Health outcomes following transition from paediatric to adult care among young people with HIV in the UK

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Declaration

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

Abstract

With increasing numbers transferring from paediatric to adult HIV care, a limited number of studies have investigated the health outcomes of young people post-transfer, with inconsistent findings reported. This thesis aims to investigate the risk of disengagement from care and health outcomes of young people and the availability of youth-friendly services following transfer to adult care.

In this thesis, data linkage algorithms were developed to link national paediatric cohort data from the Collaborative HIV Paediatric Study (CHIPS) to adult data from the UK Collaborative HIV (UK CHIC) study and two national HIV surveillances systems: Survey of Prevalent HIV Infections Diagnosed (SOPHID); and HIV and AIDS Reporting System (HARS).

By five years post-transfer, one-in-eleven young people had experienced an AIDS event and/or died, one-in-twenty became loss-to-follow-up (LTFU) and a quarter had experienced severe immunosuppression or viral failure. Young people with poorer health outcomes in paediatric care were at higher risk of AIDS/mortality, poor immunological and virological outcomes in adult care, and provision of youth-friendly adult services had no association with improved health outcomes and engagement in adult care. The lack of association is likely attributable to the cross-sectional nature of the clinic-level data. Having measured cascade of care post-transfer to adult care, the majority of young people had completed a first adult visit, were engaged and on ART, while low levels were virally suppressed and with a good immune status. However, this group had significantly better cascade outcomes when compared to young people with behaviourally-acquired HIV (BHIV) in adult care.

My findings highlight the need for additional resources for young people with pre-existing problems managing their HIV disease in paediatric care. As young people from paediatric care progressed considerably better across the adult care pathway compared to newly diagnosed young people with BHIV, HIV exposure-based interventions may be beneficial.

Impact Statement

Previous research suggests that young people with childhood acquired HIV are at greater risk of poor treatment adherence, disengagement from care and mortality compared to older adults. As young people survive into adulthood, there is a need to understand long-term impacts of growing up with HIV.

The data linkage carried out between paediatric and various adult datasets in the UK has enabled ongoing research collaborations between CHIPS, PHE's national HIV/AIDS surveillance department and the UK CHIC study, which will facilitate further monitoring of long-term health outcomes among young people as they progress through adult care. The linkage algorithm can be applied in other settings so as to identify and track young people as they progress through adult care.

My clinic survey mapped the specialist and accessibility-promoting services available to young people post-transfer to adult care. With guidelines recommending the delivery of youth-friendly services tailored to the needs of young people, my findings suggested young people's specialist services were well provided, while accessibility-promoting services were not as readily available. These findings can therefore inform health service delivery on how to make clinics more accessible to young people.

Using CHIPS and UK CHIC data, my analysis of predictors of AIDS/mortality, disengagement, severe immunosuppression and viral failure in adult care identified subsets of young people who might benefit from specialist care and closer monitoring. However, with differences observed in the clinical characteristics of those attending UK CHIC and non-UK CHIC clinics, my findings may not be generalisable to the wider population of young people with childhood acquired HIV. Nonetheless, globally, this is the first study to identify the predictors of AIDS or mortality following transfer. My research has been communicated to clinicians and researchers at multiple national and international HIV conferences, and several CHIPS and UK CHIC steering committee meetings, consisting of multidisciplinary healthcare professionals who provide care to my study population. My findings can shape the direction of future research, for example, in identifying effective risk-reduction interventions for young people at high risk of mortality in adult care.

My cascade of care research is the first to capture the national population of young people who transferred to adult care. My findings revealed those who transferred from paediatric care to have high levels of linkage to adult care, engagement and treatment uptake, but low levels of viral suppression and good immune status. Other young people with BHIV in adult care had worse cascade outcomes compared to the former group. Overall health discrepancies were found among both groups of young people when compared to the older adult HIV population, who have been reported to have excellent cascade outcomes. My cascade research can help public health policies to improve young people's progression along the care pathway.

The findings of this thesis will be used by the NHS appointed clinical reference group to advice commissioning priorities that can improve clinical care for young people who are transferring to adult care. I also aim to publish my research in peer-reviewed journals.

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"For every girl who aspires to be great.
And for every woman who helped me realize we already possess the greatness we seek"

By Elaine Welteroth who wrote 'More than Enough'

Table of Contents

List of Tables

List of Figures

Frequently used abbreviations in this thesis

a(HR)	Adjusted hazard ratio
a(RR)	Adjusted risk ratio
AIDS	Acquired immunodeficiency syndrome
ART	Antiretroviral therapy
BHIV	Behaviourally acquired HIV
BHIVA	British HIV Association
cART	Combination antiretroviral therapy
CHIPS	Collaborative HIV Paediatric Study
CHIVA	Children's HIV Association
CI	Confidence interval
HARS	HIV and AIDS Reporting System
HIC	High-income countries
HIV	Human immunodeficiency virus
LMIC	Low- and middle-income countries
LTFU	Lost to follow-up
MSM	Men who have sex with men
MTCT	Mother-to-child-transmission
PHE	Public Health England
PHIV	Perinatal HIV
PMTCT	Prevention of mother-to-child-transmission
SOPHID	Survey of Prevalent HIV Infections Diagnosed
UK	United Kingdom
UK CHIC	UK Collaborative HIV Cohort
USA	United States of America
VL	Viral load
WHO	World Health Organization

1. Chapter 1: Introduction

1.1. Overview of Human Immunodeficiency Virus (HIV)

1.1.1. History of HIV

Human Immunodeficiency Virus (HIV) was first identified as a public health concern in 1981, when young and previously healthy men were reported to have life-threatening opportunistic infections and unusual malignancies such as *Pneumocystis carinii* pneumonia and Kaposi's sarcoma [1]. These previously rare events were associated with a high death rate and were the first sign of the new HIV epidemic. Initially, the events were only reported among men who have sex with men (MSM), causing the disease that is now known as Acquired Immunodeficiency Syndrome (AIDS) to be surrounded by substantial stigma. However, more cases of individuals with similar symptoms were reported among injecting drug users [2], people with haemophilia [3], people from Haiti [4] and children of parents from these groups [2]. The common underlying factor for all of these reported cases was severe immunodeficiency [5,6].

The first paediatric AIDS cases were reported by the US Centers for Disease Control and Prevention (CDC) in 1983, characterised with opportunistic infections and unexplained cellular immunodeficiencies. However, at that stage, it was difficult to distinguish these cases from previously reported congenital immunodeficiency syndromes [7].

The name AIDS was given to the disease in 1983 by the CDC and a case definition was established to facilitate the diagnosis and surveillance of AIDS. Additional cases of AIDS were reported across various European countries [8–10] and a severe wasting disease known in Uganda as the 'slim disease' was also subsequently identified as AIDS [11].

The AIDS-causing virus was independently isolated by two laboratories from France and the USA. In 1983, the French research group published a paper stating that they had isolated a new virus from a patient which they called the virus 'Lymphadenopathy Associated Virus' (LAV) [12]. The following year, a research group from the USA published a paper on the isolation of a virus which they called 'Human T-cell Lymphotropic Virus 3' (HTLV-III) [13]. Shortly after, the two viruses were confirmed to be the same AIDS-causing virus and it was finally named Human Immunodeficiency Virus.

1.1.2. Biology of HIV

HIV is a retrovirus, belonging to the subgroup lentivirus, which in Latin means *slow*; the virus is characterised by the prolonged duration from time of infection to the onset of symptoms [14]. The virus contains two ribonucleic acid (RNA) strands that make up its genome and the viral enzymes (reverse transcriptase, integrase and protease) [15]. Like other viruses, HIV needs help from host cells in order to replicate its genome and thus complete its life cycle. HIV infects cells that express the surface protein CD4 which is predominantly found on CD4 lymphocyte cells also called CD4 T cells (CD4 cells) [16]. CD4 cells have a central role within the immune response to invading pathogens, such as activating CD8 lymphocyte cells and macrophages, and stimulating B lymphocytes to produce antibodies. Therefore, the infection of CD4 cells by HIV leads to the impairment of host cellular immunity [5].

1.1.3. HIV life cycle

The first step of the HIV life cycle is the virus binding and fusing with the host cell (Figure 1.1). When HIV encounters a CD4 cell, the viral surface proteins bind to the CD4 surface receptor and one of the following co-receptors, CXCR4 or CCR5, depending on the viral strain. The viral membrane then fuses with the host cell membrane and tethers together enabling the viral genome and HIV enzymes to enter the host cell cytoplasm [16]. The second step is when reverse transcription takes place. The reverse transcriptase (RT) viral enzyme converts HIV RNA into DNA [17,18]. This enables the converted viral DNA to be integrated into the host genome, which is the third step of the life cycle (integration). The viral DNA is incorporated into the host DNA with the help of the viral integrase enzyme. The integrated viral DNA is called the provirus [18,19]. The provirus can remain dormant and be undetected by the immune system for many years [18,20]. The fourth step of the life cycle is transcription, when the proviral DNA along with the host DNA is converted into messenger RNA (mRNA) [18,21]. The viral mRNA then leaves the nucleus and migrates to the cytoplasm where it then acts as a blueprint for the cell to translate the mRNA into a long chain of HIV proteins [18].

Figure 1.1: The multiple steps of the HIV life cycle [22]

The HIV protease enzyme separates this long protein chain into individual units. These new viral proteins along with a copy of the HIV genome are assembled together to form a new virus particle. In order to exit the cell, the new viral particle then needs to push out through the host cell membrane; known as 'budding out' (Figure 1.1) [18]. During the budding of the virus, some of the host cell membrane is taken by the virus and used as a covering envelope. This step is crucial for the virus to reach maturation and thus become infectious [18]. The new HIV virus enters the bloodstream and is ready to infect other susceptible cells.

1.2. HIV acquisition

HIV can be transmitted from person to person via bodily fluids such as blood, breast milk, semen and vaginal secretion [23]. Higher HIV RNA levels in these fluids is associated with increased risk of HIV acquisition [17]. The main routes of acquisition are via unprotected sexual intercourse, blood-to-blood contact via injecting drug use, blood transfusion and mother-to-child HIV transmission (also referred to as vertical acquisition) during pregnancy, birth or through breastfeeding. Repeated exposure is also associated with increased risk of infection [24]. Globally, the most common route of acquisition is through sexual intercourse. In the early years of the HIV epidemic, HIV was acquired through contaminated blood transfusions, but all blood products are now screened for HIV in the UK and most high-income countries (HIC).

1.2.1. Vertically acquired HIV

With effective prevention of mother-to-child- transmission (PMTCT) through interventions such as initiating antiretroviral therapy (ART) among pregnant and breastfeeding women, vertical acquisition rates can be below 1% in HIC [25]. However, in the absence of such interventions the vertical acquisition rate were reported to range from 13% to 32% in non-breastfeeding populations from HIC [26] and from 20% to 45% in low-income countries (LIC) [27]. Studies have shown maternal viral load to be an important predictor of vertical acquisition [28–30] and a UK study reported that the children of pregnant women with unsuppressed viral loads (≥10,000 copies/ml) had an acquisition rate of 9.2% compared to the children of women with a viral load <50 copies/ml who had a rate of 0.05% [31]. Other reported predictors of vertical acquisition include low maternal CD4 count [28–30] and younger gestational age of the infant at birth [30]. Children who acquire HIV from their mothers are referred to as living with perinatal HIV (PHIV).

1.3. Natural history of paediatric HIV

In the absence of ART, disease progression to AIDS is more rapid in children in comparison to adults [32,33]. In the pre-ART era, the European Collaborative Study of children living with HIV (attending one of 11 clinics across Europe) reported that 15% of all children developed AIDS or died by the first year of life with almost 50% experiencing one of these events by 10 years [34]. Birth cohorts of children with HIV in low- and middle-income countries (LMIC) reported higher mortality estimates. A pooled analysis of community-based cohorts in sub-Saharan Africa found that 60% of untreated children died before their fifth birthday [32]. The difference in mortality estimates is likely due to earlier diagnoses, better ART coverage and lower background mortality reported in Europe compared to Africa.

In the ART era, the adult HIV population in the UK and other HIC are reported to have life expectancies nearing that of the general populations [35,36]. As the first generation born with PHIV have only recently reached adulthood, it is difficult to accurately estimate their life expectancy.

1.4. HIV disease markers

With HIV predominantly infecting and causing the depletion of CD4 cells, absolute CD4 cell count is used as an immunological measure of disease severity and progression in adults with HIV. Among children younger than five years, CD4 percentage is used in addition to CD4 count, as the CD4 cell count can be very high during infancy and the early years of childhood, before

reducing to adult values by five years of age [37]. The WHO classifies severe immunosuppression in infants aged up to one year as having a CD4 percentage of less than 20%, and in children aged one to five years as having a CD4 percentage of less than 15%. Children aged over five years with a CD4 count less than 200 cells/mm$_3$ are also classified as having severe immunosuppression [38]. While CD4 count is more commonly used clinical marker in older age groups, CD4 percentage remains an important measure beyond the early years of childhood in distinguishing CD4 count declines due to the HIV disease and general transient reductions that occur due to pregnancy and other acute illnesses [39,40]. Viral load is also used as a disease marker, with plasma viral load levels reported to predict long-term progression to AIDS [41]. Viral suppression is usually defined as viral load levels below the limit of detection by a viral load assay. The detection limit may vary from 20 to 500 copies/ml depending on the sensitivity of the viral load assay, with more sensitive assays developed in recent years. The common thresholds used across studies are <50 and <400 copies/ml. Viral loads and CD4 counts can also be used in combination as prognostic markers to assess treatment efficacy. combination antiretroviral therapy (cART) has been reported by adult studies to result in rapid viral suppression and a rise in circulating CD4 count or immune recovery [42–44]. However, individuals who have achieved viral suppression have still experience other clinical health implications such as inflammation, cardiovascular disease and decline in bone health [45].

1.5. The global HIV epidemic

Since the start of the HIV epidemic in 1981, an estimated total of 76.1 million (95% confidence interval (CI) 65.2-88.0 million) people were infected, within excess of 35 million (95% CI 28.9-41.5 million) thought to have died from AIDS-related illnesses. By the end of 2016, 36.7 million (95% CI 30.8-42.9) million people were estimated to be living with HIV. The highest burden of the global epidemic is in sub-Saharan Africa where an estimated 25.6 million people are living with HIV, this region is believed to contribute almost two-thirds of the global HIV population. Approximately, 2.1 million (95% CI 1.7-2.6) million children under 15 years were estimated to be living with HIV in 2016, of whom 90% were infected during pregnancy, at delivery or through breastfeeding (UNAIDS 2016; Ciaralleno et al 2012). From 2010 to 2016, the Joint United Nations Programme on HIV/AIDS (UNAIDS) reported the global estimate of HIV among adults (aged ≥15 years) to have declined by 11% from 1.9 (95% CI 1.6-2.1) million to 1.7 (95% CI 1.4-1.9) million. Among children, a decline in incidence of 47% was reported with the number of new cases dropping from 300,000 (95% CI 230,000-370,000) in 2010 to 160,000 (95% CI 100,000-220,000) in 2016. This reduction was attributed to increased global access to ART and PMTCT programmes [46].

An estimated 1.6 million (95% CI 1.1-2.3 million) adolescents aged 10-19 years were living with HIV in 2018, the majority of whom were adolescent girls (970,000 girls compared to 680,000 boys) [47]. Adolescent girls are disproportionately affected by HIV often due gender-based violence and unequal social and economic status [48,49]. The adolescent HIV population is a complicated group including both those with PHIV and those who more recently acquired HIV horizontally during adolescence. In 2015, HIV was reported as the eighth leading cause of mortality among all adolescents (defined as those aged 10-19 years), globally [50]. Between 2005 and 2012, global

AIDS-related deaths increased by 50% among adolescents but declined by 30% among all other age groups (Figure 1.2) [51,52].

Figure 1.2: AIDS-related mortality trends among (A) Adolescents and to the global population (B), source: UNAIDS report on the global AIDS epidemic 2013 [51,52]

A global cohort collaboration reported outcomes of more than 38,000 adolescents with PHIV aged 10 to 19 years across 5 continents. Adolescents in North America and Europe presented to care and started ART at a younger age and with a higher CD4 percentage compared to adolescents in South America, Asia and Africa (Figure 1.3) [53].

Figure 1.3: Distribution of age and CD4 percent of adolescents with PHIV by region [53]

1.5.1. HIV epidemic in the UK

The UK is a country with low HIV prevalence. In 2015, 101,200 (95% CI 97,500-105,700) people aged 15 and over were estimated to be living with HIV, the majority of whom were men (69%) [54]. The UK has an effective antenatal HIV screening programme with coverage in pregnant women of around 97% [55], which enables almost all pregnant women living with HIV in the UK to receive PMTCT interventions. Due to increased screening, treatment coverage and avoidance of breastfeeding, the mother-to-child-transmission (MTCT) rate in the UK was reported in 2014 to have declined from 2.1% in 2000-2001 to 0.46% in 2010-2011 [31]. An updated publication showed a further decline in the MTCT rate during 2012-2014 to 0.27% [56] (Figure 1.4). Additionally, the number of children with HIV from abroad are also declining likely due to more widespread PMTCT interventions in LMIC, reducing the global burden of PHIV.

Figure 1.4: MTCT rates and number of live births from 2000-2014 (MTCT data for 2000-2011 were obtained from Townsend et al. 2014 and data for 2012-2014 were updated from the National Study of HIV in Pregnancy and Childhood)

The number of children with HIV born in the UK has stabilised due to PMTCT and the number of children with HIV coming from abroad are declining due to more widespread PMTCT interventions in LMIC and other settings, thus reducing the global burden of PHIV. By 2017, 2,133 children with HIV had ever been reported and followed up in the UK and Ireland's national paediatric cohort, the Collaborative HIV Paediatric Study (CHIPS), among whom 117 deaths were reported during

paediatric care [57]. In the 1990s, over three quarters of the CHIPS cohort were aged below 10 years, whereas in more recent years the majority of the children have reached adolescence and early adulthood (Figure 1.5).

*Figure 1.5: Children followed up in CHIPS by age group and calendar year, 1996-2017** [58]

**Graph includes all children and adolescents who ever received paediatric care in the UK or Ireland*

1.6. Treatment of HIV

In the early 1990s, the standard of HIV care involved the administration of the first few licensed ART drugs either on their own, as mono-therapy, or combined as dual-therapy. In the mid-1990s, highly active antiretroviral therapy (HAART) was introduced, a combination of at least three drugs usually from two or more drug classes. HAART was later referred to as cART. cART revolutionised HIV treatment, and along with increased global access to treatment has been crucial in drastically reducing morbidity and mortality among those with HIV [59].

ART is currently expected to be used lifelong and has the primary aim of preventing further damage to the immune system and related clinical sequelae and also achieving viral suppression by inhibiting viral replication, thus decreasing the risk of onward transmission. ART drugs belong to different drug classes: Nucleoside Reverse Transcriptase Inhibitors (NRTI), Non-nucleoside Reverse Transcriptase Inhibitors (NNRTI), Protease Inhibitors (PI), Integrase Strand-Transfer Inhibitors (ISTI) and Fusion Inhibitors (FI). Each class is designed to interrupt a different stage of the HIV life cycle (e.g. PIs inhibit the HIV protease enzyme, which is needed to separate newly formed HIV particles into functional forms) [60,61].

It has been shown that children who start ART at lower CD4 counts or older ages are more vulnerable to not achieving immune recovery [62,63]. It is uncertain whether the effect of ART on the CD4 count is maintained long-term, as many studies have not followed this group beyond five years. Drug toxicity and development of drug resistance are the main concerns of such long-term ART exposure. However, medication with paediatric formulations are limited due to a number of factors. Firstly, the global aim of eradicating MTCT and the declining rates limits the incentive for

pharmaceutical companies to pursue the development of new paediatric treatment options. Additionally, pharmacokinetics can vary largely with age and weight of children, which would require drug formulation to have flexible dosages. The technical complexity of carrying out research to ensure the safety and efficacy of such drugs acts as another barrier in developing new paediatric formulations [64].

1.6.1. Changes in ART guidelines over time

WHO guidelines on when to initiate ART in children have been revised several times over the last two decades. In the past, guidelines recommended initiation of ART for more symptomatic individuals, who had already experienced disease progression. The lack of evidence on the best time to initiate treatment for asymptomatic persons coupled with concerns of drug resistance and ART toxicities have previously shaped ART guidelines to prioritise the use of treatment in those with immunosuppression. At each revision, the immunological threshold for ART initiation has been increased. More recently, the age limit for immediate start of ART was also reduced to include older ages. The latest WHO guidelines now recommend universal ART in all children and adults, regardless of age or immunological status (Table 1.1) [42].

Table 1.1: Changes in WHO guidelines on when to start ART in children by age over the last decade, 2006-2016 [42,65–68]

WHO guidelines		Age				
		<12 months	12-23 months	24-35 months	36-59 months	≥60 months
2006	CD4%	<25	<20		<15	<15
	CD4 count	<1500	<750		<350	<200
2008	CD4%	All	<20		<20	<15
	CD4 count	All	<750		<350	<200
2010	CD4%	All	All	≤25		NA
	CD4 count	All	All	<750		≤350
2013	CD4%	All	All	All	All	NA
	CD4 count	All	All	All	All	≤500
2016	CD4%	All	All	All	All	All
	CD4 count	All	All	All	All	All

1.6.2. Current regimen guidelines for children and adolescents

The most recent WHO treatment guideline recommends that the standard first-line therapy for children aged 1 to 9 years and adolescents aged 10 to 19 years should consist of two NRTI and a NNRTI [69].

For children, the preferred first-line regimen includes abacavir (ABC) with lamivudine (3TC) as the two NRTI agents, in combination with dolutegravir (DTG) (with lopinavir (LPV) replacing DTG as an alternative recommended regimen) (Table 1.2) [69]. For adolescents, the preferred first-line regimen includes tenofovir disoproxil fumarate (TDF), 3TC and DTG. The alternative

recommended regimen consists of the same NRTI backbone in combination with the NNRTI efavirenz (EFV) [69]. DTG has been shown to have a high threshold against viral resistance and to result in a shorter median time to viral suppression in comparison to EFV among adolescent and adults [70] and improved safety, tolerability and efficacy among children older than 6 years [69]. However, given limited access to this drug in some settings, few children currently take it.

Table 1.2: Summary of first-line ART regimens for children and adolescents recommended in 2018 WHO treatment guidelines [69]

Age group	Preferred first-line regimen	Alternative regimen
Children (1-9 years)	ABC, 3TC and DTG[A]	ABC, 3TC and LPV
Adolescents (10-19 years)	TDF, 3TC and DTG	TDF, 3TC and EFV[B]

A: For children aged >6 years and weighing more than 15kg; B: For children aged ≥3 years

1.7. Growing up with HIV

In the ART era, children and adolescents with HIV are surviving to adulthood, with the UK's national paediatric HIV cohort having a median age of 17 years at last paediatric visit [71]. The health outcomes of the UK paediatric cohort are also improving with declines in hospital admissions, AIDS events and mortality rates over calendar time (Figure 1.6) [72,73].

Figure 1.6: Rates of AIDS and deaths combined, deaths, and hospital admissions in the UK and Ireland paediatric cohort, 1996-2006 [72]

1.7.1. Adolescents and young people living with HIV

Globally, the UK has one of the oldest adolescent cohorts living with PHIV as a result of implementation of ART (i.e. mono- and dual-therapy) in earlier calendar years compared to other settings. To understand the burden of HIV and ART from birth and early childhood, it is important to monitor the population that has survived paediatric HIV and to further research their health outcomes through their adult years. Such research can help inform clinical care in the UK as well

as other countries that do not have the means to track their paediatric cohorts as they move into adult care [74].

Adolescents and young people with HIV are reported to be at higher risk of poor adherence, disengagement from care [75], co-morbidity and mortality [76–78]. Globally, adolescents with HIV are the only age group who experienced a 50% increase in number of HIV-related deaths, while all other age groups had a 30% decline from 2005 to 2012 [79]. This rise among adolescents has been suggested to be due to a large number of young people with PHIV reaching adolescence and adulthood [80]. However, these findings were not disaggregated by mode of acquisition, so it is unclear if the PHIV population are driving the rise in mortality.

Generally, young people with chronic diseases may initiate treatment during the developmentally sensitive period of adolescence, which is characterised by immature concrete reasoning, and a sense of invincibility leading to increased risky behaviour [77,81]. These factors may negatively impact treatment adherence and the ability of the adolescent to self-manage their disease as they prepare for a more autonomous lifestyle during and after transfer to adult care. Young people with PHIV may experience additional medical and psychological difficulties that set them apart from individuals with other chronic diseases [82]. Those with PHIV may have multi-class drug exposure and resistant viral strains which limits the treatment choices that remain available to them should they experience viral rebound on their current regimen [83]. Young people with PHIV may also experience psychosocial issues, including the risk of transmitting HIV infection to sexual partners and offspring, having to disclose HIV status to family and friends, poverty, discrimination and stigma [82,84]. Migration can also result in psychosocial barriers as over half of the paediatric cohort in the UK and Ireland were born abroad, mainly in Africa, and had to adapt to cultural and social changes growing up.

1.7.2. Cascade of care

Following the advancement of HIV treatment, a new framework, the cascade of care, was created which shaped the international approach to tackling the burden of HIV. In order to reduce mortality and onward HIV transmission, individuals living with HIV have to be diagnosed, accessing HIV care, on treatment and virally suppressed [85]. In 2014, UNAIDS announced the '90-90-90' target – an ambitious target that aims to achieve 90% of people living with HIV being diagnosed, 90% of those diagnosed being on treatment, and 90% of those on treatment being virally suppressed by 2030 [86]. This global target has united the efforts of HIV programmes and countries with the shared goal of reducing the HIV burden. The conceptual clarity of the cascade makes it an appealing framework for policy makers, health providers and researchers [85]. Cascades can be used to identify where patients 'leak' out and are lost at each step due to barriers in engaging in care or adhering to treatment, and interventions can thus be tailored to such issues and 'patch the leaks' [87].

The adult HIV population aged 15 and older in the UK were reported to have met the 90-90-90 target, with 92% of those living with HIV diagnosed, 98% of those diagnosed on treatment and 97% of those on treatment being virally suppressed in 2017 [88]. However, the sub-group of young people aged 15 to 24 years were least likely to be engaged in care, to be on ART with a CD4

<350 cells/mm3 and to have achieved viral suppression (<200 copies/ml), compared to older age groups (Figure 1.7) [89].

Figure 1.7: (A) proportion of adults engaged in care for 12 months in 2012 (B) with CD4 <350 cells/mm3 and on ART in 2013, (C) virally suppressed (<200 copies/ml) and on ART in 2013 [89]

In the USA, adolescents and young people were also reported to have sub-optimal outcomes at all stages of the cascade, from diagnosis to viral suppression compared to older age groups [90]. The majority of the cascade literature has focused on adults with non-perinatal HIV [91–95] or HIV-exposed infants born to pregnant women with HIV [96–98]. Few studies have adopted the cascade approach for adolescents and young people diagnosed with HIV from birth or early childhood and with prolonged exposure to ART. Even fewer studies investigated the cascade among young people who transferred from paediatric to adult care.

1.8. Transfer from paediatric to adult care

Transferring from paediatric to adult care, also referred to as transitioning care settings, has been defined as "a purposeful, planned process that addresses the medical, psychosocial and educational/vocational needs of adolescents and young adults with chronic physical and medical conditions as they move from child-centred to adult-orientated health care systems" [99]. The terms transfer and transition have been interchangeably used in the literature, and both terms are used in this thesis. It is suggested, following transfer, young people leave behind a family-orientated and supportive environment in paediatric care for a less friendly environment in adult care, where more autonomy is often required. The difference in these care cultures can make transition a period of difficult adjustment [100] and young people are thus at risk of 'falling through the cracks' of the healthcare system and disengaging from care, thereby adversely affecting their health outcomes [84].

In the UK, some young people may transfer to specialised young people's clinics designed to be more 'youth-friendly', where services are tailored to the unique needs of young people with HIV. Others transfer to general adult HIV clinics, often within infectious diseases and genitourinary medicine (GUM) settings that tend to have a larger and predominantly older adult population with services which are less focused on trying to be 'youth-friendly'. Youth-friendliness is described as a patient-centred approach that addresses the needs of adolescents and young people [101].

There are varying models of the transition process [84,102]. Some transition models allow for a more integrated approach where adolescents can access adult services from within the paediatric clinic (e.g. a dedicated adolescent day within a paediatric clinic). Other models include transferring to a specialised young people's clinic, attended only by adolescents and young adults. This type of clinic generally offers specialised youth-friendly services. However, adolescents must then re-transfer for a second, later, time to general adult care. A third transition model consists of a simpler 'hand over' where young people transfer to adult care with preparation and a comprehensive transfer programme [84]. This latter model is described to be suitable for smaller clinics where a dedicated young people's clinic is not available. There is a fourth transition model, similar to the second model, young people transition to specialised young people's clinic but do not engage in a further transition to another care setting. A successful transition model has been described to require a flexible and age appropriate approach in order to meet the needs of the young person within the chosen model [84,103]. A randomized controlled trial has not been conducted to determine superiority of one model over another. A particular model would generally be chosen depending on the patient group, geographical location and the resources available [84]. The literature has described different transition models that exist around the world [77,104–107]. While in Europe young people tend to transfer at around 17-18 years of age and transfer is generally from paediatric to adult clinics, the USA has more of a healthcare focus on adolescent specialist care, and transfer in many of the US studies refers to the transfer from adolescent to adult care. There may be larger differences from paediatric to adult care than from adolescent to adult care, as paediatric care is described to be more family orientated and 'friendlier' than adult care settings where more autonomy is expected from the young person [102].

An increasing number of young people with PHIV are transferring to adult care in the UK. By the end of March 2017, almost half (44%) of the UK and Ireland's paediatric cohort had transferred to adult care, with 50 to 120 young people having transferred to adult care each year from 2009 to 2016 [71]. With the number of newer diagnoses in children and adolescents decreasing and a greater number of children reaching the age at which they transfer to adult care, the number of children in CHIPS is declining [57].

The success or effect of transfer is often assessed using clinical measures such as linkage and engagement in care, mortality, virological and immunological outcomes in adult care [76,78,108]. Research on young people with HIV transferring to adult care is more limited in comparison to adolescents with other chronic diseases. This may be due to the PHIV population only recently reaching adulthood, as previously children with HIV did not survive past their childhood [109]. To date, studies investigating health outcomes post-transfer have reported contradictory findings, with some reporting worsening health outcomes [77,110], as similarly reported in other childhood chronic diseases such as diabetes and cystic fibrosis [111–115]. However, other HIV studies have reported improved health outcomes post-transfer to adult care [105,116].

1.9. Youth-friendly HIV services

With the health disparities experienced by young people with HIV compared to older age groups, there has been an increased focus on youth differentiated care models [117–119]. Patient-centred HIV care is tailored to the unique and often unmet needs of these young people [118]. Within differentiated care models for young people, the WHO highlighted in recent years the importance of including family-based approaches and integration of psychosocial support, sexual health services and peer support groups [119]. Services that can accommodate and meet the unique needs of young people are referred to as youth-friendly services and while this term is widely used it is still inconsistently defined [120].

The WHO has recently assessed the effectiveness of youth-friendly services in comparison to standard care by conducting a systematic review which included eleven randomized control trials and eight observational studies with varying population groups (young people living with HIV, diabetes and mental health) [119]. The systematic review found that young people attending clinics with youth-friendly services had a small but significant improvement in several outcomes (i.e. health outcomes, knowledge, attitude, sexual risk-reduction behaviour and self-efficacy). Among just the HIV studies included in the review, a small but significant improvement in young people's outcomes (i.e. short-term viral reduction and long-term ART adherence) were reported. These findings thus shaped WHO's recommendation for the implementation of youth-friendly services, where the following qualities of care objectives were highlighted [119,121]:

1. Accessibility – where all young people can access and afford the health services (e.g. convenient clinic hours).
2. Acceptability – where young people access care in a confidential, private and non-judgemental space (e.g. separate youth waiting area).
3. Appropriateness – where health needs are addressed by the health services or via referral
4. Effectiveness – where healthcare providers have suitable competencies and adhere to guidelines when delivering health services.
5. Equity of care – where services are available to all young people.

To date, approaches used to improve the engagement or health outcomes of young people with HIV, have included individual-level interventions such as text messaging, peer support and motivational interviewing, and clinic-level interventions such as evening-hour clinic appointments, walk-in services and established youth-focused care models based within clinics.

1.10. Brief overview of HIV studies (CHIPS, SOPHID, HARS and UK CHIC) included in this thesis

CHIPS is a prospective cohort study that follows children diagnosed with HIV and receiving paediatric care in the UK and Ireland. As the cohort's data are provided by paediatric HIV clinics, the follow-up period is limited to the duration of follow-up in paediatric care. Therefore, it is not possible to undertake further long-term research on these children once they transfer to adult care as CHIPS does not have access to the adult data of former participants.

In the UK, outcomes in the adult HIV population are monitored through two national adult HIV surveillance systems coordinated by Public Health England (PHE) - Survey of Prevalent HIV Infections Diagnosed (SOPHID); and HIV and AIDS Reporting System (HARS) - as well as through the largest UK adult cohort, the UK CHIC study. Only participants aged ≥15 years are followed up in SOPHID and HARS and participants aged ≥16 years in the UK CHIC study. Therefore, these adult studies cannot assess the participants' history of health in paediatric care without access to paediatric data.

Throughout this thesis, I refer to former CHIPS participants who are in adult care as 'young people'. The WHO defines young people as individuals aged 10 to 24 years. Some CHIPS participants are aged above 24 years at last visit in adult care but are still referred to as young people. In addition, the CHIPS cohort is not exclusively a population with PHIV; whilst 91% of the cohort acquired HIV in this way, 2% acquired HIV via blood transfusion, 1% via other routes (i.e. sexually) and 6% had unknown routes of acquisition (unpublished CHIPS data, 2018). Therefore, to be inclusive of all acquisition groups in this thesis, CHIPS participants will be referred to as young people with HIV, rather than those with PHIV.

1.11. Aims and outline of this thesis

The aims of this thesis are to:

1. develop a linkage algorithm that can link young people's paediatric and adult data across the CHIPS, SOPHID, HARS and the UK CHIC studies;
2. assess service provision and level of 'youth-friendliness' of adult clinics attended by young people who transferred from paediatric care;
3. explore disengagement from care, AIDS, mortality, severe immunosuppression and viral failure following transfer to adult care; and
4. explore the cascade of care among young people who transferred from paediatric to adult care, compared to young people with BHIV.

Each of my chapters are outlined below. The clinical importance and limitations of each study are described within the respective chapter.

1.11.1. Chapter 2: Literature review

This chapter provides a detailed review of the published literature on the cascade of care among young people with HIV, as well as engagement in care and health outcomes following transfer to adult care.

1.11.2. Chapter 3: Methods and data linkage of paediatric data and adult data

Chapter 3 describes the methods of CHIPS, SOPHID, HARS and the UK CHIC studies. This includes the description of the data collection processes and limitations of each study, and standard statistical methods used in this thesis. The data linkage method and results are also presented and the overlap of participants between the linked studies is described. The data linkage algorithm and results were presented as a poster presentation at the International Workshop on HIV & Hepatitis Observational Databases [122].

1.11.3. Chapter 4: Service provision for young people with HIV following transfer to adult care

This chapter describes a national clinic survey developed and conducted within the adult HIV services available to young people with HIV who transferred out of paediatric care. Clinics were also ranked by their level of youth-friendliness, determined by the provision of services recommended by youth-friendly and transfer guidelines. The results from the survey are described and discussed.

1.11.4. Chapter 5: Mortality and disengagement from care among young people with HIV who transferred to adult care

This chapter describes progression to AIDS and/or mortality post-transfer to adult care among young people with HIV using CHIPS and UK CHIC linked data. The risk of and factors associated with progression to AIDS and/or mortality among young people with HIV post-transfer to adult care are investigated. The rate and factors associated with disengagement from adult care are also described. The AIDS/mortality analysis from this chapter was presented at the 10th International Workshop on HIV Pediatrics [123] and the 13th Annual CHIVA Conference [124], respectively.

1.11.5. Chapter 6: Immunological and virological outcomes among young people with HIV who transferred to adult care

This chapter describes the immunological and virological outcomes before and after transfer to adult care using CHIPS and UK CHIC data. The incidence and predictors of severe immunosuppression and viral failure are also assessed on a participant level and also on a clinic level (i.e. with regards to adult clinics' level of youth-friendliness). The analyses on severe immunosuppression and viral failure were presented as oral and poster presentations at the International Workshop on HIV & Hepatitis Observational Databases [125] and the 10th International Workshop on HIV Pediatrics [126].

1.11.6. Chapter 7: Cascade of care among young people with HIV following transfer from paediatric to adult care in the UK

In Chapter 7, the national cascade of care is constructed for young people who transferred to adult care using SOPHID and HARS data. This cascade is also compared to that for young people with horizontally acquired HIV (i.e. men who have sex with men and those acquiring HIV through sex between men and women) also in adult care.

1.11.7. Chapter 8: Concluding remarks

A final summary and discussion of the overall findings, their clinical significance and limitations, along with opportunities for further research are presented in Chapter 8.

2. Chapter 2: Literature review

2.1. Chapter content

An increasing number of children with HIV are surviving into adulthood, thus requiring them to transfer from paediatric to adult care. This brings into question the health status of this population following transfer to adult care. To date, most existing paediatric observational cohorts have limited follow-up data on young people with PHIV after they have transferred to adult care.

In this chapter, I summarise the literature on mortality, engagement in care and health outcomes post-transfer to adult care and the cascade of care among young people with HIV. The literature review focuses on research conducted in HIC (defined according to the World Bank country classification), as the study population for this thesis is based in the UK. My literature review will focus on the following topics, chosen to complement my analysis chapters:

1. Engagement and mortality status post-transfer to adult care
2. Immunological and virological status post-transfer to adult care
3. The cascade of care among adolescents and young people with HIV
4. The impact of youth-friendly clinic services on the engagement and health outcomes of young people with HIV

2.2. Methods

A separate literature search was carried out for each sub-topic listed in section 2.1. All searches were undertaken using the PubMed bibliographic database. In addition, the following conference abstract databases were explored: The International AIDS Society (IAS) Conference on HIV Science; the International Workshop on HIV Pediatrics; and the Conference on Retroviruses and Opportunistic Infections (CROI), the calendar years covered by the searches varied by the sub-topic. Relevant papers and published literature reviews were also searched for additional references not identified in the PubMed searches.

The inclusion criteria applied to all four sub-topics were:

Language: English publications

Dates: No date restrictions applied unless otherwise stated for each literature review

Publication type: Primary quantitative research. Although review papers and editorials were excluded, their references were checked for additional studies not captured in the PubMed search.

Participant characteristics: Characteristics varied for each literature review section. The common population of interest for all sections were young people with HIV in HIC, as the population of interest in this thesis are predominantly young people with PHIV and also small proportion with BHIV who were previously followed up in CHIPS. Additionally, no age restriction was applied, firstly, due to studies defining ‘young people’ and ‘adolescents’ differently and secondly, due to the age of transfer to adult care differing by country and region. Therefore, to include all relevant studies, search terms specific to adolescents and young people were used for all sections. Table 2.1 lists individual sets of search terms used for each section of this literature review. Further inclusion criteria applied for each literature review section are described in the methods of each literature review.

Table 2.1: Literature review search terms and databases used

Topic	PubMed database search terms	Conference database search terms (IAS, CROI, International Workshop on HIV Pediatrics)
Engagement and mortality status post-transfer to adult care	(((HIV[Title]) AND (youth OR young people OR young person* OR adolescent OR teen* OR young adult*)) AND (Transfer OR transfer OR transfer to adult care OR transfer to adult care OR transfer in care OR healthcare transfer OR transfer outpatients clinic))	Transfer to adult, adult care, transfer to adult, post-transfer OR post-transfer
Immunological and virological status post-transfer to adult care	(((((((HIV[Title]) AND Adolescents) AND ((Transfer OR transfer OR transfer to adult care OR transfer to adult care OR transfer outpatients clinic))) AND ((health outcomes OR immunosuppression OR CD4 OR immunological outcome OR virological outcomes OR viral failure OR virological OR viral OR viral rebound OR unsuppressed OR virologically suppressed OR treatment failure OR treatment outcome OR virologic suppression))) AND (young people OR youth OR young adult)))))	Transfer to adult, adult care, transfer to adult, post-transfer OR post-transfer
The effect of youth-friendly clinic services on the engagement and health outcomes of young people with HIV	((((HIV[Title]) AND (youth OR young people OR young person* OR adolescent OR teen* OR young adult*)) AND (adult care OR adult services OR outpatient clinic OR HIV care OR adolescent medicine clinics OR community-based health center OR adolescent medicine OR adolescent clinic OR adult clinic)) AND (youth friendly OR adolescent friendly OR peer support OR youth friendly technology OR clinic-specific factors OR clinic-level factors OR text message OR accessible services OR care model)) AND (HIV treatment outcomes OR medical outcomes OR HIV outcomes OR engagement OR disengagement OR engagement OR linkage to care OR viral load OR adherence OR immunological OR CD4))))	Clinic-level, youth-friendly, adolescent-friendly, text message OR peer support
Cascade of care among adolescents and young people	HIV[Title] AND (youth[Title/Abstract] OR young people[Title/Abstract] OR young person*[Title/Abstract] OR adolescent[Title/Abstract] OR teen*[Title/Abstract] OR young adult*[Title/Abstract]) AND (perinatally OR perinatal OR cascade OR continuum OR 90-90-90 OR transfer)	Cascade of care, continuum of care, cascade, continuum, 90-90-90 OR care pathway

Note: IAS, International AIDS Society; CROI, Conference on Retroviruses and Opportunistic Infections

2.3. Mortality and disengagement post-transfer to adult care

This literature review investigated mortality and disengagement status among young people with HIV post-transfer to adult care in HIC.

2.3.1. Methods

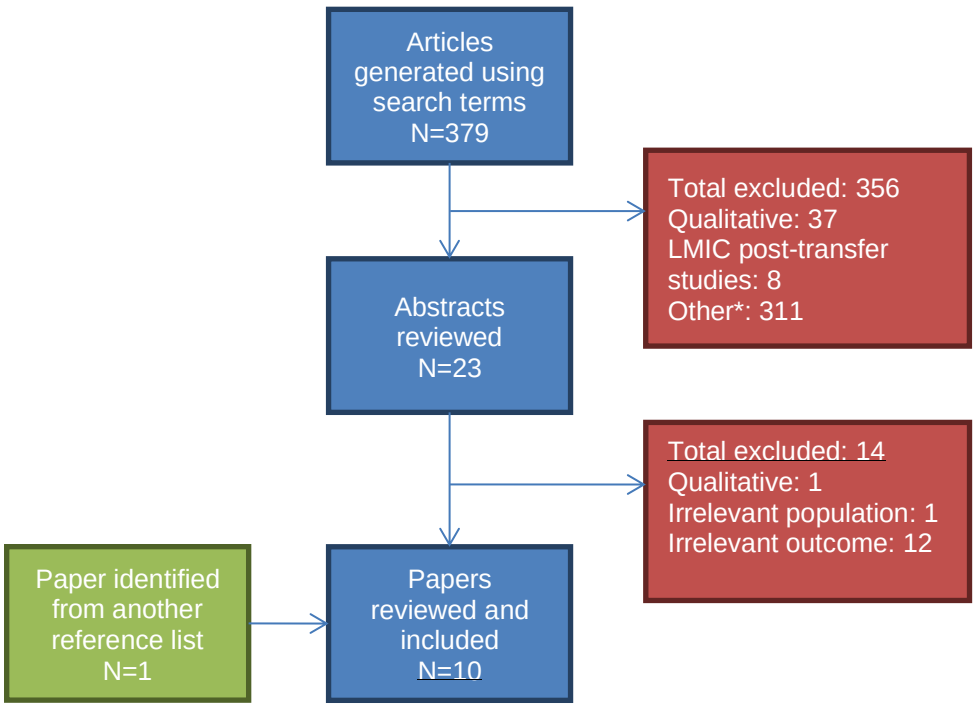
In addition to the inclusion criteria specified in section 2.2, studies were required to report mortality or disengagement from care findings.

In the wider HIV literature engagement in care is used to describe linkage to care and engagement in care interchangeably [108,127,128]. In this thesis, engagement in care is used to refer to the level to which participants remain in care following their first visit. Disengagement from care is used to describe the level at which participants are not in care. However, to allow for comparability between the studies included in this review, engagement estimates were converted into disengagement estimates. This allowed the studies included in this review to be comparable to the disengagement findings in Chapter 5 of my thesis.

2.3.2. Results

The literature search identified 379 publications. Only 10 papers met the inclusion criteria including one paper which was identified through manually reviewing the reference list of another paper. Papers that did not report post-transfer mortality and/or disengagement findings were excluded. Literature reviews were also excluded as they did not report primary data (Figure 2.1). The 10 papers were identified in the PubMed database and were published from 2014 to 2018. All studies were of young people with HIV following transfer to adult care.

Figure 2.1: Flowchart of studies considered for the mortality and disengagement literature review



**Papers with irrelevant study populations or outcomes of interest*

Six studies were from Europe; two from the UK (one multi-region and one London study), another two from Italy (Brescia and Gonoa), one from Spain (study region not described) and the

Netherlands (another study), all of which were predominantly of PHIV populations (78% to 100%) [78,104,105,129,130]. All except one [129], had longitudinal study designs, reporting mortality and/or disengagement outcomes over a two year observation period following transfer date [78,104,105,129,130].

Another four studies were from North America; one from Canada and three from the USA. The Canadian study was a single-centre longitudinal study with a median follow-up duration of 4 years post-transfer and 100% of the population had PHIV. All three US studies were multisite studies with a longitudinal study design, adult follow-up periods ranged from one to three years. One of the US studies had a population with 100% PHIV, while the other two US studies were of predominantly young people with BHIV (15% to 38% had PHIV) [108,131]. Age at transfer ranged from 17 to 22 years for all studies [78,104,105,110,130–132].

2.3.2.1. Mortality post-transfer to adult care

Within this literature review, six studies reported mortality findings among young people who transferred to adult care [78,104,129,130,133,134] of which only three described causes of deaths. None of the studies investigates risk factors of mortality following transfer to adult care.

The proportion of deaths reported by the six post-transfer cohorts across Europe and the USA ranged from 0% to 7% [78,104,129,133–135] and the majority of deaths were due to AIDS-defining illnesses and some included respiratory diseases [78,104,134]. Two of these, the Brescia and Genoa study, were single-site studies from Italy with a sample size of 24 and 45 young people with PHIV, respectively [129,135], which limits the generalisability of their estimates. The remaining studies had larger sample sizes, ranging from 209 to 735 young people, mostly with PHIV, although, there was no correlation with the sample size and number of deaths.

Only the London and New York studies described mortality rates post-transfer to adult care. The London study of 11 post-transfer deaths, reported mortality rates stratified by age and health care setting (paediatric versus adult care). The crude mortality rate increased from 0.2 per 100 person-years (95% CI 0.1, 0.6) among young people with PHIV aged 13 to 15 years in paediatric care to 0.9 (95% CI 0.3, 2.3) for those aged ≥ 21 years in adult care. The mortality rate ratio was 2.7 (95% CI 0.6, 12.2) and 4.9 (95% CI 1.1, 22.0) for those aged 16 to 20 years and ≥21 years in adult care, respectively, with young people aged 13 to 15 years in paediatric care being the reference group (p=0.18). The wide confidence intervals were due to the small number of events [78].

The New York study of used state-level surveillance data to report mortality findings of all young people with PHIV who transferred to adult care (N=735, 41 deaths). There was a large increase in the mortality rate from one year pre-transfer to one year post-transfer to adult care (0.2 to 5.6 per 100 person-years, Figure 2.2). The rise in mortality rate was suggested to be due to deteriorating clinical conditions prior to transfer as opposed to the effect of transfer itself. This explanation was supported with all deaths occurring within one year following transfer to adult care, of which almost two-thirds (61%) occurred in the first 6 months post-transfer.

Figure 2.2: Estimates of the mortality rate per 100 person-years and the 95% confidence intervals, before and after transfer to adult care among young people with PHIV in the UK and USA

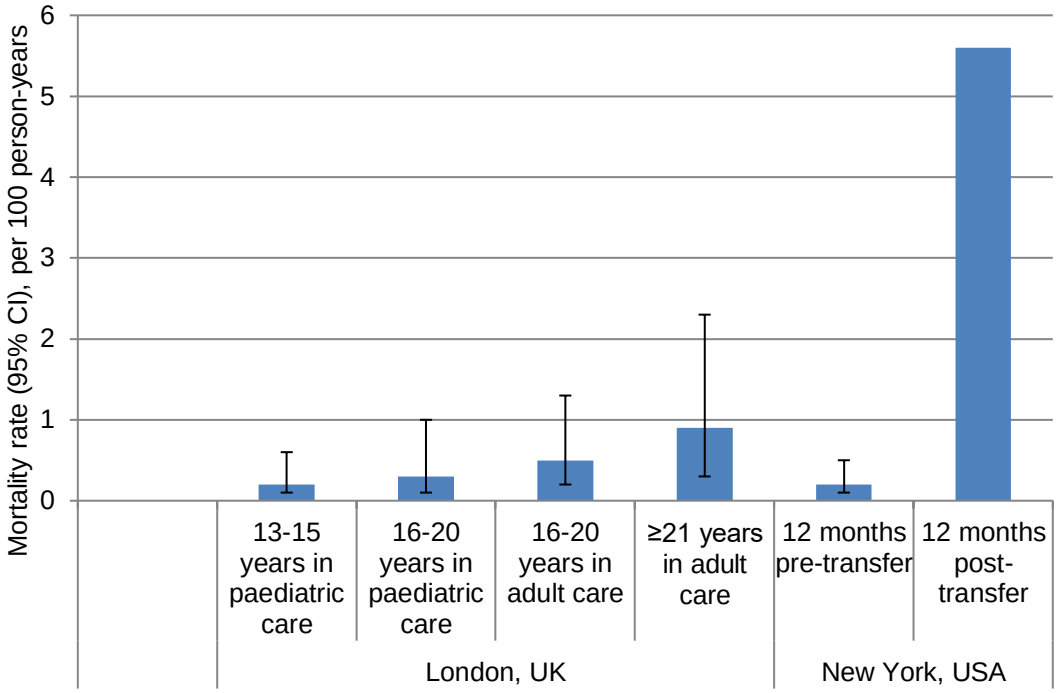


Table 2.2: Mortality estimates of young people who transferred from paediatric to adult care in HIC

First author, city, country, year[1], ref	Study design	Sample size and population	Age at transfer to adult care [A]	Inclusion criteria	Mortality estimate	Causes of death	Time point for Mortality rate	Mortality rate (95% CI) /100 person-years
Europe								
Judd, multi-region, UK, 2017, [104]	Multi-site longitudinal study	271 (93% perinatal)	Median: 17 [IQR 16-18] years	Transferred to adult care	7 (3%)	3 (42%) advanced HIV, 1 (1%) leukoencephalopathy, 1 (1%) renal failure, 1 (1%) pulmonary TB, 1 (1%) unknown	Not reported	Not reported
Fish, London, UK, 2014, [78]	Multi-site longitudinal study	248 (91% perinatal)	Range: 15-21 years	Transferred to adult care	11 (4%)	1 (1%) infective exacerbation of bronchiectasis, 1 (1%) progressive multifocal leucocephalopathy, 2 (2%) end-stage AIDS, 1 (1%) pulmonary RSV infection, 1 (1%) sepsis, 1 (1%) cerebral toxoplasmosis, 2 (2%) suicides, 1 (1%) cerebral lymphoma, 1 (1%) missing	13-15 years in paediatric care 16-20 years in paediatric care 16-20 years in adult care ≥21 years in adult care	0.2 (0.1-0.6) 0.3 (0.1-1.0) 0.5 (0.2-1.3) 0.9 (0.3-2.3)
Izzo, Brescia, Italy, 2018, [130]	Single-site longitudinal study	24 (100%) perinatal)	Median:18 years	Transferred to adult care	0 (0%)	Not reported	Not reported	Not reported
Sainz, multi-region, Spain, 2015, [133]	Multi-site cross-sectional study	209 (100% perinatal)	Median: 18 [IQR 17-19] years	Transferred to adult care	4 (2%)	Not reported	Not reported	Not reported

Table 2.2 continued on the next page

First author, city, country, year[1], ref	Study design	Sample size and population	Age at transfer to adult care [A]	Inclusion criteria	Mortality estimate	Causes of death	Time point for Mortality rate	Mortality rate (95% CI) /100 person-years
Europe								
Righetti, Genoa, Italy, 2015, [129]	Single-site cross-sectional study	45 (100% perinatal)	Median: 9 years	Transferred to adult care	3 (7%)	Not reported	Not reported	Not reported
North America								
Xia, New York, USA, 2018, [134]	Multi-site longitudinal study using surveillance data	735 (100% perinatal)	Median: 22 years	In care last year of paediatric care and transferred to adult care	41 (6%)	34 (83%) HIV-related diseases , 2 (5%) cancer-related illnesses, 1 (2%) cardiovascular disease, 1 (2%) respiratory disease, 1 (2%) homicide, 2 (5%) unknown	12 months pre-transfer	0.2 (0.1-0.5)
							12 months post-transfer	5.6 (4.1-7.6)

A - The transfer date definition varied by study (last visit date in paediatric care or first visit date in adult care); IQR - interquartile range; TB - Tuberculosis

2.3.2.2. Disengagement from care post-transfer to adult care

Eight of the studies in this literature review measured engagement and/or disengagement post-transfer to adult care across Europe and North America. As previously mentioned, all engagement estimates were converted to disengagement estimates in order to better compare between studies. Only the London and multi-region UK studies did not report disengagement or engagement estimates due to not being able to differentiate true disengagement from participants transferring to non-participating clinics [78,104].

The four European post-transfer studies all measured disengagement from care using the LTFU measure in adult care [105,129,133,135], although none of the studies specified their LTFU definition. The four post-transfer studies from North America used similarly detailed definitions to measure engagement in care: ≥2 visits in a 12 month period, ≥3 months apart [131]; ≥1 visit in each 12 month window over a three year period [134]; ≥1 visit in a 6 month window over a 12 month period [108] or a combination of the LTFU measure (no visit in 12 months) and ≥1 visit in the last 6 months of follow-up [110]. All these engagement definitions were used to describe proportions not engaged in care (Table 2.3).

Across Europe, LTFU estimates ranged from 0.4% to 20% (Figure 2.8). The Spanish study, a multisite cross-sectional study, found 12% of young people with PHIV to be LTFU in adult care, while the single-site Genoa study found 0.4% to be LTFU in adult care. Higher LTFU levels were reported by the Dutch Brescia studies, with 20% LTFU following the last adult visit and 14% LTFU by 24 months post-transfer, respectively. However, the two Italian studies were from a single-sites which limits the generalisability of their disengagement estimates to the general perinatal population in adult care.

Across Canada and USA, disengagement from care levels ranged from 11% to 50%. The New York study reported 14% of 735 young people with PHIV to take more than 12 months to link to adult care following the last paediatric visit [134]. Despite this, the proportions disengaged from adult care following transfer remained low over a three year period in adult care (5% to 6%). In Canada, the Quebec study interviewed 25 young people with PHIV who transferred to adult care and described 12% who had no clinic visit in the last year prior to the interview date [110].

Table 2.3: Disengagement estimates of young people who transferred from paediatric to adult care

First author, city, country, year	Study design	Sample size and population	Age at transfer [A]	Inclusion criteria	Disengagement definitions	Time point	Disengagement prevalence
Europe							
Weijsenfeld, multi-region, Netherlands, 2016,	Multi-site longitudinal study	59 (91% perinatal)	Range: 15-21 years	Transferred to adult care	LTFU (definition not specified)	Last adult visit	14%
Sainz, multi-region, Spain, 2015	Multi-site cross-sectional study	209 (100% perinatal)	Median: 18 [IQR 17-19] years	Transferred to adult care	LTFU (definition not specified)	12 months post-transfer	12%
Izzo, Brescia, Italy, 2018	Single-site longitudinal study	24 (100% perinatal)	Median:18 years	Transferred to adult care	LTFU (definition not specified)	12 months post-transfer 24 months post-transfer	0% 20%
Righetti, Genoa, Italy, 2015	Single-site cross-sectional study	45 (100% perinatal)	Median: 9 years	Transferred to adult care	LTFU (definition not specified)	In 2014	0.4%
North America							
Xia, New York, USA, 2018	Multi-site longitudinal study using surveillance data	735 (100% perinatal)	Median: 22 years	In care last year of paediatric care and transferred to adult care	Not engaged, following definition converted: ≥1 adult visit in each 12 months period	12 months post-transfer 24 months post-transfer 36 months post-transfer	15% 14% 14%

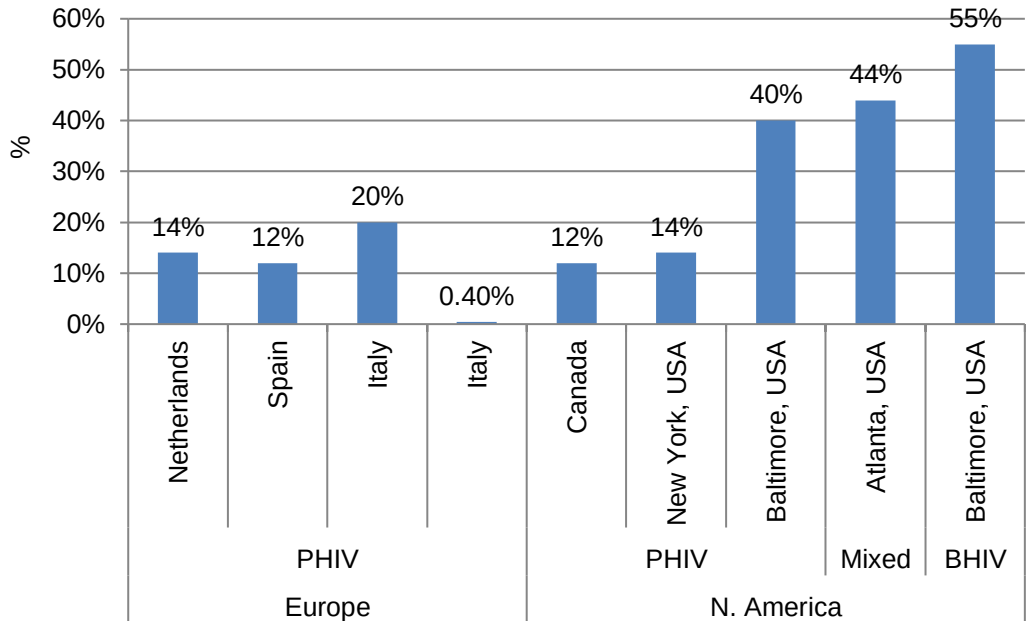
Table 2.3 continued on the next page

First author, city, country, year	Study design	Sample size and population	Age at transfer[A]	Inclusion criteria	Disengagement definitions	Time point	Disengagement prevalence
North America							
Ryscavage, Baltimore, USA, 2016	Multi-site longitudinal study	19 (100% PHIV)	At first adult visit: 19-27 years	Transferred to adult care	Disengaged from care, following definition converted: ≥2 adult visits over 12 months (1 visit in each 6 months)	12 months post-transfer 12 months post-	40%
	Multi-site longitudinal study	31 (100% BHIV)	At first adult visit: 19-27 years	Transferred to adult care	Disengaged from care, following definition converted: ≥2 adult visits over 12 months (1 visit in each 6 months)	12 months post-transfer	55%
Kakkar, Quebec, Canada, 2016	Single site longitudinal study	25 (100% perinatal)	18 years	3 visits per year in last two years prior to transfer	Self-reported disengagement from care, following definition converted: ≥1 visit in last 12 months	In the last year prior to study interview [B]	12%
Hussen, Atlanta, USA, 2017	Single site longitudinal study	72 (15% perinatal)	Median: 25 [IQR 23, 25]	Transferred to adult care	Disengaged from care, following definition converted: ≥2 visits in a 12 month period, ≥3 months apart	24 months pre-transfer 12 months pre-transfer 12 months post-transfer 24 months post-transfer	5% 5% 11% 44%

A - The transfer date definition varied by study (last visit date in paediatric care or first visit date in adult care); B – Quebec study carried out interviews (at an unknown date) where participants were asked about their engagement in care in the past year

The Baltimore study was the only one to report disengagement from care estimates post-transfer by mode of HIV acquisition (N=19 with PHIV and n=31 with BHIV) [108]. The proportion disengaged from adult care was lower among PHIV at 40% compared to 55% among BHIV youth, although this was a non-significant difference. The small sample size likely limited the statistical power needed to detect a potential trend between the exposure groups.

Figure 2.3: Estimates of disengagement from care by the latest reported adult visit following transfer date, by location and mode of HIV acquisition of study populations



The Atlanta study of 72 young people with mixed modes of HIV acquisition (28% with PHIV) assessed disengagement from care both before and after transfer from paediatric to adult care and reported 5% to be disengaged at both 12 and 24 months prior to transfer date. Among those who transferred, disengagement levels increased from 11% at 12 months post-transfer to 44% by 24 months ($p<0.001$) [131]. The majority of the Atlanta study population were those with BHIV, which may not be representative of young people with PHIV, who likely have been in care for a longer time and may therefore be more likely to be engaged in care compared to young people with BHIV [81,84]. Nonetheless, more data are needed determine which exposure group is at higher risk of disengagement.

The Atlanta study (N=72) was the only one to investigate factors associated with disengagement from adult care following transfer date. Exposure variables explored included demographic characteristics (sex, ethnicity and age at transfer), and clinical characteristics (mode of HIV acquisition and baseline CD4 count). The study found that young people with longer gaps in care between their last paediatric visit and their first adult visit had an increased risk of disengagement in the second year following transfer. This finding possibly reflects young people's unpreparedness to transfer to adult care. Younger age at transfer was also associated with increased risk of disengagement from adult care, although the study authors stated this association was likely due to unmeasured confounding and not age or participant maturity itself, as young people at this clinic all transferred to adult care at a given age (which was not specified

but described to have changed over time). Sex, ethnicity, mode of HIV acquisition (perinatal vs behavioural), immunological and virological characteristics at transfer date were not associated with disengagement from adult care.

2.3.2.3. Summary

Overall, the post-transfer mortality estimates across Europe and North America were low and ranged from 0% to 7%. However, two studies that compared mortality rates before and after transfer to adult care both found rates to increase in adult care [78,134]. One study hypothesised that poorer health outcomes at the end of paediatric care drove the increased mortality rate. With limited study follow up (1 to 2 years post-transfer) it is difficult to assess the long-term mortality trends and if mortality rate continued to increase beyond the short study periods. Disaggregated mortality data are needed to determine if the rise in HIV-related deaths reported among young people, globally, are driven by the PHIV or BHIV group.

Disengagement from adult care estimates varied from 0.4% to 50%, with poorer estimates across North America compared to Europe. The differences in disengagement estimates may be due to most European countries offering free HIV care compared to the situation in North America where healthcare is private and either paid for by patients' employee health insurance or by the government's Medicare program for those who qualify (i.e. aged ≥65 years or with a disability). Those without insurance or Medicare help would have to pay privately for health care. In general, the wide range of disengagement estimates also reflects the different definitions used. With regard to measuring disengagement from care, studies would ideally need national coverage in order to distinguish undocumented self-referrals to other clinics from true disengagement from care. Only the Spanish and Genoa studies reported the number of young people who transferred to a non-participating clinic [129,133], which suggests the other studies that measured disengagement from adult care may not know if young people have transferred to another clinic. This leads to the risk of participants being misclassified as disengaged from care and the overestimation of disengagement figures. Although, it is difficult to know how mobile the study populations are, as young people who live in smaller cities or towns with only one clinic available would be less likely to transfer to another clinic and thus result in less bias, compared to a study in a larger city where multiple clinics are available for the young person.

Only a small number of studies have investigated mortality and disengagement levels following transfer to adult care, most of which were restricted by small sample sizes, single clinics, short follow-up period and no post-transfer study has achieved national coverage. All of these limitations result in findings that cannot be easily generalised to other perinatal populations in adult care. In addition, all the post-transfer studies may be subject to survival bias as study populations consisted of young people who successfully completed their transfer to adult care [105,108,131,133,135], or had history of good engagement in paediatric care [110,134]. These inclusion criteria resulted in selection biases, where mortality and disengagement from adult care are measured among young people with better history of engagement in care compared to those who did not complete their transfer to adult care. The exclusion of the latter group likely leads to underestimated mortality and disengagement figures. The sub-populations who are LTFU prior to or during transfer to adult care are likely to not have access to ART and are at risk of disease

progression and mortality. Therefore, there is a need for data on the characteristics and outcomes of this population with linked paediatric and adult data in order to inform strategies to minimise disengagement during and following transfer to adult care.

Additionally, there is a large gap in the literature to address factors associated with mortality and disengagement following transfer to adult care. In my thesis, the data linkage of paediatric and adult cohort data has enabled me to investigate pre-transfer risk factors of post-transfer mortality and disengagement from care (in Chapter 5).

2.4. Immunological and virological outcomes post-transfer to adult care

This literature review investigated the immunological and virological status among young people with HIV post-transfer to adult care in HIC.

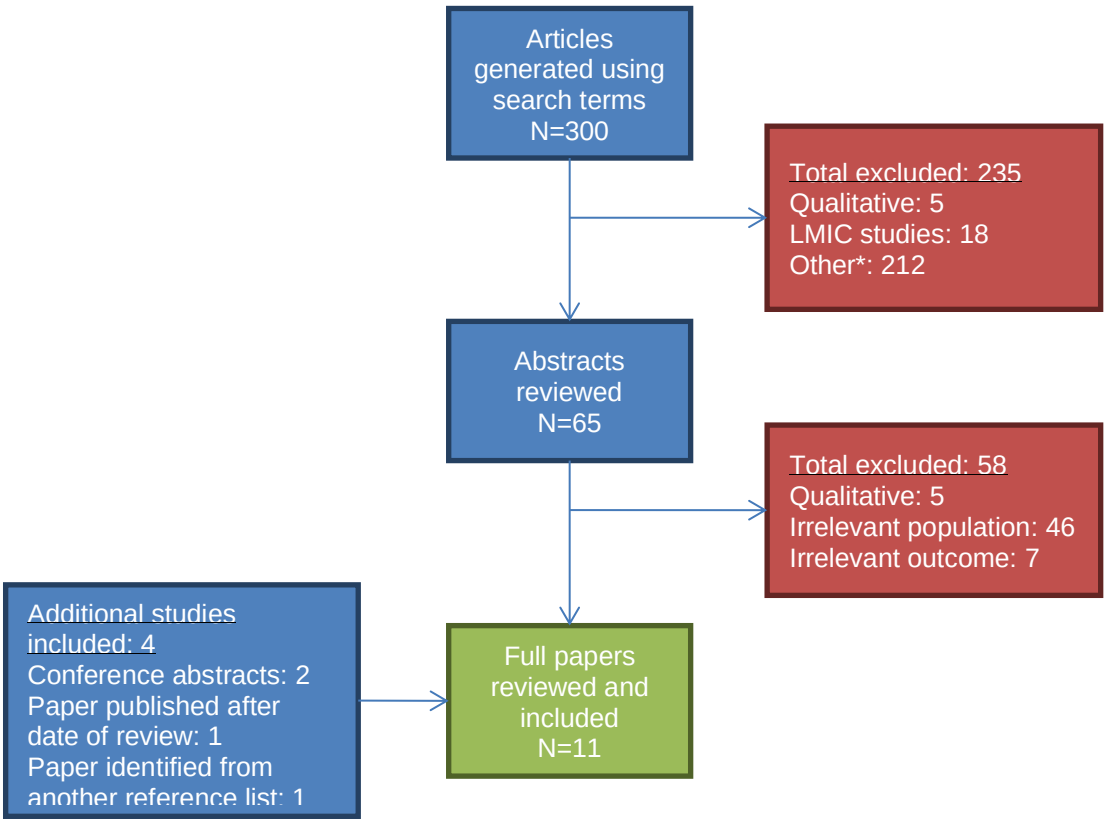
2.4.1. Methods

In addition to meeting the inclusion criteria specified in section 2.2, included studies had to report immunological and/or virological outcomes following transfer to adult care.

2.4.2. Results

The literature search resulted in 300 publications, of which only seven were papers that met my inclusion criteria described in section 2.2 and section 2.4.1. Two additional papers were identified; one from a manual search of reference lists and another published after this literature review search was carried out, and two abstracts were found in the CROI abstract database. This resulted in a total of 11 studies being included in this literature review. Most of the papers reviewed and excluded were qualitative studies, literature reviews or did not report immunological and virological outcomes among young people post-transfer to adult care (Figure 2.4).

Figure 2.4: Flowchart of studies considered for the immunological and virological literature review



**papers with irrelevant study populations or outcomes of interest*

There were seven European studies; including a multi-region UK study, a London study, two Italian studies from Brescia and Genoa, a multi-region Spanish study, one multi-region Dutch and a Stockholm study. All studies had populations primarily consisting of young people with PHIV (91% to 100%). The multi-region UK study and the London study both used patient data from the same paediatric cohort study (CHIPS), although the London study collected adult data from four selected hospitals (selection method not specified) [136], while the other UK study linked the patient data to one of the largest adult cohorts in the UK (the UK CHIC study) [104]. Another four studies were from North America; one from New York, Baltimore, Atlanta and one from Quebec, Canada. The Atlanta and Baltimore studies were of 15% and 38% young people with PHIV, respectively, while the New York and Quebec studies were of all young people with PHIV (100%).

The majority of studies had multi-centre longitudinal study designs, adult follow-up ranging from one to three years post-transfer among those studies. Only the Genoa and Stockholm studies were cross-sectional, measuring health outcomes in 2014 in the former study, while the latter measured health outcomes of the cohort in 2013 and 2015. The Genoa study had a median age at transfer date of 9 years, with the youngest age at transfer being only 2 years. This study described a Genoa clinic with an atypical transfer care model where children and adults attended together and children were provided with a child-customised environment and playground [129]. The transition model adopted by the Genoa clinic limits the comparability of the Brescia cohort to the other post-transfer cohorts across Europe and North America which have median ages at transfer

date ranging from 17 to 25 years.

Eight of the 11 post-transfer studies reported immunological outcomes across Europe and North America [104,108,110,129,130,134,136,137] and all 11 studies reported virological outcomes post-transfer to adult care. Almost all studies (9/11) compared immunological and/or virological outcomes prior to and after the time of transfer [104,105,108,110,130,131,133,134,136].

2.4.2.1. Immunological outcomes post-transfer to adult care

With regard to immunological outcomes in adult care, some studies reported proportions of young people with a CD4 count within a specified threshold (i.e. <200, <350 or ≥500 cells/mm^3) [104,110,129,134,137] and others reported median or mean CD4 counts before and after transfer to adult care [104,108,130,136] (Table 2.4). Inconsistent immunological trends were described across the European and North American studies.

The two UK studies [104,136] used more sophisticated methods, mixed effects regression methods, to measure the slope of CD4 count across paediatric and adult care compared to the other studies. Both studies reported a declining CD4 trajectory in paediatric and adult care, although the London study described the rate of CD4 decline of the 211 young people to slow down in adult care, after a median follow-up post-transfer of three years [136]. The multi-region UK study described further CD4 decline following transfer to adult care among black males, while CD4 count remained stable among black females and increased among white males and females [104]. In contrast, the Brescia study of 24 young people at a single clinic reported the median CD4 count to increase from 534 cells/mm^3 at last paediatric visit to 716 cells/mm^3 by 24 months post-transfer to adult care [130]. It is unclear if similar demographic trends as that reported in the multi-region UK study occurred in the Brescia study, as the CD4 outcome was not stratified by demographic characteristics in the latter study. Additionally, the Brescia cohort had better ART and virological outcomes compared to the other post-transfer cohorts with 100% on ART and virally suppressed (VL <50 copies/ml) by the last adult visit.

Table 2.4: Studies reporting immunological outcomes among young people who transferred to adult care

First author, country, year, ref	Study design methods	Sample size and population	Age at transfer [A]	Inclusion criteria	Immunological definitions [B]	Time point	Immunological outcome
Europe							
Judd, multi-region, UK, 2017, [104]	Multi-centre longitudinal study	271 (93% PHIV)	Median age: 17 [IQR 16, 18] years	Transferred to adult care	CD4 count <200	12 months pre-transfer	21%
						12 months post-transfer	23%
					CD4 change over time using mixed-effects model and adjusted for demographic variables	Over paediatric and adult follow-up	CD4 count declined prior to transfer, following transfer, CD4 count increased for white males and females, remained stable for black women and continued to decline for black males
Hope, London, UK, 2016, [136]	Multi-centre longitudinal study	211 (97% PHIV)	Median age: 18 [IQR 17, 18] years	Transferred to adult care	Mean CD4 count	24 months pre-transfer	420 cells/mm3
						24 months post-transfer	420 cells/mm3
					CD4 change over time using mixed-effects model	Over paediatric and adult follow-up	CD4 count declined in the 2 years prior to transfer and carried on declining post-transfer, although at a slower rate
Izzo, Brescia, Italy, 2018, [130]	Single-centre longitudinal study	24 (100% PHIV)	Median age: 18 years	Transferred to adult care	Median CD4 count	Transfer date	534 cells/mm3
						12 months post-transfer	626 cells/mm3
						Last adult visit	716 cells/mm3

Table 2.4 continued on the next page

First author, country, year, ref	Study design methods	Sample size and population	Age at transfer [A]	Inclusion criteria	Immunological definitions [B]	Time point	Immunological outcome
Europe							
Righetti, Genoa, Italy, 2015, [129]	Single-centre cross-sectional study (data collected in 2014)	45 (91% PHIV)	Median age: 9 years	Transferred to adult care	CD4 count <200	Last visit in 2014	8%
Westling, Stockholm, Sweden, 2016, [116]	Single-centre cross-sectional study	34 (91% PHIV)	Median age: 19 years	Transferred to adult care	CD4 count <350	Last visit 2013	14%
North America							
Xia, New York, USA, 2018, [134]	Multi-centre longitudinal study	735 (100% PHIV)	Median age: 22 years	In care last year of paediatric care and transferred to adult care	CD4 count ≥500	Transfer date 12 months post-transfer 24 months post-transfer 36 months post-transfer	35% 38% 39% 39%
Ryscavage, Baltimore, USA, 2016, [108]	Multi-centre longitudinal study	50 (38% PHIV)	Median age: 25 years	Transferred to adult care	Median CD4 count	Prior to transfer [C] 12 months post-transfer	347 cells/mm^3 351 cells/mm^3
Kakkar, Quebec, Canada, 2016, [110]	Single-centre longitudinal study	25 (100% PHIV)	All: 18 years	3 visits per year in last two years prior to transfer	CD4 count >500	Prior to transfer (time not specified) 12 months post-transfer	64% 29%

A – Transfer definition varied by study; last visit date in paediatric care or first visit date in adult care; B – units: cells/mm^3; C - Time not specified

The Stockholm and Genoa studies were the only two that measured CD4 count cross-sectionally at one time point, in 2013 and 2014, respectively [129,137], while the rest compared CD4 outcomes prior to and after transfer to adult care. The Genoa study found 8% of young people who transferred to adult care to have a CD4 count <200 cells/mm^3 at the last visit in 2014 while the Stockholm one reported 14% with a CD4 <350 cells/mm^3 at the last visit in 2013. However, these findings were from single sites and small samples sizes (N=25-45), which limits the representativeness and generalisability of the findings.

In North America, the New York study had the largest sample size including 735 young people with PHIV who transferred to adult care. This study reported proportion of those with CD4 count ≥500 cells/mm^3 to significantly increase from 35% at last visit in paediatric care to 38%, 39% and 39% at one, two and three years post-transfer (p=0.04) [138]. In contrast to this trend, the Quebec study of 25 young people with PHIV found the proportion with a CD4 count >500 cells/mm^3 to decline from 64% at date of transfer to 29% 12 months post-transfer (p=0.04). Further to this, the Baltimore study of 50 young people (38% with PHIV) found no significant difference in median CD4 count prior to transfer date (time point unspecified) and 12 months post-transfer (347 vs 351 cells/mm^3, respectively, p value not provided).

Comparison of immunological outcomes across the studies was made difficult with studies reporting median CD4 counts, proportion with CD4 <200 cells/mm^3, <350 cells/mm^3 or >500 cells/mm^3 and the use of varying time points in paediatric and adult care, ranging from one to two years pre-transfer and one to three years post-transfer.

2.4.2.2. Virological outcomes in adult care

Of the 11 studies reporting virological outcomes post-transfer, nine compared their findings to pre-transfer outcomes. The majority of studies reported viral suppression using various different viral load thresholds (<40, <50, ≤50, <80, ≤400 or <400 copies/ml). Three studies reported viral failure using the following thresholds: ≥50, >50 and >400 copies/ml, however, to enable comparability between studies, the proportions virally suppressed were deduced from these study findings (Table 2.5).

Table 2.5: Studies reporting virological outcomes among young people who transferred to adult care

First author, country, year	Study design	Sample size and population	Age at transfer [A]	Inclusion criteria	Virological definitions	Time point	Virological outcome
Europe							
Judd, multi-region, UK, 2017	Multi-centre longitudinal study	271 (93% perinatal)	Median age: 17 [IQR 16, 18] years	Transferred to adult care	VL ≤400 copies/ml	12 months pre-transfer	72%
						12 months post-transfer	71%
Hope, London, UK, 2016	Multi-centre longitudinal study	211 (97% perinatal)	Median age: 18 [IQR 17, 18] years	Transferred to adult care	VL <50 copies/ml	24 months pre-transfer	43%
						24 months post-transfer	63%
Sainz, multiple cities, Spain, 2015	Multi-site cross-sectional study	209 (100% perinatal)	Median: 18 [IQR 17-19] years	Virologically suppressed at transfer date	VL ≤50 copies/ml	12 months post-transfer	86%
Weijsenfeld, multiple cities, Netherlands, 2016,	Multi-site longitudinal study	59 (91% perinatal)	Range: 15-21 years	Transferred to adult care	VL ≤50 copies/ml	12 months post-transfer	50%
Righetti, Genoa, Italy, 2015	Single-centre cross-sectional study	45 (91% perinatal)	Median: 9 years	Transferred to adult care	VL ≤50 copies/ml	Last visit in 2014	91%
Izzo, Brescia, Italy, 2018	Single-centre longitudinal study	24 (100% perinatal)	Median age: 18 years	Transferred to adult care	VL <50 copies/ml	Transfer date	62%
						12 months post-transfer	71%
						Last adult visit	100%
Westling, Stockholm, Sweden, 2016	Single-centre cross-sectional study	34 (91% perinatal)	Median: 19 years	Transferred to adult care and on ART	VL <50 copies/ml	Last visit in 2013	90%
						Last visit in 2015	92%

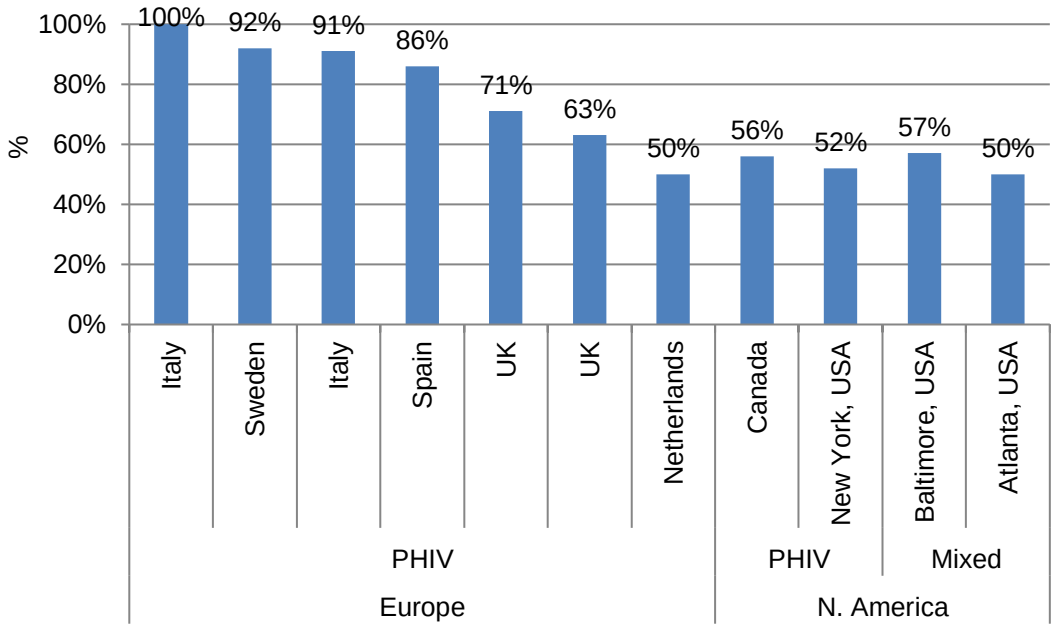
Table 2.5 continued on the next page

First author, country, year, ref	**Study design**	**Sample size and population**	**Age at transfer** [A]	**Inclusion criteria**	**Virological definitions**	**Time point**	**Virological outcome**
North America							
Xia, New York, USA, 2018,	Multi-centre longitudinal study	735 (100% perinatal)	Median: 22 years	People with PHIV and living in New York City (at least from 2014)	VL ≤200 copies/ml	Transfer date	46%
						12 months post-transfer	49%
						24 months post-transfer	51%
						36 months post-transfer	52%
Kakkar, Quebec, Canada, 2016	Single-centre longitudinal study	25 (100% perinatal)	All: 18 years	3 visits per year in last two years prior to transfer	VL <40 copies/ml	Prior to transfer (time not specified)	60%
						12 months post-transfer	56%
Hussen, Atlanta, USA, 2017	Single site longitudinal study	72 (15% perinatal)	Median: 25 [IQR 23, 25] years	Transferred to adult care	VL below detection limit	Transfer date	38%
						12 months post-transfer	53%
						24 months post-transfer	50%
Ryscavage, Baltimore, USA, 2016	Multi-centre longitudinal study	50 (38% perinatal)	Median age: 25 years	Transferred to adult care	VL <400 copies/ml	6 months post-transfer	36%
						12 months post-transfer	57%

A – The transfer definition varied by study between last visit date in paediatric care and first visit date in adult care

Virological outcomes widely varied across the post-transfer cohorts, although, the European cohorts reported higher proportions with viral suppression before and after transfer to adult care compared to the North American studies (Figure 2.5). Across Europe, two studies (the London and Brescia study) found viral suppression levels to improve in adult care from 43% and 72% prior to transfer date to 63% and 100% following transfer to adult care, respectively. The multi-region UK study found viral suppression levels (2 consecutive VL ≤400 copies/ml) to remain similar at 12 months prior to and after transfer date (72% vs 71%, respectively, p=0.85). Similar high levels of viral suppression were reported among the Spanish post-transfer cohort where 86% had a VL ≤50 copies/ml compared to 50% of a Dutch post-transfer cohort, using the same viral suppression definition. The Dutch cohort had a higher proportion of sub-Saharan African participants compared to 98% of the Spanish cohort born in Spain, this may help explain the difference in viral suppression estimates as migrants may have additional barriers to care such as cultural, language and financial barriers. However, the multi-region UK study also consisted predominantly of migrants (61%), despite reporting high viral suppression levels. The Genoa and Stockholm studies [116,129] reported similarly high viral suppression estimates (VL <50 or ≤50 copies/ml) in 2013 (90%), 2014 (91%) and 2015 (92%), although both studies were of a single clinic with 24 to 34 participants.

Figure 2.5: Estimates of the proportions with viral suppression at the latest reported adult visit following transfer date, by location and mode of HIV acquisition of study populations



Among post-transfer cohorts across North America, the viral suppression levels ranged from 50% to 57% and were considerably lower to that reported among the European cohorts. The New York study described almost half (46%) of young people to be virally suppressed at the transfer date, which then increased slightly to 49%, 51% and 52% by one, two and three years post-transfer, respectively. Despite the slight increase in the proportion virally suppressed post-transfer, a statistically significant trend was detected (p=0.001). The Atlanta study and the Baltimore study also reported an increase in the percentage of those virally suppressed following transfer date,

although test for statistical significance was not carried out by either study. In contrast to those three USA studies, the Quebec study of 25 young people attending a single clinic in Canada described a decline in the viral suppression levels from 60% prior to the transfer date (time point not specified) to 56% at 12 months post-transfer, although test for significant trend was not carried out by these study as well [110].

Though most studies described an increase in level of viral suppression from paediatric to adult care, only two multisite longitudinal studies [134,136] of predominantly PHIV populations reported that these increases were statistically significant ($p<0.05$) [134,136]. These two studies had two of the largest sample sizes which may have resulted in sufficient statistical power to detect these trends in comparison to the smaller studies. Among the remaining studies across Europe and North America, three found no significant change [108,131,139] and the rest did not compare virological outcomes before and after transfer date [105,110,129,130,133,137].

2.4.2.3. Factors associated with immunological and virological outcomes in adult care

Five studies (the Spanish, Dutch, Atlanta, London and the multi-region UK study [104,105,131,133,136]) included in this review also investigated risk factors associated with poor immunological and/or virological outcomes post-transfer to adult care (Table 2.6).

Factors associated with declining CD4 count in adult care

Two UK studies investigated factors associated with an increasing or declining CD4 trajectory following transfer to adult care [104,136]. In the London study, older current age (time-updated variable), disease progression during paediatric follow-up (not defined by study) and lack of virological failure at transfer (VL ≥50 copies/ml) were all associated with a decreasing CD4 trajectory following transfer to adult care. The multi-region UK study also found older age (based on earlier calendar year of birth) to be associated with a declining CD4 trajectory in adult care in addition to the black male demographic group, after adjusting for place of birth (abroad vs UK) and nadir CD4 count).

Factors associated with virological failure in adult care

The Dutch, Spanish and Atlanta studies all reported risk factors of viral failure using the following viral load thresholds: >50copies/ml [105,133] and ≥80 copies/ml [131] in adult care. The Dutch study explored social and clinical factors and identified unknown or low education status (vs middle and high, defined using the International Standard Classification of Education), lack of autonomy over HIV medication, and insufficient knowledge about HIV infection (e.g. difference between HIV infection and AIDS status) to be risk factors for viral failure in adult care. However, the Dutch study did not explore non-social factors such as treatment, immunological or virological status, thus making it unclear if their reported associations would have remained if these other factors were adjusted for in the model. The Spanish study reported no factors to be associated with loss of viral suppression in adult care, although the range of factors explored was not specified. Lastly, the Atlanta study described that viral failure (VL ≥80 copies/ml) at last paediatric visit, and ≥6 month gap in care between last paediatric visit and first adult visit (vs a ≤3 month gap in care) were associated with viral failure in adult care.

Table 2.6: Risk factors of declining CD4 trajectory and viral failure following transfer to adult care among young people with HIV

First author, city, country, year. ref	Study design	Sample size and population	Statistical method	Outcome of interest	Factors explored	Significant risk factors (p≤0.05)
Declining CD4 count outcome						
Judd, multi-region, UK, 2017, [104]	Multi-centre longitudinal study	271 (93% perinatal)	Random effects regression	Declining CD4 trajectory	Sex, ethnicity, born abroad, year of birth, nadir CD4 count, time-updated viral suppression status	black males, earlier birth years
Hope, London, UK, 2016, [136]	Multi-centre longitudinal study	211 (97% perinatal)	Linear regression	Declining CD4 trajectory	Demographic, clinical and socio-economic factors	Male, younger current age, disease progression during childhood, virological failure at transfer
Viral failure outcome						
Sainz, multi-region, Spain, 2015, [133]	Multi-site cross-sectional study	209 (100% perinatal)	Logistic regression	Viral failure (>50 copies/ml)	Not described	No factors
Weijsenfeld, multi-region, Netherlands, 2016, [105]	Multi-site longitudinal study	248 (91% perinatal)	Logistic regression with GEE	Viral failure (>50 copies/ml)	Time-updated variables: age, education and employment status, duration on cART, care setting (paediatric or adult care)	Low education status, lack of autonomy over ART adherence, insufficient knowledge about HIV
Hussen, Atlanta, USA, 2017, [131]	Single site longitudinal study	72 (15% perinatal)	Logistic regression	Viral failure (≥80 copies/ml)	Sex, ethnicity, age, acquisition route, baseline CD4	Viral failure at last paediatric visit, >3 months gap between paediatric and adult care

2.4.2.4. Summary

There were inconsistent immunological and virological trends from paediatric to adult care. Some cohorts reported improved health outcomes post-transfer, while other cohorts reported poorer outcomes in adult care. The majority of the latter cohorts found no significant change in immunological or virological outcomes before and after transfer to adult care, likely due to the small samples sizes and limited statistical power to investigate such trends over time.

Many of the post-transfer cohorts had limited representativeness as they only included participants attending a single adult clinic. Furthermore, the majority of the studies extracted paediatric and adult records for only a selected group of participants. Details of how studies selected these participants were not described, making it unclear how much selection bias may have affected their findings. Only one national paediatric cohort had linked their patient data to an adult HIV study; though the adult study lacked national coverage, a larger sample size was achieved with reduced selection bias in the participants included in the study [104]. There is a need for national post-transfer studies, through data linkage of national paediatric and adult cohort data. Such studies would produce more representative and generalisable findings on patient health outcomes that would help inform clinical care.

The Atlanta and Baltimore studies included in this literature review were predominantly of young people with BHIV and only the latter study disaggregated its findings by mode of HIV acquisition and found no significant difference in immunological or virological outcomes post-transfer. However, the Baltimore study, similar to other post-transfer studies, had a small sample size (N=50) and short follow-up period (12 months period post-transfer). Further data are needed of larger sample sizes to compare health outcomes post-transfer by mode of HIV acquisition (PHIV vs. BHIV). The work in this thesis aims to address the gaps in knowledge by using national paediatric and adult cohort to investigate the immunological and virological trends following transfer to adult care.

Additionally, studies that use a viral load cut-off of <400 copies/ml to describe an 'undetectable viral load' may not appropriately reflect the true extent of viral suppression achieved across the population. Those with a detectable value <400 copies/ml would be different to those who achieved full suppression to <20 or <50 copies/ml and be subject to different health outcomes. Therefore, terms such as '<400 copies/ml' instead of 'undetectable' may be more appropriate.

2.5. Cascade of care among young people with HIV

This literature review investigated the cascade of care among adolescents and young people with HIV in HIC. The primary focus of this review was the cascade of care which refers to the care pathway from linkage to care (defined as completing a first visit following diagnosis or transfer from paediatric care [88,108] to achieving viral suppression. Therefore, the first two steps of the classical UNAIDS cascade (i.e. the number of young people living with HIV and diagnosed) were not included in this literature review.

2.5.1. Methods

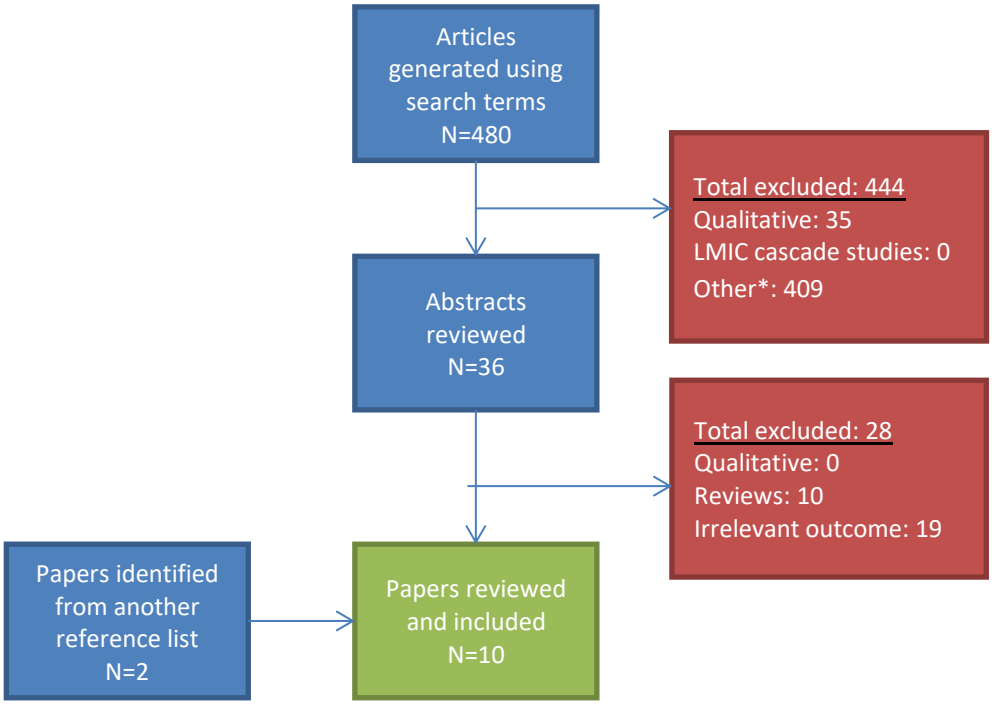
In addition to the inclusion criteria specified in section 2.2, another criterion was that studies should report at least three steps of a cascade, with any three of the following steps being

considered: linkage to care, engagement in care, ART coverage, viral suppression or CD4 status. Only literature published after 2012 was reviewed as the cascade framework is a new concept that was first published in 2011 [91].

2.5.2. Results

The literature search identified 480 publications. Based on the study title, 36 of these publications were considered relevant and the abstracts were reviewed (Figure 2.6). Of these, eight papers met the inclusion criteria. Two further papers were identified from manual searches of the reference lists in other papers and were included. The majority of papers excluded after reviewing the titles included qualitative studies (N=35), cascade studies among irrelevant study populations (i.e. HIV-negative young people and general adult populations) (N=6) and studies with no results regarding cascade of care (e.g. on mental health, reproductive health, HIV prevention etc.) (N=403).

Figure 2.6: Flowchart of studies considered for the cascade of care literature review



**Studies with non-cascade outcomes or irrelevant study populations such as older adults*

No papers were identified from the titles to report cascade outcomes in LMIC. Additionally, literature reviews relevant to cascades in HIC were only used to identify additional papers and were not included in the final list of studies identified in the PubMed search. The 10 publications included in this literature review were published between 2015 and 2018. No additional studies were identified through conference databases.

Three out of 10 studies measured cascade of care post-transfer to adult care among; one from Italy and three from USA [108,130,131]. Of these three post-transfer studies, the care settings and mode of HIV acquisition differed; the Italian study included only young people with PHIV who transferred from paediatric to adult care, while the two USA studies (from Baltimore and Atlanta) included young people with mixed modes of HIV acquisition (15-38% with PHIV) transferring from

adolescent to adult care.

Another two studies were of predominantly PHIV populations; one of which was a national paediatric UK study (CHIPS), which carried out a cross-sectional analysis of longitudinal data to assess the cascade of care among children and young people in paediatric care in 2010, 2013 and 2016. [138,139]. However, this UK study was limited as it did not report cascade findings following transfer to adult care. The cascades were stratified by current age groups, including an adolescent group (aged 15 to 21 years) in 2013 and 2016. The second study was from the New York, USA and used surveillance data to measure a cross-sectional cascade among young people with PHIV in 2014. Health care settings were not specified in this study and the population age range was 0 to 36 years, with findings stratified by age group, including 13 to 19 year olds. The remaining five studies were of young people with predominantly BHIV (with 0-29% perinatal) in adult care. Four of these studies were of young people who enrolled into a HIV program in the USA and the fifth study was a national cascade of all adults with HIV in the UK with disaggregated estimates for young people (aged 15-24 years), constructed by PHE [88,140–143].

The CHIPS cascade, New York City cascade and the PHE cascade were the only three cascades constructed in a cross-sectional manner, where the cascade steps measured were at a single point in calendar year in time for all participants. The other seven studies all reported a longitudinal cascade of care among young people with HIV (duration of follow-up ranging from one to three years). All 10 studies reported findings for ≥3 steps in their cascade of care. Table 2.7 lists the steps covered by each of the 10 studies.

