overall findings. The limitations discussed here include those that are specific to the methods used in this chapter, as well those discussed in previous chapters focusing on how they could affect my modelling.

In this analysis, the EIC outcome was measured across one year for each participant, whilst the exposure variables were measured at baseline (AALPHI interview). This approach was taken to avoid time dependent confounding, however variables including baseline viral load and adherence may have been influenced by previous EIC, thus meaning it is still not straightforward to disentangle predictors and mediators

For this analysis, variables were considered within domains and much of the selection took place prior to considering the full multivariable model including variables across these domains. Arguably some exposure variables could have been included in other domains, for example ever excluded could have been included in the risk behaviours domain rather than the sociodemographic domain. Thus between-covariate associations may have been missed, and variables might have been erroneously dropped in the modelling stages. Additionally, due to the large number of related variables, sometimes decisions were made about which variable to take forward and which to drop. It is possible that errors were made in these decisions.

As detailed in Chapter 3, a number of participants apparently attended early for their appointments, particularly where the next appointment was predicted 6 months later. This was a possible example of misclassification of time to next appointment due to the classifications in the flowcharts not being representative of countrywide practice. This

misclassification would then result in young people being classified as in care, when they in fact were out of care. This could result in a dilution of the effect of predictors or result in predictors being missed entirely. Reassuringly, when the time to next appointment was capped at 4 months (instead of 6 months) in a sensitivity analysis, the stage 4 model results were very similar to the primary stage 4 model.

A number of the additional biases resulting in a misclassification of the outcome discussed in Chapter 3 could also lead to a dilution in the strength of effect or a missed predictor. Examples include limitations resulting from the use of proxy markers; people may be attending clinic but not having a blood test or measurement, or dates might be inaccurately recorded or missed on the CHIPS forms. Additionally, serious events such as a CDC events, which would require much shorter time to next appointment schedules, may not have been reported. Again, reassuringly, results from the sensitivity analysis provides some confidence in my findings. When a more lenient $p < 0.1$ cut off was assessed (as opposed to p value <0.05) the stage 4 model was very similar to the primary stage 4 model, with only two new exposure variables becoming associated with EIC.

Another possible cause of dilution was the choice of the AALPHI interview date as the start date (baseline). It was chosen because this is the time point when the exposure measurements were taken, however 43% of participants had a clinic visit on the day of their AALPHI appointment, which could also dilute the strength of associations. For example, if baseline self-esteem was associated with poorer EIC, then no effect of low self-esteem would be apparent in participants who had a clinic visit at interview until their next visit was due (meaning they would be in care on average for 4 months despite low self-esteem). In the remaining 57% who did not have a clinic visit at baseline, a more immediate drop out in participants who had low self-esteem might be seen. If the effect of self-esteem was marginal, it might be missed. Thus a sensitivity analysis was designed to assess this, utilising a start date 3 months after the original start date (AALPHI interview). The findings in the sensitivity analysis were very similar to the primary stage 4 model, suggesting that the start date is unlikely to have caused too much dilution to the strength of association of exposure variables with EIC.

As discussed in Chapter 4, a number of biases related to the AALPHI interview may affect the EIC model. Selection of appropriate measurement tools is complicated, due to the lack of tools specifically designed and validated in young people and due to the compromises required to ensure the AALPHI interview was not too lengthy for the participants. In addition,

issues such as social desirability or misinterpretation/ misunderstanding of question can impact the answers given. For example, if the depression tool did not effectively identify depression in young people, or many young people reported that they took their medication when in fact they did not, both of these circumstances would affect the exposure variable. If, as a result of either of these problems, the measures only pick up the most extreme values, this might overestimate the strength of the association between the exposure and EIC. Conversely, if the measurements more randomly identify young people with true problems with adherence or depression, the strength of the exposure would be diluted.

Finally, if patients who were excluded from this analysis due to missing CHIPS data were not missing at random, then this would introduce selection bias. This bias could potentially limit the generalisability of the model, with the findings only being applicable to young people with CHIPS data, and not more broadly generalisable.

5.5.4. Concluding remarks

In this analysis, I was able to investigate the association between a broad range of exposure variables and EIC in young people living with PHIV. Rigorous variable investigation and four stages of modelling were performed to reduce collinearity and strengthen the stability of the final model. This is the first analysis that I am aware of that examines predictors of EIC in young people living with PHIV in the UK, and the first multi-clinic analysis in Europe. Four main predictors of EIC were identified, all of which can be considered by clinics to identify young people most at need of support in attending clinic appointments.

5.5.5. Key points from this chapter

- Rigorous variable investigation was performed across eight domains
- Four stages of modelling were carried out to identify predictors of EIC
- In the primary stage 4 final model, worse EIC was associated with Asian/mixed ethnicity, self-harm, not good/bad adherence and viral load >50c/mL
- Sensitivity analyses findings were similar to the primary stage 4 final model but also suggest there may be effects of age, travel time to clinic, language spoken at home and type of clinic attended.

Chapter 6. Exploring young people's perspectives on the predictors of engagement in care

6.1. Introduction

It is crucial to include young people in health care research about issues that affect their care for a number of reasons. Firstly, to make sure any recommendations about health care provision are patient centred, participatory work is essential to understand how young people feel about their health care.(259) Any recommendations made about health care delivery runs the risk of being disconnected from young people's realities if they are not involved in the research process.(89,259,260) Additionally, it is imperative for young people to be included in health care research to raise their profile within the health care setting and with decision makers.(260) Where meaningful youth participation occurs, it can be hugely beneficial for research, health care practice and policy and for young people themselves.(261)

In order to understand young people's experiences of, and engagement in, health care, I wanted to gain their perspectives on this research to help interpret and contextualise the quantitative findings. This would then help to better understand how to support optimum EIC for this group.(262) Importantly for this project, I hypothesised that EIC was related more to the psychosocial rather than clinical aspects of living with HIV. Therefore, experiential accounts of young people living with PHIV gathered via qualitative data collection methods were a pertinent component of understanding the psychosocial dimensions of EIC.

In this chapter, I present findings from focus groups discussions with young people with PHIV. There were two main topics. The first topic was the use of clinical markers as a proxy for clinic visit attendance in the flowcharts. I explored with young people their reasons for clinic visits and regularity of tests and measurements to analyse the strengths and limitations of using proxy markers in the flowcharts. The second topic was the exposure variables found to be associated with EIC. I presented and discussed these with young people to elucidate if the predictors of EIC found in the quantitative analysis resonated with their experiences as patients. This helped me contextualise the overall findings and gain a deeper understanding of the nuances of the factors they face when engaging in HIV care.

6.2. Objective

- To take the results from the quantitative analyses, and explore them through focus group discussions with young people with PHIV
- To assess whether the quantitative results of this study resonated with young peoples' own experiences and to enhance our understanding of them.

6.3. Methods

I chose focus groups discussions to explore the quantitative findings. The advantage of focus group discussions over other qualitative methods such as interviews is the social interaction and communication between the participants (263) which helps interrogate the quantitative data. I specifically chose focus groups as they retained the potential to help increase the group interaction around the otherwise possibly abstract topics of EIC. For example, where people in the group have different experiences or views, the subsequent debate can lead to a much more detailed and reflective discussion in a way that may not occur in individual interviews. This is especially useful when exploring sensitive issues, such as barriers to care or non-attendance. Although social interaction may inhibit some discussions, hearing other people voice their concerns and experiences can also help participants to discuss their stories more freely, moving beyond socially acceptable answers.(264)

The benefits of the focus group may be all the more pertinent when working with young people. In a study into communication among children with HIV in Uganda, Kajubi et al (265) found that the hierarchical nature of adult-child and doctor-adult-child relationships resulted in children being much less vocal in interviews where adults were present. In contrast, children communicated freely and were very interactive when they attended group activities with other children and young people living with HIV.

6.3.1. Participants

All young people living with PHIV were eligible to be involved in the focus groups as long as they were aged 16-26 years and were aware of their HIV status. Being an AALPHI participant was not an eligibility criterion. However, the age range of 16-26 was chosen to be able to include young people who may have taken part in AALPHI (the age range for AALPHI was 13-21 years but the focus groups were carried out five years after the baseline AALPHI interviews). Recruitment of focus group participants was facilitated by voluntary sector staff at two different voluntary organisations working with young people living with PHIV.

Voluntary sector staff were requested to purposively select participants to include different sexes and ages and to try and include people who had a variety of experiences in attending clinic (e.g. consistent attenders, irregular attenders, lost to follow-up) based on their knowledge (if any) of young people's attendance in clinic.

Of the participants who were approached by voluntary sector staff, two young people who initially agreed to take part did not participate. One young person who was supposed to attend focus group discussion 1 (FGD1) was ill on the day and a second young person who was supposed to attend the voluntary sector support group was unable to attend on the night. These people are therefore not included in Table 6.1. All young people were given £20 vouchers for taking part.

Table 6.1 shows the demographic characteristics of the participants. In total, three focus groups were carried out with 16 participants taking part overall. I had intended to carry out a fourth focus group but this was prevented by the national COVID-19 related lockdown in March 2020. Focus Group Discussion 1 (FGD1) had six participants, of whom half were female. The median age of the group was 20 years (min 18, max 21 years); there were four participants of black ethnic background and two of white ethnic background. The participants lived across the UK and Ireland. In FGD2, there were five male participants. This was the oldest group with a median age of 23 years (min 18, max 21 years). All the participants were of black ethnicity and lived in a city in the UK. In FGD3, there were also five participants, three of whom were female. This was the youngest group with a median age of 16 years (min 16, max 19 years). Four participants were of black ethnicity and one was of mixed back and white ethnicity and, as with FGD1, the participants were from across the UK and Ireland. Overall, the median age of the participants was 20 years (min 16, max 25 years).

