Antiretroviral therapy, drug resistance in pregnancy, and preventing mother-to-child HIV transmission in the UK

A thesis presented for the degree of Doctor of Philosophy

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Declaration

I, Laura Byrne, 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

Effective interventions have reduced the HIV vertical transmission rate in high-income countries to very low levels; the goal is now to eliminate new paediatric HIV infections. The aim of this thesis was to examine the role of antiretroviral therapy (ART) and other interventions to reduce vertical HIV transmission in the UK and Ireland in the current treatment era. I used data from the National Study of HIV in Pregnancy and Childhood (NSHPC), a national surveillance study of all pregnancies in women living with HIV and their children in the UK and Ireland; the UK HIV drug resistance database and a national survey on the management of women who decline antenatal HIV testing. The NSHPC dataset included all pregnancies reported 2000-2014.

Results highlight substantial changes in the demographics of women with reported pregnancies. There was wide variation in the management of women who decline HIV testing in pregnancy. Women with perinatal HIV in the UK had a first pregnancy incidence of 13 per 1000 woman-years (95% CI: 9 to 17 per 1000 woman-years). Perinatal HIV was an independent risk factor for detectable viral load near delivery (aOR 3.22 95% CI: 1.22-8.48), as was lower age at conception, no ART at conception, and PI-containing cART. The prevalence of transmitted drug resistance was 5.3% in women diagnosed during pregnancy (95% CI: 4.3% to 6.5%), similar to other estimates in non-B HIV-1 subtypes in the UK. Key contributing factors were identified in the 108 cases of perinatal HIV in infants born in the UK 2006-2014, including women who declined HIV testing in pregnancy; difficulties with engagement and adherence to ART during pregnancy; HIV acquisition during pregnancy or postnatal period after a negative test in early pregnancy.

This thesis identifies key improvements which can still be made on the road to eliminating paediatric HIV.

Impact statement

Since the recognition in the medical community of the first case of HIV/AIDS in 1981, researchers have strived to understand the natural history, epidemiology, virology, treatment and wider impact of the virus and its consequences for the global population. Huge advances have been made in these areas - with early diagnosis and treatment people living with HIV can have a near-normal life expectancy. One of the biggest successes has been interventions to prevent vertical transmission of HIV from mother to child – reducing the risk of transmission from 25-40% to as low as 0.3% in high-income countries. The goal worldwide is now to eliminate new paediatric HIV infections.

The National Study of HIV in Pregnancy and Childhood (NSHPC) has been collecting data on pregnant women living with HIV and their infants in the UK and Ireland for 30 years. I have focussed on pregnancies in the recent treatment era, 2000 to 2014, and combined this with data from several other sources.

In this thesis I demonstrate several new findings. The population of women living with HIV who become pregnant has changed over the time – with increasing age at conception, more sequential pregnancies reported, a rise in in the proportion of women reported from Eastern Europe and Western Africa, more pregnancies reported from outside London. I have found that the management of women who decline antenatal HIV testing varies widely and have identified themes common to cases of vertical infection in the UK. I have found there is a reassuringly low rate of transmitted drug resistance among women diagnosed during pregnancy, which is important information for guidance on recommending first-line antiretroviral therapy. My research findings have fed into the national standards of the Infection Diseases in Pregnancy Screening Programme, as well as the UK guidelines on the management of HIV in pregnancy. The enhanced data collection methodology I developed is now embedded into the NSHPC.

Women living with perinatal HIV are an important emerging population globally, with little data available on long-term outcomes. I estimated pregnancy incidence in the UK in this population and found that perinatal HIV is an independent risk factor for failing to achieve viral suppression near delivery (a risk factor for vertical

infection). This is a new insight into the complex needs of women growing up with HIV, and the results have now been replicated by a prospective multicentre study in the US.

I have disseminated my findings through presentations at several national and international conferences and two papers in international peer-reviewed journals of high impact. I have also discussed my research on an episode of the podcast 'Sex Talk' produced by Public Health England and National Prison Radio and at a patient workshop on HIV and pregnancy held at Positively UK. The work presented in this thesis has implications for both public health policy and clinical guidelines, and for researchers, including those exploring the impact HIV is having on women growing up with it and those continuing to work towards the elimination of new paediatric HIV infections, as well as women living with HIV themselves.

Acknowledgments

This thesis is dedicated to all the women living with HIV I have had the privilege of caring for.

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Acronyms and abbreviations

AIC Akaike's information criterion

AIDS Acquired immune deficiency syndrome

aOR Adjusted odds ratio

APR Antiretroviral Pregnancy Registry

ART Antiretroviral therapy

BASHH British Association of Sexual Health & HIV

BHIV Behaviourally-acquired HIV

BHIVA British HIV Association

BIC Bayesian information criterion

BMI Body mass index

cART Combined antiretroviral therapy

CD4 CD4-presenting T-cell

CHIVA Children's HIV Association

CI Confidence interval

CMV Cytomegalovirus

CS Caesarean section

DF Degrees of freedom

EDD Estimated delivery date

EECA Eastern European and Central Asian countries

ERP Expert Review Panel

GUM Genito-urinary Medicine

HEU HIV-exposed uninfected

HIC High-income country

HIV Human Immunodeficiency virus

IDPS Infectious Disease in Pregnancy Screening

IDU Injecting drug use

INSTI Integrase strand transfer inhibitor

IPV Intimate partner violence

IQR Interquartile range

KPI Key performance indicator

LMIC Low- and middle-income countries

LRTI Lower respiratory tract infection

MDT Multidisciplinary team

MTCT Mother-to-child transmission of HIV

NHS National Health Service

NNRTI Non-nucleoside reverse transcriptase inhibitor

NRTI Nucleos(t)ide reverse transcriptase inhibitor

NSHPC National Study of HIV in Pregnancy and Childhood

OR Odds ratio

PCR Polymerase chain reaction

PDR Pre-treatment drug resistance

PEP Post-exposure prophylaxis

PHE Public Health England

PHIV Perinatally-acquired HIV

PI Protease inhibitor

PMTCT Preventing MTCT

PPROM Premature prelabour rupture of membranes

PWID People who inject drugs

ROI Republic of Ireland

ROM Rupture of membranes

SOPHID Survey of Prevalent HIV Infections Database

SSA Sub-Saharan Africa

START Short term antiretroviral therapy

TAF Tenofovir alafenamide

TAMs Thymidine analogue mutations

TDF Tenofovir disoproxil fumarate

TDR Transmitted drug resistance

TDRM Transmitted drug resistance mutations

UK United Kingdom

UKHDRD UK HIV Drug Resistance Database

UNAIDS Joint United Nations Programme on HIV/AIDS

VL Viral load

WHO World Health Organisation

1 Introduction

1.1 Global epidemiology of HIV 2000-2014

By the end of 1999, there were an estimated 34.3 million people living with HIV in the world, of whom 15.7 million were women, and 1.3 million were children; 18.8 million people had died of AIDS, and 13.2 million children had been orphaned (Joint United Nations Programme on HIV AIDS 2001). According to a report published by UNAIDS in 2001, *"A decade ago, HIV/AIDS was regarded primarily as a serious health crisis. Estimates in 1991 predicted that in sub-Saharan Africa, by the end of the decade, 9 million people would be infected and 5 million would die – a threefold underestimation. Today, it is clear that AIDS is a development crisis, and in some parts of the world is rapidly becoming a security crisis too".* In sub-Saharan Africa, 16 countries had HIV prevalence risen to more than 10% of the adult population; in seven southern countries prevalence was at least 20% (Joint United Nations Programme on HIV AIDS 2001). Although eastern and southern countries had so far borne the brunt of the epidemic, at the turn of the century the prevalence of HIV in western African countries was also rising, and in Nigeria had reached 5% (Joint United Nations Programme on HIV AIDS 2001).

In Asia, overall prevalence was low, but the epidemic was concentrated in at-risk groups such as sex workers and people who inject drugs (PWID), with high geographical variability both between and within countries (Joint United Nations Programme on HIV AIDS 2001). The epidemic in South and Central America was also highly variable, with the highest infection rate in the Caribbean states of Central America, but with heterosexual epidemics in Brazil, and high rates of infection in men who have sex with men (MSM) and PWID in Mexico, Argentina and Columbia. The Caribbean islands were experiencing a major heterosexual epidemic, driven by condomless sex between men and women, with low age of sexual debut and frequent partner change (Joint United Nations Programme on HIV AIDS 2001).

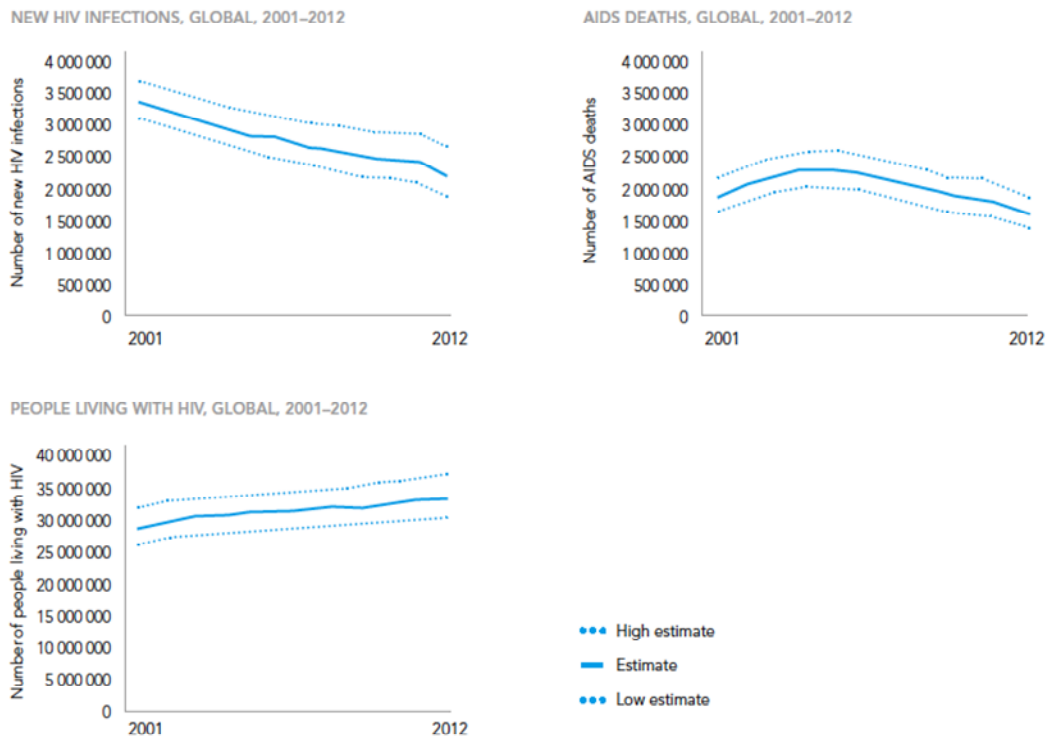
In Eastern European and Central Asian countries (EECA), HIV infection was concentrated heavily in PWID, with small absolute numbers of cases in many countries. However, in Ukraine, the epicentre of the HIV epidemic in EECA, the number of diagnosed infections had jumped from virtually zero before 1995 to around 20,000 a year from 1996 onwards, around 80% in PWID (Joint United

Nations Programme on HIV AIDS 2001). Eastern and South Eastern Europe has the highest prevalence of IDU in the world, at 1.27% of the population aged 15–64 years, versus 0.25% globally, with almost all the people who inject drugs (PWID) in this region living in Russia and Ukraine (Bailey, Turkova, and Thorne 2017). The Ukrainian epidemic at this point was fuelled by unsafe injecting practices of predominantly home-grown liquid poppy straw[1] made from poppy cultivated within Ukraine (WHO 2014a; Rhodes et al. 1999), although Ukraine was also thought part of a major trafficking route of Afghanistan-grown heroin into Russia and Eastern Europe (Layne 2010).

In the WHO European region, the rate of newly diagnosed HIV infections per 100,000 population rose from 7.3 in 2006 to 7.8 in 2012; this increase was largely driven by an accelerating epidemic in the east, with incidence of 22.0 per 100,000 population in 2012, and the highest country incidence in Ukraine of 37.1 per 100,000 population (ECDC 2013). Since 2008, the reported predominant route of transmission in the east changed evolved from injecting drug use to heterosexual contact (initially with PWID, who remain an important group within the epidemic), which accounted for 60% of new HIV infections in 2012 (ECDC 2013). The male-to-female ratio in cases of newly diagnosed HIV was 1.4 in the east, the lowest of the three regions (ECDC 2013).

[1] "Dried poppy straw (stems, poppy heads) mixed with chemicals, boiled, and strained in several steps to extract the opioids. If the final filtered product appears 'dirty,' it might be mixed with a small quantity of blood, thought to absorb the dust and dirt" (Booth et al. 2003).

Figure 1-1. Numbers of people living with HIV, new HIV infections, and AIDS deaths, 2001-2012, globally (UNAIDS 2013)[2]



By 2012 the number of people estimated to be living with HIV had risen to 35.3 million, of whom 17.7 million were women and 3.3 million children under 15 years (UNAIDS 2013). However, the estimated incidence of new HIV infections declined from 3.4 million new infections in 2001 to 2.3 million in 2012 (see Figure 1-1). By 2013, record numbers of people were receiving antiretroviral therapy (ART), and the percentage of people living with HIV who were not receiving ART had been reduced from 90% in 2013 to 63% in 2013 (UNAIDS 2014).

The scale-up of ART was not only important for the health of people living with HIV, but also for the prevention of onward transmission. In 2010, the Partners in Prevention prospective cohort study reported a much lower transmission rate in sero-discordant heterosexual African couples where the partner with HIV had initiated ART. The transmission rate was estimated at 0.37 (95% confidence interval (CI) 0.09-

[2] Figure reproduced with permission from UNAIDS, personal communication.

2.04) per 100 person-years, compared with 2.24 (95% CI 1.84 – 2.72) in couples where the person living with HIV was not taking ART (Donnell et al. 2010). This was followed in 2011 by the results of the ground-breaking HPTN052 study, which was a multicontinental randomised controlled trial comparing early versus delayed ART for patients with CD4 counts between 550 and 350 cells/mL who were in a stable sexual relationship with an HIV-negative partner. HPTN052 reported a linked transmission incidence rate of 0.1 per 100 person-years in the early treatment group (95% CI 0.0 to 0.4) and 1.7 per 100 person-years in the delayed-treatment group (95% CI 1.1 to 2.5)(Cohen et al. 2011). The Partner study, a multi-centre observational trial, published interim results in 2014 and then final results in 2016; there were no phylogenetically-linked transmissions among 888 serodiscordant couples where the HIV-positive partner was on ART with a VL < 200 copies/ml (95% CI 0.0 to 0.30 per 100 person-years) (Rodger et al. 2016).

The GAP Report, published by UNAIDS in 2014, highlighted progress achieved in the preceding decade (UNAIDS 2014), including the particularly rapid scale-up of access to ART in South Africa, India, Uganda, Nigeria, Mozambique, Tanzania and Zimbabwe. Prevention programmes providing access to condoms and male circumcision had also impacted on HIV transmission, contributing to the reduction in new infections, and increased testing programmes had reduced the number of people living with HIV who were unaware of their infection.

1.1.1 HIV and young women: a key population

The Gap Report also highlighted the disparities in progress with respect to key populations. In 2013, almost 60% of all new HIV infections among young people aged 15-24 occurred amongst adolescent girls and young women; 80% of women aged 15-24 years living with HIV were living in sub-Saharan Africa (UNAIDS 2014). Globally, women comprised 52% of all people living with HIV in low- and middle-income countries (LMIC), and in sub-Saharan Africa, the centre of the global epidemic, women still accounted for approximately 57% of all people living with HIV (UNAIDS 2013). Young women aged 15–24 years were most vulnerable to HIV, with infection rates twice as high as in young men, at 0.6%; this disparity was most pronounced in sub-Saharan Africa, where 3.1% of young women were living with HIV, versus 1.3% of young men (Joint United Nations Programme on HIV/AIDS 2012). In South Africa, the country with the world's largest HIV positive population, HIV infection rates were

eight times higher among adolescent women than among young men of the same age (Zuma et al. 2016). HIV/AIDS was the leading cause of death in women of reproductive age globally (Ribeiro et al. 2008) and the HIV epidemic in eastern and southern Africa contributed to substantial increases in maternal mortality (Hogan et al. 2010).

The 2012 UNAIDS report on the state of the global AIDS epidemic was devoted to the drivers of HIV infection among women, and stated that '"*gender inequality drives the HIV epidemic*" (Joint United Nations Programme on HIV/AIDS 2012). Worldwide, women faced (and continue to face) harmful gender norms which can act as barriers to protecting themselves from HIV: women have less economic and sexual empowerment, are at risk of gender-based violence, are more likely to be involved in sex-work, and face reproductive health challenges (Joint United Nations Programme on HIV/AIDS 2012). A 2016 review by Harrison et al. framed the complex issue of sustained high HIV incidence in young women in southern Africa within the "*gendered context of HIV risk*", which includes age-disparate sexual partnerships, and high rates of gender-based violence leading to gender inequality, relationship power differentials, and sexual coercion (Harrison et al. 2015), which have elsewhere been called the "*dynamics of hypervulnerability*" (Leclerc-Madlala 2008). Young women who experienced intimate partner violence in South Africa were 50% more likely to acquire HIV than women who did not (Jewkes et al. 2010). In addition, transactional sex with older male partners was commonplace, and this was associated with unsafe sexual practices (Leclerc-Madlala 2008).

Women are also biologically vulnerable to HIV infection, influenced by the type of sexual activity and innate biological defences of uninfected women (Chersich and Rees 2008). Women seem to be at higher risk of HIV infection by sex act, with cervical ectopy (which is more common in young women) and the presence of bacterial vaginosis and trichomonas, (as well as ulcerative sexually transmitted infections (STIs) in either partner) increasing transmission risk (Chersich and Rees 2008). Vaginal practices widespread in southern Africa have been linked with the loss of lactobacilli and disruption of the vaginal epithelium (Kilmarx et al. 1998; Hiber et al. 2007). There may be a hormonal influence, with an increased risk of HIV acquisition in pregnant and breastfeeding women, and there may be a modest

increase in risk of acquisition with the long-acting injectable progesterone DMPA (Polis et al. 2016).

1.2 Perinatal HIV

1.2.1 Global and UK epidemiology

Mother-to-child transmission of HIV (MTCT) can occur in utero, during labour or delivery, or in the postpartum period through breastfeeding. In the early years of the epidemic, the transmission rate in untreated breastfeeding resource-poor settings was estimated to be 25 to 45%, and 15 to 30% in non-breastfeeding resource-rich settings (Dabis et al. 1993; De Cock et al. 2000). The global approach to reducing the number of children infected or affected by HIV consists of four main strategies: *"1. Primary prevention of HIV among women of childbearing age; 2. Preventing unintended pregnancies among women living with HIV; 3. Preventing vertical transmission of HIV; and 4. Providing appropriate treatment, care and support to mothers living with HIV and their children and families"* (WHO and UNICEF Interagency Task Team 2007).

Successes in comprehensive antenatal screening, early initiation of combination ART (cART), and optimised obstetric management, as well as the avoidance of breastfeeding, have now reduced MTCT rates in resource-rich countries to less than 1% (Townsend et al. 2014). Despite this, 370 000 children became newly infected with HIV in 2009 worldwide, and an estimated 42 000 – 60 000 pregnant women died because of HIV. In 2011 the 'Global Plan towards elimination of new HIV infections among children by 2015 and keeping their mothers alive' was launched by UNAIDS, which set four targets to be achieved in 22 priority countries by 2015: *"1. Reduce HIV incidence in women aged 15-49 by 50%; 2. Reduce unmet need for family planning to zero; 3. Reduce MTCT to 5%; and 4. Provide 90% of pregnant women in need of ART for their own health with lifelong ART"* (Joint United Nations Programme on HIV/AIDS 2011).

Mother-to-child transmission of HIV peaked worldwide in 2001-2 with an estimated 550 000 children newly infected per year; following the scale-up of antenatal HIV testing and ART for pregnant and breastfeeding women living with HIV, there has been a 52% reduction in new infections among children worldwide between 2001 and 2012, but coverage of prevention services in priority countries is still variable, with 13 countries with generalised epidemics reaching less than 50% of pregnant women living with HIV (UNAIDS 2013). Box 1.1 shows the Gap report's priority actions for meeting the needs of pregnant women living with HIV.

Box 1.1 Priority actions for meeting the needs of pregnant women living with HIV (UNAIDS 2014)

- Improving access to voluntary counselling and testing.
- Ensuring that voluntary couples counselling and testing is available.
- Ensuring that all HIV services are voluntary, confidential and of high quality, including referrals and follow-up.
- Ensuring that women living with HIV have full and complete information and an understanding of their sexual and reproductive health options, risks and benefits and the ability to choose freely among them.
- Providing lifelong treatment for all pregnant women according to the 2013 WHO guidelines to prevent vertical transmission while at the same time safeguarding the woman's health (WHO 2013).
- Providing treatment to the remaining 30% of pregnant women living with HIV who are not receiving ART to prevent vertical transmission.
- Paying extra attention to pregnant adolescents.

1.2.2 Pregnancies in women living with HIV in the UK

In the UK there were an estimated 98,400 people living with HIV in 2012, of whom 1 in 5 were unaware of their infection, with an estimated overall prevalence of 1.5 per 1000 population and 51 per 1000 in Black African women (Public Health England 2013). Nearly half (45%) of newly diagnosed infections in 2012 were acquired heterosexually, and more heterosexual women than men were newly diagnosed with HIV (1530 women compared to 1050 men) (Public Health England 2013). From 2002 to 2011 the proportion of infections among heterosexuals acquired in the UK increased from 27% to 52%, and the proportion of those acquired abroad more than halved (Public Health England 2013). Late diagnosis (i.e. with CD4 <350 cells/μL) was highest in heterosexuals, with over half of women and two-thirds of men diagnosed late (Public Health England 2013). In the UK Collaborative HIV Cohort Study (UK CHIC), which includes around 30% of women accessing care in the UK, the median age of all women living with HIV and accessing care rose from 33 in 2000/1 to 37 years in 2008/9, and CD4 count rose from 338 to 463 cells/μL (Huntington et al. 2013).

Prevalence of HIV among pregnant women in England in 2011 was 2.2 per 1,000, and highest among sub-Saharan African-born pregnant women (23 per 1,000), with a small decline in this group over the previous decade, from 25 per 1,000 in 2002 (estimates from unlinked anonymous seroprevalence surveys based on neonatal dried blood spots)(Cortina-Borja et al. 2004). In contrast, the prevalence of HIV among UK-born women increased slowly over the same period, from 3 per 1,000 to 5 per 1,000 (HPA 2012). In the UK CHIC cohort, the pregnancy incidence was estimated at 3.5% in 2000, peaking at 4.8% in 2006, and falling slightly to 4.7% in 2009, with an increasing proportion resulting in delivery and decreasing proportion in termination (from 12.8% in 2000 to 2.9% in 2009). Women were more likely to become pregnant if they were younger, had a CD4 count greater than 200 cells/μL, and were of Black African ethnicity (Huntington et al. 2013).

The National Study of HIV in Pregnancy and Childhood (NSHPC) provides comprehensive population-based surveillance data on women living with HIV in the UK & Ireland who become pregnant (Townsend et al. 2014). Data published from the study have demonstrated striking trends in this population in the past two decades. The median age for women delivering 1990-1993 was 27.2 years (IQR 24.4 to 30.1), and this rose to 30.2 years in 2004-2006 (IQR 26.4 – 34.0) (p<0.001)(Claire Townsend et al. 2008). In the calendar period 2000-2011, approximately 70% of pregnant women living with HIV in the UK were Black African, and the proportion likely to be infected through injecting drug use declined from 3% in 2000-2006 to 1.5% in 2007-2011 (Townsend et al. 2014). The proportion of pregnant women living with HIV who were diagnosed prior to conception rose from 46.3% in 2000-2006 to 72.3% in 2007-2011 (p<0.001) (Townsend et al. 2014). There was also evidence that as the health and life expectancy of people living with HIV and the prevention of perinatal HIV improved, women were increasingly free to have the children they desired: the proportion of second or subsequent pregnancies reported in women living with HIV rose from 20.3% in 1997 to 38.6% in 2009, with a median birth-to-birth interval of 2.3 to 2.7 years (French et al. 2012).

Before the recommendation that all people with HIV should start ART and continue lifelong (BHIVA Guidelines writing group 2016), there was concern that women with CD4 counts >350 cells/ml receiving short-term ART (START) in pregnancy may be at risk of defaulting care after delivery, and that this would impact on their health

outcomes (French et al. 2014; French et al. 2013). In addition, evidence from the non-pregnant population was that treatment interruptions were associated with morbidity and mortality (SMART Study Group et al. 2006). An NSHPC analysis reported that 53% of women were not on ART at conception in their second pregnancy 2000-2010, and of these women, 40% had a CD4 count below 350 cells/μL, (nearly half of these women had a CD4 count of greater than 350 cells/μL in their first pregnancy, therefore qualifying for START as per the recommendations at that time)(French et al. 2014). These women started on ART during their second pregnancy had a 4.3 times odds of a detectable HIV viral load (VL) at delivery than women on ART at conception (French et al. 2014).

The MTCT rate in diagnosed women in the UK declined from 2.1% in 2000-2001 to 0.46% in 2010-2011, with a further decline to 0.27% in 2012-2014, as a result of comprehensive antenatal HIV testing, a reduction in the proportion of women who are untreated, and earlier initiation of ART in pregnancy; in women with VL below the level of detection near to delivery, the MTCT rate was 0.05% (Townsend et al. 2014; Peters et al. 2017).

1.2.3 Interventions to reduce perinatal HIV

Interventions to reduce perinatal HIV infection include: preventing unintended pregnancies in women living with HIV; universal antenatal voluntary screening for HIV in early pregnancy; the provision of effective ART for women diagnosed with HIV; engagement with clinical services and good adherence to ART; optimal obstetric management; post-exposure prophylaxis for the newborn; and infant feeding strategies which minimise the risk of transmission whilst maintaining optimal health for the newborn. The World Health Organisation (WHO) produces guidelines for the management of HIV in pregnant women, aimed at low and middle-income countries (LMIC), and the British HIV Association (BHIVA) produces guidelines on the management of pregnant women living with HIV in the UK. These national and international guidelines evolved substantially between 2000 and 2014, reflecting the growing body of evidence on the effectiveness of interventions to reduce vertical transmission. The mechanisms of ART and its role in preventing vertical transmission are discussed in detail in Chapter 2. The remaining interventions are reviewed here.

Antenatal screening for HIV in the UK

In 1994, the Department of Health recommended screening of all pregnant women for HIV in areas of high prevalence in the UK, and elsewhere to those of higher risk (Department of Health 1994), but in 1996 only 13.5% of women who were unaware of their infection were diagnosed by the time of delivery (Unlinked Anonymous Surveys Steering Group 1997). A subsequent audit published in 1998 found that uptake of testing was less than 10% in over 65% of units, and recommended the normalisation of antenatal HIV screening for all pregnant women in the UK (Tookey et al. 1998). This recommendation was adopted into Department of Health guidance in 1999, with a target to achieve 50% uptake by end of 2000 and 90% by end of 2002 (Department of Health 1999). Nearly all (99%) maternity units had implemented universal HIV screening for pregnant women by the end of 2003, with 36% reaching the 90% uptake target (Townsend, Cliffe, and Tookey 2006). By 2008, estimated uptake of testing had risen to 95% of pregnant women, and in 2012 was 98% (Public Health England 2013).

Antenatal screening for HIV is now part of the Infectious Diseases in Pregnancy Screening (IDPS) programme run by the National Screening Committee (NSC), under the auspices of Public Health England. Antenatal HIV testing during pregnancy in the UK remains entirely voluntary, with an 'opt-out' approach. It is offered by the midwife at the first antenatal 'booking' appointment along with other screening tests recommended by the UK National Screening Committee. Although women who decline the offer of HIV screening in pregnancy are followed up (see Chapters 4, 7 and 8), women (with capacity) retain the autonomy to decline this test. There is currently no national guidance on the testing of asymptomatic infants whose mother has declined HIV testing in pregnancy.

Obstetric management in pregnant women living with HIV

In the pre-cART era, a randomised clinical trial found that elective caesarean section (CS) prior to the onset of labour substantially reduced the risk of MTCT (Read and Newell 2005; The European Mode of Delivery Collaboration 1999). Observational data suggest there is no reduction in MTCT rates for women on cART with a VL <50 copies/ml who have elective CS compared to vaginal delivery (Townsend et al. 2014), and CS is associated with greater morbidity to both mother and infant (Read and Newell 2005). The ANRS French Perinatal Cohort found that there was no difference

in MTCT rates with elective CS or vaginal delivery in women with VL <400 copies/ml (Warszawski et al. 2008), whereas the European Collaborative Study reported that elective CS reduced MTCT risk by 80% in women with VL <400 copies/ml(European Collaborative Study et al. 2010). These conflicting findings may be due to variation in the spread of actual VL within the VL group as a result of differing limits of detection between VL assays (women in the French study may well have clustered at the bottom of the range); therefore, the findings of the French study cannot be said to apply to women with VL 50-400 copies/ml with VL assays in current use in the UK (Taylor et al. 2012). The most recent UK data suggests that for all modes of delivery, risk of MTCT was higher when VL was 50-399 copies/ml than when <50 copies/ml; the rate of transmission following elective CS was 0.77% compared to 1.6% following planned vaginal delivery, although this did not reach statistical significance and was likely underpowered due to a very small number of observations (Townsend et al. 2014).

Since 2012, women who have a VL <50 copies/ml at 36 weeks' gestation are recommended to have a vaginal delivery in the absence of obstetric contraindications, with this having been an option since 2005 (Taylor et al. 2012; Hawkins et al. 2005). Although there is similar guidance in France, recent data have shown that women with a suppressed VL and eligible for a vaginal delivery were less likely to deliver vaginally outside of the Paris area (Briand et al. 2013). Similarly, a preliminary analysis of UK data demonstrated wide variation in the proportion of women with an undetectable VL delivering vaginally in recent years, this effect was associated with the size of the unit's caseload of pregnant women with HIV: women delivering at units with a smaller caseload were less likely to deliver vaginally (Peters and Tookey 2014). This suggests that less experienced obstetricians may not be confident offering women with an undetectable VL vaginal delivery, even though this is now recommended in national guidance.

Infant post-exposure prophylaxis

Infant post-exposure prophylaxis (PEP) has been an essential component of the battery of interventions to reduce vertical transmission since the ACTG 076 trial, which used six weeks infant zidovudine monotherapy in conjunction with maternal zidovudine monotherapy and showed a significant reduction in transmission rates (Connor et al. 1994). In the 2014 update of the BHIVA pregnancy guidelines, twice-

daily zidovudine monotherapy was recommended for infants born to women with delivery VL <50 copies/ml, for a reduced duration of four weeks to minimise potential adverse effects (Guidelines writing group 2014). It was recommended that neonates born to women who were untreated or had a delivery VL >50 copies/ml were treated with a combination of three drugs, tailored to any genotypic resistance identified in the maternal virus. This was based on the findings of the randomised controlled trial published in 2012, which found that infant zidovudine monotherapy for six weeks was inferior to both zidovudine plus 3 doses of nevirapine, and to zidovudine plus nelfinavir and lamivudine for the first 2 weeks in infants born to women who were untreated in pregnancy living in the Americas and South Africa (Nielsen-Saines et al. 2012). The intrapartum transmission rates were 4.8% (95% CI 3.2 – 7.1%); 2.2% (95% CI 1.2-3.9, p=0.046); and 2.4% (95% CI 1.4-4.3%, p=0.046) respectively. In multivariable analysis, infant zidovudine monotherapy was independently associated with transmission of HIV (Nielsen-Saines et al. 2012).

Infant feeding

Exclusive breastfeeding reduces morbidity and mortality in both HIV exposed and HIV unexposed infants in LMIC. It has been estimated that breastfeeding could prevent half of diarrhoeal and a third of respiratory illnesses in infants living in LMIC (Victora et al. 2016). In settings with high HIV prevalence and where formula feeding is not "*available, feasible, affordable, sustainable*, and *safe"*, breastfeeding improves HIV-free survival by improving nutrition and growth and protecting against serious infections (World Health Organization et al. 2010). The WHO recommends that all women with HIV take cART and are supported to breastfeed their babies until 12 months of age (exclusively for the first six months) (World Health Organization and UNICEF 2016). The WHO guidance is adopted primarily by LMIC countries with high rates of diarrhoeal illnesses and mortality in infancy.

The risk of postnatal HIV transmission from untreated women is cumulative, and estimated to be 5-10% (Read et al. 2004) and it is higher with mixed feeding than exclusive breastfeeding (mixed with additional foodstuffs rather than formula) (Coutsoudis et al. 2001; Iliff et al. 2005; Coovadia et al. 2007). In women not receiving effective ART, the complete avoidance of breastfeeding reduces the risk of vertical transmission (Horvath et al. 2009; Nduati et al. 2000) and can eliminate the risk of postnatal transmission. Table 1.1 summarises studies investigating postnatal

transmission rates in breastfeeding women living with HIV. In a seminal trial conducted in Nairobi, in which women not in receipt of ART were randomised to either breastfeed or formula feed their babies, the transmission rates at the end of 24 month follow-up were 36.7% (95% CI 29.4% to 4.4%) in the breastfeeding group (median duration breastfeeding 17 months), and 20.5% (95% CI 14-27%) in the formula feeding group (p=0.001) (Nduati et al. 2000).The lowest rate of transmission at 6 months in the studies listed in Table 1-1 was from the Mma Bana study. In this study, women were randomised to receive either Trizivir (abacavir / zidovudine / lamivudine) or zidovudine/lamivudine plus ritonavir-boosted lopinavir initiated at 26-34 weeks and continued to 6 months postpartum (continued in women with CD4 count < 200 cells/uL). Infants received 6 weeks zidovudine monotherapy plus stat dose nevirapine at birth. The 6-month transmission rates were 2.1% in the Trizivir arm, and 0.3% in the PI-based ART arm.

Although the precise mechanisms of HIV transmission through breastfeeding are incompletely understood, transmission most likely occurs through multiple pathogenic pathways relating to high levels of both cell-free and cell-associated virus (Van de Perre et al. 2012). High levels of cell-associated virus may be more strongly linked with transmission in women not on cART (Ndirangu et al. 2012). There is evidence that cART does not entirely suppress cell-associated HIV DNA in breast milk despite suppression in plasma (Lehman et al. 2008; Shapiro et al. 2005), and activated CD4 T-cells producing HIV have been detected in the breast milk of women on cART with undetectable plasma VL (Valea et al. 2011), possibly because mammary epithelial cells may represent a non-T cell reservoir of HIV (Kandathil, Sugawara, and Balagopal 2016). However, in a recent study of 221 breastfeeding mothers in Malawi looking at paired plasma and breast milk RNA, none of the mothers with suppressed plasma virus transmitted to their babies (Davis et al. 2016).

Guidance for women living with HIV in the UK and other high income countries (HIC) advises avoidance of breastfeeding to reduce the risk of transmission via breast milk (Taylor et al. 2012; European Aids Clinical Society 2017; Society of Obstetricians and Gynaecologists Canada 2014). Up until BHIVA released their position statement on infant feeding in 2010, guidance was that women living with HIV thought to be breastfeeding their baby against medical advice should be reported to child safeguarding services. The statement changed this: women with undetectable VL and

good adherence to ART who chose to breastfeed their baby despite medical advice should be supported to do so with careful monitoring up to the age of six months (BHIVA CHIVA writing group 2010).

Audit of perinatal HIV in children born in England 2000-2005

In 2007 a national audit was carried out jointly by the NSHPC, the Audit Information and Analysis Unit for Specialised Services, and the Children's HIV Association (CHIVA), to look at the continuing problem of perinatal HIV infection despite the success of the antenatal screening programme(NSHPC, Audit Information Analysis Unit, and CHIVA 2007). The audit was devised to explore the circumstances surrounding 87 cases of MTCT in children born in England 2000-2005, of whom 54 were born to women who had not been diagnosed with HIV by delivery. Box 1.2 indicates some of the key recommendations in the audit report. The findings of this audit were fed into the IDPS programme standards, BHIVA guidelines on the management of HIV in pregnant women, and the CHIVA guidelines on managing HIV in children.

Box 1.2. Some of the key recommendations from the Audit of Perinatal HIV 2007 (NSHPC, Audit Information Analysis Unit, and CHIVA 2007).

- Women who decline antenatal HIV screening should be formally reoffered the test on a least one more occasion by a member of the team with specialist training
- Positive test results should be given in person within two weeks of testing
- Blood tests carried out after 20 weeks gestation should be processed urgently
- There should be a clear pathway for communicating and following up positive test results at all centres
- Women with adverse social circumstances should be identified and supported by the multidisciplinary team
- Women presenting in labour with unknown HIV status should be offered rapid testing
- Where a child is diagnosed with HIV, the paediatrician should seek permission from the mother to inform the obstetric unit of the transmission, so that procedures can be reviewed

Table I-1. Summary of observational and clinical trial data on risk of vertical transmission with breastfeeding in low-income countries 2000-2010 Adapted from (Byrne and Orkin 2017)

Study[3]	Design	Setting	Enrolment	Number of mother-infant pairs	cART regimens[4]	Estimated vertical transmission rate 6 months after delivery (per 1000 live births)
Nduati et al	RCT	Kenya	1992-1998	401	nil	28 (breastfeeding group) 16 (formula feeding group)
Mitra Plus	Prospective cohort	Tanzania	2004 -2006	378	ZDV/3TC/NVP	10
Marazzi et al	Prospective cohort	Mozambique	2005 - 2007	313	ZDV/3TC/NVP	6
Amata	Prospective cohort	Rwanda	2005 - 2007	227	D4T/3TC/NVP or ZDV/3TC/EFV	5
Mma Bana	RCT	Botswana	2006 - 2008	263	ZDV/3TC/LPV-r	3
BAN	RCT	Malawi	2004 - 2008	803	ZDV/3TC + NVP or NFV or LPV-r	26
Kesho Bora	RCT	Burkina Faso, Kenya, South Africa	2005 - 2008	349	ZDV/3TC/LPV-r	16

[3] Nduati et al (Nduati et al. 2000); Mitra Plus (Kilewo et al. 2009); Marazzi et al (Marazzi et al. 2009); Amata (Peltier et al. 2009); Mma Bana (Shapiro et al. 2013); BAN ; Kesho Bora (The Kesho Bora Study group 2011)
[4] ZDV: zidovudine; 3TC: lamivudine; D4T: stavudine; NVP: nevirapine; EFV: efavirenz; LPV-r: ritonavir-boosted lopinavir; NFV: nelfinavir

1.2.4 Women growing up with perinatal HIV

Huge advances in treatment have increased life expectancy for both adults and children infected with HIV (Nakagawa, May, and Phillips 2013), and dramatically reduced morbidity and mortality (Judd et al. 2007). The first generation of children surviving the epidemic has grown up to adulthood, and in addition there are 2.1 million adolescents aged 10 to 19 years living with HIV, with HIV believed to account for the largest number of deaths among female adolescents in the world (WHO 2014b). As the number of newly infected children reported each year in the UK falls, the average age of the cohort has risen: 31% of the nearly 2000 young people living with HIV were aged over 16 by in 2013 (CHIPS annual report 2012-13).

The aims of treatment for children and young people with HIV have progressed significantly over the last decade, moving far beyond limitation of short-term morbidity and mortality to optimizing health status for adult life and minimizing the impact of chronic HIV infection on immune system development and health in general(Bamford et al. 2015). With improvements in treatment and survival, the emphasis of care of young people living with perinatally-acquired HIV (PHIV) has shifted to the management of adherence, complex resistance, transition of care to adult services, long-term drug toxicity and sexual and mental health (Bamford and Lyall 2015).

The prevalence of sexual activity and risk-taking behaviour in young people with PHIV varies by setting. A multi-centre cohort in the US found lower rates of sexual activity in young people with PHIV compared to those with behaviourally-acquired HIV (BHIV), and factors associated with being sexually active were increasing age, having a boyfriend or girlfriend, and illicit drug use (Setse et al. 2011). A smaller single-centre US study found similar sexual risk behaviours between young people with PHIV or BHIV (Renaud et al. 2013). A US multi-centre cohort comparing young people with PHIV to those who were HIV-exposed but uninfected found a lower proportion sexually active in the former, but this did not reach statistical significance (Mellins et al. 2011). In the UK, a small cohort was noted to have higher rates of smoking, alcohol use, anxiety and depression, but lower sexual activity and drug use in adolescents with PHIV compared with HIV-negative adolescents (A Judd et al. 2013). A qualitative study of young people with PHIV in the UK showed high levels of

procreational intent, likely reflecting perceived improvements in HIV treatment and the risk of MTCT (Evangeli et al. 2014).

Pregnancy incidence rates in two cohorts of young women living with PHIV were lower than HIV-negative women of a similar age (Agwu AL et al. 2011; Brogly et al. 2007) and several studies have reported pregnancy outcomes in women with PHIV (Kenny et al. 2012a; Brogly et al. 2007; Agwu AL et al. 2011; Jao et al. 2015; Munjal et al. 2013; Badell et al. 2013; Thorne et al. 2007; Calitri et al. 2014). Half of the women described in a UK case series had problems with adherence during pregnancy(Kenny et al. 2012a), and other studies in the US have shown higher VLs during pregnancy but similar rates of MTCT compared to women with BHIV (Badell et al. 2013; Brogly et al. 2007; Munjal et al. 2013). Having a mother with PHIV was found to be an independent risk factor for low birthweight for gestational age and infants born to women with PHIV had lower length-for-age *Z*-scores (but not weight-for-age) in the first year of life compared to those born to women with BHIV (Jao et al. 2012; Jao et al. 2015). However, there is still a paucity of data on the pregnancy incidence and outcomes in this unique and high-risk group of young women.

2 ART and its use in pregnancy up to 2014

2.1 Introduction

The first drug licensed to treat HIV was zidovudine, a nucleoside reverse transcriptase inhibitor (NRTI) approved for use in 1987. However, although zidovudine monotherapy showed a reduction in VL, delayed progression to AIDS, and prolonged survival, the effect was temporary and did not significantly reconstitute immune function (Pau and George 2014). The first PI triple therapy trials demonstrated immunological recovery and sustained viral suppression (Lederman et al. 1998), and heralded the beginning of the highly active antiretroviral era.

By 2014 there were over 20 drugs licensed for the treatment of HIV in the UK, categorised according to mode of action: nucleotide/nucleoside reverse transcriptase inhibitors (NRTI); non-nucleoside reverse transcriptase inhibitors (NNRTI); PI; integrase strand transfer inhibitors (INSTI); a CCR5 inhibitor and a fusion inhibitor.

2.2 Mechanisms of action

Figure 2-1 illustrates the various stages of the HIV life cycle: HIV envelope glycoprotein gp120 attaches onto human chemokine receptors (CCR5 or CXCR4) on the CD4 cell surface; the viral and cell membranes fuse, allowing the viral proteins to enter into the cytoplasm; HIV RNA then transcribes into a double-stranded viral DNA, catalysed by the enzyme reverse transcriptase; the viral DNA enters the cell nucleus, and in the presence of the integrase enzyme, integrates into host genome; after successful integration, proviral polyproteins are made and cleaved by the viral enzyme protease, and infectious virions are formed (Pau and George 2014).

Antiretroviral drugs aim at halting viral replication at various stages of the HIV life cycle (Figure 2-1). Enfuvirtide is a fusion inhibitor which interferes with the fusion process by binding to the first heptad-repeat in the viral envelope glycoprotein gp41. However it is only available as an injectable with a high rate of injection-site reactions, so has very limited use in clinical practice (Pau and George 2014). The CCR5-inhibitor maraviroc selectively binds to human CCR5 receptors on the cell membrane, blocking the interaction of the HIV gp120 and the CCR5 receptor, and so

is only effective in CCR5-topic virus, again limiting clinical utility(Pau and George 2014). NRTIs inhibit HIV reverse transcriptase by incorporating into the nucleotide analogue causing DNA chain termination or by competing with the natural substrate of the virus, halting the conversion of viral RNA into double stranded DNA (Pau and George 2014). NNRTIs are non-competitive inhibitors of reverse transcriptase, resulting in a conformational change and thus decrease in action of the enzyme (Pau and George 2014). INSTIs block the enzyme integrase from catalysing the formation of covalent bonds between the host and viral DNA, preventing incorporation of the viral DNA into the host genome (Pau and George 2014). PIs bind to HIV proteases late in the HIV life cycle, blocking proteolysis and the formation of infectious virions (Pau and George 2014). See Table 2-1 for antiretroviral drugs licensed in the UK up to 2014.

Table 2-1. Antiretroviral agents licensed in the UK up to 2014

Drug names in grey were not recommended in the 2014 updated BHIVA pregnancy guidelines (Guidelines writing group 2014)

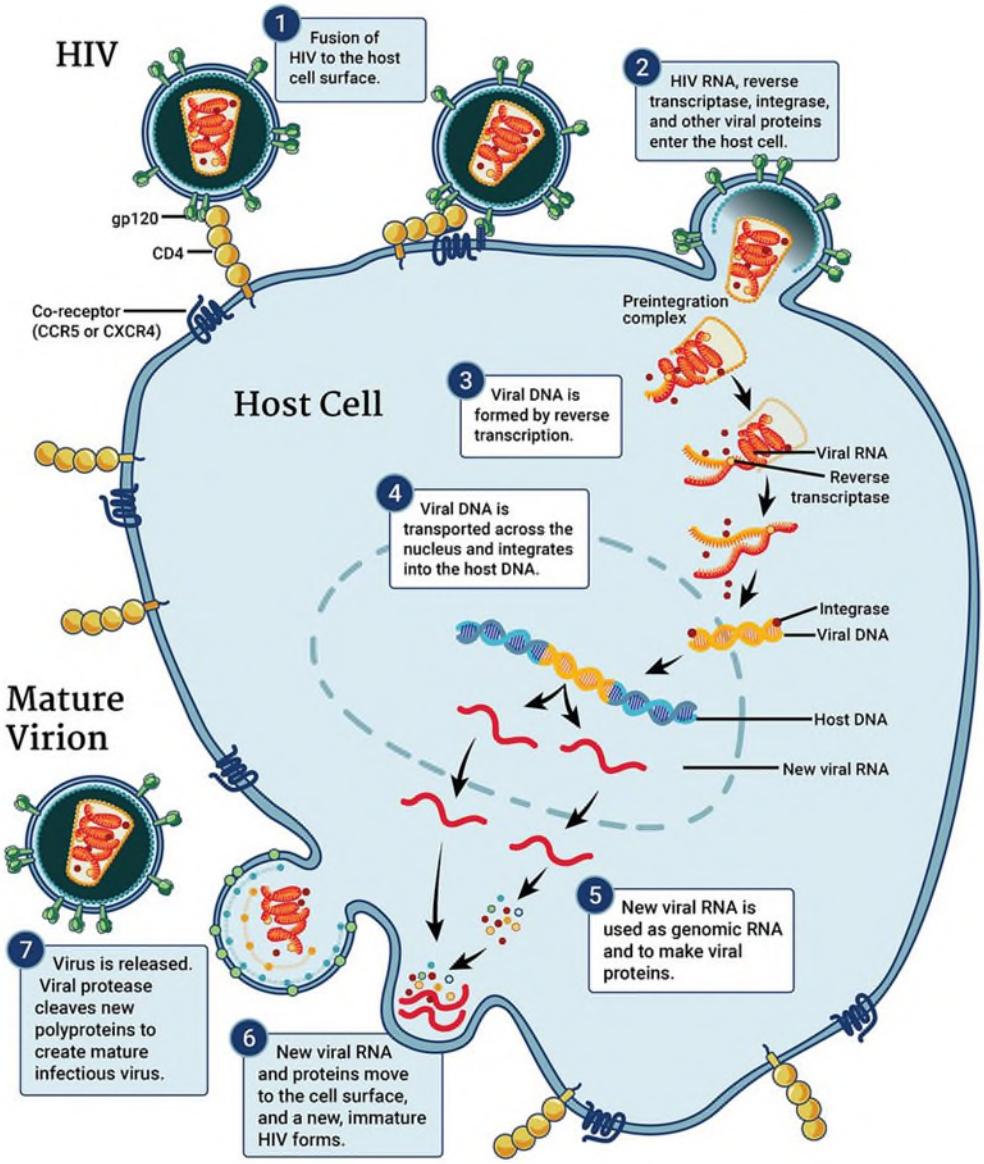
Drug class	CCR5 Antagonist	Fusion Inhibitor	NRTI	NNRTI	INSTI	PI
Drug name	Maraviroc	Enfuvirtide	Zidovudine	Nevirapine	Raltegravir	Saquinavir[6,8]
			Didanosine	Delavirdine	Elvitegravir[5,6]	Indinavir
			Zalcitabine	Efavirenz	Dolutegravir[7,6]	Ritonavir (high-dose)
			Stavudine	Etravirine[6]		Nelfinavir
			Lamivudine	Rilpivirine[6]		Amprenavir
			Abacavir			Lopinavir[8]
			Tenofovir			Fosamprenavir[6,8]
			Emtricitabine			Atazanavir[8]
						Tipranavir[6]
						Darunavir[6,8]

[5] Launched in the UK in 2013 as part of the co-formulation tenofovir DF + emtricitabine + elvitegravir + cobicistat
[6] Considered to be of unproven safety/efficacy in pregnant treatment-naïve women in 2014 BHIVA guidelines
[7] Launched in the UK Feb 2014
[8] Must be boosted with low-dose ritonavir

Table 2-2. Recommendations for first-line antiretroviral therapy in women who require treatment for their own health in BHIVA guidelines 2001-2018 (Mercy et al. 2001; Hawkins et al. 2005; de Ruiter et al. 2008; Guidelines writing group 2014; Gilleece and BHIVA pregnancy guidelines writing group 2019)

Year of guidelines	Recommended first line cART	Gestation at which ART is recommended to start by	Recommended mode of delivery for women with suppressed HIV
2001	"HAART" including zidovudine plus lamivudine plus PI/NNRTi	"Avoid first trimester"	Elective CS at 38 weeks
2005	"HAART containing zidovudine"	"After first trimester"	Elective CS at 38 weeks, or can 'opt' for SVD
2008	Zidovudine plus lamivudine plus PI/NNRTI	No recommendation	Elective CS at 38 weeks, or can 'opt' for vaginal delivery
2012	Zidovudine plus lamividine or tenofovir plus emtricitabine or abacavir plus lamivduine plus NNRTI	By week 24	Vaginal delivery
2018	Tenofovir plus emtricitabine or abacavir plus lamivudine plus efavirenz or atazanavir/ritonavir	Second trimester if baseline viral load <100,000 copies/ml First trimester if baseline viral load>100,000 copies/ml	Vaginal delivery

Figure 2-1. HIV replicative life cycle[9] (NIAID 2010)



[9] Figure reproduced under Creative Commons licence 2.0

2.3 The role of ART in pregnancy

The choice of ART regimen in an individual pregnant woman is based on a number of factors: efficacy in suppressing VL, preventing MTCT, and preserving maternal health; and, prior to the START trial results (The INSIGHT START Study Group 2015), whether the woman required cART for her own health (if her CD4 count was less than 350-500 cells/μL); ability of drugs in the regimen to cross the placenta and 'pre-load' the infant; possible adverse effects of antiretroviral drugs on the woman or pregnancy; possible adverse effects of the drugs on the foetus/infant; and the potential for the development of viral drug resistance. Worldwide, there are also programmatic and resource constraints to be considered (Aizire, Fowler, and Coovadia 2013; WHO and UNICEF Interagency Task Team 2007), as well as the public health effects of ART on onward transmission of HIV (Sigaloff, Lange, and Montaner 2014).

2.3.1 Mono- or dual therapy

The only antiretroviral drug to be licensed for use in pregnancy is zidovudine, for use in the third trimester. In 1994, the ACTG 076 study, a randomised double blind placebo-controlled trial of 409 mother-infant pairs, found that administration of the NRTI zidovudine to women with CD4 >200 cells/uL during pregnancy, labour and delivery, and to the infant after birth for six weeks led to a 68% relative risk reduction in MTCT (Connor et al. 1994). This reduced risk of MTCT with zidovudine monotherapy was replicated to different degrees in varying populations, with risk reductions of 30-60% in unselected observational studies (Mayaux et al. 1997; ECS 1998; Cooper et al. 1996; Wade et al. 1998). Further randomised controlled trials comparing zidovudine monotherapy, administered from different time points in pregnancy (and in some to the infant after birth), with placebo found significant reductions in transmission rates at 4-8 weeks of age in both breastfeeding and non-breastfeeding populations (Siegfried et al. 2011). This Cochrane review found that zidovudine monotherapy courses shorter than the ACTG 076 protocol were less effective, but nevertheless reduced transmission rates at 4-8 weeks of age (Siegfried et al. 2011). The most effective of the shorter courses was one of the regimens used in the PETRA RCT, set in a mostly breastfeeding population in sub-Saharan Africa. A combination of zidovudine with lamivudine given from 36 weeks' gestation,

continued through labour and for 7 days postpartum and given to the infant for the first week after birth resulted in estimated efficacy of around 63% (95% CI 41 to 85%) (Petra Study Team 2002).

Similarly, a single dose of the NNRTI nevirapine for both mother at the onset of labour and infant within 72 hours of birth was found to reduce MTCT by 50% in a breastfeeding population (Guay et al. 1999). However, PACTG 316 compared 'standard ART' alone (a mixture of zidovudine monotherapy and cART) to regimens with the addition of single-dose nevirapine after the onset of labour, and a single dose of nevirapine for the infant 48-72 hours after birth (Dorenbaum et al. 2002). This trial found no benefit for the addition of nevirapine and was stopped early due to lower-than-expected transmission rates.

Zidovudine monotherapy and single-dose nevirapine were combined into a regimen for women who did not require treatment for their own health, in resource-constrained settings, which continued as *Option A* in WHO guidelines for prevention of MTCT, until 2013 when it was recommended that all pregnant women be treated with cART if possible (referred to as *Option B+)* (WHO 2012; WHO 2013). In the UK, zidovudine monotherapy was an option reserved for women with a VL less than 10,000 copies/ml who did not require cART for their own health, in combination with elective CS unless they were elite controllers with a VL <50 copies/ml in the absence of treatment (Taylor et al. 2012). The use of zidovudine monotherapy to prevent MTCT in the UK declined from 12.2% 2000-2006 to 2.3% in 2007-2011 (Townsend et al. 2014). Although there was an option for adults who are suppressed on cART to simplify to monotherapy with a boosted protease inhibitor, this was not recommended for pregnant women (Taylor et al. 2012).

2.3.2 Triple drug cART

2.3.2.1 Women who required treatment for their own health

In the 2014 UK guidelines, women with CD4 less than 350 cells/μL were considered to require ART for their own health (Guidelines writing group 2014), and three drug cART had been the treatment of choice since it was first demonstrated to reduce VL to undetectable levels (Myers, Montaner, and INCAS Study Group 1996).

Women in the UK who required treatment for their own health were treated according to the adult treatment guidelines, which recommended a 'backbone' containing two NRTIs plus either one NNRTI or a PI (Ian Williams et al. 2014), with the caveat that there were very sparse data on the safety of newer agents in pregnancy and so these should be avoided if possible, as shown in Table 2-1. Drugs which were considered of unproven efficacy were the NNRTIs etravirine and rilpivirine, the INSTIs dolutegravir and elvitegravir, and the boosted PI darunavir. In addition, several older NRTIs were considered to have a prohibitive side effect profile, or risk of teratogenicity (didanosine, stavudine, zalcitabine); and unboosted PIs were not considered efficacious (Guidelines writing group 2014). Analysis of births in the UK up to 2011 found no difference in MTCT rates between PI and NNRTI-based regimens (Townsend et al. 2014). Table 2-2 shows some of the recommended PMTCT interventions recommended by BHIVA since the first guideline was published in 2001.

The NRTI backbone recommended was tenofovir plus emtricitabine, and second line was abacavir plus lamivudine, but only if the baseline VL was less than 100,000 copies/ml. The recommended NNRTI was efavirenz, or nevirapine if maternal CD4 was less than 250 cells/μL (nevirapine hypersensitivity is more common in women with CD4 > 250 cells/ μL (Coster and Kumar 2012)). Either atazanavir or darunavir were the recommended PIs, both given with a low dose of ritonavir which boosts plasma concentration. The INSTI raltegravir was a newer agent reserved as a third or fourth drug in women starting ART late in pregnancy with a high VL, since administration is associated with rapid VL decay (Trahan et al. 2015). Additional drug treatment, e.g. a single dose of nevirapine and an intravenous infusion of zidovudine during labour and delivery, were suggested for women presenting very late in pregnancy or in labour with a high VL. The addition of double-dose tenofovir was suggested in the situation of pre-term labour if the baby was unlikely to absorb oral medications, since it readily crosses the placenta (Guidelines writing group 2014).

Zidovudine has not been recommended as first-line treatment for adults with HIV infection in the UK since the revision of the national guidelines in 2008, because of concerns about, for example, twice-daily dosing, nausea, anaemia, and mitochondrial toxicity resulting in lipoatrophy and myopathy (Gazzard 2005; Waal, Cohen, and

Maartens 2013; Scruggs and Naylor 2008). An RCT directly comparing tenofovir plus emtricitabine to zidovudine plus lamivudine with efavirenz as a third agent found a greater proportion of people with virological suppression at week 96 in the tenofovir group, with a lower incidence of limb fat loss (Pozniak et al. 2006). The proportion of women on cART in pregnancy in the UK increased from 82.3% in 2000-2006 to 96.3% 2007-2011 (Townsend et al. 2014). As a result of these changes in prescribing and the increase in the proportion of women conceiving on cART, although there was most experience with a zidovudine-containing NRTI backbone in pregnant women worldwide, the proportion of women in Europe conceiving on zidovudine-sparing cART increased from 15% to 31% 2000 to 2009 ($p<0.001$)(Tariq et al. 2011). There was also a more modest increase in the proportion of women initiated on zidovudine-sparing cART during pregnancy from 4% to 12%; no difference was found in MTCT rates or the proportion of women who achieved undetectability between regimens that contain or spare zidovudine (Tariq et al. 2011).

2.3.2.2 Women who did not require treatment for their own health

In 2014, UK guidance was that women with CD4 count between 350 and 500 cells/μL could continue cART after delivery, and should be recommended to continue at this CD4 threshold if there was co-infection with hepatitis B or C (Guidelines writing group 2014). It was recommended that cART be discontinued if maternal CD4 count was greater than 500 cells/μL, unless there was discordance with her partner or hepatitis co-infection (i.e. START). For women on START the recommended combination was two NRTIs plus a PI, to minimise the risk of drug resistance developing at cessation of therapy (Guidelines writing group 2014). NNRTIs were avoided in this situation since they have a low genetic barrier to resistance, and a long half-life (Guidelines writing group 2014).

2.3.2.3 When to start cART in pregnancy

The advice on when to start cART in women not on cART at conception has evolved since 2000; in the 2001 BHIVA pregnancy guidelines, women who required cART for their own health were advised to start after the first trimester if possible, and women who were to take START were recommended to commence in the late second trimester; the 2005 and 2008 guidelines recommended commencing START between 20 and 32 weeks' gestation (Mercy et al. 2001; Hawkins et al. 2005; de Ruiter et al.

2008). In 2008, a multi-centre prospective cohort in France reported that longer duration of cART was associated with lower risk of MTCT (Warszawski et al. 2008), and the NSHPC reported a similar association between duration of cART and risk of vertical transmission in reported live births 2000 to 2006, with an estimated 10% reduction of risk for every week of cART, in women not on cART at conception (adjusted OR.0.90, 95% CI: 0.84–0.97, p=0.007) (Townsend et al. 2008). A retrospective multicentre analysis of 378 pregnancies in the UK found that when baseline VL was >10,000 copies/ml, initiation of cART after 20.4 weeks gestation made achieving an undetectable VL at delivery less likely (p=0.011) (Read et al. 2012).

The most recent analysis of NSHPC prospective national surveillance data in the UK of births 2000-2011 showed that duration of cART was strongly associated with risk of vertical transmission, with an initial rapid decline for every additional week of cART, up to about 15 weeks of treatment (Townsend et al. 2014). The probability of vertical transmission varied considerably by baseline VL, leading the authors to support the current BHIVA guidance to initiate cART earlier in women with VLs greater than 100,000 copies/ml. The 2014 guidance was that women not on cART at conception should start as soon as possible if they require treatment for their own health and that all women should start by 24 weeks gestation (Guidelines writing group 2014).

2.4 Birth outcomes in women living with HIV

2.4.1 Preterm birth and stillbirth in untreated women

Preterm births are those which occur before 37 weeks' gestation (Winson and McDonald 2005). Preterm birth occurs in approximately 9.6% of births worldwide, with the highest rates in Africa (11.9%) and North America (10.6%), and the lowest in Europe (6.2%), and is associated with significant infant mortality and short- and long-term morbidity (Beck et al. 2010). Preterm births account for 75% of perinatal mortality and more than half the long-term morbidity; although most preterm babies survive, they are at increased risk of neurodevelopmental impairments and respiratory and gastrointestinal complications (Goldenberg et al. 2008). Preterm births fall into 3 categories: 1) preterm delivery by induction or pre-labour caesarean section for maternal or foetal indications; 2) spontaneous pre-term labour with intact

membranes and 3) pre-labour premature rupture of membranes, irrespective of mode of delivery (PPROM)(Goldenberg et al. 2008). PPROM is more common in women of Black ethnicity (Goldenberg et al. 2008). The causes and mechanisms of preterm labour and PPROM are incompletely understood; the pathological processes implicated are infection, ischaemia, uterine overdistension, cervical disease, abnormal allograft reaction, allergic phenomena and endocrine disorder (Romero et al. 2006). However, certain risk factors have been elicited: Black ethnicity; short interpregnancy interval, previous preterm birth, low body mass index (BMI), multiple pregnancy, vaginal bleeding from placental abruption or praevia, oligo- or poly-hydramnios, psychological or social stress, smoking, intrauterine infection, and cervical shortening or insufficiency (Goldenberg et al. 2008).

Untreated HIV infection is also independently associated with increased risk of preterm birth; and additionally women living with HIV have a higher prevalence of established risk factors (Short and Taylor 2014). Lower CD4 count, advanced clinical disease, and detectable HIV viremia have all been shown to increase risk further (Short and Taylor 2014). A meta-analysis of studies in untreated women living with HIV (recruited between 1983 and 2006) from both sub-Saharan Africa and the Americas found a relative risk of pre-term birth of 1.50 in 14 prospective cohort studies (95% CI: 1.24 to 1.82) and 1.82 in 8 retrospective cohort studies (95% CI: 1.41 – 2.34) (Wedi et al. 2016).

The International Classification of Disease 10th revision (ICD10) defines stillbirths as late foetal deaths (from 28 weeks' gestation) or early foetal deaths (from 22 weeks' gestation), although definitions in the literature do vary (Lawn et al. 2016). Worldwide, it has been estimated that post-term pregnancy (>42 weeks' gestation) is the factor with the highest population attributable risk (14%); with pre-existing hypertension, overweight/obesity and pre-existing diabetes all contributing around 10%; maternal age over 35 years contributes around 7% (Lawn et al. 2016). Eclampsia and pre-eclampsia, active and passive smoking, bacterial and viral infections and medical disorders such as thyroid and liver disease are also implicated. In sub-Saharan Africa, which has the highest stillbirth rate worldwide at an estimated 28.7

per 1000 births (uncertainty range 25.1 to 34.2[10]), malaria has an attributable risk estimated at 20%, and syphilis 11% (Lawn et al. 2016).

Data on the attributable risk of HIV infection was noted to be sparse, but the authors of the same review and meta-analysis estimated it to be 0.7% in sub-Saharan Africa (uncertainty range 0.6 – 0.8%)(Lawn et al. 2016), based on national data from the South African surveillance programme births 2012-2013 (coverage of cART in pregnancy unknown) (Pattinson, Rhoda, and PPIP Study Group 2014). Several studies in untreated women living with HIV have shown higher rates of stillbirth, with one meta-analysis of 14 pre-cART era prospective studies estimating an odds ratio of 3.91 (CI: 2.65-5.77) in a total of 1936 women living with HIV and 28,363 HIV-negative women, but with noted heterogeneity between studies (Brocklehurst and French 1998). A later meta-analysis on perinatal outcomes only included two studies with stillbirth rates, and estimated a relative risk of HIV of 1.67 (95% CI: 1.05 – 2.66) (Wedi et al. 2016).

2.4.2 Preterm birth and stillbirth in women on ART

Preterm birth

Data on the possible effects of ART on preterm birth are conflicting. Several European cohort and national surveillance studies have shown an increased risk of preterm birth in association with cART. The European Collaborative Study (ECS) found that antenatal cART was strongly associated with preterm birth in over 4000 births in 2000-2004, with an adjusted odds ratio (AOR) of 1.88 for cART started during pregnancy (95% CI 1.34 – 2.65), and 2.05 for cART started before pregnancy (95% CI 1.43 – 2.95) compared with 1.0 for mono/dual therapy, and the effect was even more pronounced in severe prematurity (Thorne, Patel, and Newell 2004). Data from UK surveillance 1990-2005 showed increased risk of preterm birth in women on cART (AOR 1.51; 95% CI 1.19 to 1.93) compared to mono or dual therapy, and this association was even stronger for preterm birth before 35 weeks' gestation, with no

[10] This paper used maximum likelihood estimation, and uncertainty estimates were generated sing a bootsrap approach (Blencowe et al. 2016).

association between timing of treatment initiation and rate of preterm birth (Townsend et al. 2007).

A meta-analysis of 13 cohort studies In Europe, South and North America found no overall increase in risk of preterm birth in women on cART, but did note a modest increase in risk with PI versus non-PI based cART, and cART initiated before or early in pregnancy (AOR 1.71; 95% CI: 1.09 – 2.67) (Kourtis et al. 2007). However, it has been noted that there were several issues with the data included in this meta-analysis: significant heterogeneity between study populations; comparisons with women not on cART; failing to adjust for potential confounders, and dual and triple therapy being grouped together (Townsend et al. 2007). A pooled analysis of European data and the Paediatric Spectrum of HIV Disease Consortium in North America showed an increased risk of preterm birth in women on cART compared to those on dual therapy (AOR 1.5; 95% CI 1.19 – 1.87), and noted the heterogeneity of the two populations (Townsend et al. 2010). One of the issues in comparing women on cART with untreated women is that pre-term delivery may increase the likelihood that a woman is left untreated in pregnancy, and it has been argued that the comparison of women on cART to those on mono- or dual therapy is more valid (Townsend et al. 2010).In addition, the choice of therapy (mono-, dual or cART) in non-randomised trials may be indicated by the health status of women, introducing a potential source of bias. Although correction for CD4 count and the presence of symptoms may be used as a proxy for health status, this does not eliminate the potential for bias by indication (Townsend et al. 2010).

Multicentre surveillance data from the French Perinatal Cohort has shown an increase in the rate of preterm birth over time between 1990 and 2009 and prematurity was associated with cART versus zidovudine monotherapy (AOR 1.69; 95% CI 1.38 – 2.07). They looked at a sub-group of women prescribed PI-based therapy initiated during pregnancy (n=1253) and found that women prescribed boosted PI regime versus unboosted PI based regime were more likely to deliver preterm (adjusted hazard ratio 1.76, 95% CI 0.97 – 3.19) (Sibiude et al. 2012). However, it is important to note that the majority of women in the analysis (85%) were taking a boosted PI, and the majority of these were on ritonavir-boosted lopinavir. The majority of women on an unboosted PI were taking nelfinavir, so it is unclear whether the difference in preterm birth risk between the two treatment

groups is an association with ritonavir-boosting, with the protease inhibitor, or whether it may an association with virological efficacy of the regimen.

Two randomised control trials in Africa have reported differing results: the Mma Bana study randomised women to take either triple NRTI or ritonavir-boosted lopinavir cART in Botswana, and in a secondary analysis found an increased risk in preterm birth among women on the boosted PI-based regimen (adjusted OR 2.02; 95% CI 1.25 – 3.27) (Powis et al. 2011). The Kesho Bora study found no difference in preterm birth rates between women randomised to either lopinavir/r-based cART or zidovudine monotherapy plus single dose nevirapine. However, in this study gestation at initiation of therapy was 34-36 weeks (before it was revised to 28 weeks' gestation after a change in WHO guidance) which is much later than most other studies (The Kesho Bora Study group 2011). Neither of these studies were designed to examine preterm birth as a primary outcome. Overall, it does seem as though an association between cART and preterm birth is likely, this may be an effect of ritonavir-boosted lopinavir (or boosted protease inhibitors overall, although most of the data is with lopinavir), and gestation at initiation of cART may also be important.

Several potential mechanisms for the association between cART and preterm birth have been postulated. Fiore et al suggested that the Th2 to Th1 cytokine shift seen with the introduction of cART in people with HIV may contribute: "*The feto-placental unit produces Th2 cytokines throughout pregnancy, inhibiting maternal Th1 activity and thus protecting the pregnancy…Maternal production of interleukin (IL)-2 (Th1) is directly associated with unsuccessful pregnancy as it activates cytotoxic activity. There is thus a balance of cytokine production between mother, placenta and foetus, and it is likely that relatively minor perturbations of this balance can have an impact on pregnancy*" (Fiore et al. 2006). This group studied levels of IL-2 (Th1) and IL-10 (Th2) in peripheral blood mononuclear cells during pregnancy in 49 women with HIV, and found increased IL-2 and decreased IL-10 after commencement of cART, as well as an independent association between incremental increase in IL-2 and risk of preterm birth (Fiore et al. 2006). Other factors may include the immune reconstitution seen with the introduction of cART, direct effects of cART on the placenta, and the materno-foetal hypothalamic pituitary axis (Short and Taylor 2014).

Stillbirth

Analysis of UK surveillance data showed a stillbirth rate of 12.7 per 1000 births following cART exposure, compared to 5.7 per 1000 following mono- or dual therapy exposure, although this difference did not reach statistical significance (OR 2.26, 95% CI 0.96-5.41) (Townsend et al. 2007). Similarly, several smaller studies have not found an increased risk of stillbirth by treatment regimen and it may be that these studies were underpowered due to the low frequency of stillbirth as an outcome (Tuomala et al. 2002; Cotter et al. 2006; Tuomala et al. 2005; Kreitchmann et al. 2014). Similar to the issues with interpreting observational data on preterm deliveries, confounding by indication may be an issue. A small study in Botswana looking at potential aetiologies of stillbirth in HIV-infected and uninfected women found a higher rate of placental insufficiency in HIV-infected women treated with cART and HIV-uninfected women, compared with HIV-infected women not on cART, although the significance of this finding remains unclear (Shapiro et al. 2012).

2.4.3 ART in early pregnancy and the risk of congenital abnormality

The evidence on whether exposure to antiretrovirals in early pregnancy increased risk of congenital abnormality evolved extensively over the period 2000 to 2014, as a result of the increasing proportion of women conceiving on ART. The Antiretroviral Pregnancy Registry (APR) is a prospective database of antiretroviral use and congenital abnormality based in the US, recording rates of congenital birth defects in babies born to women with first-trimester exposure to ART, in comparison to background rates of congenital birth defects and second- and third-trimester only exposures to the same compounds (Antiretroviral Pregnancy Registry Steering Committee 2015). Clinicians voluntarily register pregnant women with prenatal exposures to any ART and provide foetal/neonatal outcomes prospectively. The prevalence of birth defects is calculated by dividing the number of defects by the total number of live births and is compared to the prevalence in the CDC's population-based surveillance system (Metropolitan Atlanta Congenital Defects Program, MACDP) and the Texas Birth Defects Registry (TBDR). Additionally, first trimester exposures, in which organogenesis occurs, are compared with second/third trimester exposures. Overall, a cohort of 200 exposed newborns is required to detect a doubling of overall risk, with 80% power and a Type I error rate of 5%; however for

the subgroup of CNS and eye defects (which includes, e.g. neural tube defects), around 2000 exposed births would need to be evaluated to detect a two-fold increase (Covington et al. 2004). Each year the APR enrols approximately 1300 pregnant women in the US exposed to ART (approximately 15% of the 8,700 HIV positive women who give birth to live infants annually in the US), with only 15% of reports originating from non-US countries (Antiretroviral Pregnancy Registry Steering Committee 2015).

For abacavir, darunavir, didanosine, efavirenz, indinavir, and stavudine, sufficient numbers of first trimester exposures have been monitored to detect at least a two-fold increase in risk of overall birth defects. For atazanavir, emtricitabine, lamivudine, lopinavir, nelfinavir, nevirapine, ritonavir, tenofovir, and zidovudine sufficient numbers of first trimester exposures have been monitored to detect at least a 1.5-fold increase in risk of overall birth defects and a 2-fold increase in risk of birth defects in the more common classes, cardiovascular and genitourinary systems. No increases were detected in any of these drugs (Antiretroviral Pregnancy Registry Steering Committee 2015).

For didanosine and nelfinavir, there was a modest but statistically significant increase in overall rates of defects when compared with the MACDP though not the TBDR, but no consistent pattern of birth defects was detected with didanosine or nelfinavir and the clinical relevance of this statistical finding is unclear (Antiretroviral Pregnancy Registry Steering Committee 2015). By the end of 2014, the drugs raltegravir, etravirine, maraviroc, and less commonly used older compounds saquinavir, fosamprenavir, enfuvirtide and tipranavir did not have sufficient outcomes data to excluded such risk (Antiretroviral Pregnancy Registry Steering Committee 2015).

Concerns related to efavirenz dated back to pre-clinical animal studies that were not conducted with any other ART. Twenty cynomolgus macaques were exposed to efavirenz during early pregnancy, and three of the 20 offspring had significant abnormalities at birth: one with anencephaly and anophthalmia; the second with microphthalmia; and the third with a cleft palate (Nightingale 1998). Consequently, efavirenz was classified as category C by the US Food and Drug Administration (FDA)

[11]and it was recommended that efavirenz should not be prescribed to women of child-bearing potential. After the re-classification of efavirenz, the APR received reports of seven abnormalities in 281 cases, including three reports of myelomeningocele and one of Dandy-Walker syndrome. These abnormalities had been reported retrospectively. This led to efavirenz being re-classified as category D, indicating an established risk to the human foetus. A review by R Brent in the journal *Paediatrics* stated "*There is no question that whole animal teratology studies are helpful in raising concerns about the reproductive effects of drugs and chemicals, but negative animal studies do not guarantee that these agents are free from reproductive effects. There are examples in which drug testing was negative in animals (rat and mouse) but was teratogenic in the human (thalidomide), and there are examples in which a drug was teratogenic in an animal model but not in the human (diflunisal)"* (Brent 2004).

However, since these efavirenz animal studies were published, robust prospective evidence has emerged indicating that there is no increased risk of any defect with first-trimester efavirenz exposure. As well as the APR data for efavirenz referred to above, in 2014 an updated systematic review and meta-analysis of 23 observational cohorts reported birth outcomes among women exposed to efavirenz during the first

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[11] The FDA's ABCDX catagorisation for risk in pregnancy stated "*For pregnancy category C, if animal reproduction studies have shown an adverse effect on the fetus, if there are no adequate and well-controlled studies in humans, and if the benefits from the use of the drug in pregnant women may be acceptable despite its potential risks, the labeling must state: Pregnancy Category C. (Name of drug) has been shown to be teratogenic (or to have an embryocidal effect or other adverse effect) in (name(s) of species) when given in doses (x) times the human dose. There are no adequate and well-controlled studies in pregnant women. (Name of drug) should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus*" (Food and Drug Administration 2008). This labelling system was abolished from 2015, and has been replaced with a system that requires a description of risk information, clinical considerations, and background data (Food and Drug Administration, HHS 2014).

trimester (Ford et al. 2014) (previous versions of this systematic review were published in 2010 and 2011). The primary endpoint was a birth defect of any kind and the analysis found no increased risk of overall birth defects among 2026 women exposed to efavirenz during first trimester (n = 44, 1.63% 95% CI 0.78–2.48%) compared with exposure to other antiretroviral drugs. Only one neural tube defect was observed with first-trimester efavirenz exposure, giving an estimated prevalence of 0.05% (95% CI < 0.01–0.28%); the estimated prevalence in births in the general population in Europe 1991 to 2011 was 0.1% (Khoshnood et al. 2015). Furthermore, the prevalence of overall birth defects with first-trimester efavirenz exposure was similar to the ranges reported in the general population.

Sibiude et al. published an analysis of the ANRS French perinatal cohort, analyzing just over 13,000 live births in women living with HIV 1994 – 2010. They looked at the prevalence of congenital abnormalities in infants born to women exposed to various antiretroviral drugs, from conception / in the first trimester, versus unexposed, or those only exposed after the first trimester. They found an increased risk of congenital abnormality in multivariable analysis of births with first trimester exposure to zidovudine (AOR 1.39, 95% CI: 1.06 – 1.83); didanosine (AOR 1.44; 95% CI 1.08 – 1.92); lamivudine (AOR 1.37; 95% CI 1.06 – 1.73); and indinavir (AOR 1.66; 95% CI: 1.09 – 2.53). There was a particular association between first trimester zidovudine exposure and congenital heart defects (AOR 2.3, 95% CI 1.3 – 3.4). There was no overall association between efavirenz and the prevalence of birth defects, and there was no particular pattern seen in the four differing neurological defects reported in children exposed to efavirenz in the first trimester (Sibiude et al. 2014).

There are challenges in analyzing exposures to ART in pregnancy and birth outcomes in observational cohorts: medical and obstetric practice changes with calendar period making historical controls problematic, drugs are given in common combinations due to co-formulation (e.g. zidovudine plus lamivudine), ART switching makes teasing out individual exposures challenging, and dealing with confounding by indication is very difficult. Many pregnancy cohorts have had varying capture of terminations and stillbirths, leading to the conundrum of inclusion or exclusion in analyses.

2.4.4 Other concerns regarding the health of HIV-exposed uninfected (HEU) infants

The reduction in perinatally-infected infants with increasing ART coverage for pregnant women, as shown in Figure 2-2 indicates the growing numbers of HEU children in LMIC born to women living with HIV. Concerns regarding the short- and long-term health of HEU infants are due to potential effects of HIV-exposure in utero or via breastmilk; direct toxicity of ART exposure in utero, via breastmilk or via post-exposure prophylaxis; and potential long term effects on normal development of this ART exposure. In infants who are both HIV- and ART-exposed, it is challenging to differentiate the significance of these varied exposures. Concerns include increased susceptibility to infections, especially skin, lower-respiratory tract infections (LRTI) and oral candidiasis; pre-term birth and growth and development; and other potential long term effects of *in utero* exposure to ART such as mitochondrial toxicity and possible effects on bone mineral density of *in utero* tenofovir exposure (Evans, Jones, and Prendergast 2016). The causes of increased morbidity and mortality are probably multifactorial, and might be partly driven by adverse environmental and socioeconomic conditions (Evans, Jones, and Prendergast 2016).

The apparent susceptibility of HEU children to infections was summarised in two reviews published in 2014 (Cotton, Slogrove, and Rabie 2014; Afran et al. 2014). The authors noted that HEU children have a higher prevalence of risk factors traditionally associated with morbidity: prematurity, low birth weight, and small-for-gestation, and that high maternal CD4 count is protective against infectious disease morbidity. Prior to the availability of ART in pregnancy in Zimbabwe, analysis of outcomes in the the ZVITAMBO cohort (recruited between 1997 and 2000) showed that the 2-year mortality of HEU children was more than three times greater than that of HIV-unexposed (HU) children (9·2% *versus* 2·9%); mortality for HEU children peaked at 3–6 months and was associated predominantly with LRTI (Marinda et al. 2007). Further studies in Africa then confirmed that mortality in HEU children is caused predominantly by LRTI of varied aetiology (Afran et al. 2014).

HEU children respond well to vaccination but have lower levels of vaccination-induced antibody to infections such as pertussis, tetanus, pneumococcus, *H. influenzae* B, measles and hepatitis B, between birth and vaccination. There is an estimated four-fold increased risk of *M. tuberculosis* infection, and a higher risk of

congenital CMV in HEU children (Cotton, Slogrove, and Rabie 2014). Several causes of immune dysfunction have been suggested, such as increased innate and adaptive immune cell activation and lower numbers and proportion of CD4 T cells, and lower circulating levels of specific antibodies (Evans, Jones, and Prendergast 2016). Both HIV-specific cytotoxic T-cell activity and CD4 helper T-cell responses have been reported in HEU infants, with greatest breadth and magnitude of responses reported soon after birth; these responses have not been detected in older children (aged 7 years) (Afran et al. 2014).

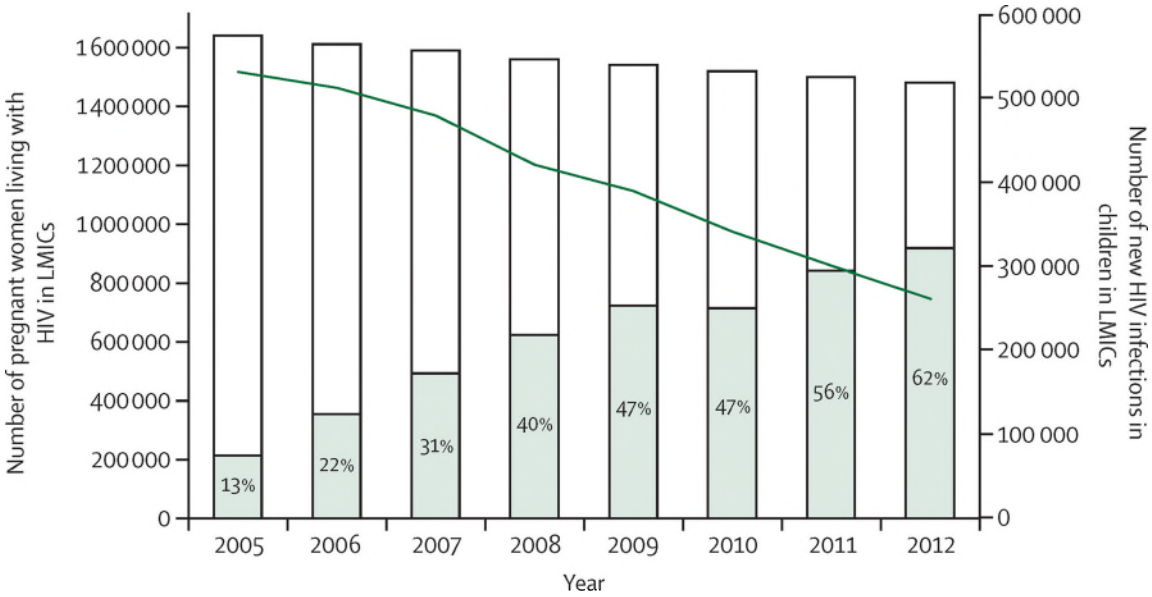
Mitochondria are cell organelles located in the cytoplasm of most eukaryotic cells; they are involved in many important cell processes, such as heat production, energy supply, cell respiration, calcium homeostasis, and the anabolism and catabolism of numerous metabolites, among others. However, in pathological conditions, mitochondria are also the main source of reactive oxygen species production and apoptosis (Morén et al. 2014). Mitochondrial toxicity caused by NRTIs is well-documented in adults on ART, especially with the older agents such as zidovudine, stavudine and didanosine; mitochondrial dysfunction induced by NRTIs is considered to result from direct inhibition of the mitochondrial polymerase, as well as drug-DNA incorporation and arrest of DNA replication(Morén et al. 2014). Clinically evident mitochondrial dysfunction is seen infrequently in HEU children, however cardiac effects have been noted, as well as the presence of biomarkers of mitochondrial dysfunction, and there are concerns regarding long-term neurodevelopment and possible increased cancer risk (Poirier et al. 2015). It is difficult to distinguish the effects of NRTI exposure from HIV exposure *in utero* when establishing the cause of indicators of mitochondrial dysfunction in later life of HEU children.

Reduction of bone mineral density with use of tenofovir disoproxil (TDF) in adults has been established (Grant et al. 2013), but long term follow-up data on the effect of TDF on neonatal and infant growth are sparse and conflicting (Wang et al. 2013). The DART trial (based in sub-Saharan Africa) showed no difference in TDF exposed or non-TDF exposed HEU infants growth outcomes from birth through infancy(Gibb et al. 2012). The US-based prospective cohort SMARTT study found no evidence for an increased risk of low birthweight or small-for-gestational age for TDF-exposed HEU infants, but did find a slightly lower mean head-circumference-for-age and length-for-age z-scores in HEU infants exposed to TDF (Siberry et al. 2012). The IMPAACT

P1025 prospective cohort did not demonstrate an increased risk of low birth weight or altered growth through 6 months of age among 2025 infants born in the US 2002-2011, although TDF exposure during the second- or third-trimester significantly predicted underweight at six months (weight-for-age z-score <5%) (Ransom et al. 2013) A much smaller US cohort looked at 74 TDF-exposed (in late pregnancy) infants and 69 non-exposed HEU infants at birth and found that late pregnancy tenofovir exposure was significantly associated with lower bone mineral content (as measured by bone densometry scans) at or shortly after birth (Siberry et al. 2015).