Table 2.7: Cascade of care steps measured by studies included in the literature review; tick implies the study measured the respective cascade step

		Cascade steps				
First author, country, year of publication	**Care settings**	**Linkage to care**	**Engagement in care**	**On ART**	**Viral suppression**	**CD4 status**
PHIV populations						
Xia, New York, USA, 2016	Unspecified	✓	✓		✓	✓
Izzo, Brescia, Italy, 2018	Transferred to adult care		✓	✓	✓	
Mixed populations [A]						
Ryscavage, Baltimore, USA, 2016	Transferred to adult care	✓	✓	✓	✓	
Hussen, Atlanta, USA, 2017	Transferred to adult care	✓	✓		✓	
Collins, national, UK, 2018	Paediatric care		✓	✓	✓	
Nash, national, UK, 2018	Adult care		✓	✓	✓	
Kahana, multistate, USA, 2016	Adult care		✓	✓	✓	
BHIV populations						
Lally, multisite, USA, 2018	Adolescent care		✓	✓	✓	
Farmer, multistate, USA, 2016	Adult care		✓	✓		✓

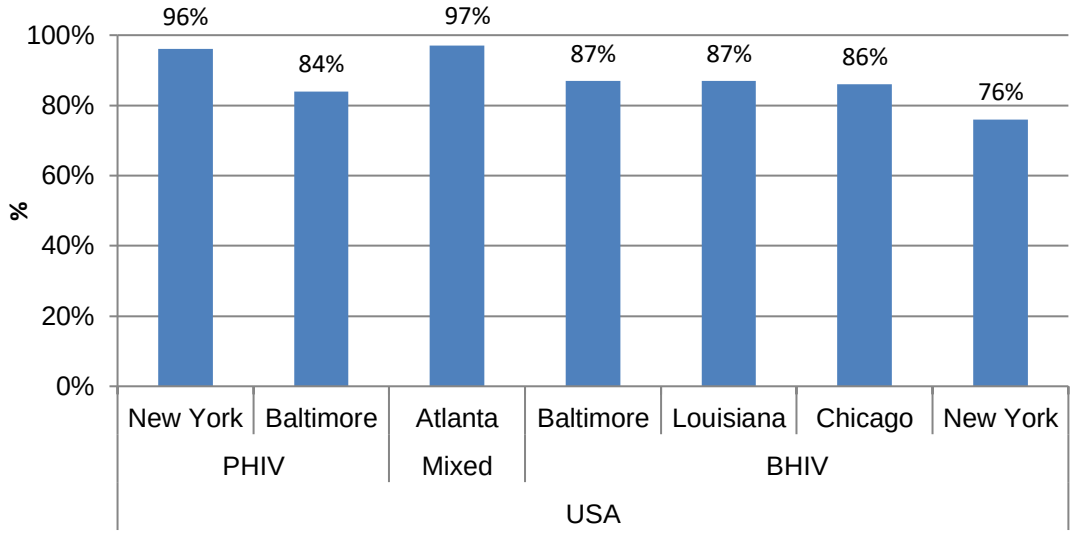
Maulsby, multisite, USA, 2015	Adult care	✓	✓	✓

A – including young people with PHIV and BHIV

2.5.2.1. Linkage to care

Within this literature review, four studies investigated linkage to care (defined as ever having a first visit following transfer to adult care or enrolment into a HIV study). Only two of the studies (the Baltimore and Atlanta studies) were among young people who transferred to adult care. Nonetheless, high levels of linkage were reported among all studies. Across the PHIV populations in the New York and Baltimore study, 84% to 96% were linked to care [108,131,138] (Figure 2.7). Similar linkage estimates were reported (76% to 97%) among predominantly young people with BHIV in three of the USA studies [108,131,140].

Figure 2.7: Estimates of the proportion of young people linked to adult care by location and mode of HIV acquisition of study population



The comparable linkage estimates across all four studies may reflect the simplistic definition used across the studies (i.e. to complete ≥1 visit during the adult study periods, with no time restriction) (Table 2.8). However, the inclusion criteria used by the New York PHIV study and the USA studies by Maulsby et al meant that participants could have had a visit in adult care prior to being followed up in these studies, while the other two post-transfer studies would capture the true first visit post-transfer to adult care. The study populations also differed with the multi-region USA study only including incarcerated participants, MSM or those in receipt of benefits who are likely a different risk group to the general PHIV population. This would thus limit the generalisability of this study's findings to young people with PHIV.

The other six cascade studies of young people included in this literature review did not measure the linkage step due to only including study participants already linked to care [130,139,141–143].

Table 2.8: Estimates of the proportion of young people linked to care in studies reporting ≥3 stages of the cascade of care

First author, city, country, year[A]	Sample size and study population	Age	Denominator	Definition of linkage	Linked to care
PHIV populations					
Xia, New York, USA, 2016	N=402 (100% PHIV)	Range in 2014: 13-19 years	Diagnosed with HIV	≥1 CD4/VL test in 2014	96%
Mixed populations					
Ryscavage, Baltimore, USA, 2016	N=19 (100% PHIV)	Range at first adult visit: 19-27 years	Documented as planning to transfer to adult care	First adult visit post-transfer	84%
	N=31 (100% BHIV)	Range at first adult visit: 19-27 years	Documented as planning to transfer to adult care	First adult visit post-transfer	87%
Hussen, Atlanta, USA, 2017	N=72 (15% PHIV)	Median age at first adult visit 25 [IQR 23, 25]	Documented as planning to transfer to adult care	First adult visit post-transfer	97%
BHIV populations					
Maulsby, Chicago, USA, 2015	N=564 (100% MSM)	At enrolment: ≤24 years (lower limit not specified)	Enrolled into the study	First adult visit after enrolment into the study, post-diagnosis or a 6 month gap in care	86%
Maulsby, Louisiana, USA, 2015	N=998 (100% BHIV assumed [B])	At enrolment: ≤24 years (lower limit not specified)	Enrolled into the study and in prison	First adult visit after enrolment into the study, post-diagnosis or a 6 month gap in care	87%
Maulsby, New York, USA, 2015	N=1053 (100% BHIV assumed [B])	At enrolment: ≤24 years (lower limit not specified)	Enrolled into the study and in receipt of benefits	First adult visit after enrolment into the study, post-diagnosis or a 6 month gap in care	76%

A - Year study was published; B – With mode of HIV acquisition is not specified, study populations were assumed to have BHIV due to consisting of young people recently diagnosed with HIV in adult care

2.5.2.2. Engagement in care

Engagement in care was measured by all 10 cascade studies included in this review (Table 2.9). Eight studies measured engagement in care, while two studies (one of the multi-region USA study and the Brescia study) measured disengagement from care. For these two studies, disengagement measures were converted into engagement measures to allow for better comparability between studies, as described in Table 2.4. The conversion of the disengagement measures also allowed for easier comparison with my cascade findings (in Chapter 7), as I measured engagement in care rather than disengagement from care. The engagement definitions used varied across the studies, including:

- LTFU post-transfer to adult care, definition not specified [135], converted to not LTFU for this review
- ≥2 visits in a 12 month period with each visit being ≥3 months apart [138,140,141,144]
- ≥1 visit in each 6 month period, over a 12 month period post-transfer [108]
- ≥1 visit in each calendar year [88,139]
- Self-reported ever missing a clinic visit [143], converted to no missed visits for this review
- ≥1 visit for each 4 month period, over the first year post-enrolment into the study and 1 visit in each 6 month period in the second and third year post-enrolment [142]

The engagement definition used by the studies is likely driven by the follow-up frequency and availability of data. For example, the Brescia post-transfer study had follow-up data of up to 24 months following transfer date compared to just 12 months of follow-up in the Baltimore post-transfer study. The former study was thus able to measure engagement at 12 and 24 months post-transfer.

Table 2.9: Estimates of the proportion of young people engaged in care in studies reporting ≥3 stages of the cascade of care

First author, city, country, year[A], ref.	Sample size and study population	Age	Denominator	Engagement definition	Time point	Engagement in care
PHIV populations						
Izzo, Brescia, Italy, 2018	N=24 (100% PHIV)	Median age at first adult visit: 18 years	Linked to adult care	Engaged in care (not defined)[C]	By 12 months post-transfer	100%
					By 24 months post-transfer	80%
Xia, New York, USA, 2016	N=402 (100% PHIV)	Range in 2014: 13-19 years	Diagnosed with HIV	≥2 visits in a 12 month period with each visit being ≥3 months apart	In 2014	89%
Mixed populations						
Ryscavage, Baltimore, USA, 2016	N=19 (100% PHIV)	Range at first adult visit: 19-27 years	Linked to adult care	≥2 adult visits over 12 months (1 visit in each 6 months)	By 12 months post-transfer	60%
	N=31(100% BHIV)	Range at first adult visit: 19-27 years	Linked to adult care	≥2 adult visits over 12 months (1 visit in each 6 months)	By 12 months post-transfer	45%
Collins, national, UK, 2018	N=396 (>95% PHIV)	Range in 2016: 15-21 years	Ever followed up in CHIPS	≥1 visit in 2016	In 2016	92%
Hussen, Atlanta, USA, 2017	N=72 (15% PHIV)	Median age at first adult visit 25 [IQR 23, 25]	Linked to adult care	≥2 visits in a 12 month period with each visit being ≥3 months apart	By 12 months post-transfer	89%
					By 24 months post-transfer	56%
Nash, national, UK, 2018	N=2622 (unknown % PHIV)	Range in 2017: 15-24 years	Seen in care in 2016	≥1 visit in 2017	In 2017	92%
Kahana, multi-region, USA, 2016	N=1891 (28% PHIV)	Range at enrolment: 12-26 years	Linked to adult care and enrolled into study	% with no missed visits in the past 12 months (self-reported) [C]	In the last year of follow-up	50%

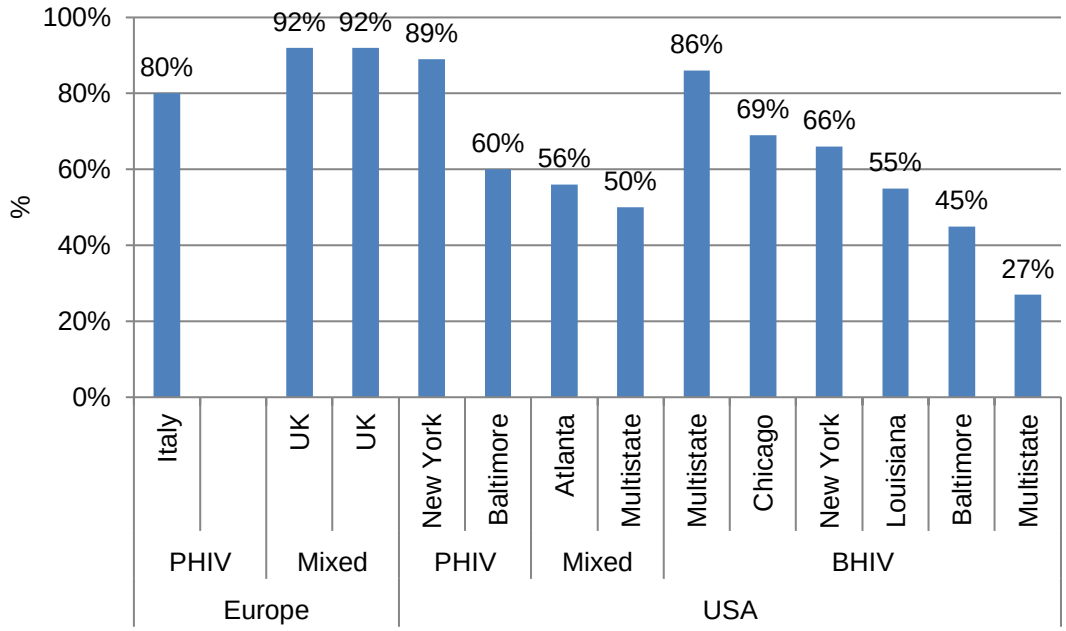
Table 2.9 continued on the next page

First author, city, country, year[A], ref.	Sample size and study population	Age	Denominator	Engagement definition	Time point	Engagement in care
BHIV populations						
Farmer, multi-region, USA, 2016	N=1160 (100% BHIV)	Range at enrolment: 12-24 years	Linked to adult care	1 visit for each 4 month period in the year 1, 1 visit in each 6 month period in year 2 and 3	In year 1-3 post-enrolment	49%
					In year 1 post-enrolment	45%
					In year 2 and 3 post-enrolment	27%
Lally, multi-region, USA, 2017	N=467 (100% BHIV)	Range at enrolment: 16-24 years	Linked to adult care	≥2 visits in a 12 month period with each visit being ≥3 months apart	In the last year of follow-up	86%
Maulsby, Chicago, USA, 2015	N=564 (100% MSM)	At enrolment: ≤24 years (lower limit not specified)	Enrolled into the study	≥2 visits in a 12 month period with each visit being ≥3 months apart	In the last year of follow-up	69%
Maulsby, Louisiana, USA, 2015	N=998 (100% BHIV assumed [B])	At enrolment: ≤24 years (lower limit not specified)	Enrolled into the study and in prison	≥2 visits in a 12 month period with each visit being ≥3 months apart	In the last year of follow-up	55%
Maulsby, New York, USA, 2015	N=1053 (100% BHIV assumed [B])	At enrolment: ≤24 years (lower limit not specified)	Enrolled into the study and in receipt of benefits	≥2 visits in a 12 month period with each visit being ≥3 months apart	In the last year of follow-up	66%

A - Year study was published; B – With mode of HIV acquisition is not specified, study populations were assumed to have BHIV due to consisting of young people recently diagnosed with HIV in adult care; C – engagement measure converted from disengagement measure reported by the studies (undefined 'LTFU' in the Italian study and 'missed visits' in the USA study

Figure 2.8 presents the engagement estimates across Europe and North America by mode of HIV acquisition, among the longitudinal studies reporting engagement estimates for multiple time points, the latest time point listed in Table 2.9 were presented. Engagement in adult care among young people with HIV across Europe and North America varied widely from 27% to 100%. The studies with predominantly PHIV populations (aged 13 to 27 years) from the Brescia, New York, Baltimore and the UK, reported engagement in care estimates of 60% to 100%. The other studies of predominantly young people with BHIV (aged 12 to 27 years) had a wider range of 27% to 89% engaged in care.

Figure 2.8: Estimates of proportion of young people engaged in care at the latest reported date, by location and mode of HIV acquisition of study populations



Only three (Atlanta study, Brescia study and the multi-region USA study by Farmer et al.) measured engagement at multiple time points and found declining trends. According to the Atlanta (15% PHIV) and Brescia (100% PHIV) post-transfer studies, engagement in care declined from 89% and 100% at 12 months post-transfer to 56% and 80% at 24 months post-transfer, respectively. The USA study (by Farmer et al.) of young people with BHIV reported a decline in the proportion engaged in care; from 45% in the first year post-enrolment to the HIV program to 27% engaged in the second and third year post-enrolment [142]. The remaining seven studies measured engagement at a single time point included in 2016 and 2017 (by the UK's national paediatric and adult studies), at 12 months post-transfer (by the Baltimore study) and in the last year of study follow-up (by the three multi-region USA studies).

The high level of variability in engagement estimates could be due to the use of different engagement definitions, populations sampled and cascade denominators used [140,142], the length of study follow-up and time points measured [131,141–143,145].

The denominator used to assess engagement in care also varied across the cascade studies. The Brescia, Baltimore and Atlanta post-transfer studies all used those linked to adult care as the

cascade denominator for measuring engagement in care [108,131,135]. In contrast, the denominators of the remaining studies included those diagnosed with PHIV [138] or those enrolled to their respective HIV program [140–143]. Only one study (the UK's national paediatric HIV study) had national coverage and was able to exclude those LTFU (defined as no visit for >3 years) [139]. The remaining studies did not exclude young people transferring to non-participating clinics or out-migrations (moving to a different region or country) following study entry, possibly resulting in underestimated engagement levels [108,131,135,138,140–143]. All studies, except for one (the New York PHIV study), used denominators of young people already linked to care, seen in care the previous calendar year or with a scheduled post-transfer visit, which leads to the study populations being biased in favour of those more likely to be engaged.

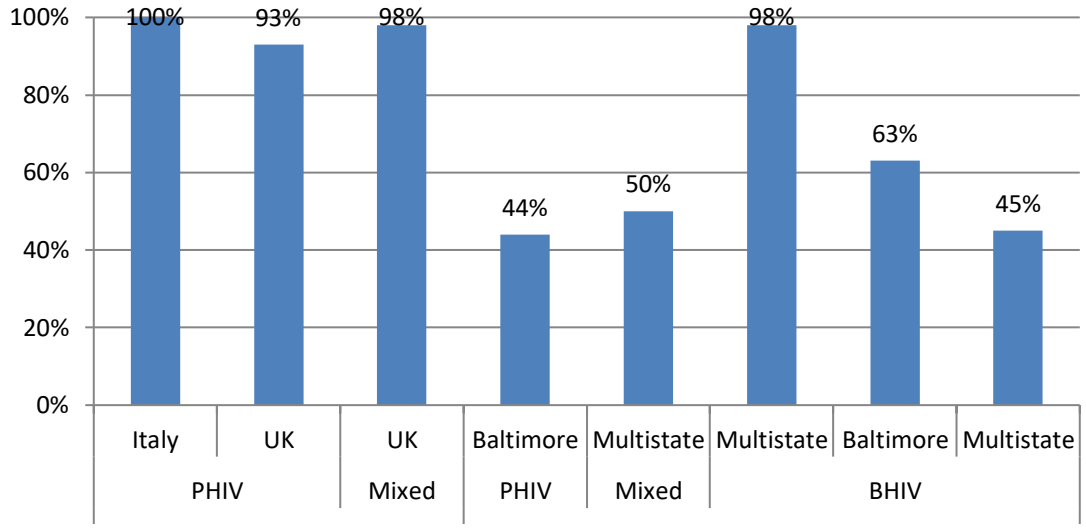
The study populations also varied widely; many of the US studies of young people with BHIV included young people with history of mental health issues (43%), previous incarceration (40%) [141], previously disengaged from care or at risk of disengagement (100%) [140] or uninsured young people (45%) [142]. These study populations also disproportionately consisted of black males from low socio-economic backgrounds [140–142]. These differences make comparability between the studies difficult.

The sample sizes varied widely across the cascade studies. Studies assessing the cascade of care post-transfer from paediatric or adolescent care to adult care were much smaller, including only 19 to 72 young people with HIV (mixed modes of HIV acquisition) across Europe and North America [108,130,131], while the studies restricted to young people with BHIV, aged 12-26 years in adult care and mostly in the USA were larger, including data on approximately 450-2600 participants [140–143]. The smaller sample sizes of the post-transfer studies are most likely due to the much lower prevalence of PHIV across the USA and the UK as a result of effective perinatal screening and PMTCT programmes.

2.5.2.3. ART coverage

In this review, seven studies measured the proportions currently on ART at varying time points. All studies used participant medical records as the data source for the ART cascade step, and only two post-transfer studies (the Brescia and Baltimore studies) limited the ART definition to those on cART [108,130], while the rest of the cascade studies measured those on any ART regimen. Similar to the engagement in care estimates, ART coverage also varied widely across the cascade studies; from 41% to 100%, with a similarly wide range of ART coverage reported among PHIV and BHIV populations (44% to 100% and 41% to 98% among PHIV and BHIV populations, respectively) (Figure 2.9). The inconsistent ART estimates may be a reflection of the wide range of time points used, from time at linkage to adult care [108] to three years post-enrolment to the respective studies [142], and the different population denominators used in each study (Table 2.10).

Figure 2.9: Estimates of ART coverage proportions, by location and mode of HIV acquisition of study populations



The three studies from Europe (one Italian and two UK studies) reported higher ART estimates among young people with HIV than that reported by studies from the USA. In the UK, the national paediatric study (aged 15 to 21 years) and national adult cascade study (aged 15 to ≥65 years) both reported ART coverage of 93% and 98% in 2016 and 2017, respectively [88,139]. The latter UK cascade did not report ART estimates stratified by age, so it is unclear how those aged <25 years compare to the general adult HIV population with the 98% ART coverage in 2017. The Brescia study reported 79% of young people with PHIV to be on cART by 12 months post-transfer and increased to 100% by 24 months post-transfer [130]. The study did not describe whether the remaining participants not on cART regimens were off treatment or on another non-cART regimen.

Table 2.10: Estimates of the proportion of young people on ART in studies reporting ≥3 stages of the cascade of care

First author, city, country, year[A], ref.	Sample size and study population	Age	Denominator	Definition	Time point	On ART
PHIV populations						
Izzo, Brescia, Italy, 2018	N=24 (100% PHIV)	Median age at first adult visit: 18 years	Linked to adult care	Any cART regimen on medical records	By 12 months post-transfer By 24 months post-transfer	79% 100%
Mixed populations						
Ryscavage, Baltimore, USA, 2016	N=19 (100% PHIV)	Range at first adult visit: 19-27 years	Linked to adult care	Any cART regimen on medical records	By 12 months post-transfer	44%
Ryscavage, Baltimore, USA, 2016	N=31(100% BHIV)	Range at first adult visit: 19-27 years	Linked to adult care	Any cART regimen on medical records	By 12 months post-transfer	63%
Collins, national, UK, 2018	N=396 (>95% PHIV)	Range in 2016: 15-21 years	Engaged in care in 2016	Any regimen on medical records	Last visit in 2016	93%
Nash, national, UK, 2018	N=2622 (unknown % PHIV)	1Range in 2017: 15 to ≥65years	Engaged in care in 2017	Any regimen on medical records	At the last visit in 2017	98%
Kahana, multi-region, USA, 2016	N=1891 (28% PHIV)	Range at enrolment: 12-26 years	Linked to adult care and enrolled into study	Any regimen on medical records	At the most recent visit	50%
BHIV populations						
Farmer, multi-region, USA, 2016	N=1160 (100% BHIV)	Range at enrolment: 12-24 years	Linked to adult care	Any regimen on medical records	By 12 months post-linkage	41%
Lally, multi-region, USA, 2017	N=467 (100% BHIV)	Range at enrolment: 16-24 years	Engaged in care	Any regimen on medical records	At the most recent visit	98%

A - Year study was published

The remaining four studies measured ART coverage from across USA. The Baltimore study, a post-transfer study, reported a higher proportion of young people with BHIV (N=31) to be on ART by 12 months post-transfer compared to young people with PHIV (N=19). A statistical test for significant difference between the estimates were not carried out, although, the small sample sizes would likely limit the statistical power needed to detect a trend.

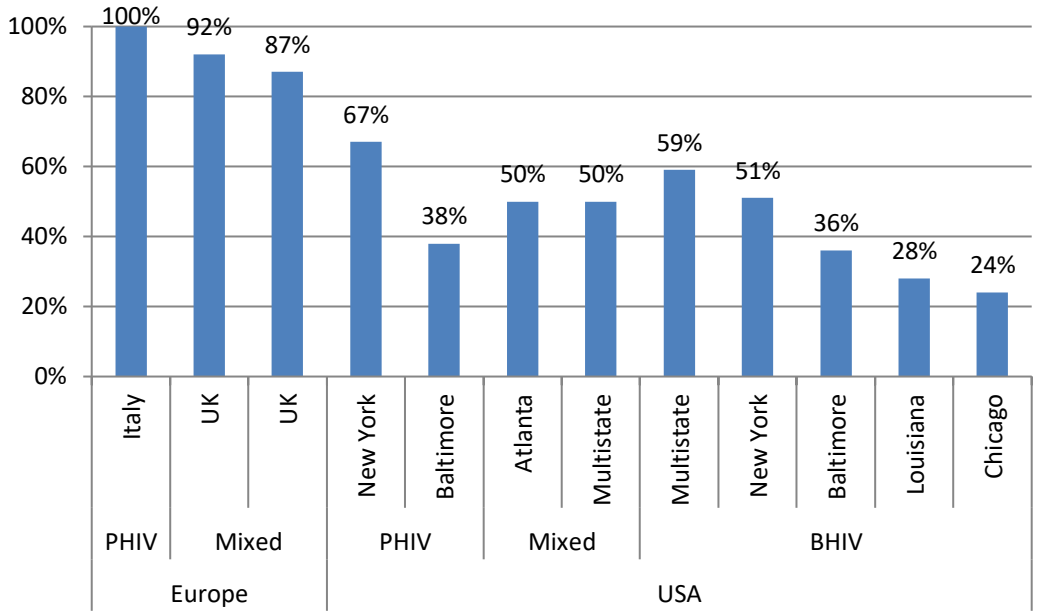
The other three studies of primarily young people with BHIV enrolled onto HIV programmes across the USA, reported varying estimates of ART coverage. The first study from 2016 (by Kahana et al.) of young people with HIV (28% with PHIV) found 50% to be on ART at the most recent visit. Similar ART estimates were reported by the second study (by Farmer et al.) where 41% were found on ART by 12 months following linkage to adult care. The third study from 2018 (by Lally et al.) reported almost all (98%) young people with BHIV were on ART at the most recent visit. Despite the varying estimates, all three study populations comprised of mostly males (63% to 79%) and African Americans (61% to 71%).

There were three other studies in this review that did not measure the ART step of the cascade due to unavailable ART data [131,138,140].

2.5.2.4. Viral suppression

In this literature review, nine studies measured viral suppression levels (under 50, 200 or 400 copies/ml) among young people with HIV in adult care. Similar to engagement in care and ART coverage, the prevalence of viral suppression varied widely among the PHIV and BHIV populations (Figure 2.10). Higher viral suppression estimates (87% and 100% with VL <200 and <50 copies/ml, respectively) were reported from PHIV from Europe (the Brescia study and the UK's national paediatric study) [139], while the third European study, the UK's national adult cascade study which consists mostly of young people with BHIV, also reported a high proportion of viral suppression (87% with a VL <200 copies/ml) [88]. In the USA, the New York study of only young people with PHIV found 67% to be virally suppressed (VL ≤200) [138]. The Baltimore post-transfer study reported only 38% of young people with PHIV to be virally suppressed (VL <400) which was similar to BHIV group's estimate of 36%. The Atlanta study, also a post-transfer study, estimated 53% of young people with HIV (15% with PHIV) to be virally suppressed (VL below detection limit, which varied by clinic) by 12 months post-transfer, which declined slightly to 50% by 24 months post-transfer.

Figure 2.10: Estimates of the proportion with viral suppression, by location and mode of HIV acquisition of study populations



Two multi-region USA studies from 2016 and 2018 of predominantly BHIV populations (by Kahana et al. and Lally et al.) found 50% and 89% to be virally suppressed (varying definitions listed in Table 2.11) at the most recent visit of study follow-up, respectively. The latter 2018 USA study (by Lally et al.) further reported 81% of participants to have ≥50% of their viral load measurements in the last 12 months of study follow-up less than 200 copies/ml and 59% had all viral load measurements in the last 12 months <200 copies/ml [141]. The longitudinal approach used in this study provided more information than other studies that considered outcomes at a single time-point (e.g. at 12 months post-transfer to adult care). The latter 2018 USA study (by Lally et al.) included only young people engaged in care and on ART while the 2016 USA study were only of young people linked to adult care. This likely resulted in this latter study having a selection bias in favour of those more likely to be engaged in care and adhere to treatment which would explain the higher viral suppression estimate reported compared to the 2016 USA study.

The lowest viral suppression levels were reported by one of the multi-region USA studies from 2015 (by Maulsby et al.), with 24% to 51% of young people across Chicago, Louisiana and New York having a VL ≤200 copies/ml at the last visit of study follow-up [140]. The low proportions is likely due to the study including participants with a history of disengagement from care, incarceration or drug abuse.

Table 2.11: Estimates of the proportion of young people with viral suppression in studies reporting ≥3 stages of the cascade of care

First author, city, country, year[A], ref.	Sample size and study population	Age	Denominator	Definition	Time point	Viral suppression
PHIV populations						
Izzo, Brescia, Italy, 2018	N=24 (100% PHIV)	Median age at first adult visit: 18 years	Linked to adult care	1 VL <50	By 12 months post-transfer	75%
					By 24 months post-transfer	100%
Xia, New York, USA, 2016	N=402 (100% PHIV)	Range in 2014: 13-19 years	Diagnosed with HIV	≥1 VL ≤200	In last visit in 2014	67%
Mixed populations						
Ryscavage, Baltimore, USA, 2016	N=19 (100% PHIV)	Range at first adult visit: 19-27 years	Linked to adult care	1 VL <400	By 12 months post-transfer	38%
Ryscavage, Baltimore, USA, 2016	N=31(100% BHIV)	Range at first adult visit: 19-27 years	Linked to adult care	1 VL <400	By 12 months post-transfer	36%
Collins, national, UK, 2018	N=396 (>95% PHIV)	Range in 2016: 15-21 years	On ART in 2016	≥1 VL <200	In 2016	92%
Hussen, Atlanta, USA, 2017	N=72 (15% PHIV)	Median age at first adult visit 25 [IQR 23, 25]	Engaged in care	≥1 VL below detection limit	By 12 months post-transfer	53%
					By 24 months post-transfer	50%
Nash, national, UK, 2018	N=1978 (unknown % PHIV)	Range in 2017: 15-24 years	On ART in 2017	≥1 VL <200	By last visit in 2017	87%
Kahana, multi-region, USA, 2016	N=1891 (28% PHIV)	Range at enrolment: 12-26 years	Linked to adult care and enrolled into study	≥1 VL below detection limit	In the last year of follow-up	50%

Table 2.11 continued on the next page

First author, city, country, year[A], ref.	Sample size and study population	Age	Denominator	Definition	Time point	Viral suppression
BHIV populations						
Lally, multi-region, USA, 2018	N=467 (100% BHIV)	Range at enrolment: 16-24 years	Engaged in care and on ART	≥1 VL <200	In the last year of follow-up	89%
				50% of VL <200	In the last year of follow-up	81%
				100% of VL <200	In the last year of follow-up	59%
Maulsby, Chicago, USA, 2015	N=564 (100% MSM)	At enrolment: ≤24 years (lower limit not specified)	Enrolled into the study	≥1 VL ≤200	In the last year of follow-up	24%
Maulsby, Louisiana, USA, 2015	N=998 (100% BHIV assumed [B])	At enrolment: ≤24 years (lower limit not specified)	Enrolled into the study and in prison	≥1 VL ≤200	In the last year of follow-up	28%
Maulsby, New York, USA, 2015	N=1053 (100% BHIV assumed [B])	At enrolment: ≤24 years (lower limit not specified)	Enrolled into the study and in receipt of benefits	≥1 VL ≤200	In the last year of follow-up	51%

A - Year study was published; B – With mode of HIV acquisition is not specified, study populations were assumed to have BHIV due to consisting of young people recently diagnosed with HIV in adult care

High levels of missing VL data can impact the study findings, and not accounting for them appropriately can introduce bias. One study assumed missing VL data equalled failure[139], while another only included young people with a VL measurement available [131]. The remaining studies had no missing data reported [135,143] or did not specify methods in handling missing data [88,108,138,141]. The studies without missing VL data used wide windows to capture the last recorded VL measurement during study follow-up.

The different viral suppression definitions, population denominators (young people linked to care, enrolled to a study, engaged in care or on ART) led to a wide range of viral suppression estimates across the USA, UK and Italy. The highest viral suppression estimates were among the PHIV populations across Europe and the lowest among the PHIV and BHIV populations across the USA.

2.5.2.5. CD4 status

Among the nine studies included in this literature review, only two reported the CD4 status of young people with HIV (Table 2.12). Some studies only provided a median CD4 count and were thus not included in this section of the review, while others did not report a CD4 outcome at all. The definition used for optimal CD4 status was a CD4 count >500 cells/mm_3, based on the World Health Organization (WHO) immunological classification [146].

In 2016, the UK's national paediatric cascade study reported 90% of all young people (aged 15 to 21 years) on ART to have a CD4 count >500 cells/mm_3, which was significantly lower than the estimates for the younger age groups also in the study (97% for those <15 years and on ART ($p<0.001$) [139]. In contrast, the multi-region USA study (by Farmer et al.) of young people with BHIV (aged 12 to 24 years) reported 39% of those engaged in the first year of study follow-up to have a CD4 count >500 cells/mm_3, this declined to 27% among those engaged in year two and three of study follow-up, and overall 31% of those engaged in all three years had a CD4 count >500 cells/mm_3[142].

Table 2.12: Estimates of the proportion of young people with CD4 >500 cells/mm3 in studies reporting ≥3 stages of the cascade of care

First author, city country, year [A]	Sample size and population	Age	Denominator	Time point	CD4 count >500 [B]
Mixed populations					
Collins, national, UK, 2018	N=396 (>95% PHIV)	15-21 years in 2016	On ART in 2016	Last visit in 2016	90%
BHIV populations					
Farmer, multistate, USA, 2016	N=1160 (100% BHIV)	At enrolment: 12-24 years	Engaged in years 1-3 post-enrolment date	At linkage to care	31%
	N=1160 (100% BHIV)	At enrolment: 12-24 years	Engaged in year 1 post-enrolment date	At linkage to care	39%
	N=1160 (100% BHIV)	At enrolment: 12-24 years	Engaged in years 2 and 3 post-enrolment date	At linkage to care	27%

A - Year study was published; B – CD4 count units are cells/mm3

2.5.2.6. Summary

The proportions of those linked to adult care among young people with HIV were consistently high (>75%) with similar linkage definitions used by all studies (i.e. completion of ≥1 visit in adult care in a given year, post-transfer or enrolment date). However, all other cascade steps varied widely. This reflected the limited comparability between the studies of young people with PHIV and BHIV. The studies had study populations with different demographic compositions and different cascade methodology. Comparability among studies can be encouraged by adopting more standardised cascade definitions, in particular with regards to engagement, viral suppression and ART status, as recommended by the European Centre for Disease Prevention and Control (ECDC) in 2017 [92].

Additionally, undocumented deaths and out-migrations are often difficult to account for due to data limitations, although deaths are well documented in the UK. This explains how only the two UK studies in my review considered the effect of deaths and out-migrations within their population. The UK's national paediatric and adult cascade studies measured cascade outcomes in 2016 and 2017, respectively, and excluded deaths and out-migrations from the cascade denominator at the start of the respective calendar years. The studies that were unable to exclude deaths and out-migrations before or during study follow-up were likely to inflate their denominators with participants that had no chance of meeting the cascade steps, thus resulting in under-estimated cascade figures [147,148].

The cross-sectional cascades reported better findings for all steps of the cascade (from linkage

to CD4 status) compared to the longitudinal cascades, although the cross-sectional cascade findings are likely to be biased due to assuming no temporal effect, when in reality the health status at all cascade steps is likely to change over time.

The Italian post-transfer study of young people with PHIV produced the highest estimates on the engagement, ART and viral suppression steps of the cascade over a two year period following transfer to adult care at ≥75% [130]. The generalisability of the study findings was limited by this being a single-site study with the smallest sample size (N=24), which makes it difficult to extrapolate these study findings beyond its settings. The Brescia, Baltimore and Atlanta study were the only three post-transfer studies to measure the cascade of care in adult care and the latter two studies had participants with mixed modes of HIV acquisition. Only the Baltimore study compared the outcomes by mode of acquisition and found the PHIV group to be higher estimates engaged in care, lower levels linked to adult care and on cART at time of linkage, while comparable viral suppression estimates were observed compared to the BHIV group. This study's comparison is limited by the small sample size (19 and 31 young people with PHIV and BHIV, respectively). Further research with larger sample sizes, national coverage and disaggregated data are needed to produce more representative findings that would allow us to better understand the care pathway of young people transferring to adult care and to identify if the poor performance of young people with HIV along the cascade is driven by the PHIV or BHIV population.

In this thesis, the gaps in literature were addressed by generating a national cascade of young people who transferred from paediatric to adult care in the UK and were also compared to young people with other modes of HIV acquisition attending adult care. Additionally, I sought to develop a cascade which maximised the use of the available data, by not only exploring the typical steps often reported by cascade studies (i.e. on ART, virally suppressed), but additional steps including percentage linked in care, engaged in care and with optimal immunological status (CD4 count >500 cells/mm_3 according to the WHO immunological classification system[38]), all following transfer to adult care.

2.6. The impact of youth-friendly clinic services on the engagement and health outcomes of young people with HIV

This literature review investigated the impact of youth-targeted clinic services on the engagement in care and health outcomes of young people with HIV attending adult clinics in HIC.

2.6.1. Methods

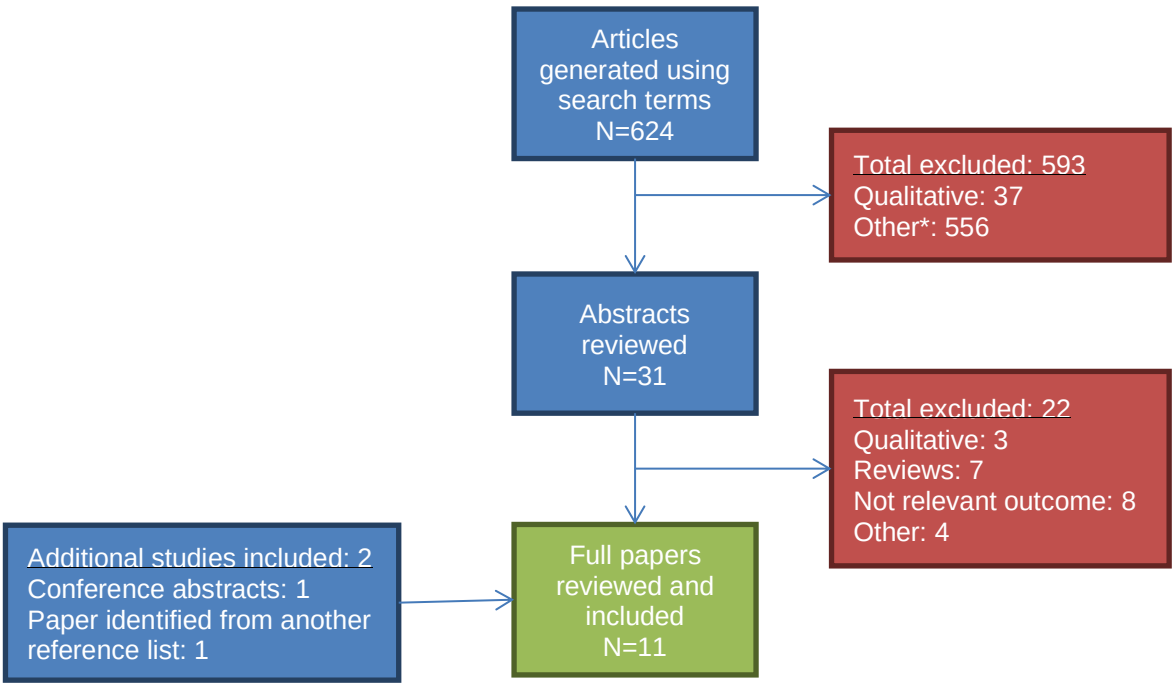
The inclusion criteria, in addition to those outlined in section 2.2, were for studies to measure the impact of youth-targeted services or features on the engagement or health outcomes of young people with HIV (all modes of HIV acquisition) in adult care. However, I note at this stage that there is no consistently used definition for 'youth-friendly services' found in the literature.

2.6.2. Results

The search resulted in 624 papers. After reviewing all titles for relevance to the inclusion criteria, 31 were selected for abstract reviewing and only nine were included in this literature review. An additional paper from another reference list and a conference abstract from the CROI abstract database were included into the literature review, resulting in a total of 11 studies (Figure 2.11). The majority of excluded papers were due to not reporting the impact of clinic level services or study population not consisting of young people with HIV.

In this review, nine of the 11 studies were from the USA and one was from the UK and France. All the USA studies were of predominantly young people with BHIV (37% to 100%), while the French and UK studies were of young people with only PHIV. The ages for all study populations ranged from 12 to 30 years in adult care.

Figure 2.11: Studies screened for the literature review on the impact of youth-friendly services



**papers with irrelevant study populations or outcomes of interest*

In this literature review, there were three randomized control trial (RCT) studies; two from multiple regions across the USA and one from Chicago. There were another four non-randomized

intervention studies without control groups; three from the USA (i.e. Los Angeles (LA), Detroit and one from multiple regions across the USA) and one from London, UK. There were also a multi-region USA cross-sectional study and three cohort studies (one from Paris, France, one from Baltimore, USA and one from multiple regions across the USA). When assessing the impact of youth-friendly interventions, only the Baltimore study and the Paris study used a comparison group who were receiving the standard of care (SOC). The study durations ranged from 3 to 12 months in adult care.

Not all studies used the term 'youth-friendly' or 'adolescent-friendly' to describe their clinic services or features. However, all were youth-focused and aimed to improve the access to care or health outcomes of young people with HIV. Therefore, in this review, I refer to those services as 'youth-friendly'. The youth-friendly services evaluated among all studies varied from group-level peer support to individual-level daily text messaging. Five studies used individual level interventions, most of which were daily text messaging services, and another six studies used clinic-level interventions (i.e. evening hours, youth-focused care models, counselling services). All studies explored the association of these services with various patient outcomes, including self-reported adherence to ART, engagement in care, virological and immunological outcomes of young people with HIV in adult care (Table 2.13).

2.6.2.1. The impact of youth-friendly clinic services on engagement and health outcomes of young people with HIV

Clinic-level interventions for engagement and virological outcomes

Five USA studies (the LA study, Detroit study, two multi-region USA studies and the Baltimore study) reported different youth-friendly services that positively impacted on the engagement in adult care of young people with HIV [101,128,149–151]. The engagement definitions used varied across all studies, including ≥2 clinic visits in the past 6 months [149], ≥1 visit every 3 months in a 12 month period [101] and ≥1 visit every 6 months in a 24 month period. All studies investigated engagement interventions that were clinic-level services or features (Table 2.13).

The LA study, a multisite intervention study, evaluated the effect of psychosocial case management on the engagement of African-American or Latino men who have sex with men (N=61) [149]. The case management consisted of a designated case manager who provided service referrals, treatment education, adherence support and risk reduction counselling, on a weekly basis for the first 2 months and on a biweekly basis for another 22 months. By three months of case management, 90% of young men were engaged in care which declined significantly to 70% by 6 months ($p<0.001$). The mean number of clinic visits also declined from 2.2 visits in the first three months to 1.7 visits in months four to six ($p<0.001$), thus reflecting the positive impact of the psychosocial case management on patient engagement in care. The generalisability of these findings are limited by the short follow-up duration and the niche study population, which predominantly consisted of young people with a history of depression and/or drug use.

Table 2.13: Summary of studies reporting the impact of youth-friendly interventions to improve engagement and health outcomes among young people with HIV in adult care

First author, city/region, country, year[A]	Study design	Main outcome(s)	Intervention and duration time	Inclusion criteria	Receiving intervention	Comparison	Receiving comparison	Impact of intervention
Clinic level intervention with engagement and viral suppression outcomes								
Wolh, LA, USA, 2011, [149]	multisite, pre-post intervention study	Engagement in care (≥2 clinic visits in the past 6 months)	Youth-focused case management (including psychosocial and adherence support and counselling) for 12 months (weekly sessions in the first 8 weeks, biweekly in the remaining period)	Aged 13-23 years, African-American or Latino men who have sex with men, newly diagnosed or in intermittent care (<2 clinic visits in last 6 months)	61 (100% MSM)	None	N/A	By 3 months: 90% engaged in care By 6 months: 70%, p<0.001
Naar-King, Detroit, USA, 2007, [150]	Single-site, intervention study	Number of engagement in care (≥1 visit every 3 month over a 12 month period) [B]	Case-management (referring to specialist services) and counselling for 6 months	Aged 16-25 years and attended the clinic for 12 months	75[b]	None	N/A	By 3 months: higher number of case-management and counselling sessions were associated with fewer number of gaps in care
Philbin, multi-region, USA, 2014, [128]	Multisite, cohort study	Engagement in care (defined as having a second visit within 16 weeks after first visit)	Youth-friendly clinic services including: outreach worker, clinic type (adolescent only vs shared paediatric and adolescent vs specialist HIV clinic)	Aged 12-24 years	1172 (4% perinatal)	None	N/A	By 32 months: Clinics with outreach workers who scored low on effectiveness (OR=0.41, 95% CI 0.30, 0.55) and did not interact with participants (OR=0.07, 95% CI 0.07, 0.07) were associated with lower levels of patient engaged in care

First author, city/region, country, year[A]	Study design	Main outcome(s)	Intervention and duration time	Inclusion criteria	Receiving intervention	Comparison	Receiving comparison	Impact of intervention
Griffith, Baltimore , USA, 2019, [151]	single site, cohort study	Engagement in care (≥1 clinic visit each 6 months over a 24 months period) and VS (viral load <200 copies/ml)	Youth-focused care model (including additional appointment reminders)	Intervention and comparison group: aged 18-30 years Intervention group: history of mental health diagnosis, history of substance abuse, known adherence issues	61 (23% perinatal)	SOC	76 (3% perinatal)	By 24 months: 49% of intervention group engaged in care vs 26% of comparison group (p=0.01) (aOR=3.26, 95% CI 1.23, 8.63), Of those engaged in care, 60% of the intervention group were VS and 89% of the comparison group
Lee, multi-region, USA, 2016, [101]	Multisite, cross-sectional study	Engagement in care (defined as ≥2 clinic visits ≥3 months apart in a 12 month period)	Youth-friendly clinic features and services including: location of clinic, youth-friendly waiting area, text messages, evening clinic hours, same day walk-in service, adolescent-trained staff	Aged 15-24 years, with ≥1 clinic visit	680 (35% perinatal /blood transfusion)	None	N/A	Young people were more likely to be engaged in care if they attended clinics with a youth-friendly waiting area (adjusted OR (aOR)=2.47, 95% CI 1.11=, 5.52), evening hours (aOR=1.94, 95% CI 1.13, 3.33) and staff with adolescent training (aOR=1.98, 95% CI 1.01, 3.86)

First author, city/region, country, year[A]	Study design	Main outcome(s)	Intervention and duration time	Inclusion criteria	Receiving intervention	Comparison	Receiving comparison	Impact of intervention
Funck-Brentano, Paris, France, 2005, [152]	single site, cohort study	Change in self-reported emotional wellbeing and % VS (viral load ≤200 copies/ml)	Group-level peer support therapy for 26 months	Aged 12-18 years, with perinatal HIV	10 (100% perinatal)	SOC	20 (100% perinatal)	By 24 months: worries about illness declined in the intervention group but stayed the same in the comparison group. Perception of treatment became less negative in the intervention group than the comparison group. Proportion with VS increased from 30% to 80%, p=0.06
Individual level intervention with adherence, immunological or virological outcomes and participants with documented poor adherence								
Garofalo, Chicago, USA, 2016, [153]	Multisite, RCT	% with self-reported ART adherence [C] of ≥90%	6 months of daily text messages	Aged 16-29 years, regular clinic follow-up and not pregnant	55 (12% perinatal)	SOC	54 (7% perinatal)	By 6 months: intervention group were more likely to have ≥90% adherence compared to comparison group (odds ratio (OR)=2.12, 95% CI 2.02, 4.45, p<0.05)
Belzer, multi-region, USA, 2014, [154]	Multisite, RCT	% with self-reported ART adherence [C] of ≥90%	6 months of mobile adherence support (incl. medication reminders, emotional support and resource referrals)	Aged 15-24 years, VL >1000 copies/ml	19 (63% perinatal)	SOC	18 (28% perinatal)	By 6 months: intervention group were more likely to have ≥90% adherence for past 3 months compared to comparison group (OR=2.85, 95% CI 1.02, 7.97, p=0.05)
Jeffries, multi-region, USA, 2016, [155]	Multisite, RCT	Viral load, units not specified	Daily text messages Text messaging for 3 months	Aged 15-24 years, with ≥1 clinic visit	91 [D]	SOC	45 [D]	By 3 and 6 months: Viral load was significantly lower among the intervention group compared to the comparison group (p<0.05)

First author, city/region, country, year[A]	Study design	Main outcome(s)	Intervention and duration time	Inclusion criteria	Receiving intervention	Comparison	Receiving comparison	Impact of intervention
Dowshen, multi-region, USA, 2012, [156]	Single site, pre-post intervention study	Mean % of adherence [C] (self-reported on a scale of 0-100%), median CD4 count and viral load	6 months of daily text messages	Aged 14-29 years	25 (12% perinatal)	None	N/A	Baseline: mean adherence was 75% By 3 months: mean adherence was 93% By By 6 months: mean adherence was 93% (week 0 vs week 24, p<0.001), no significant change in median CD4 and VL by 3 months
Foster, London, UK, 2014, [157]	Single site, pre-post intervention study	Median CD4 count and % viral suppression (VS) (defined as <50 copies/ml)	12 months of motivational interviewing and financial incentive dependant on viral load reduction	Aged 16-25 years, with perinatal HIV, CD4 count ≤200, off ART despite multiple attempts to restart ART	11 (100% perinatal)	None	N/A	Baseline: median CD4 count was 30 cells/mm3 and 0% VS By 12 months: median CD4 count was 140 cells/mm3 and 45% VS By 24 months: median CD4 count was 75 cells/mm3 and 55% VS

A – year of publication; B – engagement in care measure converted from gaps in care (no visit for ≥3 months over a 12 months period) C - Adherence measured using visual analogue scale (VAS), which allows participants to report their adherence to treatment from 0% to 100%; D - Proportion with PHIV not described

The Detroit study also investigated the impact of 6 months of case management and counselling on engagement in care (defined as ≥1 visit every 3 months) of 75 young people with HIV [150]. In this study, case management was defined as a designated professional having contact with a patient and referring them to necessary services. The counselling service was associated with increased engagement in the second 6 month period after receiving the intervention, while case management was not significantly associated with increased engagement in care. However, the study is limited by short follow-up duration and longitudinal studies with longer follow-up periods are needed to assess the long-term effects of these interventions.

The multi-region USA cohort study (N=1172) by Philbin et al assessed the impact of clinic type (paediatric/adolescent clinics vs adolescent only vs adult HIV specialist clinic), availability of an outreach worker (a designated contact person who arranges appointments) on engagement in care (≥1 visit within 16 weeks following the first visit) [128]. By 32 months of follow-up, 71% to 100% of young people were engaged in care. Young people with HIV who attended adult HIV specialist clinics were more likely to be engaged in care (odds ratio (OR)=2.93, 95% CI 1.90, 4.53, p<0.05) compared to those at adolescent only clinics not specific to HIV. Young people attending clinics without outreach workers (OR=0.38, 95% CI 0.25, 0.58), or with outreach workers judged to be less effective at engaging young people (based on opinion of staff and young people) (OR=0.56, 95% CI0.39, 0.81) were less likely to be engaged in care compared to those at clinics with 'effective' outreach workers. These findings suggest the importance of appropriate clinic settings and staff training when engaging young people in care, although, a less subjective measure of outreach workers' effectiveness would strengthen this conclusion.

The Baltimore study, a single site cohort study also from USA, evaluated the impact of a youth-focused care model on the engagement in care (defined as ≥1 visit every 6 months in a 24 month period) of young people with HIV [151]. The youth-focused care model consisted of specialist HIV and adolescent clinicians, social workers with paediatric training who all provided a developmentally sensitive approach in order to address the barriers to care. The study compared the engagement in care of 61 young people (23% perinatal) who received the youth-focused care model versus 76 young people (3% perinatal) who received the SOC. The inclusion criteria for the first group required that participants had a history of mental health diagnosis, substance abuse and/or known adherence issues. The group who received the youth-focused care model had higher odds of engagement in care after 24 months of entering the study compared to the control group (adjusted OR (aOR)=3.26, 95% CI 1.23, 8.63, p=0.01), after adjusting for various demographic and clinical characteristics. However, improved engagement in the intervention group did not result in significantly increased viral suppression (viral load <200 copies/ml) by 24 months (aOR=0.63, 95% CI 0.35, 1.14). The lack of impact detected on the participants' viral suppression may be due to the study's limited statistical power caused by the small sample size.

The multi-region USA cross-sectional study by Lee et al examined whether the following clinic features and services improved engagement (defined as ≥2 visits, ≥3 months apart, in a 12 month period) of 680 young people with HIV (35% PHIV): location of clinic, availability of separate waiting area for young people, evening hours, communication via text messaging, same day

appointments and staff being trained in adolescent care [101]. Engagement in care was associated with having a young people's waiting area (aOR=2.47, 95% CI 1.11, 5.52), evening clinic hours (aOR=1.94, 95% CI 1.13, 3.33), and staff with adolescent training (1.98, 95% CI 1.01, 3.86). These factors were adjusted for age, sex, duration in care, CD4 count and ART status.

The Paris study, a single-site cohort study, evaluated the effect of group level peer support therapy among young people with PHIV (aged 12 to 18 years) [152]. Ten young people completed 26 months of the peer support therapy, 10 refused the intervention and another 10 did not take the intervention due to living too far away from the clinic. The outcome of interest was viral suppression (VL ≤200 copies/ml) and emotional wellbeing measures: worries about HIV illness and perception of treatment. After 24 months of follow-up, patient worries about their illness declined significantly among the intervention group, but increased or remained the same among the other two groups (p=0.03) and the perception of treatment also became less negative among the intervention group compared to the other groups. The proportion of young people in the intervention group who were virally suppressed increased from 30% at enrolment to 80% after 24 months (p=0.06), while viral load levels remained unchanged in the other two groups.

Individual level interventions with adherence, immunological and virological outcomes and participants with poor adherence

Five studies (three RCTs and two intervention studies) examined individual-level interventions to improve young people's ART adherence, immunological or virological outcomes in adult care [153,155–158].

In the Chicago RCT study, young people aged 16 to 29 years were randomised to receive 6 month of daily medication reminders via text messages compared to those in SOC [153]. After a 6 month intervention period, self-reported ART adherence was compared between the trial arms; the study found the intervention group (N=55) to be twice as likely to adhere to their medication (aOR=2.12, 95% CI 2.02, 4.45, p<0.05) compared to the control group (N=54). The findings were more representative of young people who were better engaged in care as the study inclusion criteria for both arms required young people to be regularly attending care (undefined) and to not be pregnant. Additionally, the self-reported nature of the adherence outcome measure was a study limitation which allowed the potential for recall bias and even desirability bias, thus possibly leading to overestimated post-intervention adherence figures.

The multi-region USA RCT study by Belzer et al, evaluated the impact of a mobile phone support programme on self-reported ART adherence [158]. The phone support included medication reminders, emotional support and service referrals. Nineteen young people (63% PHIV) were randomized to the intervention arm and another 18 young people (28%) to the control arm and given the SOC. This and the previous RCT both used a self-reported adherence measure, where participants were given a visual analogue scale (VAS) and rated their adherence to treatment from 0% to 100%. Young people in the intervention group were almost three times as likely to report ART adherence of at least 90% compared to the control group (OR=2.85, 95% CI 1.02, 7.97, p=0.05).

The multi-region USA RCT study by Jeffries et al reported that the use of text messaging to remind young people to take their medication had resulted in significantly improved viral load levels (viral load value not specified) at 3 and 6 months following baseline ($p<0.05$) [155]. The study randomized 91 young people to receive the intervention for 3 months and 45 young people to receive the SOC.

The multi-region USA intervention study by Dowshen et al, from multiple regions across USA), investigated whether 6 months of daily text message medication reminders would improve the adherence to ART among 25 non-adherent young people (aged 14 to 29 years) [156]. Young people self-reported their adherence using the VAS measure similar to the previous two RCTs. At baseline, the average percentage of adherence was 75% which increased to 93% by 6 months of receiving the intervention ($p<0.001$). However, the adherence level did not change by 12 months following study initiation, indicating that any impact of the intervention was short-term.

The London study, a pre-post intervention study, of 11 young people attending a single clinic with CD4 counts ≤200 cells/mm_3, unsuppressed viral load (VL >50 copies/ml) and adherence issues, were provided a financial incentive and motivational interviewing with the aim of lowering their viral load levels [157]. The financial incentive received depended on viral load reduction in the first year following enrolment. After the first year, 45% had achieved viral suppression (VL <50 copies/ml) and the mean CD4 count gain was 90 cells/mm_3; by two years following enrolment, 55% were virally suppressed with a mean CD4 count gain of 122 cells/mm_3. The findings indicate longer term benefits of motivational interviewing and financial incentive, although, implementation of such interventions may not be financially feasible in all clinics.

2.6.2.2. Summary

Several individual- and clinic-level interventions were reported to significantly improve engagement in care, adherence to ART, virological and immunological outcomes among young people with HIV in adult care. Studies found the following clinics-level characteristics to be associated with better engagement in care among young people with HIV: availability of young people's waiting areas, evening hours, adolescent staff training, good outreach worker(s), psychosocial and adherence support, counselling services and individualised case management. These engagement interventions were aligned with one or more of the five objectives in the WHO's framework on youth-friendly services (described in Chapter 1, section1.9.). Some interventions promoted clinic accessibility (i.e. evening hours), some acceptability to young people (e.g. by providing separate waiting area), some were focused on being more appropriate by providing services that were specific and developmentally sensitive to the needs of young people with HIV (e.g. psychosocial, adherence support, counselling and individualised case management) and some clinics improved care efficacy by having adolescent trained staff and patient-interacting outreach workers.

With regard to improving adherence to ART among non-adherent young people with HIV, three intervention studies found the use of telephone technology as medication reminders a useful tool that is also compatible with the widespread mobile youth culture [159]. Within the WHO youth-friendliness framework, can be categorised as an appropriate type of service delivery for young

people. However, the RCTs and intervention studies only had a 6 month observation period, which thus questions the long-term effect of text message reminders.

Few studies (i.e. the London and Paris studies) also found virological and immunological outcomes of young people with HIV to be improved by services such as motivational interviewing, financial incentive and group-level peer support. All of these fall in line with WHO's objective for youth-friendly services to be appropriate in addressing young people's health needs.

It is difficult to generalise all the findings due to the small number of studies, limited sample sizes and short follow-up durations. The study designs used also varied from RCTs to cross-sectional studies. All three RCT studies in this literature review were consistent in finding text message reminders to be an effective intervention in tackling poor adherence. However, all RCTs used self-reported measures for ART adherence and studies that use more objective measures of adherence are needed to minimise any potential for reporting bias.

Among the other study designs, there was much more variation in the type of services identified as useful interventions as well as the outcomes of interests. Harmonisation of the type of services and outcomes evaluated would increase the ability to compare study findings and to collate strong evidence in support of effective youth-friendly services. Though, such harmonisation becomes difficult due to inconsistent and unclear definitions of youth-friendly services and the fact that multiple type of services can be considered youth-friendly.

All studies, except two (the London and Paris studies), were set in the USA where study populations consisting mostly of young people with BHIV. The London and Paris studies were of young people with only PHIV who likely have more extensive history of receiving HIV care compared to more newly diagnosed young people with BHIV. Therefore, it is unclear what the different needs are of these two populations and further studies are needed to evaluate youth-friendly services among the perinatal populations, in particular young people who have transferred to adult care. In my thesis, this gap in literature was addressed by assessing the impact of youth-friendly services on disengagement and health outcomes following transfer to adult care among young people with HIV.

3. Chapter 3: Methods and data linkage of paediatric data and adult data

3.1. Chapter content and aims

3.1.1. Chapter content

As part of this PhD, patient-level paediatric data from the UK and Ireland's paediatric HIV cohort (CHIPS) were linked to UK adult surveillance and cohort data from the following surveillance systems and cohort study: SOPHID, HARS and UK CHIC. None of the studies shared a unique patient identifier (e.g. NHS number), which would have allowed for a simple linkage. Instead, I developed data linkage algorithms to link the records of participants in the studies based on commonly collected identifying variables such as date of birth (dob), clinic name, partial postcode etc.

Linking patient data across the studies enabled CHIPS participants to be identified in the adult datasets, post-transfer. This, in turn, allowed me to create a longitudinal life-course dataset, from childhood diagnosis through to adulthood. With this dataset I investigated paediatric determinants of poor health outcomes and disengagement from care following transfer to adult care.

In this chapter, I describe the CHIPS, SOPHID, HARS and UK CHIC data sources as well as standard statistical methods used throughout the thesis. I then describe the data linkage methods and results.

3.1.2. Aims

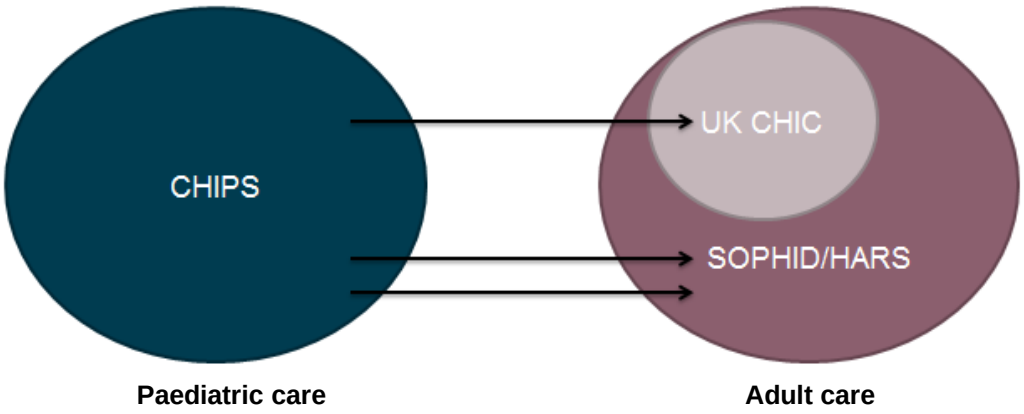
The aims of this chapter are to:

1. Describe the CHIPS, SOPHID, HARS and UK CHIC studies
2. Describe the data linkage methods used
3. Summarise the linkage results and level of linkage completeness
4. Describe the standard statistical methods used in this thesis

3.2. Paediatric and adult HIV studies and surveillance systems in the UK

In the UK, children diagnosed with HIV aged <16 years, including those born abroad, are reported to the National Study of HIV in Pregnancy and Childhood (NSHPC). NSHPC is a reporting scheme for pregnant women with HIV and their babies in the UK and Ireland. The NSHPC informs CHIPS of any HIV diagnosed children; these children are then followed up in CHIPS throughout their duration in paediatric care. Once these children transfer to adult care they are followed up in SOPHID, HARS and/or the UK CHIC study (Figure 3.1).

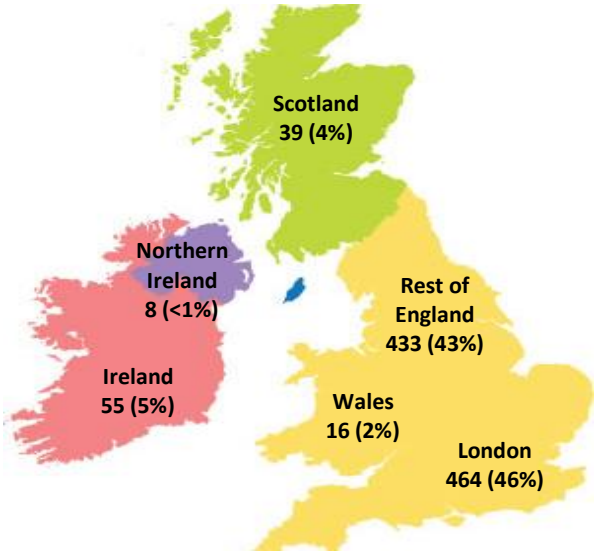
Figure 3.1: Young people followed up in paediatric and adult care and captured by the different cohorts and surveillance systems



3.2.1. Paediatric follow-up in CHIPS

CHIPS is a multicentre paediatric cohort study estimated to include over 95% of children with HIV receiving care in the UK and Ireland [160]. The study was established in April 2000 to collect more detailed follow-up data on all children diagnosed with HIV and notified to the NSHPC. The aim of CHIPS is to describe HIV-related clinical data of the paediatric population in order to inform standard of care for paediatric clinics (currently 54 clinics). Figure 3.2 presents the distribution of children followed up in CHIPS by region.

Figure 3.2: Regional distribution of 1,015 children with HIV in active follow up in CHIPS by the end of 2016*



** Excluding children who died, were LTFU, left the country or transferred to adult by the last paediatric visit*

Data collection in CHIPS

Once NSHPC has informed CHIPS of any newly diagnosed children, CHIPS sends a baseline form (Appendix 1) to the respective paediatric clinics, which is followed by prospective annual follow-up forms (Appendix 2). The CHIPS study is based at the Medical Research Council Clinical Trials Unit (MRC CTU), University College London (UCL).

CHIPS follow-up forms request detailed demographic and clinical data, including all clinical events and CDC stage B or C, growth parameters, hospital admissions, clinic attendances, AIDS or serious non-AIDS events, hepatitis B and C co-infections, CD4 count and percentage, viral load, complete ART history and death data. After all patient data are submitted to CHIPS, data inconsistencies and errors are checked and queried with clinics. The data are then cleaned and prepared into datasets by the CHIPS statistician, thereafter stored on a secure network server at the MRC CTU.

3.2.2. Follow-up in adult care

3.2.2.1. SOPHID

In 1995, PHE established an adult HIV surveillance system (SOPHID) which ran until the end of 2015 as the main surveillance system of the adult HIV population in the UK. Thereafter, an improved surveillance system (HARS) was implemented to replace SOPHID. To date, the majority of adult clinics are now reporting to HARS, but the remaining clinics are expected to keep reporting to SOPHID. SOPHID is an annual cross-sectional survey of all adults with HIV aged ≥15 years and accessing NHS-funded HIV care in England, Wales and Northern Ireland. Scottish clinics instead report to Public Health Scotland. SOPHID together with HARS data are used to monitor the health outcomes of those living with HIV and the quality of care they receive [161].

Data collection in SOPHID

The SOPHID forms are sent out biannually to all adult HIV clinics in London, as well as Brighton, Hastings and Eastbourne. For all other clinics outside of London, the survey is sent annually. It is compulsory for clinics to submit data to SOPHID as the Department of Health allocates funding by taking into account whether data has been submitted to SOPHID. Additionally, many hospital trusts in London have service-level agreements, where they are contractually bound to submit timely data to SOPHID [162]. This has resulted in SOPHID having national coverage of the adult HIV population in the UK (excluding Scotland) to the end of 2015. The SOPHID forms request limited demographic and clinical data for the last patient visit per calendar year, rather than every clinic visit in for the year (Table 3.1) [161,162]. The collected clinical data include AIDS events, CD4 and viral load measurements and ART data (SOPHID data specification in Appendix 4).

Table 3.1: Metadata description of the CHIPS, UK CHIC, SOPHID and HARS databases

Countries reporting to each database:	CHIPS	UK CHIC	HARS	SOPHID
England	✓	✓	✓	✓
Wales	✓			✓
Scotland	✓	✓		
N. Ireland	✓			✓
Ireland	✓			
Frequency of data requests	Every clinic visit per year	Every clinic visit per year	Every clinic visit per year	Last clinic visit per year

Once the data are submitted to PHE, they are stored on a secure network server in the HIV/STI surveillance department in PHE. The data are checked for inconsistent or missing data, which are then queried accordingly. Each patient who attends a NHS-funded clinic are allocated a unique hospital number, which is submitted along with a patient form to SOPHID. A patient record is then created in SOPHID based on this clinic identifier. However, patients can have multiple hospital numbers if they attend multiple clinics, thus resulting in SOPHID having two different patient records for the same person. To deal with the duplicate patient records, SOPHID undergoes a de-duplication process to ensure only one record exists per patient. Multiple records for the same individual are matched on dob, sex and Soundex (a non-unique code based on the patient's surname [163]). The dataset is then cleaned and ready for analysis.

3.2.2.2. HARS

In 2014, PHE developed HARS, which is a more comprehensive and complete HIV surveillance system that is replacing SOPHID and captures clinical data from all patient visits rather than the last patient visit per calendar year. Like SOPHID, HARS was designed to also achieve national coverage. All clinics in England currently report to HARS, with the exception of some large London clinics still reporting to SOPHID. Wales and Northern Ireland are also expected to adopt this reporting system (in due course), while Scotland will use their own reporting system [164]. HARS and SOPHID have similar aims with regards to public health monitoring and informing quality of HIV care. Using data from SOPHID and HARS, annual reports on national adult HIV surveillance are published by PHE [164,165].

Data collection in HARS

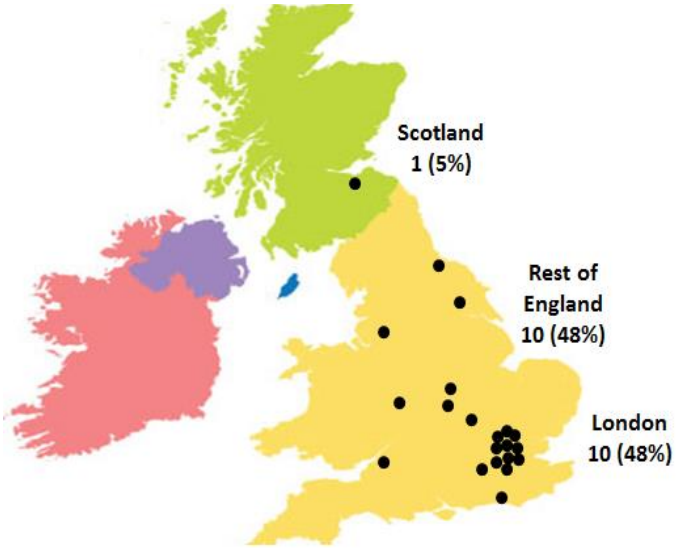
On a quarterly basis, clinics submit detailed demographic and clinical data for all patient visits to a secure web portal [165]. Clinical data include ART, CD4 and viral load measurements, AIDS events, hepatitis B and C results, ART side-effects, psychiatric care, date and cause of deaths (HARS data specification in Appendix 5). The HARS data are checked for errors and undergo a similar de-duplication process to SOPHID [165].

3.2.2.3. The UK CHIC study

The UK CHIC study is a multicentre observational cohort study of adults living with HIV aged ≥15 years in some of the largest adult HIV clinics in the UK. This collaboration began in 2001 with the aim of investigating health outcomes and treatment responses of the adult HIV population

attending UK CHIC-participating adult clinics. There are 21 adult clinics across England and Scotland reporting to the UK CHIC study (Figure 3.3). This makes the UK CHIC study the largest adult HIV cohort to collect clinical data in the UK. The UK CHIC database contains data on approximately 60,000 adults, with data going back to 1996.

Figure 3.3: Geographical distribution of HIV adult clinics participating in UK CHIC (N=21)



Data collection in the UK CHIC study

The UK CHIC data items are similar to those for CHIPS, with additional information on renal and liver function tests and ART side effects (UK CHIC, 2015). THE UK CHIC study coordinator requests an annual data submission, sending out the latest data specifications to all participating sites at the beginning of November each year with a deadline for submission of the end of December. In the following months, data quality checks and cleaning queries are carried out and resolved where possible.

Similar to SOPHID and HARS, UK CHIC data undergo a de-duplication process. The process uses a computerized algorithm to combine multiple records thought to belong to one individual, using various demographic and clinical data. The algorithm produces definite matches, indeterminate matches or definite non-matches. For indeterminate matches, the clinical data are manually checked by two investigators. If there is disagreement or uncertainty about a match, a third investigator will also check the patient records. Definite non-matches remain as separate records.

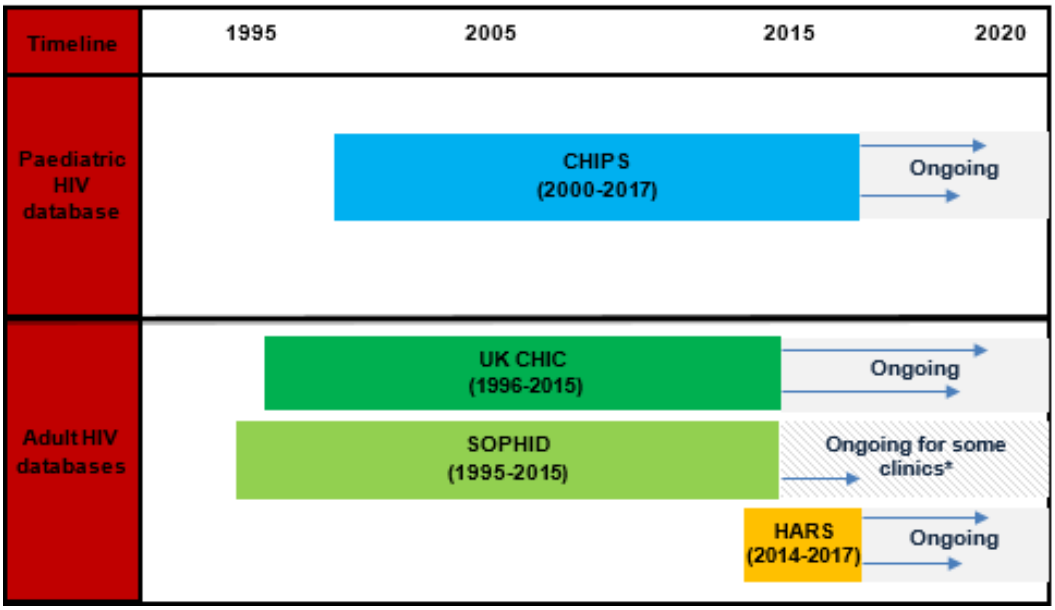
After the de-duplication process, any records that are deemed a match are merged, and a second dataset produced. The merged dataset is sent securely to the UK CHIC statistician to run some final checks and to create a final dataset for use in analyses.

3.2.3. CHIPS, SOPHID, HARS and UK CHIC datasets used in this thesis

Young people in CHIPS who transfer from paediatric care to adult care in the UK are potentially captured in SOPHID, HARS and/or UK CHIC follow-up. In September 2017, the latest available datasets were obtained from CHIPS, SOPHID, HARS and UK CHIC and were used in this thesis. The datasets included all available identifying variables to be used for the data linkage. Demographic, clinical and treatment variables were also obtained in order to carry out the analyses.

Figure 3.4 presents the timeline of follow-up periods of the paediatric and each adult dataset. The CHIPS dataset included data to 01/04/2017 and was restricted to young people aged ≥13 years by that same date. The SOPHID and UK CHIC datasets both had data from 01/01/1995 and 01/01/1996, respectively, through to 31/12/2015. As HARS is not a retrospective study, the data were from 31/12/2014 to 01/04/2017. All adult datasets were restricted to participants aged <40 years on 01/04/2017, as no CHIPS participant was older than 39 years by this date.

Figure 3.4: Timeline for the CHIPS, UK CHIC, SOPHID and HARS datasets used in this thesis



**Clinics that have not yet begun reporting to HARS*

3.2.4. Study variables

Table 3.2 lists the variables in the CHIPS, UK CHIC, SOPHID and HARS datasets used in this thesis. CHIPS, UK CHIC and HARS all collect death data, primarily from participating clinics. CHIPS obtains additional death data from NSHPC and HARS receives death data from the Office for National Statistics (ONS). The UK CHIC study gains additional death data from its annual linkage to HARS. In contrast, SOPHID does not directly collect death data. Death data are instead obtained from another HIV surveillance system: HIV & AIDS New Diagnoses Database (HANDD), which reports new HIV diagnoses, AIDS and deaths received from adult clinics.

Table 3.2: Variables from the CHIPS, SOPHID, HARS and UK CHIC datasets

	Variable	Data format	CHIPS	SOPHID	HARS	UK CHIC
Sociodemographic	Sex	Integer	✓	✓	✓	✓
	Date of birth	dd/mm/yyyy	✓	✓	✓	✓
	Country of birth	Text	✓	✓	✓	✓
	Ethnicity	Integer	✓	✓	✓	✓
	Initials	Text	✓	✓	✓	✓
	Soundex	Text	✓	✓	✓	✓
	Patient hospital number	Text	✓	✓	✓	✓
	Clinic name	Text	✓	✓	✓	✓
	Partial postcode (first part)	Text	✓	✓	✓	
First presention to care	Date of HIV diagnosis in	dd/mm/yyyy	✓	✓	✓	✓
	Date of HIV diagnosis from abroad	dd/mm/yyyy			✓	
	Mode of HIV acquisition	Integer	✓	✓	✓	✓
	Transfer date	dd/mm/yyyy	✓			
AIDS data	AIDS event	Integer/text	✓	✓	✓	✓
	AIDS event date	dd/mm/yyyy	✓	✓	✓	✓
	Serious non-AIDS event	Integer				✓
Laboratory data	CD4%	Integer	✓			✓
	CD4 count	Integer	✓	✓	✓	✓
	Viral load	Integer	✓	✓	✓	✓
Treatment data	ART regimen (incl. regimen changes)	Integer	✓	✓	✓	✓
	First ART start date in the UK	dd/mm/yyyy	✓		✓	
	Initial ART regimen	Integer	✓			
Follow-up status	Date first seen at clinic	dd/mm/yyyy	✓	✓	✓	✓
	Date last seen at clinic	dd/mm/yyyy	✓	✓	✓	✓
	Date of death	dd/mm/yyyy	✓		✓	✓
	Cause of death	Text			✓	✓

3.3. Ethics and data governance

This PhD project used secondary data collected by CHIPS, SOPHID, HARS and the UK CHIC study, all of which have NHS Research Ethics approval, therefore, ethics approval was not required for this PhD research project. All data were collected and stored in compliance with the Information Governance Framework and Caldicott Principles. Therefore, storage and usage of national adult surveillance data were limited to being on-site in the Colindale offices of PHE.

3.4. Statistical methods

A range of statistical methods were used in this thesis. At the start of each results chapter, the study design, inclusion criteria and statistical methods used are described. Below is an overview of the statistical methods used in all chapters of this thesis. All analyses were carried out using STATA version 14.2 and 15.1.

3.4.1. Descriptive analyses

In each chapter, the study population and data are described using summary statistics. Categorical variables were presented as frequencies (N) and percentages (%). Continuous variables are described as means and standard deviations for data with normal distributions and median and interquartile range [IQR] if the data were skewed. The majority of CD4 count and viral load data analysed in this thesis were skewed and, thus, presented as medians and IQRs.

Unpaired data

Where characteristics are compared between two independent groups, unpaired t tests were used. An example of two independent groups would be males and females as the two groups would not overlap in individuals. When comparing two categorical variables a chi-squared test was used. Where the categorical groups have an expected frequency below five, Fisher's Exact test was used. Continuous variables with normally distributed data were compared between two independent groups using the Student's t-test; continuous variables with non-normally distributed data were compared between two groups using the Wilcoxon signed rank sum test. Ordinal or non-normally distributed variables were compared between two independent groups and where there were more than two groups, using a Kruskal-Wallis test.

Using paired data

When characteristics were compared between two dependant groups (with paired data), paired tests were used. In my thesis, this occurred when the same group of individuals was compared at different time-points. When comparing two paired binary variables, McNemar's test was used. Paired continuous variables were compared using the t-test for normally distributed data or Mann-Whitney test for non-normal data.

3.4.2. Regression analyses

When investigating factors associated with a single outcome of interest in this thesis, various regression models were used, with the type of regression model dependent on the outcome of interest. All potential explanatory variables were defined prior to analyses and were described further in each respective chapter. Firstly, univariable analyses were carried out, where the association between each single exposure variable and outcome variable was described. A

multivariable model was then built to take into account the simultaneous effect of multiple exposure variables on an outcome, while also adjusting for potential confounders. The regression methods used in this thesis include Poisson regression and Cox proportional hazards regression. Poisson regression was used where the outcome consisted of count data, for example, the number of people with gaps in care of more than 12 months. Cox proportional hazards regression was used to investigate the time to an event (e.g. death or viral failure) from a meaningful time zero (i.e. transfer date) and where the amount of participant follow-up varied.

3.4.2.1. Statistical interactions

The presence of statistical interaction between pairs of exposure variables in a model was also investigated. A statistical interaction is when the effect of an exposure varies according to the level of another exposure, e.g. the effect of age on an outcome is greater for females than for males. When interactions were identified in a multivariable model, an interaction term was introduced.

3.4.2.2. Functional form of variables

In proportional hazards models, the appropriate functional form for a continuous explanatory variable was investigated by plotting the Martingale residual of the variable in question. The Martingale residuals represent the difference between whether an individual had the event of interest vs whether the person was predicted to have the event by the fitted model [166]. A linear relationship between the Martingale residuals and the continuous variable indicated that a linear continuous form of the variable was appropriate.

3.5. Methods for linking paediatric and adult HIV data

The large size of the CHIPS (N=1,683), SOPHID (N=33,523), HARS (N=25,849) and UK CHIC datasets (N=14,878), prevented individual participant-level matches occurring through simple linkage using only date of birth or hospital number alone. Therefore, a more complex method of data linkage using multiple identifiers was required.

Deterministic and probabilistic linking approaches are often used in studies that have linked participant records across multiple observational studies [167–169]. The probabilistic method generates a weight for each possible pair of records; this weight reflects the probability that the two records are a true match. Deterministic linkage classifies whether two records match exactly based on a set of identifying variables, such as sex and date of birth. Data linkage with a deterministic algorithm is more suited when using datasets with high quality data, while probabilistic algorithms may be better for data of poorer quality where there is a high proportion of missing data [170,171]. In this thesis, the deterministic method was considered the most appropriate approach as CHIPS, SOPHID, HARS and UK CHIC datasets have high quality data with several variables in common.

The CHIPS dataset was linked to each adult dataset, separately. The data linkage was a two-part process. In part one, CHIPS was linked to each adult datasets using stringent linkage algorithms. In part two, the linkage algorithm was relaxed to further maximise the number of CHIPS participants linked to their adult records. Overlap of CHIPS participants across the three adult

datasets is described in 3.5.4. All data linkage was carried out in STATA version 14.2 (CHIPS and the UK CHIC study) and 15.1 (CHIPS, SOPHID and HARS).

3.5.1. Inclusion criteria for data linkage

In part one, the inclusion criteria for CHIPS participants were ages ≥13 years by 01/04/2017 and ever attended CHIPS-participating clinics in the UK. Children attending only clinics in Ireland were excluded, as none of the adult studies collected data from Ireland. CHIPS participants whose data were not linked in part one and were documented in CHIPS to have transferred to adult care, were reintroduced in part two of the linkage process.

The adult datasets linked to CHIPS all had the same inclusion criterion: individuals aged ≥13 to <40 years by 01/04/2017, for part one and two.

3.5.2. Data linkage variables

Variables used to link CHIPS to SOPHID, HARS and UK CHIC are listed in Table 3.3. Most variables were well recorded with percentage of data completeness nearing 100% in each dataset. However, Soundex, patient hospital number, clinic name and partial postcode had 12% to 62% available data. The Soundex variable was introduced by all studies in later years and partial postcodes were not collected in the UK CHIC dataset thus not used to link the CHIPS and UK CHIC datasets.

Table 3.3: Data linkage variables used from the different datasets and their data completeness

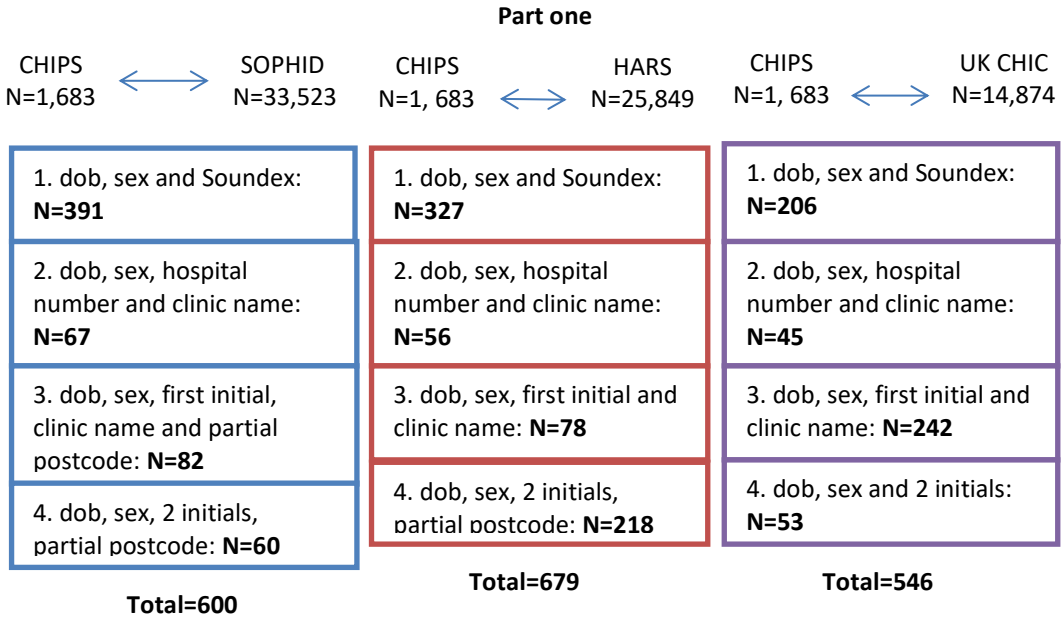
Linkage variable	**CHIPS (N=1,683)**	**SOPHID (N=33,523)**	**HARS (N=25,849)**	**UK CHIC (N=14,874)**
	percentage of data completeness			
Sex	99.8	99.9	95.9	99.8
Date of birth	100.0	100.0	100.0	100.0
Initials	99.9	99.4	100.0	100.0
Soundex	43.9	98.8	100.0	99.9
Patient hospital number	61.6	93.7	100.0	100.0
Clinic name	95.1	32.5	30.1	100.0
Partial postcode	12.3	85.6	95.1	N/A

3.5.3. Data linkage algorithms

3.5.3.1. Part one

Figure 3.5 presents the three linkage algorithms for part one. Each algorithm included four steps, consisting of different combinations of linkage variables. The first two steps of all three algorithms consist of the same combination of linkage variables. The steps in each algorithm occur in a hierarchical order, where step 1 (based on dob, sex and Soundex) is the strongest combination compared to the last step which would be the least stringent. If a CHIPS participant was linked in multiple steps to different records, the earlier step was considered the most valid. CHIPS participants can also be linked more than once in different adult datasets using the different algorithms. The overlap or inconsistencies of linked participants across the algorithms were examined as described in section 3.6.3.

Figure 3.5: Data linkage algorithms used to link CHIPS to SOPHID, HARS and UK CHIC in part one



**N: denotes the number of records linked by each step*

Step 1

In the first steps of each algorithm, CHIPS records were linked to SOPHID, HARS and UK CHIC records on *dob, sex* and *Soundex*. This step generated 391, 327 and 206 linked records identified in each adult dataset, respectively.

Step 2

In the second step of each algorithm, records were linked on *dob, sex, hospital number* and *clinic name*. The *hospital number* is unique for each individual within a hospital. However, some hospitals use the same number generator to allocate a hospital number for each person. Therefore, two people from different hospitals could be allocated the same hospital number. To avoid one-to-many matches (i.e. one paediatric record linking to multiple adult records and vice versa), the *clinic name* variable was added to the second step. The second step generated 67, 56 and 45 additional linked records between CHIPS and the SOPHID, HARS and UK CHIC datasets, respectively.

Step 3

Records of individuals not linked in the second step, were retried in the third step, by attempting linkage on *dob, sex, first initial* and *clinic name*. Since SOPHID is the largest dataset of 33,524 records, there were a high number of many-to-one matches, where one SOPHID record linked to multiple CHIPS records with the same *dob*, *sex, first initial* and *clinic name*. The CHIPS-SOPHID algorithm was therefore made stricter by adding *partial postcode* to the third step. In step three, 82, 78 and 242 CHIPS records linked to SOPHID, HARS and UK CHIC records, respectively.

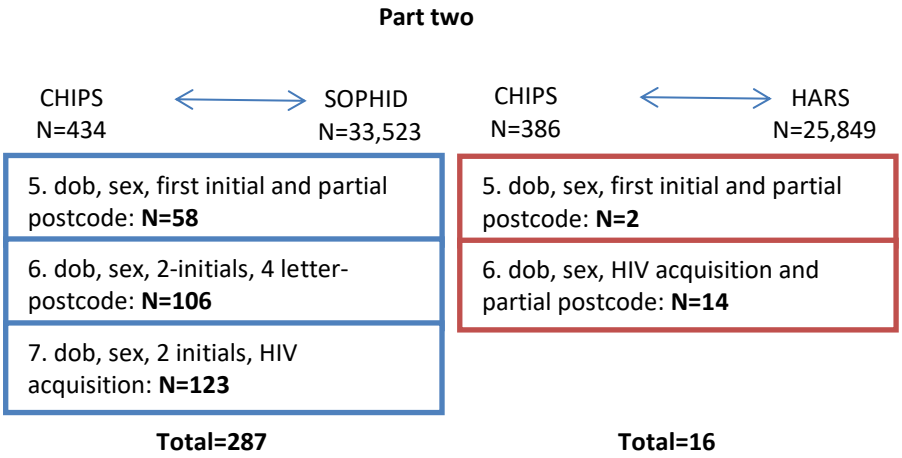
Step 4

The fourth step of the CHIPS-SOPHID and CHIPS-HARS algorithms consisted of *dob, sex, 2 initials* and *partial postcode*. The fourth step for the CHIPS-UK CHIC algorithm only had *dob, sex* and *2 initials*, as partial postcodes were not recorded in the UK CHIC dataset. For all datasets, the initials variable was reduced to the first two letters or first and last letter for participants who had three-letter initials. From step four, 60, 218 and 53 CHIPS records linked to each adult dataset, respectively.

3.4.3.2. Part two

Part two restricted the inclusion criteria of CHIPS participants to those documented in CHIPS as having transferred to adult care but who had not previously been linked in part one. The linkage algorithms for the SOPHID and HARS dataset in part two were less stringent. The CHIPS dataset was not relinked to UK CHIC in part two, as it was felt that relaxing the CHIPS-UK CHIC algorithm any further would result in potentially false matches. Figure 3.6 presents the linkage algorithms used to link CHIPS records to SOPHID and HARS. In part two, the steps in each algorithm were again followed in a hierarchical order.

Figure 3.6: Data linkage algorithms used to link CHIPS to SOPHID and HARS in part two



**N: denotes the number of records linked by each step*

Step 5

Records linked in step 5 of the SOPHID and HARS algorithms had the new combination of *dob, sex, first initial* and *partial postcode*. The remaining steps differed between the two algorithms. Step 6 of the CHIPS SOPHID algorithm linked records on *dob, sex, 2 initials* and shortened version of the *partial postcode* (first 4 letters). Records were then linked on *dob, sex, 2 initials* and *HIV acquisition*.

Steps 6 and 7

In the CHIPS HARS algorithm, step 6 linked records on *dob, sex, HIV acquisition* and *partial postcode*. Due to SOPHID being the largest dataset, an extra step was incorporated into the linkage algorithm, linking records on *dob, sex, initials* and *HIV acquisition*.

3.6. Linkage results

3.6.1. Linkage overview

From parts one and two, 887 CHIPS participants were linked to SOPHID data, 695 to HARS data and 546 to UK CHIC data. These totals are not mutually exclusive; the level of overlap is described in section 3.6.4.

3.6.2. Validating linked data

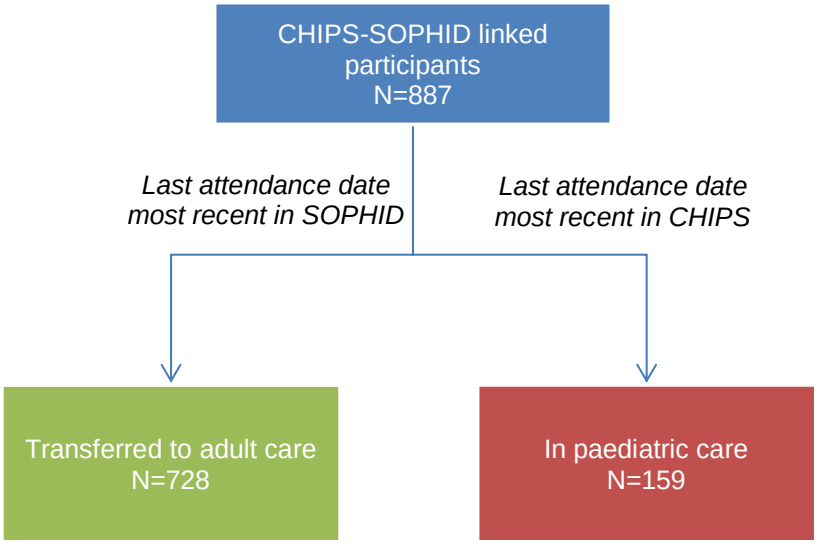
Paediatric data from CHIPS participants were present in all three adult datasets. Therefore, it was unclear if the CHIPS participants linked to the adult datasets had transferred to adult care or were just linked to their own paediatric data. Clinics with both paediatric and adult patients sometimes submit data from both groups to SOPHID, HARS and UK CHIC, despite the ≥15 age limit for the adult datasets. There are online prompts in the SOPHID, HARS and UK CHIC data submission systems, but the submission of paediatric data is not prevented (personal communication, C. Chau and T. Hill). Consequently, the fact that CHIPS participants were identified in the adult datasets did not necessarily mean that they had transferred to adult care. Additionally, participants who had transferred to adult care could still have their paediatric and adult data contained within the adult datasets.

A validation process was carried out to check that linked CHIPS participants had in fact transferred to adult care. Linked participants were confirmed as transferred to adult care if they had adult records dated after the last paediatric visit date in CHIPS. Participants with a last paediatric date more recent than any adult records were assumed to still be in paediatric care and excluded from further analyses. Next, I describe the validation results for each adult dataset.

3.6.2.1. CHIPS-SOPHID linkage

Figure 3.7 shows the overview of CHIPS and SOPHID linked records. Of the 887 participants linked between CHIPS and SOPHID, 728 (82%) had a most recent attendance date in SOPHID compared to CHIPS, which confirmed they had transferred to adult care. The remaining 159 (18%) participants with a most recent attendance date in CHIPS were assumed to not have transferred to adult care and thus were excluded from further any analyses.

Figure 3.7: Validating transfer status of CHIPS-SOPHID linked participants

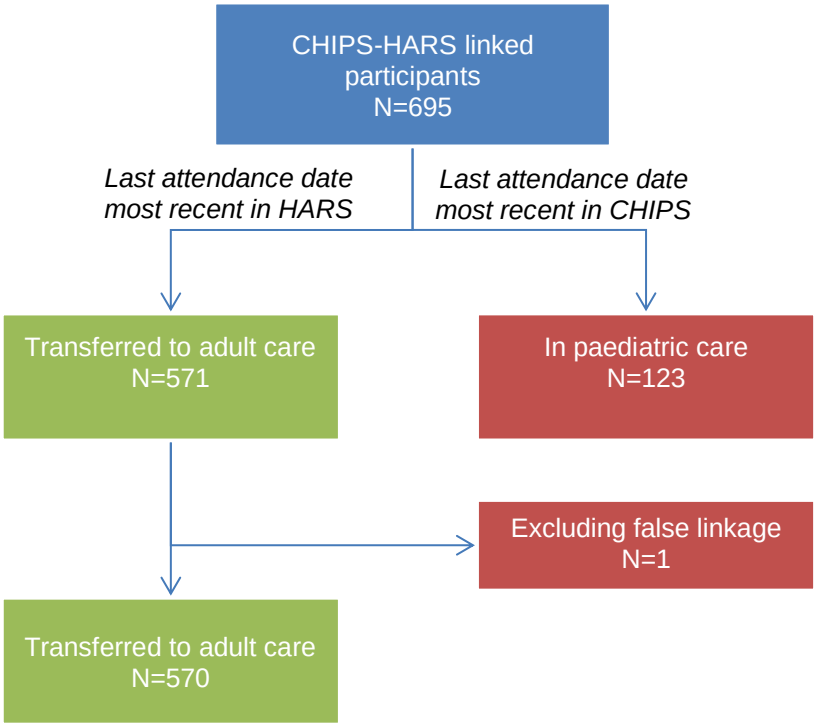


3.6.2.2. CHIPS-HARS linkage

Figure 3.8 presents the CHIPS-HARS linkage overview after comparing the attendance dates in both datasets. Of 695 participants who were linked between CHIPS and HARS, 571 (82%) participants had a most recent last attendance date in HARS and were thus assumed to have transferred to adult care.

Of the 571 confirmed as transferred to adult care, two participants were reported in CHIPS to have died in adult care. Neither of the deaths was recorded in HARS. However, one of the participants had a last HARS attendance date in 2017 when their year of death was 2003 in CHIPS. Therefore, this linkage was excluded as a false match. The second deceased participant had no follow-up data in HARS after the death date recorded in CHIPS and was thus not excluded as a false match. Altogether there were 570 participants with CHIPS-HARS linked data and assumed to have transferred to adult care.

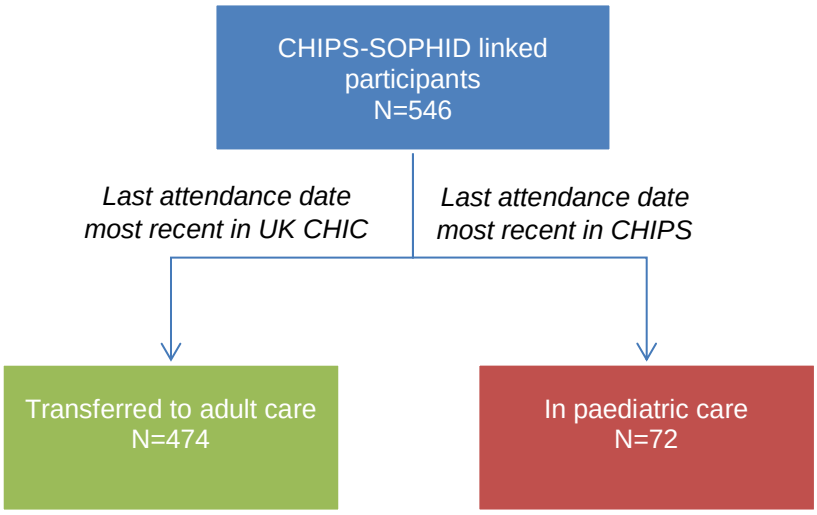
Figure 3.8: Validating transfer status of CHIPS-HARS linked participants



3.6.2.3. CHIPS-UK CHIC linkage

Figure 3.9 displays the linkage overview of CHIPS and UK CHIC records after comparing attendance dates from both datasets. Of all the 546 CHIPS and UK CHIC linked participants, 474 (87%) had a more recent attendance date in the UK CHIC dataset and were assumed to have transferred to adult care. The remaining 72 participants with a most recent attendance date in CHIPS were excluded from any further analyses.

Figure 3.9: Validating transfer status of CHIPS-UK CHIC linked participants



3.6.3. Many-to-one linkages

With the deterministic linkage approach, many-to-one linkages can occur, especially with the use of large datasets. The larger the dataset, the increased likelihood of multiple people sharing the same date of birth or initials. This can also occur if there are duplicate records of one person in either dataset as a result of datasets not undergoing complete de-duplication.

