Sequential pregnancies among women living with HIV in the United Kingdom and Ireland

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Declaration

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

Signed…… Date……..

Abstract

This thesis investigates the epidemiology of sequential pregnancies among HIV-positive women in the United Kingdom and Ireland, and explores the health, therapeutic and obstetric management, and pregnancy outcomes, of the women experiencing them. Data from the UK and Ireland's National Study of HIV in Pregnancy and Childhood (NSHPC) are analysed. This is a well-established, active, comprehensive national surveillance study with over 1500 pregnancies currently reported each year.

The findings demonstrate that a substantial and increasing proportion of pregnancies are women's second or subsequent since their HIV diagnosis (39% in 2009), with a rate of 6.7 (95% CI: 6.5-6.9) per 100 woman-years during 1990-2009. Analyses revealed potential missed opportunities for the timely initiation of antiretroviral therapy (ART) in this group of previously diagnosed women, both within and outside the context of pregnancy. Variations in women's engagement with HIV and pregnancy-related care are explored.

In the contemporary context of effective prevention of mother-to-child transmission (PMTCT) interventions there are unanswered questions around the optimal management of HIV-positive women of childbearing age. Exposure to short-course protease inhibitor-based combination ART for PMTCT did not impact on response to therapy in subsequent pregnancies, supporting current UK recommendations. However, analyses of the immunological status and virological outcomes in second pregnancies to women not on ART at conception suggest that initiating lifelong ART in pregnancy may have benefits for maternal health and the risk of vertical transmission in future pregnancies. Adverse pregnancy and perinatal outcomes are investigated among women's repeat pregnancies, which were for example, more likely to be conceived on ART than index pregnancies. Finally, patterns in mode of delivery for women's sequential births are explored.

The analyses presented in this thesis inform the evidence-base for the effective management of HIV-positive women in the context of current and potential future pregnancies.

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Abbreviations

aHR:	Adjusted hazard ratio
AIDS:	Acquired Immunodeficiency Syndrome
aOR:	Adjusted odds ratio
APR:	Antiretroviral Pregnancy Registry
ART:	Antiretroviral therapy
BHIVA:	British HIV Association
BPSU:	British Paediatric Surveillance Unit
cART:	Combination antiretroviral therapy
CDC:	(United States) Centres for Disease Control and Prevention
CI:	Confidence interval
CS:	Caesarean section
DNA	Deoxyribonucleic acid
ECS:	European Collaborative Study
El CS:	Elective caesarean section
Em CS:	Emergency caesarean section
HAART:	Highly active antiretroviral therapy
HANDD:	HIV and AIDS New Diagnoses and Deaths
HIV:	Human Immunodeficiency Virus
HR:	Hazard ratio
ICH:	Institute of Child Health
IQR:	Inter-quartile range
LR test:	Likelihood ratio test
MSM:	Men who have sex with men
MTCT:	Mother-to-child transmission (of HIV)
NHS:	National Health Service
NICE:	National Institute for Health and Care Excellence
NNRTI:	Non-nucleoside reverse transcriptase inhibitor
NRTI:	Nucleoside reverse transcriptase inhibitor
NSHPC:	National Study of HIV in Pregnancy and Childhood
OR:	Odds ratio
PCR:	Polymerase chain reaction
PHE:	Public Health England, previously the Health Protection Agency (HPA)
PI:	Protease inhibitor
PMTCT:	Prevention of mother-to-child transmission
RCOG:	Royal College of Obstetricians and Gynaecologists
RCPCH:	Royal College of Paediatrics and Child Health

RNA:	Ribonucleic acid
sdNVP:	Single dose nevirapine
SOPHID:	Survey of Prevalent HIV Infections Diagnosed
STI:	Sexually transmitted infection
UCL:	University College London
UK CHIC:	UK Collaborative HIV Cohort
UK:	United Kingdom
UNAIDS:	Joint United Nations Programme on HIV/AIDS
US:	United States
VBAC:	Vaginal birth after caesarean
WHO:	World Health Organization
WITS:	US Women and Infants Transmission Study

Publications arising from this work

Peer reviewed publications (provided in Appendix I)

French CE, Thorne C, Tariq S, Cortina-Borja M, Tookey PA. Immunologic status and virologic outcomes in repeat pregnancies to HIV-positive women not on antiretroviral therapy at conception: a case for lifelong antiretroviral therapy? *AIDS* 2014; 28:1369-1372.

French CE, Tookey PA, Cortina-Borja M, de Ruiter A, Townsend CL, Thorne C. Influence of short-course antenatal antiretroviral therapy on viral load and mother-to-child transmission in subsequent pregnancies among HIV-infected women. *Antivir Ther* 2013;18(2):183-92.

French CE, Cortina-Borja M, Thorne C, Tookey PA. Incidence, patterns, and predictors of repeat pregnancies among HIV-infected women in the United Kingdom and Ireland, 1990-2009. *JAIDS* 2012;59(3):287-93.

Conference abstracts

French CE, Thorne C, Tariq S, Cortina-Borja M, Tookey PA. Repeat pregnancies among HIV-infected women: Immunologic status and virologic outcomes among those not on antiretroviral therapy at conception. 19th Conference on Retroviruses and Opportunistic Infections, Seattle, 2012.

French CE, Thorne C, Cortina-Borja M, Tariq S, Tookey PA. Repeat pregnancies among HIV-infected migrant women in the United Kingdom and Ireland. 6th International AIDS Society Conference on HIV Pathogenesis, Treatment and Prevention, Rome, 2011.

French CE, Thorne C, Cortina-Borja M, Tookey PA. Management of repeat pregnancies among HIV-infected women in the United Kingdom and Ireland. 15th Annual Conference of the British HIV Association, Bournemouth, 2011.

French CE, Thorne C, Cortina-Borja M, Tariq S, Tookey PA. Repeat pregnancies among HIV-infected migrant women in the United Kingdom and Ireland.15th International Workshop on HIV Observational Databases, Prague, 2011.