Table 6.1: Characteristics of participants in the focus group discussions (FGD)

Demographics	FGD (number)			Total (n=16)
	FGD1 (n=6)	FGD2 (n=5)	FGD3 (n=5)	
Male sex	3	5	3	11
Median age (min, max)	20 (18-21)	23 (18-25)	16 (16-19)	20 (16-25)
Ethnicity				
Black	4	5	4	13
White	2	0	0	2
Mixed	0	0	1	1
Geographic region of participants	Across UK	Same UK city	Across UK & Ireland	-

FGD1 included a group of participants who had previously supported other young people living with PHIV, and were peer support workers or team leaders at events run by voluntary sectors organisations. Through their volunteering activities, they had spent a considerable amount of time as a group and were quite familiar with each other. FGD2 comprised of young men who usually attended the same support group. The voluntary sector staff informed me that the participants in this second group all knew each other but the voluntary sector worker did not specifically identify them as friends. FGD3 included new members of a group being brought together to work on an HIV project. When the focus group was carried out, it was only the second time they had met as a group.

6.3.2. Confidentiality and anonymity

At the start of each session, I informed all participants taking part in the focus group discussions that it is not possible to control what information other participants in the focus groups might share outside of a focus group because of the group nature of the discussion. I did ask the young people to treat each other respectfully and to respect each others privacy, but advised participants both verbally and in the consent forms not to disclose anything they would not want to be shared outside the group. The Patient Information Sheet (Appendix G) included a section that explained the processes used to protect anonymity and confidentiality.

I reassured participants that information discussed in the groups would not be fed back to the their HIV clinics. I informed participants that the only reason information would be passed on to clinic or voluntary sector staff would be at the request of the participant, or if a participant under 18 years reported something that made me worried about the participant safety or the safety of someone else under 18 years of age.

An unexected problem arose in the third FGD. I had been pre-warned that two interpreters would be present during the focus group to interpret for a participant with profound hearing loss. However, during my introduction to the discussion, an additional voluntary sector worker who organised the groups, came in the room and sat down. Unfortunately, I could not find an appropriate time to ask this person to leave because I was already facilitating the group and therefore they remained in the room for the entirety of the discussion.

6.3.3. Study setting

I conducted all three focus group discussions in England between July and November 2019. I carried out the focus groups at locations where a dedicated event or group activity was

taking place specifically for young people with HIV. I arranged FGD1 and FGD3 with the voluntary sector staff so that they piggybacked existing residential events where participants from across the UK were staying for several nights. FGD2 was held at a voluntary sector organisation on the evening that their routine support group was held.

The settings of the focus groups provided several benefits. Firstly, by carrying out the groups within organised HIV-related events and voluntary organisations, it was assured that participants' HIV status was already known to the other participants. Secondly, pre-existing groups are a useful forum to explore 'naturally occurring' topics within the social context.(266) Furthermore, safeguards were available because voluntary sector staff were well placed to provide support if any inadvertent distress was caused by the topics discussed. Finally, in all three instances, participants did not have to go out of their way to attend the session and were familiar with their surroundings by the time the focus group was carried out.

6.3.4. Focus group discussion facilitation and data collected

I facilitated all three focus groups, with the aid of a session plan I developed for use in the focus group discussions (abbreviated version shown in Appendix H). It included an overview of the aims of each section, resources required, content to include as well as possible prompts and timings. I paid attention to the order of topics to be discussed in the focus group to encourage people to feel relaxed in the groups, beginning with less sensitive issues. I also used flip charts with simple tables and spider grams to facilitate reflection and further exploration of specific messages. During each section, I wrote the main points raised by the participants on a flip chart, and read these back to the group to make sure the participants had accurately understood main points.

I developed and used a PowerPoint presentation to explain the quantitative analysis. Slides were largely pictorial to help explain examples in an understandable, lay way. After a brief introduction about EIC, I carried out a warm-up game in FGD2 and FGD3 to help people feel comfortable in the group. In FGD1, the participants had already spent all week working together as a group so I did not think this warm-up activity was necessary.

After the warm up, I gave a very brief overview of what is known about EIC in young people with PHIV. Then I carried out an exercise to familiarise young people with the idea of factors that affect EIC. I gave young people five minutes to quickly review a list of the variables

included in the quantitative analysis and then asked them to identify five factors from their experience that they thought were associated with EIC.

Next, I gave a brief explanation of the flowcharts (using PowerPoint) to the young people to provide them with enough information to start the reflection and discussion about the quantitative analysis. To help me understand how much the participants knew about what factors their clinic doctors use to determine the time to their next clinic appointment, I facilitated an initial discussion in each focus group about what reasons clinic staff give to explain when their next appointment should be. I presented a list of the clinical measurements that I used as proxy markers for clinic visits in the flowcharts. I then explored these with participants to see whether these measurements were collected at every appointment and if there were reasons that they attended clinic appointments that might not be captured by the proxy markers used.

Finally, I presented predictors of EIC from the quantitative analysis to gather participants' views about whether the findings concurred with their own perceptions of factors that affect attendance in clinic. I introduced and defined each variable found to be associated with EIC in the quantitative analysis (ethnicity, adherence, viral load and self-harm), though the discussion did not focus on ethnicity. Only one young person from the three focus groups was of mixed ethnicity and none of Asian ethnicity, and it did not feel appropriate to discuss this finding. I presented adherence and viral loads as separate entities but together due to the direct biological relationship between taking medication and viral load results. I presented adherence and viral load first so that participants could become familiar with the format of the focus group before I addressed the more sensitive topic of self-harm.

6.3.5. Audio recording and transcription

Focus groups lasted one to two hours and were audio recorded on two devices. I wrote field notes at the end of each focus group, with reflections on the interactions of the group and the topics discussed (267). I uploaded recordings to a computer the same day that I conducted the focus group and the recordings were then deleted from the recording devices.

I transcribed the focus groups verbatim to gain as much familiarity with the data as possible after the focus group, also to allow iterative data analysis from the start and so that I could explore emerging ideas and questions in subsequent focus group discussions. To protect the anonymity of participants, I removed personal identifiers from transcripts and gave all participants a study number (1-16) which I then used in combination with their focus group

number for all subsequent writing and documentation. I removed all locations, clinics and voluntary sector group names.

6.3.6. Analysis

I used both inductive and deductive approaches to thematically synthesise the data (263). Inductive analysis emerges from the data and deductive analysis starts from an *a priori* set of concepts or frameworks that is applied to the data.(268) I used inductive analysis in the process of coding the original data and in creating the themes. However, I did have some awareness of the literature before I coded the data and so I recognised some familiar patterns emerging from the coded data based on prior knowledge. I performed line to line coding to try and stay close to the data in bottom up rather than top down analysis. All analysis was carried out using NVIVO 12 software.(269)

I conducted two phases of coding. First, I coded data from the individual focus groups using discrete codes and organised the codes under similar descriptive themes (for example 'dislike of medicine', 'invisibility of HIV' and 'unquestioning attendance').(270,271) Then I reviewed, refined and compared all the codes within each focus groups and then across focus groups.(271) Next I explored relationships between codes and grouped individual codes to make more meaningful themes. I continually reviewed non-coded data to see if they challenged or fitted into existing themes or to see if new themes were emerging.

I wrote analytical memos throughout the analysis process to highlight key content and concepts and emerging ideas, which I shared with my supervisors for input and discussion alongside anonymised and coded focus group transcripts. Analysis continued throughout the process of writing up the findings as questions about the data and relationships gained more clarity when being explained in the text.

6.4. Ethical considerations

6.4.1. Consent

Voluntary sector staff who were familiar with the participants made decisions about who could be contacted to protect participants who may have been too psychologically vulnerable to take part. I obtained written consent from all participants at the beginning of each focus group. I read though the consent form (Appendix I) with the group and then gave them as much time as they needed to read through again and ask questions. The consent taking process took around 10-15 minutes in each group. I informed all participants that they

were free to withdraw their consent to participate in the focus group discussions at any time and for any reason, without it affecting their clinical treatment or involvement in the voluntary organisations. I encouraged participants that if they found any of the subjects in the focus group upsetting, they should approach staff or me from the voluntary organisation after the group. I informed all participants at the start of the session that the focus group would be audio recorded.

6.4.2. Anonymisation of data

Consent forms were scanned and stored in the UCL Data Safe Haven. Paper consent forms were shredded and emails of the scanned consent forms were deleted from the email inbox and deleted folder. Participant names, demographic details and a participant number were also stored in the Data Safe Haven separately from all study data. Only participant numbers were used in the transcripts of the focus group discussions. Anonymised transcripts were stored in a secure location on the LSHTM server.

6.5. Findings

There are three sets of findings from the focus group study. I present, firstly, a summary of participants' responses to the questions posed about the flowcharts and EIC predictors (adherence, viral load and self-harm). Secondly, I discuss the two main themes that emerged inductively from the young peoples' discussion about EIC: self-management and shared decision making, and responsibility and blame.

6.5.1. Participants feedback and response on the proxy markers and predictors of EIC

On viewing the model in the presentation at the start of the focus group, participants first commented on the proxy markers and discussed whether these clinical factors accurately reflected all of the reasons they attended clinic or whether there were factors that had not been accounted for.

I then presented and discussed the three factors that showed evidence of an association with EIC in the quantitative analysis (adherence self-assessment, viral load and self-harm).

6.5.1.1. Feedback on the proxy markers

All participants in the three focus groups agreed that the markers being used (viral load, CD4 count, weight, height, ART changes) were appropriate proxies for a clinic visit because at least one of these clinical measurements was taken at most appointments.

However, the participants also raised several additional reasons for attending clinic that were not included in the list of proxy markers. Participants in all three focus groups had been asked to attend clinic for mental health or psychological reasons, as one young man explained here:

> *'I remember I had a rough patch and they were like 'we want to keep an eye on you for a while'. Which was also linked to viral load and just keeping, making sure it didn't go too high and my CD4 didn't drop. But a lot of it was mental health and to maintain stability.' (male, 18 years old, FGD1-participant 6 (P6))*

Participants also mentioned factors other than those included as proxies for clinic visits, such as wanting to obtain advice on issues such as disclosure of HIV status, help with medical and school forms, and sexual health check-ups.