There were two types of many-to-one linkages that occurred within the algorithms: (1) many-to-one linkages from different steps (e.g. one CHIPS record can match to two different SOPHID records from step 2 and 3), and (2) many-to-one linkages that occurred within the same step (e.g. one CHIPS record matching to two different SOPHID records in step 2). The first type of many-to-one linkage was handled by selecting the record linked in the earlier step due to having more stringent combination of linkage variables. The second type of many-to-one linkage was manually checked with additional demographic and clinical data (i.e. initials, ethnicity, country of birth, HIV diagnosis date etc.); the record with the most similar data was then selected.

Many-to-one linkages were very infrequent in the CHIPS-UK CHIC and CHIPS-HARS algorithms, only occurring two and four times, respectively. All many-to-one linkages occurred in different steps and records generated in earlier more stringent steps were selected.

From the CHIPS-SOPHID algorithm, many-to-one linkages occurred more frequently. The majority of them were many-to-one linkages from different steps where records linked from the earlier steps were selected. Many-to-one linkages also occurred from the same step three times, where two different CHIPS records linked to the same SOPHID record three times. The data for each CHIPS record were manually checked, and the CHIPS record with most similar data to the respective SOPHID record was selected as the correct match.

3.6.4. Overlap of linked participants across the adult datasets

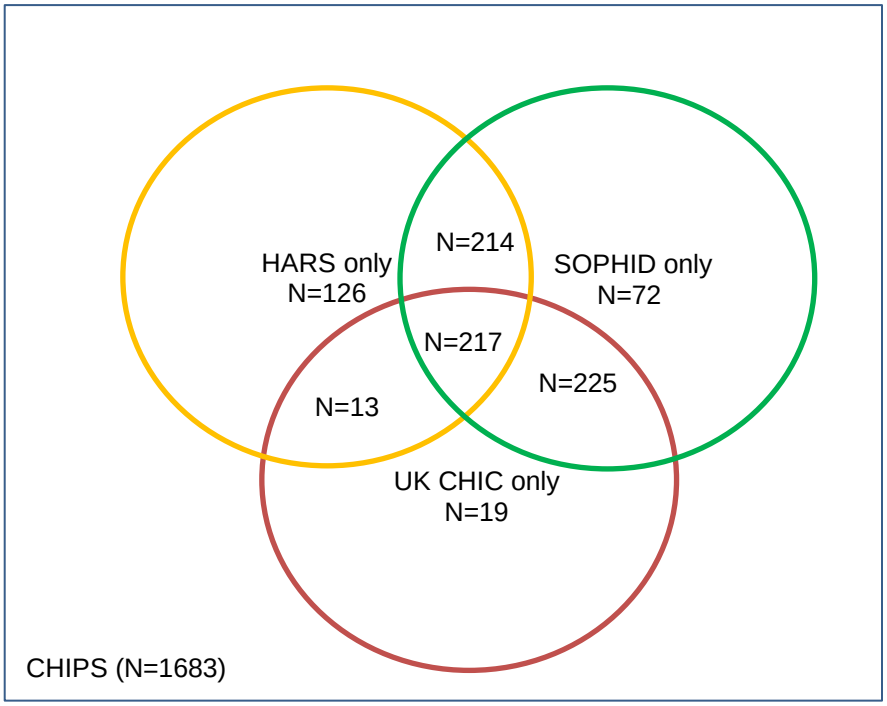
Figure 3.10 presents the overlap of linked participants who were confirmed to have transferred to adult care in SOPHID, HARS and UK CHIC. CHIPS participants linked to more than one adult dataset were checked to verify if they linked to the same individual across the adult datasets. Participant records were considered to belong to the same person if they linked on *sex, dob* and *Soundex*. This is also the technique used by the HIV/AIDS surveillance department in PHE to link duplicate records within a study as well as across studies (i.e. between SOPHID and HARS).

There were 431 CHIPS participants linked to the SOPHID and HARS datasets, of which 413 (96%) matched on *sex, dob* and *Soundex*, which suggests that these CHIPS participants were linked to the same individuals identified in SOPHID and HARS. For the remaining 18 participants who did not match on these criteria, their demographic and clinical variables (i.e. ethnicity, clinic name and postcode, CD4 and viral load trajectories) were manually checked. The additional data for the remaining 18 were checked and confirmed as likely being the same unique individuals in SOPHID and HARS.

CHIPS participants linked to SOPHID and/or HARS were then compared to those also linked to UK CHIC. There were 455 CHIPS participants linked to SOPHID and/or HARS and the UK CHIC dataset. Of those, 437 (96%) matched on *sex, dob* and *Soundex*, suggesting the same individuals

were linked across the adult datasets. The remaining 18 individuals that did not match on the criteria were manually checked using additional demographic and clinical variables and confirmed as the same participants.

Figure 3.10: The overlap of CHIPS participants linked to each adult dataset



3.6.5. Linkage completeness

Altogether, 886/1683 (53%) of eligible CHIPS participants linked to one or more adult dataset and were confirmed to be in adult care. The linkage completeness was assessed by comparing the number of linked participants with the number of young people who transferred to adult care as reported by paediatric clinics to CHIPS. Table 3.4 shows the follow-up status of CHIPS participants at the last paediatric visit by linkage status (linked vs not linked to any adult dataset).

Of the 1683 CHIPS participants eligible for linkage, 929 were reported as having transferred to adult care, of whom 797 (86%) were linked to any of the adult datasets (Table 3.4). Of those not linked to any adult dataset, 132 were reported to CHIPS to have transferred to adult care. The median year of transfer for these 132 participants was 2013 [IQR 2007, 2015]. Of the 1683 eligible participants, 797 were not linked to any adult dataset, of whom the majority (565/797 (71%)) were reported in CHIPS as still in paediatric care.

Table 3.4: Documented follow-up status in the CHIPS dataset by linkage status

Follow up status in CHIPS	Total	Linked	Not linked
Transferred to adult care	929 (100%)	797 (86%)	132 (14%)
Still in paediatric care	626 (100%)	61 (10%)	565 (90%)
LTFU in paediatric care	34 (100%)	12 (35%)	22 (65%)
Moved abroad	94 (100%)	16 (17%)	78 (83%)
Total	1683 (100%)	886 (53%)	797 (47%)

3.6.6. Deaths identified across the studies

A total of 14 deaths were identified among young people who transferred to adult care. These 14 deaths were identified in different datasets: eight were reported in CHIPS, 11 in UK CHIC and none in SOPHID or HARS. Most of the deaths (11/14) occurred before 2014 and would not have been captured in HARS as it was implemented at the end of 2014 and did not collect retrospective data.

3.7. Data linkage discussion

In this chapter, I successfully linked participant level data from the UK's national paediatric cohort (CHIPS) to two national adult surveillance systems (SOPHID and HARS) and a large adult cohort (UK CHIC). Due to these studies not sharing a unique identifier, I developed linkage algorithms, where young people's paediatric and adult records were linked using a range of different identifying variables using a deterministic linkage approach. With this strategy, 886 young people who transferred out of paediatric care were identified across the three adult studies. The majority of participants were identified in multiple adult datasets and were verified to be the same people, validating the robustness of the linkage methods.

The data linkage was mostly an automated process that was programmed in STATA, thus allowing it to be repeated in the future. Many-to-one linkages (i.e. two records from one study linking to the same record from another study) generated from the linkage process were manually reviewed using additional data. Some records were identified as duplicate records and reported to the relevant study which resulted in minor improvements to the data quality of these studies.

The data linkage completeness was assessed by comparing the number of people documented in CHIPS as transferred to adult care to those identified in my data linkage. Of 929 young people reported to have transferred to adult care, 797 (86%) were identified through the data linkage. In addition, those reported as LTFU or moved abroad by the last paediatric visit were captured in my data linkage, suggesting return to care in adult services. A small number of young people (N=61) were reported to CHIPS as still in paediatric care despite being shown, through my data linkage, to be in adult care. The use of national paediatric and adult surveillance datasets allowed for such a high level of linkage completeness. Although measuring linkage completeness in this way relies on the assumption that the CHIPS transfer status is up to date, in practice, a reporting lag can result in participants being misclassified as still in paediatric care when they are actually in adult care. It was also possible that these 61 participants were incorrectly linked, but this was

impossible to assess further in my study. With additional resources paediatric clinics could have been contacted to confirm the follow up status of these patients.

There were 132 CHIPS participants documented as having transferred to adult care but had not been identified in any adult dataset. The median year of transfer for these young people was 2013 [IQR 2007, 2015], which could suggest they may have been LTFU or moved abroad since the last paediatric visit. Non-linkage could also be due to missing data, as Soundex, hospital number and postcode are not well recorded in CHIPS with only 12% to 61% data completeness for these variables, thus potentially preventing linkage. A more relaxed algorithm could increase the chance of the 132 participants being captured; however, the accuracy of the linkage results would decline. Alternatively, these young people may not be followed up in any of the adult studies, as UK CHIC and HARS do not have national coverage and a UK linkage study has previously found that not all people are reported to SOPHID [172].

The linkage algorithms were made stringent with a total use of seven identifying variables. Each step in the algorithm had a combination of three or more identifiers. The stringent algorithms limited the likelihood of false linkages being made. Although this may lead to some level of under-linkage, as variables with even the slightest discrepancy would not be linked, under-linkage was preferred over false linkages from using more relaxed algorithms (e.g. only linking on *dob* and *sex*).

To limit false linking, personal demographic variables such as *ethnicity* and *country of birth*, which have been used in another linkage study [172], were excluded from my linkage algorithms. This was due to such variables having less heterogeneity than the other linkage variables which would result in higher number of many-to-one linkages. Clinical variables such as CD4 count, AIDS events and VL were also not used in algorithms to link records, except for in manual inspection of linked records. Participants with more clinical data available would be more likely to be linked compared to participants with less data, thus introducing a selection bias. Those with more clinical data may also have poorer health outcomes as BHIVA guidelines recommend more frequent CD4 and VL monitoring of participants with advanced disease progression [173]. Conversely, those with less clinic data may also have poorer health outcomes if they disengaged from care.

3.7.1. Limitations

The linkage methods had some limitations. For CHIPS participants, broad inclusion criteria (aged ≥13 years and previously in paediatric care) were used for the data linkage. This resulted in participants who had not transferred to adult care linked to the adult datasets, made possible by the presence of paediatric data in the adult datasets. Using a narrower inclusion criteria limited to just those documented as transferred to adult care, as previously done by a UK study [104], would result in higher proportion being linked. However, such an inclusion criteria would fail to capture 89 participants who were not reported to have transferred to adult care. Therefore, broader inclusion criteria were favoured in order to maximise potential linkages.

Another limitation of the data linkage methods was the use of some linkage variables that were not well recorded in the different studies. Also, it is possible that the linkage variables were collected by the studies inconsistently over the years, which would lead to temporal bias of

participants linked to adult care. Data collection may have improved in the more recent years, such as Soundex being introduced in later years, thus making people who transferred to adult care in more recent years more likely to be linked.

The deterministic linkage approach has some benefits and limitations compared to the probabilistic approach. Probabilistic linking is more likely to capture linkages with imperfect or missing identifiers, while deterministic linking relies on data recorded correctly and consistently over time [167,174]. Deterministic linkage was considered the most appropriate approach due to the studies having many identifiers in common and most of which were well recorded. Deterministic linking is much less likely to produce incorrect linked data due to the low chance of two people sharing multiple personal identifiers (e.g. *dob, Soundex* and *postcode*) [175]. Conversely, data entry errors can result in details such as the *dob* or *initials* values being incorrect, and postcodes can change from participants moving house, all of which can lead to under-linking, given the requirement for exact matches.

3.7.2. Implication for subsequent results chapters in this thesis

Linking CHIPS to the adult studies has created a national life course dataset of detailed clinical and treatment data from time of diagnosis in paediatric care to the last visit in adult care in the UK. This has enabled me to investigate, among young people diagnosed with HIV during their childhood, factors from paediatric care that could predict long term poor health outcomes post-transfer to adult care as described in subsequent chapters of this thesis.

The linkage algorithms developed in this chapter can potentially be used by other countries with comparable datasets including similar identifying variables. It can also help other paediatric cohort studies to track their participants following transfer. To my knowledge, this is the first national paediatric and adult linked cohort including almost all young people with HIV who have transferred to adult care.

Table 3.5: Summary of issues and errors identified in the data linkage method and the impact on the final denominators

Data source	Issue	Type of error and potential impact on linked records	Adjustment made
	Denominator		
SOPHID, HARS and UK CHIC datasets	These datasets do not include adults with HIV in care in Ireland, so young people in CHIPS who received paediatric care in Ireland could not be linked	Selection bias; denominator not representative of the population of young people in Ireland	
SOPHID dataset	High level of one-to-many linkages were produced from the CHIPS-SOPHID linkage algorithm, due to the large size of the SOPHID dataset, and multiple patients having the same date of birth or initials	Misclassification of linked records	Additional demographic and clinical data were manually reviewed to select the best matching records
	Data linkage variables		
CHIPS, SOPHID, HARS and UK CHIC datasets	Some variables used for data linkage (e.g. Soundex, hospital number) had high level of missing data	Under-linking of records due to inability to identify record linkages with confidence	
	Some variables used for data linkage may change over time (e.g. initials, hospital number)		The most recently reported data were selected for the data linkage process

4. Chapter 4: Service provision for young people with HIV following transfer to adult care

4.1. Chapter content and aims

4.1.1. Chapter content

A national clinic survey was carried out to assess the adult HIV services available to young people with HIV who transferred from paediatric to adult clinics across the UK and Ireland. It was also designed to measure the level to which adult HIV clinics adhered to international and national transfer and youth-friendly guidelines [121,176]. The clinic survey data were used to generate a youth-friendly composite score for each adult clinic. This was used in subsequent chapters to assess the association between a clinic's level of youth-friendliness and young people's engagement in care and health outcomes such as immunosuppression, viral failure and mortality.

4.1.2. Aims

The aims of this chapter are to:

1. Describe the clinic survey development and pilot study
2. Summarise the survey results, stratified by clinic type (young persons' clinic vs general adult clinic)
3. Describe the composite score for each clinic, indicating the level of youth-friendliness
4. Compare the characteristics of CHIPS participants at transfer to adult care by the adult clinic type and level of youth-friendliness (using the composite score)

4.2. Methods

4.2.1. Study design and population

A survey was carried out among adult HIV clinics across the UK and Ireland.

The initial inclusion criterion for the clinic survey was:

- All adult clinics in the UK and Ireland, where young people who transferred from paediatric HIV care were reported to CHIPS to have attended

There were 112 clinics that met this criterion. In the CHIPS database, contact details were available for a named person (name and email address of lead clinician or HIV specialist nurse) for 34 of the 112 clinics. A first wave of survey invites (as part of the survey launch) were sent to these 34 clinics in June 2017. Numerous attempts were made to obtain a relevant contact person for the remaining clinics through online searches (using hospital directories and websites), but with limited success, with only 19 more being obtained. There were several clinics which had been attended by only one person; therefore, the inclusion criterion was revised in order to focus on clinics with larger numbers of young people.

The revised inclusion criterion for the clinic survey was:

- All adult clinics in the UK and Ireland, where ≥3 young people who transferred from paediatric care were reported to CHIPS to have attended

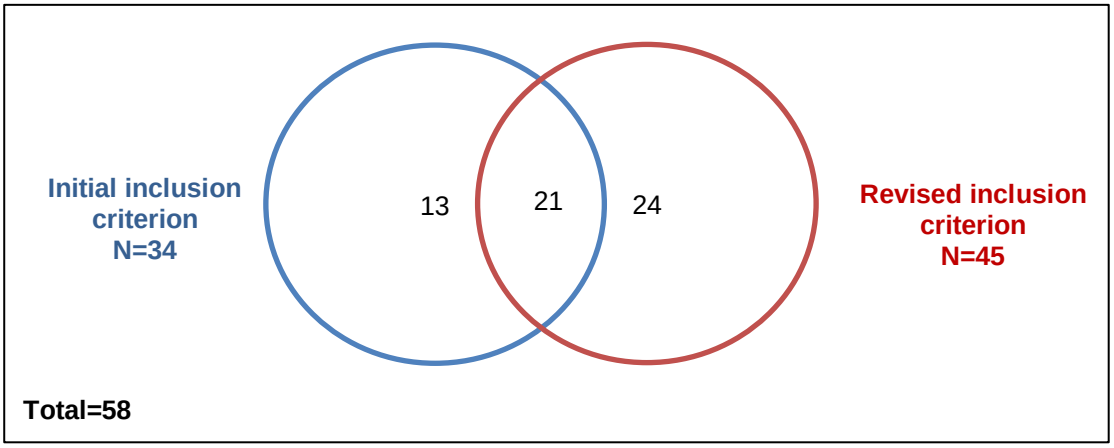
This revised inclusion criterion captured 91% of young people transferring from paediatric care. Overall, 53 clinics met this revised inclusion criterion, of which eight clinics were excluded for the following reasons:

- Not being separate clinics as they had merged with another hospital (N=2)

- No longer following those who transferred from paediatric care as they were referred to other clinics (N=5)
- Being a private hospital (N=1)

Therefore, 45 clinics met the revised inclusion criterion, of which 21 clinics had already been invited to participate in the initial wave of survey invites (Figure 4.1). The remaining 24 clinics that met the revised inclusion criterion were sent a survey invite by July 2017. The contact details of these 24 clinics were identified from the CHIPS database, hospital directories or NHS websites. Thirteen of the 34 clinics that met the initial criteria did not meet the revised inclusion criterion as they had fewer than three young people who had transferred from paediatric care. Five of these 13 clinics had responded to the survey prior to amending the inclusion criterion and were thus included in the analysis for this chapter.

Figure 4.1: Overlap of invited clinics that met the initial inclusion criterion, revised inclusion criterion and both criteria



After including the 13 clinics that met the initial inclusion criterion, a total of 58 clinics were invited to complete the survey.

4.3. Development of the clinic survey

The clinic survey was developed as an online survey due to the advantages of low cost, rapid distribution and return, as compared to postal surveys. Online surveys also allow for fast response monitoring and facilitate the use of email reminders to non-responders.

4.3.1. Developing clinic survey using REDCap software

The clinic survey was administrated using the Research Electronic Data Capture (REDCap) online software, developed by Vanderbilt University, USA. This online software can be used for creating and developing surveys, collecting, storing and managing research data in a regulated and secure manner designed for sensitive data.

The REDCap software had some benefits over other types of software that were available, such as SurveyMonkey. For example, REDCap allows for data quality checks and for a wider range of formats that could be selected for questions depending on the type of response required. Additionally, incomplete survey responses for different sections can also be queried with the respondent in order to minimise missing data.

In the clinic survey, the questions were formatted as: (a) drop down questions, where respondents can select one answer from a list of choices; (b) multiple choice questions, where multiple options can be selected from a list; (c) short and long text box answers, depending on how much depth the answer required; (d) matrix grids, which are multiple choice questions represented in a grid format, this type of question maximises the information gathered, while avoiding repeated questions. An example of a matrix grid question in the clinic survey can be found Appendix 7.

REDCap also enabled the survey to have a skip logic feature. This is also known as conditional branching or branch logic, and prevents the respondent from seeing questions which do not apply to them. This was important as not all the questions in the clinic survey relevant to general adult clinics were relevant to young persons' clinics.

4.3.2. Content of the survey

The clinic survey was divided into three sections:

1. Accessibility features
2. Specialist services targeting adolescents/young people
3. Transfer preparation and support

Each section included questions about the use of services and standard practices that were highlighted as key recommendations from transfer and youth-friendliness guidelines and published literature on youth-friendly services.

The survey consisted of 16 questions across the three sections. The first page of the survey provided a brief overview of the clinic survey objectives and requested contact details of the healthcare provider completing the survey. Completion of the first page was required to proceed, thus ensuring that the respondent's clinic and contact details were collected.

Section 1: Accessibility promoting features

Section 1 included questions about the clinic type in order to assess how each clinic provided its services for young people with HIV. Respondents were asked to classify their clinic as a (a) young persons' clinic for those with PHIV, (b) young persons' clinic dedicated for those with perinatal or horizontal HIV or (c) general adult HIV clinic. This section also included questions about clinic opening times, clinic accessibility features (i.e. availability of evening hours, weekend services, walk-in services, home visits, instant messaging or video calling) and whether there was a separate waiting area, specifically for young people.

Section 2: Specialist services targeting adolescents/young people

Section 2 included questions about whether a range of specialist services were provided, including availability of adherence support, a clinic pharmacy and/or home delivery of medication, mental health support, group peer support (which includes group activities for young people with HIV) or one-to-one peer support.

For each service, the survey respondent was asked to indicate if the service was (a) available on the same day as routine visits, (b) only available through referral on a different day, or (c) was not offered at all. This was to compare the availability of each service.

Section 3: Transfer preparation and support

Section 3 included questions about whether individualised transfer plans, joint initial paediatric and adult care appointments or more active follow-up was offered to non-attending young people who transferred from paediatric care compared to older adults with HIV.

4.4. Pilot study

4.4.1. Pre-pilot survey review by HYPNet

Prior to the piloting of the survey, the clinic survey content was reviewed in May 2016 by members of the HIV Young Persons Network (HYPNet) at their biannual meeting. HYPNet is multidisciplinary collaboration of healthcare professionals (mainly paediatric clinicians) and volunteer representatives who work with young people with HIV. Much of the feedback received related to making some questions clearer and including questions about additional clinic services. Once all feedback and suggestions from this HYPNet review were incorporated into the clinic survey, it was adapted and finalised using REDCap software for the pilot study. The online link to the clinic survey was tested by colleagues at the MRC CTU at UCL, to check survey functionality.

4.4.2. Pilot study launch

In the pilot study, clinicians from six adult HIV clinics were invited to complete the online survey. They were also asked to provide feedback on the survey content and the design. Four out of six clinicians completed the survey. Two did not respond or provide any feedback. The feedback that was provided by the four clinicians primarily suggested that I clarify several questions that were thought to be ambiguously worded, and include more free text sections to allow healthcare providers to expand on their answers. The pilot study also highlighted a technical error in the online survey which was subsequently corrected.

4.5. Clinic survey launch

The clinic survey was launched in June 2017 to the 58 clinics that met the revised inclusion criterion by sending personalised emails containing a link to the online survey.

Steps taken to maximise the response rate

In the one to three months following when the survey invitation was sent out to all clinics, non-responders were sent individualised follow-up emails to encourage survey participation. A month after these individualised follow-up emails were sent, the remaining non-responders were actively followed up by telephone. Non-responding clinics with larger numbers of young people who had transferred from paediatric care were prioritised with regards to encouraging survey participation. This was due to larger clinics having a greater contribution to the patient sample size. The online survey was active for seven months and closed at the end of January 2018 to allow time for analysis. Following the survey closure, any incomplete survey data were queried with the respective clinic. Only two clinics submitted incomplete data, with one or two missing questions each.

4.6. Variable definitions

In this chapter, the survey answers are referred to as clinic survey variables. This is because some questions allow for multiple services to be selected. A main aim of the clinic survey analysis was to compare clinic characteristics by clinic type. However, due to the relatively low number of clinics being defined as a young persons' clinic for those with PHIV (N=10), or a young persons' clinic for those with perinatal or horizontal HIV (N=8), these two groups were collapsed into a single group, labelled as "young persons' clinics".

Ranking clinics based on the level of youth-friendliness

The clinic survey variables were used to develop a youth-friendly composite score for each clinic. Table 4.1 lists the clinic survey questions, the guidelines from which they originated, and those contributing to the youth-friendly composite score. Questions 1-7 (contact details of respondent and lead clinician and clinic address) and question 16 (whether respondents would like a summary of their survey responses) are not included in Table 4.1, as they were for administrative purposes only.

Clinic survey variables recommended by transfer and youth-friendly guidelines included: evening hours, walk-in service, instant messaging, home visits, young people's waiting area, peer support, transfer plans, joint paediatric and adult appointments and systematic approaches to following up non-attenders (Table 4.1). Expert opinions included physicians' feedback from the pilot study. In this chapter, the variables incorporated in the youth-friendly composite score are also referred to as the youth-friendly services.

Table 4.1: Clinic survey questions, source guidelines, and youth-friendly composite score definition

Survey question number	Clinic survey variables	Expert opinions[1]	Transfer and youth-friendly guidelines				Adolescent HIV literature	Youth-friendly composite score
			HIV		Other chronic diseases			
			WHO, 2012/16[119,121]	CHIVA, 2011[84]	NICE, 2016[176]	NHS, 2016[177]		
Q8	Clinic type (young people's/adult's)	✓						
Q9	Frequency of opening times (categorical)	✓						
Q10	Evening hours (Y/N)	✓	✓				✓[178]	✓
	Walk-in service (Y/N)		✓			✓		✓
	Weekend services (Y/N)						✓[101]	
	Instant messaging/video call (Y/N)				✓	✓	✓[101]	✓
	Home visit (Y/N)						✓[179]	✓
Q11	Young people's waiting area (Y/N)						✓[101]	✓
Q12	Adherence support (Y/N)		✓					
	On-site pharmacy (Y/N)	✓						
	Mental health support (Y/N)		✓					
	Peer support (Y/N)				✓	✓	✓[152,178]	✓
Q13	Individualised transfer plans (Y/N)			✓	✓	✓		✓
Q14	Joint paediatric & adult appointments (Y/N)			✓	✓	✓		✓
Q15	Following up non-attenders (Y/N)				✓	✓		✓

1 - Expert opinions were based on colleagues' and HYPNet members' feedback

4.2.2. Statistical methods

Descriptive statistics were used to characterise the different clinic services, stratified by clinic type (young persons' clinic vs general adult clinic). Each clinic survey variable planned for inclusion in the composite score was also stratified by clinic type.

Variables with no data variation or where there was complete concordance with clinic type were omitted from the youth-friendly composite score in order to avoid collinearity with the clinic type variable. Lack of data variation would result in no difference being detected between the levels of youth-friendliness and patient outcomes from the different types of clinics. To create the composite variable, I summed the responses from each of the individual variables. The youth-friendly composite score was then categorised into groups with roughly equally spaced score cut-offs: low (0-2); middle (3-5); and high (6-9) scores.

The combination of services provided within each clinic was assessed to establish if some services were more likely to be offered together. The percentages of clinics offering the different youth-friendly services individually and in combination with one another were thus described. The percentages were categorised into groups: low (<30%), medium (30-59%) and high (≥60%), representing the level of availability of each youth-friendly service.

Patient-level paediatric data were linked to the clinic-level data from the survey. Patient characteristics at the start of treatment in paediatric care and at the time of transfer (defined as last paediatric visit) were compared by the adult clinic type and the level of youth-friendliness offered by the clinics.

4.7. Survey results

4.7.1 Clinic level characteristics

Fifty-eight clinics were invited to complete the survey, and 45 (78%) responded. Figure 4.2 displays the flowchart of clinics invited to participate in the survey and those who responded.

Figure 4.2: Flowchart of adult HIV clinics invited to participate in the survey

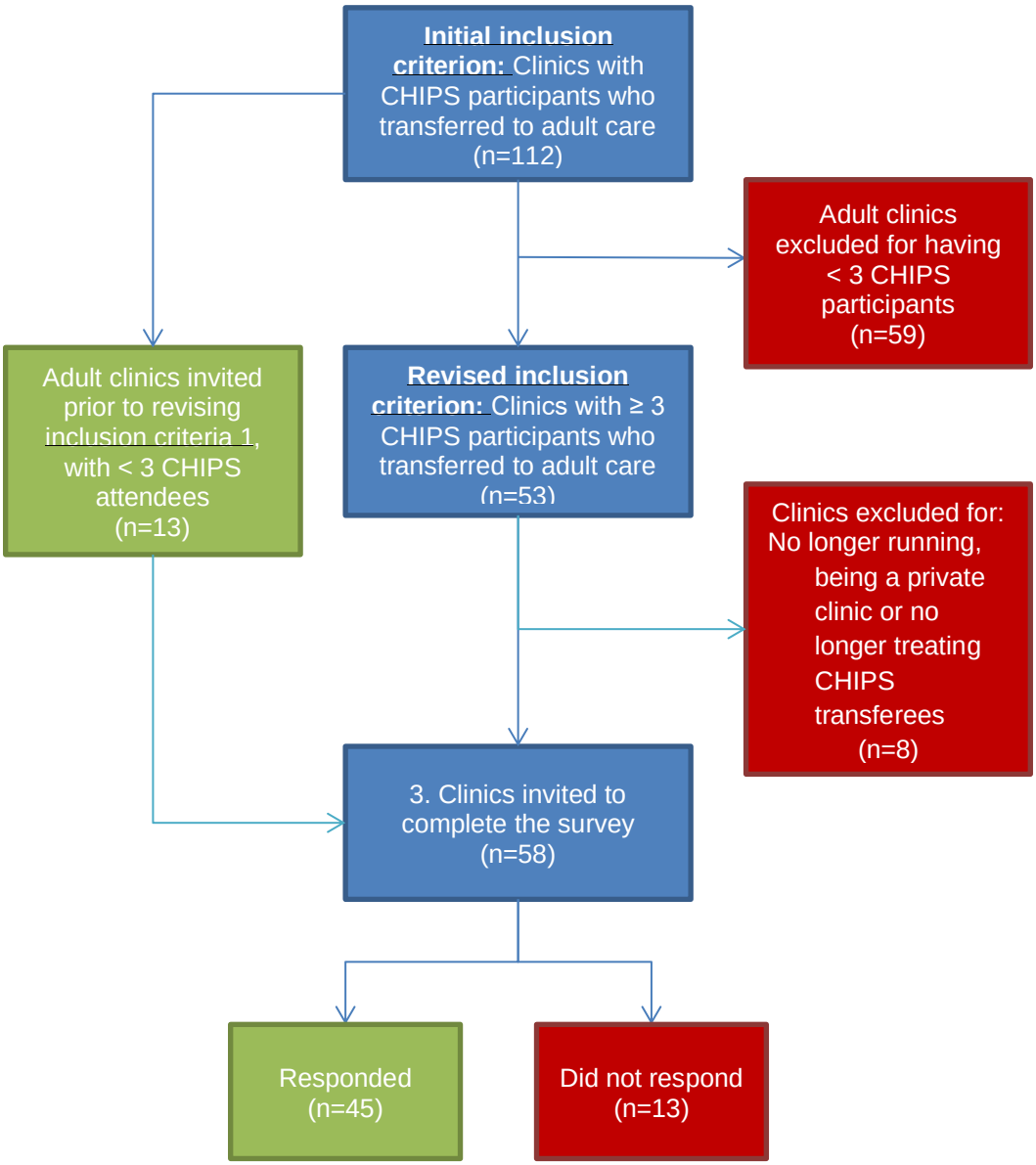


Figure 4.3 shows the geographical distribution of the 45 clinics that completed the survey as well as the number of CHIPS participants who transferred to each clinic. The majority of adult clinics with ≥30 CHIPS participants were based in London.

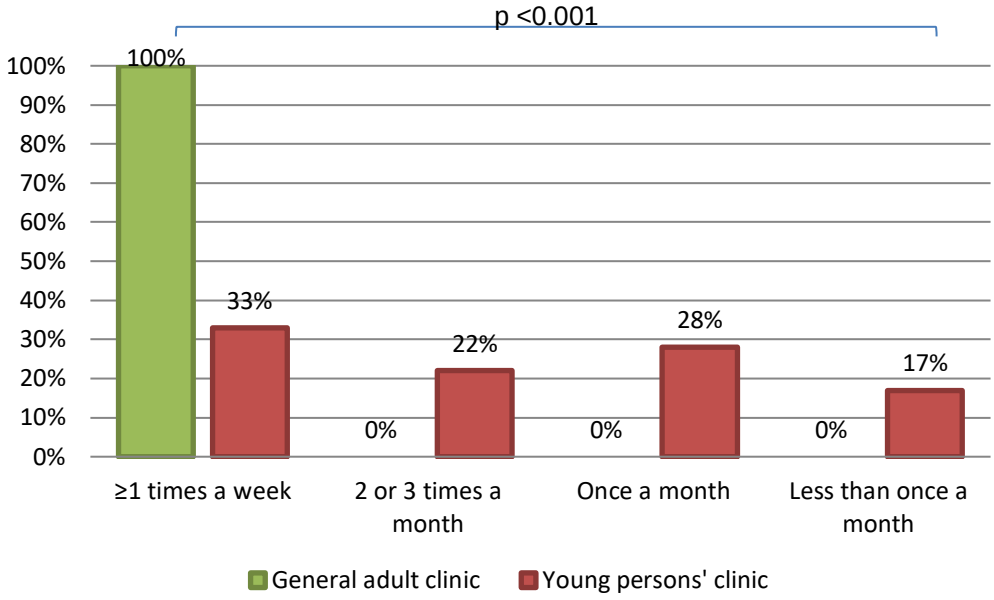
Figure 4.3: Geographical distribution of adult HIV clinics that participated in the survey across the UK and Ireland and the number of CHIPS participants who transferred to each clinic (N=45)

Of the 45 clinics that completed the survey, 27 (60%) were general adult clinics and 18 (40%) were young persons' clinics. Ten of the young persons' clinics were specifically for young people with PHIV, and the remainder were for young people with all modes of HIV acquisition.

Figure 4.4 shows the frequency of opening times by clinic type. Young persons' clinics were provided less frequently than general adult clinics. All adult clinics were open at least once a

week. For young persons' clinics, a third (33%) were open at least once a week, four (22%) were open two to three times a month, five (28%) were open once a month and the rest once a month or less frequently.

Figure 4.4: Frequency of opening times by clinic type (N=45)

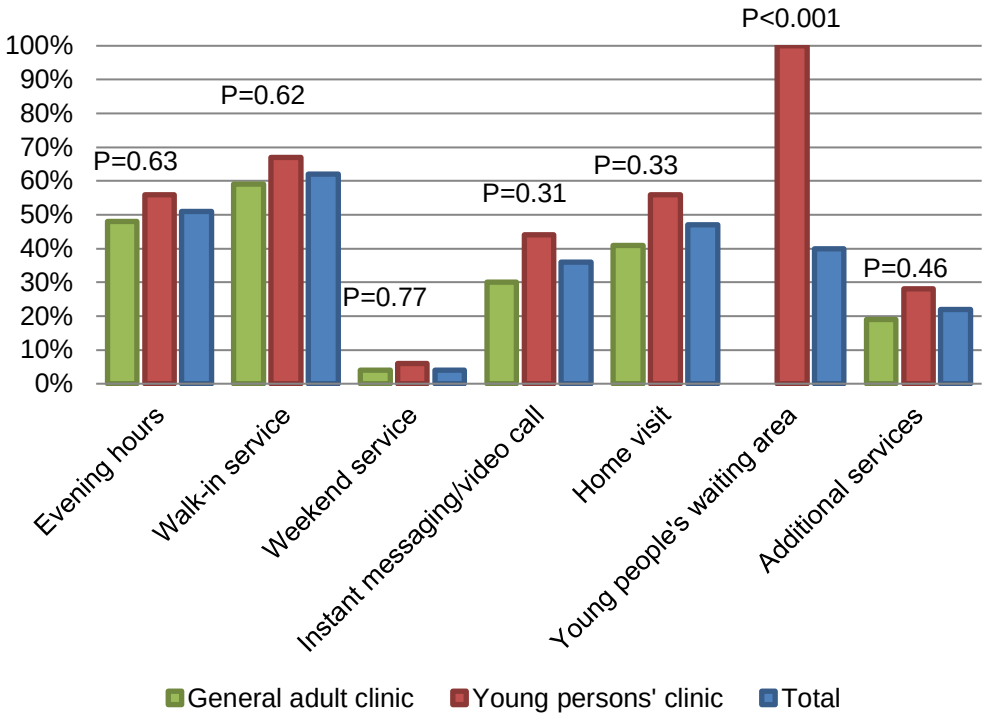


4.7.1.1. Clinic accessibility

Figure 4.5 shows the availability of different clinic accessibility services by clinic type. There was no difference in the proportion of adult clinics and young persons' clinics providing evening hours, walk-in services, weekend services, instant messaging and/or video calls, home visits by clinic type (all p>0.1). Overall, 62% of all clinics provided walk-in services, 51% evening hours, 47% home visits, 36% instant messaging and/or video calls and 4% weekend services. Eight clinics (18%) provided additional services, such as email communication (N=3) and telephone consultations (N=6).

All young persons' clinics, and no general adult clinics, provided a waiting area specifically for young people (p<0.001).

Figure 4.5: Clinic accessibility services by clinic type (N=45)



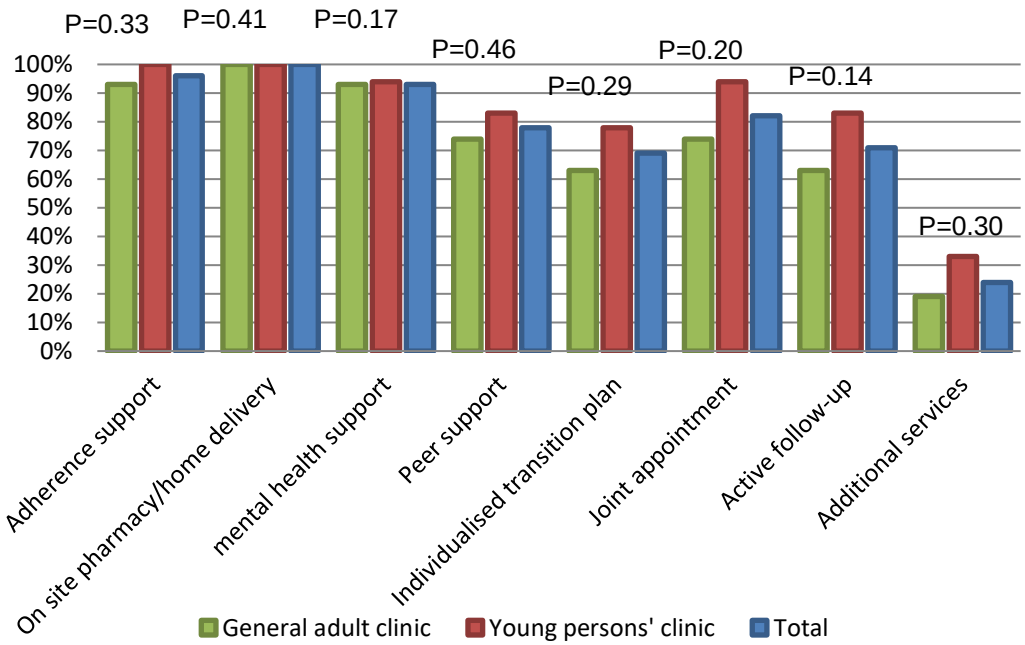
4.7.1.2. Specialist services offered by clinics

The different specialist services provided by clinic type are shown in Figure 4.6. Similar to the clinic accessibility services, there was no difference in the proportions providing each specialist service by clinic type.

All clinics provided an on-site pharmacy and/or home delivery of medication. Ninety-six per cent of clinics offered adherence support, 93% mental health support, 83% joint paediatric and adult care appointments, 77% peer support, 71% actively followed up their non-attenders and 69% offered individualised transfer plans (all >0.1).

Thirteen clinics (29%) provided access to additional services or health and social care specialists: health advisors (N=8), psychologists (N=3), social workers (N=3), dieticians (N=3), occupational therapists (N=1), young person's support nurse (N=1), sexually transmitted infection (STI) screening (N=3), contraception provision (N=3), motivational interviews (N=1) and psychosocial assessments (N=1) (Figure 4.6).

Figure 4.6: Specialist services provided by clinic type (N=45)



4.7.1.3. Youth-friendliness levels

Of the nine survey variables planned for inclusion in the youth-friendly composite score, the young people's waiting area variable was excluded as it was 100% concordant with clinic type. The eight remaining survey variables were thus included in the youth-friendly composite score. In Table 4.2, the availability of the different youth-friendly services in combination with one another were explored across the clinics.

Specialist services (peer support, transfer plan, joint paediatric and adult appointments, and following up non-attenders) were widely offered by clinics (56% to 96%) together with other specialist services and clinic accessibility services (evening hours, walk-in services, instant messaging and home visits) (Table 4.2). In contrast, the clinic accessibility services were not as available in combination (41% to 63%) as the specialist services. This indicates clinic resources are more focused on providing specialist services for young people who transferred, compared to increasing clinic accessibility. The availability of any two services offered in combination was not below 30%.

Table 4.2: Level of availability of youth-friendly services across the clinics

			Clinic accessibility services				Specialist services			
			Available services:							
		Total=45	Evening hours, (N=23)	Walk-in Service,(N=28)	Instant messaging, (N=16)	Home visit, (N=21)	Peer support, (N=35)	Transfer plan, (N=31)	Joint appointment, (N=37)	Following up non-attenders, (N=32)
Clinic accessibility services	Available services:	Evening hours								
		Walk-in service	59%							
		Instant messaging	43%	46%						
		Home visit	61%	41%	63%					
Specialist services		Peer support	96%	82%	88%	86%				
		Transfer plan	74%	71%	56%	62%	69%			
		Joint appointment	83%	79%	81%	81%	91%	84%		
		Following up non-attenders	70%	79%	94%	86%	66%	71%	70%	
		Total	100%	100%	100%	100%	100%	100%	100%	100%

Key for Table 4.2:

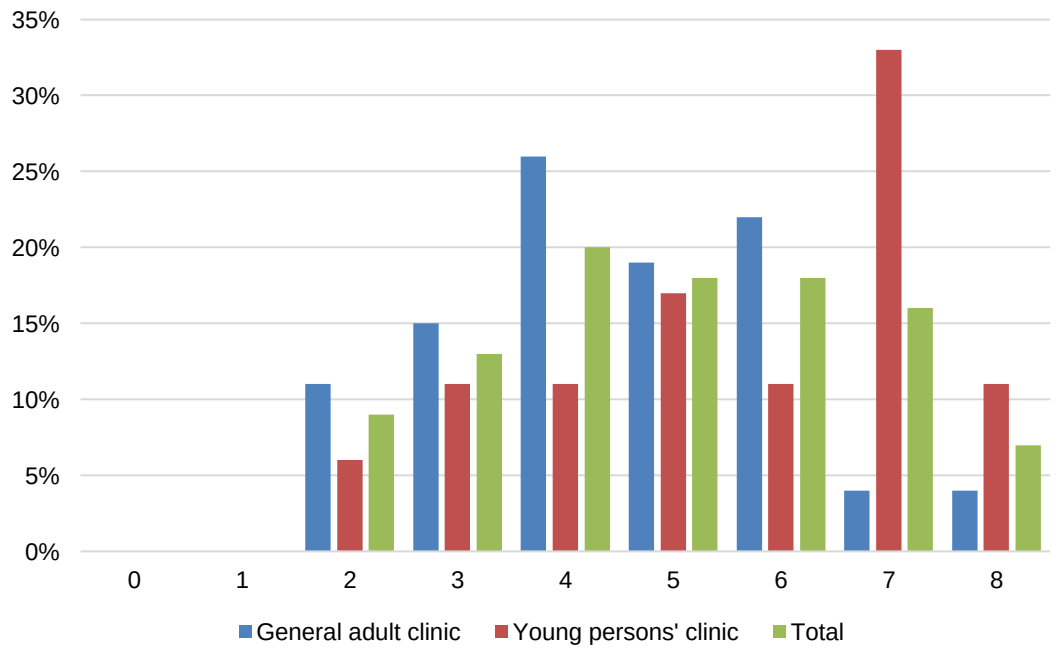
%	Level of availability
≥60%	High
30-59%	Moderate
<30%	Low

Youth-friendliness by clinic type

Figure 4.7 presents the range of youth-friendliness scores by clinic type. Although a higher proportion of young persons' clinics scored seven or eight compared to adult clinics, the level of youth-friendliness did not vary significantly by clinic type (p=0.16).

Overall, four (9%) clinics had a youth-friendliness score of two, six (13%) scored three, nine (20%) scored four, eight (18%) scored five, eight (18%) scored six, seven (16%) scored seven and three clinics (7%) scored eight. No clinics had a youth-friendliness score less than two.

Figure 4.7: Level of youth-friendliness by clinic type (N=45)



When the youth-friendliness score was grouped into low (0-2), middle (3-5) and high (6-9), two-fifths (40%) of all clinics had a high youth-friendliness score, while 38% had a medium score and 22% a low one. With regards to the geographical distribution of clinics, those with high scoring youth-friendliness did not significantly differ between clinics in London compared to those situated outside of London (p=0.16).

4.7.2. Patient level characteristics

4.7.2.1. Demographic characteristics

Of the 45 adult clinics with clinic-level survey data, 731 former CHIPS participants were identified as having transferred to one of these adult clinics. The majority (72%) of these 731 young people had transferred to young persons' clinics.

Table 4.3 compares the demographic characteristics of the 731 young people by clinic type (young persons' clinic vs adult clinic). There were no differences in demographic characteristics by clinic type (all p>0.1). Overall, half (53%) of the 731 young people were female, 61% were born abroad and the majority (82%) were of black ethnicity. Most (99%) young people were born prior to 2000, with 34% being born prior to 1993 and two thirds (66%) between 1993 and 1999.

Table 4.3: Demographic characteristics of young people attending clinics with clinic-level survey data (N=731)

		Total (N=731)	Young persons' clinic n=528	General adult clinic n=203	P-value
		n (%) or median [IQR] or range			
Sex (N=731)	Male	341 (46.7)	247 (46.8)	92 (46.0)	0.85
	Female	109 (53.4)	281 (53.2)	108 (54.0)	
Mode of acquisition (N=731)	Vertical	670 (91.7)	483 (91.5)	187 (92.1)	0.95
	Other[1]	24 (3.3)	18 (3.4)	6 (3.0)	
	Unknown	37 (5.1)	27 (5.1)	10 (4.9)	
Place of birth (N=714)	UK	281 (39.4)	203 (39.3)	78 (39.4)	0.99
	Abroad	433 (60.6)	313 (60.7)	120 (60.6)	
Ethnicity (N=712)	White/other	128 (18.0)	85 (16.5)	43 (21.7)	0.11
	Black	584 (82.0)	429 (81.3)	155 (78.3)	
Year of birth (N=731)	1979-1985	21 (2.9)	16 (3.0)	5 (2.5)	0.76
	1986-1992	224 (30.6)	161 (30.5)	61 (30.5)	
	1993-1999	482 (65.9)	349 (66.1)	132 (66.0)	
	2000-2004	4 (0.6)	2 (0.4)	2 (1.0)	

4.7.2.2. Characteristics at start of treatment

Table 4.4 presents characteristics at ART start of the 731 young people by clinic type. Characteristics at start of treatment were similar between those who transferred to young persons' clinics and adult clinics (all trends p>0.1). Overall, a third (32%) of young people had initiated ART between ages 10 to 14 years. Almost two-thirds (64%) initiated on a combination ART (cART) regimen, 19% on a mono or dual regimen, 10% on other non-cART regimens (e.g. triple NRTI or triple regimens, including unboosted PI) and 8% were ART naïve in paediatric care. A quarter (24%) of young people were severely immunosuppressed (CD4 <200 cells/mm$_3$) at the start of treatment and the overall median CD4 count was 266 [134, 475] cells/mm$_3$. The majority (98%) of young people had initiated treatment with an unsuppressed viral load (>400 copies/ml) and almost half (46%) with a viral load ≥100,000 copies/ml. At ART start, 19% had a prior AIDS diagnosis.

[1] Including sexual and blood transfusion acquisition

Table 4.4: Clinical characteristics at start of ART in the UK/Ireland of young people with HIV young people attending clinics with clinic-level survey data by adult clinic type (N=731)

		Total n=731	Young persons' clinic n=528	General adult clinic n=203	P-value
		n (%) or median [IQR] or range			
Age at ART start, years (N=672)	Median [IQR]	8.81 [4.7, 12.5]	8.5 [4.5, 12.5]	9.6 [5.1, 12.5]	0.37
	Range	0.1, 18.7	0.1, 18.7	0.2, 17.5	
	<1	40 (5.5)	34 (6.9)	6 (3.4)	0.40
	1-4	142 (19.4)	104 (21.1)	38 (21.4)	
	5-9	205 (28.0)	152 (30.8)	53 (29.8)	
	10-14	234 (32.0)	165 (33.4)	69 (38.8)	
	≥15	51 (7.0)	39 (7.9)	12 (6.7)	
First ART regimen (N=731)	Mono/dual ART	135 (18.5)	99 (18.8)	36 (17.7)	0.08
	cART	465 (63.6)	34 (6.4)	25 (12.3)	
	Other[2]	72 (9.7)	342 (64.8)	123 (60.6)	
	ART-naïve	59 (8.1)	34 (6.4)	25 (12.3)	
CD4 count, cells/mm^3 (N=485)	Median [IQR]	266 [134, 475]	266 [124, 480]	255 [153, 456]	0.99
	Range	0, 4180	0, 4180	4, 3530	
	<200	178 (24.4)	126 (36.5)	52 (37.1)	0.94
	200-349	125 (17.1)	91 (26.4)	34 (24.3)	
	350-499	70 (9.6)	48 (13.9)	22 (15.7)	
	≥500	112 (15.3)	80 (23.2)	32 (22.9)	
Viral load, copies/ml (N=479)	0-499	13 (2.7)	11 (3.1)	2 (1.7)	0.40
	500-49,999	180 (37.6)	137 (38.3)	43 (35.5)	
	50,000-99,999	67 (14.0)	45 (12.6)	22 (18.2)	
	≥100,000	219 (45.7)	165 (46.1)	54 (44.6)	
An AIDS event (N=731)	Yes	141 (19.3)	109 (20.6)	32 (15.8)	0.16
	No	590 (80.7)	419 (79.4)	171 (84.2)	

[2] *Includes triple NRTI regimens (excluding abacavir) and triple regimens (including unboosted PI)*

4.7.2.3. Characteristics at last follow-up in paediatric care

Table 4.5 presents characteristics at last paediatric visit of the 731 young people by clinic type. Those who attended young persons' clinics transferred in more recent years with a median transfer year of 2013 [IQR 2009, 2014], compared to 2011 [IQR 2008, 2013] for those transferring to general adult clinics (p<0.001). Young people transferred to general adult clinics at a slightly younger age compared to those at young persons' clinics (median age 17.6 vs 17.9, p=0.01). In terms of immunological characteristics, although there was small difference in median nadir CD4 count at last visit in paediatric care by clinic type (203 cells/mm^3 vs. 198 cells/mm^3, p=0.09), the median CD4 count at transfer was slightly higher in those transferring to young persons' clinics (512 vs. 448 cells/mm^3, p=0.06), as was the proportion with a CD4 ≥500 cells/mm^3 at transfer (51.5% vs. 43.1%, p=0.08).

Those who transferred to young persons' clinics were more likely to have a suppressed viral load at transfer (57.2% vs. 43.4% with VL ≤50 copies/ml, p=0.004), but there was no significant difference in the proportion with a prior AIDS events (27.1% vs. 22.7%, p=0.22). Young people who transferred to young persons' clinics were more likely to be on a cART regimen (81% vs 75%) and were less likely to be off treatment or ART-naïve (8% vs 15%) at the last paediatric visit, compared to those who transferred to general adult clinics (p=0.03).

Table 4.5: Clinical characteristics of young people with HIV at last paediatric visit by adult clinic type (N=731)

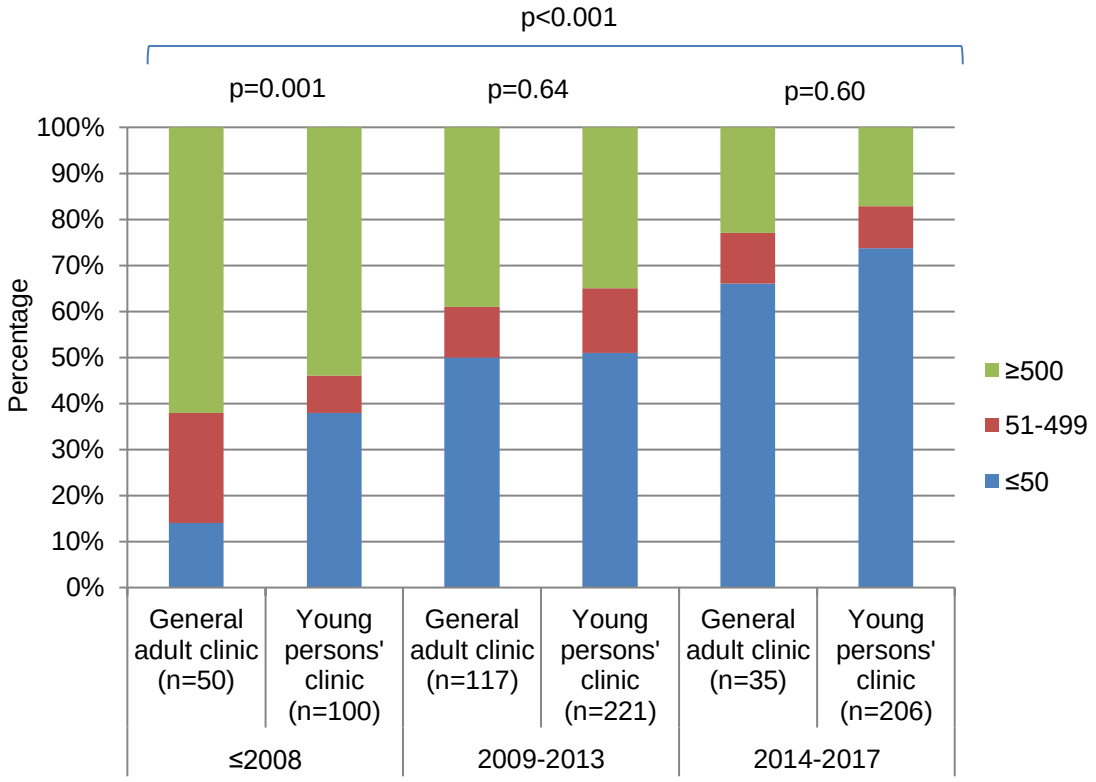
		Total (N=731)	**Young people's clinic (N=528)**	**General adult clinic (N=203)**	**P-value**
		n (%) or median [IQR]			
Age at transfer, years (N=731)	Median [IQR]	17.8 [16.9, 18.5]	17.9 [17.0, 18.6]	17.6 [16.8, 18.4]	0.01
	Range	14.8, 25.8	14.8, 25.8	14.9, 21.1	
Calendar year of transfer (N=731)	Median [IQR]	2012 [2009, 2014]	2013 [2009, 2014]	2011 [2008, 2013]	<0.001
	Range	1998, 2017	1998, 2017	2000, 2016	
Nadir CD4 count, cells/mm$_3$ (N=728)	Median [IQR]	201 [92, 305]	203 [88, 309]	198 [100, 300]	0.09
	Range	0, 990	0, 990	0, 764	
CD4 count, cells/mm$_3$ (N=728)	Median [IQR]	496 [319, 686]	512 [330, 700]	448 [306, 640]	0.06
	Range	0, 9310	0, 9310	0, 1898	
	<200	93 (12.7)	70 (13.3)	23 (11.4)	0.08
	200-349	121 (16.6)	79 (15.0)	42 (20.8)	
	350-499	156 (21.4)	106 (20.2)	50 (24.8)	
	≥500	358 (49.2)	271 (51.5)	87 (43.1)	
Viral load, copies/ml (N=729)	≤50	390 (53.5)	302 (57.2)	88 (43.4)	0.009
	51-499	87 (11.9)	58 (11.0)	29 (14.3)	
	≥500	252 (34.6)	167 (31.7)	85 (42.1)	
An AIDS event (N=731)	Yes	189 (25.9)	143 (27.1)	46 (22.7)	0.22
	No	542 (74.2)	385 (72.9)	157 (77.3)	
ART regimen (N=731)	Mono/dual ART	63 (8.6)	49 (9.3)	14 (6.9)	0.03
	cART	578 (79.1)	425 (80.5)	153 (75.4)	
	Other$_3$	16 (2.2)	11 (2.1)	5 (2.5)	
	Off ART/ART-naïve	74 (10.1)	43 (8.1)	31 (15.3)	

3 *Includes triple NRTI regimens (excluding abacavir) and triple regimens (including unboosted PI)*

4.7.2.4. Characteristics at transfer to adult care by calendar year

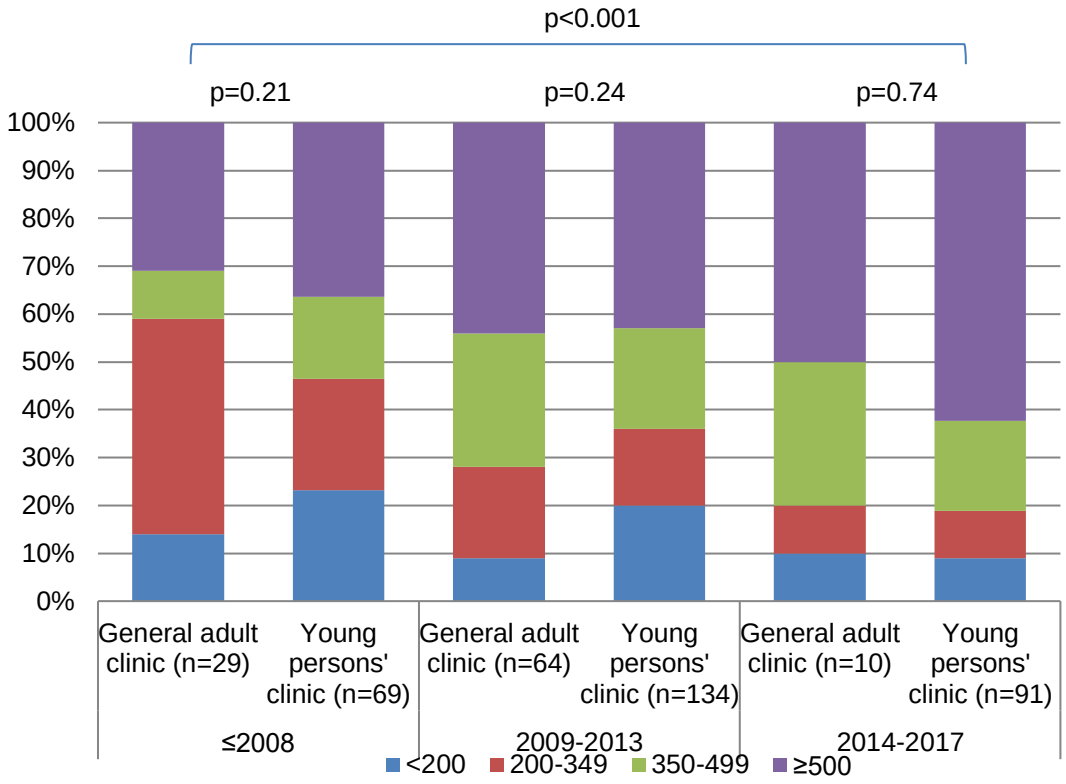
Figure 4.8 describes viral load trends by transfer year and clinic type. Overall, the proportion of young people with viral suppression (≤50 copies/ml) increased over calendar time from 38% in 2008 or earlier to 73% in 2014-2017 (p<0.001). Young people who transferred in 2008 or earlier to young persons' clinics were less likely to be virally suppressed compared to those transferring to adult clinics (p=0.001). However, viral load distributions at transfer did not differ by clinic type in the latter two calendar periods (both p>0.1).

Figure 4.8: Viral load distribution by year of transfer and clinic type



Similarly, Figure 4.9 shows that overall there was an improvement in the proportion of young people transferring with a CD4 count ≥500 cells/mm3 over calendar time, from 35% in 2008 or earlier to 61% in 2014-2017 (p<0.001). However, the CD4 status within each of the calendar year periods did not differ by clinic types (p>0.1).

Figure 4.9: CD4 count distribution by calendar years of transfer and clinic type



4.7.2.5. Characteristics at transfer to adult care by level of adult clinic's youth friendliness

Table 4.6 presents the characteristics of young people at transfer to adult care by the clinics' level of youth friendliness. Here, clinics are stratified by the youth friendliness composite score rather than by clinic type. A total of 529 (72%) CHIPS participants transferred to a high scoring clinic, 149 (20%) to a medium scoring clinic, and 53 (7%) to a low scoring clinic. There were no significant differences between the characteristics of participants and level of youth friendliness for most variables. Overall, 10% of young people were ART naïve or off ART at time of transfer, of whom a higher proportion went to adult clinics with low or medium youth friendliness score compared to high scoring adult clinics (9%, p=0.06).

Table 4.6: Demographic and clinical characteristics at last paediatric follow-up by the youth-friendly composite score

			Youth friendly composite score			P-value
		Total (N=731)	**Low (N=53)**	**Medium (N=149)**	**High (N=529)**	
		n (%) or median [IQR]				
Sex (N=731)	Males	341 (47)	24 (45.3)	66 (44.3)	251 (47.5)	0.78
	Females	390 (53)	29 (54.7)	83 (55.7)	278 (52.6)	
Transfer age, years (N=727)	Median	17.8 [16.9, 18.5]	18.0 [17.1, 18.5]	18.0 [17.1, 18.8]	17.7 [16.9, 18.5]	0.08
	14-16	198 (27)	12 (22.6)	36 (24.8)	150 (28.4)	0.17
	17-20	509 (70)	41 (77.4)	101 (69.7)	367 (69.4)	
	21-25	20 (3)	0 (0.0)	8 (5.5)	12 (2.3)	
Transfer year (N=731)	≤2008	152 (21)	16 (30.2)	36 (24.2)	100 (18.9)	0.12
	2009-2013	338 (46)	26 (49.1)	64 (43.0)	248 (46.9)	
	2014-2017	241 (33)	11 (20.8)	49 (32.9)	181 (34.2)	
CD4 count, cells/mm$_3$ (N=728)	Median	496 [319, 686]	440 [322, 640]	509 [327, 700]	499 [314, 684]	0.70
	<200	93 (13)	3 (5.7)	22 (15.0)	68 (12.9)	0.14
	200-349	121 (17)	14 (26.4)	17 (11.6)	90 (17.1)	
	350-499	156 (21)	14 (26.4)	33 (22.5)	109 (20.6)	
	≥500	358 (49)	22 (41.5)	75 (51.0)	261 (49.4)	
Viral load, copies/ml (N=729)	≤50	390 (54)	29 (54.7)	73 (49.7)	288 (54.4)	0.80
	51-499	87 (12)	7 (13.2)	17 (11.6)	63 (11.9)	
	≥500	252 (35)	17 (32.1)	57 (38.8)	178 (33.7)	
An AIDS event (N=731)	Stage A	334 (46)	27 (50.9)	76 (51.0)	231 (43.7)	0.48
	Stage B	208 (28)	15 (28.3)	37 (24.8)	156 (29.5)	
	Stage C	189 (26)	11 (20.8)	36 (24.2)	142 (26.8)	
ART regimen (N=731)	Mono/dual ART	63 (8.6)	6 (11.3)	7 (4.7)	50 (9.5)	0.06
	cART	578 (79.1)	36 (67.9)	117 (78.5)	425 (80.3)	
	Other[4]	16 (3.3)	2 (3.8)	5 (3.4)	9 (1.7)	
	Off ART/ART naïve	74 (10.1)	9 (17.0)	20 (13.4)	45 (8.5)	

[4] *Includes triple NRTI regimens (excluding abacavir) and triple regimens (including unboosted PI)*

4.8. Discussion

This chapter describes the results of a national survey conducted of the adult services available to young people with HIV who transferred from paediatric to adult care across the UK and Ireland. The survey was developed to assess the accessibility of clinics and level of youth-friendliness, guided by transfer and youth-friendly guidelines and additional input from experts in the field. Two types of adult care setting were compared: young persons' clinics and general adult clinics. Provision of services tailored for young people and supporting the transition process were available in most young persons' and general adult clinics. However, accessibility features such as evening hours, walk-in service and weekend appointments were not as readily available across the UK and Ireland.

4.8.1. Clinic survey methodology

Initially, the survey targeted all young persons' and adult clinics to which young people with HIV attended post-transfer, with 112 clinics meeting these inclusion criteria. However, without access to a clinic network or clinic database of contact details for NHS clinics, and with limited resources, it proved too ambitious to identify clinic representatives at all these clinics. As a result, I restricted the inclusion criteria to clinics where at least three young people had transferred from paediatric care. The restricted inclusion criteria resulted in a more feasible study but meant that the study findings are less representative of smaller adult clinics and with a reduced sample size.

The survey was designed to be short and administered in 10 to 15 minutes, in order to encourage a high response rate, and was self-administered. Telephone or face to face interviews could have been preferable in that they would have allowed the opportunity for questions to be further clarified or interviewees to be probed for additional information [180], but this would have required more time and with cost implications with regards to travel and/or transcribing [181]. The self-administered approach may have resulted in a better response rate compared to the other approaches as it would have been less burdensome for respondents in terms of their time. Self-administered surveys also have the advantage of allowing respondents more time to reflect on questions and for them to respond at their own convenience [180].

The survey was designed and administered using REDCap software which had several benefits over other types of software such as SurveyMonkey. For example, REDCap is secure in handling and storing sensitive data as well as having a wide range of formats, such as skip logic and matrix formatted questions, which reduced the survey length and allowed the survey to be customised to different clinic types (i.e. young persons' clinics vs general adult clinics).

The online survey was first piloted with a small group of adult physicians to test the functionality of the online instrument as well as the clarity of the questions, which resulted in the survey undergoing some revision. Respondents included in the pilot study were also included in the main survey study, as they met the inclusion criteria. There is a concern that these respondents may have responded differently to the survey questions due to pre-exposure to the survey questions and tools compared to respondents who did not participate in the pilot study [182]. These respondents may have had less enthusiasm to provide complete answers the second time they were exposed to the survey questions. However, it is unlikely this response bias had a large

impact on the study findings as most of the questions were multiple choice questions and, as a whole, the pilot process was useful in testing overall functionality and clarifying ambiguously worded questions.

After launching the clinic survey by email, most respondents required multiple emails and telephone calls to encourage participation. Due to this process, the survey was online for 7 months which led to the data collected from the different clinics being relevant to different time points through the year. This may slightly impact the comparability of service provision across the clinics due to the different dates of data collection.

A total of 78% of clinics responded, and 731 young people previously followed up in CHIPS had transferred to these clinics. This response rate was higher than another 2014 cross-sectional transition study from the UK which evaluated service provision for young people post-transfer, which had a 60% response rate [183]. The number of participating clinics in that 2014 transition study was similar to my survey with 44 and 45 clinics, respectively. Response rates for national HIV service evaluation audits co-ordinated by BHIVA have been smaller, ranging from 41% to 56%. Although, the majority of these BHIVA audits included a much higher number of participating adult clinics (N=102-143), most likely enabled by access to existing national clinical networks [184–186]. The only BHIVA post-transfer audit evaluating services for young people who transferred to adult care was conducted in 2009 and included 143 clinics, of which only 63 (44%) clinics reported having received young people from paediatric care, and another 71 (50%) were expecting young people from paediatric care. However, these figures are likely to be very different now with an increase in young people transferring from paediatric to adult care in the ten years since 2009.

My main exposure variable was clinic type which was based on a single question and self-classification by the survey respondent (i.e. doctors and nurses). It is possible that more nuanced methods could have been taken to determine the clinic type, such as the proportion of attending participants under the age of 25 years. But in favour of making the survey easier to complete by the respondents, I chose to include a simpler question on the clinic type. Consequently, it is possible that, survey respondents could self-classify as a 'young persons' clinic' when they only provide one 'young persons' day' in the month.

In my study, the majority of participating clinics were general adult clinics (60%) and were open more frequently than young persons' clinics ($p<0.001$), possibly as a result of funding restrictions for specialist services. The participating clinics were widely distributed across the UK and Ireland, although most were located in London, covering almost half (43%) of the UK's adult HIV population [54].

4.8.2. Clinic-level findings

With regard to the clinic-level data, the exposure variable was the clinic type, the outcome variables were the different service variables and my hypothesis was that young persons' clinics would offer a higher proportion of the youth-friendly services.

Provision of accessibility features and specialist services did not differ significantly by clinic type ($p>0.1$). A wide range of clinics (4% to 62%) offered the different clinic accessibility services (such

as evening hours, walk-in services etc.). In contrast, specialist services were widely available, with each service provided by ≥70% of clinics. The most commonly provided services were on-site pharmacies, mental health and adherence support, which were all offered by >90% of clinics. This positively reflects clinics recognising the importance of these services as highlighted in the consolidated WHO treatment guidelines [119]. The 2014 transition study from the UK that evaluated post-transfer service provision reported lower proportions of clinics offering mental health services (59%) than in my study (93%) [183], although this study differed in including paediatric clinics as their denominator. The 2014 transition study also reported 84% of clinics to offer STI screening and 78% contraception services, but provision of these services was not included in this survey, which limited the breadth of service provision I could compare. Nonetheless, STI screening and contraception services were not included due to not being specific services for young people. The BHIVA post-transfer audit reported that 34% of clinics with or expecting young people from paediatric care, had both paediatric and adult care staff involved in the transition process through joint meetings [187], which is considerably lower than the proportion reported in my study (83%). It is possible the increase in the level of joint transition planning increased from 2009 to 2017 due increased focus and published guidelines on transition and youth-friendliness. The BHIVA post-transfer audit also reported 34% of clinics to have a named transfer worker responsible for the transition process and 57% of clinics tracking and following up non-attending young people, whilst in my study, 77% of clinics followed-up non-attenders. Availability of named transfer workers was not included in my survey due to my focus being on services rather than professional roles within the clinics, although, the inclusion of a named transfer worker may have been beneficial, especially as two guidelines on youth-friendliness emphasised its importance. In addition, data on how well clinics are connected to public transport would also elucidate the accessibility of clinics, as previously explored in youth-friendly study from the USA [101], but this information was not asked about in the survey as this information is subjective, and may have been hard to quantify and verify by survey respondents.

Overall, the BHIVA post-transfer audit may have produced more accurate estimates of service provisions young people with HIV across the UK, due to having a larger and more nationally representative sample size. On the other hand, my study complemented and updated the BHIVA post-transfer audit and was more comprehensive in reporting on a larger variety of youth-friendly and transfer related services.

In my study, clinics were ranked on their level of youth-friendliness, using a youth-friendly composite score. The results indicated that the level of youth-friendliness did not differ by clinic type, although it is possible that the sample size reduced the statistical power to detect a significant difference. Geographically, the level of adherence to transfer and youth-friendly guidelines varied across the UK and Ireland. It is possible that clinics from larger urban areas would have larger populations and more supporting resources, including youth-friendly services, although this was not apparent in the survey findings. The 2014 transition study from the UK that evaluated the service provision of 44 clinics with young people who transferred from paediatric care, found no correlation between clinic size and number of specialist services offered, and did not describe a geographical trend [183].

4.8.3. Patient-level findings

With regard to the patient-level data, the exposure variables were the participants' health characteristics at transfer date and the outcome variables were the adult clinic type and its level of youth-friendliness. Here, I hypothesised that young people with poorer health status were more likely to be referred to young persons' clinics with higher level of youth-friendliness in order to better meet their needs. The characteristics of young people transferring from paediatric to adult care were compared by the type of adult clinic to which they transferred. There were no age or gender effects by clinic type, potentially indicating comparable maturity of young people at both clinic types. Young people who transferred to young persons' clinics presented with better CD4 count and viral load status at transfer compared to those who transferred to general adult clinics. However, the former group also transferred to adult care in more recent years (median calendar year of transfer 2013 vs 2011, $p<0.001$). After stratifying by calendar year of transfer, these differences were no longer apparent. Two factors may contribute to these trends. Firstly, international and national youth-friendliness guidelines have only been published since 2011, and thus it is likely that young persons' clinics have only existed in recent years [84,176,188]. Secondly, other analyses have reported improving health outcomes at transfer in more recent calendar years among young people with PHIV in the UK and Ireland trend [160], which would also explain the calendar year effect reported in my study.

In practice, paediatricians are likely to transfer young people to adult care based on a number of factors such as geographical feasibility [189], resources available or adult clinics that share the same trust as the paediatric clinic [84,136], young persons' preference and possibly their clinical status at transfer [84]. There is no general consensus on the best model for transferring young people and the UK's Children's HIV Association (CHIVA) guideline on transition has instead emphasised that the transition process should be tailored to the young person's individual needs [84].

4.8.4. Limitations

While the strengths of this survey lie in the relatively high response rate and the geographical spread of the responding clinics, a large number of clinics did not meet the study inclusion criteria due to only having one or two young people who had transferred from paediatric care. The inclusion criteria are thus likely to have caused a selection bias, where the clinics not invited to the study were the smaller clinics from smaller towns and cities. Subsequently, the generalisability of study findings may be limited to clinics in larger urban areas and may be an over/underestimation of the level of youth friendliness nationally. Additionally, with 22% of invited clinics not responding, it is possible these clinics may be systematically different to the responding clinics. For example, the non-responding clinics may have considerably less resources or the staff capacity to complete the survey compared to the responding clinics. Therefore, the former group of clinics may have provided different survey answers to the latter, thus potentially introducing non-response bias which may result in the overestimation of service provisions. Another bias that could impact the clinic survey data is social desirability bias, where clinic respondents might answer in a manner that will result in the respective clinic being viewed in a more favourable light, i.e. higher level of youth-friendly service provision, which may lead to an overestimation of service provision.

The clinic survey could have been designed to include more detailed questions that could discern how long services were available, however, a longer survey with more detailed questions may have resulted in a lower response rate as it would require staff with in-depth knowledge of changes in practice over time. Therefore, I made a compromise between the levels of detail collected by including less in-depth questions with the consequence of having less accurate service provision data. Another consequence of including less in-depth questions is the possibility of clinic respondents reporting that a particular service is available, e.g. evening hours, when this has only been available on one occasion or to a subgroup of participants. The cross-sectional nature of the survey precluded any analysis of how long clinics had provided a reported service. Many of the services could have been recently developed or have been in the developmental stage when the survey took place, especially with WHO guidelines promoting youth-friendliness only being published in 2012 and 2016 [119]. The information on when services were implemented by clinics could have been requested as part of my survey, however, it was felt that it would be too complicated to ask survey respondents about this, and this level of detail may have discouraged reporting and be subject to recall bias. Therefore, the clinic survey findings do not take into account changes in service provision over time and any trends detected between the patient health outcomes at transfer and the clinic-level characteristics may be affected by temporal bias. Consequently, it cannot be assumed that young people who transferred to adult care in the earlier years were exposed to the same level of service provision as reported in the survey. This methodological limitation will limit the usefulness of the youth friendliness variable in the analyses of subsequent chapters. Similarly, it cannot be assumed that young people were actually using the services offered by clinics. Therefore, my findings must be interpreted with caution. Ongoing longitudinal surveys would be the optimal methodology but these were not feasible to carry out within the time frame of this PhD project as well as the retrospective nature of the patient data that I analysed in subsequent chapters.

An uncertainty in my study is whether the services included in the youth-friendly composite score had an additive or multiplicative effect. In practice, some services could have a multiplicative effect, where services such as evening hours in combination with weekend service could have more of an impact on young peoples' engagement in comparison to the provision of evening hours and walk-in services. A study of a London HIV clinic, from 2014, found peer support to positively impact CD4 count and viral load outcomes in adult care [157]. Another study from the USA reported that the availability of youth-friendly clinic services such as evening hours, separate young persons' waiting area and adolescent-trained staff to improve engagement in adult care of young people with HIV [101]. In contrast, a Kenyan study from 2016, found no improvement in engagement following the introduction of peer support and dedicated clinic days for young people [178]. Therefore, due to the national and international guidelines on youth-friendliness not emphasising the beneficial impact of one service over the other, I chose to build the composite score assuming each service would have a similar additive effect on patient outcomes.

Despite young persons' waiting areas being previously reported to positively impact engagement in care [101], it was excluded from the youth-friendly composite variable due to having no data

variation by clinic type, as only young persons' clinics offered this feature. The different issues and biases identified in the clinic survey study are summarised in Table 4.7.

4.8.5. Implications for subsequent results chapters in this thesis

In summary this survey suggested no difference in a range of services provided to young people transferring from paediatric care by adult clinic type. It is, therefore, hypothesised that patient outcomes in adult care will not differ by clinic type after adjustment for calendar year of transfer, and this will be further explored in subsequent chapters of this thesis.

In the following results chapters, the clinic survey variables, including the youth-friendly composite score, are investigated as potential predictors of engagement in care and health outcomes in adult care. Research findings to date describe how inadequate provision of HIV services tailored to young people is a barrier to engagement in care [101,106]. It is therefore hypothesised here that more youth-friendly services would encourage young people to be better engaged in care. This would subsequently increase their access to medication and potentially improve ART adherence and lastly their health outcomes in adult care.

Table 4.7: Summary of issues and errors affecting the clinic survey findings

Issue	Type of error	Potential effect of bias on the service provision estimates (where applicable)
Denominator		
Clinics with <3 patients who transferred from paediatric care were excluded from the clinic survey study	Selection bias that may limit the generalizability of findings	-
22% of clinics invited to complete the survey did not complete it, non-responding clinics may have had less resources	Non-response bias	Overestimation of service provision
Clinic survey instrument		
Survey questions lacked detail and did not enquire about the duration of service provision or the level of access patients had to services (e.g. mental health support may only have been available to a sub-group of patients or on a particular day)	Reliability	Overestimation or underestimation of service provision
Clinic survey data were self-reported by clinic staff, who may have tended to over-report provision of youth-friendly services	Social desirability bias	Overestimation of service provision
Clinic survey respondents may not have full knowledge or memory about the services available	Reliability and recall bias	Overestimation or underestimation of service provision
Clinic survey questions may have been misunderstood by respondents	Reliability	Overestimation of service provision
Clinic survey data were collected over a 7 month period, therefore, time point of interest varied across the clinics. Service provision in clinics who responded early could have changed by month 7.	Misclassification	-
Clinic-level data were from one point in time while service provision may have changed over time	Reliability	Overestimation of service provision
The majority of clinic survey answer options were categorical as opposed to text answers and respondents could have accidently selected the wrong answer, or the answer they wanted may not have been available	Misclassification	Overestimation or underestimation of service provision
Data entry error as data were not double-entered by different individual.	Misclassification	Overestimation or underestimation of service provision
Youth-friendly composite variable		
All variables included in the composite score were assumed to have an equal and additive effect of youth-friendliness on patient outcomes, when in reality some variables may be more effective than others	Misclassification	-

5. Mortality and disengagement from care following transfer to adult care

5.1. Chapter content and aims

5.1.1. Chapter content

In this chapter, I assess the incidence rate of (i) progression to AIDS and death, and (ii) disengagement from care following the transfer of young people from paediatric to adult HIV care, and identify associated risk factors. I use two measures of disengagement from care: the first is based on "gaps in care" and utilises the complete longitudinal follow-up dataset available during adult care; the second is a binary definition of LTFU. The analyses described in this chapter are based on data linked between the CHIPS and the UK CHIC studies and not SOPHID and HARS, because the latter two surveillance systems did not collect detailed clinical data. Additionally, death data were not reported in SOPHID and were described to be largely underreported in HARS (detailed in Chapter 3, section 3.5.6). This led to only young people who transferred to UK CHIC-participating clinics being included in the analyses of this chapter. To assess the representativeness of young people at UK CHIC-participating clinics, their demographic and clinical characteristics in paediatric care are compared to those of young people who transferred to non-UK CHIC-participating clinics.

5.1.2. Aims

The aims of this chapter are to:

1. compare characteristics of young people who transferred to UK CHIC-participating clinics compared to those who transferred to non-UK CHIC clinics;
2. assess the cumulative incidence rate of progression to AIDS and death after transfer to adult care in UK CHIC clinics and associated factors; and
3. assess the rate of (i) gaps in care and (ii) LTFU after transfer to adult care and their associated factors.

5.2. Characteristics of young people with HIV who transferred to UK CHIC-participating clinics vs non-UK CHIC clinics

5.2.1. Methods

5.2.1.1. Study population

All young people with HIV aged ≥13 years by 01/04/2017 who had received paediatric care and were documented to have transferred to adult care were included. The study population was split into two groups: (1) young people who transferred to a UK CHIC-participating clinic (i.e. identified in the CHIPS and UK CHIC linkage), and (2) young people who transferred to a non-UK CHIC clinic (i.e. not identified in the CHIPS and UK CHIC linkage) but were documented to have transferred to adult care.

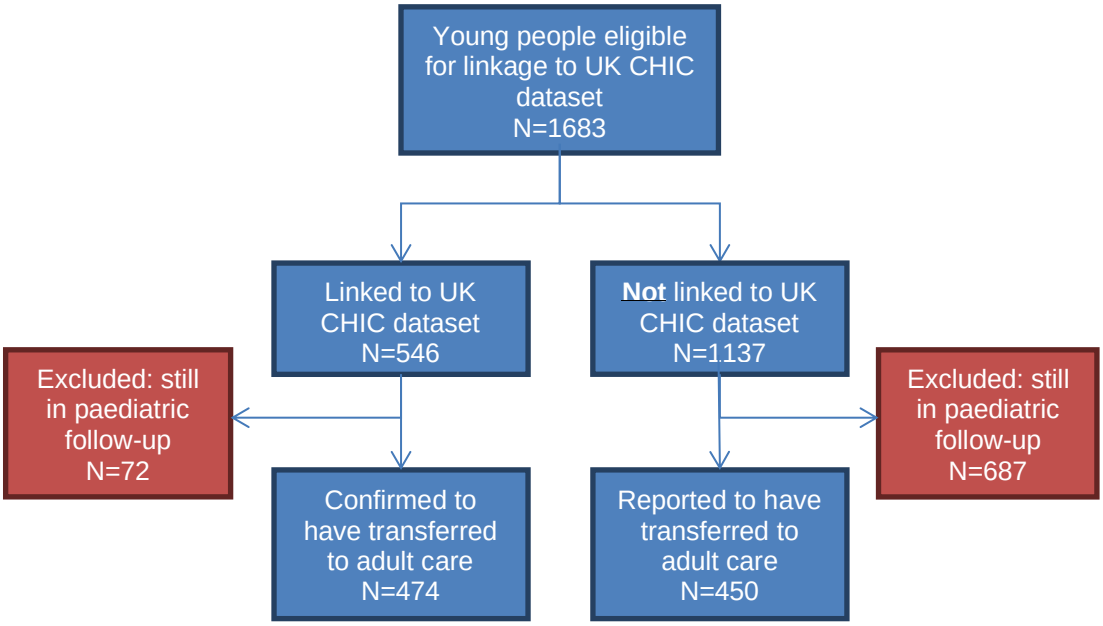
5.2.1.2. Statistical analysis

To assess the representativeness of the young people who transferred to UK CHIC clinics, the demographic and clinical characteristics at the last paediatric visit were compared to those who transferred to non-UK CHIC clinics (i.e. those not linked to the UK CHIC dataset but documented in CHIPS to have transferred to adult care).

5.2.2. Results

Among 1683 eligible young people with HIV, 546 (32%) were linked to UK CHIC, of whom 474 were confirmed as having transferred to adult care. Among the remaining 1137 young people not linked to the UK CHIC dataset, 450 were documented in CHIPS to have transferred to adult care (Figure 5.1).

Figure 5.1: Young people with HIV linked and not linked to UK CHIC dataset



5.2.2.1. Demographic characteristics

Table 5.1 presents the demographic characteristics of young people who transferred to a UK CHIC clinic (i.e. linked to the UK CHIC dataset) and at a non-UK CHIC clinic (i.e. not linked). Some characteristics were similar between the two groups with 96% with PHIV, just over half (53%) being female and 62% born abroad. A slightly higher proportion of the UK CHIC group were black (82% vs 79%, respectively, p=0.02) and born at an earlier median year (year of birth 1993 vs 1994, p<0.001) compared to the non-UK CHIC group. Young people who transferred to UK CHIC clinics were diagnosed with HIV at a younger age compared to those who transferred to non-UK CHIC clinics (median age 6 vs 7 years, respectively, p=0.05).

Table 5.1: Demographics of young people with HIV who were and were not linked to UK CHIC

Demographic characteristics		Total (N=924)	UK CHIC clinic (N=474)	Non-UK CHIC clinic (N=450)	P-value
		n (%) or median [IQR] or range			
Mode of HIV acquisition (N=846)	Perinatal	809 (95.6)	414 (96.1)	395 (95.2)	0.53
	Other [A]	37 (4.4)	17 (3.9)	20 (4.8)	
Sex (N=924)	Male	435 (47.1)	233 (49.2)	202 (44.9)	0.19
	Female	489 (52.9)	241 (50.8)	248 (55.1)	
Ethnicity (N=904)	Black	718 (79.4)	380 (82.4)	884 (79.3)	0.02
	White/Other	186 (20.6)	81 (17.6)	338 (76.3)	
Place of birth (N=908)	UK	350 (38.6)	184 (39.6)	105 (23.7)	0.52
	Abroad	558 (61.5)	281 (60.4)	281 (60.4)	
Calendar year of birth (N=924)	Median [IQR]	1994 [1991, 1996]	1993 [1990, 1995]	1994 [1992, 1997]	<0.001
	Range	1979, 2001	1982, 1999	1979, 2001	
Age at HIV diagnosis, years (N=911)	Median [IQR]	6.6 [2.5, 11.0]	6.0 [2.2, 10.7]	7.3 [3.0, 11.1]	0.05
	Range	0.0, 16.0	0.0, 16.0	0.0, 15.9	

[A] – *includes sexual modes of acquisition and via blood transfusions*

5.2.2.2. Last visit in paediatric care

Table 5.2 presents the clinical and treatment characteristics at last visit in paediatric care among young people who transferred to UK CHIC clinics vs non-UK CHIC clinics. The overall median age at last visit in paediatric care was 17.7 years and did not significantly differ between the groups. Among the UK CHIC group, six were aged under 13 years at the last paediatric visit, at which point all, except one, were known to be LTFU or to have moved abroad prior to re-entering care at a UK CHIC-participating adult clinic. Young people who transferred to UK CHIC clinics transferred in earlier calendar years (2011 vs 2012, p<0.001) compared to those who transferred to non-UK CHIC clinics. The UK CHIC group had poorer immunological and virological characteristics at last visit in paediatric care compared to the other group. The median CD4 nadir was slightly lower among the former group compared to the latter (median CD4 nadir 200 vs 210 cells/mm_3, p=0.07). Similarly, the median CD4 count at last visit was lower among the UK CHIC group (median CD4 count 471 vs 511 cells/mm_3, p=0.002). A significantly lower proportion of the UK CHIC group were virally suppressed at last visit in paediatric care compared to the non-UK CHIC group (60% vs 71%, p<0.001).

At the last paediatric visit, overall 26% had ever been diagnosed with AIDS in paediatric care, and 77% of all young people with HIV were on cART, 10% were on a mono or dual regimen and 11% were ART-naïve or on a treatment interruption. The proportion of young people diagnosed with AIDS by the last paediatric visit, and treatment regimens, did not vary significantly between the two groups.

Table 5.2: Clinical and treatment characteristics at last visit in paediatric care of young people with HIV who were and were not linked to UK CHIC

Characteristics at last visit in paediatric care		Total (N=924)	UK CHIC clinic (N=474)	Non-UK CHIC clinic (N=450)	P-value
		n (%) or median [IQR] or range			
Age, years (N=917)	Median [IQR]	17.7 [16.8, 18.5]	17.7 [16.7, 18.5]	17.7 [16.8, 18.4]	0.47
	Range	6.9, 23.1	6.9, 22.5	12.1, 23.1	
Calendar year (N=897)	Median [IQR]	2011 [2009, 2014]	2011 [2008, 2013	2012 [2009, 2014]	<0.001
	Range	1998, 2017	2000, 2015	1998, 2017	
Nadir CD4 count, cell/mm$_3$ (N=912)	Median [IQR]	203 [98, 310]	200 [90, 293]	210 [110, 321]	0.07
	Range	0, 990	0, 733	0, 990	
CD4 count, cells/mm$_3$ (N=912)	Median [IQR]	494 [315, 686]	471 [280, 663]	511 [351, 699]	0.002
	Range	0, 1898	0, 1898	0, 1848	
	<200	110 (12.1)	72 (15.6)	38 (8.5)	0.004
	200-349	156 (17.1)	85 (18.4)	71 (15.8)	
	350-499	196 (21.5)	94 (20.3)	102 (22.7)	
	≥500	450 (49.3)	212 (45.8)	238 (53.0)	
Viral load, copies/ml (N=910)	≤400	580 (59.9)	278 (59.9)	302 (67.7)	0.01
	>400	330 (36.3)	186 (40.1)	144 (32.3)	
AIDS events (N=924)	Yes	241 (26.1)	131 (27.6)	110 (24.4)	0.27
	No	683 (73.9)	343 (72.4)	340 (75.6)	
ART regimen$_1$ (N=917)	Mono/dual	91 (9.9)	51 (10.9)	40 (8.9)	0.47
	cART	708 (77.2)	352 (75.4)	356 (79.1)	
	Other$_1$	19 (2.1)	12 (2.6)	7 (1.6)	
	Naïve/off ART	99 (10.8)	52 (11.1)	47 (10.4)	

1 triple NRTI or triple regimens (including unboosted PI)

5.3. AIDS and mortality following transfer to adult care

5.3.1. Methods

5.3.1.1. Study population

Young people with HIV were included if they had paediatric and adult data linked between the CHIPS and UK CHIC dataset.

5.3.1.2. Statistical analysis

The outcome of interest was the composite endpoint of mortality or a new AIDS event following transfer to adult care. Due to the relatively small number of deaths among young people who transferred to UK CHIC clinics (N=14), a composite endpoint was used to increase statistical power. Demographic and clinical characteristics at last visit in paediatric care were compared between young people who progressed to AIDS/mortality in adult care vs those who did not.

Among young people who died in adult care, the CD4 count, viral load, AIDS and treatment status at last visits in paediatric and adult care were described. The CD4 count and viral load trajectories of those who died were plotted by age during follow-up in paediatric and adult care until the date of death.

Using the AIDS/mortality composite endpoint, time to event analyses were carried out. Time at risk started from the date of transfer (last paediatric visit) until the earliest of a new AIDS event, death or last clinic visit in adult care. Crude AIDS/mortality rates were calculated according to sex, ethnicity (black vs white/other), place of birth (UK vs abroad), time-updated age and calendar year of transfer. Factors associated with AIDS/mortality in adult care were identified using a Cox proportional hazards model with a step-wise backwards elimination approach. Variables associated with the outcome in the univariable analysis ($p<0.2$) were considered for multivariable analysis, those with highest p-values (≥0.1) were sequentially removed from the multivariable model until all remaining variables had a p-value <0.1. The following variables, selected *a priori*, were included in all models, regardless of statistical significance: sex, age at HIV diagnosis in the UK, and age and calendar year at the transfer date. Previous paediatric HIV studies having reported age at HIV diagnosis to be associated with mortality [190–192]. Calendar year of transfer was also selected *a priori* as virological and immunological characteristics have shown to significantly differ by calendar year within my study population (Figure 4.8 and 4.9).

Factors considered as potential risk factors for AIDS/mortality in adult care included the following individual-level factors:

- place of birth (UK vs abroad),
- ethnicity (black vs white/other),
- nadir CD4 count by transfer,
- CD4 count at transfer,
- Viral failure in the last year of paediatric care (≥1 VL >400 copies/ml),
- ART status (on ART vs ART naïve/off ART) at transfer,
- prior AIDS events in paediatric care, and
- gap in care (duration between the last paediatric visit and first adult visit).

The following clinic-level factors were also considered as potential risk factors:

- adult clinic's level of youth-friendliness, and
- clinic type (young persons' clinic vs general adult clinic).

With regards to the clinic-level factors, the potential for a cluster effect at a clinic-level was explored by fitting a frailty model [193]. For continuous variables, the optimal functional form of the association between each potential risk factor and the outcome was determined by plotting the Martingale residual against each variable in question. A straight line relationship between the Martingale residual and the respective variable indicated that a linear term was appropriate; therefore, the variable was engaged in its continuous (untransformed) form. If non-linearity was detected (i.e. not a straight line), the variable was categorised and further described in results section of this chapter. Virological and immunological characteristics at transfer were shown to differ by calendar year of transfer (Figure 4.8 and 4.9), therefore interactions between calendar year at transfer and all other potential risk factors were explored in the final model. Additionally, the proportional hazards assumption was tested for each potential risk factor; where there were factors that violated this assumption, an interaction was fitted between the fixed covariate and calendar time. The cumulative incidence of AIDS/mortality in adult care was also calculated using Kaplan-Meier methods and stratified by variables included in the final multivariable regression model.

Among young people who did not die in adult care, clinical characteristics at the last adult visit were descriptively compared between those with and without AIDS events in adult care.

5.3.2. Results

5.3.2.1. Demographic characteristics among young people with HIV by AIDS/mortality status in adult care

Of the 474 young people linked between the CHIPS and UK CHIC datasets, 14 were excluded from any analyses due to missing a subsequent visit date after the first adult visit which meant their time at risk could not be estimated. Of the remaining 460 young people who transferred to UK CHIC-participating clinics and were included, 35 (8%) experienced the composite endpoint of AIDS and/or mortality in adult care. Of these, 28 young people experienced a new AIDS event and 14 died in adult care. Of the 14 young people who died, four were censored at their first AIDS event in adult care and the remaining 10 did not have an AIDS diagnosis in adult care prior to death.

Causes of death were advanced HIV disease (N=3), HIV wasting (N=1), non-HIV/AIDS related (N=1), suicide (N=1), renal failure (N=1), respiratory disease (N=2), multifocal leukoencephalopathy (N=1) and unknown/missing (N=4). Twenty-eight participants experienced at least one AIDS event, of whom 22 only had one AIDS event, three experienced two events and two experienced three AIDS events and one experienced four events in adult care. The AIDS events in adult care included candidiasis (N=7), cryptosporidiosis (N=2), herpes simplex disease (N=1), HIV encephalopathy (N=2), Kaposi's sarcoma (N=1), Burkitt's lymphoma (N=1), respiratory diseases (N=9), progressive multifocal leukoencephalopathy (N=1), cerebral toxoplasmosis (N=2), HIV wasting syndrome (N=1) and unknown diagnoses (N=1).

Table 5.3 presents the demographic characteristics of young people with HIV by AIDS/mortality status in adult care. A higher proportion of those who experienced AIDS/mortality were female compared to the event-free group (63% vs 37%, p=0.13), although this was not a significant trend. Young people who experienced AIDS/mortality in adult care had an earlier median year of birth compared to the AIDS/mortality-free group (1989 vs 1993, p<0.001). A higher proportion of participants with an event were born abroad (78% vs 58%, p=0.02) compared to young people to the latter group. Overall, 82% were black with a median age at HIV diagnosis of 6 years and neither characteristic differed significantly by AIDS/mortality status in adult care.

Table 5.3: Demographic characteristics of young people with HIV by AIDS/mortality status in adult care

Demographic characteristics		**Total (N=460)**	**Experienced AIDS/mortality in adult care**		
			Yes (N=35)	**No (N=425)**	**P-value**
		n (%) or median [IQR] or range			
Sex (N=460)	Female	233 (50.7)	22 (62.9)	211 (49.7)	0.13
	Male	241 (49.4)	13 (37.1)	214 (50.4)	
Ethnicity (N=449)	White/other	79 (17.6)	4 (11.4)	75 (18.1)	0.23
	Black	370 (82.4)	31 (88.6)	339 (81.9)	
Place of birth (N=451)	UK	179 (39.7)	8 (22.9)	171 (41.1)	0.05
	Abroad	272 (60.3)	29 (77.1)	245 (58.9)	
Calendar year of birth (N=460)	Median [IQR]	1993 [1990, 1995]	1989 [1986, 1991]	1993 [1991, 1995]	<0.001
	Range	1982, 1999	1983, 1996	1982, 1999	
Age at HIV diagnosis [A], years (N=453)	Median [IQR]	6.0 [2.2, 10.7]	6.1 [3.7, 11.6]	6.0 [2.0, 10.3]	0.23
	Range	0.0, 16.0	0.2, 15.0	0.0, 16.0	

[A]: this is age at HIV diagnosis in the UK

5.3.2.2. Clinical characteristics at last visit in paediatric care among young people with HIV by AIDS/mortality status in adult care

Table 5.4 presents the clinical characteristics at last visit in paediatric care by AIDS/mortality status in adult care. The AIDS/mortality group transferred to adult care at a slightly younger age than the other group (median age at transfer 17.1 vs 17.8 years, p=0.05) and in significantly earlier calendar years (median calendar year of transfer 2006 vs 2011, p<0.001).

Young people who progressed to AIDS/mortality in adult care had poorer immunological and virological characteristics at time of transfer compared to those without an event. The group with AIDS/mortality had a lower median nadir CD4 count (median nadir CD4 count 110 vs 200 cells/mm_3, p=0.07) and a lower CD4 count at transfer compared to the latter group (median CD4 count 298 vs 482 cells/mm_3, p<0.001). The ART usage at transfer did not differ significantly between the groups. A higher proportion of participants with AIDS/mortality in adult care had prior AIDS diagnosis in paediatric care compared to those without an event (54% vs 26%, p<0.001), respectively.

Overall, for all young people the median gap in care between last paediatric visit and first adult visit was 3.2 months and the majority (87%) had transferred to a young persons' clinic, neither characteristic differed significantly by AIDS/mortality status in adult care.