French CE, Thorne C, Cortina-Borja M, Tookey PA. Are sequential pregnancies in HIV-Infected women associated with an increased risk of mother-to-child transmission? 18th Conference on Retroviruses and Opportunistic Infections, Boston, 2011.

French CE, Thorne C, Cortina-Borja M, Tookey PA. Increasing repeat pregnancies among HIV-infected women in the United Kingdom and Ireland. XVIII International AIDS Conference, Vienna, 2011.

Chapter 1 Introduction

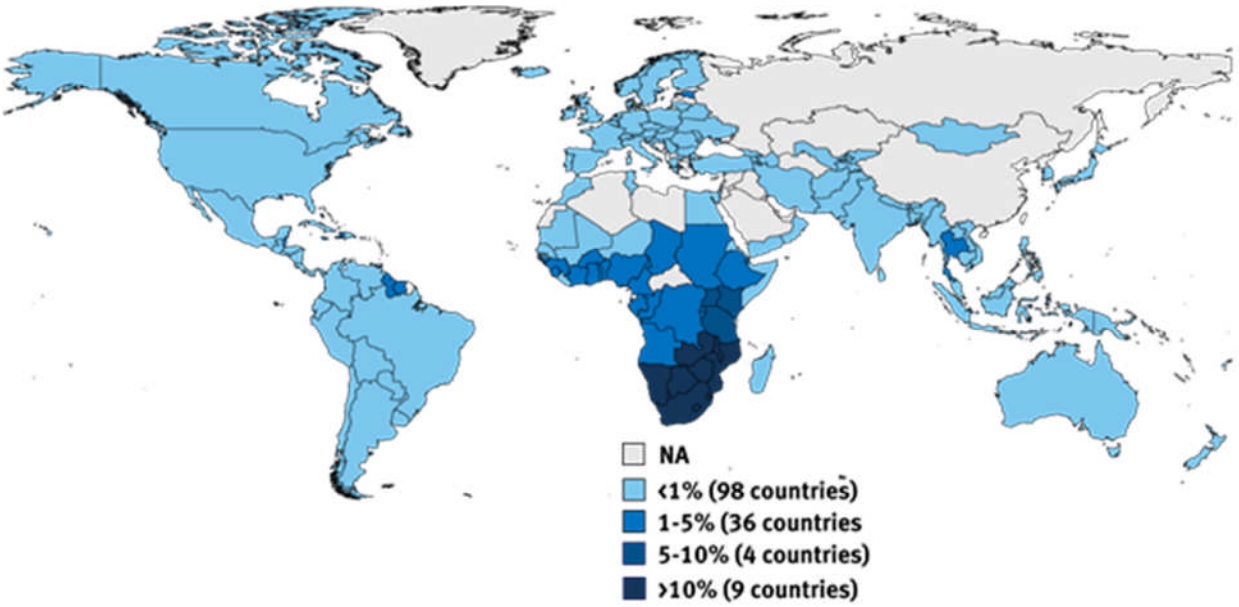
1.1 Overview of HIV

1.1.1 Global epidemiology of HIV

In 2012 an estimated 35.3 million adults were living with Human Immunodeficiency Virus (HIV) worldwide, half of whom were women. Over the last decade there has been a 33% reduction in the annual number of new infections among adults and children (from 3.4 million in 2001 to 2.3 million in 2012). This reflects the natural course of the epidemic, combined with the impact of prevention measures, particularly behaviour change programmes which have resulted in the adoption of safer sexual practices, together with expanded access to antiretroviral therapy (ART). Although there have been recent increases in the number of people living with HIV, this is due to the expansion of treatment programmes, and consequent reduction in HIV-related deaths (which declined from 2.3 million in 2005 to 1.6 million in 2012). There are, however, significant geographic variations. Globally, the highest prevalence of HIV is in sub-Saharan Africa where 4.7% of adults aged 15-49 years were living with HIV in 2012, with particularly high prevalence in the countries of Southern Africa (Figure 1.1) (UNAIDS, 2013).

There are variations across sub-Saharan Africa, but many countries are now experiencing generalised epidemics (i.e. prevalence of HIV among the general population exceeds 1% (World Health Organization, 2013)). In this region women are at disproportionate risk, now accounting for 57% of all those living with HIV. Significant gender inequalities exist in many areas making women particularly vulnerable to HIV, with factors such a gender-based violence, poorer access to education and economic opportunities, as well as women's greater physiological vulnerability to HIV all thought to play a role (UNAIDS, 2013). Many other regions of the world have epidemics that are concentrated among specific high risk groups which include men who have sex with men (MSM), people who inject drugs and sex workers. In much of Western Europe and the United States (US), migrants from high prevalence areas of the world and MSM bear the greatest burden of HIV, while the epidemic in much of Central Asia and Eastern Europe is particularly focused among injecting drug users and their sex partners (Centers for Disease Control and Prevention, 2012; European Centre for Disease Prevention and Control/ WHO Regional Office for Europe, 2013; UNAIDS, 2011b).