6.5.1.2. Adherence and viral load

Participants confirmed the face validity of the finding that young people with better adherence and a supressed viral load are more likely to come to attend clinic: *'Because if they are undetected it means they are OK with what they are doing. If they have an appointment, they will go for it. They know how to take their medicines and they do it,'* explained one participant (male, 21 years old, FGD2-P7).

Participants often reported that the combination of having an undetectable viral load, taking ART and attending clinic meant that the young person was in a '*good place'* in terms of their HIV acceptance and management.

Conversely, several participants admitted that if they thought their viral load might be detectable due to recent problems taking their medication, they would avoid clinic. *'My viral load was awful so I just didn't go clinic'*, explained one young man (male, 20 years old, FGD1-P4), while another participant imagined other young people would do the same:

> *'And I was supposed to go to clinic but I didn't because I didn't need medication and like I didn't want to go… because I was thinking my viral load is bad, and what if my body is all messed up. Because I felt fine, but...' (female, 20 years old, FGD1-P3)*

Another male participant went as far as asking: *'what's the point of coming to hospital if you are not drinking medicines?*' (male, 18 years old, FGD1-P6). This suggests that young people's concerns about how their adherence might show up in their viral load shape their decisions to engage in care. For example, one young man used an analogy to explain why young people might not attend clinic if they had forgotten to take their medication:

> *'It's a bit like you know when you spent a lot of money and then you don't want to look at your bank account. It's a bit like that. So you know you haven't done something that you wanted to so you kind of don't want to find out the results or check your account basically.' (male, 25 years old, FGD2- P9)*

By contrast, three of the 16 focus group participants were surprised at the finding that better adherence and having a supressed viral load was associated with better EIC, since, for example, a low viral load might signal better health and less reason to attend clinic.

6.5.1.3. Self-harm

The third finding from the quantitative analysis was that young people who self-harm are less likely to be EIC. I presented to focus group participants a definition of self-harm as '*hurting yourself on purpose in any way for example by taking an overdose of pills or by cutting yourself'.* Focus group participants seemed to understand self-harm as an indication of deeper psychological or psychosocial suffering that may prevent people from being able to seek or engage in care. One male participant explained:

> *'..a lot of people that do it like they try to keep it a secret and they don't want anyone to find out. So, yeah, I think one reason is that they may not go to clinic is because they might get found out and have to talk about it.' (male, 25 years old, FGD2- P9)*

Participants also voiced concerns about the consequences of clinic staff finding out that they self-harmed and a subsequent lack of control over both their personal information and the situation in general. One participant expressed concern about their parents being involved: *'You don't want them to know because they might tell your parents who might not know,'* explained one young woman (female, 16 years old, FGD3- P16). Another young woman talked about an influx of additional support from other services and clinic staff:

> *'Also the fear of consequence. Like if I self-harm or do this, what is going to happen? Because like personally, and I don't know if other people feel the same, they haven't said anything because they are like what if I get taken away or put in the hospital and*

I don't want to be put in the hospital, I don't have time to be put in the hospital.' (male, 20 years old, FGD1- P4)

Possible fear about being forcibly detained in hospital if they disclosed their self-harm was relayed by one participant:

'I feel like maybe if they do *go to the doctor, like what he says, when you like take drugs, and they take you to like rehab. They might take them somewhere and you might not want them to do that.' (male, 18* years old*, FGD3- P13*)

For one female participant who disclosed a history of self-harm in the focus group, this fear of the clinic staff members' reaction meant she continued to attend clinic so as not to arouse concern, but hid her self-harm:

'For me I still went to the doctor, to my appointments, I knew what I was doing was wrong but I still wanted to maintain the appointments maintaining like everything was OK. I feel like if I told them, they would want to help, and they will help in the wrong way. So I just go to maintain it.' (female, 21 years old*, FGD1-P2*)

Participants postulated a further relationship between the quantitative results, suggesting that non-attendance and non-adherence could be forms of self-harm in themselves. One young male participant seemed to suggest a period of time when he stopped his medicines was actually suicidal ideation because he knew it would eventually make him ill. Another participant explained:

'For some people, they think if the meds are keeping them alive then if they stop taking them they won't stay alive.' (male, 25 years old, FGD2-P9)

'So they feel they want to die?' (facilitator)

'Yeah, they are suicidal and that could be a type of self-harm.' (male, 25 years old, FGD2-P9)

This, however, was not a universally held view. For example, one young woman who talked a lot about her problems attending clinic and taking ART, did not identify with these issues as a form of self-harm.

6.5.2. Self-management and shared decision making

The previous findings were based specifically on participant responses to questions and prompts about the EIC flowcharts and quantitative findings. The next two themes were based on participant's experiences and emerged inductively from the discussions. The first theme to emerge from the analysis based on young people's discussions in the focus group was about self-management and shared decision making. The theme had three components: influence of age on EIC, communication and involvement in decision making and control and choice in attending clinic appointments.

6.5.2.1. Influence of age on engagement in care

During the focus groups, participants initiated a discussion about age as a factor in EIC and, specifically, how personal responsibility to engage in care and attend clinic increased with age. Participants had conflicting views however, on whether this increased responsibility made attending appointments harder or easier. One participant explained that '*once you reached puberty, and you are living your life, then you would maybe go to clinic more'* (female, 20 years old, FGD1-P3), while another highlighted the challenges of motivation associated with young adulthood: *'Because when you are a kid, your parents or guardian take you. So you just go. But when you are like 18 it is on you to go and that is a lot of effort to drag yourself out of bed'* (male, 20 years old, FGD1-P4).

Participants also had contrasting experiences of support provided by their parents/carers to attend clinic as younger children, which may have subsequently shaped their later EIC:

> *'I say for me when I was younger I probably messed up a lot more than when I got older. Because when I was older, I was a lot more independent and more in charge of my medication and my appointments. Whereas before, it was kind of like through my mum. And my mum, my mum is a busy woman (laughter).' (male, 23 years old, FGD2-P10)*

> *So my experiences was the opposite. When I was young, my grandparents helped me. So I was taking medicines twice a day and I was always taking it on time every day because they always reminded me. Then as I got older, because it was my responsibility I kept forgetting it a lot. (male, 21 years old, FGD2-P7)*

A participant also highlighted the conflict young people face between attendance in clinic and attendance at school and how this becomes more challenging with age:

When you are like 16+ you have actually got to attend school. Before that, you can just go out of school for a day and it's not a problem. But when you have got A'levels and GCSEs it's not like you can take a day off and its fine, because you can't. (male, 20 years old, FGD1-P4)

6.5.2.2. Communication and involvement in decision making

During the discussions about the information participants were given by clinical staff regarding the rationale for the time interval to their next appointment, a broader conversation emerged about the benefits of being involved in decision making about follow-up appointments, as well as the consequences of not being involved.

A number of the participants reported that the staff at the clinic actively updated them on their results and or health status and made clear links between their health status and the amount of time to their next appointment. As one young man relayed, *'they show me a graph and say that is where your CD4 count is and your viral load and that's when we need to see you'* (male, 25 years old, FGD2-P9). The participants seem to see the clear link between health status and timing of subsequent appointments. One participant explained:

'Aahh yeah. It just depends, it really depends on what you are doing next. For example, so if I am changing my meds they say they want you to come back, you know, to see like if you have any side effects. And one time when I was very ill, very ill, they said I needed to come back to see if you are doing well and sometimes they just want to check your blood test and check everything is going well.' (male, 18 years old, FGD1-P6)

In FGD2, which was the oldest group, all of the participants described being well informed by clinic staff about their health status. Furthermore, they were also involved in the decision of when their next appointment should be so that clinic appointments could fit into participants' lives:

'Like every 4 to 6 months. They usually give me a choice of when I am seen. So like when I usually go they say do you want to be seen this month or next month? And then basically depending on what I have got planned.' (male, 25 years old, FGD2-P9)'I feel like for me, if I am undetectable (viral load <50 c/mL), it's just like usually just say come in whenever my meds start finishing, but because I have been at University for 3 or 4 years, you just try to fit in when I am back from holidays basically. And it's just

worked out fine. Then if I do need to come in earlier, they will text me and say based on your blood results can you come back in.' (male, 23 years old, FGD2-P10)

One young person also talked about being offered the choice of being seen earlier, even if his health did not require it, which may be an intimation of the wider supportive role clinics can provide in addition to clinical monitoring.

In contrast, some of the participants came away from their clinic appointment feeling unclear about the state their health status. One young person described times in their past when they used the length of time to their next appointment as an indicator to try and deduce their health status:

'When it is less time your brain kind of works it out naturally, oh OK I guess I need to do this sooner. But when it is more time in-between, it is like 6 months, it's like oh OK, why so long?' (male, 20 years old, FGD1-P4).

This young person described how this lack of information led to anxiety about their health status:

'I had a weird period of time when I was there every month. So I just got into the routine but I was like I don't know why I am showing up every month. And they jumped to four months and I was like OK I guess it was every four months now. And then recently, I went to a new clinic and they said come back in a month and I had this deep fear something was wrong again but they were like no we just need to see if you are on the system properly and I was like that's the first time I was given a reason'. (male, 20 years old, FGD1-P4)

6.5.2.3. Choice and control in attending clinic appointments

Participants presented differing positions as to the amount of control they had concerning their health and attendance in clinic. Some participants appeared able to exercise some sense of control and choice in their health care whereas with some other participants there seemed to be less chance to be involved in decision making.

A number of participants expressed a desire to attend clinic to stay informed about their health status, such as this participant: *'Because there is a reason why I missed them (ART medication) and I would go there and see if everything is alright. Say I missed a week (of ART), I wanna go there and go and see if I am OK in my bloods.'* (male, 18 years old, FGD3-P13).