Table 5.4: Clinical characteristics of young people with HIV at last visit in paediatric care by AIDS/mortality status in adult care

Characteristics at last visit in paediatric care		Total (N=460)	Experienced AIDS/mortality in adult care Yes (N=35)	No (N=425)	P-value
		n (%) or median [IQR] or range			
Age, years (N=447)	Median [IQR]	17.8 [16.8, 18.5]	17.1 [16.7, 18.0]	17.8 [16.8, 18.6]	0.05
	Range	12.6, 22.5	14.8, 20.2	12.6,22.5	
Calendar year (N=437)	Median [IQR]	2011 [2008, 2013]	2006 [2003, 2009]	2011 [2008, 2013]	<0.001
	Range	2000, 2016	2000, 2013	2000, 2016	
Nadir CD4 count, cells/mm$_3$ (N=451)	Median [IQR]	196 [88, 291]	110 [60, 260]	200 [90, 293]	0.07
	Range	0, 733	0, 655	0, 733	
CD4 count, cells/mm$_3$ (N=451)	Median [IQR]	470 [280, 662]	298 [120, 450]	482 [286, 672]	<0.001
	Range	0, 1898	2, 752	0, 1898	
Viral load, copies/ml (N=452)	≤400	201 (44.5)	8 (22.9)	193 (46.3)	0.007
	>400	251 (55.5)	27 (77.1)	224 (54.7)	
ART status (N=455)	On ART	404 (88.8)	30 (85.7)	374 (89.1)	0.57
	ART naïve/Off ART	51 (11.2)	5 (14.3)	46 (11.0)	
Ever had AIDS events (N=474)	Yes	130 (28.3)	54 (54.3)	111 (26.1)	<0.001
	No	330 (71.7)	16 (45.7)	325 (73.9)	
Gap in care between last paediatric visit and first adult visit, months (N=450)	Median [IQR]	3.2 [1.6, 6.2]	3.5 [1.6, 7.7]	3.2 [1.6, 6.2]	0.58
	Range	0.0, 159.4	0.0, 70.9	0.0, 159.4	
Adult clinic type (N=376)	Young persons' clinics	328 (87.2)	24 (92.3)	304 (87.9)	0.56
	General adult clinics	48 (12.8)	2 (7.7)	46 (13.1)	

A: Duration between date of diagnosis in the UK and the last visit in paediatric care

5.3.2.3. Clinical characteristics of young people with HIV who died in adult care

Table 5.5 presents the sex, age, calendar year, ART status, CD4 count, viral load and AIDS events at the last paediatric visit and last adult visit prior to death as well as cause of death among the 14 young people who died post-transfer. The participants are presented in order of their year of death, starting with the earliest calendar year. Almost two-thirds (64%) were female; age at the last paediatric visit ranged from 14 to 18 years and the median calendar year of transfer was 2006. At the last paediatric visit, 12 (86%) were on ART, of whom 10 (71%) were on a cART regimen. The overall median CD4 count was 150 cells/mm_3, under a third (29%) were virally suppressed (≤400 copies/ml) and 71% had an AIDS diagnosis.

At the last visit prior to death, ages ranged from 18 to 23 years and the median calendar year was 2010. Young people had a median CD4 count of 30 cells/mm_3 and 31% were virally suppressed (≤400 copies/ml). All of the four participants who were virally suppressed at the last paediatric visit remained virally suppressed at their last measurement in adult care prior to their date of death. Only one person who was unsuppressed at the last paediatric visit date achieved viral suppression prior to their death. The deaths occurred at a median of 3 [IQR 2, 4] years following transfer to adult care (data not shown) and only four participants experienced a new AIDS event in adult care.

Figure 5.2 shows the longitudinal CD4 counts and viral load trajectories by age of the 14 young people who died following transfer to adult care. The viral loads were expressed on a log_{10} scale, where 2.6 log_{10} copies/ml is equivalent to 400 copies/ml, and viral load values above this threshold were considered unsuppressed.

None were diagnosed with HIV and started on ART in the UK during infancy or early childhood with a median age at diagnosis of 6 [IQR 4, 10] years and a median age at ART start of 10 [IQR 5, 12] years (data not shown). However, there was a broad range of ages young people had their first CD4 or viral load measurements in paediatric care (ranging from 5 to 13 years).

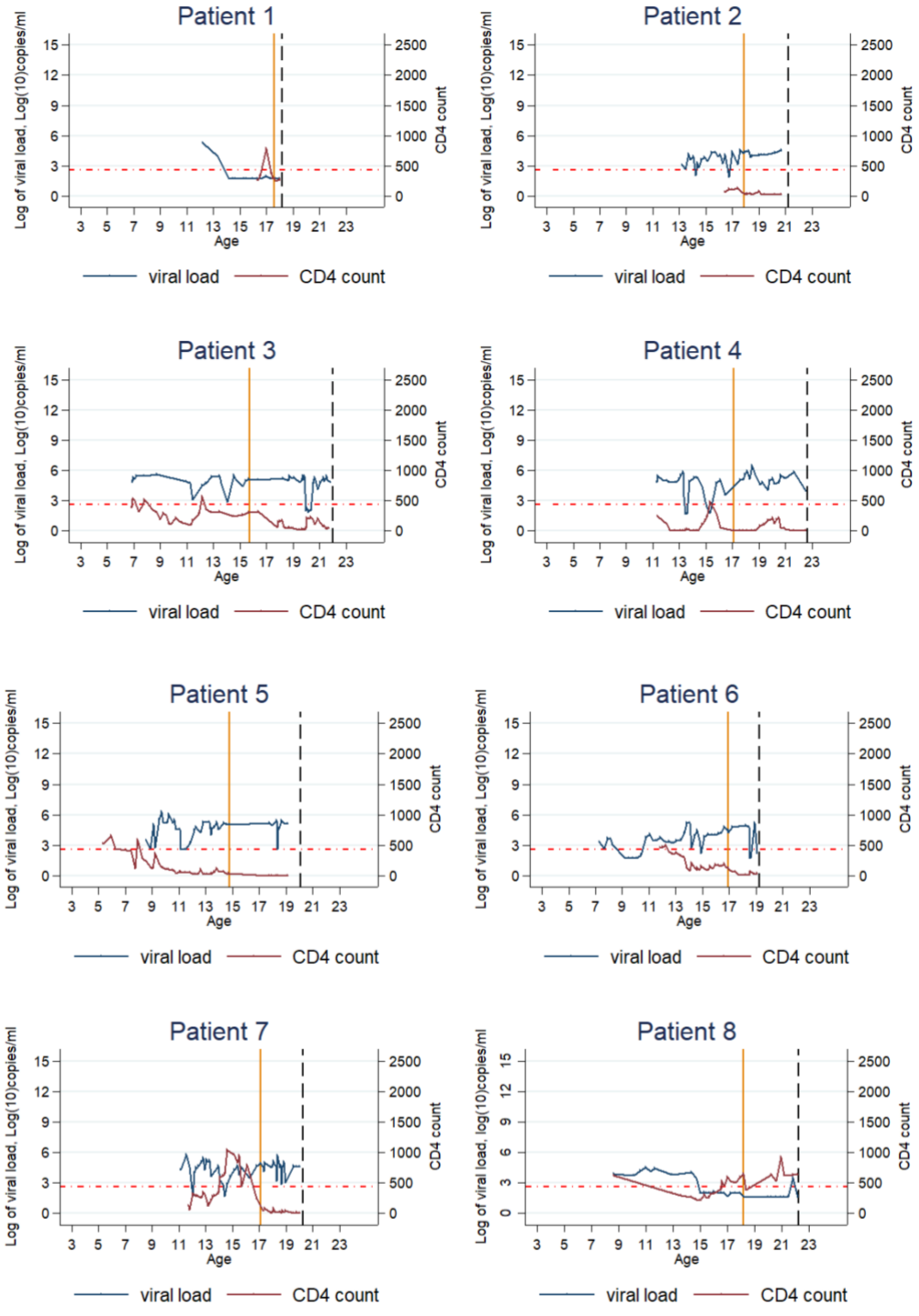
There were some similarities in CD4 and viral load trajectories of the 14 young people. During paediatric follow-up, two patients had a consistently suppressed viral load (patients 11 and 13), however, most had an increasing trajectory prior to and after transfer date, leading to 11 out of 14 young people being unsuppressed throughout their follow-up in adult care. Similarly, most had persistently low CD4 counts and ≤500 cells/mm_3, often nearing 0 cells/mm_3 in adult care (Patients 1, 3, 4, 5, 7, 9, 10 and 12).

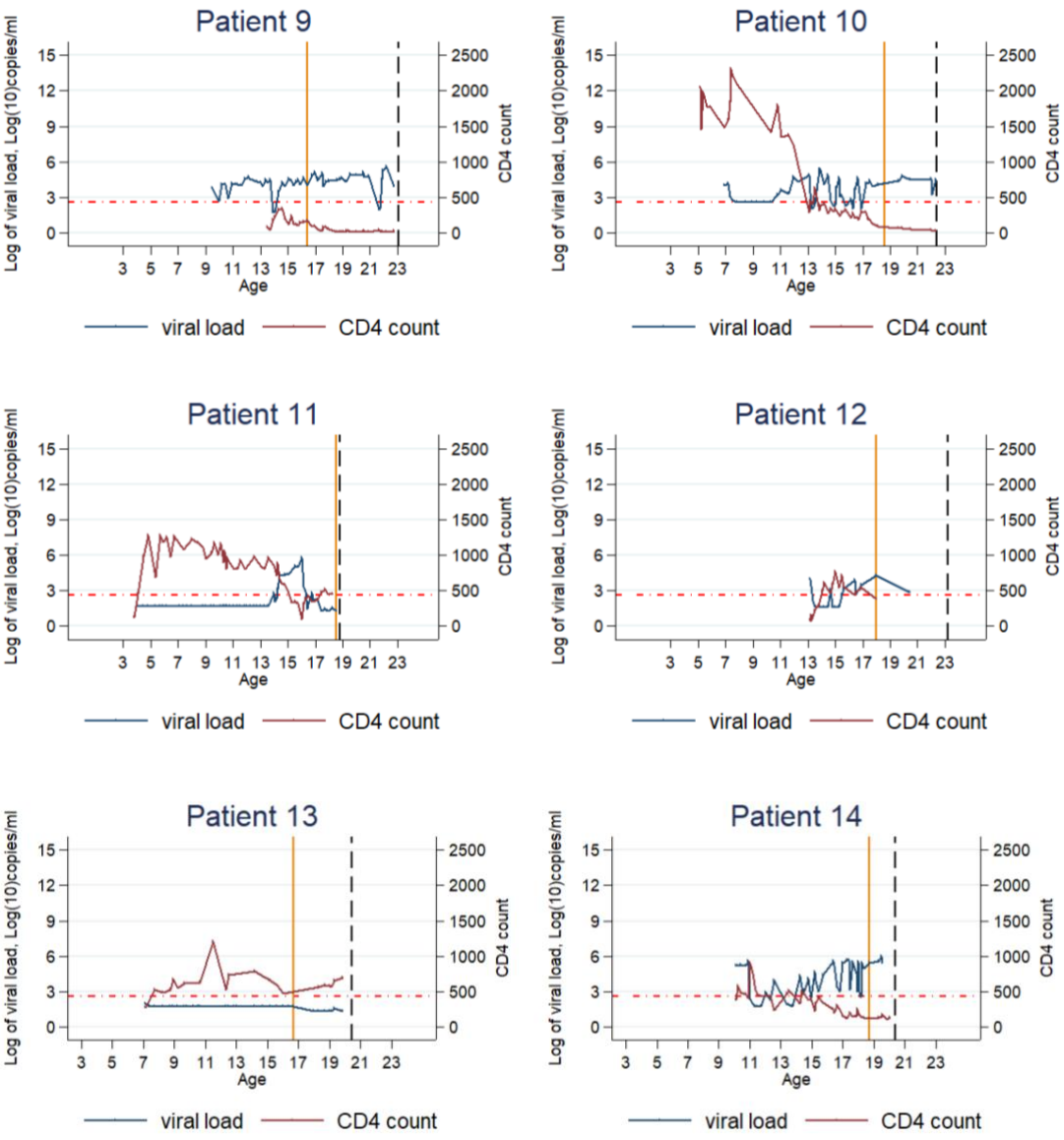
Table 5.5: Clinical and treatment characteristics at date of transfer and last visit prior to death among young people who died in adult care (N=14), ordered by calendar year of death

	At last paediatric visit							Last visit priori to death						
Patient	**Sex**	**Age**	**Year**	**On ART**	**CD4**	**VL**	**AIDS event**	**Age**	**Year**	**On ART**	**CD4[A]**	**VL[B]**	**AIDS event**	**Cause of death**
1	Female	17	2003	Yes	290	<50	Bacterial pneumonia	18	2003	Yes	270	<50	no new event	Respiratory disease and failure
2	Female	17	2002	Yes	70	18400	PCP	21	2005	no	20	36100	no new event	Renal failure
3	Male	15	2001	Yes	306	135000	Failure to thrive	21	2007	Yes	40	72689	PCP	Suicide
4	Male	17	2003	Yes	2	4041	MAI	22	2009	Yes	10	9914	HIV wasting syndrome	-[C]
5	Female	14	2003	Yes	40	112795	Bacterial pneumonia, failure to thrive	20	2009	-[C]	0	136258	no new event	Advanced HIV disease, general deterioration
6	Female	16	2006	Yes	130	29208	Failure to thrive	19	2009	Yes	40	160	no new event	PML
7	Female	17	2006	No	120	75934	Bacterial pneumonia	20	2009	No	10	39583	no new event	Advanced HIV disease
8	Female	18	2006	Yes	651	<50	no new event	22	2010	Yes	630	<50	no new event	-[C]
9	Male	16	2004	Yes	170	11019	no new event	23	2011	Yes	30	8500	Oesophageal candida	Advanced HIV disease
10	Female	18	2009	No	94	11760	no new event	22	2013	Yes	26	28300	no new event	-[C]
11	Female	18	2013	Yes	450	<50	no new event	18	2013	Yes	-[C]	-[C]	Oesophageal candida	Pulmonary tuberculosis
12	Female	17	2011	Yes	383	20705	Oesophageal candida, PCP	23	2016	-[C]	-[C]	694	no new event	-[C]
13	Male	16	2012	Yes	477	<50	Other bacterial infection	20	2016	Yes	690	<50	no new event	HIV wasting
14	Male	15	2011	Yes	110	246000	Bacterial pneumonia	20	2016	Yes	130	248530	no new event	Heart failure

[A] - CD4 count (units cells/mm3); [B] - viral load (units copies/ml); [C] - missing data; PCP - Pneumoncystis carinii pneumonia; MAI - Mycobacterium avium; PML - Progressive multi-focal-leukoencephalopathy

Figure 5.2: CD4 count, log$_{10}$ (viral load) and age at transfer date and death among the 14 young people who died in adult care





Age at transfer date

Age at last visit prior to death

VL=2.6 $\log_{10}$ copies or 400 copies/ml

5.3.2.4. Rates of AIDS/mortality, and mortality, in adult care

Table 5.6 presents the AIDS/mortality rates in adult care by sex, ethnicity, place of birth, current age, and calendar year of transfer. The crude rate of AIDS/mortality was 1.8 (95% CI 1.3, 2.5) per 100 person-years and the mortality rate was 0.6 (95% CI 0.4, 1.1) per 100 person-years in adult care.

The crude AIDS/mortality rates were comparable by sex and ethnicity with overlapping confidence intervals. Young people who were born abroad had a slightly higher AIDS/mortality rate compared to those born in the UK (crude rate: 2.4 (95% CI 1.6, 3.4) vs 1.1 (95% CI 0.5, 2.1) per 100 person-years, respectively), although the confidence intervals had some overlap. The AIDS/mortality crude rate rose from 0.5 (95% CI 0.2, 1.3) per 100 person-years for young people with a current age less than 19 years to 1.6 (95% CI 1.0, 2.7) per 100 person-years for young people aged 20 to 24 years and 8.1 (95% CI 4.9, 13.5) for those aged ≥25 years, although, the last group only contributed 185 person-years. The AIDS/mortality crude rate was highest among young people who transferred to adult care ≤2008 (crude rate: 2.5 (95 CI 1.7, 3.7) per 100 person-years). Young people who transferred between the calendar years 2009 to 2012 had a crude rate of 0.9 (95% CI 0.5, 2.0) per 100 person-years and 1.1 (95% CI 0.3, 4.4) per 100 person-years for those who transferred in 2013 to 2016.

When the outcome was restricted to only mortality events instead of the AIDS/mortality composite outcome, similar rates were observed across the different demographic categories. While the AIDS/mortality rate was highest among young people aged ≥25 years compared to younger age groups, there were no mortality events in this age group.

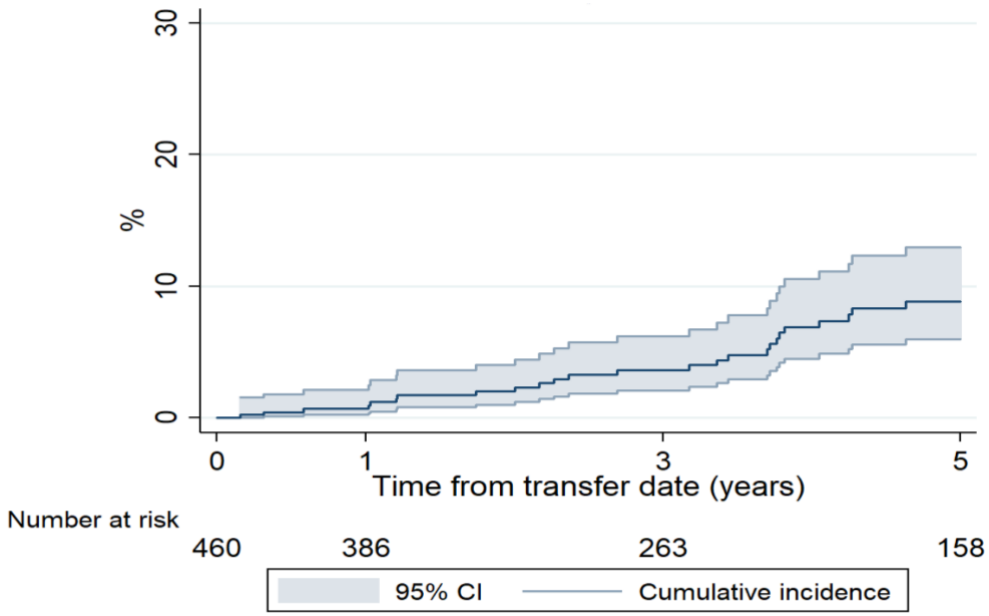
Table 5.6: AIDS/mortality rates of young people with HIV per 100 person-years by demographic characteristics

Demographic characteristics	AIDS/mortality outcome			Mortality outcome		
	Number of events	Person-years	Rate (95% CI)	Number of events	Person-years	Rate (95% CI)
Overall	35	1944.4	1.8 (1.3, 2.5)	14	1135.9	0.6 (0.4, 1.1)
Sex						
Female	22	1019.3	2.2 (1.4, 3.3)	9	1155.1	0.8 (0.4, 1.5)
Male	13	925.1	1.4 (0.8, 2.4)	5	1020.8	0.5 (0.2, 1.2)
Ethnicity						
White/other	4	394.8	1.0 (0.4, 2.7)	2	422.7	0.5 (0.1, 1.9)
Black	31	1509.9	2.1 (1.4, 2.9)	12	1696.0	0.7 (0.4, 1.2)
Place of birth						
UK	8	758.1	1.1 (0.5, 2.1)	3	808.8	0.4 (0.1, 1.2)
Born abroad	27	1141.8	2.4 (1.6, 3.4)	11	1319.4	0.8 (0.5, 1.5)
Current age						
<19	5	941.5	0.5 (0.2, 1.3)	4	927.0	0.3 (0.1, 1.1)
20-24	15	936.1	1.6 (1.0, 2.7)	10	925.5	0.9 (0.4, 1.8)
≥25	15	184.9	8.1 (4.9, 13.5)	0	184.9	0 (0, 0)
Calendar year of transfer						
≤2008	26	1022.6	2.5 (1.7, 3.7)	7	1039.6	0.7 (0.3, 1.4)
2009-2012	7	741.0	0.9 (0.5, 2.0)	3	783.9	0.5 (0.1, 1.2)
2013-2016	2	110.6	1.1 (0.3, 4.4)	1	195.4	0.6 (0.1, 3.6)

5.3.2.5. Risk of AIDS/mortality in adult care

The cumulative incidence of AIDS/mortality in adult care is presented in Figure 5.3. In the first three years after the last paediatric visit, there was a steady increase in cumulative incidence of AIDS/mortality, followed by a steeper rise in the incidence between years three and five of adult follow-up. In the first year of adult care follow-up, 1% (95% CI 0%, 2%) had experienced AIDS/mortality. By the third year, the cumulative incidence increased slightly to 4% (95% CI 2%, 6%) and by the fifth year following transfer, 9% (95% CI 6%, 13%) had experienced AIDS/mortality in adult care.

Figure 5.3: Cumulative incidence of experiencing AIDS/mortality in adult care (N=460)



5.3.2.6. Factors associated with AIDS/mortality after transfer to adult care

Table 5.7 shows the factors associated with AIDS/mortality in adult care from the univariable and multivariable analysis using Cox proportional hazard models.

In the univariable analysis, young people who transferred to adult care in earlier calendar years, those born abroad and those who had poorer immunological and virological status and prior AIDS diagnosis at the last paediatric visit were at a significantly greater risk of experiencing AIDS/mortality in adult care. Young people born in the UK (HR: 0.4 (95% CI 0.2, 1.0), p=0.04) and those who transferred in later calendar years (HR: 0.9 (0.8, 1.0) per year increase, p=0.002) had a lower risk of AIDS/mortality. At transfer, higher CD4 nadir (HR per 100 cells/mm$_3$ increase: 0.8 (95% CI 0.6, 1.0), p=0.07), and higher CD4 count (HR per 100 cells/mm$_3$ higher: 0.8 (95% CI 0.7, 0.9), p=0.002) also had protective effects, while viral failure in the last paediatric year (HR: 2.2 (95% CI 1.0, 4.8), p=0.05) and a prior AIDS diagnosis in paediatric care (HR: 3.3 (95% CI 1.7, 6.5), p<0.001) increased hazard of experiencing AIDS/mortality in adult care.

In the multivariable analysis, the following variables were selected *a priori*: sex, age at HIV diagnosis, age and calendar year at transfer date. The protective effect of UK-born participants persisted within the adjusted model (adjusted HR (aHR): 0.4 (95% CI 0.2, 0.9) vs born abroad,

p=0.03). An interaction was found between calendar year and CD4 count at date of transfer (p=0.002). In earlier calendar years, CD4 count at transfer date was not significantly associated with the AIDS/mortality outcome in adult care. However, from 2006, higher CD4 count at transfer had a significantly protective effect against AIDS/mortality post-transfer. Prior AIDS diagnosis from paediatric care remained significantly associated in the multivariable analysis (aHR: 3.2 (95% CI 1.6, 6.4), p=0.001). The other demographic characteristics, ART status at transfer date, gap between the last paediatric visit and the first adult visit, and the clinic-level characteristics did not have an association with the outcome of interest in the univariable and multivariable models (p≥0.2). Additionally, a cluster effect was not observed with any of the clinic-level factors (both p=0.50) and none of the exposure variables violated the proportional hazard's assumption (all p≥0.1).

Table 5.7: Factors associated with AIDS/mortality in adult care, results from Cox proportional hazards models (N=460)

		N (%)	Unadjusted hazard ratio (95% CI)	P-value	Adjusted hazard ratio (95% CI)	P-value
Variables selected for inclusion *a priori*						
Sex	Male	227 (49)	1.0		1	
	Female	233 (51)	1.5 (0.8, 3.1)	0.21	1.7 (0.8, 3.5)	0.15
Age at HIV diagnosis, per year increase		453 (100)	1.0 (1.0, 1.1)	0.38	1.0 (0.9, 1.1)	0.91
Age at transfer, per year increase		460 (100)	0.9 (0.8, 1.1)	0.52	1.0 (0.8, 1.2)	0.87
Demographic variables						
Ethnicity	Black	370 (82)	1.0			
	White/other	79 (18)	0.5 (0.2, 1.4)	0.18		
Place of birth	Born abroad	272 (60)	1.0		1	
	UK	179 (40)	0.4 (0.2, 1.0)	0.04	0.4 (0.2, 0.9)	0.03
Variables at the last paediatric visit						
CD4 nadir, per 100 cell/mm$_3$ increase		451 (100)	0.8 (0.6, 1.0)	0.07		
Viral failure in last year of paediatric care (>400 copies/ml)	Yes	251 (56)	2.2 (1.0, 4.8)	0.05		
	No	201 (45)	1.0			
Calendar year of transfer, per year increase		460 (100)	0.9 (0.8, 1.0)	0.002		
CD4 count, per 100 cell/mm$_3$ increase		451 (100)	0.8 (0.7, 0.9)	0.002	Test for interaction	p=0.02
Effect of CD4 count among those who transferred in 2000, per 100 cell/mm$_3$ increase					1.1 (0.9, 1.5)	0.38
Effect of CD4 count among those who transferred in 2002, per 100 cell/mm$_3$ increase					1.0 (0.8, 1.3)	0.83
Effect of CD4 count among those who transferred in 2004, per 100 cell/mm$_3$ increase					0.9 (0.8, 1.1)	0.36
Effect of CD4 count among those who transferred in 2006, per 100 cell/mm$_3$ increase					0.8 (0.7, 1.0)	0.02
Effect of CD4 count among those who transferred in 2008, per 100 cell/mm$_3$ increase					0.8 (0.6, 0.9)	0.002
Effect of CD4 count among those who transferred in 2010, per 100 cell/mm$_3$ increase					0.7 (0.5, 0.9)	0.002
Effect of CD4 count among those who transferred in 2012, per 100 cell/mm$_3$ increase					0.6 (0.5, 0.8)	0.002
Effect of CD4 count among those who transferred in 2014, per 100 cell/mm$_3$ increase					0.6 (0.5, 0.8)	0.002
Effect of CD4 count among those who transferred in 2016, per 100 cell/mm$_3$ increase					0.5 (0.3, 0.8)	0.003
Prior AIDS diagnosis	Yes	130 (28)	3.3 (1.7, 6.5)	<0.001	3.2 (1.6, 6.4)	0.001
	No	330 (72)	1.0		1	
ART status	On ART	409 (89)	1.0			
	ART naïve/off ART	51 (11)	1.1 (0.4, 2.8)	0.87		
Gap in care$_2$, per month increase		450 (100)	0.997 (0.979, 1.015)	0.72		

Table 5.8 continued on the next page

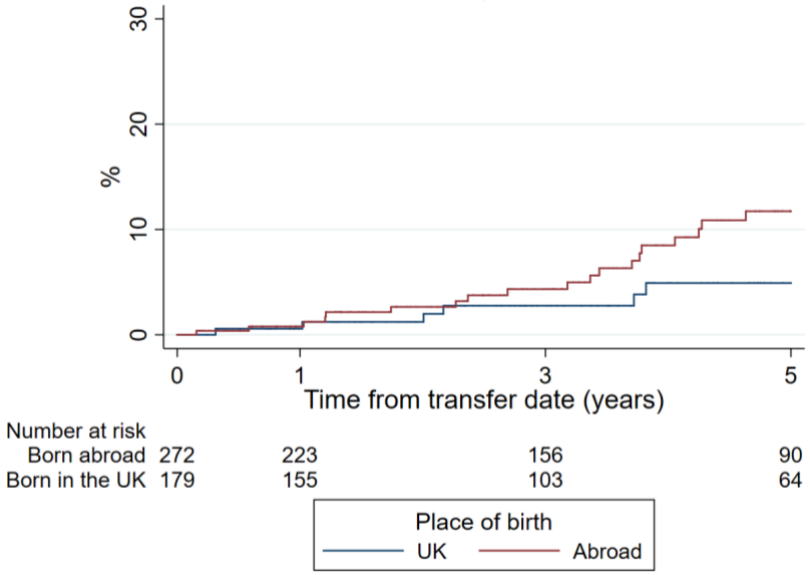
		N (%)	Unadjusted hazard ratio (95% CI)	P-value	Adjusted hazard ratio (95% CI)	P-value
Adult clinic-level variables						
Clinic type	Young persons' clinic	328 (87)	1.0			
	General adult clinic	48 (13)	0.5 (0.1, 2.0)	0.30		
Level of youth-friendliness, per 1 unit increase		376 (100)	1.2 (0.9, 1.7)	0.17		

2: gap in care between the last paediatric visit and the last adult visit

5.3.2.7. Risk of AIDS/mortality in adult care by identified risk factors

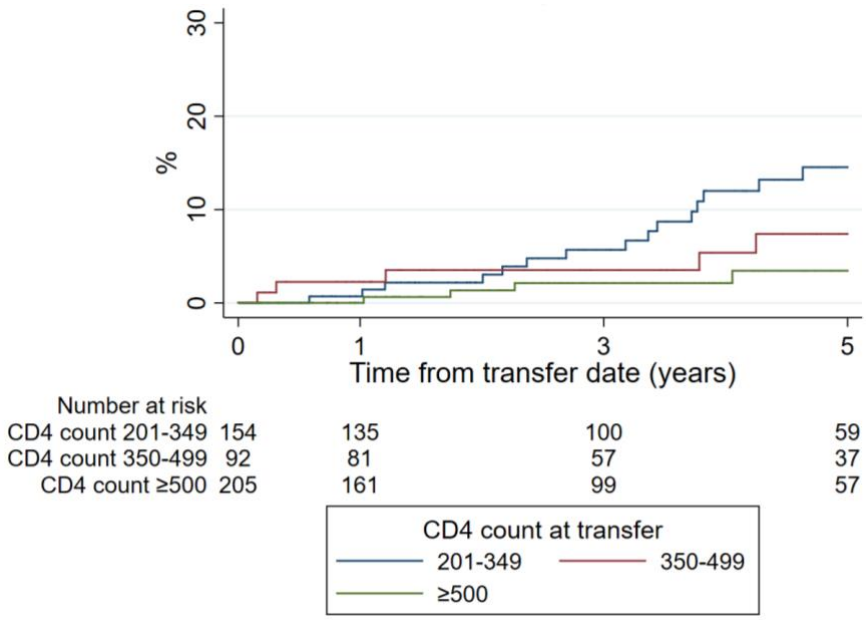
In the first year of adult follow-up, the incidence of AIDS/mortality were the same irrespective of place of birth. However, after two years of follow-up, young people who were born abroad had a higher AIDS/mortality risk compared to those born in the UK (Figure 5.4). At 3 years following transfer, those born abroad had a cumulative incidence of 4% (95% CI 2%, 8%) compared to 1% (95% CI 1%, 7%) among those born in the UK. The difference in cumulative incidence was greater by five years post-transfer, with 12% (95% CI 8%, 18%) of the born abroad group having experienced AIDS/mortality compared to only 5% (95% CI 2%, 11%) of the UK-born group by this time.

Figure 5.4: Cumulative incidence of experiencing AIDS/mortality in adult care by place of birth (p=0.04)



The cumulative risk of AIDS/mortality in adult care by CD4 count at transfer is presented in Figure 5.5. In the first year of follow-up, young people with a CD4 count between 201-349 cells/mm$_3$ at last paediatric visit had a cumulative incidence of 1% (95% CI 0%, 5%) and those with a CD4 count between 350-499 cells/mm$_3$ had an incidence of 2% (95% 1%, 9%), while those with a CD4 count ≥500 cells/mm$_3$ had no AIDS/mortality events. By three years post-transfer, those in the lowest CD4 group had a slightly higher cumulative incidence of 6% (95% 3%, 12%) compared to 4% (1%, 11%) and 2% (95% CI 1%, 6%) among those with a CD4 count between 350-499 cells/mm$_3$ and ≥500 cells/mm$_3$, respectively. By five years, the incidence was 15% (95% CI 9%, 23%), 7% (95% CI 3%, 17%) and 3% (95% CI 1%, 9%), respectively.

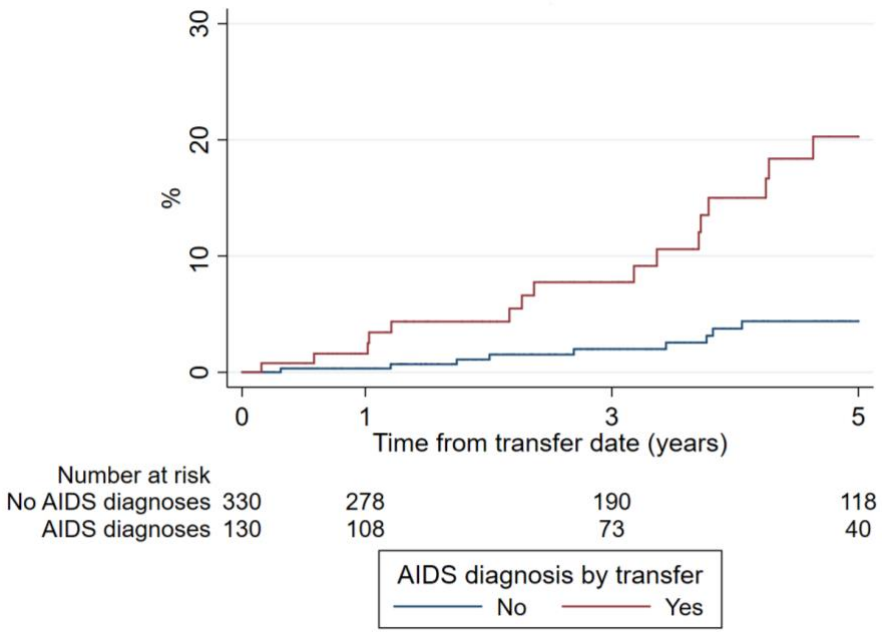
Figure 5.5: Cumulative incidence of experiencing AIDS/mortality in adult care by CD4 count at transfer date (p=0.02)*



**CD4 count groups reflect the WHO's immunological classification system*

Young people with a prior AIDS diagnosis from paediatric care had a higher risk of progressing to AIDS/mortality from the first year of follow-up to the fifth year (Figure 5.6). By three years of adult follow-up, the cumulative incidence was 2% (95% CI 1%, 5%) and 4% (95% CI 2%, 8%) for the AIDS-free group, respectively. Among the group with prior AIDS diagnosis by the transfer date, the cumulative incidence for AIDS/mortality in adult care remained significantly higher than that of the AIDS-free group at 8% (95% CI 4%, 15%) and 20% (95% CI 13%, 32%) by three and five years post-transfer, respectively.

Figure 5.6: Cumulative incidence of AIDS/mortality in adult care by prior AIDS status at transfer date (p<0.001)



5.3.2.8. Clinical characteristics at last visit in adult care among young people with HIV by AIDS status in adult care

Next the clinical characteristics at the last adult visit were compared between those who did and did not progress to AIDS in adult care (Table 5.8). Young people with AIDS events in adult care had a longer duration in adult care (6 years vs 3 years, respectively, p<0.001) and were significantly older by the last adult visit (age 27 vs 22, respectively, p<0.001) compared to the AIDS-free group. By the last visit in adult care, the overall median CD4 count was 527 cells/mm$_3$ and the majority of young people were virally suppressed (VL ≤400 copies/ml) (75%) and on ART (94%), although neither characteristic differed by AIDS status in adult care (p>0.1).

Table 5.8: Clinical characteristics of young people with HIV at last visit in adult care visit by AIDS status

Characteristics at last visit in adult care		Total (N=446)	Experienced AIDS in adult care		P-value
			Yes (N=21)	No (N=425)	
		n (%) or median [IQR]			
Duration in adult care, years (N=437)	Median [IQR]	3.3 [1.2, 6.4]	8.6 [6.6, 10.4]	3.1 [1.2, 5.9]	<0.001
	Range	0.0, 14.0	2.6, 14.0	0, 13.3	
Age, years (N=446)	Median [IQR]	21.7 [19.6, 24.5]	26.6 [24.9, 28.5]	21.5 [19.5, 24.1]	<0.001
	Range	16.3, 31.6	19.0, 30.7	16.3, 31.6	
Calendar year (N=446)	Median [IQR]	2015 [2014, 2015]	2015 [2015, 2015]	2015 [2014, 2015]	0.45
	Range	2003, 2016	2011, 2016	2003, 2016	
CD4 count, cells/mm$_3$ (N=420)	Median [IQR]	527 [326, 740]	430 [300, 690]	540 [330, 740]	0.24
	Range	4, 1567	9,1002	4, 1567	
Viral load, copies/ml (N=421)	≤400	315 (74.8)	18 (85.7)	297 (74.3)	0.31
	>400	106 (25.2)	3 (14.3)	103 (25.8)	
ART status (N=388)	On ART	363 (93.6)	19 (90.5)	344 (93.7)	0.64
	Naïve/off ART	25 (6.4)	2 (9.5)	23 (6.3)	

5.4. Disengagement from care following transfer to adult care

5.4.1. Methods

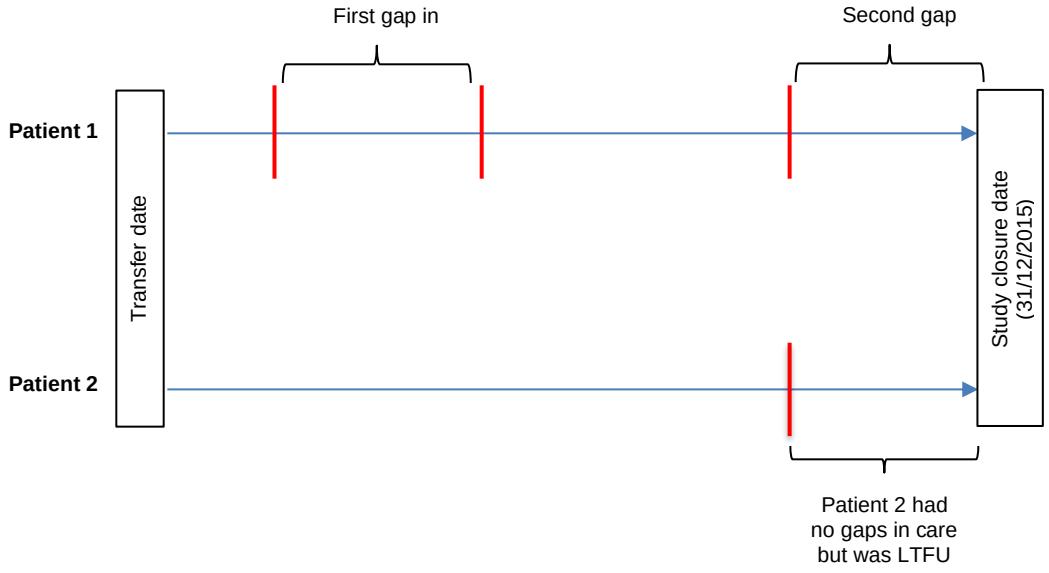
5.4.1.1. Study population

Young people with HIV who transferred to UK CHIC-participating adult clinics with ≥1 adult visit and ≥12 months potential follow-up after the first adult visit were included.

5.4.1.2. Statistical analysis

There were two outcomes of interest: gaps in adult care defined as no visit for >12 months at any point in adult care, and LTFU defined as no visit in the 12 months prior to study closure date. Young people could experience multiple gaps in care, and there was some overlap between the definitions. If a patient experienced a gap and then became LTFU, with no visit in the last 12 months of study follow-up, the LTFU period was classified as an additional gap in adult care, despite the fact that the person had not returned to care (Patient 1 in Figure 5.7). However, participants who had no prior gaps in care before becoming LTFU in adult care were classed as having no gaps in care, only becoming LTFU (Patient 2 in Figure 5.7).

Figure 5.7: Disengagement scenarios during adult follow-up of two hypothetical patients



As the UK CHIC study does not have national coverage, and individuals may move to a non-UK CHIC clinics. To assess the accuracy of the disengagement estimates, the UK CHIC data were validated with national SOPHID and HARS data from PHE. Therefore the status of young people who were identified to have experienced any type of disengagement using the UK CHIC data was validated using national SOPHID and HARS data from PHE. If a visit date was recorded in SOPHID/HARS during a period that the patient was categorised as 'disengaged from care' in the UK CHIC dataset, they would be reclassified as not disengaged from care during that period. For example, if UK CHIC data suggested that a participant was out of care for the whole of 2011, but a visit to another HIV clinic during 2011 was recorded in SOPHID or HARS, this patient was classed as being in care in 2011. This validation technique applied to gaps in care and LTFU outcomes.

Demographic and clinical characteristics at last paediatric visit, using UK CHIC data, were compared by the two types of disengagement from adult care. The crude rates of gaps in care and LTFU events were estimated and were stratified by the following demographic characteristics: sex, ethnicity (black vs white), place of birth (UK vs born abroad), current age in adult care and calendar year of transfer. Age was originally categorised as ≤19 years, 20 to 24 years, and ≥25 years to reflect adolescent, young adult and adult age groups, as defined by the WHO (WHO, 2011). However, due to the small number of participants with events in the oldest age group (i.e. ≥25 years) for both disengagement outcomes, age was subsequently grouped as <19 years, 20-22 years and ≥23 years.

As the gaps in care outcome consisted of count data (i.e. 1, 2, 3 gaps in care etc.), Poisson regression was used to investigate factors associated with more gaps in adult care. The Poisson assumption of events occurring at constant rate over time was checked by comparing the rate of the first gap occurring vs the rate of the second gap occurring. If the rate was not constant, the gaps in care outcome was turned into a binary variable (any gaps vs no gaps in care). In the Poisson model, the optimal functional form was identified by plotting functional polynomials, if a linear relationship was detected, then the exposure variable was kept in its continuous form. If non-linearity was detected, the variable was categorised. In the univariable analysis, variables associated with gaps in care ($p<0.2$) were considered in the multivariable analysis in addition to the *a priori* variables. Variables with the highest p-values (≥0.1) were sequentially removed from the multivariable model until all remaining variables had a p-value <0.1. The following variables, selected *a priori*, were included in all models, regardless of statistical significance: sex, and age and calendar year at the transfer date. The effect of age at transfer rather than current age was explored in order to give insight into whether there was an optimal age for young people to transfer to adult care. Factors considered as potential risk factors for LTFU in adult care included the following individual-level factors:

- place of birth (UK vs abroad),
- ethnicity (black vs white/other),
- nadir CD4 count by transfer,
- CD4 count at transfer,
- viral failure in the last year of paediatric care (≥1 VL >400 copies/ml),
- ART status (on ART vs ART naïve/off ART) at transfer,
- prior AIDS events in paediatric care,
- duration in paediatric follow-up,
- any prior gaps in paediatric care (no visit for >12 months in paediatric care), and
- gap in care between the last paediatric visit and first adult visit.

The following clinic-level factors were also considered as potential risk factors:

- adult clinic's level of youth-friendliness, and
- clinic type.

As with the AIDS/mortality analysis, the potential for cluster effects of clinic-level variables were explored by fitting a frailty model. If a cluster effect was detected, the frailty model remained in the multivariable model.

With the LTFU outcome, time to event analysis was carried out. Time at risk began from the date of transfer (last visit in paediatric care), until the earliest of death date or last visit date in adult care. Young people were not at risk during periods of gaps in care and the LTFU periods, therefore person-time was not contributed during these periods. Risk factors for LTFU were investigated using Cox proportional hazards models and the cumulative incidence of LTFU was calculated using Kaplan-Meier methods. For the Cox regression model with LTFU as the outcome, the same model building approach and potential risk factors were explored as detailed for the gaps in care analysis. The optimal functional form of the continuous exposure variables were determined using the same methods as described for the AIDS/mortality analysis (Section 5.3.1.2. Statistical analysis).

By the last adult visit, characteristics were compared by the two type of disengagement from adult care.

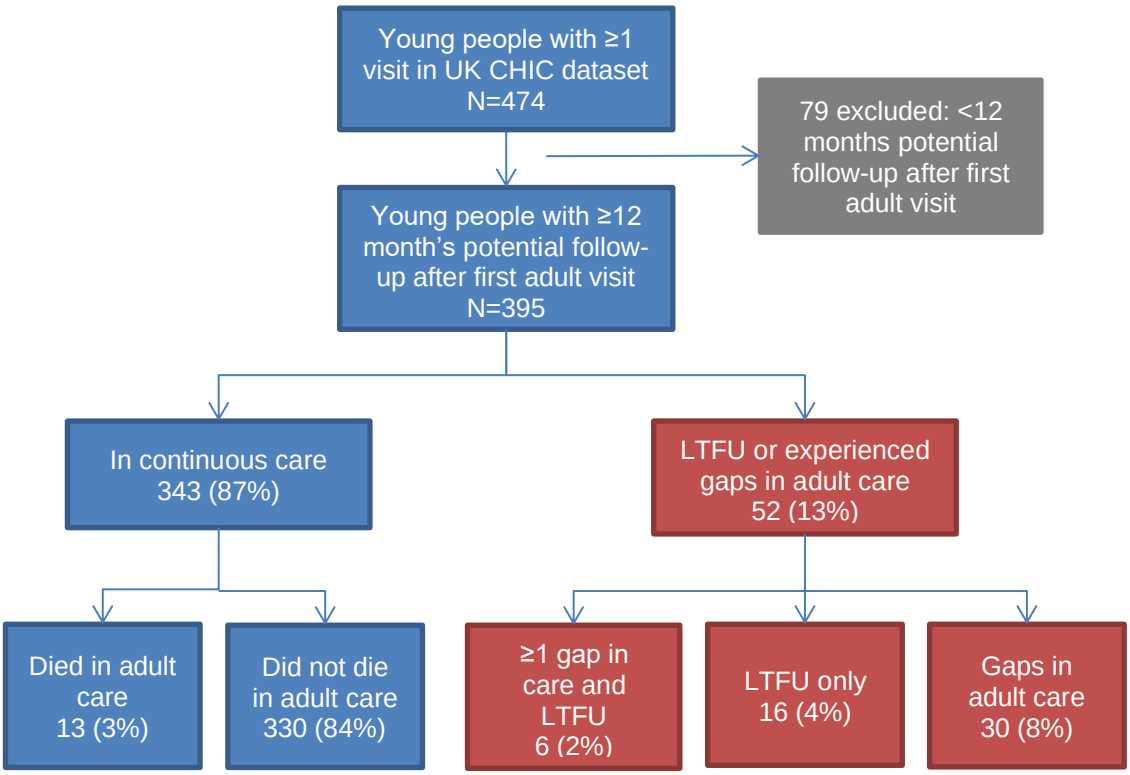
In sensitivity analyses, the risk factors for LTFU was investigated after redefining LTFU as no visit in the two years prior to the UK CHIC database closure date. The same statistical methods as described previously were used to identify risk factors.

5.4.2. Results

5.4.2.1. Demographic characteristics by type of disengagement from adult care

Of 474 young people with ≥1 visit at a UK CHIC-participating clinic, 395 (87%) had ≥12 months potential follow-up after their first adult visit (i.e. duration between first adult visit and UK CHIC study closure date) and included in the analysis (Figure 5.8). Using the UK CHIC data, 212 (54%) of young people with ≥12 months potential adult follow-up met the disengagement definition, of whom 102 (26%) had ≥1 gap in care and 146 (37%) were LTFU. After validating both disengagement outcomes using SOPHID/HARS data, only 52 (13%) had experienced either type of disengagement from adult care, while the remaining 343 (87%) were in continuous care. All young people who died following transfer date were in continuous care prior to date of death. Of the 52 young people who experienced any disengagement from adult care, 16 (4%) were LTFU prior to study closure date, 30 (8%) experienced ≥1 gap in adult care (defined as no visit >12 months) and 6 (2%) experienced both types of disengagement from care. Of the 36 young people who experienced any gaps in adult care, 23 had one gap in care and 13 had two gaps in care. The median duration of a gap in care or LTFU period were 1.5 years and 2.8 years, respectively.

Figure 5.8: Young people with ≥1 adult visit at a UK CHIC-participating clinic who experienced different types of disengagement from adult care



5.4.2.2. Clinical characteristics at last visit in paediatric care by type of disengagement in adult care

Table 5.9 presents the demographic and clinical characteristics at last visit in paediatric care among young people with ≥12 months potential follow-up after their *first* adult visit (N=395). Characteristics were compared by each type of disengagement from adult care. Overall, young people who experienced gaps in care or were LTFU had a number of different demographic and clinical characteristics at last paediatric visit to those engaged in adult care. Those with gaps in care had a higher proportion of males compared to those without gaps in care (64% vs 46%, p=0.04). There was no difference in age at transfer, place of birth and ethnicity between the groups with and without gaps in adult care (p>0.1). Young people with gaps in adult care had an earlier calendar year of birth (1990 vs 1993, p<0.001) and year of transfer to adult care (2008 vs 2010, p<0.001) compared to those who had no gaps in care. Immunological, virological and treatment status at last visit in paediatric care did not differ between those with and without gaps in adult care (p>0.1). Likewise, duration in paediatric follow-up and history of gaps in paediatric care did not differ by gaps in adult care status. However, young people with gaps in adult care had a lower proportion with AIDS diagnoses by the last paediatric visit compared to those without gaps in care (14% vs 30%, p=0.05).

Similar to young people who experienced gaps in adult care, those who were LTFU in adult care were born in earlier calendar years and transferred to adult care in earlier calendar years (p=0.008 and 0.007, respectively). They were also more likely to be born abroad (85% vs 57%, p=0.02) and were followed up in paediatric care for a shorter duration than those not

LTFU in adult care (median duration 8 years vs 12 years, p=0.02). However, there were no other significant difference in any of the other demographic characteristics (sex, age at transfer date and ethnicity) or clinical characteristics at last paediatric visit (CD4 count, viral load, ART and AIDS status).

Table 5.9: Demographic characteristics of young people with HIV at last paediatric visit by type of disengagement from adult care (N=395)

Characteristics at last visit in paediatric care		Total N=395	No gaps in care N=359	≥1 gaps in care N=36	P-value	Not LTFU N=373	LTFU N=22	P-value
		N (%) or median [IQR]						
Sex	Male	189 (47.9)	166 (46.2)	23 (63.9)	0.04	178 (47.7)	11 (50.0)	0.84
	Female	206 (52.2)	193 (53.8)	13 (36.1)		195 (52.3)	11 (50.0)	
Age, years	Median	18 [17, 18]	18 [17, 18]	17 [16, 18]	0.17	18 [17, 18]	17 [16, 18]	1.00
	Range	7, 22	7, 22	11, 21		9, 22	7, 20	
Place of birth	UK	159 (41.2)	148 (42.1)	11 (32.4)	0.27	156 (42.6)	3 (15.0)	0.02
	Abroad	227 (58.8)	204 (58.0)	23 (67.7)		210 (57.4)	17 (85.0)	
Ethnicity	White/other	68 (17.6)	63 (18.0)	5 (14.3)	0.82	65 (17.9)	3 (13.6)	0.78
	Black	318 (82.4)	288 (82.1)	30 (85.7)		299 (82.1)	19 (86.4)	
Year of birth	Median	1992 [1990, 1994]	1993 [1990, 1995]	1990 [1988, 1992]	<0.001	1993 [1990, 1994]	1991 [1988, 1992]	0.008
	Range	1982, 1998	1982, 1998	1984, 1994		1982, 1998	1985, 1997	
Duration in paediatric care, years	Median	12 [7, 15]	11 [7, 16]	12 [6, 14]	0.45	12 [7, 16]	8 [3, 13]	0.02
	Range	0, 22	0, 22	2, 19		0, 22	1, 16	
Previous gaps in paediatric care[1]	Yes	128 (32.4)	116 (32.3)	12 (33.3)	0.90	121 (32.4)	7 (31.8)	0.95
	No	267 (67.6)	243 (67.7)	24 (66.7)		252 (67.6)	15 (68.2)	
Calendar year	Median	2010 [2007, 2012]	2010 [2007, 2012]	2008 [2004, 2009]	<0.001	2010 [2007, 2012]	2008 [2005, 2010]	0.007
	Range	1991, 2014	1991, 2014	1999, 2012		1991, 2013	1999, 2014	
CD4 nadir, cells/mm^3	Median	193 [85, 290]	191 [82, 289]	228 [139, 307]	0.30	193 [83, 290]	184 [91, 304]	0.93
	Range	0, 700	0, 700	2, 530		0, 700	0, 500	
CD4 count, cells/mm^3	<200	65 (16.8)	62 (17.7)	3 (8.3)	0.11	62 (16.9)	3 (15.0)	0.82
	≥200	321 (83.2)	228 (82.3)	33 (91.7)		304 (83.1)	17 (85.0)	

Table 5.9 continued on the next page

Characteristics at last visit in paediatric care		Total N=395	No gaps in care N=359	≥1 gaps in care N=36	P-value	Not LTFU N=373	LTFU N=22	P-value
		N (%) or median [IQR]						
Viral load, copies/ml	≤400	166 (42.9)	155 (44.2)	11 (30.6)	0.12	156 (42.4)	10 (52.6)	0.38
	>400	221 (57.1)	196 (55.8)	25 (69.4)		212 (57.6)	9 (47.4)	
AIDS events	Yes	111 (28.1)	106 (29.5)	5 (13.9)	0.05	107 (28.7)	4 (18.2)	0.29
	No	284 (71.9)	253 (70.5)	31 (13.9)		266 (71.3)	18 (81.8)	
On ART	Yes	340 (87.2)	312 (88.1)	28 (77.8)	0.11	323 (87.3)	17 (85.0)	0.73
	No	50 (12.8)	42 (11.9)	8 (22.2)		47 (12.7)	3 (15.0)	

5.4.2.3. Rates of gaps in care and LTFU in adult care

Table 5.11 presents the crude rates of gaps in care and LTFU in adult care by sex, ethnicity, place of birth, current age in adult care and calendar year of transfer. The overall crude rate of gaps in care and LTFU 1.8 (95% CI 1.3, 2.5) per 100 person-years and 1.1 (95% CI 0.7, 1.7) per 100 person-years, respectively.

With gaps in care as the outcome of interest, males had double the rate of females (crude rate 2.5 (95% CI 1.6, 3.7) vs 1.2 (95% CI 0.7, 2.1), per 100 person-years, respectively). Young people of black ethnicity also had a higher rate of gaps in care compared to those of non-black ethnicities (crude rate 1.9 (95% CI 1.3, 2.7) vs 1.3 (95% CI 0.5, 3.1) per 100 person-years, respectively). Young people born abroad experienced 1.9 (95% CI 1.6, 2.9) gaps in care per 100 person-years compared to 1.5 (95% CI 0.8, 2.7) per 100 person-years in those born in the UK. The crude rate was 0.1 (95% CI 0.0, 0.8) among those aged ≤19 years in adult care, 2.0 (95% CI 1.2, 3.1) in those aged 20 to 24 years and increased by five times to 9.7 (95% CI 6.0, 15.6) for those aged ≥25 years. The crude rate did not differ by calendar year of transfer, those who transferred ≤2008 or 2009 to 2012 had a rate of 2.0 (95% CI 1.3, 3.1) and 1.8 (1.0, 3.1) per 100 person-years, respectively. There were no gaps in care among the cohort who transferred after 2012.

The crude rate for LTFU in adult care was similar by sex and ethnicity (Table 5.11). Those born abroad had a higher LTFU rate of 1.4 (95% CI 0.9, 2.3) per 100 person-years compared to young people born in the UK with 0.4 (95% CI 0.1, 1.2) per 100 person-years. Young people aged 20 to 24 years in adult care had a higher LTFU rate at 1.5 (95% CI 0.9, 2.6) per 100 person-years compared to young people aged ≤19 years (crude rate: 0.7 (95% CI 0.3, 1.5) per 100 person-years) and those aged above 24 years in adult care (crude rate: 1.1 (95% CI 0.3, 4.6) per 100 person-years). Young people who transferred in the most recent years (2013-2015) had a higher LTFU rate (1.4 (95% CI 0.4, 5.7) per 100 person-years) compared to a LTFU rate of 1.2 (95% CI 0.7, 2.0) and 0.9 (95% CI 0.4, 5.7) among young people who transferred ≤2008 and during 2009 to 2012, respectively.

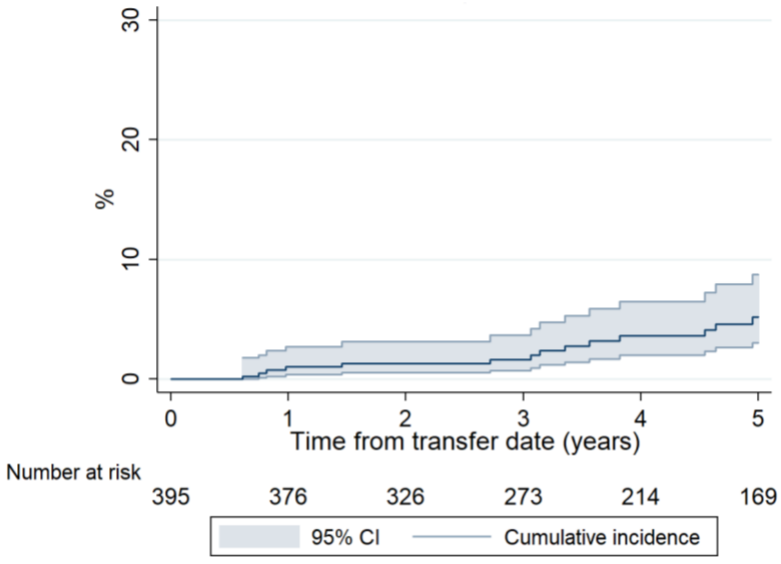
Table 5.10: Rates of gaps in adult care per 100 person-years by demographic characteristics among young people with HIV (N=395)

	Gaps in care outcome			LTFU outcome		
	No. of events	**Person-years**	**Rate (95% CI)**	**No. of events**	**Person-years**	**Rate (95% CI)**
Overall	36	1993.7	1.8 (1.3, 2.5)	22	2002.4	1.1 (0.7, 1.7)
Sex						
Female	13	1056.1	1.2 (0.7, 2.1)	11	1061.2	1.0 (0.6, 2.1)
Male	23	937.6	2.5 (1.6, 3.7)	11	941.2	1.2 (0.6, 1.9)
Ethnicity						
White/other	5	387.3	1.3 (0.5, 3.1)	3	388.3	0.8 (0.2, 2.4)
Black	30	1565.3	1.9 (1.3, 2.7)	19	1572.6	1.2 (0.8, 1.9)
Place of birth						
UK	11	747.0	1.5 (0.8, 2.7)	3	749.4	0.4 (0.1, 1.2)
Born abroad	23	1201.9	1.9 (1.3, 2.9)	17	1207.8	1.4 (0.9, 2.3)
Current age, years						
≤19	1	901.8	0.1 (0.0, 0.8)	6	905.3	0.7 (0.3, 1.5)
20-24	18	916.2	2.0 (1.2, 3.1)	14	921.4	1.5 (0.9, 2.6)
≥25	17	175.7	9.7 (6.0, 15.6)	2	175.7	1.1 (0.3, 4.6)
Calendar year of transfer						
≤2008	20	1016.3	2.0 (1.3, 3.1)	13	1113.1	1.2 (0.7, 2.0)
2009-2012	13	728.1	1.8 (1.0, 3.1)	7	747.1	0.9 (0.4, 2.0)
2013-2015	0	134.9	0.0 (0.0, 0.0)	2	141.5	1.4 (0.4, 5.7)

5.4.2.4. Risk of LTFU in adult care

The cumulative incidence of LTFU in adult care is presented in Figure 5.9. At one, three and five years following transfer the cumulative incidence of LTFU was 1% (95% CI 0.4%, 3%), 2% (95% CI 1%, 4%) and 5% (95% 3%, 9%), respectively.

Figure 5.9: Cumulative incidence of becoming LTFU in adult care (N=395)



5.4.2.5. Factors associated with gaps in adult care

Table 5.12 presents the factors associated with any gaps in adult care following the transfer date using a Poisson regression model. The rates of gaps in care occurring was not constant over time, therefore, the gaps in care outcome was converted into a binary outcome: experiencing no gaps vs any.

In the univariable analysis, females were 50% less likely to experience gaps in care compared to males (rate ratio (RR):0.5, 95% CI 0.2, 1.0, p=0.04). None of the other demographic characteristics (including age and calendar year of transfer, ethnicity and place of birth) as well as follow-up duration in paediatric care and previous gaps in paediatric care were significantly associated with the gaps in care (p>0.2). Similarly, CD4 nadir, CD4 count and viral failure in the year prior to transfer date were not associated with gaps in adult care (p>0.2). However, young people were at a lower risk of experiencing gaps in care if they had a prior AIDS diagnosis in paediatric care (RR:0.4, 95% CI 0.2, 1.1, p=0.07). The ART status, duration of linkage to adult care, clinic type and level of youth-friendliness of the adult clinic young people attended were not associated with the outcome of interest (p>0.2).

In the multivariable analysis, being female continued to have a strong protective association with gaps in adult care (adjusted RR (aRR):0.5, 95% CI 0.2, 0.9, p=0.03). Young people with previous AIDS events from paediatric care still had 60% reduction in risk of gaps in adult care (aRR:0.4, 95% CI 0.1, 1.0, p=0.05) compared to those without AIDS diagnosis in paediatric care. No other variables were associated with gaps in care.

5.4.2.6. Factors associated with LTFU status following transfer to adult care

Table 5.13 presents the association between various factors and LTFU in adult care using Cox proportional hazard models. In the univariable analysis, young people who were born in the UK had a 70% lower risk (HR: 0.3, 95% CI 0.1, 1.0, p=0.06) of becoming LTFU compared to young people born abroad. The type of adult clinic was not included in the regression model as no events occurred among those who transferred to a general adult clinic. All other demographic, clinical and clinic-level characteristics had no association with the outcome of interest (p>0.1). After adjusting for *a priori* variables, no variables, including place of birth, were significantly associated with LTFU in adult care. No cluster effect was observed with any of the clinic-level factors (both p>0.3) and none of the exposure variables violated the proportional hazard's assumption (all p≥0.2).

Table 5.11: Factors associated with any gaps in adult care (gaps of care of >12 months), results from Poisson model (N=395)

		N (%)	Unadjusted rate ratio (95% CI)	P-value	Adjusted rate ratio (95% CI)	P-value
Variables selected for inclusion *a priori*						
Sex	Male	189 (48)	1		1	
	Female	206 (52)	0.5 (0.2, 1.0)	0.04	0.5 (0.2, 0.9)	0.03
Age at transfer, per year increase		395 (100)	1.0 (0.9, 1.2)	0.71	1.0 (0.8, 1.2)	0.95
Calendar year of transfer, per year increase		395 (100)	1.4 (0.8, 2.6)	0.22	1.4 (0.8, 2.6)	0.25
Demographic variables						
Ethnicity	Black	318 (82)	1			
	White/other	68 (18)	0.7 (0.3, 1.7)	0.40		
Place of birth	Born Abroad	227 (59)	1			
	UK	159 (41)	0.8 (0.4, 1.6)	0.48		
Variables at the last paediatric visit						
Duration in paediatric care, years		380 (100)	1.0 (0.9, 1.1)	0.88		
Previous gaps in paediatric care[1]	Yes	128 (32)	0.9 (0.4, 1.7)	0.70		
	No	267 (68)	1			
CD4 nadir, per 100 cell/mm^3 increase		386 (100)	1.1 (0.9, 1.2)	0.56		
CD4 count, per 100 cell/mm^3 increase		386 (100)	1.1 (1.0, 1.2)	0.19		
Viral failure in last paediatric year (>400 copies/ml)	Yes	221 (57)		0.31		
	No	166 (43)	1			
AIDS events	Yes	111 (28)	0.4 (0.2, 1.1)	0.07	0.4 (0.1, 1.0)	0.05
	No	284 (72)	1		1	
ART status	On ART	340 (87)	1			
	ART naïve/Off ART	50 (13)	1.6 (0.7, 3.6)	0.22		
Gap between paediatric and adult care[2], per month increase		390 (100)	1.0 (1.0, 1.0)	0.31		
Adult clinic-level variables						
Clinic type	Young persons' clinic	278 (87)	1			
	General adult clinic	42 (13)	1.3 (0.5, 3.5)	0.56		
Level of youth-friendliness, per 1 unit increase		320 (100)	1.1 (0.9, 1.4)	0.48		

1: gaps in care defined as no visit for >12 months in paediatric care; 2 duration between the last paediatric visit and the first adult visit

Table 5.12: Factors associated with LTFU (no visit for >12 months prior to study closure), results from Cox proportional hazards models (N=395)

		N (%)	Unadjusted hazard ratio (95% CI)	P-value	Adjusted hazard ratio (95% CI)	P-value
Variables selected for inclusion *a priori*						
Sex	Male	189 (48)	1		1	
	Female	206 (52)	0.9 (0.4, 2.0)	0.72	1.0 (0.4, 2.7)	0.95
Age at transfer, per year increase		395 (100)	0.8 (0.6, 1.2)	0.34	0.8 (0.5, 1.2)	0.24
Calendar year of transfer, per year increase		395 (100)	1.0 (0.8, 1.2)	0.81	1.0 (0.9, 1.3)	0.63
Demographic variables						
Ethnicity	Black	318 (82)	1			
	White/other	68 (18)	0.6 (0.2, 2.1)	0.42		
Place of birth	Born Abroad	227 (59)	1			
	UK	159 (41)	0.3 (0.1, 1.0)	0.06		
Variables at the last paediatric visit						
Duration in paediatric care, years		380 (100)	1.1 (1.0, 1.2)	0.15		
Previous gaps in paediatric care[1]	Yes	128 (32)	0.8 (0.3, 1.9)	0.60		
	No	267 (68)	1			
CD4 nadir, per 100 cell/mm^3 increase		386 (100)	1.0 (0.7, 1.3)	0.79		
CD4 count, per 100 cell/mm^3 increase		386 (100)	1.0 (0.9, 1.2)	0.85		
Viral failure in last paediatric year (>400 copies/ml)	Yes	221 (57)	0.5 (0.2, 1.3)	0.15		
	No	166 (43)	1			
AIDS events	Yes	111 (28)	0.6 (0.2, 1.7)	0.30		
	No	284 (72)	1			
ART status	On ART	340 (87)	1			
	ART naïve/Off ART	50 (13)	1.0 (0.3, 3.5)	0.98		
Gap between paediatric and adult care[2], per month increase		390 (100)	1.002 (0.987, 1.017)	0.76		
Adult clinic-level characteristics						
Clinic type	Young persons' clinic	278 (87)	-			
	General adult clinic	42 (13)	-			
Level of youth-friendliness, per 1 unit increase		320 (100)	1.3 (0.8, 2.2)	0.28		

[1]: gaps in care defined as no visit for >12 months in paediatric care; [2]: duration between the last paediatric visit and the first adult visit

5.4.2.7. Clinical characteristics at last visit in adult care by type of disengagement in adult care

Table 5.13 presents the characteristics at last visit in adult care by type of disengagement from care. Young people with any gaps in adult care had a significantly longer median follow-up duration in adult care (duration 6 vs 4 years, p<0.001) and older at the last visit (age 25 vs 22 years, p<0.001) compared to those without gaps in care. There was no significant difference in type of adult clinic between the two groups (p=0.37).

Overall, 17% had a CD4 count <200 cells/mm_3, 28% were virally unsuppressed (VL >400 copies/ml) and 13 had died in adult care. As previously mentioned, all deaths occurred among young people who did not previously have gaps in adult care or LTFU prior to study closure date, and the clinical characteristics were comparable across all groups (p>0.2).

5.4.2.8. Sensitivity analysis: factors associated with any LTFU in adult care (no visit for >24 months in adult care)

In the sensitivity analysis, LTFU was redefined as no visit in the last 24 months prior to study closure date. The cumulative incidence of the LTFU was 1% (95% CI 0%, 3%), 1% (95% CI 0%, 3%) and 3% (95% CI 2%, 7%) by one, three and five years following transfer, respectively (data not shown).

Table 5.14 presents the factors associated with the redefined LTFU outcome in adult care, using Cox proportional hazards models. In the univariable analysis, only duration in paediatric care had an association with the LTFU outcome (HR: 0.9 (95% CI 0.7, 1.0) per year increase, p=0.04). In the multivariable analysis, after adjusting for sex, age and calendar year at transfer date, longer duration of paediatric follow-up still had a protective effect against LTFU (aHR: 0.8 (95% CI 0.7, 1.0) per year increase, p=0.04). Place of birth and adult clinic type variables were not included in the regression model as there were no LTFU events among those born in the UK and transferred to general adult clinics.

Table 5.13: Clinical characteristics of young people with HIV at last adult visit by type of disengagement from adult care (N=395)

Characteristics at last visit in adult care		Total N=395	No gaps in care N=359	≥1 gaps in care N=36	P-value	Not LTFU N=373	LTFU N=22	P-value
		N (%) or median (IQR)						
Duration between last paediatric visit and first adult visit, months (N=390)	Median	3 [2, 6]	3 [2, 6]	5 [1, 14]	0.11	3 [2, 6]	4 [2, 14]	0.23
	Range	0, 159	0, 159	0, 97		0, 128	1, 159	
Duration in adult care, years (N=395)	Median	4 [2, 6]	4 [2, 6]	6 [5, 8]	<0.001	4 [2, 6]	3 [1, 6]	0.22
	Range	0, 14	1, 14	1, 13		0, 14	0, 10	
Adult clinic type (N=320)	Young persons' clinic	278 (86.9)	256 (87.4)	22 (81.5)	0.37	267 (86.4)	11 (100.0)	0.37
	General adult clinic	42 (13.1)	37 (12.6)	5 (18.5)		42 (13.6)	0 (0.0)	
Age, years (N=395)	Median	22 [20, 25]	22 [20, 24]	25 [23, 26]	<0.001	22 [20, 25]	21 [17, 23]	0.14
	Range	16, 32	16, 32	19, 31		16, 32	17, 29	
CD4 count, cells/mm3 (N=379)	<200	66 (17.4)	57 (16.6)	9 (25.0)	0.25	63 (17.5)	3 (15.8)	1.00
	≥200	313 (82.6)	286 (83.4)	27 (75.0)		297 (82.5)	16 (84.2)	
Viral load, copies/ml (N=384)	≤400	277 (72.1)	251 (72.1)	26 (72.2)	0.99	265 (72.8)	12 (60.0)	0.21
	>400	107 (27.9)	97 (27.9)	10 (27.8)		99 (27.2)	8 (40.0)	
Death in adult care	Yes	13 (3.3)	13 (3.6)	0 (0.0)	0.62	13 (3.5)	0 (0.0)	1.00
	No	382 (96.7)	346 (96.4)	36 (100.0)		360 (96.5)	22 (100.0)	

Table 5.14: Factors associated with LTFU (no visit for >24 months prior to study closure), results from Cox proportional hazards models (N=339)

		N (%)	Unadjusted hazard ratio (95% CI)	P-value	Adjusted hazard ratio (95% CI)	P-value
Variables selected for inclusion *a priori*						
Sex	Male	161 (48)	1		1	
	Female	178 (53)	0.7 (0.2, 2.7)	0.63	0.9 (0.2, 3.6)	0.87
Age at transfer, per year increase		329 (100)	0.8 (0.5, 1.4)	0.48	1.1 (0.6, 2.0)	0.74
Calendar year of transfer, per year increase		323 (100)	1.0 (0.8, 1.2)	0.86	1.0 (0.8, 1.3)	0.78
Demographic variables						
Ethnicity	Black	271 (82)	1			
	White/other	61 (18)	0.5 (0.1, 4.3)	0.55		
Place of birth	Born Abroad	198 (60)	-			
	UK	134 (40)	-			
Variables at the last paediatric visit						
Duration in paediatric care, per year increase		326 (100)	0.9 (0.7, 1.0)	0.04	0.8 (0.7, 1.0)	0.04
Previous gaps in paediatric care[1]	Yes	109 (32)	0.8 (0.3, 2.1)	0.59		
	No	230 (68)	1			
CD4 nadir, per 100 cell/mm^3 increase		330 (100)	0.9 (0.6, 1.4)	0.76		
CD4 count, per 100 cell/mm^3 increase		330 (100)	1.1 (0.9, 1.4)	0.36		
Viral failure in last paediatric year (>400 copies/ml)	Yes	193 (58)	0.3 (0.1, 1.3)	0.12		
	No	138 (42)	1			
AIDS events	Yes	93 (27)	0.8 (0.2, 3.6)	0.73		
	No	246 (73)	1			
ART status	On ART	289 (87)	1			
	ART naïve/Off ART	45 (13)	1.4 (0.2, 11.1)	0.78		
Gap in care[2], per month increase		334 (100)	0.999 (0.961, 1.039)	0.97		
Adult clinic-level variables						
Clinic type	Young persons' clinic	230 (85)	-			
	General adult clinic	39 (15)	-			
Level of youth-friendliness, per 1 unit increase		269 (100.0)	2.2 (0.6, 8.0)	0.23		

1: gaps in care defined as no visit for >12 months in paediatric care; 2: duration between the last paediatric visit and the first adult visit

5.5. Discussion

In this chapter, I described the mortality and disengagement from adult care among young people who transferred to UK CHIC-participating clinics. While my findings suggest similar demographic groups of young people transferred to UK CHIC and non-UK CHIC clinics, young people with poorer health outcomes at transfer date were more likely to be referred to a UK CHIC clinic which may introduce a selection bias into my study. Among the UK CHIC cohort, my study findings highlight the clinical complexities of this group with one in eleven progressing to a new AIDS event or dying by five years following transfer date. Young people were at higher risk for AIDS/mortality in adult care if they were born abroad or had prior AIDS diagnosis in paediatric care. There was also evidence of an interaction between calendar year of transfer and CD4 count at transfer date, where low CD4 count was associated with an increased risk, but only in later calendar years.

This chapter also explored two measures of disengagement from care: gaps in care and LTFU status following transfer. Overall, one and two young people experienced any gaps in care or became LTFU, respectively, per 100 person-years in adult care. Those with gaps in care were more likely to be males, and without prior AIDS events from paediatric care, while none of the explored characteristics were associated with LTFU in adult care.

5.5.1. Findings interpretation and comparison to wider literature

5.5.1.1. AIDS/mortality following transfer to adult care

In my study, I investigated the risk factors of AIDS/mortality as a composite outcome due to the low number of mortality events, which would have drastically reduced the statistical power needed to detect possible associations in an adjusted model. Ideally, I would have investigated the risk factors of mortality separately from AIDS events but was limited by the small number of events. Six other post-transfer studies have previously investigated mortality as a separate outcome, but have only reported descriptive findings with no analysis of the risk factors.

Among my UK CHIC cohort of 474 young people, 37 (8%) progressed to AIDS or mortality in adult care, including 14 (3%) who died. The deaths mostly occurred in earlier calendar years (median year of death: 2010), possibly reflecting improvements in HIV treatment and management which has led to reduced morbidity and mortality with time [59]. Additionally, in earlier calendar years, treatment guidelines did not recommend immediate initiation of ART, universally. This was reflected in the late median age at ART initiation (10 years) among the deceased participants. Nonetheless, similarly low proportions of deaths were reported by other post-transfer studies from across Europe and North America (0-7%). Only a single-site study of 24 young people from North Italy reported 0% deaths, although, this study population was unique with all adhering to treatment and achieving viral suppression (VL <50 copies/ml) at the most recent adult visit [130].

The overall rate of AIDS/mortality in my study was 1.8 (95% CI 1.3, 2.5) per 100 person-years and the rate for mortality only was 0.6 (95% 0.4, 1.1) per 100 person-years. Another study of 735 young people with PHIV in New York City reported a considerably higher mortality rate of 5.6 (95% CI 4.1, 7.6) per 100 person-years at 12 months post-transfer to adult care. Although, the

majority of deaths in that cohort occurred within the first 6 months following transfer date, while young people from my cohort died after a median of three years of adult follow-up. In my study, the AIDS/mortality and mortality rates were similar across various demographic characteristics including place of birth and calendar year of transfer. There were some differences in crude mortality rates by current age in adult care, although confidence intervals overlapped. Younger participants (aged ≤19 years) had a lower mortality rate (0.3 (0.1, 1.1) per 100 person-years) compared to those aged 20 to 24 years (0.9 (95% CI 0.4, 1.8) per 100 person-years) with overlapping confidence intervals. No deaths occurred above the age of 24 years, although the person-years in this group was considerably smaller than the younger two age groups. Nonetheless, previous studies have described young people's brains to reach full maturation by the age of 25 years thus suggesting increased maturity and less risk-taking behaviour that could lead to poorer health outcomes [194–196]. Similar increasing mortality trend with age up until the age of 24 years was reported by another study of 248 young people with PHIV attending adult clinics in London [78]. This study found a mortality rate of 0.5 (95% CI 0.2, 1.3) among young people aged 16-20 years which rose to 0.9 (95% CI 0.3, 2.3) for 21-24 year olds.

To put these findings into context, the mortality rate for young people in the UK's general population for males and females was 0.03 and 0.02 among ≤19 year olds and increased to 0.05 and 0.02 among 20 to 24 year olds and 0.06 and 0.03 among 25 to 29 year olds, respectively [197]. The mortality rates in my study were more than ten times higher than the general population, thus highlighting my study's unique and vulnerable population, despite wide access to ART.

In the unadjusted and adjusted model for AIDS/mortality, there was no significant age effect. Despite comparable crude rates for AIDS/mortality by place of birth, in the adjusted model, young people born abroad had double the hazard of progressing to AIDS/mortality compared to those born in the UK. This finding is in line with other European studies that described adult migrants to be more susceptible to poorer HIV outcomes and HIV-related deaths in comparison to the native populations [198–201]. The increased risks for poorer health outcomes and mortality among migrants may reflect barriers to HIV care, including stigma, social isolation, and language, cultural and legal barriers. Although, many of these studies consisted of older adults who may be more mobile compared to my study population which largely consisted of younger migrants who entered healthcare in the UK at a younger age and have since engaged in care for several years. A large pooled European paediatric HIV study described migrant children to have a higher but non-significant risk of AIDS/mortality compared to non-migrant children (adjusted HR=1.45, 95% CI 0.9, 2.3, p=0.13) [202]. Although, this study differed from mine in that the population were in paediatric care and were considerably younger at their most recent visit, which may help explain the difference in findings. Nonetheless, longer term research is needed to further explore the migrant effect on young people's risk of disease progression and mortality following transfer to adult care.

None of the other demographic or *a priori* variables were significantly associated with AIDS/mortality in adult care. Of all the clinical exposure variables explored, young people with lower CD4 count at transfer had an increased hazard of experiencing AIDS/mortality post-transfer, although this association was only significant in recent calendar years of transfer, as the

association was weaker in years prior to 2006. Having shown higher proportion with good immunological status at transfer in more recent calendar years, it is possible young people with poorer CD4 outcomes in recent years represent a group of more complex cases. Prior AIDS diagnosis in paediatric care was also associated with AIDS/mortality in adult care. These findings were consistent with a previous post-transfer study from London [78] which described young people who died in adult care to have poor immunological outcomes (median CD4 count of 27 cells/mm$_3$), although, this was a descriptive analysis and not adjusted for any potential confounders. Similarly, a collaborative study of paediatric HIV cohorts from Europe and Thailand [203] reported prior AIDS diagnosis and low CD4 count in paediatric care to be predictive of mortality among children with HIV. These findings are particularly relevant to my study population, as both used CHIPS data; the London study population were of former CHIPS participants and a third of the collaborative European and Thai study were of the current CHIPS cohort. Altogether, these findings reflect how a compromised immune system is more vulnerable to opportunistic infections (i.e. AIDS) and death.

To my knowledge, this study is the first to explore the impact of clinic-level youth-friendly services on the progression of AIDS/mortality in adult care. Studies have only explored such clinic factors among older adult populations with BHIV and in the context of disengagement from care [101]. The clinic-level data were obtained from my 2017 cross-sectional adult clinic survey study (Chapter 4). There I hypothesised that young people who transferred to adult clinics with higher levels of youth-friendliness were more likely to be engaged in care and thus have better clinical outcomes in adult care. The lack of association found in this chapter between the clinic-level factors and AIDS/mortality should be interpreted with caution as it is unlikely that youth-friendly services have no benefit, in particular as a number of studies across the USA and UK have found such services to improve levels of engagement in adult care and virological suppression [101,152,157]. The lack of association between the clinic-level variables and AIDS/mortality is maybe due to the effect of youth-friendly clinics being confounded by calendar year as many youth-friendly services were developed in the past decade following recent publication of transfer and youth-friendly guidelines [84,176,204]. The lack of association may also be due to the cross-sectional nature of how the clinic-level data were collected, leading to potential misclassification of exposure. For example, young people may have transferred to an adult clinic in 2008 which only started offering youth-friendly services in 2017 but was classified as a youth-friendly clinic throughout. Therefore, such participants would not have been exposed to the same level of youth-friendly services throughout the years of follow-up. Future studies investigating the impact of youth friendly services using longitudinal clinic level data is warranted.

5.5.1.2. Gaps in adult care and LTFU

Here, I developed two disengagement measures, gaps in care and LTFU, in order to investigate rates of disengagement following transfer to adult care within the UK CHIC cohort and associated factors. A previous post-transfer study from the UK was unable to measure disengagement from adult care using UK CHIC data as the UK CHIC study lacks national coverage and young people who appear to have gaps in care could in fact have attended a non-UK CHIC participating clinic. I overcame this limitation by using national surveillance data from SOPHID and HARS to validate

true gaps in care or LTFU periods, thus avoiding misclassification of young people at non-UK CHIC clinics. The UK CHIC data showed more than half (54%) of the UK CHIC cohort to have met either definition for gaps in care or LTFU status, this estimate reduced to 13% after the disengagement measures were validated with SOPHID and HARS. This highlights the difficulty of detecting transfers to non-participating clinics within cohort studies that lack national coverage. Comparable to my LTFU measure, four other European post-transfer studies measured LTFU in adult care, although none specified a threshold period for no visits [105,129,130,133]. Another four post-transfer studies from North America used more detailed disengagement definitions with each requiring a different number of visits over various periods of follow-up [108,110,131,134]. In my study, such a detailed disengagement definition was not used in order to enable better comparability of my study to the European post-transfer studies.

Overall, the rate of experiencing gaps in care was 2.2 (1.7, 2.9) per 100 person-years and 1.1 (95% CI 0.7, 1.7) per 100 person-years for LTFU in adult care. The rates for gaps were similar by ethnicity, place of birth and calendar year of transfer. However, the results indicated a higher rate of gaps in care among males and older ages in adult care. Males had double the gaps in care rate compared to females (2.5 vs 1.2 per 100 person-years) and the crude rate rose with age, from 0.1 per 100 person-years among ≤19 year olds to 2.0 among 20-24 year olds and 9.7 among ≥25 year olds. None of the confidence intervals overlapped. In the univariable and multivariable model for gaps in care, the sex effect persisted (females: adjusted HR=0.5 (95% 0.2, 0.9) vs males, p=0.03), while no age effect was observed. The association of sex with disengagement from care has been inconsistent across studies. Several adult studies from the UK have reported females to be at higher risk of disengagement [75,205–207], while some USA studies have found no sex effect [208–211] and there were also studies that were in line with my findings that reported males to be at greater risk of having gaps in care [212–215]. However, any sex effect may vary across different settings and cultures, and could likely be due to other unmeasured demographic or social factors.

While my study found no effect of age with gaps in care, a national report of the UK has described that young people with HIV aged under 25 years in 2015 were less likely to be engaged in care compared to older age groups (92% vs 97%) [88], although this was only a descriptive comparison and their denominator was largely made up of young people with BHIV. Similar to my study, another post-transfer study from USA found no age effect with disengagement from care (defined as <2 visits in a 12 month period and ≥3 months apart) [131]. In this USA study, consisting of predominantly young people with BHIV (85%), a similar lack of association between clinical characteristics and disengagement from care was found. Instead, that study found young people with longer gaps between the last paediatric visit and the first adult visit and those who were younger at transfer date to be more likely to disengage from adult care. In contrast, this was not observed in my study, which may reflect differences in health systems where in the USA health insurance is required during adulthood which may pose a barrier to care while in the UK there is free universal access to care.

In this study young people who died in adult care did not meet the definition of gaps in adult care or LTFU prior to date of death. Further to this young people who progressed to AIDS in paediatric

care had a decreased likelihood of having gaps in adult care, which suggests that young people with AIDS events may have been more closely monitored by physicians and thus less likely to have gaps in care. This would be in line with 2016 BHIVA monitoring guidelines which recommends increased monitoring for patients with poorer health outcomes.

In the LTFU model, none of the demographic, clinical and clinic-level characteristics were associated with LTFU status in adult care. In the univariable analyses, being born abroad was significantly associated but this association weakened after adjusting for age, sex, and calendar year of transfer. In terms of limitations, it is possible that there are other factors that may act as barriers to care not explored in my study, such as mental health diagnoses, socio-economic status and poor ART adherence.

For both gaps in care and the LTFU outcome, none of the clinic-level factors had a significant effect, which was similar to the lack of association found with AIDS/mortality earlier in this chapter. As previously stated, several other studies from the USA reported that youth-friendly clinic services and features such as adherence and counselling services, having a designated contact person, adolescent-specific clinics and evening hours had beneficial associations with patient engagement in adult care [101,128,149–151]. In my study, the gaps in care were more likely to occur in earlier calendar years and due to the cross-sectional nature of the clinic-level factors, services available in earlier calendar years were not captured. Therefore, I cannot conclude that increased youth-friendliness by clinics has no impact on the engagement in care of young people and more detailed analysis which captures the time of service provision may be more informative. Furthermore, 21% had no clinic-level data, because the adult clinic they attended did not report to my cross-sectional survey study, this missing data further limits the statistical power to detect a trend between these factors and the outcomes.

My study had several strengths. Internationally, this is one of the largest studies that has linked data of young people followed up in a national paediatric cohort (CHIPS) and utilises data from one of the largest adult cohort studies (UK CHIC study). This method led to a more representative cohort of young people in adult care, in contrast to other post-transfer studies from the USA that have obtained data for a number of young people who attended selected paediatric and adult clinics (selection process not specified), many of which were clinics described to serve populations with low socioeconomic statuses [108,131]. I was able to provide a detailed picture of the immunological, virological and clinical state of the participants throughout paediatric and adult follow-up, in particular those who experienced AIDS/mortality – this was made possible with the rich clinical data collected by CHIPS and the UK CHIC study. My study is the first to investigate risk factors for AIDS/mortality among young people who transferred to adult care, taking into account characteristics at time of transfer.

5.5.2. Limitation

There were also several limitations in my study. As previously mentioned, the UK CHIC study does not have national coverage and comprises mostly of the large clinics in London and likely consists of more specialised, tertiary care HIV clinics that may be less generalisable to other settings. Young people transferred to UK CHIC clinics with poorer immunological and virological

outcomes at time of transfer compared to young people who transferred to non-UK CHIC clinics. Subsequently, my study may have some selection bias in favour of patients with poorer health, and the AIDS/mortality and disengagement estimates may therefore be overestimated in the context of the UK population of young people in adult care. However, While my study sample is demographically representative of the wider population, clinically it is not, which makes it is difficult to extrapolate the AIDS/mortality and disengagement findings beyond the UK CHIC population.

Time at risk to AIDS/mortality and LTFU outcome starting at the last paediatric visit as a proxy for 'time of transfer', however, participants may have transferred before or after this date, in particular if they had a period of shared care. This may therefore effect the estimated rate of AIDS/mortality and LTFU.

Another limitation of all analyses was the inclusion of young people with at least one visit in adult care. This excluded young people who were documented as transferred but had no visit in UK CHIC adult clinics, which may affect the overall generalisability of the findings. Therefore, my findings ignore a vulnerable population of young people who did not turn up in adult care or may have transferred to a non-UK CHIC clinic. An additional inclusion criteria applied in the gaps in care and LTFU analyses were for participants to have at least 12 months potential adult follow-up, so they could have the potential to experience the disengagement outcome. However, this would also exclude young people with considerably less follow-up duration and thus also impact the generalisability of the findings.

The mortality, gaps in care and LTFU findings must be interpreted with caution as only demographic, clinical factors and adult clinic-level factors were explored. Disengagement from care may be due to other unexplored factors such as stigma, geographical distance from clinics, understanding of the HIV disease, lack of travel funding among other social factors, which were not feasible to capture in this study.

The LTFU outcome was defined as no visit in the last 12 month prior to study closure date, which may be too narrow of a time frame that could result in overestimated LTFU as young people may have been misclassified as LTFU when they in fact returned to care shortly following the study closure date. However, it is unlikely this had a large impact on the accuracy of the LTFU estimate, as similar estimates were produced in the sensitivity analysis where LTFU was redefined as no visit in the last 24 months.

With regards to the exposure variables, the VL and CD4 measurements were taken from the last paediatric visit date and may not reflect the exact date of transfer which could cause the exposure effects from the multivariable model to be diluted from the real value. Similarly, there may be some unmeasured confounding and reporting errors in the exposure variables that could also dilute the exposure effects.

The data issues and biases detected in this study is summarised in Table 5.15, along with the impact of bias on the study findings.

5.5.3. Conclusion

In summary, young people most at risk of AIDS progression and mortality in adult care were those with poorer health indicators at transfer and as well as migrants. Young people who died had poor immunological status and virological control throughout paediatric and adult follow-up. Therefore, greater investment in multidisciplinary specialised adult services are needed to address this cohort's high risk of morbidity and mortality. Engagement in care is important in ensuring access to ART and thus achieving optimal health outcomes. Further research using non-clinical data is needed to explore participants at increased risk of disengagement from care.

Table 5.15: Summary of issues and errors affecting the AIDS/mortality and disengagement results

Issue	Type of error	Potential effect of bias on exposure or outcome effect estimates (where applicable)	Adjustment made
Denominator			
CHIPS patients who transferred to non-UK CHIC clinics were excluded	Selection bias that may limit the generalizability of findings	-	
CHIPS patients who did not have at least 1 adult visit were excluded	Selection bias that may limit the generalizability of findings	-	
Outcome variables			
Time at risk to AIDS/mortality and disengagement were calculated from the last paediatric visit date but transfer to adult care may have happened after this date, or before this date if there was a period of shared care	Misclassification	Unclear effect on rate	
AIDS events and deaths in patients may not have been reported to UK CHIC	Misclassification	Underestimation of AIDS/mortality outcome	
LTFU definition used narrow time frame (no visit in the last 12 months prior to UK CHIC study closure date) which may not give participants enough time to engage in care as clinic visits could occur following study closure date	Misclassification of disengagement status	Overestimation	Sensitivity analyses defined LTFU as no visit in the last 24 months prior to closure date
Exposure variables			
Clinic-level variables were from one point in time while service provision may have changed over time	Temporal bias and misclassification of youth friendliness and clinic type variables	Diluted exposure effect	
Errors in reporting of potential confounding factors (e.g. calendar year of transfer)	Misclassification of exposure	Diluted exposure effect	
Laboratory measures (CD4, viral load) may not be measured at the actual transfer date, and may have changed by the transfer date	Misclassification of exposure	Diluted exposure effect	
Unmeasured confounders	Residual confounding	Diluted exposure effect	

6. Immunological and virological outcomes following transfer to adult care

6.1. Chapter content and aims

6.1.1. Chapter content

In this chapter, I assess the incidence and risk factors of (i) severe immunosuppression, and (ii) viral failure following transfer to adult care among young people with HIV already on ART. The demographic and clinical characteristics at last visit in paediatric care were compared between young people who were on ART for ≥6 months prior to transfer and those who were ART naïve or with less than 6 months on ART at transfer. Similar to Chapter 5, the analyses in this chapter is based on the cohort of young people with data linked between the CHIPS and UK CHIC dataset due to UK CHIC study offering more detailed VL and CD4 data compared to SOPHID and HARS.

6.1.2. Aims

The aims of this chapter are to:

1. compare characteristics of young people who transferred to UK CHIC-participating clinics by duration on ART use in paediatric care;
2. describe the trends over calendar time in the immunological and virological status of young people with HIV at the time of transfer to UK adult clinics;
3. describe the immunological and virological characteristics of young people with HIV who transferred to adult care at 12 months prior to and 12 months after the transfer date; and
4. assess the cumulative incidence rate of severe immunosuppression and viral failure post-transfer to UK CHIC clinics and associated factors.

6.2. Characteristics in paediatric and adult care among young people with and without ART experience

6.2.1. Methods

6.2.1.1. Study population

Young people with HIV were included if they had paediatric and adult data linked between the CHIPS and UK CHIC dataset.

6.2.1.2. Statistical analysis

Demographic and clinical characteristics at the last paediatric visit were compared between young people linked to the UK CHIC dataset who were on ART for ≥6 months by the last paediatric visit (hereafter referred to as the 'ART-experienced' group) and those who were either ART-naïve or were on ART for <6 months by the last paediatric visit (referred to as the 'ART-naïve' group). Young people on ART for ≥6 months were distinguished from those who were on ART <6 months, as viral suppression is typically achieved by 6 months following ART initiation [216].

Trends in immunological and virological characteristics at the last paediatric visit in the ART-experienced group were described over calendar time (from 2000 to 2016). The proportion with a CD4 cell count ≥500 cells/mm^3 of transfer was explored. This cut off was selected to represent the optimal immunological criteria, in line with the WHO immunological classification system [146], whereas HIV viral load values were dichotomised into ≤400 vs >400 copies/ml. Additionally, the median CD4 and viral load at the last paediatric visit were also described over calendar time using box plots to represent the 25th, 50th and 75th quartile ranges. Calendar years were evenly grouped

into approximately 3-year groups: 2000-2003, 2004-2006, 2007-2009, 2010-2012 and 2013-2016. These analyses excluded the ART-naïve group as they were not the focus in this chapter.

Additionally, the clinical characteristics at 12 months before and after the last paediatric visit were compared among the ART-experienced group so as to make comparable to several other post-transfer studies [104,108,110,129,130,134]. For these analyses, the earliest recorded CD4, VL and ART regimen in the last 12 months of paediatric follow-up and latest recorded CD4, VL and ART regimen in the first 12 months following last paediatric visit were selected for analysis. Thus, the time interval between measurements could be no longer than 24 months. Applying a window of three or six months around each of the time points considerably reduced the number of records available for analysis, and would therefore have been too restrictive for meaningful analyses. Categorical variables were compared between the dependant groups (the group at the 12 month time point pre-transfer vs the group at the 12 month time point post-transfer) using McNemar's test.

This chapter is separated into three sections: (1) patient characteristics, and immunological and virological trends over time, (2) severe immunosuppression (≥1 CD4 count <200 cells/mm^3) in adult care, and (3) viral failure (≥2 consecutive viral loads >400 copies/ml) in adult care. In sections (2) and (3), time to event analyses were carried out to investigate severe immunosuppression and viral failure as the outcomes of interest among ART-experienced young people. Those with a CD4 count <200 cells/mm^3 at transfer were excluded from the severe immunosuppression analysis, and those with ≥2 consecutive viral loads >400 copies/ml were excluded from the viral failure analysis. Therefore, participants were excluded if they had already experienced the outcome of interest at the time of transfer (time zero).

The methodology for the severe immunosuppression and viral failure analysis are further detailed at the beginning of sections (6.3.1.) and (6.4.1.).

6.2.2. Results

6.2.2.1. Demographic and clinical characteristics at the last paediatric visit by ART status

Of the 474 young people linked to the UK CHIC dataset, 47 (10%) had never received ART and 5 (1%) were on ART for <6 months – the ART-naïve group therefore comprised 52 (11%) young people. Four-hundred and twenty-two (89%) young people were on ART for ≥6 months prior to transfer and comprised the ART-experienced group.

Table 6.1 presents the demographic characteristics of the ART-experienced and –naïve group. Some characteristics differed between the two groups. A higher proportion of the former group were males compared to the latter group (51% vs 31%, p=0.005). Ethnicity and place of birth did not differ by ART status at transfer (p=0.31 and p=0.30, respectively). The ART-experienced group were born in later calendar years (median calendar year of birth 1993 vs 1991, p=0.001) but were diagnosed with HIV at a significantly younger age (median age at diagnosis 6 vs 10 years, p=0.004) in comparison to the other group.

Table 6.1: Demographic characteristics of young people with HIV by ART status

		Total (N=474)	**ART-experienced group (N=422)**	**ART-naïve group (N=52)**	**P-value**
		N (%) or median [IQR]			
Sex (N=474)	Female	241 (50.8)	205 (48.6)	36 (69.2)	0.005
	Male	233 (49.2)	217 (51.4)	16 (30.8)	
Ethnicity (N=461)	Black	380 (82.4)	339 (81.7)	41 (89.1)	0.31
	White/other	81 (17.6)	76 (18.3)	5 (10.9)	
Place of birth (N=465)	UK	184 (39.6)	168 (40.4)	16 (32.7)	0.30
	Abroad	281 (60.4)	248 (59.6)	33 (67.4)	
Calendar year of birth (N=474)	Median [IQR]	1993 [1990, 1995]	1993 [1990, 1995]	1991 [1989, 1994]	0.001
	Range	1982, 1999	1982, 1999	1984, 1997	
Age at HIV diagnoses, years (N=467)	Median [IQR]	6.0 [2.2, 10.7]	5.8 [2.1, 10.3]	9.6 [2.7, 13.8]	0.004
	Range	0.0, 16.0	0.0, 16.0	0.2, 15.7	

Table 6.2 presents the clinical and treatment characteristics at the last paediatric visit by ART status. The ART-experienced group had a slightly older age at transfer date (18 vs 17 years, p=0.01) and transferred to adult care in later calendar years (2011 vs 2008, p<0.001) compared to the ART-naïve group. The ART-experienced group had a significantly lower median nadir CD4 count (188 vs 350 cells/mm_3, p<0.001) compared to the other group, but the median CD4 count by the last paediatric visit did not significantly differ (p=0.15). As expected, a significantly higher proportion of young people in the former group were virally suppressed (≤400 copies/ml) by the same date compared to the ART-naive group (65% vs 7%, p<0.001). Overall, 28% had experienced an AIDS event in paediatric care, although the ART-experienced group had a higher proportion with AIDS events compared to the ART-naive group (31% vs 4%, p<0.001). The majority (75%) of the ART-experienced group were on a cART regimen by the last paediatric visit.