Figure 1.1 Global HIV prevalence among adults, 2012



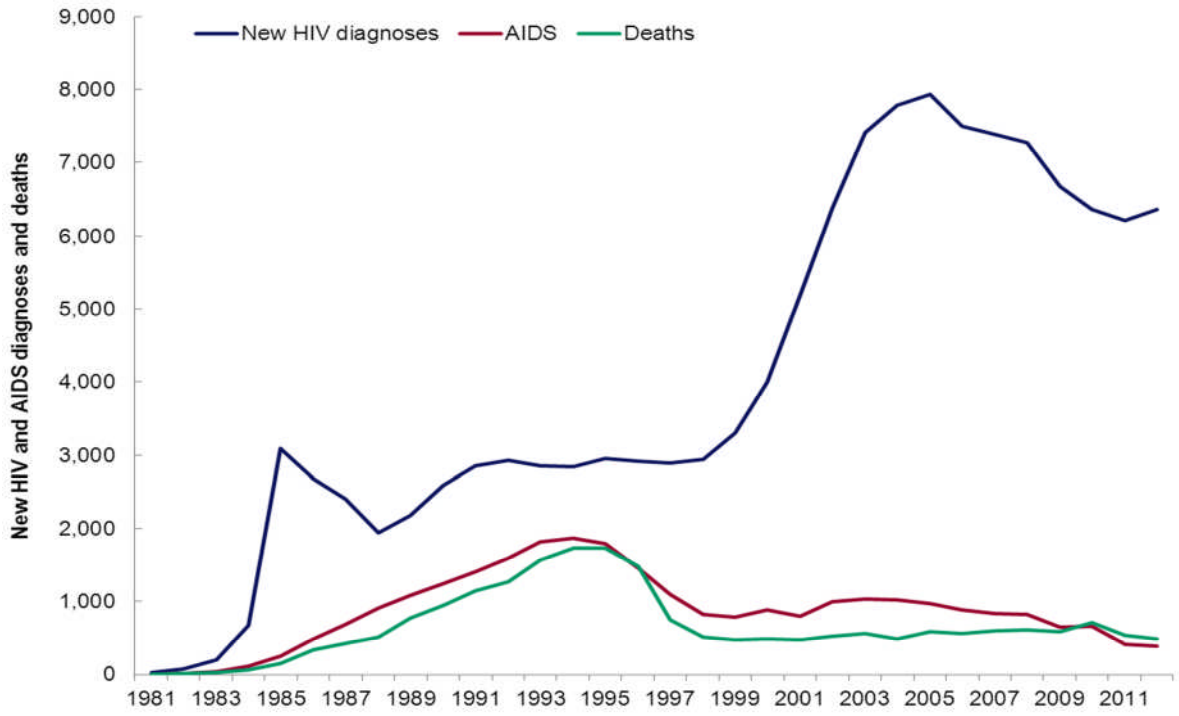
NOTES: Data are estimates. Prevalence rates include adults ages 15-49. The estimate for Sudan represents data for South Sudan. An estimate was not provided for Sudan.
SOURCE: Kaiser Family Foundation, www.GlobalHealthFacts.org, based on UNAIDS, Report on the Global AIDS Epidemic; 2013.

1.1.2 Epidemiology of HIV in the United Kingdom (UK)

In the UK[1] there were an estimated 98,400 people living with HIV in 2012, one in five of whom (21,900) were unaware of their status. Approximately one third (31,700) were women, and the majority (82%) of diagnosed women are of childbearing age (15-49 years)[2]. There were 6360 new HIV diagnoses overall (1800 in women) during 2012. New diagnoses increased substantially to a peak of almost 8000 in 2005 but have since been declining (Figure 1.2), as a result of reductions in new diagnoses among heterosexuals originating from high prevalence areas of the world. Diagnoses among MSM have, however, continued to increase and accounted for just over half of diagnoses in 2012 (Aghaizu *et al*, 2013).

[1] Data from Ireland are not collected as part of routine HIV surveillance by Public Health England (PHE), therefore information is presented for the UK only.
[2] The proportion of women who were of childbearing age was calculated among those with *diagnosed* HIV attending HIV care during in 2012. Data obtained from (Aghaizu *et al*, 2013, Appendix 6).

Figure 1.2 Annual new HIV and AIDS diagnoses and deaths, UK, 1981-2012



Source: (Aghaizu *et al*, 2013)

The overall prevalence of HIV among the UK population was 0.15% in 2012 (0.1% in women and 0.2% in men), but is much higher in certain population groups with one in 20 MSM (0.47%) living with HIV (one in 12 in London). Meanwhile, 5.1% of black African women and 2.6% of black African men in the UK were living with HIV in 2012, reflecting the high prevalence of HIV in sub-Saharan Africa. Black African women were less likely to have undiagnosed HIV than men, most likely due to the effectiveness of the antenatal screening programme (which is discussed further in Section 1.2.1 of this chapter). There are also geographic variations in prevalence; 20% of local authorities (18 of which were in London) have been classed as 'high prevalence' areas with ≥0.2% of the adult (15-59 year old) population living with diagnosed HIV (Aghaizu *et al*, 2013).

1.1.3 Natural history and transmission

HIV is a retrovirus that causes Acquired Immunodeficiency Syndrome (AIDS). There are currently two known types of HIV: HIV-1 and HIV-2. HIV-1 is both more virulent and more infectious (Peeters *et al*, 2013). HIV-1 is the dominant type throughout most of the world while HIV-2 is confined largely to West Africa (Lemey *et al*, 2003; Peeters *et al*, 2013). HIV-1 is divided into four main groups, 'M' being the most common, and these groups are further divided into a number of types and sub-types reflecting the high genetic variability of the virus (Peeters *et al*, 2013).

HIV contains two copies of single-stranded ribonucleic acid (RNA), together with various enzymes, including reverse transcriptase, integrase and protease, required for the development of new virus particles. Glycoproteins (gp120 receptors) on the surface of the virus particles enable virons to bind with CD4 lymphocytes ('T helper cells'); viral RNA can subsequently enter the nucleus of the host cell. From here viral RNA is converted to deoxyribonucleic acid (DNA) by reverse transcriptase, and then enters the nucleus of the host cell where it is spliced into the DNA of the host cell. When the host lymphocyte becomes active, new virus particles are produced via the replication processes of the host cell. These new virus particles subsequently bud off and infect other CD4 cells (Mortimer *et al*, 2001). Through this process HIV systematically destroys CD4 cells (Pantaleo *et al*, 1993), thereby causing a decline in the host's immune function.

In the natural course of HIV disease, the initial 'acute phase' is characterised by rapid viral replication and consequent sharp decline in CD4 T-lymphocyte cell count, hereafter referred to as CD4 count. An immune response to HIV is elicited within the first three months which results in some recovery in CD4 count and a substantial reduction in viral load. Then ensues a clinically latent phase of around 10 years, during which there is a gradual decline in CD4 cells. This continues until the immune system is weakened to such a degree that opportunistic diseases begin to occur (Pantaleo *et al*, 1993). AIDS is defined as a CD4 count of <200 cells/µl or the diagnosis of an AIDS-definition condition (World Health Organization, 2007)[3]. In the absence of treatment, death from AIDS usually occurs within around two years (Lemp *et al*, 1990; Mocroft *et al*, 1997).