Another participant voiced how attending clinic helped him re-gain control after a period of not taking medicines:

> *'To be able to be like I have grabbed my life and I have taken control and I know that a few other people feel the same way with their viral load. Because if they can get it to undetectable then they know what they are doing OK.' (male, 20 years old, FGD1-P4)*

In stark contrast, one participant explicitly says that attending clinic was not a choice. They attend because it was a better option than being chased by clinic staff. A third group of young people expressed their attendance in clinic with resignation – something they have always done and know that they need to carry on doing. It was hard to ascertain in the focus group if these participants, by attending clinic, were passively behaving as expected, or if they had more simply accepted the role clinic played in their lives:

> *'I have never had a time when I have been stressed and don't take my meds. I go to clinic because I just go to hospital. I have never had times where stuff is going on and I don't want to go to clinic…So I am going to clinic, I move to adult clinic, and I just go there and I never miss my meds. So yeah.' (male, 18 years old, FGD1-P1)*

> *'Me like I feel like what he say. It's the same thing. I just go to my clinic like every appointment and they pay for my travel and everything is just sorted. So I like just go and they are just like nice people.' (male, 18 years old, FGD1-P6)*

6.5.3. Responsibility and blame

The second theme that emerged from the data was that of responsibility and blame. There were a number of ways young people expressed feeling the burden of responsibility for their HIV: judgement, pressure and threats from others, responsibility for others, and internalisation of responsibility.

6.5.3.1. Judgement, pressure and threats from others

Being 'told off' and feeling judged by health care staff was a common theme in focus group discussions. Participants explained that fear of scolding was a possible reason for avoiding clinic if they had missed doses of their medication. Participants did not anticipate understanding from clinic staff about their adherence problems, as one participant explained: *'Because by the time you go to the hospital, they are just going to say the same thing like 'Take your meds' so why should I go if they are just going to say the same thing.*'

(male, 18 years old, FGD1-P6). Participants expressed that there was a: 'pressure to take your medication' (female, 21 years old, FGD1-P2) and said: '*You don't want to be judged if you are doing that (missing medication)'* (female, 20 years old, FGD1-P3).

Participants also said clinical staff tried to encourage them to take their medication by highlighting the risks associated with missing medication:

> *'The nurses are like, 'If you don't take your medication you're are going to die the next time'. And you're like, OK! I just love it when people tell me I am going to die soon. It really makes me feel like I want to return!' (female, 21 years old, FGD1-P2)*

One young woman expressed a concern that there could be repercussions from missing clinic appointments: 'let's say you haven't been to the hospital for some time, and you decide to go, you feel they may kind of discriminate you, there may be disadvantages and consequences' (female, 16 years old, FGD3-P16). Young people seemed to perceive the reactions they had from clinic staff in regards to their problems taking medication as an attempt at discipline them into 'behaving'.

When asked what might make someone not come to clinic if they had been having problems taking their medicines, participants in in one group instantly reeled off a list of people they felt they were under pressure from: the doctor, themselves and their parents. They expressed concerns about wasting the doctor's time and disappointing everyone. This was the conversation in the focus groups to mention pressure from families in relation to managing HIV as well as from health care professionals.

There seemed to be a consensus from much of the group that this approach meant clinic staff did not properly address the problems they were dealing with. However, one young man defended clinic staff arguing that HIV was linked to everything:

> *'But at the same time, I understand their point, the doctor's point about giving everything to HIV. Because HIV is like you, that's you, so everything that happens to you is somehow it can link to HIV. So for example, how can I say this? Getting stressed it links to your HIV like taking your meds, going to hospital, it all links to HIV.' (male, 18 years old, FGD1-P6)*

There seems to be a tension between on the one hand, the messages young people receive about taking individual responsibility and the message that they almost have no personal accountability because everything problematic is caused by HIV.

6.5.3.2. Responsibility towards others

As well as fear of being disciplined for not taking their medication, participants also expressed a feeling that their actions had a negative effect on clinic staff and the unease made them not want to attend clinic. Young people regularly attend the same paediatric clinic for many years and had developed very close relationships with doctors and nurses in the clinics. They talked about not wanting to *'disappoint your doctor' (male, 19 years old, FGD3-P15), and 'worry about wasting the doctor's time'* (male, 16 years old, FGD3-P12). Another participant talked about the worry of upsetting clinic staff after a period of not taking medication having historically managed taken medication well:

> *For me, I just don't want to let people down who have watched me grow up. They are always like 'we are so proud of you we are so proud of you and we see you grow'… Then all of a sudden you are not taking your meds and not doing well and it's like you don't want to burden them with your problems. (male, 20 years old, FGD1-P4)*

By being praised and labelled as a 'good adherer' this young person then felt pressure to always be a 'good adherer'.

Participants also recounted interactions with clinic staff in which they were told how much their drugs cost, which they experienced as a form of reprimand and made them feel responsible for the cost of their treatment. After experiencing side effects on a new ART combination, a young person described the clinic staff reaction prompting both agreement and outrage in the focus group:

> *'And eventually I went back and said can I have my old ones and she said they are expensive and I was like 'I don't care, I want my old ones' and she was like OK!' (male, 20 years old, FGD1-P4)*
>
> *'Wow.' 'They shouldn't talk to you about money'. (female, 20 years old, FGD1-P5)*
>
> *'But they do.' (General, FGD1)*
>
> *'But they shouldn't because that is like a guilt thing'. (female, 20 years old, FGD1-P5)*
>
> *'But they do.' (female, 21 years old, FGD1-P2)*
>
> *'Some adult clinics put the prices on the bottle so you feel grateful for having them.' (male, 20 years old, FGD1-P4)*

'Mmmmhmm.' (female, 20 years old, FGD1-P3)

'They don't do it for cancer medications because it's not the persons fault if they have cancer but it is the persons fault if they have HIV'. (male, 20 years old, FGD1-P4)

The stigma associated to HIV adds to the existing pressure these young people have to adhere to their treatment and puts pressure on their relationship with clinic staff.

6.5.3.3. Internalisation of responsibility

It was apparent that a few of the participants saw any problems they had taking their medicines (and attend clinic in one case) as entirely their own fault. One young woman openly discussed her current problems with attending clinic as well as taking ART. She understood the health risks of not taking medicines, and unlike some of the other participants in the group, she did not feel judged by the clinic staff in the paediatric or adult clinics for having problems attending clinic or taking medication. In fact, she was shocked by some of the reports from other participants where they were scolded for non-adherence or told the cost of the ART by clinic staff. Although this young woman later discussed her dislike of what she describes as the formal nature of adult services, she never attributed any blame to anyone but herself:

'I think for me it's a personal thing I think. So it's like, I know I need to and I tell myself I need to, I just don't. For me, I think that is something for me I am just trying to figure out why I don't even though I know I need to.' (female, 20 years old, FGD1-P5)

Likewise, another young woman talks about the shame one might feel if they became immunocompromised after not taking ART:

'Let's say your CD4 is really low they are going to have to keep you in the clinic for some time and you might feel ashamed with yourself – oh why did I miss it?' (female, 16 years old, FGD3-P16)

Another young man had a long history of problems taking his medicine. He explicitly expressed a feeling of unconditional support from his clinic. He had no problems engaging in care and attended very regular appointments mainly for social and psychological support. He very much seemed to blame himself entirely for making the management of his HIV difficult:

'It's not hard! It's not hard! No I mean, it's the person who's using it. Some people make it harder than it seems. Because there are people who are using it who have more than me and I am very aware of it. And that there are younger kids who are using it better than I can.' Male, 18 years old, (FGD2-P11)

These young people were very critical of themselves and did not seem to be aware that the difficulties they were having were widely shared among other young people with HIV.

6.6. Discussion

6.6.1. Summary of findings

In this chapter, I detailed the methods I adopted to conduct three focus groups discussions with 16 young people living with PHIV, aged 16-25 years old. I presented findings from the analysis in three parts: firstly, participants' feedback about the use of proxy markers for clinic appointments, and predictors from the quantitative analysis: viral load, adherence and self-harm. This was followed by the findings from the two themes that emerged from the data, namely, self-management and shared decision making and responsibility and blame.

6.6.2. Comparison to the literature

6.6.2.1. Reflections on the use of proxy markers and the predictors of engagement in care

Participants in all of the three focus groups agreed that proxy markers were routinely collected at most of their clinic visits. However, participants also reported additional reasons for attending clinic that would be missed using this approach. For example, participants across all three focus groups reported attending clinic for psychological support. Mental health challenges are well documented in young people living with PHIV in both low- and high-income countries. Studies suggest that young people living with PHIV face a higher burden of a range of metal health problems such as anxiety and depression, (272,273) post-traumatic stress disorder,(273) suicidality,(273) and lower self-esteem, (114). Consequently, mental health support is often an integrated, central part of HIV health care. When developing the adult algorithm on which the flowcharts in this study are based, Howarth *et al* (151) acknowledged as one of the main limitations of their study, the inability to measure appointment made for psychosocial wellbeing. An interesting point not captured in other EIC studies, is the breadth of other reasons for attending clinic that participants mentioned. Participants reported attending for disclosure support, help with medical and disability forms

as well as school forms and routine sexual health check-ups (in concurrently running sexual health clinics). The range of reasons participants attended clinics appointments outside of their clinical management calls attention to the wider support role that HIV clinic staff provide for many young people and their families.

One of the reasons I sought participant's feedback was to see if the quantitative results resonated with young people's experiences. Most of the participants felt it made sense that young people might engage less in care if their viral load was >50 c/ml or their adherence self-assessment was not so good/bad, as indicated by the model discussed in chapter 5. Interestingly, three different explanations emerged from the discussion. Firstly, in contrast to the quantitative results, two young people described having a long history of problems taking ART, but reported that this never affected their attendance in clinic. Secondly, participants described that attendance in clinic was more likely if they were taking their medicines and managing with their HIV. They felt this meant that that young people were generally more in control and had taken responsibility to adhere to their medicines as well as attend clinic. Finally, participants described using biomarkers as a reference point to decide for themselves whether to attend clinic or not. If young people had a period of non-adherence, they would actively avoid clinic because their perception was that their viral load would be high so they did not want to have their blood test taken. Both of these last two accounts are in alignment with the quantitative findings, and with other literature,(256) although they suggest that the relationship between viral load and EIC is not uni-directional, but rather dynamic and changing over time.