Table 6.2: Clinical and treatment characteristics of young people with HIV at the last paediatric visit by ART status

		Total N=474	**ART-experienced group N=422**	**ART-naïve group N=52**	**P-value**
		N (%) or median [IQR]			
Age, years (N=461)	Median [IQR]	17.8 [16.8, 18.5]	17.8 [16.8, 18.6]	17.2 [16.5, 17.8]	0.01
	Range	14.0, 22.5	14.0, 22.5	14.6, 19.8	
Calendar year (N=465)	Median [IQR]	2011 [2008, 2013]	2011 [2008, 2013]	2008 [2004, 2011]	<0.001
	Range	2000, 2016	2000, 2016	2001, 2014	
Nadir CD4 count, cells/mm$_3$ (N=463)	Median [IQR]	200 [90, 293]	188 [83, 280]	350 [239, 480]	<0.001
	Range	0, 733	0, 733	0, 670	
CD4 count, cells/mm$_3$ (N=463)	Median [IQR]	471 [280, 663]	480 [280, 676]	410 [281, 565]	0.15
	Range	0, 1898	2, 1898	0, 870	
Viral load, copies/ml (N=464)	≤400	278 (59.9)	275 (65.3)	3 (7.0)	<0.001
	>400	186 (40.1)	146 (34.7)	40 (93.0)	
Ever had AIDS events (N=474)	Yes	131 (27.6)	129 (30.6)	2 (3.9)	<0.001
	No	343 (72.4)	293 (69.4)	50 (96.2)	
ART regimen (N=467)	Mono/dual	51 (10.9)	51 (12.1)	0 (0.0)	<0.001
	cART	352 (75.4)	348 (82.5)	4 (8.9)	
	Other	12 (2.6)	11 (2.6)	1 (2.2)	
	ART naïve/off treatment	52 (11.1)	12 (2.8)	40 (88.9)	

6.2.2.2. Changes in CD4 count and viral load outcomes at transfer by calendar time among ART-experienced young people

Figure 6.1 shows the trend in proportions with a VL ≤400 copies/ml and a CD4 count >500 cells/mm$_3$ at the time of transfer by calendar year among the ART-experienced group (N=422). Firstly, the number of participants transferring out of paediatric care increased from 2 individuals in 2000 to 56 in 2014, but then declined to 6 in 2016. The proportion of young people with a VL ≤400 copies/ml or a CD4 count >500 cells/mm$_3$ at transfer increased in the first five years (2000-2004), although numbers who transferred were low in these periods. After 2004, there was a steady increase in the proportions virally suppressed or with a CD4 count >500 cells/mm$_3$. By 2015, the proportions with a VL ≤400 copies/ml or a CD4 count >500 cells/mm$_3$ at transfer reached 85% and 69%, respectively.

Figure 6.1: Trends over calendar time in the proportion of young people with a VL ≤400 copies/ml and CD4 count >500 cells/mm$_3$ at transfer (2000 to 2016) (N=422)

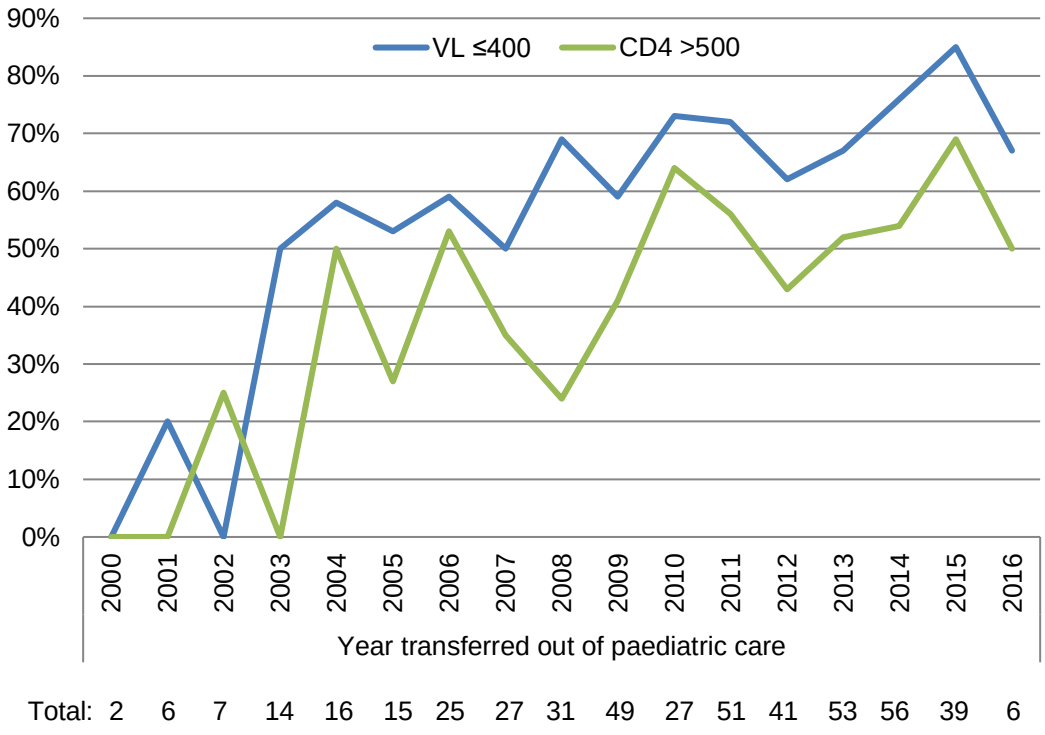
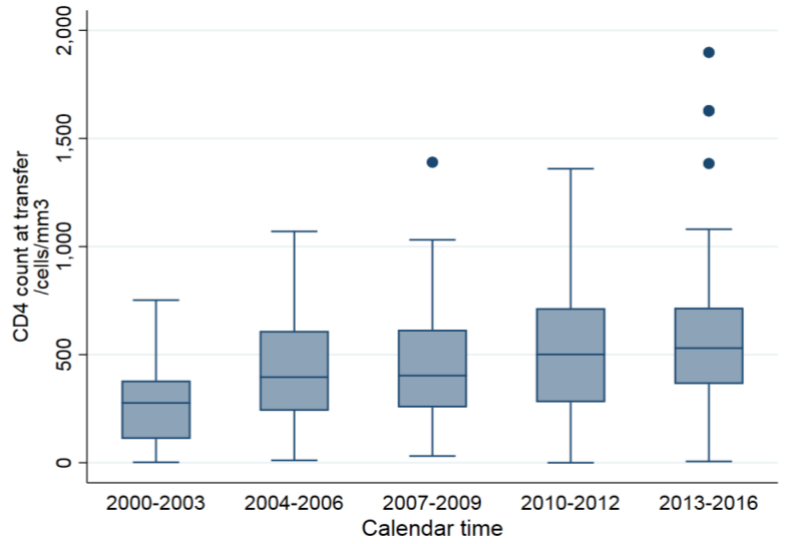


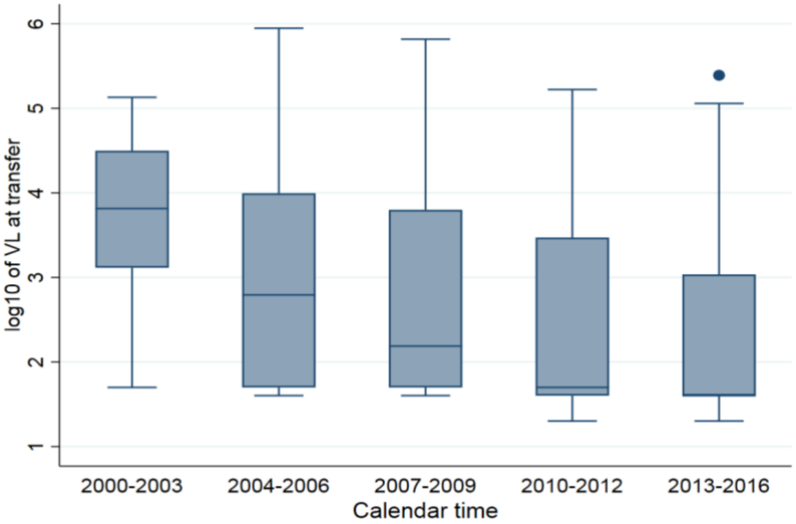
Figure 6.2 illustrates the distribution of the median CD4 count at transfer among ART-experienced young people transferring during the years 2000 to 2016. Among those who transferred to adult care from 2000 to 2003, the median CD4 count at transfer was 277 [IQR 110, 380] cells/mm$_3$, which improved to 544 [369, 704] cells/mm$_3$ for young people who transferred in 2014 to 2016 ($p<0.001$).

Figure 6.2: The distribution of the CD4 count at transfer among young people on ART in different calendar periods (N=422)



The median log_{10}(viral load) at transfer also improved among young people on ART over calendar time (Figure 6.3). The median (IQR) viral load at transfer was 3.8 [3.1, 4.5] log_{10} copies/ml among young people who transferred in the earlier calendar years (2000-2003) but this halved to 1.6 [1.4, 2.2] log_{10} copies/ml among those transferring from 2014 to 2016 ($p<0.001$). However, a quarter of the young people had a viral load ≥5 log_{10} copies/ml, indicated by the upper quartiles of the viral load distributions for most calendar years of transfer. To determine whether the decline in median viral load in the past two decades were genuine or due to the emergence of more sensitive viral load assays in recent years, the lower limit of the viral load values were recoded to 400 copies, which reflects the detection threshold of one of the least sensitive assays. Using the recoded viral load values at transfer, the median viral load declined from 2000 to 2009, and thereafter, remained stable between 2009 and 2016 (data not shown).

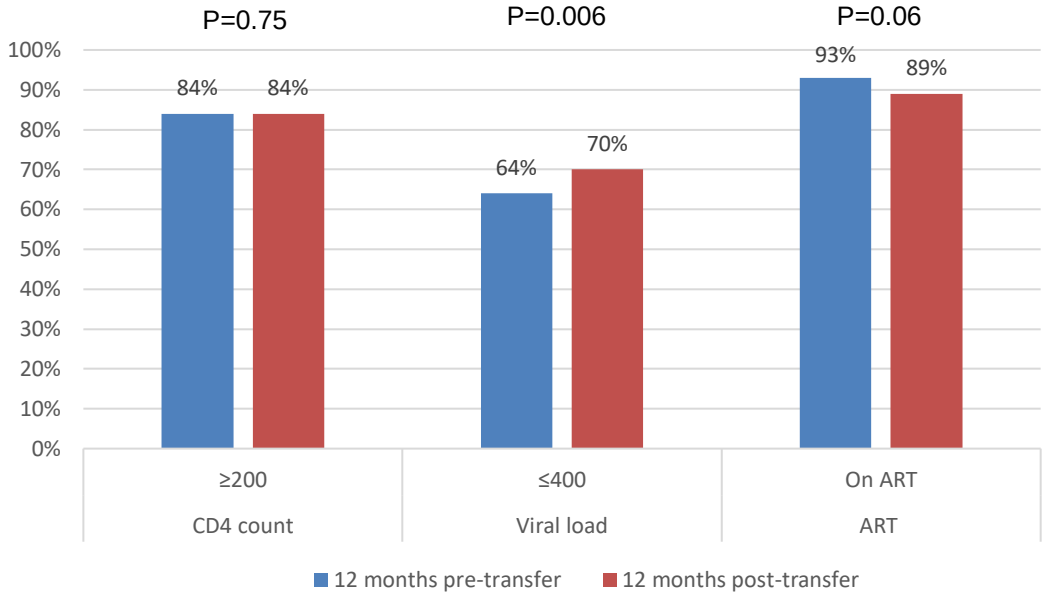
Figure 6.3: The distribution of log_{10}(viral load) at transfer among young people on ART in different calendar periods (N=422)



6.2.2.3. Changes in CD4 count and viral load outcomes before and after transfer among ART-experienced young people

Figure 6.4 presents the immunological, virological and treatment status at 12 months before and 12 months after transfer to adult care among ART-experienced young people with HIV (N=422). Overall, there was no significant change in the percentage with a CD4 ≥200 cells/mm$_3$ following transfer to adult care (p=0.75), though, the proportion virally suppressed (VL ≤400 copies/ml) improved from 64% at 12 months prior to transfer to 70% at 12 months following transfer to adult care (p=0.006). The proportion on ART between the two time points declined slightly from 92% to 89% (p=0.06).

Figure 6.4: A summary of CD4 count, viral load and treatment use at 12 months pre- and 12 months post-transfer to adult care (N=422)



6.3. Severe immunosuppression post-transfer to adult care among ART-experienced young people with HIV

6.3.1. Methods

6.3.1.1. Study population

Young people were included if they were on ART for ≥6 months and had a CD4 count ≥200 cells/mm$_3$ by the last paediatric date and had ≥1 CD4 measurement in the UK CHIC dataset.

6.3.1.2. Statistical analysis

The outcome of interest was severe immunosuppression, defined as the first CD4 count <200 cells/mm$_3$ in adult care. To ensure that the sample size was sufficient for robust analyses, I only required a single CD4 count <200 cells/mm$_3$ for individuals to meet the definition of severe immunosuppression. However, the majority (70%) of those who met this criterion did have a subsequent CD4 count <200 cells/mm$_3$ in adult care, and would therefore have also met a more stringent criteria based on ≥2 consecutive CD4 counts <200 cells/mm$_3$.

Time to event analyses were carried out with time at risk starting from the last paediatric visit date until the earliest of a severe immunosuppression event, death or last visit in adult care. Crude rates for severe immunosuppression in adult care were calculated according to sex, ethnicity (black vs white/other), place of birth (UK vs abroad), time-updated age and calendar year of transfer. Factors associated with severe immunosuppression in adult care were identified using a Cox proportional hazards model using a step-wise backwards elimination approach. Variables associated with the outcome in the univariable analysis ($p<0.2$) were considered for multivariable analysis, those with highest p values (≥0.1) were sequentially removed from the multivariable model until all remaining variables had a p-value <0.1. The following variables, selected *a priori*, were included in the final model, irrespective of statistical significance: sex, and age and year of transfer date. This was because age and sex are commonly reported confounders and calendar year at transfer was also selected *a priori* as immunological and virological characteristics have shown to improve with recent calendar years of transfer among this study population (Figure 6.2). Factors considered as potential individual-level risk factors for severe immunosuppression in adult care were:

- place of birth (UK vs abroad),
- ethnicity (black vs white/other),
- CD4 count at ART start,
- viral load at ART start,
- duration on ART by transfer,
- nadir CD4 count by transfer,
- CD4 count at transfer,
- viral failure in the last year of paediatric care (≥1 VL >400 copies/ml),
- prior AIDS events in paediatric care, and
- gap in care (duration between the last paediatric visit and first adult visit).

The following clinic-level factors were also explored as potential risk factors for severe immunosuppression in adult care:

- adult clinic's level of youth-friendliness, and
- clinic type (young persons' clinic vs general adult clinic).

With regards to the clinic-level factors, the potential for a cluster effect at a clinic-level was explored by fitting a frailty model, and where a cluster effect was identified, the frailty model was retained in the multivariable model [193]. Where variables were continuous, the optimal functional form of the association between each potential risk factor and the outcome was determined by plotting the Martingale residual against each variable in question. A straight line relationship between the Martingale residuals and the respective variable indicated that a linear term was appropriate; therefore, the variable was engaged in its continuous form without any further transformation. If non-linearity was detected, the variable was categorised and described in results section of this chapter. Additionally, the proportional hazards assumption was tested for each potential risk factor; where factors violated this assumption, an interaction term was fitted between the respective covariate and the follow-up time. Having observed changes in clinical characteristics at transfer by calendar time within this population of interest, interactions between

calendar year at transfer and all other potential risk factors were explored in the final model. The Kaplan-Meier survival curves for the cumulative incidence of severe immunosuppression in adult care were calculated and stratified by the variables engaged in the final multivariable model.

In the sensitivity analysis, the outcome was defined on the basis of the first of ≥2 consecutive CD4 counts <200 cells/mm$_3$ in adult care, instead of only a single CD4 count <200 cells/mm$_3$.

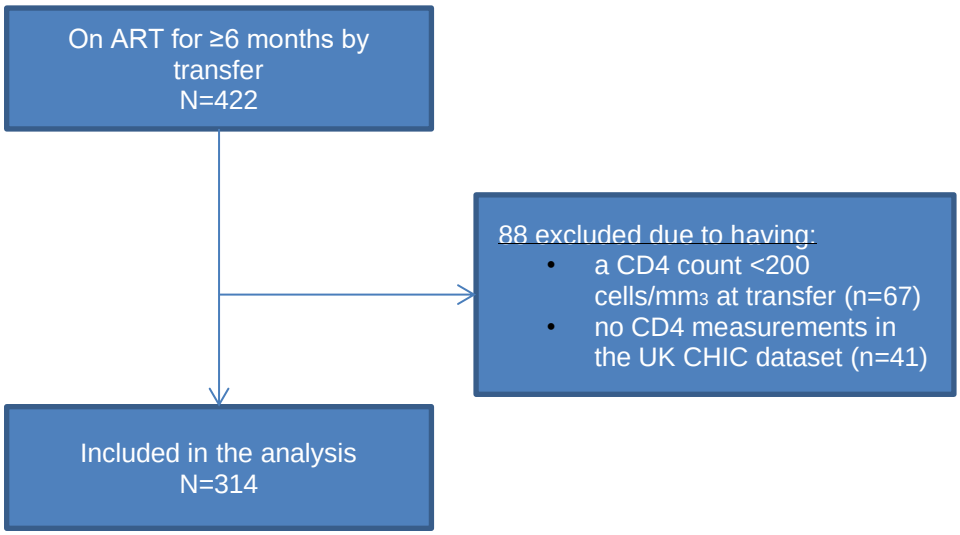
6.3.2. Results

6.3.2.1. Characteristics of young people on ART and with a CD4 count >200 cells/mm$_3$ at transfer

Of the 422 ART-experienced young people, 314 (79%) were not severely immunosuppressed (CD4 count >200 cells/mm$_3$) on the last paediatric visit and were thus included in the analysis of severe immunosuppression in adult care (Figure 6.5). The other 67 were excluded for already experiencing severe immunosuppression (CD4 <200 cells/mm$_3$) at the time of transfer, of these 75% remained severely immunosuppressed after 12 months of adult follow-up.

Of the 314 who met the inclusion criteria, 153 (49%) were female, 251 (81%) were of black African/Caribbean origin and 187 (61%) were born abroad. The median age at the last paediatric visit was 18 [17, 19] years and their median duration in adult care was 3.4 [1.3, 6.2] years. At transfer, the median CD4 count was 524 [374, 714] cells/mm$_3$. Among those included in the severe immunosuppression analysis, 66 (21%) experienced severe immunosuppression in adult care. The median duration to experiencing the first event was 1.6 [IQR 0.8, 3.7] years following transfer date. Of these, 36% had first event of severe immunosuppression in the first year of adult care and 26% in the second year.

Figure 6.5: ART-experienced young people included in the analysis for severe immunosuppression in adult care



6.3.2.2. Rates of severe immunosuppression post-transfer to adult care

Table 6.3 presents the crude rates of severe immunosuppression in adult care by sex, ethnicity, place of birth, current age in adult care and calendar year of transfer. The overall crude rate of severe immunosuppression was 0.5 (95% CI 0.4, 0.6) per 100 person years in adult care, and were comparable across the demographic groups except current age. The rate of severe immunosuppression increased with older age from 1.1 per 100 person-years among for those aged ≤19 years to 18.2 per 100 person-years for those aged ≥25 years, however, the confidence interval widened for the oldest age group reflecting the small amount of person-years.

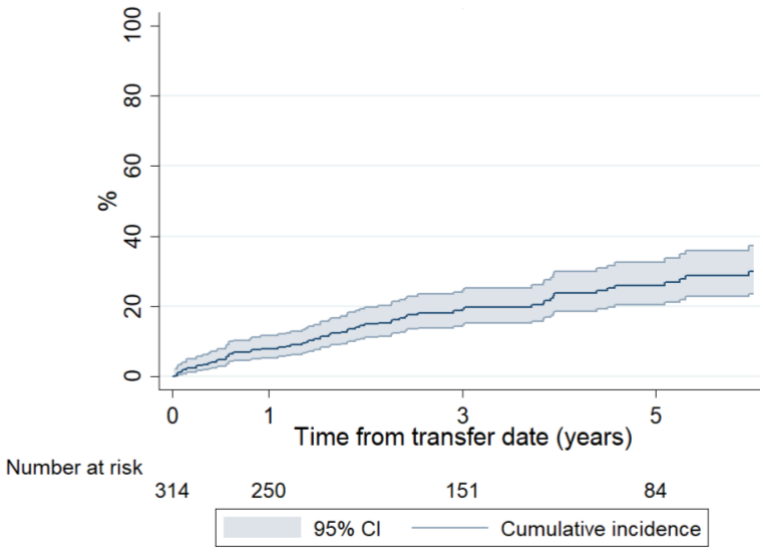
Table 6.3: Severe immunosuppression rates of young people with HIV per 100 person-years by demographic characteristics

Demographic characteristics	Severe immunosuppression outcome		
	Number of events	Person-years	Rate (95% CI)
Overall	66	13482.5	0.5 (0.4, 0.6)
Sex			
Female	38	6200.1	0.6 (0.4, 0.8)
Male	28	7282.5	0.4 (0.3, 0.6)
Ethnicity			
White/other	12	3144.4	0.4 (0.2, 0.7)
Black	54	10100.1	0.5 (0.4, 0.7)
Place of birth			
UK	28	4998.8	0.6 (0.4, 0.8)
Born abroad	38	8105.3	0.5 (0.3, 0.6)
Current age			
≤19	7	646.4	1.1 (0.5, 2.3)
20-24	32	711.1	4.5 (3.2, 6.4)
≥25	27	148.5	18.2 (12.5, 26.5)
Calendar year of transfer			
≤2008	34	5796.4	0.6 (0.4, 0.8)
2009-2012	24	6082.4	0.4 (0.3, 0.6)
2013-2016	8	1603.7	0.5 (0.2, 1.0)

6.3.2.3. Risk of severe immunosuppression in adult care

The cumulative incidence of severe immunosuppression in adult care increased steadily in adult care (Figure 6.6). In the first year of adult follow-up, 8% (95% CI 5%, 12%) of young people had experienced severe immunosuppression, rising to 19% (95% CI 14%, 24%) and 26% (95% CI 21%, 33%) by three and five years of follow-up in adult care, respectively. The confidence intervals were wider at the later time points due to a smaller number of people under follow-up and at risk.

Figure 6.6: Cumulative incidence of experiencing severe immunosuppression (1 CD4 count <200 cells/mm3) in adult care (N=314)



6.3.2.4. Factors associated with severe immunosuppression after transfer to adult care

Table 6.4 presents the factors associated with severe immunosuppression in adult care from the univariable and multivariable analyses using Cox proportional hazard models. In the univariable analysis, there was evidence to suggest being female (HR: 1.6 (95% CI 0.9, 2.6) vs males, p=0.09), experiencing viral failure in the last year of paediatric care (HR: 5.1 (95% CI 2.8, 9.4), p<0.001), transferring to a general adult clinic (HR: 2.1 (95% CI 1.1, 4.3) vs young persons' clinic, p=0.03) increased the hazard of experiencing severe immunosuppression following transfer to adult care. Transferring in earlier calendar years (HR: 0.9 (95% CI 0.8, 1.0) per year increase, p=0.01), higher CD4 nadir count (unadjusted HR: 0.7 (95% CI 0.6, 0.9) per 100 cells/mm3 increase, p=0.002), higher CD4 counts at the last paediatric visit (HR: 0.6 (95% CI 0.5, 0.7) per 100 cells/mm3 increase, p<0.001) and transferring to adult clinics with higher level of youth-friendliness (HR: 0.8 (95% CI 0.7, 1.0) per 1 unit score increase, p=0.07) all had a protective effect against severe immunosuppression in adult care.

In the multivariable analysis, viral failure in the last paediatric year of follow-up (adjusted HR: 2.6 (95% CI 1.4, 5.0), p=0.003), CD4 count at the last paediatric visit (aHR: 0.6 (95% CI 0.5, 0.7) per 100 cells/mm3 increase, p<0.001) continued to have a significant association with the outcome of interest. Prior AIDS status also had a significant association with severe immunosuppression (aHR: 1.9 (95% CI 1.1, 3.3) vs no prior AIDS diagnosis, p=0.03), despite the weak association found in the univariable analysis. None of the demographic characteristics, including the *a priori* variables were significantly associated with the outcome of interest (all p≥0.1). Being female had a strong but non-significant association with severe immunosuppression in adult care (aHR: 1.5 (95% 0.9, 2.6) vs male, p=0.14). CD4 nadir count and the clinic-level characteristics no longer had an effect in the multivariable analysis, and there was no evidence to suggest a clinic-level cluster effect (both p=0.50). None of the exposure variables violated the proportional hazards assumption.

Table 6.4: Factors associated with severe immunosuppression (≥1 CD4 count <200 cells/mm$_3$), results from Cox proportional hazards model (N=314)

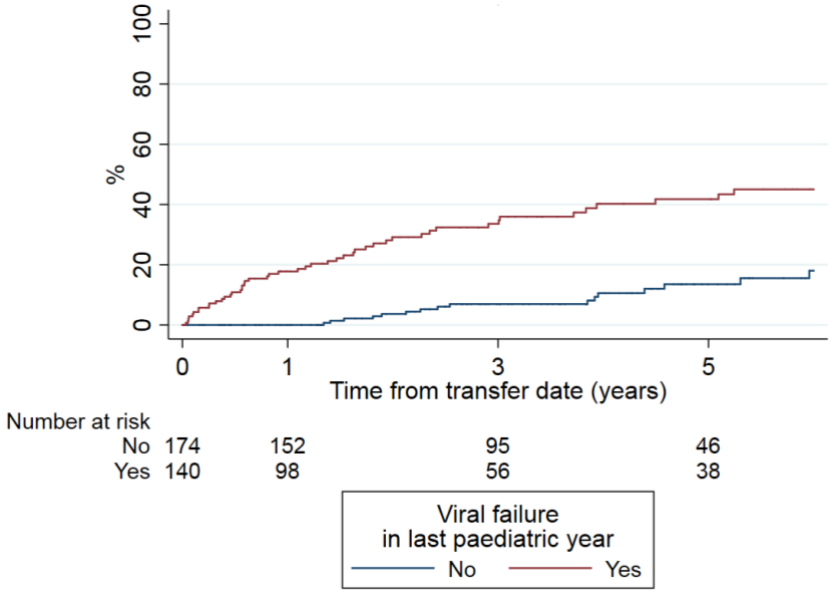
		N (%)	Unadjusted hazard ratio (95% CI)	P-value	Adjusted hazard ratio (95% CI)	P-value
Variables selected for inclusion *a priori*						
Sex	Male	161 (51)	1		1	
	Female	153 (49)	1.6 (0.9, 2.6)	0.09	1.5 (0.9, 2.6)	0.14
Age at transfer, per year increase		313 (100)	1.0 (0.8, 1.2)	0.92	0.9 (0.8, 1.1)	0.54
Calendar year of transfer, per year increase		314 (100)	0.9 (0.8, 1.0)	0.01	1.0 (0.9, 1.1)	0.92
Demographic variables						
Ethnicity	Black	251 (81)	1			
	White/other	58 (19)	0.7 (0.4, 1.5)	0.40		
Place of birth	Born Abroad	187 (61)	1			
	UK	121 (39)	1.3 (0.8, 2.1)	0.38		
Variables at the last paediatric visit						
CD4 nadir, per 100 cell/mm$_3$ increase		312 (100)	0.7 (0.6, 0.9)	0.002		
CD4 count, per 100 cell/mm$_3$ increase		312 (100)	0.6 (0.5, 0.7)	<0.001	0.6 (0.5, 0.7)	<0.001
Viral failure in last paediatric year, copies/ml (>400 copies/ml)	Yes	140 (45)	5.1 (2.8, 9.4)	<0.001	2.6 (1.4, 5.0)	0.003
	No	174 (55)	1		1	
AIDS diagnosis	Yes	88 (28)	1.4 (0.9, 2.4)	0.17	1.9 (1.1, 3.3)	0.03
	No	226 (72)	1		1	
ART regimen	Combination ART	265 (84)	1			
	Non-combination ART	49 (16)	1.4 (0.7, 2.7)	0.30		
Duration on ART, per year increase		314 (100)	1.0 (1.0, 1.1)	0.22		
Gap in care$_1$, per month increase		314 (100)	0.996 (0.976, 1.016)	0.67		
Adult clinic-level variables						
Clinic type	Young persons' clinic	241 (100)	1			
	General adult clinic	29 (11)	2.1 (1.1, 4.3)	0.03		
Level of youth-friendliness, per 1 unit lower		287 (100)	0.8 (0.7, 1.0)	0.07		

$_1$: duration between the last paediatric visit and the first adult visit

6.3.2.5. Risk of severe immunosuppression in adult care by identified risk factors

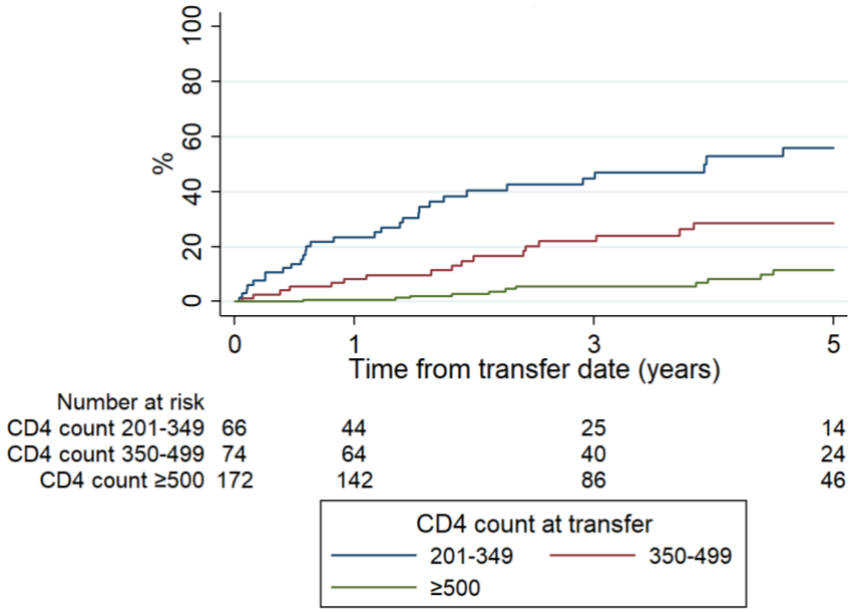
Young people who experienced viral failure in their last year of paediatric follow-up had a higher cumulative incidence of experiencing severe immunosuppression in adult care than those who did not have viral failure prior to the transfer date (Figure 6.7). In the first year following transfer date, young people who had viral failure in the last paediatric year had a cumulative incidence of severe immunosuppression of 18% (95% CI 13%, 25%), while the other group had no severe immunosuppression events. After three years post-transfer, the cumulative incidence among the former group increased to 34% (95% CI 26%, 43%) compared to only 7% (95% CI 4%, 13%) of the latter group and by five years post-transfer, the cumulative incidence was 42% (95% CI 33%, 52%) vs 14% (95% CI 8%, 22%) in the two groups, respectively.

Figure 6.7: Cumulative incidence of experiencing severe immunosuppression in adult care by viral failure status in last year of paediatric care (N=314)



The cumulative risk of severe immunosuppression in adult care by CD4 count at transfer date is presented in Figure 6.8. The cumulative incidence for severe immunosuppression in adult carewas higher among those with lower CD4 count at transfer date. The difference in cumulative incidence between the CD4 count groups (i.e. 200-349, 350-499 and ≥500 cells/mm$_3$ at transfer) was bigger in the later years of adult follow-up. By the fifth year of adult follow-up, the incidence was 56% (95% CI 42%, 70%) for those with a CD4 count of 200-349 cells/mm$_3$ at transfer, 29% (95% CI 19%, 42%) for those with a CD4 count of 350-499 cells/mm$_3$ and 11% (95% CI 6%, 20%) for those with a CD4 count ≥500 cells/mm$_3$ at transfer.

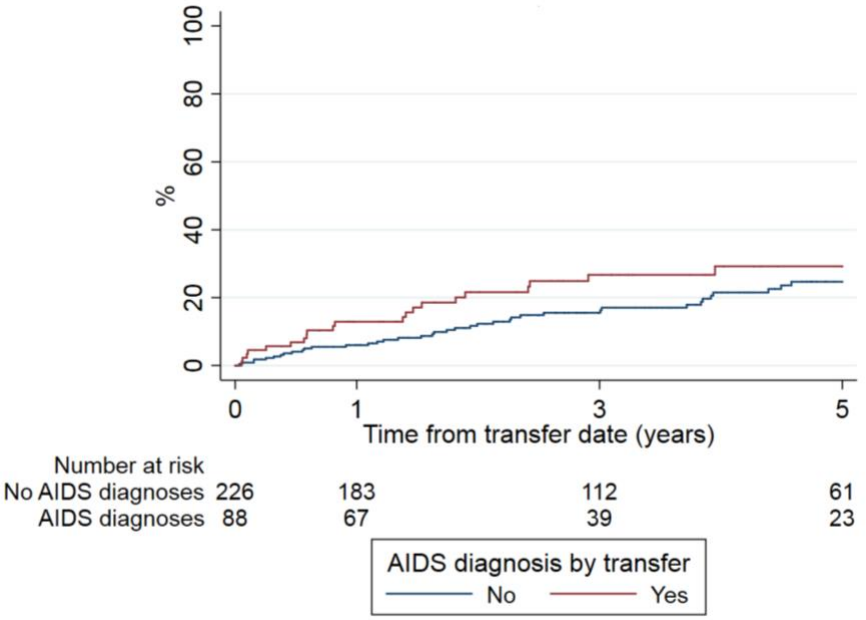
Figure 6.8: Cumulative incidence of experiencing severe immunosuppression in adult care by CD4 count at transfer date (N=314)



**CD4 count groups reflect the WHO's immunological classification system*

Young people with a prior AIDS diagnosis by transfer date had a greater risk of experiencing severe immunosuppression in adult care compared to those without AIDS diagnosis (Figure 6.9). After one year post-transfer, the group with prior AIDS diagnoses the cumulative incidence of severe immunosuppression was 13% (95% CI 7%, 22%) compared to almost half the incidence (6%) of the AIDS free group. After five years following transfer date, there was a smaller difference in cumulative incidence between the two groups: 29% (95% CI 20%, 42%) and 25% (95% CI 18%, 33%), respectively.

Figure 6.9: Cumulative incidence of experiencing severe immunosuppression in adult care by AIDS status at transfer date (N=314)



Of the 66 young people who ever experienced severe immunosuppression in adult care, almost half (42%) remained severely immunosuppressed at the last visit in adult care.

6.3.2.6. Sensitivity analysis

In the sensitivity analysis, I re-defined severe immunosuppression on the basis of the first of two consecutive CD4 counts <200 cells/mm3. There were 313 young people who met the inclusion criteria for the sensitivity analysis (who, at transfer, were on ART with a CD4 count >200 cells/mm3, and had ≥2 CD4 measurements in the UK CHIC dataset). Figure 6.10 presents the cumulative incidence of severe immunosuppression based on this revised definition. By one year following transfer to adult care, 4% (95% CI 2%, 7%) had experienced the outcome of interest. By three and five years post-transfer, the cumulative incidence increased to 12% (95% CI 8%, 16%) and 16% (95% CI 11%, 21%), respectively. Expectedly, these incidence estimates were lower at all three time points compared to those obtained when a more relaxed definition of severe immunosuppression was used (i.e. 1 CD4 <200 cells/mm3).

Figure 6.10: Cumulative incidence of experiencing severe immunosuppression (2 consecutive CD4 counts <200 cells/mm3) in adult care (N=313)

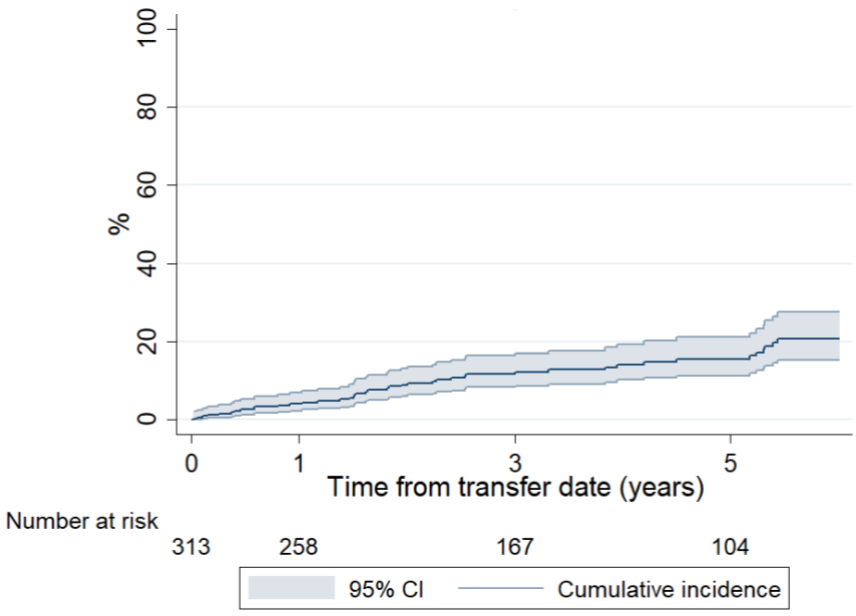


Table 6.5 presents the results from the Cox proportional hazards model to identify factors associated with severe immunosuppression in adult care. In the unadjusted model, higher CD4 nadir, higher CD4 count at transfer date and viral failure (VL >400 copies/ml) in the last paediatric year were all associated with severe immunosuppression in adult care, which is consistent with the main model. However, prior AIDS diagnosis in paediatric care was found to have a significant association calendar year of transfer and the adult clinic-level characteristics were not associated in this sensitivity analysis. In the multivariable analysis, higher CD4 count (aHR: 0.6 (95% CI 0.5, 0.8) per 100 cells/mm3 increase, p<0.001), viral failure in the last year of paediatric care (aHR: 3.1 (95% CI 1.3, 7.2), p=0.008) and prior AIDS diagnosis (aHR: 2.1 (95% CI 1.0, 4.2), p=0.04) by transfer were still significantly associated with severe immunosuppression. After redefining severe immunosuppression, higher CD4 nadir (aHR: 0.7 (95% CI 0.6, 1.0) per 100 cells/mm3

higher, p=0.04) and being on ART for a longer duration (aHR: 1.1 (1.0, 1.2) per year longer, p=0.04) had a significant effect in the sensitivity analysis but not in the main model. None of the other characteristics had a significant association with the outcome of interest (all p>0.1).

Table 6.5: Factors associated with severe immunosuppression (≥2 CD4 count <200 cells/mm3), results from Cox proportional hazards model (N=313)

		N (%)	Unadjusted hazard ratio (95% CI)	P-value	Adjusted hazard ratio (95% CI)	P-value
Variables selected for inclusion *a priori*						
Sex	Male	161 (51)	1		1	
	Female	152 (49)	1.3 (0.7, 2.3)	0.46	1.0 (0.5, 2.0)	0.89
Age at transfer, per year increase		312 (100)	1.0 (0.8, 1.3)	0.78	0.8 (0.7, 1.1)	0.16
Calendar year of transfer, per year increase		302 (100)	0.9 (0.8, 1.0)	0.11	1.0 (0.9, 1.2)	0.82
Demographic variables						
Ethnicity	Black	252 (82)	1			
	White/other	57 (18)	0.5 (0.2, 1.3)	0.15		
Place of birth	Born Abroad	191 (62)	1			
	UK	118 (38)	1.2 (0.7, 2.2)	0.58		
Variables at the last paediatric visit						
CD4 nadir, per 100 cell/mm3 increase		311 (100)	0.6 (0.5, 0.8)	<0.001	0.7 (0.6, 1.0)	0.04
CD4 count, per 100 cell/mm3 increase		311 (100)	0.5 (0.4, 0.7)	<0.001	0.6 (0.5, 0.8)	<0.001
Viral failure in last paediatric year, copies/ml (>400 copies/ml)	Yes	135 (43)	5.9 (2.7, 12.8)	<0.001	3.1 (1.3, 7.2)	0.008
	No	178 (57)	1		1	
AIDS diagnosis	Yes	96 (31)	2.1 (1.1, 3.8)	0.02	2.1 (1.0, 4.2)	0.04
	No	217 (69)	1		1	
ART regimen	Combination ART	271 (87)	1			
	Non-combination ART	42 (13)	1.4 (0.6, 3.0)	0.41		
Duration on ART, per year increase		313 (100)	1.1 (1.0, 1.1)	0.11	1.1 (1.0, 1.2)	0.04
Gap in care1, per month increase		306 (100)	0.992 (0.967, 1.018)	0.54		
Adult clinic-level variables						
Clinic type	Young persons' clinic	231 (90)	1			
	General adult clinic	25 (10)	1.8 (0.8, 4.4)	0.18		
Level of youth-friendliness, per 1 unit increase		256 (100)	0.8 (0.7, 1.0)	0.12		

1: Duration between the last paediatric visit and the first adult visit

6.4. Viral failure post-transfer to adult care among all those on ART

6.4.1. Methods

6.4.1.1. Study population

Young people on ART for ≥6 months and with a viral load ≤400 copies/ml by the last paediatric visit, and had ≥2 viral load measurements in the UK CHIC dataset were included.

6.4.1.2. Statistical analysis

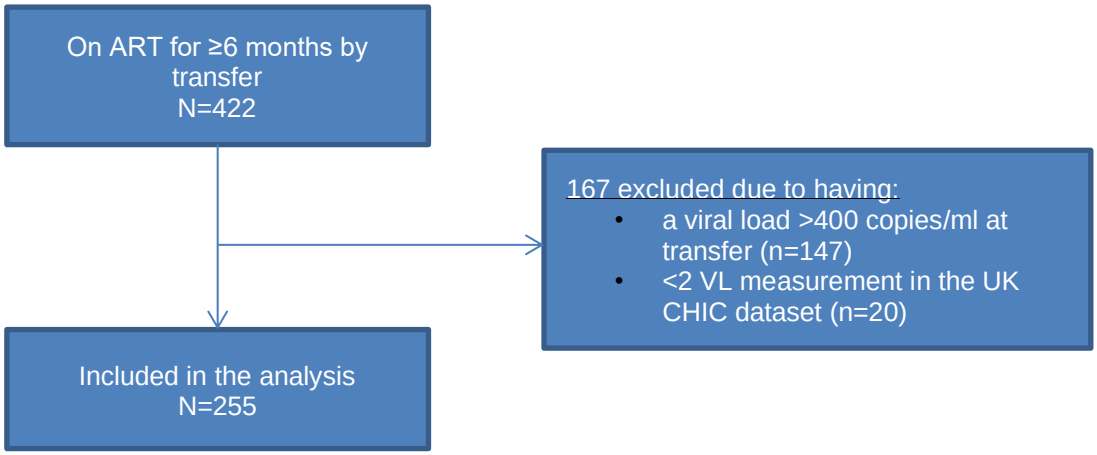
The outcome of interest was viral failure, defined as ≥2 consecutive viral loads >400 copies/ml to take into account the high variability of viral loads [217], and avoids the misclassification of a single viral load blip as viral failure. Time to event analyses were carried out with time at risk starting from the last paediatric visit date until the earliest of viral failure event, death or last visit in adult care. The cumulative incidence of and factors associated with viral failure in adult care were identified using the same methods outlined for severe immunosuppression and the same set of potential risk factors were explored (described in section 6.3.1.2. Statistical analysis). In the sensitivity analysis, the viral failure outcome was redefined as the first of ≥2 consecutive viral loads >1000 copies/ml in adult care.

6.4.2. Results

6.4.2.1. Characteristics of young people on ART and with a VL <400 copies/ml at transfer

Of the 422 ART-experienced young people, 255 (60%) were virally suppressed (VL ≤400 copies/ml) at the last paediatric visit and were thus included in the analysis of viral failure in adult care (Figure 6.11). Of the 167 young people who were excluded, almost all (98%) were virally unsuppressed at the time of transfer and 20 individuals were excluded due to insufficient VL data in the UK CHIC dataset. Among those with unsuppressed VL at transfer date, 69% still had a VL >400 copies/ml at 12 months following transfer to adult care. Of the 255 young people included in the analysis, half were female (47%), 81% were black and 60% were born abroad. The median age at the last paediatric visit was 18 [IQR, 17, 19] years and the median duration in adult care was 2.9 [1.2, 5.4] years. Among the 255 young people, 57 (22%) ever experienced an episode of viral failure (≥2 VL >400 copies/ml) whilst in adult care and the median duration to the first event was 1.6 [IQR 0.8, 3.7] years post-transfer. Over half (53%) of those who ever experienced viral failure had their first event within the first two year of adult follow-up.

Figure 6.11: ART-experienced young people included in the viral failure analysis



6.4.2.2. Rates of viral failure post-transfer to adult care

The crude rates of viral failure in adult care are presented in Table 6.6 by sex ethnicity, place of birth, current age in adult care and calendar year of transfer. The overall crude rate was 0.6 (95% CI 0.4, 0.7) per 100 person-years and rates were similar by the demographic characteristics. Similarly with the severe immunosuppression analysis, the viral failure rate also increased with current age. The viral failure rate increased substantially from 1.6 per 100 person-years among those aged ≤19 years to 22.2 per 100 person-years among those aged ≥25 years, although the confidence interval was wide for the last age group, reflecting the small amount of person-time.

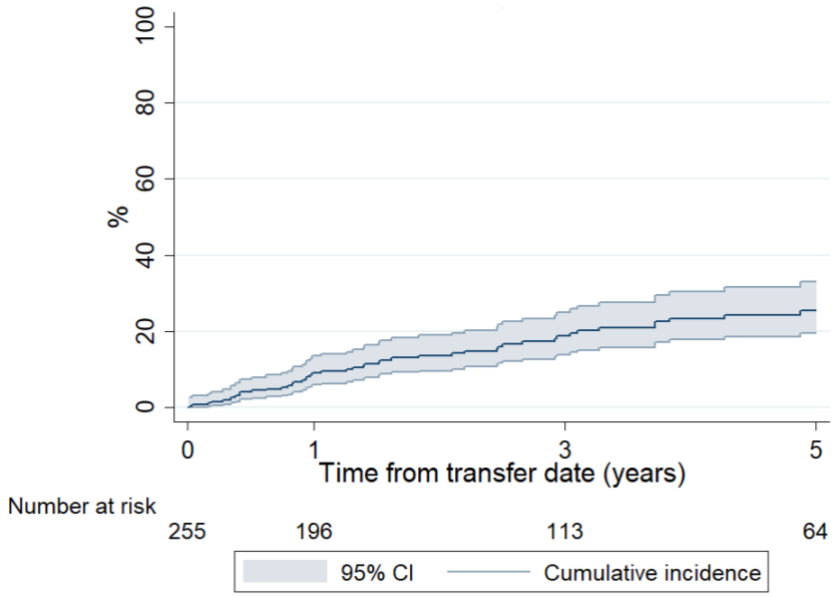
Table 6.6: Viral failure rates of young people with HIV per 100 person-years by demographic characteristics

Demographic characteristics		**Viral failure outcome**		
		Number of events	Person-years	Rate (95% CI)
Overall		57	10346.2	0.6 (0.4, 0.7)
Sex				
	Female	33	4559.3	0.7 (0.5, 1.0)
	Male	24	5787.8	0.4 (0.3, 0.6)
Ethnicity				
	White/other	10	2498.3	0.4 (0.2, 0.7)
	Black	47	7609.9	0.6 (0.5, 0.8)
Place of birth				
	UK	24	3848.7	0.6 (0.4, 0.9)
	Born abroad	33	6228.3	0.5 (0.4, 0.7)
Current age				
	<19	8	5071.2	1.6 (0.8, 3.2)
	20-24	31	5044.6	6.1 (4.3, 8.7)
	≥25	18	812.6	22.2 (14.0, 35.2)
Calendar year of transfer				
	≤2008	20	4233.2	0.5 (0.3, 0.7)
	2009-2012	31	4681.9	0.7 (0.5, 0.9)
	2013-2016	6	1383.6	0.4 (0.2, 1.0)

6.4.2.3. Risk of viral failure in adult care

Figure 6.12 presents the cumulative incidence of viral failure after transfer to adult care. After one year, 9% (95% CI 6%, 14%) had experienced viral failure, increasing to 19% (95% CI 14%, 25%) and 26% (95% CI 19%, 33%) by three and five years, respectively. The confidence intervals widened with time as the numbers still at risk declined.

Figure 6.12: Cumulative incidence of experiencing viral failure (defined as two consecutive viral loads >400 copies/ml) in adult care (N=255)



6.4.2.4. Factors associated of viral failure after transfer to adult care

Table 6.7 presents the factors associated with viral failure in adult care using Cox proportional hazard model. In the unadjusted analysis, being female (HR: 2.3 (95% CI 1.2, 4.2), p=0.008), experiencing viral failure in the last year of paediatric care (HR: 2.0 (95% CI 1.1, 3.7), p=0.02) and being on a non-cART regimen at transfer date (HR: 2.1 (95% CI 1.0, 4.4), p=0.05) were all associated with viral failure in adult care.

After adjusting for sex, age and year of transfer, being female (aHR: 2.3 (95% CI 1.2, 4.2), p=0.009) and experiencing viral failure in the last paediatric year (aHR: 2.0 (95% CI 1.1, 3.7), p=0.04) remained associated with viral failure in adult care. An interaction was found between calendar year and ART regimen at time of transfer. Among young people on non-cART regimens at transfer, those who transferred in later calendar years had an increased hazard of viral failure (aHR: 1.4 (95% CI 1.1, 1.9) per calendar year increase, p=0.02). Among those on a cART regimen at transfer, there was no significant calendar year effect (aHR: 0.9 (95% CI 0.8, 1.0) per year increase, p=0.17). None of the other demographic, clinical and clinic-level characteristics were significantly associated and there was no evidence to suggest a clinic-level cluster effect (both p=0.50).

Table 6.7: Factors associated with viral failure (≥2 VL >400 copies/ml), results from Cox proportional hazards model (N=255)

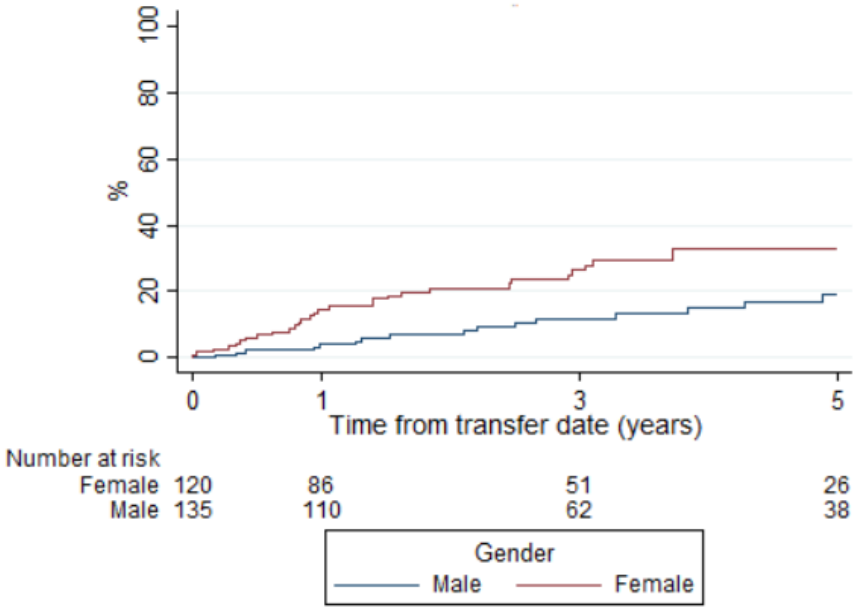
		N (%)	Unadjusted hazard ratio (95% CI)	P-value	Adjusted hazard ratio (95% CI)	P-value
Variables selected for inclusion *a priori*						
Sex	Male	135 (53)	1		1	
	Female	129 (47)	2.3 (1.2, 4.2)	0.008	2.3 (1.2, 4.2)	0.009
Age at transfer, per year increase		254 (100)	0.9 (0.7, 1.1)	0.23	0.9 (0.7, 1.1)	0.27
Demographic variables						
Ethnicity	Black	202 (81)	1			
	White/other	48 (19)	0.8 (0.4, 1.6)	0.50		
Place of birth	Born Abroad	150 (60)	1			
	UK	100 (40)	1.0 (0.5, 1.8)	1.00		
Variables at the last paediatric visit						
CD4 nadir, per 100 cell/mm$_3$ increase		255 (100)	1.1 (0.9, 1.3)	0.41		
CD4 count, per 100 cell/mm$_3$ increase		255 (100)	1.1 (1.0, 1.2)	0.22		
Viral failure in last paediatric year, copies/ml (>400 copies/ml)	Yes	63 (25)	2.0 (1.1, 3.7)	0.02	2.0 (1.0, 3.7)	0.04
	No	192 (75)	1		1	
AIDS diagnosis	Yes	184 (72)	1			
	No	71 (28)	1.6 (0.9, 2.9)	0.14		
ART regimen						
	Combination ART	226 (89)	1			
	Non-combination ART	29 (11)	2.1 (1.0, 4.4)	0.05		
Calendar year of transfer, per year increase		249 (98)	1.0 (0.9, 1.1)	0.80	Test for interaction with ART regimen, p=0.007	
Effect of calendar year at transfer date among those on a cART regimen at transfer date, per year increase					0.9 (0.8, 1.0)	0.17
Effect of calendar year at transfer date among those on a non-cART regimen at transfer date, per year increase					1.4 (1.1, 1.9)	0.02
Duration on ART, per year increase		255 (100)	1.0 (1.0, 1.1)	0.34		
Gap in care$_1$, per month increase		248 (97)	1.0 (0.9, 1.0)	0.16		
Adult clinic-level variables						
Clinic type	Young persons' clinic	193 (91)	1			
	General adult clinic	19 (9)	1.3 (0.5, 3.3)	0.57		
Level of youth-friendliness, per 1 unit increase		212 (83)	0.9 (0.7, 1.1)	0.19		

1: duration between the last paediatric visit and the first adult visit

6.4.2.5. Risk of viral failure in adult care by identified risk factors

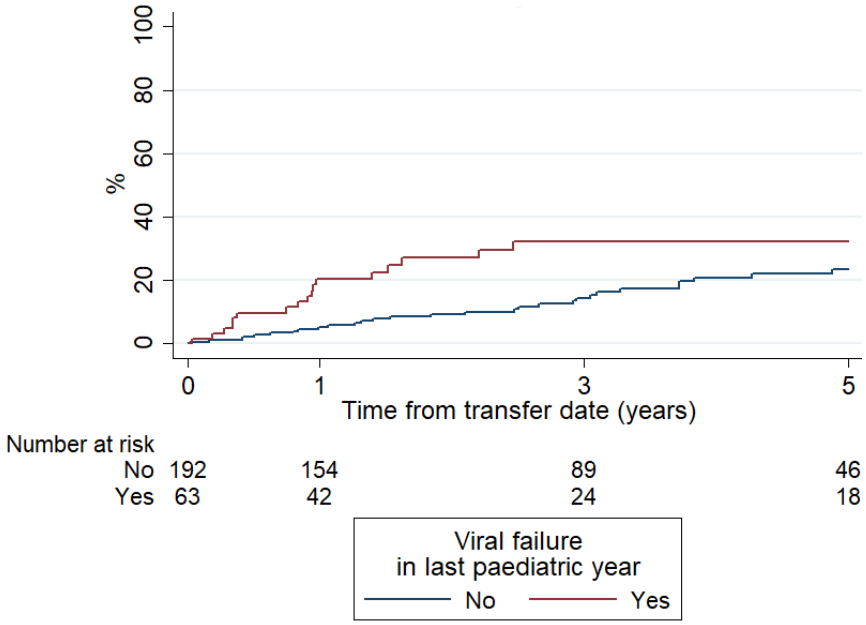
Figure 6.13 presents the cumulative incidence of viral failure in adult care by sex. Females had a two-fold increased risk of experiencing viral failure in adult care compared to males. One year following transfer, the cumulative incidence among females was almost three times the incidence for males (15% (95% CI 9%, 23%) vs 4% (95% CI 2%, 10%)). By three and five years post-transfer, the cumulative incidence of viral failure in adult care for both groups were 27% (95% CI 19%, 37%) vs 12% (95% CI 7%, 20%), and 33% (95% CI 24%, 44%) vs 19% (95% CI 12%, 30%), respectively. However, the confidence intervals overlapped between the different time points.

Figure 6.13: Cumulative incidence of experiencing viral failure in adult care by sex (N=255)



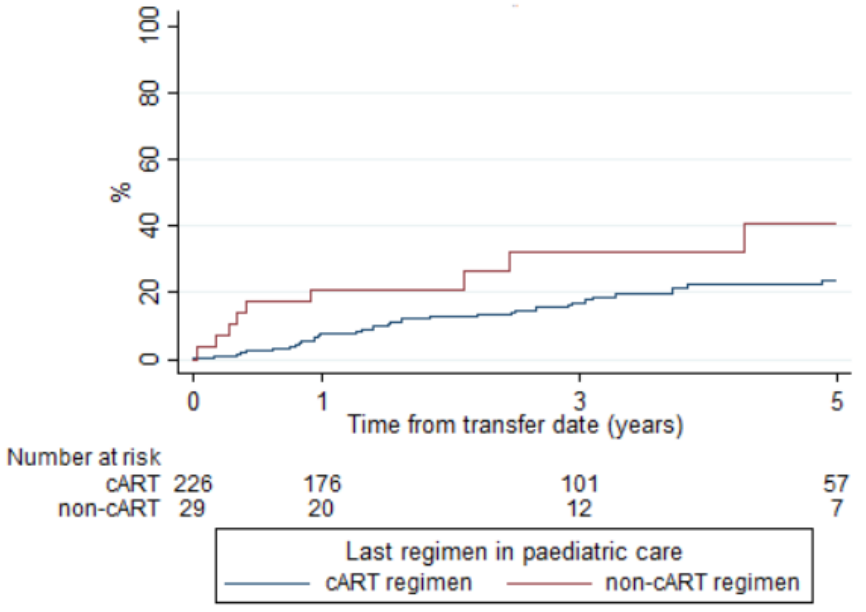
Despite all young people being virally suppressed by the last paediatric visit, having experienced viral failure during the last paediatric year had higher risk of experiencing viral failure in adult care compared to those with no viral failure in the last year of paediatric care (Figure 6.14). The cumulative incidence of viral failure in adult care for both groups were 20% (95% CI 12%, 33%) vs 5% (95% CI 3%, 10%) by one year post-transfer and 32% (95% CI 21%, 48%) vs 14% (95% CI 10%, 21%) by three years post-transfer, respectively. Those who experienced viral failure in their last paediatric year experienced no new viral failure events following the third year of adult follow-up, while the other group had an incidence of 23% (95% CI 17%, 33%) by five years.

Figure 6.14: Cumulative incidence of experiencing viral failure in adult care by viral failure status in the last year of paediatric care (N=255)



Young people who were on a non-cART regimen at transfer had greater risk of experiencing viral failure in adult care compared to those on a cART regimen (Figure 6.15). At one year post-transfer, the cumulative incidence of viral failure was 21% (95% CI 10%, 41%) vs 7% (95% CI 5%, 12%), rising to 32% (95% CI 17%, 55%) vs 17% (95% CI 12%, 24%) by three years post-transfer and 41% (95% CI 22%, 67%) vs 24% (95% CI 17%, 32%) by five years, respectively.

Figure 6.15: Cumulative incidence of experiencing viral failure in adult care by ART regimen at transfer (N=255)



Among the 57 young people who experienced viral failure in adult care, just over half (53%) still had viral failure at the last visit in adult care.

6.4.2.6. Sensitivity analysis

In the sensitivity analysis, viral failure was re-defined as the first 2 consecutive VL >1000 copies/ml. There were 271 young people on treatment with a VL ≤1000 copies/ml at the date of transfer who were eligible for inclusion in the sensitivity analysis. Of these, 55 (20%) young people had experienced two consecutive VL >1000 copies/ml in adult care. The cumulative incidence of the redefined viral failure outcome was slightly lower than the main analysis at 8% (95% CI 6%, 13%) at one year, increasing to 17% (95% CI 13%, 23%) and 23% (95% CI 17%, 30%) by three and five years of adult follow-up (Figure 6.16).

Figure 6.16: Cumulative incidence of experiencing viral failure (≥2 consecutive viral loads >1000 copies/ml) in adult care (N=271)

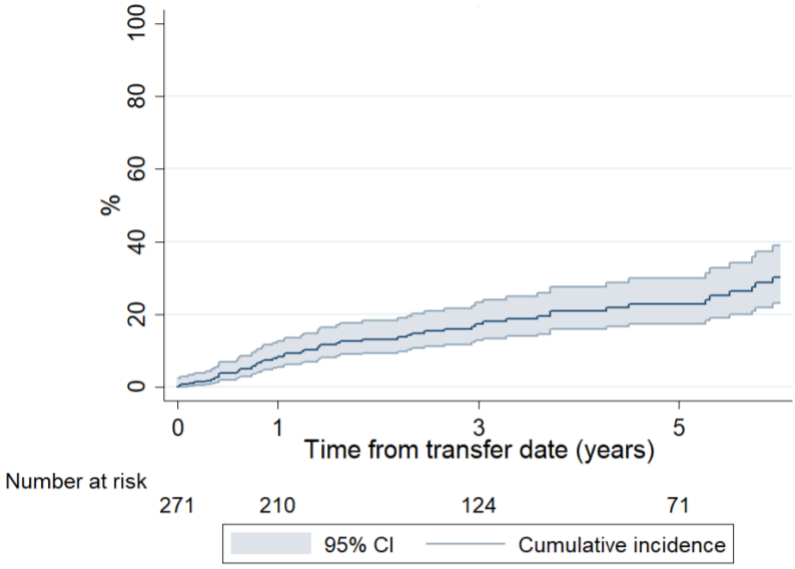


Table 6.8 presents the factors associated with viral failure (2 VL >1000 copies/ml) from the univariable and multivariable analysis using Cox proportional hazards models. In the sensitivity analysis, being female (HR: 1.8 (95%1.0, 3.2), p=0.04) and experiencing viral failure in the last year of paediatric care (HR: 3.1 (95% CI 1.8, 5.4), p<0.001) were associated with viral failure in adult care, which is consistent with the main univariable analyses. In contrast to the main analyses, younger age at transfer date became significantly associated (HR: 0.8 (95% CI 0.7, 1.0) per year younger, p=0.05) in the sensitivity analysis, while being on a non-cART regimen no longer had an effect on the redefined viral failure outcome.

In the multivariable analysis, sex, age and year at transfer were selected *a priori*. Females were 63% more likely to experience viral failure than males (aHR: 1.7 (95% CI 1.0, 3.0), p=0.06). Having viral failure (VL >400) in the last paediatric year (aHR: 3.3 (95% CI 1.9, 5.7), p<0.001) more than tripled the risk of viral failure in adult care. In contrast to the main analysis, calendar year of transfer and non-cART regimens were no longer had a significant effect in the sensitivity analysis.

Table 6.8: Factors associated with viral failure (≥2 VL >1000 copies/ml), results from Cox proportional hazards model (N=271)

		N (%)	Unadjusted hazard ratio (95% CI)	p-value	Adjusted hazard ratio (95% CI)	p-value
Variables selected for inclusion *a priori*						
Sex	Male	147 (54)	1		1	
	Female	124 (46)	1.8 (1.0, 3.2)	0.04	1.7 (1.0, 3.0)	0.06
Age at transfer, per year increase		270 (100)	0.8 (0.7, 1.0)	0.05	0.9 (0.7, 1.1)	0.16
Calendar year of transfer, per year increase		265 (98)	0.9 (0.8, 1.0)	0.11	0.9 (0.8, 1.0)	0.18
Demographic variables						
Ethnicity	Black	216 (81)	1			
	White/other	50 (19)	0.9 (0.4, 1.8)	0.71		
Place of birth	Born Abroad	158 (60)	1			
	UK	106 (40)	1.3 (0.8, 2.3)	0.34		
Variables at the last paediatric visit						
CD4 nadir, per 100 cell/mm^3 increase		271 (100)	1.0 (0.9, 1.2)	0.79		
CD4 count, per 100 cell/mm^3 increase		271 (100)	0.9 (0.8, 1.1)	0.28		
Viral failure in last paediatric year, copies/ml	Yes	79 (29)	3.1 (1.8, 5.4)	<0.001	3.3 (1.9, 5.7)	<0.001
	No	192 (71)	1		1	
AIDS diagnosis	Yes	194 (72)	1			
	No	77 (28)	1.1 (0.6, 1.9)	0.87		
ART regimen	Combination ART	238 (88)	1			
	Non-combination ART	33 (12)	1.8 (0.9, 3.6)	0.10		
Duration on ART, per year increase		271 (100)	1.0 (1.0, 1.1)	0.32		
Gap in care[1], per month increase		264 (97)	1.0 (1.0, 1.0)	0.39		
Adult clinic-level variables						
Clinic type	Young persons' clinic	205 (91)	1			
	General adult clinic	21 (9)	0.6 (0.2, 2.0)	0.43		
Level of youth-friendliness, per 1 unit increase		226 (83)	1.0 (0.8,1.3)	0.95		

1: duration between the last paediatric visit and the first adult visit

6.5. Discussion

In this chapter, I described the immunological and virological outcomes of young people with HIV who transferred to adult care in the UK. The analyses in this chapter were based on linking young peoples' paediatric records from CHIPS to their adult records from the UK CHIC study. This approach has enabled me to extend follow-up after the transfer date and thus create a life-course dataset with a median duration of three years of adult follow-up. Among this cohort, there has been significant improvements in immunological and virological characteristics over calendar years of transfer, which likely reflects advancements in HIV treatment options, clinical care and the recent shift towards universal ART, irrespective of immunological status. My findings also identified a sub-group of young people with prior history of poor VL control who were more susceptible to severe immunosuppression and viral failure in adult care. Young people with suboptimal CD4 outcomes and a previous AIDS diagnosis in paediatric care were more likely to experience severe immunosuppression following transfer to adult care.

6.5.1. Findings interpretation and comparison to wider literature

6.5.1.1. Changes in immunological and virological characteristics before and after transfer date

The number of young people who transferred from paediatric to adult care increased from 2 in 2000 to 56 in 2014, reflecting the aging CHIPS cohort. Subsequently, the numbers declined to 39 and 6 in 2015 and 2016, respectively. The low number of young people observed in 2016 is likely due to a CHIPS reporting lag but could also reflect the drastically reducing MTCT rates over the years as a result of the effective PMTCT programmes in the UK [56].

Following transfer to adult care, immunological characteristics did not significantly change, with 16% having a CD4 count <200 cells/mm$_3$ at 12 month before and after transfer (p=0.75). This finding is comparable with several other studies that also found no significant change in CD4 outcomes by 12 and 24 months before and after transfer [104,108,136]. Contradictory findings were reported by one study of 24 young people with PHIV, where the median CD4 count had improved from 534 cells/mm$_3$ at last paediatric visit to 716 cells/mm$_3$ at last adult visit [130]. However, this was a single-site study in Italy with a much smaller sample size than the other mentioned studies, which considerably limits the generalisability of those study findings. In addition, the small sample size could have meant that the differences detected were due to chance, although the small sample size would increase the likelihood of a type II error (i.e. false negative finding) [218]. A previous multi-region UK study of 271 young people whose records were linked between CHIPS and the UK CHIC study, modelled the CD4 slopes over time in paediatric and adult care follow-up using mixed effects regression methods [104]. The CD4 trajectory was found to already be declining in the last years of paediatric care leading up to transfer but increased following transfer among white males and females, continued to decline among black males and remained stable among black females. In contrast, no effect of ethnicity or sex were found in my study in the multivariable model, although the statistical methods differed where time to event analyses were carried out in my study.

In my study, the percentage severely immunosuppressed at 12 months post-transfer (i.e. 16%) was slightly higher than the 10% reported to ever be severely immunosuppressed among the general adult HIV population in the UK CHIC study in the last 24 months of follow-up by 2013 (S. Jose, personal communication). However, as the UK CHIC estimate is not stratified by age, the difference may be due to differences in mode of HIV acquisition. Also the vast majority of the UK CHIC population have non-perinatal HIV acquisition, were diagnosed in adult care and aged >30 years [95].

In my cohort, there was a significant improvement in the proportion virally suppressed increasing from 64% to 70% from 12 months before and after transfer date (p=0.006). Similar virological improvements post-transfer was reported by a London study of 201 young people who transferred to one of four adult clinics [136] and another New York study of 735 young people who transferred to adult care [138]. Although, the percentage increase in level of virally suppression differed between these two studies, at 20% and 3%, respectively. However, my proportion (70%) virally suppressed at 12 months post-transfer were considerably higher than the London (63%) and New York study (49%). In contrast, studies from the UK, USA (i.e. Atlanta and Baltimore), Canada, Sweden and the Netherlands reported viral suppression levels to not significantly differ before and after transfer date [104,105,108,110,116,131]. The various virological trends reported across the literature could reflect the different VL cut-offs (i.e. <40, ≤50, ≤200, and ≤400 copies/ml), settings and time points used before and after transfer. The improved level of virological suppression in my study population could possibly be due to a calendar year effect and the availability of better ART regimens in the later years [134]. The improvements is likely not due to increased maturity, as the rate of viral failure in adult care was found to substantially increase with current age, although the small amount of person-years in the oldest age group (≥25 year olds) resulted in less accurate estimates evident in the wide confidence intervals.

6.5.1.2. Severe immunosuppression and viral failure following transfer to adult care

After five years of follow-up in adult care, the incidence of severe immunosuppression and viral failure was high (both 26%) in this analysis which was restricted to participants on ART and with a CD4 count >200 cells/mm$_3$ and VL <400 copies/ml at transfer. This is the first post-transfer study to report cumulative incidence of either outcome, but these estimates refer to the first events of severe immunosuppression and viral failure and do not represent a persistent clinical state. Of those who experienced severe immunosuppression or viral failure in adult care, over half experienced their first event in the first two years following the transfer date. It is difficult to discern whether the poor immunological and virological outcomes in the first couple of years of adult follow-up are due to transferring to adult care or due to pre-existing health conditions from paediatric care. There is, however, previous evidence to support the latter point with two previous UK studies having reported a declining CD4 count trajectory among young people in the last few years of paediatric care, prior to transfer date [104,136]. Of those who ever experienced severe immunosuppression or viral failure in adult care, 42% and 53% were still experiencing severe immunosuppression and viral failure by the last adult visit, respectively. These findings indicate that for half the population who experienced poor immunological and virological outcomes, these

poor outcomes persisted after a median follow-up of three years post-transfer, highlighting the need for further clinical support for this vulnerable population.

In adult care, the overall rate of severe immunosuppression was 0.5 (95% CI 0.4, 0.6) per 100 person-years. The rates were comparable by sex and calendar year of transfer, although, in unadjusted analysis, there was some evidence to suggest being female (HR: 1.6 (95% CI 0.9, 2.6), p=0.09) or transferring in earlier calendar years (HR: 1.1 (95% 1.0, 1.2), per year earlier, p=0.01) increased the hazard of experiencing severe immunosuppression in adult care. After adjusting for age, virological and immunological characteristics at transfer, the sex and calendar year effect disappeared. Results from the multivariable analysis for severe immunosuppression indicated young people who transferred with lower CD4 count or had prior AIDS diagnosis or viral failure in the last year of paediatric care had a significant risk of severe immunosuppression in adult care. No effect of sex, ethnicity, place of birth or calendar year at transfer was detected. These findings highlight a subset of young people with poorer health outcomes towards the end of paediatric care who continue to struggle managing their HIV disease post-transfer, suggesting the need for additional support while in paediatric care. The multi-region UK study and London study also explored risk factors for poor CD4 outcomes in adult care [104,136]. The London study reported virological failure and disease progression in paediatric care to also predict declining CD4 trends, although disease progression was not specified. Nonetheless, neither study explored the effect of prior AIDS diagnosis or CD4 count at transfer on poorer immunological outcomes in adult care. Similar findings were reported by a Thai study of 13 to 16 year olds who were attending a transfer clinic where the viral load and CD4 count was closely associated with immunological status at the last visit following transfer, although the different settings and the younger adolescent cohort limits this study's comparability to my findings [219]. There were no demographic predictors of severe immunosuppression following transfer. In contrast, the multi-region UK study and the London study found black males [104] and younger ages [104,136] to be associated with declining CD4 trajectory in adult care. However, the immunological outcome differed between my study and the two other UK studies differed, with mine looking at time to the first CD4 count <200 cells/mm3 and the other two studies looking at the CD4 trajectory in adult care.

In adult care, the overall rate for viral failure was similar to that of severe immunosuppression at 0.6 (95% CI 0.4, 0.7) per 100 person-years. The viral failure rate did not differ by sex or calendar year, evident with the overlapping confidence intervals. Despite this, a sex and calendar year effect was observed in the univariable and multivariable analysis for viral failure in adult care, which showed females to have double the hazard (aHR: 2.3 (95% CI 1.2, 4.2), p=0.009) of experiencing viral failure in adult care compared to males and a strong sex effect persisted in the sensitivity analysis. Of the only two post-transfer studies from Spain and the USA, to date, that have explored the effect of sex on viral failure in adult care both reported no significant association [131,133]. Thus one possibility is that the sex effect found in my study may be attributable to chance. In addition, a consistent relationship between sex and treatment outcomes has not been established [36,220–222] and any sex effect could potentially be confounded by unassessed behavioural factors [222]. In my study, transferring in later calendar years while on a non-cART regimen was significantly associated with viral failure post-transfer. This group of young people

not on cART in recent calendar years likely reflects a vulnerable sub-population who failed to be on cART (as a first line recommendation from BHIVA and WHO ART guidelines [119,223]), which may be due to limited treatment options caused by possible development of multi-class drug resistance and/or adherence issues [224]. None of the other demographic characteristics, including age, ethnicity and place of birth, were significantly associated with viral failure in adult care. The Spanish post-transfer study found that none of their explored demographic factors were associated with viral failure in adult care, although the factors explored were not specified by the study authors [133]. In my study, prior viral failure in the last year of paediatric care was predictive of both severe immunosuppression and viral failure in adult care. These findings are in line with a post-transfer study from Atlanta, USA, which reported viral failure prior to transfer to be a significant risk factor of viral failure at the most recent visit in adult care [131]. The Atlanta study also stated gap in care (i.e. duration between the last paediatric visit and first adult visit) of >3 months to be predictive of viral failure post-transfer, although, my study identified no such association between time to linkage and viral failure post-transfer. The difference in findings may be due to the US study comprising predominantly of young people with BHIV (85%) compared to our study in which 92% of young people had PHIV, as well as differences in healthcare settings, where the UK has free national healthcare compared to the USA.

In my study, the impact of youth-friendly services available in adult clinics was assessed on severe immunosuppression and viral failure in adult care, using clinic-level data obtained from my 2017 clinic survey study. In Chapter 4, I hypothesised that higher provision of youth-friendly services by adult clinics would be associated with better immunological and virological outcomes as an indirect result from increasing engagement in care. However, the clinic-level characteristics had no significant effect on severe immunosuppression or viral failure in adult care, as observed with the AIDS/mortality and disengagement outcomes in Chapter 5. Only on a univariable level was there some evidence to suggest young persons' clinics or clinics with higher youth-friendliness scores had reduced risks of experiencing severe immunosuppression, but this association was not significant after adjusting for sex, age and calendar year at transfer. This is likely a reflection of the cross-sectional nature of the clinic-level data collected and not a lack of efficacy of youth-friendly services. The effect of youth-friendliness in this study was likely confounded by calendar year as many youth-friendly services were developed in the recent decade following the publication of transfer and youth-friendly guidelines [84,176,204]. In my study, young people may have transferred to an adult clinic in 2008 that only started offering youth-friendly services in 2017. Therefore, such individuals would not have been exposed to the youth-friendly services. The benefits of clinic interventions on immunological outcomes in adult care have been investigated by other studies [156,157]. A London study investigated the effect of motivational interviewing and financial incentive on 11 non-adherent young people with PHIV and a CD4 count <200 cells/mm_3 at the study enrolment date. After a 12 month intervention period and an overall 24 month follow-up period, the mean CD4 count increased by 122 cells/mm_3. However, the small sample size of immunosuppressed patient in a single clinic setting highly limits the generalizability of this study's findings. Contrasting findings were reported by another youth-friendly intervention study of 25 young people who received 6 months of daily text messages that acted as medication reminders. That study found no significant change in CD4 or

VL outcomes [156]. The inconsistent study findings are likely due to the high variability of youth-friendly interventions investigated, thus making any study comparability difficult.

6.5.2. Limitations

This study has several limitations, one of which is the study comprising of only young people who transferred to UK CHIC-participating adult clinics. As previously mentioned, the UK CHIC study does not have national coverage. In Chapter 5, my cohort of young people who transferred to UK CHIC clinics had similar demographic characteristics to those who transferred to non-UK CHIC clinics, but poorer clinical characteristics at time of transfer. As a result, my study likely has a selection bias where the severe immunosuppression and viral failure risks post-transfer may be overestimations when compared to the wider population of young people with HIV. Therefore, the generalisability of my findings are likely limited beyond the UK CHIC cohort of young people. On the other hand, my inclusion criteria for the severe immunosuppression and viral failure analyses were restricted to young people on ART for ≥6 months in paediatric care and with a CD4 ≥200 cells/mm_3 or VL ≤400 copies/ml at transfer, respectively. This allowed me to investigate the risk of experiencing either of these outcomes in adult care among young people who were event free prior to entering the analysis period. The small group of young people with limited ART use (N=52) were not included in the immunosuppression and viral failure analyses as their health outcomes would expectedly be different to those with several years of ART experience. This was evident as the majority the ART-naïve group were virally unsuppressed at transfer date which would have made it difficult to investigate the risk of viral failure among this group. Additionally, the inclusion of the ART-naive group would have caused the effect of ART inexperience to dominate the effect of all other exposures when investigating immunosuppression or viral failure in adult care, and the analyses were not repeated for ART-naive group due to their small number (N=52). Nonetheless, my inclusion criteria for the severe immunosuppression and viral failure analyses resulted in the study sample being representative of young people with better treatment, immunological and virological outcomes at transfer.

Similar to the time to event analyses in Chapter 5, time at risk was calculated using the last paediatric visit as time zero and a proxy for transfer date. However, if participants had periods of shared care between paediatric and adult care, the exact date of transfer is unclear which may affect the accuracy of the estimates rates for severe immunosuppression and viral failure.

Due to missing CD4 and/or VL data, 41 young people were excluded from the severe immunosuppression analysis due to not having ≥1 CD4 measurements in the UK CHIC dataset. Similarly for the viral failure analysis, 20 young people were excluded for not having ≥2 VL measurements in the UK CHIC dataset which was needed to meet the viral failure outcome. However, as the proportions excluded due to missing data were relatively low (10% and 5% missing CD4 and VL data, respectively), it is unlikely for the findings to be affected by substantial bias.

A single CD4 measurement was used to define severe immunosuppression, which increased the sample size, but also increased the risk of capturing a blip in CD4 count, and thus resulting in a less accurate incidence estimate. This was confirmed in the sensitivity analysis, where severe

immunosuppression redefined using ≥2 CD4 measurements, and a lower cumulative incidence was found. This suggests a sub-group of young people soon recovered and only experienced a blip in CD4 count. However, risk factors identified in the main severe immunosuppression analysis still had a significant effect when severe immunosuppression was redefined in the sensitivity analysis.

Another limitation of my study was only exploring demographic and clinical factors as potential risk factors of severe immunosuppression and viral failure due to the CHIPS and UK CHIC datasets being limited to such data. The Dutch post-transfer study reported non-clinical factors such as lower educational attainment level, knowledge of the HIV disease and autonomy over ART regimens to be predictive of viral failure following-transfer [105]. A London audit study of 11 young people who died following transfer found high levels of mental health diagnoses (82%), poor adherence (82%) and ART resistance (73%) [78]. These factors were not assessed in my study due to data on mental health diagnoses, drug resistance and ART adherence not being collected by either the CHIPS or UK CHIC study. It is therefore possible that the exposure effect may be diluted due to not taking into account these unmeasured confounders [225]. Similarly, there may be reporting errors in the exposure variables that could also result in the dilution of the detected exposure effects.

As my research aimed to identify risk factors of poor health following transfer, the outcomes of interest were of specific endpoints in adult care rather than broader outcomes such as the evolution of CD4/VL in adult care. While the broader approach is more informative in describing the CD4/VL trajectories, the more specific approach helped address risk groups who were more susceptible to severe immunosuppression and viral failure. On the other hand, my study was limited by the short term outcomes due to insufficient numbers with longer term follow-up which was evident in the wider confidence intervals observed during the later years of adult follow-up. Longer-term data are needed to assess if the effect of the identified risk factors persist. All issues and biases identified in this study are summarised in Table 6.9, along with the direction of bias on the study findings.

6.5.3. Conclusion

In summary, the findings in this chapter highlight the clinical complexities of this population. Despite the population of interest consisting of young people with good CD4 and VL outcomes and on ART at transfer, the risk of severe immunosuppression and viral failure among this population is still a concern that requires additional clinical care and monitoring following transfer to adult care.

Table 6.9: Summary of issues and errors impacting the study findings

Issue	Type of error	Potential effect of potential bias on exposure or outcome effect estimates (where applicable)	Adjustment made
Denominator			
CHIPS patients who transferred to non-UK CHIC clinics were excluded	Selection bias that may limit the generalizability of findings	-	
CHIPS patients who did not have at least 1 adult visit were excluded	Selection bias that may limit the generalizability of findings	-	
Participants with missing CD4/VL data were excluded	Missing data	Either	
Inclusion criteria of participants on ART without severe immunosuppression or viral failure at transfer	Selection bias that may limit the generalizability of findings	Underestimation	
Outcome variables			
Time at risk to AIDS/mortality and disengagement were calculated from the last paediatric visit date but transfer to adult care may have happened after this date, or before this date if there was a period of shared care	Misclassification	Unclear effect on rate	
One rather than two consecutive CD4 measurements used to define severe immunosuppression	Misclassification	Overestimation	Sensitivity analysis used two consecutive CD4 measurements
Exposure variables			
Clinic-level variables were from one point in time while service provision may have changed over time	Temporal bias and misclassification of youth friendliness and clinic type variables	Diluted exposure effect	
Errors in reporting of potential confounding factors (e.g. calendar year of transfer)	Misclassification of exposure	Diluted exposure effect	
Laboratory measures (CD4, viral load) may not be measured at the actual transfer date, and may have changed by the transfer date	Misclassification of exposure	Diluted exposure effect	
Unmeasured confounders	Residual confounding	Diluted exposure effect	

7. Chapter 7: Cascade of care following transfer to adult care

7.1. Chapter content and aims

7.1.1. Chapter content

This chapter provides a national overview of the cascade of care among young people with HIV transferring from paediatric to adult care, taking a public health perspective. This chapter also combines the engagement in care and health outcomes explored in the previous chapters. The cascades were designed to measure how successfully young people with HIV progressed through the adult care pathway, from linkage to care, engagement in care and treatment uptake to achieving viral suppression. As an additional last step in the cascades, I explored the possibility of measuring young people's CD4 status using surveillance data. The cascade of young people with HIV who transferred from paediatric care, the large majority of whom have PHIV, was then compared to that of young people with BHIV in adult care. The cascade work used national adult surveillance data from SOPHID and HARS. Separate cascades using different definitions were constructed for the SOPHID and HARS datasets to take into account differences in frequency of data collection between these two data sources.

In this chapter, young people who transferred from paediatric to adult care are referred to as 'young people with PHIV' or the 'perinatal group', despite 4% diagnosed with BHIV and 3% with an unknown mode of acquisition in paediatric care. This allowed for simpler comparison with young people with BHIV.

7.1.2. Aims

The aims of this chapter are to:

1. describe the cascade of care at 12 months after the first adult visit, and in the last year of adult care follow-up, among young people with PHIV following transfer;
2. describe the cascade of care at 12 months after the first adult visit, and in the last year of adult care follow-up, among young people with BHIV; and
3. compare the cascades at 12 months after the first adult visit, and in the last year of adult care follow-up by mode of HIV acquisition (PHIV vs BHIV group).

7.2. Methods

7.2.1. Study design and population

The cascades of care were measured among young people with PHIV who were documented in CHIPS as transferred to adult care. The initial plan was to measure the cascade among young people with data linked between CHIPS and SOPHID/HARS. However, by definition these participants would require at least one adult visit to be captured in SOPHID/HARS, which would pose a selection bias including only those who engaged in care post-transfer. Young people known to have moved abroad or LTFU from paediatric care were excluded from the denominator due to the majority (65% and 82%, respectively) of whom could not be linked to records in the SOPHID/HARS datasets, suggesting they had not attended adult care at all.

Young people with BHIV in the SOPHID and/or HARS database were selected as a comparison group. For both the PHIV group and the BHIV group, cascades were measured at 12 months following the first adult visit following transfer and in the last year of adult follow-up prior to study

closure date. The cascades all had a longitudinal study design as the different cascade steps captured different time points (e.g. date of transfer, first adult visit and the 12 month visit in adult care).

7.2.2. Data source used for the cascades of care

The development of definitions for the cascade steps varied by the adult data source (SOPHID vs HARS). As some participants had adult care data only in the SOPHID dataset, others only HARS data, and some both, different approaches were explored to ascertain the best method to define the cascade across these groups.

I determined the best approach to separate the total population into two groups: (1) participants with SOPHID data, with or without subsequent HARS data; and (2) participants with only HARS data. This approach allowed for consistent cascade definitions to be used within each group, although, for group (1), this required reducing the HARS data to only one patient record per calendar year, thus mimicking the SOPHID dataset. This approach also allowed group (1) to be based on a larger sample size (N=689) than if this group was split into those with only SOPHID data (N=271) vs only HARS data (N=53). Throughout this chapter, group (1) will be referred to as those with SOPHID +/- HARS data and group (2) as those with HARS only data.

Prior to this, I considered constructing the cascades for a single population, which would include all participants with SOPHID and/or HARS data. However, this approach was inappropriate due to the differences in data collection frequency and time periods covered by the two surveillance systems. The different cascade step definitions required for each data source would in turn complicate the interpretation of the findings and limit comparability. Additionally, with HARS covering a shorter period of time, participants only in HARS would have less adult data and a higher proportion would be excluded from analyses than SOPHID participants. Therefore, this approach was not pursued.

Another considered approach was to divide participants into two groups: 271 participants with only SOPHID data (first and last visit in SOPHID) and 53 participants with only HARS data (first and last visit in HARS). However, this approach excluded the majority of participants (N=418) with initial SOPHID follow-up and subsequent HARS follow-up, and was thus not pursued further.

7.2.2.1. Inclusion criteria for young people who transferred from paediatric to adult care

As HARS is the newer surveillance system implemented to phase out SOPHID, 'SOPHID-participating adult clinics' refers to clinics that have not yet started reporting to HARS during a period of interest, while HARS-participating clinics refer to those who have started reporting to HARS.

Cascades using SOPHID +/- HARS data included those who:

a) were aged ≥13 years by 01/04/2017 (CHIPS database closure date);
b) were documented in CHIPS to have transferred to a SOPHID-participating adult clinic; and
c) had a CHIPS transfer date prior to 01/01/2015 (i.e. allowing for ≥12 months potential follow-up prior to SOPHID database closure date).

Cascades using HARS data only included participants who:

a) were aged ≥13 years by 01/04/2017 (CHIPS database closure date);
b) were documented in CHIPS to have transferred to a HARS-participating adult clinic; and
c) had a CHIPS transfer date between 31/12/2014 and 01/04/2016 (i.e. allowing for ≥12 months potential follow-up prior to HARS database closure date).

7.2.2.2. Inclusion criteria for young people with BHIV in adult care

To ensure young people with BHIV had a median age and calendar year of entry into adult care that were similar to young people with PHIV (median age 17 years and median calendar year 2011), the former group was required to be aged 15-19 years and have entered adult care on or after 01/01/2008.

Cascades using SOPHID +/- HARS data included those who:

a) were aged 15-19 years at first visit in SOPHID;
b) had no record of attendance at a paediatric clinic, and were not in the CHIPS dataset;
c) were in the MSM or heterosexual exposure group; and
d) had a first visit date between 01/01/2008 and 31/12/2014 at a SOPHID-participating clinic (i.e. allowing for ≥12 months potential follow-up prior to SOPHID database closure date).

Cascades using HARS data only included those who:

a) were aged 15-19 years at first visit in HARS;
b) had no record of attendance at a paediatric clinic, and were not in the CHIPS dataset;
c) were in the MSM or heterosexual exposure group; and
d) had a first visit date between 31/12/2014 to 01/04/2016 at a HARS-participating clinic (i.e. allowing for ≥12 months potential follow-up prior to HARS database closure date).

There was potential for overlap between the 12 month and last visit time point where both could be based on the same patient visit date. This would occur if a participant had a 12 month visit that was also their last visit in adult care, therefore, such participants were excluded from the cascade in the last year of follow-up. In addition, young people who transferred to adult care and were identified in UK CHIC dataset as having died subsequently, were excluded from the last year cascade but not the 12 month cascade. This was so I could examine engagement of all

participants who transferred out of paediatric care in the 12 month cascade. HARS death data were not used due to substantial underreporting identified among young people who transferred to adult care (described in section 3.5.6), and SOPHID does not report death data.

7.2.3. Cascade definitions

As the SOPHID +/- HARS dataset is restricted to the last visit per calendar year, the first adult visit would actually be the last visit in the first calendar year of follow-up. In the HARS only dataset, the follow-up only covered between 31/12/2014 to 01/04/2017, there was not enough follow-up of young people to measure the HARS only cascade in the last year of follow-up – had I done this, there would have been a risk that values used to calculate this cascade would overlap with the 12 month HARS only cascade. Altogether, six cascades were measured with varying time points, data sources and populations of interest (Figure 7.1).

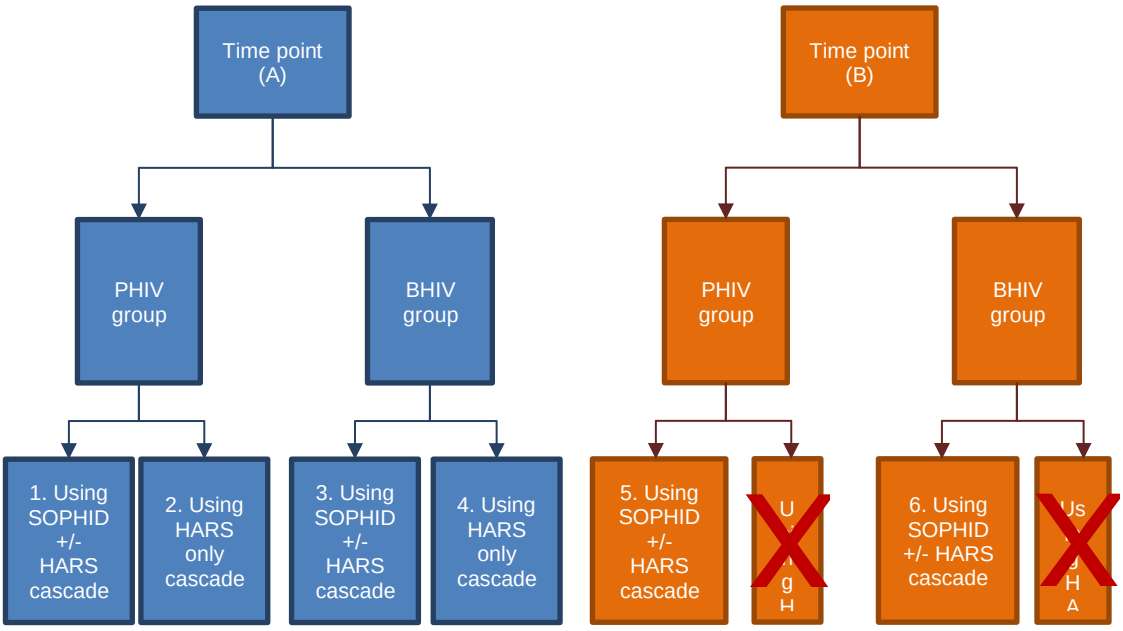
At the 12 month time point, cascades were measured:

1. among young people with PHIV using SOPHID +/- HARS data;
2. among young people with PHIV using HARS only data;
3. among young people with BHIV using SOPHID data +/- HARS data; and
4. among young people with BHIV using HARS only data.

In the last year of follow-up, two cascades were measured:

5. among young people with PHIV using SOPHID +/- HARS data; and
6. among young people with BHIV using SOPHID data +/- HARS data.

Figure 7.1: Flowchart of cascades measured at different time points by mode of HIV acquisition and data source used



7.2.4.1. Cascades measured at 12 months following the first adult visit

Table 7.1 describes the steps and respective definitions used for 12 month time point by data source and mode of HIV acquisition.

Young people transferring from paediatric to adult care

Using SOPHID +/- HARS data, the cascade at 12 months after first adult visit included the following steps: (1) transferred out of paediatric care; (2) linked to adult care; (3) engagement at 12 months; (4) on ART (any regimen); (5) VL ≤400 copies/ml; and (6) CD4 >500 cells/mm_3. The 'linkage to adult care' step refers to having a first adult visit following the transfer date. Engagement at the 12 month time point was defined as having a visit in the calendar year subsequent to the year of the first adult visit. For example, a participant reported as transferred to adult care in 2012 and had a first adult visit in December 2013 needed a visit at any point in 2014 to meet the 12 month engagement in care definition. The relaxed engagement definition was used to take into account the fact that SOPHID only collected data on the last visit in a given year rather than all visits. The ART, VL and CD4 estimates were based on the data recorded in the SOPHID +/- HARS dataset for that '12 month' visit. As part of a sensitivity analysis, the VL and CD4 status steps were also estimated using different cut-offs (VL ≤200 copies/ml and CD4 >350 cells/mm_3).

Using HARS only data, I was able to explore a more stringent definition for engagement in care at 12 months following the first adult visit. Rather than one engagement step as was used in the SOPHID +/- HARS cascade, the HARS cascade included two engagement steps. Participants needed ≥1 visit in the first 6 months and in 6 to 12 months following the first adult visit to qualify as engaged in care. In the HARS cascade the ART, VL and CD4 estimates used the same definitions as those used in the SOPHID +- HARS cascades and was based on the data recorded in the HARS only dataset for the '12 month visit'.

Young people with BHIV in adult care

The cascades for young people with BHIV used the same definitions as those used for the PHIV population. The only difference was the BHIV cascades starting from the 'linked to adult care' step and not the 'transferred out of paediatric care' step as young people with BHIV were diagnosed in adult care and did not previously attend paediatric care.

Table 7.1: Cascade steps and definitions used for the 12 month cascades by mode of HIV acquisition and data source

Cascade step	PHIV group			BHIV group	
	CHIPS	**SOPHID**	**HARS**	**SOPHID**	**HARS**
Step 1: Transferred out of paediatric care	✓	×	×	×	×
Step 2: Linkage to adult care (date of first adult visit)	×	✓	✓	✓	✓
Step 3: Engaged at 6 months	×	×	✓ (≥1 visit within 6 months after first visit)	×	✓ (≥1 visit within 6 months after first visit)
Step 4: Engaged at 12 months	×	✓ (visit in the calendar year subsequent to the calendar year of the first visit)	✓ (≥1 visit between 6 and 12 months after the first visit)	✓ (visit date in the calendar year subsequent to the calendar year of the first visit)	✓ (≥1 visit between 6 and 12 months after the first visit)
Step 5: On any ART at 12 months	×	✓	✓	✓	✓
Step 6: Viral suppression ≤400copies/ml at 12 months	×	✓	✓	✓	✓
Step 7: CD4 >500cells/mm$_3$ at 12 months	×	✓	✓	✓	✓

7.2.4.2. Cascade measured in the last year of adult follow-up

Table 7.2 presents the steps and definitions used for the last year of follow-up by mode of HIV acquisition. The engagement step in the last year of follow-up was taken in the last calendar year prior to the database closure date. The cascade step definitions were the same as those used in the 12 month cascades, with the exception of the engagement step. Engagement in care in the last year of follow-up was defined as having a visit within the last 12 months prior to the database closure date. The closure date varied by whether participants last visit date was recorded in the SOPHID or HARS dataset. To meet the engagement definition, participants with a last date in SOPHID needed a visit date between 01/01/2015 and 31/12/2015, and participants with a last date in HARS needed a visit between 01/04/2016 and 01/04/2017. For participants with both SOPHID and HARS data, the latest available date was selected. The cascade definitions were the same between young people with PHIV and BHIV. The BHIV cascades differed with the first step beginning with those 'linked to adult care and not 'transferred out of paediatric care'.