[3] The WHO provides a comprehensive list of AIDS-defining conditions. Examples include *Pneumocystis* pneumonia, active tuberculosis disease, HIV wasting syndrome, and Kaposi sarcoma (World Health Organization, 2007).

HIV can be present in bodily fluids including blood and blood products, semen, vaginal secretions and breast milk. The virus can thus be transmitted through unprotected sex (the most common route of transmission globally), receipt of infected blood, blood products or organs, the use of contaminated needles and from mother to child (Adler, 2001). The likelihood of transmission is highly dependent on the circulating viral load (Quinn *et al*, 2000; Tovanabutra *et al*, 2002).

1.1.4 Diagnosis

There are several methods for the diagnosis of HIV, including both serological and virological tests. Serologic methods detect antibodies to the virus and/or the p24 viral antigens (p24) in the blood, while the presence of viral DNA and RNA can be detected by means of the polymerase chain reaction (PCR) (Fearon, 2005). Current UK guidelines recommend the use of serological assays which detect both antibodies and antigens simultaneously. HIV RNA viral load tests are not recommended for diagnosis due to the potential for false-positive results (British HIV Association *et al*, 2008).

In the UK, both the estimated proportion of HIV infections that remain undiagnosed (22% in 2012), and the proportion of infections diagnosed late[4] (47% in 2012) (Aghaizu *et al*, 2013), remain worryingly high. Individuals diagnosed at a late stage of disease have greater morbidity and mortality (Aghaizu *et al*, 2013; Chadborn *et al*, 2006; May *et al*, 2011a). Furthermore, undiagnosed and hence untreated infection presents a major barrier to HIV control at the population level as the virus may, for example, be unwittingly passed on to sexual partners, particularly in the presence of high viral loads (Marks *et al*, 2006). In light of this, concerted efforts have been made to increase the uptake of HIV testing among high risk groups (Health Protection Agency, 2011b). UK national guidelines for HIV testing published in 2008 recommend universal testing of adults presenting to general practice or other medical services in areas where the prevalence exceeds 0.2%. Universal testing is also recommended in certain settings such as sexual health clinics and antenatal services, and for all those falling into high risk groups e.g. MSM and partners of diagnosed individuals (British HIV Association *et al*, 2008). More recently, innovative strategies such as the use of home sampling kits, available to order online with samples sent to the laboratory for testing, have been implemented (Aghaizu *et al*, 2013; Nardone *et al*, 2013).

[4] Based on a 'late diagnosis' definition of CD4 <350 cell/µl within three months of HIV diagnosis (Aghaizu *et al*, 2013). The definition of late diagnosis (or presentation to care) has changed over time with a threshold of <200 cells/µl previously used in the UK (Chadborn *et al*, 2006).

1.1.5 Treatment

The advent and impact of ART

There have been significant advances in the treatment of HIV since the first antiretroviral drug, zidovudine, a nucleoside reverse transcriptase inhibitor (NRTI), was found to be effective against HIV in 1987 (Fischl *et al*, 1987). With the subsequent identification of further agents that prevent HIV viral replication, including both non-nucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs), in the mid-1990's it was demonstrated that treating patients with a combination of antiretrovirals suppressed viral load more effectively than zidovudine alone (Hammer *et al*, 1996). This hailed the advent of highly active antiretroviral therapy (HAART), a combination of three or more antiretrovirals (also now known as combination antiretroviral therapy (cART)), commonly consisting of two NRTIs and either an NNRTI or a PI. There are now a number of different classes of antiretrovirals, each targeting a different phase of the HIV lifecycle. The main classes and their mechanisms of action are provided in Table 1.1. The most commonly used classes are NRTIs, NNRTIs and PIs. Ritonavir, a PI, is prescribed alongside cART, not for its own antiretroviral activity but because it inhibits the host enzyme that breaks down other PIs thus leading to higher concentrations ("boosting") of these drugs in the patient. The World Health Organization (WHO) recommends that first line HIV therapy consists of two NRTIs plus one NNRTI (tenofovir and lamivudine or emtricitabine) plus efavirenz, assuming no contraindications (World Health Organization, 2013). Meanwhile, UK guidelines for the treatment of adults recommend that two NRTIs are combined with either an NNRTI, a ritonavir-boosted PI or an integrase inhibitor (INI), the preferred regimen being tenofovir and emtricitabine plus either boosted atazanavir, boosted darunavir, efavirenz or raltegravir (Williams *et al*, 2012).

cART has dramatically improved the lives of people living with HIV. With early diagnosis and appropriate treatment, HIV-positive[5] people can now have a near normal life expectancy (May *et al*, 2011b; Nakagawa *et al*, 2012; Samji *et al*, 2013; van Sighem *et al*, 2010). Adherence to treatment is paramount for maintaining high levels of viral suppression, though required levels of adherence vary by regimen (Maggiolo *et al*, 2007; Nachega *et al*, 2007; Paterson *et al*, 2000; Shuter, 2008).

[5] "HIV-positive" is largely used in place of "people (or women) living with HIV" in this thesis for brevity (both refer to the *diagnosed* population).

Table 1.1 Main classes of antiretrovirals

Drug class	Mechanism of action	Examples
Non-nucleoside reverse transcriptase inhibitors (NNRTIs)	Inhibit the function of the reverse transcriptase enzyme required for HIV replication	nevirapine (NVP), efavirenz (EFV)
Nucleoside reverse transcriptase inhibitors (NRTIs)	Inhibit the function of the reverse transcriptase enzyme required for HIV replication	zidovudine (ZDV, AZT), tenofovir (TDF), emtricitabine (FTC), abacavir (ABC), lamivudine (3TC), stavudine (d4T)
Protease inhibitors (PIs)	Block the protease enzyme	atazanavir (ATV), darunavir (DRV), nelfinavir (NFV)
Fusion (or entry) inhibitors	Blocks the virus from entering host CD4 lymphocytes	maraviroc (MVC)
Integrase inhibitors (INI)	Blocks the intergrase enzyme	raltegravir (RAL)

Source: Based on information from the US Department of Health and Human Sciences. Available at: http://www.niaid.nih.gov/topics/HIVAIDS/Understanding/Treatment/pages/arvdrugclasses.aspx (Accessed January 2014).