The active decision-making about whether to attend clinic or not was also reported in a study by Taylor *et al* (274) of adults with HIV (n=40) in the USA. They found that irrespective of whether participants were attending their appointments, they conveyed high self-efficacy and felt in control. In the context of young people who have grown up with HIV, this management of appointments, actively deciding whether or not to attend, may well be an extension of the strategy that children adopt in relation to adherence. Kawuma et al, (257) interviewed 11-13 year olds (n=26) to explore their perceptions and experiences of children taking treatment. In their findings they noted that non-adherence was not a passive activity as many adults presumed but was actually a deliberate and strategic choice.(257)

Two main points came out of discussions in my study about why young people who self-harm may not attend clinic. Firstly, participants felt that feelings of shame may drive this disengagement because young people want to avoid clinic to keep the self-harm a secret.

The other factor from discussions in all three focus groups was the fear of what would happen if clinic staff found out. These fears ranged from worry about more intense, unwanted clinic staff attention to being forcibly institutionalised. Both of these points about self-harm are in accordance with the quantitative finding, although the concerns young people expressed about the consequences of the discovery of self-harm broaden the understanding of the issues. In contrast to the quantitative findings, the one young woman who disclosed she had self-harmed in the past however, reported she attended all her appointments so as not to arouse suspicion in the health care professionals.

6.6.2.2. Self-management and shared decision making

Young people relayed different experiences of the increasing responsibility and self-management of their HIV care that came with age and how this affected their EIC. Some participants described finding the increased responsibility difficult and reported either not feeling like they wanted to attend their appointments or forgetting to attend. A second group of young people described that their EIC and adherence improved as they took responsibility and were living a more independent life.

Studies have found young people can feel worried about the shift in responsibility for their health care from their parents/carers to themselves.(275) The importance of continued support for young people even as they increasing take on more responsibility for their own care has been found to be associated with better self-management.(172) Again, the participants' experiences were not universal, but, interestingly, the young man who described how his mother was not able to support him in managing his HIV when he was younger reported both his adherence and attendance in clinic improved once he was able to be responsible for this himself.

Across the focus groups, there were mixed reports from the participants about their experiences of communication in clinic and how well informed they were about their state of health. What transpired from the discussions was that young people who reported feeling well informed, also reported greater involvement in decision making about the time to their next appointment. Of course, this focus on time to next appointment was specifically related to the questions I was posing about my flowcharts. However, from the responses it seems clear that participants' answers are more than just about appointments. Young people were actually describing being given a choice of when an appointment would fit into their lives, which is arguably not only shared decision making but also a recognition, by the health care workers, of the need for young people to manage living with HIV within the broader

psychosocial context of their lives. The young people who described better communication and shared decision making were mainly from FGD2. The young people in this group were older and received their HIV care in large adolescent clinics both of which may have contributed to this improved communication.

In contrast, some of the younger participants described feeling less clear about their health status and, particularly in FGD3, the youngest of the three groups, there was no discussion about any shared decision making. One young person described the possible consequences of being left with uncertainty about one's health. He relayed times in the past when he became quite anxious in his attempts to try to interpret what the status of his health was based on whether his next appointment was sooner or further away.

Shared decision making in health care has been shown to improve patient autonomy, health satisfaction, adherence and outcomes (172,276,277) but shared decision-making is complicated for young people who have grown up with chronic illness. These children have grown up with communication about their health occurring in a triad between themselves, their parents/carers and the clinician. Adult input often dominates the interaction in the consultation leaving the child in a relatively passive role.(275,276) As young people develop through adolescence, this relationship needs to be modified so that shared decision making is between the clinician and the young person which can be difficult for all parties involved. This process is also complicated by the dynamic nature of adolescent development that means this relationship is constantly shifting as the young person matures.(275,276)

For young people growing up with PHIV, the move to shared decision making can be further compounded by the stigma of living with HIV, which for many young people manifests as silence about HIV across most aspects of their lives. (83,256,257,265) For some young people, clinic is one of the only spaces where they can talk about HIV.(256) Still, having grown up with this silence about HIV, can make the transition to having open shared decision making about their health care even more complicated for some young people.

There were three distinct responses in respect to young people's sense of control in attending their clinic appointments. The first group of young people saw attending clinic as a choice. If the attended clinic they could and find out their viral load and this gave them a sense of control over the management of their HIV. This sense of control was not always a constant state. One young person describes a transient period of disengagement and how he gained a sense of control when he made the decision to start attending clinic once more.

Conversely, a second group, describe having no choice at all in attending clinic, they just feel they have to attend and also want to avoid being chased and told off by clinic staff. The third group seemed very indifferent to their need to attend clinic appointments, they attended because that is just what they do.

For some young people, it appears that attending clinic is a way to keep on top of the information about their own health as part of their self-management and engagement in their HIV care. However, for other young people, although they report attending their clinic appointments, their passive experience does not seem to equate with active engagement in care.

6.6.3. Responsibility and blame

There were a number of ways young people described being told off and disciplined, mainly at clinic but also at home and by the voluntary sector staff. In their findings from interviews with 26 young people (11-13 year old) in Uganda, Kawuma *et al* (257) found that, similarly to adults, children have to navigate complex social contexts to manage their HIV medication long-term, but that these problems were not taken seriously by clinic staff. In their accounts from 10-24 year olds (n=147) from across five low and high income countries, Bernays *et al* (104) found that health care providers emphasised the need to take ART rather than how they might support young people to take it. Instead of offering practical support, discussion around adherence was largely limited to being scolded after they had missed medication or just a reiteration that they needed 'perfect' adherence. (104)

These findings are not unique to HIV research. Renedo *et al* (278) found comparable patterns of interactions between staff and young people in their research based on interviews with 13-21 year olds with sickle cell disease. Little or no consideration was given to the social context of managing living with sickle cell, and participants were likewise reminded of previous episodes of illness as a motivation to adhere to their treatment.

Niehaus (279) maintains that there is far too much emphasis in biomedicine on the concept of 'treatment literacy', and an assumption that there is a direct link between HIV and ART knowledge and education, and therapeutic adherence and efficacy. Treatment literacy as a construct can obscure the multiplicity of social and economic factors that affect adherence to ART. These factors can be both supportive of adherence, such as the role of one's community, or create barriers, such as poverty and stigma. Either way, they are essential issues when thinking about adherence to treatment and achieving therapeutic success. (279)

Young people in my study did have a clear understanding that they should take their medication as directed; however, managing this in their day-to-day lives remained challenging. If the clinic staff do not acknowledge the multiplicity of factors related to adherence, clinic can become a place of discipline that young people might avoid when facing difficulties taking their medicines, or any other problems such as conflicting priorities attending clinic.

Another reason young people may have for missing clinic appointments or disengaging in care is the responsibility they feel towards health care workers and worries they have about letting them down. Many young people have had long and close relationships with the doctors and nurses in their clinic and are grateful to them. Interestingly, praising young people for being a 'good' adherer became a burden for young people because it made it very difficult for them to open up about instances of non-adherence. Bernays *et al* (104) found that young people were worried that that any imperfection in their management of ART could negatively affect their relationship with clinic staff. *'Scolding and praising are respectively linked to the ideas of young patients as being either 'failures' or 'successes', with very little space in the middle and no apparent accommodation of shifts and changes in young people's capacity to take their treatment.'* (p 65) Similarly, findings from focus groups with adults (n=43) in the USA show that this concept of a 'good' patient was also relevant to EIC. (280) Patients saw the 'engaged' patient within a moral framework as a 'good' patient. While this framework was a positive influence for people hopeful of being a 'good' patient, it also had the opposite effect for patients who were felt they were failing at being a 'good' patient. (280)

In addition, there were instances where participants in my focus groups were incredibly critical about themselves for their perceived failures in managing their HIV. Two participants in particular, who both had long-term problems taking their ART and/or attending clinic, were very defensive of their clinic staff and very much internalised the blame for these 'failures' as their own responsibility, with no reference to psychosocial or structural barriers. Renedo et al (278) describe this internalised narrative of needing to 'improve', as young people echoing the discourse of the adults around them which young people use as a form of self-discipline. Paparini & Rhodes (258) contend that the acceptance of HIV as a normalised chronic illness has diminished consideration of the challenges and constraints to individual behaviours that can be brought by the different psychosocial contexts of living with HIV. This dictum about the 'manageability of HIV' has placed the responsibility of taking

medicines and engaging in care completely on the individual, making them morally responsible for poor health.(281) This is echoed in this study in instances when staff pointed out the costs of treatments and reminded one participant about their risk of death if they did not improve their adherence.

6.6.4. Reflections, strengths and limitations of the focus group study

All three groups had common aspects in their dynamics. Focus groups were conducted alongside an existing event or, as in the case of FGD2, at the same time as a regular support group. This meant that all the young people were in a safe space, they were with people they knew to some extent and, perhaps most importantly, they had already shared their HIV diagnosis by being in that space.

However, differences about the three environments and pre-existing relationships could have affected the dynamics of the specific groups. FGD1 took place on a Friday and the young people had spent the week together as camp leaders in addition to previous training residential weekends together and existing friendships. One of the key benefits of this relationship - and the strengths it added to the data collection - was that the young people in this group elaborated more, and by their open discussion helped each other to elaborate. This was the case both when young people were agreeing about things and when they had opposite experiences. An example of interaction in the group is displayed when they discuss why people who are having problems taking their medication may not attend clinic.