Table 7.2: Cascade steps and definitions used for the last year of follow-up cascades by mode of HIV acquisition and data source

Cascade steps	PHIV group		BHIV group
	CHIPS	SOPHID	SOPHID
Step 1: Transferred out of paediatric care	✓	×	×
Step 2: Linkage to adult care (date of first visit in adult care)	×	✓	✓
Step 3: Engagement at last visit	×	✓ (visit in the last 12 months prior to database closure date)	✓ (visit in the last 12 months prior to database closure date)
Step 4: On any ART at last visit in adult care	×	✓	✓
Step 5: Viral suppression (≤400 copies/ml) at last visit	×	✓	✓
Step 6: CD4 >500 cells/mm$_3$ at last visit	×	✓	✓

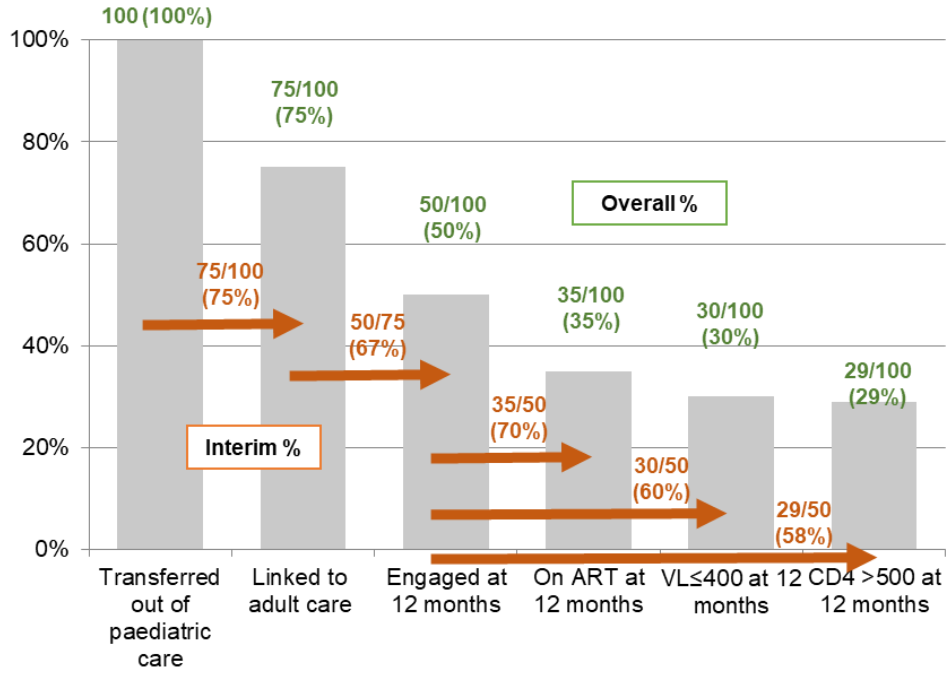
7.2.4. Statistical methods

In order to assess comparability between participants in the SOPHID +/- HARS dataset and the HARS only dataset, the demographic and clinical characteristics at last visit in paediatric care, using CHIPS data, were compared.

Overall and interim cascade percentages

A hypothetical example of the cascade for young people who transferred from paediatric to adult care is shown in Figure 7.2. In the cascades of this chapter, two sets of percentages are described which I will refer to as: (1) the overall percentages and (2) interim percentages. The overall percentage is the number of participants who have reached a given cascade step, divided by the total number of participants entering the entire cascade (i.e. step 1 - those who transferred from paediatric care). For example, if 100 participants met step 1 (transferred out of paediatric care), 75 participants met step 2 (linked to adult care) and 50 met step 3 (engaged by 12 months), and the overall percentage of the engagement step would be 50% (50/100). The interim percentage engaged in care would be 67% - the number reaching that step (i.e. 50 participants) divided by the number of participants reaching the previous cascade step (i.e. 75 participants linked to adult care, 50/75). In all cascades, the interim percentages for the ART, VL and CD4 steps all had the engagement step as their denominator, which allowed the treatment and health outcomes to be described of all those who were in care.

Figure 7.2: Hypothetical example of a cascade at 12 months following first adult visit for young people who transferred from paediatric to adult care



For young people with PHIV, all the SOPHID+/-HARS cascades were stratified by sex, place of birth (UK vs born abroad), ethnicity (black vs white/other), age group at transfer date (14-16, 17-19, 20-23 years) and grouped calendar year of transfer date (≤2008, 2009-2012 and 2013-2016). For young people with BHIV, all SOPHID +/- HARS cascades were stratified by sex, ethnicity and mode of HIV acquisition (MSM vs heterosexual group). All cascade

estimates were compared by the above demographic characteristics using chi-squared tests, or Fisher's exact tests. None of the HARS cascades were compared by demographic characteristics due to the low number of participants in the HARS only dataset.

Where inconsistencies were identified in the data collected in SOPHID/HARS, for example, mode of HIV acquisition for a patient may have been reported differently over time, in such a case the most recent visit was used (following methods used at PHE, P. Kirwan, personal communication).

Missing data

In the HARS only cascades, if ART, CD4 or VL data were not available at the 12 month time point, a window of +/- three months was applied to obtain the nearest available measurement to this date. The method was not relevant for SOPHID as the SOPHID dataset only included a single measurement for each variable for a given calendar year.

When estimating the overall percentages for the CD4 and VL steps, the denominators were of all young people who met the first cascade step, including those with missing CD4 and VL measurement. However, when calculating the interim percentages for the CD4 and VL steps, the denominators were restricted to those engaged in care at the respective time point and with a CD4 or VL data available. This approach was used to avoid the strong assumption of 'missing equals failure', as UK adult guidelines recommend patients engaged in care and with sustained viral suppression and good immunological status to not need frequent VL and CD4 monitoring [226].

To assess if the missing VL and CD4 data were missing at random, demographic and clinical characteristics were compared for participants engaged in care and with available CD4 and VL data vs those without CD4 and viral load data, and chi-squared tests were applied. This comparison was only conducted for young people with PHIV as they were the main focus of the PhD.

Sensitivity analyses

Due to a high level of missing CD4 and VL data in the SOPHID and HARS datasets, sensitivity analyses were conducted to determine the impact of the missing CD4 and VL data on the cascade estimates for young people who had transferred to adult care.

Due to HARS-related data collection issues, the SOPHID +/- HARS cascades at the 12 month time point and in the last year of adult follow-up were reconstructed using SOPHID only data, after removing all subsequent HARS follow-up data. This was to determine if the level of missing VL and CD4 data reduced without the HARS data and to compare the cascade estimates between the two data sources (SOPHID +/- HARS vs SOPHID only).

Secondly, the SOPHID +/- HARS cascade was reconstructed at both time points using UK CHIC only data as the UK CHIC dataset was known to have more complete VL and CD4 data recorded. The UK CHIC dataset was reduced to one patient record per calendar year so as to mimic the SOPHID dataset and allow for fairer comparison. The group of young people captured in the 12 month UK CHIC cascade were those who met the engagement in care step

of the 12 month cascade using SOPHID +/- HARS data. Similarly, the last year cascade using UK CHIC only data captured young people engaged by the last year of follow-up in the SOPHID +/- HARS cascade. The ART, VL and CD4 cascade estimates were then compared between the two data sources (UK CHIC only vs SOPHID +/- HARS) to determine whether the SOPHID +/- HARS cascades produced over- or underestimates of the VL and CD4 step due to the high level of missing data observed in the latter data source.

7.3. Results

7.3.1. Young people with PHIV

Among the 872 young people with PHIV by 01/04/2017, 689 (79%) transferred to a clinic reporting to SOPHID and 53 (6%) to a clinic reporting to HARS and had ≥12 months potential follow-up (Figure 7.3). A further 130 young people transferred after 01/01/2015 to clinics reporting to SOPHID, and were excluded due to having less than 12 months potential follow-up prior to database closure.

Figure 7.3: Flowchart of young people with PHIV by the type of reporting by the adult clinic

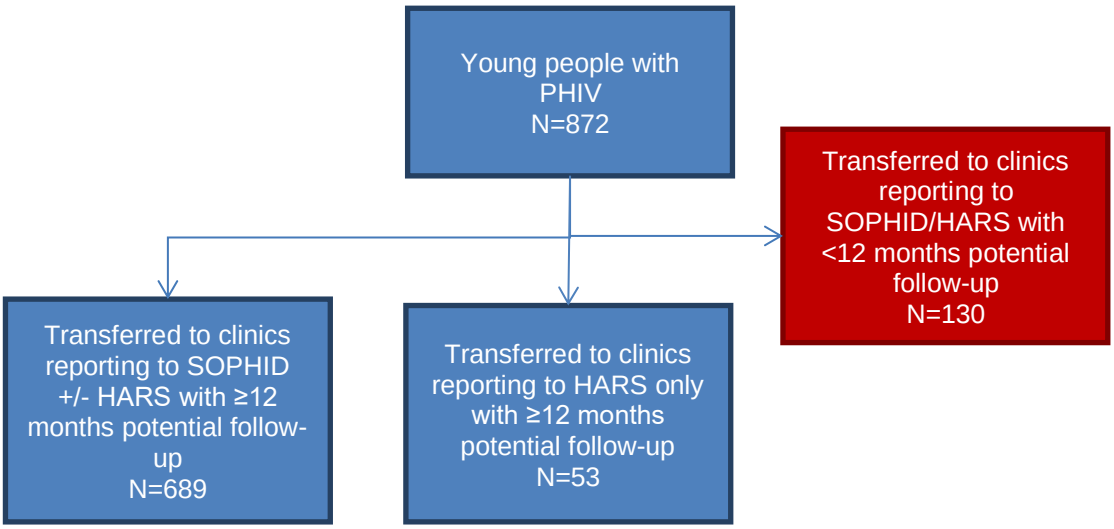


Table 7.3 compares the demographic and clinical characteristics of the included young people at their last paediatric care visit prior to transfer to either SOPHID or HARS clinics. Around half of both groups were female (53% and 45%, respectively, p=0.29). A lower proportion of those transferring to SOPHID clinics were born abroad compared to those who transferred to HARS clinics (62% vs 81%, respectively, p=0.007). Those who transferred to SOPHID clinics were slightly younger at their last paediatric visit compared to those who transferred to HARS clinics (median 17.5 years vs 18.2 years, respectively, p<0.001). Additionally, the median year of the last paediatric visit for young people who transferred to a SOPHID clinic was 2011 and 2015 for those who transferred to HARS clinics (p<0.001). Young people who transferred to HARS clinics were more likely to be on ART (96% vs 78%, respectively p<0.001) with better CD4 (59% vs 45% with CD4 >500 cell/mm$_3$, respectively, p=0.06) and viral load measures (77% vs 60%, with VL ≤400 copies/ml, respectively, p=0.01) at the last paediatric visit compared to those transferring to SOPHID clinics.

Table 7.3: Demographic and clinical characteristics at last paediatric care visit of young people transferring to clinics reporting to SOPHID vs HARS

		SOPHID (N=689)	HARS (N=53)	P-value
		N (%) or median [IQR] or range		
Sex				
	Female	364 (52.8)	24 (45.3)	
	Male	325 (47.2)	29 (54.7)	0.29
Place of birth				
	UK	257 (38.0)	10 (19.2)	
	Abroad	419 (62.0)	42 (80.8)	0.007
Ethnicity				
	Black	559 (82.6)	44 (86.3)	
	White/other	118 (17.4)	7 (13.7)	0.33
Age at last paediatric visit				
	Median	17.5 [16.7, 18.4]	18.2 [17.7, 18.9]	
	Range	14.0, 23.1	14.9, 23.6	<0.001
Year of last paediatric visit				
	Median	2011 [2008, 2013]	2015 [2015, 2015]	
	Range	1998, 2014	2015, 2016	<0.001
On ART at last paediatric visit				
	Yes	536 (77.8)	51 (96.2)	
	No	153 (22.2)	2 (2.8)	<0.001
CD4 count at last paediatric visit, cells/mm3				
	≤500	377 (54.7)	22 (41.5)	
	>500	308 (44.7)	31 (58.5)	0.06
Viral load at last paediatric visit, copies/ml				
	≤400	412 (60.2)	41 (77.4)	
	>400	272 (39.8)	12 (22.6)	0.01

7.3.1.1. SOPHID +/- HARS Cascades at 12 months after first adult visit and in the last year of follow-up among young people with PHIV

The 689 young people with PHIV who transferred to a SOPHID clinic were included in the first cascade measured at 12 months following the first adult visit. Of these, 601 met the inclusion criteria to be included in the second cascade measured in the last year of adult follow-up. Figure 7.4 compares the SOPHID +/- HARS cascade estimates at these two time points.

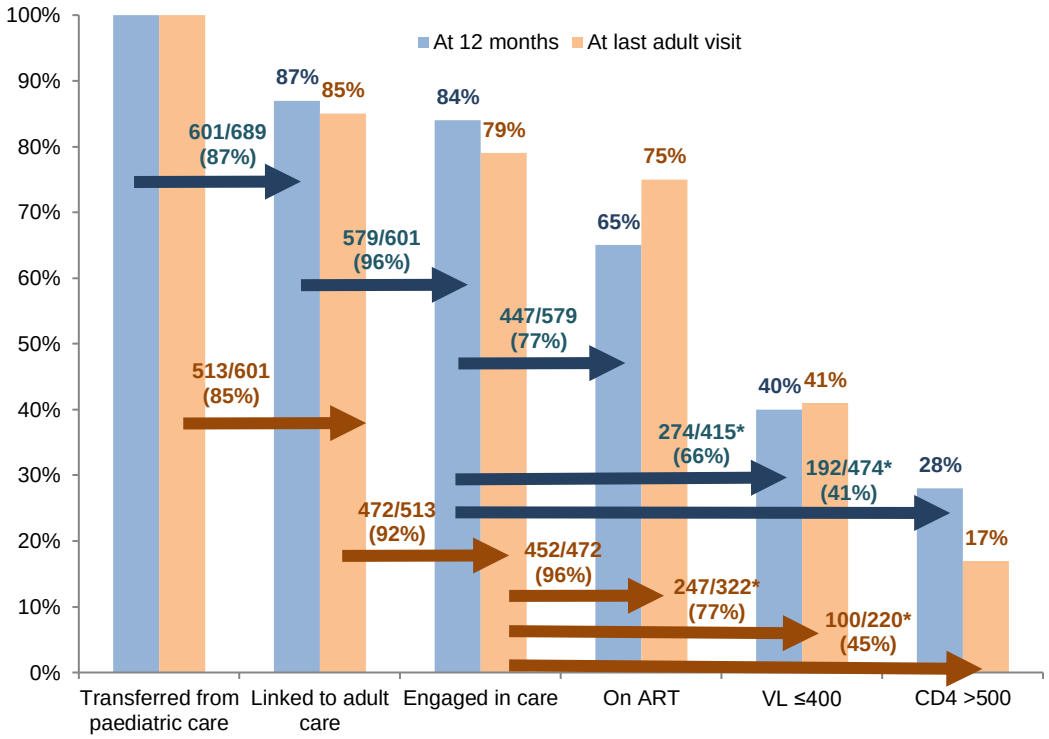
Interim percentages

For the 12 month cascade, the interim percentages show 601/689 (87%) had at least one adult visit and were thus linked to adult care, and of this group, 579 (96%) were engaged in care at 12 months. In the SOPHID +/- HARS dataset, the median duration between the date of linkage to adult care and the 12 month visit was 364 days. At the 12 month time point, 447/579 (77%) were on ART, of the 415 with VL data, 274/415 (66%) had a VL ≤400 copies/ml and of the 474 with CD4 data, 192/474 (41%) had a CD4 count >500 cells/mm3. In the sensitivity analysis, among those with VL and CD4 data, 261 (63%) had a VL ≤200 copies/ml and 298 (63%) had a CD4 count >350 cells/mm3, respectively. The largest fall in percentage

among the interim steps occurred between engagement in care at 12 months and having a CD4 count >500 cells/mm3, demonstrated by the fall in overall percentages from 84% to 28%, although the proportion of missing CD4 count increased from 18% to 53%, respectively.

In the last year of follow-up cascade, 601 young people had more than 12 months of follow-up and were included. Of these, 513/601 (85%) were linked to adult care, 472/513 (92%) were engaged in care in the last year of follow-up, of whom 452/513 (96%) were on ART. Of those engaged in care and with VL data 247/322 (77%) were virally suppressed (VL ≤400 copies/ml) and of the 220 with CD4 data, 100/220 (45%) had a CD4 count >500 cells/mm3.

Figure 7.4: SOPHID +/- HARS cascades at the 12 month and last visit time point among young people who transferred to adult care (N=689)



** Denominator includes only participants with available VL/CD4 data*

Overall percentages

Comparing the 12 month and last year cascade estimates, the overall percentages shows a slight decline in proportions engaged in care (84% vs 79%, respectively). In contrast to this trend, the proportion on ART increased from 65% at 12 months to 75% by the last visit in adult care, and the proportion virally suppressed (VL ≤400 copies/ml) remained similar (40% vs 41%, respectively).

Missing VL and CD4 data

Among young people engaged in care at 12 months post-linkage, 28% and 18% had missing VL data and CD4 data at the 12 month visit, respectively; these proportions increased to 32% and 53% by the last visit in adult care. To assess which demographic groups were more likely to have missing data, the level of missing VL and CD4 data among those engaged in care at

both time points were stratified by sex, place of birth, ethnicity, age and calendar year of the last paediatric visit (Table 7.4). The VL data at 12 months post-linkage were more frequently missing among young people who transferred in later calendar years compared to those who transferred in earlier years (34% missing for 1998-2008, 12% for 2009-2012 and 41% for 2013-2014, p=0.002). The level of missing VL or CD4 data did not differ significantly by any of the other demographic characteristics.

Table 7.4: Missing VL and CD4 data at the 12 month and last visit time points by characteristics at the last paediatric visit among young people engaged in care at the respective time points

	At the 12 month visit			**At the last visit**		
	Engaged in care	Missing VL data	Missing CD4 data	Engaged in care	Missing VL data	Missing CD4 data
	D	N/D (%)		D	N/D (%)	
Total	579	164/579 (28)	105/579 (18)	472	150/472 (32)	252/472 (53)
Sex						
Female	308	82/308 (27)	48/308 (16)	249	91/249 (37)	136/249 (55)
Male	271	82/271 (30)	57/271 (21)	223	59/223 (26)	116/223 (52)
P-value	-	0.84	0.57	-	0.23	0.98
Place of birth						
UK	220	63/220 (29)	36/220 (16)	185	52/185 (28)	40/185 (22)
Abroad	347	99/347 (29)	65/347 (19)	278	95/278 (34)	58/278 (21)
P-value	-	1.00	0.72	-	0.13	0.48
Ethnicity						
Black	476	130/476 (27)	91/476 (19)	378	126/378 (33)	204/378 (54)
White/other	93	33/93 (36)	12/93 (13)	86	22/86 (26)	42/86 (50)
P-value	-	0.61	0.43	-	0.22	0.48
Age at last paediatric visit (years)						
14-16	205	64/205 (31)	36/205 (18)	175	57/175 (33)	92/175 (53)
17-19	350	92/350 (26)	65/350 (19)	281	88/281 (31)	151/281 (54)
20-23	24	8/24 (33)	4/24 (17)	16	5/16 (31)	9/16 (56)
P-value	-	0.54	0.93	-	0.54	0.91
Year of last paediatric visit						
1998-2008	169	58/169 (34)	22/169 (13)	151	44/151 (29)	76/151 (50)
2009-2012	270	48/270 (18)	51/270 (19)	254	88/254 (35)	144/254 (57)
2013-2014	140	58/140 (41)	32/140 (23)	67	18/67 (27)	32/67 (48)
P-value	-	0.002	0.18	-	0.48	0.61

In the 12 month cascade using SOPHID +/- HARS data, 579 were engaged in care, of these 374 (65%) had both measurements available, 515 (89%) had VL or CD4 measurement available and 64 (11%) had both VL and CD4 data missing. To determine if the VL/CD4 data were missing at random, demographic and clinical characteristics at the last paediatric visit were compared between the latter two groups (515 with available VL or CD4 data vs the 64 with missing VL and CD4 data at the 12 month time point) (Table 7.5). The latter group had a higher proportion born abroad (83% vs 60%, respectively, p<0.001) but a smaller proportion of black ethnicity (68% vs 84%, respectively, p=0.008). However, sex, viral load status, calendar year and age at transfer date did not differ missing VL/CD4 status (all p>0.1).

Table 7.5: Characteristics at last paediatric visit among young people with PHIV and were engaged at 12 months post-linkage, by status of missing VL and CD4 data (N=579), using SOPHID +/- HARS data

	With VL and/or CD4 data (N=515)	**With missing VL and CD4 data (N=64)**	**P-value**
	n (%) or median [IQR]		
Sex			0.20
Female	279 (54.2)	29 (45.3)	
Male	236 (45.8)	35 (54.7)	
Place of birth			<0.001
UK	200 (39.7)	11 (17.2)	
Abroad	304 (60.3)	53 (82.8)	
Ethnicity			0.008
Black	423 (83.8)	43 (68.3)	
White/other	82 (16.2)	20 (31.8)	
Age at last paediatric visit, years			
14-16	183 (35.5)	22 (34.4)	0.77
17-19	311 (60.4)	39 (60.9)	0.89
20-23	21 (4.1)	3 (4.7)	1.00
Year of last paediatric visit			
1998-2008	149 (28.9)	20 (31.3)	0.76
2009-2012	237 (46.0)	33 (51.6)	0.40
2013-2014	129 (25.1)	11 (17.2)	0.17
Median CD4 count at last paediatric visit, cells/mm$_3$			
Median [IQR]	479 [330, 736]	440 [281, 627]	0.51
Viral load at last paediatric visit, copies/ml			0.66
≤400	303 (59.1)	39 (61.9)	
>400	210 (40.9)	24 (38.1)	

In the SOPHID +/- HARS cascade in the last year of follow-up among those from paediatric care, 472 were engaged by the last visit, of these 390 (83%) had a VL or CD4 data available and 123 (26%) had both VL and CD4 measurement missing at the last visit. Table 7.6 presents the demographic and clinical characteristics at last paediatric visit between these two groups. Demographic characteristics (i.e. sex, place of birth, ethnicity, age and year of last paediatric visit) were comparable between the two groups. However, the group with missing VL and CD4 data had a higher proportion virally suppressed at the last paediatric date compared the other group (58% vs 38% with VL ≤400 copies/ml, respectively, p=0.005).

Table 7.6: Characteristics at last paediatric visit among young people with PHIV and were engaged at last adult visit, by status of missing VL and CD4 data (N=513), using SOPHID +/- HARS data

	With CD4 or viral load data (N=390)	With missing VL and CD4 data (N=123)	P-value
	N (%) or median [IQR]		
Sex			
Female	198 (50.8)	71 (57.7)	0.32
Male	192 (49.2)	52 (42.3)	
Place of birth			0.24
UK	161 (41.9)	42 (34.0)	
Abroad	223 (58.1)	81 (65.9)	
Ethnicity			0.44
Black	314 (81.8)	106 (86.2)	
White/other	70 (18.2)	17 (13.8)	
Age at last paediatric visit, years			
14-16	133 (34.1)	43 (35.0)	0.88
17-19	240 (61.5)	74 (60.2)	0.88
20-23	17 (4.4)	6 (4.9)	1.00
Year of last paediatric visit			
1998-2008	112 (28.7)	24 (19.5)	0.33
2009-2012	177 (45.4)	64 (52.0)	0.67
2013-2014	101 (25.9)	35 (28.5)	0.64
Median CD4 count at last paediatric visit, cells/mm3			
Median [IQR]	425 [281, 616]	462 [284, 649]	0.20
Viral load at last paediatric visit, copies/ml			
≤400	148 (38.1)	96 (57.8)	0.005
>400	240 (61.9)	70 (42.2)	

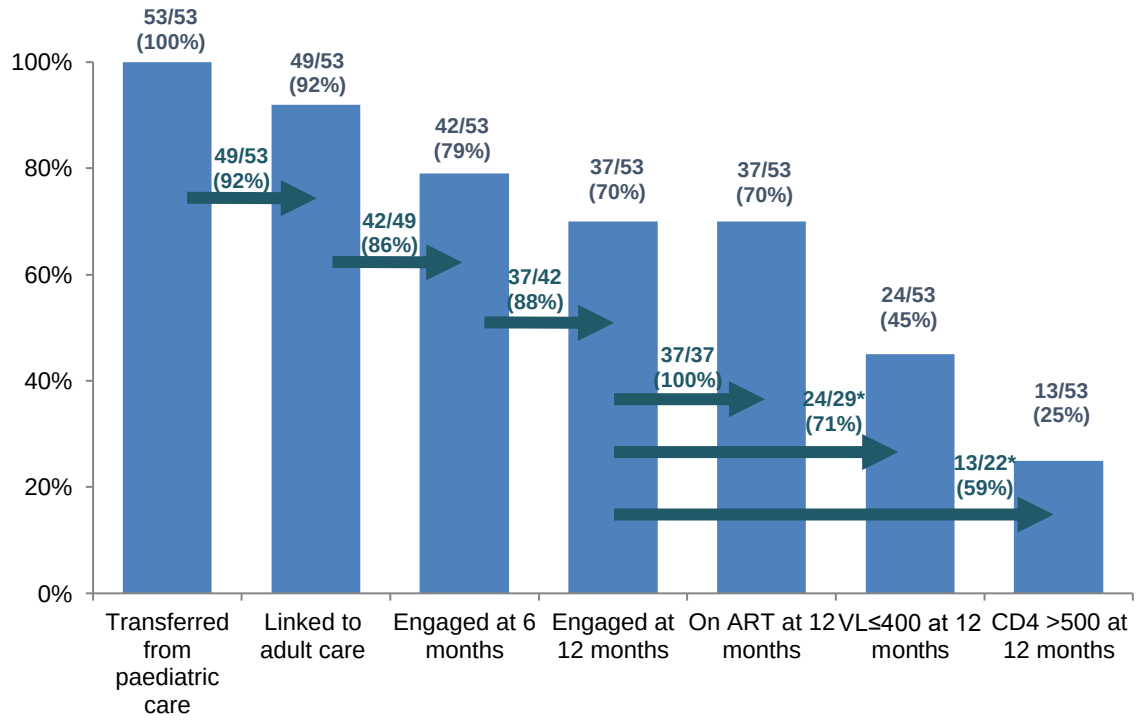
7.3.2.1. HARS only cascade at 12 months after first adult visit among young people with PHIV in HARS clinics

Figure 7.5 presents the 12 month cascade of care for the 53 young people who transferred from paediatric to adult clinics reporting to HARS only.

Interim percentages

With respect to the interim cascade percentages, of the 53 transferred from paediatric care to HARS clinics 49 (92%) were linked to adult care with at least one adult visit, 42/49 (86%) were engaged in care at 6 months post-linkage and of whom 37/42 (88%) were engaged at 12 months. Among the 37 participants engaged at 12 months, all (100%) were on ART, of the 29 with VL data, 24/29 (71%) were virally suppressed (VL ≤400 copies/ml), and of the 22 with CD4 data, 13/22 (59%) had a CD4 count >500 cells/mm3 (in the sensitivity analysis, 77% had a VL ≤200 copies/ml and 82% had a CD4 count >350 cells/mm3). The largest drop out of the cascade occurred engagement in care at 12 months and the CD4 step, with only 59% of those engaged in care having a CD4 count >500 cells/mm3.

Figure 7.5: HARS only cascade at 12 months following first adult visit among young people with PHIV (N=53)



** Denominator includes only participants with available VL/CD4 data*

Overall percentages

For the overall cascade percentages, among the total who transferred from paediatric care, 79% and 70% were engaged in care at 6 and 12 months, respectively, 70% were on treatment, 45% were virally suppressed (VL ≤400 copies/ml) and a quarter (25%) had a CD4 count >500 cells/mm3 at the 12 month time point. Of all those engaged in care at 12 months post-linkage, none had missing ART data, 8/37 (22%) and 15/37 (41%) had missing VL and CD4 data, respectively (data not shown).

7.3.2. Young people with BHIV in adult care

A total of 592 young people with BHIV had initiated adult care at a SOPHID clinic whilst aged 15 to 19 years and during or after 2008. Of these, 38% had acquired HIV via heterosexual sex, 45% were MSM, 12% were people who inject drugs (PWID) and 16% had unknown modes of acquisition.

A further 209 young people with BHIV had initiated care at a HARS clinic whilst aged 15 to 19 years and during or after 2008. Over half (54%) of this group were MSM, 54 (26%) were in the heterosexual exposure group, one (0.5%) was a PWID and the remaining 41 (20%) had unknown modes of acquisition.

Table 7.7 presents the demographic and treatment characteristics of all young people attending a SOPHID clinic with at least one adult visit, by mode of HIV acquisition. Characteristics were described among young people who entered in or after 2008 which

allowed for better comparability between the PHIV and BHIV group as then the median year of entry to adult care across the groups were more similar (2008-2012).

In total, 56% of young people with PHIV were female compared to none of MSM, 14% of PWID, 79% of the heterosexual group and 49% of the unknown acquisition group. Eighty four per cent of young people with PHIV were black compared to 10% of MSM, none of PWID, 56% of the heterosexual group and 64% of the unknown group. Young people with PHIV, PWID, the heterosexual group and those with unknown mode of acquisition had a high proportion born abroad (ranging from 50% to 64%) compared to the MSM group (17%). The median age at HIV diagnosis among the PHIV group was 7 years, but 18 to 19 years among the other groups.

The median age at first visit in adult care ranged from 18 to 19 years across all groups. High proportions had ever been on ART in adult care across all groups (96% of the PHIV group, 86% of MSM, 86% of PWID, 86% of heterosexual participants, and 67% of the unknown group). Young people with PHIV had initiated ART at a median age of 9 years and had been on ART for a median of 13 years during paediatric and adult follow-up. The other groups initiated ART between the ages 18 to 20 years and had median durations on ART of 3 to 4 years in adult care. At the last adult visit, those with PHIV, MSM, heterosexual and the unknown group had comparable median ages (23 to 24 years) and durations of adult follow-up (4 to 5 years). The PWID group were older at the last visit (27 years) and with a longer duration of follow-up (7 years).

The unknown exposure group shared similar demographic characteristics (i.e. gender, ethnicity and place of birth) with the PHIV group. Indicating a likelihood of them also having PHIV, Further investigation of the unknown group found that 12 matched with CHIPS participants on date of birth and sex. Of these 7 had missing data linkage variables from the CHIPS and/or SOPHID dataset, in particular Soundex and patient hospital number. The remaining 5 participants with unknown mode of HIV acquisition who matched CHIPS participants on date of birth and sex were relinked using the CHIPS-SOPHI linkage algorithm, but none matched on any linkage step. Due to potential overlap of participants with the PHIV group, the unknown exposure group was not included in any of the cascades of young people with BHIV. The PWID group were also excluded due to the small number (N=7) that entered adult care during or after 2008, older age at last visit and this population often has complex health needs and increased risk of poor health outcomes which makes comparison to this group difficult.

Table 7.7: Demographic and treatment characteristics in adult care among young people with HIV by mode of acquisition

Characteristics		PHIV group N=536	BHIV group			
			MSM (N=269)	PWID (N=7)	Heterosexual (N=223)	Unknown (N=93)
		n (%) or median [IQR]				
Sex	Female	299 (55.8)	0 (0.0)	1 (14.3)	176/223 (78.9)	46 (49.4)
	Male	237 (44.2)	265 (100.0)	6 (85.7)	47 (21.1)	47 (50.5)
Ethnicity	Black	444 (84.1)	21 (10.1)	0 (0.0)	88/157 (56.1)	33 (63.5)
	White/other	84 (15.9)	187 (89.8)	6 (100.0)	69 (43.9)	19 (36.5)
Place of birth	Born abroad	311 (58.0)	36 (17.2)	4 (66.7)	81 (50.0)	29 (64.4)
	UK	225 (42.0)	173 (82.8)	2 (33.3)	81 (50.0)	16 (35.6)
Age at HIV diagnosis, years	Median [IQR]	7 [3, 11]	19 [18, 19]	19 [19, 20]	19 [18, 19]	18 [17, 19]
Year of adult care entry	Median [IQR]	2012 [2010, 2013	2011 [2009, 2013]	2008 [2008, 2011]	2010 [2009, 2012]	2011 [2009, 2013]
Age at first adult visit, years	Median [IQR]	18 [17, 19]	19 [19, 20]	20 [19, 20]	19 [18, 20]	19 [17, 19]
Ever on ART in adult care	Yes	448 (95.7)	230 (85.5)	6 (85.7)	191 (86.0)	62 (67.4)
	No	20 (4.3)	39 (14.5)	1 (14.3)	61 (14.0)	30 (32.6)
Age at ART start, years	Median [IQR]	9 [5, 13]	20 [19, 22]	21 [19, 23]	20 [19, 21]	19 [17, 20]
Duration on ART	Median [IQR]	13 [10, 18]	3 [2, 4]	3 [2, 4]	3 [2, 6]	4 [3, 6]
Age at last adult visit, years	Median [IQR]	23 [21, 25]	24 [22, 25]	27 [21, 28]	24 [22, 25]	23 [22, 25]
Duration in adult care, years	Median [IQR]	4 [2, 6]	5 [3, 6]	7 [2, 8]	5 [3, 6]	5 [3, 6]

7.3.2.1. Cascades at 12 months after first adult visit and in the last year of follow-up among young people with BHIV in adult clinics reporting to SOPHID

Young people with BHIV included in the cascade analyses included young people with MSM or heterosexual modes of acquisition who had entered adult care ≥2008. As these young people were diagnosed in adult care, the first step of the cascades were not based on those who transferred out of paediatric care. Figure 7.6 presents the SOPHID +/- HARS cascade at the 12 month and last visit time points among young people with BHIV in adult care. A total of 492 met the inclusion criteria for the 12 month SOPHID +/- HARS cascade and 482 met the inclusion criteria for the last visit cascade. Of the young people who met these inclusion criteria, 492 (55% MSM 45% heterosexual) had initiated care at an adult clinic reporting to SOPHID.

Interim percentages

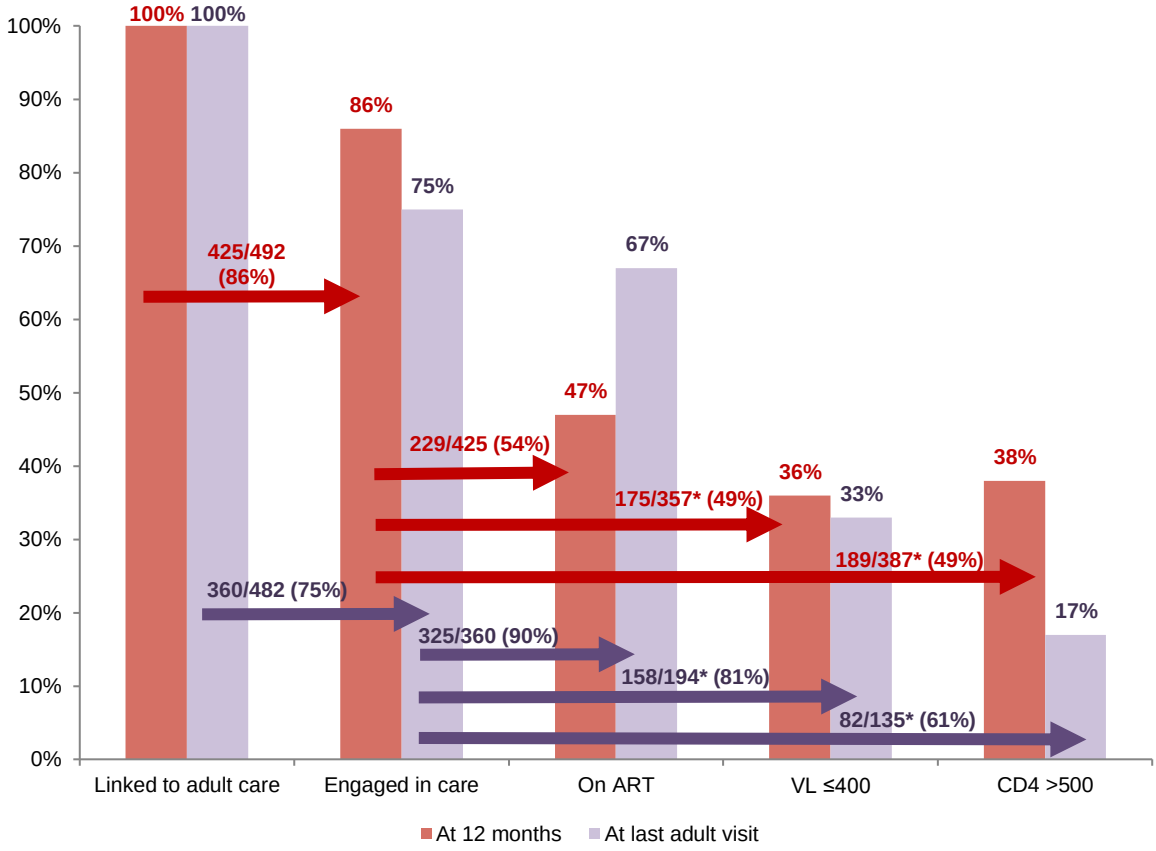
For the 12 month cascade, of 492 linked to adult care, 425 (86%) were engaged in care at 12 months, of whom 229/425 (54%) were on ART. Of those engaged in care and with VL data, 175/357 (49%) were virally suppressed (VL ≤400 copies/ml) and of the 387 with CD4 data, 189 (49%) had a CD4 count >500 cells/mm3. In the sensitivity analysis, among those with VL and CD4 data, 163/357 (46%) had a VL ≤200 copies/ml and 317/387 (82%) had a CD4 >350 cells/mm3 at the 12 month visit. The largest drop off of participants was between the 12 month engagement step and the viral suppression step, with only 49% of those engaged in care being virally suppressed by 12 months post-linkage.

For the last year in follow-up cascade, 482 had more than 12 months of follow-up and were included. Of these, 360 (75%) were engaged in care in the last year of follow-up, of whom 325/360 (90%) were on ART, of the 194 with VL data 158 (81%) were virally suppressed and of the 135 with CD4 data, 82 (61%) had a CD4 count >500 cells/mm3.

Overall percentages

Comparing the cascade estimates between the 12 month hand last visit time points, using the overall cascade percentages, the proportion of young people engaged in care at 12 months post-linkage declined from 86% to 75% by the last adult visit. In contrast to this trend, the proportion on ART increased from 47% at 12 months to 67% at the last adult visit. The proportions virally suppressed remained stable between the time points (36% vs 33%, respectively), while the proportion with a CD4 count >500 cells/mm3 halved from 38% at 12 months to 17% at the last visit.

Figure 7.6: SOPHID +/- HARS cascades at the 12 month and last visit time point among young people with BHIV (N=492)



** Denominator includes only participants with available VL/CD4 data*

Missing VL and CD4 data

Among young people engaged at 12 month post-linkage, 16% and 8% had missing VL and CD4 data at the 12 month time point, respectively. Among those engaged in the last year of follow-up cascade, the missing VL and CD4 data increased to 46% and 63%, respectively. Next, the group of young people more likely to have missing VL and CD4 data at either time point was assessed. Table 7.8 presents the level of missing VL and CD4 data by demographic characteristics (sex, mode of acquisition and ethnicity). The level of missing VL and CD4 at either time point did not differ by any of the demographic characteristics (all p>0.1).

Table 7.8: Missing VL and CD4 data at the 12 month and last visit time points by characteristics at the last paediatric visit among young people with BHIV engaged in care at the respective time points

	At the 12 month visit			At the last visit		
	Engaged in care	**Missing VL data**	**Missing CD4 data**	**Engaged in care**	**Missing VL data**	**Missing CD4 data**
	D	N/D (%)		D	N/D (%)	
Total	425	68/425 (16.0)	38/425 (8.9)	360	166/360 (46.1)	225/360 (62.5)
Sex						
Female	152	26/152 (17.1)	12/152 (7.9)	126	57/126 (45.2)	75/126 (59.5)
Male	269	42/269 (15.6)	26/269 (9.7)	232	109/232 (47.0)	149/232 (64.2)
P-value	-	0.85	0.62	-	0.78	0.77
Mode of acquisition						
MSM	233	35/233 (15.0)	22/233 (9.4)	205	98/205 (47.8)	137/205 (66.8)
Heterosexual	192	33/192 (17.2)	16/192 (8.3)	155	68/155 (43.9)	88/155 (57)
P-value	-	0.70	0.80	-	0.78	0.25
Ethnicity						
Black	101	13/101 (12.9)	10/101 (9.9)	98	42/98 (42.9)	62/98 (63.3)
White/other	239	37/239 (15.5)	19/239 (8.0)	231	110/231 (47.6)	151/231 (65.4)
P-value	-	0.55	0.62	-	0.48	0.93

7.3.2.2. Cascade at 12 months after first adult visit among young people with BHIV in adult clinics reporting to HARS only

A total of 167 young people with BHIV (68% MSM and 32% heterosexual) had initiated care at an adult clinic reporting to HARS and were aged under 20 years. Figure 7.7 presents the 12 month HARS only cascade for young people with BHIV.

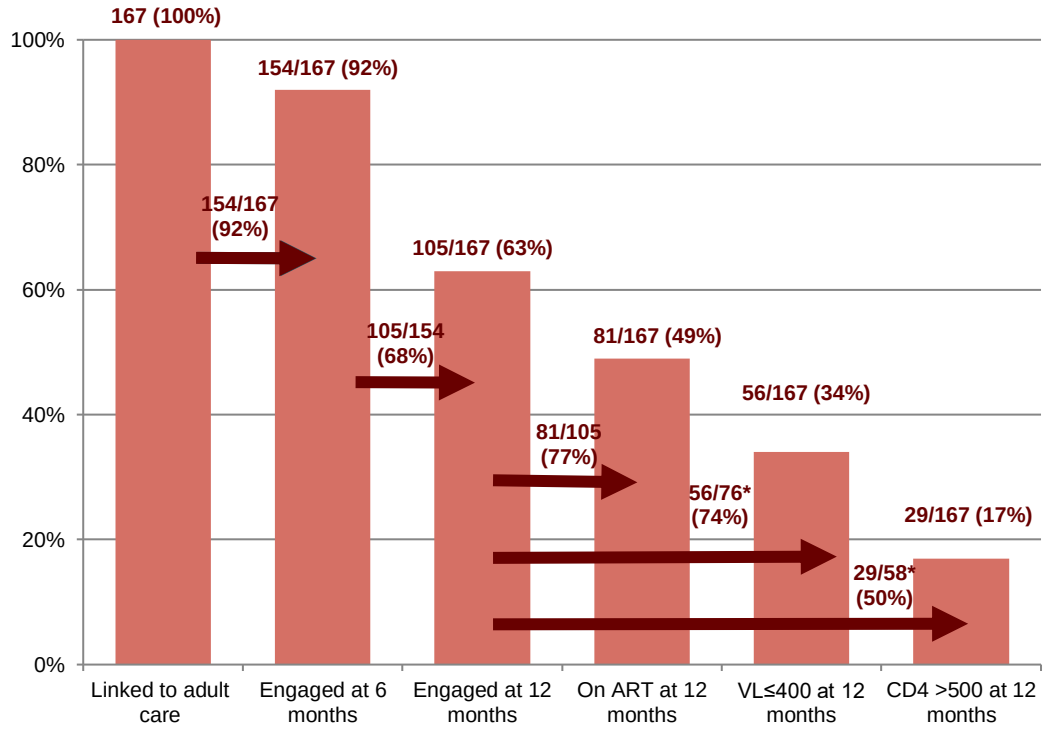
Interim percentages

Using the interim percentages, 154/167 (92%) were engaged with a second visit at 6 months, of whom 105/154 (68%) had a third visit at 12 months after the first adult visit. Of those engaged at 12 months post-linkage, 81/105 (77%) were on ART, among the 76 with VL data, 56/76 (74%) were virally suppressed (VL ≤400 copies/ml) and of the 58 with CD4 data, 29/58 (50%) had a CD4 count >500 cells/mm$_3$ (in the sensitivity analysis, 74% had a VL ≤200 copies/ml and 78% had a CD4 >350 cells/mm$_3$). The largest drop off of participants was observed between the 12 month engagement step and the CD4 step, with half (50%) of those engaged and with a CD4 count >500 cells/mm$_3$.

Overall percentages

Using the overall percentages, of the total linked to adult care, 92% and 63% were engaged in care by 6 and 12 months post-linkage, 49% were on ART, 34% were virally suppressed and 17% had a CD4 count >500 cells/mm3 at the 12 month time point (Figure 7.7). Among those engaged in care by 12 months, 28% and 45% had missing VL and CD4 data, respectively (data not shown).

Figure 7.7: HARS only cascade at 12 months following first adult visit among young people with BHIV (N=167)



** Denominator includes only participants with available VL/CD4 data*

7.3.3. Cascade of care by mode of acquisition

Next, the cascade of care were compared between the PHIV and BHIV groups. The former group were restricted to those aged under 20 years by the first adult visit to allow for better age comparability between the groups. All cascades were compared between the perinatal, MSM and heterosexual group only included the overall percentages and not the interim percentages. Additionally, the cascade steps began from those 'linked to adult care' and not 'transferred out of paediatric care' to allow for comparability of the steps between the groups of young people.

7.3.3.1. SOPHID +/- HARS cascades

A total of 547 young people with PHIV were identified in the SOPHID +/- HARS dataset and were aged under 20 years by the first adult visit, along with 492 young people with BHIV which included 269 (55%) MSM and 226 (46%) heterosexual participants. Figure 7.8 compares the SOPHID +/- HARS cascade at 12 month post-linkage by mode of acquisition (perinatal vs MSM vs heterosexual groups). Only the overall percentages were described.

Overall percentages

Among all young people with a first visit in adult care, the perinatal group had the highest proportion engaged in care at the 12 month time point (97% of perinatal group vs 87% of MSM group vs 86% of heterosexual groups (p<0.001), overall 75% of perinatal group, 44% of MSM group and 50% of heterosexual group were on ART, respectively (p<0.001), the proportion virally suppressed with a VL ≤400 copies/ml was 45%, 33% and 38% respectively (p<0.001). In contrast, there was no significant difference in proportions with a CD4 count >500 cells/mm3 at the 12 month time point across the exposure groups at 32%, 39% and 38%, respectively (p=0.12).

Figure 7.8: SOPHID +/- HARS cascade of care at 12 months after first visit in adult care by mode of acquisition (PHIV (N=547), MSM (N=269) and heterosexual (HS) (N=226) groups)

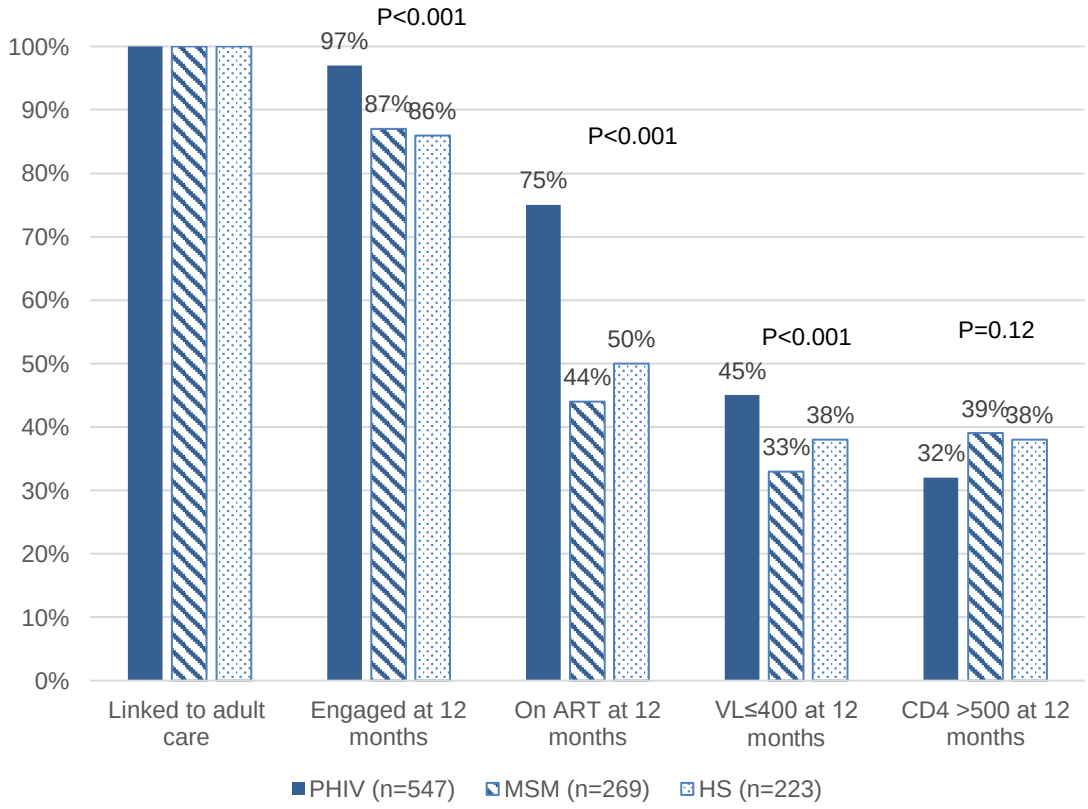


Figure 7.9 presents the same 12 month cascade by mode of acquisition and also by level of missing VL and CD4 data. The PHIV group had a significantly higher proportion with missing VL and CD4 data at the 12 month visit compared to the other two exposure groups with 27% missing VL data vs 13% and 15%, respectively (p<0.001) and 18% missing CD4 data vs to 8% and 7%, respectively (p=0.005).

Figure 7.9: The level of missing VL and CD4 data in the 12 month cascade using SOPHID +/- HARS data by mode of acquisition (PHIV (N=547), MSM (N=269) and heterosexual (HS) (N=226) groups)

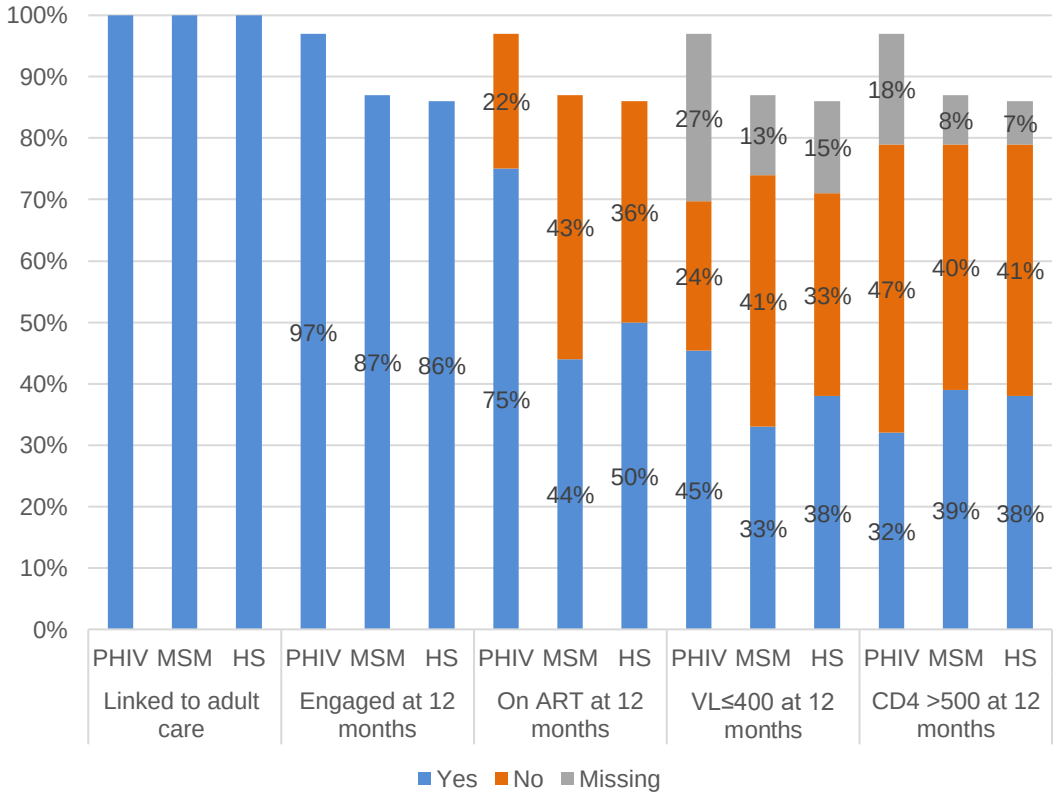


Figure 7.10 compares the cascade of care in the last year of follow-up among young people linked to adult care at a SOPHID clinic, by mode of acquisition. Similar to the trends observed in Figure 7.8, the PHIV group had a significantly higher percentage engaged in care in the last year of follow-up (93% of perinatal group vs 79% of MSM group and 71% of heterosexual groups, p<0.001), as well as higher proportion on ART (88% vs 72% of MSM group and 62% of heterosexual groups, p<0.001) and virally suppressed at the last visit (48% vs 36% for MSM group and 29% for heterosexual group, p<0.001) compared to the other two exposure groups. However, there was no significant difference in the proportions with a CD4 count >500 cells/mm$_3$ between the three exposure groups (p=0.67).

Figure 7.10: SOPHID +/- HARS cascade of care at last visit in adult care by mode of acquisition (perinatal (N=495), MSM (N=261) and heterosexual (HS) (N=221) groups)

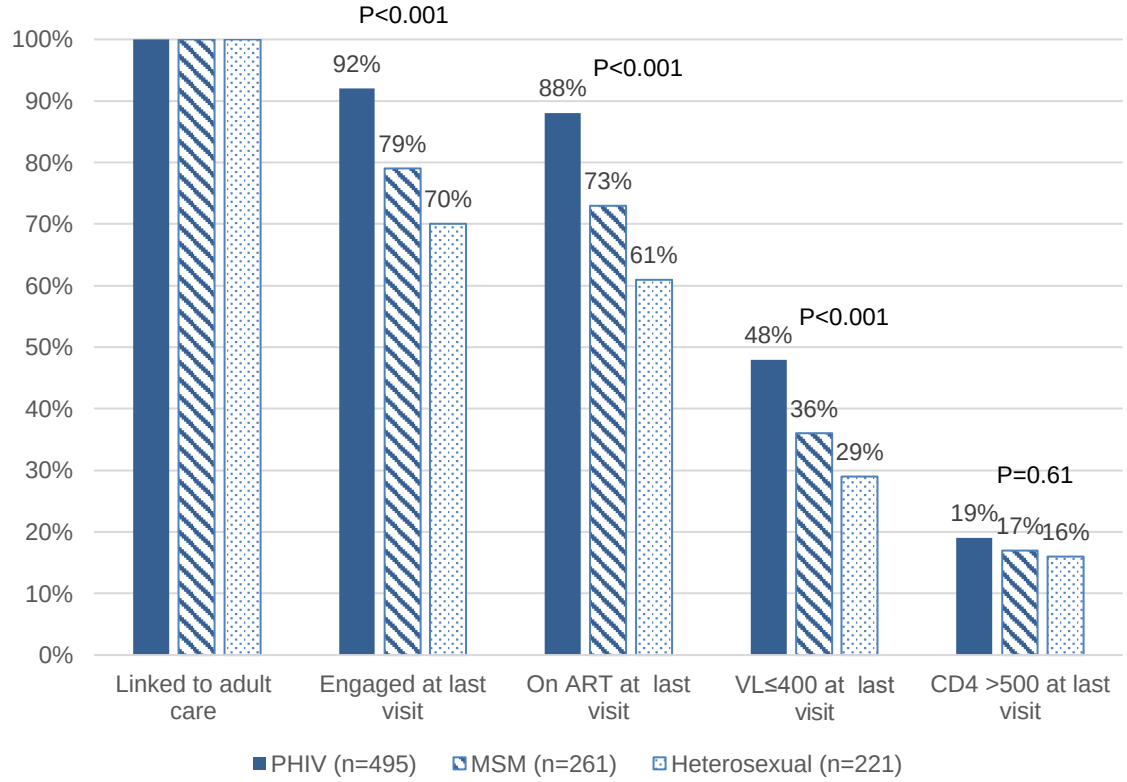
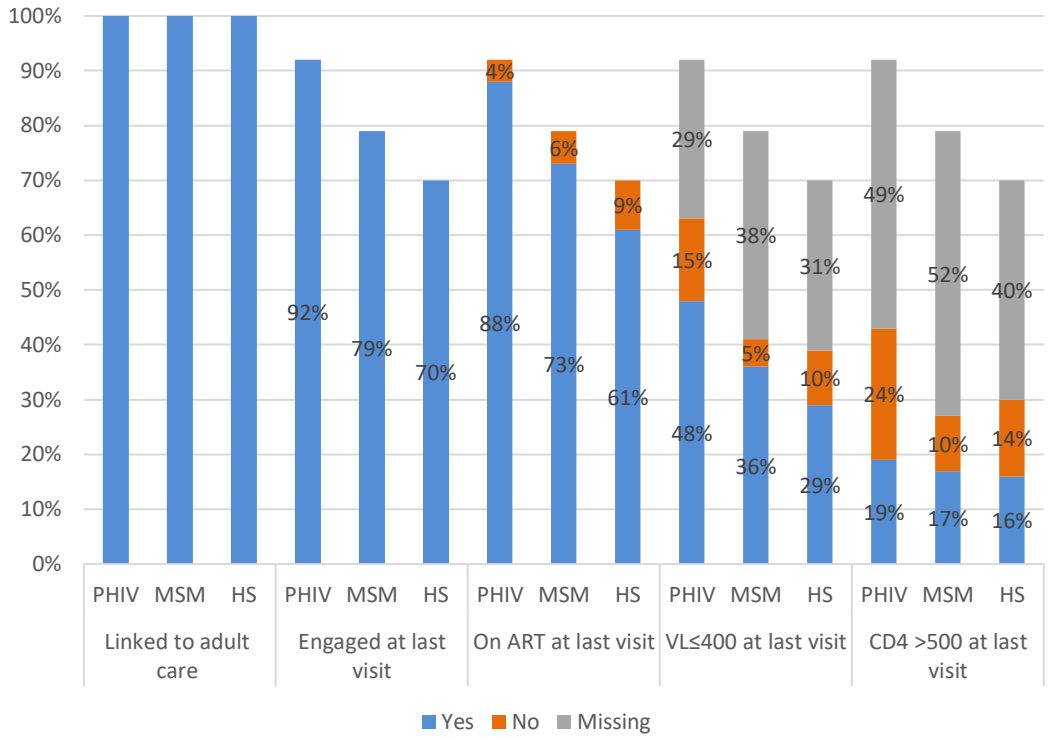


Figure 7.11 presents the SOPHID +/- HARS cascade in the last year of follow-up by mode of acquisition and level of missing VL and CD4 data at the last visit. Here, the MSM group had the highest level of missing data at 38% compared to 29% and 31% for the PHIV and heterosexual group, respectively (p<0.001). The level of missing CD4 data was similar between the MSM and PHIV group (52% and 49%, respectively), while the heterosexual group had lower proportion of missing CD4 data (40%, p<0.001).

Figure 7.11: The level of missing VL and CD4 data in the last year of follow-up cascade using SOPHID +/- HARS data by mode of acquisition (perinatal (N=495), MSM (N=261) and heterosexual (HS) (N=221) groups)

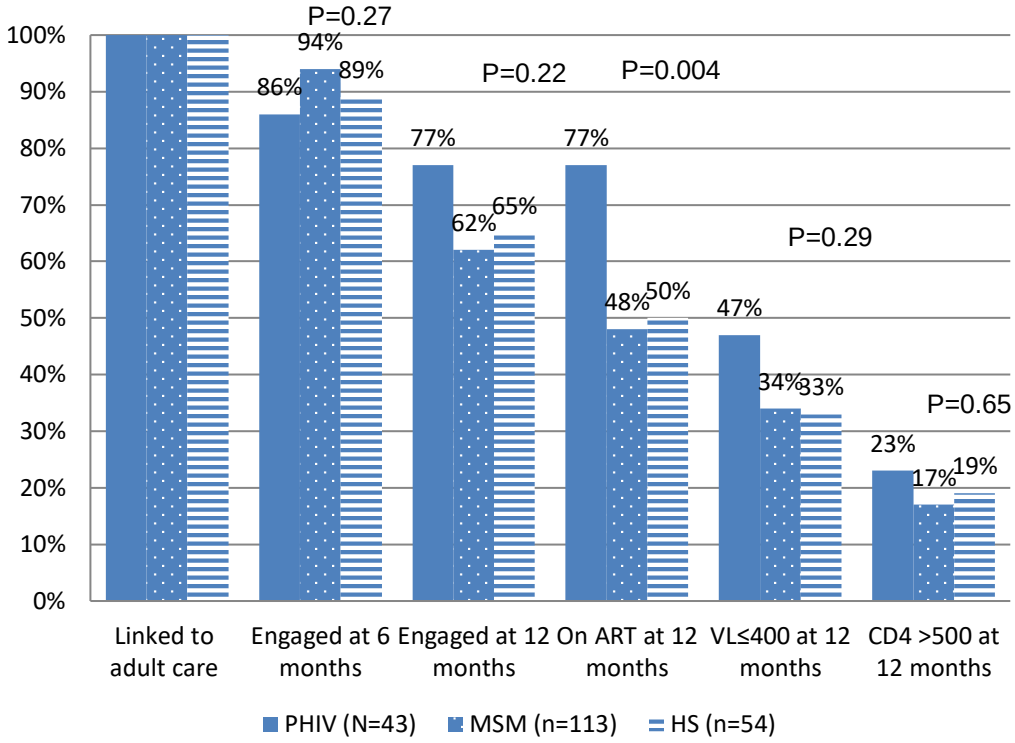


7.3.3.2. HARS only cascade

There were 43 young people with PHIV aged under 20 years, who transferred to adult clinics reporting to HARS only and who were compared to 167 young people with BHIV attending adult clinics reporting to HARS only. Of the latter group, 113 (68%) were MSM and 54 (32%) were heterosexual.

Figure 7.12 presents the 12 month HARS cascade for young people by mode of acquisition. In contrast to the trends observed in the SOPHID +/- HARS cascades by mode of acquisition, there were no difference in the proportions engaged in care at the 6 and 12 month time points, virally suppressed and with a CD4 count >500 cells/mm3 across the exposure groups (p>0.1). This was despite a substantially higher proportion of the PHIV group engaged by the 12 month time point compared to the other groups (77% vs 62% and 65% of the MSM and heterosexual groups, respectively, p=0.22). Young people with PHIV had a significantly higher proportion on ART compared to the other two groups (77% vs 48% and 50%, respectively, p=0.004).

Figure 7.12: HARS only cascade of care at 12 months after first visit in adult care by mode of acquisition (PHIV (N=43), MSM (N=113) and heterosexual (HS) (N=54) group)

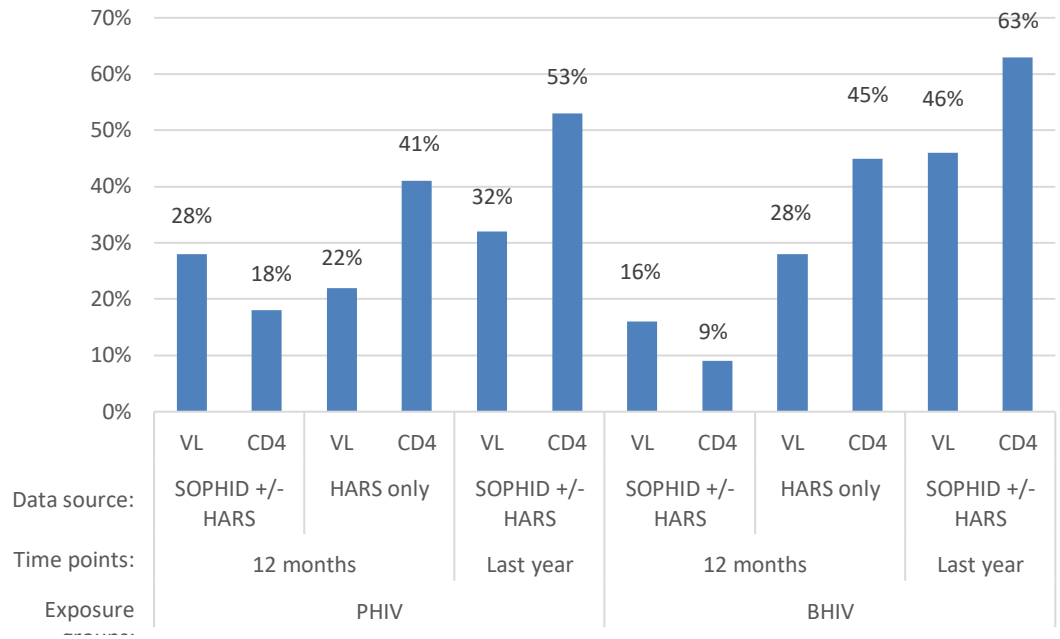


7.3.4. Sensitivity analyses among young people with PHIV

There were varying levels of missing VL and CD4 data in the SOPHID +/- HARS and HARS only cascades at the 12 month and last year of follow-up time points. Figure 7.13 displays the percentage of missing VL and CD4 data at 12 months post-linkage and at last visit in adult care among young people by mode of HIV acquisition and data source used. Among both groups of young people who were engaged by the 12 month time point, 16-28% had missing VL data and 9% to 45% had missing CD4 data in SOPHID and HARS. Among those engaged in the last year of follow-up, the ranges increased to 32% to 46% for missing VL data and 53% to 63% for missing CD4 data. There were similar distributions of missing data by mode of acquisition and data source.

Several sensitivity analyses were carried out to assess the impact of the missing VL and CD4 data on the SOPHID +/- HARS and the HARS only cascade estimates of young people who transferred to adult care. This was done by reconstructing the cascades using different data sources: (1) SOPHID only (without any subsequent HARS data) and (2) UK CHIC only.

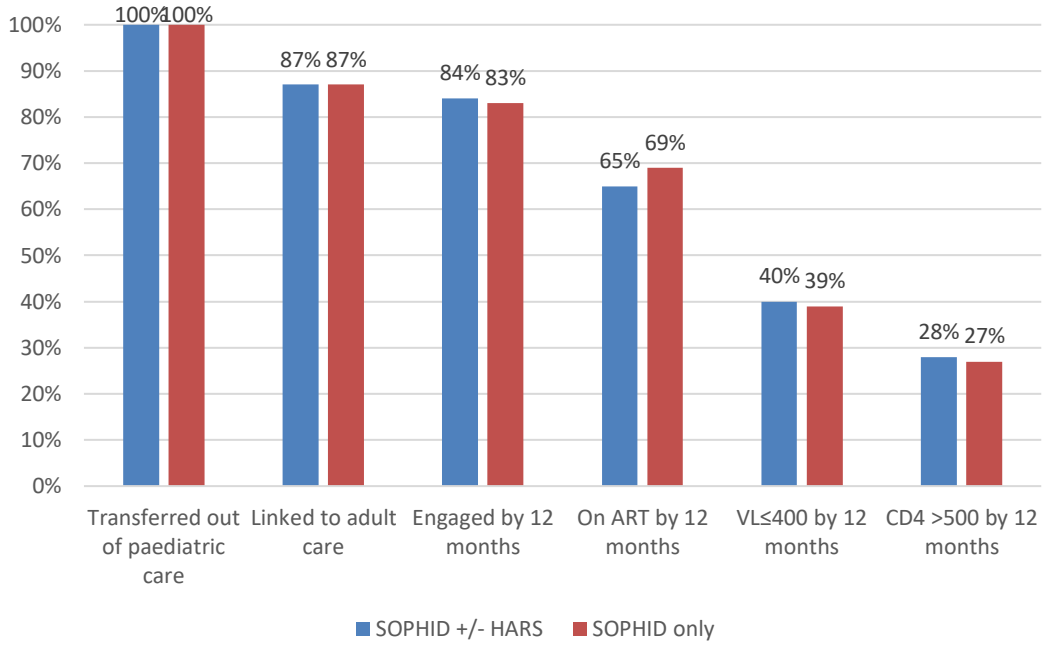
Figure 7.13: The level of missing CD4 and VL data by mode of HIV acquisition and data source used



7.3.4.1. Cascades of care using SOPHID +/- HARS vs only SOPHID data

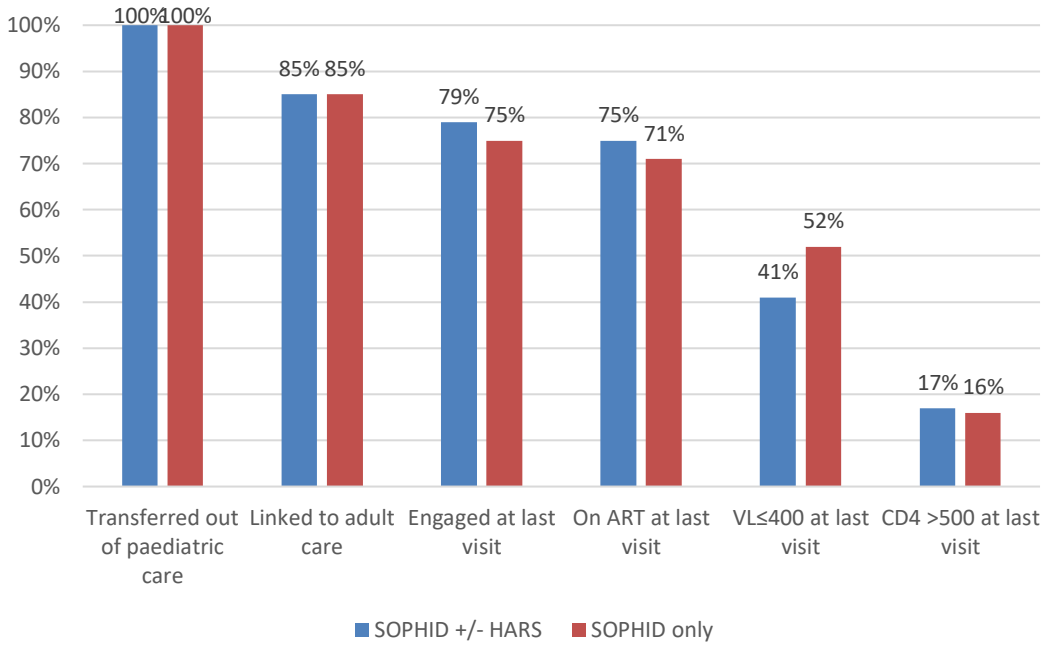
The 12 month cascade of care using SOPHID +/- HARS data was compared to the 12 month cascade using SOPHID only data (Figure 7.14). The cascade estimates across all the steps were comparable between the two data sources and the level of missing VL and CD4 data did not change from 28% and 18%, respectively.

Figure 7.14: Cascade of care at the 12 month visit among young people with PHIV by data source (SOPHID +/- HARS vs only SOPHID data)



Next, the cascade in the last year of follow-up were compared by data source (SOPHID +/- HARS data vs SOPHID only) (Figure 7.15). Similar to the 12 month time point, the cascade estimates were similar across the steps between the SOPHID +/- HARS cascade and the SOPHID only cascade. The proportion of missing VL was lower in the SOPHID only cascade (11%) compared to the SOPHID +/- HARS cascade (31%). However, the level of missing CD4 data did not differ by data source (52% vs 53%, respectively).

Figure 7.15: Cascade of care in the last year of follow-up among young people with PHIV by data source (SOPHID +/- HARS vs only SOPHID data)

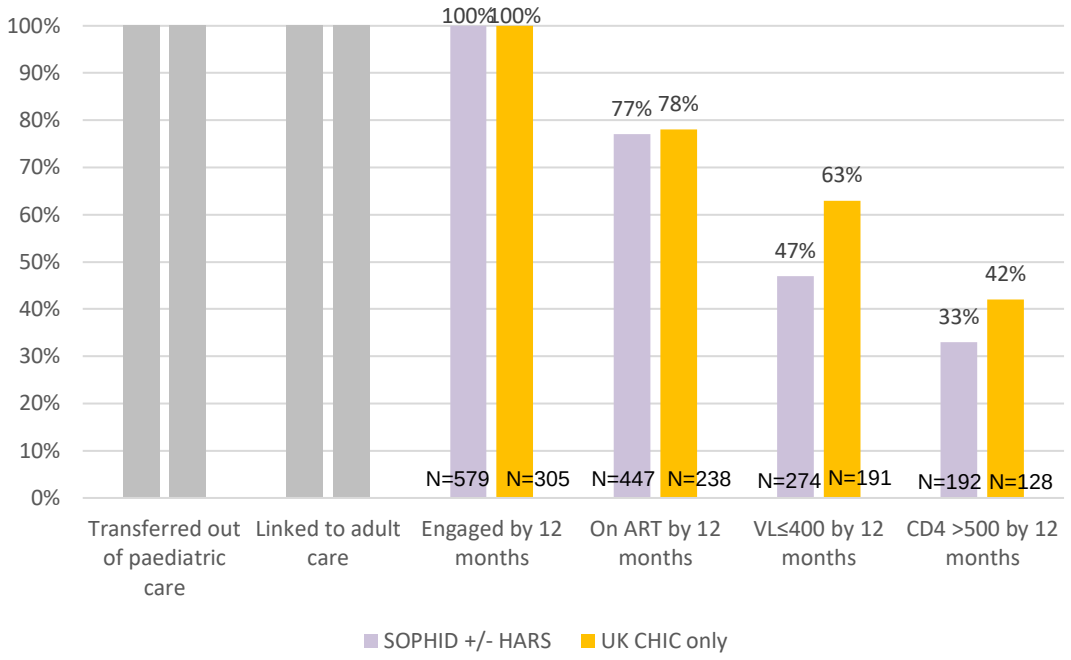


7.3.4.2. Cascade of care using SOPHID +/- HARS data vs only UK CHIC data

The SOPHID +/- HARS cascade at 12 months was reconstructed using only UK CHIC data among only young people with PHIV who met the engagement step of the SOPHID +/- HARS cascade (N=579). Among these 579, 344 had UK CHIC data, of who, 305 were engaged at the 12 month step in the UK CHIC cascade. Figure 7.16 compares the 12 month cascade by data source (UK CHIC only vs SOPHID +/- HARS). Both cascades began from the engagement in care at 12 month step so as to make a fair comparison by data source.

Using the overall percentages, the proportion on ART at the 12 month visit between the SOPHID +/- HARS cascade and the UK CHIC only cascade (77% vs 78% on ART, respectively). However, the viral suppression estimates were higher in the cascade using UK CHIC only data at 63% compared to 47% in the SOPHID +/- HARS cascade. Similarly, the former cascade also had a higher proportion with a CD4 count >500 cells/mm$_3$ compared to the latter (42% vs 33%, respectively). In the UK CHIC cascade, only 2% and 5% had missing VL and CD4 data, respectively, compared to 28% and 18% with missing VL and CD4 data in SOPHID +/- HARS 12 month cascade.

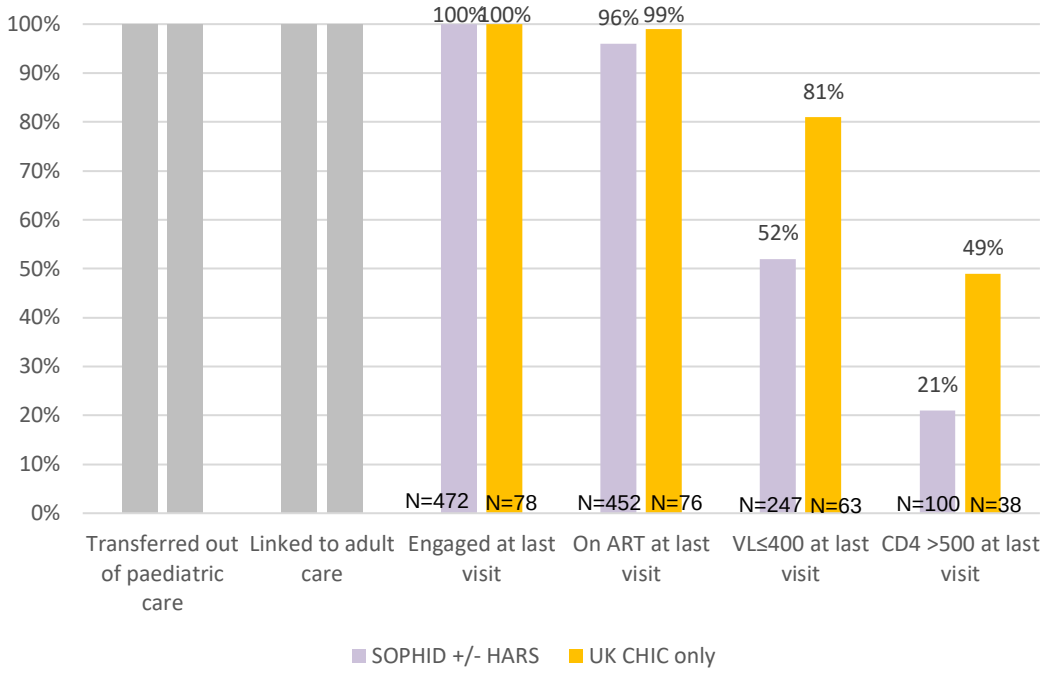
Figure 7.16: Cascade of care at the 12 month visit among young people with PHIV by data source (SOPHID +/- HARS vs only UK CHIC data)



The SOPHID +/- HARS cascade in the last year of follow-up was also reconstructed using only UK CHIC data among young people with PHIV who met the engagement step of the SOPHID +/- HARS cascade (N=472). Among the 472 engaged in care in the SOPHID +/- HARS cascade, 167 had UK CHIC data, of whom, 78 were engaged in the last year of follow-up.

Figure 7.17 compares the last visit cascade by data source (UK CHIC only vs SOPHID +/- HARS). Using the overall percentages, among those engaged in the last year of follow-up, 96% and 99% were on ART in the SOPHID +/- HARS cascade and the UK CHIC only cascade, respectively. Similar to the trends observed at the 12 month time point, the UK CHIC cascade had higher VL and CD4 estimates compared to the SOPHID +/- HARS cascade with 81% vs 52% virally suppressed, respectively, and 49% vs 21% with a CD4 count >500 cells/mm$_3$, respectively. However, the viral suppression estimates were higher in the cascade using UK CHIC only data at 63% compared to 47% in the SOPHID +/- HARS cascade. Similarly, the former cascade also had a higher proportion with a CD4 count >500 cells/mm$_3$ compared to the latter (42% vs 33%, respectively). In the last visit cascade using UK CHIC data, there were 1% with missing ART data, none with missing VL data and 12% with missing CD4 data. These proportions were considerably less than the proportions of missing VL and CD4 data observed in the last visit cascade using SOPHID +/- HARS data (32% and 53%, respectively).

Figure 7.17: Cascade of care in the last year of follow-up among young people with PHIV by data source (SOPHID +/- HARS vs only UK CHIC data)



7.4. Discussion

In this chapter I present the first national cascades of young people who transferred from paediatric to adult care and compared to those of young people with BHIV in adult care. The cascades measured the progress of young people through their adult care pathway; from linkage to adult care, engagement in care and treatment uptake to achieving viral suppression and attaining immune restoration (CD4 count >500 cells/mm_3). One of the first strengths of this work is the use of national surveillance data (SOPHID and HARS) that were linked to the national paediatric cohort study (CHIPS). The surveillance data allowed me to account for silent transfers of participants to other clinics and, thus, measure true engagement in care, which was not possible in previously published cascade studies of young people that lacked national coverage [108,130,131]. Secondly, the SOPHID data allowed the cascades to be measured longitudinally over a median adult follow-up of five years among both groups of young people. In contrast, other post-transfer studies had limited adult follow-up of up to two years [108,130,131]. Thirdly, immunological status (CD4 count >500 cells/mm_3) in adult care was also explored as a rare last step in the cascade using the CD4 data collected in the surveillance systems, although the VL and CD4 estimates were limited by the high levels of missing data. Fourthly, the cascades are also the first to use such a large sample size of young people who transferred to adult care (N=689), as all other post-transfer cascade studies had sample sizes ranging from 24 to 402 [108,135,138].

Overall, the findings of this chapter have shown that the majority of young people who transferred from paediatric care had completed a first adult visit (85-92%), were engaged in care (70-84%) and on ART (65-75%) by 12 month post-linkage and in the last year of adult follow-up, irrespective of data source. In comparison, young people with BHIV had significantly poorer levels of engagement in care (63-86%), on ART (47-67%) and virally suppressed (33-36%) at both the 12 month and last visit time points.

7.4.1. Data sources used to construct the cascades

Different cascade steps and definitions were used to account for the difference in data collection frequency between SOPHID and HARS. The HARS cascades were more recent and detailed and allowed me to apply stricter engagement definitions; requiring young people to have a visit by 6 and 12 months post-linkage to adult care compared to SOPHID's engagement definition of just one visit in the calendar year following the first year of adult follow-up. The use of more relaxed engagement definitions in the SOPHID cascades can potentially lead to less accurate engagement estimates. With regards to the 12 month cascades using SOPHID +/- HARS data, the nature of the data collection resulted in the engagement, ART, VL and CD4 cascade steps being based on a clinic visit not precisely 12 months post-linkage. Instead, the cascade was based on the last clinic visit of the second calendar year of SOPHID follow-up. If a participant had a first adult visit date recorded in the SOPHID +/- HARS dataset in January 2013 and a second visit in December 2014, this individual would meet the engagement in care definition at the 12 month time point despite the two consecutive visits being separated by almost 24 months. Nevertheless, this was not a common issue as the median duration between the first and second adult visit recorded in SOPHID +/- HARS dataset was 364 days for young people who transferred to adult care.

Additionally, the SOPHID +/- HARS cascades were based on far larger sample sizes and had higher geographical coverage compared to HARS only cascades which did not have national coverage and included only young people who transferred to adult care between 2014 and 2016 (due to HARS having been implemented only in 2014). The small numbers included in the HARS cascades thus impacts the reliability and generalisability of the HARS only cascade estimates to the wider population of young people. Therefore, it is clear that both data sources have their strengths and weaknesses, and the large differences in data collection and cascade definitions means caution is required when comparing outcomes between the two types of cascades.

Those who were captured in the SOPHID +/- HARS cascades vs the HARS only cascade had different characteristics at time of transfer. For instance, the latter group transferred to adult care at a significantly later period compared to the former group (median calendar year 2015 vs 2011, $p<0.001$), reflecting the later years of HARS implementation in comparison to SOPHID. Those at HARS-reporting clinics also transferred with better virological and immunological outcomes and were more likely to be on ART at transfer compared to the other group. These differences likely reflect improvements in disease management in recent years and changes in ART guidelines towards immediate ART initiation [42].

7.4.2. Missing data in SOPHID and HARS

The level of missing CD4 and VL data was high in both SOPHID +/- HARS and the HARS only datasets, irrespective of the participants' mode of HIV acquisition, missing CD4 data was higher (reaching 63%) compared to missing VL data (46%). Such a high percentage of missing data can lead to biased cascade estimates, loss of information, decreased statistical power and increased standard error [227]. In the HARS only dataset, missing VL and CD4 measurements were imputed from clinic visits within a three month window on either side of the visit date of interest. The same could not be done in the SOPHID dataset as this only included a single patient visit per calendar year. According to the HIV/AIDS surveillance team at PHE, the implementation of HARS in recent years has involved some data collection issues. This included a number of quarterly submission periods where some adult clinics had not submitted data to HARS, issues with the HARS online submission portal which contributed to the high level of missing VL and CD4 data in HARS and may have resulted in biased VL and CD4 cascade estimates with potential for over- or underestimation. In addition, these data collection issues would also result in underreported attendance visits, which would cause my cascades having underestimated engagement in care figures.

The level of missing VL and CD4 data led me to investigate with the sensitivity analyses, if the level of missing VL and CD4 would remain high when I constructed cascades using only SOPHID data and no subsequent HARS follow-up data. The proportion of missing VL and CD4 data remained high, ranging from 11-28% and 18-52%, respectively. This suggests that the missing data are not down to just the HARS-related issues described above. PHE runs another surveillance system, called the CD4 Surveillance Scheme, which collects CD4 data among the adult HIV population from 60 laboratories across the UK. The low level of available CD4 data in SOPHID reported by the clinics may be due to the CD4 Surveillance Scheme which monitor

immunological trends [228]. Unfortunately, data from the CD4 Surveillance Scheme were not available for use in this study, therefore, it is unclear if the CD4 data are more completely recorded in this system.

Another important possible factor behind the missing VL and CD4 data in SOPHID and HARS is the possibility that the cascades may be capturing a visit at the engagement step where participants completed a clinic visit but did not have their laboratory measurements (i.e. viral load and CD4 count). The national monitoring guideline published by BHIVA have recommended adult clinics to monitor participants' viral load and CD4 counts in relation to their health status, with more frequent monitoring among participants with poorer immunological and virological outcomes [226]. Those established on ART and virally suppressed (VL <50 copies/ml) are recommended to have their viral load monitored every 6 to 12 months, and those with a CD4 count >200 cells/mm_3 should have their CD4 count monitored annually. Participants with a CD4 count >350 cells/mm_3 who have been virally suppressed on two or more occasions within a year are not required to have their CD4 count monitored, until subsequent viral rebound or onset of HIV-related symptoms. Therefore, missing CD4 data may be due to stable immunological status. On the other hand, participants with a viral load >200 copies/ml are recommended to have their viral load measured every 3 to 4 months while participants with a CD4 count <200 cells/mm_3 who are virally suppressed should have their CD4 count monitored every 6 months. As the latest BHIVA guideline recommends less frequent laboratory monitoring for individuals with more stable health outcomes, it is possible that those with missing they are more likely to have missing CD4 and VL data in my cascades.

When the cascades were reconstructed using only UK CHIC data, the VL and CD4 figures were considerably higher than those reported using the SOPHID +/- HARS data. This suggests that the SOPHID +/- HARS and HARS only cascades produced underestimated levels of viral suppression and levels with a CD4 count >500 cells/mm_3. The bias caused by the missing data would have a larger impact on the set of overall percentages as those included people with missing data in the denominator in contrast to the interim percentages which were based on only those with available VL and/or CD4 data. This, therefore, explains why the interim percentages were higher than the overall percentages and less biased by the missing data.

7.4.3. Cascade outcomes among young people who transferred to adult care

Overall, 87% of young people with PHIV were linked to adult care with a first visit in the SOPHID +/- HARS dataset. It is unclear whether the other 13% not identified in the SOPHID dataset were missing due to being LTFU, having moved abroad or simply not captured in the CHIPS-SOPHID/HARS linkage algorithm. Between the 12 month visit date and the last visit date in adult care cascade estimates remained fairly stable. The overall percentages showed 84% and 79% as engaged in care, 65% and 75% on ART, 40% and 41% virally suppressed and 28% and 17% had a CD4 count >500 cells/mm_3 at the 12 month and last visit time points, respectively. The high level of linkage to adult care among this group is comparable to linkage estimates of young people with PHIV and BHIV reported in Italy and USA [108,131,138,140]. Varying levels of engagement in adult care have been reported by cascade studies of young people with HIV, ranging from 56% to

100% among perinatal populations [108,130,131,138] and 45% to 86% among those with BHIV [140–143]. ART and viral suppression levels have also been shown to vary between different cascade studies, likely due to the use of different definitions and cascade denominators, making direct comparison to these studies difficult.

While the HARS only participants had better clinical characteristics at the last paediatric visit compared to the SOPHID +/- HARS participants, the former group had higher levels linked to adult care, on ART, but lower levels engaged by 12 months post-linkage and comparable levels virally suppressed and with a CD4 count >500 cells/mm$_3$ in adult care compared to the latter group. It is unclear if these trends between the SOPHID +/- HARS and the HARS only cascades are attributable to the different cascade methodologies used, time periods of follow-up covered or due to HARS only cascade findings having limited representativeness with including 53 young people with a median follow-up duration of 9 months post-transfer.

The overall and the interim percentage are equally important cascade percentages; the first shows the overall proportion of young people who transferred out of paediatric care and met each cascade step whereas the interim percentages show the proportion of young people progressing between each consecutive step allowing the extent of drop off between steps to be determined. Nonetheless, the overall percentages in particular should be interpreted with caution as the denominator includes young people who did not have the chance to meet the respective step, for example, someone who was not engaged in care at a certain time point, would not have the chance to be on ART at that same time point according to my cascades.

7.4.4. Cascade outcomes by mode of acquisition

Cascades were also generated for young people with BHIV aged 15 to 19 years by the first adult visit and had entered adult care during or after 2008 so as to make the age and year of entry more comparable to young people who transferred from paediatric care. The strict inclusion criteria applied to the BHIV group of young people enabled better comparability with the PHIV group. However, the BHIV inclusion criteria also limited the generalisability of the cascade estimates to other young people with BHIV who entered adult care in earlier years or were slightly older.

Among the BHIV group captured in the SOPHID +/- HARS cascades, engagement in care declined from 12 months post-linkage to last visit in adult care (86% vs 75%), which is comparable to a USA study that reported a decline in levels engaged in care among young people with BHIV (aged 12 to 24 years), although the USA study was over a three year period post-transfer [142]. On the other hand, the proportions on ART (47% vs 67%) increased in the SOPHID +/- HARS cascade from 12 months post-linkage to the last adult visit, while the levels of viral suppression and those with a CD4 count >500 cells/mm$_3$ was low and remained comparable between the two time points.

Next, the cascades were compared by mode of HIV acquisition, including the PHIV group (i.e. young people from paediatric care) and the BHIV group (i.e. including MSM and heterosexual exposure groups). In the SOPHID +/- HARS cascades, the perinatal group had significantly higher

proportions engaged in care and on ART and virally suppressed at 12 months and last adult visit compared to both the MSM and heterosexual groups. In the HARS only cascade, the perinatal group still had a higher proportion engaged in care, on ART and virally suppressed by the 12 month visit, although only the ART step showed a significant trend by mode of acquisition. The perinatal group having better cascade outcomes likely reflects this group having better adjusted in adult care after being in paediatric care for majority of their lives. In contrast, many of the BHIV group were newly diagnosed young people dealing with the responsibility of the HIV disease and its therapy for the first time. There was little difference in cascade estimates between the MSM and heterosexual group, which indicates less benefit in having exposure group-based interventions in adult care. However, all young people with HIV fared the worst at the CD4 step of the cascade, irrespective of mode of acquisition and data source used. Overall, 17-39% of all young people with HIV had a measured CD4 count >500 cells/mm$_3$ at the 12 month post-linkage and last visit in adult care, although these estimates are very likely biased and impacted by the high level of CD4 count data (9% to 61%). Therefore, firm conclusions cannot be drawn from the CD4 count estimates. However, similarly low CD4 count estimates were reported by a longitudinal cascade study in the USA, where 27% to 39% of young people (aged 12-24 years) achieved a CD4 count >500 cells/mm$_3$ over a three year follow-up period. Only one other post-transfer study from the USA compared cascade estimates between young people with PHIV vs BHIV [108]. Dissimilar to my study, the USA study found no significant difference in the cascade estimates by mode of acquisition, although their sample size (N=50) was considerably smaller than mine , which may have limited the statistical power for the USA study to detect any difference exposure group.

7.4.5. In the context of the UNAIDS global '90-90-90' goal

The cascade findings for young people who transferred to adult care and those with BHIV were not easily comparable to the UNAIDS 90-90-90 goal, as the first 90 refers to number of people with HIV diagnosed. This step was not measured in my cascades as all young people in the CHIPS, SOPHID and HARS dataset were already diagnosed in paediatric care. Therefore, only the last two steps (ART and viral suppression step) of the 90-90-90 framework were comparable to the young people's cascade findings. Despite the difference in denominators, young people with PHIV in the SOPHID +/- HARS cascade did not meet any the UNAIDS goals by the 12 month time point. However, they did surpass the 90% goal for the ART step with 96% on ART of those engaged at the last visit using the SOPHID +/- HARS data. Among young people with PHIV in the HARS only cascade who were engaged in care at 12 months post-linkage, all were on ART (100%) and 71% virally suppressed, which was encouraging. Young people with BHIV had not reached the 90% goal for either step (ART or viral step) at any time points. In contrast, a 2018 PHE report (using SOPHID and HARS data) showed the national population of adults with HIV to have passed the 90-90-90 goal with 92% diagnosed, of those 98% on ART and of those 97% virally suppressed (VL <200 copies/ml) [88]. From this it is clear that the population of young people in the UK have some progress to make to reach achievements made by the older adult population. My findings are consistent with other adult HIV studies from the UK, USA and Canada that reported poorer cascade outcomes among young people with HIV [229–233]. Therefore, These young

people with HIV, in particular those more recently diagnosed with BHIV, may benefit from more intense monitoring and additional multidisciplinary adult services to prevent disengagement from care, improve ART adherence and virological control. However, with the high level of missing VL and CD4 data observed, the low estimates, in particular the CD4 estimates, are likely biased and deserve to be interpreted with much caution.

7.4.6. Limitations

The cascade work in this chapter has several limitations. Firstly, the infrequent data collection in SOPHID led to the use of relaxed engagement definitions compared to cascades using HARS data, thus resulting in less accurate estimates in the SOPHID cascades. Another limitation is the level of missing CD4 and viral load data. In this chapter, the proportions that met each cascade step were presented as observed, which included participants with missing data in the denominators. My current approach of calculating the cascade estimates by including those with missing data meant the missing equals failure (i.e. unsuppressed viral load or CD4 count <500 cells/mm$_3$) assumption applied, which is not reflective of participants who completed a visit but did not have their laboratory measurements taken. Alternatively, the exclusion of those with missing data from the denominators would mean the missing at random assumption applied, which would also not be appropriate, especially as differences in demographic and clinical characteristics were observed between those with missing and not missing data. With cascades, there is no gold-standard approach in dealing with missing data. Among post-transfer cascade studies for young people in adult care, one study assumed missing equals failure [139], another limited their sample size to those with no missing data [131], two studies reported no missing data in their studies [135,143], while the majority of cascade studies did not specify their methods in dealing with missing data [88,108,138,141].

In these cascades, high cut offs were used when defining the VL (≤400 copies/ml) and CD4 step (≥500 cells/mm$_3$) which may result in an overestimation of the proportion of young people who met both steps compared to other studies that used lower cut offs (e.g. VL <50 copies/ml). However, in the sensitivity analyses, lower cut-offs were used (i.e. VL <200 copies/ml and CD4 ≥350 cells/mm$_3$), the viral suppression estimates remained very similar to that in the main analyses, while the proportion meeting the CD4 step were considerably higher when the threshold was reduced to >350 cells/mm$_3$. This suggests a large group of individuals had a CD4 count between 350-500 cells/mm$_3$ at the respective time points.

The cascades of care methodology used a unidirectional and simplistic framework with fixed endpoints at the 12 month and last visit time points, where it was not possible to capture the backward movement of participants between the cascade steps (i.e. being on and off ART). A more sophisticated cascade methodology was used for the adult HIV population by the UK CHIC study [95]. The status of participants along the cascade was time-updated by a month-by-month basis which was more reflective of real-life patient scenarios and enabled backward and forward movement along the cascade to be taken into account. Additionally, in my study, the cascades of care comparisons by mode of HIV acquisition were limited by descriptive analyses and potential confounders were not taken into account. Another limitation of the cascade methodology was not

taking into account young people's eligibility to be on ART. The study period occurred during the years when ART eligibility was dependent on patients' immunological status and prior to the recent recommendation for universal ART coverage. Therefore, there will be participants in my study who were classified as 'off ART' when they were not eligible to receive ART. However, due to the high level of missing CD4 data in the SOPHID and HARS data sources, it was difficult to properly assess ART eligibility for all individuals.

When young people with HIV were compared by mode of acquisition, there were differences that could not be accounted for between the different modes of acquisitions. For example, the majority of young people with HIV transferred to adult care with prior exposure to HIV and ART for most of their lives in contrast to more recently diagnosed young people with BHIV. The demographic composition of each exposure group also differed. The population that transferred from paediatric care, with predominantly PHIV (95%) were mostly black African with equal sex distribution, whereas the MSM group were all male and predominantly white while the heterosexual group were black and female. Furthermore, young people who transferred from paediatric care may exhibit more care seeking behaviour as the majority of them have over a decade of experience in attending paediatric clinic visits compared to young people with BHIV who were more recently diagnosed with HIV in adult care. This would also result in potential survival bias among the former group, which may explain why their engagement, ART and viral suppression estimates were higher than the latter group.

Another limitation is including participants who transferred out of paediatric care over a long period of time (1998 to 2016), particularly in the SOPHID +/- HARS cascades. The more historic participants entered adult care during a period when monitoring guidelines were very different treatment options were less effective and more limited compared to young people entering adult care in more recent years.

A limitation that is often inevitable with national surveillance systems is the collection of inconsistent data. Variables such as mode of acquisition were inconsistently recorded in SOPHID and HARS. Therefore, in such instances, a standardised approach was taken, where the last submitted record was selected in line with standard of practice of the HIV/AIDS surveillance team at PHE (P. Kirwan, personal communication). Importantly, national mortality estimates were not investigated in the cascade analyses due underreported death data for young people who transferred to adult care, as described in Chapter 3. According to the HIV/AIDS surveillance department, HARS captures deaths through linkage with the Office of National Statistics, which have experienced data processing issues. Consequently, deaths were not excluded from the SOPHID and HARS cascades in the last year of follow-up, which could result in young people who are linked to adult care, not reaching the later steps of the cascades (i.e. engagement, ART etc.) due to having died years prior. This could possibly result in underestimation of cascade estimates. However, the cumulative mortality incidence was 9% by five years of adult follow-up among young people who transferred to UK CHIC-participating clinics.