Drug resistance

Due to the rapid and error-prone replication of HIV, the development of resistance to antiretrovirals is a major issue (Clavel *et al*, 2004; Tang *et al*, 2012). Resistance may be transmitted, whereby an individual is infected with a resistant strain, or acquired, when an individual develops resistance through drug selection pressure (Clavel *et al*, 2004; Tang *et al*, 2012). Resistance to PIs occurs less frequently than for NNRTIs as they have a higher 'genetic barrier' to the development of resistance; several mutations are required for resistance to occur (Clavel *et al*, 2004; de Mendoza *et al*, 2004; Tang *et al*, 2012). Meanwhile, resistance occurs less frequently under cART regimens than with single or dual drug therapy since the high levels of viral suppression maintained by cART minimise the replication of any resistant virus that may emerge. Resistance mutations can, however, still occur in the presence of cART (Clavel *et al*, 2004; Dolling *et al*, 2012; Paredes *et al*, 2010; Phillips *et al*, 2005).

Timing of ART initiation

There is uncertainty and debate with regards to the optimal timing of ART initiation among HIV-positive adults. Though the benefits of ART initiation among those with CD4 counts of <350 cells/µl are now widely agreed (European AIDS Cinical Society, 2013; Panel on Antiretroviral Guidelines for Adults and Adolescents, 2013; Williams *et al*, 2012; World Health Organization, 2013), the benefits and risks of starting ART in asymptomatic people with higher CD4 counts are uncertain. A recent review of national and international HIV treatment guidelines highlighted the disparities in recommendations and the differing methodologies used to assess the evidence-base (Sabin *et al*, 2013). Although current UK guidelines do not recommend ART for those with CD4 counts of ≥350 cells/µl, except for some specific groups such as those with certain co-infections (Williams *et al*, 2012), they do allow for the continuation of ART after pregnancy in women with CD4 counts of 350-500 cells/µl who wish to stay on treatment (Taylor *et al*, 2012). Meanwhile, recent WHO guidelines recommend the initiation of ART when CD4 counts fall to ≤500 cells/µl (the threshold was previously <350 cells/µl) (World Health Organization, 2013), and the latest European guidelines state that treatment may be considered for those with CD4 counts of ≥350 cells/µl (European AIDS Cinical Society, 2013). Some guidelines now recommend treatment for all people living with HIV, even those with CD4 counts >500 cells/µl (Panel on Antiretroviral Guidelines for Adults and Adolescents, 2013; Thompson *et al*, 2012). The Strategic Timing of Antiretroviral Therapy (START) is a large, international clinical trial currently underway to assess the risks and benefits of starting ART among people with CD4 counts of >500 cells/µl (Babiker *et al*, 2013), the results of which should contribute to the evidence-base.

HIV treatment as prevention

The effectiveness of cART in reducing viral load to undetectable levels has led to "HIV treatment as prevention" becoming an area of active research and growing interest (Cohen *et al*, 2007; Eaton *et al*, 2012; Granich *et al*, 2009; Hosseinipour *et al*, 2002; Montaner *et al*, 2006; Montaner *et al*, 2010; World Health Organization, 2013). The move towards the earlier initiation of ART, including new WHO recommendations (World Health Organization, 2013), is being driven not only by the clinical benefits for the individual, but also evidence that people on effective treatment with undetectable viral loads have a very low risk of onward transmission of HIV (Cohen *et al*, 2011; Quinn *et al*, 2000; Tovanabutra *et al*, 2002)[6]. The trial by Cohen *et al*, conducted in nine countries, was hailed as a major breakthrough in HIV prevention. Patients with CD4 counts of 350-550 cells/µl in serodiscordant partnerships were randomised to either

[6] Indeed, the title of the most recent (2013) WHO guideline on the use of antiretrovirals is "Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection".

immediate ART initiation or delayed initiation (at CD4 ≤250 cells/μl). Of the 28 transmissions that could be genetically linked to the HIV-positive partner, only one occurred in the immediate therapy group (hazard ratio (HR): 0.04, 95% CI: 0.01-0.27). Current UK guidelines recommend that patients are made aware that being on ART reduces the risk of passing HIV to their sexual partners (Fidler *et al*, 2013).