Figure 2-2. Reduction in perinatally HIV-infected infants with increasing PMTCT coverage, from (Evans, Jones, and Prendergast 2016)[12]

The number of pregnant women living with HIV in low-income and middle-income countries (white bars) declined between 2005 and 2012, from 1·64 million to 1·48 million. In the same period, the proportion of HIV-infected pregnant women receiving effective PMTCT interventions (green bars) increased substantially from 13% in 2005 to 62% in 2012, leading to a reduction in the number of HIV-infected infants (green line). The number of HIV-exposed uninfected infants is, therefore, increasing. Data from WHO and UNAIDS. LMICs=low-income and middle-income countries. PMTCT=prevention of mother-to-child transmission.



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2.5 HIV genetic variation and drug resistance

2.5.1 HIV-1 genetic diversity

The genetic variability of HIV is the result of the high error rate and recombinogenic properties of the reverse transcriptase enzyme during viral replication, together with the high turn-over of viral particles (Peeters, Jung, and Ayouba 2013). HIV-1 strains are divided in four groups (M, N, O and P), originating from four separate cross-species transmissions from chimpanzees and/or gorillas to humans. The current epidemic of HIV-1 worldwide is caused by group M virus; based on phylogenetic analysis, HIV-1 group M can be further subdivided into nine subtypes (A–D, F–H, J, K). Inter-subtype recombinant viruses are observed in many instances; these are classified as circulating recombinant forms (CRF) if there has been further spread of the recombinant viruses within the human population, and as unique recombinant forms (URF) if they remain restricted to a limited number of individuals. Currently, there are 58 CRFs and numerous URFs have been reported (Peeters, Jung, and Ayouba 2013). Figure 2-3 shows the geographical distribution of HIV-1 M subtypes in 2007.

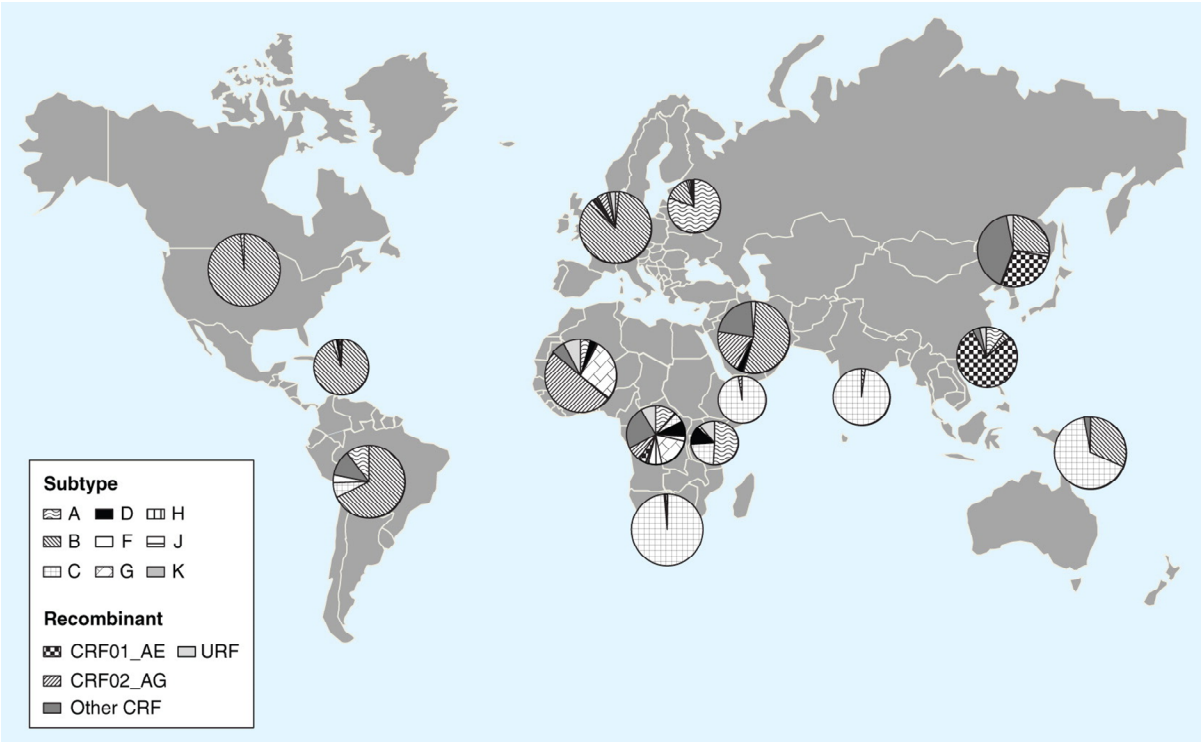
In Europe, HIV-1 subtype is closely related to the person's country of origin. Analysis of subtypes in European countries from sequences obtained between 2002 and 2005 showed that the proportion newly diagnosed with subtype B was higher in patients from Western Europe (76.6%), Latin America (78.2%) and Eastern Europe and Central Asia (86.6%) (Abecasis et al. 2013). In patients from South and South-East Asia, the most prevalent subtype was CRF01_AE (63.9%). In patients from Sub-Saharan Africa, almost all subtypes were found, but subtype C was most prevalent (31.2%). Subtype B was the most prevalent subtype in patients originating from North Africa and Middle East (58.3%), but subtype C was also a large group in these patients (16.7%)(Abecasis et al. 2013).

Analysis of HIV-1 subtypes in newly diagnosed individuals in the UK 2002 – 2010 showed that men who have sex with men (MSM) predominantly, though not exclusively, have subtype B virus (88.4%)(the UK Collaborative Group on HIV Drug Resistance 2014). In patients with heterosexually-acquired HIV, subtype C was the most frequent subtype, although a greater proportion of women (n = 12 789; 55.0%) had this subtype than men (n = 7331; 46.7%; $p < 0.001$) (the UK Collaborative Group on HIV Drug Resistance 2014). Subtype B infections were more common in

heterosexual men (n = 2947; 18.8%) than women (2246; 9.7%; p < 0.001). Subtype A was also frequent in those with heterosexual contact as well as a variety of CRFs. Finally, novel recombinants were frequent in both men and women and occurred in greater numbers within heterosexuals than MSM; this reflects historical differences in viral diversity between these population (the UK Collaborative Group on HIV Drug Resistance 2014). Trends over time were similar for black African men and women, with an increase in the proportion of patients diagnosed with non-B non-C subtypes and a decrease in the proportion of subtype C. The declining trend was most prominent for subtypes A, D and other CRFs, but was partially offset by an increase in the number of people infected with novel recombinant virus (the UK Collaborative Group on HIV Drug Resistance 2014). White heterosexual women were had roughly equal prevalence of subtype B, C and non-B non-C, whereas white heterosexual men were more likely to have subtype B infections (41.1% of overall infections) and proportionately fewer subtype C infections (22.5% of overall infections) compared with women (p<0.001) (the UK Collaborative Group on HIV Drug Resistance 2014).

There is evidence that HIV-1 subtype may be associated with speed of disease progression: two studies have suggested that people with subtype D are more likely to progress faster than those with subtype A (Camacho 2006; Amornkul et al. 2013). One study in Kenya found that the risk of vertical transmission was higher in women with subtype D than those with subtype A (relative risk 2.0, p=0.002) (Yang et al. 2003). Although overall, cART achieves excellent outcomes regardless of the infecting subtype (Geretti et al. 2009), some differences in disease progression and response to ART between subgroups have been suggested. Analysis of data from the Swiss cohort showed that in white patients with HIV-1 on cART, those with non-B subtypes were less likely to have virological failure than those with subtype B (adjusted hazard ratio 0.68, 95% CI 0.51 – 0.91) (Scherrer et al. 2011). A similar analysis of UK CHIC data estimated a hazard ratio of 0.78 in patients on cART with non-subtype B (unboosted PI regimens excluded), but this did not reach statistical significance (95% CI 0.4 – 1.4). The authors of this analysis suggested that the possible increased risk of virological failure was related to an increased risk of viral rebound after suppression, rather than a failure to suppress initially after the start of cART (Dolling et al. 2013).

Figure 2-3. The geographic distribution of HIV-1 M subtypes and CRFs circulating in 2007 (Peeters, Jung, and Ayouba 2013)[13]



2.5.2 HIV antiretroviral drug resistance

Mechanisms

Resistance to ART occurs if HIV continues to replicate in the presence of drug pressure or can be transmitted from person to person, and therefore be present at diagnosis of HIV (this is known as transmitted drug resistance (TDR))(Clutter et al. 2016). The development of drug resistance mutations (DRM) results from high rate of HIV-1 reverse transcriptase processing errors, recombination when multiple viral variants infect the same cell, and the accumulation of proviral variants during the course of infection (Clutter et al. 2016). The selection of virus containing DRMs depends on the extent to which viral replication continues during incompletely suppressive therapy, the ease of acquisition of a particular DRM, and the effect of DRMs on drug susceptibility and virus replication (Clutter et al. 2016). Although

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naturally occurring drug-resistant viruses arise every day in untreated patients, these variants occur mainly below the limit of detection because they are less fit than drug-susceptible viruses in the absence of selective drug pressure (Clutter et al. 2016). Indeed, nearly all clinically significant DRMs arise only as a result of selective drug pressure and are otherwise non-polymorphic. For some ART agents, multiple DRMs are required to reduce susceptibility, while for others a single DRM is sufficient (Clutter et al. 2016). Figure 2-4 illustrates potency of ART versus genetic barrier to resistance. In the absence of drug pressure, the viral population may revert to wild-type, but a small proportion of drug resistant strains persist below the limit of detection of current assays, and may emerge if drug pressure is re-introduced (Clutter et al. 2016).

Drug resistance testing

HIV-1 drug testing can be performed phenotypically or genotypically. Phenotypic *in vitro* susceptibility assays measure ART susceptibility in cell culture, but due to cost and lengthy turnaround time, phenotypic testing is usually reserved for drug development, drug resistance research or complex clinical cases (Clutter et al. 2016). Standard genotypic resistance testing involves the use of dideoxy terminator Sanger sequencing of protease, reverse transcriptase and/or integrase to identify clinically significant DRMs. The lower limit of standard genotypic resistance tests is generally agreed to be around 20%, but both point-mutation assays and next generation deep sequencing technologies often detect drug resistant variants at well below the 20% threshold, although the clinical significance of these are uncertain (Clutter et al. 2016).

Interpretation of genotypic resistance tests is complex, and the VL at the time of testing, time from last drug exposure and the treatment history of the patient are all important context. The Stanford HIV Drug resistance database (Rhee 2003) provides an online genotypic resistance interpretation resource to aid interpretation. DRMS can be inputted to the program, and this returns penalty scores based on DRM characteristics and the consensus of clinical significance of a DRM among experts in the field, such as the IAS-USA Drug Resistance Mutations Group (Wensing et al. 2014). An estimate of the efficacy of individual drugs is given, with explanatory notes.

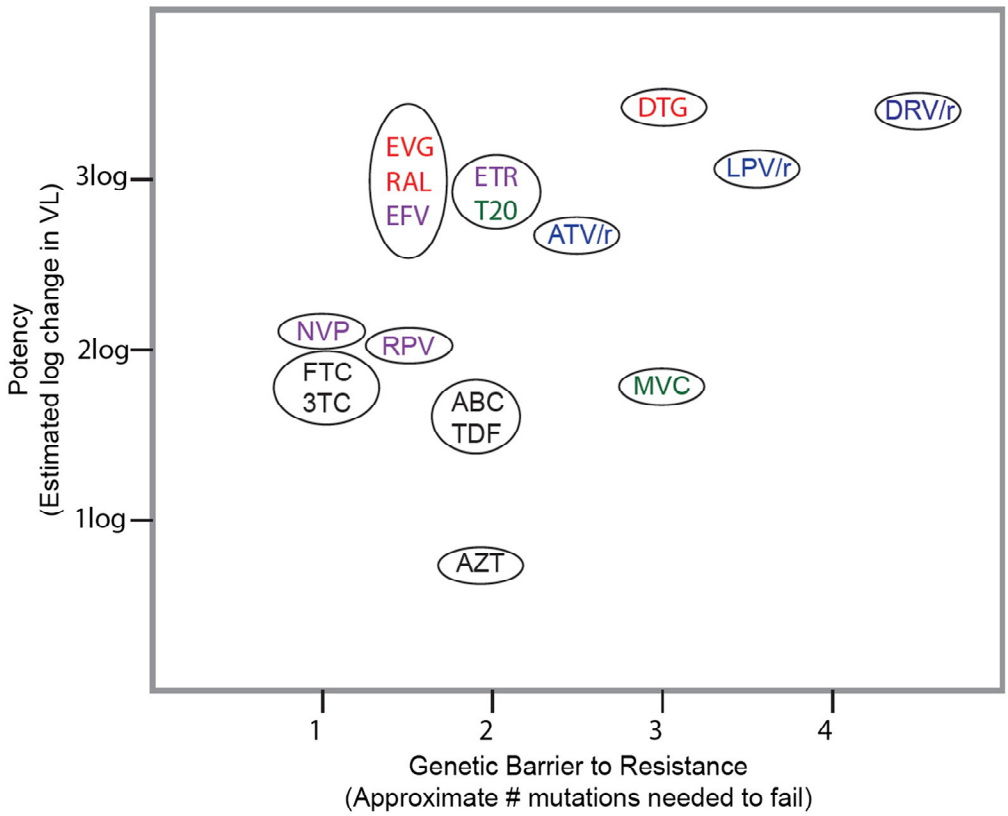
In the UK, genotypic drug resistance testing is recommended for all people newly diagnosed with HIV, to detect the presence of TDR at baseline. In addition, genotypic

drug resistance testing is recommended if there is evidence of viral failure, or upon cessation of ART for whatever reason(Williams et al. 2014). Resistance testing is also considered for pregnant women who have not achieved a VL <50 copies/ml at 36 weeks' gestation (Guidelines writing group 2014). Due to resource limitations, the availability of genotypic resistance testing is limited in LMIC, restricting the surveillance of TDR and the ability of clinicians to tailor ART regimens to the presence of DRMs.

Transmitted drug resistance

TDR increases the risk of treatment failure in patients receiving at least one compromised drug, and it may be that patients with TDR who are prescribed drugs with a low genetic barrier to resistance have a higher chance of virological failure even if all drugs are considered fully active (Wittkop et al. 2011). See Figure 2-5 for estimated risk of virological failure according to presence of TDR in patients in 25 cohorts in the EuroCoord network. Previous work from the UK Antiretroviral Drug Resistance Database (UKDRD) up to 2006 showed a lower prevalence of TDR among ART-naïve people with non-subtype B compared to subtype B, a declining prevalence with non-subtype B; and a higher prevalence in rarer recombinant forms. More recently, a stabilisation in the decline in TDR among subtype B infection in the UK was reported (UK Collaborative Group on HIV Drug Resistance 2012).

Figure 2-4. ARV potency versus genetic barrier to resistance, from (Clutter et al. 2016) [14]



Abbreviations and key: ARV: antiretroviral; VL: viral load; ABC: abacavir; ATV/r: boosted atazanavir; DRV/r: boosted darunavir; DTG: dolutegravir; EFV: efavirenz; FTC: emtricitabine; EVG: elvitegravir; T20: enfuvirtide; ETR: etravirine; 3TC: lamivudine; LPV/r: boosted lopinavir; MVC: maraviroc; NVP: nevirapine; RAL: raltegravir; RPV: rilpivirine; and TDF: tenofovir. ARVs in black font are nucleoside or nucleotide reverse transcriptase inhibitors (NRTIs), those in purple font are NNRTIs, those in blue font are PIs, those in red font INSTIs, and those in green font are entry inhibitors. ARVs appearing together in the same ellipse should be considered to have roughly equivalent potencies and genetic barriers to resistance.

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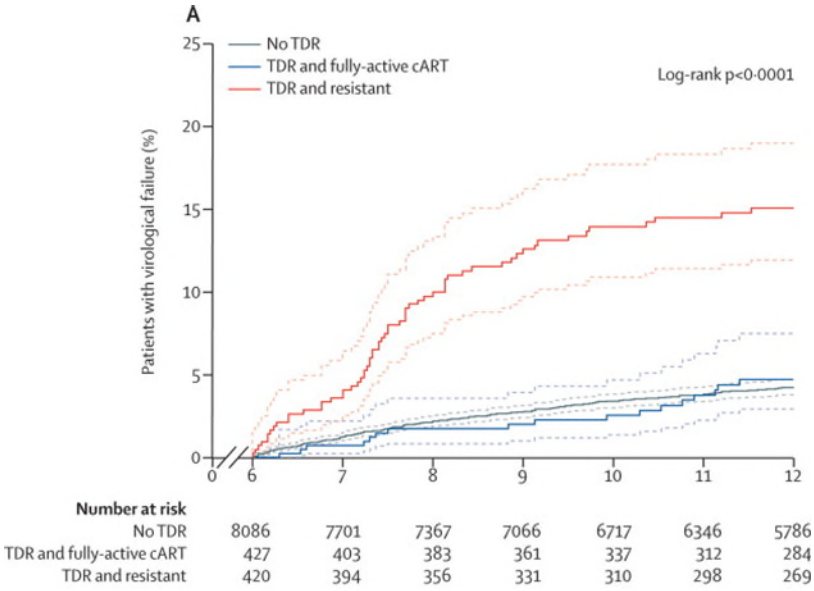
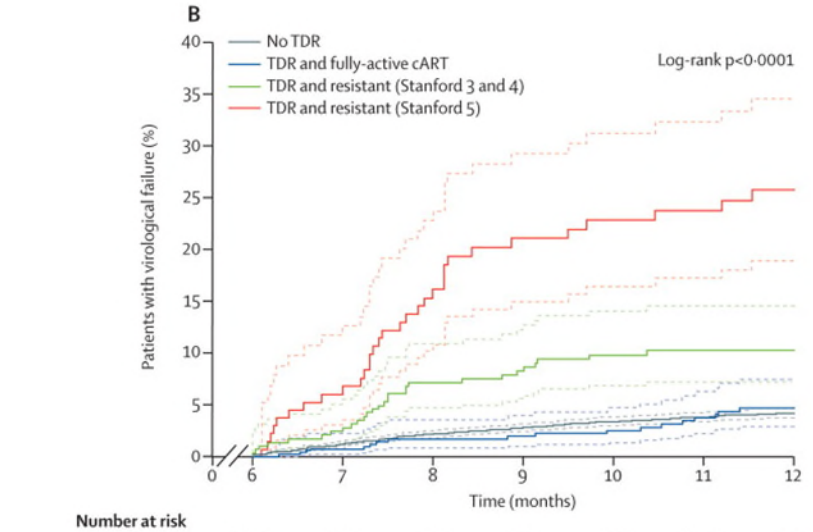
Figure 2-5. Kaplan-Meier estimates of the proportion of patients with virological failure, from (Wittkop et al. 2011)[15]

A. Risk of virological failure according to patient groups
B. Risk of virological failure in patients with intermediate and high-level resistance
Dotted lines=95%CI



Number at risk							
No TDR	8086	7701	7367	7066	6717	6346	5786
TDR and fully-active cART	427	403	383	361	337	312	284
TDR and resistant	420	394	356	331	310	298	269



Number at risk							
No TDR	8086	7701	7367	7066	6717	6346	5786
TDR and fully-active cART	427	403	383	361	337	312	284
TDR and resistant (Stanford 3 and 4)	287	273	250	239	225	217	199
TDR and resistant (Stanford 5)	133	121	106	92	85	81	70

[15] Reprinted from The Lancet Infectious Diseases, with permission from Elsevier via Rightslink.

2.5.3 Drug resistance and pregnancy

Single dose nevirapine for prevention of MTCT is widely associated with the development of NNRTI resistance. Until recently single dose nevirapine was given in conjunction with zidovudine during pregnancy, and zidovudine plus lamivudine for a week after delivery, to prevent the development of resistance, but this regimen is no longer recommended by WHO (WHO 2013). Zidovudine monotherapy is itself associated with the development of drug resistance in women with high VLs, low CD4 counts, repeated exposure, or long duration of treatment (Welles et al. 2000). However, a UK study of 80 women with low baseline VL on zidovudine monotherapy for prevention of MTCT in accordance with UK guidelines found no emergence of drug resistance (Read et al. 2008). In addition, data from the UK CHIC cohort have shown that women previously treated with zidovudine monotherapy for prevention of MTCT according to the UK guidelines (those with low VL and high CD4 count) have similar rates of viral suppression with subsequent cART, when compared to ART-naïve women (Huntington et al. 2014).

There is limited data on risk of resistance with START: two studies found high rates associated with nevirapine or nelfinavir-based START (Paredes et al. 2010; Ellis et al. 2011), but neither of these drugs is currently recommended in the UK for START. The Mma Bana study, a randomised controlled trial in Botswana, found no clinically significant mutations after ART-naïve women took either triple NRTI or zidovudine/lamivudine/lopinavir/ritonavir regimens in pregnancy and for six months through the breastfeeding period (Souda et al. 2013). An audit looking at HIV-infected infants born in England 2002-2005 found that failure to act upon suboptimal virological response to ART contributed to transmission in some cases (NSHPC, Audit Information Analysis Unit, and CHIVA 2007). There are no data on the prevalence or incidence of drug resistance in pregnant women in the UK.

Vertical transmission of DRM

DRM-containing virus can be transmitted vertically, as well as via sexual transmission, and this pre-treatment drug resistance (PDR) has important implications for antiretroviral treatment of children diagnosed with PHIV. A meta-analysis of 10 studies recruiting 2000 – 2006 examining the prevalence of PDR in children with PHIV found a pooled estimate of 52.6% prevalence of nevirapine resistance in children who had only been exposed to maternal single-dose nevirapine

(95% CI 37.7 – 67.0%), and 16.5% prevalence of nevirapine resistance in children born to mothers treated with single-dose nevirapine plus either maternal zidovudine monotherapy or maternal zidovudine plus lamivudine during pregnancy (95% CI 8.9 – 28.3%) (Arrive et al. 2007). A later systematic review of drug resistance in the paediatric population worldwide examined 18 studies of PDR in children naïve to ART, with recruitment periods between 1993 and 2011, and found a wide range of resistance rates: NRTI resistance rates ranged 0 to 17%, NNRTI resistance 0–37% and major PI resistance 0-18% (Rojas Sánchez and Holguín 2014). An analysis of children with PHIV initiating cART 1998-2008 with at least one pre-treatment genotypic resistance test across 18 cohort studies in 11 European countries, found an estimated prevalence of at least one PDR mutation in 7.8% (95% CI 5.5 – 10.6). Children were stratified into 'PDR with resistance to treatment' or 'PDR with fully active cART or no PDR'(Ngo-Giang-Huong et al. 2016). Children in the 'PDR with resistance' group tended to a higher cumulative risk of virological failure at 12 months after cART initiation than children in the 'PDR + fully active cART or no PDR) group, but this did not reach statistical significance (32.1% vs 19.4%, p=0.095). In multivariable analysis, the presence of PDR and resistance to ≥1 ART drug was not associated with risk of virological failure (Ngo-Giang-Huong et al. 2016).

3 Aims and Methods

3.1 Rationale for this work

The life expectancy of people living with HIV has improved dramatically over the past 20 years, and is likely to continue to do so (May et al. 2011; Rodger et al. 2013). Women living with HIV are diagnosed earlier, and have a better life expectancy than men, and pregnancy incidence and the number of sequential pregnancies is increasing in the UK. Although the population of women living with HIV who become pregnant and give birth in the UK has been well described previously (Townsend et al. 2008), recent work has mostly focussed on specific subgroups of this population, and since the demographics and characteristics of these women are changing, there is a need for an up-to-date characterisation of the population to inform the planning of health services and clinical guideline development.

The UK MTCT rate in diagnosed women decreased to 0.46% in 2010-2011 (Townsend et al. 2014), but the rising pregnancy incidence and proportion of women diagnosed prior to conception has led to increasing numbers of infants being exposed to ART *in utero* throughout gestation, and to newer drugs. This means that concern now goes beyond transmission to include maternal health, pregnancy outcome, and the long-term health of HIV-exposed uninfected children. Rates and risk factors for other adverse pregnancy outcomes such as stillbirth need to be investigated in this population. This is a fast-moving field of research; clinical guidelines for the management of HIV in pregnant women are updated regularly and are often 'catching up' on changes in practice that have already occurred, so there is a need for a picture of current clinical practice and trends in the management of these women in recent years, to sit alongside outcomes.

Globally, adolescents and young people living with PHIV are an emerging population for which there are scant long-term data. Pregnancy outcomes in young women with PHIV have only been investigated in small cohorts, mostly single-centre. The longstanding NSHPC surveillance methods, collecting data both on children exposed and infected with HIV, and on women living with HIV who become pregnant, present a unique opportunity to estimate country-level incidence of pregnancy in young women with PHIV living in the UK, and would enable a robust analysis of pregnancy

outcomes in these women, comparing them with women of a similar age who acquired their HIV behaviourally.

Drug resistance testing is a key component of the management of all people living with HIV in the current treatment era to ensure effective ART, but data on the prevalence of resistance in pregnant women in the UK are scarce. To date there has not been a UK national study examining the burden of resistance in HIV-positive pregnant women, and there is a valuable opportunity to do so by using our two existing comprehensive surveillance studies, the NSHPC and the UK HIV Drug Resistance Database (UKDRD). Data linkage between the NSHPC and the UKDRD would provide a unique opportunity to describe viral subtype and transmitted drug resistance in pregnant women. Evaluating the prevalence and nature of transmitted drug resistance on a population level is important for decision in the clinical management of pregnant women living with HIV and their infants. Given that most women with heterosexually-acquired HIV have non-subtype B infection, an analysis of recent trends in the prevalence of TDR in women diagnosed in pregnancy (and therefore ART-naïve) would assist in mapping the epidemic in this group of women. Estimating the impact of viral subtype and TDR on the likelihood of women achieving an undetectable VL prior to delivery may influence choice of drugs and timing of initiation of ART in pregnant women, especially in the case where a woman presents late in pregnancy and ART must be initiated prior to resistance results becoming available (Taylor et al. 2012).

Despite the very low MTCT rate, vertical transmission to children born in the UK still occurs. In previous work looking at infected children born in England in 2000-2005, mothers in the majority of cases had significant social issues, and two-thirds of these children were born to undiagnosed mothers. Since then there has been development of the standards for antenatal screening, and changes in clinical guidelines; examination of cases of transmission in recent years would inform future policy for the prevention of MTCT in the UK. There is a need for an up-to-date investigation into the circumstances of the small number of children still acquiring HIV from their mothers in the UK and Ireland, in order to identify missed opportunities to prevent PHIV to enable clinicians and policy-makers to strive for sustaining the very low level of paediatric HIV acquired in the UK.

3.2 Aims and objectives

Aim

To examine the role of antiretroviral therapy and other interventions to reduce MTCT of HIV in the UK and Ireland in the current treatment era.

Hypothesis The epidemiology, diagnosis and clinical management of women living with HIV in the UK is likely to have evolved since 2000. The management of women who decline antenatal HIV testing is likely to vary between antenatal services.

Objective 1 To assess the epidemiology, circumstances of diagnosis and clinical management of pregnant women living with HIV in the UK since 2000; and survey the clinical management of women who decline antenatal HIV screening.

Hypothesis Pregnancy outcomes in women living with HIV in the UK may have changed since 2000. Based on previous research, the pregnancy incidence of women living with perinatal HIV has not been previously estimated. Women with PHIV are likely to have an increased risk of adverse pregnancy outcome.

Objective 2 To examine pregnancy outcomes in women living with HIV in the UK since 2000 overall; to estimate incidence of first pregnancy in women with perinatal HIV; and to describe prevalence and risks of specific outcomes (adverse pregnancy outcomes and undetectable VL at delivery) in women with PHIV, comparing with an age-matched group of women with behaviourally-acquired HIV.

Hypothesis The pattern of ART prescribing for pregnant women is likely to have changed since 2000. Between 2000 and 2014, the proportion of women with a resistance test is likely to have increased. Pregnant women living with HIV are more likely to have non-subtype B virus, and a low prevalence of transmitted drug resistance.

Objective 3 To describe trends in the use of ART in pregnancy in the UK since 2000; examine patterns of antiretroviral resistance testing in pregnancy; and estimate the prevalence of and factors associated with transmitted antiretroviral drug resistance in women diagnosed with HIV in pregnancy in the UK.

Hypothesis There are likely to be themes common cases of perinatal transmission of HIV in the UK which can help to identify missed opportunities to prevent perinatal PHIV, and improve policy and practice in PMTCT HIV in the UK.

Objective 4. To explore the circumstances of perinatal HIV transmission in infants born in the UK since 2006 in order to provide evidence to improve policy and practice in the prevention of PHIV.

3.3 Data sources

3.3.1 National Study of HIV in Pregnancy and Childhood

All pregnancies in diagnosed women living with HIV in the UK and Ireland, regardless of outcome, are reported to the National Study of HIV in Pregnancy and Childhood (NSHPC), based at the UCL Great Ormond Street Institute of Child Health, London. This population-based surveillance study comprises two active confidential reporting schemes: an obstetric and a paediatric scheme.

Obstetric scheme

Obstetric data is reported from maternity units using a scheme that was established under the auspices of the Royal College of Obstetricians and Gynaecologists in 1989. All maternity units in the UK and Ireland have a named respondent, often a specialist midwife or antenatal screening coordinator, who reports all pregnancies occurring in women diagnosed with HIV, whether they were diagnosed before or during the reported pregnancy. Every quarter, respondents are requested to return a reporting card indicating the number of pregnancies to women diagnosed with HIV during the previous quarter, including null returns. The NSHPC requests that all pregnancies are reported, regardless of outcome. Demographic and clinical information on each reported pregnancy is then obtained from respondents using a standardised notification form. For pregnancies expected to continue to term, a pregnancy outcome form is sent to the respondent close to the expected date of delivery. Information on maternal demographic characteristics such as age, country of birth, ethnicity, parity, timing of HIV diagnosis, clinical factors related to HIV infection, as well as clinical management in pregnancy, during labour and delivery and pregnancy outcome are collected. New pregnancy reports are linked to previous reports for the same woman based on date of birth as well as other information, e.g. country of birth, timing of HIV diagnosis, partial postcode, or NHS number. All stages of the reporting process are actively managed by the NSHPC team, and units noted to not be reporting are followed up, resulting in high reporting rates. The data items on the obstetric reporting forms have been added to during the study period; this is commented on in the text where relevant.

Paediatric scheme

Children diagnosed with HIV and children born to mothers living with HIV are reported to the study via the British Paediatric Surveillance Unit's (BPSU) 'orange

card' system, run by the Royal College of Paediatrics and Child Health (Verity & Preece, 2002), or directly reported to the NSHPC. The paediatric reporting scheme began in 1986 (reporting of AIDS diagnoses only) and was extended to include children born to women with HIV and children diagnosed with HIV when the obstetric scheme began in 1989. The BPSU routinely sends a monthly 'orange card' to all consultant paediatricians in the UK and Ireland registered with the RCPCH. Paediatricians are requested to return the card indicating whether or not they have seen a child with any of the listed conditions (including HIV or born to a woman diagnosed with HIV) during the past month. The BPSU notifies the NSHPC of any paediatric cases or exposed infants via an electronic spreadsheet on a weekly basis (The BPSU do not collect any patient identifiable information). The NSHPC then sends out a paediatric notification form to the reporting paediatrician, which is then completed and returned to the NSHPC. Increasingly, paediatric units with a larger caseload of HIV exposed children report cases directly to the NSHPC. Following the initial report, a follow-up form is sent in order to obtain the HIV status of exposed children. Similarly, to the obstetric scheme, there is active monitoring and follow-up at all stages. Obstetric and paediatric reports are linked based on dates of birth, geographic location of the report, NHS number and other demographic information, and pregnancies reported from the same woman are also linked. Infants born to women with HIV in the UK and Ireland should be independently reported through both the obstetric and paediatric schemes. Children diagnosed with HIV born abroad and born to women who were undiagnosed during pregnancy will only be reported through the paediatric scheme. Children diagnosed with HIV are subsequently followed up by the Collaborative HIV Paediatric Study (CHIPS) based at the MRC Clinical Trials Unit at UCL (MRC CTU).

Data items

All data are collected using standardised data collection forms (Appendix 10.1) which are periodically reviewed by the steering committee; new variables have been added during the study period (this is commented on as appropriate in the relevant section). No names or addresses, aside from residential postcodes excluding the last digit, are collected. Women are assigned a unique NSHPC study number. Demographic information collected includes women's date of birth, ethnic origin, country of birth and date of arrival into the UK or Ireland if born abroad, and previous reproductive history (live births, stillbirths, terminations and miscarriages). Information on

probable source of maternal HIV infection is requested, including whether it was likely acquired in either the UK or Ireland or abroad (and if abroad which country), and the likely route of acquisition (heterosexual, injecting drug use, vertical transmission or other). Timing of diagnosis includes date of first positive HIV test, whether the woman was diagnosed prior to or during the current pregnancy, where she was diagnosed (antenatal, GUM clinic or elsewhere), and whether there is any evidence of seroconversion during this pregnancy. Pregnancy information including booking date, expected date of delivery and/or date of last menstrual period, whether the pregnancy is continuing to term (and if so, whether the planned mode of delivery is vaginal or caesarean section), and whether the pregnancy has already ended in a miscarriage or termination (and if so, the date or gestation at pregnancy end). Information on ART, including whether the woman was on treatment at conception, together with drugs received and start and stop dates is requested. Items indicating maternal clinical status include whether the woman has ever had CDC Stage C disease (AIDS), whether she has had HIV/AIDS symptoms during the pregnancy and concurrent infections (specifically requesting details on hepatitis B and C and syphilis status). The earliest antenatal CD4 count and VL measurement are also collected.

The obstetric outcome form includes the date of delivery, pregnancy outcome, gestational age, planned and actual mode of delivery, whether rupture of membranes (ROM) occurred prior to delivery and duration of ROM. Information on pregnancy complications such as pre- eclampsia and gestational diabetes is requested. Maternal clinical status (HIV/AIDS symptoms) at delivery, together with CD4 count and VL closest to delivery are also collected. Details of ART during pregnancy and delivery, as well as any other non-HIV drugs such as tuberculosis treatment or methadone taken during pregnancy are requested on both notification and outcome forms to ensure completeness and record any switches in ART.

Information on the infant includes birth-weight, the presence of perinatal infections and congenital abnormalities, as well as details of post-partum prophylaxis. The paediatric notification form requests some of the child's demographics, their likely source of infection (including mother's demographic and HIV exposure details for those infants likely exposed to maternal HIV), perinatal details including mode of delivery, ART received by the mother and/or infant, the presence of any congenital abnormalities, whether or not the child was breastfed, initial infection status and

clinical details. A paediatric follow-up form to establish the infant's HIV status is subsequently sent to the appropriate paediatric respondent.

Data collection and management

At the time of the data collection for the dataset used in this thesis, data were held and managed in a Microsoft Access database (Microsoft Corp., Redmond, Washington, USA). Data were entered by hand from the paper paediatric and obstetric forms into the database by the data management team, and checks and data cleaning were performed, including checking for duplicate reporting. Incomplete forms or forms including inconsistent information were queried with the respondent by telephone or secure nhs.net email. At the end of each calendar quarter, a set of standard queries was run to check the quality of data, and data for analysis was extracted from the database; the outputs of these queries were then compiled into a single analysis dataset via R (R Development Core Team, Vienna), with the analysis dataset subsequently imported into Stata (Stata Corporation, College Station, Texas, USA) where further routine data checks were carried out; a Stata dataset was compiled every quarter. Recently the study has migrated its database to a new platform, and at the time of this PhD was trialling a bespoke secure web-reporting system for obstetric reporting.

To ensure data quality in analyses presented in this thesis, additional range checks were carried out on the variables of interest within the Stata dataset to make sure that no variables were coded outside the expected range, and cross tabulations were used to check consistency between variables. Where inconsistencies or errors were identified, corrections were made by referring back to the original paper report if possible or recoding them as missing if not.

The NSHPC Stata dataset is in long form, with one row per pregnancy, a unique identifier for each pregnancy and a unique identifier for each woman, thus pregnancies for the same woman can be identified. Stata script for labelling sequential pregnancies was developed by Clare French utilising the inbuilt _n and _N variables for creating group identifiers (French 2014), and I used this when recoding the dataset in order to identify sequential pregnancies from the same woman.

Data on individual drugs is not routinely extracted as part of the compilation of the quarterly NHPC Stata dataset. This was extracted separately and merged into the

dataset using the unique identifiers of the woman and pregnancies. Individual drugs had been entered into the database with both generic and commercial names, so the data was cleaned and recoded after merging in Stata. Commonly used NRTI 'backbones' of two co-formulated drugs (i.e. zidovudine plus lamivudine; abacavir plus lamivudine; tenofovir plus emtricitabine) were coded if the start date of both NRTIs matched (see Chapter 6).

3.3.2 Categories and definitions

Definitions and categorisation of key variables utilised throughout this thesis are outlined here. Specific groupings appropriate to each analysis, as well as the definitions of variables that pertain to a single analysis only, are specified in the relevant chapter.

Maternal demographic characteristics

Maternal age at conception was defined as women's age at estimated conception date, derived using women's date of birth. *Maternal age at delivery* was derived using women's date of birth and the date of delivery (for live and stillbirths) or end of pregnancy for other outcomes.

Parity was defined as the number of live and stillbirths (of gestational age ≥24 weeks (Winson and McDonald 2005). Women were classified as nulliparous if they were reported to have had no previous live or stillbirths at the time of their first pregnancy reported to the NSHPC, and parous if they had one or more previous live or stillbirths.

For data collection purposes *maternal ethnicity* is defined as white, black African, black Caribbean, black other, Asian/Indian Subcontinent, Asian other/Oriental and other/mixed. *Maternal ethnicity* was recoded as white, black African and other in some analyses.

Migrant woman/women is used to describe women who had country of birth other than UK/Ireland.

World region of birth was largely grouped as UK or Ireland, sub-Saharan Africa and elsewhere. For some analyses the following more detailed breakdown was used: UK or Ireland, rest of Europe, Eastern Africa, Middle Africa, Western Africa, Southern Africa, Africa (unspecified) and elsewhere. The division of sub-Saharan Africa into

regions was based on the United Nations definitions (UN Statistics Division 2018). Occasionally specific maternal country of origin is commented on where appropriate.

Likely route of maternal HIV acquisition was categorised as either 'heterosexual', 'injecting drug use' or 'perinatal HIV'. The perinatal period is defined by the WHO as commencing at 22 weeks' gestation, and ending 7 days after birth (WHO 2015) but 'perinatal HIV' or HIV which is 'perinatally-acquired' are generally accepted terms used to describe when an infant or child has acquired HIV 'vertically' from their mother either during pregnancy, at the time of labour and delivery, or through breastfeeding, and this is the definition used here.

Region of report was the geographical region of the UK and Ireland that the obstetric report originated from, based on PHE regions.

Estimated date of conception and gestational age

Date of conception was estimated as 280 days prior to expected date of delivery, a widely used estimation of the average duration of pregnancy (Jukic et al. 2013). If only a paediatric report had been received for the pregnancy (the expected date of delivery is not recorded on the paediatric form), date of conception was approximated by date of delivery minus gestational age.

The *first, second* and *third trimesters* of pregnancy were defined as 1-12 completed gestational weeks, 13-26 weeks and ≥27 weeks respectively. Pregnancies resulting in a live or stillbirth delivered at <37 gestational weeks were classified as being *preterm*, and <32 weeks being *very preterm*.

Timing of antenatal booking

Gestation at antenatal booking was estimated by the number of days from estimated date of conception to reported date of booking for antenatal care.

Maternal clinical and immunological characteristics

CD4 count in pregnancy refers to the CD4 count available on the earliest date during pregnancy (cells/μL).

VL near to delivery was restricted to those taken within 28 days prior to and seven days after delivery. An *undetectable VL* was defined as <50 copies/ml. The detectability limit of assays has changed over time. Those reported as being below a

higher detection limit than 50 copies/ml (e.g. '<200 copies/ml') were recoded as the mid-point, thus the example given was recoded as 100 copies/ml.

Antiretroviral therapy

Class of ART received during pregnancy was broadly classified as mono/dual therapy or cART (defined as any combination of three or more antiretrovirals). For some analyses cART was further classified as PI-based (either ritonavir boosted or unboosted), NNRTI-based, PI- and NNRTI-based (triple class therapy) and NRTI only. There were a small number of pregnancies where women had been treated with raltegravir plus two NRTIs (these are described separately), and a small number of cases where raltegravir was added to an already established cART regimen. In some analyses pregnancies were grouped according to whether the woman had been in receipt of ART at conception or not.

Mode of delivery and pregnancy outcomes

Deliveries were classified as vaginal (planned or unplanned), elective CS (conducted before the onset of labour or the rupture of membranes), or emergency CS (conducted after rupture of membranes or onset of labour) (elective or emergency CS were classified by the respondent). Information on whether vaginal deliveries were planned or unplanned has been collected since 2002, with planned mode requested for all pregnancies since 2007.

Pregnancy outcomes were categorised as live births, stillbirths (deaths occurring from 24 weeks onwards), miscarriages (foetal deaths occurring before 24 weeks gestation) (Royal College of Obstetricians and Gynaecologists, 2013), terminations, or continuing to term. Outcome was recorded as 'other' when women were reported to have gone abroad during pregnancy, or to have died.

Infant HIV status

Infants were categorised as being 'presumed HIV-positive' if they had a positive HIV polymerase chain reaction (PCR) test at over one month of age. A confirmed diagnosis was based on a subsequent positive PCR test on infants aged over three months, or a positive antibody test at >18 months of age. Infants were 'presumed HIV-negative' if they had a negative initial PCR. They were confirmed as being negative based on a repeat negative PCR test, or a negative antibody test. Because it is rare that later tests do not confirm the initial results, no distinction was made

between infants with a 'presumed' or 'confirmed' diagnosis in the analyses (Townsend et al. 2008)

In some analyses, timing of infant HIV acquisition was estimated according to the results of HIV DNA PCR tests carried out on infant blood, which are recommended to be performed at birth, 6 weeks, and 12 weeks for infants born to women who have been diagnosed with HIV, with a final HIV antibody test at 18 months of age

Infants were presumed infected in utero if HIV PCR was positive within 72 hours of birth; presumed infected intrapartum if PCR at birth was negative, but positive at 6 weeks; and infected postnatally if PCR negative at 6 weeks but PCR or HIV antibody positive thereafter (Newell 1998).

3.3.3 Ethical approval

The ethical approval for the study has evolved during the study period, these are the current details (NSHPC 2018):

Principal Investigator:	Dr. Claire Thorne
Sponsor:	UCL Great Ormond Street Institute of Child Health
Data Protection Reg No:	Z6364106 Section 19
Current funding bodies:	Public Health England National Screening Committee
Ethics approval:	London REC ref: MREC/04/2/009 Reviewed 28 January 2004, and approved Amendment (1), Perinatal HIV Audit 2002-2005, reviewed 2 February 2006, and approved. Amendment (2), Perinatal HIV Audit Protocol, reviewed 8 November 2012, and approved.
PIAG/NIGB/CAG:	NIGB Ref: PIAG/BPSU 2-10(a)/2005 IG Toolkit Ref: EE133902-SLMS Version 14 (2017) Confidentiality Advisory Group (CAG) Ref: 15/CAG/0190 (previously 15/CAG/0153

3.3.4 Data set for analysis

The NSHPC dataset for analysis in Chapters 4, 5 and 6 includes all pregnancies reported by the 30th September 2014, with estimated or actual delivery date between 1st January 2000 and 31st December 2014.

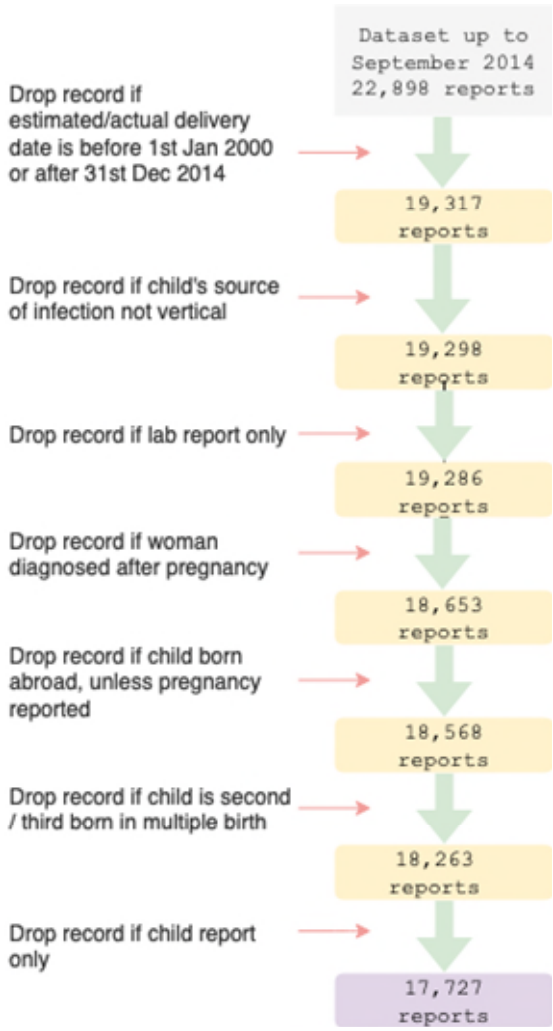
Further exclusion criteria were:

- Paediatric reports where the child's source of HIV exposure was not vertical (for example, haemophiliacs exposed to infected blood products).

- Pregnancies for which only a laboratory report was received since these contain very minimal demographic and clinical information. Aside from this limitation, it was also difficult to confirm that they are not duplicates of reports received through the obstetric and/or paediatric scheme.
- Pregnancies reported retrospectively – these are historical reports largely from prior to the initiation of the NSHPC.
- Pregnancies (or children born to) women who had not been diagnosed prior to delivery, except in Chapter 7 which uses an additional data set as specified in the chapter methods.
- Children who were born abroad and subsequently came to the UK (unless the mother was also reported to the NSHPC i.e. she was in the UK or Ireland at some point during pregnancy).

See Figure 3-1 for a schematic diagram of the exclusions made from the original dataset.

Figure 3-1. Diagram of exclusions made from original dataset



3.3.5 Survey of Prevalent HIV Infections Diagnosed (SOPHID)

The Survey of Prevalent HIV Infections Diagnosed (SOPHID) began in 1995 and was a cross-sectional survey of all persons with diagnosed HIV infection who attended for HIV care at an NHS site in England, Wales and Northern Ireland. Paediatric data (children <16 years of age) were provided from the NSHPC. All patients receiving care in NHS-funded clinics were reported. The survey ran twice a year in London and annually outside London. Since individuals were allocated a unique SOPHID personal identifier, which remains constant, it is possible to trace HIV-care attendance for individuals, or population sub-groups over time.

In the analyses presented in Chapter 6, the NSHPC dataset was matched to SOPHID unique identifiers to enable merging with the UK HIV drug resistance database, and specific methods on the matching process are provided in Chapter 6. No data items other than the unique identifier were utilised from SOPHID.

3.3.6 Drug Resistance Database

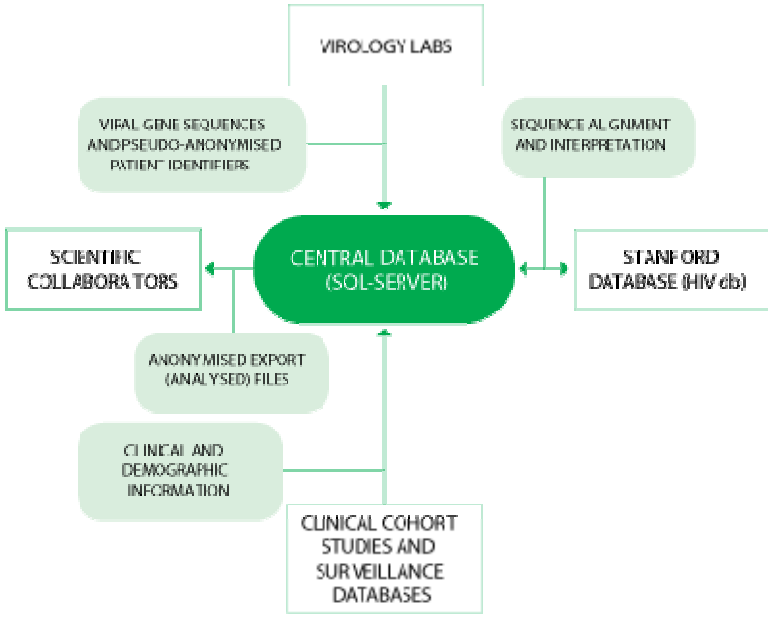
Genotypic HIV resistance test results are nucleotide sequences (of protease, portions of reverse transcriptase, integrase or gp41) indicating point mutations which may confer resistance to ART, produced by Sanger PCR sequencing (Tang and Shafer 2012). The UK HIV Drug Resistance Database is a central repository for genotypic HIV resistance tests performed as part of routine clinical care throughout the UK. Established in 2001, by the end of 2016 over 135,000 test results, most in the form of viral gene sequences, had been received and curated (UK HIVDRD 2018).

The Database is overseen by an inclusive Steering Committee and is coordinated by the UCL Institute for Global Health in London. The project was originally funded by the Department of Health and is currently funded by the UK Medical Research Council (grant 164587).

Data collection and processing

Data on routine resistance tests are received annually from 15 participating virology laboratories in the UK and imported into a central SQL database. The nucleotide sequences are then processed through the Stanford University Genotypic Resistance Interpretation Algorithm (HIVdb) to obtain aligned sequences, amino acid mutations and drug susceptibility data. These are stored in the database along with subtype data from the Rega Institute.

Figure 3-2. Schematic of data collection and processes in the UK HIV drug resistance database



Where possible, tests are linked (using pseudo-anonymised patient identifiers) to UK CHIC clinical data, the UK Seroconverter Register, CHIPS and to surveillance data at Public Health England. After extensive data cleaning, a final dataset is created for analysis. Relevant variables from this are made available to collaborators. Full details of the linking process to SOPHID and the NSHPC datasets are in the chapter methods described in Chapter 6.

Centres contributing data

- **Addenbrooke's Hospital**, Cambridge
- **Chelsea and Westminster Hospital NHS Trust,** London
- **Guy's and St Thomas' NHS Foundation Trust,** London
- **PHE Birmingham Public Health Laboratory,** Birmingham
- **PHE London**
- **King's College Hospital**, London
- **Leeds Teaching Hospitals NHS Trust**, Leeds
- **Liverpool Specialist Virology Centre**, Royal Liverpool University Hospital

- **Manchester Specialist Virology Centre,** Central Manchester Foundation Trust
- **Royal Free Hospital**, London
- **Royal Infirmary of Edinburgh**, Edinburgh
- **Royal Victoria Infirmary,** Newcastle
- **South Tees Hospitals NHS Trust**, Middlesbrough
- **St George's Hospital**, London
- **Barts and The London NHS Trust,** London
- **St Mary's Hospital, Imperial College Health NHS Trust**, London
- **University College London Hospitals,** London
- **West of Scotland Specialist Virology Centre,** Gartnavel General Hospital, Glasgow

3.3.7 Missing data

Through the data process described on page 81, the amount of missing data is minimised as far as possible. However, as with any surveillance study some missing data are inevitable. This was dealt with by examining the extent of missing data on key outcome and exposure variables and assessing whether this was likely to significantly bias the findings, by comparing the characteristics of those with and without missing data, as appropriate to each analysis (these data are presented within each relevant chapter).

Multiple imputation, generating a number of different imputed datasets based on the distribution of the available data, is often used as a technique in epidemiological studies to deal with missing data (Rubin 1988; Sterne et al. 2009). The application of such an approach to dealing with missing data in the NSHPC dataset has been previously assessed (French 2014) and has been deemed largely inappropriate because

i) the NSHPC dataset has a complex structure, consisting of pregnancies with some women potentially having more than one pregnancy reported, therefore some variables would need to remain constant across pregnancies in the same woman e.g. maternal ethnic group, while others are pregnancy-specific e.g. antenatal CD4 count measurements;
ii) the dataset consists of a range of variable types including continuous variables which are mainly non-normally distributed;
iii) multiple imputation relies on the assumption that data are missing at random (Jonathan AC Sterne et al. 2009). While for some NSHPC variables missing at random could be a reasonable assumption e.g. the respondent may have simply missed the question, for many this assumption is unlikely to hold e.g. maternal demographic and clinical details may be less likely to be reported for women who present late in pregnancy or only at delivery, and are also more likely to have been collected for women with more than one pregnancy reported;
iv) finally, of course the outcome variable of interest cannot be imputed, and the NSHPC dataset contains a number of potential outcomes of interest.

3.4 Statistical analysis

Data were managed in Access 2010 (Microsoft Corp., Redmond, Washington, USA), compiled using R version 2.14.2 (R Development Core Team., Vienna, 2012), and analysed using Stata version 13 (Stata Corp. LP, College Station, Texas, USA). Where Stata commands are referred to, they are written in Courier New font.

3.4.1 Descriptive analyses and tests of significance

Proportions were calculated among cases with known information on the variable of interest and were compared using the χ^2 or Fisher's exact test (if there were less than five observations in any cell); trends in proportions were assessed using the χ^2 test-for-trend (Kirkwood & Sterne, 2003). A Bonferroni correction for multiple comparisons was used where required (Bland & Altman, 1995). For non-normally distributed variables medians were compared using the Wilcoxon-Mann-Whitney test ('`ranksum`') (Kirkwood and Sterne 2003; Mann and Whitney 1947) and trends in medians using Cuzick's non-parametric test for trend across ordered groups ('`nptrend`') which is an extension of the Wilcoxon-Mann-Whitney test (Cuzick 1985); whether variables were normally distributed was tested using the Shapiro-Wilk test (Shapiro and Wilk 1965). The statistical significance level was 0.05, unless otherwise stated.

3.4.2 Construction of multivariable models

Multivariable models using logistic regression were fitted to investigate the relationship between exposure and outcome variables in Chapters 5 and 6. The approach taken is slightly different between the chapters and is therefore discussed in the specific methods within the results chapters.

3.5 The role of the researcher

This work was conducted in the context of an ongoing national surveillance study, so I take this opportunity to clarify my role. Data collection at the NSHPC was the responsibility of clinicians at each participating centre and I had limited involvement with data verification and entry done at the UCL GOS Institute of Child Health. I conducted data checks prior to each analysis and collaborated with the study staff to resolve data queries.

For the survey of clinical management of women who decline HIV testing in pregnancy, I designed and created the data collection tools in collaboration with Dr Amanda Williams, Dr Bhanu Williams and my supervisor Dr Pat Tookey.

For the analysis of the combined UK HIVDRD NSHPC dataset, I wrote the study proposal and applied to the UKHIV DRD for permission to use their data, created the matched dataset and performed the analysis with support from my supervisors, and Professor David Dunn.

For the audit of PHIV in children born in the UK 2006 onwards, I revised and refined the telephone interview questionnaire that had been previously been developed and trained the research assistant HP[16] to conduct the telephone interviews. I oversaw the data collection, troubleshooting with the research assistant. I coordinated the expert review panel meetings, presented the data, and kept minutes of the meeting in conjunction with HP.

I performed all analyses presented in this thesis, with guidance from my supervisors Dr Pat Tookey, Dr Claire Thorne, and Dr Mario Cortina Borja. To date this work has led to two original research papers, and several conference abstracts (included in Appendix 10.5).

[16] Helen Peters, now NSHPC study manager

4 Women living with HIV who become pregnant

4.1 Introduction

Since the turn of the 21st century, the worldwide epidemic of HIV has evolved rapidly, and patterns of migration into the UK from high-prevalence countries have changed. Life expectancy of people living with HIV has increased, and well as the proportion of people treated with ART. Therefore, it can be expected that the population of women living with HIV in the UK and Ireland who become pregnant has also changed over time, in terms of their demographics and health status. This chapter aims to assess the epidemiology and circumstances of diagnosis in women living with HIV with a reported pregnancy and survey the clinical management of women who decline antenatal HIV screening. The dataset used in the analyses presented in 4.2 contains all reported pregnancies with estimated or actual delivery date between 1st January 2000 and 31st December 2014 and reported by 30th September 2014.

Women living with HIV can only be reported to the NSHPC if they have been diagnosed. The work presented in Chapter 7 looks at the circumstances of perinatal transmission in the UK; one of the themes explored is women who decline HIV testing in pregnancy. Anecdotally, it seemed there was wide variation in local policy and practice in managing women who decline HIV testing in pregnancy. From informal discussion with clinicians, I learned that some maternity units had developed detailed and robust pathways, but there was no formal evidence of the variation in policy and practice between maternity units. The objective of the survey presented in 4.3 was to survey clinicians at maternity units in the UK and Ireland to find out: the number of women who delivered at the unit and the proportion of those who declined antenatal HIV testing during the calendar year 2014; whether the unit had a local policy in place for women who decline the offer of HIV testing in pregnancy; what the policy consisted of, and whether it contained an offer of HIV testing for the infants born to women who decline antenatal HIV testing; and how the multidisciplinary team had resolved cases where women declined antenatal HIV testing.

4.2 Demographics, health status of women

There were 12,014 women living with HIV with 17,730 pregnancies reported to the study with EDD / delivery date between 2000 and 2014, reported by April 2014. In their first reported pregnancy, 49.5% of women had been diagnosed before that pregnancy (5921/11951), and 50.5% were diagnosed during that pregnancy (6030/11951). The proportion of women diagnosed before their first reported pregnancy increased from 36.7% in 2000-2002 (623/1077) to 70.7% in 2012-2014 (1,186/1677).

Forty-three percent of women were reported to be nulliparous at their first reported pregnancy (7702/10885)[17]; this rose from 37% in calendar period 2000-2002 (560/1505) to 47% in 2012-2014 (745/1585) (p<0.001). In women reported to be nulliparous at first reported pregnancy, the proportion diagnosed before the reported pregnancy rose from 28% in 2000-2002 (155/559) to 68.4% in 2012-2014 (509/744) (p<0.001).

Table 4-1 shows the baseline characteristics of women in their first reported pregnancy, by timing of HIV diagnosis: a greater proportion of white women were diagnosed before first reported pregnancy (56.7%), compared with Black African (48.5%) or women of other ethnicity (46.3%); a higher proportion of women born in the UK/Ireland were diagnosed before pregnancy (56.7%) compared with those born in Sub-Saharan Africa (SSA)(48.6%) or elsewhere (46.7%). Whereas slightly more women who acquired HIV heterosexually were diagnosed during the first reported pregnancy (52.3%), most women who acquired HIV through injecting drugs had been diagnosed prior to pregnancy (72.0%), and as expected the vast majority of women reported with perinatal HIV had been diagnosed prior to their first reported pregnancy (94.3%). Age at maternal diagnosis was slightly lower for women diagnosed before the first reported pregnancy than those diagnosed during the pregnancy (28 versus 29 years respectively). Women were reported to have hepatitis

[17] Since only pregnancies with EDD/ delivery date 2000-2014 were included in the dataset analysed, parous women may either have had one or more previous pregnancies prior to diagnosis (and therefore not reported to the study), or they may have had one or more pregnancies reported during an earlier calendar period and therefore not included in this dataset.

B co-infection in 1.8% pregnancies (326/17730), and hepatitis C co-infection in 0.8% (137/17730).

Table 4-1. Characteristics of women at first reported pregnancy with EDD/delivery date 2000-2014

	Timing of maternal diagnosis at first reported pregnancy		
Characteristic	Before	During	*p*-value
N=11,951	5921	6030	
Ethnicity (grouped) (*n*=11,919)			<0.001
White	998 (16.9%)	762 (12.7%)	
Black African	4445 (75.3%)	4721 (78.5%)	
Other	460 (7.8%)	533 (8.9%)	
Region of birth (*n*=11,744)			<0.001
UK/Ireland	877 (15.1%)	703 (11.8%)	
Sub-Saharan Africa	4350 (75.1%)	4605 (77.4%)	
Elsewhere	565 (9.8%)	644 (10.8%)	
HIV risk (*n*=11,951)			<0.001
Heterosexual	5130 (86.6%)	5629 (93.3%)	
IDU	180 (3.0%)	70 (1.2%)	
Unknown	545 (9.2%)	327 (5.4%)	
Perinatal HIV	66 (1.1%)	4 (0.07%)	
Age at diagnosis, median (IQR) (*n*=10,833)	27.6 (23.9, 31.2)	29.1 (25.4, 32.9)	<0.001
Parity (*n*=10,860)			<0.001
0	2111 (39.0%)	2582 (47.4%)	
1	1863 (34.4%)	1681 (30.9%)	
2	939 (17.4%)	766 (14.1%)	
3	499 (9.2%)	419 (7.7%)	
Age at conception, median (IQR) (*n*=11,949)	31.8 (27.6, 35.5)	28.7 (25.1, 32.6)	<0.001

Median age at conception in first reported pregnancy increased from 28 years in 2000-2002 (IQR 25 to 32 years) to 32 years in 2012-2014 (IQR 28 to 36) (p<0.001). In women who were nulliparous at first reported pregnancy, median age at conception increased from 26 years (IQR 23 to 30 years) in 2000-2002 to 30 years in 2012-2014 (IQR 26 to 34 years) (p<0.001).

The proportion of women with injecting drug use as their likely route of HIV acquisition fell from 4.4% in 2000-2002 (75/1704) to 1.2% in 2012-2014 (20/1692) and the proportion of women reported to have PHIV rose from none in 2000-2002 to 1.7% in 2012-2014 (28/1692) (p<0.001).

Median gestation week at antenatal booking was 12.3 weeks (IQR 10 to 16 weeks). The median gestation week at antenatal booking fell from 13.9 weeks in 2008[18] (IQR 11.3 to 18.7 weeks) to 11.4 weeks in 2014 (IQR 9.3 weeks to 13.6 weeks) (p<0.001). Median booking week was 12 weeks for women diagnosed before conception (IQR 9.7 to 15.1 weeks) and 13.9 weeks for women diagnosed during conception (IQR 10 to 16 weeks) (p<0.001).

Figure 4-1 shows maternal region of birth and maternal ethnicity by calendar period of first reported pregnancy. Overall, over three quarters (76.7%) of women were of Black African ethnicity (9166/11951); and 76.3% were born in SSA (8955/11793). The proportion of women born in Europe (not UK/Ireland) increased from 3.0% in 2000-2002 (50/1694) to 9.3% in 2012-2014 (150/1,617), and this was largely driven by the increasing number of women with a reported pregnancy from Poland, Latvia, Ukraine and Romania, as illustrated by Figure 4-2[19]. Figure 4-3 shows maternal country of birth for women born in SSA. The largest group of women were born in Zimbabwe: the proportion of women from Zimbabwe rose from 17.7% in 2000-2002 (226/1279) to 33.0% in 2006-2008 (803/2432) and then fell to 29.2% in 2012-2014 (330/1131); the proportion of women born in Nigeria rose from 9.8% in 2000-2002 (125/1279) to 16.3% in 2012-2014 (184/1131); the proportion of women born in Uganda fell from 14.3% in 2000-2002 (183/1279) to 5.6% in 2012-2014 (63/1131) (p<0.001).

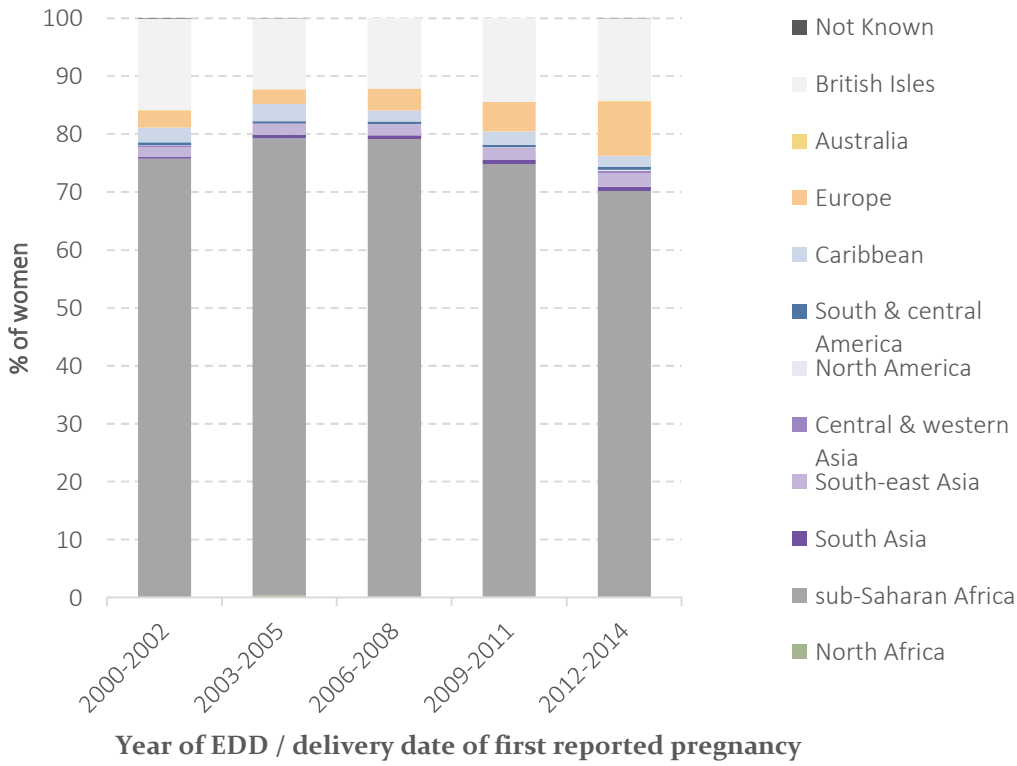
The date that migrant women arrived in the UK was reported in 61.3% of first reported pregnancies in women born in SSA (5519/8996); 49.3% of women born in Europe (249/505); and 58.8% of women born elsewhere (416/707). The median length of time between all migrant women arriving in the UK and delivery date / EDD was 3.6 years (IQR 1.5 to 7.8); rising from 2.2 years in 2000-2002 (IQR 0.8 to 5.99

[18] Gestation week was routinely collected by the NSHPC from 2007 and was reported in 60.1% of pregnancies reported by 2008

[19] In 2004 the largest single expansion of the European Union (EU) occurred when the "A10 countries" Cyprus, Czech Republic, Estonia, Hungary, Latvia, Lithuania, Malta, Poland, Slovakia, and Slovenia joined. Bulgaria and Romania joined in 2007 (Wikipedia 2019)

years) to 7.4 years in 2012-2014 (IQR 2.9 to 10.8 years) (p<0.001). The median length of time between a migrant woman arriving in the UK and her delivery date / EDD was 4.1 years for women born in SSA (IQR 1.7 to 7.4); 3.4 years for women born in Europe (IQR 1.3 to 6.8 years); and 3.6 years for those born elsewhere (IQR 1.5 years to 7.7 years): this variation was not statistically significant (p=0.25). There were 281 women who were reported to have arrived in the UK within 3 months of their delivery date / EDD: 91.8% (256/279) were born in SSA, including 86 born in Nigeria; there was no evidence of a trend by calendar period (p=0.49).

Figure 4-1. A. Maternal region of birth by calendar period



B. Maternal ethnicity by calendar period

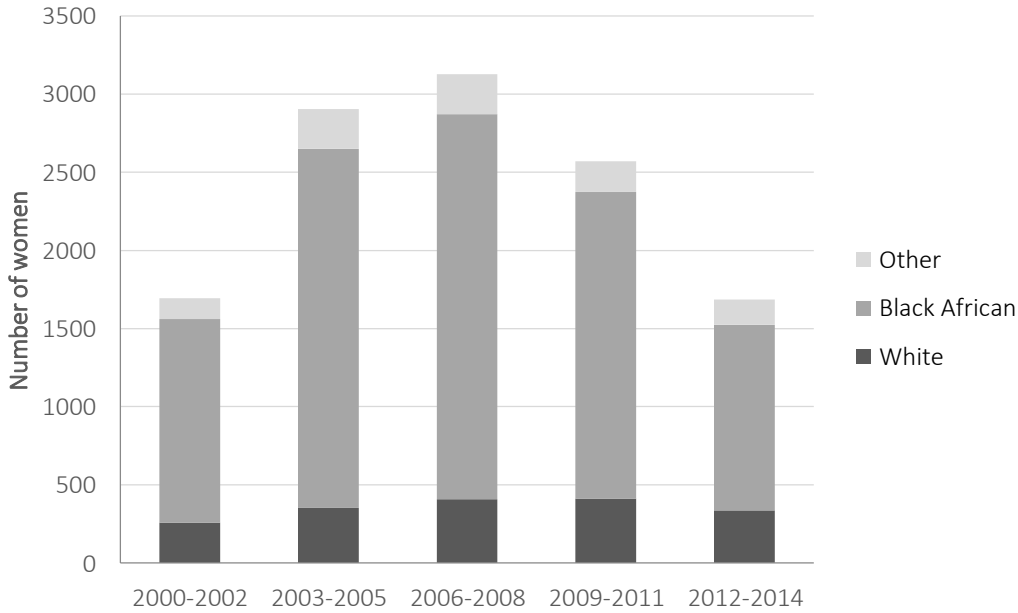


Figure 4-2 Maternal country of birth for women born in Europe with a reported pregnancy 2000-2014

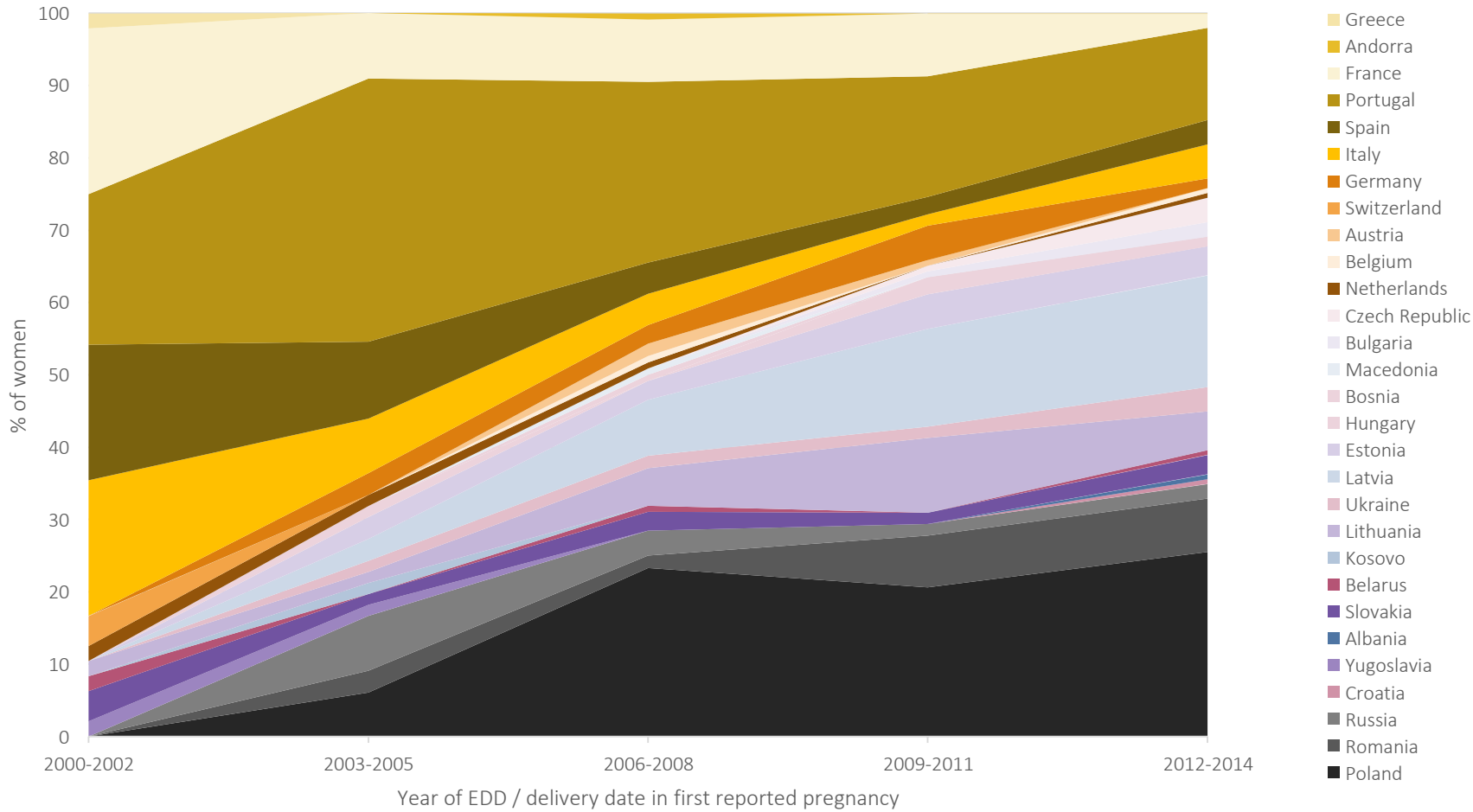
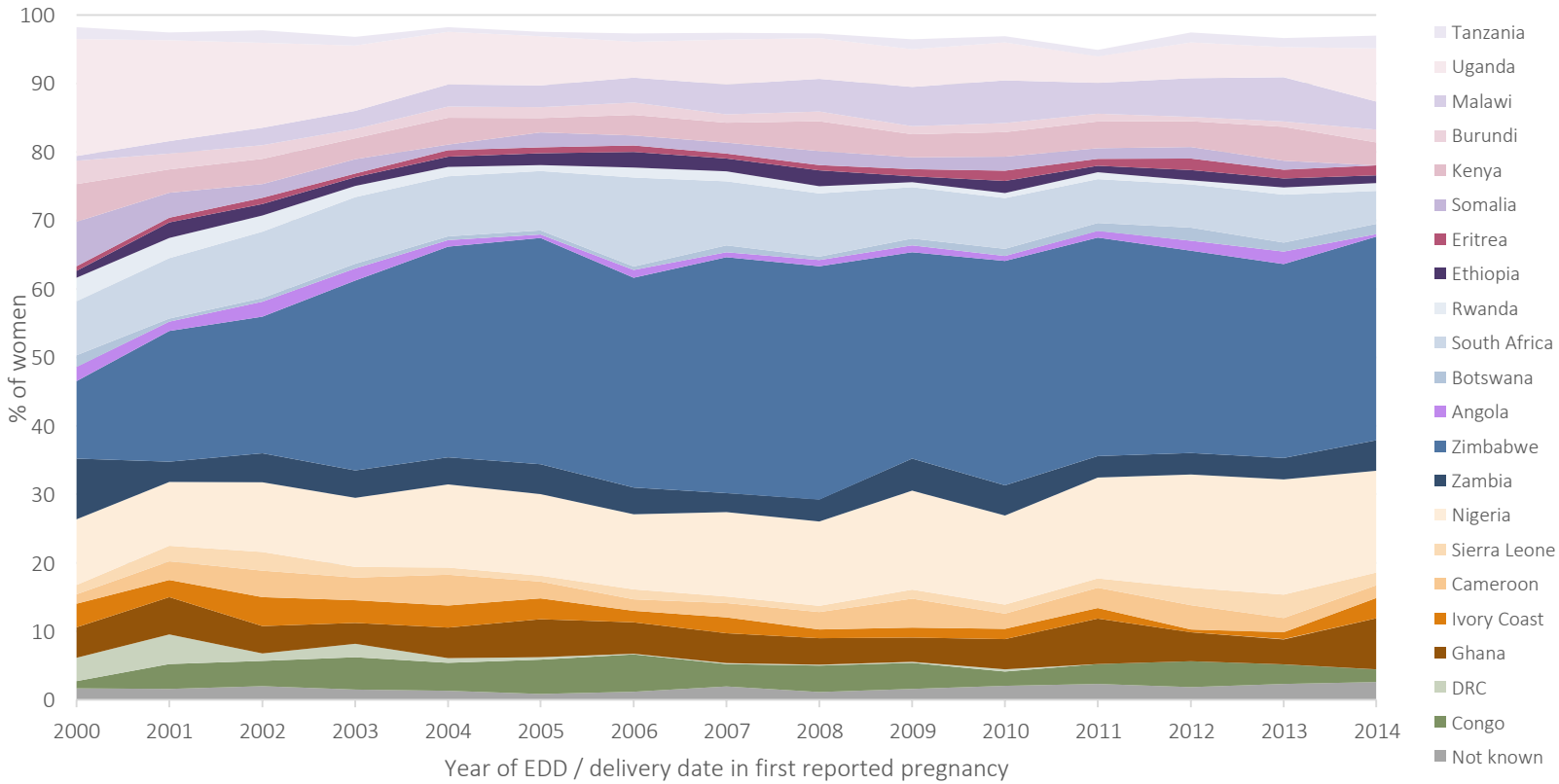


Figure 4-3. Maternal country of origin for women born in sub-Saharan Africa with a pregnancy reported 2000-2014[20]



[20] Excluding SSA countries with proportion of women <1%

4.2.1 Women known to have gone abroad or pregnancy outcome unknown

Known pregnancy outcomes are explored in Chapter 5, but there are a group of women with a reported pregnancy who were reported to have gone abroad before the outcome was known, or where outcome was unknown. Overall, 1.7% of women were reported to have gone abroad before the outcome of their first reported pregnancy (203/12,014) and outcome was unknown in 2.0% of first reported pregnancies (237/12,014). The proportion of first reported pregnancies where outcome was unknown fell from 3.0% in 2000-2002 (51/1704) to 0.1% in 2012-2014 (2/1692), and the proportion of first reported pregnancies where the woman went abroad was 1.7% in 2000-2002 (29/1704), rose to 1.8% in 2006-2008 (57/3131) and then fell to 1.4% in 2012-2014 (24/1692). Table 4-1 shows the characteristics of women in their first reported pregnancy by whether pregnancy outcome was known, not known or they were reported to have gone abroad.

The geographical region with the highest proportion of unknown pregnancy outcome was North West England with 4.0% of first pregnancies having unknown outcome (29/717), compared with 2.2% of first pregnancies reported from London (115/5150), and 0.8% of first pregnancies reported from Scotland (3/374), which was the lowest proportion ($p<0.001$).

Table 4-2. Maternal characteristics by reporting of pregnancy outcome in first reported pregnancies 2000-2014

Characteristic	Outcome known	Gone abroad	Outcome not known	*p*-value
N	11574	203	237	
Maternal ethnicity				0.001
White	1728 (15.0%)	22 (11.1%)	17 (7.4%)	
Black African	8850 (76.6%)	163 (80.3%)	200 (87.3%)	
Other	975 (8.4%)	13 (6.4%)	12 (5.2%)	
Maternal region of birth				<0.001
UK/Ireland	1568 (13.8%)	2 (1.0%)	15 (6.8%)	
Sub-Saharan Africa	8649 (76.0%)	157 (80.1%)	190 (85.6%)	
Elsewhere	1158 (10.2%)	37 (18.9%)	17 (7.7%)	
Maternal HIV risk				0.033
Heterosexual	10407 (89.9%)	179 (88.2%)	206 (86.9%)	
IDU	246 (2.1%)	4 (2.0%)	2 (0.8%)	
Unknown	851 (7.4%)	20 (9.9%)	29 (12.2%)	
Vertical	70 (0.6%)	0 (0.0%)	0 (0.0%)	
Maternal age at diagnosis, median (IQR)	28.4 (24.6, 32.1)	27.2 (24.2, 30.7)	28.1 (25.4, 32.1)	0.048
Parity				<0.001
0	4523 (42.9%)	92 (54.8%)	87 (47.0%)	
1	3459 (32.8%)	49 (29.2%)	46 (24.9%)	
2	1653 (15.7%)	15 (8.9%)	42 (22.7%)	
3	897 (8.5%)	12 (7.1%)	10 (5.4%)	
Age at conception, median (IQR)	30.2 (26.2, 34.3)	28.2 (24.3, 32.8)	29.6 (25.8, 33.1)	<0.001
Week gestation at booking, median (IQR)	12.4 (10.0, 16.4)	14.4 (11.3, 20.9)	14.4 (12.0, 18.0)	<0.001
ART at conception	3247 (28.6%)	32 (16.4%)	37 (16.6%)	<0.001

4.2.2 CD4 count in pregnancy

CD4 count closest to delivery was available in 81.6% of pregnancies overall (14,467/17,730)., and 81.3% of first reported pregnancies in the dataset (2,244/12014 missing). The median number of days between the date of the CD4 measurement and the estimated delivery date of the pregnancy was 49 days (IQR 28 to 99 days). Table 4-3 shows CD4 count closest to delivery in all pregnancies, by timing of diagnosis and treatment at conception.

Table 4-3. CD4 count closest to delivery in all reported pregnancies

	CD4 count closest to delivery				
	Median (IQR)	CD4 < 200 *N* (%)	CD4 200-349 *N* (%)	CD4 350-499 *N* (%)	CD4 ≥500 *N*(%)
Diagnosed pre-conception, not on art at conception					
N=4035	440 (314 to 605)	333 (8.3)	966 (23.9)	1140 (28.3)	1596 (39.6)
Diagnosed pre-conception, on ART at conception					
N=5558	434 (317 to 573)	413 (7.4)	1309 (23.6)	1747 (31.4)	2,089 (37.6)
Diagnosed during pregnancy					
N=4835	410 (275 to 581)	647 (13.4)	1206 (24.9)	1232 (25.5)	1750 (36.2)

The proportion of women diagnosed before their first reported pregnancy, and not on ART at conception with a CD4 count below 350 cells/uL fell from 43.3% in 2000-2002 (90/208) to 26.5% in 2012-2014 (66/249) (test-for-trend $p<0.001$). Similarly, the proportion of women previously diagnosed and on ART at conception at their first reported pregnancy with CD4 count <350 cells/uL fell from 51.5% in 2000-2002 (121/235) to 22.2% in 2012-2014 (149/672) (test-for-trend $p<0.001$). There was some evidence of a trend in the proportion of women diagnosed during pregnancy with CD4 <350 cells/uL: this was 41.5 in 2000-2002 (307/739), fell to a nadir of 35.8% in 2009-2011 (301/841) and then rose slightly to 37.7% in 2012-2014 (148/393) (test-for-trend $p=0.04$).

Table 4-4 shows the variation in maternal characteristics by CD4 count in pregnancies to women not on ART at conception. A greater proportion of women with low CD4 (<200 cells/uL) were black African ethnicity vs. other ethnicities, born

in sub-Saharan Africa vs. UK/Ireland or elsewhere, and had acquired PHIV rather than heterosexually or IDU-acquired HIV. Maternal age at conception and age at diagnosis were both slightly higher for women with a low CD4 count, and median gestation weeks at booking was also slightly higher.

Table 4-4. Maternal characteristics by CD4 count near delivery in pregnancies to women not on ART at conception

	CD4 count near EDD/delivery			
	≥500	200-499	<200	*p*-value
N	3346	4546	980	
Maternal ethnicity				<0.001
white	699 (53.3%)	543 (41.4%)	69 (5.3%)	
black African	2305 (34.2%)	3601 (53.4%)	839 (12.4%)	
other	339 (41.9%)	400 (49.4%)	71 (8.8%)	
Maternal region of birth				<0.001
UK/Ireland	665 (52.3%)	537 (42.2%)	69 (5.4%)	
Sub-Saharan Africa	2273 (34.3%)	3523 (53.2%)	831 (12.5%)	
Elsewhere	383 (42.2%)	454 (50.0%)	70 (7.7%)	
Maternal HIV risk				0.005
heterosexual	3111 (37.7%)	4232 (51.3%)	905 (11.0%)	
IDU	73 (39.9%)	93 (50.8%)	17 (9.3%)	
Unknown	156 (38.3%)	204 (50.1%)	47 (11.5%)	
PHIV	6 (17.6%)	17 (50%)	11 (32.4%)	
Woman's age at diagnosis, median (IQR)	27.4 (23.7, 31.2)	28.1 (24.3, 31.9)	29.3 (25.7, 33.0)	<0.001
Parity				0.41
0	1176 (38.8%)	1517 (50.0%)	338 (11.2%)	
1	1087 (38.1%)	1464 (51.3%)	305 (10.7%)	
2	540 (35.4%)	803 (52.9%)	176 (11.6%)	
3	337 (38.0%)	460 (51.9%)	89 (10.0%)	
Age at conception, median (IQR)	28.9 (25.0, 33.1)	29.6 (25.9, 33.3)	30.8 (27.2, 34.1)	<0.001
Week gestation at booking, median (IQR)	12.9 (10.4, 16.6)	13.0 (10.4, 17.6)	14.0 (11.1, 20.0)	<0.001

4.2.3 Patterns of reporting

Region of report (London, rest of England, Wales, Scotland, N. Ireland and Republic of Ireland (ROI)) was available for 17717/17730 pregnancies. Overall, 44% pregnancies were reported from London (7793/17717), 44% from the rest of England (7707/17717), 1.3% from Wales (221/17717), 2.8% from Scotland (502/17717), 0.6% from N. Ireland (98/17717), and 7.9% from ROI (1396/17717).

The proportion of pregnancies reported form London fell from 63.5% in 2000-2002 (1158/63.5) to 39.5% in 2012-2014 (1324/3353), and conversely the proportion of pregnancies reported from the rest of England rose from 22.3% in 2000-2002 (406/1824) to 49.1% in 2012-2014 (1647/3353) (p<0.001). This change over time was even more pronounced for women diagnosed prior to their first reported pregnancy: 69% of first reported pregnancies were reported from London in 2000-2002 (430/622), falling to 36% in 2012-2014 (428/1186), and 18% of first reported pregnancies were reported from the rest of England (112/622), rising to 53.5% in 2012-2014 (634/1186) (p<0.001). Figure 4-4 is a choropleth map of England divided up into Health Protection Agency (HPA)[21] regions, which illustrates the number of pregnancies reported from each region over the whole study period. Figure 4-5 contains five choropleth maps illustrating the number of pregnancies reported in England per HPA region by calendar period, showing changes in regional patterns of reporting over time.