> *Can you think of some examples, from yourself or other people you know, if you are having problems taking your medicines, why would that stop you going to clinic? (facilitator)*
>
> *Pressure to take your medication. (female, 21 years old, FGD1-P2)*
>
> *Who puts you under pressure? (facilitator)*
>
> *The nurses. (female, 21 years old, FGD1-P2)*
>
> *You don't want to be judged if you are doing that. (female, 20 years old, FGD1-P3)*
>
> *Or told off. Doctors are sometimes like 'You're gonna die' no one wants to be told they are going to die. (male, 20 years old, FGD1-P4)*
>
> *Yeah they are like threatening. (female, 20 years old, FGD1-P3)*

Every single time. (female, 21 years old, FGD1-P2)

Who has told you this? (female, 20 years old, FGD1-P5)

The nurses are like, 'If you don't take your medication you're are going to die the next time'. And you're like, OK! (female, 21 years old, FGD1-P2)

It's never like the main doctor. It's sometimes the one taking your bloods and you just sat there like, OK! (male, 20 years old, FGD1-P4)

Mine are so lovely. (female, 20 years old, FGD1P5)

This is a good example of how the story is built through the interaction between participants. When presenting different opinions, young people started differing accounts with phrases such as 'for me' or 'personally' which felt like a respectful way to offer an alternative experience.

In FGD2, the young people all knew each other to some extent from attending the same support group. However, the interaction was different to FGD1. Young people seemed happy to share their personal experiences even if they differed to the other member, but instead of the conversations being interactive, the young people in this group took turns to speak and often waited for me to invite them to answer a question. This group had five members, and after answering two questions one member declined to speak for the rest of the session, so in fact there were only four young people interacting. Three of the members in this group were in their twenties and in their discussion of interactions with the group conveyed a lot of choice and autonomy in the management of their HIV that may have reflected their older age. They were also all receiving their HIV care in specialist adolescent clinics, which may have contributed to their involvement in decision-making.

Participants in FGD3 were the youngest, and the group in which the participants seemed most reticent about offering their opinions. I tried to adapt the session as I went along, for example by repeating questions using comments young people had made, and using more spider grams and pictorial aids to try and stimulate conversation in a less direct way. In addition to this group being younger, the presence of three additional adults is likely to have had an effect on dynamics was. In my view, the unexpected presence of the voluntary worker may have been problematic for the participants of this focus group. In all of the focus groups I encouraged open discussion and reassured young people it would not be fed back to their parents/carers or NHS clinics. Having the voluntary sector worker in the room who knows

their parents/carers and the clinic they attend could potentially have undermined young people's trust in the confidentiality of the session.

Despite the difference between the interactions across the three focus groups, in this analysis I paid extreme attention to try to ensure data from all three groups shaped the findings as fairly as possible.

One potential limitation of the study is that all participants were purposively selected from a group of young people already engaged in voluntary sector organisations, whose views are potentially not representative of those young people living with PHIV in the UK who are struggling with EIC even more. Although young people in two of the focus groups openly discussed periods where they had problems attending clinic or taking medication, they unlikely to represent the most disengaged young people in the population. In addition, the participants in the first group had been involved in the voluntary sector for a number of years, which is likely to have made them more aware of the issues discussed in the focus groups and more used to thinking critically about their health care.

I am aware that reference to the broader social and structural challenges young people face managing their HIV on a day to day basis is missing from the focus group discussions. This is a gap noticeable against the literature on this group. It is possible that the emphasis of the focus groups on the topic of health care and clinic attendance precluded other kinds of discussions. It would be very interesting to find out more about what support young people are given from their families to attend clinic and to manage their HIV more generally.

6.6.5. Concluding remarks

In this chapter, I present the findings from focus groups with young people living with PHIV. In the focus groups, the findings from the quantitative analysis were presented to young people to see if they resonated with their experiences and to better contextualise the quantitative findings. Findings from the focus groups were presented in three parts: feedback on the use of proxy markers and the quantitative findings; and then from two themes that emerged from the data: self-management and shared decision-making.

Young people in the focus groups reported that the results from the quantitative methods largely resonated with their experiences of attending clinic and engaging in care. However, findings from the focus group discussions revealed that young people's experiences are much more nuanced than the quantitative findings can depict. Therefore, these findings extend the quantitative results and uncover issues not considered in the quantitative

analysis. In addition, these findings deepen the understanding of the tensions and ambiguities young people experience engaging in care.

The findings from this focus group clearly highlighted the importance and benefit of including young people in health care research. Without the findings from the focus group, the range and dynamic nature of the different explanations for the individual predictors of EIC from the quantitative model would be lost. Crucially, what emerged from this work is the suggestion that attendance at clinic appointments for young people with PHIV does not necessarily equate to engagement in care. Similarly, participants' active choice to not attend clinic visits suggests that there is more to non-attendance in clinic than being disengaged in care.

There is an emerging body of work on young people's experiences of adhering to HIV medications, but comparatively little on EIC. Further work with young people is required to broaden our understanding of EIC and how to improve it.

6.7. Key messages from this chapter

- Participants largely agreed with the use of proxy markers in the quantitative analysis but highlighted visits that would be missed by using this method
- Young people reported that the quantitative findings largely resonated with their experiences of EIC. However, discussions highlighted a much more nuanced and complex picture than suggested by the quantitative findings emphasising the importance of consulting young people on this work
- Young people who reported clear communication with healthcare workers also reported more positive experiences of shared decision-making and better EIC
- Communication about adherence from clinic staff was usually reactive when problems occurred and was in the form of being scolded and told off. Young people reported little acknowledgment of the wider context of managing their HIV treatment which can cause disengagement
- For young people with PHIV, attendance in clinic did not necessarily equate to EIC, and nonattendance may not mean that young people were disengaged
- If young people believe they will be scolded for missing ART doses, clinic can become a place of discipline that young people may choose to avoid, particularly when having problems with adherence.

Chapter 7. Discussion

7.1. Introduction

Combined antiretroviral therapy has dramatically changed outcomes for people living with HIV, improving morbidity and mortality. For children and young people, this means they are surviving into adolescence and young adulthood. However, there are many familial, social and developmental complexities growing up with PHIV, which makes the required ongoing self-management of living with a stigmatised chronic condition complicated. These complexities are demonstrated by the poorer outcomes of young people living with PHIV compared to other age groups. EIC has been reported to be associated with improved patient outcomes and is thus increasingly becoming a focus of global and national targets as an important component to help improve outcomes for people living with HIV in the cART era. Studies mainly in adults living with HIV, have shown improved outcomes in people who are engaging in care. EIC is arguably especially important in young people with PHIV, who have worse outcomes compared to adults and are therefore particularly vulnerable. However, few studies have measured EIC in children and young people with PHIV in Europe, and none have looked at predictors of EIC which could be used to identify and support young people most at risk of disengagement. In this thesis, I developed a sensitive measure of EIC for young people with PHIV that could pick up changes in their health status and treatment. The resulting flowcharts were then applied to a dataset of young people in the AALPHI cohort study, and this dataset included both CHIPS national surveillance data as well as a wide range of other potential predictors of EIC. Finally, predictors of EIC which emerged from the quantitative analysis were explored in focus group discussions with young people living with PHIV to explore if they aligned with young people's own experiences, and to gain a fuller understanding of the findings.

In this discussion chapter, I summarise the key findings from each of my results chapters (chapters 3 to 6). I then offer some concluding remarks, which encompass a description of my findings' relevance, the main strengths and limitations of my work and its generalisability, and finally I explore future possible uses for the EIC flowcharts and for improvements to EIC.

7.2. Summary of key findings

In chapter 3, I adapted the Howarth *et al* algorithm which had measured EIC in adults, for use in young people with PHIV. Guidelines and clinical expertise were used to develop three

flowcharts that classified clinical management for this population. These flowcharts were then utilised to measure EIC in young people with PHIV in the AALPHI cohort. Across 3,585 months of follow-up for the participants, 34% were months with a visit. At those visits, 61% of participants had an undetectable viral load (Flowchart A), 27% were on ART with a detectable viral load (Flowchart B) and 9% were off ART (Flowchart C). Using the flowcharts, participants were most frequently scheduled to have a follow-up appointment 4 months later. However, 37% of participants had at least one of their appointments scheduled in a month's time, suggesting the changing health needs in these patients over the course of the year. Overall EIC over the 12 month period of study was 87% person-months.

European and Sub-Saharan African estimates of EIC range from 80-98%,(153–155,157–160) so my estimate of EIC falls in the middle of this range, and is in line with the upper end of estimates from the USA (56-99%).(123,161–168) Within chapter 3, I considered various limitations to both the development of the flowcharts and the available datasets (CHIPS and AALPHI). Two key limitations were that actual attended appointments were not reported in CHIPS, and therefore proxy visits were used for this analysis. In addition, all data in CHIPS measured clinical aspects of HIV management and therefore visits for psychological aspects of HIV care (which were also not available in AALPHI) were not captured in this analysis.

In chapter 4, I describe how I compiled the exposures potentially related to EIC for the AALPHI cohort. A large number of exposures were available for consideration so these were grouped in "domains" of related factors. I then presented the potential exposures using descriptive statistics and compared my summary findings to other relevant studies and population data. This included comparison of *a priori* and HIV markers to PHIV in the wider CHIPS cohort, and comparison of other variables from the remaining domains (sociodemographic, risk behaviour practices, mental health, cognition and clinic) to HIV negative youth. Participants in the AALPHI cohort were broadly similar to CHIPS participants, except they had on average lower CD4 nadir counts, suggesting that AALPHI participants are broadly representative of the wider UK population of children living with PHIV. When compared to HIV negative young people, again AALPHI participants were broadly similar, but they were more likely to have experienced the death of one or both parents and had increased prevalence of mental health problems across the majority of the included measures. Young people with PHIV in my analyses also had lower cognition scores when compared to normative data. One of the main limitations highlighted in this chapter was the possibility of selection bias of the participants in the AALPHI cohort, who were recruited in NHS clinics and voluntary sector organisations.