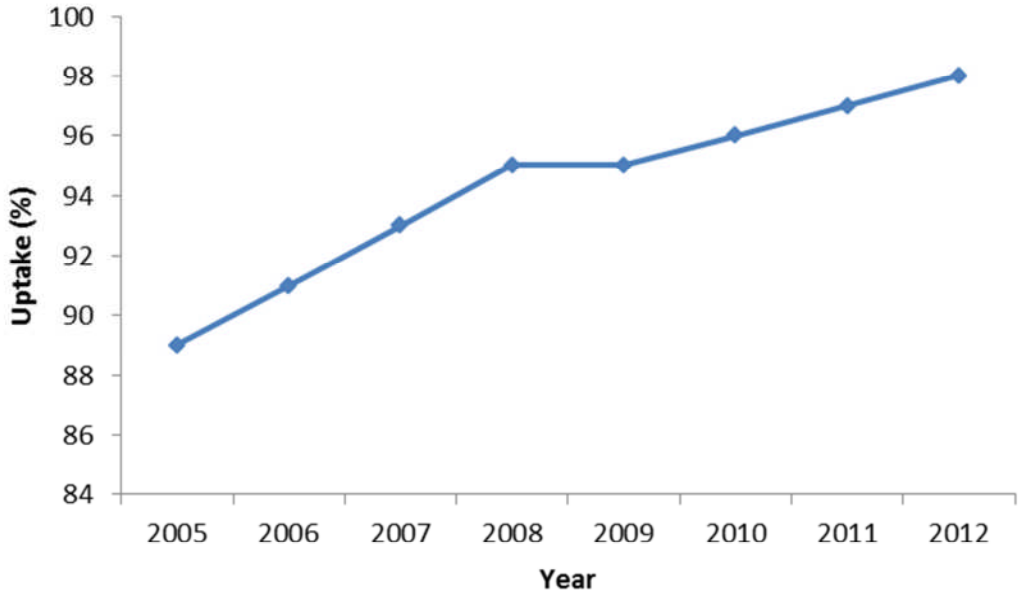
1.2 HIV in pregnant women

1.2.1 Antenatal HIV screening

Ensuring that women living with HIV are diagnosed during, if not before, pregnancy is an essential component of interventions for the prevention of vertical transmission, as well as improving the woman's prognosis[7]. During the 1990's there were high levels of undiagnosed HIV among pregnant women (an estimated two-thirds of pregnant women were undiagnosed in 1997), reflecting the low uptake of the existing 'opt-in' approach to HIV antenatal screening (Gibb, 2000; Tookey *et al*, 1998). Recognising the importance of diagnosing HIV in pregnant women, in 1999 the Department of Health for England introduced a policy to offer and recommend a voluntary antenatal HIV test to all pregnant women with a target of 80% uptake by the end of 2002 (NHS Executive, 1999). Similar policies were subsequently adopted in Wales, Scotland and Northern Ireland. Uptake of antenatal HIV screening has risen substantially since then with national uptake in England reaching 98% in 2012 (Figure 1.3) (Public Health England, 2013a; Townsend *et al*, 2006).

[7] As a consequence of earlier diagnosis (Aghaizu *et al*, 2013; Chadborn *et al*, 2006; May *et al*, 2011a).

Figure 1.3 Trends in uptake of antenatal HIV screening in England, 2005-2012



Source: Based on data from Public Health England; data are collected through the National Antenatal Infections Screening Monitoring (NAISM). Data tables for 2005-2012. Available at: http://www.hpa.org.uk/web/HPAweb&HPAwebStandard/HPAweb_C/1245581538007 (Accessed December 2013).

1.2.2 Epidemiology of HIV in pregnant women in the UK and Ireland

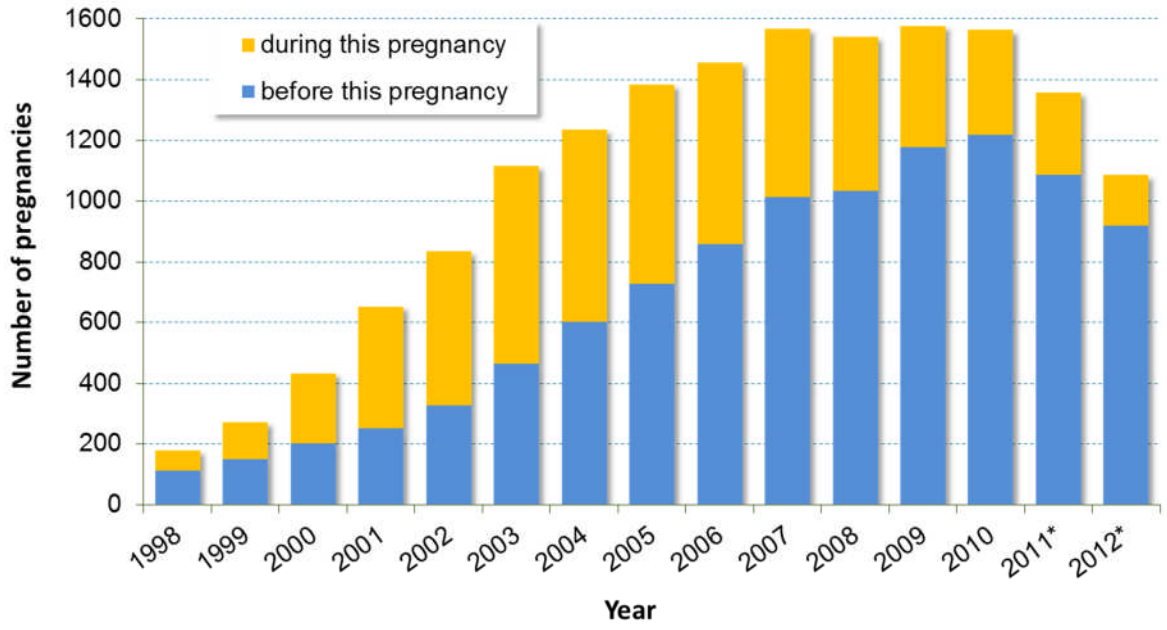
In 2012, 0.19% of women tested through the voluntary antenatal scheme had a positive result, and this has been relatively stable in recent years (Public Health England, 2013a). Meanwhile, based on data from the neonatal dried blood spot survey (an unlinked anonymous survey of maternal HIV infection using neonatal dried blood spots which therefore includes all women giving birth, regardless of whether diagnosed or not) the estimated prevalence was 0.22%[8]. Consistent with what is known about the distribution of HIV among the UK population, the highest prevalence was in women from sub-Saharan Africa (2.3%) (Aghaizu *et al*, 2013).

By the end of 2012, over 16,000 pregnancies to diagnosed HIV-positive women had been reported to the UK and Ireland National Study of HIV in Pregnancy and Childhood (NSHPC) since surveillance began in 1989, with over 1500 reported each year since 2007 (National

[8] The unlinked anonymous pregnant women surveys use leftover neonatal dried blood spots routinely taken from newborns around 10 days after birth to test for maternal HIV infection. The survey includes >60% of births in England (www.hpa.org.uk). The lower HIV prevalence estimate obtained based on the results of voluntary antenatal screening (0.19%) is due to a combination of factors such as some previously diagnosed women not being screened antenatally, while others may acquire HIV during pregnancy.