[21] The Health Protection Agency was a non-departmental public body, whose role was to provide an integrated approach to protecting UK public health through the provision of support and advice to the NHS, local authorities, emergency services, other Arms Length Bodies, the Department of Health and the others. It was set up in 2003, and merged with Public Health England in 2013 (Health Protection Agency 2018).

Figure 4-4. Map of England showing total number of pregnancies reported 2000-2014 by HPA region

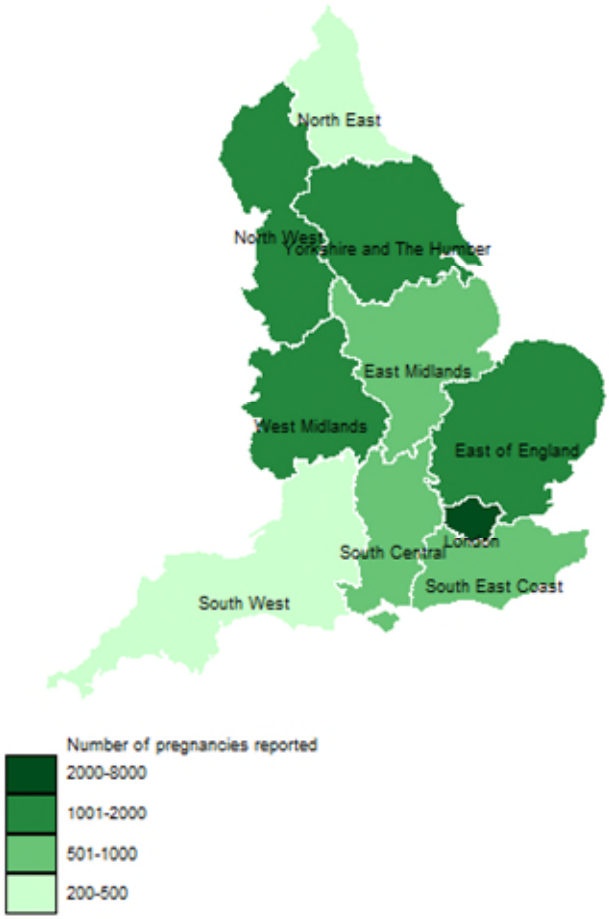
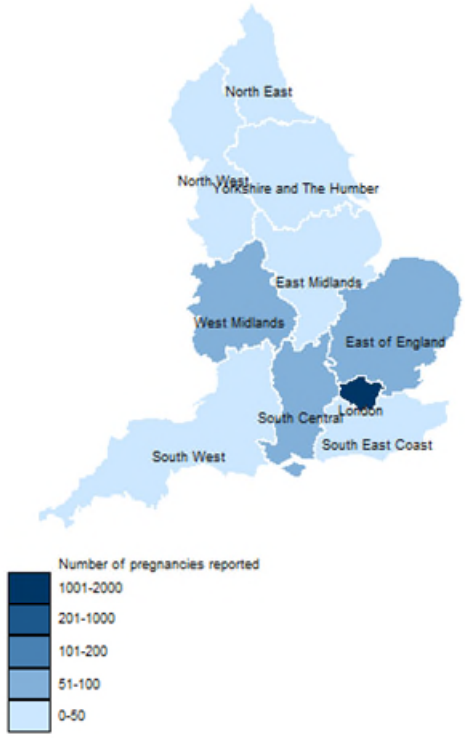


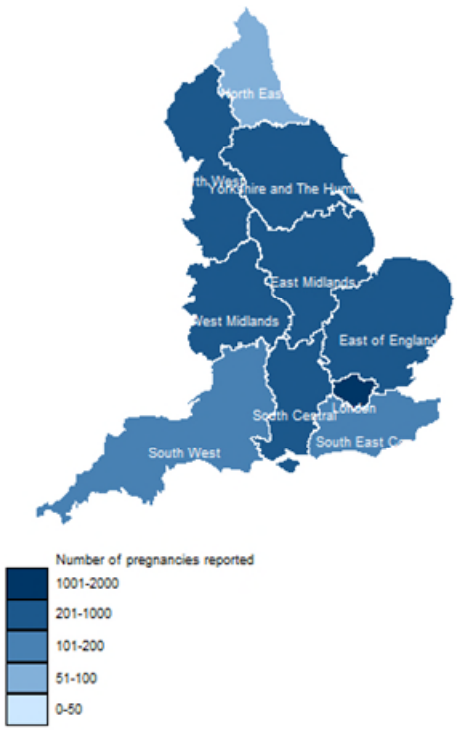
Figure 4-5. All pregnancies reported in England by year of EDD/delivery date and HPA region

A. 2000-2012

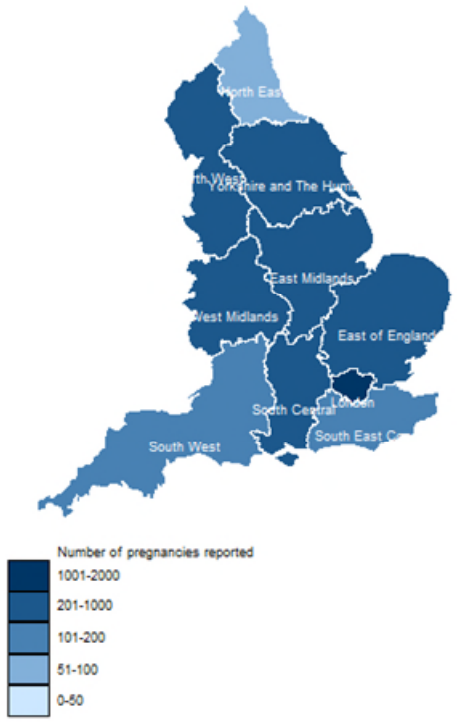


B. 2003-2005

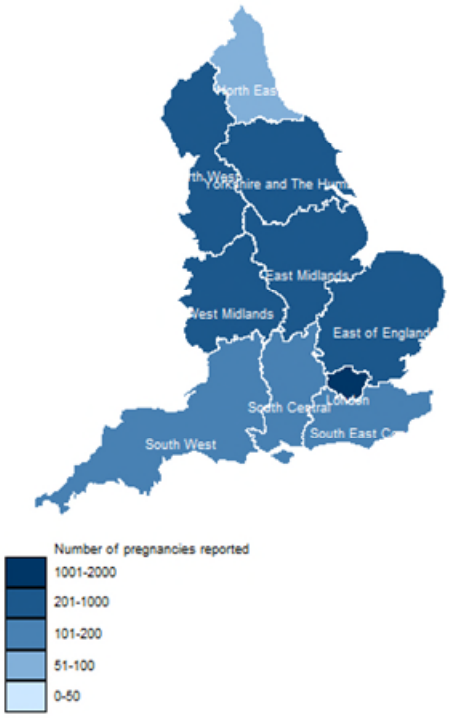
C. 2006-2008



D. 2009-2011



E. 2012-2014


East Midlands
West Midlands
East of England
South West
Number of pregnancies reported
1001-2000
201-1000
101-200
51-100
0-50

The mode of maternal HIV acquisition varied by region of report (first reported pregnancies only): The region with lowest proportion of women who likely acquired HIV through IDU was 1.2% in London (64/5150), followed by the 1.3% in the rest of England (68/5448); 1.4% in N. Ireland (1/70), 2.6% in Wales (4/152), 7.0% in Scotland (26/374), and 11.0% in ROI (89/811) (p<0.001). Over half of the 70 women with PHIV were reported from London (36/70), 23 were reported from the rest of England, and 10 from ROI. Maternal ethnic group also varied by region of report (first reported pregnancies only). The proportion of women reported from London who were Black African was 81% (4201/5135), whereas the proportion of women reported from ROI (70.5%, 570/809), Wales (50.1%, 77/152), Scotland (57.6%, 215/373), and N. Ireland (35.7%, 25/70) who were Black African was much lower (p<0.001).

When restricting to first reported pregnancies, there was evidence of a variation in region of report by timing of maternal diagnosis: 43.4% of women diagnosed during their first reported pregnancy were reported from London (2617/6028) and 44.2% were reported from the rest of England, (2664/6028). This was in comparison to 42.6% of those diagnosed before pregnancy reported from London (2522/5914) and 46.3% reported from the rest of England (2738/5914) (p<0.001).

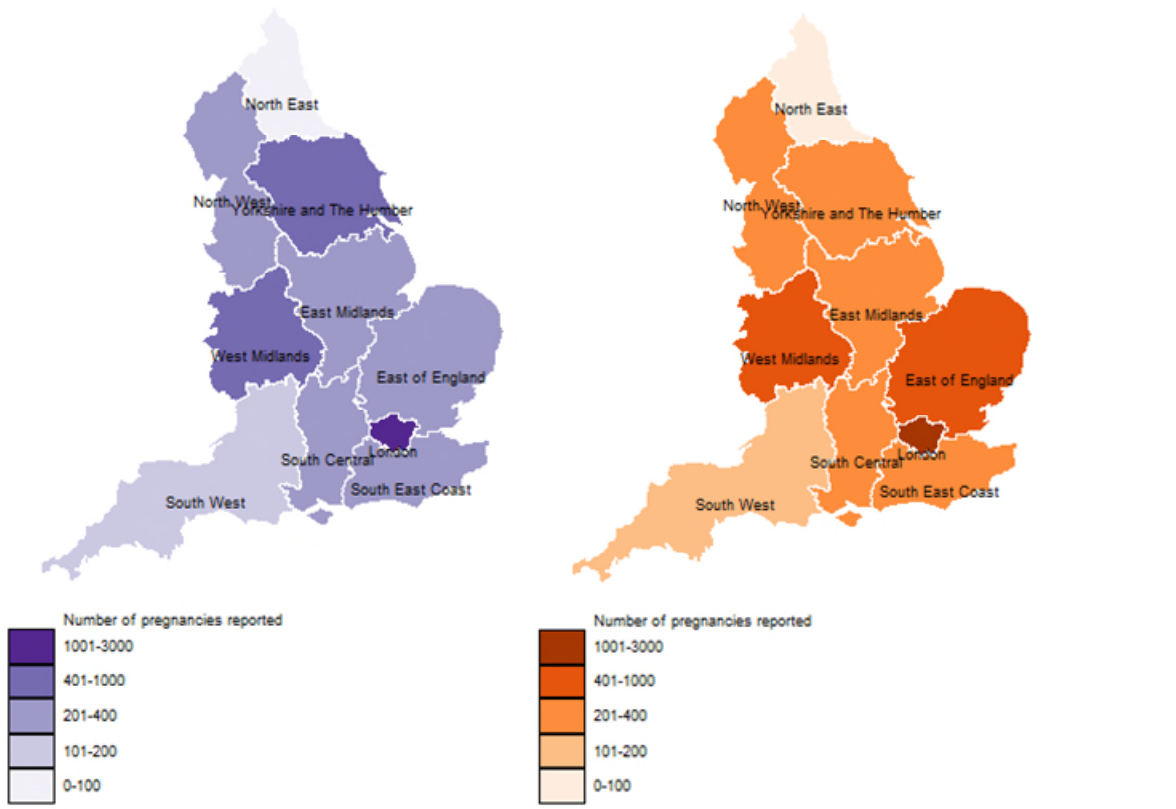
The region with the highest proportion of women diagnosed during their first reported pregnancy was N. Ireland (58.6%, 41/70), and the lowest was Scotland (46.0%, 172/374), with London somewhere in the middle (50.1%, 2617/5150) (p<0.001). Figure 4-6 is a choropleth map showing the number of first pregnancies reported by HPA region in A) women diagnosed before pregnancy and B) women diagnosed during the first reported pregnancy. There was a difference in median gestation week at antenatal booking by region: 12.1 weeks for London (IQR 9.9 to 15.4 weeks), the rest of England (IQR 9.7 to 15.6 weeks) and Wales (IQR 10.4 to 16.7 weeks); 13.1 weeks in Scotland (IQR 11.3 to 16.7 weeks), 13.7 weeks in N. Ireland (IQR 11.1 to 18.4 weeks), and 14.7 weeks in ROI (IQR 11.9 to 19.6 weeks, p<0.001).

Being on ART at conception was also associated with region of report: the highest proportion was in Wales, with 41% (88/213), the lowest in N. Ireland with 23.7% (23/97), and 39.5% of women reported from London were on ART at conception (3,003/7611) (p<0.001). As expected, when restricting to first reported pregnancy, a lower proportion were on ART at conception: 18.5% in ROI (145/784); 28.0% in the rest of England (1477/5281), and 29.9% in London (1523/5093) (p<0.001). I also

examined whether CD4 count near delivery varied by region of report in women not on ART at conception of their first pregnancy: 13.5% of women who were reported in London (first pregnancy only) had a CD4 count near delivery <200 cells/uL (409/3037), compared with 11.1% of those from the rest of England (343/3093), 9.6% of those from Wales (8/83); 10.7% of those from Scotland (23/215); 6.1% of those from N. Ireland (3/49) and 12.0% of those reported from ROI (47/393), however this variation did not reach the level of significance (p=0.06).

Figure 4-6. First pregnancies reported in England by timing of diagnosis and HPA region 2000-2014[22]

A. Women diagnosed before first pregnancy **B. Women diagnosed during first pregnancy**



[22] First pregnancy reported in the dataset, but may have had pregnancies reported with EDD/delivery date before 1st January 2000

4.2.4 Place of diagnosis and reason for test

Setting of HIV diagnosis was reported for 77.2% of women diagnosed before pregnancy (4575/5921) and 97.9% of women diagnosed during pregnancy (5849/6030).

Over half (60.8%) of women diagnosed before the first reported pregnancy were diagnosed in sexual health services (2780/4575); 3.4% in primary care (155/4575); 13.9% in another hospital department (637/4575); 10.9% were diagnosed elsewhere (500/4575), and 11.0% in antenatal services (in a previous pregnancy) (503/4575)[23]. Figure 4-7 shows setting of HIV diagnosis in A) women diagnosed before first reported pregnancy; and B) women diagnosed before first reported pregnancy and who were nulliparous.

In women diagnosed before pregnancy (Figure 4-7 A), over half (60.8%) had been diagnosed in sexual health services (2780/4575); 11.0% in antenatal services in a previous pregnancy (503/4575); 3.4% in primary care (155/4575); 13.9% in another hospital department (637/4575); and 10.9% elsewhere (500/4575). The proportion of these women who had been diagnosed in sexual health services dropped from 63.1% in 2000-2002 (325/515) to 55.3% in 2012-2014 (462/835). Over the same time period, the proportion of women who had been diagnosed in primary care rose from 2.1% in 2000-2011 (11/515) to 4.8% in 2012-2014 (40/835). These trends are more distinct in women diagnosed before pregnancy who were reported as nulliparous in their first reported pregnancy (Figure 4-7B): the proportion of women diagnosed in sexual health services fell from 74.6% (97/130) to 62.7% (244/389) over the calendar period, whereas the proportion of women diagnosed in primary care rose from 0.8% (1/130) to 6.4% (25/389); the proportion of women diagnosed in other hospital departments was 10.0% in 2000-2002 (13/130) and plateaued at around 16% in 2009-2011 (73/443) and 2012-2014 (63/389) (p=0.01). Around 3.7% of these nulliparous women had been diagnosed in a previous pregnancy: 38.8% of women reported as nulliparous in their first reported pregnancy had at least one termination or miscarriage prior to this reported pregnancy (764/1969). The vast majority (94.0%)

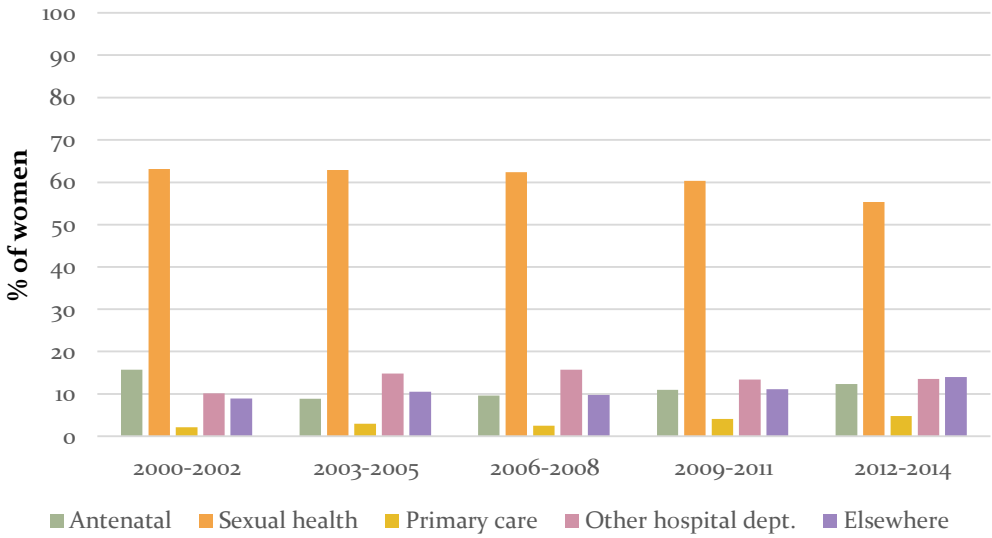
[23] 'Elsewhere' includes drug unit, private clinic, testing for insurance purposes, asylum screening, tested abroad.

of women diagnosed during the first reported pregnancy were diagnosed in antenatal services (5495/5849).

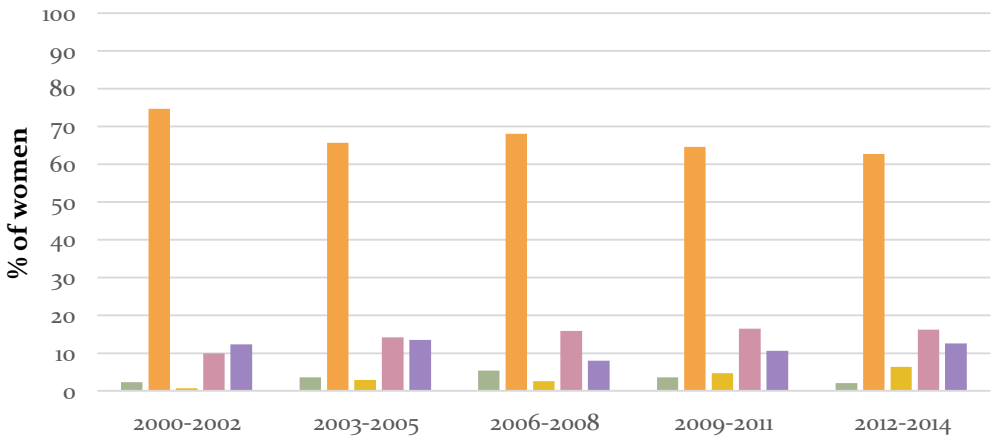
For women previously diagnosed with HIV, low CD4 during pregnancy may indicate lack of engagement after diagnosis (either with or without initial diagnosis being made at a late stage). Therefore, following on from the analysis of CD4 in pregnancy presented in 4.1, I examined the proportion of women diagnosed before the first reported pregnancy and not on ART at conception who had a low CD4 count in their first reported pregnancy (<350 cells/µl). This was a third (33.2%) of those diagnosed in sexual health services (356/1071); 35.9% of those diagnosed in primary care (19/53); 36.4% of those diagnosed in other hospital departments (60/165); 37.8% of those diagnosed in antenatal services (74/196); and 38.0% of those diagnosed elsewhere (70/184). The lowest proportion of women with CD4 count in pregnancy <350 cells/uL were those diagnosed at a sexual health clinic, indicating either that they were diagnosed earlier in their disease, or that they were less likely to disengage from care between diagnosis and reported pregnancy (since those with a low CD4 would be recommended to start ART if engaged with services), however these variations in CD4 count did not reach statistical significance (p=0.57).

Figure 4-7. Setting of HIV diagnosis by calendar year of first reported pregnancy

A) Women diagnosed before first reported pregnancy (*N*=4575)



B) Women diagnosed before first reported pregnancy and nulliparous (*N*=1696)



4.3 Survey on women who decline HIV testing in pregnancy

4.5.1. Specific Methods

This national electronic survey was a collaboration between the NSHPC and the Children's HIV Association (CHIVA). CHIVA is a registered charity working across the UK and Ireland to improve care for HIV positive children and their families. CHIVA membership consists of health and social care professionals involved in caring for children living with HIV.

My role

The Chair of CHIVA, Dr Amanda Williams (AW) had previously approached my primary supervisor, Dr Pat Tookey (PT), to collaborate on a survey of clinicians aiming to map policy and practice for women who decline HIV testing in pregnancy. There had not been any progress on this after initial discussions until I met informally with AW at the CHIVA conference 2014 (where I was presenting the initial findings from the perinatal audit (see Chapter 7)), and we discussed how best we could administer the survey. After discussion with my supervisors, PT and Dr Claire Thorne (CT), we decided that the survey fitted with my PhD objectives, so I would take on the role for refining the proposed survey questions, data collection and analysis. AW provided me with a first draft of the proposed survey questions, which I revised with input from PT, AW, and Bhanu Williams[24].

I created the survey forms in RedCap (see below); I then piloted the survey with two NSHPC obstetric respondents for content validity, who gave feedback in telephone interviews. I collected and analysed the data from respondents.

Data collection

All NSHPC respondents, and all CHIVA professional members were invited by email to complete the electronic survey in January 2015, covering 214 maternity units (169 in England, 45 in Wales, Rep Ireland and Northern Ireland, and Scotland). The survey was open for responses for a period of 3 weeks; regular reminders were sent out during this time, and queries addressed via email correspondence. The recipients of the survey invitation could pass it on to a colleague with more information to hand,

[24] Dr Bhanu Williams, Consultant Paediatrician, North West London University Healthcare NHS Trust

and only one response per maternity unit was requested. During the survey period, respondents who had submitted partial responses were individually contacted (NSHPC respondents only) to encourage them to complete the survey response. Due to data protection considerations, CHIVA were unable to share their email address list with the NSHPC, so individual troubleshooting with CHIVA members (who were not NSHPC respondents) could only be done if they had initiated contact with me (my contact details were sent out in the CHIVA emails).

Survey data were collected and managed using REDCap electronic data capture tools hosted at University College London (Harris et al. 2009). The survey questions are included in Appendix 10.2. Respondents were asked to give responses that referred to the calendar year 2014. Smaller than expected denominators indicate missing data. Percentages which total more than 100 indicate questions for which more than one answer could be given.

4.3.1 Results

There were 111 survey responses at the close of the survey; 19 responses were excluded because another response from the same unit was received which contained more complete information and a further response from a respondent at a health care facility which did not have a maternity unit was also excluded. There was a 43% response rate (91 responses from the 214 units). The response rate was 45% in England (76/169), and 43% in Scotland, Wales, Northern Ireland and the Republic of Ireland (15/45). The respondents varied in their clinical role: the majority (65%) were antenatal screening coordinators and HIV specialist midwives (59/91). The median number of deliveries during calendar year 2014 was 5000 with a range of 250 to 10,500 (interquartile range 3600 to 6300 deliveries).

Women who decline antenatal HIV testing

Seventy-four percent of respondents stated that their unit recorded the number of women who declined antenatal HIV testing in 2014 (67/91); 10% stated they did not record this information (9/91), and 17% of respondents did not know (15/91). Knowledge of this policy was strongly associated with the clinical specialty of the respondent: 60% of clinicians in paediatrics and genitourinary medicine did not know, compared to 2% of midwives ($p<0.001$).

The proportion of women who declined antenatal HIV testing in 2014 was provided by 50 of the 67 units who stated they recorded this information. The median decline rate was 0.05% (interquartile range 0% to 0.35%). Four units had a decline rate exceeding 1% of deliveries, the highest was almost 3%. The proportion of women who declined HIV testing varied by maternity unit region: the median decline rate in units in London was 0.02% (9/50 units), in units in the rest of England the median decline rate was 0.13% (36/50 units) and the decline rate in the five units in the rest of the UK and Republic of Ireland was 0% (p=0.005) There was no evidence of an association between the number of deliveries per unit in 2014 and the decline rate (p=0.21).

Policies for the management of women who decline HIV testing

The vast majority (80%) of respondents stated their unit had a local policy on management of women who decline antenatal HIV testing (73/91); 11% stated they did not (10/91); and 9% did not know (8/91). The presence of a local policy was not associated with the number of deliveries at the unit in 2014 (p=0.74), or region (p=0.18).

In the 73 units with a local policy, women declining the initial antenatal HIV test were re-offered a test by a community or antenatal clinic midwife in 71% (52/73), the screening coordinator in 26% (19/73), a specialist midwife in 26% (14/73) and by an obstetrician or Genito-urinary medicine (GUM) specialist or other consultant in 16% (12/73); 4% stated another policy (3/73). In the situation of a woman declining the re-offer of an antenatal HIV test, local policy was for this not to be pursued further in 41% (30/71) of units; 27% respondents stated that support was sought from GUM, paediatrics or other members of the multidisciplinary team (20/73); 15% stated that there would be intensive input from the midwifery team (11/73); 10% stated that it was their policy to inform the GP or health visitor (7/73); and 23% units had a different policy (17/73).

Respondents were asked to describe their unit's policy if it did not fit one of the specified options. One respondent stated that the HIV test was re-offered at each antenatal visit by the community midwife; if the woman continued to decline she received a letter from the screening coordinator explaining the importance of the screening tests and was then referred to a women's health advisor, who contacted the woman by telephone to discuss the reasons for the decline, and to offer saliva or

finger-prick testing to women who are needle-phobic. Several respondents stated that the level of intervention or support offered depended on the perceived risk of maternal HIV infection, for example women from countries with high HIV prevalence or with additional risk factors such as a history of injecting drug use would be more likely to be referred to the MDT.

Reasons women decline antenatal HIV testing

The reason women gave for declining antenatal HIV testing was routinely recorded in 43% of maternity units (39/91); in 72% this was recorded in the handheld maternity notes (28/39), in 36% in maternity case notes (14/39), in 36% in the maternity electronic record (14/39); and in 3 units this would be recorded somewhere else (3/39). The most common reason recorded for women declining antenatal HIV testing in 2014 are given in Table 4-5.

Table 4-5 Most common reasons recorded for women who decline initial offer of antenatal HIV screening (2014)

(number of respondents = 39)

Reason for declining HIV test	Yes	
	n	%
The woman did not feel she was at risk of HIV infection	22	56
The woman did not want to know if she has HIV	5	13
The woman was needle-phobic	21	54
The woman had a prior negative HIV test	16	41
No reason was given	10	26
Declined all antenatal screening	2	5
Other	2	5

Women attending in labour without a documented HIV test result

84% of respondents stated that their maternity unit had a local policy in place for women who attended in labour without a documented HIV test result (76/90); 10% stated they did not have a policy; and 6% did not know (5/90). Where units had a local policy in place, in 92% the woman would be offered a test immediately (69/75), in 4% a test would be offered if risk factors for HIV were identified (3/75), in 1% a test would be offered before hospital discharge (1/75) and in 3% a test would not routinely be offered (2/75).

Table 4-6 shows the method of HIV testing offered to women presenting in labour.

Table 4-6. Method of testing women who present in labour without a documented HIV test result

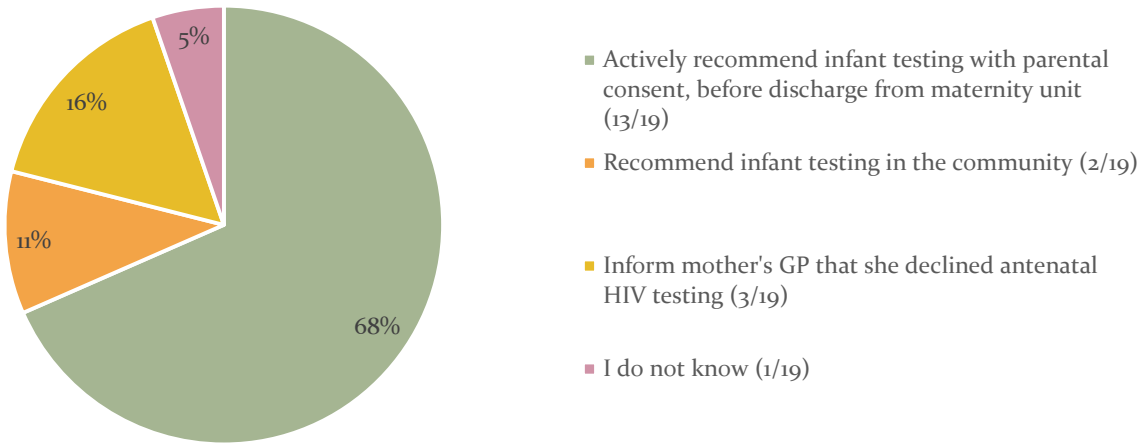
(no. of respondents = 91)

HIV test	Yes	
	n	%
Urgent HIV serology from hospital laboratory	68	75
Routine HIV serology from hospital laboratory	4	4
Rapid point-of-care HIV test, available 24 hours a day	19	21
Rapid point-of-care test, only during 'office hours'	2	2
I don't know	7	8
Other	1	1

Infant testing

Only a fifth (21%) of respondents stated that their maternity unit had a local policy on testing infants born to women who declined antenatal HIV testing (19/90); the majority (68%) stated that their unit did not have a policy (61/90) and 11% did not know (10/90). Units in London were more likely to have a policy (50% of units based in London vs. 15% in the rest of England, and 20% in other regions (p=0.01)). Of those units which did have a policy, over half (58%) stated that the recommendation of infant testing would depend on a risk assessment (11/19). The most common risk factors that were considered: mother born in high prevalence country (10/11); maternal history of injecting drug use (10/11), and mother's sexual history (10/11). Figure 4-8 shows child testing policies for those units which had one.

Figure 4-8. Child testing policies for women who declined antenatal HIV testing



Respondents who stated they did have a policy on offering infant testing were asked what would be done if the parents declined HIV testing for their child despite a recommendation; 11% said they would not pursue testing any further (2/18) and one respondent stated they would only pursue if the baby was unwell. Table 4-7 shows the actions taken for those 16 respondents who would pursue child testing further.

Table 4-7. Actions taken in the case of parents declining child testing[25]

(no. of respondents = 16)

Risk factor	Yes	
	n	%
Discuss the case in a multidisciplinary setting	12	75
Discuss with trust child safeguarding, and consider referring to child protection services	11	69
Get advice from a specialist paediatric HIV service	10	63
Inform the child's GP	5	31
Consider going to court to test child	8	50

[25] Answers could include multiple options

The respondents were asked whether their maternity unit had an accessible legal team who were able to offer advice on the best course of action if necessary: 64% answered yes (58/90); 9% answered no (8/90), and 27% did not know (24/90).

The majority (79/91) of respondents were able to state the number of cases that they were aware of in their unit during 2014 where a woman had declined all antenatal HIV testing for herself, and 39% were not aware of any cases (31/79). Of those with at least one case, 60% had between 1 and 5 cases (29/48); 21% had 6 to 20 cases (10/748); 15% had 21 to 50 cases (7/48), and two respondents had over 50 cases. Table 4-8 shows how these cases were resolved.

Table 4-8. Actions taken and outcomes achieved in cases where antenatal and infant HIV testing were declined

(no. of respondents = 48)

Action / outcome	Yes	
	n	%
No further action was taken	24	50
The parents did not consent for infant testing despite intervention by the MDT	3	6
The parents consented to infant testing after intervention by the MDT	6	13
Parents consented to infant testing after notification that the case would be referred to child safeguarding services	3	6
A court order enabled the infant to be tested	0	0
Other	4	8
I don't know	9	19

4.4 Key points

- There were 12,014 women in the dataset, with 17,730 reported pregnancies. Only 43% of women were reported to be nulliparous at first reported pregnancy – this means the remainder either had a pregnancy prior to their HIV diagnosis, or had a pregnancy reported to the NSHPC prior to 2000.
- Around half of the women in the dataset had been diagnosed prior to their first reported pregnancy, and half after. There were several trends in demographics over time in the dataset. The proportion of women diagnosed prior to their first reported pregnancy rose significantly from 37% to 71% over the study period; in nulliparous women this increase was 28% to 68%. Median age at conception in first reported pregnancy rose from 28 years to 32 years over the study period. The majority of women were thought to have acquired HIV heterosexually; the proportion of women who likely acquired HIV through IDU fell from 4% to 2% over the study period (p<0.001).
- Women who were diagnosed before their first reported pregnancy had a younger median age at diagnosis but an older median age at conception compared with those diagnosed during pregnancy (27 vs 29 years and 31 years vs 28 years respectively).
- The majority of women were Black African ethnicity, 76.3% were born in SSA. The largest group of SSA women were born in Zimbabwe, peaking at 33% of those from SSA in 2006-2008. The proportion of SSA women born in Nigeria rose across the calendar period from 10% to 16 %. The proportion of women born in Europe (not UK/Ireland) rose from 3% to 9.3% over the study period, largely driven by increasing number of women from Poland, Latvia, Ukraine and Romania. Overall, the median time from migrant women arriving in the UK/Ireland to first reported delivery date rose from 2.2 years to 7.4 years over the study period (p<0.001).
- There was a small proportion (2%) of pregnancies where women were reported to have gone abroad before the outcome of their first pregnancy was known; and outcome was unknown in a further 2% of first reported pregnancies. The proportion of unknown outcome in first reported pregnancies fell over the study period from 3% to 0.1% (p<0.001). A higher proportion of women with an unknown outcome were Black African ethnicity (87% vs. 80% for gone abroad and 77% for known outcome) and born in SSA

(86% vs. 80% of those gone abroad, and 76% for known outcome). A greater proportion of women gone abroad were nulliparous (55% compared with 47% of those with an unknown outcome, and 43% of those with a known outcome); median gestation week at antenatal booking was greater for women with unknown pregnancy outcome and known to have gone abroad (14 weeks) compared with women with a known pregnancy outcome (12 weeks); a greater proportion of women with a known pregnancy outcome were on ART at conception (29% vs. 16% for gone abroad and 17% for outcome unknown).

- Low CD4 count near delivery is a marker of advanced disease. Median CD4 count nearest delivery was lower in women diagnosed during the reported pregnancy (410 cells/uL) than those diagnosed pre-conception not on ART (434 cells/uL) or on ART (440 cells/uL). The proportion of women previously diagnosed who had a CD4<350 cells/uL fell during the study period. A greater proportion of women with low CD4 (<200 cells/uL) were black African ethnicity vs. other ethnicities, born in sub-Saharan Africa vs. UK/Ireland or elsewhere, and had acquired PHIV rather than heterosexually or IDU-acquired HIV. Maternal age at conception and age at diagnosis were both slightly higher for women with a low CD4 count, and median gestation weeks at booking was also slightly higher.
- The greatest number of pregnancy reports came from London (44%) and the rest of England (44%), 1.3% from Wales, 2.8% from Scotland, 0.6% from N. Ireland, and 7.9% from ROI. There was a clear trend over the calendar period of the study, with the proportion of women being reported from London falling from 64% to 40%, and the proportion of women being reported from the rest of England rising from 22% to 49% by the end of the study (p<0.001). In univariable comparative analysis, region of pregnancy report was associated with mode of maternal HIV acquisition, maternal ethnic group, timing of maternal diagnosis, median gestation week at antenatal booking, and being on ART at conception.
- The majority of nulliparous women diagnosed before pregnancy were diagnosed in sexual health services; however, this fell from 75% in 2000-2002 to 63% in 2012-2014. The proportion diagnosed in primary care rose from 1% to 6% over the same time period, and the proportion diagnosed in other

hospital departments rose from 10% to 16% over the study period. As would be expected, the vast majority of women diagnosed during pregnancy were diagnosed in antenatal services. A small proportion of nulliparous women were diagnosed in a previous pregnancy (4%); this may be explained by the fact that nearly 40% of women reported as nulliparous were also reported as having a previous termination or miscarriage.

- The survey of clinicians examining the management of women who decline antenatal HIV testing had a response rate of 43% (91/214 units responded). The sample contained maternity units of a range of 'sizes' (i.e. number of deliveries overall per year).
- The majority of respondents stated that their unit recorded the number of women who declined antenatal HIV testing (71%). The median decline rate was 0.05%, but four units had a decline rate exceeding 1%. The reported decline rates varied by region of maternity unit: 0.02% in London, 0.13% in the rest of England (no women were reported to have declined in the remaining five units).
- Although the majority did, 11% of respondents stated their unit did not have a policy on managing women who decline antenatal HIV testing. In those units which did have a policy (73), an HIV test was re-offered by varying clinical staff groups, but the majority (71%) of re-offers were by a community or antenatal clinic midwife (i.e. a staff member without specialist HIV experience). If a woman declined the re-offer, 41% of units would not pursue this further.
- The most common reasons recorded for declining HIV testing in pregnancy were that the woman did not feel she was at risk of HIV infection (56% of responses); that she was needle-phobic (54% of responses); and that she had previously tested negative (41% of responses).
- The majority of units did not have a policy for testing infants of women who declined antenatal HIV testing (68%). Units based in London were more likely to have a policy (p=0.01). For those units which did have a policy (n=19), the most common was to offer infant testing to parents before discharge from the maternity unit (13/19); of these respondents, the majority (16/18) units would pursue infant testing further if the parents declined the offer.

- Around 60% of respondents were aware of cases where the woman had declined all antenatal HIV screening during 2014; the majority (60%) had between 1 and 5 cases. Half of respondents said that no further action was taken. In the remaining cases, a variety of outcomes were achieved. In no cases was a court order obtained to achieve infant testing.

5 Pregnancy outcomes in women living with HIV in the UK

5.1 Introduction

The characteristics of pregnant women with HIV reported to the NSHPC have changed over time, with increasing age, increasing proportion already diagnosed and on ART at conception, and an increasing number of sequential pregnancies, which has now stabilized (French et al. 2012; Townsend et al. 2014; Townsend et al. 2008). In this chapter I describe outcomes in reported pregnancies to the NSHPC delivered or due to deliver between 2000 and 2014. In the first part of the chapter I concentrate on describing reported miscarriages, terminations, live births and stillbirths in the population overall, and examine trends in pregnancy outcome over time. I briefly examine ART taken by women during pregnancy over the study period (a more detailed look at individual drugs and patterns of prescribing is presented in Chapter 6). I also describe and compare pregnancies in which women did and did not achieve an undetectable VL, and trends over time, as background to the multivariable analysis of factors associated with detectable VL at delivery presented later in the chapter.

In the second half of this chapter I estimate the incidence of first pregnancy in women with PHIV first reported to the NSHPC as children and examine in detail the pregnancy outcomes of women with PHIV, comparing outcomes with an age-matched comparison group of women who acquired HIV behaviourally. Since all children diagnosed with HIV are reported to the study, and then all pregnancies in women living with HIV are reported, this gave me a unique opportunity to calculate a national pregnancy incidence rate for women with PHIV in the UK for the first time.

Young people living with PHIV have a higher risk of treatment failure and multiclass drug resistance than those with behaviourally-acquired HIV (BHIV) for many reasons: previous exposure to obsolete and suboptimal antiretroviral therapy (ART); the limited range of ART licensed for use in childhood; and difficulties with adherence because of stigma, discrimination, and HIV-associated neurocognitive deficits, among others (Sohn and Hazra 2013). Several studies have compared women with PHIV to those with BHIV to estimate the effects of mode of HIV acquisition on

pregnancy and infant outcomes (Agwu et al. 2011; Badell et al. 2013; Jao et al. 2015; Munjal et al. 2013) however, such comparisons have been limited by key differences between groups regarding age, parity, and treatment era. In order to minimise these differences, I constructed a comparison group of women with BHIV who were nulliparous at first reported pregnancy; diagnosed with HIV before the first reported pregnancy and had similar age distribution to the women with PHIV. My analysis finishes with multivariable analysis of factors associated with an undetectable VL near delivery, and factors associated with adverse pregnancy outcome in these two groups.

5.2 Pregnancy outcomes overall

There were 17,730 pregnancies reported in 12,014 women who delivered or were due to deliver between 1st January 2000, and 31st Dec 2014, reported to the study by Sep 2014. Of these 17, 730 pregnancies, outcome was not known in 2.8% of pregnancies (505/17,730), in 2.3% the outcome was recorded as 'continuing' (404/17,730), and 36 were reported to be ectopic pregnancies. These 945 pregnancies were excluded from the descriptive analysis presented in 5.3 and 5.4.

After these exclusions, 67.5% of 16,785 pregnancies in the dataset were the woman's first pregnancy reported to the NSHPC which delivered or was due to deliver after 1st January 2000; 23.9% the second reported pregnancy; 6.8% the third reported pregnancy; and 1.9% the fourth or subsequent pregnancy reported.[26]

Women were reported to be nulliparous in 43.0% of first reported pregnancies in the dataset. In the remaining 57%, the woman either had a live- or stillbirth prior to January 2000 reported to the NSHPC, or a live or stillbirth before she was diagnosed with HIV or before she arrived in the UK that was therefore not reported to the study. The maximum number of reported pregnancies in the dataset for one woman was seven.

Table 5-1 and Figure 5-1 show outcome of pregnancy by first or subsequent reported pregnancy per woman. There was evidence of a significant variation in outcome of

[26] Only sequential pregnancies with delivery date or estimated delivery date between 1st January 2000 and 31st December 2014 included in the dataset, therefore a woman may have had a previous pregnancy reported to the NSHPC not included in the dataset

pregnancy by rank of sequential pregnancy reported per woman (i.e. first, second, third pregnancy etc.). For example, the proportion of terminations was highest in 1st reported pregnancies (3.5%) and ≥4th pregnancy, and the proportion of miscarriages rose from 5.6% in first reported pregnancies to 10.5% in ≥4th reported pregnancy (χ^2 p<0.001). However, there was no evidence of a significant ordinal trend in pregnancy outcome with increasing rank of sequential pregnancy reported (test-for-trend p=0.54).

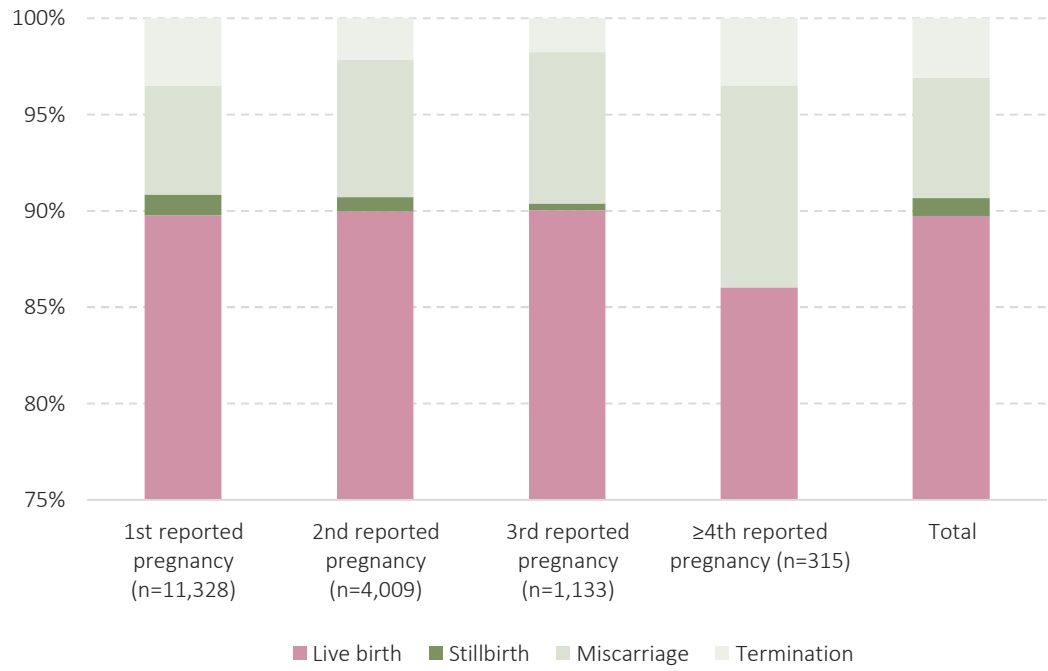
Overall, 5.2% of women were not on ART during the pregnancy (843/16,294); 6.6% were treated with mono- or dual therapy (1,069/16294); and 88.3% were treated with cART of 3 drugs or more (14,382/16,294). The proportion of women treated with cART rose from 65.6% in 2000-2002 (1125/1,714) to 96.1% in 2012-2015 (2,741/2,851) (p<0.001).

Table 5-1. Outcome of pregnancy by number of sequential pregnancy reported per woman

		1st reported pregnancy per woman	2nd reported pregnancy per woman	3rd reported pregnancy per woman	≥4th reported pregnancy per woman	Total
Live birth	*n*	10169	3607	1020	271	15067
	(%)	(89.8)	(90.0)	(90.0)	(86.0)	(89.8)
Stillbirth	*n*	122	30	4	0	156
	(%)	(1.1)	(0.7)	(0.4)	(0)	(0.9)
Miscarriage	*n*	638	285	89	33	1,045
	(%)	(5.6)	(7.1)	(7.9)	(10.5)	(6.2)
Termination	*n*	399	87	20	11	517
	(%)	(3.5)	(2.2)	(1.8)	(3.5)	(3.1)
Total	*n*	11328	4009	1133	315	16785

NOTE: Women may have had a pregnancy reported to the NSHPC delivered or due to deliver before 1st Jan 2000 not included in the dataset

Figure 5-1. Outcome of pregnancy by number of sequential pregnancy reported per woman



5.2.1 **Terminations & miscarriages**

Overall, 3.1% of reported pregnancies ended in termination (517/16785) and 6.2% ended in miscarriage (1045/16785). Table 5-2 shows pregnancy outcomes by calendar period.

Table 5-2 shows that the proportion of reported pregnancies ending in miscarriage rose from 4.8% in 2000-2002 to 8.6% in 2012-2014 ($p<0.001$). In 1,045 reported miscarriages, 84% of women were diagnosed before the pregnancy (878/1,045); 14.6% were diagnosed during the pregnancy (153/1,045), and in 1.3% pregnancies timing of maternal diagnosis was missing (14/1045). Table 5-3 shows timing of maternal diagnosis by calendar period in pregnancies ending in miscarriage. The proportion of women diagnosed prior to pregnancy rose from 72.6% in 2000-2002 to 90.1% in 2012-2014 (test-for-trend $p<0.001$) (a higher proportion than overall in all pregnancy outcomes (see page 91). When restricting to women diagnosed before pregnancy, the proportion of miscarriage was 4.8% in 2000-2002 (84/1742), dropping slightly to 4.3% in 2003-2006 (149/3476), and then rising to 5.4% 2006-2008 (231/4291), 7.6% 2009-2011 (328/4338) and 8.6% in 2012-2014 (253/2938) (test-for-trend $p=0.008$).

Table 5-2. Pregnancy outcome by year of delivery or estimated delivery date (grouped)

		Year of delivery or EDD*					
		2000-2002	2003-2005	2006-2008	2009-2011	2012-2014	Total
Livebirth	*n*	1540	3141	3896	3876	2614	15067
	(%)	(88.4)	(90.4)	(90.8)	(89.4)	(89.0)	89.8)
Stillbirth	*n*	15	41	43	42	15	156
	(%)	(0.9)	(1.2)	(1.0)	(1.0)	(0.5)	(0.9)
Miscarriage	*n*	84	149	231	328	253	1045
	(%)	(4.8)	(4.3)	(5.4)	(7.6)	(8.6)	(6.2)
Termination	*n*	103	145	121	92	56	517
	(%)	(5.9)	(4.2)	(2.8)	(2.1)	(1.9)	(3.1)
Total	*n*	1742	3476	4291	4338	2938	16785

*Year of birth for live and stillbirths, year of estimated delivery date for terminations and miscarriages

Table 5-3. Timing of maternal diagnosis in pregnancies ending in miscarriage, by year of EDD

		Year of estimated delivery date					
		2000-2002	2003-2005	2006-2008	2009-2011	2012-2014	Total
Before pregnancy	n	61	116	184	289	228	878
	%	72.6	77.9	79.7	88.1	90.1	84.0
During pregnancy	n	23	33	46	34	17	153
	%	27.4	22.1	19.9	10.4	6.7	14.6
Unknown / missing	n	0	0	1	5	8	14
	%	0	0.0	0.4	1.5	3.2	1.3
Total	n	84	149	231	328	253	1,045

Table 5-2 shows that the proportion of pregnancies reported that ended in termination fell from 5.9% in 2000-2002 to 1.9% in 2012-2014 (p<0.001). In 517 reported pregnancies ending in termination, 68.2% of women were diagnosed before the pregnancy (353/517), 31.3% were diagnosed during the pregnancy (162/517), and in 2 pregnancies timing of diagnosis was missing.

Median age at conception was 33 years for pregnancies ending in miscarriage (IQR: 28 to 37 years) and 30 years for pregnancies ending in termination, live birth or stillbirth (IQR: 26 to 34 for each); this variation in median age at conception reached statistical significance (p<0.001). The median age at conception for pregnancies ending in miscarriage rose from 30 years in 2000-2002 to 34 years in 2012-2014 (IQR: 27.5 years to 36 years, and 29 years to 38 years respectively). The median age at conception for pregnancies ending in termination was 29 years in 2000-2002 (IQR: 25 to 32), 32 years in 2009-2011 (IQR: 27 to 36) and 31 years in 2012-2014 (IQR 27 to 37). Figure 5-2 shows median age at conception by time period for live births and stillbirths (A), and miscarriages and terminations (B).

In pregnancies ending in miscarriage, 74.5% of women were of black African origin (779/1039), 15.5% were white (161/1039), and 9.5% (99/1039) were of another ethnicity; 15.5% of women with a reported miscarriage were born in the UK or Ireland (156/1005), 74.4% were born in sub-Saharan Africa (758/1005), and 9.1% were born elsewhere (91/1005). In pregnancies ending in termination, 76.8% of women were black African (393/512), 13.9% were white (71/512), and 9.4% were of another ethnicity (48/512); 76.7% of women with a reported termination were born in sub-Saharan Africa (376/490), 13.1% were born in the UK or Ireland (64/490), and 10.2% were born elsewhere (50/490).

There was significant association between outcome of the pregnancy reported and the route of maternal HIV acquisition. In pregnancies ending in termination, 2.3% of women were reported to have perinatal HIV (PHIV) (12/517), compared to <0.5% in all other outcomes (p<0.001). Of the 97 reported pregnancies in women with PHIV[27],

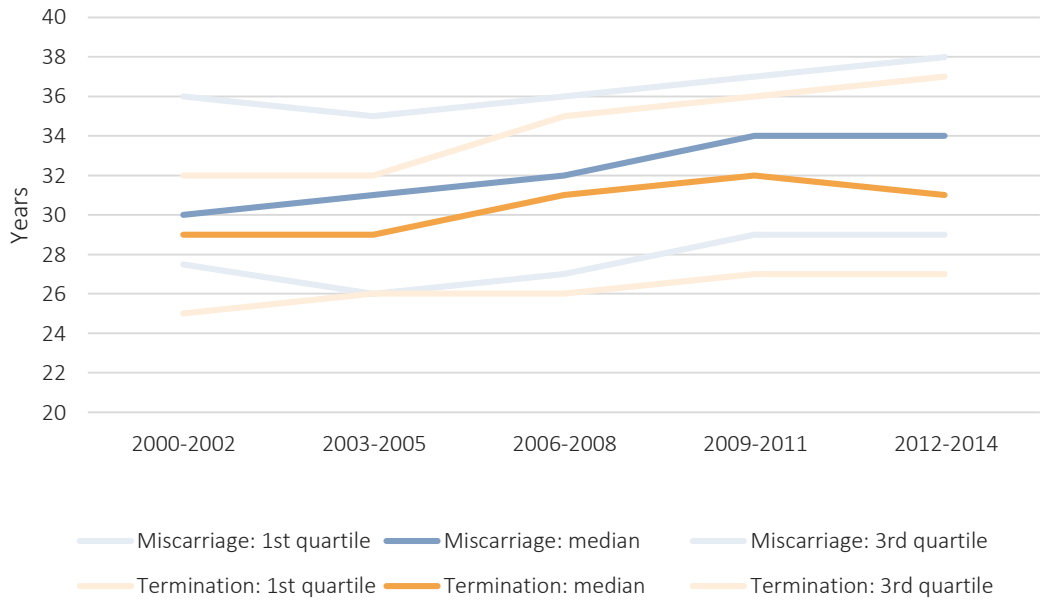
[27] These are all the pregnancies in women reported to be perinatally infected in the dataset, and not subject to the additional inclusion / exclusion criteria in the subsequent analysis of pregnancy outcomes in women with PHIV.

12.4% ended in termination, compared to 3.0% of the 15,354 pregnancies in women with behaviourally-acquired HIV (BHIV) (see Table 5-4).

There were 32 women who had two reported terminations in the dataset (no women had more than two reported). These women had a slightly lower median age at conception (28.5 years for women with two reported terminations, IQR: 26 to 31; compared with 30 years for women with only one termination reported (30 years, IQR: 26 to 34). Women with two reported terminations were slightly less likely to have acquired their HIV heterosexually (87.5%, 28/32) than women with only one reported (89.5% 434/485), with 6.2% of women with two reported terminations having likely acquired HIV through injecting drug use (2/32) compared with 1.7% of women with one reported (8/485), and 6.3% of women with two reported terminations had PHIV (2/32), compared with 2.1% of women with one reported termination (10/485) (p=0.04). There was no significant difference in maternal ethnicity between women with one and two reported terminations (p=0.95).

Figure 5-2. Median age at conception by year of birth (or EDD)

(A)



(B)

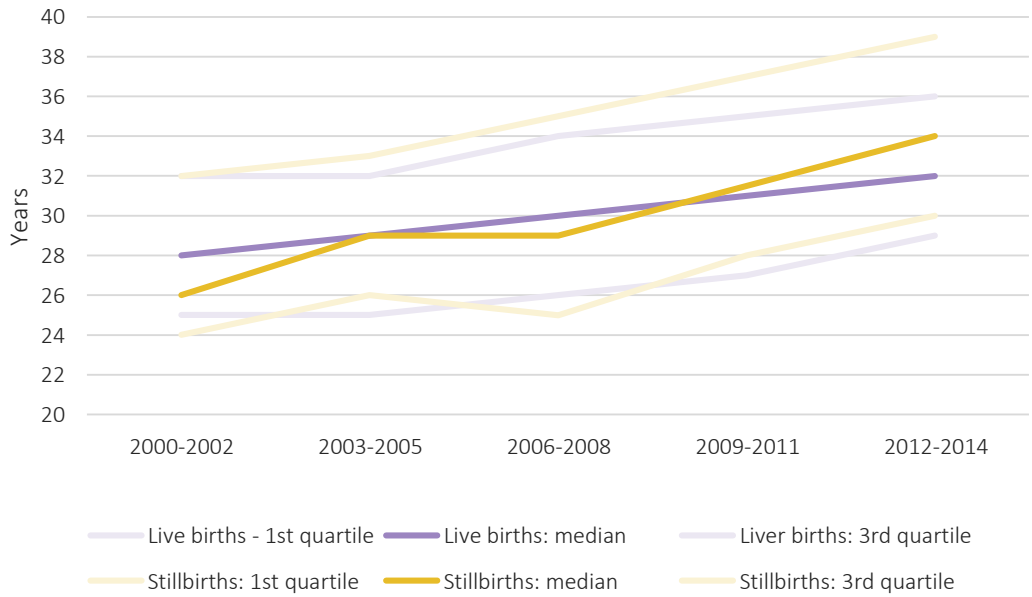


Table 5-4. Outcome of pregnancy by reported route of maternal HIV acquisition

		Live birth	Stillbirth	Miscarriage	Termination	Total
Heterosexual	*n*	13,839	140	913	462	15,354
	%	90.1	0.9	6.0	3.0	100
Injecting drug use	*n*	313	3	31	10	357
	%	87.7	0.8	8.7	2.8	100
Unknown	*n*	835	13	96	33	977
	%	85.5	1.3	9.8	3.4	100
Perinatal	*n*	80	0	5	12	97
	%	82.5	0	5.2	12.4	100
Total	*n*	15,067	156	1,045	517	16,785

The proportion of women not treated with any ART in pregnancies ending in miscarriage fell from 61% (41/77) in 2000-2002 to 17.6% in 2012-2014 (34/193), and the proportion treated with cART rose from 35.1% (27/77) to 80.3% (155/193) (p<0.001). The proportion of women untreated in pregnancies ending in termination fell from 69.9% in 2000-2002 (65/93) to 20.4% in 2012-2014 (10/49), and the proportion treated with cART rose from 25.8% in 2002-2012 (24/93) to 77.6% in 2012-2014 (38/49).

The proportion of women on ART at conception was 52.4% in pregnancies ending in miscarriage (483/922) and 39.4% in pregnancies ending in termination (192/487). The proportion of women on ART at conception in pregnancies ending in miscarriage rose from 33.8% in 2000-2002 (27/80) to 70.6% in 2012-2014 (151/214) (p<0.001). The proportion of women on ART at conception in pregnancies ending in termination rose from 32.7% in 2000-2002 (32/98) to 66.0% in 2012-2014 (35/53) (p<0.001).

In women treated with cART, 48.5% of women with a miscarriage were treated with PI-based cART (249/513); 44.8% were treated with NNRTI-based cART (230/513); 2.3% had NRTI-only cART (12/513); and 4.3% had cART containing both a PI and NNRTI (22/513). A slightly higher proportion of women with a pregnancy ending in termination were treated with NNRTI-based cART (52.4%, 99/189); 38.1% were treated with PI-based cART (72/189); 4.8% had NRTI-only cART (9/189); and 4.8% had both NNRTI and PI-based cART (9/189). Women received the NNRTI efavirenz in pregnancy in 10.3% of terminations (53/517), compared with 6.7% in pregnancies

ending in live birth (992/15,067), 6.9% of miscarriages (72/1,045), and 7.1% of still births (11/156) (p=0.01).

Table 5-5. Congenital abnormalities in terminated pregnancies

Name of congenital abnormality	Number of affected terminations	Woman in receipt of ART at conception	
		n	%
Chromosomal abnormalities			
Down syndrome	10	5	50.0
Trisomy 18	6	5	83.3
Turner syndrome	1	0	0
Other	4	1	25.0
Heart defects			
Unspecified	2	2	100
Tricuspid atresia	1	1	100
Cephalic abnormalities			
Anencephaly	4	0	0
Enlarged cerebral ventricles	1	1	100
Skeletal / spinal abnormality			
Spina bifida	4	3	75.0
Unspecified	1	-	-
Achondroplasia	1	0	0
Renal abnormality			
Hydronephrosis	1	0	0
Renal agenesis	1	0	0
Gastrointestinal abnormality			
Exomphalos	2	1	50.0
Diaphragmatic hernia	1	0	0
Bowel obstruction / unspecified	1	0	0
Cleft palate and/or hare lip	1	0	0
Unspecified abnormality	2	2	100
TOTAL	44	21	47.7

In 8.5% of reported terminations, the foetus was found to have congenital abnormality (44/517)[28], compared with 2.8% of livebirths (415/15,067), 1.1% of

[28] For congenital abnormality reporting, 105/517 terminations were reported as having no congenital abnormality, and in 368/517 this variable was not reported. I have assumed that

reported miscarriages (11/1045) and 9.0% of reported stillbirths (14/156) (p<0.001). One woman had two terminations with congenital abnormality reported in both foetuses. Table 5-5 shows the range of congenital abnormalities reported in terminations. The proportion of reported congenital abnormality was 7.1% in women not on ART at conception (21/295) and 11.5% in women on ART at conception (22/192) but this difference did not reach statistical significance (χ^2 p=0.10).[29] The proportion of terminations affected by congenital abnormality was 0.74% in pregnancies terminated at 12 weeks' gestation or less (2/272), 9.0% in pregnancies terminated at 13 to 18 weeks' gestation (14/155); 29.9% of pregnancies terminated at 19 to 24 weeks gestation (26/87), and two out of three pregnancies terminated after 24 weeks gestation (p<0.001).

5.2.2 Live births & stillbirths

Overall, 89.8% of pregnancies in the dataset ended in live birth (15,067/16,785), and 0.9% of pregnancies ended in stillbirth (156/16,785). The proportion of both outcomes remained fairly constant over calendar time (see Table 5-2). The proportion of multiple pregnancy was 1.9% in live births (286/15,067) and 3.2% in stillbirths (5/156) (p<0.001).[30]

Characteristics of the women

Similarly to pregnancies ending in miscarriage and termination, the proportion of women diagnosed before conception in livebirths rose from 37.8% in 2000-2002 (582/1540) to 84.6% in 2012-2014 (2,212/2,614) (p<0.001). However, there was no evidence of trend over time in the proportion of women with a reported stillbirth who were diagnosed before conception (test-for-trend p=0.70); the overall proportion was 60.9% (95/156).

There was a steeper rise in age at conception for stillbirths compared with live births across year groups (see Figure 5-2B). Median age at conception for live births rose

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these terminations where congenital abnormality was not reported were unaffected. Timing of diagnosis of congenital abnormality is not reported, so I cannot infer whether terminations were as a result of congenital abnormality diagnosed antenatally, but this is likely to be a reason for termination especially in terminations at later gestation.

[29] In half of the terminations with congenital abnormality reported, individual drugs were not reported, precluding analysis of individual drugs.

[30] Second (or higher) order infants from multiple births are excluded from analyses unless otherwise stated.

from 28 in 2000–2002 to 32 years in 2012-2014, whilst that for stillbirths rose from 26 to 34 years over the same period.

In pregnancies to women of black African ethnicity, 90.0% ended in live birth (11, 636/12, 934), and 0.97% in stillbirth (126/12,934); 89.9% of pregnancies to white women ended in live birth 2,188/2,435), and 0.62% ended in stillbirth (15/2,435); 88.4% of pregnancies to non-white non-black African women ended in live birth (1,236/1,398), and 1.1% ended in stillbirth (15/1398), however this difference in outcomes did not reach statistical significance (p=0.16). Similarly, there was no evidence of a significant difference in the proportion of live and still birth by maternal region of birth: the proportion of live births was 89.8% in women born in the UK/Ireland (2,091/2,328), 91.3% in those born in the rest of Europe (548/600); 90.1% in women born in Africa (11,460/12,714), and 88.9% in women born elsewhere (848/954) the proportion of stillbirths was 0.94% in women born in Africa (120/12,714); 0.73% in women born in the UK/Ireland (17/2328); 0.83% in women born in the rest of Europe (5/600) and 1.26% in women born elsewhere (12/954) (p=0.6).

Gestational age and birthweight

The median gestational age at delivery for live births was 38 weeks in year groups 2000-2002, 2003-2005, 2006-2008, 2009-211 (IQR 38 to 39 weeks) and 39 weeks in 2012-2014 (IQR 38 to 40 weeks). The proportion of live births born at less than 37 weeks' gestation fell over the time period: 14.3% in 2000-2002 (218/1528); 13.1% in 2003-2005 (409/3115), 13.6% in 2006-2008 (528/3876), 11.1% in 2009-2011 (94273865), and 11.1% in 2012-2014.(289/2594) (p<0.001). The proportion of live births born at less than 32 weeks' gestation was lower in deliveries in the latter calendar periods, but this did not reach statistical significance: 2.8% in 2000-2002 (42/1528); 3.0% in 2003-2005 (94/3115), 2.9% in 2006-2008 (111/3876), 2.5% in 2009-2011 (98/3865), and 2.31% in 2012-2014 (60/2594) (p=0.12). The proportion of live births delivered before 37 weeks' gestation was 14.8% in white women (321/2165), 12.0% in black African women 1385/11,575), and 13.4% in women of non-white non-black African ethnicity (165/13.4) (p=0.001).

Overall, 86.3% of live born infants weighed 2.5kg or more (12,052/13,958). In live births at or after 37 weeks' gestation, 94.3% of infants weighted 2.5kg or more (11,520/12,223); 5.7% weighed 1.5 to <2.5kg (702/12,223) and one infant weighed <1.5

kg. Of infants born at term to women of black African ethnicity, 94.7% weighed ≥2.5kg (9009/9517), compared with 93.0% of infants born to white women (1603/1723), and 91.9% of infants born to non-black African non-white women (921/1002) (p=0.001).

5.2.3 Antiretroviral therapy in pregnancies ending in live birth[31]

In pregnancies ending in live birth, 91.2% of women were treated with cART[32] (13,545/14,851)[33]; 5.9% of women were treated with monotherapy (880/14,851); 1.0% with dual therapy (150/14851); and 1.8% were untreated (265/14850).

Mono- and dual therapy

In women treated with monotherapy, 99.4% were treated with zidovudine (849/854). The proportion of women treated with monotherapy fell from 18.4% in 2000-2002 (320/1742) to 1.1% in 2012-2014 (32/2938) (test-for-trend p<0.001).

Of the 150 women who were recorded as being treated with dual therapy, 54% received zidovudine plus lamivudine (81/150). 15 women coded as being on dual therapy were on a PI boosted with ritonavir, which is considered functional monotherapy. The remaining 54 women were treated with either 2 NRTIs (not zidovudine + lamivudine) or one NRTI plus an NNRTI.

Combination ART

Overall, 39.3% of women treated with cART with a live birth were on ART at conception (5,202/13,245). Over the time period, the proportion of women on cART at conception rose from 25.4% (264/1039) in 2000-2002 to 60.1% in 2012-2014 (1488/2475) (test-for-trend p<0.001).

Women treated with cART received a PI-based regimen in 61.0% of pregnancies (8,266/13,545); an NNRTI-based regimen in 32.0% (4,337/13,545); both a PI and an

[31] This is a brief outline of antiretrovirals in pregnancy - trends in individual and combinations of drugs are explored in Chapter 6.
[32] cART refers to combination antiretroviral therapy of three or more drugs (not including the pharmacological boosters low-dose ritonavir or cobicistat)
[33] There were a total of 15,067 live births in the dataset, so any antiretroviral treatment information is missing in 416 live births (2.3%).

NNRTI in 5.1% (684/13,545); NRTI-only cART in 1.6% (214/13,545); and NRTI plus raltegravir in 0.32% (44/13,545).

Viral load at delivery

Overall, women achieved a VL <50 copies/ml near delivery in 71% of live births (9835/13,803); 14.8% had a VL 51-400 copies/ml (2,038/13,804); 3.5% had a VL 401-1000 copies/ml (481/13,804); 5.8% had a VL 1001-10,000 copies/ml (804/13,804); and 4.7% had a VL >10,000 copies/ml (646/13,804). The proportion of women with a VL <50 copies/ml near delivery increased from 40.3% in 2000-2002 (495/1229) to 86.8% in 2012-2014 (2,173/2,504) (test-for-trend $p<0.001$). Table 5-6 shows the association between maternal and pregnancy characteristics and undetectable VL during delivery.

For women with live births not on ART at conception, there was an association between class of cART and achieving an undetectable VL near delivery: 65.4% of women treated with PI-based cART achieved an undetectable VL (3606/5509) compared with 57.9% of women treated with NNRTI-based cART (984/1699), and 80.1% of women treated with NRTI-only cART or raltegravir plus 2 NRTIs (117/146) ($p<0.001$). Median start of cART for women not on ART at conception was 22.6 weeks for women who achieved an undetectable VL near delivery (IQR 19.4 to 25.7 weeks) compared with 25.1 weeks for women who had a detectable VL near delivery (IQR 21 to 29 weeks) ($p<0.001$).

There was also an association between class of cART and undetectable VL near delivery for women with livebirths on cART at conception: 94.7% of women on NNRTI-based cART achieved an undetectable VL (2152/2272) compared with 89.0% of women on PI-based cART (2021/2270, 92.2% of women on NRTI only or raltegravir + 2 NRTIs (94/102); and 77% of women on both a PI and NNRTI (314/403) ($p<0.001$).

Table 5-6. Maternal and pregnancy characteristics by viral load near delivery in live births

	Maternal viral load near delivery (copies/ml)		
	<50	≥50	*p*-value
Number of pregnancies	9835	3969	
Maternal ethnicity			0.37
white	1409 (70.2%)	582 (29.2%)	
black African	7613 (71.5%)	3035 (28.5%)	
other	808 (69.7%)	352 (30.3%)	
Maternal region of origin			0.11
UK/Ireland	1314 (69.3%)	582 (30.7%)	
Africa	7514 (71.6%)	2974 (28.4%)	
elsewhere	933 (70.8%)	384 (29.2%)	
Maternal HIV risk			<0.001
heterosexual	9033 (71.1%)	3666 (28.9%)	
injecting drug use	163 (60.4%)	107 (39.6%)	
unknown	587 (77.3%)	172 (22.7%)	
perinatal	52 (68.4%)	24 (31.6%)	
Woman's age at diagnosis, median (IQR)	27.9 (24.3, 31.3)	27.6 (23.9, 31.4)	0.071
Parity			<0.001
0	2701 (67.5%)	1300 (32.5%)	
1	3391 (72.2%)	1243 (26.8%)	
2	2066 (75.7%)	663 (24.3%)	
3	1172 (71.9%)	457 (28.1%)	
Age at conception, median (IQR)	31.5 (27.5, 35.1)	29.3 (25.5, 33.1)	<0.001
Gestation at booking (weeks), median (IQR)	12.3 (10.0, 15.6)	13.7 (10.7, 20.0)	<0.001
Woman on ART at conception	4603 (90.6%)	478 (9.4%)	<0.001
Type of ART			<0.001
untreated	27 (17.3%)	129 (68.4%)	
mono	250 (31.6%)	541 (68.4%)	
dual	72 (62.6%)	43 (37.4%)	
cART	9460 (74.5%)	3239 (25.5%)	
CD4 count nearest delivery			<0.001
≥500	3887 (77.0%)	1162 (23%)	
350-499	2845 (74.5%)	974 (25.5%)	
200-349	2137 (67.3%)	1040 (32.7%)	
<200	673 (54.5%)	561 (45.5%)	

5.2.4 Mode of delivery in pregnancies ending in live birth

The dataset covers a time period with evolving evidence on the role of mode of delivery in preventing vertical transmission of HIV, with UK guidelines changing to reflect this. In the first UK pregnancy guidelines published by BHIVA in 2001, elective CS was recommended for all women living with HIV (Mercy et al. 2001); in 2005 vaginal delivery emerged as an 'option' for women with undetectable VL at 36 weeks' gestation (Hawkins et al. 2005); since 2012 vaginal delivery has been recommended for all women with undetectable VL, in the absence of obstetric indication for CS (Taylor et al. 2012). Among 15,014 live births over the study period, 31.9% of women gave birth vaginally (4,796/15,014), 44.1% had an elective caesarean section (CS) (6626/150,14) and 23.9% had an emergency CS (3592/15,014). The proportion of live births delivered vaginally rose from 17.6% in 2000-2002 (270/1533) to 45.0% in 2012-2014 (1174/2609) (test-for-trend $p<0.001$). Figure 5-3 shows mode of delivery by year of birth for A) all live births B) women with VL near delivery <50 copies/ml C) women on ART at conception and D) women not on ART at conception.

In the 6860 live births where planned mode of delivery was available[34], 32.6% of women who planned vaginal delivery had an emergency CS (1282/3931), and 23.0% of women who planned elective CS delivered by emergency CS (673/2929) ($p<0.001$)[35].

The emergency CS rate for women who planned vaginal delivery was 41.1% in 2006-2008 (293/713); 33% in 2009-2011 (534/1603); and 28.0% in 20012-2014 (451/1604). The emergency CS rate for women who planned elective CS was 30.1 in 2006-2008 (267/888); 20.0% in 2009-2011 (235/1179); and 19.4% in 2012-2014 (161/828).

There were 286 multiple live births, 185 of these were in women with VL near delivery <50 copies/ml, and in 113/185 planned mode of delivery was reported: 17.7% women planned vaginal delivery (20/113) and 82.3% planned elective CS (93/113). Among women who planned vaginal delivery, 35.0% had an emergency CS (7/20)

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[34] Planned mode of delivery was requested from obstetric respondents from 2006. In births 2006-2008, 41.1% of livebirths had planned mode of delivery reported; 2009-2011 had planned mode of delivery reported in 71.8%; and 2012-2014 planned mode of delivery was reported in 93.1% of live births.

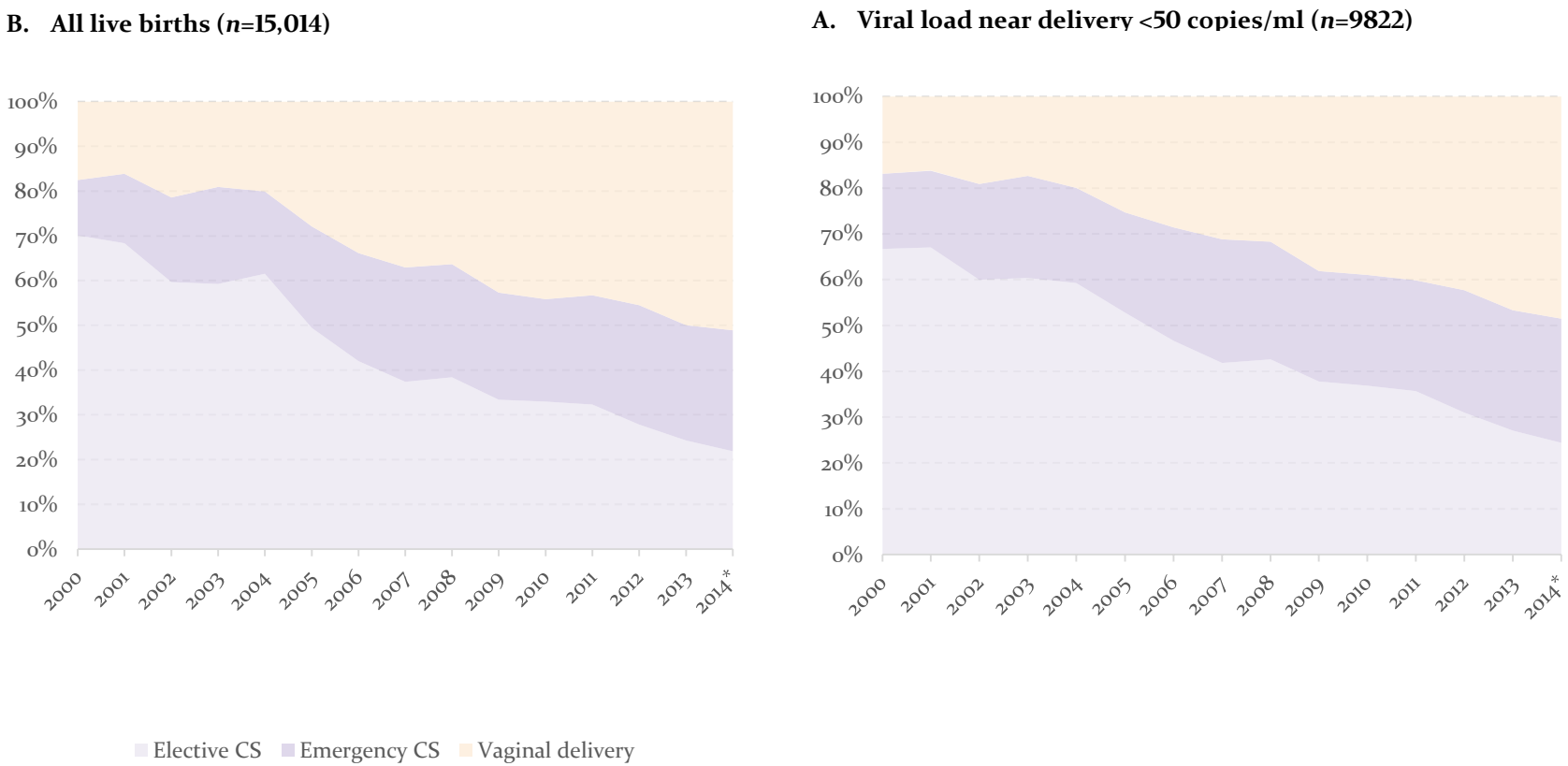
[35] Indication for caesarean section has been collected on the obstetric reporting form since 2006 but has not been consistently reported or coded so I have not used this variable in this analysis.

and 65.0% had a vaginal delivery (13/20); 34.4% of women who planned elective CS had an emergency CS (32/93), and 3.2% had a vaginal delivery (3/93).

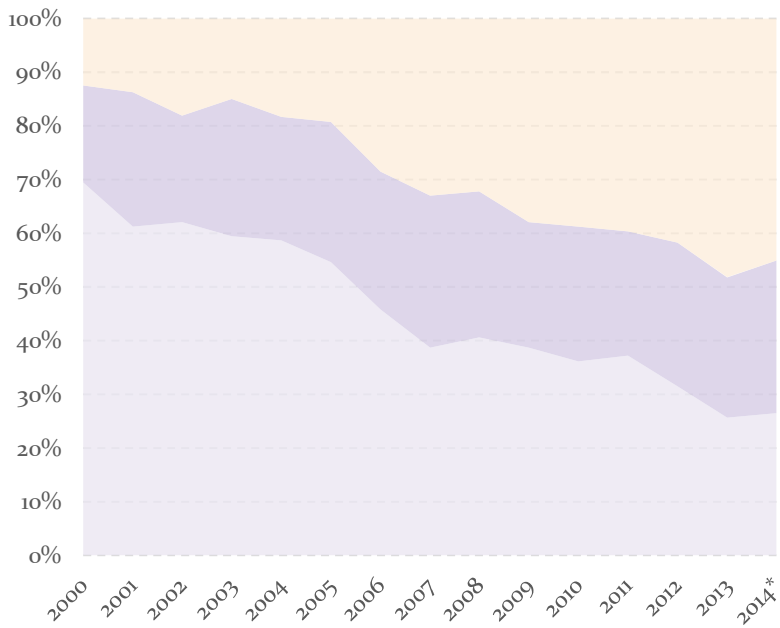
In singleton pregnancies to women with VL <50 copies/ml, the proportion of planned elective CS rose from 29.5% in a woman's first pregnancy reported in the dataset (880/2987) to 52.5% by a woman's 4th or subsequent pregnancy reported in the dataset (85/162) (p<0.001). Excluding women who had a previous CS reported in the dataset, 75.0% of women with undetectable VL and a singleton pregnancy planned vaginal delivery (2.908/3876); rising from26.1% in 2000-2002 (6/23) to 83.2% in 2012-2014 (1214/1460) (test-for-trend p<0.001). The proportion of actual vaginal delivery in women with singleton pregnancy, no previously reported CS and VL<50 copies/ml rose from 19.6% in 2000-2002 (91/465) to 59.5% in 2012-2014 (902/1515); the emergency CS rate in this group rose from 16.1% on 2000-2002 (75/465) to 26.6% in 2012-2014 (403/1515) (p<0.001).

In women with a singleton pregnancy and an undetectable VL near delivery, the emergency CS rate was 19.3% in deliveries at ≥37 weeks of gestation 1686/8717), and 64.0% in pregnancies delivered before 37 weeks' gestation (p<0.001). When restricting to women with a singleton pregnancy delivered at ≥37 weeks' gestation, with an undetectable VL near delivery and no previous CS reported in the dataset, the vaginal delivery rate increased from 20.1% in 2000-2002 (82/409) to 61.6% in 2012-2014 (848/1,376); the elective CS rate decreased from 70.4% in 2000-2002 (288/409) to 14.5% (200/1376) and the emergency CS rate increased from 9.5% (39/409) to 23.8% (328/1376) in the same calendar period (p<0.001). Where planned mode of delivery had been reported, 76.2% had planned vaginal delivery (2,682/3,518).

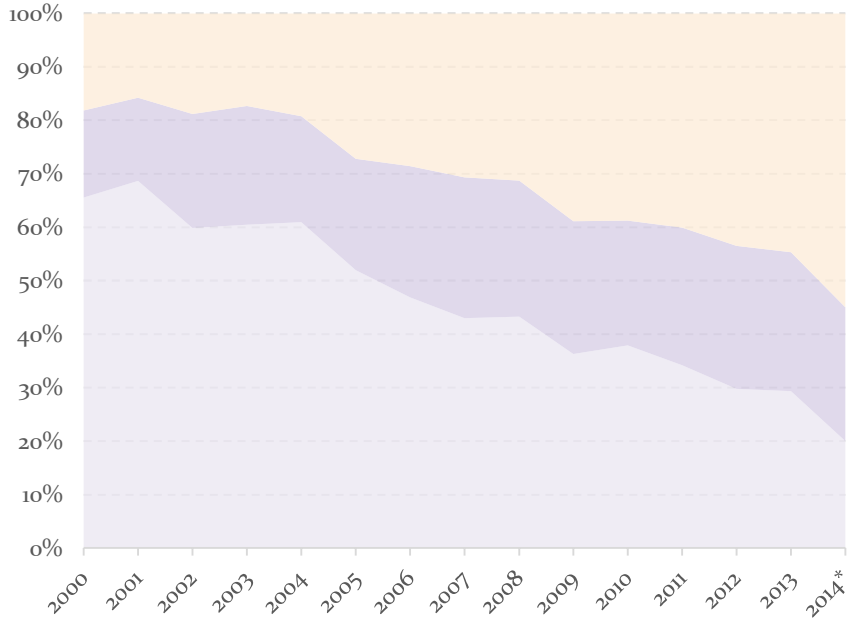
Figure 5-3. Mode of delivery and year of birth for live births



D. Women on art at conception (*n*=5234)



C. Women not on ART at conception (*n*=9338)



* data incomplete

5.3 Pregnancy incidence and outcomes in women with perinatally-acquired HIV in the UK

5.3.1 Specific methods

Women with perinatally-acquired HIV

Several published series describing pregnancies in women with PHIV did not specifically define inclusion criteria (Munjal et al. 2013; Agwu et al. 2011; Cruz et al. 2010; Phillips et al. 2011). The largest study in the US was part of Paediatric AIDS Clinical Trials Group (PACTG) Protocol 219C that longitudinally followed HIV-infected children and young people (enrolment up to age 21); inclusion criteria for the PHIV analysis were that women had been born to mothers who were diagnosed with HIV by the time of delivery but there was no criterion for the age at which the woman was diagnosed (Brogly et al. 2007). One case series of 20 women in the US stated that women had a documented positive HIV test in infancy or childhood or a family history which suggested perinatal acquisition (Badell et al. 2013). Thorne et al described 11 pregnancies in European women with PHIV: women were included if their mother had been diagnosed with HIV, the woman had been diagnosed herself prior to her 14th birthday and vertical infection was the route of acquisition reported. Kenny et al described pregnancies in women diagnosed before their 16th birthday, their mothers reported as having presumed or confirmed HIV and where no other risk factors were identified (Thorne et al. 2007; Kenny et al. 2012b).

To aid comparison with other cohorts and case series and to avoid misclassification of likely route of acquisition, women in this analysis were considered to have perinatally-acquired HIV if they had been coded as vertically infected with no other possible risk reported, and they had been diagnosed with HIV before their 14th birthday.

Estimating incidence rates of first pregnancy reported in women with perinatally-acquired HIV

Two studies have estimated a pregnancy incidence rate in women with perinatal HIV. Brogly et al reported pregnancy incidence in vertically infected females enrolled at primarily university-affiliated paediatric infectious disease clinics across the US from September 2000 (Brogly et al. 2007). Females were followed until loss of

contact, death or their 25th birthday. Incidence rate of first pregnancy was estimated per 1000 woman-years from the girl's 13th birthday to the date of conception of first pregnancy or the last cohort visit, whichever occurred first. Agwu et al reported pregnancy incidence rates in all vertically-infected and behaviourally-infected females aged 13 to 24 years attending four high-volume urban academic clinics between 1997 and 2009 in the US (Agwu et al. 2011).

The NSHPC has been collecting data on all children diagnosed with HIV seen for care in the UK (as well as HEU children) via the British Paediatric Surveillance Unit since 1990 (Verity and Preece 2002). In this analysis, the population considered 'at-risk' of pregnancy were all females with perinatal HIV (see definition above) who had been reported to the NSHPC as children. The time (in years) that they were 'at-risk' of first pregnancy was considered to be from their 13th birthday (the youngest age at which a woman with PHIV had a reported pregnancy) up to the 30th June 2014 (referred to in this analysis as the 'study end date') or date of censoring. Time (in years) to the estimated conception date of first pregnancy during the study period was calculated if a pregnancy had been reported. Individuals without a reported pregnancy were censored at date of death or date of last contact with UK health services if they were lost-to-follow-up or known to have gone abroad before the study end date. The incidence rate ratio was calculated using the Stata command `poisson [outcome], exposure[pyears] irr` and the confidence interval level was set at 95%.

In addition, incidence rate of first pregnancy was also calculated for women aged between 16 and 24 years. In this case, the time considered 'at risk' of first pregnancy was from 16th birthday up to but not including the 25th birthday. Individuals were censored at date of death or date of last contact as applicable if this date fell before the 25th birthday. Multiple pregnancies ending in live birth were treated as a single birth event, but the total number of infants born is included when 'infant' is used.