Reassuringly, AALPHI participants were broadly similar to CHIPS participants, however, comparison was only on quite a crude level. At the end of this chapter I discussed in detail many potential biases that could have been introduced into my work, including potential measurement and data collection errors common to many cohort studies.

In Chapter 5, I put together the exposure variables described in Chapter 4 and the flowcharts described in Chapter 3 to investigate predictors of EIC in the AALPHI cohort. Due to the large number of exposure variables included in this analysis, multiple stages of model building investigations were carried out to examine between-covariate associations to avoid introducing collinearity in the modelling stages. Then, four stages of multivariable logistic regression modelling were carried out (allowing for clustered data) to investigate predictors of EIC.

Four factors were found to be associated with EIC in the primary stage 4 model, each from a different domain. Young people were less likely to be in care if they: were of Asian/mixed ethnicity compared to being of black or white ethnicity (*a priori* domain); reported having ever self-harmed compared to not (mental health domain); reported having not so good/bad adherence to ART or if they were not on ART compared to excellent/good adherence to ART (HIV experience and management domain); and had a viral load >50c/mL compared to ≤50c/mL (clinical markers domain). In addition, four further exposure variables were found to be associated with worse EIC in sensitivity analyses: older age (*a priori* domain); speaking a language other than English at home compared to English or English and another language (sociodemographic domain); increased travel time to clinic and attending a paediatric clinic compared to an adolescent or adult/GUM clinic (both clinic domain). Older age was found to have an association with EIC in all three sensitivity analyses (one only marginally), which is in line with the literature which suggests EIC declines through older adolescence and early adulthood. Other studies also found similar associations between age,(151,161,162) viral load,(158) clinic type (possible proxy for clinic youth friendliness),(164) and travel time.(218) A number of studies also found an association between ethnicity and EIC although trends varied.(151,161,162) I found no other studies that identified self-harm, adherence or language spoken at home as predictors of EIC.

I describe a number of limitations in Chapter 5. Despite the investigations, variables' covariate associations may have been missed if I had placed exposure variables in the wrong domains. In addition, misclassification of the outcome, discussed in Chapter 3, had the

potential to cause dilution in the strength of effect or missed predictors. However, sensitivity analyses provided some reassurance due to the relative consistency of the findings.

In Chapter 6, I used focus group discussions with young people living with HIV to explore the wider relevance and meaning of using of clinical markers for proxy visits (Chapter 3), and predictors of EIC (from the primary stage 4 model, Chapter 5). Three focus groups discussions were conducted with 16 young people aged 16-26 years. I facilitated all three focus groups and conducted them alongside existing voluntary sector events. Focus group discussion were recorded, transcribed and analysed using thematic analysis. First, I explored with young people their reasons for clinic visits and regularity of tests and measurements, to analyse the strengths and limitations of using proxy markers in the flowcharts. Secondly, I presented the exposure variables found to be associated with EIC and discussed these with young people to elucidate if the predictors of EIC found in the quantitative analysis resonated with their experiences as patients. This helped me contextualise the overall findings and gain a deeper understanding of the nuances of the factors they face when engaging in HIV care.

Findings were presented in three parts. Firstly, I described feedback on the use of proxy markers and the quantitative findings. Then I presented two themes that emerged from the data, which were self-management and shared decision making. Young people reported that the quantitative findings were largely aligned with their experiences of EIC, however, discussion highlighted a much more nuanced and complex picture than suggested by the quantitative findings alone. Poor communication with health care providers left some young people feeling anxious due to subsequent negative assumptions they made about their health care status. Conversely, young people who reported clear communication with healthcare workers also reported more positive experiences of shared decision-making. Other young people described avoiding clinic appointments when they thought that their missed ART doses might be detected through viral load testing, and lead to in reproach from health care workers. I described a number of limitations in the chapter. The two main limitations were that ethnicity as a predictor of EIC was not discussed in the focus groups, resulting in less understanding of the context of this finding. In addition, all participants were purposively selected from pre-existing groups of young people already engaged in voluntary sector services, which might make their views unrepresentative of young people struggling with EIC.

Table 7.1 summarises the objectives, key findings and limitations from each of the results chapters.

Table 7.1: Summary of the objectives, key findings and limitations from each of the results chapters

	Objective	Key findings	Key limitations
Chapter 3	• To develop a sensitive measure of EIC in order to take into account changes over time in treatment and health status for young people with perinatal HIV in England • To apply the measure to describe EIC in young people with perinatal HIV in England through quantitative analysis of the AALPHI cohort dataset	• Development of a flexible new approach to measuring EIC that takes into account changing health status • Classifications are based on both clinical guidelines and clinician's experience • 87% of 3,585 person months of follow-up across 306 participants were engaged in care • Two thirds of clinic visits were in participants on ART with a viral load ≤50c/mL • Participants off ART accounted for led than 10% of months with a visit • Nearly half of appointments were categorised as requiring the next scheduled appointment after 4 months • Participants were most likely to attend their appointment early if their time to next scheduled appointment was at 6 months.	• Flowcharts were complex and time consuming to develop and keep up-to-date • Time to next scheduled appointments may not be reflective of national practice • Use of clinical measures for proxy markers may not capture some appointments for other reasons (e.g. psychosocial issues) and may incorrectly classify other visits as actual clinic appointments (e.g. phlebotomy) • Less frequent monitoring of HIV markers may have resulted in missed visits • Leniency added into the model may have resulted in an underestimation of time out of care • The decision to drop patients and rows with no clinical data may have introduced selection bias • Missing data and data entry errors may have affected the estimation of EIC.
Chapter 4	• To describe the characteristics of AALPHI participants • To compare findings from analysis of AALPHI participants' data to the national HIV cohort or the wider general population where comparisons are available	• Due to the breadth of the data collected in the AALPHI study, a large number of variables were available for consideration for inclusion in this analysis • Variables were justified for inclusion based on evidence form the literature or expert opinion • Participants in AALPHI were broadly similar to participants in CHIPS except AALPHI participants were more likely to be female than CHIPS participants, and have a lower CD4 nadir • AALPHI participants were also broadly similar to the UK population in many ways. Where they differed was that more young people in AALPHI had lost a parent and were in foster care or adopted. In addition, AALPHI participants had a lower cognitive score and had worse mental health than young people in the general population.	• Risk of selection bias due to recruitment of AALPHI participants in the clinic and voluntary sector • Possible selection bias from specific young people not being referred by clinic staff to participants in AALPHI, for example young people with cognitive delay and newly diagnosed young people (due to AALPHI inclusion criteria) • A number of possible sources of measurement error could have been introduced by the use of self-completed questionnaires in the AALPHI interview, such as social desirability, recall bias and poorly phrased questions. In addition, there was a risk of poor execution of the protocol due to the multiple research nurses • Key exposure variables for EIC may not have been included in AALPHI • Errors in data collection and data processing may have occurred.

Chapter 5	• To investigate the relationship between a range of exposures and EIC in AALPHI participants, through quantitative analysis	• Rigorous variable investigation was performed across eight domains • Four stages of modelling were carried out to identify predictors or EIC • In the primary stage 4 model, worse EIC was associated with Asian/mixed ethnicity, self-harm, not so good/bad adherence and viral load >50c/mL • Sensitivity analyses findings were similar to the primary stage 4 final model but also suggested there may be effects of age, travel time to clinic, language spoken at home and type of clinic attended.	• Longitudinal outcome measures and baseline exposure variables many have been influenced by previous EIC • Between-covariate associations may have neem missed causing possible collinearity and model instability • Misclassification of the outcome variable may have caused dilution of effect or missed predictors of EIC • Choice of start date may also have caused dilution of effect or missed predictors of EIC • Poor selection of appropriate measurement tools in AALPHI could lead to an over or underestimation of EIC • Exclusion of patients with data not missing at random could limit the generalisability of the analysis.
Chapter 6	• To explore the predictors of EIC discussed in Chapter 5 through focus groups with young people in order to assess if they resonate with young people's experiences and to enhance our understanding of the findings	• Participants largely agreed with the use of proxy markers in the quantitative analysis but highlighted visits that would be missed by using this method • Young people reported that the quantitative findings largely resonated with their experiences of EIC. However, discussions highlighted a much more nuanced and complex picture than suggested by the quantitative findings emphasising the importance of consulting young people on this work • Young people who reported clear communication with healthcare workers who reported more positive experiences of shared decision-making and better EIC • Communication about adherence from clinic staff was usually reactive when problems occurred and was in the form of being scolded and told off. Young people reported little acknowledgment of the wider context of managing their HIV treatment which can cause disengagement • For young people with PHIV, attendance in clinic did not necessarily equate to EIC, and nonattendance may not mean that young people were disengaged • If young people believe they will be scolded for missing ART doses, clinic can become a place of discipline that young people may choose to avoid, particularly when having problems with adherence.	• Ethnicity as a predictor was not discussed in the focus groups, resulting in less understanding of the context of this finding • All participants were purposively selected from pre-existing groups of young people already engaged in voluntary sector services and therefore may not be representative of young people struggling with EIC • Young people in the first focus group had been involved in the voluntary sector for a number of years and may be more used to critically thinking about health care than other young people.

7.3. Concluding remarks

The aim of this doctoral project was to describe engagement in HIV care in young people with PHIV in England and to assess whether psychosocial factors predicted EIC. In this thesis, I hypothesised that psychosocial issues were more important in influencing EIC than clinical aspects of living with HIV. To address whether my hypothesis may be correct, I will consider the four predictors of EIC from the primary stage four model of my analysis, which were ethnicity, self-harm, adherence and viral load, as well as age, which was identified in all three sensitivity analyses. Based on the quantitative findings alone, it could be assumed that only self-harm and adherence bear out the hypothesis. These variables were in mental health and HIV experience and management domains, while ethnicity and age were in the sociodemographic markers domain, and viral load in the HIV markers domain.