Study of HIV in Pregnancy and Childhood, 2013). There have been major shifts in the demographic profile of HIV-positive pregnant women since the early years of the HIV epidemic. For example, there has been a decline in the proportion of women born in the UK or Ireland (from 49% during 1990-1993 to 14% in 2007-2011), and in those who likely acquired their HIV infection from their own or their partner's injecting drug use (from 49% to 1.5% over the same period). Meanwhile, the proportion who originated from sub-Saharan Africa increased substantially (from 44% to 77%) (Townsend *et al*, 2014; Townsend *et al*, 2008b). There have been significant increases over time in the proportion of women reported to the NSHPC who were diagnosed prior to their current pregnancy, now accounting for over 80% of pregnancies reported annually (Figure 1.4). In 2012, among those women diagnosed prior to their current pregnancy, around 40% were diagnosed antenatally during a previous pregnancy, with a further 40% having been diagnosed in a genitourinary medicine (GUM) clinic, and the remaining 20% in other settings e.g. general practice (Byrne *et al*, 2013).

Figure 1.4 Trends in timing of maternal HIV diagnosis, UK and Ireland, 1998-2012



*Incomplete data due to reporting delays

Note: Based on year of delivery for live and stillbirths and expected date of delivery for other outcomes.

Source: National Study of HIV in Pregnancy and Childhood (NSHPC), data reported by end of December 2012.

1.2.3 Mother-to-child transmission (MTCT) of HIV

HIV can be transmitted from mother to child in utero, during labour and delivery, and through breastfeeding. In utero transmissions may occur via the placenta, particularly in the presence of placental tears or disruption. Transmissions occurring during labour and delivery may result from exposure of the infant to the virus in maternal blood and genital secretions in the birth canal, ascent of infection from the vagina or cervix, and maternal-fetal transfusions during contractions (Kourtis *et al*, 2010; Newell, 1998). In the absence of interventions, the risk of MTCT was around 14-25% among non-breastfeeding populations in Western settings (The Working Group on Mother-To-Child Transmission of HIV, 1995). The relative contributions of antepartum, intra-partum and post-partum transmission are not entirely clear but in non-breastfeeding populations most transmissions are thought to occur in late pregnancy or during delivery (Kourtis *et al*, 2001).

Maternal HIV RNA level ("viral load") is the pre-eminent risk factor for MTCT (Cooper *et al*, 2002; European Collaborative Study, 1999; Garcia *et al*, 1999; Mayaux *et al*, 1997; Mofenson *et al*, 1999; Warszawski *et al*, 2008), and there is clear evidence that the risk of transmission increases with increasing viral load. For example, a recent analysis of UK data reported a transmission rate of 9.2% in women with delivery viral loads of ≥10,000 copies/ml compared with just 0.05% in women with undetectable (<50 copies/ml) viral loads (Townsend *et al*, 2014). Viral load may be considered as a proxy for the potential risk of vertical transmission.

1.2.4 Prevention of mother-to-child transmission (PMTCT) of HIV

Antenatal ART

In 1994, a landmark randomised controlled trial demonstrated that zidovudine monotherapy given to pregnant women and their newborns reduced the risk of MTCT of HIV by 68% (Connor *et al*, 1994), an intervention which was then rapidly adopted. Meanwhile, the Ugandan HIVNET 012 trial demonstrated that a single dose of intra-partum nevirapine (sdNVP) reduced MTCT risk by 50% (Guay *et al*, 1999), and this was found to be beneficial when added to a short-course of antenatal zidovudine (Lallemant *et al*, 2004). The use of sdNVP for PMTCT in resource-limited settings is discussed further in Chapter 2, Section 2.5. The effectiveness cART in preventing vertical transmission of HIV has been widely demonstrated (Siegfried *et al*, 2011), and is now generally the recommended regimen in resource-rich settings (Aebi-Popp *et*

al, 2013b; Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission, 2012; Taylor *et al*, 2012).

The aim of ART administered during pregnancy is to suppress viral replication, ideally reducing maternal viral load to an undetectable level by the time of delivery; this is the mechanism through which ART reduces the risk of vertical transmission (Siegfried *et al*, 2011). The therapeutic management of HIV in pregnancy is complex, not least due to the many physiological changes that women undergo during this period. These changes may alter the pharmacokinetics of drugs, including absorption, distribution and metabolism (Abduljalil *et al*, 2012; Mirochnick *et al*, 2010). Achievement of an undetectable viral load by delivery is dependent on a range of factors including baseline viral load, timing and duration ART, type of drugs and dosing, drug pharmacokinetics (including the potential for differential penetration into genital tract tissues), and adherence (Aziz *et al*, 2013; Dumond *et al*, 2007; Read *et al*, 2012; Taylor *et al*, 2012).

Current British HIV Association (BHIVA) guidelines on the management of HIV in pregnancy recommend short-term cART commenced after the first trimester, and discontinued after delivery, for pregnant women not requiring treatment for their own health (Taylor *et al*, 2012). Boosted-PI based cART is the recommended regimen for PMTCT (Taylor *et al*, 2012) owing to the long half-life of NNRTIs which increases the risk of the development of drug resistance following short-course therapy (Mackie *et al*, 2004). If NNRTI-based cART is used efavirenz or nevirapine are the recommended drugs. In the UK and Ireland zidovudine monotherapy remains an alternative to cART for women who do not require treatment for their own health, have a baseline viral load of <10,000 copies/ml and plan to deliver by caesarean section (Taylor *et al*, 2012), though the majority of women receive cART (Townsend *et al*, 2014). A brief summary of how the key recommendations for the management of HIV have changed over the last decade is provided in Appendix II.

The timing of antenatal ART initiation requires a balance of the risks and benefits to both mother and child. This includes consideration of possible teratogenicity of first trimester ART exposure, toxicities e.g. mitochondrial, the precipitation of pregnancy complications such as pre-eclampsia, risk of adverse pregnancy outcomes such as preterm delivery, and women's health (Newell *et al*, 2013). International and national guidelines have evolved over time with a more recent move towards the earlier initiation of antenatal ART among women not requiring ART for their own health. The WHO now recommends that women start ART as early as 14 weeks gestation (World Health Organization, 2013), while in the US it is recommended women

start at 12 weeks, with initiation during the first trimester also being an option taking into consideration women's health status (Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission, 2012). The 2012 UK guideline states that all women should have commenced ART by 24 weeks, and at the start of the second trimester for those with very high viral loads (>30,000 copies/ml) (Taylor *et al*, 2012). Prior to this the recommended timing was 20-28 weeks according to the 2008 guideline (de Ruiter *et al*, 2008), while the 2005 guideline provided a broader recommendation of 'during the second trimester' (Hawkins *et al*, 2005).