Constructing a comparison group (women with BHIV and at least one reported pregnancy)

Several studies have included a comparison group of women with BHIV in order to estimate the effects of mode of acquisition on pregnancy outcomes (Badell et al. 2013; Munjal et al. 2013; Jao et al. 2015; Agwu et al. 2011). This methodology has several limitations and there are potential confounding factors. Women with PHIV in the

referenced studies had a significantly lower median age of first conception compared to pregnant women with BHIV, so in planning this analysis the comparison group should ideally be age-matched given that the circumstances of pregnancy during adolescence and young adulthood may be very different to those at an older age. Improvements in health and life expectancy mean that pregnancies reported in women living with BHIV in the referenced studies were more likely to be second or subsequent pregnancies, whereas most pregnant women with PHIV were nulliparous. Therefore, this analysis comparing with women with PHIV and BHIV needed to account for parity. In addition, the management of pregnancies in women with HIV in the UK has changed considerably since the early 2000s, and pregnancy outcomes and MTCT rates have improved dramatically, so any comparison should also account for the time period in which the pregnancies occurred.

In this analysis, women were included in the initial BHIV group if they:

- Had a first pregnancy reported with estimated or actual delivery date between January 2006 and September 2014
- Were nulliparous at first reported pregnancy (or if parity at first reported pregnancy was missing)
- Were diagnosed with HIV prior to their first reported pregnancy
- Had a mode of acquisition reported that was not vertical infection
- Were diagnosed with HIV after their 13th birthday if mode of acquisition was known
- Were diagnosed with HIV after their 15th birthday if mode of acquisition was not known
- Were aged 29 years or less at the estimated conception date of their first reported pregnancy

Once these exclusions/inclusions had been made, women were grouped according to their age at first reported pregnancy (<16 years, 16-19 years, 20-24 years, 25-29 years). In order for the age distribution of the PHIV group and the final BHIV group to be similar, I planned to include three times as many BHIV women in each age band (if available) as included in the PHIV group (see Table 5-7).

Table 5-7. Age at conception of first reported pregnancy of women with PHIV and number of women planned to be included in the BHIV comparison group

Age at first conception	PHIV women		Number of women planned to be in BHIV comparison group	
	n	%	*n*	%
<16	3	7	9	7
16-19	24	53	72	53
20-24	16	36	48	36
25-29	2	4	6	4
TOTAL	45	100	135	100

In age bands with excess numbers of BHIV women, women to retain were selected randomly. This was done by assigning a random number (using the Stata command runiform()), to each record of BHIV women in the dataset then reordering the records numerically within each age band by their assigned random number, and retaining the number of records required within each age band starting with the record with the lowest assigned random number. For women included in the final BHIV group, all their reported pregnancies up to September 2014 were included in the analysis.

Analysis of association between maternal route of HIV acquisition and detectable VL near delivery and adverse pregnancy outcome[36]

Logistic regression models were fitted to estimate odds ratios (OR) and adjusted odds ratios (aOR) to examine, firstly, factors associated with detectable VL near delivery[37], and secondly, factors associated with an adverse pregnancy outcome.

Adjustment for clustering

In this analysis, some women contributed more than one pregnancy to the dataset, therefore the data was clustered at the pregnant woman level. If clustered observations (in this case, pregnancies) were treated as independent, as is the case with standard statistical approaches, the resulting standard errors of the models'

[36] Professor Cortina-Borja advised and assisted me with the modelling methodology
[37] For common (often cited as >10%) outcomes, the odds ratio does not provide a close approximate of the risk ratio (as it does for rare outcomes) (Bland and Altman 2000; McNutt et al. 2003). However, it remains a valid measure of association.

parameter estimates are too small, and corresponding confidence intervals too narrow due to intra-cluster correlation (i.e. variation between pregnancies in the same woman may be less than between pregnancies to different women).

In the first risk factor analysis I initially planned to account for this woman-level clustering by introducing one or more random effects into the model at the woman-level (Kirkwood and Sterne 2003). I constructed a model with a random intercept, and in the univariable analysis with the first few explanatory variables, a likelihood-ratio test (LR test) comparing to ordinary logistic regression (without the random effect) was highly significant, indicating that including the random effect improved the goodness-of-fit of the model. However, for the explanatory variable looking at whether the woman was on ART at conception in that pregnancy, the univariable model took many more iterations and failed to converge, and estimated a crude odds ratio which was very far from what would be predicted from a simple 2×2 analysis, or ordinary logistic regression, and with an extremely wide confidence interval. This indicated that the model had converged to a local maximum of the likelihood function, rather than to the global maximum (B.S. Everitt 1987). I attempted several optimization methods, used different starting values for the optimization procedure, and modified the optimization algorithms' tuning parameters (e.g. length of gradient steps, and tolerances); none of these changes made the optimization process to converge for this model.

Therefore, an alternate statistical method for accounting for clustering was used: robust standard errors were obtained using a clustered sandwich estimator (W.H. Rogers 1993). This method adjusts the standard errors (and thus the 95% confidence intervals) based on the variability within the data rather than variability determined by a statistical model, without altering the point estimate, and is appropriate where the total number of clusters is large ≥30 (Kirkwood and Sterne 2003). This adjustment was applied using the `'(vce) cluster'` option with the '`logistic`' Stata command.

Model selection

The likelihood required for clustered models is not a true likelihood since the individual observations are no longer independent, instead a log pseudo-likelihood is calculated, and the standard LR test for nested model comparison should not be used. The Wald test is often recommended to be used instead (Kirkwood and Sterne 2003)

but this procedure does not take into account the number of parameters in the model. Penalized model selection criteria such as Akaike's information criterion (AIC) and the Bayesian information criterion (BIC) favour a parsimonious model unless the improvement in fit achieved by the more complex model is sufficiently large (Kuha 2004). Here, the AIC and BIC were calculated using the pseudo-likelihood function (Pan 2001). Using the BIC in clustered data also has its controversies since the equation utilizes the number of observations in the dataset (*N*). In clustered data it is often difficult to decide which *N* should be used (i.e. the number of observations or the number of clusters or something in between), but using the number of observations is generally considered conservative, and so this approach is followed here (StataCorp LP 2015). When comparing models, the model with the smallest AIC or BIC was selected.

Univariable analyses were carried out to obtain crude ORs with 95% CIs. The corresponding *p*-values were obtained using the Wald test. Multivariable models were developed using a forward-fitting strategy. Since this analysis examined the association between a defined exposure and outcome, potential confounders were identified in bivariate analyses (considered a significant confounder if $p<0.05$ in the bivariable model); if adjusting for a variable changed the crude OR by at least 10%, and the variable was not believed to be on the causal pathway, it was considered a potential confounder. Each potential confounder was then added to the model starting with the one for which there was the strongest evidence of confounding (based on the results of the bivariable analysis, $p<0.05$ was considered significant). Variables were kept in the model if they improved the fit (based on extent of change in the crude OR, and the AIC/BIC). Once the model had been built, other variables that were not identified as potential confounders in the bivariable analysis were added to the model to see if they improved the fit. If not, they were removed. Potential collinearity between explanatory variables was examined by calculating variance inflation factors for the regression model estimates in the final model (O'Brien 2007).

Combined adverse pregnancy outcome

A combined outcome measure for 'adverse pregnancy outcome' was created and used for the second logistic regression analysis. Adverse pregnancy outcome was recorded if pregnancies ending in live or stillbirth were either delivered preterm (before 37

weeks' gestation), were stillborn, or the infant delivered was of low birth weight at term (<2500g as per the WHO definition (Wardlaw 2004)).

5.3.2 RESULTS

Incidence of first reported pregnancy in women with PHIV

A total of 775 female children with PHIV diagnosed before their 14th birthday and aged 13 or older during the study period were reported, 630 of these did not die or go abroad before their 13th birthday and so comprised the denominator. The total follow-up time was 3568 woman-years. Of these, 45 (6%) women went on to have at least one pregnancy reported to the study, with 21 second pregnancies, three third pregnancies and one fourth pregnancy, giving a total of 70 pregnancies. The incidence rate of first pregnancy in these PHIV women was 13 per 1000 woman-years (95% CI: 9 to 17 per 1000 woman-years). The incidence rate of first pregnancy in 470 women aged 16 to 24 years was 22 per 1000 woman-years (95% CI: 16 to 30 per 1000 woman-years), with a total follow-up time of 1911 woman-years. Age at first estimated conception date ranged from 13 to 27 years for this group of women with PHIV (see Table 5-7).

Aged-matched comparison group of pregnant women with BHIV

There were 943 women who met the inclusion criteria for the BHIV group; 87% of these women likely acquired their HIV heterosexually, 2% likely through injecting drug use, and in 11% likely route of acquisition was unknown (though no evidence of vertical transmission). Median age at first estimated conception date was 26 years (IQR 23 to 28, range 16 to 29 years). The age distribution of the 943 women in the initial BHIV group is shown in Table 5-8.

Table 5-8. Age distribution of planned BHIV group and final BHIV group

Age at first conception	Number of women planned to be in BHIV comparison group		Number of women meeting BHIV inclusion criteria		Number of women in final BHIV comparison group	
	n	%	*n*	%	*n*	%
<16	9	7	0	0	0	0
16-19	72	53	64	7	64	54
20-24	48	36	291	31	48	41
25-29	6	4	588	62	6	5
TOTAL	135	100	943	100	118	100

The final BHIV comparison group comprised 118 women with 184 pregnancies (48 second pregnancies, 15 third pregnancies and 3 fourth pregnancies).

Ideally, the comparison group would also have been matched to the PHIV group by country of birth but given the low numbers of comparison women available at younger age at first conception, this would have skewed the age distribution.

Baseline characteristics

Demographic characteristics of the 45 women with PHIV and 118 women with BHIV who had at least one reported pregnancy are shown in Table 5-9. Although ethnicity was similar across the two groups, country of birth differed, with nearly 60% of women with PHIV born in the UK or Ireland compared to 30% of women with BHIV (p=0.02). Among women with BHIV, 10% were not born in the UK/Ireland or Africa; of these 12 women, 6 were born in the Caribbean, and 3 in Europe (2 in Eastern Europe) and 3 in South-East Asia.

Among women with PHIV, 15% of were born to mothers who injected drugs (data available in 39/45); region of birth of their mothers was Africa for 71% of women and UK/Ireland for 18% (data available in 34/45); and 91% of their mothers were only diagnosed with HIV after delivery (data available in 43/45).

Age at diagnosis differed between the two groups: women with PHIV had median age of diagnosis of 5 years, compared to 19 years in women with BHIV (p<0.001). In the BHIV group, there was one woman who was reported to have been diagnosed prior to the age of 14; she had been diagnosed with heterosexually-acquired HIV at the age of 13 in Malawi.

Median age at conception of first reported pregnancy was very similar in both groups, at around 20 years, although the marginal difference did reach statistical significance. Year of birth for women with a reported pregnancy, and year of conception for all reported pregnancies in these women is shown in Figure 5-4.

The region of the UK/Ireland that the pregnancy had been reported from also differed between the PHIV and BHIV groups. Half (53%) of the pregnancies in women with PHIV were reported from units in London (37/70) compared to 40% of pregnancies in women with BHIV (73/183); 24% of pregnancies in women with PHIV were reported from the rest of England (17/70) compared with 42% of those in

women with BHIV (77/183); and 23% of pregnancies in women with PHIV were reported from the rest of the UK & Ireland (16/70) compared with 18% of pregnancies in women with BHIV (33/184) (p=0.03).

Management of pregnancy, lab test results and outcome of pregnancy

Table 5-10 shows antenatal ART, earliest antenatal CD4, VL close to delivery, outcome of pregnancy and median gestation at antenatal booking appointment in pregnancies across the two groups. There was no evidence of a significant difference between median gestation at antenatal booking appointment between the two groups in pregnancies ending in live birth or continuing to term with a median gestation of around 12 weeks in both groups (50/220 data missing) (p=0.20). Women with PHIV were more likely to be on ART at conception (65% vs. 41% in women with BHIV, p<0.001), but there was no evidence of a difference in the number of drugs they received (94% of women with PHIV received cART compared with 95% of women with BHIV, p=0.25).

Women with PHIV were more likely to have a low CD4 count in pregnancy: 55% of women with PHIV had CD4 count below 350 cells/μL and 21% below 200 cells/μL, vs. 32% and 6% in women with BHIV respectively, (p<0.001). There was also evidence that women with PHIV were less likely to achieve an undetectable VL close to delivery (56% of women with PHIV had VL <50 copies/ml close to delivery vs. 76% in women with BHIV, p=0.015).

Pregnancy outcome differed between the two groups: 83% of pregnancies to women with PHIV resulted in live birth, including one twin pregnancy, compared with 89% of pregnancies to women with BHIV; a higher proportion of reported pregnancies in women with PHIV ended in termination (13% vs. 3% in the BHIV group); and a higher proportion of the pregnancies in women with BHIV ended in miscarriage (7% vs. 3% in women with PHIV) (p=0.023); there was one stillbirth in the BHIV group. Median age at conception in reported live births across both groups 21 years (IQR 19 to 23 years); 19.5 years in miscarriages (IQR 19 to 22) 18 years in reported terminations (IQR 16 to 20.); and 24.5 years in continuing pregnancies (IQR 24 to 26; p=0.003).

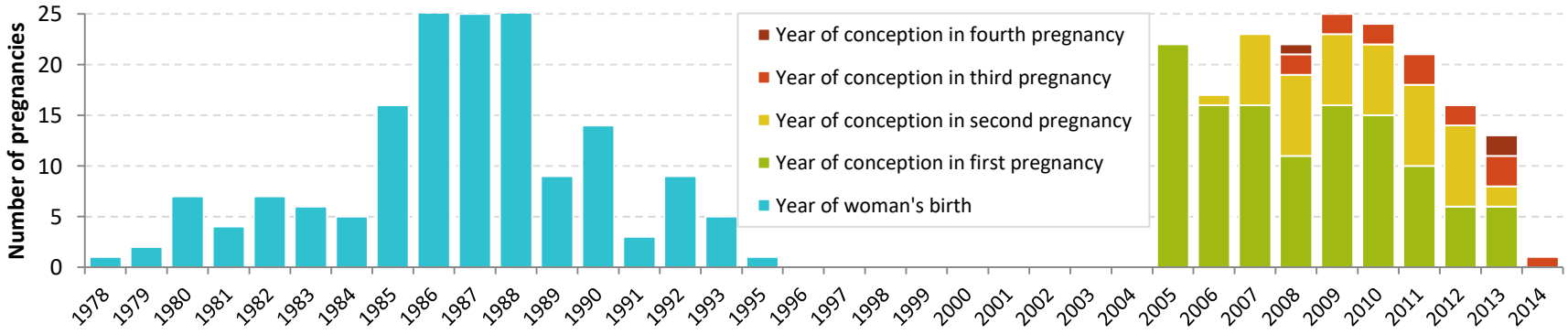
Table 5-9. Baseline characteristics of 118 women with BHIV & 45 women with PHIV

Maternal characteristic	Women with BHIV (*N*=118)		Women with PHIV (*N*=45)		
	n	%	*n*	%	*p*-value
Ethnic group					0.43
White	37	32	11	24	
Black African	67	57	26	58	
Other	13	11	8	18	
Region of birth					0.021
UK/Ireland	41	36	26	58	
Africa	62	54	18	40	
Elsewhere	12	10	1	2	
Injecting drug use*	3	3	0	0	0.28
Age at diagnosis, median (IQR)	19.1 (17.4, 20.5)		5.6 (2.7, 11.1)		<0.001
Age at conception of first reported pregnancy, median (IQR)	20.1 (18.8, 23.0)		19.8 (17.7, 21.4)		0.022

* Women with injecting drug use as likely route of acquisition of HIV

Figure 5-4. Year of birth and conception in women with BHIV and PHIV

A) Year of birth and year of conception in 118 women with BHIV and their 184 reported pregnancies



B) Year of birth and year of conception in 45 women with PHIV and their 70 reported pregnancies

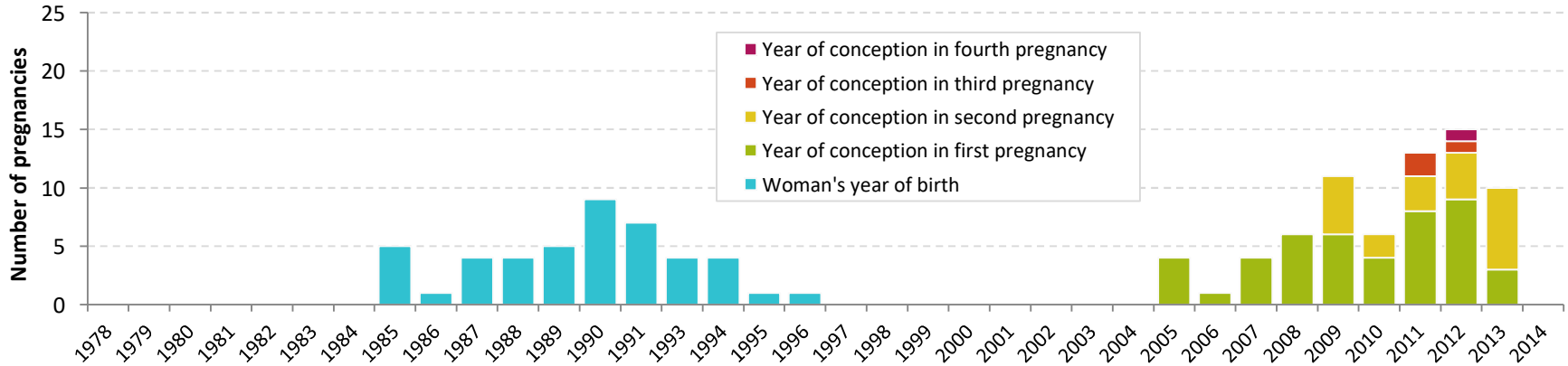


Table 5-10. Treatment in pregnancy, CD4 count, viral load, outcome of pregnancy and gestation at booking in pregnancies to women with PHIV and BHIV

	Pregnancies in women with BHIV (*N*=184)		Pregnancies in women with PHIV (*N*=70)		*p*-value
	n	%	*n*	%	
On ART at conception	(*n*=181)		(*n*=69)		
	69	39	45	65	<0.001
Type of ART	(*n*=178)		(*n*=69)		
No treatment	5	3	4	6	0.32
Monotherapy	4	2	0	0	
cART	169	95	65	94	
Earliest CD4 count in pregnancy (cells/μL)	(*n*=171)		(*n*=66)		
≥500	63	37	21	32	<0.001
350-499	54	31	9	14	
200-349	44	26	22	33	
<200	10	6	14	21	
VL nearest delivery (copies/ml)	(*n*=173)		(*n*=63)		
<50	131	76	35	56	0.015
50-999	26	15	19	30	
1000-9999	8	5	6	10	
≥10,000	8	5	3	5	
Outcome of pregnancy	(*n*=184)		(*n*=70)		
Live birth*	163	89	58	83	0.02
Stillbirth	1	1	0	0	
Miscarriage	12	6	2	3	
Termination	5	3	9	13	
Continuing	3	2	1	1	
Median weeks gestation at booking**, (IQR)	(*n*=115)		(*n*=57)		
	12.1 (10.3, 15.4)		11.6 (9.4, 13.9)		0.20

*There was one twin pregnancy in the PHIV group ending in live birth, so total 59 infants were born in this group.

**Pregnancies ending in live birth or continuing to term only

NOTE: smaller than expected denominators indicate missing data

Mode of delivery

There was no evidence of a difference in planned mode of delivery between the two groups in pregnancies ending in live birth (where data available): planned mode of delivery was vaginal in 53% of live births in women with PHIV (24/44) and 56% of live births in women with BHIV (64/114, p=0.75). There was no evidence for a difference in actual mode of delivery either: 41% of live births to women with PHIV were delivered by elective caesarean section (CS) (23/56); 27% by emergency CS (15/56); and 32% were delivered vaginally (18/56). In the BHIV group, 37% were delivered by elective CS (61/163); 28% by emergency CS (45/163); and 35% vaginally (57/163, p=0.88).

Among women with VL<50 copies/ml near delivery, the proportion of women with PHIV who delivered vaginally rose to 52% (17/33) with a smaller rise to 39% in women with BHIV (49/126, p=0.38 for comparison of mode of delivery between risk groups). When pregnancies to women who had had a previous CS were excluded (all VLs), 40% of women with PHIV and 43% of women with BHIV delivered vaginally; the proportion of emergency CS was 26% and 27% respectively (p=0.87 for comparison between risk groups). There was no evidence of a trend in the proportion of vaginal deliveries by delivery year across the study period for either women with PHIV or BHIV (p=0.5, p=0.4 respectively).

Antiretroviral therapy in pregnancy

All women with PHIV in their 59 live births and continuing pregnancies and 97% of women with BHIV (160/165) were treated with cART (p=0.4). One woman with BHIV presented in advanced labour having had no antenatal care and was untreated, four women with BHIV were treated with zidovudine monotherapy, and one woman received treatment, but the type is unknown. Median gestation at initiation of cART for those not on ART at conception was 21 weeks (IQR 17, 24 weeks) in women with BHIV and 17 weeks in women with PHIV (IQR 10, 24 weeks) (p=0.03).

Class of cART prescribed did not significantly differ between the two groups amongst live births and continuing pregnancies: 26% of women with PHIV received NNRTI-based ART (42/161), compared with 14% of women with BHIV (8/59), and 80% of women with PHIV had PI-based cART (47/59) vs. 67% of women with BHIV (109/161, p=0.18). 2/161 women with BHIV had triple NRTI therapy (a combination of abacavir, zidovudine and lamivudine); 4/59 women with PHIV and 8/161 women with BHIV

had both PI and NNRTI based ART during pregnancy. However, drug class did differ significantly when restricted to women not on ART at conception: 18% of women with PHIV started NNRTI-based cART (7/39), compared to 48% of women with BHIV (32/67), and 74% of women with PHIV started PI-based cART (29/39) compared to 42% of BHIV women (28/67, p=0.004).

There was a difference in NRTI combination prescribed between the two groups in live births and continuing pregnancies: 85% of women with PHIV were prescribed tenofovir plus emtricitabine (33/39), compared with 33% of women with BHIV (38/115); 10% of women with PHIV were prescribed zidovudine plus lamivudine compared with 64% of women with BHIV; and 5% vs 11% respectively were prescribed abacavir plus lamivudine (p<0.001). This difference was still apparent when the groups were restricted to women not on ART at conception (88% of women with PHIV were prescribed tenofovir plus emtricitabine whereas 74% of women with BHIV were prescribed zidovudine plus lamivudine (p<0.001)); but there was no evidence of a significant difference in NRTI combination between the two groups in women on ART at conception (p=0.49).

In live births and continuing pregnancies 43% of women with PHIV who received PI-containing cART were prescribed ritonavir-boosted darunavir (19/44), compared with 6% of women with BHIV (6/104); 25% of women with PHIV were prescribed ritonavir-boosted lopinavir (11/44) compared with 52% of women with BHIV (55/102); 30% of women with PHIV (13/44) and 14% of women with BHIV (15/104) were prescribed ritonavir-boosted atazanavir; and 2% of women with PHIV were prescribed ritonavir-boosted saquinavir (1/44), compared with 27% of women with BHIV (28/104) (p<0.001). One woman with PHIV was prescribed unboosted atazanavir.

Women received the integrase inhibitor raltegravir in 27% of live births and continuing pregnancies in women with PHIV (16/59) and 0.6% of pregnancies in women with BHIV (1/166) (p<0.001). The one woman with BHIV on raltegravir initiated this at 35 weeks, having commenced her main cART at 15 weeks' gestation; she had a delivery VL of 50-999 copies/ml. Of the PHIV women, seven conceived on

raltegravir[38]. Gestation week at start of raltegravir was available in five of the remaining nine live births or continuing pregnancies to women with PHIV not on ART at conception; raltegravir was initiated as part of the main combination in 4 of these pregnancies and was prescribed at 35 weeks in one pregnancy (after main cART commenced at 22 weeks' gestation).

Gestation at delivery, birthweight, and congenital abnormalities[39]

There was no evidence of a difference in gestation at delivery of live born infants: 88% of infants born to women with BHIV were born at or after 37 weeks' gestation (143/163), compared with 84% of infants born to women with PHIV (47/56); 6% of infants born to women with BHIV and 11% of infants born to women with PHIV were born at less than 35 weeks' gestation, and 4% of infants born to women with BHIV born at less than 32 weeks' gestation compared with 2% of infants born to women with PHIV (p=0.47) .

There was no evidence of a difference in birth weight in live infants born to women with BHIV compared with infants born to women with PHIV (p=0.8). Birth weight was 2.5kg or greater for 91% of live infants born at term (≥37 weeks' gestation) to women with BHIV (127/139), compared with 93% of infants born to women with PHIV (43/46, p=0.65).

In the BHIV group, 1.9% (95% CI: 0.34 – 5.4, 3/160 infants) infants had a major congenital abnormality versus 5.7% (95% CI: 1.2 – 15.7, 3/53) in those born to women with PHIV (p=0.15)[40]. Four of the six infants with defects had first trimester exposure to ART (three from conception and one from 11 weeks' gestation). See Table 5-11 for a description of congenital abnormalities reported.

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[38] 5/7 did not have a raltegravir start date reported, but raltegravir was part of the initial combination reported, and the woman was reported to have been on ART at conception

[39] There were 163 live-born infants in the BHIV group and 59 live-born infants in the PHIV group (including one twin pregnancy). Smaller denominators indicate missing data.

[40] All of these congenital abnormalities were reported in live births (there were no other pregnancies with a reported congenital abnormality)

Table 5-11. Description of congenital abnormalities and ART exposure in first trimester

Case number	Congenital abnormality	Maternal HIV acquisition	ART exposure in 1st trimester	Individual drugs in first trimester
1	Heart defect	BHIV	Yes	Zidovudine, lamivudine, lopinavir (+ritonavir)
2	Bowel abnormality	BHIV	No	-
3	Pulmonary stenosis	BHIV	No	-
5	Missing / malformed digits	PHIV	Yes	Tenofovir, emtricitabine, atazanavir (+ritonavir)
6	Missing / malformed digits	PHIV	Yes	Raltegravir, darunavir (+ritonavir)
6	Intestinal malrotation	PHIV	Yes (from 11 weeks)	Zidovudine, abacavir, lamivudine, lopinavir (+ ritonavir)

Infant HIV status

Of the entire study cohort only one infant was known known to have acquired HIV perinatally and was born to a woman with PHIV with longstanding adherence issues and the infant was likely infected in utero; the remaining 163 of infants born to women with BHIV and 58 infants born to women with PHIV were reported as confirmed uninfected.

Examining the association between maternal HIV acquisition and detectable VL near delivery in live births

The proportion of women with a detectable VL near delivery was 20% in women with BHIV and 40% in women with PHIV. The results of the univariable analysis of factors associated with a detectable VL near delivery are shown in Table 5.12. Mode of HIV acquisition of PHIV was significantly associated with greater odds of detectable VL near delivery: PHIV had an odds ratio of 2.63 (95% CI: 1.24 – 5.55) compared with BHIV (p=0.01). Other factors associated with increased odds of detectable VL near delivery were: previous AIDS-defining illness, age at first conception, age at conception of the current pregnancy, having a CD4 count <200 copies/ml and being on ART which contained a protease inhibitor (PI). Being on ART at conception was associated with a lower odds of detectable VL (OR 0.28, 95% CI 012 – 0.63) compared to those not on ART at conception. There was a large proportion of missing data for the variable on previous AIDS-defining illness (59% in BHIV live births and 46% in PHIV live births) so it was not appropriate to include this in the bivariable or multivariable analysis. Age at first conception, age at conception of current pregnancy, ART at conception, CD4 near conception and PI-containing ART were all found to be potential confounders of the association between maternal mode of acquisition and detectable VL at delivery (see Table 5-13).

Table 5-12. Univariable analysis of factors associated with a detectable VL near to delivery in live births

Explanatory variable	VL >50 copies/ml	Univariable Analysis		
	N (%)	OR	95% CI	*p* -value
Maternal HIV acquisition				
BHIV	32/158 (20)	1		
PHIV	22/55 (40)	2.63	1.24 – 5.55	0.01*
Age at first conception (continuous, years)		0.83	0.73 – 0.95	<0.01*
Parity				
Nulliparous	37/127 (29)	1		
Multiparous	17/86 (20)	0.41	0.34 – 1.07	0.08
Previous AIDS-defining illness**				
No	22/101 (22)	1		
Yes	7/12 (58)	5.03	1.32 – 19.17	0.02*
Age at conception (continuous, years)		0.80	0.71 – 0.90	<0.01*
Maternal region of birth				
UK/Ire./Europe	26/89 (29)	1		
Africa/Elsewhere	28/121 (23)	0.73	0.36 – 1.47	0.38
CD4 count near conception				
≥500 cells/μL	13/80 (16)	1		
200-499 cells/μL	29/111 (26)	1.82	0.97 – 3.82	0.11
<200 cells/μL	10/19 (53)	5.73	1.59 – 20.61	0.01*
On ART at conception				
No	40/113 (35)	1		
Yes	13/99 (13)	0.28	0.12 – 0.62	<0.01*
PI-containing ART				
No	4/48 (8)	1		
Yes	48/161 (30)	4.67	1.64 – 13.34	<0.01*
Gestational age at delivery				
≥ 37 weeks	44/184 (24)	1		
< 37 weeks	10/29 (34)	1.67	0.76 – 3.70	0.20
Year of delivery				
2006-2008	18/63 (29)	1		
2009-2011	21/84 (25)	0.83	0.40 – 1.75	0.63
2012-2014	15/66 (23)	0.74	0.33 – 1.63	0.45

*p-value reaches the level of significance (<0.05)

** The variable 'previous AIDS-defining illness' has a high proportion of missing data and so was not included in the bivariable or multivariable analysis

OR: odds ratio, CI: confidence interval,

Table 5-13. Bivariable analysis of association between maternal mode of HIV acquisition and detectable VL near delivery in live births

Explanatory variable	Bivariable Analysis		
	aOR for PHIV acquisition**	95% CI	*p*-value
None	2.63	1.24 – 5.55	0.01
Age at first conception*	2.33	1.12 – 4.85	0.02
Parity	2.53	1.17 – 5.46	0.02
Age at conception*	2.34	1.1 – 4.98	0.03
Maternal region of birth	2.48	1.12 – 5.48	0.02
CD4 count near conception*	2.23	1.00 – 4.96	0.05
On ART at conception*	4.84	1.95 – 12.03	<0.01
PI-containing ART*	2.51	1.16 – 4.43	0.02
Gestational age at delivery	2.59	1.22 – 5.46	0.01
Year of delivery	3.40	1.54 – 7.52	<0.01

*Meets criteria for inclusion in multivariable model

**Versus OR 1.0 for BHIV acquisition, when outcome is detectable VL near delivery

aOR: adjusted odds ratio, CI: confidence interval.

Table 5-14 shows the explanatory variables included in each of the 10 multivariable models fitted to the data and Table 5-15 shows the goodness-of-fit characteristics (AIC and BIC) for those models. ART at conception, age at conception and CD4 near conception improved the fit and were included in the final model (M6). Although age at first conception was identified as a potential confounder, once age at conception in the current pregnancy was added to the model, this effect disappeared, and it did not improve the AIC or BIC.

Table 5-16 shows the results of the final multivariable model. The aOR for PHIV (versus BHIV) rose to 3.22 in the final model, and this reached statistical significance (p=0.02). Being on a PI also significantly increased the odds of having a detectable VL at delivery (aOR=3.52). For every year older at age of conception in the current pregnancy the aOR was protective at 0.89 (p=0.04). Being on ART at conception reduced the odds of detectable VL near delivery considerably (aOR= 0.27) and this

was highly significant. Having a CD4 count <200 cells/μL was associated with an increased odds of detectable VL, but this did not reach significance (aOR= 3.39, *p*=0.05). The variance inflation factors calculated for the explanatory variables in the final model were all <1.5, indicating no significant collinearity between the variables (Craney and Surles 2002).

Table 5-14. Explanatory variables included in multivariable models

Model number	Explanatory variables in multivariable model									
	Maternal mode of HIV acquisition	ART at conception	Age at conception (current pregnancy)	Age at first reported conception	CD4 count in pregnancy	PI-containing ART	Parity	Year of delivery	Gestation at delivery	Maternal region of birth
M0	✓									
M1	✓	✓								
M2	✓	✓	✓							
M3	✓	✓	✓	✓						
M4	✓	✓		✓						
M5	✓	✓	✓		✓					
M6	✓	✓	✓		✓	✓				
M7	✓	✓	✓		✓	✓	✓			
M8	✓	✓	✓		✓	✓		✓		
M9	✓	✓	✓		✓	✓			✓	
M10	✓	✓	✓		✓	✓				✓

Table 5-15. Goodness of fit characteristics for fitted multivariable models

Model number	Multivariable Analysis							
	OR for PHIV acquisition*	95% CI	*p*-value	Number of observations	Pseudo log-likelihood	DF	AIC	BIC
M0	2.63	1.24 – 5.55	0.01	213	-116.63	2	237.26	243.98
M1	4.84	1.95 – 12.03	0.01	212	-104.20	3	214.40	224.47
M2	4.18	1.66 – 10.49	<0.01	212	-100.96	4	209.92	223.34
M3	4.47	1.79 – 11.12	<0.01	212	-100.46	5	210.91	227.70
M4	4.31	1.76 – 10.56	<0.01	212	-103.04	4	214.08	227.50
M5	3.51	1.36 – 9.08	0.01	210	-97.72	6	207.44	227.53
M6**	3.22	1.22 - 8.48	0.02	206	-92.49	7	198.98	222.27
M7	3.26	1.24 – 8.56	0.02	206	-92.33	8	200.66	227.28
M8	2.80	1.01 – 7.79	0.05	206	-92.20	9	202.40	232.35
M9	3.11	1.20 – 8.10	0.02	206	-91.37	8	198.73	225.36
M10	3.32	1.19 – 9.23	0.02	203	-92.00	8	200.00	226.50

* OR (or adjusted OR) versus 1.0 for BHIV acquisition, when outcome is detectable VL near delivery

** Selected as final multivariable model

aOR: adjusted odds ratio, CI: confidence interval, DF: degrees of freedom, AIC: Akaike's information criterion, BIC: Bayesian information criterion

Table 5-16. Results of the final multivariable model: association between maternal mode of HIV acquisition and detectable VL near delivery in live births (n=206)

Explanatory variable	Univariable Analysis			Multivariable Analysis		
	OR	95% CI	*p*-value	aOR	95% CI	*p*-value
Maternal HIV acquisition						
BHIV	1			1		
PHIV	2.63	1.24 – 5.55	0.01*	3.22	1.22 – 8.48	0.02*
Age at conception						
(Per year older)	0.80	0.71 – 0.90	<0.01*	0.89	0.78 – 0.99	0.04*
CD4 count near conception						
≥500 cells/µL	1			1		
200-499 cells/µL	1.82	0.97 – 3.82	0.11	1.97	0.86 – 4.51	0.11
<200 cells/µL	5.73	1.59 – 20.61	0.01*	3.49	1.00 – 12.10	0.05
On ART at conception						
No	1			1		
Yes	0.28	0.12 – 0.62	<0.01*	0.27	0.11 – 0.70	<0.01*
PI-containing ART						
No	1			1		
Yes	4.67	1.64 – 13.34	<0.01*	3.52	1.16 – 10.69	0.03*

*Factors reaching statistical significance with p<0.05

OR: odds ratio, aOR: adjusted odds ratio, CI: confidence interval

Factors associated with adverse pregnancy outcome

In pregnancies ending in live birth or stillbirth, there was no difference in the proportion of adverse pregnancy outcome in women with PHIV compared with women with BHIV (18% and 19% respectively, *p*=0.82). Table 5-17 shows the results of univariable logistic regression analysis of factors associated with adverse pregnancy outcomes. The only factor with an association reaching statistical significance was year of delivery 2009-2011, which had a lower crude OR of 0.36 compared with delivery year 2006-2008 (OR 1.0). Maternal HIV VL near delivery of 50-999 copies/ml, had a crude OR of 2.09 compared with HIV VL of <50 copies/ml (OR 1.0), but this did not quite reach the level of significance since *p*=0.05.

In the bivariable analysis, the OR for PHIV acquisition changed by more than 10% only for being on ART at conception (from 1.09 to 1.21, see Table 5-18). However, whether ART contained a PI, CD4 count in pregnancy, VL near delivery and year of delivery all produced an AIC which was lower than the univariable model, indicating

improved goodness-of-fit. Therefore, these variables were added first in the forward-fitting of the multivariable model (see Table 5-19 for explanatory variables included in the various fitted multivariable models, and Table 5-20 for their corresponding goodness-of-fit characteristics).

Multivariable model number M6 produced the lowest AIC, and so was selected as the best multivariable model (see Table 5-21). The only explanatory variable with a statistically significant association with adverse pregnancy outcome was delivery year 2009 – 2011, with a lower adjusted OR of 0.36 versus 1.0 for delivery year 2006 – 2008 (p=0.04). Having a VL of 50-999 copies/ml near delivery increased the adjusted OR of adverse pregnancy outcome to 2.03 compared with a VL <50 copies/ml, but this did not quite reach statistical significance (p=0.06). There was no evidence that maternal mode of HIV acquisition, PI-containing ART in pregnancy, or ART at conception were associated with adverse pregnancy outcome.

Table 5-17. Univariable analysis of factors associated with adverse pregnancy outcome in pregnancies ending in live or stillbirth

Explanatory variable	Proportion with adverse pregnancy outcome (%)	Univariable Analysis		
	N (%)	OR	95% CI	*p*-value
None (empty model) (*n*=229)				
Maternal HIV acquisition (*n*=229)				
BHIV	33/171 (19)	1		
PHIV	12/58 (18)	1.09	0.49 – 2.42	0.83
Age at first conception (*n*=229) (per year older)		1.01	0.90 – 1.14	0.81
Parity (*n*=229)				
Nulliparous	29/132 (22)	1		
Multiparous	16/97 (16)	0.70	0.35 – 1.40	0.31
Previous AIDS-defining illness (*n*=116) **				
No	20/104 (19)	1		
Yes	5/12 (42)	3.00	1.15 – 7.82	0.03*
Age at conception (*n*=229) (continuous)		0.97	0.86 – 1.09	0.61
Maternal region of birth (*n*=226)				
UK/Ire./Europe	20/96 (21)	1		
Africa/Elsewhere	25/130 (19)	0.90	0.43 – 1.90	0.79
CD4 count (*n*=222)				
≥500 cells/μL	14/83 (17)	1		
200-499 cells/μL	26/117 (22)	1.41	0.65 – 3.04	0.38
<200 cells/μL	5/22 (23)	1.45	0.45 – 4.67	0.53
ART contains PI (*n*=224)				
No	8/54 (15)	1		
Yes	36/170 (21)	1.54	0.61 – 3.88	0.36
On ART at conception (*n*=227)				
No	27/121 (22)	1		
Yes	18/106 (17)	0.71	0.36 – 1.40	0.33
Year of delivery (*n*=229)				
2006-2008	18/68 (26)	1		
2009-2011	10/88 (11)	0.36	0.14 – 0.89	0.03*
2012-2014	17/73 (23)	0.84	0.36 – 1.97	0.69
HIV VL near delivery (*n*=223)				
<50 copies/ml	29/164 (18)	1		
50-999	13/42 (31)	2.09	0.99 – 4.40	0.05
≥ 1000	2/17 (12)	0.62	0.13 – 3.04	0.56

*p-value reaches the level of significance (<0.05)

** The variable 'previous AIDS-defining illness' has a high proportion of missing data and so was not included in the bivariable or multivariable analysis

OR: odds ratio, CI: confidence interval,

Table 5-18. Bivariable analysis of association between maternal mode of HIV acquisition and adverse pregnancy outcome in pregnancies ending in live or stillbirth

Explanatory variable	Bivariable Analysis						
	aOR for PHIV acquisition	95% CI	*p*-value	Pseudo log-likelihood	DF	AIC	BIC
None	1.09	0.49 – 2.42	0.83	-113.45	2	230.90	237.76
ART contains PI	1.03	0.47 – 2.30	0.94	-110.42	3	226.83	229.66
Age at first conception	1.11	0.49 – 2.52	0.80	-113.40	3	232.81	243.11
Parity	1.05	0.47 – 2.34	0.90	-112.93	3	231.85	242.16
Age at conception	1.06	0.47 – 2.40	0.88	-113.28	3	232.55	242.85
Maternal region of birth	1.04	0.45 – 2.36	0.92	-112.76	3	231.53	241.79
CD4 count near conception	1.09	0.49 – 2.46	0.83	-111.41	4	230.81	244.42
On ART at conception	1.21	0.53 – 2.81	0.65	-112.40	3	230.81	241.08
VL near delivery	1.00	0.46 – 2.20	0.99	-108.66	4	225.32	238.95
Year of delivery	1.11	0.49 – 2.54	0.80	-110.04	4	228.08	241.81

*Meets criteria for inclusion in multivariable model

**Versus OR 1.0 for adverse pregnancy outcome with BHIV acquisition

aOR: adjusted odds ratio, CI: confidence interval, DF: degrees of freedom, AIC: Akaike's information criterion, BIC: Bayesian information criterion

Table 5-19. Explanatory variables included in multivariable models for adverse pregnancy outcome in livebirths and stillbirth

Model number	Explanatory variables in multivariable model									
	Maternal mode of HIV acquisition	ART contains PI	CD4 count in pregnancy	On ART at conception	HIV VL near delivery	Year of delivery	Maternal region of birth	Age at conception (current pregnancy)	Age at first conception	Parity
M0	✓									
M1	✓	✓								
M2	✓	✓	✓							
M3	✓	✓	✓	✓						
M4	✓	✓		✓						
M5	✓	✓		✓	✓					
M6	✓	✓		✓	✓	✓				
M7	✓	✓		✓	✓	✓	✓			
M8	✓	✓		✓	✓	✓		✓		
M9	✓	✓		✓	✓	✓			✓	
M10	✓	✓		✓	✓	✓				✓

Table 5-20. Goodness of fit characteristics of multivariable models for adverse pregnancy outcome in live births and stillbirths

	Multivariable Analysis							
Model number	aOR for PHIV acquisition*	95% CI	*p*-value	Number of observations	Pseudo log-likelihood	DF	AIC	BIC
M0	1.09	0.49 – 2.42	0.83	229	-113.45	2	230.90	237.76
M1	1.03	0.47 – 2.30	0.94	224	-113.42	3	226.83	237.07
M2	1.06	0.47 – 2.38	0.89	218	-108.89	5	227.77	244.69
M3	1.18	0.51 – 2.73	0.70	218	-108.49	6	228.99	249.30
M4	1.15	0.50 – 2.66	0.75	223	-109.89	4	227.78	241.41
M5	1.07	0.46 – 2.47	0.88	218	-105.41	6	222.81	243.12
M6**	1.12	0.46 – 2.73	0.80	218	-102.45	8	220.91	247.98
M7	1.13	0.44 – 2.92	0.80	215	-101.67	9	221.34	251.67
M8	1.13	0.43 – 2.98	0.80	218	-102.45	9	222.91	253.37
M9	1.22	0.47 – 3.13	0.69	218	-101.98	9	221.96	252.42
M10	1.07	0.44 – 2.59	0.88	218	-102.24	9	222.49	252.95

* adjusted odds ratio versus 1.0 for BHIV acquisition, for adverse pregnancy outcome

** Selected as final multivariable model

aOR: adjusted odds ratio, CI: confidence interval, DF: degrees of freedom, AIC: Akaike's information criterion, BIC: Bayesian information criterion

Table 5-21. Final multivariable analysis of factors associated with adverse pregnancy outcome in live births and stillbirths (*N*=218)

Explanatory variable	Univariable Analysis			Multivariable Analysis		
	OR	95% CI	*p*-value	aOR	95% CI	*p*-value
Maternal HIV acquisition						
BHIV	1			1		
PHIV	1.09	0.49 – 2.42	0.83	1.12	0.46 – 2.73	0.80
ART containing PI						
No	1			1		
Yes	1.54	0.61 – 3.88	0.36	1.02	0.36 – 2.90	0.97
VL near delivery						
<50 copies/ml	1			1		
50-999 copies/ml	2.09	0.99 – 4.40	0.05	2.03	0.97 – 4.23	0.06
≥1000 copies/ml	0.62	0.13 – 3.04	0.56	0.64	0.12 – 3.46	0.60
On ART at conception						
No	1			1		
Yes	0.71	0.36 – 1.40	0.33	0.73	0.31 – 1.69	0.46
Year of delivery						
2006 - 2008	1			1		
2009 - 2011	0.36	0.14 – 0.89	0.03	0.36	0.14 – 0.97	0.04*
2012 - 2014	0.84	0.36 – 1.97	0.69	0.79	0.30 – 2.12	0.64

*Factors reaching statistical significance with $p<0.05$

OR: odds ratio, aOR: adjusted odds ratio, CI: confidence interval

5.4 Key Points

5.4.1 Terminations and miscarriages

- The proportion of reported miscarriages rose significantly from 4.8% in 2000-2002 to 8.6% in 2012-2014, this rise was similar in women diagnosed before conception.
- Median age at conception was significantly higher in reported miscarriages (33 years) than other pregnancy outcomes (30 years).
- The proportion of reported terminations declined over the study period from 5.9 to 1.9%.
- In reported terminations, women were more likely to have acquired HIV perinatally than in other pregnancy outcomes. The proportion of terminations was significantly higher in women who acquired HIV perinatally (12.4% compared with 3.0% in women with BHIV).
- 32 women had two terminations reported in the dataset; these women had a lower median age and were more likely to have acquired HIV through injecting drug use or perinatally.
- A greater proportion of women with a reported termination were treated with the NNRTI efavirenz (10.3% compared with around 7% in other pregnancy outcomes), this reached the level of significance.
- The proportion of reported congenital abnormality was highest in stillbirths (9%) and terminations (8.5%), compared with 2.8% of live births.
- There was a wide range of reported congenital abnormality.
- The proportion of terminations affected by congenital abnormality rose with increasing gestation at termination, indicating that the presence of congenital abnormality may have been a deciding factor in the decision to terminate in these pregnancies.

5.4.2 Live births and stillbirths

- The proportion of live and stillbirths remained fairly constant over time
- The median age at conception for women with reported stillbirths rose from 26 years at the beginning of the study period, to 34 years at the end. In comparison,

median age for women with live births rose from 28 to 32 years over the study period.

- There was a slightly higher proportion of stillbirth in women of black African and non-white non-black African ethnicity, but this did not reach statistical significance.
- The proportion of live births delivered before 37 weeks' gestation fell from 14.3% to 11.1% over the study period.
- The proportion of pre-term birth was significantly higher in white women (14.8%) than black African (12.0%) or non-white non-Black African women (13.4%). A higher proportion of infants born at term to black African women weighed ≥2.5kg.

5.4.3 Antiretroviral therapy

- A large majority of women were treated with cART (91.3%), and only 1.8% were untreated.
- The proportion of women treated with monotherapy fell during the study period from 18.4% to 1.1%, the vast majority of these women received zidovudine.
- The proportion of women on cART at conception rose significantly from 25.4% to 60.1% during the study period.

5.4.4 Women who achieved an undetectable viral load near delivery

- The majority of women achieved an undetectable VL near delivery (71%), and this proportion increased from 40.3% to 86.8% during the study period.
- In univariable comparative analysis, women with undetectable VL were more likely to: have acquired HIV heterosexually, compared with perinatally or via injecting drug use; be parous; have a higher median age at conception, have booked earlier in the pregnancy, have received cART rather than mono- or dual therapy; and be on cART at conception.
- Women not on cART at conception were more likely to achieve an undetectable VL if they received PI-based cART, compared with NNRTI-based cART, and median gestation at start of cART was lower in women with undetectable VL (22.6 weeks compared with 25.1 weeks in women with VL >50 copies/ml).
- In women on cART at conception, a higher proportion of women on NNRTI-based regimens achieved undetectable VL (94.7% compared with 89.0% of women on PI-based cART).

5.4.5 Mode of delivery

- The overall proportion of vaginal delivery was 31.9%, and this rose from 17.6% to 45.0% over the study period.
- In live births where planned mode of delivery was available, 32.6% of women who planned vaginal delivery ended up delivering by emergency CS.
- The majority of women with multiple pregnancy planned delivery by CS (82.3%).
- In women with singleton pregnancy, undetectable VL near delivery and no previous reported CS, who delivered at term, 76.2% had planned vaginal delivery. In these women the proportion of vaginal delivery rose from 20.1% to61.6% over the study period; correspondingly, the emergency CS rate increased from 9.5% to 23.8% over the study period.

5.4.6 Pregnancy incidence and outcomes in women with PHIV in the UK

- Women who had been reported as children to the NSHPC with PHIV, and were aged ≥ 13 years, had a pregnancy incidence of 13 per 1000 woman-years. This rose to 22 per 1000 woman-years when restricted to women aged 16 to 24 years.
- The women in the BHIV group were fairly well-matched to the PHIV group: age at conception of first reported pregnancy was 19.8 in women with PHIV compared with 20.1 years in women with BHIV. There were no significant differences in reported ethnicity, region of birth or reported injecting drug use (as route of HIV infection).
- There were significant differences in pregnancy characteristics between women with PHIV and BHIV:

  - more conceptions on ART in women with PHIV (65% vs. 39%, $p<0.001$)

  - women with PHIV had a lower baseline CD4 count in pregnancy (21% had a CD4 count < 200, vs. 6% of women with BHIV, $p<0.001$)

  - a greater proportion of women with PHIV delivered with a detectable VL (45% vs. 20% in women with BHIV, $p=0.015$).

- Women with PHIV not already on cART were initiated at an earlier gestational age than women with BHIV (17 weeks versus 21 weeks, p=0.03), despite no difference in gestation at antenatal booking date.
- There was no significant difference in mode of delivery between the two groups.
- Overall, there was no significant difference in class of ART prescribed between the two groups, but women with PHIV not on ART at conception were more likely to start a PI-based regimen (74% vs 42%, p=0.004). Many more women with PHIV were treated with raltegravir (27% vs. 0.6% of pregnancies in women with BHIV, p<0.001).
- More reported pregnancies ended in termination in women with PHIV (13% vs. 3%, p=0.02), and there was a modest difference in the proportion of miscarriage (3% vs 6% in women with BHIV).
- There were no significant differences in the rate of pre-term birth, low birth weight or congenital abnormality between the groups.
- PHIV was found to be an independent risk factor for a detectable VL near delivery, with an odds ratio of 2.63 vs. 1 in women with BHIV (95% CI: 1.22– 8.48, p=0.02).
- Other independent risk factors for detectable VL at delivery were younger age at conception, lower CD4 count near conception, not being on ART at conception, and receiving PI-containing ART during pregnancy.
- There was no significant association between maternal mode of HIV acquisition and adverse pregnancy outcome.

6 ART prescribing patterns, resistance testing in women with a reported pregnancy, and TDR in women diagnosed during pregnancy

6.1 Introduction

Combination antiretroviral therapy is now the standard of care for preventing vertical transmission for all women living with HIV, as well as for maintaining their own health (Guidelines writing group 2014; BHIVA Guidelines writing group 2016; WHO 2013). However, these guidelines and the recommended agents used have evolved over the study period of the analyses presented in this thesis. In the first part of this Chapter, I describe patterns of antiretroviral prescribing in women on cART with livebirths whose estimated or actual delivery date fell between 1st January 2000 and 31st December 2014, and who were reported to the NSHPC by 30 September 2014. I describe the class of ART (i.e., which class of third agent was used), and how this changed over the study period. I also describe common NRTI backbones, and how the prescriptions of these have changed over time, and differences in cART regimens used in women on treatment at conception, and those starting treatment in pregnancy.

Choice of ART is in part influenced by any HIV drug resistance that may have either been transmitted to or accumulated by a woman requiring treatment. The NSHPC does not collect information on evidence of drug resistance either during or prior to reported pregnancies. In the second half of the chapter, I present an analysis using a combined dataset of NSHPC and the UK HIV Drug Resistance Database (UKHDRD), where women with reported pregnancies were matched to resistance tests held by the UKHDRD. Specific methods for the derivation and analysis of this dataset are described in 6.3.1. I examine the characteristics of women who were able to be matched to at least one resistance test and use multivariable logistic regression to examine factors associated with being matched to at least one resistance test. I describe patterns of viral subtype in matched women, and the association with region of birth. I describe the prevalence of transmitted drug resistance in women matched to a resistance test and analyse risk factors for the presence of TDR and describe the

mutations identified in women with TDR. Finally, I test whether the presence of TDR is associated with non-suppression of VL at delivery and infant infection status.

6.2 Patterns of antiretroviral prescribing in live births to women receiving cART 2000 – 2014

6.2.1 Combination ART

There were 13,545 live births in women treated with cART 2000 – 2014. A brief summary of classes of cART prescribed is included in Chapter 5. To recap, women treated with cART received a PI-based regimen in 61.0% of pregnancies (8,266/13,545); an NNRTI-based regimen in 32.0% (4,337/13,545); both a PI and an NNRTI in 5.1% (684/13,545); NRTI-only cART in 1.6% (211/13,545); and NRTI plus raltegravir in 0.32% (44/13,545).

Women received additional raltegravir in 0.4% of pregnancies where they were treated with an NNRTI regimen (18/4,337), 2.3% of women on PI regimens (191/8,266) and 5.3% of women treated with both a PI and NNRTI (36/684)[41].

There were 211 women treated with NRTI-only regimens (no additional raltegravir or maraviroc); of these 81.6% were reported as treated with the combination abacavir + lamivudine + zidovudine (155/190)[42]. The proportion of women who received NRTI-only cART varied significantly by calendar year group, but there was no evidence of an ordinal trend with later calendar period: 1.4% in 2000-2002 (15/1062); 2.0% in 2003-2005 (53/2600); 1.1% in 2006-2008 (40/3634), 1.3% in 2009-2011 (47/3608); and 2.4% in 2012-2014 (56/2341) (χ^2 p<0.001; test-for-trend p=0.26).

Excluding the 21 women with individual drug information missing, the proportion of women on NRTI-only cART treated with abacavir + lamivudine + zidovudine was 80.0% in 2000-2002 (12/15); 82.3% in 2003-2005 (42/51); 70.0% in 2006-2008 (28/40); 84.4% in 2009-2011 (38/45) and 89.7% in 2012-2014 (35/39) (p=0.18). Table 6-1 shows common NRTI backbones in pregnancies ending in live birth with an NNRTI or a PI-based cART regimen, by period of delivery. The proportion of women on zidovudine + lamivudine as a backbone fell from 97.2% in 2000-2002 to 18.1% in 2012-2014; the use of tenofovir + emtricitabine emerged at 0.2% in 2003-2005, rising

[41] Raltegravir can be added to the main cART regimen for intensification purposes. See Page 183 for details of women not on ART at conception who received additional raltegravir in addition to their main combination; the majority of women had raltegravir added at a later gestation than their initial cART start date.
[42] 25 women were reported as being on NRTI-only regimen but individual drug information was missing.

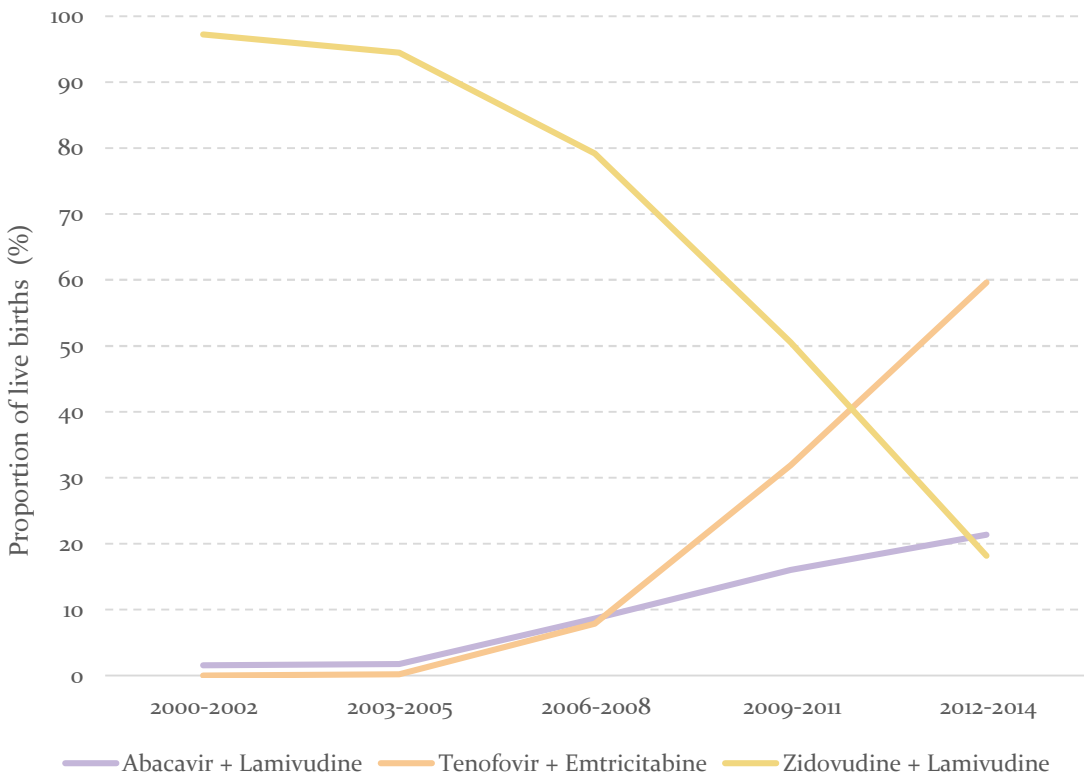
to 59.6% in 2012-2014; and similarly, the use of abacavir rose but to a lesser extent, from 1.6% in 2000-2006 to 21.4% in 2012-2014. This pattern is illustrated in Figure 6-1, showing the three most common NRTI backbones by year of delivery in women treated with NNRTI- or PI-based cART.

Table 6-1. Common NRTI backbones used in women treated with a PI- or NNRTI-based regimen)[43][44]

NRTI combination		Year of birth 2000-2002	2003-2005	2006-2008	2009-2011	2012-2014	Total
Abacavir + lamivudine	n	13	39	288	545	397	1,282
	%	1.6	1.8	8.7	16.0	21.4	11.0
Tenofovir + emtricitabine	n	0	5	262	1,084	1,108	2,459
	%	0	0.2	7.9	31.9	59.6	21.2
Abacavir + lamivudine + zidovudine	n	10	22	37	18	8	95
	%	1.2	1.0	1.1	0.5	0.4	0.8
Zidovudine + lamivudine	n	805	2,095	2,627	1,717	338	7,582
	%	97.2	94.5	79.2	50.5	18.1	65.2
Tenofovir + lamivudine	n	0	57	105	35	8	205
	%	0	2.6	3.2	1.0	0.4	1.8
Total	n	828	2,218	3,319	3,399	1,859	11,623

[43] There were 13,298 live births to women treated with cART and treated with a PI or NNRTI (or both) in pregnancy; 876/13,298 of these reports were missing specific drug information; 11,623/13,298 women were treated with one of the common NRTI combinations listed in this table; therefore the remaining 799/13,298 women were treated with an NRTI combination other than those listed in the table, or were not taking an NRTI in addition to the PI/NNRTI (although they were taking a minimum of 3 drugs, so this is unlikely), or had start dates missing.
[44] The individual NRTIs listed within each combination had the same start date.

Figure 6-1. The most common NRTI backbones in women treated with PI- or NNRTI-based regimens by year of birth (live births only)



Women on ART at conception

Women with a live birth and on ART at conception were treated with PI-based cART in 45.0% of pregnancies (2338/5200); NNRTI-based cART in 45.0% of pregnancies (2350/5200); cART containing both PI and NNRTI in 7.8% (407/5200); NRTI-only cART in 1.7% of pregnancies (87/5200); and 18 women were treated with the integrase inhibitor raltegravir plus an NRTI-backbone. Women received additional maraviroc in 10 pregnancies in women on a PI-based regimen, and in 4 pregnancies received maraviroc plus an NRTI-backbone.

Women treated with NNRTI-based cART regimens were treated with nevirapine in 70.2% of live births (1,536/2,187); efavirenz in 29.3% (641/2187); etravirine in 0.3% (7/2187); and rilpivirine in three live births (in 2012-2014). Within women treated with NNRTI-based regimes, the proportion treated with nevirapine declined from 94% in 2000-2002 (138/146) to 43% in 2012-2014 (218/504), and the use of efavirenz rose from 5.5% in 2000-2002 (8/146) to 55.2% in 2012-2014 (278/504) (p<0.001).

The prescription of individual PIs in women on PI-based cART also varied over time, as shown in Figure 6-2.

Women not on cART at conception

Women with pregnancies ending in live birth and not on ART at conception were treated with a PI-based regimen in 71.2% of pregnancies (5,717/8,034); NNRTI-based therapy in 23.6% (1897/8034); both a PI and NNRTI in 3.4% (271/8034); NRTI-only therapy in 1.5% of pregnancies (124/8034); 0.3% were treated with two NRTIs plus raltegravir (25/8034). The proportion of women treated with PI-based regimen increased from 17.4% in 2000-2002 (135/775) to a peak of 87.3% in 2009-2011 (1684/1928), with a slight drop to 80% in 2012-2014 (789/986). The proportion of women treated with an NNRTI dropped from 77.2% in 2000-2002 (598/775) to a nadir of 7.5% in 2009-2011 (145/1928), and then rose slightly to 10.6% in 2012-2014 (104/986). The proportion of women treated with NRTI-only regimen increased from 0.65% in 2000-2002 (5/775) to 6.3% in 2012-2014 (62/986). The proportion of women treated with both PI and NNRTI decreased from 4.8% in 2000-2002 (37/775) to 2.4% in 2006-2008 (58/2417), and then rose slightly to 3.1% in 2012-2014 (31/986). The increase in the proportion of PI-containing cART over the time period was statistically significant (*test-for-trend p*=0.001).

The median gestational age at start of cART in 7708 women was 23.6 weeks (IQR: 20.1 to 27.2 weeks). The median gestation at start of cART decreased from 27 weeks in 2000-2002 (IQR: 22.6 to 30.4 weeks) to 20 weeks in 2012-2014 (IQR: 16.6 to 23.1 weeks; $p<0.001$). The median gestation at start of cART also varied by drug class: 24.6 weeks for women treated with an NNRTI (IQR: 20.4 to 28.6 weeks); 23.4 weeks for women treated with a PI (IQR: 20.1 to 26.6 weeks); 23.3 weeks for women treated with NRTIs only (IQR: 20.3 weeks to 27 weeks); and 22.6 weeks for women treated with a PI and NNRTI (IQR: 17.4 weeks to 26.9 weeks) ($p<0.001$).

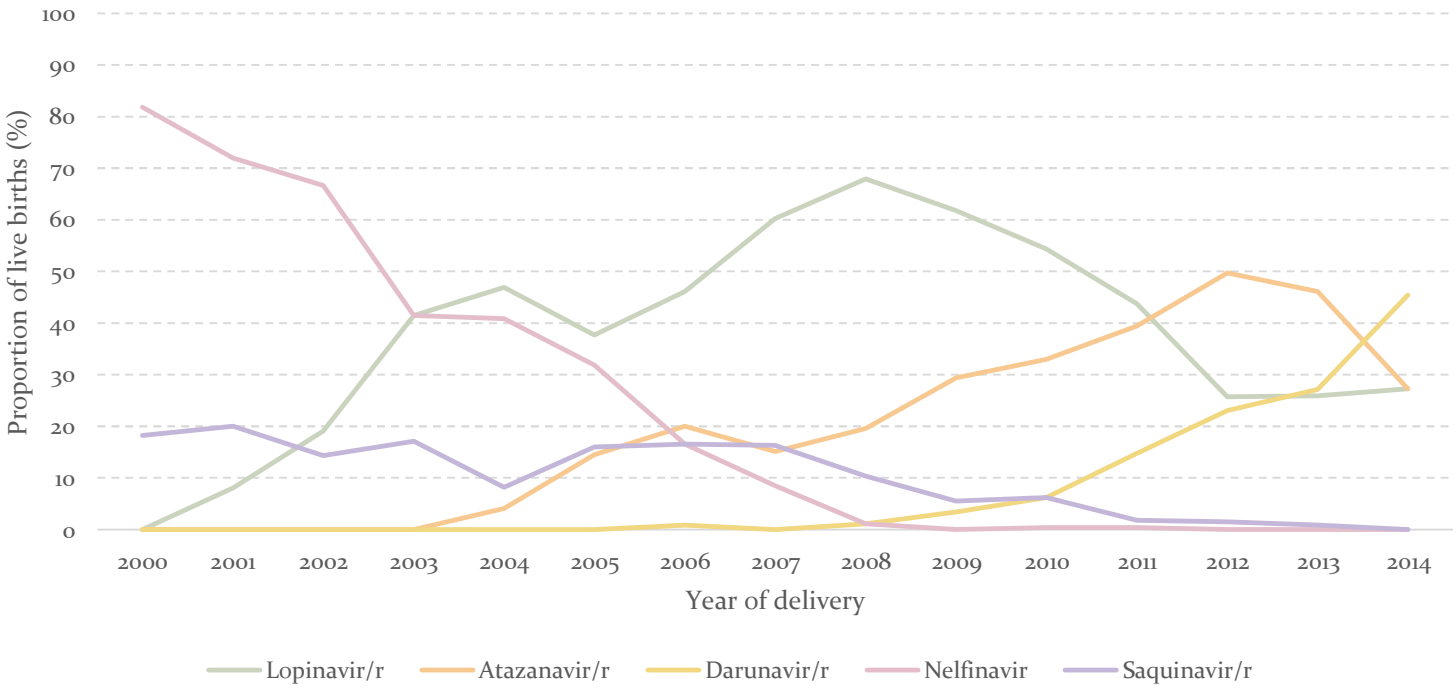
Women were treated with raltegravir in addition to their main regimen in 2.3% of live births (183/8034): 0.5% of women with NNRTI regimen received raltegravir (9/1897); 2.3% of women treated with a PI (129/5717); and 7% of women treated with both a PI and NNRTI (19/271) ($p<0.001$); one woman received triple NRTI therapy and raltegravir. The median gestation at start of raltegravir was 32.8 weeks (IQR: 24 to 35.9 weeks). The start date of raltegravir was subsequent to the start date of the

main ART regimen in 60.1% women (104/173; start dates missing in 10/183 women who took additional raltegravir). Three women who received PI-based therapy also received maraviroc.

Of the 23.6% of women treated with NNRTI based therapy, the overwhelming majority were treated with nevirapine (94.6%; 1742/1841); only 5.3% were on efavirenz (98/1841) and one woman was treated with rilpivirine. The proportion of women initiated on efavirenz rose from 0.5% in 2000-2002 (3/582) to 54.9% in 2012-2014 (45/82). Figure 6-2B. shows individual PIs in women not on ART at conception prescribed a PI-based regimen over time.

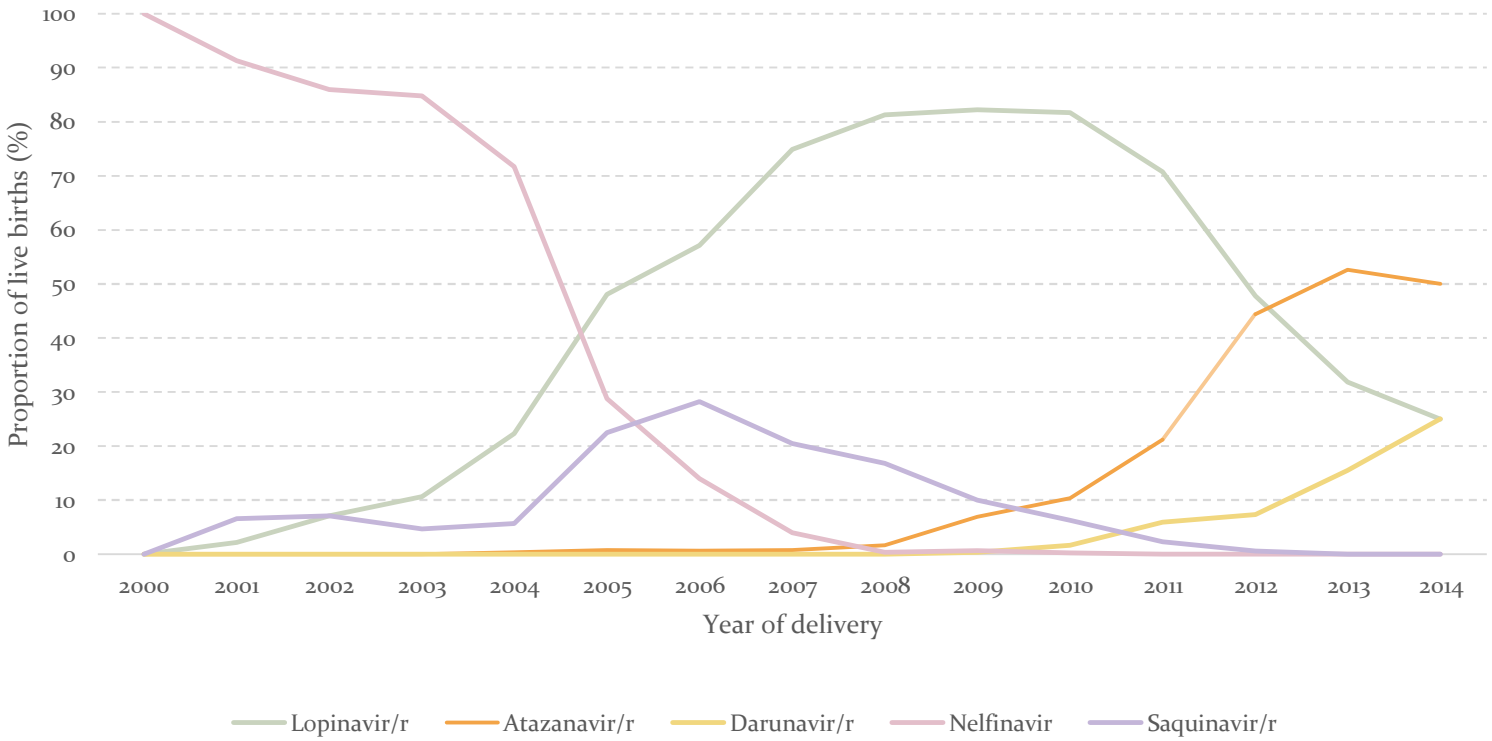
Figure 6-2. Prescribing patterns of protease inhibitors in women on PI-based combination ART by year of delivery[45]

A) Women on ART at conception



[45] This is the proportion of women treated with cART who had a live birth and were treated with a PI-based regimen (so excludes women who received an NNRTI, both an NNRTI and a PI, and raltegravir)

B) Women not on ART at conception



6.3 Patterns of resistance testing overall, prevalence and risk factors for transmitted drug resistance in women diagnosed during pregnancy

6.3.1 Specific methods

Matching procedures: NSHPC to SOPHID

A cleaned extract of the NSHPC dataset (all pregnancies reported 2000 – 2014) was provided securely to the HIV and STI service at PHE in February 2015. The dataset included various demographic and clinical variables on which to match the dataset with SOPHID, including partial postcode (i.e., minus the final letter, which is not collected by the NSHPC), country of birth, site of treatment, site of delivery and date of diagnosis. Women attending HIV care during their pregnancy should have been independently reported to both SOPHID and the NSHPC (see Chapter 3 for full description of reporting methods for both studies).

Data linkage procedures were carried out by the HIV and STI department of PHE[46]. Matching was based on a range of variables collected by both NSHPC and SOPHID, this hierarchical algorithm is detailed in Appendix 10.3. Where potential duplicates were identified, for example one NSHPC record matching to more than one SOPHID record, these were excluded. The analysis was restricted to pregnancies reported from England and Wales, since SOPHID does not collect data from the Republic of Ireland, and data from Scotland did not provide a reliable linkage. An account of matching a previous SOPHID NSHPC combined dataset with the same methodology has been published (Tariq, Pillen, et al. 2012)

There were 10,115 women in the NSHPC dataset whose pregnancies had been reported from England and Wales, and 8,801 of these were successfully matched to a SOPHID record (87% matched).

Matching procedures: SOPHID to UKHDRD

UKHDRD provided their 2013 dataset (all resistance tests received up to the end of 2013) to the HIV and STI Department at PHE, where they were matched to SOPHID

[46] The matching process was developed by Shema Tariq, Clare French, Janet Masters and Cuong Chau in previous joint work. Many thanks to Cuong Chau at the HIV and STI who carried out the matching procedures for this analysis.

records with a similar hierarchical matching procedure, as detailed in Appendix 10.3[47].

In previous matching procedures, around 50% of SOPHID records have been matched to at least one UKHDRD record. Generally, SOPHID records are matched more successfully to UKHDRD records from UK CHIC sites, as these records contain additional variables and the quality of the data is better; it has also been noted that UKHDRD records from laboratories based in Manchester and Birmingham have lower matching rates, for reasons unclear at the time of this analysis [personal communication, Cuong Chau, PHE].

Merging the UKHDRD and NSHPC datasets.

The NSHPC dataset with SOPHID unique identifier incorporated was reshaped into a simplified wide format, with one record per woman and limited variables for each pregnancy reported (NSHPC datasets are originally in long format with one record per reported pregnancy). This dataset was then merged with the UKHDRD, based on the SOPHID unique identifier. The new merged dataset was therefore in long form, with each record signifying an individual resistance test.

Definitions

The term 'transmitted drug resistance mutations' (TDRMs) describes the presence of one or more mutations from the WHO 2009 surveillance list (Bennett et al. 2009) with the addition of E138K, a mutation known to cause resistance to the second-generation NNRTI rilpivirine, and all changes at codon T215 as they are likely to be ancestrally related to T215F or Y mutations (Mitsuya et al. 2008).

Predicted phenotypic resistance to ART drugs was examined using the Stanford HIVdb algorithm v7.0 (TF Liu and RW Shafer 2006). Scores of low-level, intermediate or high-level resistance were used to predict phenotypic resistance.

HIV-1 subtypes were determined using the REGA v3.0 genotyping tool (REGA Institute, Katholieke Universiteit Leuven, Belgium).

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[47] Cuong Chau, PHE, and Anna Tostevin, UKHDRD, developed this matching procedure.

6.3.2 Results

Characteristics of women matched and not matched to at least one resistance test

In the matched dataset, there were 10,115 distinct women with 14,416 reported pregnancies with EDD / delivery date in 2000 – 2014. The number of pregnancies ranged from 1 to 6 per women, with a mean 1.42 pregnancies per woman; 87.0% of women were matched to a SOPHID unique identifier (8801/10,115).

Nearly half (49.4%) of these women were matched to at least one resistance test (4994/10,115). The year of first matched resistance test ranged from 1996 to 2015, with a median year of 2007.

In women matched to a resistance test, year of maternal diagnosis ranged from 1985 to 2013 (4637/4994 available). The proportion of women matched was similar in calendar periods: 56.4% in those diagnosed 2006 onwards (2029/3596), compared with 56.8% of those diagnosed 2010 (524/923).

The reason for the resistance test was only recorded in 47.2% of women matched to a resistance test (2,358/4994). Women were reported as being ART-naïve or ART-experienced at the time of the resistance test; the proportion of women classified as ART-experienced at first matched resistance test fell from 74.1% in women diagnosed 1985-1995 to 17.6% in women diagnosed 2010-2013 (p<0.001), as shown in Table 6-2.

Table 6-3 shows maternal demographic characteristics in women matched, and not matched to at least one resistance test. Women of Black African ethnicity, and those born in sub-Saharan Africa were least likely to be matched (48.6% matched for both). The small number of women reported from Wales were more likely to be matched (54.2%), than those from London (53.9%), and women from elsewhere in England the least likely (45%). The proportion of women matched increased with later calendar period for the first reported pregnancy: those with first pregnancy in 2009-2013 were 53.2% matched. Women with the 3 or more pregnancies in the dataset were the most likely to be matched: 59%. The proportion of women diagnosed during pregnancy who were matched was slightly, and significantly, higher at 50% than those who were diagnosed before (48.9%).Women who were diagnosed with HIV in 1996-2000 had the lowest matched proportion (43.7%), whilst those diagnosed in 2010-2013 had the highest (56.8%). Women with younger age at conception of first reported pregnancy

were more likely to be matched: 58.9% of those aged 13 to 20, compared with 37.5% of those aged 45 or older.

Table 6-2. Classification of ART-naïve or ART-experienced at time of first matched resistance test, by year of maternal HIV diagnosis

	Year woman diagnosed with HIV											
	1985-1995		1996-2000		2001-2005		2006-2009		2010-2013		Total	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
Experienced	120	74.1	316	65.2	872	44.5	277	18.4	92	17.6	1677	36.2
Naïve	38	23.5	162	33.4	1057	53.9	1195	79.4	425	81.1	2877	62.0
Not classified	4	2.47	7	1.44	32	1.63	33	2.19	7	1.3	83	1.8
Total	162	100	485	100	1961	100	1505	100	524	100	4637	100

Table 6-3. Maternal demographics in women matched and not matched to at least one resistance test

	Matched to at least one resistance test						
		No		Yes		Total	*p*-value
	n	%	*n*	%	*n*	%	
Maternal ethnicity							
White	620	48.7	652	51.3	1272	100	
Black African	4073	51.4	3844	48.6	7917	100	
Other	409	45.4	491	54.6	900	100	0.001
Maternal region of birth							
UK/Ireland	547	45.6	652	54.4	1199	100	
Europe	178	47.8	194	52.2	372	100	
Africa	3974	51.4	3762	48.6	7736	100	
Elsewhere	308	49.0	321	51.0	629	100	0.002
Maternal mode of HIV acquisition							
Other risk	5046	50.5	4940	49.5	9986	100	
IDU	75	58.4	54	41.9	129	100	0.09
Area first pregnancy reported from							
London	2247	46.1	2628	53.9	4875	100	
Rest of England	2800	55.0	2289	45.0	5089	100	
Wales	65	45.8	77	54.2	142	100	<0.001
Year first pregnancy reported							
2000-2003	1304	59.5	886	40.4	2190	100	
2004-2008	2184	49.3	2248	50.7	4432	100	
2009-2013	1633	46.8	1860	53.2	3493	100	<0.001
Total no of pregnancies reported							
One	3750	54.6	3119	45.4	6869	100	
Two	1025	42.6	1378	57.3	2403	100	
3 or more	346	41.0	497	59.0	843	100	<0.001
Timing of maternal diagnosis							
Before first reported pregnancy	2566	51.1	2455	48.9	5021	100	
During first reported pregnancy	2530	50.0	2525	50.0	5055	100	<0.001
Year of maternal HIV diagnosis							
1985-1995	154	48.7	162	51.2	316	100	
1996-2000	626	56.3	485	43.7	1111	100	
2001-2005	2269	53.6	1961	46.4	4230	100	
2006-2009	1168	43.7	1505	56.3	2673	100	
2010-2013	399	43.2	524	56.8	923	100	<0.001
Age at conception in first reported pregnancy							
Age 13 to 20	233	41.1	334	58.9	567	100	
Age 21 to 28	1791	49.2	1846	50.8	3637	100	
Age 29 to 36	2424	51.9	2249	48.1	4673	100	
Age 37 to 44	651	54.1	553	45.9	1204	100	
Age 45+	20	62.5	12	37.5	32	100	<0.001

Factors associated with being matched to at least one resistance test

Table 6-4 shows the results of univariable logistic regression analysis of factors associated with being matched to at least one resistance test. Being younger at conception in first reported pregnancy was associated with a greater likelihood of being matched. Women diagnosed 1996-2000 and 2001-2005 were less likely to be matched compared with women diagnosed 2010-2013. Similarly, women with year of first reported pregnancy prior to 2006 were less likely to be matched compared with women with first reported pregnancy 2006 onwards. Women with more than one reported pregnancy in the dataset were more likely to be matched. Women born in the UK/Ireland were more likely to be matched then those born in sub-Saharan Africa. Women of white ethnicity had a slightly higher odds ratio than those of Black African ethnicity, though this did not quite reach the level of significance (p=0.07), however women of 'other' ethnicity were more likely to be matched (p=0.001). Finally, women with first reported pregnancy in London were more likely to be matched to a resistance test than those with first pregnancy reported from the rest of England.

Table 6-4. Factors associated with being matched to at least one resistance test: univariable analysis

	Univariable Analysis		
Explanatory variable	OR	95% CI	*p*-value
Age at conception in first reported pregnancy (*n*=10,113)			
13 to 20 years	1.39	1.16 – 1.66	<0.001
21 to 28 years	1	-	-
29 to 36 years	0.90	0.83 – 0.98	0.02
37 to 44 years	0.82	0.72 – 0.94	0.01
Age 45+ years	0.58	0.28 – 1.19	0.14
Year of maternal diagnosis (*n*=9,253)			
1983 - 1995	0.80	0.62 – 1.03	0.09
1996 - 2000	0.59	0.49 – 0.70	<0.001
2001 - 2005	0.66	0.57 – 0.76	<0.001
2006-2009	0.98	0.84 – 1.14	0.81
2010-2013	1	-	-
Year of first reported pregnancy (*n*=10,115)			
2000-2002	0.63	0.55 – 0.72	<0.001
2003 - 2005	0.77	0.68 – 0.87	<0.001
2006 - 2008	1.02	0.92 – 1.14	0.68
2009 - 2011	1		
2012 - 2014	1.06	0.92 – 1.22	0.46
Number of pregnancies reported (*n*=10,115)			
1 pregnancy	1		
2 pregnancies	1.61	1.47 – 1.78	<0.001
3 or more	1.73	1.49 – 1.99	<0.001
Maternal region of birth (*n*=9936)			
UK/Ireland	1.26	1.11 – 1.42	<0.001
Europe	1.15	0.93 – 1.41	0.19
Sub-Saharan Africa	1		
Elsewhere	1.1	0.94 – 1.30	0.25
Maternal ethnicity (*n*=10,089)			
Black African	1		
White	1.11	0.99 – 1.25	0.07
Other	1.27	1.11 – 1.46	0.001
Area first pregnancy reported from (*n*=10,106)			
London	1		
Rest of England	0.70	0.64 – 0.76	<0.001
Wales	1.01	0.72 – 1.42	0.94

Table 6-5. Model selection for analysis of factors associated with being matched to at least one resistance test

Model number	Explanatory variables in multivariable model											
	No. of pregs. reported	Region reported from	Year of first reported preg.	Year of maternal diagnosis	Maternal region of birth	Age at conception in first preg.	Maternal ethnicity	Injecting drug use	Pseudo log-likelihood	DF	AIC	BIC
M0									-7010.4	1	14022.8	14030.0
M1	✓								-6942.5	3	13891.1	13912.8
M2	✓	✓							-6902.7	5	13815.5	13851.6
M3	✓	✓	✓						--6812.7	9	13643.5	13708.5
M4	✓	✓	✓	✓					--6213.0	13	12452.0	12544.7
M5	✓	✓	✓	✓	✓				--6124.4	16	12280.7	12394.6
M6*	✓	✓	✓	✓	✓	✓			-6114.1	20	12268.3	12410.7
M7	✓	✓	✓	✓	✓	✓	✓		-6119.0	18	12274.1	12402.2
M8	✓	✓	✓	✓	✓	✓		✓	-6113.37	21	12268.7	12418.2

*Selected as most parsimonious model

Table 6-5 shows the model selection process with AIC and BIC for each multivariable model; Model 6 was selected as the most parsimonious (lowest AIC and BIC) and contained all explanatory variables that were significantly associated in the univariable analysis except for maternal ethnicity. Goodness-of-fit of the final model was assessed with the Hosmer-Lemeshow chi square test, which was reassuring (p=0.71), indicating no significant difference between the estimated and actual values.

After adjusting for potential confounding variables in the final multivariable model (see Table 6-6), women who were diagnosed in 1996-2000 and 2001-2005 remained less likely to have been matched to a resistance test than those diagnosed in 2010-2013 (OR 0.67, 0.73 respectively, p=0.001 for both). In the univariable analysis, being younger at conception in first reported pregnancy was associated with a greater likelihood of being matched, but in the multivariable analysis this only remained significant in two age categories: women aged 13 to 20 years were more likely to be matched (OR 1.29, p= 0.01), and women aged 37 to 44 years were less likely to be matched (OR 0.83, p=0.02) than those aged 21 to 28 years at conception.

The significant association with higher number of pregnancies reported in the univariable analysis remained in the multivariable analysis: women with a higher number of pregnancies reported were more likely to be matched (OR 1.63 for two pregnancies, OR 1.89 for three or more pregnancies, p<0.001 for both). The likelihood of being matched for women born in the UK or Ireland remained the same in univariable and multivariable analysis; these women were more likely to be matched than women born in sub-Saharan Africa (OR 1.26 vs 1, p=0.001). The association with region of pregnancy report grew stronger in the multivariable analysis: women whose first reported pregnancy was from the rest of England were less likely to be matched compared with those reported from London (OR 0.63 and 1, p<0.001). Similarly, the effect of calendar period of first reported pregnancy remained after adjustment: women whose first reported pregnancy was in 2005 or before were less likely to be matched than those whose expected or actual delivery date was in 2006 onwards (OR 0.57 for pregnancies 2000-2002, p<0.001; OR 0.78 for pregnancies 2003-2005, p=0.001).