However, findings from the focus groups give an insight into the psychosocial context of viral loads, with young people making decisions about whether or not to attend clinic based on their beliefs of what their viral load measurement may be; and the subsequent interaction they would have with clinic staff based on this. Likewise, for age, young people reported different experiences of the increasing responsibility and self-management of their HIV care that came with age and how this affected their EIC. In my analysis, young people of Asian/mixed ethnicity were less likely to be engaged in care. Unfortunately, ethnicity was not discussed in the focus groups, however, previous studies have highlighted how social contexts such as racism and medical distrust may account for disparities in EIC between people of different ethnicities.(161) However, these findings were not specific to young people of Asian or mixed ethnicity so may not be relevant for the findings from my analysis. I think it is therefore possible to argue that the hypothesis was broadly correct, even though some of the variables found to be associated with EIC fell in the sociodemographic and HIV markers domains.

As discussed previously, the estimate of EIC from this study falls in the middle of the European estimates and at the higher end of estimates from the USA. Compared to the two other European studies from the UK and Italy, this study was the only one to focus on EIC (as opposed to the cascade of care,(155) and outcomes at transition (157)). Additionally, the Italian paper (157) did not define EIC and the UK study (155) required participants to have an appointment in the year prior to the analysis which is likely to explain the high proportion of young people found to be EIC.

Results from the Howarth *et al* (151) study, where the original algorithm to measure EIC in adults in the UK was developed, are probably the most appropriate comparison. Howarth *et al* estimated EIC using surveillance data from the UK CHIC study, which included data from the largest clinics across the UK.(126) The estimate of EIC from this PhD analysis is similar to that found in the overall UK CHIC cohort (87% vs 84% respectively) but is substantially higher than the estimate in young people aged <25 years (77%). There is no stratification for perinatal acquisition in Howarth *et al*'s analysis, presumably because either the data were not available or the numbers too small. It is likely that young people in the <25 years age group were largely young people with BHIV, and studies have shown that this group are less likely to be engaged in care than young people with PHIV (161,168) which may account for the difference between the estimates. However, the other consideration is that young people in AALPHI were consented, and so were willing to be involved in the study, and they were also recruited from HIV clinics. When setting up the AALPHI study, consideration was given to how to recruit young people who may be less engaged in care or LTFU and was one of the key rationales for recruiting in the voluntary sector as well as HIV clinics. Inevitably, however, young people in AALPHI were likely to be a cohort of young people who have better EIC than the wider cohort of young people with PHIV in the UK. It is therefore plausible that my estimate of EIC is an overestimate due to the selection bias of this group. However, it is likely that the true number of young people engaged in care falls somewhere in between the estimate from this study and Howarth *et al*, and is reassuringly higher than many estimates from the USA where most of the studies in this field have been conducted to date.

In many ways, the predictors of EIC found in this analysis are unsurprising because they point to the most vulnerable young people in this cohort. The findings from this analysis suggest a number of ways to potentially identify young people most at risk of future disengagement, such as through simple adherence, self-esteem or depression self-assessment (as a proxy for self-harm) questionnaires. In addition, these identified predictors of EIC provide supporting evidence for future interventions to improve EIC in this group in the future. However, findings from my focus groups reveal greater nuance in factors underpinning decisions to engage in care and how engagement is a precursor for improved outcomes in subsequent steps of the cascade of care in young people living with PHIV. Findings from the focus groups, substantiated by the literature,(256) highlight how supportive clinic staff are key to making this engagement – outcome relationship work. A number of young people described a perceived lack of understanding from clinic staff about the difficulties of maintaining long-term ART adherence and clinic attendance, and reported being scolded if they had missed ART doses. These findings

suggest that in the post-cART era, improvements in outcomes in this complex group may be less about simply ensuring that young people attend clinic, but also about the communication that occurs once young people are in clinic, and the wider recognition of support required by young people in self-managing a stigmatised, complex, lifelong condition.

7.3.1. Strengths and limitations

The specific strengths of this thesis have been previously described in detail in each chapter and summarised in Table 7.1. Here I will discuss strengths and limitations that are relevant to the whole thesis.

One of the major strengths of my approach is the definition used to measure EIC. The flowcharts allowed health care status of participants to be taken into account; I examined whether participants were attending clinic when they need to, based on their individual health care requirements as opposed generic predefined times or missed visits. The flowcharts highlight the heterogeneity of the young people in the AALPHI cohort and therefore the need for a sensitive measure of visit constancy in this cohort. In addition, my analysis benefited from measuring EIC longitudinally because it was possible to show how a cross sectional snapshot of time to next scheduled visit was quite different to the proportion of scheduled time to next visit classifications across the whole year. However, there was only one year of follow-up in my analysis, and this could be extended in future analyses.

The second strength of my approach was in utilising the CHIPS and AALPHI datasets. Very few such comprehensive datasets exist globally, and access to these data allowed much broader examination of relevant factors that could potentially confound or predict EIC. Without access to these data, it would not have been possible to characterise EIC in this group in such detail. Finally, the use of mixed methods in my work has enhanced the understanding of the research. In general, the findings from the quantitative analysis were aligned with the experiences of the young people living with HIV who took part in the focus groups. Discussions highlighted a much more nuanced and complex picture than suggested by the quantitative findings, emphasising the importance of consulting young people on this work. While the quantitative results are generalisable and can be framed in context of the existing literature, the addition of the qualitative component provides a more complete picture of EIC and reminds us that this complex group are heterogeneous and have different experiences.

There are some key limitations that need to be considered in addition to the strengths. Firstly, I did not have access to actual attended clinic visits for this analysis and therefore proxy clinic

visits were used based on clinical markers collected in clinic. The use of proxy markers is common in the EIC literature and nearly half of the papers in the literature review used this approach. Clinic visits for mental health support were also highlighted in all three focus groups as a reason young people attended clinic, and they were not captured in my measure.

One of the main strengths of the flowchart approach, of taking individual health status factors into account, is also one of its main disadvantages. Monitoring and treatment guidelines are constantly evolving and therefore the flowcharts need regular updates. At the time of submitting this thesis, the flowcharts are already out of date because, for example, at the time of their development there was much less information about the use of integrase inhibitors in young people, and time to switch was treated the same as for NNRTIs rather than PIs as it is now.

7.3.2. Generalisability

I believe that my findings may be generalisable to other young people in living with HIV in the UK because young people in the AALPHI cohort were broadly similar in many characteristics to young people in the national CHIPS surveillance cohort. In addition, my findings may also be generalisable to other countries in Western Europe with patients of similar demographics (for example the Netherlands,(282) France,(283)). Generalisability with the USA may be more limited due to the very different health care and sociodemographic circumstances in that country. However, many of the issues highlighted in this analysis may be common across young people living with PHIV in high income countries and so results may be useful. Certainly, many of the explanations from the focus groups echo findings from other qualitative studies, especially around relationships between health care staff and young people, and the narratives around chronic disease management, suggestive of common patterns and experiences.

In theory, the flowcharts used to measure EIC here could be extended for use in other high income countries. The main prerequisite for these flowcharts is that routine HIV monitoring is conducted at every clinic visit to allow the scheduling of the next appointment. Although the flowcharts would need updating for current guidelines and adapting to national practices, the paediatric guidelines on which they are based are the PENTA European treatment guidelines, and so for many European high income countries the adaptations required would be quite minor. The main limiting factor is the complexity of the flowcharts and the time that the underlying programming would take to revise and check.

7.3.3. Opportunities for future work

There are a few important questions that could be investigated in future research. Firstly, from a methodological point of view, it would be interesting to measure engagement in care in this cohort using a simpler definition. The benefits of the flowcharts developed for this analysis are that they take an individual's health status into account, but the downside is the complexity and time consuming nature of developing and adapting the measure. To justify continued use of this complex measure, one could produce comparative estimates of EIC in the same cohort using a simpler measure, to see if the findings correlate. A previous study compared three measures of EIC, gaps in care, visit constancy and a measure combining gaps in care and visit constancy. Moderate to strong correlation was found between visit constancy and gaps in care.(132) If high correlation was found between the flowchart and a subsequent simpler analysis, it might be hard to justify the additional time required to carry out this flowchart method.

Another aspect of the flowcharts that could warrant further work is the classification of time to next scheduled appointment. This could be done by conducting an audit of patient notes to examine actual time between attended appointments and the clinical status at each appointment. This would need to be carried out in both a paediatric and adolescent or adult/GUM clinic. To address the issue of selection bias in the AALPHI study, it would also be interesting to apply the flowcharts to all young people aged ≥13 years of age in the CHIPS cohort to see how the prevalence of EIC compares.

A possible use for the flowcharts could be to help gather evidence for HIV commissioning. NHS England commission all HIV services in the UK and are in the process of developing a national outpatient tariff system whereby all patients can be classified as new, stable or complex patients. Children and young people with HIV are yet to be classified and findings from this analysis, or from a similar analysis across the whole of the CHIPS cohort, could help classification in this cohort by measuring and capturing the complex and changing needs of this group.

Finally, as already discussed, one of the key messages that came out of the focus groups was about the importance of effective, non-judgemental communication between young people and clinic staff. I had an initial meeting with a voluntary sector organisation about the possibility of creating a comprehensive resource for both young people and professionals to address these communication issues that arose in the focus groups. The voluntary sector organisation work closely with both professionals and young people living with HIV and so would be ideally placed to help take this forward, and would potentially be a key way of raising the impact of my findings.

7.4. Conclusion

The aim of this work was to develop a quantitative measure to estimate EIC in the AALPHI cohort. A wide range of predictors were investigated in a series of logistic regression models. The findings from the quantitative analysis were explored in focus groups discussions with young people with PHIV to see whether they resonated with young peoples' own experiences of living with PHIV and to help enhance our understanding. Eighty seven per cent of young people were found to be engaged in care. Ethnicity, self-harm, adherence, viral load and age were all found to be associated with EIC. Focus groups discussions highlighted the much more nuanced and complex picture underlying these quantitative findings. Results from both quantitative and qualitative aspects provide pointers to services about how they might improve engagement in care in young people with HIV.

Chapter 8.References

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