Lastly, the cascade of care constructed in this chapter were limited to only clinical measures and due to data limitation did not take into account psychosocial issues such as HIV stigma,

depression and anxiety, that has previously been described among young people living HIV [84]. Nonetheless, this may not be the most appropriate cascade framework to use when measuring the success of young people's progression through adult care. In recent years, there is increased understanding that the ultimate goal for the HIV population should go beyond achieving viral suppression, which is where the original '90-90-90' UNAIDS developed framework ends. Instead, the WHO recently recommended for the extension of the cascade to include a fourth '90' called the 'quality of life'. This additional step takes into account that individuals who achieve viral suppression may still contend with the issue that impact their quality of life such as depression, anxiety, financial issues, comorbidities and pain management [90,104,234–236]. Therefore, future research measuring the cascade with this additional step would provide valuable insight into the care progression of young people, although, it is not yet clear the best approach to consistently measure 'quality of life' and how such a measure could be incorporated into national surveillance systems. All issues and biases identified in this study are summarised in Table 7.18.

7.4.7. Conclusion

My research highlights the need for caution when interpreting cascades as they provide different estimates depending on whether the overall or interim percentages are described. Some differences were also noted among the estimates using SOPHID +/- HARS data vs HARS only data, although the steps could not be properly compared due to HARS cascades being based on a different definition of engagement compared to the SOPHID cascades. The ideal cascade would use follow-up data from all clinics visits in each year and would be based on longitudinal data spanning a longer period than is currently available for HARS. All things considered, young people who transferred from paediatric to adult care were shown to progress through the adult care pathway better than young people with BHIV who were more recently diagnosed. Further work comparing their virological and immunological trajectories through adult care, with more complete data, is needed to better understand if and how their disease progression differs.

Table 7.18: Summary of issues and errors affecting the cascade estimates

Issue	Type of error	Potential effect of biases on cascade estimates (where applicable)	Adjustment made
Overall cascade denominator			
Small number of participants captured in the HARS cascades, restricted to only those who entered adult care between 31/12/2014 to 01/04/2016	Reliability	Overestimation/ underestimation of all cascade steps	
Large differences between patients with different modes of acquisition in demographic characteristics and duration of exposure to HIV	Limited comparability	-	
Participants who were documented in CHIPS as moved abroad or were LTFU from paediatric care were excluded from analyses, but may have re-entered adult care	Selection bias that may limit the generalizability of findings	-	
Engagement in care cascade numerator			
In the SOPHID +/- HARS cascades, a sophisticated engagement in care definition could not be used as the SOPHID dataset only includes the last visit per patient per calendar year	Accuracy	Overestimation/ underestimation of the proportion engaged in care	
ART cascade numerator			
The ART cascade step does not take into account ART eligibility, as study follow-up occurred prior to the recommendation of universal ART uptake, when eligibility was dependent on patients' immunological status	Misclassification (young people who were not eligible to be on ART may be misclassified as 'off ART)	Underestimation of the proportion off ART	

Table 7.18 continued on the next page

VL and CD4 cascade numerators			
The VL and CD4 steps were defined using only one measurement each, while these biological measures vary over time, a blip in VL/CD4 count may have been captured in the cascade steps	Reliability	Overestimation/ underestimation of proportion meeting the VL and CD4 step	
High level of missing CD4 and VL data in SOPHID and HARS datasets	Missing data	Overestimation/ underestimation of proportion meeting the VL and CD4 step	Sensitivity analyses reconstructed the cascade using only UK CHIC data

8. Chapter 8: Concluding remarks

8.1. Key findings and relevance

In this thesis, a broad aim was to investigate the health status of young people who grew up with HIV, following their transfer from paediatric to adult HIV care. As there is no gold-standard approach to measuring a successful transfer, I have taken a broad approach of measuring the risk and predictors of key clinical outcomes in the follow-up period after entry to adult care, such as severe immunosuppression, viral failure, new AIDS events or mortality and disengagement from care. In addition, I have adapted the HIV cascade of care to be applied to this population for the period following entry to adult care, focusing on outcomes of retention in care, being on ART, achieving viral suppression and good immune status among young people with childhood acquired HIV (mostly due to perinatal HIV acquisition) was compared to a young people with newly diagnosed HIV upon direct entry to adult care.

8.1.1. Chapter 3: Data linkage of paediatric and adult data

The analyses used in this thesis required data linkage of individual patient level data across multiple cohorts and national surveillance data. Deterministic data linking is a useful and automated method that can link large number of records [171], but had not been widely used among HIV studies that collect paediatric and adult data. The majority of post-transfer studies have described collecting and using paediatric and adult data from participating clinics, although without specifying the methods for combining the data sources (i.e. review of medical records or using shared unique identifier). Therefore, it is unclear if the patient data were extracted from a small number of specific clinics which may impact the representativeness of the study populations. Prior to my study, deterministic data linkage method was used by only one other post-transfer study [104], which linked CHIPS and UK CHIC cohort data, the latter includes data from some of the largest adult HIV clinics in the UK. In my study, this linkage was updated using a more detailed linkage algorithm and was expanded to include linkage to PHE's national HIV surveillance datasets to provide national coverage.

Of the CHIPS participants who met the broad inclusion criteria for data linkage, half (53%) were successfully linked to adult datasets, among those not linked, 90% were reported to still be in paediatric care. Of those documented in CHIPS as transferred to adult care, the majority (87%) were linked with adult care data. The robustness of the data linkage was checked through a validation process where the linked records underwent both manual and automated checks. The linkage was largely limited by missing data of some of the linkage variables which increases the risk of under-linking, however as 87% of those transferred to adult care were successfully linked, the under-matching is relatively low for a national cohort. For future research, emphasis on complete collection of key identifying variables such as *Soundex* and *patient hospital number* within the CHIPS, UK CHIC, SOPHID and HARS databases will be critical in ensuring the success of future linkage studies.

This study demonstrates that with appropriate linkage algorithms, the creation of a life course dataset for young people who transferred to adult care is feasible, thus providing the opportunity

to research the long term impact of patients born with HIV and lifelong exposure to ART. The algorithms developed are intended for automated usage which promotes efficiency and utilisation of existing cohort or surveillance databases, the methods used here could be applied to numerous other settings, building upon or adapting this algorithm as needed, depending on the availability of the unique identifying variables (i.e. *date of birth, sex, partial postcode, clinic, hospital number* etc.).

8.1.2. Chapter 4: Service provision for young people with HIV following transfer to adult care

International and national transition and youth-friendliness guidelines have recommended the importance for adult clinics to offer differentiated care to young people, also called 'youth-friendly services', tailored to the unique needs of young people [84,121,176,177]. Studies across various settings have shown the benefits of youth-friendly services on the engagement in care and health outcomes of young people with HIV, although these services have varied in their content, from provision of peer support to availability of evening hours and financial incentives [101,106,128,154,155]. To date, no study has explored range of youth-friendly clinic-level services which are currently available in the UK nor their effect on key outcomes such as engagement in care, viral suppression and immune response of young people who have transferred from paediatric to adult care.

In Chapter 4, I developed a clinic survey to carry out a national mapping of youth-friendly services available to young people who transferred to adult care. The survey data were used to assess the level of youth-friendliness across regions and by clinic type (young persons' clinics vs general adult clinics). The findings from this survey study provides a detailed overview of the range of services available to young people in the UK along with gaps in service provision. My survey findings indicated a high provision of specialist services (ranging from 69% to 93%) tailored to young people and the transition process, while the proportion of adult clinics providing accessibility promoting services such as evening hours, walk-in and weekend services was lower ranging from 4% to 62%. The lower proportion of clinics offering accessibility promoting services may be considered as a potential barrier to care for some young people, although, my work in Chapter 5 found no association between the clinic-level characteristics and disengagement outcomes. In contrast to my findings, adult HIV studies from USA, Kenya and South Africa reported various youth-friendly clinic services to improve engagement in care [101,128,237,238], and most of which had also adjusted for key clinical patient characteristics. However, the cross-sectional nature of the survey data used in this study is a key limitation as it reflect the current status as of 2017 among responding centres and may not reflect the services provided over the previous calendar years. Ideally cluster randomised clinical trials would address this question of the impact of different service delivery models, although they are very expensive to conduct and there may not be sufficient number of patients transferring to meet the required sample size to detect a difference in key clinical outcomes such as AIDS or death. An alternative approach may be the introduction of regular surveys to map evolving services over time which would provide data for future analyses on their impact on patient outcomes before and after these services were introduced.

8.1.3. Chapter 5: Mortality and disengagement from care following transfer to adult care

With the first generation of children born to mothers with HIV reaching adulthood in recent years, it is difficult to estimate their life expectancy and the long-term effects of life-long exposure to ART and HIV is not yet well understood. In Chapter 5, I explored the incidence and risk factors of experiencing AIDS and/or mortality post-transfer as well as disengagement from adult care, using CHIPS and UK CHIC linked data.

Young people who transferred to UK CHIC clinics were found to be broadly similar to the young people who transferred to non-UK CHIC clinics, although, the former group were more likely to have poorer immunological and virological status at transfer. This is likely due to the UK CHIC study consisting of most of the larger and more specialised adolescent and adult clinics which are more likely to receive clinically complex patient referrals. Therefore, the findings in Chapter 5 should be interpreted in the context of the UK CHIC cohort who transferred from paediatric care. In my study, 3% of patients died in adult care, one in eleven patients experienced a new/recurrent AIDS event or death and one in twenty were LTFU by five years of follow-up in adult care. Similar overall mortality estimates were reported by post-transfer studies from HIC (ranging from 0-7%) [78,104,130,133,134] and LMIC (ranging from 0-6%), although their durations of follow-up ranged from one to three years. In this study, young people at higher risk of AIDS/mortality were those born abroad, transferred in later calendar years, with lower CD4 counts and prior AIDS diagnosis at time of transfer. The majority of deaths observed in my study occurred in earlier calendar years (median year 2006), many of whom had exposure to sub-optimal mono and dual therapy, prior to availability of cART.

Overall, 8% of this cohort ever became LTFU in adult care. The literature has described varying disengagement levels (0.4% to 20%) from 12 months post-transfer to last visit in adult care across Europe [105,129,130] and wider ranges reported across North America (14% to 55% by 12 to 24 months post-transfer), although disengagement definitions varied widely and many of the studies were based on data from single sites and/or had small sample sizes of up to 72 participants [105,108,110,116,129,131]. Similar LTFU estimates to my study were found in post-transfer cohorts across LMIC; 10% in a Dominican Republic cohort and 13% in a Thai cohort of young people enrolled on a transfer preparedness program, although, studies were of one or two sites and both had small sample sizes (N=67-81). While none of the demographic, clinical or clinic-level factors explored in my study were found to be associated with the LTFU outcome, being male or not having prior AIDS diagnoses in paediatric care were associated with gaps in adult care. Only one other post-transfer study of 72 young people from USA explored predictors of disengagement from adult care and found no gender effect, while prior AIDS status was not explored [131]. That study also found none of the clinical characteristics at transfer to have a significant effect with the outcome, which was in line with my findings.

While this study explored both patient-level characteristics at time of transfer and clinic-level services, other non-clinical factors which may be pertinent such as: unemployment status, mental health, other comorbidities, financial stability and housing status, were not explored due to such

data not being available in this study. In addition, cultural or language barriers may be particularly relevant to my study populations, as two thirds of the CHIPS cohort were born abroad.

8.1.4. Chapter 6: Immunological and virological outcomes following transfer to adult care

The literature has described inconsistent immunological and virological trends following transfer, although most studies are limited by small sample sizes.

CHIPS and UK CHIC linked data were used to assess the incidence of severe immunosuppression and viral failure in adult care among young people on treatment for ≥6 months, with good immunological and virological outcomes at transfer. Despite the stringent inclusion criteria, high incidence of severe immunosuppression and viral failure were found, with a quarter experiencing either outcome by five years after transfer. Sub-groups at higher risk for severe immunosuppression and viral failure were young people with higher viral load, lower CD4 (although >200 cells/mm$_3$) and a previous AIDS diagnosis at transfer. My findings are further supported by other post-transfer studies from the UK [136], USA [131], Thailand [219] that similarly found poor clinical outcomes prior to transfer to predict poor immunological or virological outcomes in adult care.

These findings suggest that this sub-group of young people that transfer to adult care with sub-optimal health outcomes are at risk of continued poor health in adult care and could benefit from additional clinical support and resources prior to and following transfer, especially as the public health impacts of uncontrolled viral load are the possibility of onward transmission as many young people begin to engage in sexual activity during this period of adolescence/young adulthood [239]. The findings regarding risk of severe immunosuppression findings also indicate that young people with borderline health outcomes, i.e. CD4 count of 200-500 cells/mm$_3$, can benefit from more frequent monitoring to prevent CD4 count declining to below 200 cells/mm$_3$. As CD4 decline is driven by high VL, a key factor not previously measured is adherence to treatment. Researching trends in adherence in paediatric and adult care could help inform the optimum time to provide young people with adherence support that could potentially reduce their risk of experiencing poor outcomes in adult care. It would be useful to also assess the effect of previously unmeasured social factors such as mental health issues, educational attainment and lack of social support on the immunological and virological outcomes in adult care that could add further context to my findings.

8.1.5. Chapter 7: Cascade of care following transfer to adult care

The literature has described young people with HIV to perform poorer along each step of the cascade of care when compared to older adults [54,90,229–233]. However, there is a lack of data disaggregated by mode of acquisition with the majority of cascade studies consisting of young people with BHIV [54,140,141,143]. It was unclear if young adults with childhood acquired HIV also had poorer retention in the cascade of care as compared to adults.

In Chapter 7, national cascades of care were measured of young people, by mode of HIV acquisition, after entry to adult care to provide a public health overview for this population. The study was strengthened with the use of national adult surveillance data which resulted in a large

and representative sample size. The cascade estimates suggest that young people had better engagement in care, were more likely to be on ART and be virally suppressed as compared to young people with BHIV. However, when compared to the national adult HIV population, young people had lower proportions engaged in care, on treatment and virally suppressed, irrespective of mode of acquisition. These findings were consistent with two USA studies which describe the cascade of care among young people (15% to 38% with PHIV) who transferred from paediatric to adult care, reporting similar low proportions progressing through the cascade and achieving viral suppression [108,131]. However, in South-Africa and sub-Saharan Africa, substantially lower proportions of young people with HIV have managed to successfully progress through the care pathway and achieve viral suppression (ranging from 10% to 24%), driven by the low numbers accessing ART (14% to 32%) [52,240]. Young people with BHIV in some African countries are also heavily marginalised, in particular in countries (e.g. Uganda) that have passed anti-homosexuality laws that criminalizes young MSM, which may act as additional barriers to care [241].

In my study, the different exposure groups had vast demographic and clinical differences that could not be matched. The majority of the PHIV group had around close to two decades of HIV and ART exposure at last visit and many years of engagement in HIV care, as compared to young people with BHIV, who were more recently diagnosed and initiated on ART, which may result in different care seeking behaviours. These differences may go some way to explain why the latter group had poorer cascade outcomes, although, the divergent trends may not persist as the populations age and mature over time. Therefore, additional longer term research on the cascade of care by age would be useful in assessing such a trend with age.

These findings highlight the public health concern and vulnerability of young people compared to older adults with HIV, in particular when considering the low proportion with viral suppression at last visit (41 and 33% among the PHIV and BHIV group, respectively) and the impact this may have on risk of AIDS and death. Furthermore, the cascade of care steps were limited to clinical outcomes, extending the cascade by including 'quality of life', as recently recommended by the WHO, would allow broader wellbeing to be taken into account when measuring the success of young people's progression through the care pathway [234,235]. Further to this, my findings also have health research relevance, as using different cascade definitions, steps and population denominators have shown to produce slightly different estimates. The high variation in cascade methodology across settings, often guided by the study's data source, limits the comparability of cascade findings, and guidelines have thus highlighted the need for global standardised cascade methodology. However, this is often difficult to achieve due to data limitations.

In Table 8.1, I further summarised the main objectives, findings, clinical significance and limitations of each results chapter.

Table 8.1: Summary of the objectives, key findings, clinical significance and limitations of the chapters in this thesis

Chapter number: key objectives	Key findings	Clinical significance and/or strengths	Limitations
Chapter 3: To link paediatric and adult data among young people with HIV	• 53% of eligible participants were linked to adult care data • 86% of patients transferred to adult care were linked to adult care data	• Life-course dataset created • Linkage algorithm is for automated use and can be repeated for future studies	General limitations: • No shared unique identifier, therefore, cannot rule out falsely linked records • Potential under linkage due to missing data on key variables Biases: • Temporal bias: linkage variables will have more missing data for young people who transferred in earlier calendar years in comparison to recent years due to improvements in data collection methods. Those who transferred in more recent years would therefore be more likely to be captured in the linkage
Chapter 4: To describe the range of youth friendly services in adult HIV clinics (data source: clinic survey)	• 78% response rate for clinic survey • Level of youth-friendly services did not differ by clinic type (young persons' vs general adult clinic) • Specialist services were more widely available than accessibility promoting services	• Inform gaps in service provision for young people with HIV • Enabled assessment of impact of youth friendly services on engagement in care and clinical outcomes	General limitations: • Findings based on cross-sectional data which may not be extrapolated beyond the year of data collection (2017) • Clinic survey questions lacked detail Biases: • Selection bias: clinic survey only included larger clinics with ≥3 young people from paediatric care • Social desirability bias by survey respondents

Chapter number: key objectives	Key findings	Clinical significance and/or strengths	Limitations
Chapter 5: To measure the risk of and factors associated with AIDS/mortality and disengagement from care following transfer date (data source: CHIPS and UK CHIC datasets)	• 1 in 11 progressed to AIDS or died in adult care • Mortality burden declined over time with most of the deaths occurring in earlier calendar years (median year of death - 2010) • Young people born abroad and with prior AIDS events in paediatric care were more likely to experience AIDS/mortality in adult care • 1 in 20 were LTFU • LTFU group had similar demographic and clinical characteristics at transfer to those who were not LTFU in adult care	• Migrants and those with poorer health outcomes at transfer need additional clinical support in adult care • As all deceased participants had access to ART, it is possible there are non-clinical factors that contributed to their death that had not been explored in my study • The mortality burden in this study has declined in recent years likely due to improvements in HIV care management •	General limitations • Small number of deaths, so had to use composite outcome of AIDS and/or mortality • Non-clinical factors not explored as potential predictors of mortality and disengagement from care • Could not ascertain the number of deaths • Short follow-up duration Bias: • Selection bias: (1) only young people with at least one visit were included in this study (2) only included young people at UK CHIC clinics and the UK CHIC group had poorer health outcomes at transfer compared to the non-UK CHIC group, (3) survival bias: study consists of young people who have survived during paediatric and adult follow-up

Chapter number: key objectives	Key findings	Clinical significance and/or strengths	Limitations
Chapter 6: To measure the risk of and factors associated with severe immunosuppression and viral failure following transfer date (data source: CHIPS and UK CHIC datasets)	• 1 in 4 of young people on ART with good CD4 and VL outcomes at transfer experienced severe immunosuppression or viral failure at least once in adult care • Half of those who ever experienced an episode of severe immunosuppression or viral failure had experienced another episode by the last visit in adult care • Young people with poorer virological and immunological outcomes in paediatric care were at higher risk of experiencing either outcome in adult care • CD4 and VL status at transfer has improved over the years	• Young people with poorer health outcomes at transfer and borderline CD4 count (between 200-500 cells/mm_3) may require closer monitoring • The risk of experiencing either outcome is considerably high despite the population of interest consisting of those with optimal health outcomes and adherent to treatment	General limitations: • Not representative of young people with viral failure or severe immunosuppression at transfer • Short follow-up duration • Non-clinical factors not explored as potential risk factors for severe immunosuppression and viral failure Bias: • Selection bias: (1) only young people with at least one visit were included in this study (2) only included young people at UK CHIC clinics and the UK CHIC group had poorer health outcomes at transfer compared to the non-UK CHIC group, • survival bias: study consists of young people who have survived during paediatric and adult follow-up

Chapter number: key objectives	Key findings	Clinical significance and/or strengths	Limitations
Chapter 7: To describe the national cascade of care among young people who transferred to adult care compared to those with BHIV in adult care (data source: CHIPS and SOPHID/HARS datasets)	• Young people who transferred to adult care had better cascade outcomes than those with BHIV • All young people had worse cascade outcomes, irrespective of mode of HIV acquisition compared to the general adult population living with HIV	• Young people with HIV in adult care could benefit from additional clinical support compared to older adults with HIV • 12 month cascade shows the health status of both those who transferred in recent years and those who transferred in more historic years, while the last visit cascade can be viewed as a more recent snapshot of all young people in 2015 • Cascade outcomes have improved compared to earlier years, although, further progress is still needed	General limitations: • SOPHID infrequent data collection, which resulted in more relaxed engagement definitions • Missing CD4 and VL data in the SOPHID/HARS datasets • National mortality estimates not produced due to underreporting of mortality data in the SOPHID and HARS dataset • Inability to make a fair match between the different exposure groups, as demographic characteristics and likely behavioural characteristics are expected to differ by mode of acquisition • Cascade findings have to be interpreted with caution as different cascade methodology produced slightly different estimates • Descriptive analyses, not adjusted for any known confounders • Short follow-up duration

8.2. Limitations

The limitations specific to each of the five analyses chapters have been described in depth within the relevant chapters. Further to this, there are general limitations that affect all chapters as a consequence of using observational data, and these limitations have to be taken into account when interpreting the findings. Randomised control trials are the gold-standard for evidence-based research, however, young people have been transitioning from paediatric to adult care without RCTs to inform optimal healthcare delivery. Therefore, without 'gold-standard' randomised data, the most appropriate approach was to utilise existing routine care observational data which were readily available to explore health outcomes and engagement in care following transfer to adult care. In terms of future research, in particular in regions where perinatal HIV populations are only just entering adolescence, such as in sub-Saharan Africa [242], cluster randomised trials exploring different types or range of youth-friendly services and transition preparation processes and their impact on engagement in care and health outcomes post-transfer to adult care would be highly informative, as well as the cost-effectiveness of such interventions to assess their economical viability for resource limited settings. An RCT design would improve the ability to clearly ascertain the impact of the intervention (e.g. service delivery model), removing any bias and controlling for known and unknown confounding through the randomisation process. However, a large number of clinics would need to be recruited and would be best suited to settings with high burden of paediatric and adolescent HIV. Additionally, there may be ethical implications of the control arm withholding WHO recommended youth-friendly services.

8.2.1. Data representativeness and generalisability

One of the limitations of my research is the use of different populations and data sources for different analyses within this thesis, this was largely guided by the research questions and the availability of data within each data source. The use of different populations across the analyses can lead to a lack of internal consistencies, and limited representativeness between the populations [85]. However the characteristics of patients included in the UK CHIC datasets were broadly similar to those in the HARS and SOPHID datasets. Figure 8.1 presents the different patient-level study populations included in this thesis.

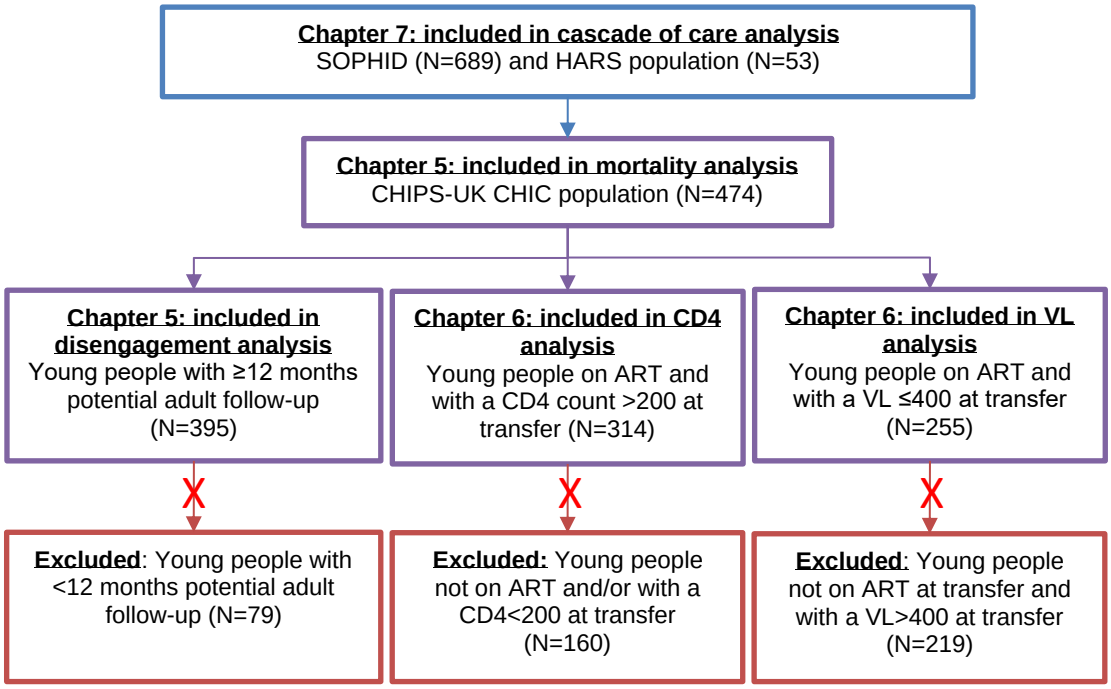
The largest study population and most representative of young people who transferred to adult care was the SOPHID population included in the analyses of Chapter 7. The SOPHID population had national coverage and thus enabled the cascade of care analysis, including national-level engagement in care to be measured. The strength of this dataset was the ability to capture patients who had transferred across clinics over time, these transfers would not have been captured if using the UK CHIC dataset, if patients transferred to other clinics outside of the UK-CHIC network of clinics. The SOPHID/HARS surveillance systems have the advantage of ensuring compliance in data submission from all adult HIV clinics due to the contractual obligation placed on clinics by the Department of Health, which is not the case with the UK CHIC study, therefore, the UK CHIC data may be more complete. One limitation of the more comprehensive national HARS dataset is that it only included young people who transferred in the most recent calendar years (>2014) compared to the SOPHID dataset. The former population transferred to

adult care with significantly better ART uptake, CD4 count and viral load characteristics compared to the SOPHID population, which consists of a more historic group of young people.

In Chapters 5 and 6, patient-level data linked between the CHIPS and UK CHIC dataset were used, as detailed clinical data were required to carry out in-depth analyses on incidence of mortality, disengagement, severe immunosuppression and viral failure following transfer and the associated factors. The disengagement analyses among the UK CHIC sub-populations (Chapter 5) were strengthened by validating true LTFU or gaps in care from silent transfers with the use of SOPHID/HARS data. Although this validating step highlighted a discrepancy in data submitted by adult clinics to the UK CHIC study and to SOPHID and HARS. The CHIPS-UK CHIC cohort formed a sub-population of those identified in SOPHID and HARS and therefore had more limited representativeness of the national population.

The sub-population captured in the CHIPS and UK CHIC data linkage may not be as representative of the wider population of young people as the SOPHID and HARS population. The majority of UK CHIC-participating adult clinics are mostly large tertiary centres based in London or large cities. Young people transferring to UK CHIC clinics were more likely to have poorer health outcomes to those at non-UK CHIC clinics. Therefore, the findings of the CHIPS-UK CHIC cohort cannot be generalised to the entire UK population of young people who transferred to adult care. Nonetheless, the findings can still be useful in informing clinical care within the UK CHIC-participating adult clinics, which captures around half the population of young people transferring out of paediatric care in the UK. The mortality analyses were carried out among all young people identified in the UK CHIC study, while additional inclusion criteria were applied for the disengagement, severe immunosuppression and viral failure analyses. Consequently, the mortality findings were more generalizable to the wider population of young people at UK CHIC adult clinics compared to the other analyses. As a result of the inclusion criteria applied, there are sub-groups of young people not captured in many of these analyses. For example, young people who were off-ART or on ART but with viral loads>400copies/mL at transfer were excluded from the virological failure analysis of Chapter 6 (Figure 8.1). Further research are needed to explore the outcomes of these particularly vulnerable patient groups with already poor outcomes at time of transfer.

Figure 8.1: Different study populations included in the results chapters of this thesis



Another issue that affects all study populations of this thesis, is the fact that all analyses were based on only young people linked to the adult datasets with at least one completed adult visit. Therefore, young people who transferred out of paediatric care but did not enter adult care are not represented here. This group may have different demographic and clinical characteristics, likely poorer health outcomes due to not accessing to care. Alternatively, it is also possible some patients did successfully engage with adult care but was simply not captured in my data linkage due to missing or changing identifiers (e.g. change in surname and Soundex upon entry to adult care).

Even though my data linkage resulted in a total of 886 young people identified across the adult databases, the sample size used for the different analyses were considerably smaller due to the different inclusion criteria applied, ranging from 255 to 689. The smallest sample size was used in the virological analysis (N=255). Despite this, the sample sizes used in all the analyses of this thesis still exceed almost all the published post-transfer studies across HIC, to date. An exception to this is a large New York based post-transfer study of 735 young people with PHIV that investigated health outcomes in adult care. In this thesis, the different study populations had short to medium length follow-up durations in adult care (median 3 to 5 years) due to most young people transferring to adult care over the last decade. The limited follow-up periods may have resulted in an overestimated disengagement figures, as some young people may not have had the opportunity to return back to care due to the database cut-off date applied [243].

Overall, my findings would be relevant in informing clinical care in HIC as well as LMIC, especially with two-thirds of the CHIPS cohort consisting of children who were born abroad, mostly from African countries and were diagnosed and initiated ART late, at older ages which is often also observed in LMIC [243]. However, the generalisability of my findings is limited by the vast differences

in healthcare systems, resource availability and transition processes adopted across the different settings. For example, in many sub-Saharan settings children and adults are all seen in one primary health care setting with no physical transition from paediatric to adolescent or adult care [244]. Nonetheless, it would be important to have similar analyses conducted in these settings, to explore outcomes of patients with PHIV as they enter adolescence and adulthood. Further to this, it is unclear if my findings will remain the same for future generations of youth entering adult care across the UK as new and improved treatments emerge, repeat of similar analyses would be important to assess how the trends evolve over time.

8.3.2. Data availability and missing data

While the CHIPS and UK CHIC study providing detailed clinical information, my analyses were limited by the lack of non-clinical data collected such as adherence data that would allow me to contextualise the viral failure and mortality findings. Adherence is, however, seldom captured in HIV cohorts across the UK [245] due to the difficulties in measuring this over prolonged periods and the fact that there is no standardised measurement tool used in routine care across all settings [246].

Missing data was particularly an issue in the cascade chapter as substantial missing VL and CD4 measurements in the SOPHID and HARS dataset. This may have led to an under or over-estimate of the immune and virological outcomes. In the cascade of care sensitivity analysis based on the more complete UK CHIC data, the CD4 and VL outcomes were shown to be better than that seen in the main analysis. Another issue regarding data availability and missingness, was the underreporting of mortality data in SOPHID and HARS, which meant mortality events could not be described on a national level, and was only done within the UK CHIC cohort. It is possible that some deaths among patients in in the UK CHIC dataset were not captured; therefore, the UK CHIC mortality estimate described in Chapter 5 should be interpreted as a minimum estimate for the UK CHIC cohort. However, as the UK CHIC group were found to have poorer health outcomes at transfer compared to the non-UK CHIC group, the mortality estimate may be a possible overestimation for the UK's national population of young people who transferred to adult care

Lastly, despite having created a life-course dataset, most analyses did not utilise the full extent of paediatric data, as my focus was on characteristics at transfer date that may predict negative health outcomes in adult care.

8.2.3. Biases and unmeasured confounding

As with all observational studies, the potential for uncontrolled biases and unmeasured confounding cannot be eliminated. With the study samples from each chapter being based on the data linkage between the relevant parent studies, the validation process of the data linkage required young people to have at least one completed adult visit. This, therefore, introduced an inevitable selection bias in favour of those more likely to complete their transition process, which would in turn result in underestimations of the mortality, disengagement, viral failure and severe immunosuppression figures. Another common bias identified across the chapters is survival bias

as the young people captured in the study populations are those who survived during paediatric and adult follow-up.

To remove potential biases and adjust for potential confounders identified in the general HIV and post-transfer literature, in particular age, sex and poor clinical characteristics, I used multivariable regression methods, although, there may still be some unmeasured confounding. Socioeconomic status and adherence to ART are two important confounders that were not adjusted for in any of the analyses due to inaccessibility to such data. A Dutch post-transfer cohort identified that a lower educational attainment was associated with an increased risk of experiencing viral failure post-transfer [105]. Another study from the UK, that investigated mortality among young people who transferred to adult care, found a high prevalence of mental health conditions among the deceased participants [78]. As all the young people who died in adult care in my study had access to ART, it is very possible that there are other non-clinical factors driving the mortality risk. It is possible that young people who do not have family support are more susceptible to adherence problems compared to young people who are more supported at home and given medication reminders. Unfortunately, this was an unexplored theory as data on familial support were also not collected.

Further to this, there could be residual confounding, as a result of inaccuracies in the measurement of some variables or inadequate adjustment of captured confounders, which could all lead to the effect estimates being distorted from the true value. Conducting a randomized clinical trial would avoid the effect estimates from being affected by such confounding, although, this is not always financially and practically feasibly to implement.

8.3. Lessons learnt

From the research conducted in this thesis, overall, seven main lessons have been learnt that could be relevant to populations living with HIV as well as other childhood acquired chronic diseases. Lessons learnt could also be useful to current and future studies using big data, in particular with the increased focus in using big data in HIV research [247–251], characterised by large and complex data collection as well as the linkage between multiple data sources. Big data have been recognised as a powerful tool with potential to advance existing data systems and improve the quality of health research.

1. This research has highlighted the clinical vulnerability of young people with HIV transferring from paediatric care as compared to the general adult population with HIV, in terms of higher than expected mortality, incidence of severe immunosuppression and virological failure. This may be partly due to the developmentally sensitive adolescent phase and losing the familiarity of paediatric care settings. Young people with HIV, in particular those with sub-optimal health outcomes at time of transfer out of paediatric care may benefit from additional clinical support in the period prior to and after transfer as well as closer monitoring. This could be highlighted in the national monitoring guidelines that currently do not differentiate young people from older adults, although there are recommendations for closer monitoring of patients not on stable and suppressive ART. Further research is still needed to identify and evaluate effective clinical and

non-clinical interventions to help improve the adherence, viral control and disease progression of this population of young people.

2. This research has highlighted a range of poor clinical outcomes observed in this population but does not focus on the reasons driving these poor health outcomes compared to older adults. The research did not explore non-clinical risk factors of poor health outcomes and is further limited by the lack of patient and public involvement (PPI), which could have offered unique insight into the research findings. Therefore, qualitative and quantitative studies investigating barriers to care, social-demographic, economic and mental health-related risk factors of poor health, mortality and disengagement from care would be very informative in shaping and advancing clinical care. Similarly, measuring the cascade of care with only quantitative measures may not be the best approach for young people who transferred to adult care. Instead, extending the cascade by adding the quality of life as an additional step would be more reflective of young people's the successful progression through the care pathway. However, it is unclear how to consistently measure and incorporate patient reported outcomes such as quality of life into national surveillance systems and observational studies.

3. An important concern within the healthcare transition field is whether the health of young people who transferred to adult care, is largely worsening, improving or remaining constant. Using the research of this thesis, it is difficult to answer this question due being heavily focused on the health outcomes and disengagement status in adult care. Importantly, the evolution of young people's CD4 count before and after transfer [104] has previously been modelled in the UK, where the CD4 trajectory was found to already be declining in the years prior to transfer and continue to decline post-transfer for some demographic groups, while stabilising in other groups. Further research building on the life course dataset created across CHIPS, SOPHID, HARS and UK CHIC can be used to explore the long term immune and virological trajectory, disengagement and mortality trends before and after transfer.

4. The cascade of care research highlights the need for caution when interpreting cascades, as estimates varied by data source, time points and cascade percentage used (interim vs overall percentage). This is relevant to HIV and Hepatitis C cascade frameworks among all age groups, and additional caution must be used when comparing cascades constructed with different methodology.

5. Improvements in the quality of the mortality, VL and CD4 surveillance data are needed to enable future research to more accurately assess the HIV population's health and mortality status in adult care. Due to underreporting of death in the surveillance systems, national burden of mortality could not be fully estimated in this thesis and the number of deaths identified in UK CHIC may be underestimated.

The following two lessons are relevant to adolescent populations living with all childhood acquired chronic diseases, such as type 1 diabetes, sickle cell disease and cystic fibrosis, where young people are required to transfer from paediatric to adult care.

6. There is a need for unique patient identifiers (e.g. NHS number) or commonly collection of patient identifiers (e.g. date of birth, soundex, sex etc) used across paediatric and adult databases. Harmonization across studies and healthcare settings would allow for participants to be more easily linked to enable research on long-term outcomes of young people with chronic diseases. In this thesis, all the data linkage was carried out retrospectively, and future data linkage carried out prospectively may result in higher linkage coverage of these young people as they progress through adult care. However, this would ideally require the patient's consent or assent at first entry to care.

7. The impact and cost effectiveness of youth-friendly services on the disengagement from care and health outcomes of young people need to be assessed using gold standard methods such as RCT to provide a strong evidence base for policy recommendations, particularly in resource limited settings where there are large number of competitions demands for scarce resources and the most effective and cost-effective interventions need to be identified. Importantly, interventions which work well in HIC need to be confirmed to be feasible and as effective in LMIC where very different health care systems exist.

As the UK has one of the oldest cohorts of young people growing up with HIV, the lessons learnt in this thesis, would be particularly beneficial to settings with an existing and emerging burden of adolescent HIV, including central and Eastern Europe, and sub-Saharan Africa. The research in this thesis can help inform health care providers on expected clinical outcomes and associated risk factors, as well as informing the direction of future research in this population. Some of the lessons learnt can also be useful to studies linking multiple large databases or researching post-transfer health outcomes among populations with HIV and other chronic diseases.

8.4. Recommendations

The research carried out in this thesis has informed the following recommendations for the benefit of other researchers, policy makers and healthcare service providers:

1. Studies evaluating the efficacy of youth-friendly services lack input from young people living with HIV who could provide insight on what they may define as 'youth-friendly'. Therefore, future research and HIV clinics evaluating and implementing youth-friendly services would likely benefit from engaging young people with HIV, seeking their perspective, to ensure the services better meet their needs.

2. Paediatric and adult HIV studies collecting unique patient identifiers such as NHS number, would enable better monitoring of young people with HIV and other chronic diseases as they progress through paediatric and adult care. This would also avoid the need for time and resource intensive cross-study data linkages.

3. Comprehensive surveillance systems and cohort studies such as HARS and the UK CHIC study provided detailed and rich data (on all patient visits) which enabled informative research, such as measuring the national post-transition cascade for young people in the UK and to identify

the risk factors of AIDS and/or mortality. Therefore, other settings would benefit from setting up such comprehensive systems and studies with regards to carrying out informative research.

4. There is an increasing evidence on poor social factors (i.e. low educational attainment) and mental health co-morbidities being associated with poorer HIV health outcomes. Therefore, national HIV surveillance systems such as HARS and SOPHID could better monitor the health and wellbeing of the HIV population (regardless of age), by also collecting non-clinical markers such as mental health diagnoses, poverty and educational attainment. Though the logistics of capturing data on factors such as poverty may be difficult to incorporate into a national surveillance system.

8.5. Further research

The analyses in this thesis were focused on exploring the different health statuses of young people with HIV, which helped identify clinically vulnerable groups in need of additional clinical support. It is also important to know what interventions are effective in helping such groups improve their engagement in care and health outcomes in adult care. Qualitative research, gaining the perspective of young people, on the drivers of disengagement from care and poor health outcomes in adult care would be vital when tailoring effective interventions to this population. In the coming years, it would also be important to repeat the data linkage across the paediatric and adult cohorts and surveillance systems, with more complete data for the linkage variables, which would likely result in higher potential matches.

Further to the descriptive cascade work carried out in Chapter 7, future research identifying the risk groups less likely to meet each step of the cascade could help inform recommendations on how to improve young people's cascade estimates and close the health gap between older adults. Additionally, a more complex cascade which allows for participants' forward and backward movement between cascade steps, as previously done in a UK adult HIV study [95] would also ensure a more accurate depiction of young people's progression through the care pathway.

As previously mentioned, the research in this thesis could be extended by assessing young people's success in completing the transition process. This could be investigated by comparing the different health outcomes and disengagement patterns before, during and after transfer to adult care. With the lack of consensus on how to properly assess a 'successful transition experience', a proposed research initiative (Creating a Global fRAmework of Data collection Used for Adolescent HIV Transition Evaluation (GRADUATE)) has recently aimed to harmonise the data collected by post-transfer studies, particularly, in LMIC, by guiding the demographic, socio-economic, clinical and laboratory data that should be collected to describe the transition period [252]. The global implementation of such a standardised approach would enable easier comparison and evaluation of transition processes across the different settings.

The literature has described young people's brain development to mature by the age of 25 years associated thereafter with less impulsivity and risk-taking behaviour, which may result in better health outcomes and progression through the care pathway [194–196]. Therefore, it would be

interesting for future research to focus on trends in engagement and health outcomes by age to see if young people's health improves with increased maturity during older adulthood.

8.6. Conclusion

This thesis aimed to investigate the risk of AIDS/mortality, disengagement from care, severe immunosuppression and viral failure following transfer to adult care. I identified a sub-group with poorer health outcomes prior to transferring at greater risk of experiencing viral failure, severe immunosuppression and AIDS/mortality in adult care. I also found young people who transferred from paediatric care progressed significantly better across the cascade of care following transfer compared to more newly diagnosed young people with BHIV.

I believe this thesis has enabled future data sharing between CHIPS, SOPHID, HARS and the UK CHIC study as well as providing the findings to inform adult clinical care and intervention targets that can help bridge the widely reported health gaps between young people and older adults with HIV on a national and international level.

Appendices

Appendix 1: CHIPS baseline form

MRC Clinical Trials Unit | UCL

CHIPS Baseline form

Version 12.8 Jan 2018

CHIPS Number: ..... Soundex: _ _ _ _ PENTA Trial Number: .....

CSTU Number: ..... Hospital Number: .....

Date of birth: ..... Initials: ..... Gender: .....

Paediatrician: ..... Main hospital: .....

Date of most recent examination: d d m m y y y y

1. Is this child in shared care with another hospital? Yes ☐ No ☐

1a. If Yes, where? .....

For the purpose of CHIPS study, virtual or satellite clinics are not shared care clinics and do not need to be reported here. Transfers must be reported in Q13.

2. Has the child ever had any CDC category B or C events? Yes ☐ No ☐

If Yes, please complete the table below

a. Category B or C events Please list below	b. Date of onset dd/mm/yyyy	c.Category (please tick)		d. Diagnosis Definitive or Presumptive*		e. Drugs/treatment administered (not ART)
		B	C	D	P	
	__/__/____					
	__/__/____					
	__/__/____					
	__/__/____					
	__/__/____					

for definitions of category B, please see appendix 1 and for category C, please see appendix 2

3. Has the child had any hospital inpatient stays since diagnosis? Yes ☐ No ☐

If Yes, please complete the table below (continue on page 3 if needed)

a. Name of Hospital	b. Date of admission dd/mm/yyyy	c. Date of discharge dd/mm/yyyy	d. Diagnosis and drugs/treatments administered (not ART)	e. Related Event (specify if related to B/C/ART event as above)
	__/__/____	__/__/____		
	__/__/____	__/__/____		

4. Has the child ever had: 4a Hep B Pos ☐ Neg ☐ Never tested ☐ Missing ☐ **4b. Hep C** Pos ☐ Neg ☐ Never tested ☐ Missing ☐

5. Please give all results from initial date of diagnosis (only 1 height/weight measurement required per year)

(continue on page 3 if needed)

a.Date dd/mm/yyyy	b.Weight	c.Height	d.Blood Pressure	e.Date of sample dd/mm/yyyy	f.CD4	g.CD4 %	h.Total Lymph	i.Date of sample dd/mm/yyyy	RNA viral load k.copies/ml	l.cut off
__/__/____	. kg	cm	__/__/____	__/__/____		%		__/__/____		
__/__/____	. kg	cm	__/__/____	__/__/____		%		__/__/____		
__/__/____	. kg	cm	__/__/____	__/__/____		%		__/__/____		
__/__/____	. kg	cm	__/__/____	__/__/____		%		__/__/____		

6. Does the child have lipodystrophy? *(for definition please see Appendix 3)* Yes ☐ Probable ☐ No ☐ Not Known ☐

6a. If Yes, or Probable, please specify onset date: d d m m y y y y

6b. What type is it? Lipohypertrophy ☐ Lipoatrophy ☐ Both ☐

7. Most recent blood lipids: Not done ☐

7a. Triglycerides: . mmol/l **7b.** Cholesterol: . mmol/l

7c. Date: d d m m y y y y **7d.** Fasting: Yes ☐ No ☐ Not known ☐

(If the patient is male please go to question 10)

8a. Has the girl experienced menarche? Yes ☐ No ☐ **8b.** If Yes, give date of onset: m m y y y y

9. Has the girl ever been pregnant? Yes ☐ No ☐

9a. If Yes, what was the outcome? Continuing ☐ Termination ☐ Miscarriage ☐ Still birth ☐ Live birth ☐

9b. If it was a live birth, what was the date of birth? d d m m y y y y

All pregnancies must be reported to the NSHPC. For more information see www.ucl.ac.uk/nshpc/reporting/pregnancies

10. Has the child ever received ART in the UK/Ireland? (incl. post-partum prophylaxis) Yes ☐ No ☐

If Yes, please complete the table below. See appendix 4 for coding of reasons (continue on page 3 if needed)

a. Drug (FDC)	Individual dose b. mg	c. frequency	d. Formulation	e. Date started dd/mm/yyyy	f. Date stopped dd/mm/yyyy	g. Reason(s) for start	h. Reason(s) for stop/change

10i. If born abroad, has the child previously received ART (incl. post-partum prophylaxis) in their home country before arriving in the UK/Ireland?

Yes, details known ☐ Yes, details not known ☐ No ☐ Don't know ☐ Not applicable (born UK/Ireland) ☐

If details known, please include in the table above. See appendix 4 for coding of reasons (continue on page 3 if needed)

ART related adverse events:

Has the child ever had any adverse events possibly related to ART? (Grade 2 or above) Yes ☐ No ☐

If yes, please complete the table below (for definitions please see Appendix 5 (continue/add comments on page 3)

a. Event (specify)	b. Date of onset dd/mm/yyyy	c. Date resolved dd/mm/yyyy (or tick box if ongoing)	d.Worst grade	e. Related drug (if known)	f. Possibly, probably or definitively related or unknown?	g.ART stopped? (see 10f) Yes	g.ART stopped? (see 10f) No	h. Reported to Yellow Card Yes	h. Reported to Yellow Card No
	__/__/____	__/__/____ ☐							
	__/__/____	__/__/____ ☐							

11. Has the child's HIV antibody status been tested in the last 2 years? Yes ☐ No ☐

11a. If Yes, date tested: d d m m y y y y **11b.** Result: Pos ☐ Neg ☐ **11c.** Assay used:.....

12. Postcode of child's residence at most recent examination (without last letter):

13. If you have not seen this child since diagnosis, is s/he:

13a. Due for an appointment? ☐ If so, appointment date d d m m y y y y

Or the child is no longer seen at this clinic because they have (please tick only one):

13b. Transferred to another paediatric clinic? ☐ **13c.** If so, date and clinic?.....

13d. Completed transfer to adolescent clinic? ☐ **13e.** If so, date and clinic?.....

13f. Completed transfer to adult care? ☐ **13g.** If so, date and clinic?.....

13h. Known to have left the country? ☐ **13i.** Lost to follow up? ☐

13j. Died? **Give details on Death form.** ☐ **13k.** If died, date of death: d d m m y y y y

13l. Other: .....

(Only tick "Completed transfer" if the young person has been *fully discharged* from paediatric care).

14. Comments (if any): .....

.....

.....

Signature:	Printed Name:	Date Completed: d d m m y y y y

For office use only: Date form entered onto database : dd - mm - yyyy Initials of data enterer:

MRC Clinical Trials Unit | UCL

CHIPS Baseline form

Version 12.8 Jan2018—Continuation sheet

CHIPS Number: _____ Hospital Number: _____

Date of Birth: _____ Initials: _____

Please provide all data which does not fit in pages 1 or 2 below:

Q3. Has the child had any hospital inpatient stays since diagnosis? (continued from page 1)

a. Name of Hospital	b. Date of admission dd/mm/yyyy	c. Date of discharge dd/mm/yyyy	d. Diagnosis and drugs/treatments administered (not ART)	e. Related Event (specify if related to B/C/ART event as above)
	__/__/____	__/__/____		
	__/__/____	__/__/____		
	__/__/____	__/__/____		

Q5. Please give all results from initial date of diagnosis (only 1 height/weight measurement required per year)

(continued from page 1)

a.Date dd/mm/yyyy	b.Weight	c.Height	d.Blood Pressure	e.Date of sample dd/mm/yyyy	f.CD4	g.CD4 %	h.Total Lymph	i.Date of sample dd/mm/yyyy	RNA viral load k.copies/ml	l.cut off
__/__/____	. kg	cm	__/__	__/__/____		%		__/__/____		
__/__/____	. kg	cm	__/__	__/__/____		%		__/__/____		
__/__/____	. kg	cm	__/__	__/__/____		%		__/__/____		
__/__/____	. kg	cm	__/__	__/__/____		%		__/__/____		
__/__/____	. kg	cm	__/__	__/__/____		%		__/__/____		
__/__/____	. kg	cm	__/__	__/__/____		%		__/__/____		

Q10. Has the child ever received ART in UK/Ireland? (incl. post-partum prophylaxis) & 10i. If born abroad, has the child previously received ART (incl. post-partum prophylaxis) in their home country before arriving in UK/Ireland (continued from page 2)

a. Drug (FDC)	Individual Dose b. mg	c. frequency	d. Formulation	e. Date started dd/mm/yyyy	f. Date stopped dd/mm/yyyy	g. Reason(s) for start	h. Reason(s) for stop/change

ART related adverse events:

Has the child ever had any adverse events possibly related to ART? (Grade 2 or above) (continued from page 2)

a. Event (specify)	b. Date of onset dd/mm/yyyy	c. Date resolved dd/mm/yyyy (or tick box if ongoing)	d.Worst Grade	e. Related drug (if known)	f. Possibly, probably or definitively related or unknown?	g.Reported to Yellow Card Yes	g.Reported to Yellow Card No	h. ART stopped? (see 10f) Yes	h. ART stopped? (see 10f) No
	__/__/____	__/__/____ ☐							
	__/__/____	__/__/____ ☐							
	__/__/____	__/__/____ ☐							

Comments. _____

_____

Signature: | Printed Name: | Date Completed: d d m m y y y y

Thank you for completing this form. **Call us with any queries on 020 7670 4612 or email:** chips.mrcctu@ucl.ac.uk. Please keep a copy for your clinic records and return this form to **CHIPS Data Manager, MRC Clinical Trials Unit at UCL, Institute of Clinical Trials & Methodology, 90 High Holborn, 2nd Floor, London, WC1V 6LJ**

These data are being collected in collaboration with the NSHPC study —call with NSHPC queries on: 020 7905 2692 or email: nshpc@ucl.ac.uk

For office use only: Date form entered onto database : dd - mm - yyyy Initials of data enterer:

Appendix 2: CHIPS follow-up form

CHIPS : Follow up visit

Version 12.10 Jan 2018

CHIPS No.: ----------

PENTA Trial No.: ----------

Main hospital: ----------

Hospital No.: ----------

Date of birth: ----------

Date of most recent examination: d d m m y y y y

Date of last report: ----------

Please approach this patient to consent to the UK Register "CHIPS+" study, if s/he is ≥16, and return the CHIPS+ registration form to us. Thank you.

1. Has the child been in shared care with another hospital since ? Yes ☐ No ☐

1a. If Yes, where? .....

For the purpose of CHIPS study, virtual or satellite clinics are not shared care clinics and do not need to be reported here. Transfers must be reported in Q13.

2. Has the child had any new CDC category B or C events since Yes ☐ No ☐

If Yes, please complete the table below

a. Category B or C events Please list below	b. Date of onset dd/mm/yyyy	c.Category (please tick)		d. Diagnosis Definitive or Presumptive*		e. Drugs/treatment administered (not ART)
		B	C	D	P	
	/ /					
	/ /					

for definitions of category B, please see appendix 1 and for category C, please see appendix 2

ART related adverse events

Has the child had any adverse events (Grade 2 or above) possibly related to ART since ? Yes ☐ No ☐

If Yes, please complete the table below and add comments in Q14 if needed (for definitions please see Appendix 5)

Please use the continuation sheet if not enough space.

a. Event (specify)	b. Date of onset dd/mm/yyyy	c. Date resolved dd/mm/yyyy (or tick box if ongoing)	d.Worst grade	e. Related drug (if known)	f. Possibly, probably or definitively related or unknown?	g. ART stopped? (see 10f) Yes	g. ART stopped? (see 10f) No	h.Reported to Yellow Card Yes	h.Reported to Yellow Card No
	/ /	/ / ☐							
	/ /	/ / ☐							

3. Has the child had any hospital inpatient stays since ? Yes ☐ No ☐

If Yes, please complete the table below . Please use the continuation sheet if not enough space.

a. Name of Hospital	b. Date of admission dd/mm/yyyy	c. Date of discharge dd/mm/yyyy	d. Diagnosis and drugs/treatments administered (not ART)	e. Related Event (specify if related to B/C/ ART event as above)
	/ /	/ /		
	/ /	/ /		
	/ /	/ /		

4. Has the child ever had: 4a. Hep B Pos ☐ Neg ☐ Never tested ☐ Missing ☐ **4b. Hep C** Pos ☐ Neg ☐ Never tested ☐ Missing ☐

5. Please give all results from the routine clinic visit assessments since ?

Please use the continuation sheet if not enough space.

a.Date dd/mm/yyyy	b.Weight	c.Height	d.Blood Pressure	e.Date of sample dd/mm/yyyy	f.CD4	g.CD4 %	h.Total Lymph	i.Date of sample dd/mm/yyyy	RNA viral load k.copies/ ml	RNA viral load l.cut off
	kg	cm				%				
/ /	kg	cm		/ /		%		/ /		
/ /	kg	cm		/ /		%		/ /		
/ /	kg	cm		/ /		%		/ /		
/ /	kg	cm		/ /		%		/ /		
/ /	kg	cm		/ /		%		/ /		

6. Does the child have lipodystrophy? *(for definition please see appendix 3)* Yes ☐ Probable ☐ No ☐ Not Known ☐

6a. If Yes, or Probable, please specify onset date: d d m m y y y y

6b. What type is it? Lipohypertrophy ☐ Lipoatrophy ☐ Both ☐

7. Most recent blood lipids: Not done ☐

7a. Triglycerides: ☐☐.☐☐ mmol/l **7b.** Cholesterol: ☐☐.☐☐ mmol/l

7c. Date: d d m m y y y y **7d.** Fasting: Yes ☐ No ☐ Not known ☐

(If the patient is male please go to question 10)

8. Onset of menarche previously reported as:

8a. If not previously reported, onset of menarche since last visit?: Yes ☐ No ☐

8b. If Yes, give date of onset: d d y y y y

9. Since has the girl been pregnant? Yes ☐ No ☐

9a. If Yes, what was the outcome? Continuing ☐ Termination ☐ Miscarriage ☐ Still birth ☐ Live birth ☐

9b. If it was a live birth, what was the date of birth? d d m m y y y y

All pregnancies must be reported to the NSHPC. For more information see www.ucl.ac.uk/nshpc/reporting/pregnancies

10. Has there been any change in antiretroviral therapy and/or doses since ? Yes ☐ No ☐

If Yes, please complete the table below. See appendix 4 for coding of reasons. Please use the continuation sheet if not enough space.

a. Drug (FDC)	Individual Dose b. mg	c. frequency	d. Formulation	e. Date started dd/mm/yyyy	f. Date stopped dd/mm/yyyy	g. Reason(s) for start	h. Reason(s) for stop/ change

11. Has the child's HIV antibody status been tested in the last 2 years? Yes ☐ No ☐

11a. If Yes, date tested: d d m m y y y y **11b.** Result: Pos ☐ Neg ☐ **11c.** Assay used:.....

12. Postcode of child's residence at most recent examination (without last letter): ☐☐☐☐ ☐☐■

13. If you have not seen this child since is s/he:

13a. Due for an appointment? ☐ If so, appointment date d d m m y y y y

Or the child is no longer seen at this clinic because they have (please tick only one):

13b. Transferred to another paediatric clinic? ☐ **13c.** If so, date and clinic?.....

13d. Completed transfer to adolescent clinic? ☐ **13e.** If so, date and clinic?.....

13f. Completed transfer to adult care? ☐ **13g.** If so, date and clinic?.....

13h. Known to have left the country? ☐ **13i.** Lost to follow-up? ☐

13j. Died? **Give details on Death form.** ☐ **13k.** If died, date of death: d d m m y y y y

13l. Other: .....

NB: Only tick "Completed transfer..."if the young person has been *fully discharged* from paediatric care.

14. Comments (if any): .....

.....

Signature:	Printed Name:	Date Completed: d d m m y y y y

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These data are being collected in collaboration with the NSHPC study —call with queries on: **020 7905 2692** or email: nshpc@ucl.ac.uk

For office use only: Data entry date: dd - mm - yyyy Initials of data enterer: ☐☐☐☐

Appendix 3: CHIPS data specification (10/04/2017)

Overview

CHIPS data are contained in a series of 12 datasets (including one summary dataset) linked by the unique CHIPS identifier (trialno). There are two copies of these datasets stored in separate folders, these are:

- **FinalDatasets_All** – datasets in this folder contain all data entered into the CHIPS database, including, for some participants, data after transfer to adult care. The majority of data available after transfer to adult care are from follow up of young people participating in the AALPHI cohort or notifications of deaths. Note that data on deaths after transfer are received ad-hoc from clinics and are not routinely collected. If using FinalDatasets_All data after transfer, it is important to acknowledge the limitations of the data and that they are available only for a subset of the CHIPS cohort.
- **FinalDatasets_Paed** –All datasets in this folder are censored at date of transfer to adult care (using variable 'transferdate' found in both summary.dta files). Any visits, viral load, CD4, inpatient events, BC events, or ART adverse events measured or commencing after transfer are dropped from their respective datasets. Summary variables (for example 'everpregnant' and 'artstatus_recent') reflect status at the final visit prior to transfer.

Data specification

Baseline and follow-up chips forms each contain 14 questions plus additional demographic and administrative data in the header of the form. The baseline and follow-up forms differ only in the information collected in the header, the recording of ART related adverse events (follow up only) and ART before arrival in UK (baseline only).

In the following tables the source of each variable is provided (CHIPS question number, CHIPS form header, CHIPS death form or additional data supplied by NSHPC). Distinction between baseline and follow-up forms is only made where the information appears on only one.

Summary.dta (1 record per child in CHIPS)

This file contains basic demographic data for all CHIPS children. This includes identifiers, date of birth, sex, current hospital(s), follow-up status, etc.

Variable name	Source	Description	Format & codes
Demographics			
trialno	Admin	CHIPS number	String
cstuno	NSHPC	NSPHC child study number	String
patinit	Header (B/line only)	Initials	String
soundex	Header (B/line only)	Soundex code	String
sex	Header (B/line only)	Gender	Integer 1 (male) 2 (female)
dob	Header	Date of birth	Date
ethnicity	NSHPC	Ethnicity	String
countryofbirth	NSHPC	Country of birth	String
bornabroad	NSHPC	Born outside of the UK	Integer 1 (yes) 0 (no)
postcode	Q12	Postcode of residence	String
regdate	Admin	Date of registration into CHIPS	Date
menarche	Q8a	Menarche or not	Integer 1 (yes) 0 (no)
menarchedate	Q8b	Date at menarche	Date
everpregnant	Q9	Ever been pregnant	Integer 1 (yes) 0 (no)

nochipsform	Q9b	No CHIPS forms entered - Registered in CHIPS but no baseline form returned (yet). Only limited data from NSHPC available.	Integer 1 (yes) 0 (no)
Clinics and transfers			
c_centre	Header	Current clinic number (from last CHIPS follow-up form).	Integer
c_centrename	Header	Current clinic name (from last CHIPS follow-up form).	String
c_hospno	Header	Current hospital number (from last CHIPS follow-up form)	String
c_region	Derived from c_centrename	Region of current clinic	Integer 1 (London) 2 (South - England) 3 (Midlands - England) 4 (North - England) 5 (Scotland) 6 (Wales) 7 (N. Ireland) 8 (Rep. Ireland)
sharedcare	Q1	In shared care (on last follow up form)	Integer 1 (Yes) 0 (No)
sharedcentre	Q1a	Shared care clinic code name (from last CHIPS follow-up form).	Integer
sharedcentrename	Q1a	Shared care clinic name (from last CHIPS follow-up form).	String
c_fupstat_cactus	Derived from Q13	Current follow-up status as recorded on CACTUS based on data from last received on last CHIPS form. Note that lost to follow up is only used when a clinic states a child is lost. Some children may not have been seen for several years but not defined by a clinic as lost to follow-up.	Integer 1 (Transfer to another paediatric clinic) 2 (Due to be seen) 3 (Left country) 4 (Lost to follow-up) 5 (Other) 6 (Transfer to adult care) 7 (Transfer to adolescent clinic) 9 (Died)
c_fupstat	Derived from Q13	Follow-up status (grouped). Note that lost to follow up is only used when a clinic states a child is lost. Some children may not have been seen for several years but not defined by a clinic as lost to follow-up.	Integer 1 (Still in CHIPS follow up) 2 (Lost to follow-up) 3 (Left country) 4 (Transfer to adult/adolescent care) 5 (Died)
transferdate	Q13c	Date transferred to adult care (defined as the first day in a recorded Adolescent, GUM or Infectious Diseases clinic)	date
transfer_centrename	Q13c	Clinic transferred to	String
First diagnosed/presented			
mumdiag	NSHPC	Whether maternal infection was diagnosed before delivery or not	Integer 1 (Before/During) 2 (After)
datearrivedinuk	NSHPC	Date arrived in UK (equal to NSHPC variable DateArrivedInUK)	date
firstuklab	NSHPC	Date of first UK positive lab (always before or equal to fdiaguk)	date
fdiaguk	NSHPC	Date infection is first established in the UK (equal to NSHPC variable DateInfectionEstab)	date
fdiagever			
fdatcareuk	Derived using dob, mumdiag, bornabroad, firstuklab	Date first presented to medical care in the UK (defined as dob if mumdiag=Before/During & bornabroad=No, OTHERWISE defined as minimum of firstuklab and fdiaguk)	date

	and fdiaguk		
fknage	Derived using and fdatcareuk	Age first presented to medical care in UK/Ireland (age at fdatcareuk)	numeric
Antiretroviral treatment*			
prophylaxis_ever	Derived from Q10	Whether received MTC prophylaxis (see appendix 3 for definition of prophylaxis)	Integer 1 (Yes) 0 (No)
proph_start	Derived from Q10e & prophylaxis	Date started MTC prophylaxis (see appendix 3 for definition of prophylaxis)	date
proph_end	Derived from Q10f & prophylaxis	Date stopped MTC prophylaxis(see appendix 3 for definition of prophylaxis)	Date
proph_drugs	Derived from Q10a & prophylaxis	ART drugs received for MTC prophylaxis (see appendix 3 for definition of prophylaxis)	String
artstart	Derived from Q10e & prophylaxis	Date started ART, excluding MTC prophylaxis	Date
artstart_regimen	Derived from Q10a & prophylaxis	First ever ART regimen	String
artstart_regimenclass	Derived from Q10a & prophylaxis	Class of first ever ART regimen	String
artstart_age	Derived from artstart & dob	Age at start of ART	numeric
artstart_cd4	Derived from artstart, Q5e & Q5f	CD4 count at start of ART (closest measurement within 6 months before and 1 month after ART start)	Integer
artstart_cd4p	Derived from artstart, Q5e & Q5g	CD4 percentage at start of ART (closest measurement within 6 months before and 1 month after ART start)	Integer
artstart_vl	Derived from artstart, Q5i, Q5k & Q5l	Viral load at start of ART (closest measurement within 6 months before and 1 week after ART start)	Integer
artstart_cdcstatus	Derived from artstart, Q2b & Q2c	CDC status at start of ART	Integer
cartstart	Derived from Q10a, Q10e & prophylaxis	Date started cART (cART is defined as a regimen of ≥3 drugs from ≥2 classes (excluding 2 class regimens where second class is an unboosted PI) OR a regimen of ≥3 NRTIs which includes abacavir)	Date
cartstart_naive	Derived from Q10a	Naïve at start of cART (cART is defined as a regimen of 3+ drugs from 2+	Integer 1 (Yes)

	& cartstart	classes (excluding 2 class regimens where second class is an unboosted PI) OR a regimen of at least 3 NRTIs which includes abacavir)	0 (No)
n_drugsever	Derived from Q10a	Number of unique drugs ever taken	Integer
artline_recent	Derived from Q10a, Q10e & Q10f	A summary of ART line. For those never on cART, recent regimens are classed as mono, dual, triple or none (naïve (with or without MTC prophyaxis) or treatment interruption). Once cART has been initiated subsequent regimens are classes as being after initial cART or after a switch to a subsequent line.	Integer 1 (On mono) 2 (On dual) 3 (On triple (3 NRTI – excl ABC)) 4 (On triple (inc unboosted PI)) 5 (Started initial cART) 6 (Switched to second cART) 7 (switched to third of later cART) 8 (ART naive) 9 (Treatment interruption)
artstatus_recent	Derived from Q10a, Q10e & Q10f	Most recent ART status. Summarises the most recent ART regimen.	Integer 1 (On mono) 2 (On dual) 3 (On triple (3 NRTI – excl ABC)) 4 (On triple (inc unboosted PI)) 5 (cART) 8 (ART naive) 9 (Treatment interruption)
Last exam and most recent clinical measurements*			
lastseen	Derived from header, Q5a/e/l, Q7c, Q10e/f, Q11a	Date of latest examination or lab value. Defined as most recent date of last exam on most CHIPS form, viral load date, ART change, CD4 date, height/ weight date, lipid date or antibody test date.	Date
cdcstatus	Derived from Q2c	Most recent CDC stage (maximum CDC stage reached at any point)	String
firstBdate	Derived from Q2b & Q2c	Date of first ever B event	Date
firstCevent	Derived from Q2b & Q2c	Date of first ever C event	Date
lastcd4date	Derived from Q5e	Date of most recent CD4	Date
lastcd4	Derived from Q5e & Q5f	Most recent CD4 count	Integer
lastvldate	Derived from Q5i	Date of most recent viral load	Date
lastvl	Derived from Q5i, Q5k & Q5l	Most recent viral load	Integer
lastvlsign	Derived from Q5i, Q5k & Q5l	Sign of most recent viral load	Integer
Death**			
datedeath	Q13j/Death form Q1	Date of death	date
deathdateacc	Q13j/Death form Q1	Accuracy of date of death	Integer 1 (yyyy) 2 (mm/yyyy) 3 (form date) 4 (approx)
deathcause1	Death form Q2	Specific cause of death 1 (code)	Integer
deathcause1_name	Death form Q2	Specific cause of death 1 (name)	String

deathcause2	Death form Q2	Specific cause of death 2 (code)	Integer
deathcause2_name	Death form Q2	Specific cause of death 2 (name)	String
deathcause3	Death form Q2	Specific cause of death 3 (code)	Integer
deathcause3_name	Death form Q2	Specific cause of death 3 (name)	String
Other studies			
in_aalphi	Admin	Participant in AALPHI cohort	Integer 1 (Yes) 0 (No)
aalphino	Admin	AALPHI number	String
in_ukreg	Admin	Participant in UKReg	Integer 1 (Yes) 0 (No
in_chipsplus	Admin	Consented to CHIPS+	Integer 1 (Yes) 0 (No)

ART.dta (multiple records per child in CHIPS)

One line per drug change per patient. Dataset created using data in ARToriginal.dta (where data are arranged with each drug (and drug change) appearing on a separate line). Here data are rearranged into regimens with a new line for each change to a regimen (dose or drug change). Treatment interruptions after start of ART are included.

Variable name	source	Description	Format & codes
trialno	Admin	CHIPS number	String
artdatefrom	Q10e	Start date of this ART regimen	date; 11,11,1911 (unknown)
artdateto	Q10f	End date of this ART regimen	date
NRTI	Derived from Q10a	Number of NRTI drugs in this regimen	Integer
NNRTI	Derived from Q10a	Number of NNRTI drugs in this regimen	Integer
PI	Derived from Q10a	Number of PI drugs in this regimen	Integer
ENTRY	Derived from Q10a	Number of ENTRY drugs in this regimen	Integer
INI	Derived from Q10a	Number of INI drugs in this regimen	Integer
FUSION	Derived from Q10a	Number of FUSION drugs in this regimen	Integer
Other	Derived from Q10a	Number of Other drugs in this regimen	Integer
artname1	Q10a	Name of first drug in the regimen	String
artdose1	Q10b	Individual dose of first drug in the regimen	Integer
artfreq1	Q10c	Frequency of first drug in the regimen	Integer
artsplit1	Q10b/c	Split dosing of first drug in the regimen. Used to identify regimens where drug is taken >1 times per day and the doses differ at different times of day. Here the average individual dose is entered in artdose1.	Integer 1 (yes)
artdaily1	Derived from Q10b/c	Total daily dose of first drug in the regimen	Integer
artform1	Q10d	Form of first drug in the regimen	Integer 1 (capsules) 2 (syrup) 3 (powder) 4 (soft gel) 5 (hard gel) 6 (intravenous) 7 (tablet) 8 (syrup+tablet)
artfdc1	Q10a	FDC of first drug in the regimen	Integer 1 Combivir (AZT+3TC) 2 Trizivir (AZT+3TC+ABC) 3 Kaletra (LPV+RTVl) 4 Kivexa (ABC+3TC)

			5 Truvada (TDF+FTC) 6 Atripla (EFV+EMT+TDF) 7 Eviplera (EMT+RPV+TDF) 8 Stribild (ELV+COB+EMT+TDF) 9 Triumeq (DTG+ABC+3TC) 10 Evotaz (ATV+COBI) 11 Rezolsta (DRV+COBI)
artdatefromacc1	Q10e	Accuracy of artdatefrom for first drug in the regimen	Integer 1 (yyyy) 2 (mm/yyyy) 3 (form date) 4 (approx)
artdatetoacc1	Q10f	Accuracy of artdateto for first drug in the regimen	Integer 1 (yyyy) 2 (mm/yyyy) 3 (form date) 4 (approx)
artcomment1	Q14	Comment on first drug in the regimen	String
artcode1	Q10a	Code of first drug in the regimen	Integer
artstartreascode1	Q10g	Reason (code) for starting first drug in the regimen	Integer
artstartreasname1	Q10g	Reason for starting first drug in the regimen	String
artstartreasother1	Q10g	Other reason for starting first drug in the regimen	String
artstopreascode1	Q10h	Reason (code) for stopping first drug in the regimen	Integer
artstopreasname1	Q10h	Reason for stopping first drug in the regimen	String
artstopreasother1	Q10h	Other reason for stopping first drug in the regimen	String
class1	Derived from Q10a	Class of first drug in the regimen	String
…N		All above …1 variables for second, third etc drug	
n_drugsever	Derived from Q10a	Number of unique drugs ever taken by that patient	Integer
n_drugs	Derived from Q10a	Number of unique drugs in that regimen	Integer
class_comb	Derived from Q10a	Class combination of the regimen (ignores low dose RTV and COBI)	String
class_comb2	Derived from Q10a	Class combination of the regimen (including low dose RTV and COBI)	String
n_class	Derived from Q10a	Number of classes in that regimen	Integer
drug_comb	Q10a	Drug combination in the regimen (full drug names)	String
drug_comb2	Q10a	Drug combination in the regimen (abbreviated drug names)	String
prophylaxis	Derived from Q10	The regimen has been identified as prophylaxis	Integer
prophylaxis_ever	Derived from Q10	This patient has had prophylaxis at some point	Integer
cart	Derived from Q10a	This regimen is identified as cART (cART is defined as a regimen of 3+ drugs from 2+ classes (excluding 2 class regimens where second class is an unboosted PI) OR a regimen of at least 3 NRTIs which includes abacavir)	Integer 1 (Yes) 0 (No)
startedcart	Derived from Q10a	The patient has started a cART regimen at some point in the past, regardless of whether current regimen meets definition of cART (cART is defined as a regimen of 3+ drugs from 2+ classes (excluding 2 class regimens where second class is an unboosted PI) OR a regimen of at least 3 NRTIs which includes abacavir)	Integer 1 (Yes) 0 (No)
art_line	Derived from drug_comb2 & artdatefrom	For those never on cART recent regimens are classed as mono, dual, triple or none (naïve or treatment interruption). Once cART has been initiated subsequent regimens are	Integer 1 (On mono) 2 (On dual) 3 (On triple (NRTI – excl ABC)) 4 (On triple – unboosted PI)

		classed as being after initial cART or after a switch to a subsequent line.	5 (Started initial cART) 6 (Switched to second cART) 7 (Switched to third of later cART) 9 (Treatment interruption)
art_status	Derived from drug_comb2 & artdatefrom	Summary of ART used in current regimen	Integer 1 (On mono) 2 (On dual) 3 (On triple (NRTI – excl ABC)) 4 (On triple – unboosted PI) 5 (cART) 9 (Treatment interruption)
art_line_num	Derived from drug_comb2 & artdatefrom	ART line number, First line starts at initiation of cART. A new line is defined as addition of a new class, a change or addition of second PI, addition of second NNRTI or switch to NRTI based regimen.	Integer
class_reg	Derived from artdatefrom, art_line_num & class_comb2	Class of drugs used at start of each new line (as defined by art_line_num above).	String
drug_reg	Derived from artdatefrom, art_line_num & drug_comb2	Specific drugs used at start of each new line (as defined by art_line_num above).	String

ARToriginal.dta (multiple records per child in CHIPS)

One line per drug change per patient. This is the original form of ART.dta. All data in ARToriginal.dta are also in ART.dta

Variable name	Source	Description	Format & codes
trialno	Admin	CHIPS number	String
artname	Q10a	Name of drug	String
artabr	Q10a	Abbreviated name of drug	String
artcode	Q10a	Code of drug	Integer
artdose	Q10b	Individual dose of drug	Integer
artfreq	Q10c	Frequency of individual dose (per day)	Integer
artsplit	Q10b/c	Split dosing of drug in the regimen. Used to identify regimens where drug is taken >1 times per day and the doses differ at different times of day. Here the average individual dose is entered in artdose.	Integer 1 (yes)
artdaily	Derived from Q10b/c	Total daily dose of first drug in the regimen	Integer
artform	Q10d	Form of drug	Integer 1 (capsules) 2 (syrup) 3 (powder) 4 (soft gel) 5 (hard gel) 6 (intravenous) 7 (tablet) 8 (syrup+tablet)
artfdc	Q10a	Part of FDC	Integer 1 Combivir (AZT+3TC) 2 Trizivir (AZT+3TC+ABC) 3 Kaletra (LPV+RTVI) 4 Kivexa (ABC+3TC) 5 Truvada (TDF+FTC) 6 Atripla (EFV+EMT+TDF) 7 Eviplera (EMT+RPV+TDF) 8 Stribild (ELV+COB+EMT+TDF) 9 Triumeq (DTG+ABC+3TC) 10 Evotaz (ATV+COBI) 11 Rezolsta (DRV+COBI)
artdatefrom	Q10e	Start date of this drug/dose	Date
artdatefromacc	Q10e	Accuracy of start date	Integer

			1 (yyyy) 2 (mm/yyyy) 3 (form date) 4 (approx)
artdateto	Q10f	End date of this drug/dose	Date
artdatetoacc	Q10f	Accuracy of end date	Integer 1 (yyyy) 2 (mm/yyyy) 3 (form date) 4 (approx)
artstartreascode	Q10g	Reason (code) for starting drug	Integer
artstartreasname	Q10g	Reason for starting drug	String
artstopreascode	Q10h	Reason (code) for stopping drug	Integer
artstopreasname	Q10h	Reason for stopping drug	String
artstartreasother	Q10g	Other reason for starting drug	String
artstopreasother	Q10h	Other reason for stopping drug	String
artcomment	Q14	Comment on drug	String

ARTevents.dta (multiple records per child in CHIPS)

This file contains any adverse events (grade 2 or above) possibly related to ART

Variable name	Source	Description	Format & codes
trialno	Admin	CHIPS number	String
eventnameart	Q2p2a (F/up only)	Code of ART event.	Integer.
eventnameart_name	Q2p2a (F/up only)	Name of ART event.	String.
eventnameartdesc	Q14 (F/up only)	Description of ART event – free text comment	String
dateonsetartevent*	Q2p2b (F/up only)	Date ART event began	Date
dateonsetaccuracyartevent	Q2p2b (F/up only)	Accuracy of date ART event began	Integer 1 (yyyy) 2 (mm/yyyy) 3 (form date) 4 (approx)
dateresolvedartevent	Q2p2b (F/up only)	Date ART event resolved	Date
dateresolvedaccuracyartevent	Q2p2c (F/up only)	Accuracy of date ART event resolved	Integer 1 (yyyy) 2 (mm/yyyy) 3 (form date) 4 (approx)
ongoingartevent	Q2p2c (F/up only)	Whether the ART event is ongoing	Integer
worstgrade	Q2p2d (F/up only)	Worst grade for that ART event	Integer 2 (2 – Moderate) 3 (3 – Severe) 4 (4- Life threatening)
relatedartdrug1	Q2p2e (F/up only)	ART drug 1 (code) event related to.	Integer See
relatedartdrug1name	Q2p2e (F/up only)	ART drug 1 (name) event related to.	String
artrelationship1	Q2p2f (F/up only)	How related to drug 1	Integer 1 (Possibly) 2 (Probably) 3 (Definitively) 9 (Unknown)
artstopped1	Q2p2g (F/up only)	Drug 1 stopped	Integer 1 (Yes) 0 (No)
…N		All above …1 variables for second, third etc drug	
yellowcard	Q2p2h (F/up only)	Yellow card	Integer 1 (Yes) 0 (No)

BCEvents.dta (multiple records per child in CHIPS)

Variable name	Source	Description	Format & codes
trialno	Admin	CHIPS number	String
bccondition	Q2a	B/C event code	Integer
bccondition_name	Q2a	B/C event name	String
bcconditiondesc	Q2a	B/C event free-text description	String
dateonsetbcevent	Q2b	Onset date of B/C event	Date
dateaccuracybcevent	Q2b	Accuracy of onset date	Integer 1 (yyyy) 2 (mm/yyyy) 3 (form date) 4 (approx)
categorytype	Q2c	B or C event category	Integer 1 (B) 2 (C)
diagnosisbcevent	Q2d	Definitive or presumptive diagnosis	Integer 1 (Presumptive) 2 (Definitive)
drugstreatment1bcevent	Q2e	Drug/treatment 1 – code	Integer
drugstreatment1bceventname	Q2e	Drug/treatment 1 - name	String
drugstreatment2bcevent	Q2e	Drug/treatment 2 – code	Integer
drugstreatment2bceventname	Q2e	Drug/treatment 2 – name	String
drugstreatment3bcevent	Q2e	Drug/treatment 3 – code	Integer
drugstreatment3bceventname	Q2e	Drug/treatment 3 - name	String

CD4.dta (multiple records per child in CHIPS)

Variable name	Source	Description	Format & codes
trialno	Admin	CHIPS number	String
cd4date	Q5e	CD4 test date	Date
cd4	Q5f	CD4 count	Integer
cd4percentage	Q5g	CD4 percentage	Integer
totlymph	Q5h	Total lymphocytes	Integer
centre	Header	Clinic code	Integer
centrename	Header	Clinic name	String

Clinical.dta (multiple records per child in CHIPS)

Variable name	Source	Description	Format & codes
trialno	Admin	CHIPS number	String
htwtdate	Q5a	Date of height/weight/BP measurement	Date
weight	Q5b	Weight (kg)	numeric
height	Q5c	Height (cm)	numeric
systolicbp	Q5d	Systolic BP	Integer
diastolicbp	Q5e	Diastolic BP	Integer
centre	Header	Clinic code	Integer
centrename	Header	Clinic name	String

InpatientEvents.dta (multiple records per child in CHIPS)

Variable name	Source	Description	Format & codes
trialno	Admin	CHIPS number	String
hospitalname	Q3a	Hospital name code.	Integer
hospitalname_desc	Q3a	Hospital name.	String
ward	Q3a	Hospital ward	Integer 6 (Paediatric) 8 (HDU) 9 (ICU)
admissiondate	Q3b	Date of admission	Date
dischargedate	Q3b	Date of discharge	Date

diagnosis1	Q3d	Diagnosis 1 – code	Integer
diagnosis1_name	Q3d	Diagnosis 1 – name	String
diagnosis2	Q3d	Diagnosis 2 – code	Integer
diagnosis2_name	Q3d	Diagnosis 2 - name	String
diagnosis3	Q3d	Diagnosis 3 – code	Integer
diagnosis3_name	Q3d	Diagnosis 3 – name	String
drugstreatment1	Q3d	Drug/treatment 1 – code	Integer
drugstreatment1name	Q3d	Drug/treatment 1 - name	String
drugstreatment2	Q3d	Drug/treatment 2 – code	Integer
drugstreatment2name	Q3d	Drug/treatment 2 – name	String
drugstreatment3	Q3d	Drug/treatment 3 – code	Integer
drugstreatment3name	Q3d	Drug/treatment 3 - name	String
relatedevent1	Q3e/Q2a	Related event 1 – code	Integer
relatedevent1_name	Q3e/Q2a	Related event 1 – name	String
onsetrelatedevent1	Derived from Q3e, Q2a & Q2b	Onset date of related event 1	Date
relatedevent2	Q3e/Q2a	Related event 2 – code	Integer
relatedevent2_name	Derived from Q3e/Q2a & Q2b	Related event 2 – name	String
onsetrelatedevent2	Q2b	Onset date of related event 2	Date
relatedevent3	Q3e/Q2a	Related event 3 – code	Integer
relatedevent3_name	Q3e/Q2a	Related event 3 – name	String
onsetrelatedevent3	Q2b	Onset date of related event 3	date
inpatientextrainfo	Q14	Additional related info – free text	String

MainClinics.dta (multiple records per child in CHIPS)

Variable name		Description	Format & codes
trialno	Admin	CHIPS number	String
maincountry	Header	Country of main clinic - code	Integer
maincountryname	Header	Country of main clinic - name	String
maincentre	Header	Clinic attended – code	Integer
maincentrename	Header	Clinic attended – name	String
maindept	Header	Department attended	Integer 1 (Adolescent) 2 (GUM) 3 (Haemophilia) 4 (Infectious diseases) 5 (Medical) 6 (Paediatric) 7 (Thoracic)
mainclinicno	Header	Patient's hospital number	String
maindatefrom	Admin & Q13	Date started at clinic. Date of registration in CHIPS entered as maindatedate for original registering clinic.	Date
maindateto	Q13	Date left clinic	Date

SharedClinics.dta (multiple records per child in CHIPS)

Variable name	Source	Description	Format & codes
trialno	Admin	CHIPS number	String
sharedcountry	Q1a	Country code of shared care clinic	Integer
sharedcountryname	Q1a	Country name of shared care clinic	String
sharedcentre	Q1a	Clinic attended – code	Integer
sharedcentrename	Q1a	Clinic attended – name	String
shareddept	Q1a	Department attended	Integer 1 (Adolescent) 2 (GUM) 3 (Haemophilia) 4 (Infectious diseases) 5 (Medical) 6 (Paediatric) 7 (Thoracic)
shareddatefrom	Derived from Header	Date started at clinic. Exact dates are not reported by clinics. When a form is returned indicating shared care since the previous form was completed, date of the previous form returned is entered as shareddatefrom	Date
shareddateto	Derived from Header	Date left clinic. Exact dates are not reported by clinics. When a form is returned indicating shared care, date of last examination is taken as shareddateto	Date

ViralLoad.dta (multiple records per child in CHIPS)

Variable name	source	Description	Format & codes
trialno	Admin	CHIPS number	String
vlsign	Q5k	Viral load sign	Integer 0 (=) 1 (<) 2 (>)
vload	Q5k	Viral load (copies/ml)	Integer
vlcutoff	Q5l	Viral load test cut-off value	Integer
vldate	Q5i	Viral load test date	Date
centre	Header	Clinic code	Integer
centrename	Header	Clinic name	String

VisitForm.dta (multiple records per child in CHIPS)

Variable name	Source	Description	Format & codes
trialno	Admin	CHIPS number	String
centre	Header	Clinic code	Integer
centrename	Header	Clinic name	String
dob	Header	Date of birth	Date
visitid	admin	Visit id	Integer 0 (Baseline/First CHIPS form) 999 (Unscheduled/Follow up form)
lastexam	Header	Date of last exam	Date
datasupplied1_12	Q1-12	Indicates whether data were provided ib CHIPS Q1 to 12. Where datasupplied1_12=0 indicates that the centre returned a form with information about a transfer, death or LTF only (in Q13).	Integer 1 (Yes) 0 (No)
sharedcare	Q1	Shared care since the last report	Integer 1 (Yes) 0 (No)
bcevents	Q2	New category B/C events	Integer 1 (Yes) 0 (No)
artae	Q2p2 (F/up only)	Adverse events possibly related to ART	Integer 1 (Yes) 0 (No)
inpatient	Q3	Any hospital inpatient stays	Integer 1 (Yes) 0 (No)
hepb	Q4a	Ever had hepatitis B	Integer 0 (Negative) 1 (Positive) 2 (Never tested) 9 (Not known)
hepc	Q4b	Ever had hepatitis C	Integer 0 (Negative) 1 (Positive) 2 (Never tested) 9 (Not known)
lipoyn	Q6	Child has lipodystrophy	Integer 0 (No) 1 (Yes) 2 (Probable) 9 (Not known)
lipodate	Q6a	Lipodystrophy onset date	Date
lipodateacc	Q6a	Accuracy of lipodystrophy onset date	Integer 1 (yyyy) 2 (mm/yyyy) 3 (form date) 4 (approx)
lipotype	Q6b	Lipodystrophy type	Integer 1 (Lipohypertrophy) 2 (Lipoatrophy) 3 (Both)

lipidsdone	Q7	Recent blood lipid done	Integer 1 (Yes) 0 (No)
testdate1	Q7c	Lipid test date 1 (Note: Most recent test date is requested from Clinics. However, some provide a second set of recent lipids and where two sets of results are provided, the second set are entered under 'testdate2')	Date
trig1	Q7a	Triglycerides result 1	Numeric
chol1	Q7b	Cholesterol result 1	Numeric
fasting1	Q7d	Fasting at time of test 1	Integer 0 (No) 1 (Yes) 9 (Not known)
testdate2	Q7c	Lipid test date 2 (Note: Most recent test date is requested from Clinics. However, some provide a second set of recent lipids and where two sets of results are provided, the second set are entered under 'testdate2')	Date
trig2	Q7a	Triglycerides result 2	Numeric
chol2	Q7b	Cholesterol result 2	Numeric
fasting2	Q7d	Fasting at time of test 2	Integer 0 (No) 1 (Yes) 9 (Not known)
menarche	Q8a	Onset of menarche since last report	Integer 1 (Yes) 0 (No)
menarchedate	Q8b	Date of menarche onset	Date
preg	Q9	Pregnant since last report	Integer 1 (Yes) 0 (No)
pregoutcome	Q9a	Pregnancy outcome	Integer 1 (Continuing) 2 (Terminating) 3 (Miscarriage) 4 (Still birth) 5 (Live birth)
pregdob	Q9b	Live birth date	Date
artchange	Q10 (F/up only)	Any change in ART/doses	Integer 1 (Yes) 0 (No)
artabroad	Q10i (B/line only)	Received ART in home country before arrival in UK	Integer 1 (Yes, details known) 2 (Yes, details not known) 3 (No) 4 (Don't know) 5 (Not applicable)
antibody	Q11	HIV antibody status tested in last 2 years	Integer 1 (Yes) 0 (No)
antibodydate	Q11a	HIV antibody test date	Date
antibodyresult	Q11b	HIV antibody test result	Integer 1 (Positive) 0 (Negative)
antibodyassay	Q11c	HIV antibody assay used	String
postcode	Q12	Postcode at most recent exam (without last letter)	String
fupstatus	Q13	Reason child not seen	Integer 1 (Transfer to another paediatric clinic) 2 (Due for an appointment) 3 (Known to have left the country) 4 (Lost to follow-up) 5 (Other) 6 (Transfer to adult care) 7 (Transfer to adolescent clinic) 8 (Transfer to UK Register) 10 (Died)
apptdate	Q13a	Date due for an appointment	Date

fupother	Q13l	Other reason child not seen	String
comments	Q14	Comments	String
completedate	CF – footer after Q14	Date form completed	Date

Appendix 4: SOPHID data specification

Public Health England

SOPHID metadata files

The Survey of Prevalent HIV Infections Diagnosed (SOPHID)

1	What is SOPHID?	The Survey of Prevalent HIV Infections Diagnosed (SOPHID) began in 1995 and is a cross-sectional survey of all persons with diagnosed HIV infection who attend for HIV care at an NHS site in England, Wales and Northern Ireland (E, W & NI). Scottish data is collected by Health Protection Scotland. Paediatric data (children<16 years of age) were from the Institute of Child Health (ICH). All those data are incorporated to produce United Kingdom (UK) totals.
2	What is being measured?	Key output from SOPHID include: 1. Number of individuals living with a diagnosed HIV infection in the UK by age, sex, probably route of HIV transmission, ethnicity, ART status, CD4 cell count, region of residence and region of providing care 2. Diagnosed HIV prevalence among population aged 15 – 59 years old in Local Authorities in England 3. Together with New HIV and AIDS Diagnoses and Deaths Database and CD4 Surveillance Scheme, proportion of individuals diagnosed late (CD4 cell count less than 350 cells/mm^3 in Local Authorities are generated. 4. Quality of care indicators are generated annually to measure • Early access to HIV testing, • Prompt integration into care • Access to ART • Achieving viral load suppression • Preventing symptomatic infection • Retention into care
3	Why is it being measured?	Timely data from SOPHID provide essential information on the changing profile of people living with diagnosed HIV infection for public health monitoring, prevention monitoring and the commissioning of HIV-related services. Three national decisions based on information from SOPHID include: 1. HIV testing guidelines (2008) indicate that primary care trusts with a diagnosed HIV prevalence over 2/1000 population should expand HIV testing from traditional GUM settings to community settings. SOPHID provides this is information to commissioners and policy makers. 2. In 2010, data collected through SOPHID was used to develop the HIV outpatient care pathway as part of the Department of Health's payment by results initiative. Work is underway to ensure data fields to support the resultant tariff will be collected through SOPHID. 3. SOPHID is continually used by HIV and sexual health commissioners to fund and allocate HIV services.
3	How is the indicator defined?	Data were de-duplicated to ensure that a patient has a record of attendance in each calendar year. Patients can be tracked between clinics and over time.
4	Who does it measure?	All HIV-diagnosed individuals receiving NHS-funded HIV care within the survey period.
5	When does it measure it?	The survey is run bi-annually in London (includes Brighton, Hastings and Eastbourne) covering attendances from January to June and from July to December, whereas the survey outside London covers attendances for the whole calendar year.
6	Will it measure absolute numbers or proportions?	Results can be presented in absolute numbers, proportions or rate per 1,000 population
7	Where does the data come from?	SOPHID returns collected and collated by the HIV & STI Department, PHE, Colindale

Frequently Asked Questions

How does SOPHID complement other national HIV surveillance systems?
Difference between *newly diagnosed* and *prevalent* diagnosed infections.
The HIV and AIDS new diagnoses database collects information on individuals with newly diagnosed HIV and AIDS. Neither annual, nor cumulative reports of new HIV diagnoses can give a measure of individuals who are currently living with diagnosed HIV in the UK since these cannot take into account movement out of the UK or unreported deaths. SOPHID collects reports of individuals living with HIV who have been in contact with the NHS and is therefore a good measure of the annual prevalent HIV diagnosed population and the demand on services.

Estimating the number of HIV-infected but undiagnosed individuals
Some individuals infected with HIV and living in the UK have not yet been diagnosed. These individuals cannot be detected by either surveillance of new diagnoses or SOPHID. The total estimated national number of HIV-infected individuals (diagnosed and undiagnosed) can be estimated using multiple sources of information including SOPHID, unlinked anonymous surveys, the National Survey of Sexual Attitudes and Lifestyles and census data. Annual estimates of the total number of individuals living with (diagnosed and undiagnosed) HIV in the UK are available in the annual HIV report.

Why does the number of records I reported to SOPHID differ from the number of records in the tables I received back?
The following procedures may often cause final SOPHID figures to differ from those originally reported:

- The SOPHID survey can be used to allocate an individual to a LA if the residence information provided by the site of treatment maps to one LA only. Records where LA cannot be ascertained are marked as 'not known' and not allocated to an area of residence. This may result in a discrepancy between the number of individuals reported and final number included into LA/regional tables.
- A single site of treatment sometimes reports duplicate records of the same individual - these are identified and removed.
- If insufficient information was provided for an individual to enable de-duplication (no soundex, date of birth or sex) then the record is removed following consultation with the reporting site.
- If an individual has been reported but later found to have actually been seen outside of the survey period then the individual is removed following consultation with the reporting site.
- More than one record of the same individual are often reported from more than one site of treatment - these are identified and removed.

What data are collected for the SOPHID survey?
Fields we require on each individual are as follows:

Field Name	Details	Description / comment
SDEX	Soundex	Code of surname used to link reports from the same patient
DOB	Date of birth	Used to link reports from the same patient and to calculate age (dd/mm/yyyy)
SEX	Sex	Male or female
INIT	Initial	Used to link reports from same patient
CLINID	Clinic identification code	Treatment centre's GUM clinic id code - used to link reports from the same patient
PCTres	PCT of residence	Primary Care Trust code - if postcode not available
LA/UAres	LA/UA of residence	Local/Unitary Authority Code - if postcode not available
POSTCODE	Postcode (last letter may be removed for added confidentiality)	Used for derivation of LA, Upper tier LA, PHE Centre and Region of residence.
SITE	Site of care	Place where patient received HIV-related care
PEXP	Infection route	How infection was probably acquired
DATEAIDS	Date of most recent AIDS	Date of diagnosis of most recent AIDS defining illness in survey period (not defined by CD4 count)

ETHN	Ethnic group	Ethnic group classification (NHS classification accepted)
ARV	Anti-retroviral therapy	Level of antiretroviral therapy prescribed by your clinic/site when last seen in the survey period
ARVSTART	Date of start of ARV	Date this patient first ever started a course of antiretroviral therapy - may not be HAART and may not be at your clinic/site (please estimate if exact date not known)
CD4	CD4 cell count	CD4 cell count per micro litre at date last seen.
VL	Most recent viral load	Most recent viral load (number of copies per millilitre) Number e.g. 35000
VLDATE	Date of most recent viral load	Date of most recent viral load in the survey period.
DATEPOS	Date first positive on site or date of first attendance on site	If no previous care (PREVCARE = no), enter date of patient's first positive test (including immediate referrals), or If PREVCARE = yes, enter date of patient's first attendance at your clinic/site
PREVCARE	Previous care at another site	Did the patient ever receive HIV treatment or care elsewhere before attending at your clinic/site? (consider as 'NO' those who have had a first positive test and then been immediately transferred to your clinic/site)
DLSEEN	Date patient last seen at this site or date of death in the survey period	Date patient was last seen for care within the survey period OR date of death if the person is known to have died within the period dd/mm/yyyy

For information on the codes we use for these fields please request our SOPHID protocol.

Is reporting to SOPHID voluntary?
Participation in SOPHID is not compulsory. However Department of Health allocations for each clinical commissioning group (CCG) include an adjustment for HIV-infected residents, which are calculated using SOPHID data: therefore it is in each CCGs interest to respond. In addition, many London trusts have Service Level Agreements that contractually require timely SOPHID reporting.

What about individuals who are seen at more than one centre? What is de-duplication?
At the end of the year when all the data are received multiple reports of an individual are removed through the process of "de-duplication". These are identified based on matched clinic-attributed patient ID number, soundex, date of birth and sex. Individuals who are seen at more than one centre are assigned to the centre at which they were seen most recently. All routine survey summaries are then prepared using this de-duplicated dataset.

Are children included in the final data?
Children reported by ICH include infants reported to have been born to HIV-infected mothers during the survey year regardless of their infection status. These infants will have received HIV-related care while their infection status was being established (many of whom will subsequently be confirmed as uninfected). Children who are uninfected or whose infection status has not yet been confirmed will not be included in the final numbers of individuals living with diagnosed HIV infection but are included in separate national tables.

What confidentiality procedures are in place?
We ask that all data be sent to us electronically via the secure HIV & STI web portal. All staff are briefed on Caldicott guidelines and are aware of the sensitive nature of the data. When ad hoc queries come in we do not provide any breakdowns below LA level.
To maintain patient confidentiality, soundex codes are used instead of names. All data are stored on restricted and secure databases, with strict adherence to the Data Protection Act and Caldicott Guidelines. SOPHID has approval under the section 60 regulations of the Health and Social Care Act 2001.
For confidentiality reasons, data is not broken down within a region smaller than a LA and all outputs are presented in aggregate form. No identifiers are provided.
For further information on safeguarding the confidentiality of patient information whilst protecting public health please see: http://www.hpa.org.uk/confidentiality/

What is the HIV & STI Web Portal and how do I use it?
The web portal is a secure Internet site recommended by PHE, which allows transfer of data discreetly and confidentially to a secure server located within PHE. The SOPHID data can be placed into the SOPHID folder which is accessible only by SOPHID staff and themselves. For instructions on using the web portal please contact the SOPHID team (sophid.sophid@phe.gov.uk).