Table 6-6. Factors associated with being matched to at least one resistance test: multivariable analysis

Explanatory variable	Multivariable analysis (*n*=9119)		
	Adjusted odds ratio	95% confidence interval	*p*-value
Year of maternal diagnosis			
1983-1995	0.92	0.68 – 1.23	0.56
1996-2000	0.67	0.54 - 0.84	0.001*
2001-2005	0.73	0.60 – 0.87	0.001*
2006-2009	1.00	0.84 - 1.19	1.00
2010-2013	1	-	-
Age at conception of first reported pregnancy			
Age 13 to 20	1.29	1.06 - 1.57	0.01*
Age 21 to 28	1	-	-
Age 29 to 36	0.93	0.84 - 1.02	0.12
Age 37 to 44	0.83	0.72 - 0.97	0.02*
Age 45+	0.46	0.20 - 1.03	0.06
Number of pregnancies reported			
One	1	-	-
Two	1.63	1.47 - 1.81	<0.001*
3 or more	1.89	1.62 - 2.21	<0.001*
Maternal region of birth			
UK/Ireland	1.26	1.10- 1.44	0.001*
Europe	1.11	0.88 - 1.39	0.37
Africa	1	-	-
Elsewhere	1.08	0.91 - 1.29	0.37
Area first pregnancy reported from			
London	1		-
Rest of England	0.63	0.58 - 0.69	<0.001*
Wales	0.75	0.52 - 1.08	0.125
Year of first reported pregnancy			
2000-2002	0.57	0.47 - 0.67	<0.001*
2003-2005	0.78	0.67 - 0.90	0.001*
2006-2008	0.96	0.84 - 1.08	0.48
2009-2011	1	-	-
2012-2013	1.12	0.95 - 1.3	0.17

Viral subtype in women matched to at least one resistance test

Table 6-7 shows viral subtypes in women matched to at least one resistance test, by maternal region of birth. The most common viral subtype, present in nearly half of women matched to a resistance test, was subtype C (2248/4881). Subtype CRF02_AG was the next most prevalent subtype, with 13.3% of women, and subtypes A and B were both present in around 10% of women. Other recombinant forms were found in

8.2%, with substantially lower numbers of subtype D, subtype G, other pure and unclassified subtypes.

Viral subtype was highly associated with region of birth (p<0.001). Over half (52.2%) of the matched women born in sub-Saharan Africa had subtype C infection, 15.2% had CRF02_AG, and 11.8% had subtype A. Only 1.1% of women born in sub-Saharan Africa had subtype B virus. Of the 643 women born in the UK or Ireland, over a third (37.2%) had subtype B virus, and just under a third had subtype C virus (32.5%). In women born in Europe (not UK/Ireland), subtype B was most prevalent (32.6%), and a greater proportion of women had subtype A virus (17.6%) than those born in the UK or Ireland (7.2%). The prevalence of subtype C virus was lower in women born in Europe than those born in the UK or Ireland (14% vs 32.5%). The prevalence of subtype B virus was highest in women born elsewhere (46.3%), and around a fifth of these women had subtype C (21.3%) and other recombinant forms (20.0%).

All of the subtypes and other pure and recombinant forms were dominated by women born in sub-Saharan Africa, with the exception of subtype B. The majority, 86.4%, of women with subtype C were born in sub-Saharan Africa (1,944/2248); and 9.3% were born in UK/Ireland (209/2248) (p<0.001). Over half (54.5%) of women with subtype C virus who were born in sub-Saharan Africa were born in Zimbabwe (1059/1944) ; 11.1% were born in South Africa (216/1944), and 8.3% were born in Malawi (158/1944).

The next most prevalent subtype was CRF02_AG, found in 13.3% of women. Similarly, 86.9% of these women were born in sub-Saharan Africa (565/650), with the most common countries of birth being in West Africa: Nigeria 36.8% (208/565); Ghana 20.0% (208/565) and Ivory Coast 12.9% (73/565). 11.8% of women born in sub-Saharan Africa had subtype A (438/3725), with 29.9% of these women born in Uganda (131/438), 13.2% born in Kenya (58/438) and 7.3% born in the Democratic Republic of Congo (DRC) (32/438). 7.1% of women born in sub-Saharan Africa had another recombinant subtype (266/3725); the most common countries of birth in these women were Nigeria 21.1% (56/266); DRC 13.5% (36/266), and Ghana 12.0% (32/266).

Overall 8.2% of women had a recombinant subtype (other than CRF02_AG) (399/4881): two-thirds of these women were born in sub-Saharan Africa (266/399),

and 16.0% were born elsewhere (64/399). Of those born elsewhere, 60.9% were born in Thailand (39/64).Figure 6-3 A. shows region of birth in women matched to at least one resistance test over time (year of first reported pregnancy, and B shows country of birth over time in women matched to at least one resistance test and born in sub-Saharan Africa,

Figure 6-5 illustrates that the prevalence of subtype C rose from 28.1% 2000 to 53.3% in 2010, fell to 42.8% in 2012, and then rose to 48.5% in 2013. The proportion of women born in Zimbabwe (over half of women from sub-Saharan Africa with subtype C infection were born in Zimbabwe) also rose from 12.1% in 2000 to 35.6% in 2008, and then fell to 28.8% in 2013. The rise in the proportion of subtype C infections 2012 to 2013 may be accounted for by the concurrent rise in women from South Africa and Malawi in the same years. The proportion of women born in Nigeria rose steadily from 8.3% in 2000 to 16.2% in 2012; the proportion of women born in Ghana fluctuated between 3.0% and 6.7% over the calendar period; and proportion of women from the Ivory Coast fell from 3.8% in 2000 to 1.13% in 2013. The prevalence of CRF02_AG virus rose from 9.4% in 2000 to 15.5% in 2005 and fell slightly to 13.5% in 2012.

The prevalence of subtype B fell from 14.1% in 2000 to 8.0% in 2008, and then rose to 12.5% in 2013. This may be explained by the fall in the proportion of women born in the UK/ Ireland from 13.2% in 2000 to 9.8% in 2006, with a rise to 14.2% in 2013. In addition, there was a small rise in the proportion of women born in Europe (non-UK / Ireland) and elsewhere in the later years of the calendar period.

Table 6-7. Viral subtypes in women matched to at least one resistance test, by maternal region of birth

	Viral subtype (n=4881)																	
	A		CRF02_AG		B		C		D		Other recombinant		Other pure		G		Unclassified	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
Maternal region of birth																		
UK/Ireland (*n*=643)	46	7.2	53	8.2	239	37.2	209	32.5	19	3.0	49	7.6	3	0.5	24	3.7	1	0.2
Europe (*n*=193)	34	17.6	16	8.3	63	32.6	27	14.0	2	1.0	20	10.4	10	5.2	19	9.8	2	1.0
Sub-Saharan Africa (*n*=3,725)	438	11.8	565	15.2	40	1.1	1,944	52.2	186	5.0	266	7.1	52	1.4	208	5.6	26	0.7
Elsewhere (*n*=320)	13	4.1	16	5.0	148	46.3	68	21.3	4	1.3	64	20.0	0	0.0	7	2.2	0	0.0
Total	531	10.9	650	13.3	490	10.0	2,248	46.1	211	4.3	399	8.2	65	1.3	258	5.3	29	0.6

Figure 6-3. Maternal region of birth by year of first reported pregnancy in women matched to at least one resistance test

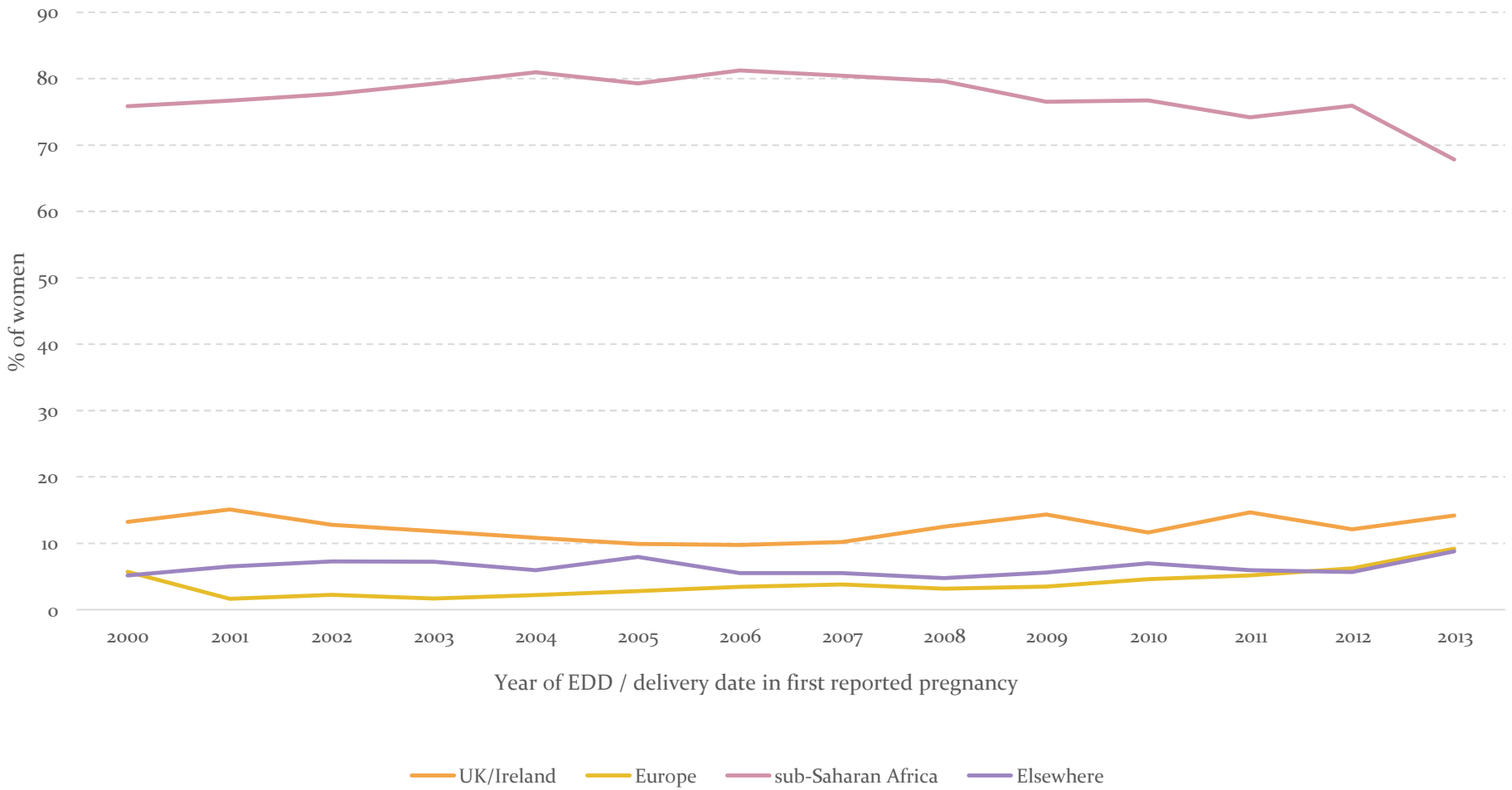
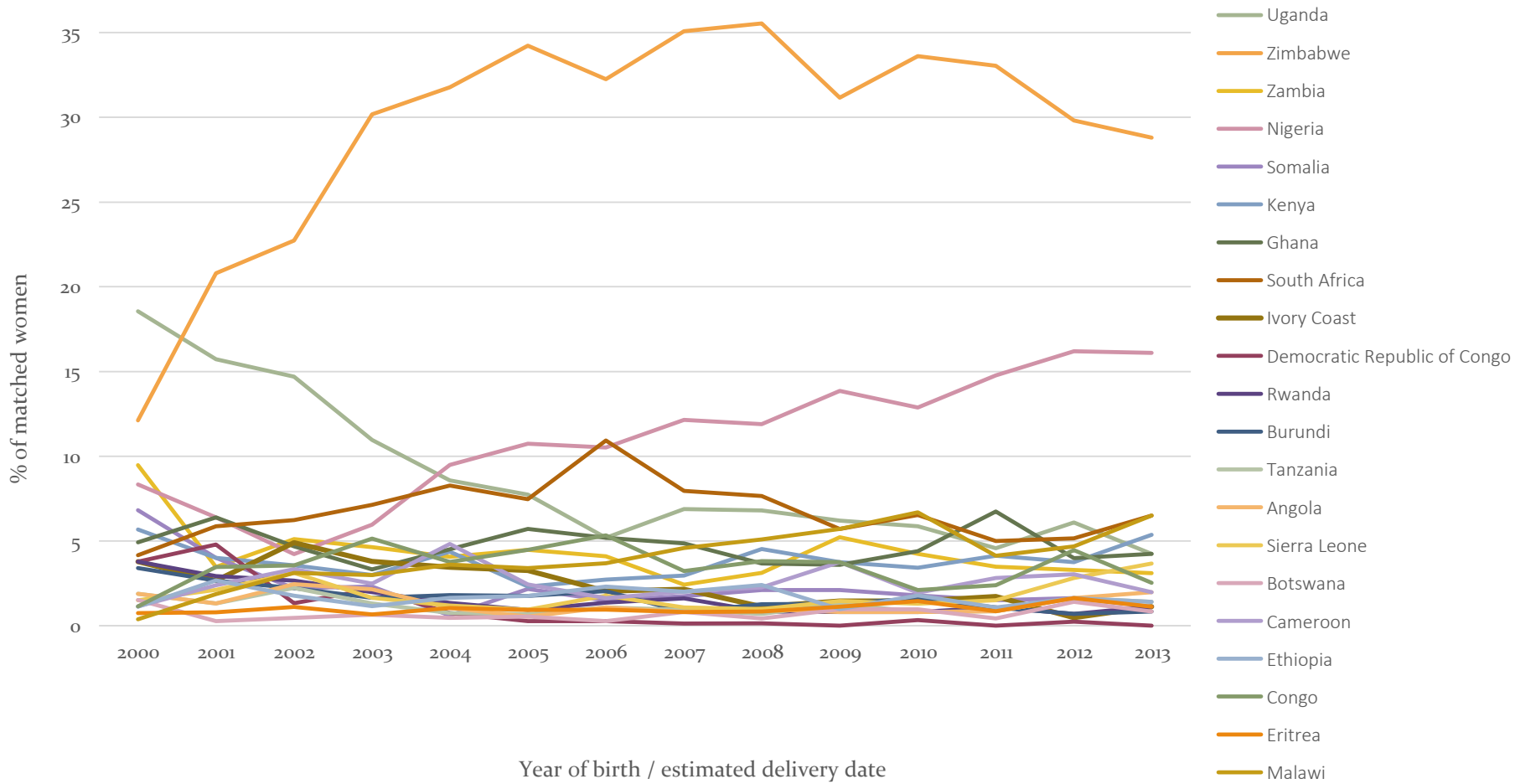
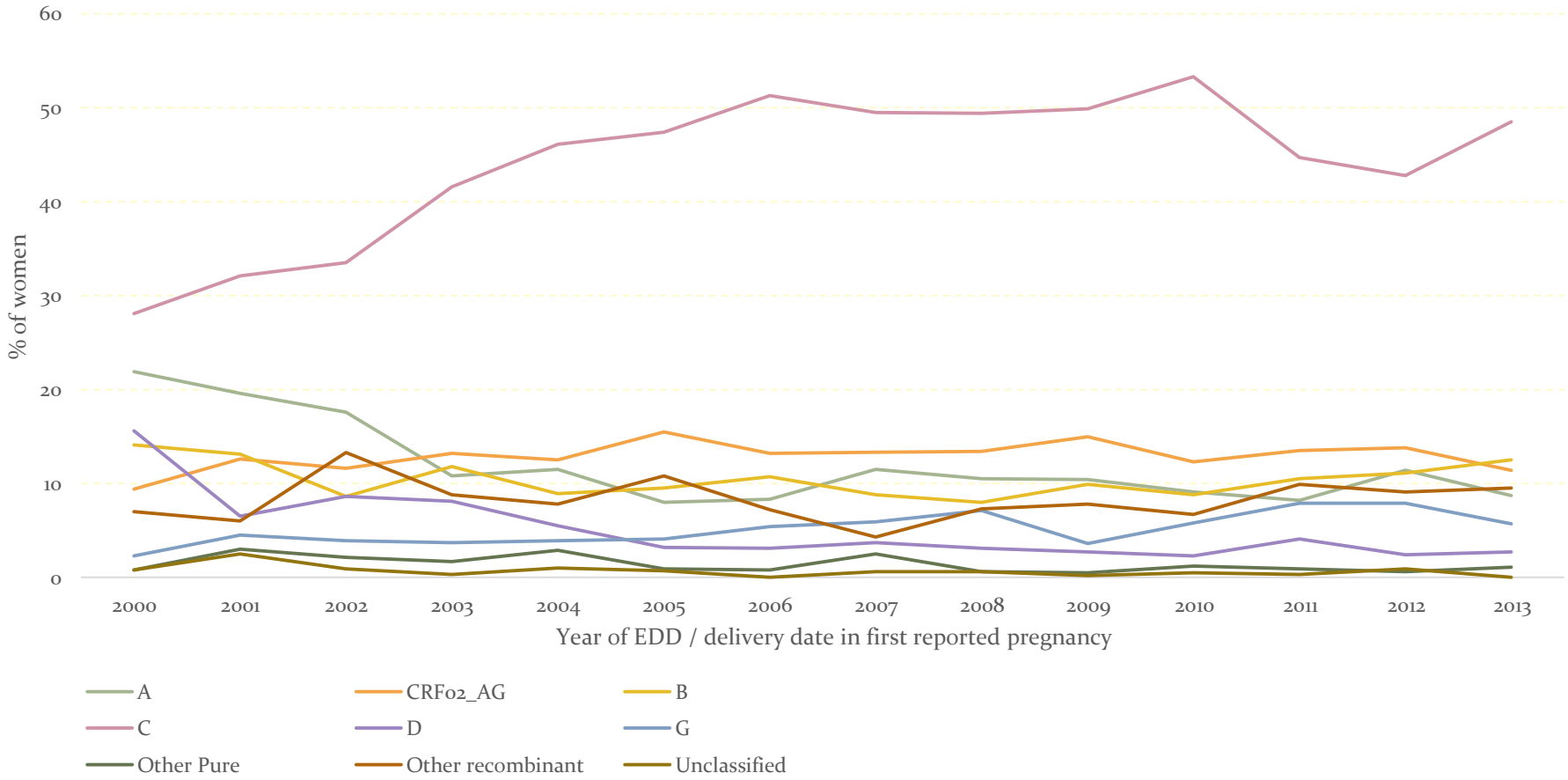


Figure 6-4 Country of birth by year of first reported pregnancy in matched women born in sub-Saharan Africa*



*countries shown if >1% reported pregnancies in any given year

Figure 6-5. Viral subtype by year of first reported pregnancy in women matched to at least one resistance test



Transmitted drug resistance in women diagnosed during pregnancy

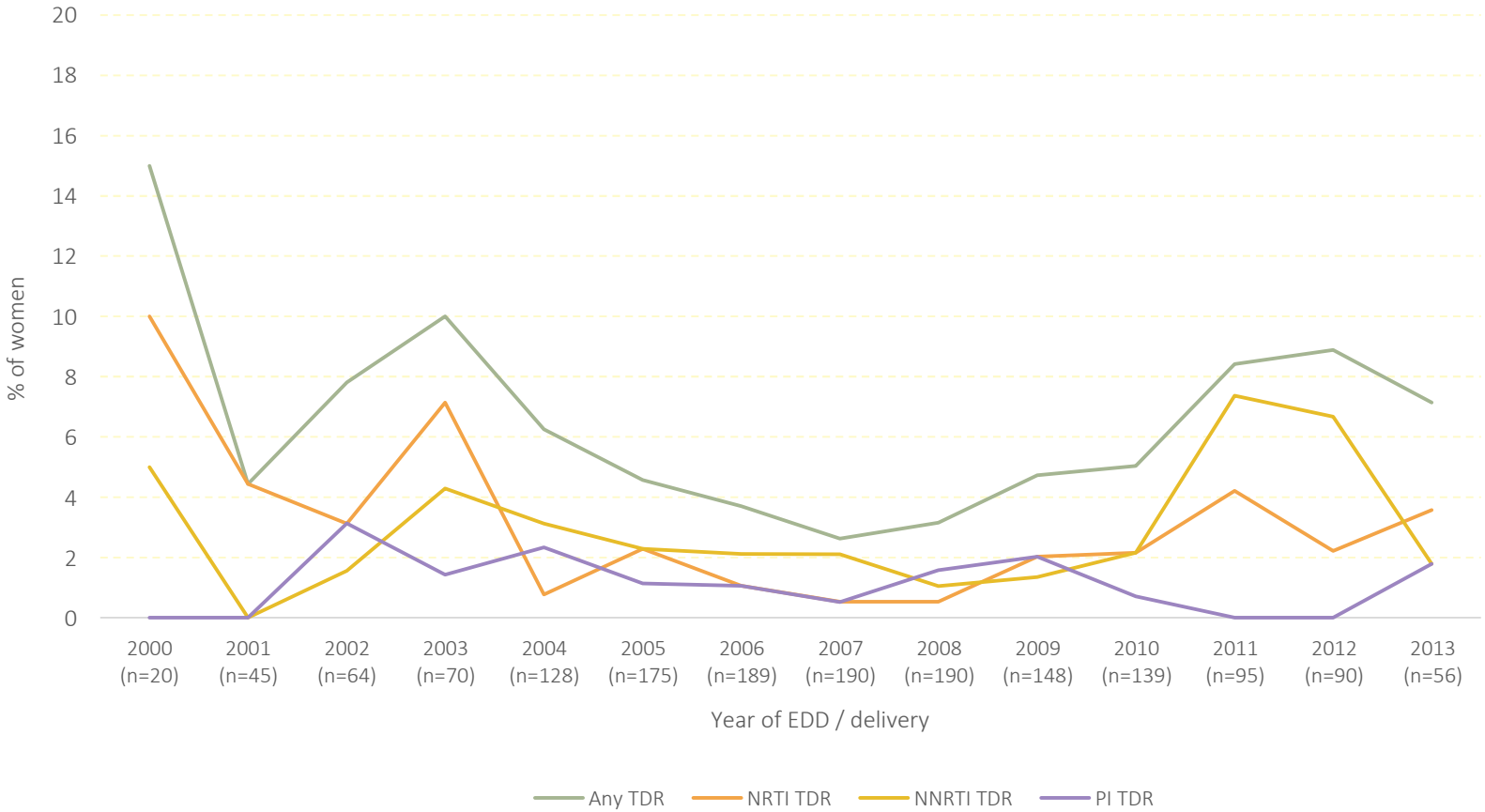
Of the 4994 women matched to at least one resistance test, 2525 (50.6%) were diagnosed with HIV infection during the first reported pregnancy in the dataset. Of these, 1599 women were recorded as naïve to ART at the time of their first matched resistance test. Table 6-8 shows the proportion of women diagnosed during pregnancy matched to a resistance test, and those classified as naïve to ART at first resistance test, by year of pregnancy. Overall, 5.3% had any TDR at this first matched resistance test (85/1599; 95% CI: 4.3% to 6.5%). The prevalence of TDR varied by year of pregnancy: 7.8% in women diagnosed during pregnancy in 2000-2002 (10/119); 6.2% in 2003-2005 (23/373); 3.2% in 2006-2008 (18/569); 5.8% in 2009-2011 (22/360) and 8.2% in 2012-2013 (12/146) (p=0.04). There was no evidence of a linear trend by calendar period (test-for-trend p=0.94). The prevalence of TDR varied with HIV subtype, but this did not reach statistical significance; the subtype categories with the highest prevalence of TDR were 'other pure' with a prevalence of 13.3% (2/15); 'other recombinant' with a prevalence of 9.1% (14/154); and subtype B with a prevalence of 7.8% (11/145); subtype D had the lowest prevalence of TDR at 2.6% (1/39), and subtype C also had a low prevalence at 4.6% (33/721) (p=0.26).

Figure 6-6 shows the prevalence of TDR (overall and by antiretroviral class) in women diagnosed during pregnancy and who were matched to a resistance test by calendar period. The prevalence of NRTI TDR varied by year: 4.7% in 2000-2002 (6/129), 2.8% in 2003-2005 (10/373), 0.7% in 2006-2008 (4/569), 2.6% in 2009-2011 (10/382), and 2.7% in 2012-2014 (4/146) (Fisher's exact p=0.01). However, there was no evidence of a linear trend by calendar period (test-for-trend p=0.4). The variation in the prevalence of NNRTI TDR did not reach statistical significance: 1.6% in 2000-2002 (2/129); 3.0% in 2003-2005 (11/373); 1.8% in 2006-2008 (10/569); 3.1% in 2009-2011 (12/382); and 4.8% in 2012-2013 (7/146) (p=0.23). Similarly, the variation in PI TDR did not reach statistical significance either: 1.6% in 2000-2002 (2/129); 1.6% in 2003-2005 (6/373); 1.1% in 2006-2008 (6/569); 1.1% in 2009-2011 (4/382), and 0.7% in 2012-2014 (1/146) (p=0.9).

Table 6-8. Proportion of women diagnosed during first reported pregnancy who were matched to a resistance test and classified as naïve on first resistance test

Year of estimated / actual delivery date														
	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013
Women classified as naïve on 1st resistance test														
n	20	45	64	70	128	175	189	190	190	148	139	95	90	56
(%)	(10)	(14)	(17)	(14)	(24)	(32)	(38)	(41)	(44)	(44)	(47)	(42)	(50)	(38)
Women matched to ≥ 1 resistance test														
n	70	118	159	195	259	293	290	261	233	172	169	124	122	60
(%)	(38)	(37)	(42)	(38)	(49)	(53)	(58)	(56)	(54)	(51)	(58)	(55)	(67)	(41)
Total number of women diagnosed during pregnancy														
n	183	321	380	514	529	552	497	467	429	334	292	225	181	146
(%)	(100)	(100)	(100)	(100)	(100)	(100)	(100)	(100)	(100)	(100)	(100)	(100)	(100)	(100)

Figure 6-6. Prevalence of TDR in women diagnosed during pregnancy and who were matched to a resistance test



What risk factors were associated with the presence of transmitted drug resistance in women diagnosed during pregnancy?

In the univariable logistic regression analysis shown in Table 6-9, having EDD/delivery date 2006 – 2008 was associated with a lower risk of TDR compared to 2000-2002 (OR 0.39 p=0.02). Having a low CD4 count in pregnancy (and therefore near to diagnosis) was associated with increased risk of TDR (OR 2.08 vs. 1.0 in CD4 ≥ 500 cells/uL, p=0.04). The model with the lowest AIC was chosen, M7 in Table 6-10 (see page 188). Goodness-of-fit of the final model was assessed with the Hosmer-Lemeshow chi square test, which was reassuring (p=0.31), indicating no significant difference between the estimated and actual values. In the multivariable analysis (Table 6-11), the only explanatory variable which reached the level of significance was the association between year of EDD/delivery date 2006-2008, which was still associated with a lower risk of TDR (AOR 0.39 vs. 2000-2002, p=0.02); the increased risk of TDR with CD4 count <200 cells/uL did not reach the level of significance in the multivariable model (AOR 2.02 vs. CD4 ≥ 500 cells/uL, p=0.05).

Table 6-9. Univariable analysis of risk factors for TDR in women diagnosed during pregnancy

	Univariable analysis		
Explanatory variable	Odds Ratio	95% confidence interval	*p*-value
Age at conception (*n*=1599)			
13 to 20 years	0.32	0.10 – 1.03	0.06
21 to 30 years	0.70	0.44 – 1.10	0.12
31 to 40 years	1	-	-
>40 years	1.32	0.30 – 5.84	0.71
Year (*n*=1599)			
2000-2002	1	-	-
2003-2005	0.78	0.36 - 1.69	0.53
2006-2008	0.39	0.18 - 0.86	0.02*
2009-2011	0.73	0.33 - 1.58	0.42
2012-2014	1.07	0.44 - 2.56	0.89
Maternal region of birth (*n*=1581)			
Sub-Saharan Africa	1	-	-
UK/Ireland	1.03	0.52 - 2.04	0.94
Europe	1.08	0.33 - 3.54	0.90
Elsewhere	1.27	0.60 - 2.72	0.53
Maternal ethnicity (*n*=1,598)			
Black African	1	-	-
White	1.19	0.61 - 2.30	0.61
Other	1.16	0.59 - 2.31	0.67
Area first pregnancy reported from (*n*=1599)			
London	1	-	-
Rest of England	0.82	0.53 - 1.28	0.38
Wales	0.50	0.07 - 3.77	0.50
HIV subtype (*n*=1595)			
Non-subtype C	1	-	-
Subtype C	0.76	0.48 - 1.19	0.23
CD4 count in first pregnancy (*n*=1423)			
≧500 cells/ μ L	1	-	-
350-499 cells/ μ L	1.6	0.88 - 2.92	0.13
200-349 cells/ μ L	1.27	0.67 - 2.42	0.47
<200 cells/ μ L	2.08	1.04 - 4.19	0.04*

* reached level of significance ($p<0.05$

Table 6-10. Model selection for multivariable analysis of risk factors for TDR in women diagnosed during pregnancy

Model number	Explanatory variables in multivariable model										
	CD4 in pregnancy	Year	Age at conception	Area reported from	HIV subtype	Maternal region of birth	Maternal ethnicity	Pseudo log-likelihood	DF	AIC	BIC
M1	✓							-297.1	4	602.1	623.1
M2		✓						-327.0	5	664.1	691.0
M3		✓	✓					-323.9	8	663.8	706.84
M4	✓	✓	✓					-290.0	11	602.1	659.92
M5	✓	✓						-293.4	8	602.8	644.9
M6	✓	✓	✓	✓				-289.9	13	605.8	674.2
M7*	✓	✓	✓		✓			-288.9	12	601.8	665.0
M8	✓	✓	✓		✓	✓		-288.2	15	606.3	685.1
M9	✓	✓	✓			✓		-289.2	14	606.4	679.9
M10	✓	✓	✓		✓		✓	-288.6	14	605.2	678.9
M11	✓	✓	✓	✓	✓	✓	✓	-287.3	19	612.6	712.4

* Selected as most parsimonious model

DF: degrees of freedom, AIC: Akaike's information criterion, BIC: Bayesian information criterion

Table 6-11. Multivariable analysis of factors associated with TDR in women diagnosed during pregnancy

Explanatory variable	Multivariable analysis (n=1420)		
	Adjusted odds ratio	95% confidence interval	*p*-value
Age at conception			
13 to 20 years	0.23	0.05 – 0.98	0.05
21 to 30 years	0.67	0.41 – 1.07	0.10
31 to 40 years	1	-	-
>40 years	0.63	0.08 - 4.93	0.66
Year			
2000-2002	1	-	-
2003-2005	0.78	0.33 – 1.84	0.58
2006-2008	0.39	0.16 - 0.94	0.04*
2009-2011	0.72	0.31 - 1.69	0.45
2012-2014	0.73	0.27 – 2.00	0.54
HIV subtype			
Non-subtype C	1	-	-
Subtype C	0.74	0.46 - 1.19	0.21
CD4 count in first pregnancy			
≥500 cells/ μ L	1	-	-
350-499 cells/ μ L	1.51	0.82 – 2.77	0.18
200-349 cells/ μ L	1.25	0.65 – 2.39	0.51
<200 cells/ μ L	2.02	0.99 – 4.10	0.05

Was the presence of TDR associated with a detectable VL at delivery or infant infection status?

There was no evidence in univariable analysis that the presence of TDR was associated with a detectable VL at delivery: 4.9% of women with a delivery VL <50 copies/ml had evidence of any TDR (41/835) compared with 5.4% of women with a detectable VL (30/551) (p=0.66) and OR of having detectable VL at delivery in the presence of TDR was 1.12, (95% CI 0.69 – 1.80, p=0.66). There was a similar result when looking at the individual associations of NRTI TDR, NNRTI TDR, and PI TDR with VL at delivery [data not shown].

Infant infection status was available for 89.7% women diagnosed with HIV during pregnancy and matched to a resistance test (1297/1446). Overall, 12 infants were vertically infected; 0.9% of infants born to women with no TDR detected acquired PHIV (11/1227) and 1.4% of those whose mothers had TDR detected (1/70) (p=0.48). Regarding the one infant who acquired PHIV from a woman with TDR, the woman had entered the UK from Zimbabwe during pregnancy and had been diagnosed with HIV a month before delivery. She had intrapartum ZDV only, delivered by elective caesarean section in 2000, and the baby received PEP. There were no VL data available for the pregnancy or delivery, and she was recorded as having T215D mutation at baseline.

Resistance mutations identified in women with TDR diagnosed during pregnancy

Of the 85 women identified as having at least one TDRM (transmitted drug resistance mutations), 24/85 women had one or more TDRM conferring resistance to only NRTIs, 35/85 had TDRM conferring resistance to only NNRTIs, and 16/85 had only TDRM conferring resistance to PIs, 3/85 women had resistance to both NRTIs and PIs, and 7/85 women had resistance to both NRTIs and NNRTIS but not PIs. There were no women with triple-class resistance.

In terms of TDRM in reverse transcriptase that confer resistance to NRTIs, thymidine analogue mutations (TAMs), selected by the thymidine analogues zidovudine and stavudine, were present in 11/34 women (41L was the most common in 9/34 women). M184VI was identified in 8/34 women, a mutation which is selected by and confers resistance to emtricitabine and lamivudine (and to a lesser extent abacavir and didanosine). TAM variants selected by zidovudine at codon 219 were present in 4/34 women (219E/N/R) and at codon 67 were found in 2/34 women (67E/G). T215

revertants, which increase the risk of virological failure to zidovudine-containing ART regimens, were identified in 3/34 women (215/D/E/V).

The most common TDRMs identified in reverse transcriptase which confer resistance to NNRTIs were 103N (20/41 women), a mutation selected by nevirapine and efavirenz which reduces nevirapine susceptibility; 101E,(8/41 women), which is selected by exposure to any of the NNRTIs and reduces susceptibility to nevirapine by 3- to 10-fold, to efavirenz by 1 to 5-fold, and to etravirine and rilpivirine by about 2-fold; 106A/M (3/41 women); 181C (3/41 women); and 138K (3/41 women). The most common protease TDRMs were 46I/L (7/19), which are selected primarily by indinavir, nelfinavir, fosamprenavir, atazanavir, and lopinavir, and occur in about 0.1%-0.4% of viruses in people naïve to treatment, with highest prevalence in CRF01_AE; 90M (5/19), which is selected primarily by saquinavir, nelfinavir, indinavir and lopinavir and reduces susceptibility to all PIs except tipranavir and darunavir; and 85V (4/19), which has minimal, if any, effect on PI susceptibility (Liu and Shafer 2006).

6.4 Key points

- The pattern of combination antiretroviral drug prescribing in pregnancy in the UK and Ireland changed over time. Median gestation at start of ART in women not on ART at conception fell from 27 weeks in 2000-2002 to 20 weeks in 2012-2014 (p<0.001).
- Women were treated with a PI-based regimen in nearly two-thirds of live births (61%) and an NNRTI-based regimen in a third. Women on cART at conception were equally likely to be prescribed PI- or NNRTI-based cART; women not on ART at conception were treated with a PI-based regimen in over 70% of cases, and the proportion of these women on a PI increased from 17% in 2000-2002 to a peak of 87% in 2009-2011.
- Women are commonly prescribed an NNRTI 'backbone' (of two drugs, often co-formulated) plus a third agent. Few women (211) received treatment with triple-NRTI therapy, most commonly the co-formulated combination abacavir + lamivudine +zidovudine (brand name Trizivir). Use of the NRTI backbone zidovudine + lamivudine (co-formulated as Combivir) fell dramatically from 97% in 2000-2002 to 18% in 2012-2014. Tenofovir + emtricitabine (co-formulated as Truvada) use rose from 0.2% of livebirths in 2003-2005 to become the most widely prescribed NRTI backbone in 2012-2014 (60%). Abacavir + lamuvidine (co-formulated as Kivexa) also rose in popularity but to a lesser extent, with a high of 21% in 2012-2014.
- A small number of women received additional raltegravir in (0.4% live births overall; 2.3% of live births in women not on ART at conception).
- Patterns of NNRTI use also evolved over the calendar period of the study. In women on ART at conception treated with NNRTI-based cART, nevirapine use fell from 94% in 2000-20002 to 43% in 2012-2014. Conversely, the use of efavirenz as a third agent rose from 6% in 2000-2002 to 55% in 2012-2014 (p<0.001). Similarly, women not on ART at conception treated with an NNRTI were mostly treated with nevirapine (95%), but efavirenz use in this group rose from 0.5% to 54.9% in 2012-2014.
- At the start of the study period, nelfinavir was the most widely used PI, but dropped dramatically to negligible levels by 2008. The use of ritonavir-boosted lopinavir rose from zero in 2000, peaked at 82% in 2010 in women not on ART at conception before dropping to only a quarter of women by the

end of the study. Ritonavir-boosted atazanavir use emerged in 2003 and became the most widely used PI in both women on and not on ART at conception in 2012. Ritonavir-boosted darunavir use emerged in 2007-2008 and use steadily rose over time, particularly in women on ART at conception, of whom nearly half were on darunavir in 2014.

- Nearly half of women with a reported pregnancy 2000-2014 were matched to at least one resistance test in the UK HIV Drug Resistance Database.
- Factors associated with being matched to at least one resistance test included younger age (aOR 1.29 for those aged 13 to 20; AOR 0. 83 for those aged 37 to 44), more pregnancies reported (aOR 1.63 for two pregnancies, aOR 1.89 for three or more pregnancies) and being born in the UK/Ireland (OR 1.26 vs. 1 for women born in sub-Saharan Africa). Women diagnosed in earlier calendar periods were less likely to have been matched than those diagnosed 2010-2013 (aOR 0.67 for 1996-2000, 0.73 for 2001-2005 respectively), as were women whose first reported pregnancy was from the rest of England versus London (aOR 0.63); women whose first reported pregnancy was in 2005 or before were less likely to be matched than those with later pregnancies (aOR 0.57 for pregnancies 2000-2002, aOR 0.78 for pregnancies 2003-2005).
- The most common viral subtype, present in nearly half of women matched to a resistance test, was subtype C , followed by Subtype CRF02_AG (13% of women), and subtypes A and B (both in around 10% of women).
- Subtype was highly correlated with region of birth. All of the subtypes and other pure and recombinant forms were dominated by women born in sub-Saharan Africa, with the exception of subtype B. Over half of women with subtype C virus born in SSA were born in Zimbabwe. The vast majority of women with cRF02_AG virus were born in sub-Saharan Africa; most commonly in the West African countries Nigeria (37%), Ghana (20%) and the Ivory Coast (13%). Overall, 10% of women had subtype B; of these women, nearly half were born in UK/Ireland, 18% in Jamaica, and 4% in Poland.
- 1599 women who were matched to at least one resistance test were diagnosed during the first reported pregnancy and reported as ART-naïve on the request for the resistance test. Of these 1599 women, 5% had evidence of TDR (95% CI 4.3% to 6.5%).
- Year of pregnancy 2006-2008 (and therefore diagnosis) was associated with a

lower risk of TDR (aOR 0.39, *p*=0.04); low CD4 count in pregnancy (and therefore at diagnosis) was associated with a higher risk of TDR (aOR 2.02 vs. 1.0) but did not quite reach the level of statistical significance (*p*=0.05).

- There was no evidence that the presence of TDR increased the risk of detectable VL at delivery or was associated with the infection status of the infant. In both cases, the low rates of TDR and of detectable VL at delivery, and the low vertical infection rate would have contributed to a lack of statistical power.
- The largest group of women with TDRMs had resistance to only NNRTIs (35/85); only 10 women had dual class resistance, and none had triple class resistance. The most common TDRM conferring NNRTI resistance was 103N (20/41), followed by 101E (8/41), 181C (3/41) and 138K (3/41). The most common TDRMs conferring NRTI resistance were TAMs (present in 11/34 women), and 184V (8/33). The most common TDRMs conferring resistance to PIs were 46I/L (7/19), 90M (5/19), and 85V (4/19).

7 Eliminating vertical transmission of HIV in the UK: what is left to do?

7.1 Introduction

In 2011 UNAIDS published Countdown to Zero: the Global Plan towards the elimination of new HIV infections among children by 2015 and keeping their mothers alive, which set out the goals of reducing the number of new childhood HIV infections by 90% and reducing the number of AIDS-related maternal deaths by 50% (Joint United Nations Programme on HIV/AIDS 2011). In 2014, the WHO set out guidance for evaluating the elimination of vertical transmission, defining it as less than 50 new paediatric infections per 100,000 live births, plus a transmission rate of less than 2% in non-breastfeeding populations (World Health Organization 2014). In the UK there were between 750,000 and 810,000 live births per year 2006 to 2013 (Office for National Statistics 2015), so the first threshold would equate to less than 350 new paediatric infections per year, which is certainly the case. In addition, the transmission rate from women diagnosed with HIV before delivery in the UK had fallen to less than 0.5% in 2010-2011, and continued to decline to 0.27% in 2012-2014 (Townsend et al. 2014; Peters et al. 2017).

So, the UK already meets the WHO criteria for the elimination of vertical transmission; but those targets are global targets aimed at the epidemic in mainly resource-poor settings. There are still new paediatric HIV infections being diagnosed in children born in the UK, a resource-rich country with universal healthcare free at the point of access for nearly everyone. How can we reduce the number of new paediatric HIV infections to virtually zero? This chapter presents a piece of work looking at the circumstances of the pregnancy and birth of all children born in the UK since 2006 who acquired HIV from their mothers, in order to identify missed opportunities for preventing these vertical transmissions, and areas of national policy and clinical practice that can be strengthened to reduce the number of new paediatric infections in the UK even further.

7.2 Specific Aims & Methods

7.2.1 Aims and objectives[48]

Aim

To provide information to the Infectious Diseases in Pregnancy Screening (IDPS) Programme about the antenatal screening and management of women whose infants acquire HIV perinatally in the UK, in order to contribute to:

- The monitoring and improvement of antenatal HIV screening protocols;
- A further reduction in the risk of perinatal acquisition of HIV infection by improving our understanding of the timing and circumstances of maternal and infant acquisition of infection.

Objectives

1. To explore the circumstances of perinatal HIV transmission in infants born in the UK since 2006 by designing and implementing additional data collection tools to perform enhanced data collection in these cases, to supplement surveillance data collected within the NSHPC.
2. To analyse this additional data in the light of current standards and guidelines to identify areas of potential improvement in practice, guidance, and research in the prevention of MTCT.

7.2.2 Methods

Ethics

Ethical approval was granted in November 2012 in the form of a substantial amendment to the NSHPC approval from the London multicentre research ethics committee (reference MREC/04/2/009).

[48] These aims and objectives were initially written by Pat Tookey for the original audit proposal submitted to the IDPS Programme in 2011.

Clinical audit methodology

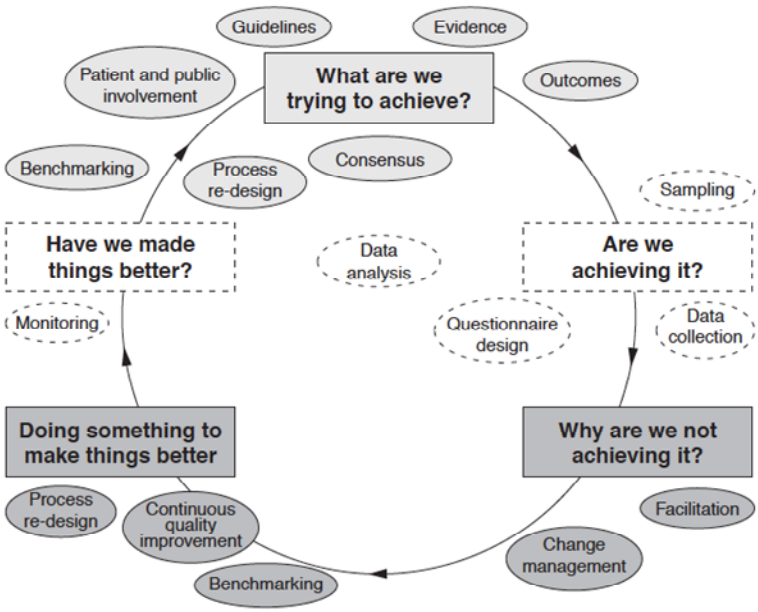
The planning and data collection methods for this enhanced surveillance study were modelled on clinical audit methodology. According to the National Institute for Health and Clinical Excellence (NICE)

"Clinical audit is a quality improvement process that seeks to improve patient care and outcomes through systematic review of care against explicit criteria and the implementation of change. Aspects of the structure, processes, and outcomes of care are selected and systematically evaluated against explicit criteria. Where indicated, changes are implemented at an individual, team, or service level and further monitoring is used to confirm improvement in healthcare delivery."

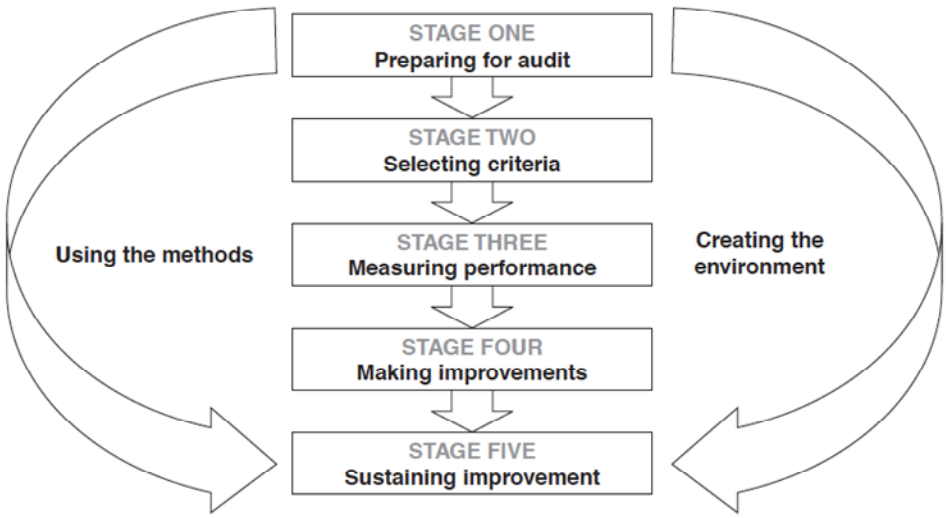
The clinical audit cycle is shown in Figure 7-1A, and the stages of clinical audit in Figure 7-1B. Stages 1 and 2 of clinical audit refer to the processes of identifying a topic for audit, identifying criteria for measurement by reviewing relevant current clinical guidelines and best practice standards, and preparing data collection tools. I identified a model of care for pregnant HIV positive women, which is shown in Figure 7-2. This model of care is the pathway that a pregnant woman diagnosed with HIV should follow in the 'best case' scenario. Since the MTCT rate in women in the UK with an undetectable VL by delivery is 0.1%, the ultimate goal of this pathway is a healthy woman with suppressed virus, who is engaged in HIV care and an HIV negative child. The national guidelines and standards which cover this model of care are: the NICE guidelines on antenatal care (NICE 2008); the IDPS Programme standards (UK National Screening Committee 2010); the IDPS laboratory handbook (National Screening Committee 2012) and the BHIVA guidelines on managing HIV infection in pregnant women (Taylor et al. 2012). I developed the data collection tools in reference to these documents and my clinical experience. Problems at any stage of the model of care for pregnant HIV-positive women can result in the transmission of HIV to the child, and so it is important that the data collection tools were designed to capture this level of detail wherever possible.

Figure 7-1. The clinical audit cycle and the stages of clinical audit (from Scrivener et al, Principles and Best Practice of Clinical Audit (Scrivener et al. 2004))[49]

A. The clinical audit cycle



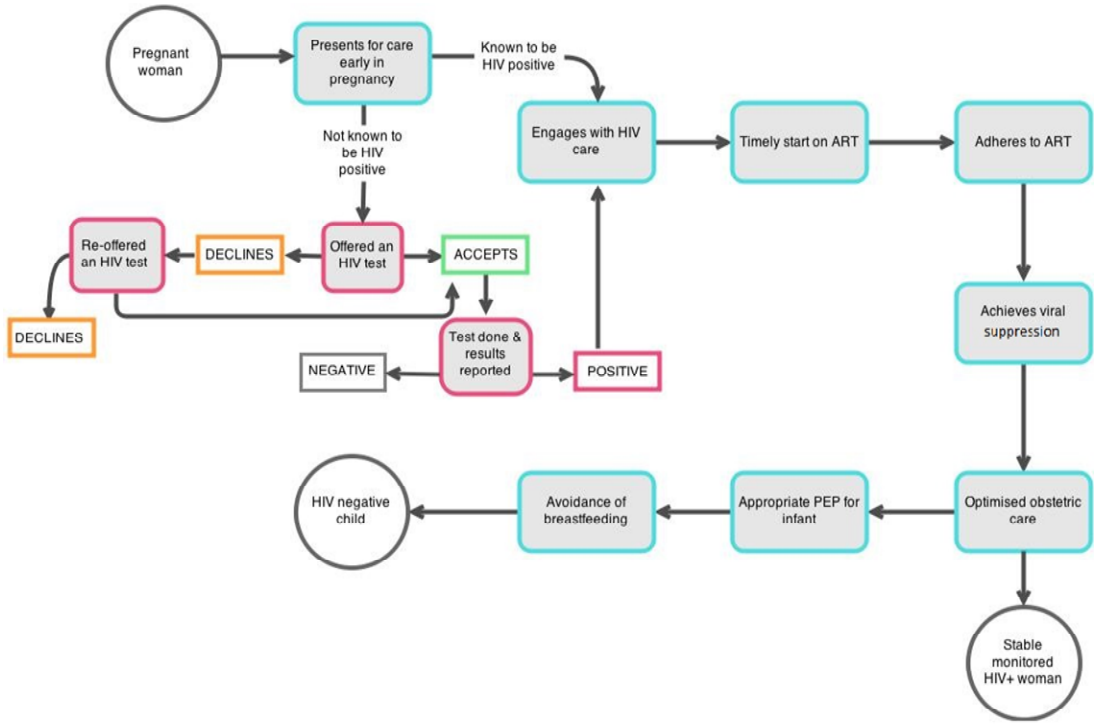
B. The stages of clinical audit



[49] Reproduced with permission from NICE (material may be freely reproduced for educational and not-for-profit purposes).

Figure 7-2 Simplified model of care for women diagnosed with HIV before or during pregnancy[50]

Adapted from the BHIVA pregnancy guidelines (Taylor et al. 2012) and the IDPS programme infectious diseases screening standards (UK National Screening Committee 2010).



Development of telephone interview questionnaires

Enhanced data collection was performed by structured form-based telephone interviews with reporting clinicians. It had been decided (prior to my involvement) that telephone interviews would provide the best opportunity to capture the individual details of each case, and would enhance response rates from participating clinicians (since a postal or web-based survey would likely result in a lower response rate and a larger proportion of missing data items, lack of flexibility in terms of follow-up questions branching logic, and face-to-face interviews were not feasible with the resources available). These forms had initially been designed by a previous NSHPC research assistant[51], and I revised them when I took over responsibility for

[50] This model of care reflects guidance at the time of the audit data collection – breastfeeding advice in the BHIVA guidelines has evolved over the time period, although is still recommended to avoid breastfeeding to minimise the risk of vertical transmission.
[51] Dr Cassandra Nan

data collection. Three different data collection forms were developed: for women who had been diagnosed prior to delivery, women undiagnosed by delivery, and the child.

For women diagnosed prior to or during pregnancy, questions focussed on the circumstances of maternal HIV diagnosis; language barriers and interpretation; possible adverse social circumstances the woman was experiencing; clinician perception of her engagement with HIV and obstetric care and acceptance of diagnosis; details of ART prescribed, including timing of initiation, and any changes to initial regimen; adherence to ART and any resistance she may have developed; and the circumstances of her labour and delivery. For women diagnosed after delivery (or not diagnosed) questions focussed on timing and circumstances of booking for antenatal care; transfers of antenatal care; social problems and language barriers; details of antenatal HIV screening including evidence of being offered an HIV test, evidence of decline, test re-offers, and whether there was a problem with the test or communicating the result; whether there was evidence of HIV seroconversion in the antenatal or postnatal periods, and the circumstances of labour and delivery. For interviews pertaining to the child, questions focussed on delivery details, timing and administration of post-exposure prophylaxis; infant feeding; and the circumstances of HIV diagnosis and any preceding contact with health services (see Appendix 10.4 for the three interview forms).

In order to validate the content of the data collection forms (Lynn 1986), I conducted pilot interviews with two members of the NSHPC steering group (one obstetrician and one paediatric infectious disease nurse specialist). The content, relevance, structure and flow of the questions were assessed, and any other feedback gathered from the pilot respondents. After refinement post-pilot, the forms were finalised, and I trained the research assistant to carry out the structured interviews by telephone. I took maternity leave from July 2013 to February 2014, and during this time HP[52] continued with data collection. A timeline of the audit from conception to publication is given in Figure 7-4.

[52] Helen Peters: initially research assistant to the NSHPC, now Data Manager and Statistician

Identification of cases of perinatal HIV

Children diagnosed with perinatal HIV are reported by paediatric respondents to the NSHPC as per the standard protocol (see section 3.3.1). Women diagnosed prior to delivery are reported to the NSHPC routinely, with child and mother study numbers matched to produce mother-child pairs. However, women not diagnosed prior to delivery cannot be reported to the NSHPC, so these children are not matched with a maternal record. All reported children diagnosed with perinatal HIV, who were born in the UK between 1st January 2006 and 31st December 2013, and reported by 31st March 2014, were identified in the NSHPC database and were considered the study population; where possible their matched maternal record was also included.

Data collection

The paediatric respondent for each case was contacted with a brief outline of the audit, including the aims and ethical approval, and asked to participate. Once contact had been established, the respondent was asked whether they required further information, and full audit protocols were sent if requested. The data collection forms, with basic clinical details pre-completed using existing NSHPC data extracted by myself or the research assistant, were sent by secure electronic transfer to the respondent, to enable them to prepare for the telephone interview (e.g. retrieving case notes, looking up electronic information). The telephone interview was carried out at a convenient, pre-arranged time, and information recorded in writing by the interviewer as close to verbatim as possible. For children born to women diagnosed with HIV prior to delivery, we then contacted the obstetric respondent at the appropriate maternity unit to provide information in the same manner.

In the case where a child was diagnosed with perinatal HIV and the mother was undiagnosed by the time of delivery, it is recommended by CHIVA that the paediatric unit informs the responsible obstetric unit of the transmission, so that practices can be scrutinised and improved (NSHPC, Audit Information Analysis Unit, and CHIVA 2007). For these children, we asked the paediatric respondent whether they had reported the case back to the relevant obstetric unit, and if this had been done, we contacted the obstetric unit for further information. If the obstetric unit had not been notified, we requested that the paediatric respondent report the case to the obstetric unit and inform them about the audit, so that we could then contact them to participate; this was necessary to ensure that previously unknown clinical

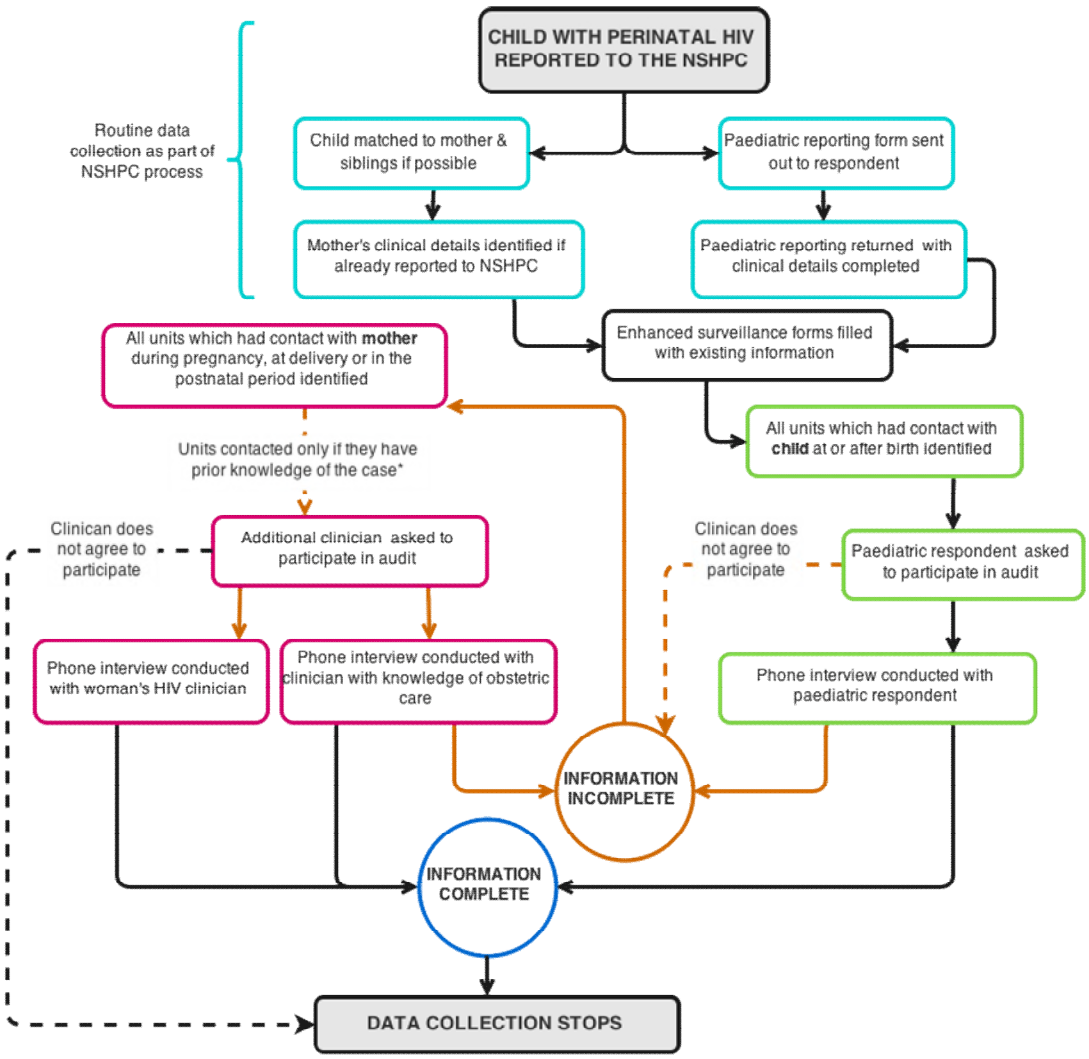
information was not shared with respondents by audit staff. If the paediatric respondent did not agree to this or felt that it was inappropriate to inform the obstetric unit, we did not pursue further data collection. See Figure 7-3 for a diagram of data collection processes.

Cases with incomplete information

Where cases were still missing valuable clinical information after paediatric and obstetric interviews, we sought contact details of other clinicians who might have been able to provide further information, e.g. the woman's HIV clinician after diagnosis. In cases where the mother or child was seen at more than one obstetric or paediatric unit, every effort was made to contact these units if information was incomplete.

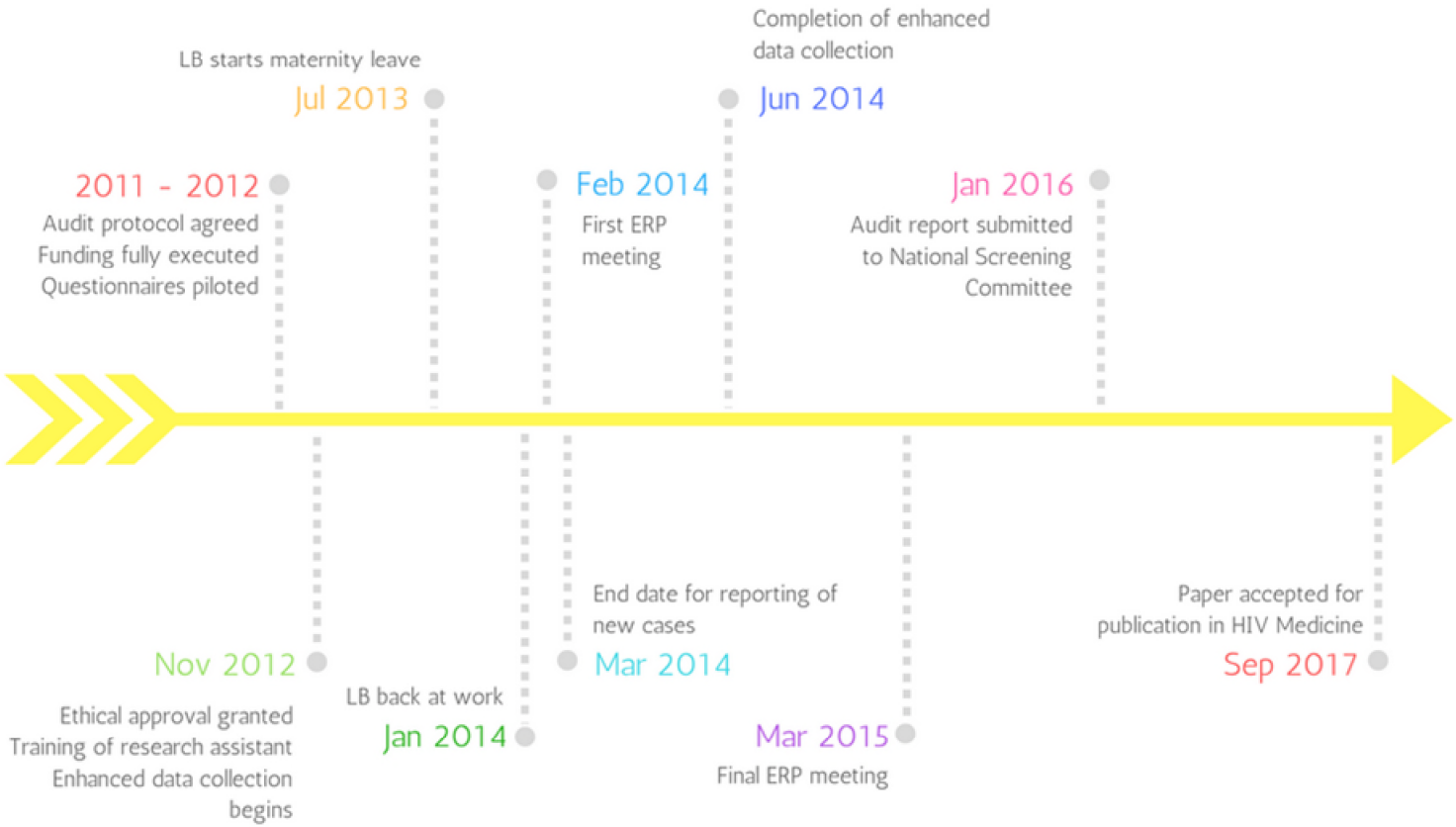
There were a few instances where respondents did not agree to take part in the audit, or initially agreed but then stopped responding to phone or email contact. In these cases repeated attempts to obtain data from respondents were made, but we ceased when we had not obtained data, or the promise of data, six months after initial contact. In some cases, although the respondent had agreed to participate, clinic notes could not be retrieved, and the respondent had no personal knowledge of the case, so we could not collect the additional data. Missing data is discussed in 7.2.3.

Figure 7-3. Diagram of audit data collection processes



*In cases where the antenatal unit was unaware of the infected infant, we requested that the paediatric respondent notify them and ask them to participate in the audit. If this was not possible, the antenatal unit was not contacted for information governance reasons.

Figure 7-4. Timeline of key milestones during the audit



Definitions

Antenatal units

Antenatal units were classified according to the total number of pregnancies in women living with HIV reported to the NSHPC between 2006 and 2013. Units were classified as 'small' if they had reported fewer than 20 pregnancies; 'medium' if they had reported 20-99 pregnancies; and 'large' if they had reported 100 or more pregnancies over the study period.

Cases

Each mother-child pair where a vertical transmission occurred is referred to as a 'case'.

Diagnosed & undiagnosed women

Women in each mother-child pair were described as 'diagnosed' if they had been diagnosed with HIV prior to or during labour or delivery. Women were described as 'undiagnosed' if they had been diagnosed with HIV after delivery of the child or their HIV status remained unknown.

Late booking for antenatal care

BHIVA recommend that all pregnant women with HIV are started on ART by 24 weeks gestation (Guidelines writing group 2014). In this analysis late booking for antenatal care is therefore defined as first antenatal visit at or after 24 weeks gestation, since this is the point at which potential duration of treatment would be impacted. However, it is worth noting that the NICE Guidelines for Antenatal Care state that women should be ideally seen for their first antenatal care visit ('booking visit') prior to 10 weeks' gestation, and define late presentation for antenatal care as presentation after 13 weeks and 6 days for purposes of auditing the guidelines (National Institute of Health and Care Excellence 2008).

Timing of infant acquisition of HIV

Timing of infant acquisition of HIV can be estimated according to the results of HIV DNA polymerase chain reaction (PCR) tests carried out on infant blood, which are

recommended to be performed at birth, 6 weeks, and 12 weeks for infants born to women diagnosed with HIV, with a final HIV antibody test at 18 months of age[6].

Timing of tests and likely timing of infection:

- **In utero:** positive PCR test within 3 days of birth
- **Intrapartum or in utero:** no test within 3 days of birth, and positive PCR test within 6 weeks
- **Intrapartum:** negative PCR test within 3 days of birth, and positive PCR test within 6 weeks
- **Intrapartum or postnatal:** negative PCR test within 6 weeks of birth, and positive PCR test after 6 weeks of age
- **Postnatal:** negative PCR after 6 weeks of age, with a later positive test (including a positive HIV antibody test after 18 months of age)
- **Unknown:** positive PCR test after 6 weeks of age (or positive HIV antibody test after 18 months of age) with no previous test results

Mortality rates

Crude mortality rates were calculated using the time 'at risk' being from the child's date of birth to the end of the data collection period (31/03/2014) or date of death if the child had died.

Complicating issues at the time of pregnancy

During the interviews respondents were asked whether they knew (or had evidence from the case notes) that the woman had experienced any adverse social circumstances or complicating issues at the time of the pregnancy. The specific issues asked about were: uncertain immigration status, housing problems, diagnosed mental health problems, drug or alcohol use, and known intimate partner violence (IPV).

Contributing factors for transmission

HP and I drew up anonymised case summaries for each case. These case summaries were prepared in the order in which data collection on the cases was completed. It was apparent on review of these case summaries that although many were clearly multifactorial, a large proportion shared similar features. In order to better describe and quantify these themes, I identified 'contributing factors' in each case. This was

done by reviewing the events of the case and identifying which characteristics or circumstances may have contributed to the failure to prevent vertical transmission to the infant. The contributing factors identified are shown in Table 7-1 and were defined after consideration of common themes among the cases, knowledge of relevant literature, and the findings of the previous perinatal audit, as well as my own clinical experience.

Main contributing factor

Once all known 'contributing factors' had been identified for each case, one 'main contributing factor' was assigned to each case. This was done by reviewing all the contributing factors and deciding clinically which factor was likely to be most important in contributing to the failure to prevent the transmission, taking into account any evidence on the timing of maternal and infant infection. For example, if a woman had not presented for antenatal care until 34 weeks' gestation, tested positive for HIV at booking, was started on treatment at 36 weeks, and then delivered at 38 weeks by caesarean section (CS), but the infant was PCR positive for HIV within 72 hours of birth (a likely in utero transmission), then the main contributing factor would be the fact that she booked late for antenatal care, which had impacted on the duration of treatment and reduced the opportunity to prevent in utero transmission. If, however, the infant had been PCR negative at birth and six weeks, and then positive at 3 months (a likely postnatal transmission), and other routes of transmission had been ruled out by the paediatric team, then the main contributing factor identified would have been 'postnatal transmission likely due to breastfeeding'. Cases were assigned to groups by the main contributing factor identified.

Table 7-1. Contributing factors identified in cases

Contributing factor	Description
Seroconversions	Women who acquired HIV during pregnancy or in the postnatal period after testing negative at first antenatal visit
Declines	Women who declined antenatal HIV testing
Failure in the HIV testing pathway	Cases in which there had been a problem with the antenatal HIV testing process (taking the sample, processing or reporting the test results)
Engagement	Women who had difficulty engaging with HIV care and/or adhering to ART in pregnancy
Late presenters	Women who presented late for antenatal care where this impacted on duration of treatment
Preterm delivery	Women with preterm delivery that impacted on duration of treatment
Breastfeeding	Infants who were likely to have acquired HIV in the postnatal period through breastfeeding
Transfer of care	Women who transferred care during pregnancy and this was thought to have impacted on their care
None identified	Cases where none of these factors was identified
Insufficient information	Cases where only minimal information was available.

Expert review panel

An expert review panel (ERP) was convened to discuss anonymised case summaries. The ERP included clinicians with expertise in managing HIV in pregnant women and children from a variety of clinical specialties, as well as the IDPS programme director; the IDPS clinical advisor; members of the NSHPC; and community representatives (for a full list of members please see Appendix 10.4.2).

Clinicians with expertise in managing HIV in pregnant women were identified from a variety of sources: members of the NSHPC steering group; members of the London Perinatal HIV Research Group[53]; NSHPC respondents; and clinicians recommended

[53] An informal group made up of clinicians and scientists based in London and the South-East with a research interest in perinatal HIV, which meets once every 3 months to discuss, collaborate on and support research projects.

by existing members. Clinicians were drawn from various specialities and disciplines: paediatrics, obstetrics, midwifery, and HIV medicine/infectious diseases.

The aims & objectives of the ERP were to:

- Reach consensus on likely timing of maternal acquisition of HIV in women not diagnosed prior to pregnancy, and timing of perinatal transmission where possible
- Identify missed opportunities for identifying undiagnosed women with HIV as early as possible during their pregnancy
- Identify missed opportunities for preventing MTCT in women with diagnosed HIV in pregnancy
- Make recommendations to strengthen national policy to reduce the MTCT rate in the UK even further
- Feedback at a local level to the relevant NHS organisations to avoid further missed opportunities for the prevention of perinatal HIV in children born in the UK if relevant and feasible

The first meeting of the ERP was held in February 2014 (see Appendix 10.4 for an example of an ERP meeting agenda); in total six meetings were required to discuss all 108 cases that had been reported by end of March 2014. The cases were discussed in the order that data collection had been completed and were grouped in themes according to main contributing factor within each meeting (so not all themes were discussed at each meeting). HP and I both minuted the discussion points in each meeting, and then I combined our minutes after the meetings and circulated them to the ERP participants for feedback. The minutes were then revised and formally agreed at the following meeting (they were agreed as a *record of the discussion*, and not as formal recommendations).

Once all six meetings had taken place, I prepared a report[54] containing a short descriptive analysis of the audit data; a summary of all discussion points that had come up during the six meetings; and suggested points which could become ERP recommendations. This report was circulated to the ERP members by email. A final

[54] Helen Peters, Pat Tookey and members of the ERP contributed to this report

ERP review meeting was held in March 2015 in which HP and I presented a short descriptive analysis of the audit data. The ERP members reviewed the 'discussion points' and possible recommendations for each theme and suggested and agreed revisions to the final recommendations. I then drafted a final report for submission to the National Screening Committee and this report was revised and agreed by email with the ERP members before submission in January 2016.

7.2.3 Results

Overall characteristics of women and children

Approximately 9,200 live births to women with diagnosed HIV in the UK between 2006 and 2013 were reported by April 2014. There were 108 children born in the UK during the same period diagnosed with perinatal HIV and reported by April 2014. Detailed data collection was performed for these cases.

Women had been diagnosed before or at delivery in nearly 40% (41/108) of the cases of perinatal transmission and after delivery in the remaining 60% (67/108). Overall, nearly 80% of the mothers of these infected children were born in Africa, and only 2% were likely to have acquired HIV through injecting drug use. Women's median age at delivery was 29 years, (IQR 26 to 34 years). Table 7-2 shows the timing of maternal HIV diagnoses, where women likely acquired their infection, how or where women were diagnosed with HIV and the likely route of HIV infection and Table 7.3 shows socio-demographic characteristics of the women at the time of pregnancy.

Table 7-2. Maternal HIV acquisition and diagnosis (*N*=108)

Characteristic	n	%
Timing of maternal diagnosis		
Before pregnancy	15	14
During pregnancy or at delivery	26	24
After delivery or undiagnosed	67	62
Where HIV acquired		
Abroad	43	40
UK/Ireland	26	24
Not known	39	36
How or where HIV identified		
Antenatal screening	35	32
Following diagnosis in child	25	23
Following diagnosis in partner	3	3
Genito-urinary medicine clinic testing	12	11
Testing in another hospital department	12	11
Other/not known	21	19
Likely route of maternal HIV acquisition		
Heterosexual	90	83
Injecting drug use	2	2
Vertical transmission	1	1
Not known	15	14

Table 7-3. Maternal socio-demographic characteristics at the time of pregnancy (*N*=108)

Characteristic	Diagnosed (*N*=41) *n*	%	Undiagnosed (*N*=67) *n*	%
Age (years) at delivery				
<20	3	7	3	5
20-29	20	49	27	40
30-39	17	42	30	45
≥40	1	2	2	3
Not known	0	0	5	7
Marital status				
Married/cohabiting	30	73	49	73
Separated	5	12	7	10
Single	6	15	7	10
Not known	0	0	4	6
Employment status				
Employed (healthcare worker)	1	2	11	16
Employed (other)	7	17	22	33
Student	8	20	4	6
Unemployed	20	49	29	43
Not known	6	14	12	18
Partner employment status			)	
Employed	15	50	24	49
Student	5	17	0	0
Unemployed	4	13	7	14
Not known	17	20	18	37
Region of birth				
Africa	34	83	51	76
UK	4	10	10	15
Elsewhere in Europe	1	2	4	6
Asia	2	5	1	2
Caribbean	0	0	1	2
Time in UK prior to delivery if born abroad (years)	(n=27)		(n=30)	
<1	6	22	5	17
1-5	10	37	14	47
6-10	7	26	9	30
>10	4	15	2	7

The number of cases reported by child's year of birth declined during the study period (see Figure 7-5). The number of perinatally infected children born each year declined from 31 children in 2006 to six in 2012, and one in 2013. In addition, the number of children born to undiagnosed women who were diagnosed at or under the age of one year also substantially declined over the study period (see Figure 7-6). It is important to note that although most children with perinatal HIV born to mothers known to have HIV during pregnancy will be diagnosed by 18 months of age, children born to undiagnosed women tend to be reported at an older age since they are not subject to testing at birth; the latter group will either be diagnosed as a result of a clinical manifestation of HIV or as a result of their mother being diagnosed at some point after the pregnancy. Therefore, additional children with perinatal HIV born in the UK during the study period are likely to be reported in the future, especially those born to undiagnosed women, and Figure 7-5 should be interpreted with caution. However, these numbers do suggest a substantial reduction in the actual number of perinatally infected children born in the UK over the study period.

Figure 7-5. Timing of maternal diagnosis by child's year of birth (n=108)

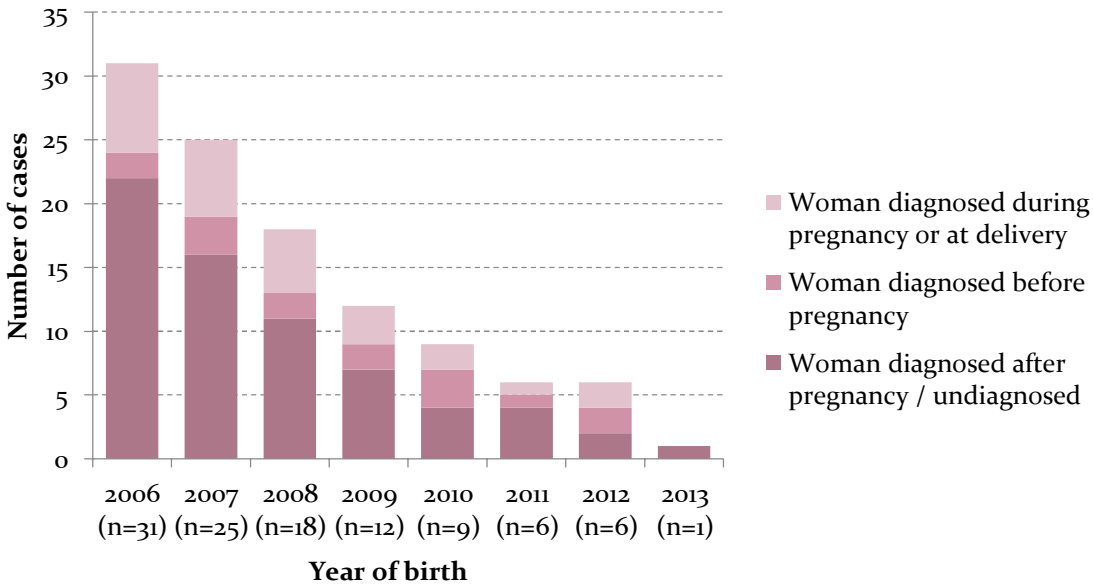
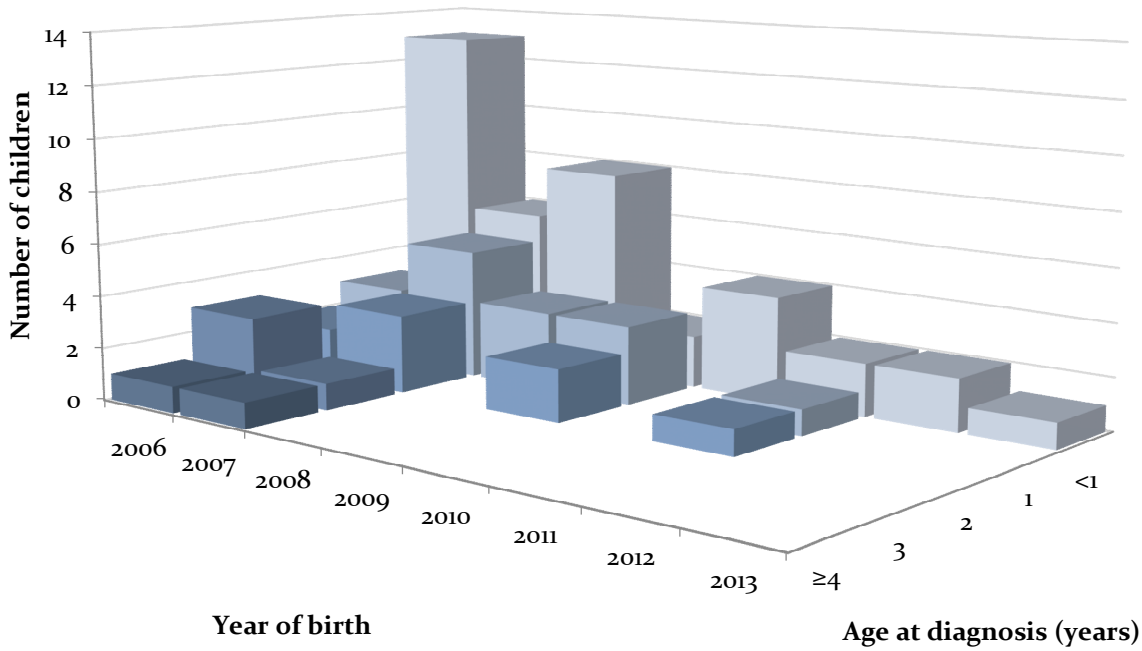


Figure 7-6. Age at diagnosis of children by year of birth

A. Children born to undiagnosed women (*N*=67)



B. Children born to diagnosed women (*N*=41)

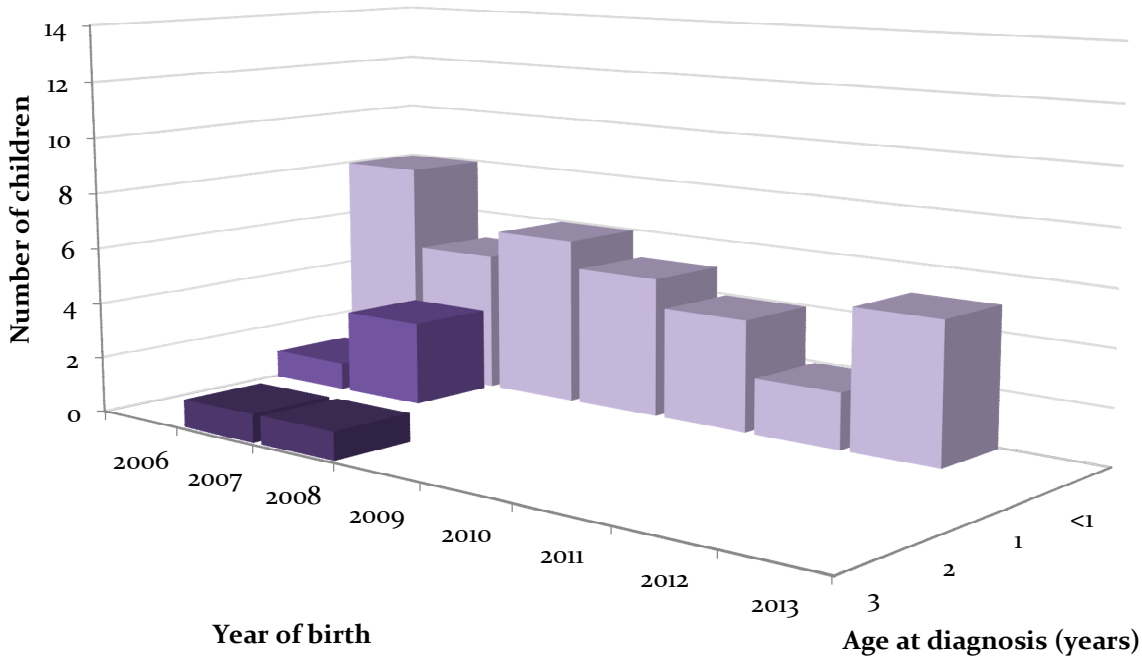


Table 7-4 shows the clinical and treatment characteristics of women diagnosed before or at delivery, stratified by timing of diagnosis (before or after conception). Nearly two-thirds of this group of women overall had a CD4 count at the beginning of pregnancy of less than 350 cells/μL. Almost three-quarters of women diagnosed during the reported pregnancy had a baseline VL over 10,000 copies/ml, and a third over 100,000 copies/ml. Nearly 60% of 14 women diagnosed before pregnancy were on ART at conception.

Table 7-4. Maternal clinical markers for women diagnosed before or at delivery (*N*=41)

	Women diagnosed before pregnancy		Women diagnosed during pregnancy or at delivery	
	n	%	*n*	%
Viral load nearest conception (copies/ml)	(*n*=14)		(*n*=26)	
<1000	3	21	2	8
1000-99,999	10	71	16	61
≥100,000	1	7	8	31
Viral load nearest delivery (copies/ml)	(*n*=14)		(*n*=25)	
<50	7	50	3	12
50-999	3	21	9	36
1000-99,999	3	21	10	40
≥100,000	1	8	3	12
CD4 count nearest conception (cells/μL)	(*n*=13)		(*n*=26)	
<250	4	31	10	39
250-349	5	38	6	23
350-499	1	8	6	23
≥500	3	23	4	15
ART	(*n*=15)		(*n*=26)	
Any ART in pregnancy	14	93	25	96
On ART at conception	6	40	-	-

Between 2006 and 2013, there were 9,172 live births reported in women diagnosed with HIV in the UK and Ireland: 9% delivered in small units; 33% delivered in medium-sized units and 58% delivered in large units. Just over a quarter (28%) of 41

infants born to diagnosed women had been delivered at small units, 37% at medium-sized units and 34% at large units. The vertical transmission rate in diagnosed women over the whole time period (2006 to 2013) was 1.5% in small units, 0.5% in medium sized units, and 0.2% in large units (p<0.0001). This does not take into account differences in the obstetric population living with HIV, distribution of cases over time, or other potential confounding factors. A lower proportion of the 67 undiagnosed women delivered at small units (13%), 59% delivered at medium-sized units and 32% delivered at large units.

Timing of infant HIV acquisition

Likely timing of infant infection could be estimated in 44% of cases overall (48/108). Just over half of the infants born to diagnosed women were likely infected *in utero*, nearly 20% around the time of delivery (intrapartum) and 20% in the postnatal period through breastfeeding (see Table 7-5). Timing of HIV acquisition could not be established in the majority of infants born to undiagnosed women.

Table 7-5. Likely timing of infant HIV acquisition

	Infants born to women diagnosed before or at delivery (*N*=41)		Infants born to women diagnosed after delivery (*N*=67)	
	n	%	*n*	%
In utero	23	56	3	4
In utero or intrapartum	1	2	1	2
Intrapartum	7	18	1	2
Intrapartum or postnatal	1	2	0	0
Postnatal	8	20	3	4
Unknown	1	2	59	88

Just over half of the 67 infants born to undiagnosed women were diagnosed because they presented with symptoms of HIV (35/67); 12/67 as a result of the mother subsequently being diagnosed, 19/67 after another family member was diagnosed, and in one case there is no information. Of the 41 infants born to diagnosed women, 39 received post-exposure prophylaxis(PEP) (one infant did not receive PEP; information was not available for one case).

Likely in utero infections (n=26)

Women were diagnosed with HIV prior to pregnancy in 31% of these cases (8/26), and all these women had problems with engagement with HIV care and/or adherence to treatment during pregnancy as the main contributing factor identified. The woman was diagnosed during the pregnancy in 16/26 of in utero transmissions, the main contributing factor in half (8/16) of these women was late presentation for antenatal care, in a quarter was issues with engagement and/or adherence (4/16). Two women acquired HIV in pregnancy after testing negative at booking and this was found to be the main contributing factor, one infant was born preterm, and in one case there was a problem in obtaining the result of the HIV test and therefore a delay in starting treatment. In the remaining 2/26 cases the woman had not been diagnosed by delivery, but the infant was tested at birth due to indications that the mother had acquired HIV.

Likely intrapartum transmissions (n=8)

In half of these cases (4/8), no main contributing factor could be identified, and all four women had achieved an undetectable HIV VL on combined ART prior to delivery at 35-37 weeks' gestation (one spontaneous vaginal delivery, three CS carried out prior to the onset of labour).

In the remaining four cases, one woman diagnosed before pregnancy was delivered by emergency CS after pre-term pre-labour rupture of membranes. She had a detectable VL, and prolonged rupture of membranes (>24hours) because there was a delay in performing the CS due to a lack of neonatal beds. Two women were diagnosed during the pregnancy: one presented late for antenatal care and only received 4 days ART prior to delivery by elective CS; the other woman had significant problems with engagement with HIV care and was delivered by emergency CS after the onset of labour by court order. One woman delivered very preterm by emergency CS for

obstetric indications. She had not been tested at booking (circumstances unclear), and despite being tested in labour the results were not noted until 5 days later (no further information was available).

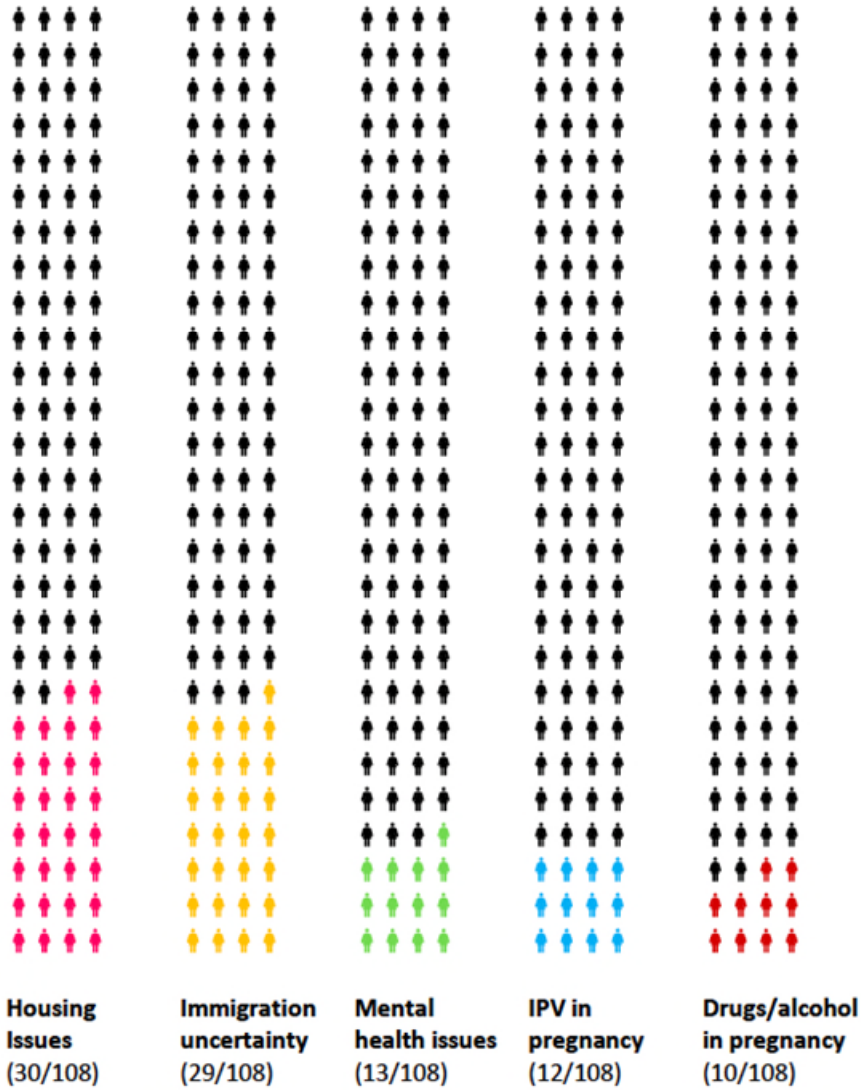
Likely postnatal transmissions are presented in Contributing factors.

Complicating issues

Overall, based on clinician reports 57 (53%) women had experienced at least one of the five specific complicating issues in pregnancy that we asked about; 19% had experienced two and 7% three complicating issues. Since we could only ascertain complicating issues that reporting clinicians were aware of or had documented in the notes, these are minimum estimates. Table 7-7 for reported complicating factors by main contributing factor. Figure 7-7 illustrates the proportion of cases in which each of the main complicating factors was reported. The two most commonly reported were housing issues (30/108) and immigration uncertainty (29/108).

Figure 7-7. Main complicating issues reported in 108 cases

Each icon represents a woman included in the audit



IPV= intimate partner violence reported during the pregnancy

Thirty-eight percent of women had a complicating issue reported by respondents other than the five presented in Figure 7-7 (41/108). It was reported that in 17/108 cases women had contact with social services during or prior to the pregnancy, three women had been incarcerated either during or prior to the pregnancy, and three women had a partner who had been incarcerated at the time of the pregnancy. Two women were under the age of 18 at delivery. Women were reported as not being fluent English speakers in 16 cases; half of these had independent interpretation at

their appointments; two women declined interpretation and two women had a friend or family member translate.

The median duration of stay in the UK before delivery for those women reported to have uncertain immigration status was 3 years (IQR 1 to 5 years, n=20), compared with 5 years in women born abroad but not reported to have uncertain immigration status (IQR 2 to 8 years, *n*=43). Of women born abroad, 46% of those who had been in the UK less than 5 years were reported to have uncertain immigration status (16/35) compared with 18% of those who had been in the UK more than 5 years (4/18, *p*=0.03).

Employment status was reported for 90/108 women (83%); 41% of those in employment had at least one of the five complicating issues reported (12/29), compared with 63% of women reported to be unemployed (31/49), and 83% of women with student status (10/12, *p*=0.03). There was also evidence of an association between employment status and uncertain immigration status: 10% of employed women had uncertain immigration status (3/29), compared with 37% of unemployed women (18/49) and 42% of women who were students (5/7, *p*=0.02). There was no evidence of an association between employment status and either reported housing problems, IPV or a diagnosed mental health problem. Eighteen percent of women who were unemployed were reported to be using drugs or excessive amounts of alcohol during the pregnancy (9/49) compared with 3% of those in employment, but this did not reach statistical significance (1/28, *p*=0.07).

There was no evidence of a difference in median age of women who had problems with drugs or alcohol compared to those who did not (median 31 years, 29 years respectively; *p*=0.46). Women were reported to be subject to IPV in 33% of cases where she was separated in the pregnancy (4/12), 15% of cases where she was reported to be single (2/13), and 8% of cases where she was married or cohabiting during the pregnancy (6/79; *p*=0.02). There was no evidence of an association between IPV and maternal diagnosis before or after delivery (*p*=0.73); similarly, there was no evidence of an association between IPV and uncertain immigration status (*p*=0.94) [data not shown].

Contributing factors

Overall, 62% (67/108) of cases had one contributing factor identified, 22% (24/108) had two factors identified, 5% (5/108) had three factors identified and one case had four factors identified. Figure 7-8 illustrates all the factors identified for each case in undiagnosed women, and highlights that many of the cases were multifactorial. Table 7-6 shows the number of cases in which the contributing factors were identified, and the main contributing factor identified in each case. In 5 cases no significant contributing factor could be identified and in a further 5 cases only minimal information was available.

Main contributing factor

The largest group of cases in diagnosed women was those who had problems with engagement and/or adherence (14/41), followed by women who presented late for antenatal care, with an impact on their duration of treatment (9/41) (see Table 7-6).

The largest group in undiagnosed women were women who declined antenatal HIV testing (28/67), followed by women who acquired HIV in pregnancy or in the postnatal period after testing negative in pregnancy (23/67).

Overall, 17% of women presented after 24 weeks gestation for antenatal care (or presented in labour unbooked). Nearly half of women diagnosed before delivery had problems with engagement with HIV care or adherence to ART (19/41).

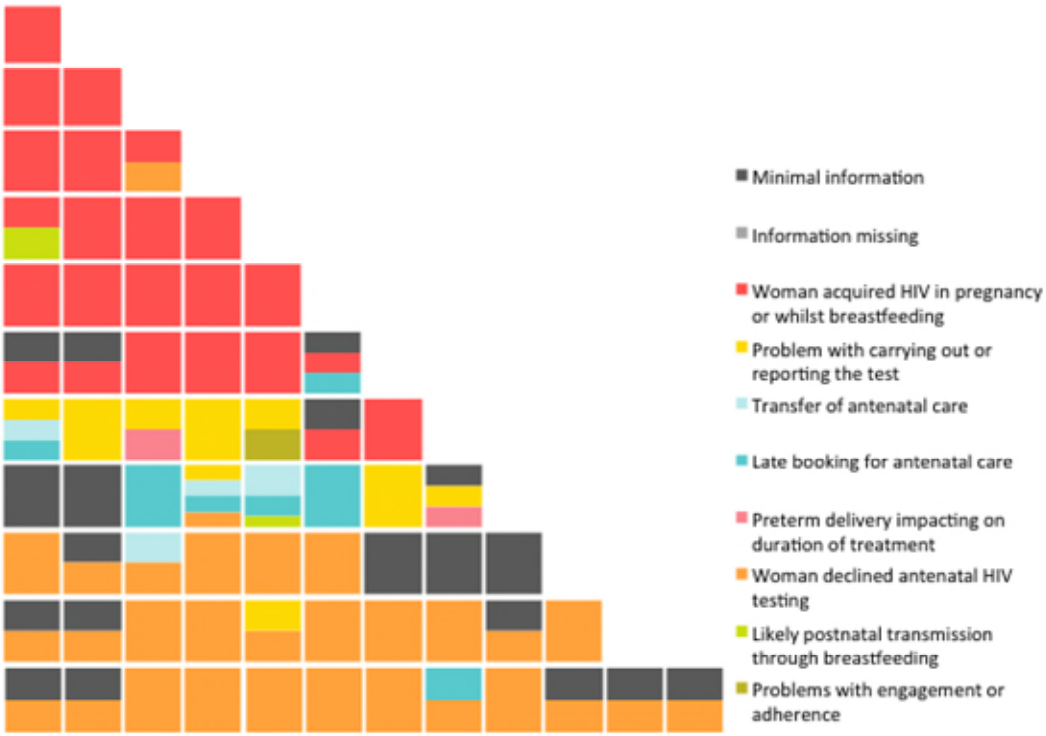
Table 7-6. Contributing factors identified in each case, by maternal diagnosis status

*Adjusted to total 100%

Contributing factor	Diagnosed women (*n*=41)			Undiagnosed women (*n*=67)		
	Identified as a contributing factor	Identified as the *main* contributing factor		Identified as a contributing factor	Identified as the *main* contributing factor	
	n	n	%*	n	n	%*
Woman declined antenatal HIV testing	2	-	-	31	28	42
Seroconversion in pregnancy/postnatal period	2	2	5	23	23	34
Engagement/treatment adherence issues	19	14	34	-	-	-
Postnatal transmission likely due to breastfeeding	7	7	17	1	1	2
Woman presented late for antenatal care	11	9	22	7	3	4
Woman transferred centre of antenatal care	4	-	-	-	-	-
Pre-term delivery impact on duration of treatment	3	3	7	2	-	-
Problem with antenatal HIV test	1	1	3	8	7	10
No specific contributing factor identified	5	5	12	-	-	-
Missing information	2	0	0	19	5	8
Total		41	100		67	100

Figure 7-8. Factors identified in each case of perinatal HIV in undiagnosed women (n=67)

Each square represents one mother-child pair.



Main contributing factor: woman declined HIV testing in pregnancy

The main contributing factor identified was women declining HIV testing in 26% of cases (28/108). Year of birth for their infants ranged 2006 to 2010 with the majority of infants born 2006 to 2007 (18/28). Median maternal age at delivery was 30.9 years (IQR 26.6 to 34.1 years, 1/28 missing). Twenty-three women were considered to be fluent in English and not requiring interpretation by clinicians, and one woman was not fluent, but it is not known whether an interpreter was used for her antenatal appointments (in 4/28 cases this information was unavailable).

Two women had reported past uncertainties with blood test results as the reason for declining antenatal HIV testing in this pregnancy; two woman reported needle-phobia (one of these accepted the first offer but the phlebotomist failed to draw an adequate sample, and the woman declined another attempt); three women stated

they did not feel they were at risk of acquiring HIV; one woman had confidentiality concerns (her stay in the UK depending on her job as a nurse); one woman wanted to discuss it with her husband and there was no evidence of this being followed up; one woman misunderstood the information given to her and thought there was a risk to the baby from the test (she was considered fluent in English); one woman was seeking asylum in the UK after fleeing violence (including sexual violence) in her home country and did not think she could cope with a positive result; and in one case the antenatal team documented that the woman declined the HIV test at multiple points in pregnancy, but after her child had been diagnosed the woman stated to the paediatric team that she had not been offered the test. In the remaining 16/28 cases the reason for the decline was not documented or accessible.

In 6/28 cases the woman was re-offered HIV testing later in pregnancy (and declined the re-offer); in three of these cases this re-offer involved a senior member of staff such as a supervisor of midwives, a consultant or a health advisor. In 12/28 cases the woman was not re-offered a test after the initial decline and in 10/28 cases it is not known whether she was re-offered an HIV test.

Women experienced significant complicating issues at the time of the pregnancy in 17/28 cases (Table 7-7); a third had housing issues, and a third had uncertain immigration status. Five of the 28 women were reported to have been working as healthcare professionals at the time of the pregnancy. In 9/28 cases the woman's partner was also diagnosed with HIV following her or the child's diagnosis.

Data were not available on previous HIV testing at the time of the pregnancy for 11 women; among the remaining 17 women, the majority (15, 88%) had not had a previous HIV test and two women had reported having had a negative HIV test in the past. In two cases where previous testing was unknown, it subsequently transpired that the woman had received a previous positive HIV diagnosis that she had not disclosed at the time of the pregnancy. Median interval between birth of the infant and maternal HIV diagnosis was 6.8 months (IQR 3.5 to 32.8 months, 22/28 available). For 19 of the 28 women, HIV diagnosis occurred as a result of their child's diagnosis, six following diagnosis of another family member, one in a subsequent pregnancy, and one following an inpatient admission with tuberculosis (1/28 not known).

Among the 26 infants with infant feeding data available, 15/28 infants were exclusively breastfed; eight were fed a combination of breast milk and formula and three were fed exclusively with formula. Median age at HIV diagnosis for the infants was 8.1 months (IQR 3.6 to 32.0 months). Three infants were known to have died of HIV-related causes at 4 months, 6 months and 25 months of age.

Table 7-7. Reported complicating issues by main contributing factor

		Complicating issue reported										
	Total cases	Housing problems		Uncertain immigration status		Intimate partner violence		Drug or alcohol problems		Mental health diagnosis		
Main contributing factor	*n*	*n*	% (Total cases)	*n*	% (Total cases)	*n*	% (Total cases)	*n*	% (Total cases)	*n*	% (Total cases)	
Declined HIV test	28	9	32	9	32	5	18	4	14	3	11	
Seroconversion	25	4	16	4	16	3	12	2	8	1	4	
Adherence/engagement	14	4	29	3	21	1	7	1	7	4	29	
Late booking	12	4	33	7	58	2	17	0	0	1	8	
Postnatal (breastfeeding)	8	4	50	4	50	0	0	0	0	1	13	
Problem with HIV test	8	1	13	0	0	0	0	0	0	1	13	
Preterm delivery	3	0	0	2	67	0	0	0	0	0	0	
No contributing factor identified	5	1	20	0	0	1	20	1	20	1	20	
Information missing	5	1	20	0	0	0	0	1	20	0	0	
TOTAL	108	28	26	29	27	12	11	9	8	12	11	

Main contributing factor: woman acquired HIV in the pregnancy or postnatal period

Women acquired HIV in the pregnancy or postnatal period in 23% of cases (25/108) after a documented negative HIV test in pregnancy. Median gestation at woman's negative HIV test (done at antenatal booking) was 12 weeks (IQR 9 to 17 weeks); this was available in 19/25 cases. Two women booked late in pregnancy and their negative antenatal HIV tests were performed at 29- and 35-weeks' gestation.

Three women had HIV infection diagnosed during pregnancy/delivery: two were diagnosed with likely HIV seroconversion illness during pregnancy (one woman was diagnosed after being admitted with suspected primary herpes simplex at 39 weeks and the other with a seroconversion illness at 29 weeks following IDU); one woman was diagnosed in labour at 40 weeks' gestation as she was known to have a partner with HIV and had declined numerous re-offers during pregnancy. In the remaining 22/25 women, median interval to mother's first positive HIV test was 8.6 months after delivery (IQR 3.3 to 24.0 months after delivery, data available in 19/22 cases), therefore timing of HIV acquisition was uncertain.

Year of birth for these children ranged from 2006 to 2013. Median age at delivery for these 25 mothers was 28.3 (IQR 23.9 to 31.5 years). One woman was thought to have acquired HIV in pregnancy through injecting drug use (IDU), the remaining 24 women heterosexually.

In 20/24 cases where the woman likely acquired HIV heterosexually, the woman was married or co-habiting at the time of pregnancy; two women were separated, one single, and marital status of one was not known. Seventeen current male partners of the 20 married/cohabiting women were diagnosed with HIV; current partner's HIV status was unknown in 2/20 and one current partner tested negative. Four of the 17 current partners diagnosed with HIV had been diagnosed prior to the woman: two of these women were aware of their partners' positive HIV status, the other two male partners did not disclose their HIV status and continued to have condomless sex during pregnancy and the postnatal period. In the 2/24 case where the woman was separated at the time of the pregnancy, one ex-partner was diagnosed with HIV following her diagnosis, and one ex-partner was negative (she had acquired a new partner in the pregnancy, but his HIV status was unknown). There was no

information available on previous male partners in the 1/24 women who was single at the time of the pregnancy and the 1/24 women who's marital status was unknown.

At least one complicating issue was reported for 13/25 women who seroconverted (Table 7-7). Two of the women had been identified as vulnerable in pregnancy because of their young age. Four women had previous contact with social services; in two cases their older children had been subject to child protection plans.

Thirteen of the 25 infants born to women who seroconverted were exclusively breastfed until maternal or child HIV diagnosis; eight were fed with a combination of breast milk and formula, and four were exclusively formula fed. Median age at infants' HIV diagnosis was 8.3 months (IQR 2.7 to 20.7 months, data available 23/24 cases).

For the majority of infants born to women who seroconverted, the timing of infant acquisition of infection was unknown (20/25). Three infants were likely infected *in utero* since they had a positive HIV PCR within 72 hours of birth; one of these infants was born to a woman perceived by the antenatal team to be at very high risk of acquiring HIV from her known HIV-positive partner, therefore the infant was tested shortly after birth despite no confirmation of maternal infection; two infants with *in utero* acquisition were born to women diagnosed with primary HIV during pregnancy. Two infants were thought to have likely acquired HIV in the postnatal period; in one case the mother tested negative at booking and her partner was diagnosed with primary HIV in the postnatal period, and the child and mother were both diagnosed as a result of this. In the other case the woman tested negative at booking but acquired a new partner in the postnatal period and was diagnosed with HIV 14 months after the birth of the child following her new partner's diagnosis. She was breastfeeding her infant, who was diagnosed at the same time.

Main contributing factor: problem with the antenatal HIV test

In 7% of cases the main contributing factor was a problem with the processing of the HIV test (8/108); these infants were born between 2006 and 2008. One woman consented to antenatal HIV testing at the booking appointment, but the blood was not drawn from her; the NHS Trust was successfully sued for breach of care.

One woman twice consented to the test, and blood was drawn but on both occasions the virology laboratory did not receive the sample; a third offer of HIV testing was

declined; the infant born to this mother was diagnosed whilst seriously ill at 3 months and died shortly after.

One woman consented to the test, blood was drawn from her, but the sample was labelled incorrectly and was not processed by the laboratory. This was not recognised by antenatal services and she delivered the baby without a documented HIV test result.

Two women consented to the test, blood was drawn, the sample reached the lab, but the HIV test was not processed by the laboratory; in one of these cases the absent result was noted by antenatal services, but the woman was not informed, and she was not re-offered a test.

One woman consented to the test, blood was drawn and the laboratory processed the sample but when the result was put on the electronic patient record it stated 'HIV positive as before' and antenatal services assumed the woman knew her positive status, and did not communicate the result to the woman or refer her to specialist services (she had been previously diagnosed but did not disclose this to antenatal services, and assumed she had been 'cured' when not informed of the most recent test result). The positive result was noted shortly after delivery and the infant was HIV PCR positive within 72 hours of birth, indicating likely *in utero* HIV acquisition.

One woman booked at 8 weeks' gestation and was offered an HIV test; it was not carried out, and it is unclear whether she declined. The infant was delivered by emergency section at 27 weeks' gestation and the woman was diagnosed with HIV before discharge (the details remain unclear). The infant was HIV PCR negative at 5 days but positive within 6 weeks, indicating acquisition of HIV during labour/delivery or in the early postnatal period.

One woman declined antenatal HIV testing, but the test was requested in error, blood was drawn, the HIV test was processed by the lab and was positive. There was a significant delay in communicating this result to the woman: the test was at 15 weeks' gestation, but she was not informed until 28 weeks. She started ART with good adherence, had an undetectable VL by delivery, but the infant was HIV PCR positive at birth, with likely *in utero* HIV acquisition.

At least four of these eight cases were investigated as a 'serious incident'[55] by the NHS Trust responsible. Two of the eight infants were likely infected with HIV *in utero*, one likely during labour/delivery or the early postnatal period and in the remaining five cases timing of infection is unknown.

Main contributing factor: woman had problems with engagement with HIV specialist care and/or adherence to ART

The main contributing factor was identified as the woman having problems engaging with HIV specialist services and/or adherence to ART in 34% of cases in which the woman was diagnosed before delivery (14/41). Seven women were diagnosed before and seven during the pregnancy. Median maternal age at delivery was 27.9 years (IQR 25.3 to 32.5). One woman was reported as having been vertically infected herself, and for 11 women HIV acquisition was likely heterosexual (2/14 unknown). Median interval between HIV diagnosis and delivery was 28.3 weeks (IQR 25.1 to 31.6 weeks) in the seven women diagnosed during pregnancy.

Eleven of the 14 women had at least one significant complicating factor at the time of pregnancy (Table 7-7); 8/14 had significant complicating issues in addition to these, including four women who had very strong religious beliefs that appeared to conflict with their ability to accept their HIV diagnosis and engage with specialist care. Median gestation at antenatal booking was 13 weeks (IQR 11-19 weeks, 1/14 booking date unknown). Three of the seven women who were diagnosed prior to pregnancy booked after 13 weeks' gestation, and one at 24 weeks (1/7 unknown); 3/7 women who were diagnosed during pregnancy booked after 13 weeks, and none at/after 24 weeks gestation. Of the five women who were not fluent English speakers, independent

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[55] The Serious Incidents Framework (NHS England Patient Safety Domain 2015) defines a serious incident as "*In broad terms…events in health care where the potential for learning is so great, or the consequences to patients, families and carers, staff or organisations are so significant, that they warrant using additional resources to mount a comprehensive response*."

interpretation was used in appointments for three women, with one woman declining interpretation and no data for the remaining woman.

Six of the seven women diagnosed before pregnancy had previous ART: three for prevention of MTCT in a previous pregnancy, two had three or more previous therapeutic regimens and conceived on ART, for one indication for ART was unknown; ART details not available for the seventh woman. Three of these women had previous unstructured treatment breaks, four had previous problems with adherence, and four had evidence of virological resistance to ART during the pregnancy. Two of the seven women diagnosed during pregnancy disengaged from specialist care after receiving their positive result and did not return for specialist care until very late in pregnancy.

All 14 women were treated with PI-based cART in pregnancy. The 12 women starting ART in pregnancy initiated at a median gestation of 23 weeks (IQR 17-33 weeks, 1 missing). Six women had VL <1000 copies/ml at delivery; five VL 10,000-100,000 copies/ml and three VL >100,000 copies/ml. Ten infants were delivered by CS; three of these were emergency CS (in one a court order for a CS was obtained after the woman had gone into labour); four infants were delivered vaginally (two women declined CS and one delivered unattended having just arrived in the unit in preterm labour at 31 weeks).

The majority (11/14) of infants in this group likely acquired HIV *in utero* (positive HIV PCR within 72 hours of birth), one was a likely intrapartum or early postnatal transmission (negative within 72 hours of birth and positive PCR within 6 weeks), one infant likely acquired their infection through breastfeeding (negative PCR at ≥6 weeks, positive thereafter).

Main contributing factor: woman booked late in pregnancy or presented in labour having had no antenatal care

There were 12/108 cases where late antenatal booking was thought to be the most important factor contributing to the transmission; eight of these women were diagnosed during the pregnancy, three were diagnosed during or very shortly after labour/delivery and one was diagnosed after delivery. Median maternal age at delivery was 28 years in this group (IQR 23 to 34 years). All but one of these women had one or more significant complicating issues in pregnancy; over half were reported

to have uncertain immigration status (Table 7-7). Eight women had an additional complicating factor such as recent incarceration or detention, having suffered traumatic sexual violence in home country, or concealing the pregnancy from family members. Seven of the 12 women were known to have been abroad during some part of the pregnancy, all in in Africa. 4/12 women were not fluent in English; 2/4 women were reported as having independent interpretation at appointments, and 1/4 used a family member.

Of the eight women diagnosed prior to labour, median gestation at booking was 36 weeks (IQR 25 to 36 weeks). Two women received less than 1 week ART; three women received 1-2 weeks ART and three women received 9-11 weeks of ART prior to delivery. One of these women had a spontaneous vaginal delivery at 40 weeks' gestation (it is unknown whether this was planned); one delivered by emergency CS at 37 weeks' gestation after going into labour prior to a planned elective CS; and six delivered by elective CS. Of the 3/12 women diagnosed during labour/delivery, two were unbooked and presented in labour without a documented HIV test at 39 weeks; the third woman presented with placental abruption at 32 weeks and delivered by emergency CS. The woman who was diagnosed after delivery had presented unbooked in labour at term but was not tested; she was diagnosed 21 months after delivery when she developed symptoms.

Nine of the 12 infants likely acquired their HIV *in utero* since they had a positive HIV PCR within 72 hours of birth; one infant likely acquired their infection either in *utero* or during delivery (no test done at birth, positive PCR within 6 weeks); one infant likely acquired HIV during delivery or in the early postnatal period (negative HIV PCR at birth, positive within 6 weeks); and for one infant the timing of transmission is unknown (infant diagnosed at 21 months).

Main contributing factor: postnatal transmission likely due to breastfeeding

There were 8/41 cases in women diagnosed before delivery in which breastfeeding was thought to be the main factor contributing to the transmission and the infant had a negative HIV PCR at ≥6 weeks age and a positive PCR thereafter (indicating postnatal transmission). Four women were diagnosed prior to pregnancy; three during the pregnancy; and one was tested just prior to delivery but the result was not available until a few days after. All were thought to have acquired HIV through

heterosexual contact. One woman who was diagnosed in pregnancy had declined an HIV test, but the test had been requested and processed in error, and she had difficulty accepting her diagnosis. Median maternal age at delivery was 31 years (IQR 29 years to 35 years).

Seven of the eight women had at least one significant complicating issue at the time of pregnancy (Table 7-7); in addition, one woman had strong religious beliefs that were thought to have conflicted with acceptance of her HIV diagnosis. Four women had difficulty with adherence to ART in pregnancy. In none of these eight cases did the woman express a desire to breastfeed to the antenatal team, but in one case the diagnosis of HIV was not communicated to the community midwifery team by antenatal services or the mother, and community midwife assisted the mother to breastfeed at home. In the other six cases breastfeeding against medical advice was suspected following the child's HIV diagnosis but not confirmed by the mother; in one case the mother was reported to be breastfeeding by another family member. Three women were on cART for the prevention of MTCT only and stopped therapy at delivery; four women were on cART for their own health and were continuing after the birth of the child, of whom two had achieved an undetectable VL prior to delivery. Median age at diagnosis of the infants was 11.8 months (IQR 4.5 to 22.1 months).

Main contributing factor: preterm delivery

There were 3/108 cases in which preterm delivery was thought to be the main contributing factor to the transmission. Two women were diagnosed during the pregnancy and one woman had been diagnosed prior to the pregnancy. Two women had uncertain immigration status, but no other significant complicating issues at the time of the pregnancy (Table 7-7). Gestation at antenatal booking appointment ranged 12-16 weeks; ART was started at 22-26 weeks, and VL at delivery ranged 100-1000 copies/ml. All three infants were delivered by emergency CS, at 26, 30 and 35 weeks' gestation; indication for delivery in two cases was pre-term pre-labour rupture of membranes (PPROM) and in once case severe pre-eclampsia. In one case of PPROM there was a delay in delivery because of a lack of appropriate paediatric beds. One infant was likely infected *in utero*, one infant either *in utero* or during labour/delivery (positive HIV PCR 4 days after birth), and one infant was likely

infected during labour/delivery or the early postnatal period (negative HIV PCR at birth, positive PCR at 6 weeks).

No significant contributing factor identified

There were 5/108 cases where no significant contributing factor was identified, with three women diagnosed prior to pregnancy and two during the pregnancy. The deliveries took place between 2010 and 2012. Maternal age at delivery ranged from 28 to 37 years. Three women had at least one complicating factor at the time of pregnancy (Table 7-7). Gestation at antenatal booking appointment was at 6-15 weeks. Two women transferred antenatal care to a different unit during pregnancy. One woman was on ART at conception and for the remaining four, gestation at start of ART was 13-22 weeks. Four women had undetectable VL prior to delivery, one woman had VL 50-100 copies/ml near delivery, and gestation at delivery was 38-41 weeks. Two infants were delivered by elective CS; two by emergency CS; and one woman had a planned vaginal delivery. Four infants probably acquired HIV during labour/delivery and one infant could have acquired HIV during labour/delivery or in the postnatal period (negative PCR at birth, positive at 10 weeks of age). One woman received intravenous iron infusions during pregnancy; a report on this case has been published (Thompson et al. 2014).

Mortality

Overall, eight children were known to have died by the end of the study period, one of prematurity-related disease, and seven of HIV-related causes. Six children died aged less than 6 months, and two aged 18 to 24 months. Year of birth for these children ranged 2006 to 2010.

All of these children were born to undiagnosed women: in three cases the main contributing factor was that the woman declined antenatal HIV testing; in two cases the main contributing factor was a problem with the HIV test; one woman acquired HIV after testing negative; and in two cases information was insufficient to determine possible contributing factors.

The proportion of children who had died by age two years was 7.8% overall (8/102); the crude mortality rate was 1.4 deaths per 100 child-years overall (95% confidence interval 0.67 to 2.70) (excluding from the denominator those children who had not yet reached 2 years at the end of the data collection period).

Missing information

There was a substantial amount of missing information for 21 of the 108 cases (19%); nevertheless at least one main contributing factor that helped to explain the circumstances of the transmission was identified for 16 of these.

For 9/21 cases we could not contact the antenatal unit since the mother had been diagnosed after the pregnancy and the antenatal unit was not aware of her diagnosis, including 3 cases where either the child or mother had died. In addition there was one case where the antenatal unit could not identify the mother with the limited identifying information we held, and one where archived antenatal notes were not accessible.

In total 116 paediatric respondents were contacted for an interview, 110 agreed to an interview and 107 interviews took place; 72 obstetric respondents were contacted, 62 agreed, and 45 interviews took place; 58 HIV clinicians were contacted, 46 agreed and 37 interviews took place.[56] Antenatal notes were not available to the interviewee for 18/53 cases in women who seroconverted or declined a test in pregnancy.

In 5/108 cases there was insufficient information gathered to ascertain the main contributing factor to the transmission; four of these cases were in 2006-2007, and one in 2009-10. In all 5 cases the woman was not diagnosed with HIV until after delivery but the reasons for this remain unclear. Age at diagnosis for the infants ranged 3 to 33 months, two infants subsequently died of HIV-related causes, and one woman was known to have died shortly after her diagnosis.

[56] Interviews were not pursued if the details of the case were complete prior to the scheduling of the interview

7.3 Key Points

- The data suggest that the number of new vertical transmissions in children born in the UK fell over the study period 2006-2013, taking into account the delay in diagnosing and reporting infected children born to undiagnosed mothers.
- There were 67 children born to undiagnosed women and 41 children born to diagnosed women. However, children with PHIV born to undiagnosed women are likely to be diagnosed at a later age, presenting with symptoms or because a family member has been diagnosed with HIV, therefore further cases of children born to undiagnosed women during the audit time period are likely to be reported.
- The crude vertical transmission rate was higher in units which saw small numbers of pregnant women living with HIV (<20 over study period) compared with units which saw more women.
- The majority of children born to diagnosed women were likely infected *in utero*, with 20% likely infected during labour/delivery and 20% likely infected postnatally through undisclosed breastfeeding.
- The proportion of children who died by age 2 years was 8% overall.
- Just over half of women had at least one complicating factor reported, though this data is not collected for uninfected children, so a comparison could not be made.
- Nearly a third of cases had more than one contributing factor identified, highlighting the complexity of many cases.
- The most frequent main contributing factor identified was women who declined HIV testing (26% of cases); the majority of these infants were born 2006 to 2007, and all by the end of 2010. The second biggest group were women who acquired HIV after testing negative in pregnancy (23% of cases); these were spread through the study period. Just over 70% of these women had a current or previous male partner who was either known to have HIV or was subsequently diagnosed with HIV. Other main contributing factors were women who had problems with engagement and/or adherence to ART; cases where there was a problem with the HIV test; women who booked late impacting on duration of ART; postnatal transmissions likely due to undisclosed breastfeeding; and pre-term delivery.

- There were 5 cases in which no contributing factor could be identified, despite adequate information being available. All women achieved a VL near delivery <100 copies/ml; 4 infants were likely infected around the time of labour/delivery, and one either at labour/delivery or postnatally.
- There were 5 cases in which insufficient information was available to identify a contributing factor.

8 Discussion

8.1 Introduction

The aim of this thesis is to 'examine the role of antiretroviral therapy and other interventions to reduce HIV MTCT in the UK in the current treatment era'. As you have read so far, the data and analyses I have presented show that the population of women living with HIV and becoming pregnant in the UK and Ireland has changed since the turn of the 21st Century. Towards the end of the calendar period of this study, women were more likely to be already diagnosed by the time of pregnancy, more likely to be on treatment at conception, started on treatment earlier in their pregnancy, less likely to deliver by CS, more likely to have a suppressed viral load at delivery, and less likely to have a child that was also living with HIV. Women have grown up with HIV acquired from their own mothers, survived, become adults, and have started families of their own – how do we best meet their needs? I have successfully linked two large national data sets to show that women diagnosed during pregnancy (a shrinking group) have a reassuringly low rate of transmitted drug resistance, but with the global scale-up of ART – will this always be the case? The audit of perinatal HIV presented in Chapter 7 identifies themes common to cases of perinatal transmission in order to better understand why these transmissions occurred.

There are cross-cutting themes pertinent to the different aspects of PMTCT which I examine: how policy and practice have evolved over the study period; the shift to put women in the centre of their care and support shared decision-making; and the need to maintain a low risk of MTCT whilst improving the holistic health and wellbeing of pregnant women and increasing access to choice and autonomy. I am writing this discussion in 2019, 5 years since the end of the study period. In Chapters 1&2 I set the scene by assessing the context of my research in terms of published literature up to 2014 - how has the PMTCT landscape changed since then and what implications does that have for my results?

This discussion will pull together the key results and interpret them in the context of other evidence to date; assess the implications of my results both from a public health and clinical viewpoint; discuss the strengths and weaknesses of the data and the

study methodology; and identify and discuss remaining issues and questions following on from my research.

8.2 How has the epidemiology of pregnant women living with HIV changed?

There were 12,014 women in the main dataset, with 17,730 reported pregnancies, as described in Chapter 4. Only 43% of women were reported to be nulliparous at first reported pregnancy – so the remainder either had a pregnancy prior to their HIV diagnosis or had a pregnancy reported to the NSHPC prior to 2000. Around half of the women in the dataset had been diagnosed prior to their first reported pregnancy, and half after. There were several trends in demographics over time in the dataset. The proportion of women diagnosed prior to their first reported pregnancy rose significantly from 37% to 71% over the study period; in nulliparous women this increase was 28% to 68%.

The increase in the proportion of women diagnosed before pregnancy reflects the overall reduction of undiagnosed HIV in the UK over the same time period. The estimated undiagnosed proportion of people living with HIV was 19% in 2009 (Harker 2010), and had fallen to 8% (credible interval 6 to 12%) by 2017 (Nash et al. 2018). The estimated proportion of undiagnosed infection in heterosexual women was 6% (credible interval 5 to 8%), which is lower than that of heterosexual men (7%, credible interval 5 to 15%), gay and bisexual men (9%, credible interval 5 to 16%), and PWID (10%, credible interval 5 to 18%). This is largely due to the extremely successful national antenatal HIV screening programme (now coordinated by the PHE Infectious Diseases in Pregnancy Screening Programme) and an increased rate of HIV testing in sexual health services in women compared to heterosexual men (Nash et al. 2018). As described in Chapter 1, the antenatal HIV screening programme in the UK was initiated in 1999, and by 2008 had an uptake of 95%. The uptake of antenatal HIV screening is now a Key Performance Indicator (KPI) for the NHS IDPS Programme and for 2016/17 stood at 99.5% in England (Public Health England 2019).

Women in England and Wales are likely to have had at least one child by the time they reach 45 years; the proportion of women remaining childless at age 45 in 2017 (therefore born in 1972) was 18% (compared to 10% of women aged 45 born in 1945)

(Office for National Statistics 2018), and this does not take into account the additional numbers of terminations, miscarriages and stillbirths. In addition fertility rates are higher in women who are non-white ethnicity in the UK, with estimated number of children per 35 woman-years of 2.79 in Black African women, compared with 1.79 in White British-born women (births 1975-2006) (Coleman and Dubuc 2010). HIV does impact on fertility intentions (Cliffe et al. 2011), but within the population of women living with HIV and accessing care in the UK, the incidence of pregnancy increased over the calendar period 2000-2009 (Huntington et al. 2013). So, the increasing proportion of women diagnosed before pregnancy in this study is likely to be a complex mix of higher rates of testing in heterosexual women and a changing birth rate in women already diagnosed with HIV (although absolute numbers of pregnancies reported in women diagnosed before conception peaked in 2010 (NSHPC 2019)). For parous women, the increase (and subsequent plateau) in the number of sequential pregnancies reported (French 2014) is another factor. In terms of outcomes, being diagnosed prior to conception is likely to be beneficial: diagnosis of HIV whilst pregnant can be traumatizing during an already stressful life event (Treisman, Jones, and Shaw 2014) and diagnosis pre-conception allows for earlier engagement with HIV services and start on ART. Outcomes for women diagnosed before and during pregnancy will be discussed later in this chapter.

Median age at conception in first reported pregnancy rose from 28 years to 32 years. The majority of women were thought to have acquired HIV heterosexually; the proportion of women who likely acquired HIV through IDU fell from 4% to 2% over the study period ($p<0.001$). Women who were diagnosed before their first reported pregnancy had a younger median age at diagnosis but an older median age at conception compared with those diagnosed during pregnancy (27 vs 29 years and 31 years vs 28 years respectively). The ageing of this cohort has already been noted (French et al. 2012), and is likely to again be related to a mixture of factors. Overall, the population of people living with HIV in the UK is ageing, due to increased life expectancy and reduced numbers of new diagnoses. Conception rates in women over 30 in the general population in England are rising, due to increased female participation in higher education and the labour force, the increased importance of a career, the rising opportunity costs of childbearing, labour market uncertainty and housing factors. In addition, the conception rate in very young women is falling (Littleboy 2019), and the number of pregnancies per woman living with HIV reported

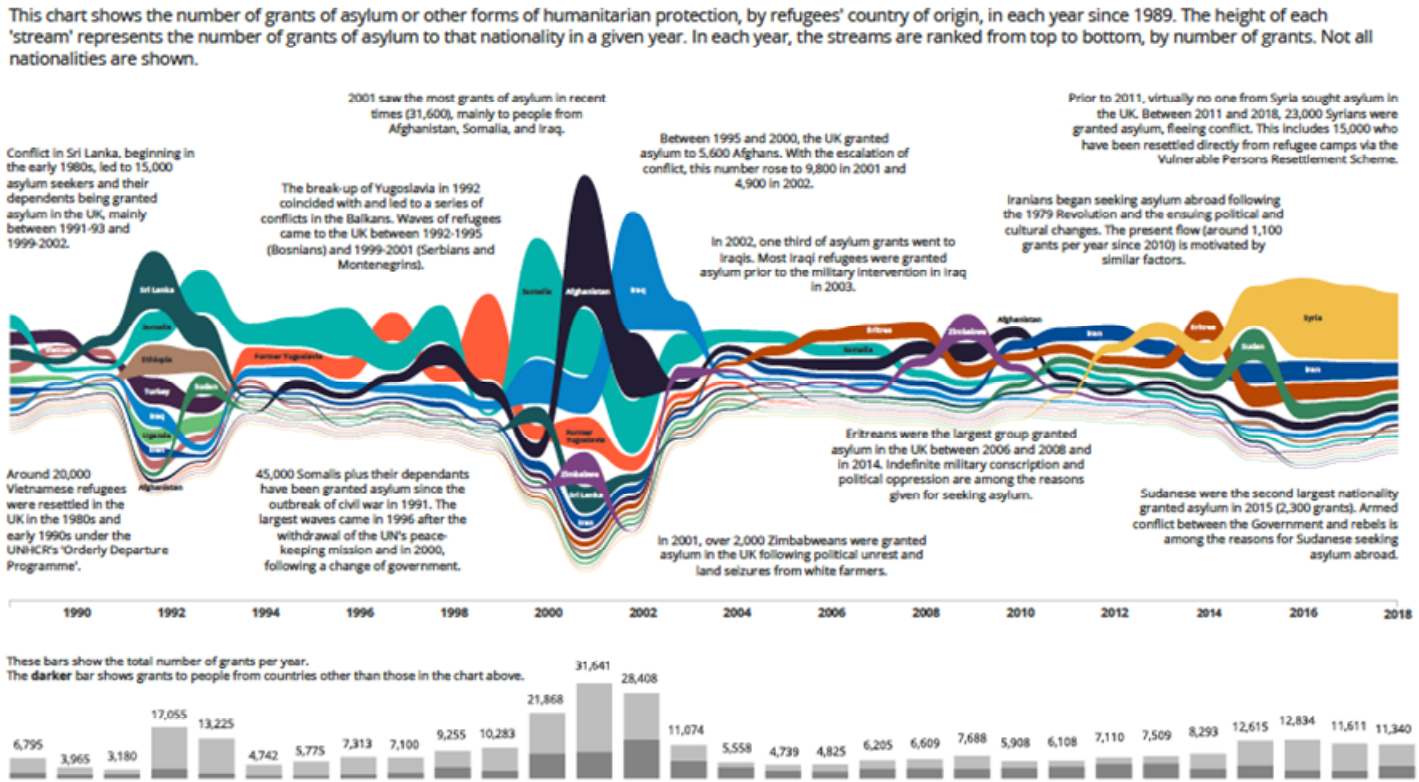
over the study period has increased, as previously noted (French et al. 2012). An analysis of pregnancies in older women with HIV reported in the UK & Ireland found that the proportion of pregnancies in women aged 40 and older rose from 2.1% to 8.9% across the calendar period, and that these pregnancies were more likely to result in multiple birth, stillbirth, or an infant with a chromosomal abnormality than pregnancies to younger women(Townsend et al. 2017).

There were also changes in ethnicity and region of birth in the main dataset over the study period. The majority of women were Black African ethnicity, with 76.3% born in SSA. The largest group of SSA women were born in Zimbabwe, peaking at 33% of those from SSA in 2006-2008. The proportion of SSA women born in Nigeria rose across the calendar period from 10% to 16%. These changes (see section 4.2) are reflective of immigration patterns from SSA to the UK and Ireland before and during the study period. Data from the Labour Force Survey shows that migration of Black Africans to the UK increased slowly in the early 1990s, and then rapidly at the turn of the century, and remained around 30,000 people per year during the first decade of the 21st century (Owen 2009). Migration from West and Central Africa increased steadily during this period, whereas migration from East Africa peaked in early 1990s and then again in the early 2000s, and migration from Southern Africa peaked around the year 2000 (Owen 2009). Migration for asylum was a major factor underlying African migration to the UK, and peaked in around 2002, however migration for employment overtook migration for asylum between 2002 and 2008 (Owen 2009). The emigration of Zimbabweans has been classified into three phases: the 1980s following Zimbabwe's independence from Britain; the 1990s, after economic hardship resulting from Zimbabwe's struggles to keep up with the World Bank and IMF Structural Adjustment Programme, and the third wave which began in 1998 following the political and social unrest under the Mugabe regime (Zanamwe et al. 2010). *Figure 8-1* shows which countries refugees come from to the UK and illustrates the second and third wave.

The proportion of women born in Europe (not UK/Ireland) rose from 3% to 9.3% over the study period, largely driven by increasing number of women from Poland, Latvia, Ukraine and Romania. As noted in Chapter 1, this was due to the enlargement of the EU to include Central and Eastern European countries (Czech republic, Estonia, Hungary, Latvia, Lithuania, Poland, Slovakia and Slovenia), in 2004

(Wikipedia 2019), as well as the evolving HIV epidemic in EECA (see Chapter 1). Despite efforts to scale up HIV diagnosis, treatment and prevention in EECA, a recent survey of 24 countries found there are still major disparities in the provision of HIV care in the region (Gokengin et al. 2018). In my analysis the median time from migrant women arriving in the UK/Ireland to first reported delivery date rose 2.2 years to 7.4 years over the study period ($p<0.001$). One of the reasons for this may be that as economic migration overtook asylum seeking as a reason to emigrate, women waited until economically established after arrival into the UK until conceiving. A large cohort collaboration looking at inequalities in PMTCT for migrant women giving birth in Europe found that migrant women were more likely to be diagnosed with HIV during pregnancy than native-born women, and were more likely to have a CD4<200 cells/uL at diagnosis during pregnancy (Favarato et al. 2018). In addition, they found that women from North Africa and the Middle East, sub-Saharan Africa and Eastern Europe were most likely to be diagnosed at a late stage of their pregnancy (>20 weeks' gestation) (Favarato et al. 2018).

Figure 8-1 Which countries do refugees to the UK come from? (Sturge 2019)[57]



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Low CD4 count near delivery is a marker of advanced disease. Median CD4 count nearest delivery was lower in women diagnosed during the reported pregnancy (410 cells/uL) than those diagnosed pre-conception not on ART (434 cells/uL) or on ART (440 cells/uL). These differences may be because women diagnosed during pregnancy are diagnosed at a more advanced stage in their disease. In addition, women previously diagnosed but not on ART at conception may have had treatment previously, and therefore maintained a higher CD4 after immune reconstitution. Low CD4 at diagnosis increases the risk of morbidity and mortality, and 'early' diagnosis (i.e. diagnosed with a CD4 >500 cells/uL) is one of the most important contributors to life expectancy in people living with HIV (Nakagawa, May, and Phillips 2013). The proportion of women previously diagnosed who had a CD4<350 cells/uL fell during the study period - this reflects the success of HIV testing programmes in the UK and Ireland reducing the proportion of late diagnoses as reported overall (Nash et al. 2018).

In this study, a greater proportion of women with low CD4 (<200 cells/uL) were black African ethnicity vs. other ethnicities, born in sub-Saharan Africa vs. UK/Ireland or elsewhere, and had acquired PHIV rather than heterosexually or IDU-acquired HIV. Overall in the UK, the proportion of people of Black African ethnicity diagnosed late has been consistently higher than the proportion of people with white ethnicity. In 2013, 66% of newly diagnosed Black African men and 57% of Black African women were diagnosed with a CD4 count <350 cells/uL, compared with 66% white men and 42% of white women (Public Health England 2014b). It has been estimated that between 33 and 45% of HIV infections among black African people were acquired after migration to the UK (Arco et al. 2017), and qualitative studies early in the 2000s indicated that migrants from SSA did not recognise the risk of HIV acquisition after arrival into the UK, and lacked awareness of the benefits of knowing HIV status (Burns et al. 2007; Doyal and Anderson 2005).

Efforts to increase testing rates to reduce late diagnosis in heterosexual women and men of black African ethnicity have not been entirely successful - a recent survey of Black African men and women in London found worryingly low levels of HIV testing (Fakoya et al. 2019). In the same sample, nearly half of those testing positive in anonymous HIV testing had reported that they were HIV-negative (though the authors note caution in interpreting this finding since it is considerably higher than

the estimated undiagnosed fraction reported from national surveillance data (Nash et al. 2018)). *Figure 8-2* shows the number of people diagnosed at a late stage of infection (CD4<350 cells/uL) by exposure category in the UK 20004-2014 (from PHE surveillance data). As can be seen, the absolute numbers of women diagnosed late have been higher than heterosexual men throughout the calendar period, but particularly between 2005 and 2009, with the gap narrowing towards the end of the 2000s (Public Health England 2015); this reduction in late diagnosis is related to the reduction in undiagnosed infection in women discussed earlier (in part due to the highly successful antenatal screening programme). *Figure 8-3* shows the proportion of late diagnoses by various exposure variables in the UK in 2013 (near the end of the calendar period of this study). The proportion of late diagnoses was highest in heterosexual men (around 60%), but nearly half of heterosexual women were diagnosed late, much higher than the rate in MSM (around 30%)(Public Health England 2015).

In addition to those women diagnosed with a low CD4 count in pregnancy (or who fall pregnant shortly after a late diagnosis), are those women previously diagnosed who have dropped out of care or stopped their ART before the reported pregnancy, and therefore are immunosuppressed during the reported pregnancy. Prior to the latest iteration of the BHIVA HIV and pregnancy guidelines which recommend lifelong treatment for all (Gilleece and BHIVA pregnancy guidelines writing group 2019), women who did not require ART for their own health could opt for short term antiretroviral therapy (START) stopped shortly after delivery (Guidelines writing group 2014). French et al. examined second pregnancies in previously diagnosed women not on ART at conception reported 2000-2010, and found that 40% of women had a CD4 count <350 cells/uL in this second pregnancy (first CD4 count before initiation of ART), and 10% were severely immunosuppressed with a CD4 <200 cells/uL (French et al. 2014). Tariq et al. combined data from the NSHPC and SOPHID to look at pregnancies in women reported 2000 to 2009, and found that loss-to-follow-up (LTFU) in the year after pregnancy was independently associated with the woman having been born in SSA, with the strongest association in women born in SSA who arrived in the UK after conception (AOR 3.19, 95% CI 1.94-3.23) (Tariq, Elford, Chau, et al. 2016). LTFU was also associated with younger age, last CD4 count in pregnancy ≥350 cells/uL, last viral load in pregnancy detectable (>50

copies/ml); shorter time since HIV diagnosis, and last pregnancy being reported from outside London (Tariq, Elford, Chau, et al. 2016).

In the analyses presented in this thesis, there was a small proportion (2%) of pregnancies where women were reported to have gone abroad before the outcome of their first pregnancy was known; and outcome was unknown in a further 2% of first reported pregnancies. The proportion of unknown outcome in first reported pregnancies fell over the study period from 3% to 0.1% (p<0.001). A higher proportion of women with an unknown outcome were Black African ethnicity (87% vs. 80% for gone abroad and 77% for known outcome) and born in SSA (86% vs. 80% of those gone abroad, and 76% for known outcome). It is likely that a large proportion of those with unknown outcome travelled out of the UK without notifying their antenatal service (since those who transferred care to another unit within the UK would be reported to the study from there). A greater proportion of women gone abroad were nulliparous (55% compared with 47% of those with an unknown outcome, and 43% of those with a known outcome), perhaps reflecting differing intentions in women with an established family life in the UK. Median gestation week at antenatal booking was greater for women with unknown pregnancy outcome and known to have gone abroad (14 weeks) compared with women with a known pregnancy outcome (12 weeks); this may be because women considering relocating outside the UK engage less swiftly with antenatal services, but also may be confounded by ethnicity (the link between late booking and ethnicity is previously discussed). A greater proportion of women with a known pregnancy outcome were on ART at conception (29% vs. 16% for gone abroad and 17% for outcome unknown); women already engaged in HIV care are less likely to emigrate.

Figure 8-2. Number of people diagnosed at a late stage of infection (CD4<350 cells/uL) by exposure category: UK 2004-2014 (Public Health England 2015)[58]

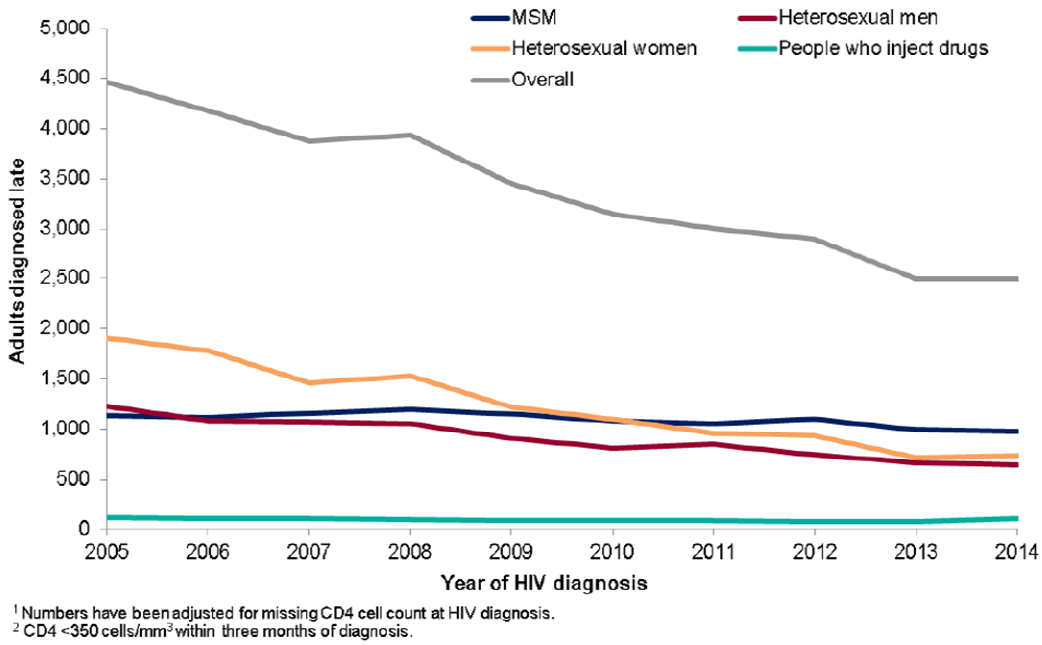
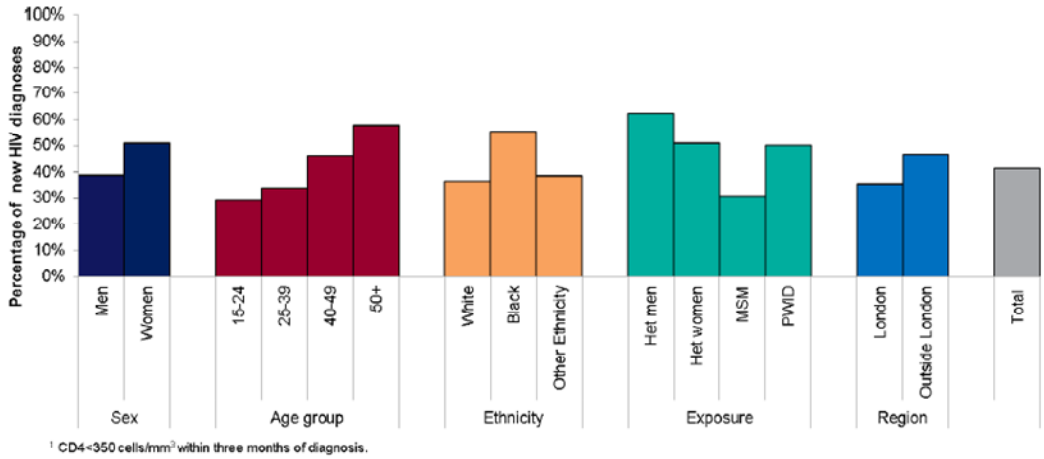


Figure 8-3. Late diagnoses: proportion of adults diagnosed with a CD4 count <350 cells/uL in the UK 2013 (Public Health England 2014b)[59]



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The greatest number of pregnancy reports came from London (44%) and the rest of England (44%), 1.3% from Wales, 2.8% from Scotland, 0.6% from N. Ireland, and 7.9% from ROI. There was a clear trend over the calendar period of the study, with the proportion of women being reported from London falling from 64% to 40%, and the proportion of women from the rest of England rising from 22% to 49% by the end of the study (p<0.001). One of the UK policies that may have impacted on this changing regional distribution of pregnancy report is the dispersal of asylum seekers, which was introduced in 2000. Under section 95 of the *Immigration and Asylum Act 1999*, asylum seekers can apply for support while waiting their claim (or appeal) to be considered - as part of this accommodation is offered in a dispersal area (i.e. away from London and the South-East) (Politowski and McGuinness 2016). There is Home Office guidance on maintaining safety and continuity of care for the dispersal of people living with HIV, and pregnant women in particular, however a survey of health care professionals raised serious concerns, noting that dispersals were often enacted with little notice and without the appropriate transfer of medical details (Creighton et al. 2004).

In univariable comparative analysis, region of pregnancy report was associated with mode of maternal HIV acquisition, maternal ethnic group, timing of maternal diagnosis, median gestation week at antenatal booking, and being on ART at conception. Just over a third of pregnancy reports in women with likely IDU-acquired HIV were from ROI; 25% from London and 10% from Scotland. In England and Wales, prevalence of HIV in PWID rose between 2000-2011, with an incidence peak in the mid 2000s in areas outside of London linked to an increase in the sharing of drug-taking equipment (Hope et al. 2014). The proportion of non-Black African women was also much higher in pregnancies reported from Wales, Scotland, N. Ireland and ROI compared with London, and this is likely to be associated with mode of acquisition. Women with a history of injecting drug use are likely to be more vulnerable and have complex needs, requiring the support of harm reduction services in addition to HIV care. Women who inject drugs are at higher risk of intimate partner violence (IPV), are more likely to be engaging in sex work and risky sexual behaviours, face more barriers to accessing care, and are more likely to be affected by poverty, unstable housing and other social issues (Pinkham, Stoicescu, and Myers 2012). Regions with larger numbers of women who inject drugs and are living with HIV need to ensure they have well-linked addiction, maternity and HIV services, and

may need to take an outreach approach in order to optimise the care of such a marginalised community.

The majority of nulliparous women diagnosed before pregnancy were diagnosed in sexual health services; however, this fell from 75% in 2000-2002 to 63% in 2012-2014. The proportion diagnosed in primary care rose from 1% to 6% over the same time period, and the proportion diagnosed in other hospital departments rose from 10% to 16% over the study period. In 2008, BHIVA published HIV testing guidelines which recommended population-level screening of adults (new GP registrations, A&E attenders and hospital admissions) in areas where the diagnosed prevalence of HIV was greater than 2 in 1000 people (based on US cost-effectiveness data), in addition to testing people who present with *indicator conditions* (British HIV Assocation, British Association for Sexual Health and HIV, and British Infection Society 2008). The change in the pattern of testing over time presented in Chapter 1 is in keeping with an analysis of national surveillance data for all HIV diagnoses in England, Wales and N. Ireland overall, which reported an increase in HIV diagnosis in non-traditional settings over the calendar period, due to multiple efforts to promote testing in GP surgeries, outpatient departments, and A&E/admissions departments (Croxford et al. 2018). As would be expected, in my analysis the vast majority of women diagnosed during pregnancy were diagnosed in antenatal services. A small proportion of nulliparous women were diagnosed in a previous pregnancy (4%); this may be explained by the fact that nearly 40% of women reported as nulliparous were also reported as having a previous termination or miscarriage.

In the main study, median gestation week at antenatal booking was 12.3 weeks, and fell significantly from 13.9 weeks in 2008 to 11.4 weeks in 2014. Women diagnosed before conception booked earlier than women diagnosed during pregnancy (median 12 weeks vs. 13.9 weeks respectively). French et al. examined live and stillbirths reported to the NSHPC 2009-2014 and found that 42% of women had booked late (≥ 13 weeks' gestation); late booking in women diagnosed before pregnancy was more likely in pregnancies reported earlier (2009-2011 vs 2012-2014), in women born abroad, and pregnancies reported from outside London. Women diagnosed during the reported pregnancy were more likely to have booked late if they were born in SSA, and had higher parity (French et al. 2017).

In my analysis, median gestation at booking was later in women with a low CD4 count (12.9 weeks for women with CD4 > 500 cells/uL, 13.0 weeks for women with CD4 count 200-499 cells/uL, and 14.0 weeks for women with CD4 <200 cells/uL near delivery). This could reflect poor engagement and barriers to accessing health services in women already diagnosed with HIV when they become pregnant.

Tariq et al. examined pregnancies due to deliver in 2008 and 2009, and demonstrated that about half of women booked late (≥13 weeks' gestation) for antenatal care in the UK; this was associated with Black African and other African ethnicity, and that women were more likely to have booked late if they had been diagnosed with HIV during the reported pregnancy compared to those diagnosed before (Tariq, Elford, et al. 2012). In the general population, a large survey of women giving birth in the UK in 2014 showed that 9% of women had not attended their antenatal booking appointment by 12 weeks' gestation, and women of Black ethnicity were more likely to book later (Maggie Redshaw and Jane Henderson 2015); this had declined from 14% in a similar survey in 2010 (Maggie Redshaw and Katriina Heikkila 2010). However, a study conducted in an ethnically-diverse London borough (which also had a high prevalence of HIV) found that 38% of women delivering between 2008 and 2011 had booked at or after 13 weeks, and 12.1% later than 20 weeks' gestation (Cresswell et al. 2013). Overall, women who book late are also more likely to be younger, multiparous, and have lower educational attainment (Feijen-de Jong et al. 2012).

In 11% of the perinatal audit cases presented in Chapter 7, the main contributing factor was that the mother booked late for antenatal care, which compromised the duration of her antenatal treatment. Two-thirds of these women were diagnosed during pregnancy, so late antenatal booking meant that HIV screening was delayed, and therefore initiation of treatment was delayed. In the latest published IDPS standards, confirmed positive or negative HIV screening tests should be reported to maternity services within eight days of receipt in the laboratory, and women should be seen within 10 working days of a confirmed positive result (Public Health England 2018). The results of the audit suggest that practice varied prior to the publication of these standards. Three-quarters of the infants in this group of women who booked late were likely infected *in utero,* which late initiation of ART is a risk factor for, as previously discussed. All but one woman had at least one significant complicating

factor during pregnancy and over half had been in Africa during some portion of their pregnancy. A report on increasing the early initiation of antenatal care by Black and minority ethnic women suggested that a complex approach was needed to address barriers, including an increase in outreach maternity services; staff training for cultural sensitivity; education to address cultural perceptions on pregnancy not requiring monitoring/intervention; and financial and practical support for very marginalised groups such as asylum seekers to reach clinics (Hollowell et al. 2012).

The changes in the population of pregnant women living with HIV in the UK and Ireland that I have reported have significant implications for clinical services. A woman with HIV conceiving and attending care in 2014 was more likely to be on treatment at conception, be older, have had previous pregnancies, have been diagnosed in a non-traditional setting, and to have been in the UK longer before her pregnancy than a woman attending in 2000. There have been improvements in the immunological status of women with reported pregnancies, and an overall reduction in the proportion of women who acquired HIV through IDU. However, disparities in health were still apparent – a higher proportion of Black African women had a low CD4 near delivery, as did women with PHIV. The increase in proportion of pregnancy reports outside of London over the study period indicates the need for access to expertise in the management of HIV and pregnancy in these regions. Late booking was the main contributing factor in a small group of cases from the perinatal audit, and this is particularly pertinent for women diagnosed during pregnancy, or those not on ART at conception.

8.3 Why do women decline HIV testing in pregnancy, and how is that managed?

The results from the perinatal audit presented in Chapter 7 show that the largest group of children were born to women who declined antenatal HIV testing: this was the main contributing factor in 26% of cases and was identified as contributing to the transmission in 31% of cases overall. The IDPS programme standards and the accompanying laboratory handbook, which set the standard of care and technical standards for antenatal HIV screening in England, were published in September 2010 with the target of full implementation by April 2012. The results of the perinatal audit and the decline survey I present in Chapter 4 were fed back to the IDPS programme and informed the most recent updates of their standards implemented in 2016 and 2018 (Public Health England 2016; Public Health England 2018). The 2012 standards stated that women who have declined HIV testing at the antenatal booking appointment should be re-offered a test by 28 weeks, and that if appropriate this discussion could involve the antenatal screening coordinator (UK National Screening Committee 2010), this re-offer was then recommended by 20 weeks in the later standards versions and it was recommended that women who decline should be referred to an MDT.

In the survey examining the management of women who decline antenatal HIV testing (Chapter 4), the majority of respondents stated that their unit recorded the number of women who declined antenatal HIV testing (71%); the median decline rate in 2014 was 0.05%, but five units had a decline rate exceeding 1%. Two of the five units with decline rates exceeding 1% were in high prevalence areas (not London) (>2/1000 adult population), which is of concern since these units may be proportionately more at risk of missing positive diagnoses. The reported decline rates varied by region of maternity unit: 0.02% in London, 0.13% in the rest of England (no women were reported to have declined in the remaining five units). The coverage of antenatal HIV screening is a Key Performance Indicator of the IDPS Programme, and all maternity units in England submit this data on a quarterly basis. For comparison, the mean coverage in England during the first quarter of the financial year 2013/2014 was 98.6% (78.8% of units had returned their data), with a range between units of 82.3% to 100% (Public Health England 2014a). There were two cases in the audit of perinatal HIV (Chapter 7) where women who knew their HIV-positive status concealed this and declined screening. In addition, one woman identified she was at

risk of HIV but declined screening because she could not cope with a positive diagnosis. These cases highlight the worry that women who decline may be at higher risk of having HIV than those who don't; there is no recent data on the prevalence of HIV in women who decline antenatal screening.

In the audit of perinatal HIV (Chapter 7), nearly half of women who declined an HIV test in the audit were not re-offered a test, and for 10/28 it was not possible to ascertain test re-offer. These cases were all prior to the full national implementation of the 2010 standards, so at this time a re-offer would be according to local rather than national policy. In the survey of clinicians on women who decline antenatal testing (Chapter 4), which was performed after the implementation of the first IDPS standards, only 11% of respondents stated their unit did not have a policy on managing women who decline antenatal HIV testing. In the majority of units with a policy, an HIV test was re-offered by varying clinical staff groups, but most re-offers were by a community or antenatal clinic midwife (i.e. a staff member without specialist HIV experience). If a woman declined the re-offer, 41% of units would not pursue this further. The publication of the audit findings (Chapter 7)(Peters et al. 2018) and the report of the Expert Review Panel to the IDPS Programme, led to the changes in the HIV screening standards, which now state that a woman who declines the initial offer should be referred to the antenatal screening coordinator for further counselling, and if she declines the re-offer should be referred to a specialist MDT. The quality of the information given to the pregnant woman whilst being offered an HIV test may have an effect on whether she accepts or declines the test; although there is now clear guidance on the content and process of counselling women for antenatal HIV screening in the UK, there is no data on the quality of these discussions. The variation in decline rate between regions in England is currently unexplained; the IDPS Programme is planning a detailed audit to examine this [personal communication, Sharon Webb, IDPS Programme Manager, PHE]. Now that the IDPS standards have become even more specific about referring women who decline to an MDT, this may change in the future with units becoming more proactive in their counselling of these women.

The overall reduction in the number of children diagnosed with HIV born to undiagnosed women over the audit study period, and the absence of cases associated with a declined test after 2010 suggests that the implementation of the IDPS

programme standards may have improved the uptake of HIV testing and contributed to reducing the proportion of women who remain undiagnosed through pregnancy in more recent years, but this needs to be interpreted with caution given that infants born to undiagnosed women are likely to be reported at an older age.

In the US, where the American College of Obstetricians and Gynaecologists has recommended universal antenatal testing since 2004, a recent analysis of US national surveillance data looking at testing rates in live births 2004-2013 found overall 75% coverage, with large state-by-state variations; these results were similar to a previous survey in 2006; women were less likely to be offered testing if they were married, white, non-Hispanic or multiparous (Koumans et al. 2018). States with specific laws or statutes relating to antenatal HIV testing have higher rates of testing (FitzHarris et al. 2018), and a survey of clinicians found that common reasons for not offering opt-out testing to pregnant women were physician's perception of low HIV risk, lack of time or resources, and overly burdensome pre-test discussion guidelines. These clinicians were less likely to offer opt-out testing if they were a solo practitioner or based in a non-urban setting (Anderson et al. 2012). A survey of clinicians in Switzerland found that 95% of those surveyed offered opt-out antenatal HIV testing to women in their care (Aebi-Popp, Kahlert, et al. 2016), and a survey of women in the Lazio region of Italy found testing rates of around 90% (Valle et al. 2014).

The most common reasons recorded for declining HIV testing in pregnancy were that the woman did not feel she was at risk of HIV infection, needle-phobia, and that she had previously tested negative; this was similar to the findings from the audit in Chapter 7. As previously discussed, there is evidence in Black African communities of a lack of awareness of the ongoing risk of HIV acquisition after arrival to the UK (Burns et al. 2007; Fakoya et al. 2019), and the higher proportion of undiagnosed infection in heterosexual men obviously impacts on the risk of acquisition to a woman in the UK prior to a pregnancy (the estimated proportion of undiagnosed infection in Black African heterosexual men was 38% in 2013 (Public Health England 2014b)). There is little data in other HIC on the proportion of women who decline offered antenatal HIV tests, and what their reasons might be.

In the decline survey (Chapter 4) the just over two-thirds of units surveyed did not have a policy for testing infants of women who declined antenatal HIV testing, and units based in London were more likely to have a policy (p=0.01). The most common

policy (where present) was to offer infant testing to parents before discharge from the maternity unit; the majority of these units would pursue infant testing further if the parents declined the offer. A variety of outcomes were achieved in the cases where women had declined all antenatal HIV screening in 2014; in no cases was a court order obtained to achieve infant testing. There were units that had a developed pathway including all these stages, with a multidisciplinary approach. The best practice model of care from these units could be shared with other units through academic publication, clinical and research networks and via the IDPS Programme, and all units encouraged to develop their own pathway for women who decline HIV testing in pregnancy (including whether and when to offer infant testing).

Within the Expert Review Panel, and at the BHIVA conference where I presented the results of the decline survey, opinions of health professionals and patient representatives differed in how to manage cases where women have declined all antenatal HIV testing. The rights of a woman with capacity to decline screening interventions is balanced against the rights of a child to know whether they are at risk of HIV and its related morbidity and mortality. I have shown that very few units have a transparent written policy on how to manage these cases, and the survey also shows that clinicians rely heavily on a 'risk assessment', which is not specified in any guidelines but is likely to include risk factors such as history of injecting drug use, sex work, or more commonly being from a country with high HIV prevalence. Therefore migrant women of Black African origin who decline HIV testing in pregnancy (where there are no clinical indicators of HIV infection) may face more pressure to consent to testing of their infant than women with lower perceived risk who have also declined. It is of utmost importance that the integrity of the voluntary screening programme is maintained and that women's trust in maternity and paediatric health services to respect their autonomy is not eroded.

8.5 Women with PHIV who get pregnant – who are they, are they at risk of adverse pregnancy outcomes, and why is this important?

As discussed in Chapter 1, advances in treatment of paediatric HIV and increased life expectancy mean there is now a generation of young adults and adolescents living with PHIV. A recent cross-global cohort analysis of nearly 40,000 adolescents with PHIV across 5 regions of the world found more than two-thirds of adolescents with PHIV living in SSA and South and Southeast Asia were born between 2000 and 2005, compared with only 7% in North America; half of these adolescents were female. So, although the number of new diagnoses in children is falling and clinics in HIC are seeing a large proportion of their patients transition to adult care (Judd et al. 2017), globally there are still very large numbers of children with PHIV who will become adults in the next 5-10 years and beyond.

Adolescents with PHIV face many potential health problems; including infections and malignant disease; chronic lung disease; cardiac disease; growth failure; neurocognitive disorders; chronic skin disease; and renal failure (Lowenthal et al. 2014). In addition to physical health problems, young people with HIV have high rates of anxiety and depression (41% of young people with PHIV in a prospective cohort in the UK (Le Prevost et al. 2018)). Five year-survival of children and adolescents with PHIV after initiating cART in high- and middle-income countries in Europe and Thailand was 97.6% overall and improved between 1997 and 2008 (EuroCoord et al. 2018). The health status of young people with PHIV on transition to adult services has improved over the period 2000 to 2014 in the UK and Ireland – nearly 70% had a viral load <50 copies/ml on transition 2012-2014 (Collins et al. 2017). However, there is still inequality in mortality and morbidity rates both between high-, middle- and low-income countries, and across country income groups within sub-Saharan Africa (where the majority live) (CIPHER Global Cohort Collaboration 2018). As the paediatric and adolescent population ages, there is a growing need for data on longer term outcomes. Strategies or interventions to support pregnant adolescents with PHIV and improve both maternal and child health outcomes have been identified as research priorities (Lowenthal et al. 2014; Armstrong et al. 2018).

In Chapter 5 I estimated pregnancy incidence in women with PHIV aged at least 13 in the UK and Ireland to be 13 per 1000 woman-years. This rose to 22 per 1000 woman-years when restricted to women aged 16 to 24 years. To my knowledge, this is the first estimated national pregnancy incidence rate for women with PHIV. This estimate was possible because the NSHPC collects data on all children diagnosed with HIV, and all women with HIV who become pregnant. It has a high level of completeness, being embedded within NHS commissioned antenatal screening services with extremely high uptake, as previously discussed. This estimated pregnancy incidence is lower than two studies from the US, which found incidence rates of 19 and 53 pregnancies per 1000 woman-years in females aged 13 and above (Agwu AL et al. 2011; Badell et al. 2013). It is also lower than the national conception rates for England and Wales for a similar age group, which were 41 per 1000 in women aged under 20 years, and 96 per 1000 in women aged 20-24 years in 2013 (ONS 2015).

Pregnancy incidence is influenced by level and type of sexual behaviour, fertility, procreational intent and the prevention of unintended pregnancies with contraception. There have been several studies in the US examining sexual activity in young people with HIV. A multicentre prospective longitudinal observational study of adolescents with PHIV 2007-2010 found that 28% of 330 youth surveyed had had sexual intercourse, and this rose to 53% of 16 year olds; 62% of sexually active youth reported condomless sexual intercourse (Tassiopoulos et al. 2013). A multicentre observational comparison of young people with PHIV and BHIV found lower rates of sexual activity in the PHIV group; older age, having a boyfriend or girlfriend, and use of illicit drugs were associated with sexual activity (Setse et al. 2011). Judd et al. recently compared the sexual health of 296 young people with PHIV with 96 HIV-affected young people (HIV-negative but living in a household with a PHIV participant, had a sibling, friend, or partner with PHIV, or had an HIV-positive parent). They found similar rates of ever having had sexual intercourse between the two groups (32% of PHIV and 40% HIV- young people), with no gender differences (Judd et al. 2018). Two-thirds of PHIV- and a third of HIV- participants reported always using a condom; and six PHIV- and five HIV- females had ever been pregnant. Increasing age, higher deprivation score, use of alcohol or recreational drugs were all independently associated with a higher likelihood of having sex (Judd et al. 2018). A qualitative study of seven young people from one clinical centre in London found high levels of procreational intent (Evangeli et al. 2014). A small single-centre case

series of 119 female patients with PHIV aged >16 years found that three had diagnosed infertility, eight women were being investigated for menstrual irregularity, and 15% had successfully conceived (Teh et al. 2019).

In the analysis presented in Chapter 4, I found that more reported pregnancies ended in termination in women with PHIV (13% vs. 3%, p=0.02), and there was a modest difference in the proportion of miscarriages (3% vs 6% in women with BHIV). The higher number of reported terminations in women with BHIV may reflect differences in clinical care between the two groups. It is possible that women with PHIV access care more often, since they are known to have higher rates of AIDS-related complications, adherence and drug resistance (Kenny et al. 2012b), leading to greater case ascertainment for termination of pregnancy in women with PHIV. In addition, lower procreational intent and a higher unmet need for effective contraception could also be part of the picture(Judd et al. 2018). These results underline the importance of integrated sexual health providing easily accessible effective contraception for young women with PHIV accessing care in the UK, both in adolescents and after transition of care to adult services.

I also found significant differences in pregnancy characteristics between women with PHIV and BHIV: women with PHIV were more likely to conceive on ART; had a lower baseline CD4 count in pregnancy and nearly half of women with PHIV delivered with a detectable viral load compared with 1 in 5 women with BHIV. Women with PHIV not already on cART started treatment at an earlier gestational age than women with BHIV despite no difference in gestation at antenatal booking date. Gestation at start of ART, and whether a woman is prescribed PI-containing ART are both likely to be associated with viral load at baseline and history of drug resistance. Women with PHIV may be more likely to have accumulated resistance and may have a higher baseline viral load at the start of pregnancy, but this information is not collected by the NSHPC so the effect of these factors could not be estimated in the model. In addition, clinicians may also be anticipating slow viral load decay and / or suboptimal adherence in women with PHIV, leading them to initiate cART earlier and choosing PI-based regimens.

In the multivariable analysis of factors associated with detectable viral load near delivery, significant factors were PHIV (aOR 3.22, vs 1 for BHIV), age at conception (aOR 0.89 for every year older); on ART at conception (aOR 0.27 vs. 1.0 for not on

ART at conception); PI containing ART (aOR 3.52; vs 1.0 for non-PI-containing ART). Women with PHIV are at higher risk of detectable viral load at delivery, independent of the other risk factors in the model. This is likely to be due to a combination of factors: young people with PHIV have a higher risk of treatment failure and multiclass ART resistance because of previous exposure to obsolete and non-suppressive ART; the limitations of paediatric ART drug formulations and research into safety and efficacy; difficulties with adherence due to stigma, discrimination, social complexity; and HIV-associated neurocognitive deficits, among others (Sohn and Hazra 2013). Adolescents living with HIV have the lowest rates of viral suppression, and high quality studies of interventions to improve linkage to and retention in care are starkly lacking (Enane, Vreeman, and Foster 2018). Older age at conception was protective for both young women with BHIV and PHIV, suggesting that factors such as adherence improve with age. The protective effect on ART at conception is important (although one of the reasons for this is likely to be that adhering to ART at conception predicts adherence near delivery) and must be a reminder to clinicians that treatment breaks are detrimental not only for a woman's own health but also for potential planned or unplanned future pregnancies.

My findings have subsequently been replicated by a multicentre cohort study in the US looking at 2123 mother-infant pairs, of whom 232 (10%) were women with PHIV, delivering 2007 to 2015. In this analysis, Goodenough et al. found that women with PHIV were significantly more likely to have a viral load >1000 copies/ml near delivery, and a CD4 count < 200 cells/uL; they also started antenatal care earlier, started ART earlier in pregnancy, and received more complex ART regimens (Goodenough et al. 2018). Similar results have also been found in small retrospective single-centre studies (Lundberg et al. 2018; Cecchini et al. 2018; Prieto et al. 2017).

Examining whether women with PHIV had an increased risk of adverse birth outcomes was a key objective of the analysis presented in Chapter 5. There were no significant differences in the rate of pre-term birth, or low birth weight between the groups of infants born to women with PHIV or BHIV. Although a higher proportion of women with PHIV had an infant with a reported birth defect, compared with women with BHIV, this did not reach the level of significance and was based on small numbers and therefore lacked power. In contrast, in a US study, women with PHIV had a nearly six-fold increased risk of a small-for-gestational age infant compared

with BHIV women. However, this study did not restrict the BHIV group to nulliparous women, and did not account for gravidity or timing of diagnosis, unlike my analysis (Jao et al. 2015).

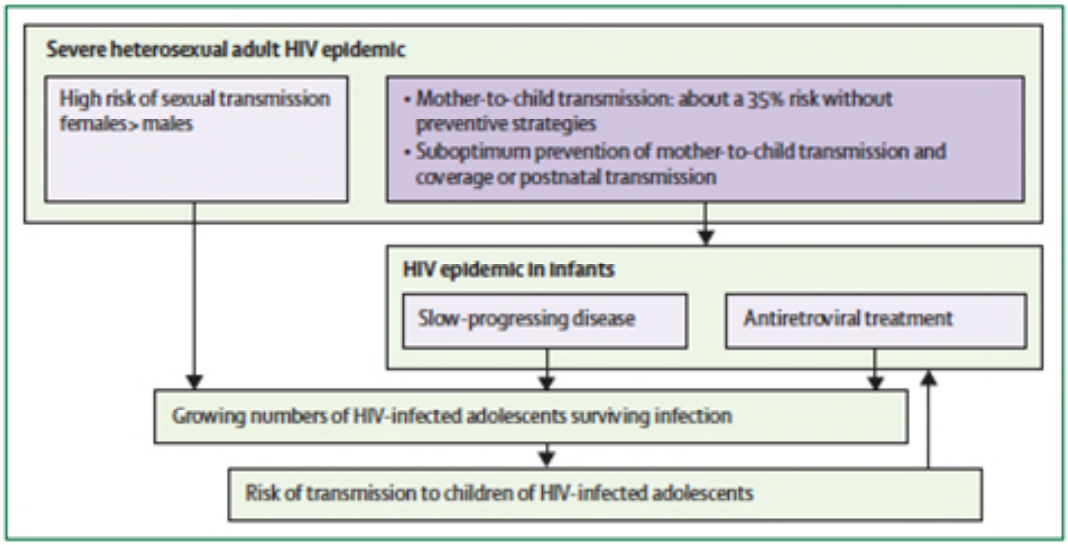
A more recent large prospective multicentre cohort study in the US by the same lead author compared 270 pregnancies to women with PHIV and 2422 pregnancies to women with BHIV (Jao et al. 2017). In multivariable analysis, the authors were able to adjust for maternal age, ethnicity, earliest CD4 count in pregnancy, maternal substance use in pregnancy, tobacco use, pre-pregnancy body mass index (BMI), most potent ART regimen and calendar year of delivery (however, timing of maternal diagnosis in the BHIV group was not described or adjusted for, nor was ART at conception). In this study, Jao et al. found no overall association between maternal PHIV status and preterm delivery or infant birthweight outcomes, although there were higher rates of low birth weight in young women aged 23-30 years with PHIV. The authors commented that the differing results between these two US studies may be due to differences in immune status of the two groups of women with PHIV, or the standard of overall healthcare and antenatal care. I was unable to adjust for BMI, substance use or tobacco use as the NSHPC does not collect these data. However, in the AALPHI cohort of young people with PHIV and HIV-negative young people affected by HIV living in the UK, young people with PHIV had similar rates of having ever smoked compared with HIV-negative young people (19% vs 25%), and a significantly lower rate of ever having tried illicit recreational drugs (15% vs. 29%)(Le Prevost et al. 2018).

It is important to note that in my analysis of pregnancy outcomes in women with PHIV in the UK and Ireland, most of the women with PHIV with a reported pregnancy were born prior to 1994, when ART for PMTCT began being used. Therefore, these women were not exposed to ART *in utero*. The growing body of work examining the long-term effects of ART exposure in utero in HIV-exposed but uninfected (HEU) children and young people will be extremely important in delineating what (if any) effects in utero exposure to ART may also have had in young women with PHIV; reproductive health outcomes in this group are of increasing importance (Afran et al. 2014; Cotton, Slogrove, and Rabie 2014; Evans, Jones, and Prendergast 2016; Thorne 2015).

Across the world, and most importantly in SSA where the epidemic is concentrated, cohorts of women with PHIV are growing older, gaining better access to more effective ART, living longer and with better health outcomes. Therefore, it is likely that the incidence of planned pregnancies in these women will rise, as women are able to choose to have the children they may wish for. In the UK, high rates of procreational intent have already been demonstrated (Evangeli et al. 2014), although low rates of sexual activity have been reported (Judd et al. 2018). Much work has been done to improve health outcomes through transition to adult services (Collins et al. 2017; Judd et al. 2017; Judd and Davies 2018), the hope is that by better addressing the sexual and reproductive health needs of adolescents and young people with HIV, the unplanned pregnancy rate in this group in the UK will fall. Women with PHIV wishing to conceive may have more complex health and psycho-social care needs than women with BHIV, and it is of utmost importance that their needs are recognised and addressed by health services. There may be relatively small numbers of young people with PHIV living in resource-rich settings, but with well-established long-term surveillance systems, lessons gained will help inform the long-term management of young people with PHIV in high-prevalence, low-income settings (Mofenson and Cotton 2013). Prevention of transmission from women with PHIV to their infants is the last link in the chain of actions towards eliminating paediatric HIV (see

Figure 8-4).