Can you provide data showing an individual's soundex?
No, no information with identifiers will be disseminated.

Appendix 5: HARS data specification

6 HARS data set:

Category/ Process ID/ Field name		DD Data Element Name	Description	Surveillance/ Quality care indicator/ Commissioning/All	Mandatory / required / optional	New/modified /existing field
Service information	Org_ID	ORGANISATION CODE (CODE OF PROVIDER)	Organisation code (of provider). A code that identifies the trust of care. Patients can only have one code for one date of attendance.	A	M	M
	Site code	SITE CODE (OF TREATMENT)	Site code (of treatment) provides unique identifier for each site of an organisation providing the HIV care. Patients can only have one code for one date of consultation	A	M	M
	Pt_care_status	PATIENT HIV CARE STATUS	Describes patient's current status at for HIV care to provide start and end dates for care at that clinic. Shared care means that the patient is on the books at the current site, but seen for aspects of their HIV care at another site. In conjunction with date of consultation, the start and end date of the care at a particular site can be deducted from this. Patients can only have one code for one date of consultation.	A	M	M
	Prev_HIV_site	SITE CODE (OF PREVIOUS HIV CARE)	The Org_ID of the HIV clinic where the patient previously received HIV care (where patients have received care at more than one site, the most recent should be given). Patients can only have one code for one date of consultation.	A	R	M
	Ref_to_Org	SITE CODE (REFERRED TO FOR HIV CARE)	HIV Organisation to which the patient is currently referred for shared HIV care.	A	R	N

HIV clinic consultation	Consultation Medium Used	CONSULTATION MEDIUM USED	CONSULTATION MEDIUM USED identifies the communication mechanism used to relay information between the CARE PROFESSIONAL and the PERSON who is the subject of the consultation, during a CARE ACTIVITY. A record of the telephone or telemedicine consultation must be retained in the PATIENT's records. Telephone contacts solely for informing PATIENTS of results are excluded. Patients can only have one code for one date of consultation.	A	R	N
	HIVCare_type	CLINIC consultation PURPOSE CODE (HIV)	Whether the patient attended to seek medical consultation or for a diagnostic test.	S	R	N
	HIVCare_Date	consultation DATE	Date of patient consultation; should be coded for every episode of HIV care consultation (including bloods).	A	M	M
Demographics	Patient_ID	LOCAL PATIENT IDENTIFIER (EXTENDED)	Patient's assigned ID at the clinic . Patients can only have one code for one date of consultation.	A	M	E
	GP_Practice_Code	GENERAL MEDICAL PRACTICE CODE (PATIENT REGISTRATION)	Organisation code of patient's GP (where available). Patients can only have one code for one date of consultation.	S/Q	R	N
	GP_disclosure	PATIENT CONSENT OBTAINED INDICATOR (CARE PROFESSIONAL CONTACT)	Has the patient consented for their GP to be contacted about the care of their HIV infection?	S/Q	R	N
	Sdex	PERSON SURNAME SOUNDEX CODE	Patient's surname soundex. (Scrambled surname). Patients can only have one code for one date of consultation.	A	M	E
	Initial	PERSON INITIAL (FIRST)	Patient's initial of first name	A	R	E
	Date of birth	PERSON BIRTH DATE	Patient's date of birth	A	R	E

	Gender_birth	PERSON GENDER CODE AT REGISTRATION	Patient's gender at birth (as reported by the patient).	S	M	E
	Gender_identity	GENDER IDENTITY CODE (HIV)	Patient's current gender identity (reported by the patient)	S/Q	M	N
	Ethnicity	ETHNIC CATEGORY	Patient's ethnicity, specified by the patient.	S/Q	R	M
	Country_Birth	COUNTRY CODE (BIRTH)	Patient's country of birth	S/Q	R	E
	LSOA	LOWER LAYER SUPER OUTPUT AREA (RESIDENCE)	LOWER SUPER OUTPUT AREA of residence. Derived at the site from postcode of residence.	A	M	E
	Prisoner	PRISONER INDICATOR	Is the patient CURRENTLY a prisoner?	S	R	N
	Sex_worker	SEX WORKER INDICATOR	Is the patient CURRENTLY a sex worker?	S	R	N
	Disability	DISABILITY CODE	The PERSON has been diagnosed as disabled or the PERSON considers themselves to be disabled. A PERSON can have more than one DISABILITY CODE.	S/Q	R	N
Diagnosis information	New_diagnosis_UK	NEW HIV DIAGNOSIS IN UNITED KINGDOM INDICATOR	Was the patient newly diagnosed in the UK with HIV at this consultation?	A	M	M
	Dx_UK_date	DIAGNOSIS DATE IN UNITED KINGDOM (HIV)	Date the patient was first diagnosed as HIV positive in the UK. If patient was not first diagnosed in the UK, leave blank.	A	R	E
	Dx_abroad_year	YEAR OF DIAGNOSIS OUTSIDE UNITED KINGDOM (HIV)	If the patient was diagnosed with HIV BEFORE the UK diagnosis date, the year of diagnosis outside of the UK. If the patient was not diagnosed outside of the UK before the UK diagnosis date, leave blank.	S	O	E
	Firstseen_date	DATE FIRST SEEN	Date the patient was first seen for HIV care in this service	A	M	E

	Patient_exposure	PATIENT EXPOSURE TO HIV	Patient's exposure to HIV i.e. the patient's MOST LIKELY infection route. Please capture the most relevant code at every consultation.	S/Q	M	M
	Country_infection	COUNTRY CODE (HIV INFECTION)	Country where patient was likely to have been infected with HIV. Patients can only have one code for this date of consultation. If unknown leave blank.	S	R	E
	Year_UK_arrival	YEAR OF UK ENTRY	Year patient arrived in the UK. If patient is UK born, leave blank. Used to ascertain whether infection was acquired in UK or abroad.	S	R	E
	Diagnosis setting	INITIAL DIAGNOSIS CARE SETTING (HIV)	To be captured at the first HIV consultation only. This field captures the setting where the patient was diagnosed with HIV infection.	S/Q	R	E
	Prev test	PREVIOUS NEGATIVE HIV TEST IN UNITED KINGDOM INDICATOR	Has the patient ever had a negative HIV test?	S	R	E
	Last_HIVneg	DATE LAST NEGATIVE HIV TEST IN UNITED KINGDOM	Date patient last tested HIV negative. Used in algorithm to ascertain length of HIV infection	S	R	E
	Seroconversion	PATIENT DIAGNOSIS INDICATOR (SEROCONVERSION ILLNESS)	Does the patient have evidence of seroconversion illness? The typical symptoms include a combination of any of: fever; rash; maculopapular); myalgia; pharyngitis; headache/aseptic meningitis	S	R	E

	TRI_result	TEST OF RECENT INFECTION RESULT (HIV)	Result of the test of recent infection laboratory test (avidity index). If test is invalid/sample insufficient, enter "999"	S	R	M
	CN_number	NUMBER OF HIV CONTACTS	To be assessed at the first consultation in each calendar year. How many contacts (sexual or injecting) has the patient had in the past year? If patient does not know or does not answer, leave blank.	S	O	N
	CN_contact	NUMBER OF HIV CONTACTABLE CONTACTS	How many contacts (sexual or injecting) the patient had in the past year that are contactable? If patient does not know or does not answer, leave blank.	S	O	N
	CN_tested	NUMBER OF HIV CONTACTABLE CONTACTS TESTED FOR HIV	How many contacts (sexual or injecting) the patient had in the in the past year tested for HIV? If patient does not know or does not answer, leave blank.	S	O	N
Treatment information	First_ARV_UK	FIRST ANTIRETROVIRAL THERAPY IN UNITED KINGDOM INDICATOR	Did the patient start ARV for the first time in the UK at this consultation? If yes then First_ARV_start and Site_ARV_start are automatically populated with consultation date.	A	M	E
	First_ARV_start	YEAR AND MONTH FIRST STARTED ANTIRETROVIRAL THERAPY	The month and year the patient first ever started ARV (either abroad or in the UK). The patient does not necessarily have to be treated currently.	A	R	E
	Site_ARV_start	START DATE (ANTIRETROVIRAL THERAPY AT CURRENT PROVIDER)	Date the patient FIRST started ARV at this site. The patient does not necessarily have be treated currently.	S	R	M
	Prep_PEP	POST AND/OR PRE EXPOSURE PROPHYLAXIS CODE	For newly diagnosed persons only, was the patient receiving post exposure prophylaxis and/or pre-exposure prophylaxis in the 6 months prior to HIV diagnosis?	S	R	N

	ARVcode	ANTIRETROVIRAL THERAPY DRUG PRESCRIBED CODE	This is the specific regimen of anti-retroviral therapy the patient has been prescribed, i.e. the individual drugs. "Anti-retroviral therapy" is the medication	A		N
	ARVband	ANTIRETROVIRAL THERAPY GROUP CODE	Name of HIV ARV drug administered to the patient. Leave blank if patient is not receiving ARV.	A	M	N
	Homedelivery	ANTIRETROVIRAL THERAPY HOME DELIVERY INDICATOR	Is the patient receiving home delivery of ARVs that are currently being prescribed? This means the patient was prescribed ARVs by their HIV provider, but receives the physical drug delivery at home.	A	R	N
	Clinical Trial indicator	CLINICAL TRIAL INDICATOR	CLINICAL TRIAL INDICATOR is used to record whether an individual episode of care within a Cancer Care Spell is being delivered to a PATIENT as part of a CLINICAL TRIAL.	S/C	R	N
Clinical information	CD4_taken	CD4 CELL COUNT PERFORMED INDICATOR	CD4 count taken at this clinic consultation?	A	M	M
	CD4	CD4 CELL COUNT	The patient's CD4 count at this consultation. If no CD4 has been recorded, leave blank. CD4+ T-lymphocytes provide an indication of an HIV patient's immunosuppression. CD4 counts are used to assess whether patients should start ARV and to evaluate whether ARV is effective.	A	R	E
	VL_taken	VIRAL LOAD COUNT PERFORMED INDICATOR	VL taken at this consultation (per mL)?	A	M	M
	VL	VIRAL LOAD COUNT	The patient's viral load count at this consultation. If no VL has been recorded, leave	A	R	E

			blank. Viral loads provide an indication of the levels of virus within the patient. It is used to assess how well ARV is working.			
	AIDS_illness	AIDS DEFINING ILLNESS TYPE	This AIDS defining illness. Patients can have multiple AIDS illnesses. Leave field blank if not needed.	S/C	R	E
	TB_treatment	TUBERCULOSIS TREATMENT INDICATOR (HIV)	The patient is currently on anti-tuberculosis treatment	S/C	M	N
	Liver_antiviral_treatment	CHRONIC VIRAL LIVER DISEASE INDICATOR (HIV)	The patient is currently on antiviral treatment for chronic viral liver disease	S/C	M	N
	Hep_B	HEPATITIS B INFECTION INDICATOR	Laboratory evidence of acute or chronic hepatitis B infection	S	M	N
	Hep_C	HEPATITIS C INFECTION INDICATOR	Laboratory evidence of acute or chronic hepatitis C infection	S	M	N
	Malignancy_treatment	MALIGNANCY TREATMENT INDICATOR (HIV)	The patient is currently receiving oncological treatment	S/C	M	N
	End_organ	PATIENT DIAGNOSIS INDICATOR (HIV END ORGAN DISEASE)	The patient has severe unstable HIV-associated end organ disease	S/C	M	N
	Psych_care	PSYCHIATRIC CARE INDICATOR (HIV)	The patient is under the active psychiatric care of a consultant.	S/C	M	N
	Pregnancy	PREGNANCY INDICATOR (HIV)	The patient is currently pregnant (from first positive pregnancy test to 1 month post delivery)	S/C	M	N
	Social_care	SOCIAL WORKER CARE INDICATOR (HIV)	The patient is currently under the care of a social worker	S/C	M	N
Death	Date of Death	PERSON DEATH DATE	Date of death. If the patient has deceased, the date of death of the patient	S/Q	R	E
	Deathcause	DEATH CAUSE ICD CODE (CONDITION)	Cause of patient death. Patients can have multiple causes of death. Leave all blank if the patient has not died.	S	R	M

Appendix 6: UK CHIC data specification

UK CHIC Data Submission Guidelines: Tables 1-12, November 2015

We are now requesting the next data download from centres. It is appreciated that some centres may not be able to provide all of this data electronically for all files. If certain data items are not available at present, could you let me know if they may be available in future?

If you have any queries, please contact Teresa Hill (020 7670 4730 or 020 7794 0500 ext 36762)
or email teresa.hill@ucl.ac.uk

Thank you.

Deadline

We ask that you submit all data by Wednesday 23rd December 2015.

Format

Please provide data on all HIV positive patients aged 16 year and over, seen for care at any time at your HIV clinic. The data submission should include data up until as recent a date as possible, and include all historical data going back as far as possible (unless updates only for laboratory data from your centre have been specifically requested)

All data can be submitted as Access tables, Excel spreadsheets, or text files with the variables comma or tab delimited

All dates should be provided in dd/mm/yyyy format, including leading zeros, and without time after dates

All files should include the clinic ID and date of birth for each patient so that the files can be easily merged

DO NOT send patient names, addresses or postcodes

Coding

Codes for the variables in the data tables (Files 1 – 12) are listed on page 5 onwards. Data must be coded using UK CHIC codes otherwise it will not be accepted. If you need help with coding or mapping your data please contact us

How to submit data securely (Encryption plus secure transfer)

Data encryption: please encrypt data using either 7-Zip or Winzip (select 256-bit AES encryption).

Please DO NOT USE AXCRYPT as this is no longer an approved encryption software. The encryption password (minimum 10 characters long, include upper/lowercase, numbers and special characters, do not use 'ukchic', or the clinic name), should be communicated by telephone or separate email

Secure Data transfer/submission: submit the encrypted files by the FTP secure transfer system.

Email teresa.hill@ucl.ac.uk or telephone if you need FTP details

Feedback on data quality

Following data submission and some general format checks, we will contact you if there are issues that need to be resolved. At a later date, we may send you more detailed data queries for resolution where possible.

Anything new this time?

As a result of Steering Committee discussions, we may collect new data some years. These items will be highlighted in blue here and in the data specifications. NO NEW DATA ITEMS THIS YEAR.

No longer collected - File 8 PCP prop – please do not send this table

File 1 – PATIENTCENTRE table

Field Name	Description	Type
ClinicNo	HIV Clinic's unique patient identifier	text (12)
DOB	Date of birth	dd/mm/yyyy
Soundex	Soundex code	text (4)
Initial	Patient initial/s	text (2)
SexID	Patient sex code	integer
HIVPos	Date of first known positive HIV antibody test	dd/mm/yyyy
HIVNeg	Date of last negative HIV antibody test	dd/mm/yyyy
Firstseen	Date of first HIV attendance at centre	dd/mm/yyyy
Lastseen	Date when last seen by a clinician at the centre	dd/mm/yyyy
ExposureID	HIV exposure category	integer
EthnicityID	Ethnicity code	integer
CountryID	Country of birth code	text (30)
DiedID	Is patient known to have died code	integer
DDeath	Date of death	dd/mm/yyyy
Cause	Cause of death (where known)	text (100)

TransferFr	Transfer in from which previous centre	text (100)
TransferFrDate	Transfer in from previous centre date	dd/mm/yyyy
TransferTo	Transfer out to which other centre	text(100)
TransferToDate	Transfer out to other centre date	dd/mm/yyyy

File 2 – AIDSEVENT table

Field Name	Description	Type
ClinicNo	HIV Clinic's unique patient identifier	text (12)
DOB	Date of birth	dd/mm/yyyy
DAIDS	Date of AIDS event	dd/mm/yyyy
AIDSID	AIDS event code	integer

File 3 – ANTIRETRO table

Field Name	Description	Type
ClinicNo	HIV Clinic's unique patient identifier	text (12)
DOB	Date of birth	dd/mm/yyyy
DStart	Date started taking drug	dd/mm/yyyy
DStop	Date stopped taking drug	dd/mm/yyyy
DrugID	Drug code	integer (15)
ReasonStopID1	Reason for stopping drug	integer
ReasonStopID2	Reason for stopping drug (if multiple codes)	integer
ReasonstopID3	Reason for stopping drug (if multiple codes)	integer

File 4 – CD4 table

Field Name	Description	Type
ClinicNo	HIV Clinic's unique patient identifier	text (12)
DOB	Date of birth	dd/mm/yyyy
Dlab	Date of lab measurement	dd/mm/yyyy
CD4A	Absolute CD4 count in cells/mm3	integer
CD4P	CD4 percentage	number (1dp)
CD8A	Absolute CD8 count in cells/mm3	integer
CD8P	CD8 percentage	number (1dp)

File 5 – RNA/HIV Viral Load table

Field Name	Description	Type
ClinicNo	HIV Clinic's unique patient identifier	text (12)
DOB	Date of birth	dd/mm/yyyy

Dlab	Date of lab measurement	dd/mm/yyyy
RNA	HIV Viral Load level in copies/ml	long integer
UndetID	Result status: below/within/above assay limit	integer
AssayID	HIV RNA assay code	integer

File 6 – HEPATITIS table

Field Name	Description	Type
ClinicNo	HIV Clinic's unique patient identifier	text (12)
DOB	Date of birth	dd/mm/yyyy
DHeptest	Date of hepatitis test	dd/mm/yyyy
HepTestID	Hep test code	integer
HepResultID	test result (-/+/indet)	integer
Hepvalue	test result value, e.g. RNA copies	long integer
UndetID	Result status: below/within/above assay limit	integer
HepUnitID	test result units	integer
HepAssayID	please ignore this	integer

File 7 – ADHERENCE table

Field Name	Description	Type
ClinicNo	HIV Clinic's unique patient identifier	text (12)
DOB	Date of birth	dd/mm/yyyy
DAdherence	Date of clinic visit	dd/mm/yyyy
AdherPeriodID	Adherence period codes	integer
AdherPerOther	Adherence period other	text (50)
DosesMiss	Number of doses missed (approximately)	integer/text
ReasonMissID	Reason for missing treatment code	integer
AdhComment	Text description relating to adherence	text (50)

File 8 – PCPPROP table (PCP prophylaxis data are no longer required - PLEASE DO NOT SEND)

File 9 – TOXICITY table

Field Name	Description	Type
ClinicNo	HIV Clinic's unique patient identifier	text (12)
DOB	Date of birth	dd/mm/yyyy
DToxtest	Date of toxicity test	dd/mm/yyyy
ToxTestID	Tox test code	integer
ToxResult	Test result value	integer/number,single (if dec places in result)
ToxUnitID	Test result units, coded	integer

File 10 – HLA-B57 table

Field Name	Description	Type
ClinicNo	HIV Clinic's unique patient identifier	text (12)
DOB	Date of birth	dd/mm/yyyy
DHLAB57	Date of HLA-B*5701 test	dd/mm/yyyy
HLAB57ResultID	test result (-/+/indet)	integer

File 11- Attendance table

Field Name	Description	Type
ClinicNo	HIV Clinic's unique patient identifier	text (12)
DOB	Date of birth	dd/mm/yyyy
DAttend	Date of attendance	dd/mm/yyyy
AttSeenBy	Who patient is seen by eg doc, nurse, virtual, dietician, psycologist, other etc	integer
AttType	Attendance: scheduled, walk-in, virtual, in-patient, other	integer
Ddischarge	Date of discharge if in-patient	dd/mm/yyyy

File 12 - SeriousNonAIDS

Field Name	Description	Type
ClinicNo	HIV Clinic's unique patient identifier	text (12)
DOB	Date of birth	dd/mm/yyyy
DSerNA	Date of serious Non-AIDS event	dd/mm/yyyy
SNAID	Serious Non-AIDS event code	integer
SNAConf	Serious Non-AIDS event status, whether Confirmed/Probable/Status unknown	integer
ICDcode	ICD code if used	text (15)
SNOMEDcode	SNOWMED code if used	text (15)

Coding/Mapping Tables – see below

CODING / MAPPING TABLES

Coding	Description
AdherPeriodID	AdherPeriod
1	Last 3 days
2	Last 14 days/2 weeks
3	Last 30 days/1 month
4	Last 90 days/3 months
98	Other adherence period
99	Not known
AIDSID	AIDS

1	Bacterial infections (multiple or recurrent) at age < 13 years
2	Candidiasis, oesophageal
3	Candidiasis, trachea/bronchi/lungs
4	Candidiasis, site unknown
5	Cervical cancer, invasive
6	Coccidioidomycosis, extrapulmonary
7	Cryptococcosis, extrapulmonary
8	Cryptosporidiosis, duration > 1 month
9	Cytomegalovirus retinitis
10	Cytomegalovirus disease, other
11	Cytomegalovirus, site unknown
12	Herpes simplex disease, duration > 1 month
13	Histoplasmosis, extrapulmonary and/or disseminated
14	HIV Encephalopathy
15	Isosporiasis, duration > 1 month
16	Kaposi's sarcoma
17	Lymphoid interstitial pneumonia or pulmonary lymphoid hyperplasia at age <13 years
18	Lymphoma, Burkitt's, immunoblastic or equivalent
19	Lymphoma, primary in brain
20	Mycobacterium avium, extrapulmonary (MAI/MAC)
21	Mycobacterium tuberculosis, pulmonary
22	Mycobacterium tuberculosis, extrapulmonary
23	Mycobacterium, other (disseminated)
24	Pneumoncystis carinii pneumonia (P. jiroveci)
25	Pneumonia, recurrent in a 12-month period
26	Progressive multifocal leukoencephalopathy
27	Salmonella Septicaemia, recurrent
28	Toxoplasmosis, cerebral
29	HIV wasting syndrome
31	Lymphoma Site Unknown
51	Mycobacterium tuberculosis, Site Unknown
98	AIDS disease, not specified
99	Not Known
AssayID	Assay
1	Roche Amplicor HIV-1 Monitor v1.0 (<400)
2	Roche non-B (<400)
3	Roche Amplicor HIV-1 Monitor v1.5 (<400)
4	Roche Amplicor HIV-1 Monitor v1.5 US (<50)
5	Roche – version unknown
6	Cobas v1.5 (<400)
7	Cobas v1.5 US (<50)
9	Cobas – version unknown
10	NASBA (<400)
11	NASBA US
12	NASBA – version unknown
13	Chiron b-DNA v1.0
14	Chiron b-DNA v2.0 (<500)
15	Chiron b-DNA v3.0 US (<50)
16	Chiron – version unknown
17	Nuclisens (<400)
18	Nuclisens US (<50?)
19	Nuclisens – version unknown
21	Cobas<10 copy assay
22	Abbott RealTime HIV-1 (ultra-sensitive)

23	Abbott LCx HIV RNA
29	Roche Cobas TaqMan v1.0 (<40)
30	Roche Cobas TaqMan v2.0 (<20)
31	Abbott RealTime HIV-1 (<40)
98	Other
99	Not known
AttSeenBy	Attendance
1	Clinician
2	Nurse
3	Health advisor
4	Pharmacy/Pharmacist
5	Dietician
6	Psychologist / Counsellor
98	Other
99	Not known
AttType	Type of attendance
1	Scheduled or booked
2	Walk-In
3	Virtual – telephone or email contact
4	In-patient
98	Other
99	Not known
DiedID	Died
0	No
1	Yes
99	Not known
DrugID	Drug
1	Zidovudine (AZT)
2	Zalcitabine (ddC)
3	Didanosine (ddI)
4	Stavudine (d4T)
5	Lamivudine (3TC)
6	Abacavir
7	Combivir (AZT+3TC)
8	Lodenosine
9	Trizivir (AZT + 3TC + abacavir)
10	Tenofovir (TDF)
11	Emtricitabine (FTC)
12	Kivexa (3TC + abacavir)
13	Truvada (tenofovir/TDF + emtricitabine /FTC)
14	Tenofovir alafenamide fumarate (TAF)
19	Other NRTI
20	Nevirapine
21	Efavirenz
22	Loviride
23	Delavirdine
24	Etravirine / TMC125
25	Rilpivirine (RPV)
26	Eviplera (rilpivirine + tenofovir/TDF + emtricitabine/FTC)
39	Other NNRTI
40	Saquinavir hard gel (invirase)
41	Indinavir
42	Ritonavir – any dose
43	Nelfinavir
44	Saquinavir soft gel (fortovase)

45	Amprenavir
46	Lopinavir (ABT 378) (kaletra)
47	Saquinavir (form unknown)
48	Atazanavir
49	Other PI
50	Hydroxyurea / hydroxycarbamide
51	IL-2
60	Acyclovir
61	Fos amprenavir
62	Tipranavir
63	Darunavir / TMC114
70	Enfuvirtide / T20
80	Adefovir
90	Blinded treatment in clinical trial
95	Maraviroc
96	Vicriviroc
97	Other Entry (CCR5) Inhibitor
98	Other ART drug (ART drug is known, but not on this list)
99	Not known (ART, but not known which drug)
110	Raltegravir / MK-0518
111	elvitegravir
112	dolutegravir
119	Other Integrase Inhibitor
120	Atripla (Efavirenz/Tenofovir/Emtricitabine)
121	STRIBILD™ (QUAD) ((elvitegravir + cobicistat + emtricitabine + tenofovir disoproxil fumarate)
122	(dolutegravir/lamivudine/abacavir)
130	cobicistat
131	cobicistat/atazanavir
132	cobicistat/darunavir
133	cobicistat/elvitegravir
EthnicityID	Ethnicity
1	White
2	Black-Caribbean
3	Black-African
4	Black – unspecified/black-other
5	Indian/Pakistani/Bangladeshi
6	Other Asian/Oriental
7	Other/mixed
98	Other
99	Not known
ExposureID	Exposure
1	Homosexual/bisexual (including homo / bi sex who also injected drugs)
2	Injecting drug use
3	Heterosexual
4	Blood/blood products recipient
5	Mother-to-child transmission
98	Other
99	Not Known
HepResultID	HepResult
0	Negative
1	Positive
2	Indeterminate /weakly reactive/equivocal

HepTestID	HepTest
1	Hep A antibody (total IgG+IgM)
2	Hep B surface antigen (HbsAg)
3	Hep B surface antibody (anti-HBs)
4	Hep B core antibody (anti-HBc)
5	Hep B e antigen
6	Hep B e antibody
7	Hep C antibody
8	Hep C virus PCR/bDNA
9	Hep B core antibody (IgM)
10	Hep A antibody (IgM)
11	Hep B DNA (Genotype unknown)
12	Hep D antibody (total)
13	Hep B surface antigen (titre)
14	Hep D antibody (IgM)
98	Other
99	Not known
HepUnitID	HepUnit
1	IU/mL
2	copies/mL
3	mIU/ml
98	Other
99	Not known
HLAB57ResultID	HLAB57Result
0	Negative
1	Positive
2	Indeterminate /weakly reactive/equivocal
PCPpDrugID	PCPpDrug (PCPp Drug data no longer collected - please do not send)
1	Co-trimoxazole/septrin
2	Dapsone
3	Pentamidine
4	Atovaquone
5	Azithromycin
6	Clarithromycin
7	Clindamycin
8	Fansidar (=pyrimethamine + sulphadoxine)
9	Primaquine
10	Pyrimethamine
11	Sulphadiazine
12	Sulphadimidine
13	Sulfametopyrazine
14	Trimetrexate
15	Trimethoprim
16	Sulfadoxine
17	Maloprim (pyrimethamine + dapsone)
18	Eflornithine
98	Other
99	Not known
ReasonMissID	ReasonMiss
1	Forgot
2	Ran out of medicaiton
3	Wanted a short break

4	Side effects
5	Away from home/supply
6	In company
7	Treatment holiday
98	Other
99	Not known
ReasonStopID	ReasonStop
10	Failure-cause unknown
11	Virological
12	Immunological
13	Clinical
14	VL / CD4
20	Toxicity-type unknown
30	Skin
31	Hypersensisity – Abacavir
32	Rash
40	GI
41	Nausea/Vomiting
42	Diarrhoea
43	Pancreatitis
44	Abnormal LFT
50	Neuro
51	CNS Disturbance
52	Peripheral Neuropathy
53	Headache
60	Metabolic
61	Lipids
62	Glucose Intolerance
63	Hyperlactataemia
64	Osteopaenia
70	Lipodystrophy
80	Myelotoxicity
81	Anaemia
82	Neutropenia
83	Thrombocytopenia
91	Myotoxicity
92	Nephrolithiasis/Renal Dysfunction
100	Patient Choice
110	Clinician decision
120	Interaction
130	Simplification
140	Poor Adherence
150	Joined clinical trial
160	Study/Trial End
170	New drug available
180	Known treatment interruption
190	Protocol amendment
200	Pregnancy
201	At start/during pregnancy
202	End of short-course ART
210	Intercurrent illness, not HIV/ drug related
220	VL sufficiently low
230	CD4 sufficiently high
240	Regimen change

250	Transfer of care
260	Drug Experience / Resistance
998	Other
999	Not Known
SNAConf	Serious Non-AIDS event Confirmed
1	Confirmed
2	Probable
99	Status Unknown (not known whether Confirmed or Probable)
SNAID	Serious Non-AIDS
10	Acute Myocardial Infarction (AMI)
11	Congestive Heart Failure (CHF)
12	Coronary Artery Disease Requiring Drug Treatment
13	Coronary Revascularization (coronary angioplasty, artery by-pass grafting, stent, carotic endarterectomy
50	Decompensated Liver Disease (DLD)
51	Alcoholic liver disease
52	Liver Cirrhosis
53	Liver Fibrosis
56	liver disease (including HAART associated, non-alcoholic steatohepatosis, nodular regenerative hyperplasia, hepatoportal sclerosis)
58	Liver disease, other
59	Liver disease, chronic, unspecified
70	Diabetes Mellitus (DM)
75	Lactic acidosis, symptomatic
80	End Stage Renal Disease (ESRD)
81	HIV nephropathy
82	renal failure (including HAART associated, Fanconi syndrome, renal tubular acidosis and tubular proteinuria)
89	Renal disease, other
100	Anal cancer
101	Bowel cancer
102	Breast cancer
103	Castleman's disease
104	Cervical cancer
105	Hodgkins Lymphoma (HL)
106	Liver cancer
107	Lung cancer
108	Stomach cancer
109	Prostate cancer
110	Other Non-AIDS-Defining cancer (NADC), unspecified
120	Peripheral Arterial Disease (PAD)
121	Pulmonary Embolism (PE)
122	Deep Vein Thrombosis (DVT)
123	Stroke
129	Other vascular / thromboembolic disease
130	Osteopenia
131	Osteoporosis
132	Fracture, fragility
133	Fracture, traumatic
134	Fracture, mixed (traumatic+fragility)
135	Fracture, unspecified
138	Other bone disease
139	Bone disease, unspecified
140	Sepsis (or Sepsis Syndrome)

141	Multi-organ failure
142	Haemophagocytic Syndrome
143	Bacterial infection, severe (non-sepsis)
144	Fungal infection, severe
145	Viral infection, severe
149	Infection, severe, unspecified (non-AIDS), other
998	Serious Non-AIDS event, other
999	Serious Non-AIDS event, not specified
SexID	Sex
1	Male
2	Female
99	Not known
ToxTestID	ToxTest
1	ALT
2	Albumin
3	Alkaline phosphatase
4	Amylase
5	AST
6	Bilirubin
7	Cholesterol total (non fasting or unknown)
8	CPK (creatine phosphokinase)
9	Creatinine (serum)
10	Glucose
11	GGT(g-glutamyl transferase)
12	Haemoglobin
13	HDL
14	Lactate
15	LDL
16	Triglycerides
17	Urea
18	Lactate dehydrogenase
19	Cholesterol (fasting)
20	Protein Total (urine)
21	Creatinine (urine)
22	Protein/Creatinine Ratio (PCR) (urine)
23	Albumin (urine)
24	Albumin/Creatinine Ratio (ACR) (urine)
25	Protein 24hr (urine)
26	Platelet count
27	Vitamin D
28	Phosphate (serum)
29	Calcium (serum)
30	Parathyroid hormone (PTH)
31	Calcium (serum, corrected)
98	Other
99	Not known
ToxUnitID	ToxUnit
1	IU/L
2	g/L
3	U/L
4	μmol/L
5	μmol/L (plasma)
6	mmol/L
7	mmol/L (urine)
8	g/dL

9	mg/L
10	mg/mmol
11	g/day
12	mg/day
13	μg/L
14	ng/L
15	10^9/L
16	mg/dL
17	pg/ml
18	nmol/L
19	pmol/L
98	Other
99	Not known
UndetID	Undet
-1	< Below lower limit of detectability
0	Any value that is detectable but below the upper limit of quantification
1	> Above upper limit of quantification

Appendix 7: Clinic survey

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CHIPS+ Clinic Survey

CHIPS+ is an extension of the CHIPS cohort that will follow-up adults with perinatal HIV (PHIV+) who have transitioned to adult care.

We are carrying out a study to look at health services that are provided to young people with PHIV+. This survey will help provide us with an up-to-date classification of the clinic types and services available to PHIV+ young people. Data from this survey will be used to describe service provision to young people with perinatal HIV in the UK. It will also be linked to CHIPS and CHIPS+ data to assess whether specific types of services offered are associated with improved health outcomes in young people.

We would be very grateful if you could complete the following questions for your adult HIV clinic. To give us as accurate information as possible, it would be best if someone with in-depth knowledge of the services provided for PHIV+ young people at your clinic complete this form. If you would like more information on the study please contact us at: hibo.asad.14@ucl.ac.uk.

Throughout the survey when we refer to ‘your clinic’ we mean the clinic in which you see PHIV+ young people, and ‘your adult service’ the whole of the adult HIV service provided at your hospital (including horizontally and vertically infected adults). 'Young people' or 'patient' refers to the person with perinatal HIV, of any age, who is being seen at the adult clinic.

Contact Details

1. Your name _____
2. Position _____
3. Phone number (without space) _____
4. Email _____
5. Name of clinic _____
6. Lead clinician _____
7. Address of clinic _____

Section 1: Clinic Details

8. What type of clinic are PHIV+ young people generally seen in?
- ○ Specific PHIV+ clinic
- ○ Clinic for PHIV+ and horizontally-infected young people
- ○ General adult clinic

9. How often does your clinic run?
- ○ 1 or more times a week
- ○ 2 to 3 times a month
- ○ Once a month
- ○ Less than once a month

10. Which of the following services are provided with regard to accessibility? (tick all that apply)
- ☐ Evening clinic/s (after 5pm)
- ☐ Walk in/drop-in services/same day appointment
- ☐ Weekend services (i.e. face to face appointments/phone support)
- ☐ Instant messaging/Video call (personal communication)
- ☐ Home visits
- ☐ Other

If 'Other' was selected, please specify? _____

11. For young people (with all routes of infection) who attend this clinic, is there a separate waiting area?
- ○ Yes
- ○ No

Section 2: Staffing and Services

12. Which services are available for PHIV+ young people in your clinic? (Tick all that apply)

	Same day service within your clinic	Referral on different day/outside of clinic	Not offered
Adherence support programme	○	○	○
Pharmacy within your clinic/home delivery	○	○	○
Mental health support	○	○	○
Group level peer support (group activities)	○	○	○
1 to1 peer support	○	○	○
Other	○	○	○

If 'Other' was selected, please specify? _____

Section 3: Preparation and Transition from Paediatric to Adult care

13. Working with the paediatric team, are PHIV+ patients offered a written, individually tailored transition plan, following transition into your clinic?
- ○ Yes
- ○ No

14. Does your clinic have joint appointments with paediatric clinic staff members during young people's transition to your clinic?
- ○ Yes
- ○ No
- ○ Sometimes

15. When PHIV+ young people do not attend, are they managed in a more active way from the way you follow-up your other HIV patients in the wider HIV service?
- ○ Yes
- ○ No

a. If 'Yes' was selected, please specify.

_____

16. Would you like a summary of your survey responses?
- ○ Yes
- ○ No

References

1. CDC. Pneumocystis Pneumonia - Los Angeles. *MMWR*. 1981;30:250-252. https://pubmed.ncbi.nlm.nih.gov/16714472/

2. Jarlais D Des, Friedman SR, Hopkins W. Risk Reduction for the Acquired Immunodeficiency Syndrome Among Intravenous Drug Users. *Ann Intern Med*. 1985;103(5):755-759.

3. Stehr-green JK, Holman RC, Jason JM, Evatt BL. Hemophilia-Associated AIDS in the United States, 1981 to September 1987. *Am J Public Health*. 1988;78(4):439-442. https://pubmed.ncbi.nlm.nih.gov/3126675/

4. Centre for Disease Control. *Opportunistic Infections and Kaposi's Sarcoma among Haitians in the United States*.; 1982. https://www.cdc.gov/mmwr/preview/mmwrhtml/00001123.htm

5. Okoye AA, Picker LJ. CD4+ T cell depletion in HIV infection: mechanisms of immunological failure. *Immunol Rev*. 2013;254(1):54-64. https://pubmed.ncbi.nlm.nih.gov/23772614/

6. Hymes KB, Cheung T, Greene JB, et al. Kaposi's sarcoma in homosexual men- a report of eight cases. *Lancet*. 1981;19(2):598-600. https://pubmed.ncbi.nlm.nih.gov/6116083/

7. CDC. Current Trends Acquired Immunodeficiency Syndrome (AIDS) Update -- United States. *MMWR*. 1983;32(24):309-311. https://www.cdc.gov/mmwr/preview/mmwrhtml/00000137.htm

8. Vilaseca J, Arnau JM, Bacardi R, Mieras C, Serrano A, Navarro C. Kaposi's sarcoma and Toxoplasma gondii brain abscess in a Spanish homosexual. *Lancet*. 1982;1:572. https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(82)92086-4/fulltext

9. Rozenbaum W, Coulaud J, Saimot AG, Klatzmann D, MAyaud C, Carette MF. Multiple opportunistic infection in a male homosexual in France. *Lancet*. 1982;319(8271):572-573. https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(82)92087-6/fulltext

10. Francioli P, Vogt M, Schadelin J, et al. Acquired immunologic deficiency syndrome, opportunistic infections and homosexuality. Presentation of 3 cases studied in Switzerland. *Swiss Med Wkly*. 1982;112(47):1682-1687. https://pubmed.ncbi.nlm.nih.gov/6294820/

11. Serwadda D, Sewankambo NK, Carswell JW, et al. Slim Disease: a New Disease in Uganda and Its Association With Htlv-Iii Infection. *Lancet*. 1985;326(8460):849-852.

12. Barré-Sinoussi F, Chermann JC, Rey F, et al. Isolation of a T-lymphotropic retrovirus from a patient at risk for acquired immune deficiency syndrome (AIDS). *Science (80-)*. 1983;220(4599):126-129. https://science.sciencemag.org/content/220/4599/868.full

13. Gallo R, Salahuddin S, Popovic M, Shearer G, Kaplan M, Haynes B. Frequent detection and isolation of cytopathic retroviruses (HTLV-III) from patients with AIDS and at risk of AIDS. *Science (80-)*. 1984;224(4648):500-503.

14. Goto T, Nakai M, Ikuta K. The Life-cycle of Human Immunodeficiency Virus Type 1. *Micron*. 1998;29(2-3):123-138. https://pubmed.ncbi.nlm.nih.gov/6200936/

15. Sarafianos S, Marchand D, Das K, et al. Structure and function of HIV-1 reverse transcriptase: molecular mechanisms of polymerization and inhibition. *J Mol Biol*. 2009;385(3):693-713. https://pubmed.ncbi.nlm.nih.gov/19022262/

16. Weiss R. HIV Receptors and Cellular Tropism. *Life*. 2002;53(1):201-205.

17. Hu W-S, Hughes SH. HIV-1 Reverse Transcription. *Cold Spring Harb Perspect Med*. 2012;2(10):55-70. https://pubmed.ncbi.nlm.nih.gov/23028129/

18. Mailler E, Bernacchi S, Marquet R, Paillart JC, Vivet-Boudou V, Smyth RP. The life-cycle of the HIV-1 gag–RNA complex. *Viruses*. 2016;8(9):1-19. https://pubmed.ncbi.nlm.nih.gov/27626439/

19. Craigie R, Bushman FD. HIV DNA Integration. *Cold Spring Harb Perspect Med*. 2012;2(7):1-21. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3385939/

20. Ruelas D, Greene W. An Integrated Overview of HIV-1 Latency. *Cell*. 2015;155(3):519-529. https://pubmed.ncbi.nlm.nih.gov/22355797/

21. Karn J, Stoltzfus CM. Transcriptional and posttranscriptional regulation of HIV-1 gene expression. *Cold Spring Harb Perspect Med*. 2012;2(2):1-17. https://pubmed.ncbi.nlm.nih.gov/22355797/

22. Weiss RA. Gulliver's travels in HIVland. *Nature*. 2001;410(1):963-967. https://www.nature.com/articles/35073632

23. Shaw GM, Hunter E. Factors That Influence HIV Transmission. *Cold Spring Harb Perspect Med*. 2012;2(11):1-23. https://retrovirology.biomedcentral.com/articles/10.1186/1742-4690-4-52

24. Mortimer PP. The virus and the tests. *Br Med J*. 1987;294(6587):1602-1605. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4937118/

25. Kellerman SE, Ahmed S, Feeley-summerl T, et al. Beyond PMTCT: Keeping Exposed and Positive children healthy and alive. *AIDS*. 2013;27(2):1-15. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4087192/

26. Dabis F, Msellati P, Dunn D, et al. Estimating the rate of mother-to-child transmission of HIV. Report of a workshop on methodological issues Ghent (Belgium), 17-20 February 1992. The Working Group on Mother-to-Child Transmission of HIV. *AIDS*. 1993;7(1):1139-1148. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4850214/

27. World Health Organization. *PMTCT Strategic Vision 2010–2015 : Preventing Mother-to-Child Transmission of HIV to Reach the UNGASS and Millennium Development Goals*. World Health Organization; 2015.

28. Tubiana R, Le Chenadec J, Rouzioux C, et al. Factors Associated with Mother-to-Child Transmission ofHIV-1 Despite a Maternal Viral Load !500 Copies/ mL at Delivery: A Case-Control Study Nested in the French Perinatal Cohort (EPF-ANRS CO1). *Clin Infect Dis*. 2010;50(4):585-596. https://pubmed.ncbi.nlm.nih.gov/20070234/

29. Mmiro F, Aizire J, Mwatha A, et al. Predictors of Early and Late Mother-to-Child Transmission of HIV in a Breastfeeding Population: HIV Network for Prevention Trials 012 Experience, Kampala, Uganda. *J Acquir Immune Defic Syndr*. 2009;52(1):32-39. https://pubmed.ncbi.nlm.nih.gov/19617849/

30. European Collaborative Study. Mother-to-Child Transmission of HIV Infection in the Era of Highly Active Antiretroviral Therapy. *HIV/AIDS*. 2005;40(1):458-465.

31. Townsend CL, Byrne L, Cortina-Borja M, et al. Earlier initiation of ART and further decline in mother-to-child HIV transmission rates, 2000-2011. *AIDS*. 2014;28(1):1049-1057. http://www.ncbi.nlm.nih.gov/pubmed/24566097

32. Newell M, Brahmbhatt H, Ghys PD. Child mortality and HIV infection in Africa: a review. *AIDS*. 2004;18(Suppl 2):27-34. https://journals.lww.com/aidsonline/fulltext/2004/06002/child_mortality_and_hiv_infection_in_africa___a.4.aspx

33. Welch SB, Gibb D. When should children with HIV infection be started on antiretroviral therapy? *PLoS Med*. 2008;5(335-338):73. https://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.0050073

34. Gray LM-LN. Fluctuations in Symptoms in Human Immunodeficiency Virus-Infected Children: The First 10 Years of Life. *Pediatrics*. 2001;108(1):116-122. https://pubmed.ncbi.nlm.nih.gov/11433063/

35. Gueler A, Moser A, Calmy A, et al. Life expectancy in HIV-positive persons in Switzerland: Matched comparison with general population. *AIDS*. 2017;31(3):427-436. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5302412/

36. Samji H, Cescon A, Hogg RS, et al. Closing the gap: Increases in life expectancy among treated HIV-positive individuals in the United States and Canada. *PLoS One*. 2013;8(12):6-13. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3867319/

37. Collins IJ. Paediatric HIV-infection in Thailand: Long-term survival and response to antiretroviral therapy & cost effectiveness of different diagnosis and treatment strategies. Published online 2013.

38. World Health Organization. *Interim WHO Clinical Staging of HIV/AIDS and HIV/AIDS Case Definitions for Surveillance*. World Health Organization; 2005.

39. Wall KM, Rida W, Haddad LB, et al. Pregnancy and HIV Disease Progression in an Early Infection Cohort from Five African Countries. *Epidemiology*. 2017;28(2):224-232. https://pubmed.ncbi.nlm.nih.gov/27893488/

40. Ahn Y, Boettiger D, Law M, et al. Effects of CD4 monitoring frequency on clinical endpoints in clinically stable HIV-infected patients with viral suppression. *J Acquir Immune Defic Syndr*. 2015;69(3):e85-e92. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4506699/

41. Eller MA, Opollo MS, Liu M, et al. HIV type 1 disease progression to AIDS and death in a rural ugandan cohort is primarily dependent on viral load despite variable subtype and T-cell immune activation levels. *J Infect Dis*. 2015;211(10):1574-1584. https://pubmed.ncbi.nlm.nih.gov/25404522/

42. World Health Organization. *Guidelines Guideline on When To Start Antiretroviral Therapy and on Pre-Exposure Prophylaxis for Hiv*.; 2015. doi:978 92 4 150956 5

43. Autran B, Carcelain G, Li TS, et al. Positive effects of combined antiretroviral therapy on CD4 + T cell homeostasis and function in advanced HIV disease. *Science (80-)*. 1997;277(1):112-116. https://pubmed.ncbi.nlm.nih.gov/9204894/

44. Lederman MM, Connick E, Landay A, et al. Immunologic Responses Associated with 12 Weeks of Combination Antiretroviral Therapy Consisting of Zidovudine, Lamivudine, and Ritonavir: Results of AIDS Clinical Trials Group Protocol 315. *J Infect Dis*. 1998;178(1):70-79. https://pubmed.ncbi.nlm.nih.gov/9652425/

45. Crowell TA, Hatano H. Clinical outcomes and antiretroviral therapy in “elite” controllers: a review of the literature. *J virus Erad*. 2015;1(2):72-77. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4844069/

46. Joint United Nations Programme on HIV/AIDS. Fact sheet 2016 - Global statistics. Published 2016. Accessed March 23, 2018. http://www.unaids.org/sites/default/files/media_asset/UNAIDS_FactSheet_en.pdf

47. United Nations Children’s Fund. Adolescent HIV prevention. Published 2019. Accessed August 5, 2019. https://data.unicef.org/topic/hivaids/adolescents-young-people/

48. Joint United Nations Programme on HIV/AIDS. *Women and HIV*. Joint United Nations Programme on HIV/AIDS; 2019.

49. Subedar H, Barnett S, Chaka T, et al. Tackling HIV by empowering adolescent girls and young women: a multisectoral, government led campaign in South Africa. *Br Med J*. 2018;363(4585):1-15. https://www.bmj.com/content/363/bmj.k4585

50. Global Burden of Disease 2013 Collaboration. Global and National Burden of Diseases and injuries among children and adolescents netween 1990 and 2013 findings from the Global Burden of Disease 2013 Study. *J Am Med Assoc*. 2016;170(3):267-287. https://pubmed.ncbi.nlm.nih.gov/26810619/

51. Kasedde S, Luo C, McClure C, Chandan U. Reducing HIV and AIDS in adolescents: opportunities and challenges. *Curr HIV/AIDS Rep*. 2013;10(1):159-168. https://pubmed.ncbi.nlm.nih.gov/23563990/

52. Joint United Nations Programme on HIV/AIDS. *Global Report: UNAIDS Report on the Global AIDS Epidemic 2013*.; 2013. http://www.unaids.org/en/media/unaids/contentassets/documents/epidemiology/2013/gr2

013/unaids_global_report_2013_en.pdf

53. Slogrove A, Judd A, Leroy V. The global epidemiology of perinatally HIV-infected adolescents. In: *AIDS*. ; 2016. http://regist2.virology-education.com/2016/8Pediatrics/18_Slogrove.pdf

54. Kirwan P, Chau C, Brown A, Gill O, Delpech V. *HIV in the UK: 2016 Report*. Public Health England; 2016.

55. Skingsley A, Yin Z, Kirwan P, et al. *HIV in the UK – Situation Report 2015 Incidence, Prevalence and Prevention*.; 2015.

56. Peters H, Francis K, Sconza R, et al. UK mother-to-child HIV transmission rates continue to decline: 2012-2014. *Clin Infect Dis*. 2017;64(4):527-528. https://academic.oup.com/cid/article/64/4/527/2623961

57. Collaborative HIV Paediatric Study. *Collaborative HIV Paediatric Study (CHIPS) Annual Report 2015/16*.; 2016.

58. Collaborative HIV Paediatric Study. *Data from the Collaborative HIV Paediatric Study (CHIPS) - Reports up to April 2016*.; 2016.

59. Adamma Aghaizu, Brown A, Nardone A, Gill O, Delpech V. *HIV in the United Kingdom : 2013 Report*.; 2013.

60. Hare S, Vos AM, Clayton RF, Thuring JW, Cummings MD, Cherepanov P. Molecular mechanisms of retroviral integrase inhibition and the evolution of viral resistance. *Proc Natl Acad Sci U S A*. 2010;107(46):20057-20062. https://academic.oup.com/cid/article/64/4/527/2623961

61. Hicks C, Gulick RM. Raltegravir: The First HIV Type 1 Integrase Inhibitor. *Rev Anti-Infective Agents*. 2009;48(1):931-939. https://pubmed.ncbi.nlm.nih.gov/19231980/

62. Patel K, Hernán M a, Williams PL, et al. Long-term effects of highly active antiretroviral therapy on CD4+ cell evolution among children and adolescents infected with HIV: 5 years and counting. *HIV/AIDS*. 2008;46(1):1751-1760. https://pubmed.ncbi.nlm.nih.gov/18426371/

63. Puthanakit T, Kerr SJ, Ananworanich J, Bunupuradah T, Boonrak P, Sirisanthana V. Pattern and Predictors of Immunologic Recovery in Human Immunodeficiency Virus-Infected Children Receiving Non-Nucleoside Reverse Transcriptase Inhibitor-Based Highly Active Antiretroviral Therapy. *Pediatr Infect Dis J*. 2009;28(6):488-492. http://content.wkhealth.com/linkback/openurl?sid=WKPTLP:landingpage&an=00006454-200906000-00007

64. Schlatter AF, Deathe AR, Vreeman RC. The need for pediatric formulations to treat children with HIV. *AIDS Res Treat*. 2016;2016(1):1-8. https://pubmed.ncbi.nlm.nih.gov/27413548/

65. World Health Organization. *Antiretroviral Thereapy of HIV Infection In Infants And Children: Towards Universal Access*. World Health Organization; 2006.

66. World Health Organization. *Report of the WHO Technical Reference Group, Paediatric HIV/ART Care Guideline Group Meeting*.; 2008.

67. World Health Organization. *Antiretroviral Therapy for HIV Infection in Infants and Children: Towards Universal Access*.; 2010.

68. World Health Organization. *Consolidated Guidelines on the Use of Antiretroviral Drugs for Treating and Preventing HIV Infection: Recommendations for a Public Health Approach*. World Health Organization; 2013.

69. World Health Organization. *Updated Recommendations on First-Line and Second-Line Antiretroviral Regimens and Post-Exposure Prophylaxis and Recommendations on Early Infant Diagnosis of HIV: Interim Guidelines. Supplement to the 2016 Consolidated Guidelines on the Use of Antiretrovir*. World Health Organization; 2018.

70. McCormack PL. Dolutegravir: A review of its use in the management of HIV-1 infection in adolescents and adults. *Drugs*. 2014;74(1):1241-1252. https://pubmed.ncbi.nlm.nih.gov/25005775/

71. Collaborative HIV Paediatric Study (CHIPS). *Collaborative HIV Paediatric Study (CHIPS) Annual Report 2017/18*.; 2018.

72. Judd A, Doerholt K, Tookey PA, et al. Morbidity , Mortality , and Response to Treatment by Children in the United Kingdom and Ireland with Perinatally Acquired HIV Infection during 1996 – 2006 : Planning for Teenage and Adult Care. *HIV/AIDS*. 2007;45:918-924. https://pubmed.ncbi.nlm.nih.gov/17806062/

73. Foster C, Judd A, Sc M, et al. Young People in the United Kingdom and Ireland with Perinatally Acquired HIV : The Pediatric Legacy For Adult Services. *AIDS Patient Care STDS*. 2009;23(3):159-166. https://discovery.ucl.ac.uk/id/eprint/124097/

74. Mofenson LM, Cotton MF. The challenges of success : adolescents with perinatal HIV infection. *J Int AIDS Soc*. 2013;16:15-17. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3687076/

75. Rice BD, Delpech VC, Chadborn TR, Elford J. Loss to follow-up among adults attending human immunodeficiency virus services in England, wales, and Northern Ireland. *Sex Transm Dis*. 2011;38(8):685-690. https://pubmed.ncbi.nlm.nih.gov/21844719/

76. Kim S, Gerver SM, Fidler S, Ward H. Adherence to antiretroviral therapy in adolescents living with HIV : systematic review and meta-analysis. *AIDS*. 2014;28(13):1945-1956. https://pubmed.ncbi.nlm.nih.gov/24845154/

77. Ryscavage P, Anderson E, Sutton S. Clinical Outcomes of Adolescents and Young Adults in Adult HIV Care. *J Acquir Immune Defic Syndr*. 2011;58(2):193-197.

78. Fish R, Judd A, Jungmann E, O'Leary C, Foster C. Mortality in perinatally HIV-infected young people in England following transition to adult care: an HIV Young Persons Network (HYPNet) audit. *HIV Med*. 2014;15(4):239-244. doi:10.1111/hiv.12091

79. World Health Organization. Coming to terms with HIV in adolescence. Published 2013. Accessed April 3, 2017. https://www.who.int/features/2013/adolescents-hiv/en/

80. Slogrove AL, Mahy M, Armstrong A, Davies M. Living and dying to be counted: What we know about the epidemiology of the global adolescent HIV epidemic. *J Int AIDS Soc*. 2017;20(Suppl 3):4-15. https://pubmed.ncbi.nlm.nih.gov/28530036/

81. Agwu AL, Fairlie L. Antiretroviral treatment, management challenges and outcomes in perinatally HIV-infected adolescents. *J Int AIDS Soc*. 2013;16:1-13. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4358185/

82. Chakraborty R, Dyke RB Van. Transitioning HIV-infected youth into adult health care. *Pediatrics*. 2013;132(1):192-197. doi:10.1542/peds.2013-1073

83. Van Dyke RB, Patel K, Kagan RM, et al. Antiretroviral Drug Resistance Among children and youth in the U.S. with Perinatal HIV. *Clin Infect Dis*. Published online 2016:1-20. http://cid.oxfordjournals.org/content/63/1/133.full.pdf+html

84. Children's HIV Association. *CHIVA Guidance on Transition for Adolescents Living with HIV*. Children's HIV Association; 2011.

85. Haber N, Pillay D, Porter K, Ba T. Constructing the cascade of HIV care: methods for measurement. *Curr Opin HIV AIDS*. 2016;11(1):102-108. https://pubmed.ncbi.nlm.nih.gov/28530036/

86. Joint United Nations Programme on HIV/AIDS. *90-90-90 An Ambitious Treatment Target to Help End the AIDS Epidemic*.; 2014.

87. Kilmarx PH, Mutasa-apollo T. Patching a leaky pipe : the cascade of HIV care. *Curr Opin HIV AIDS*. 2013;8(1):59-64. doi:10.1097/COH.0b013e32835b806e

88. Nash S, Desai S, Croxford S, et al. *Progress towards Ending the HIV Epidemic in the*

United Kingdom: 2018 Report.; 2018.

89. Delpech V. Quality of HIV care in the UK is excellent and improving. In: *22nd Annual Conference of the British HIV Association*. ; 2016.

90. Zanoni BC, Mayer KH. The adolescent and young adult HIV cascade of care in the United States: exaggerated health disparities. *AIDS Patient Care STDS*. 2014;28(3):128-135. http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3948479&tool=pmcentrez&rendertype=abstract

91. Gardner EM, Mclees MP, Steiner JF, Rio C, Burman WJ. The Spectrum of Engagement in HIV Care and its Relevance to Test-and-Treat Strategies for Prevention of HIV Infection. *Clin Infect Dis*. 2011;52(6):793-800. https://pubmed.ncbi.nlm.nih.gov/21367734/

92. Gourlay A, Noori T, Pharris A, et al. The Human Immunodeficiency Virus Continuum of Care in European Union Countries in 2013 : Data and Challenges. *Clin Infect Dis*. 2017;64(12):1644-1656. https://pubmed.ncbi.nlm.nih.gov/28369283/

93. Yehia BR, Stephens-shields AJ, Fleishman JA, et al. The HIV Care Continuum : Changes over Time in Retention in Care and Viral Suppression. *PLoS One*. 2015;10(6):1-10. https://pubmed.ncbi.nlm.nih.gov/26086089/

94. Horberg MA, Hurley LB, Klein DB, et al. The HIV Care Cascade Measured Over Time and by Age, Sex, and Race in a Large National Integrated Care System. *AIDS Patient Care STDS*. 2015;29(11):582-590. https://pubmed.ncbi.nlm.nih.gov/26505968/

95. Jose S, Delpech V, Howarth A, et al. A continuum of HIV care describing mortality and loss to follow-up: a longitudinal cohort study. *Lancet*. 2018;5(1):301-308. https://bmcmedicine.biomedcentral.com/articles/10.1186/s12916-016-0640-4

96. Rawizza HE, Chang CA, Chaplin B, et al. Loss to Follow-Up within the Prevention of Mother-to-Child Transmission Care Cascade in a Large ART Program in Nigeria. *Curr HIV Res*. 2017;13(3):5-18. https://pubmed.ncbi.nlm.nih.gov/25986371/

97. Sirirungsi W, Khamduang W, Collins IJ, Pusamang A. Early Infant HIV Diagnosis (EID) and Entry to HIV Care Cascade: Seven-year Experience in Thailand. *Lancet*. 2018;3(6):259-265. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6047735/

98. Hofer CB, Egger M, Davies M, et al. The cascade of care to prevent mother-to-child transmission in Rio de Janeiro, Brazil, 1996–2013 : improving but still some way to go. *Trop Med Int Heal*. 2017;22(10):1266-1274.

99. Department of Health. *Transition: Getting It Right for Young People, Improving the Transition of Young People with Long Term Conditions from Children's to Adult Health Services*. Department of Health; 2006.

100. Philbin MM, Tanner AE, Chambers BD, et al. Transitioning HIV-infected adolescents to adult care at 14 clinics across the United States: using adolescent and adult providers' insights to create multi-level solutions to address transition barriers. *AIDS Care - Psychol Socio-Medical Asp AIDS/HIV*. 2017;29(10):1227-1234. doi:10.1080/09540121.2017.1338655

101. Lee L, Yehia BR, Gaur AH, et al. The Impact of Youth-Friendly Structures of Care on Retention Among HIV-Infected Youth. *AIDS Patient Care STDS*. 2016;30(4):170-177. https://doi.org/10.1080/09540121.2017.1338655

102. Judd A, Davies M. Adolescent transition among young people with perinatal HIV in high and low income settings. *Curr Opin HIV AIDS*. 2018;13(3):236-248. https://pubmed.ncbi.nlm.nih.gov/28530042/

103. Health Service Exectutive. Paediatric to Adult Services. Published 2013. Accessed June 23, 2016. http://www.hse.ie/eng/about/Who/clinical/natclinprog/epilepsyprogramme/services/paedtoadult/

104. Judd A, Collins I, Parrott F, Hill T, Jose S, Ford D. Growing up with perinatal HIV: changes in clinical outcomes before and after transfer to adult care in the UK. *J Int AIDS Soc*. 2017;20(Supp 3):71-80. https://pubmed.ncbi.nlm.nih.gov/28530042/

105. Weijsenfeld AM, Smit C, Cohen S, et al. Virological and Social Outcomes of HIV-Infected Adolescents and Young Adults in The Netherlands Before and After Transition to Adult Care. *Clin Infect Dis*. 2016;63(8):1105-1112. doi:10.1093/cid/ciw487

106. Beima-Sofie K, Mutisya I, Begnel E, et al. Assessment of adolescent HIV service delivery in Kenya: The PHASE study. In: *AIDS Conference*. ; 2018.

107. Hansudewechakul R, Pongprapass S, Kongphonoi A, Denjanta S, Watanaporn S, Sohn AH. Transition of Thai HIV-infected adolescents to adult HIV care. *J Int AIDS Soc*. 2015;18(1):2014-2015. doi:10.7448/IAS.18.1.20651

108. Ryscavage P, Macharia T, Patel D, Palmeiro R, Tepper V. Linkage to and retention in care following healthcare transition from pediatric to adult HIV care. *AIDS Care*. 2016;28(5):561-565. doi:10.1080/09540121.2015.1131967

109. Bundock H, Fidler S, Clarke S, et al. Crossing the Divide: Transition Care Services for Young People with HIV—Their Views. *AIDS Patient Care STDS*. 2011;25(8):465-473. doi:10.1089/apc.2010.0279

110. Kakkar F, Van der Linden D, Valois S, et al. Health outcomes and the transition experience of HIV-infected adolescents after transfer to adult care in Québec, Canada. *Biomed Cent Pediatr*. 2016;16(109):1-7.

111. Mcdonagh JE. *Growing Up Ready for Emerging Adulthood but We Can Build Our Youth for the Future*. University of Birmingham and Birmingham Children's Hospital NHS Trust; 2006.

112. Watson AR. Non-compliance and transfer from paediatric to adult transplant unit. *Pediatr Nephrol*. 2000;14(December 1997):469-472.

113. Hersh AO, Pang S, Curran ML, Milojevic DS, von Scheven E. The challenges of transferring chronic illness patients to adult care: reflections from pediatric and adult rheumatology at a US academic center. *Pediatr Rheumatol*. 2009;7(13):1-7. doi:10.1186/1546-0096-7-13

114. Lee YA. Diabetes care for emerging adults : transition from pediatric to adult diabetes care systems. *Ann Pediatr Endocrinol &Metabolism*. 2013;18(1):106-110.

115. Lebensburger JD, Bemrich-Stolz CJ, Howard TH. Barriers in transition from pediatrics to adult medicine in sickle cell anemia. *J Blood Med*. 2012;3:105-112. http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3460672&tool=pmcentrez&rendertype=abstract

116. Westling K, Naver L, Vesterbacka J, Belfrage E. Transition of HIV-infected youths from paediatric to adult care, a Swedish single-centre experience. *Infect Dis (Auckl)*. 2016;48(6):449-452. doi:10.3109/23744235.2016.1143964

117. Grimsrud A, Bygrave H, Doherty M, et al. Reimagining HIV service delivery: The role of differentiated care from prevention to suppression. *J Int AIDS Soc*. 2016;19(1):10-12. doi:10.7448/IAS.19.1.21484

118. Reif LK, McNairy ML, Lamb MR, Fayorsey R, Elul B. Youth-friendly services and differentiated models of care are needed to improve outcomes for young people living with HIV. *Curr Opin HIV AIDS*. 2018;13(3):249-256.

119. World Health Organization. *The Use of Antiretroviral Drugs for Treating and Preventing Hiv Infection: Recommendations for a Public Health Approach*. World Health Organization; 2016.

120. Tanner AE, Philbin MM, Duvalc A, Ellenc J, Kapogiannisd B, Fortenberry JD. "Youth friendly" clinics: Considerations for linking and engaging HIV-infected adolescents into care. *AIDS Care*. 2014;26(2):199-205. doi:10.1080/09540121.2013.808800.

121. World Health Organization. *Making Health Services Adolescent Friendly - Developing National Quality Standards for Adolescent Friendly Health Services*. World Health Organization; 2012.

122. Asad H, Collins I, Goodall R, Sabin C, Judd A. Linking patients with perinatal HIV across paediatric and adult care in the UK. In: *22nd International Workshop on HIV and Hepatitis Observational Databases (IWHOD)*. ; 2018.

123. Asad H, Collins I, Goodall R, Sabin C, Judd A. Mortality and AIDS-defining events among young people with PHIV following transition to adult care in the UK. In: *10th International Workshop on HIV Pediatrics*. ; 2018.

124. Asad H, Collins I, Goodall R, Sabin C, Judd A. Clinical outcomes of young people with perinatal HIV following transfer from paediatric to adult care in the UK. In: *Children's HIV Association (CHIVA) 13th Annual Conference*. ; 2019.

125. Asad H, Sabin C, Collins I, Goodall R, Judd A. Severe immunosuppression in adult care in antiretroviral therapy-experienced young people with perinatal HIV in the UK. In: *22nd International Workshop on HIV and Hepatitis Observational Databases (IWHOD)*. ; 2018.

126. Asad H, Sabin C, Collins I, Goodall R, Judd A. Severe immunosuppression and viral failure in adult care among antiretroviral therapy-experienced young people with HIV in the UK. In: *10th International Workshop on HIV Pediatrics*. ; 2018.

127. Mugavero MJ, Davila J a, Nevin CR, Giordano TP. From access to engagement: measuring retention in outpatient HIV clinical care. *AIDS Patient Care STDS*. 2010;24(10):607-613. https://pubmed.ncbi.nlm.nih.gov/20858055/

128. Philbin MM, Tanner AE, DuVal A, et al. Factors affecting linkage to care and engagement in care for newly diagnosed HIV-positive adolescents within fifteen adolescent medicine clinics in the United States. *AIDS Behav*. 2014;18(8):1501-1510. https://doi.org/10.1080/09540121.2017.1338655

129. Righetti A, Fornoni L, Viscoli C, Biagio A Di. Transitioning HIV-infected children and adolescents into adult care: An Italian real-life experience. *J Assoc Nurses AIDS Care*. 2015;26(5):652-659. https://europepmc.org/article/med/26116060

130. Izzo I, Quiros-Roldan E, Saccani B, et al. Perinatally HIV-Infected Youths After Transition from Pediatric to Adult Care, a Single-Center Experience from Northern Italy. *AIDS Res Hum Retroviruses*. 2018;34(3):241-243. https://pubmed.ncbi.nlm.nih.gov/29061072/

131. Hussen SA, Chakraborty R, Knezevic A, et al. Transitioning young adults from paediatric to adult care and the HIV care continuum in Atlanta, Georgia, USA: a retrospective cohort study. *J Int AIDS Soc*. 2017;20(1):1-9. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5705166/

132. Ryscavage P, Tepper V. Clinical Outcomes Following Transition from Pediatric to Adult HIV Care. In: *ID Week 2013 Conference*. ; 2013. https://idsa.confex.com/idsa/2013/webprogram/Paper39557.html

133. Sainz T, Navarro ML. HIV-Infected Youths: Transition in Spain Compared to the Netherlands. *Clin Infect Dis*. 2017;64(August):230-235. https://academic.oup.com/cid/article/64/2/230/2698915

134. Xia Q, Abraham B, Shah D, Ramaswamy C, Braunstein SL, Torian L V. Transition from paediatric to adult care among persons with perinatal HIV infection in New York City, 2006–2015. *AIDS*. 2018;32(13):1821-1828. https://pubmed.ncbi.nlm.nih.gov/29894382/

135. Izzo I, Quiros-roldan E, Saccani B, et al. Perinatally HIV-Infected Youths After Transition from Pediatric to Adult Care, a Single-Center Experience from Northern Italy. *AIDS Res Hum Retroviruses*. 2018;34(3):241-243. https://pubmed.ncbi.nlm.nih.gov/29061072/

136. Hope, Rebecca; Judd, Ali; Foster, Caroline; Prime, Katia; Tookey, Pat; Jungmann, Eva; Viner R. Clinical Outcomes in Adults with Perinatal HIV After Transfer From Pediatric Care. In: *Conference on Retroviruses and Opportunistic Infections*. ; 2016.

137. Westling K, Navér L, Vesterbacka J, et al. Transition of HIV-infected youths from paediatric to adult care , a Swedish single-centre experience. *Infect Dis (Auckl)*. 2016;4235(1). https://pubmed.ncbi.nlm.nih.gov/26950534/

138. Xia Q, Shah D, Gill B, Torian L V, Braunstein SL. Continuum of care among people living with perinatally acquired HIV infection in New York city, 2014. *Public Health Rep*. 2016;131(4):566-573. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4937118/

139. Collins J, Chappell E, Peters H, Francis K, Thorne C, Judd A. The cascade of care for children with HIV in the UK and Ireland in 2015. In: *The 9th International Workshop on HIV Pediatrics*. ; 2017.

140. Maulsby C, Charles V, Kinsky S, Riordan M, Jain K, Holtgrave D. Positive Charge: Filling the Gaps in the U.S. HIV Continuum of Care. *AIDS Behav*. 2015;19(11):2097-2107. www.link.springer.com/article/10.1007/s10461-015-1015-0

141. Lally MA, Berg JJ Van Den, Westfall AO, et al. HIV Continuum of Care for Youth in the United States. *J Acquir Immune Defic Syndr*. 2018;77(1):110-117. https://pubmed.ncbi.nlm.nih.gov/28991884/

142. Farmer C, Yehia BR, Fleishman JA, et al. Factors Associated With Retention Among Non – Perinatally HIV-Infected Youth in the HIV Research Network. *J Pediatr Infect Dis Soc*. 2016;5(1):39-46. https://pubmed.ncbi.nlm.nih.gov/26908490/

143. Kahana SY, Jenkins RA, Bruce D, et al. Structural Determinants of Antiretroviral Therapy Use , HIV Care Attendance , and Viral Suppression among Adolescents and Young Adults Living with HIV. *PLoS One*. 2016;11(4):1-19. https://pubmed.ncbi.nlm.nih.gov/27035905/

144. Hussen S a, Andes K, Gilliard D, Chakraborty R, Del Rio C, Malebranche DJ. Transition to adulthood and antiretroviral adherence among HIV-positive young Black men who have sex with men. *Am J Public Health*. 2015;105(4):725-731. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4358185/

145. Tepper V, Zaner S, Ryscavage P. HIV healthcare transition outcomes among youth in North America and Europe: A review. *J Int AIDS Soc*. 2017;20(Suppl 3):60-70. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5577703/

146. World Health Organization. *WHO Case Definitions of HIV for Surveillance and Revised Clinical Staging and Immunological Classification of HIV-Related Disease in Adults and Children*. World Health Organization; 2007.

147. A Medland N, H McMahon J, PF Chow E, H Elliott J, F Hoy J, K Fairley C. The HIV care cascade: a systematic review of data sources, methodology and comparability. *J Int AIDS Soc*. 2015;18(1):1-8. https://pubmed.ncbi.nlm.nih.gov/26626715/

148. Drew RS, Rice B, Delpech V, et al. HIV continuum of care in Europe and Central Asia. *HIV Med*. 2017;18(7):490-499. https://pubmed.ncbi.nlm.nih.gov/28117527/

149. Wohl AR, Garland WH, Wu J, et al. A youth-focused case management intervention to engage and retain young gay men of color in HIV care. *AIDS Care*. 2011;23(8):988-997. https://pubmed.ncbi.nlm.nih.gov/21390879/

150. Naar-King S, Green M, Wright K, Outlaw A, Wang B, Liu H. Ancillary services and retention of youth in HIV care. *AIDS Care*. 2007;19(2):248-251. https://pubmed.ncbi.nlm.nih.gov/17364406/

151. Griffith D, Snyder J, Dell S, Nolan K, Keruly J, Agwu A. Impact of a youth-focused care model on retention and virologic suppression among young adults with HIV cared for in an adult HIV clinic. *J Acquir Immune Defic Syndr*. 2019;80(2):41-47. https://pubmed.ncbi.nlm.nih.gov/30422910/

152. Funck-Brentano I, Dalban C, Veber F, et al. Evaluation of a peer support group therapy for HIV-infected adolescents. *AIDS*. 2005;19(1):1501-1508. https://pubmed.ncbi.nlm.nih.gov/16135904/

153. Garofalo R, Kuhns LM, Hotton A, Johnson A, Muldoon A, Rice D. A randomized

controlled trial of personalized text message reminders to promote medication adherence among HIV-positive adolescents and young adults. *AIDS Behav*. 2016;20(5):1049-1059. https://pubmed.ncbi.nlm.nih.gov/26362167/

154. Belzer ME, Naar-King S, Olson J, et al. The use of cell phone support for non-adherent HIV-infected youth and young adults: An initial randomized and controlled intervention trial. *AIDS Behav*. 2014;18(4):686-696. https://pubmed.ncbi.nlm.nih.gov/24271347/

155. Jeffries C, Ross P, Matoff-Stepp S, Thompson R, Harris J, Uhrig J. Ucare4life: Mobile texting to improve HIV care continuum outcomes for minority youth. In: *Topics in Antiviral Medicine*. ; 2016. http://www.iasusa.org/sites/default/files/tam/24-e1-4.pdf%5Cnhttp://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed18b&NEWS=N&AN=613268941

156. Dowshen N, Kuhns LM, Johnson A, Holoyda BJ, Garofalo R. Improving Adherence to Antiretroviral Therapy for Youth Living with HIV/AIDS: A Pilot Study Using Personalized, Interactive, Daily Text Message Reminders. *J Med Internet Res*. 2012;14(2):51. https://pubmed.ncbi.nlm.nih.gov/22481246/

157. Foster C, McDonald S, Frize G, Ayers S, Fidler S. "Payment by Results"—Financial Incentives and Motivational Interviewing, Adherence Interventions in Young Adults with Perinatally Acquired HIV-1 Infection: A Pilot Program. *AIDS Patient Care STDS*. 2014;28(1):28-32. https://pubmed.ncbi.nlm.nih.gov/24428797/

158. Belzer ME, S N-K, Olson J, et al. The Use of Cell Phone Support for Non-adherent HIV-Infected Youth and Young Adults: An Initial Randomized and Controlled Intervention Trial. *AIDS Behav*. 2014;18(4):686-696. https://pubmed.ncbi.nlm.nih.gov/24271347/

159. Goggin G. Youth culture and mobiles. *SAGE journals*. 2013;1(1):83-88. https://journals.sagepub.com/doi/10.1177/2050157912464489

160. Collins I, Foster C, Tostevin A, et al. Clinical Status of Adolescents with Perinatal HIV at Transfer to Adult Care in the UK / Ireland. *Clin Infect Dis*. 2017;64(1):1105-1112. https://pubmed.ncbi.nlm.nih.gov/28329212/

161. Public Health England. *The Survey of Prevalent HIV Infections Diagnosed (SOPHID) Metadata Files*. Public Health England; 2013.

162. Public Health England. *Select Committee on HIV and AIDS in the United Kingdom, HIV and AIDS in the United Kingdom*. Public Health England; 2011.

163. National Archives and Records Administration. The Soundex Indexing System. Published 2005. Accessed July 12, 2017. https://www.archives.gov/research/census/soundex.html

164. Brown A, Chau C. *The HIV and AIDS Reporting System Specification*. Public Health England; 2012.

165. Cuong C. *HIV and AIDS Reporting System: Implementation Guidance*. Public Health England; 2016.

166. Ganguli B, Naskar M, Malloy EJ, Eisen EA. Determination of the functional form of the relationship of covariates to the log hazard ratio in a Cox model. *J Appl Stat*. 2015;42(5):1091-1105. https://www.tandfonline.com/doi/full/10.1080/02664763.2014.995607

167. Harron K, Goldstein H, Wade A, Muller-Pebody B, Parslow R, Gilbert R. Linkage, evaluation and analysis of national electronic healthcare data: Application to providing enhanced blood-stream infection surveillance in paediatric intensive care. *PLoS One*. 2013;8(12):1-11. https://pubmed.ncbi.nlm.nih.gov/24376874/

168. Huntington SE, Bansi LK, Thorne C, et al. Using two on-going HIV studies to obtain clinical data from before, during and after pregnancy for HIV-positive women. *Br Med J Med Res Methodol*. 2012;12(1):1-9. https://pubmed.ncbi.nlm.nih.gov/22839414/

169. Schmidlin K, Clough-Gorr KM, Spoerri A, Egger M, Zwahlen M. Impact of unlinked deaths and coding changes on mortality trends in the Swiss National Cohort. *BMC Med*

Inform Decis Mak. 2013;13(1):1-11. https://pubmed.ncbi.nlm.nih.gov/23289362/

170. McDonald J. An introduction to probabilistic record linkage. *Inst Educ*. Published online 2010:1-8. http://www.bristol.ac.uk/media-library/sites/cmm/migrated/documents/problinkage.pdf

171. Dusetzina S, Tyree S, Meyer A. *Linking Data for Health Services Research: A Framework and Instructional Guide*. Agency for Healthcare Research and Quality; 2014.

172. Huntington S, Chadborn T, Masters J, Delpech V, Tookey P. Comparison of the clinical and demographic characteristics of HIV-infected pregnant women with HIVinfected non-pregnant women seen for care in England, Wales and Northern Ireland. *HIV Med*. 2009;10(Suppl 1):24. https://www.researchgate.net/publication/295701826_Comparison_of_the_clinical_and_demographic_characteristics_of_HIV-infected_pregnant_women_with_HIV-infected_non-pregnant_women_seen_for_care_in_England_Wales_and_Northern_Ireland

173. Ahmed N, Angus B, Boffito M, et al. *BHIVA Guidelines for the Treatment of HIV-1-Positive Adults with Antiretroviral Therapy 2015 (2016 Interim Update)*. British HIV Association; 2016.

174. Zhu Y, Matsuyama Y, Ohashi Y, Setoguchi S. When to conduct probabilistic linkage vs deterministic linkage? A simulation study. *J Biomed Inform*. 2015;56(1):80-86. https://pubmed.ncbi.nlm.nih.gov/26004791/

175. Shaun J. Grannis MD, J. Marc Overhage MD PhD CJMM. Analysis of identifier performance using a deterministic linkage algorithm. *Proc AMIA Symp*. 2002;1(1):305-309. https://pubmed.ncbi.nlm.nih.gov/12463836/

176. National Institute for Care Excellence (NICE). *Transition from Children's to Adults' Services for Young People Using Health or Social Care Services*. National Institute for Health and Care Excellence; 2015.

177. National Health Service. *Diabetes Transition Service Specification*. National Health Service; 2016.

178. Teasdale CA, Alwar T, Chege D, Hawken MP, Abrams EJ. Impact of Youth and Adolescent Friendly Services on Retention of 10–24-Year-Olds in HIV Care and Treatment Programs in Nyanza, Kenya. *J Acquir Immune Defic Syndr*. 2016;71(2):1-6. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5466163/

179. Fatti G, Meintjes G, Shea J, Eley B, Grimwood A. Improved survival and antiretroviral treatment outcomes in adults receiving community-based adherence support. *J Acquir Immune Defic Syndr*. 2012;61(4):e50-e58. doi:10.1097/QAI.0b013e31826a6aee

180. Armstrong B, White E, Saracci R. *Principles of Exposure Measurement in Epidemiology*. Oxford Scholarship Online; 1992.

181. Bowling A. Mode of questionnaire administration can have serious effects on data quality. *J Public Health (Bangkok)*. 2005;27(3):281-291. https://pubmed.ncbi.nlm.nih.gov/15870099/

182. Peat JK, Mellis C, Williams K, Xuan W. *Health Science Research: A Handbook of Quantitative Methods*. SAGE publications; 2002.

183. Coppack K, Hope R, Ferran E, Foster C, Prime K. Mapping care: clinical services for young people with HIV in the UK and Ireland. *HIV Med*. 2014;15(1):Abstract only.

184. Cresswell F V, Levett T. Specialist care of older adults with HIV infection in the UK : a service evaluation. *HIV Med*. 2017;18(7):519-524. https://pubmed.ncbi.nlm.nih.gov/28117544/

185. Raffe S, Curtis H, Tookey P, et al. UK national clinical audit: management of pregnancies in women with HIV. *BMC Infect Dis*. 2017;17(1):1-6. https://pubmed.ncbi.nlm.nih.gov/28219333/

186. Miller JH, Clarke E, Patel R, Kell P, Desai M, Nardone A. How are sexual health clinics in England managing men who have sex with men who refuse to be tested for HIV? *Int J STD AIDS*. 2017;28(13):1305-1310. https://pubmed.ncbi.nlm.nih.gov/28457201/

187. British HIV Association. *Adolescent Transition to Adult HIV Care, BHIVA Audit*.; 2010.

188. World Health Organization. *HIV and Adolescents: Guidance for HIV Testing and Counselling and Care for Adolescents Living with HIV*. World Health Organization; 2013. http://apps.who.int/iris/bitstream/10665/94334/1/9789241506168_eng.pdf?ua=1

189. Ahmed N, Scott D, Matin N, Waters L, Whitlock G. Reasons for transferring HIV care in London. *Int J STD AIDS*. 2017;28(14):1447-1449. https://pubmed.ncbi.nlm.nih.gov/28509659/

190. Zanoni BC, Phungula T, Zanoni HM, France H, Feeney ME. Risk factors associated with increased mortality among HIV infected children initiating antiretroviral therapy (ART) in South Africa. *PLoS One*. 2011;6(7):4-9. https://pubmed.ncbi.nlm.nih.gov/21829487/

191. Gebremedhin A, Gebremariam S, Haile F, Weldearegawi B, Decotelli C. Predictors of mortality among HIV infected children on anti-retroviral therapy in Mekelle Hospital, Northern Ethiopia: A retrospective cohort study. *BMC Public Health*. 2013;13(1):2-7. https://bmcpublichealth.biomedcentral.com/articles/10.1186/1471-2458-13-1047

192. Bunney, P. E., Zink, A. N., Holm, A. A., Billington, C. J., & Kotz CM. Survival of HIV-1 vertically infected children. *Curr Opin HIV AIDS*. 2017;176(5):139-148. https://pubmed.ncbi.nlm.nih.gov/27716730/

193. Austin PC. A tutorial on multilevel survival analysis: Methods, models and applications. *Int Stat Rev*. 2017;85(2):185-203. https://pubmed.ncbi.nlm.nih.gov/29307954/

194. Colver A, Longwell S. New understanding of adolescent brain development: Relevance to transitional healthcare for young people with long term conditions. *Arch Dis Child*. 2013;98(11):902-907. https://pubmed.ncbi.nlm.nih.gov/23986559/

195. Casey B, Jones R, Hare T. The Adolescent Brain. *Ann New York Acad Sci*. 2008;1124(1):111-126. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2475802/

196. Arain M, Haque M, Johal L, et al. Maturation of the adolescent brain. *Neuropsychiatr Dis Treat*. 2013;9(1):449-461. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3621648/

197. Office for National Statistics. Death registrations summary tables - England and Wales (2017). Published 2018. Accessed May 1, 2019. https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/datasets/deathregistrationssummarytablesenglandandwalesreferencetables

198. Staehelin C, Rickenbach M, Low N, et al. Migrants from Sub-Saharan Africa in the Swiss HIV Cohort Study: Access to antiretroviral therapy, disease progression and survival. *AIDS*. 2003;17(15):2237-2244. https://pubmed.ncbi.nlm.nih.gov/14523281/

199. Monge S, Jarrín I, Mocroft A, et al. Mortality in migrants living with HIV in western Europe (1997-2013): A collaborative cohort study. *Lancet HIV*. 2015;2(12):540-549. https://pubmed.ncbi.nlm.nih.gov/26614968/

200. Jarrin I, Pantazis N, Gill MJ, et al. Uptake of combination antiretroviral therapy and HIV disease progression according to geographical origin in seroconverters in Europe, Canada, and Australia. *Clin Infect Dis*. 2012;54(1):111-118. https://pubmed.ncbi.nlm.nih.gov/22109944/

201. Thierfelder C, Weber R, Elzi L, et al. Participation, characteristics and retention rates of HIV-positive immigrants in the Swiss HIV Cohort Study. *HIV Med*. 2012;13(2):118-126. https://pubmed.ncbi.nlm.nih.gov/22107170/

202. Kohns M, Goodall R, Galli L, et al. Are HIV+ migrant children in Europe at increased risk of poor outcomes on ART? In: *CROI*. ; 2018.

203. Judd A, Chappell E, Turkova A, et al. Long-term trends in mortality and AIDS-defining events after combination ART initiation among children and adolescents with perinatal

HIV infection in 17 middle- and high-income countries in Europe and Thailand: A cohort study. *PLoS Med*. 2018;15(1):1-19. https://pubmed.ncbi.nlm.nih.gov/29381702/

204. Asboe D, Aitken C, Boffito M, et al. British HIV Association guidelines for the routine investigation and monitoring of adult HIV-1-infected individuals 2011. *HIV Med*. 2012;13(1):1-44. https://www.bhiva.org/monitoring-guidelines

205. Howarth AR, Burns FM, Apea V, et al. Development and application of a new measure of engagement in out-patient HIV care. *HIV Med*. 2017;18(1):267-274. https://pubmed.ncbi.nlm.nih.gov/27535219/

206. Lourenço L, Nohpal A, Shopin D, Colley G, Nosyk B, Montaner J. Non-HIV related healthcare utilization, demographic, clinical, and laboratory factors associated with time-to-initial retention in HIV care among HIV-positive individuals linked to HIV care. *HIV Med*. 2016;17(4):269-279. https://pubmed.ncbi.nlm.nih.gov/26216126/

207. McManus H, Petoumenos K, Brown K, et al. Loss to follow-up in the Australian HIV Observational Database. *Antivir Ther*. 2015;20(7):731-741. https://pubmed.ncbi.nlm.nih.gov/25377928/

208. Tedaldi EM, Richardson JT, Debes R, et al. Retention in Care within 1 Year of Initial HIV Care Visit in a Multisite US Cohort: Who's in and Who's Out? *J Int Assoc Provid AIDS Care*. 2014;13(3):232-241. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4657738/

209. Olatosi B, Probst J, Stoskopf C, Martin A, Duffus W. Patterns of engagement in care by HIV-infected adults: South Carolina, 2004-2006. *AIDS*. Published online 2009:725-730. https://pubmed.ncbi.nlm.nih.gov/19197194/

210. Kerr JC, Stephens TG, Gibson JJ, Duffus WA. Risk factors associated with inpatient hospital utilization in HIV-positive individuals and relationship to HIV care engagement. *J Acquir Immune Defic Syndr*. 2012;60(2):173-182. https://pubmed.ncbi.nlm.nih.gov/22293549/

211. Rebeiro P, Althoff KN, Buchacz K, et al. Retention Among North American HIV-Infected Persons in. *Epidemiol Prev*. 2013;62(3):356-362. https://pubmed.ncbi.nlm.nih.gov/23242158/

212. Fleishman JA, Yehia BR, Moore RD, Korthuis PT, Gebo KA. Establishment, Retention, and Loss to Follow-Up in Outpatient HIV Care. *Jounral Acquir Immune Defic Syndr*. 2012;60(3):249-259. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3383913/

213. Yehia BR, Fleishman J a, Metlay JP, et al. Comparing different measures of retention in outpatient HIV care. *AIDS*. 2012;26(9):1131-1139. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3693494/

214. Adeyemi OM, Livak B, McLoyd P, Smith KY, French AL. Racial/Ethnic disparities in engagement in care and viral suppression in a large Urban HIV clinic. *Clin Infect Dis*. 2013;56(1):1512-1514.

215. Torian L V., Xia Q, Wiewel EW. Retention in care and viral suppression among persons living with HIV/AIDS in New York City, 2006-2010. *Am J Public Health*. 2014;104(9):2006-2010. https://pubmed.ncbi.nlm.nih.gov/25033144/

216. Cohen MS, Chen YQ, McCauley M, et al. Antiretroviral Therapy for the Prevention of HIV-1 Transmission. *N Engl J Med*. Published online 2016. https://www.nejm.org/doi/full/10.1056/NEJMoa1600693

217. Chapman R, Wolf F De, Hanage WP, Fraser C. Variation in HIV-1 set-point viral load: Epidemiological analysis and an evolutionary hypothesis. 2007;104(44):17441-17446. https://pubmed.ncbi.nlm.nih.gov/17954909/

218. Columb MO, Atkinson MS. Statistical analysis: sample size and power estimations. *BJA Educ*. 2016;16(5):159-161. https://academic.oup.com/bjaed/article/16/5/159/2389876

219. Chokephaibulkit K, Kariminia A, Bunupuradah T, et al. Characterizing HIV Manifestations and Treatment Outcomes of Perinatally Infected Adolescents in Asia. 2014;33(3):291-294. https://pubmed.ncbi.nlm.nih.gov/23942457/

220. Barber T, Geretti A, Anderson J, et al. Outcomes in the first year after initiation of first-line HAART among heterosexual men and women in the UK CHIC Study. *Antiretrovir Ther*. 2011;16(6):805-814.

221. Scully E. Sex Differences in HIV Infection. *Curr HIV/AIDS Rep*. 2018;15(2):136-146. https://pubmed.ncbi.nlm.nih.gov/29504062/

222. Bonolo P de F, Ceccato M das GB, Rocha GM, Acúrcio F de A, Campos LN, Crosland Guimarães MD. Gender differences in non-adherence among Brazilian patients initiating antiretroviral therapy. *Clinics*. 2013;68(5):612-620. https://www.thelancet.com/journals/lanhiv/article/PIIS2352-3018(14)00033-2/fulltext

223. British HIV Association. *BHIVA Guidelines for the Treatment of HIV-1-Positive Adults with Antiretroviral Therapy*.; 2015. http://www.bhiva.org/documents/Guidelines/Treatment/2015/2015-treatment-guidelines.pdf

224. Tsegaye AT, Wubshet M, Awoke T, Alene KA. Predictors of treatment failure on second-line antiretroviral therapy among adults in northwest Ethiopia: a multicentre retrospective follow-up study. *BMJ Open*. 2016;6(12):1-8. https://bmjopen.bmj.com/content/6/12/e012537.citation-tools

225. Fewell Z, Smith GD, Sterne JAC. Practice of Epidemiology The Impact of Residual and Unmeasured Confounding in Epidemiologic Studies: A Simulation Study. *Am J Epidemiol*. 2007;166(6):646-655. https://academic.oup.com/aje/article/166/6/646/89040

226. Britsh HIV Association (BHIVA). *BHIVA Guidelines for the Routine Investigation and Monitoring of HIV-1 Positive Individuals*.; 2016. http://www.bhiva.org/documents/Guidelines/Monitoring/2016-BHIVA-Monitoring-Guidelines.pdf

227. Dong Y, Peng CJ. Principled missing data methods for researchers. *Springerplus*. 2013;2(222):1-17. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3701793/

228. Delpech V, Desai S. *CD4 Surveillance Metadata Files*. Public Health England; 2013.

229. Backus L, Czarnogorski M, Yip G, et al. HIV care continuum applied to the US department of veterans affairs: HIV virologic outcomes in an integrated health care system. *J Acquir Immune Defic Syndr*. 2015;69(4):474-480. https://europepmc.org/article/med/25835603

230. Wiewel EW, Braunstein SL, Xia Q, Shepard CW, Torian L V. Monitoring outcomes for newly diagnosed and prevalent HIV cases using a care continuum created with New York City surveillance data. *J Acquir Immune Defic Syndr*. 2015;68(2):217-226. https://pubmed.ncbi.nlm.nih.gov/25394192/

231. Lourenço L, Colley G, Nosyk B, Shopin D, Montaner JSG, Lima VD. High levels of heterogeneity in the hiv cascade of care across different population subgroups in British Columbia, Canada. *PLoS One*. 2014;9(12):1-18. https://pubmed.ncbi.nlm.nih.gov/25541682/

232. Hall HI, Frazier EL, Rhodes P, et al. Differences in human immunodeficiency virus care and treatment among subpopulations in the United States. *JAMA Intern Med*. 2013;173(14):1337-1344. https://pubmed.ncbi.nlm.nih.gov/23780395/

233. Mangal JP, Rimland D, Marconi VC. The continuum of HIV care in a veterans' affairs clinic. *AIDS Res Hum Retroviruses*. 2014;30(5):409-415.

234. Lazarus J V., Safreed-Harmon K, Barton SE, et al. Beyond viral suppression of HIV - the new quality of life frontier. *BMC Med*. 2016;14(1):10-14. https://pubmed.ncbi.nlm.nih.gov/21900712/

235. Webster P. UNAIDS survey aligns with so-called fourth 90 for HIV/AIDS. *Lancet*. 2019;393(1):2188. https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(19)31231-0/fulltext

236. Dahourou DL, Gautier-Lafaye C, Teasdale CA, et al. Transition from paediatric to adult

care of adolescents living with HIV in sub-Saharan Africa: Challenges, youth-friendly models, and outcomes. *J Int AIDS Soc*. 2017;20(3):34-49. https://pubmed.ncbi.nlm.nih.gov/28530039/

237. Ojwang'a V, Pennera J, Blata C, Agotd K, Bukusia E, Cohen C. Loss to follow-up among youth accessing outpatient HIV care and treatment services in Kisumu, Kenya. *AIDS*. 2014;28(4):500-507. doi:10.4172/2157-7633.1000305.Improved

238. Zanoni B, Cairns C, Sibaya T, Heberer J. High retention and viral suppression rates in a dedicated adolescent-friendly HIV clinic in South Africa. In: *8th International Workshop on HIV Pediatrics*. ; 2016.

239. Judd A, Foster C, Thompson L, et al. Sexual health of young people with perinatal HIV and HIV negative young people in England. *PLoS One*. 2018;13(10):1-14.

240. Zanoni BC, Archary M, Buchan S, Katz IT, Haberer JE. Systematic review and meta-analysis of the adolescent HIV continuum of care in South Africa: The Cresting Wave. *BMJ Glob Heal*. 2016;1(3):1-9. https://pubmed.ncbi.nlm.nih.gov/28588949/

241. IAS. IAS Statement: Anti-homosexuality Bill poses severe threat to human rights of LGBT community in Uganda. Published 2019. Accessed October 26, 2019. https://www.iasociety.org/The-latest/News/ArticleID/239/IAS-Statement-Anti-homosexuality-Bill-poses-severe-threat-to-human-rights-of-LGBT-community-in-Uganda

242. Slogrove AL. Inequality in outcomes for adolescents living with perinatally acquired HIV in sub-Saharan Africa: A Collaborative Initiative for Paediatric HIV Education and Research (CIPHER) Cohort Collaboration analysis: A. *J Int AIDS Soc*. 2018;21:35-46. https://pubmed.ncbi.nlm.nih.gov/29485724/

243. Slogrove AL, Schomaker M, Davies M-A, et al. The epidemiology of adolescents living with perinatally acquired HIV: A cross-region global cohort analysis The Collaborative Initiative for Paediatric HIV Education and Research (CIPHER) Global Cohort Collaboration. *PLoS Med*. 2018;15(3):1-21. https://pubmed.ncbi.nlm.nih.gov/29494593/

244. Tsondai P, Sohn A, PHiri S, et al. Characterizing the double-sided cascade of care for HIV-infected adolescents transitioning to adult-centred care in the IeDEA Southern Africa Collaboration. In: *10th International Workshop on HIV Pediatrics*. ; 2018. Amsterdam, Netherlands

245. Cozzi-Lepri A, Phillips AN, Clotet B, et al. Detection of HIV drug resistance during antiretroviral treatment and clinical progression in a large European cohort study. *AIDS*. 2008;22(16):2187-2198. https://pubmed.ncbi.nlm.nih.gov/18832882/

246. Simoni JM, Kurth AE, Pearson CR, Pantalone DW, Merrill JO, Frick PA. Self-report measures of antiretroviral therapy adherence: A review with recommendations for HIV research and clinical management. *AIDS Behav*. 2006;10(3):227-245. https://pubmed.ncbi.nlm.nih.gov/16783535/

247. Vermund S. Use of big data to identify risk of adverse HIV outcomes. *Lancet*. 2019;6(1):e488-e489. https://pubmed.ncbi.nlm.nih.gov/31303556/

248. Bushman FD, Barton S, Bailey A, et al. Bringing it all together: Big data and HIV research. *AIDS*. 2013;27(5):835-838. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3671485/

249. Olatosi B, Zhang J, Weissman S, Hu J, Haider MR, Li X. Using big data analytics to improve HIV medical care utilisation in South Carolina: A study protocol. *BMJ Open*. 2019;9(e027688):1-11. https://pubmed.ncbi.nlm.nih.gov/19197194/

250. Adibuzzaman M, DeLaurentis P, Hill J, Benneyworth BD. Big data in healthcare - the promises, challenges and opportunities from a research perspective: A case study with a model database. *J Heal Syst Reform*. 2017;1(4):384-392.

251. Rana A, Mugavero M. How Big Data Science can improve linkage and retention in care. *Infect Dis Clin North Am*. 2019;33(3):807-815. https://pubmed.ncbi.nlm.nih.gov/31395146/

252. NIH institute. Creating a global framework of data collection used for adolescent HIV transition evaluation (GRADUATE). Accessed July 12, 2019. https://projectreporter.nih.gov/project_info_description.cfm?aid=9321396&icde=37799104