Figure 8-4. Evolution of the paediatric HIV epidemic in sub-Saharan Africa, from (Lowenthal et al. 2014)[60]



[60] Reprinted from The Lancet, Vol. number 14, Lowenthal et al., Perinatally acquired HIV infection in adolescents from sub-Saharan Africa: a review of emerging challenges, Pages 627-693., Copyright (2014), with permission from Elsevier."

8.6 What are the patterns of resistance testing for women who become pregnant, and which women diagnosed during pregnancy are at risk of TDR?

In the second half of Chapter 6, I presented the analysis of HIV drug resistance testing in pregnancy. Nearly half of women with a reported pregnancy 2000-2014 were matched to at least one resistance test in the UK HIV Drug Resistance Database. As discussed in the specific methods (section 6.3.1) this is similar to the proportion of successful matches in previous analysis between SOPHID and UKHDRD datasets. Therefore, the remaining 51% of women in the dataset who were not matched are likely to have not had a drug resistance test requested before the study end date or had a drug resistance test but failed to be matched during the three-way matching process.

Women diagnosed in earlier calendar periods were less likely to have been matched to one or more resistance tests than those diagnosed in 2010-2013 (aOR 0.67 for 1996-2000, 0.73 for 2001-2005 respectively). Resistance testing of polymerase (*pol)* (protease and reverse transcriptase genes) started in the UK in 1998, but testing of ART-naïve individuals only became widespread from 2005 following the release of the BHIVA guidelines recommending routine monitoring of transmitted resistance in this population (Tostevin et al. 2017). In the first UK HIV and pregnancy guidelines published in 2001, drug resistance testing was recommended for all women on non-suppressive ART regimens, and consideration given to testing women diagnosed during pregnancy (Mercy et al. 2001). Therefore, prior to 2005 we can expect that resistance testing was largely done on the basis of suspected / confirmed virological failure. The proportion of women matched to a resistance test increased with calendar year of reported pregnancy: from 20.4% in pregnancies 2000-2003 to 53.2% in pregnancies 2009-2013.

Women who were younger at conception were more likely to be matched (aOR 1.29 for those aged 13 to 20; aOR 0. 83 for those aged 37 to 44). This may be associated with route of maternal HIV acquisition, since the few women with PHIV in the original dataset were much younger at conception than women with BHIV, and would be likely to be more treatment experienced, and therefore more likely to have had a resistance test requested (route of acquisition was not adjusted for in the multivariable model). This finding is in keeping with the multivariable analysis of

factors associated with a detectable viral load at delivery in Section 5.3.2, where older age at conception was associated with a lower risk of detectable viral load at delivery, suggesting that adherence may improve with age. Women with more pregnancies reported were more likely to be matched (aOR 1.63 for two pregnancies, aOR 1.89 for three or more pregnancies). This may be due to a combination of factors: women repeatedly reported to the NSHPC may be more likely to be matched to a SOPHID record due to increased data quality for the matching algorithm. Given that pregnant women not on suppressive ART require resistance testing in order to optimise ART for rapid viral load decay, it may also be that women with repeat pregnancies have more frequent resistance tests.

The fact that women born in the UK/Ireland were more likely to be matched than women born in SSA (aOR 1.26 vs. 1, $p<0.01$)) is difficult to unpick. In the model which also included ethnicity as a variable, the significant effect of region of birth was still present, making racial bias less likely to be a factor (i.e. are Black women less likely to be tested for resistance?). It is perhaps more likely that migrant women have been engaged in care for less time, or perhaps migrant women are more likely to be established on suppressive ART. This merits further investigation. Women whose first pregnancy was reported from the rest of England were less likely to be matched compared with those reported from London (OR 0.63 vs. 1). Since resistance testing other than at baseline is a marker of sub-optimal adherence and/or virological failure, it may be that women in areas outside of London are more likely to be established on suppressive ART, and therefore less likely to need repeat resistance testing (and therefore less likely to be matched). It could also be that areas outside London were slower to adopt routine baseline resistance testing after recommendations were published, and / or that they faced structural barriers to implementing these recommendations. I did not include region of report in the multivariable analysis of factors associated with detectable viral load, but this could be examined in the future.

The genetic diversity of HIV-1 reflected in subtypes and recombinant forms has implications for the diagnosis of, natural history and treatment and prevention of HIV (Lihana et al. 2012). Subtype has an impact on diagnostic testing for HIV and viral load testing (Aghokeng et al. 2009; Depatureaux et al. 2011; Plantier et al. 2009; Sire et al. 2011). HIV-1 subtypes and recombinant forms may have an impact on transmissibility and disease progression, although this is not yet established (Walter

et al. 2009; Price et al. 2019.; Wright et al. 2011; Kiwanuka et al. 2009; Omondi et al. 2019), and there are associations between subtype and the development of drug resistance (Chan and Kantor 2009; Skhosana et al. 2015; Sunpath et al. 2012; Smit et al. 2017); and implications for vaccine research (Fleury et al. 2017). A study of incident HIV infections in women in SSA 2006-2011 found that women with subtype C or D had more rapid clinical progression than those with subtype A (which is also the case in men)(Wall et al. 2017; Amornkul et al. 2013).

The most common viral subtype, present in nearly half of women matched to a resistance test, was subtype C, followed by subtype CRF02_AG (13% of women), and subtypes A and B (both in around 10% of women). This is similar to the findings of a UKHDRD study of resistance tests 2002-2009 in the UK overall, which found that subtype C was the most prevalent subtype in women overall (UK Collaborative Group on HIV Drug Resistance 2014). All the subtypes and other pure and recombinant forms were dominated by women born in SSA, with the exception of subtype B. Over half of women with subtype C virus born in SSA were born in Zimbabwe. The vast majority of women with CRF02_AG virus were born in sub-Saharan Africa; most commonly in the West African countries Nigeria, Ghana and the Ivory Coast . Overall, 10% of women had subtype B; of these women, nearly half were born in UK/Ireland, 18% in Jamaica, and 4% in Poland. In my analysis subtype was highly correlated with region of birth, which has already been well-established in other studies of genetic diversity of HIV-1 (Camacho 2006; Hemelaar et al. 2006; Bbosa, Kaleebu, and Ssemwanga 2019), and the pattern of subtypes found in my analysis fits with patterns of birth-region and migration to the UK, as discussed in section 4.2. The similarity between the distribution of subtypes in my analysis of pregnant women and the UKHDRD study (UK Collaborative Group on HIV Drug Resistance 2014) demonstrates that the subgroup of women with HIV in the UK who become pregnant are likely to be similar to women with HIV in the UK overall in terms of region of birth.

TDR in those diagnosed during pregnancy

In the analysis I present in section 6.3.2, 1599 women matched to at least one resistance test were diagnosed during the first reported pregnancy and reported as ART-naïve on the request for the resistance test. Of these 1599 women, 5% had evidence of TDR (95% confidence interval 4.3% to 6.5%). This is similar to the 4.6%

prevalence of TDR found in people with non-B subtypes in the UK 2001-2006, and lower than a more recent analysis of TDR overall in the UK (which included subtype B virus) (Chilton et al. 2010; Tostevin et al. 2017). The prevalence of TDR in women diagnosed during pregnancy over the calendar period is shown in Figure 6.6; there were small numbers pre-2004 as would be expected according to guidelines on routine baseline testing (see table 6.8). The prevalence of TDR fell to a nadir of 3.2% in 2006-2008, and rose to 8.2% in 2012-2014; this variation by calendar period just reached the threshold of statistical significance *(p*=0.04). The prevalence of NRTI TDR also followed a similar trajectory, with a prevalence of 4.7% in 2000-2002, a nadir of 0.7% in 2006-2008, rising to 2.7% in 2012-2014 (p=0.01). The lowest prevalence of NNRTI TDR was also in the year group 2006-2008, but this variation by year group did not reach statistical significance; the prevalence of PI TDR fell from 1.6% in 2000-2002 to 0.7% in 2012-2014, but this did not reach statistical significance either. So, the variation of TDR overall may be driven by the changes in NRTI and possibly NNRTI resistance, and in addition it may be that there was a trend in falling PI TDR, but my analysis lacked statistical power to demonstrate this. In multivariable analysis of risk factors associated with presence of TDR, year of pregnancy 2006-2008 (and therefore diagnosis) was associated with a lower risk of TDR (AOR 0.39, p=0.04); low CD4 count in pregnancy (and therefore at diagnosis) was associated with a higher risk of TDR (AOR 2.02 vs. 1.0), but did not quite reach the level of statistical significance (p=0.05). There was no evidence that the presence of TDR increased the risk of detectable viral load at delivery or was associated with the infection status of the infant. In both cases, the low rates of TDR and detectable viral load at delivery, and the low vertical infection rate would have contributed to a lack of power.

My findings are not entirely in keeping with a published analysis of drug resistance tests in adults reported to be ART-naive in the UKHDRD 2005-2013, which found that the prevalence of TDRMs in women who acquired HIV heterosexually had remained stable between 2010 and 2013; Figure 8-5 shows the prevalence of TDRMs by risk group in this UKHDRD analysis 2005-2010 (Tostevin et al. 2017). We can consider the group of women diagnosed in pregnancy in the analysis presented in this thesis as a sub-group of the heterosexual women presented in the UKHDRD analysis, given that the UKHDRD population consisted of all heterosexual women in the UK reported as naïve to ART with a resistance test, with 83% successfully matched to

demographic data. Figure 8-6 shows the estimated number of new HIV diagnoses in the UK by risk group; by comparing with table 6.8 we can see that in 2005 there were 3,243 women diagnosed overall and 552 of these were diagnosed during a reported pregnancy, representing 17% of all women diagnosed that year; similarly in 2011 overall 1809 women were diagnosed, and 225 were diagnosed during pregnancy (12%). Baseline characteristics of the heterosexual women in the UKHDRD analysis are not presented disaggregated, so it is not possible to compare differences in the two groups, but it is likely that women diagnosed during pregnancy differ in characteristics such as age at diagnosis, region of HIV acquisition, and length of time in the country for migrant women. Interestingly, the UKHDRD also performed multivariable analysis of factors associated with presence of TDRMs - the only factor which remained significant in their multivariable model was region of report, with a higher risk of TDRMs in tests reported from London compared to other regions (aORs 0.48-0.80 for regions outside London, except 1.02 for North of England, compared with 1.0 for London, $p<0.01$). However, this analysis included other risk groups, and MSM and people with subtype B virus have a higher rate of TDRMs than women who acquired HIV heterosexually (Tostevin et al. 2017; Hofstra et al. 2016; Frentz et al. 2014).

In my analyses, two-fifths of women with TDRMs had resistance to only NNRTIs; only 10 women had dual class resistance, and none had triple class resistance. The most common NNRTI TDRM was 103N (occurring in half) followed by 101E, 181C, 138K; the most common NRTI TDRMs conferring NRTI resistance were TAMs and 184V; the most common PI TDRMs were 46I/L, 90M , and 85V. This is in keeping with the pattern of TDR overall in the UK and Europe (Tostevin et al. 2017; Hofstra et al. 2016; Frentz et al. 2014).

As far as I am aware, the results I present in Chapter 6 are the first analysis of TDR in women diagnosed during pregnancy with national surveillance data, and the first data from a high-income country. A study of nearly 90 women diagnosed during pregnancy in Rio de Janeiro found an overall TDR rate of 17%, but this is a very different population with majority subtype B infection (Delatorre et al. 2016). Another small study in the Republic of Congo found a rate of 8.2% in women diagnosed during pregnancy 2005-2008 (Bruzzone et al. 2015). Pregnancy provides a unique context to a new HIV diagnosis, with an urgent need to suppress viral load to

prevent both in utero and intrapartum transmission, therefore knowledge of UK trends and type of TDRMs in women diagnosed during pregnancy is important. I found an increase in the overall prevalence of TDR between 2006-8 and 2012-14 in pregnant women, with a corresponding rise in NRTI TDR and possibly in NNRTI TDR. This is of concern and requires further surveillance on a national level.

Figure 8-5 Prevalence of TDRMs by transmission group in the UKHDRD 2005-2013 (Tostevin et al. 2017)[61]

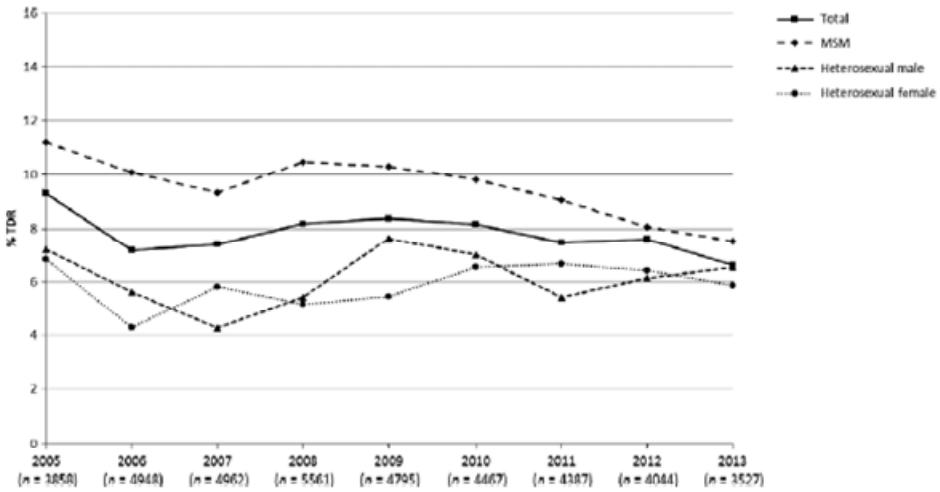


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Figure 8-6. Annual new HIV and AIDS diagnoses and deaths by year of diagnosis or death: United Kingdom 1982-2011, from (HPA 2012)[62]

Report type and sex		1996 or earlier	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	Cumulative total [1,2,3]
HIV diagnoses	Men	28,021	2,180	2,152	2,262	2,553	3,172	3,679	4,118	4,504	4,671	4,496	4,705	4,607	4,449	4,338	4,471	84,378
	Women	4,976	705	789	1,032	1,449	2,013	2,716	3,291	3,288	3,243	2,974	2,660	2,647	2,193	2,026	1,809	37,811
Total[1]		33,031	2,886	2,942	3,296	4,002	5,186	6,395	7,409	7,792	7,914	7,470	7,365	7,254	6,642	6,364	6,280	122,228
First AIDS diagnoses	Men	13,240	678	619	586	626	531	636	584	592	609	525	548	506	447	450	321	21,698
	Women	1,592	225	202	204	262	262	359	451	417	355	353	285	313	205	229	136	5,850
Total		14,832	1,103	821	790	888	793	995	1,035	1,009	964	878	833	819	652	679	457	27,548
Deaths[2]	Men	10,988	600	416	391	366	359	417	402	340	443	417	425	454	418	444	375	17,275
	Women	1,136	150	97	79	98	119	106	164	149	148	150	172	152	163	168	129	3,180
Total[3]		12,126	751	513	470	484	478	523	566	489	591	567	597	606	581	612	504	20,458

Will include some records for the same individuals which are unmatchable because of differences in the information supplied.
Numbers will rise as further reports are received, particularly for recent years.
[1] Includes 39 HIV diagnoses of individuals with sex not reported (the majority of which are in earlier years).
[2] Includes all reported deaths (all cause) in HIV diagnosed individuals.
[3] Includes 3 death reports of individuals with sex not reported.
Note: Appendices show actual numbers. Numbers presented in text are rounded.

8.7 What ART were women prescribed over the study period?

The HIV drug pipeline was, and still is, extremely active – with new drugs enabling lower doses, less frequent dosing, better side effect profiles and higher genetic barriers to resistance. In addition, there are now effective dual drug cART regimens, and novel long-acting modes of drug delivery (Orkin 2018; Singh, Sarafianos, and Sönnerborg 2019; Puhl et al. 2019; de Miguel Buckley et al. 2018). The pattern of combination antiretroviral drug prescribing in pregnancy in the UK and Ireland changed over time. I found that the median gestation at start of ART for women who were not on ART at conception fell from 27 weeks to 20 weeks over the study period (during the same period the proportion of women on cART at conception increased from a quarter to three-fifths.) This is similar to the reduction in gestation at initiation of cART in pregnancies reported to the NSHPC in the UK and Ireland 2000-2011 demonstrated by Townsend et al. (Townsend et al. 2014). I was able to identify the classes of ART and key combinations of drugs used in pregnancy over the duration of the study for both women on and not on ART at conception. Of course, by the end of the study period the majority of women were already on ART at the time of conception, so these drugs at conception were prescribed outside of

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pregnancy (though of course drug regimens may be switched for reasons pertaining to the pregnancy after conception).

Women are commonly prescribed an NRTI 'backbone' (of two drugs, often co-formulated) plus a third agent. Up until the most recent version of the UK guidelines, this third agent would usually be a NNRTI or a PI (but may now be an integrase inhibitor). Considerations taken into account when selecting regimens suitable for pregnancy include: efficacy at suppressing viral load (particularly important for the 50% of women in my dataset who were diagnosed during the pregnancy, and those women not on cART at conception who accessed care late in pregnancy), genetic barrier to resistance (5% of the women in my dataset matched to a resistance test had TDR, mostly resistance to NNRTIs), tolerability, pharmacokinetics in pregnancy, ease of adherence and pill burden, risk of adverse effects, risk of teratogenicity if given in early pregnancy, potential for drug-drug interactions, and the ability of the drugs to cross the placenta (although there is on average a 6 year gap between drug licensing and data on safety and pharmacokinetics in pregnancy becoming available (Colbers et al. 2019)). During the study period 2000-2014, there were four version of UK guidelines, as well as European and WHO guidelines, and the recommended first line regimens have evolved over time. Although now all women are recommended to start lifelong cART, on the basis of the START trial results (The INSIGHT START Study Group 2015), in previous guidelines women could opt for short term antiretroviral therapy if they had a CD4>350 cell/uL, or even zidovudine monotherapy if they had a baseline viral load <10,000 copies/ml and were planning a caesarean section (de Ruiter et al. 2008).

A small number of women (211) received treatment with triple-NRTI therapy, most commonly the co-formulated combination abacavir + lamivudine +zidovudine (brand name Trizivir). This may have been used by clinicians during pregnancy cautious about emerging data on preterm delivery (where women did not require treatment for their own health) and PIs, or in women where there is a need to avoid a PI or NNRTI (e.g. because of resistance, or to avoid drug-drug interactions or adverse effects). At the beginning of the study period, the NRTI backbone zidovudine + lamivudine (co-formulated as Combivir) was the most widely prescribed, but this fell dramatically from 97% in 2000-2002 to 18% in 2012-2014. Tenofovir + emtricitabine (co-formulated as Truvada) rose from 0.2% of live births in 2003-2005 to become the

most widely prescribed NRTI backbone in 2012-2014 (60% of women on cART). Use of abacavir + lamuvidine (co-formulated as Kivexa) also rose but to a lesser extent, with a high of 21% in 2012-2014. Zidovudine was of course the first drug that showed a reduction in the rate of vertical transmission MTCT back in the 1990s, and remains the only antiretroviral drug to be licensed in pregnancy (Sperling et al. 1996; Connor et al. 1994). As part of an NRTI-backbone with a third agent, it was very widely used in Europe until NRTIs with fewer adverse events and once-daily dosing became available and surveillance data demonstrated they were safe in pregnancy (Tariq et al. 2011).

Women were treated with a PI-based regimen in nearly two-thirds of live births (61%) and an NNRTI-based regimen in a third. Women on cART at conception were equally likely to be prescribed PI- or NNRTI-based cART. Historically, NNRTIs have been first-line third agent in non-pregnant women naïve to ART without baseline resistance. Patterns of NNRTI use evolved over the calendar period under study. In women on ART at conception treated with NNRTI-based cART, nevirapine use fell over the study period from 94% in 2000-20002 to 43% in 2012-2014. Conversely, the use of efavirenz as a third agent rose from 6% in 2000-2002 to 55% in 2012-2014 ($p<0.001$). Similarly, women not on ART at conception treated with an NNRTI were mostly treated with nevirapine (95%), but efavirenz use in this group rose from 0.5% to 54.9% in 2012-2014. Nevirapine was the first NNRTI to be licensed (in 1996), with similar virological and clinical efficacy to efavirenz, but the risk of rash and hepatoxicity limits its use to women with CD4 <250 cell/uL at initiation (Coster and Kumar 2012).

There was a period in time when concerns about conceiving on efavirenz (originating from animal studies and a small number of case reports) meant that women of reproductive age were advised to avoid efavirenz, particularly if they were planning conception(Ford et al. 2014). Therefore, if nevirapine was not suitable (e.g. women with a high CD4 count) women planning a pregnancy may have been initiated on a PI despite the absence of resistance. Further data from women conceiving on efavirenz was reassuring with no increased risk of teratogenicity (the Antiretroviral Pregnancy Registry now has 1061 first trimester efavirenz exposures reported with a congenital abnormality prevalence of 2.4% (Thorne 2019)), and since 2012 the BHIVA HIV and pregnancy guidelines have no longer advised women planning conception avoid

taking efavirenz (Ford et al. 2014; Antiretroviral Pregnancy Registry Steering Committee 2015; Taylor et al. 2012). Further data on the safety of ART in pregnancy is discussed in section 8.7.

Women not on ART at conception were treated with a PI-based regimen in over 70% of cases, and the proportion of these women on a PI increased from 17% in 2000-2002 to a peak of 87% in 2009-2011. In this situation, women were recommended to initiate a PI-based regimen if they had either baseline or accumulated drug resistance to NRTIs or NNRTIs, or if they were initiating START to be stopped at delivery, or if there were concerns regarding adherence, or another reason that NNRTI therapy would not be clinically suitable (Mercy et al. 2001; Hawkins et al. 2005; de Ruiter et al. 2008; Taylor et al. 2012). In my dataset, in the early 2000s nelfinavir was the most widely used PI, but dropped dramatically to negligible levels by 2008. Nelfinavir, which is prescribed un-boosted and needs to be taken with a high-fat meal, was licensed in 1996 and by 2008 was unavailable in the UK (de Ruiter et al. 2008). There is very little evidence presented on nelfinavir in pregnancy in the 2001 and 2005 BHIVA pregnancy guidelines (Mercy et al. 2001; Hawkins et al. 2005), but nelfinavir levels were found to be low in the second and third trimesters of pregnancy (Fang et al. 2012; Nellen et al. 2004), as well as low placental transfer (McCormack and Best 2014) and increased time to undetectable viral load compared with NNRTIs (European Collaborative Study et al. 2007).

The use of ritonavir-boosted lopinavir rose from just under 10% in 2001 (year of EMA licensing), peaked at 82% in 2010 in women not on ART at conception before dropping to only a quarter of women by the end of the study. Lopinavir/ritonavir is effective in pregnancy, but has a higher rate of gastrointestinal upset than darunavir/ritonavir or atazanavir/ritonavir, and is dosed twice-daily (Bánhegyi et al. 2012). Ritonavir-boosted atazanavir use emerged in 2003 and use rose to becoming the most widely used PI in both women on and not on ART at conception in 2012. Atazanavir can cause an unconjugated hyperbilirubinaemia which can cause visible scleral icterus, and increases the risk of renal stones, but it has not been implicated in the conflicting evidence on preterm delivery and has high levels of placental transfer compared with other PIs (McCormack and Best 2014), and so is still first line where a PI needs to be initiated during pregnancy (Gilleece and BHIVA pregnancy guidelines writing group 2019). Ritonavir-boosted darunavir use emerged in 2007-2008 and use

steadily rose toward the end of the study period, particularly in women on ART at conception, of whom nearly half were on darunavir in 2014. There is limited data on the safety and efficacy of darunavir in pregnancy, so it is currently second-line in UK guidelines.

A small number of women received additional raltegravir in addition to their main regimen (0.4% live births overall; 2.3% of live births in women not on ART at conception). The integrase inhibitor raltegravir is associated with rapid viral load decay and during the study period was used as an adjunct where viral load was not falling, or there was short time before expected delivery in which to suppress maternal viral load (60% of women in my dataset who received raltegravir started after the initiation of their main regimen, and median gestation at start of raltegravir was 33 weeks' gestation) (Brites et al. 2018; MJ Trahan et al. 2015; Murray et al. 2007; Puthanakit et al. 2018). More evidence on the role of integrase inhibitors is emerging, particularly in the situation where a woman has a very high viral load (>100,000 copies/ml) at baseline or where rapid viral load decay is of utmost importance. Raltegravir is dosed at 400mg bd in pregnancy because the pharmacokinetic profile of once daily 1200mg dosing is not sufficient. It is well tolerated except for infrequently reported mild transaminase rises (Maliakkal, Walmsley, and Tseng 2016), and seems to transfer well across the placenta (McCormack and Best 2014). A recent randomised control trial of raltegravir-based cART compared with efavirenz-based cART initiated during pregnancy showed a more rapid viral load decay in the raltegravir arm, with more women suppressed at delivery (Mirochnick et al. 2019). A recent NSHPC analysis of pregnancy outcomes in women on raltegravir and elvitegravir at conception found rates of congenital abnormalities similar to national rates in the UK (Rasi et al. 2019).

In the analysis if pregnancy outcomes of women with PHIV and BHIV presented in Chapter 5, overall there was no significant difference in class of ART prescribed between the two groups, but women with PHIV not on ART at conception were more likely to start a PI-based regimen and many more women with PHIV were treated with raltegravir. There are several reasons for PIs to be prescribed in pregnancy. Historically, women who did not require ART for their own health (CD4 >350 cells/ul) could opt for short term ART during pregnancy, and this would be a PI-containing regimen to reduce the risk of developing viral resistance on cessation of

ART (Taylor et al. 2012). In addition, because of the high genetic barrier to resistance, PIs are used in women who have already developed resistance, or in whom adherence is anticipated to be suboptimal. Women with PHIV are likely to be highly treatment exposed (Flynn and Abrams 2019), and may already have developed resistance to antiretroviral therapy, since self-reported adherence in adolescents with PHIV is lower than adults with HIV (Agwu and Fairlie 2013).

Change of practice in the use of cART in pregnancy has often evolved before guidelines are updated. There are very few RCTs conducted in pregnant women, and data on suppression of viral load is often extrapolated from trials in non-pregnant patients. A recent paper has called for a coordinated and comprehensive approach to ensure the needs of children, adolescents and pregnant and lactating women are considered when developing long-acting ART formulations, which have the potential to improve treatment outcomes substantially (Nachman et al. 2019). However, as previously discussed, without this kind of coordinated approach, data can emerge after drugs have been adopted into the pregnancy arsenal which then discourages use. For example, the combination of the NRTIs stavudine and didanosine was shown to cause an unacceptably high risk of lactic acidosis and should no longer be co-prescribed in pregnancy (WHO 2001); the concern on the potential teratogenicity of efavirenz which is discussed above, and the recent safety data on dolutegravir which I discuss in section 8.9.

Data on the teratogenicity of drugs comes largely from observational cohort and surveillance studies (such as the Tsepamo study) and a prospective US surveillance registry, The Antiretroviral Pregnancy Registry (Antiretroviral Pregnancy Registry Steering Committee 2015). These studies collect real-world data, so the safety data only emerges after a number of women have been prescribed the drug and become pregnant whilst taking it. Rare outcomes, such as neural tube defects, require large numbers of first trimester exposures to demonstrate to demonstrate no increased risk (Thorne 2019). So, although evidence evolves and guidelines change, real-world practice both influences and is influenced by these recommendations.

8.8 Why is engagement in care and adherence to ART important for pregnant women – and how can we improve this?

The most important risk factor for MTCT is detectable viral load – during pregnancy and at delivery for in utero and intrapartum transmission, and whilst breastfeeding for postnatal transmission. The three main factors which may prevent viral load suppression by the time of delivery are: 1) duration of cART prior to delivery (viral suppression can take around 3 months, and is longer with higher baseline viral load); 2) suboptimal adherence; and 3) the presence of baseline or accumulated resistance rendering cART less effective(Townsend et al. 2014; Hodgson et al. 2014; Hofstra et al. 2016). Therefore, the earlier start of cART in women not on ART at conception that I have demonstrated is important; this is reflected in the changing recommendations over the study period, and has contributed to the reduction in the rate of MTCT in the UK (Townsend et al. 2014; Peters et al. 2017). In addition, I have demonstrated that 5% of women diagnosed with HIV during pregnancy have TDR. Baseline resistance testing, and resistance testing at the time of viral failure are important as discussed earlier, and are now part of routine care of pregnant women with HIV (Gilleece and BHIVA pregnancy guidelines writing group 2019). Finally, we need to identify and support women at risk of suboptimal adherence.

In the analysis of factors associated with detectable viral load at delivery presented in Chapter 5, having PHIV was associated with an increased risk (aOR 2.63, p=0.02), older age at conception reduced the risk (aOR 0.8 per year older, p=0.04), being on ART at conception was protective (aOR 0.27, p<0.01), and being on PI-containing ART was associated with increased risk (aOR 3.52, p=0.03). As discussed earlier, PHIV is of course associated with extensive treatment history, higher risk of accumulated resistance, and high levels of social complexity and adversity during childhood and adolescence (Enane, Vreeman, and Foster 2018).

There is limited data on the risks and causes of non-adherence and resistance in pregnant women with PHIV: a retrospective multicentre study in the US of 41 women with PHIV and 41 women with BHIV delivering 2000-2014 found that women with PHIV were more likely to have resistance in their virus, and more likely to have multiclass resistance, then women with BHIV (Lazenby et al. 2016). A retrospective single-centre US study of a small number of women with PHIV with or

without a history of depression, found that mean viral load at delivery was higher and reported adherence was lower in women with a history of depression (Sheth et al. 2015). In another single-centre US study of 245 pregnancies, a multivariable analysis of pregnancies to women with PHIV, BHIV and HIV-uninfected women, maternal PHIV was associated with a higher risk of antepartum depression (Angrand et al. 2018).

The effect of age on viral load at delivery was independent of PHIV status, showing the importance of developing interventions to improve adherence among all adolescents and young people living with HIV (Enane, Vreeman, and Foster 2018). This protective effect of age on adherence and retention in care has also been noted in several studies included in a systematic review of adherence in pregnant and postpartum woman (Hodgson et al. 2014). Other risk factors identified were lower educational attainment, lack of knowledge of healthcare services, lack of disclosure to friends / partners, fears and stigma, practical demands such as travel away from home, study and work commitments, and food and/or water insecurity (Hodgson et al. 2014). A cross-sectional survey of antenatal and postnatal women with HIV in Ukraine found that lower adherence was associated with younger age, lower self-efficacy and unplanned pregnancy (Bailey et al. 2014). Tariq et al looked at characteristics of women who disengaged from care following a pregnancy reported to the NSHPC; women born in SSA were twice as likely as white UK-born women to be lost-to-follow-up in the year following their pregnancy (Tariq, Elford, Chau, et al. 2016). Women who arrived in the UK after conception were the group most likely to become lost-to-follow-up (Tariq, Elford, Chau, et al. 2016). An analysis of women with HIV who gave birth in Switzerland 1996-2011 found a loss-to-follow-up rate (>365 days since last contact) of 12%; factors independently associated with loss-to-follow-up were history of IDU and detectable viral load at delivery (Aebi-Popp, Kouyos, et al. 2016).

In the perinatal audit presented in Chapter 7, the main contributing factor to perinatal infections was suboptimal engagement and/or adherence in 14/108 cases; half of these women had been diagnosed before pregnancy and half during. Adherence to ART for people living with HIV is complex with many potential barriers, such as fear of disclosure, suspicion of treatment, pill burden or complex regimens, forgetfulness and work and family responsibilities (Mills et al. 2006). In

addition, women have been found to have lower adherence than men in a multicentre cross-sectional survey in the US, and a study of PWID in Canada; a meta-analysis of adherence studies showed that these sex differences are more apparent in studies which contain a greater proportion of MSM, and that higher rates of adherence in women were found in studies based in Africa, Asia and South America (Beer and Skarbinski 2014; Tapp et al. 2011; Ortego et al. 2012). Women diagnosed during their pregnancy experience shock and disbelief, feel threatened by illness or death, experience 'otherness' and self-stigma, and worry about their baby's health (Kelly et al. 2012). This may bring adherence challenges, since women in this situation have a short time period to process their thoughts and feelings before commencing ART, and they may have additional worries about the effect of medication on their baby.

Women of Asian and Black ethnicity have been found to have higher rates of nausea and vomiting in pregnancy in the UK than women of white or Chinese ethnicity (Fiaschi et al. 2019), which may interfere with pill-taking. A meta-analysis of studies conducted in low-, middle- and high-income countries found that only 72% of pregnant HIV-positive women had adequate adherence (Mills et al. 2006); adherence was better during pregnancy compared to the postnatal period, which may because concerns about their baby's health during pregnancy motivate women to take their treatment, whereas the postnatal period can be stressful and isolating with increased risk of depression (Nachega et al. 2012). Factors which improve adherence include strong social support, disclosure to family and friends, acceptance of HIV-positivity, having a routine into which taking ART could be easily incorporated, and using reminder tools (Mills et al. 2006).

Eighty percent of women in the audit whose main contributing factor was suboptimal engagement and/or adherence had at least one complicating factor whilst pregnant (slightly higher than the 70% overall): significant mental health issues, inadequate housing, uncertain immigration status, drug and/or alcohol use and reported IPV among others. In addition, 36% were not fluent English speakers. It is very difficult to improve adherence without addressing individual-level and structural barriers which may be present, and care of women in pregnancy needs to be holistic and may involve multiple agencies. The BHIVA guidelines recommend that all pregnant women with HIV are managed by an experienced multidisciplinary team, that at a minimum

consists of an HIV specialist doctor, a specialist midwife, a paediatrician and an obstetrician; recommends involvement of the woman's GP and health visitor; and recommends all pregnant women living with HIV have access to peer support and voluntary organisations (Taylor et al. 2012). In addition, women with specific needs may require the involvement of clinical psychology, counselling, substance abuse midwife, psychiatry, social services, dietetics, interpreters, advocates and specialist pharmacists among others.

Mentor mothers are mothers living with HIV who are trained and employed to support, empower and educate pregnant women and new mothers about their and their babies' health (Joint United Nations Programme on HIV/AIDS 2011). Although clinical evidence that peer support improves adherence is currently lacking (Nieuwlaat et al. 2014), mentor mother programmes are at the heart of global strategies to increase community involvement and reduce stigma in order to eliminate MTCT (Joint United Nations Programme on HIV/AIDS 2011). The charity Positively UK had a project 'From Pregnancy, to Baby and Beyond' which provided workshops and one-to-one mentoring for pregnant and postnatal women living with HIV, and built confidence and provided a 'safe space' for women to explore their feelings and difficulties in managing HIV and being a mother (Knudsen-Strong and Positively UK 2011). There is now a network of mentor mothers in the UK (4M: My health, my choice, my child, my life) who can support women living with HIV in pregnancy and afterwards (Namiba et al. 2017). Information on access to peer support was not available for the audit cases, but most children were born to women experiencing complex psychosocial issues in addition to coping with their diagnosis of HIV, and it is likely they would have benefitted from access to peer support during pregnancy.

8.9 What are the outcomes in pregnancies in women living with HIV overall?

Untreated maternal HIV infection is associated with an increased risk of pre-term birth, low birthweight, small for gestational age, and stillbirth, especially in sub-Saharan Africa (Wedi et al. 2016), however there is also evidence (as discussed in Chapter 2) that ART is implicated in increased risk adverse birth outcomes such as pre-term delivery, and there have been concerns around the safety of ART taken at the time of conception.

The proportion of live and stillbirths in the pregnancy outcomes analysis presented in Chapter 5 remained fairly constant over time. The median age at conception for women with reported stillbirths rose from 26 years at the beginning of the study period, to 34 years at the end. In comparison, median age for women with live births rose from 28 to 32 years over the study period. There was a slightly higher proportion of stillbirth in women of black African and non-white non-black African ethnicity, but this did not reach statistical significance. A recent analysis of stillbirth in pregnancies reported to the NSHPC 2007-2015 found a crude stillbirth rate 8.5 per 1000 (95% confidence interval 6.9 to 10.5 per 1000); risk factors in this population were pre-eclampsia, diabetes, CD4 count <350 cells/uL, older age, primiparity and Asian origin (Favarato et al. 2019). This study found no differences between cART regimens in terms of stillbirth rates, but adjusted analyses of cART regimens were precluded by small sample sizes (Favarato et al. 2019). A meta-analysis of perinatal outcomes associated with HIV included two studies with stillbirth as an outcome (n=1168), and found a risk ratio of 1.67 (95% confidence interval 1.05-2.66) compared with women who were HIV negative (Wedi et al. 2016). A meta-analysis looking at timing of ART and adverse pregnancy outcomes included two studies on stillbirth, and found an association with timing of ART start (before and after conception)(Uthman et al. 2017). An analysis of pregnancies in older women >40 years in pregnancies reported to the NSHPC 2000-2014 found that pregnancies in older women were more likely to result in multiple birth, stillbirth, or an infant with a chromosomal abnormality (Townsend et al. 2017). There was no increased risk of pre-term birth, low birth weight or risk of vertical transmission (Townsend et al. 2017).

The proportion of live births delivered preterm before 37 weeks' gestation fell from 14.3% to 11.1% over the study period. The proportion of pre-term birth was

significantly higher in white women (14.8%) than black African (12.0%) or non-white non-Black African women (13.4%). A higher proportion of infants born at term to black African women weighed ≥2.5kg. In the perinatal audit presented in Chapter 7 there were only three cases in which the main contributing factor was identified as preterm birth. ART was initiated at 22 to 26 weeks, and none of the women had an undetectable viral load by the time of delivery; the infants were likely infected *in utero* or at the time of delivery. Preterm birth shortens the duration of antenatal ART, as well as increasing neonatal morbidity. Women living with HIV are at increased risk of preterm delivery, as well as having a higher prevalence of non-HIV related risk factors (Wedi et al. 2016).

In Chapter 2 I described the evidence for the role of ART in pre-term birth up to 2014. The debate about the role of ART in preterm delivery rages on, with two key questions – is the risk of pre-term birth associated with timing of start of cART, and is there an increased risk with PI-based cART? A meta-analysis of timing of cART and adverse pregnancy outcome found that women who started cART prior to conception were more likely to deliver pre-term or very pre-term and their infants to have low birthweight, but with the quality of evidence rated low or very low (Uthman et al. 2017). However, the authors of a birth cohort simulation have pointed out that when comparing outcomes in women started on cART before and during pregnancy, those women who deliver pre-term and therefore do not start cART before delivery are excluded from such analyses (they will be untreated), which means any difference between starting cART before or during pregnancy is affected by selection bias in the group initiating cART during pregnancy (Stoner et al. 2018). The only way to counter this selection bias is to follow an intention-to-treat analysis and include women delivering before cART is initiated (Stoner et al. 2018). Selaska et al. conducted a systematic review of adverse birth outcomes in low- and middle-income countries in women with HIV, and found that compared with NRTI-based cART, and zidovudine monotherapy, the regimen lopinavir/ritonavir plus zidovudine/lamivudine was associated with an increased risk of pre-term birth, after adjusting for CD4 and WHO disease stage; there was no consistent association between pre-term birth and other PI-based cART regimens (Saleska et al. 2018).

The PROMISE trial randomised 3529 pregnant women in six SSA countries and India with CD4>350 to receive either zidovudine monotherapy + intrapartum single-dose

nevirapine, or cART with zidovudine/lamivudine + lopinavir/ritonavir (ZDV-cART), or tenofovir/emtricitabine + lopinavir/ritonavir (TDF-cART), on an open-label basis (Fowler et al. 2016). All regimens were continued through to 6-14 days post-partum. In both the lopinavir/ritonavir arms, the dose was increased in the third trimester to 600mg/150mg twice daily, although there is now evidence that this is not required (Salem et al. 2015). The PROMISE trial found a significantly lower transmission rate in the two cART arms compared with the zidovudine monotherapy arm (0.5% vs. 1.8%). They also found that the rate of pre-term delivery < 37 weeks' gestation did not differ between the ZDV-cART arm and the TDF-cART arm, but the rate of very preterm birth (<34 weeks) was higher in the TDF-cART arm and the zidovudine monotherapy arm, compared with the AZT-cART arm; this difference just reached the level of statistical significance (p=0.04)(Fowler et al. 2016). The rate of early transmission or death was significantly lower with the ZDV-cART arm, compared with zidovudine monotherapy or the TDF-cART arm.

Largely on the basis of this evidence, a BMJ rapid recommendation clinical practice guideline and meta-analysis recommended that the NRTI-backbone of zidovudine/lamivudine be used preferentially over tenofovir/emtricitabine in pregnant women (Siemieniuk et al. 2017). The PROMISE team responded to this recommendation stating they did not support it because of assumptions made in the meta-analysis, and aspects of the PROMISE trial design which made interpretation of the small differences found difficult (PROMISE Study Team 2017). There is also potentially an interaction between tenofovir and lopinavir/ritonavir that may reduce tenofovir renal clearance and increase intracellular levels, but the pharmacokinetics of tenofovir plus lopinavir/ritonavir in pregnancy have not been studied (PROMISE Study Team 2017).

A secondary analysis of factors associated with adverse pregnancy outcome in the PROMISE trial has just been published – they have reported that both ZDV-cART and TDF-cART ere associated with an elevated risk of pre-term birth <37 weeks' gestation, low birth weight <2500g, and a composite outcome including stillbirth and miscarriage compared with zidovudine monotherapy (Sebikari et al. 2019). The risk of severe outcomes was significantly higher in the TDF-cART arm, but only in relation to the zidovudine monotherapy arm; relative to the TDF-cART arm, the zidovudine monotherapy arm was associated with a significantly lower risk of the

severe outcomes (very preterm birth, very low birthweight), but not the moderate outcomes. The authors postulate that the mechanisms of the effect of PIs on adverse birth outcomes could be related to lower progesterone levels, chronic immune activation, and placental insufficiency; whether there is an independent effect of tenofovir/emtricitabine alone or in combination with lopinavir/ritonavir is still unknown (Sebikari et al. 2019).

Multiple reports of observational cohort data of women taking lopinavir/ritonavir in pregnancy have not found differences between NRTI backbones. Rough et al. looked at 4646 pregnancies in the US and found no difference in risk of adverse pregnancy outcome in women treated with either tenofovir/emtricitabine + lopinavir/ritonavir, zidovudine/lamivudine + lopinavir/ritonavir, or tenofovir/emtricitabine + atazanavir/ritonavir(Rough et al. 2018). An analysis of NSHPC surveillance data of pregnancies 2003-2013 included nearly 5000 pregnancies with lopinavir/ritonavir exposure found similar rates of adverse pregnancy outcomes compared with other populations, and no difference in adverse pregnancy outcome between NRTI backbones (Tookey et al. 2016). A surveillance study in Botswana (with 45% coverage of all births nationwide) examined adverse pregnancy outcome for women treated with multiple PI- and NNRTI-based regimens on ART from conception with differing NRTI backbones, and found a lower rate of adverse pregnancy outcomes in women on a combination of tenofovir/emtricitabine + efavirenz (Zash et al. 2017). A systematic review and meta-analysis of adverse pregnancy outcomes in studies comparing tenofovir disoproxil (TDF) and non-TDF-based ART found no evidence of an increased risk, although the authors commented that further data was required, particularly to assess neonatal mortality and growth/bone effects (Nachega et al. 2017).

The proportion of reported miscarriages rose significantly from 4.8% in 2000-2002 to 8.6% in 2012-2014, this rise was similar in women diagnosed before conception. Median age at conception was significantly higher in reported miscarriages (33 years) than other pregnancy outcomes (30 years). A recent analysis of reported pregnancies in the US Women's Interagency HIV Study, a multicentre prospective cohort study of women with and without HIV, found that risk of miscarriage in all women was associated with drinking alcohol, using marijuana, and cigarette smoking. Age group 25-30 and 30-35 was protective compared with age group <25 years (age >35 did not

meet statistical significance); however, in the analysis restricted to women with HIV, age at conception was not significant (Wall et al. 2019). Miscarriage was not associated with HIV status but was associated with higher viral load in women with HIV (Wall et al. 2019). Most studies in the general population have found a background miscarriage rate of 12% to 15% of recognised pregnancies by 20 weeks' gestation, although studies are hampered by case ascertainment bias (Rossen, Ahrens, and Branum 2018; Ammon Avalos, Galindo, and Li 2012). It is also likely that there is under-reporting of miscarriage to the NSHPC, and that certain subgroups of women (for example women with PHIV) may have better case ascertainment since they may be more closely followed in clinical care. The association between increased miscarriage rate and older age is well established; in an analysis of pregnancy outcomes in Norway 2009-2013, which has a national surveillance registry, women under the age of 20 had a moderately increased risk, risk was lowest aged 27 (9.5%) and then rose linearly after the age of 30 to reach 54% at age 45 and over (Magnus et al. 2019).

The proportion of reported terminations declined over the study period from 5.9 to 1.9%. In reported terminations, women were more likely to have acquired HIV perinatally than in other pregnancy outcomes. The proportion of terminations was significantly higher in women who acquired HIV perinatally (12.4% compared with 3.0% in women with BHIV). 32 women had two terminations reported in the dataset; these women had a lower median age and were more likely to have acquired HIV through injecting drug use or perinatally. A greater proportion of women with a reported termination were treated with the NNRTI efavirenz (10.3% compared with around 7% in other pregnancy outcomes), this reached the level of significance. The proportion of reported congenital abnormality was highest in stillbirths (9%) and terminations (8.5%), compared with 2.8% of live births ($p<0.001$). There was a wide range of reported congenital abnormality in terminated pregnancies. The proportion of terminations affected by congenital abnormality rose with increasing gestation at termination, indicating that the presence of congenital abnormality may have been a deciding factor in the decision to terminate in these pregnancies.

Although it is likely that terminations are underreported to the NSHPC, since HIV clinicians are not always aware that women under their care have opted for termination, the decline in rate of terminations reported is significant and probably

reflects the improvements in PMTCT over the study period, and a growing confidence in women to proceed with wanted pregnancies. There were very significant concerns about the potential teratogenicity of efavirenz, as previously discussed, which have now been dispelled by reassuring data. A meta-analysis of pregnancy outcomes in women taking efavirenz also found an increased termination rate in women on efavirenz, in one of the studies included termination requests were based on verbal advice rather than ultrasound findings (i.e. the foetus was not known to have abnormality) (Ford et al. 2014). In my analysis, only 8.5% of terminations reported overall were due to congenital abnormality, and the proportion of terminations affected by congenital malformation was 0.74% in pregnancies ending at 12 weeks' gestation or less. It may well be that with heightened concern about congenital abnormality, women conceiving on efavirenz opted for termination based on these concerns which turned out to be unfounded. This is important because concerns about teratogenicity of antiretrovirals are still relevant and affect the reproductive choices of women living with HIV.

Since the study end date of my analyses another integrase inhibitor (dolutegravir) has been licensed for the treatment of adults with HIV and is also being used in pregnancy. Its advantages are rapid viral load decay, good tolerability, minimal drug-drug interactions and a high genetic barrier to resistance. It has been rolled out as first line therapy in some low-income countries such as Botswana, which meant women were conceiving on it before any real pregnancy safety data were available. In May 2018 preliminary data from women conceiving on dolutegravir in an observational study in Botswana were released, the researchers found 4 cases of neural tube defects out of 426 women who conceived on dolutegravir; this rate of 0.9% compares to a 0.1% risk of neural tube defects in infants born to women taking other cART. A global alert was put out, and the WHO advised that women of child-bearing age should be prescribed cART with adequate safety data, and dolutegravir could only be considered for women on consistent contraception (WHO 2018). The latest data from the Tsepamo study was presented at the International AIDS Conference in July 2019: there was a rate of neural tube defects of 0.3% (5/1683 births) in women conceiving on dolutegravir up to March 2019. This is still higher than their control group of women conceiving on efavirenz (approximately 0.1%), but significantly lower than the previous estimate (0.94%) and a low absolute risk (R Zash et al. 2019). As a result of this and other data, the WHO has issued new

guidance that dolutegravir should be the preferred first-line third agent for all populations(WHO 2019).

Neural tube defects are a rare congenital abnormality, and incidence is lower in countries with folic acid fortification; it has been estimated that 2000 exposures to dolutegravir at conception would be needed to detect a threefold increased risk (Mofenson 2019). The APR and European Pregnancy and Paediatric HIV Cohort Collaboration (EPPICC) together have published data on pregnancy outcomes in women on dolutegravir at conception, totalling 240 mother-infant pairs and found no increased risk with dolutegravir and there were no neural tube defects, although the number of women exposed was too small to rule out an association (Vannappagari and Thorne 2019).

8.10 How often does vertical transmission of HIV occur in the contemporary UK, and why?

The UK and Ireland has one of the lowest vertical transmission rates in the world, falling from 2.1% in 2000-2001 to 0.46% in 2010-2011, and then falling further to 0.27% in 2012-2014 (Townsend et al. 2014; Peters et al. 2017); this has been attributed largely to earlier initiation of cART during pregnancy, and a higher proportion of women on cART before conception (Townsend et al. 2014). In France, women conceiving on cART had a transmission rate of 0.27% (Mandelbrot et al. 2015). In contrast, surveillance data from Ukraine has shown vertical transmission rate of 5.9% for non-IDU women and 10.8% in IDU women in births 2000-2010 (Thorne, Semenenko, and Malyuta 2012).

However, despite considerable success in preventing vertical infection, there were 108 cases of perinatal HIV in infants born in the UK between 2006 and 2013 (reported by April 2014) (Chapter 7). The mother was undiagnosed at the time of delivery in around 60% of cases. This is a slightly lower proportion to the previous audit of children with perinatal HIV born in England between 2002 and 2005 (NSHPC, Audit Information Analysis Unit, and CHIVA 2007). Women were of a similar age, had similar distribution of region of birth and likely route of HIV acquisition (only 2% were likely infected through injecting drug use) as the cohort of pregnant women living with HIV as a whole (see section 4.2). At least one significant contributing

factor was identified in 91% of cases (98/108); there were 5 cases in which no contributing factor was identified despite adequate information available, and 5 cases in which there was minimal information available. However, Figure 7.7 illustrates that there was also complexity of contributing factors, and more than one contributing factor was identified in 18% of cases in women not diagnosed by delivery.

The number of cases of perinatal HIV reported each year declined over the time period, as seen in Figure 7.6, from 31 children born in 2006 to six born in 2012 and one born in 2013. However, infants born to women who are not diagnosed by delivery are only diagnosed themselves if they become symptomatic of HIV-related disease, or as a result of their mother being diagnosed at some point after pregnancy. This means these children are diagnosed later than children born to women diagnosed before delivery and so will be reported to the study at an older age, so it would be expected that additional infected infants are reported after the study end date. This would be in keeping with the previously demonstrated decline in the MTCT rate in women diagnosed before delivery over a similar time period (Townsend et al. 2014), and suggests that there may also have been a decline in the proportion of pregnant women living with HIV not diagnosed by the time they give birth.

MTCT can occur *in utero*, at the time of delivery (intrapartum) or in the postnatal period through breastfeeding, with approximate risks of transmission in an untreated breastfeeding population of 5-10%, 10-20% and 10-20% respectively(De Cock et al. 2000). In untreated non-breastfeeding women the majority of vertical HIV transmission occurs around the time of delivery (Newell 1998), but the intrapartum transmission rate in diagnosed women in the UK has declined significantly with improvements in treatment and obstetric care, so that between 2007-2011 over half of infected infants born to diagnosed women acquired HIV *in utero* (Townsend et al. 2014). In the audit presented in Chapter 7, over half of the infected infants born to women diagnosed by delivery were known to have been likely infected *in utero*, 17% at the time of delivery, and 20% in the postnatal period. The timing of infant acquisition of infection was unknown in the majority of infants born to women who were not diagnosed by delivery.

The mechanisms of *in utero* transmission are incompletely understood, but risk factors include high maternal viral load, primary HIV infection, delayed ART and

chorioamnionitis (Jourdain et al. 2007; Lehman and Farquhar 2007). The risk of *in utero* transmission in early pregnancy is thought to be low, with risk increasing with gestational age (Newell 1998), and indeed there may be some infants who are not PCR positive within 72 hours of birth who were actually infected *in utero* close to the time of delivery (Kourtis and Bulterys 2010). In 7/26 cases of likely *in utero* infection in the audit, women were diagnosed prior to the pregnancy and in all these women the main contributing factor was lack of engagement with HIV care and/or problems with adhering to ART, therefore being on ART at conception or early in pregnancy with good adherence may have prevented these transmissions. Sixteen of the 26 likely *in utero* transmissions were in women diagnosed during pregnancy, half of these women booked late for antenatal care and therefore HIV diagnosis and initiation of therapy were also delayed.

Risk factors for intrapartum transmission of HIV include high viral load at the time of delivery, ascending genital tract infection, active genital ulcer disease and increasing duration of ruptured membranes in untreated women (although data from the NSHPC shows no increase in MTCT risk for women on cART with duration of ruptured membranes over 4 hours vs. < 4 hours)(Lehman and Farquhar 2007; Kourtis and Bulterys 2010; Peters et al. 2015). Evidence suggests that in order to attain a supressed viral load by delivery, women should start ART by around 20 weeks' gestation, with BHIVA guidelines recommending an earlier start for women who have high viral loads(Read et al. 2012; Gilleece and BHIVA pregnancy guidelines writing group 2019). In half of the 8 likely intrapartum transmissions, there was no main contributing factor identified and women had achieved an undetectable viral load shortly before delivery, although the date of the last viral load was between 3 and 5 weeks prior to delivery. As discussed previously, in the multivariable analysis of factors associated with detectable viral load at delivery presented in Chapter 5, overall 71% of women achieved an undetectable viral load near delivery, and this proportion increased from 40.3% to 86.8% during the study period. PHIV (vs. BHIV) was found to be an independent risk factor for a detectable viral load near delivery, as was younger age at conception, lower CD4 count near conception, not being on ART at conception, and receiving PI-containing ART during pregnancy.

As I outlined in Chapter 1, delivery by planned CS was the first intervention identified that reduced the risk of intrapartum transmission, but in the era of effective cART

and the high proportion of women virally suppressed at delivery many more women can now plan vaginal delivery. In the pregnancy outcomes analysis presented in Chapter 5, the overall proportion of vaginal delivery was 32%, and this rose from 18% to 45% over the study period. In live births where planned mode of delivery was available, 32.6% of women who planned vaginal delivery ended up delivering by emergency CS. In women with singleton pregnancy, undetectable viral load near delivery and no previous reported CS, who delivered at term, three-quarters had planned vaginal delivery. In these women the proportion of vaginal delivery rose from one-fifth to three-fifths over the study period; correspondingly, the emergency CS rate increased from one in 10 to nearly a quarter of live births. In the general population in England, in women with no risk factors for CS (previous CS, multiple pregnancy, placental issues, foetal distress, shoulder dystocia, diabetes, hypertension, eclampsia/pre-eclampsia, preterm delivery), 5% had a CS in 2008, and 29% of these were emergency deliveries; the overall emergency CS rate for all women in that year was 15% of all deliveries. (Bragg et al. 2010).

So, the emergency CS rate in women living with HIV is higher than the national average. As well as indications for emergency CS such as foetal distress, placental abruption and dystocia, it may be that women with ruptured membranes are having emergency CS where the intention of the clinical team is to reduce the risk of perinatal HIV. Although the NSHPC did not collect data on all obstetrical factors which may contribute to delivery by emergency CS over the study period, the study now collects data on the duration of rupture of membranes (ROM). An analysis of deliveries to women on cART reported to the NSHPC 2007-2013 found no increased risk of transmission in women with VL <50 copies/ml near delivery with ROM less than 4 hours versus more than 4 hours, but with the caveat that there were very few data on women with ROM >24 hours (Peters et al. 2015). The majority of women with pre-labour ROM at term spontaneously go into labour within 24 hours, and guidelines for the general population are that delivery can be expedited 24 hours after membrane rupture to reduce the risk of infection (or alternatively women may opt for expectant management(NICE 2014)). However, due to the paucity of data in women with HIV with ROM >24 hours, the latest BHIVA guidelines state that women with VL< 50 copies/ml should have delivery expedited so that they deliver within 24 hours.

It is important to note that in the audit of perinatal HIV (Chapter 7) no significant contributing factor was identified in five cases. These women all commenced ART prior to 22 weeks' gestation and four of them achieved an undetectable viral load prior to delivery, with the remaining woman achieving a viral load of 50-100 copies/ml. Four of the five infants likely acquired HIV during delivery, and the remaining one either at delivery or in the postnatal period (there was no indication of breastfeeding, but the first positive PCR had not been carried out until 10 weeks of age). On the basis of these findings, although we can be very reassuring to women who achieve an undetectable viral load by delivery that the risk of MTCT is very low at around 0.1% (Townsend et al. 2014), clinicians must be wary of stating that the risk is negligible. One of these cases was published as a case report by the centre involved – the mother was on PI-based cART and undetectable at conception, her pregnancy progressed uneventfully apart from a lower respiratory tract infection requiring antibiotics and bronchodilators at the beginning of the third trimester. Her viral load remained undetectable throughout the pregnancy, but she became anaemic and was treated with three intravenous iron infusions at 3 day intervals at 33-34 weeks. The baby was born by planned CS at 39 weeks, was PCR negative at birth, commenced 4 weeks zidovudine PEP, but had a seroconversion illness after cessation of PEP at 6 weeks of age, and was diagnosed with perinatal HIV (Thompson et al. 2014).

Seroconversion during pregnancy and the postnatal period leads to a high risk of vertical infection because of high rates of uncontrolled viral replication (Dinh et al. 2015). In the audit (Chapter 7) women had acquired HIV during pregnancy or the postnatal period after testing negative in nearly a quarter of cases; 2/25 of these women were diagnosed with primary HIV during the pregnancy and it was suspected that one woman had acquired HIV during the pregnancy but she would not consent to be tested; these three infants acquired their HIV likely *in utero* (in the remaining 22 infants, timing of HIV acquisition was unknown). As previously discussed, from the results of the decline survey (Chapter 4) and the perinatal audit (Chapter 7), common reasons women give for declining antenatal HIV testing are low perception of risk, needle phobia and that they have previously tested negative, however the woman who had a recognised high risk of HIV acquisition was counselled extensively for re-testing without success.

More than 90% of women acquiring HIV subsequent to antenatal booking who went on to have an infected infant were undiagnosed by the time of delivery. However, a substantial proportion may not have actually acquired infection by this time. There was evidence from clinical assessment that two women likely acquired their HIV during the postnatal period and their babies were infected through breastfeeding, in the remaining 21 infants timing of infection was unknown. The majority of these infants were breastfed, so infant acquisition of infection could have been at any time prior to the cessation of breastfeeding. MTCT rates are higher in women who acquire HIV during the pregnancy or postnatal period due to high viral loads prior to seroconversion (Drake et al. 2014).

Of the 25 women in the audit who acquired HIV during pregnancy or the postnatal period, 18 were in a sexual relationship with a male partner who was either known to be HIV positive or was subsequently diagnosed with HIV as a result of maternal diagnosis. It is probably a fair assumption that these men acquired their HIV infection first, although of course it is possible women acquired HIV infection from outside their main relationship. Heterosexual men have a higher proportion of undiagnosed HIV infection in the UK compared to heterosexual women and MSM(Public Health England 2014b), and efforts to increase the diagnosis rate of the positive partners of women who test negative at booking would contribute to preventing women acquiring HIV infection during pregnancy or the postnatal period. There have been many potential barriers identified to including men in the PMTCT process: a systematic review of 24 studies mainly in sub-Saharan Africa identified societal perception that antenatal services were a woman's domain, men's beliefs that their female partner's negative status was a proxy for their own, and women's reluctance to include male partners for fear of violence, stigmatization or divorce, as well as health system factors such as long waiting times and antenatal services being male unfriendly among others (Morfaw et al. 2013).

Two pilot studies offering HIV testing to male partners of women attending antenatal services have been conducted to date in high prevalence areas in London. One study conducted in 2008 offered a 'streamlined' HIV testing service to male partners of pregnant women attending antenatal clinic, but found very poor uptake(Noble et al. 2010). The second study promoted and offered STI screening (including HIV) to men attending antenatal ultrasound department with their pregnant partners: 52% of

women were accompanied by a male partner, and of these men 35% accepted STI testing (Dhairyawan et al. 2012). The testing was carried out by a member of GU services situated within the antenatal ultrasound department; no HIV diagnoses were made among the 432 tested men, but 16 were positive for another STI including hepatitis B and C. HIV screening of male partners is likely to be cost-effective in areas with an HIV prevalence of greater than 2 in 1000 (British HIV Assocation, British Association for Sexual Health and HIV, and British Infection Society 2008); further research looking into the feasibility and effective delivery of HIV testing for male partners who attend antenatal services is required.

Clinicians are recommended to take a sexual history from all people diagnosed with HIV at six-monthly intervals including plans for conception, encourage disclosure and contact tracing, and counsel on risk-reduction (Asboe et al. 2012). There were four cases in the audit where the male partner had been diagnosed prior to the woman's diagnosis, in two of these cases he had not disclosed his HIV status (and we can assume had condomless sex since they conceived), and in two cases the woman was aware but continued having condomless sex. It is of vital importance that male partners are involved in the PMTCT process, and this includes those men whose partners are *at risk* of pregnancy (an estimated one in six pregnancies are unplanned in Britain (Wellings et al. 2013)), not just those who are planning to conceive. In addition to the current guidance, clinicians looking after these men should ascertain pregnancy risk of female partners at regular intervals and discuss the need for contraception if not planning a pregnancy *even in the absence of the female partner at the clinic visit*, ensure male patients' understanding of serodiscordance and the risks of acquiring HIV in pregnancy and the postnatal period for mother and child (WHO 2017a; Thomson et al. 2018). In addition, maternity and sexual health services should assess whether a woman is at high risk of HIV acquisition would benefit from PrEP (BHIVA and BASHH Guidelines Group 2019; WHO 2017a)(although this is currently not available for pregnant women under NHS care in England) – PrEP is further discussed in section 8.13.1.

Maternal acquisition of HIV after testing negative during pregnancy was also identified in 20% of cases in the previous audit of perinatal HIV in England (NSHPC, Audit Information Analysis Unit, and CHIVA 2007), and the case for the introduction of third trimester repeat screening for all women was considered by the National

Screening Committee (Marshall and Peckham 2009), but a report commissioned at this time found that repeat third trimester screening for all women who test negative at booking was unlikely to be effective at reducing transmissions since it would not diagnose maternal infection acquired at the end of pregnancy or in the postnatal period [unpublished report, courtesy of Dr Pat Tookey]. A pilot study of repeat screening in the third trimester in a high prevalence antenatal population in London achieved 70% offer and uptake of the second HIV test, but despite testing around 2000 women did not pick up any new HIV infections (B. Williams et al. 2014). In the US, women at high risk of HIV acquisition, including those living in areas with estimated HIV prevalence (>1 per 1000 adult population)(National Institute of Health 2018). In Canada it is recommended that pregnant women who continue to be at risk of HIV acquisition (ongoing risk behaviour, partner who is HIV-positive) are offered repeat testing in pregnancy (Public Health Agency of Canada 2013). There is currently no provision for routine repeat antenatal HIV testing in the national screening programme, however women can request repeat testing at any time should they consider themselves at risk (IDPS Programme 2016). Around 800,000 women give birth in the UK every year (Great Britain and Commission for Healthcare Audit and Inspection 2008; NISRA 2015; ISD Scotland 2015; Welsh Government 2015), and the vast majority of women are HIV negative and do not acquire HIV after their negative test. In addition to this, it is still the case that repeat testing during pregnancy would not prevent vertical infection caused by maternal HIV acquisition in very late pregnancy or the postnatal period. The majority of women who did acquire HIV after testing negative in the audit in Chapter 7 likely acquired their HIV from their positive male partner; offering re-testing to women in high prevalence areas may not impact on these cases since background prevalence does not predict the probability of a positive current partner. Reducing the fraction of undiagnosed HIV in men, identifying male patients who may have pregnant partners or who are trying to conceive and facilitating disclosure, treatment as prevention, and PrEP for women at high risk of acquiring HIV will all contribute to reducing these cases of seroconversion.

All HIV-positive mothers in the UK are strongly recommended to avoid breastfeeding their infants. The cumulative risk of postnatal transmission through breastfeeding can be as high as 20% in the absence of ART(Lehman and Farquhar 2007), but studies in African settings (where replacement feeding is not acceptable, feasible,

affordable, sustainable or safe) with mothers on cART whilst breastfeeding have shown transmission rates of 1-3% (Homsy et al. 2010; Marazzi et al. 2009; Kilewo et al. 2009; Shapiro et al. 2010; Peltier et al. 2009; Chasela et al. 2010; Flynn et al. 2018). In the IMPAACT PROMISE trial, breastfeeding women-infant pairs were randomized at 1 week post-partum to maternal cART or infant nevirapine (the infants included tested negative at the first visit); both arms showed a similar rate of vertical transmission, this was estimated to be 0.8% overall at 12 months postnatal (Flynn et al. 2018). However, the MTCT rate in the UK (where breastfeeding is not recommended) has fallen to 0.5%, and is 0.1% in women who achieve an undetectable viral load before delivery (Townsend et al. 2014), so breastfeeding on cART may pose a small risk of transmission in the postnatal period in addition to this.

There were eight likely postnatal transmissions in the audit, with year of birth ranging 2006 to 2011. None of these women discussed the desire to breastfeed with their clinicians. Prior to publication of the BHIVA and CHIVA position statement on infant feeding in November 2010 (Taylor et al. 2010), HIV-positive women who were thought to be breastfeeding their infants were likely to be referred to child protection services. The position statement changed this guidance: current recommendations are women who choose to breastfeed against medical recommendation should be supported by their clinician to minimise the risk of MTCT by continuing cART with frequent monitoring of viral load to breastfeeding cessation, and there would not be a child protection issue if she complied with this intensive support (Gilleece and BHIVA pregnancy guidelines writing group 2019).

The postnatal transmissions in the audit are covered by the earlier guidelines, however, and these cases highlight that some women were clearly breastfeeding (most likely mixed feeding) their babies but were unable to disclose this to the clinicians looking after them. Infant feeding is a social practice, involving not only the mother and her infant, but also the social context of that interaction(Lazarus, Struthers, and Violari 2013). In cultures where breastfeeding is the norm, women who formula feed their babies face stigma, and may fear the practice will risk disclose of their HIV status(Horvath et al. 1996). Qualitative work on HIV-positive women in the UK showed that the avoidance of breastfeeding came at great personal cost, and women felt that their identity as a 'good mother' was compromised (Tariq, Elford, et al. 2012). Formula feeding is also expensive and requires sterilising equipment, and

financial support for HIV-positive women to formula feed in the UK is patchy and provided (or not) on a local level to women not in receipt of welfare. The risk that women who are advised and agree not to breastfeed will find themselves breastfeeding at some point needs to be recognised by clinicians. In addition, given that the WHO recommends breastfeeding for infants born to women with HIV, women may be receiving 'mixed messages' about the benefits and risks of breastfeeding. Clinicians caring for these women in pregnancy need to have an open and honest discussion about infant feeding choices, and elicit the woman's fears and desires, as well as communicating risk and recommendations. This conversation needs to continue into the postnatal period, and be revisited at regular intervals, in case circumstances change and women face new pressures. In addition, communication between hospital-based and community staff responsible for supporting HIV-positive women in the postnatal period needs to be clear and effective.

So, although the risk of vertical transmission in the UK is now very low, there are still a handful of children born in the UK and Ireland who acquire HIV from their mothers each year. The main factors contributing to these cases are women having difficulties with engagement with clinical services, and difficulty adhering to their ART, women acquiring HIV after having tested in early pregnancy, and women presenting late for antenatal care. The cases where women declined testing or had a processing problems with their test were clustered at the beginning of the study period, so it would appear the changes to the antenatal screening programme already had a positive impact. There were also a very small number of cases in which vertical transmission would not be anticipated, with no obvious contributing factor, so clinicians must be prepared for this eventuality.

8.11 Strengths and limitations of the studies, data and analyses

This thesis uses data from multiple sources (NSHPC surveillance study (Chapters 4, 5 and 6); the survey on women who decline HIV testing in pregnancy (Chapter 4); UK HIV Drug Resistance Database (Chapter 6); and the Audit of perinatal HIV 2006-2014 (Chapter 7)). Therefore, I will discuss strengths and limitations of each data source and analysis (where pertinent).

8.11.1 NSHPC

The NSHPC is a well-established prospective surveillance study with a very high (>90%) response rate from respondents (Townsend 2009). Notifications of pregnancies in women living with HIV are sought through the obstetric scheme, and children born to women diagnosed with HIV are notified through the paediatric scheme; these two parallel data collection systems ensure the high case ascertainment rate. All maternity units in the UK and Ireland are surveyed and incomplete notifications are actively followed up by NSHPC staff members, providing a near-complete picture of management and outcomes of pregnancies in women living with HIV. The study is anonymous and does not require individual consent, which adds to the completeness of the data. Data collection for the study dates back to 1989, therefore long-term trends in 'real world' management of HIV in pregnancy and outcomes can be analysed. Data items of interest evolve over time as management changes and new evidence for PMTCT emerges, therefore the study is responsive, and additions and modifications are made to data collection forms when required.

Due to the very large number of health professionals that report to the study and the need to maintain high response rates, the data items collected are limited to those that are considered of utmost interest and relevance. This does mean that some potential confounders are not collected and thus cannot be adjusted for. Because of the way the NHS (and ROI health system) work, paediatric notes are usually separate from maternity notes, which are separate from maternal hospital records and GP records. Since data often comes from a single obstetric and/or paediatric respondent involved the woman's clinic care, the respondent may not have access to all of a woman or child's health care records, which may lead to undetected data quality

issues, or missing data. My approach to missing data was described in Chapter 3, comments on specific analyses are below.

The NSHPC does not fit into the standard definition of a cohort study (Bhopal 2008), since it only collects data on women and their children at specific time-points in their lives (i.e. during and shortly after a pregnancy), and because it is non-consented, women are not 'enrolled'. This means that data on health status, drug resistance, ART, adherence and engagement before, in between, and after pregnancy is not captured by the study.

8.11.2 Survey on the management of women who decline antenatal HIV testing

The specific methods of the survey on women who decline antenatal HIV testing are described in section 4.5.1. Conducting a national survey with the ability to estimate response rate is challenging (a denominator of units surveyed is required). Purposive sampling was used (i.e. individuals were selected because they met specific criteria): the survey was sent out to all CHIVA members (via their email distribution list) and all NSHPC obstetric respondents. Therefore because of the national coverage of the NSHPC the sampling frame was in fact all maternity units in the UK and Ireland. Due to data protection considerations CHIVA were unable to share their email distribution list with me, but because of the established working of the NSHPC I was able to match up responses to the maternity units in the network of NSHPC respondents to estimate a response rate.

The questions included in the survey were designed to be pragmatic, and as much as possible limited to information that would be recorded in some format at the unit (i.e. a written local policy). The draft questions were piloted with two NSHPC respondents to ensure face and content validity.

The response rate was 43%, which is much lower than the recognised desirable response rate of 60-70% for external validity (Burns et al. 2008). However, the survey did capture responses from a range of maternity units in terms of 'size' (number of deliveries per year) and geographical location. Since the aim of the survey was to investigate variation in management of women who decline antenatal HIV testing across the UK and Ireland, I think the responses captured by the survey are valid in demonstrating this variation across the country and examples of good practice,

however, given the low response rate generalisability is limited. Strategies that have been shown to improve response rates in written and internet-based surveys are reminders and incentives, and it is also recommended to advertise the upcoming survey prior to the response period (Burns et al. 2008). I was able to advertise the upcoming survey in CHIVA and NSHPC communications, and was able to actively chase incomplete responses, and sent out several reminders during the response period. However, with hindsight, extending the response period of three weeks may have increased the response rate.

The survey responses may have been subject to recall bias since the responses relied on a knowledge of the institution's local policy (and therefore the focus was the presence and content of a written policy, to minimise recall bias). The finding that knowledge of whether their unit recorded the number of women who declined antenatal HIV testing was strongly associated with the clinical speciality of the respondent also suggests potential interrater reliability issues (midwives were much less likely to answer 'I don't know' compared with paediatricians and genitourinary medicine specialists).

8.11.3 Analysis of pregnancy incidence and outcomes in women with PHIV

The specific methods for this analysis are described in 5.3.1. In summary, national pregnancy incidence rates in women with PHIV were estimated and a group of age-matched women with BHIV with a similar age distribution to women with PHIV with a reported pregnancy was constructed. Multivariable logistic regression analyses were used to identify risk factors associated with detectable viral load at delivery and adverse pregnancy outcome.

Because of the national surveillance design of the NSHPC, which has collected information on the pregnancies and children born to women living with HIV for more than 25 years, it was possible to estimate a national pregnancy incidence rate for this group of women for the first time. However, as previously noted, the case ascertainment for miscarriages and terminations is likely to be lower than that for live births, and therefore these pregnancy incidence rates are minimum estimates, and median age at conception at first pregnancy could be lower than my estimate. The estimates in these analyses were based on national surveillance data, and therefore highly generalisable to similar high-income settings.

In order to ensure the validity of the comparison between women with BHIV and PHIV, a very strict definition of PHIV was used to ensure the reliability of this risk factor within the population studied. This was possible because the women with PHIV had been reported to the NSHPC as children, ensuring high completeness of age of diagnosis and route of acquisition. The comparison group of women were selected at random from the dataset as a whole, but with an age (at first conception) distribution that was as similar as possible to the women with PHIV to minimise confounding. However, there were very few women with BHIV reported to the study with very young age at first conception, so the groups were not exactly matched. Ideally, the BHIV comparison group would also have been matched to the PHIV group by other demographic factors such as county of birth, but low numbers of age-matched BHIV women precluded this.

In addition to the likely difference in case ascertainment by outcome of pregnancy, it is also possible that case ascertainment was different between the two comparison groups, particularly for outcomes other than live birth, since women with PHIV may be followed more closely in a clinical setting than women with BHIV. Because the sample size was limited by the number of women who met my criteria of PHIV, the analysis of risk factors associated with adverse pregnancy outcome may well have been limited by lack of power, since the outcome had low prevalence. As discussed previously, there are maternal risk factors for adverse pregnancy outcomes such as smoking, other substance use, hypertension, body mass index, prior treatment history and adherence, that the NSHPC does not routinely collect and which therefore could not be accounted for.

The comparison group of women with BHIV was age-matched to reduce confounding, since age at conception is strongly associated with detectable viral load at delivery and pregnancy outcomes such as miscarriage and stillbirth as previously discussed, and therefore would be a very strong confounder. Overall, the median age of women with BHIV in the whole NSHPC dataset was much higher than women with PHIV. However, using a matched comparison group rather than using all women with BHIV reduced the statistical power to detect significant differences and it has been argued that matching in epidemiological studies may be unnecessary (Faresjö and Faresjö 2010). In addition, the small number of women in the PHIV

group contributed to lack of power in some analyses of rare outcomes (such as congenital abnormality).

8.11.4 Analyses of the matched NSHPC UKHDRD dataset

As far as I am aware, the analyses presented in 6.3 are the first analyses of HIV drug resistance testing in pregnant women and the first estimate of prevalence and risk factors for TDR in women diagnosed with HIV during pregnancy in a national surveillance study. All three studies used to create the matched dataset are national surveillance studies in England and Wales, with long-established prospective data collection and successfully established matching algorithms.

The specific methods of these analyses are described in Section 6.3.1. The main limitation specific to this set of analyses is that of missing data. The process of matching the women in the NSHPC dataset led to a successful match in the SOPHID dataset in 87% of women. In 2012-2013, the matching between UKHDRD and SOPHID led to around 80% of resistance tests in the repository successfully matched to a SOPHID record, with around 50% of all patients in SOPHID linked to at least one resistance test, and 45-55% of SOPHID patients who were newly diagnosed linked to a resistance test [personal communications from Anna Tostevin (UKHDRD) and Cuong Chau (PHE)]. In my analysis, 49% of women in the NSHPC dataset reported from England and Wales were matched to at least one resistance test, and in women diagnosed during pregnancy 10-50% per calendar year of diagnosis were matched to a resistance test and categorised as 'naive to ART' on that test (Table 6.8).

As previously discussed, resistance testing was recommended for all people newly diagnosed with HIV since 2005 (Gazzard 2005), therefore it would be expected that the majority of women diagnosed after this point would have had a baseline resistance test, although no estimates of coverage have been published. In addition, it was recommended that women have resistance test if there was evidence of viral failure. In my analysis, women were less likely to be matched to at least one resistance test if they were diagnosed 1996-2005 (vs. 2006 onwards), if they were aged over 37 years at conception, if they only had one pregnancy reported, if they were born in Africa (vs. UK/Ireland), if they had been reported from England but outside of London, and if their first reported pregnancy had been before 2005. The missing data makes it difficult to interpret these findings which are likely to be due to

a combination of data quality affecting the matching process as well as lack of resistance testing in these women. The wide confidence intervals in the multivariable analysis of factors associated with TDR indicate that this model is limited by the small number of women included and the rarity of the outcome.

8.11.5 The audit of perinatal HIV in children born in the UK and Ireland since 2006

As previously noted, since the NSHPC is a long-established study, we[63] were able to utilise the existing relationships between the study and its paediatric and obstetric respondents in order to carry out the enhanced data collection for the audit. The reporting of infants infected with HIV was initially made via the BPSU 'orange card' surveillance system, which is a national scheme with good reporting rates and therefore enables a near 'complete' picture of perinatal HIV in infants born in the UK (Verity and Preece 2002), with the caveats discussed earlier around the delay in diagnosis and reporting of infants born to undiagnosed women.

The established protocols of the study meant that we could actively chase delayed responses and request that clinicians without personal knowledge of a case retrieve notes and participate in data collection interviews. Collecting detailed data by telephone interview was very secure in terms of information governance, and also meant that although this was mostly a quantitative exercise, we could capture the 'narrative' of a case by adjusting the flow of the interview if needed. My clinical experience as a physician managing HIV-positive women in pregnancy allowed me to re-design the interview questionnaires so that the order and flow of the questions would make sense to a clinical respondent. It also allowed me to train HP (a non-clinician) to carry out interviews initially under my supervision and then independently. I could review completed responses and query data items that did not seem to make clinical or practical sense, and we could go back to the respondent for clarification if needed.

There are of course limitations to the study methodology. The enhanced data collection was retrospective, and subject to recall bias from the respondents. In

[63] HP and I

addition, it was often difficult to obtain notes in cases from the beginning of the study period, especially the handheld antenatal notes where screening information is recorded. Recall bias is likely to have affected the estimates of additional complicating issues during pregnancy: this information is often not well documented, and in some cases was just a recollection of the respondent. This means that they are very much minimum estimates, and that the true prevalence of these complicating issues may well be higher.

The questionnaires were complex, and the process of retrieving archived notes and setting up and participating in interviews was time-consuming for busy clinicians. Some centres did not respond to the request to participate or stated that they did not have the resources to participate – 95% of paediatric respondents contacted agreed to participate, 86% of obstetric respondents, and 79% of HIV clinicians. This meant that in 21 cases there was significant missing information, and in five of these we were unable to ascribe a main contributing factor. Four out of five of these cases were in 2006-8, and one was in 2009-10, highlighting that it was more challenging to obtain detailed information in cases from the beginning of the study period. The enhanced surveillance was only conducted for infected infants, precluding analysis of the associations or predictors of perinatal transmission. The analysis method of assigning each case a main contributing factor enabled common themes between cases to be explored, but this may have resulted in some loss of complexity. Similarly, the data were coded and analysed quantitatively rather than qualitatively, so the descriptions of cases were simplified, and detail reduced.

The audit methodology is now embedded into the main NSHPC study, and this enhanced surveillance will be conducted prospectively for each case of perinatal HIV reported to the NSHPC. This should improve the data quality and minimise the problems with missing data, irretrievable notes and recall bias. It should also improve participation rates since respondents will be contacted much sooner after the case is reported.

8.12 Conclusions

The epidemiology of women living with HIV who get pregnant has changed considerably over the time period of my analysis – women are now more likely to conceive on cART, are older, and more likely to have had sequential pregnancies than

at the beginning of the dataset. We are seeing a higher proportion of women from Western Africa and eastern Europe with reported pregnancies, and an increasing number of pregnancies are being reported from outside of London. The examination of these changes in the population will help plan clinical services and help understand the needs of pregnant women living with HIV in the UK.

I have identified a wide variation in practice within antenatal screening services with regards women who decline HIV screening in pregnancy, and I have identified that since 2006, a large proportion of children who acquired HIV vertically were born to women who declined antenatal screening. I have also identified that adherence and engagement issues, acquisition of HIV during pregnancy and the postnatal period, and unsupported breastfeeding have also contributed to vertical transmission in the UK.

My comparison of pregnancy outcomes in women with PHIV and BHIV has demonstrated that PHIV is an independent risk factor for detectable viral load near delivery, a finding that has since been replicated; other risk factors identified were lower CD4 count near conception and being prescribed PI-based cART. Older age at conception and being on cART at conception were protective.

My analysis of TDR in women diagnosed during pregnancy showed a reassuringly low overall prevalence of 5%, but with a possible increase towards the end of the dataset that requires ongoing surveillance. This finding contributes to the evidence needed to recommend first- line ART for women diagnosed during pregnancy.

8.13 Future work

8.13.1 How can we prevent HIV infection in pregnant women?

As previously discussed, HIV acquisition during pregnancy and breastfeeding leads to high risk of vertical transmission, and there is evidence that women may be more susceptible to HIV acquisition at this time, for both biological and behavioural reasons (WHO 2017a). Preventing HIV infection in pregnant and breastfeeding women is one of the central tenets of PMTCT, and early diagnosis of newly acquired HIV of is utmost importance for both mother and baby during this time. Prevention can now include the diagnosis and treatment (for prevention) of male partners and pre-exposure prophylaxis (PrEP) for women at ongoing risk; early identification of newly acquired infection may require repeat testing in pregnancy and the postnatal period either on a population level in areas of high prevalence or in women identified as being high risk. Innovative prevention strategies such as long-term injectable PrEP, intra-vaginal rings, vaccines and monoclonal antibody infusions are also being trialled, but safety concerns have so far precluded the inclusion of pregnant women in early-stage clinical trials. Once innovative strategies are established as effective and safe in non-pregnant women, safety data during pregnancy or in women trying to conceive will be of utmost importance.

The PopART trial in Zambia and South Africa randomised communities to universal treatment with a community intervention provided by specially trained community health workers, ART according to local guidelines plus the community intervention, or standard government-delivered care according to local guidelines only. The communities receiving the community intervention (annual household visits including HIV testing, linkage to ART treatment and PMTCT, screening for TB and STIs, and condom provision) had an HIV incidence that was 30% lower than the communities receiving standard government care (Hayes et al. 2019). As discussed in Chapter 1, young women in high incidence areas are disproportionately affected by HIV, so future trials could focus on whether community intervention can reduce HIV acquisition in this group.

The trials of PrEP in women have had very mixed results. Five randomized trials of oral PrEP included women, and three of these reported outcomes in subgroups of women, and two further trials included only women (VOICE and Fem-PrEP). Partners-PrEP was performed in East Africa in serodiscordant heterosexual couples

(tenofovir/emtricitabine or only tenofovir) and showed a relative risk reduction of 0.30 in the PrEP arm, with 77-80% reported adherence. TDF2-Botswana and Bangkok-TDF showed non-significant trends towards reduced risk with 81% and 66% reported adherence respectively; VOICE and Fem-PrEP reported no reduction in risk (with 29% and 24% reported adherence respectively)(Hanscom et al. 2016). A meta-analysis of these five trials showed high predicted effectiveness with moderate and high levels of adherence (>50% and >75% respectively)(Hanscom et al. 2016). Another large meta-analysis examining oral PrEP concluded that it was effective for all populations at risk of HIV (Fonner et al. 2016) and led to the WHO strongly recommending oral PrEP for any person at high risk of HIV acquisition as part of a combination of HIV prevention approaches. Oral tenofovir disoproxil-containing PrEP is considered safe in pregnancy and breastfeeding and so the benefits outweigh any potential risks to women and their babies. However, ongoing active surveillance of PrEP in pregnancy and breastfeeding women is needed as countries roll this out (WHO 2017a).

Scotland funded PrEP for all at risk in 2017, and pilot PrEP studies in Wales and N. Ireland have uncapped place numbers. In England, after NHS England failed to commission PrEP for routine clinical care, it set up the IMPACT Trial, which is designed to study PrEP administration in real-world settings with a capped number of places (NHS England 2019). Although places for MSM filled rapidly, the trial has had done poorly recruiting women, heterosexual men and transgender people, and there have been calls for the trial to improve its reach in these underserved groups (The Lancet HIV 2019). The results from the audit of perinatal HIV (Chapter 7) show the importance of preventing new HIV diagnoses in women who tested negative at the start of pregnancy (in a country of overall low prevalence where population-level interventions may not be cost effective). This means identifying those at high risk of HIV infection, either because of risk behaviour, risk group or having a partner with undiagnosed or untreated infections. As previously discussed, two small pilot studies looking at increasing diagnosis rates in male partners were not successful and this is an important area for ongoing real-world research.

8.13.2 How safe is ART in pregnancy?

The dolutegravir and neural tube defects issue raised by the preliminary unscheduled analysis of surveillance data from the Tsepamo study in Botswana in 2018 and subsequent interim guidance from the WHO and other regulatory bodies illustrates the important evidence gaps for safety of ART in pregnancy, particularly the issue of safety at conception and in very early pregnancy when the embryo is forming, and congenital abnormalities may develop.

The interim guidance in some countries which restricted dolutegravir to women past reproductive age was seen by many as inequitable – dolutegravir is highly effective, has a high genetic barrier to resistance and a low rate of adverse events, and therefore pre-2018 was rolled-out as first line therapy in many LIC (Vitoria et al. 2018). The background prevalence of neural tube defects varies by country and folate fortification policies, so data from HIC is not necessarily generalisable to pregnant women with HIV in LIC, where the majority live. Many of the existing pregnancy cohorts in high-income countries and the Antiretroviral Pregnancy Registry which can examine pharmacovigilance issues are underpowered to detect rare outcomes, it is only large-scale surveillance such as the Tsepamo study that can provide enough data to answer some of these pharmacovigilance questions.

As I discussed in Chapter 2 and Section 8.7, there is strong evidence from randomised control trials and observational studies that that cART plays a role in the risk of preterm birth in women living with HIV. Preterm birth is a complex syndrome where early delivery is the final common outcome of several distinct disease processes, and phenotypes can be classified as spontaneous (e.g. spontaneous ROM) or provider-initiated (e.g. emergency CS for the treatment of pre-eclampsia)(J. T. Price et al. 2019). Mechanisms for the role of ART in increasing the likelihood of preterm birth, the importance of timing of initiation and class of ART need to be further delineated in carefully designed studies that are able to differentiate phenotypes. Better understanding of these mechanisms will aid the effort to develop interventions to reduce the risk of pre-term birth (Price et al. 2019). As well as better understanding of the mechanisms that drive pre-term birth in women on ART, we need comparisons of ART regimens to delineate the safest combinations for pregnant women.

I have only touched upon the body of research examining the long-term effects of *in utero* exposure to ART of HEU children, but this remains an extremely important area

of research. As well as growth outcomes, infectious disease morbidity and neurocognitive outcomes, of particular relevance to the findings presented in this thesis is whether ART exposure *in utero* will have any effect on the fertility of either women living with PHIV or HEU.

More pregnancy safety data on dolutegravir and other established and emerging treatments are required, and there is a growing realisation that this is essential to achieve gender parity in effective HIV treatment (Rebecca Zash et al. 2019). A comprehensive approach to responding to drug safety signals has been proposed, which includes: highlighting the need for clear principles in evaluating and communicating risks and benefits; the need for earlier availability of preclinical reproductive toxicity data (with the caveat that animal models do not necessarily concur with teratogenicity in humans, as discussed in Chapter 2); the inclusion of pregnant women in clinical trials so that pregnancy risks can be examined with intensive safety monitoring; improved post-marketing surveillance and the funding of expanded sentinel-site surveillance studies like the Tsepamo study in LIC; improved counselling of women of reproductive age on the risks and benefits of ART in pregnancy; involvement of the community in policy making; and flexibility of the guideline-writing process to allow for rapid revision in the light of new evidence (Mofenson et al. 2019). Implementation of this multi-pronged approach should ensure that drug safety signals emerge earlier, are studied more comprehensively, and that women have high quality information on outcomes with which to make their treatment decisions.

8.13.3 How important will HIV drug resistance be in pregnant women?

There has been a rapid scale-up in access to ART in LMIC in the last decade (WHO 2014b). Globally, pre-treatment HIV drug resistance is rising, and is predicted to continue to rise as a result of an increase in the number of people acquiring HIV from people on ART with an unsuppressed viral load, or not on ART but previously treated (WHO 2017b). By 2017, of the 11 countries reporting nationally representative survey data, six (Argentina, Guatemala, Namibia, Nicaragua, Uganda, and Zimbabwe) had prevalence estimates of TDR to NNRTIs exceeding 10%, and two greater than 15% (Haile-Selassie et al. 2017). A recent systematic review of TDR in children living in SSA found alarming rates, with a pooled prevalence of >40% in children < 18 months

of age; children exposed to PMTCT (ART during pregnancy, breastfeeding or as infant PEP) were more likely to have TDR, but the rate of TDR in PMTCT-unexposed children rose from 0% in 2004 to 27% in 2013 (Boerma et al. 2017). This rise in TDR is one of the reasons that dolutegravir is now recommended by the WHO as first-line therapy for all adults and adolescents initiating ART, with efavirenz as an alternative only in countries with a NNRTI TDR rate of <10% (WHO 2019).

Genotypic antiretroviral drug resistance testing is not widely available for routine clinical care in LMIC, and viral load testing was only available in 7 out of 40 LMIC monitored by the WHO in 2017 (Bertagnolio 2019), meaning that treatment failure is often detected late in these settings, and second-line therapy may not be optimised as resistance sequences are not available. In a systematic review of cohorts and trial data across Europe, SSA, Latin and North America and Asia, over half of patients had tenofovir resistance, and of those with tenofovir resistance, 83% also had resistance to emtricitabine and lamivudine (Gregson et al. 2016). The increasing availability of dolutegravir in LMIC is not a panacea - although the results of the EARNEST trial and other studies set up to evaluate alternatives for second line treatment in resource-limited setting, suggest that NRTIs retain high levels of efficacy despite the predictions of failure from genotypic resistance tests (Hill and Venter 2018), a secondary analysis of the DAWNING study comparing dolutegravir with ritonavir-boosted lopinavir in patients with virological failure to first-line NNRTI-based ART showed a reduced efficacy of 76% for patients switched to dolutegravir but maintained on NRTI drugs used in first-line ART, compared with 87% for those who were also switched to newer NRTIs according to WHO recommendation (Aboud et al. 2018). This suggests the continuing importance of NRTI optimisation.

The rising prevalence of TDR and high prevalence of resistance in people failing first-line NNRTI therapy has implications for pregnant women globally. Women not on treatment at conception (those diagnosed before and during pregnancy) have a need for rapid viral load suppression to reduce the risk of vertical transmission as well as for their own health outcomes, therefore surveillance of both pre-treatment and accumulated resistance in pregnant women will be important going forward. As well as making their own treatment more challenging, resistant virus may also be passed on the children of women not on suppressive therapy. Although rates of TDR in the UK have reduced overall, the possible rise in TDR I detected in recent years in women

diagnosed in pregnancy and the continued predicted rise in pre-treatment resistance globally mean this is an important area of continuing surveillance. Further research into the optimisation of ART regimens in pregnant women with resistance is also needed.

8.13.4 Women with PHIV: an emerging population

Despite the huge successes in the scale-up of ART for pregnant women and the drop in vertical transmission rates, in 2018 there were still over 400 estimated new HIV infections in children *per day* world-wide (UNAIDS 2019). As well as women born in the 1980s -2000s who are now of reproductive age, there is a generation of girls behind them who have vastly improved life expectancy and who will require lifelong ART. Growing up with perinatal HIV has effects on neurocognitive development, growth, kidney function, pulmonary function, bone health, metabolic health, pubertal onset, mental health as well as adverse effects of ART, adherence issues and accumulated resistance (Flynn and Abrams 2019). The studying of risks and long-term outcomes in observational cohorts is essential as the population ages. Given that these women will have the earliest start on ART in life, and the longest duration of treatment, it is essential that they are included in trials of innovative treatments and regimens.

Women with PHIV of reproductive age are now conceiving and having their own children; I have demonstrated that women with PHIV in the UK are less likely to have a suppressed viral load at delivery, and these findings have now been replicated. Questions remain regarding pregnancy outcomes in women with PHIV – are women with PHIV more at risk of adverse pregnancy outcomes such as stillbirth, preterm birth and congenital abnormality? Does their increased risk of detectable viral load at delivery translate to a higher risk of further vertical infection? What effect will in utero HIV exposure, and in utero ART exposure have on their HEU and (hopefully few) vertically-infected offspring? The NSHPC will continue to collect data on outcomes in these women when they are pregnant, and the infection status of their children, but currently there is no mechanism for the long-term follow up of HEU children. A separate consented prospective cohort study of women living with PHIV and their children would be required.

8.13.5 What are the evidence gaps in the guidelines, and can women with an undetectable VL make the same choices as women who are HIV-negative?

As stated in the introduction to the current BHIVA HIV and pregnancy guidelines 'Despite the few RCTs for the use of ART in pregnancy or obstetric intervention, clinical practice still continues to evolve. This is largely informed by observational data, theoretical considerations and expert opinion' (Gilleece and BHIVA pregnancy guidelines writing group 2019). Pregnant women or women planning a pregnancy are most often excluded from RCTs of ART as previously discussed, so evidence on the efficacy, safety and pharmacokinetics of antiretroviral drugs in pregnancy is limited. As well as the need for these data on existing drugs, there is also a need for pregnancy data for drugs in development, innovative delivery systems such as long-acting injectables and novel regimens using fewer than three active drugs. We need to know whether to avoid certain drugs in women with risk factors for preterm birth, or whether to avoid initiating them at a particular gestation in women not already on ART at conception. The body of research into safety, absorption and pharmacokinetics of antiretrovirals in neonates and young children for both PEP and treatment is also limited. The current guidelines have reduced the duration of PEP in neonates born to women who are 'very low risk' to two weeks, but there is currently little evidence on whether these children benefit from those two weeks of PEP. Very few antiretroviral drugs have been established as safe and efficacious in very preterm babies.

In terms of obstetric management of women, there are many unanswered questions. In the pre-cART era, longer duration of ruptured membranes, invasive procedures during labour (such as foetal blood sampling and foetal scalp electrodes) and ascending infection (chorioamnionitis) were associated with increased risk of vertical infection. As discussed earlier, there is now reassuring observational data from the NSHPC that women with SROM at term and an undetectable load with duration ROM > 4 hours but < 24 hours do not have an increased risk of transmission compared with women with ROM <4 hours, but there is very scant data on women with duration ROM >24 hours (Peters et al. 2015). According to NICE guidance, HIV-negative women at term with no signs of infection can choose induction after 24 hours of ROM or expectant management with regular monitoring, however women with HIV are advised to deliver within 24 hours of SROM, which may mean on

induction or CS depending on the situation. Further data on transmission risk for women with an undetectable viral load and SROM > 24 hours is needed before women with HIV can be given the same choice.

Other interventions in which there is little or no outcome data in women living with HIV are external cephalic version (ECV) for women with breech presentation, non-invasive prenatal testing for foetal aneuploidies to avoid invasive diagnostic tests, and amniocentesis, and outcomes for vaginal birth after CS (VBAC), which are recommended for women with VL<50 copies/ml but these recommendations are mostly based on theoretical considerations and expert opinion. In addition, there are now recommendations in the UK on place of birth and water birth. Women living with HIV are recommended to plan their delivery in a place where immediate access to paediatrics is possible, because of the time-sensitive need to administer PEP. This means that women living with HIV are not currently able to plan delivery in a stand-alone midwifery unit, or have their baby at home. The latest guidelines state that women with an undetectable viral load may choose a water birth, but there is no safety data on complication rate or transmission risk in women living with HIV.

Another area in which women living with HIV are currently not able to make the same choices in is infant feeding. In the UK, women without HIV are encouraged to breastfeed as part of The Healthy Child Programme which promotes early years health, and it is recommended that all maternity services in the UK become accredited to the Baby Friendly Initiative which promotes breastfeeding to improve chid health outcomes (UNICEF 2019). As discussed earlier, the BHIVA recommendation for women living with HIV is that they formula feed their babies, but women who have a consistently undetectable viral load and good adherence who choose to breastfeed will now be supported to do so (Gilleece and BHIVA pregnancy guidelines writing group 2019). Other recommendations in low-prevalence HIC are similar (National Institute of Health 2018; European Aids Clinical Society 2017), but the WHO recommends breastfeeding for all infants born to women with or without HIV because of the very strong evidence on reduced morbidity and all-cause mortality in breastfed infants in LMIC (World Health Organization and UNICEF 2016). As previously discussed, the disparities in these recommendations and strong cultural breastfeeding norms may lead women living with HIV in the UK to

experience very negative feelings when deciding not to breastfeed (Tariq, Elford, Tookey, et al. 2016).

With the emergence of clinical trial data demonstrating a very low risk of vertical infection through breastfeeding in mothers on cART in LMIC (Flynn et al. 2018), and the fact that these data from LMIC may overestimate the risk of transmission in HIC where the majority of women start cART before conception, and the remainder initiate earlier in pregnancy (Waitt et al. 2018), the debate on whether women with HIV in HIC should breastfeed continues. Many gaps in the evidence have been identified: the risk of postnatal vertical transmission in women on suppressive cART prior to conception; evaluation of cell-free and cell-associated HIV in breastmilk in women on established and suppressive cART; examining the role of latently-infected resting T-cells, and their subsequent activation and secretion of HIV antigen in breastmilk, and the role other cells at risk of HIV infection within breast tissues; the effect of mastitis on virus and transmission; the effects on HEU infants of ART exposure through breastmilk; the risk of resistance in virus transmitted through breastfeeding; the risks of non-optimal adherence in the postnatal period; and establishing the optimal frequency and method of HIV viral load monitoring in breastfeeding women and infants (Waitt et al. 2018)

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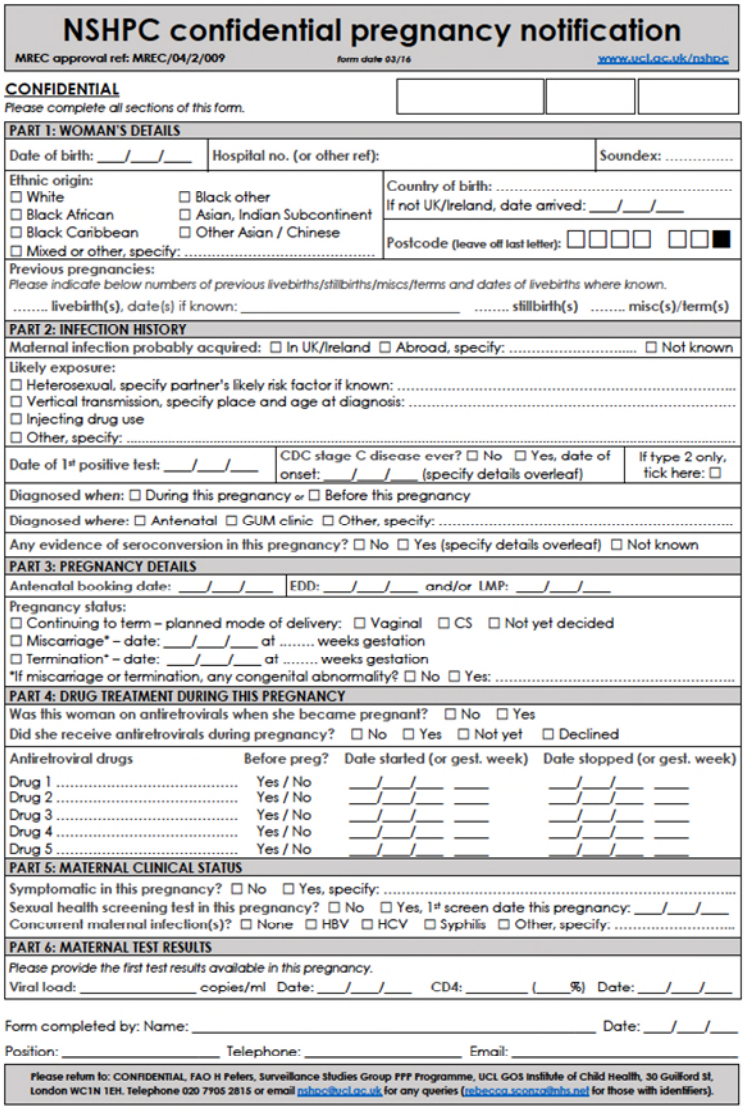
10 Appendices

10.1 NSHPC Reporting Forms (2016 editions)

10.1.1 Obstetric notification form



NSHPC confidential pregnancy notification

MREC approval ref: MREC/04/2/009 — form date 03/16 — www.ucl.ac.uk/nshpc

CONFIDENTIAL
Please complete all sections of this form.

PART 1: WOMAN'S DETAILS

Date of birth: ___/___/___ | Hospital no. (or other ref): | Soundex: .....

Ethnic origin:
☐ White ☐ Black other
☐ Black African ☐ Asian, Indian Subcontinent
☐ Black Caribbean ☐ Other Asian / Chinese
☐ Mixed or other, specify: .....

Country of birth: .....
If not UK/Ireland, date arrived: ___/___/___

Postcode (leave off last letter): ☐☐☐☐ ☐☐■

Previous pregnancies:
Please indicate below numbers of previous livebirths/stillbirths/miscs/terms and dates of livebirths where known.
..... livebirth(s), date(s) if known: _____ ..... stillbirth(s) ..... misc(s)/term(s)

PART 2: INFECTION HISTORY

Maternal infection probably acquired: ☐ In UK/Ireland ☐ Abroad, specify: ..... ☐ Not known

Likely exposure:
☐ Heterosexual, specify partner's likely risk factor if known: .....
☐ Vertical transmission, specify place and age at diagnosis: .....
☐ Injecting drug use
☐ Other, specify: .....

Date of 1st positive test: ___/___/___ | CDC stage C disease ever? ☐ No ☐ Yes, date of onset: ___/___/___ (specify details overleaf) | If type 2 only, tick here: ☐

Diagnosed when: ☐ During this pregnancy or ☐ Before this pregnancy

Diagnosed where: ☐ Antenatal ☐ GUM clinic ☐ Other, specify: .....

Any evidence of seroconversion in this pregnancy? ☐ No ☐ Yes (specify details overleaf) ☐ Not known

PART 3: PREGNANCY DETAILS

Antenatal booking date: ___/___/___ | EDD: ___/___/___ and/or LMP: ___/___/___

Pregnancy status:
☐ Continuing to term – planned mode of delivery: ☐ Vaginal ☐ CS ☐ Not yet decided
☐ Miscarriage* – date: ___/___/___ at ..... weeks gestation
☐ Termination* – date: ___/___/___ at ..... weeks gestation
*If miscarriage or termination, any congenital abnormality? ☐ No ☐ Yes: .....

PART 4: DRUG TREATMENT DURING THIS PREGNANCY

Was this woman on antiretrovirals when she became pregnant? ☐ No ☐ Yes
Did she receive antiretrovirals during pregnancy? ☐ No ☐ Yes ☐ Not yet ☐ Declined

Antiretroviral drugs	Before preg?	Date started (or gest. week)	Date stopped (or gest. week)
Drug 1	Yes / No	___/___/___ ____	___/___/___ ____
Drug 2	Yes / No	___/___/___ ____	___/___/___ ____
Drug 3	Yes / No	___/___/___ ____	___/___/___ ____
Drug 4	Yes / No	___/___/___ ____	___/___/___ ____
Drug 5	Yes / No	___/___/___ ____	___/___/___ ____

PART 5: MATERNAL CLINICAL STATUS

Symptomatic in this pregnancy? ☐ No ☐ Yes, specify: .....
Sexual health screening test in this pregnancy? ☐ No ☐ Yes, 1st screen date this pregnancy: ___/___/___
Concurrent maternal infection(s)? ☐ None ☐ HBV ☐ HCV ☐ Syphilis ☐ Other, specify: .....

PART 6: MATERNAL TEST RESULTS

Please provide the first test results available in this pregnancy.
Viral load: _____ copies/ml Date: ___/___/___ CD4: _____ (____%) Date: ___/___/___

Form completed by: Name: _____ Date: ___/___/___
Position: _____ Telephone: _____ Email: _____

Please return to: CONFIDENTIAL, FAO H Peters, Surveillance Studies Group PPP Programme, UCL GOS Institute of Child Health, 30 Guilford St, London WC1N 1EH. Telephone 020 7905 2815 or email nshpc@ucl.ac.uk for any queries (rebecca.sconza@nhs.net for those with identifiers).

10.1.2 Obstetric Outcome Form

NSHPC outcome of notified pregnancy

MREC approval ref: MREC/04/2/009 form date 04/16 www.ucl.ac.uk/nshpc

CONFIDENTIAL

Please complete all sections of this form.

Your ref: EDD: Hospital of delivery:

PART 1: CHILD INFORMATION

☐ Livebirth or ☐ Stillbirth
If twins*, tick here: ☐
*Please give details of second twin overleaf

Date of birth: ___/___/___ ☐ Male or ☐ Female

Gest ..... wks Birthweight ..... kg Paediatrician .....

Hospital no. .....
NHS no. .....

Congenital abnormalities? ☐ No ☐ Yes: .....
Other perinatal problems? ☐ No ☐ Yes: .....
Planned mode of infant feeding?
☐ Planning to formula feed only ☐ Planning to breastfeed*
*please give details overleaf

PART 2: PREGNANCY AND DELIVERY DETAILS

Postcode at delivery (leave off last letter): ☐☐☐☐ ☐☐■

Pregnancy complications:
☐ None
☐ Pre-eclampsia*
☐ Gestational diabetes
☐ Other: .....
*please give details overleaf

Invasive procedures in pregnancy:
☐ None ☐ Amniocentesis
☐ CVS ☐ Cordocentesis
If yes, date of procedure: ___/___/___
Viral load at time of procedure:
..... copies/ml Date: ___/___/___

Mode of delivery:
☐ 1. Elective CS to prevent mother-to-child transmission
☐ 2. Planned vaginal delivery
☐ 3. Elective CS for any other reason
☐ 4. Unplanned vaginal delivery
☐ 5. Emergency CS
Reason for delivery by 3, 4, or 5: .....
Planned mode of delivery: ☐ Vaginal ☐ Elective CS ☐ Not known

Invasive procedures at delivery (tick all that apply):
☐ None
☐ Ventouse
☐ Forceps, type: .....
☐ Scalp monitor
☐ FBS
Symptomatic at delivery?
☐ No ☐ Yes: .....
If died, date of death: ___/___/___

Rupture of membranes? ☐ No / Only at delivery ☐ Yes, duration: ..... hours ..... minutes

PART 3: DRUG TREATMENT DURING PREGNANCY

Antepartum treatment? ☐ No ☐ Yes
If yes, reason for treatment: ☐ Prevention of mother-to-child transmission *only*
☐ Maternal health *and* prevention of mother-to-child transmission

Antiretroviral drugs:	Date started (or gest. week)	Date stopped (or gest. week)
Drug 1	___/___/___ ____	___/___/___ ____
Drug 2	___/___/___ ____	___/___/___ ____
Drug 3	___/___/___ ____	___/___/___ ____
Drug 4	___/___/___ ____	___/___/___ ____
Drug 5	___/___/___ ____	___/___/___ ____

Any other significant drugs (e.g. PCP prophylaxis, TB treatment, methadone, illicit drugs):
Drug 1 ..... Date: ___/___/___ Drug 2 ..... Date: ___/___/___
Additional treatment intra-partum:
☐ None ☐ IV AZT ☐ Single dose nevirapine ☐ Other oral antiretrovirals: .....
Post-partum for infant:
☐ None ☐ Oral AZT ☐ IV AZT ☐ Triple, specify: .....

PART 4: MATERNAL TEST RESULTS NEAR DELIVERY

Viral load: _____ copies/ml Date: ___/___/___ CD4: _____ (____%) Date: ___/___/___
Resistance testing done this pregnancy? ☐ No ☐ Yes ☐ Not known Clade of virus if known: _____

Form completed by: Name: _____ Date: ___/___/___
Position: _____ Telephone: _____ Email: _____

Please return to: CONFIDENTIAL, FAO H Peters, Surveillance Studies Group PPP Programme, UCL Institute of Child Health, 30 Guilford St, London WC1N 1EH. Telephone 020 7905 2815 or email nshpc@ucl.ac.uk for queries (rebecca.sconza@nhs.net for those with identifiers).

Please complete parts 5 and 6 in the case of a twin pregnancy.

PART 5: CHILD INFORMATION FOR SECOND TWIN

☐ Livebirth or ☐ Stillbirth

Date of birth: ___/___/___ ☐ Male or ☐ Female

Birthweight ..... kg Paediatrician .....

Hospital no. .....
NHS no. .....

Congenital abnormalities? ☐ No ☐ Yes: .....
Other perinatal problems? ☐ No ☐ Yes: .....
Planned mode of infant feeding?
☐ Planning to formula feed only ☐ Planning to breastfeed*
*please give details overleaf

PART 6: TWIN CHORIONICITY AND AMNIONICITY

☐ Monochorionic	☐ Monoamniotic
☐ Dichorionic	☐ Diamniotic
☐ Chorionicity not known	☐ Amnionicity not known

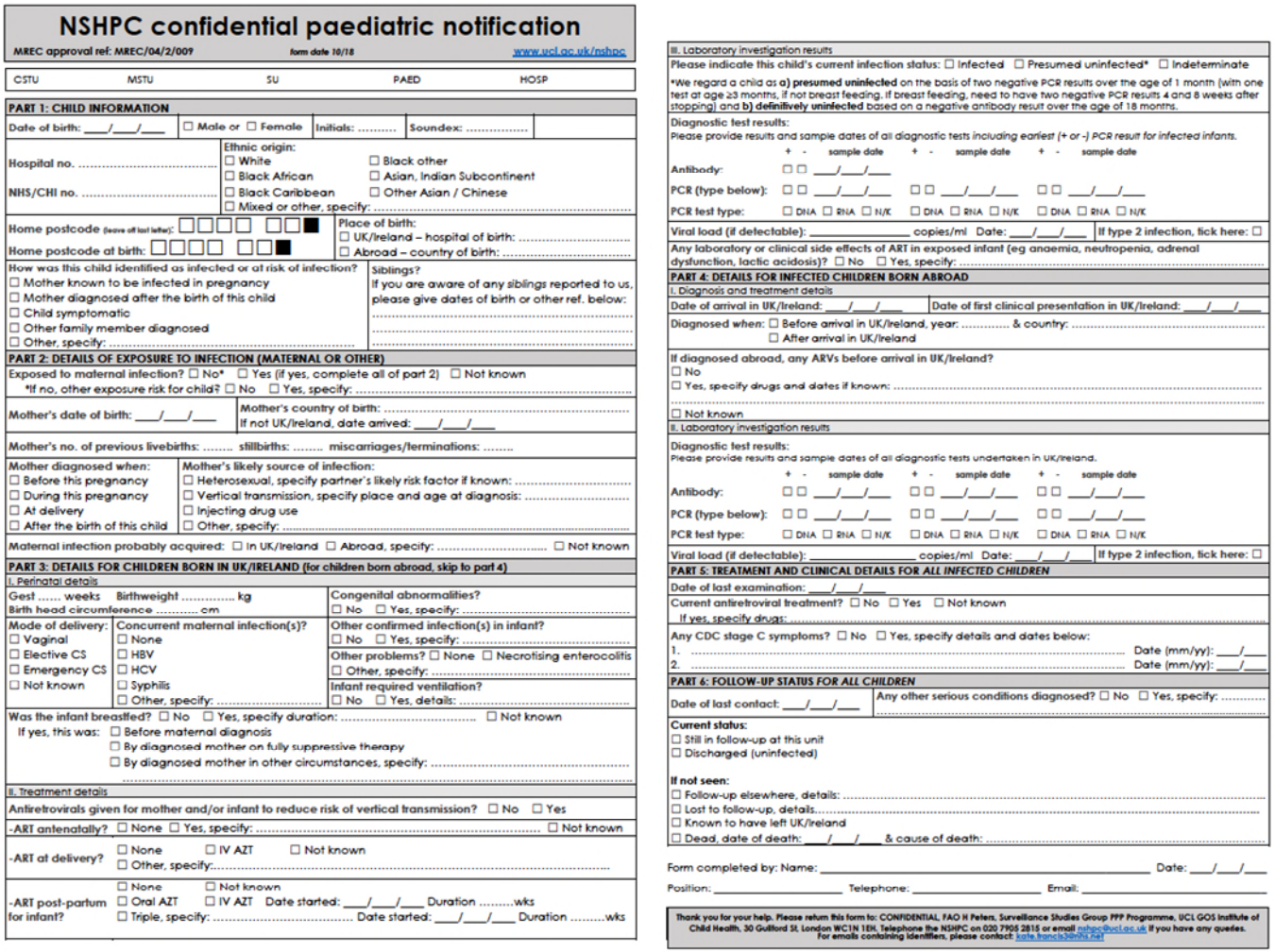
Please complete the following question *if this mother is planning to breastfeed.*

If this mother is planning to breastfeed, is this being managed in line with current BHIVA Guidelines*? Please give any relevant details below:

*Please be aware that breastfeeding is not recommended in the current BHIVA Guidelines. See BHIVA Guidelines 8.4 Infant Feeding: http://www.bhiva.org/documents/Guidelines/Pregnancy/2012/hiv1030_6.pdf.

Thank you for completing this form. If you have any further details to share about this pregnancy, please write them in the space below:

10.1.3 Paediatric Notification Form



NSHPC confidential paediatric notification

MREC approval ref: MREC/04/2/009 form date 10/18 www.ucl.ac.uk/nshpc

CSTU MSTU SU PAED HOSP

PART 1: CHILD INFORMATION

Date of birth: ___/___/___ ☐ Male or ☐ Female Initials: ..... Soundex: .....

Hospital no. .....
NHS/CHI no. .....

Ethnic origin:
☐ White ☐ Black other
☐ Black African ☐ Asian, Indian Subcontinent
☐ Black Caribbean ☐ Other Asian / Chinese
☐ Mixed or other, specify: .....

Home postcode (leave off last letter): ☐☐☐☐ ☐☐☐
Home postcode at birth: ☐☐☐☐ ☐☐☐

Place of birth:
☐ UK/Ireland – hospital of birth: .....
☐ Abroad – country of birth: .....

How was this child identified as infected or at risk of infection?
☐ Mother known to be infected in pregnancy
☐ Mother diagnosed after the birth of this child
☐ Child symptomatic
☐ Other family member diagnosed
☐ Other, specify: .....

Siblings?
If you are aware of any siblings reported to us, please give dates of birth or other ref. below:
.....
.....
.....

PART 2: DETAILS OF EXPOSURE TO INFECTION (MATERNAL OR OTHER)

Exposed to maternal infection? ☐ No* ☐ Yes (if yes, complete all of part 2) ☐ Not known
*If no, other exposure risk for child? ☐ No ☐ Yes, specify: .....

Mother's date of birth: ___/___/___
Mother's country of birth: .....
If not UK/Ireland, date arrived: ___/___/___

Mother's no. of previous livebirths: ..... stillbirths: ..... miscarriages/terminations: .....

Mother diagnosed when:
☐ Before this pregnancy
☐ During this pregnancy
☐ At delivery
☐ After the birth of this child

Mother's likely source of infection:
☐ Heterosexual, specify partner's likely risk factor if known: .....
☐ Vertical transmission, specify place and age at diagnosis: .....
☐ Injecting drug use
☐ Other, specify: .....

Maternal infection probably acquired: ☐ In UK/Ireland ☐ Abroad, specify: ..... ☐ Not known

PART 3: DETAILS FOR CHILDREN BORN IN UK/IRELAND (for children born abroad, skip to part 4)

I. Perinatal details

Gest ..... weeks Birthweight ..... kg
Birth head circumference ..... cm

Congenital abnormalities?
☐ No ☐ Yes, specify: .....

Mode of delivery:
☐ Vaginal
☐ Elective CS
☐ Emergency CS
☐ Not known

Concurrent maternal infection(s)?
☐ None
☐ HBV
☐ HCV
☐ Syphilis
☐ Other, specify: .....

Other confirmed infection(s) in infant?
☐ No ☐ Yes, specify: .....

Other problems? ☐ None ☐ Necrotising enterocolitis
☐ Other, specify: .....

Infant required ventilation?
☐ No ☐ Yes, details: .....

Was the infant breastfed? ☐ No ☐ Yes, specify duration: ..... ☐ Not known
If yes, this was: ☐ Before maternal diagnosis
☐ By diagnosed mother on fully suppressive therapy
☐ By diagnosed mother in other circumstances, specify: .....
.....

II. Treatment details

Antiretrovirals given for mother and/or infant to reduce risk of vertical transmission? ☐ No ☐ Yes

-ART antenatally? ☐ None ☐ Yes, specify: ..... ☐ Not known

-ART at delivery? ☐ None ☐ IV AZT ☐ Not known
☐ Other, specify: .....

-ART post-partum for infant? ☐ None ☐ Not known
☐ Oral AZT ☐ IV AZT Date started: ___/___/___ Duration .....wks
☐ Triple, specify: ..... Date started: ___/___/___ Duration .....wks

III. Laboratory investigation results

Please indicate this child's current infection status: ☐ Infected ☐ Presumed uninfected* ☐ Indeterminate

*We regard a child as **a) presumed uninfected** on the basis of two negative PCR results over the age of 1 month (with one test at age ≥3 months, if not breast feeding. If breast feeding, need to have two negative PCR results 4 and 8 weeks after stopping) and **b) definitively uninfected** based on a negative antibody result over the age of 18 months.

Diagnostic test results:
Please provide results and sample dates of all diagnostic tests including earliest (+ or -) PCR result for infected infants.

	+ -	sample date	+ -	sample date	+ -	sample date
Antibody:	☐☐	___/___/___				
PCR (type below):	☐☐	___/___/___	☐☐	___/___/___	☐☐	___/___/___
PCR test type:	☐ DNA ☐ RNA ☐ N/K		☐ DNA ☐ RNA ☐ N/K		☐ DNA ☐ RNA ☐ N/K	

Viral load (if detectable): _____ copies/ml Date: ___/___/___ If type 2 infection, tick here: ☐

Any laboratory or clinical side effects of ART in exposed infant (eg anaemia, neutropenia, adrenal dysfunction, lactic acidosis)? ☐ No ☐ Yes, specify: .....

PART 4: DETAILS FOR INFECTED CHILDREN BORN ABROAD

I. Diagnosis and treatment details

Date of arrival in UK/Ireland: ___/___/___
Date of first clinical presentation in UK/Ireland: ___/___/___

Diagnosed when: ☐ Before arrival in UK/Ireland, year: ..... & country: .....
☐ After arrival in UK/Ireland

If diagnosed abroad, any ARVs before arrival in UK/Ireland?
☐ No
☐ Yes, specify drugs and dates if known: .....
.....
☐ Not known

II. Laboratory investigation results

Diagnostic test results:
Please provide results and sample dates of all diagnostic tests undertaken in UK/Ireland.

	+ -	sample date	+ -	sample date	+ -	sample date
Antibody:	☐☐	___/___/___	☐☐	___/___/___	☐☐	___/___/___
PCR (type below):	☐☐	___/___/___	☐☐	___/___/___	☐☐	___/___/___
PCR test type:	☐ DNA ☐ RNA ☐ N/K		☐ DNA ☐ RNA ☐ N/K		☐ DNA ☐ RNA ☐ N/K	

Viral load (if detectable): _____ copies/ml Date: ___/___/___ If type 2 infection, tick here: ☐

PART 5: TREATMENT AND CLINICAL DETAILS FOR *ALL INFECTED CHILDREN*

Date of last examination: ___/___/___

Current antiretroviral treatment? ☐ No ☐ Yes ☐ Not known
If yes, specify drugs: .....

Any CDC stage C symptoms? ☐ No ☐ Yes, specify details and dates below:
1. ..... Date (mm/yy): ___/___
2. ..... Date (mm/yy): ___/___

PART 6: FOLLOW-UP STATUS *FOR ALL CHILDREN*

Date of last contact: ___/___/___
Any other serious conditions diagnosed? ☐ No ☐ Yes, specify: .....

Current status:
☐ Still in follow-up at this unit
☐ Discharged (uninfected)

If not seen:
☐ Follow-up elsewhere, details: .....
☐ Lost to follow-up, details: .....
☐ Known to have left UK/Ireland
☐ Dead, date of death: ___/___/___ & cause of death: .....

Form completed by: Name: _____ Date: ___/___/___
Position: _____ Telephone: _____ Email: _____

Thank you for your help. Please return this form to: CONFIDENTIAL, FAO H Peters, Surveillance Studies Group PPP Programme, UCL GOS Institute of Child Health, 30 Guilford St, London WC1N 1EH. Telephone the NSHPC on 020 7905 2815 or email nshpc@ucl.ac.uk if you have any queries. For emails containing identifiers, please contact: kate.francis3@nhs.net

10.1.4 Paediatric Outcome Form

NSHPC follow-up to establish infection status

MREC approval ref: MREC/04/2/009 *form date 10/18* www.ucl.ac.uk/nshpc

CSTU MSTU HOSP

PART 1: CHILD INFORMATION

Date of birth: ___/___/___ | **Sex:** ..... | Initials: ..... | Soundex: .....

NHS/CHI no. .....

PART 2: INFECTION STATUS AND LABORATORY INVESTIGATIONS

Has an antibody test been carried out at ≥18months?

☐ No, details ..... ☐ Yes, please provide below:

	+ -	sample date
Antibody (≥18months):	☐ ☐	___/___/___

If 18 month antibody not done please provide any PCR results (with dates) undertaken since ___/___/___.

	+ -	sample date	+ -	sample date	+ -	sample date
PCR (type below):	☐ ☐	___/___/___	☐ ☐	___/___/___	☐ ☐	___/___/___
PCR test type:	☐ DNA ☐ RNA ☐ N/K		☐ DNA ☐ RNA ☐ N/K		☐ DNA ☐ RNA ☐ N/K	

*We regard a child as **a) presumed uninfected** on the basis of two negative PCR results over the age of 1 month (with one test at age ≥3 months, if not breast feeding. If breast feeding, need to have two negative PCR results 4 and 8 weeks after stopping) and **b) definitively uninfected** based on a negative antibody result over the age of 18 months.

Part 3: Infant feeding

Was the infant breastfed? ☐ No ☐ Yes, specify duration: ..... ☐ Not known

If yes, this was: ☐ Before maternal diagnosis
☐ By diagnosed mother on fully suppressive therapy
☐ By diagnosed mother in other circumstances, specify: .....

PART 4: ART EXPOSURE SIDE EFFECTS

Any laboratory or clinical side effects of ART in exposed infant (e.g. anaemia, neutropenia, adrenal dysfunction, lactic acidosis)? Update if any additional side effects since

☐ No ☐ Yes, specify: .....

PART 5: FOLLOW-UP STATUS

Date of last contact: ___/___/___ | **Any other serious conditions diagnosed?** ☐ No ☐ Yes, specify: .....

Current status:
☐ Still in follow-up at this unit
☐ Discharged (uninfected)

If not seen:
☐ Follow-up elsewhere, details: .....
☐ Lost to follow-up, details.....
☐ Known to have left UK/Ireland
☐ Dead, date of death: ___/___/___ & cause of death: .....

Thank you for completing this form. If you have any further details, please write them on the back of this form.

Form completed by: Name: _____ Date:___/___/___

Position: _____ Telephone: _____ Email: _____

Thank you for your help. Please return this form to: CONFIDENTIAL, FAO H Peters, Surveillance Studies Group PPP Programme, UCL Institute of Child Health, 30 Guilford St, London WC1N 1EH. Telephone the NSHPC on 020 7905 2815 or email kate.francis@ninis.net if you have any queries.

10.2 Data collection form for survey on the management of women who decline antenatal HIV testing

CHIVA survey: maternity unit policy on women who decline antenatal HIV testing

Some UK cases of perinatal HIV infection have occurred in children born to women who declined HIV testing in pregnancy. We are therefore seeking to gather evidence about the number of women who decline HIV testing in pregnancy, and to find out how clinicians are dealing with these cases.

This survey has been developed by the National Study of HIV in Pregnancy and Childhood (NSHPC), in collaboration with CHIVA.

If you have any queries, please contact nshpc@ucl.ac.uk

Please complete the survey below.

Thank you!

1 Which trust or unit do you work in?

- ☐ Aintree University Hospital NHS Foundation Trust
- ☐ Airedale NHS Foundation Trust
- ☐ Alder Hey Children's NHS Foundation Trust
- ☐ Ashford and St Peter's Hospitals NHS Foundation Trust

1.1 If your unit is not listed above, please state name here: _____

2 Which of these descriptions best describes your role at [unit_name]?

- ☐ Doctor - consultant
- ☐ Doctor - non-consultant
- ☐ Nurse consultant
- ☐ Clinical nurse specialist
- ☐ Nurse
- ☐ Screening coordinator
- ☐ Specialist midwife
- ☐ Non-specialist midwife
- ☐ Administrator
- ☐ Other

3 Which of these options best describes your clinical specialty at [unit_name]?

- ☐ Paediatrics
- ☐ Obstetrics
- ☐ Midwifery
- ☐ Genitourinary medicine
- ☐ Infectious disease
- ☐ Not applicable
- ☐ Other

4 Approximately how many women delivered at your unit in 2013? (leave blank if you don't know) _____

5 Approximately how many pregnant women attending your maternity unit have declined all routine antenatal screening since the start of 2013? _____

6 Since the start of 2013, approximately how many pregnant women attending your maternity unit have declined routine antenatal screening for bloodborne infections (e.g. HIV, hepatitis B, syphilis) but accepted other screening tests? _____

7 Since the start of 2013, approximately how many pregnant women attending your maternity unit have declined routine antenatal HIV testing alone (and accepted other screening tests)? _____

8 Does your maternity unit have a local policy on the management of pregnant women who decline routine antenatal HIV testing?

- ☐ Yes
- ☐ No
- ☐ I don't know

8.1a According to this policy, what happens when a pregnant woman declines the initial offer of a routine antenatal HIV test? (Please check all that apply)

- ☐ She is re-offered an HIV test by a non-specialist midwife at her next appointment
- ☐ She is counselled and re-offered test by a specialist midwife
- ☐ She is counselled and re-offered a test by an obstetrician or genitourinary medicine specialist or other consultant
- ☐ Other

Please state _____

8.1b What do you think usually happens at your unit when a pregnant woman declines the initial offer of a routine antenatal HIV test? (Please check all that apply)

- ☐ She is re-offered an HIV test at her next appointment by a non-specialist midwife
- ☐ She is counselled and re-offered test by a specialist midwife
- ☐ She is counselled and re-offered a test by an obstetrician/GU specialist or other consultant
- ☐ Other
- ☐ I don't know

Please state _____

8.2a According to this policy, how does your unit manage women who decline HIV testing in pregnancy despite being re-offered the test? (Please check all that apply)

- ☐ Intensive input from the midwifery team
- ☐ Support sought from GUM, paediatrics and other members of the MDT
- ☐ GP or health visitor informed
- ☐ Not pursued further
- ☐ Other

Please state _____

8.2b How does your unit usually manage women who decline antenatal HIV testing despite the test being re-offered? (Please check all that apply)

- ☐ Intensive input from the midwifery team
- ☐ Support sought from GUM and other members of the MDT
- ☐ GP or health visitor informed
- ☐ Not pursued further
- ☐ I don't know
- ☐ Other

Please state _____

9 Is the reason women give for declining an antenatal HIV test normally recorded at your maternity unit?

- ☐ Yes
- ☐ No
- ☐ I don't know

9.1 Where is this normally recorded? (check all that apply)

- ☐ Handheld maternity notes
- ☐ Confidential hospital notes
- ☐ Electronic patient record
- ☐ Other

9.2a According to this documentation, what are the reasons most often given by women for declining an antenatal HIV test?

- ☐ Doesn't think she is at risk of having HIV
- ☐ Doesn't want to know whether she has HIV
- ☐ Is worried the result will not be confidential
- ☐ Needle-phobia
- ☐ She has had a prior negative test
- ☐ No reason given
- ☐ Other

Please state: _____

9.2b What do you think are the reasons most often given by women for declining an antenatal HIV test? (Check all that apply)

- ☐ Doesn't think she is at risk of having HIV
- ☐ Doesn't want to know whether she has HIV
- ☐ Is worried the result will not be confidential
- ☐ Needle-phobia
- ☐ She has had a prior negative test
- ☐ No reason given
- ☐ Other

Please state: _____

10 Does your unit have a policy for the situation where a woman attends in labour without a documented HIV test result?

- ☐ Yes
- ☐ No
- ☐ I don't know

10.1a What is your unit's policy if a woman attends in labour without a documented HIV test result?

- ☐ She is offered a test immediately
- ☐ She is offered a test before she leaves hospital
- ☐ She would not be routinely offered a test
- ☐ Other

Please state: _____

10.1b What do you think usually happens in your unit if a woman attends in labour without a documented HIV test result?

- ☐ She is offered a test immediately
- ☐ She is offered a test before she leaves hospital
- ☐ She would not be routinely offered a test
- ☐ Other

Please state: _____

10.2b If she would be offered a test, who would do this? (check all that apply)

- ☐ Non-specialist nurse or midwife
- ☐ Specialist nurse or midwife
- ☐ Antenatal screening coordinator
- ☐ Obstetrician
- ☐ Health advisor
- ☐ GU medicine doctor
- ☐ Other

Please state: _____

11 If a woman is tested for HIV during labour, what test would be used? (check all that apply)

- ☐ Rapid 'point-of-care' test (available 24 hours a day)
- ☐ Rapid 'point-of-care' test (if during office hours)
- ☐ Urgent serum HIV antibody test (regular blood test)
- ☐ I don't know
- ☐ Other

Please state: _____

11.1 How quickly will your lab give you the result of an urgent serum HIV antibody test?

- ☐ Within 1 hour
- ☐ Within 2 hours
- ☐ Within 4 hours
- ☐ Within 8 hours
- ☐ Within 24 hours
- ☐ Within 48 hours
- ☐ Over 48 hours
- ☐ I don't know

12 Does your maternity unit have a policy on testing the baby of a woman who has declined antenatal HIV testing?

- ☐ Yes
- ☐ No
- ☐ I don't know

12.1a What is this policy? (check all that apply)

- ☐ We would actively recommend the baby is routinely tested for HIV and carry out the test prior to discharge
- ☐ We would actively recommend the baby is routinely tested for HIV and arrange for testing in the community
- ☐ We would consider recommending an HIV test for the baby depending on a risk assessment
- ☐ We would inform the mother's GP that she had declined HIV testing in pregnancy
- ☐ We would not offer routine HIV testing for the baby
- ☐ Other
- ☐ I don't know

Please state: _____

12.1b What do you think usually happens in your unit when a woman declines antenatal HIV testing? (check all that apply)

- ☐ We would actively recommend the baby is routinely tested for HIV and carry out the test prior to discharge
- ☐ We would actively recommend the baby is routinely tested for HIV and arrange for testing in the community
- ☐ We would consider recommending an HIV test for the baby depending on a risk assessment
- ☐ We would inform the mother's GP that she had declined HIV testing in pregnancy
- ☐ We would not offer routine HIV testing for the baby
- ☐ Other
- ☐ I don't know

Please state: _____

12.2 What would be the factors taken into consideration in this risk assessment? (check all that apply)

- ☐ Mother born in country of high HIV prevalence
- ☐ Mother's ethnicity if born in the UK
- ☐ Partner born in country of high HIV prevalence
- ☐ Partner's ethnicity if born in the UK
- ☐ Maternal history of injecting drug use
- ☐ Partner history of injecting drug use
- ☐ Mother's sexual history
- ☐ Other
- ☐ I don't know

Please state: _____

12.3a According to this policy, what would happen if the mother declined HIV testing in pregnancy and the parents declined HIV testing for their baby despite your recommendation? (check all that apply)

- ☐ We would not pursue this any further
- ☐ We would discuss the case with a specialist paediatric HIV centre
- ☐ We would inform the baby's GP
- ☐ We would discuss this case with the child protection team or similar
- ☐ We would consider going to court
- ☐ We would always go to court in this situation
- ☐ Other
- ☐ I don't know

12.2 Would any of these factors make it more likely that you would take this case further? (check all that apply)

- ☐ Mother born in country of high HIV prevalence
- ☐ Mother's ethnicity if born in the UK
- ☐ Partner born in country of high HIV prevalence
- ☐ Partner's ethnicity if born in the UK
- ☐ Maternal history of injecting drug use
- ☐ Partner history of injecting drug use
- ☐ Mother's sexual history
- ☐ Other
- ☐ I don't know
- ☐ None of the above

Please state _____

12.3b What usually happens if the mother has declined HIV testing in pregnancy, and the parents decline HIV testing for their baby despite your recommendation? (check all that apply)

- ☐ We would not pursue this any further
- ☐ We would inform the baby's GP
- ☐ We would discuss the case with a specialist paediatric HIV unit
- ☐ We would recommend paediatric follow up for the baby
- ☐ We would discuss this case with the child protection team or similar
- ☐ We would consider going to court
- ☐ We would always go to court in this situation
- ☐ Other
- ☐ I don't know

12.2 Would any of these factors influence your decision to take this case further? (check all that apply)

- ☐ Mother born in country of high HIV prevalence
- ☐ Mother's ethnicity if born in the UK
- ☐ Partner born in country of high HIV prevalence
- ☐ Partner's ethnicity if born in the UK
- ☐ Maternal history of injecting drug use
- ☐ Partner history of injecting drug use
- ☐ Mother's sexual history
- ☐ Other
- ☐ I don't know
- ☐ None of these factors would influence my decision

Please state _____

13 Does your unit have an easily accessible legal team who are able to offer advice on the best course of action if necessary?

- ☐ Yes
- ☐ No
- ☐ I don't know

14 Since the start of 2013, how many cases are you aware of in which a woman delivered at your unit having declined all HIV testing?

- ☐ None
- ☐ 1-2
- ☐ 3-5
- ☐ 6-10
- ☐ 11-20
- ☐ 21-50
- ☐ More than 50

14.1 How were these cases resolved? (check all that apply)

- ☐ No further action was taken
- ☐ The parents did not consent for the child to be tested despite intervention by the MDT
- ☐ Parent(s) consented to child being tested after discussion with clinicians and MDT
- ☐ Parent(s) consented to child being tested after notification that case would be discussed with child protection team
- ☐ Parent(s) consented to child being tested after notification that the case would be brought to court if necessary
- ☐ A court order enabled the child to be tested
- ☐ Other
- ☐ I don't know

Please state: _____

10.3 Standard operating procedures for matching databases in the analysis of resistance testing in women with reported pregnancies

10.3.1 Matching SOPHID to UKHDRD

Data sent to HPA from MRC

The following identifiers for all samples in the UK HIV Drug Resistance Database are provided to the HPA for matching:

- Labsampid (unique, anonymous sample identifier)
- Clinic Number
- Up to 5 alternative clinic numbers, where the patient is known to have changed clinics – Available for UK CHIC patients in HIVrdb only
- Centre/Hospital ID
- Up to 5 alternative centre IDs as above– Available for UK CHIC patients in HIVrdb only
- Date of Birth
- Soundex
- Sample Date (date of blood sample)
- Report Date (date the resistance test was performed)

Matching at HPA

The UK HIV DRD data is matched separately to the Survey of Prevalent HIV Infections Diagnosed (SOPHID) data and HIV and AIDS new diagnoses and deaths (HANDD) using the same method for matching. Seven different categories (matching criteria) are used:

Matches:

- ClinicID and Site (Hospital/Centre)
- ClinicID and Region
- Soundex DoB Region
- Site and modifying the clinicID
- CID DoB SiteNK
- Any further matches that are feasible

Modify after reviewing the SOPHID-HANDD-Linking Table

The first three categories are considered the 'stronger' matches while the next four are considered to be more 'fuzzy'. In the last matching exercise ClinicID and Region accounted for the majority of the matches for both data sets (74%HANDD, 86% SOPHID).

<u>Matched dataset sent to MRC</u>

The matched dataset (csv txt file) is then sent to the MRC contains the following fields

- Earliest event date (date of diagnosis)
- Sex (HANDD and SOHID separately)
- Infection route (HANDD and SOHID separately)
- Country of infection
- Country of birth

- Ethnicity (HANDD and SOPHID separately)
- Last negative date
- Year of arrival
- Recent (RITA test result)
- Avidity score
- Detuned Score
- CD4 count
- CD4 date
- AIDS date
- Age Diagnosis
- Region of diagnosis
- Treatment status rank
- ARV Start Date

Treatment status

The HPA has two ways of calculating the ARV start date for SOPHID records:

1) ARVSTART – this field is collected as part of SOPHID and the definition is "Date this patient first ever started a course of anti-retroviral therapy – may not necessarily be at your clinic/site (please estimate if exact date not known)". As SOPHID collects this field every year the ARVSTART field used in the analysis is the earliest date recorded for an individual. This is because this field is not validated across time and collecting this data every survey allows for multiple dates to be recorded for the same person so the earliest

ARVSTART date is the best indicator as to when a patient first started treatment. When only a year is reported, this is coded to "01/07/YYYY".

2) FirstARVdate – there is a field in SOPHID called ARV which collects information on the level of anti-retroviral therapy prescribed by the clinic/site when last seen. The HPA can therefore use this field to work out which survey period a person started treatment. The HPA allocates to this field the date last seen in the survey period when a person is first recorded as being on treatment. In reality the person would have likely started treatment before the date they were last seen so FirstARVdate is recorded as "01/07/YYYY" (The HPA may change the name of this field to "FirstSurveyARV" as FirstARVdate can be misleading).

The HPA creates and provides a ranking variable indicating how the ARV start date provided by the HPA is calculated.

Rank	Description
0) Naive	No ARVSTART and no FirstARVdate so assumed Naïve.
1) Consistent	Consistent ARVSTART and FirstARVdate i.e. in the same survey period. The earlier of the 2 dates was provided and in almost all cases this was ARVSTART.
2) No start only first	ARV but no ARVSTART therefore FirstARVdate.
3) Start but no first	ARVSTART but no FirstARVdate therefore ARVSTART.
4) Start before survey	ARVSTART before survey period therefore ARVSTART.

5) Inconsistent	Inconsistent ARVSTART and FirstARVdate i.e. in different survey periods. Either date can be before the other, therefore provided with the earlier of the 2 dates.

To initially check the accuracy of the ARV start dates provided by the HPA these are compared to those of the UK CHIC patients. Resistance samples are categorised using the ART start dates provided and compared to the % susceptibility levels of the samples.

Resistance data sent back to HPA

A dataset of the HPA SOPHID and HANDD IDs with treatment susceptibility information is then sent back to the HPA. The following variables are sent:

Variable list:

- labsampid Test identifier
- dbsample Date of blood sample
- SOPHID SOPHID patient identifier
- HANDDID HANDD patient identifier
- n_PI Number of major PI mutations
- n_NRTI Number of major NRTI mutations
- n_NNRTI Number of major NNRTI mutations
- n Sum of n_PI, n_NRTI, n_NNRTI
- NRTIcomb NRTI major mutations
- NNRTIcomb NNRTI major mutations

- PROcomb PRO major mutations
- resPI 1 or more PI mutations
- resNRTI 1 or more NRTI mutations
- resNNRTI 1 or more NNRTI mutations
- resn 1 or more mutations
- perm Permutations of resistance to the 3 classes
- countperm Number of classes with resistance

10.3.2 Matching SOPHID to NSHPC

12 Jan 2012

Joint SOPHID and NSHPC database: Procedure to build joint dataset

Shema Tariq and Clare French

1. Matching process
    a. NSHPC provided the HPA with a list of pregnancies by year of report (no pregnancies are represented twice if they cross over from Dec/January) between 2000-2009
    b. NSHPC provided MSTU, postcode at notification and delivery, woman's DOB and country of birth
    c. HPA checked each NSHPC pregnancy to see if it matched with any women on the SOPHID database. Matches were given a SOPHID ID and this is used for other pregnancies in the same woman. This SOPHID ID is constant over time even if the woman moves to a different clinic.

d. Matching based on increasingly fuzzy criteria detailed on the spreadsheet –

    i. Sex, dob

    ii. Full postcode SOPHID = NSHPC (notification)

    iii. Full postcode SOPHID = NSHPC (del)

    iv. Fuzzy postcode matching e.g E9

    v. SHA

    vi. COB (SOPHID got this from HANDD)

    vii. Part postcode notification = treatment site

    viii. Delivery site and treatment site

    ix. Date of diagnosis within 30/7 on SOPHID and NSHPC

e. For each year matches are classed as S (reported to SOPHID), P (pregnant) and SP (pregnant and reported to SOPHID). Some women may not have been reported to SOPHID during pregnancy.

2. Duplicates

    a. 1 SOPHID ID: >1 NSHPC MTSU (Same woman on SOPHID but different women on NSHPC – Table 5 on spreadsheet

        i. Do not know which MSTU to match on therefore drop these from analysis

        ii. They have been saved as a list as a separate csv (duplicates.csv)

b. 1 NSHPC MTSU: >1 SOPHID ID (Same woman on NSHPC (sequential pregnancies) but different women in SOPHID – list in spreadsheet).

    i. Coded yellow – Cuong has looked through them and has chosen best SOPHID match according to matching algorithm and allocated that SOPHID attendance pattern to that MSTU.

    ii. Coded blue – Coung has looked through and decided they are SOPHID duplicate reports (i.e. same woman). The attendance patterns were amalgamated.

c. Further matches: sometimes another pregnancy hasn't been matched with SOPHID but linked by MTSU. These have been allocated same SOPHID ID.

3. HPA spreadsheet

    a. Merge Table 2a (sent recently by Cuong and has SOPHID ID) with Table 2 (most recent matching with new columns on Scottish reports and matching)

    b. Replace SP=1 P=0 S=2 (SO must be coded first)

    c. Replace "nomatch" 0=1

    d. Rename columns so compatible for Stata – mstu, scotland, sophid_id, sophid*,nomatch

    e. Replace "Scotland" Y=1

    f. Save as sophid.csv

    g. Also save list of death dates (HANDD) as deaths.csv

4. Stata:

a. Import duplicates, sophid and deaths into stata and save as separate .dta files

b. Merge sophid.dta with Q87

c. Drop _merge=1 or 2 (either not on Q87 – more recent reports- or not on SOPHID – not obstetric or pre 1999 etc)

d. Only keep sophid related variables and drop _merge

e. Merge in death dates and drop _merge

f. Merge in duplicates – drop if duplicates==1 as these are the ones with 1 SOPHID:>1 NSHPC

g. Data from Scotland is unreliable – prior to 2008 Scottish reports were assigned random ID numbers so you could not track patients over time (would have diff ID numbers each year). This was done as Scottish data was only used for yearly estimates as the data quality was poor. Therefore Scottish data is unreliable pre-2008. Using Scottish data may overestimate loss to follow up. Drop Scotland==1

5. Notes for dataset

a. SOPHID covers England, Scotland, NI and Wales

b. There is no RoI data

c. Data from Scotland is unreliable

d. 46 patients were flagged by Cuong as omitted from previous matching process – this was an error in the query used – not due to characteristics of these women.

e. The analysis should exclude women from Ireland and Scotland otherwise they will come up as simply unmatched when actually they should not be included due to the above.

f. We have no way of identifying these women as denominators easily. Best strategy is to exclude women who have only ever been notified as pregnant in Scotland or Ireland. Cannot use area of delivery (even if it is more recent) as some women do not deliver e.g. TOP. If a woman has had other pregnancies elsewhere she will be kept in the matched dataset. The assumption is that if you have only been pregnant once and it was in Ireland or Scotland you are likely to have stayed there for HIV care (at least in the short term). In Cuong's spreadsheet, only 6 women had moved between Scotland and the rest of the UK. Even if Scootish/Irish women turn up for care in England etc. you cannot comment on what may have happened in the intervening period in Scotland or Ireland. The alternative is to keep them all in, but they are counted as denominators in the matching process as though you would expect them to have care in England, Wales or NI. This will underestimate the matching success. You can probably demonstrate this by tabulating reporting region and nomatch.

6. Analysis:

    a. Women with an EDD/delivery 1998-2009

    b. Who were reported as pregnant at least once in England, Wales and N Ireland

    c. Looking at access to HIV care in England, Wales and N Ireland

10.3.3 Algorithm used to match NSHPC with SOPHID

Match level	Sex	Date of birth	Postcode/region	Other
1	x	X	Full/part PC (PS+) at Notification	
2	X	X	Full/part PC (PS+) at Delivery	
3	X	X	Part PC (PS) at Notification	
4	X	X	Part PC (PS) at Delivery	
5	X	X	Scotland	
6	X	X	Part PC (PD) at Notification	Country of birth via new HIV diagnosis
7	X	X	Part PC (PD) at Delivery	Country of birth via new HIV diagnosis

8	X	X	Part PC (PD) at Notification	Site of treatment
9	X	X	Part PC (PD) at Delivery	Site of delivery
10	X	X	Part PC (PD) at Notification	Date diagnosis within 30 days of date of first positive test
11	x	x	Part PC (PD) at Delivery	Date diagnosis within 30 days of date of first positive test

Definitions:

PC (postcode)

PS+ (postcode sector plus): full postcode minus the last character e.g. NW9 5E

PS (postcode sector): full postcode minus the last two characters e.g. NW9 5

PD (postcode district): 1st half of postcode e.g. NW9

Source: Provided by Cuong Chau, HIV and STI Department, Public Health England.

10.4 Audit of Perinatal HIV

10.4.1 Telephone data collection forms

Form 1: Child

1. Identifiers

Initials: .....

Hospital number: .....

DOB:

NHS number: .....

Soundex: .....

2. Demographics

Ethnicity: .....

Is the child alive?

☐No, date of death: ..... Cause of death: .....Was a post-mortem performed?.....

☐Yes

☐Lost to follow-up, specify: .....

3. Exposure to maternal infections

3.1. How was the infant fed?

☐ Exclusive formula feeding DURATION.....weeks

☐ Exclusive breastfeeding DURATION: ..... weeks

Was mother on ART? YES / NO

WHAT.....

Was mother's HIV VL undetectable? YES / NO / UNKNOWN

If NO, please give VLs with date taken.....

.....

.....

☐ Combination breast & formula feeding DURATION.....weeks

3.2. Was the child exposed to any other maternal infections?

☐No

☐Yes, **specify:** .....

4. Child's HIV diagnosis and treatment

4.1. How was the child's HIV infection identified?

☐Mother known to be infected in pregnancy **OR** ☐Mother diagnosed after the birth of this child

☐Child symptomatic

☐Other / Other family member diagnosed, specify:

.....

4.2. When was child's HIV infection identified?

.....

4.3. Where was the child's HIV infection identified?.....

4.4. Previous to child's HIV diagnosis, was the child offered screening which was either refused, or not adequately followed up? YES / NO

If YES,

DETAILS.....
.....

4.5. Was the child investigated for medical problems before the diagnosis of HIV was made?

☐No

☐Yes

If YES, DETAILS including all specialties seen, circumstances of events leading up to diagnosis, and missed opportunities for testing:

4.6. When was the child referred to a specialist HIV clinic?

.....

For the paediatric respondent:

4.7. If the mother was not diagnosed before/during the pregnancy, is the HIV unit aware of this case?

☐No ☐Yes

4.8. Could you initially contact the unit and introduce the audit so that we can take over?'

☐No ☐Yes

4.9. Could we contact the unit for further information?

☐**No** ☐**Yes, complete contact details on 'call log'**

4.10. Child's earliest test results

Test: PCR / Antibody When: .... Result: Positive / Negative

Viral load: .... copies/ml **CD4:** .... (..........%)

Test: PCR / Antibody When: .... Result: Positive / Negative

Viral load: .... copies/ml **CD4:** .... (..........%)

Test: PCR / Antibody When: .... Result: Positive / Negative

Viral load: .... copies/ml **CD4:** .... (..........%)

Test: PCR / Antibody When: .... Result: Positive / Negative

Viral load: .... copies/ml **CD4:** .... (..........%)

Test: PCR / Antibody When: .... Result: Positive / Negative

Viral load: .... copies/ml **CD4:** .... (..........%)

Test: PCR / Antibody When: .... Result: Positive / Negative

Viral load: .... copies/ml **CD4:** .... (..........%)

4.11. Did the infant/child receive PCP prophylaxis?

☐No

☐Yes at birth **What:** .....**Date from:** .....

☐Yes when diagnosed with HIV **What:** .....**Date from:** .....

4.12. Did the infant receive post-exposure prophylaxis after birth?

☐ No

☐Yes Time of 1st dose after birth (hrs)?.....

If there was a delay, why was this?.....

Which antiretroviral/s?.....

Duration of PEP (weeks).....

4.13.Has the infant/child received any HIV treatment since diagnosis?

☐No **Why:** .....

☐Yes **Drug: ..... Start date: ..... End date: .....**

Drug: ..... Start date: ..... End date: .....

Drug: ..... Start date: ..... End date: .....

Drug: ..... Start date: ..... End date: .....Reason.....

Drug: ..... Start date: ..... End date: ..... Reason.....

Drug: ..... Start date: ..... End date: ..... Reason.....

Drug: ..... Start date: ..... End date: ..... Reason.....

4.14. Did the parent/carer attend appointments regularly with the child?

☐No **Why:** .....

☐Yes

4.15. Respondent's perception of likely timing of transmission

4.16. Any other comments?

4.17. Can we contact you again if we need to follow this up any further? (Record on 'call log')

Form 2 – Mother diagnosed before or during pregnancy

Mother's details

1 Identifiers

1.1 Hospital number: .....

1.2 NHS number: .....

1.3 Soundex: .....

2 **Demographics**

2.1 Date of birth: .....

2.2 Country of birth: .....

2.2a If not UK/Ireland, date arrived: .....

2.3 Ethnicity: .....

2.4 Occupation: .....☐Full-time ☐Part-time ☐Unemployed ☐N/K

2.5 Marital status

☐Married / co-habiting with partner ☐Single ☐Separated from partner ☐N/K

2.6 If with partner, what is partner's occupation: .....

☐Full-time ☐Part-time ☐Unemployed ☐N/K

2.7 Any social issues?

- Immigration
- Housing
- Intimate partner violence

Details:

- Drug or alcohol problems
- Mental health problems

2.8 Other known HIV-positive family members?

☐No

☐Yes Relationship to mother: ..... When diagnosed: .....

Relationship to mother: ..... When diagnosed: .....

3 **Maternal HIV infection**

3.1 When was this woman diagnosed?

☐Before this pregnancy ☐During this pregnancy ☐ During labour/delivery,

DETAILS:.....
.....

3.2 Where was this woman diagnosed?

☐Antenatal screening ☐GUM clinic screening (& reason for attendance) .....

☐Other screening program DETAILS.....

☐Testing because of symptoms WHERE.....

☐Other, specify: .....

3.3 Any evidence of seroconversion in this pregnancy?

☐No ☐Not known

☐Yes, specify: .....

3.4 Prior negative test? ☐No

☐Yes When: ..... Where: .....

3.5 Details available on first positive HIV test?

☐No

☐Yes When: ..... Where: .....

Viral load: ..... copies/ml CD4: ..... (.....%)

☐Not known

3.6 Is it likely that the woman acquired her HIV infection in the UK/Ireland?

☐No ☐Yes ☐Not known

3.7 What is the likely source of infection?

☐Injecting drug use ☐Vertical transmission ☐Heterosexual
☐Not known ☐Other, specify: .....

3.8 Any significant past medical history? ☐No ☐Not known

☐Yes DETAILS.....

3.9 Has she had a previous AIDS-defining illness? ☐No
☐Not known

☐Yes DETAILS.....

3.10 If the woman was diagnosed before this pregnancy, has she has previous ART?

☐No ☐Not known

☐Yes ☐PMTCT only ☐1 regimen ☐2 regimens ☐≥3 regimens

3.11 Has she had previous unstructured treatment breaks?

☐No ☐Not known ☐Yes
DETAILS.....

3.12 Is she known to have drug resistance? ☐No ☐Not known

☐Yes ☐NRTI ☐NNRTI ☐PI ☐Other

3.13 Has she had difficulties with adherence? ☐No ☐Not known ☐Yes

4 Antenatal care

4.1 Gestation at booking for antenatal care (in UK): .....wks ☐Not booked ☐Not known

4.2 Estimated date of delivery: .....

4.3 Where did the woman receive antenatal care (include all centres and outside UK)?

When: ..... Where: .....

When: ..... Where: .....Reason for change.....

When: ..... Where: ..... Reason for change.....

4.4 Did she attend antenatal appointments regularly? ☐Yes ☐No ☐Not known

If NO, why? .....

4.5 Did she attend HIV appointments regularly? ☐Yes ☐No ☐Same as antenatal appts

If NO, why? ..... ☐Not known

4.6 Were there any problems engaging with the HIV service? ☐No ☐Yes

If YES, why?.....

4.7 Is English this woman's first language? ☐No ☐Yes ☐Not known

4.8 Is she fluent in English? ☐No ☐ Yes ☐Not known

4.9 Did she require translation services?

☐No ☐Yes ☐Not known

If yes, did she get when required? .....

4.10 What type of interpreter did she have (tick more than one if needed and give details)?

☐Friend/family ☐Independent person (phone or present in the room)

☐Not available ☐Not known

5 Maternal HIV treatment

5.1 Did the woman receive treatment during the pregnancy?

☐No, why: ..... continue to 4.1

☐Yes Drug: ..... Start date: ..... End date: .....

Drug: ..... Start date: ..... End date: .....

Drug: ..... Start date: ..... End date: .....

Drug: ..... Start date: ..... End date: .....

Drug: ..... Start date: ..... End date:
.....Reason.....

Drug: ..... Start date: ..... End date: .....
Reason.....

Drug: ..... Start date: ..... End date: .....
Reason.....

Drug: ..... Start date: ..... End date: .....
Reason.....

5.2 Was there evidence of resistance in this pregnancy? ☐No ☐Not known ☐Not tested

☐Yes ☐NRTI ☐NNRTI ☐PI ☐Other

Test date: .....

5.3 Any evidence of problems with adherence during the pregnancy?

☐No

☐Yes,
DETAILS.....
.....

5.4 Were any invasive investigations undertaken in pregnancy? E.g amniocentesis, foetal blood sampling etc.

☐No

☐Yes

Was HIV infection status known at the time? ☐No ☐Yes

What: ..... When: .....

ARV cover? ☐No ☐Yes Viral load: ..... copies/ml

What: ..... When: .....

ARV cover? ☐No ☐Yes Viral load: ..... copies/ml

What: ..... When: .....

ARV cover? ☐No ☐Yes Viral load: ..... copies/ml

5.5 Did the woman have any concurrent illnesses or infections in pregnancy or at delivery? E.g. hepatitis, malaria etc., other complications of pregnancy e.g. chronic nausea, strep B

☐No

☐Yes What: ..... When: .....

Treatment details:

.....

.....

What: ..... When: .....

Treatment details:

……

……

5.6 Please list all viral loads done during the pregnancy:

Date…… VL…… log……

Date…… VL…… log……

Date…… VL…… log……

Date…… VL…… log……

Date…… VL…… log……

Date…… VL…… log……

Date…… VL…… log……

Date…… VL…… log……

5.7 Did the woman travel overseas during pregnancy?

☐No

☐Yes Where: …… When: ……

Where: …… When: ……

Pregnancy outcomes

6 Outcomes related to the infant

6.1 Child's date of birth: .....

6.2 Child's hospital number: .....

6.3 Gestation at delivery (completed weeks):.....

6.4 Gender ☐Male ☐Female

6.5 Birth weight (kg): .....

6.6 Were there any congenital abnormalities?

☐No ☐Yes, specify: .....

6.7 Where there other perinatal infections/problems?

☐No ☐Necrotising enterocolitis ☐Other, specify:
.....

6.8 Did the infant require ventilation?

☐No ☐Yes, specify: .....

7 Outcomes related to the mother

7.1 Viral load near delivery: ..... copies/ml CD4: ..... (.....%)
Date: .....

7.2 Planned mode of delivery: ☐Vaginal ☐Caesarean section
☐Unknown

7.3 Actual mode of delivery: ☐Vaginal ☐ELCS
☐EMCS

Reason for EMCS: ……

Reason for change, if different from planned:

……

7.4 Was foetal blood sampling (FBS) used ☐No ☐Yes

7.5 Was a foetal scalp clip used? ☐No ☐Yes

7.6 Was there an instrumental delivery?

☐No

☐Yes Type of instrument: ……

7.7 Were the membranes ruptured?

☐No

☐Yes, duration: ……..hours……..minutes ☐Duration unknown

☐At delivery

Length of labour: …… hours ….. minutes ☐Duration unknown

☐Not known

7.8 Were there any other pregnancy complications?

☐No ☐Pre-eclampsia ☐Gestational diabetes

☐Other, specify: ……

7.9 Was the mother symptomatic of HIV at delivery?

☐No ☐Yes, specify: ……

If woman has died, Date of death: .....

Cause of death.....

7.10 Did the mother receive any extra drug treatment during labour or delivery?

☐No ☐IV AZT ☐Single dose nevirapine ☐Other oral ART: .....

Form 3: Women diagnosed after pregnancy or undiagnosed

1. For the paediatric respondent

1.1. If the mother was not diagnosed before/during the pregnancy, is the antenatal unit aware of this case?

☐No ☐Yes

1.2. If yes, could you initially contact the unit and introduce the audit so that we can take over?'

☐No ☐Yes

1.3. Could we contact the unit for further information?

☐No ☐Yes, complete contact details on 'call log'

1.4. Has the mother subsequently been diagnosed with HIV?

☐No ☐Yes

1.5. If yes, can we contact the HIV unit for further information?

☐No ☐Yes

2.

2. Mother's details

2.1. Identifiers

Hospital number: .....

NHS number: .....

Soundex: .....

2.2. **Demographics**

Date of birth: .....

Country of birth: .....

2.2.1.1.1.If not UK/Ireland, date arrived: .....

2.3. Ethnicity: .....

2.4. Occupation: ..... ☐Full-time ☐Part-time ☐Unemployed ☐N/K

2.5. Marital status when pregnant

☐ Married / co-habiting with partner ☐Single ☐Separated from partner ☐N/K

2.6. If with partner, what is partner's occupation: .....

☐Full-time ☐Part-time ☐Unemployed ☐N/K

2.7. Any social/complicating issues?

Immigration

Housing

Intimate partner violence

Drug or alcohol problems

Mental health problems

Other

3. Antenatal care

3.1. Did the women receive antenatal care outside the UK?

☐No ☐Not known ☐Yes

DETAILS.....

3.2. When did she book for antenatal care in the UK?

Date..... Approx weeks gestation.....

3.3. **Did the woman attend more than one hospital for antenatal care?**

☐No ☐Not known ☐Yes

When: ..... **Where:** .....

3.4. Did she attend antenatal appointments regularly? ☐Yes ☐No ☐Not known

If NO, why? ..... ☐Not known

3.5. Is English this woman's first language? ☐No ☐Yes ☐Not known

3.6. **Is she fluent in English?** ☐No ☐ Yes ☐Not known

3.7. Did she require translation services?

☐No ☐Not known

☐Yes If yes, did she get when required? .....

3.8. What type of interpreter did she have?

☐Friend/family ☐Independent person (phone or present in the room)

☐Not available ☐Not known

3.9. Was she offered an HIV screening test at booking visit during this pregnancy?

☐No ☐Not known ☐Yes **Date offered:** .....**Approx weeks gestation.....**

Accepted? ☐Yes, **result:** negative / positive

☐No, **If no, were reasons given and documented in the notes**?

.....

.....

Was a senior health professional involved?

DETAILS.....

.....

.....

If the initial offer was declined, was a repeat test offered?

☐Yes **Gestation**: ..... **Result**: negative / positive

☐No, why: .....

☐Not known

3.9.1.If the first test was negative, was a risk assessment carried out?

Yes/No

DETAILS.....

.....

If Yes, was she considered high risk for acquiring HIV? YES/NO

WHY? .....

If Yes, was she offered a repeat HIV test later during pregnancy? YES/NO

Accepted? YES/NO

Result: POSITIVE/NEGATIVE

If the first test was negative, was there any evidence of subsequent seroconversion during the pregnancy? YES / NO

DETAILS.....

.....

3.10. Other known HIV-positive family members?

☐No

☐Yes **Relationship to mother:** ..... **When diagnosed:** .....

Relationship to mother: ..... **When diagnosed:** .....

4. **Maternal HIV infection** (if the mother has been subsequently diagnosed with HIV)

4.1. **Where was this woman diagnosed?**

☐Antenatal screening **☐GUM clinic screening (& reason for attendance) .....**

☐Other screening program **DETAILS.....**

☐Testing because of symptoms **WHERE.....**

☐Other, specify: .....

4.2. Any evidence of seroconversion in this pregnancy or in the postnatal period?

☐No ☐Not known

☐Yes, **specify:** .....

Prior negative test? ☐No

☐Yes When: ..... Where: .....

4.3. Details available on first positive HIV test?

☐No ☐Not known

☐Yes **When**: ..... **Where**: .....

4.3.1.1.1.1.1. **Viral load:** ..... copies/ml **CD4:** ..... (.....%)

4.4. Is there any evidence that this woman acquired HIV in the postnatal period?

☐No ☐Yes ☐Not known

Details .....

Is it likely that the woman acquired her HIV infection in the UK/Ireland?

☐No ☐Yes ☐Not known

What is the likely source of infection?

4.5. ☐Injecting drug use ☐Vertical transmission ☐Heterosexual ☐Not known ☐Other, **specify:** .....

4.6. **Any significant past medical history?** ☐No ☐Not known

☐Yes DETAILS.....

4.7. **Has she had an AIDS-defining illness?** ☐No ☐Not known

☐Yes DETAILS.....

Did the woman travel overseas during pregnancy?

☐No

☐Yes **Where:** ..... **When:** .....

Where: ..... **When:** .....

Pregnancy outcomes

Outcomes related to the infant

1.1 Child's date of birth: .....

1.2 Child's hospital number: .....

1.3 Gestation at delivery (completed weeks):.....

1.4 Gender ☐Male ☐Female

1.5 Birth weight (kg): .....

1.6 Were there any congenital abnormalities?

☐No ☐Yes, specify: .....

1.7 Where there other perinatal infections/problems?

☐No ☐Necrotising enterocolitis ☐Other, specify: .....

1.8 Did the infant require ventilation?

☐No ☐Yes, specify: .....

2 Outcomes related to the mother

2.1 Mode of delivery: ☐Vaginal ☐ELCS ☐EMCS

Reason for EMCS: .....

Reason for change, if different from planned:

.....

2.2 Was foetal blood sampling (FBS) used ☐No ☐Yes

2.3 Was a foetal scalp clip used? ☐No ☐Yes

2.4 Was there an instrumental delivery?

☐No

☐Yes **Type of instrument:** .....

2.5 Were the membranes ruptured?

☐No

☐Yes, **duration:** .....hours.....minutes ☐Duration unknown

☐At delivery

Length of labour: ..... hours ..... minutes ☐Duration unknown

☐Not known

2.6 Were there any other pregnancy complications?

☐No ☐Pre-eclampsia ☐Gestational diabetes

☐Other, **specify:** .....

6.7 If woman has died, Date of death: .....

Cause of death.....

10.4.2 Members of the Expert Review Panel 2014

Pat Tookey NSHPC Principal Investigator and Senior Lecturer, UCL Institute of Child Health

Helen Peters Data Manager & Statistician to the NSHPC, UCL Institute of Child Health

Laura Byrne MRC Clinical Research Training Fellow, UCL Institute of Child Health

Catherine Peckham Clinical Advisor to the NHS Infectious Diseases in Pregnancy Screening Programme; Chair of the NSHPC Steering Group

Sharon Webb Programme Manager, NHS Infectious Diseases in Pregnancy Screening Programme

Hermione Lyall Consultant in Paediatric Infectious Disease, Imperial College Healthcare NHS Trust

Annemiek de Ruiter Consultant in HIV Medicine, Guys & St Thomas' NHS Trust

Kate Harding Consultant in Obstetrics, Guys & St Thomas' NHS Trust

Sheila Donaghy Paediatric Nurse Consultant, St George's Healthcare NHS Trust

Shema Tariq NIHR Postdoctoral Clinical Research Fellow & Honorary Consultant HIV/Sexual Health, University College London

Sarah Dermont Specialist Midwife, Chelsea and Westminster Hospital NHS Foundation Trust

Sophie Strachan Community Representative, Positively UK

Paddy McMaster Consultant in Paediatric Infectious Diseases, North Manchester General Hospital

Sally Farthing Specialist Midwife, West Middlesex Hospital

Angelina Namiba Community Representative, Positively UK

Ali Wright Consultant Obstetrician, Royal Free

Chris Wood Lead HIV Clinician, North Middlesex Hospital

10.4.3 Example of an ERP meeting agenda

NSHPC Audit of Perinatally Acquired HIV

Expert Review Panel Meeting Agenda October 2014

Attendees:

Kate Harding – Consultant obstetrician, Guys & St Thomas' NHS Trust

Hermione Lyall – Consultant in paediatric infectious diseases, Imperial College Healthcare NHS Trust

Sophie Strachan- Lay representative, Positively UK

Angelina Namiba - Lay representative, Positively UK

Sally Farthing – Specialist midwife, West Middlesex Hospital

Paddy McMaster – Consultant paediatric infectious diseases, North Manchester General Hospital

Chris Wood – Consultant GU/HIV medicine, North Middlesex University Hospital NHS Trust

NSHPC Audit Group

Pat Tookey – Principal investigator, NSHPC (Chair)

Laura Byrne – MRC clinical research training fellow, NSHPC

Helen Peters – Research assistant, NSHPC

Apologies

Catherine Peckham - IDPS programme director, Chair NSHPC Steering Group

Annemiek de Ruiter - Consultant in HIV medicine, Guys & St Thomas' NHS Trust

Ali Wright - Consultant obstetrician, Royal Free Hospital

Sharon Webb - IDPS programme manager

Graham Taylor - Reader in Communicable Disease, Imperial College Healthcare NHS Trust

Sheila Donaghy - Paediatric Nurse Consultant, St George's Healthcare NHS Trust

Sarah Dermont - Specialist Midwife, Chelsea and Westminster Hospital NHS Foundation Trust

Shema Tariq - Fullbright Scholar in Public Health, Columbia University

Time: Thursday 4th October 2014 0930-1230.

Venue:

Lower ground Floor Seminar Room,

Institute of Child Health, 30 Guilford Street WCIN 1EH

Agenda items

1. Apologies and introductions
2. Review of last meeting's minutes
3. Update on progress through cases:

Cases reported so far: 111 up to April 2014 (backlog)

3 new cases reported since then

Interview stage	**No of cases**
No response from any respondent	3
Agreed to take part but no interview	1
All ints still to carry out	1
One int done+other to carry out	12
Complete Cases	94
Total cases	**111**

No. of cases discussed by ERP (July 2014): **75**

4. Case summaries:

- Quick discussion of factors in each case
- Outcome form to be filled and agreed for each case
- Cases are grouped together in themes; there will be additional time for discussion after all cases of a particular theme are discussed

10.5 Publications and presentations of the research presented in this thesis

10.5.1 Papers

National audit of perinatal HIV infections in the UK, 2006–2013: what lessons can be learnt?

H Peters C Thorne PA Tooke, and L Byrne. HIV Medicine, 2018 Apr; 19(4):280-289.

Pregnancy incidence and outcomes in women with perinatal HIV.

L Byrne, R Sconza, C Foster, PA Tookey, and C Thorne. AIDS, 2017 Jul 31; 31(12): 1745-1754.

10.5.2 Oral presentations

Audit of perinatally acquired HIV in UK-born infants reported 2014–2017.

H Peters, L Byrne, P Tookey, S Webb and C Thorne. Presented at the Joint BHIVA BASHH Annual Conference 2018, Edinburgh, UK.

Women who decline antenatal HIV testing: a national survey of local policy and practice .

L Byrne .. CHIVA Parallel Sessions at the BHIVA Autumn Conference, Friday 13th November 2015, London, UK.

Antiretroviral drug resistance in pregnant women living with HIV in the UK: preliminary results from the matching of three national HIV surveillance databases.

L Byrne, C Chau, V Delpech, D Dunn, P A Tookey, A Tostevin, and C Thorne. Presented at 21st Annual Conference of the British HIV Association, Brighton, April 2015.

Antiretroviral drug resistance in pregnant women living with HIV in the UK: preliminary results from the matching of three national HIV surveillance databases.

L Byrne, C Chau, VDelpech, D Dunn, PA Tookey, ATostevin, and C Thorne. Presented at the 19th International Workshop on HIV Observational Databases, Catania Sicily, March 2015.

Audit of Perinatal HIV in the UK since 2006: an update.
L Byrne, HPeters, PA Tookey. Prize for Best Oral Research Presentation, annual CHIVA conference, Manchester, May 2014.

.An audit of children with perinatal HIV born in the UK since 2006.
L Byrne. Prevention of Perinatal HIV Infection: Aiming for zero transmission. BHIVA multidisciplinary event marking World AIDS Day, Friday 27 November 2015, London, UK.

10.5.3 Research Posters

Pregnancy outcomes in women growing up with perinatally acquired HIV in the UK and Ireland.
Byrne L, Thorne C, Foster C, Tookey PA. International Congress on Drug Therapy for HIV Infection 2014, Glasgow.

Pregnancy outcomes in women growing up with perinatally acquired HIV in the UK and Ireland.
Byrne L, Thorne C, Foster C, Tookey PA. International Congress on Drug Therapy for HIV Infection 2014, Glasgow.

Place of diagnosis and CD4 count in pregnant HIV-positive women diagnosed before conception in the UK and Ireland (2007-2012)
Byrne L, Townsend C, Thorne C, Tookey P. BHIVA Spring Conference 2013, Manchester.

Place of diagnosis and CD4 count in pregnant HIV-positive women diagnosed before conception in the UK and Ireland (2007-2012)
Byrne L, Townsend C, Thorne C, Tookey P. International Workshop on HIV Observational Databases 2013, Cavtat, Croatia.