This shift reflects the growing evidence that longer duration of antenatal ART decreases the risk of detectable viral load at delivery, and hence MTCT (Chibwesha *et al*, 2011; Denoeud-Ndam *et al*, 2013; Hoffman *et al*, 2010; Patel *et al*, 2007; Rachas *et al*, 2013; Read *et al*, 2012; Townsend *et al*, 2014; Warszawski *et al*, 2008). For example, an analysis of data on over 5000 mother-child pairs reported to the French Perinatal Cohort demonstrated a non-linear association between antenatal ART duration and the risk of MTCT. There was a rapid decline in risk during the first 12 weeks, with a much slower decline beyond this (Warszawski *et al*, 2008). Similarly, a recent analysis of the NSHPC data revealed that with each additional week of antenatal ART the risk of MTCT rapidly declined over the first few weeks with a continued, though slower, decline up to 15 weeks from initiation, though this varied by baseline viral load (Townsend *et al*, 2014). Preterm birth is of concern here, particularly in women starting ART late in pregnancy, since early delivery limits the duration of ART received. Meanwhile, in line with the increasing proportion of pregnancies to women who were diagnosed prior to that pregnancy (as was shown in Figure 1.4), an increasing proportion of women are conceiving on ART (41% during 2007-2011) (Townsend *et al*, 2014), with similar trends documented in Europe (Bailey *et al*, 2013; Floridia *et al*, 2006). For these women it is now recommended that treatment should usually be continued throughout pregnancy (Taylor *et al*, 2012), in accordance with other national (Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission, 2012) and international guidelines (World Health Organization, 2013). Not only shorter durations of antenatal ART, but also treatment interruptions during pregnancy, have been associated with an increased risk of MTCT (Galli *et al*, 2009; Townsend *et al*, 2008a; Warszawski *et al*, 2008), thus continuation of regimens initiated prior to pregnancy is desirable.

ART is generally well tolerated during pregnancy and is associated with relatively few maternal toxicities (Tuomala *et al*, 2005; Watts *et al*, 2004). However, that is not to say that it is without potential adverse consequences. cART in pregnancy has been linked with possible increased

risks of pre-eclampsia, hypertension and gestational diabetes (Newell *et al*, 2013; Suy *et al*, 2006; Thorne *et al*, 2007a), while an increased risk of preterm delivery has been widely documented (Short *et al*, 2014). With regard to infant outcomes, some studies have raised concerns about increased risks of conditions such as anaemia in the newborn (El Beitune *et al*, 2006; Pacheco *et al*, 2006), mitochondrial disorders (Ross *et al*, 2012) and low birthweight (Ekouevi *et al*, 2008; Machado *et al*, 2009) in exposed infants. Though the benefits of antenatal ART are widely accepted to outweigh the risks (Newell *et al*, 2013; Thorne *et al*, 2007a; Townsend *et al*, 2010b; Tuomala *et al*, 2005), it remains essential to carefully monitor and minimise any potential short and long-term adverse consequences of antenatal ART. This topic, including risks of congenital abnormalities among infants exposed to ART in utero is discussed further in Chapter 2, Section 2.6.

Mode of delivery

The effectiveness of elective caesarean section in reducing the risk of MTCT was reported in several European observational studies during the 1990's (European Collaborative Study, 1994; Kind *et al*, 1998; Maguire *et al*, 1997; Mandelbrot *et al*, 1998), a finding which was subsequently borne out in a meta-analysis of 15 prospective cohort studies in Europe and the US in which elective caesarean section was associated with a 50% reduction in the risk of transmission (The International Perinatal HIV Group, 1999). In the same year these observational findings were upheld by the results of a randomised controlled trial in which 436 HIV-positive women were allocated to either a vaginal or elective caesarean section delivery, around 65% of whom also received zidovudine prophylaxis. The risk of transmission was 3.4% in infants delivered by caesarean section compared with 10.2% in those delivered vaginally (p=0.009) (European Mode of Delivery Collaboration, 1999). Elective caesarean section was thus recommended for PMTCT in resource-rich settings (Tovo *et al*, 1999).

In the current era, there is uncertainty regarding the additional benefit of elective caesarean section in women on cART with low viral loads. Although some studies demonstrate a protective effect (Boer *et al*, 2010; Ioannidis *et al*, 2001; Thorne *et al*, 2005), others have found no significant benefit in those with undetectable viral loads delivering at term (Briand *et al*, 2013; Townsend *et al*, 2014; Warszawski *et al*, 2008), though some potential benefit among those with low but detectable levels of the virus cannot be ruled out (Townsend *et al*, 2014). There is, however, difficulty in conducting studies that are sufficiently powered to address this question. In light of the very low vertical transmission rates in women on cART (Townsend *et al*, 2014; von Linstow *et al*, 2010; Warszawski *et al*, 2008), there has been a move towards the

normalisation of delivery for HIV-positive women over the last decade with many countries allowing for vaginal deliveries in those on suppressive therapy (Aebi-Popp *et al*, 2013b). However, the viral load threshold below which there is no additional benefit is unknown. This uncertainty is reflected in variations in national and international guidelines. A recent review of European guidelines reported that the threshold below which a vaginal delivery may be considered was <50 copies/ml in 11 countries, <400 in three countries, and <1000 copies/ml in five (Aebi-Popp *et al*, 2013b).

Despite comprehensive UK guidelines for the obstetric management of HIV in pregnancy, which recognise the range and complexity of cases seen, there is a lack of specific recommendations for the management of those experiencing a repeat delivery as a diagnosed woman (Taylor *et al*, 2012).

Infant feeding

Since HIV infection can be passed from mother to child via breast milk (Dunn *et al*, 1992), the avoidance of breastfeeding is recommended in countries where infant feeding formulas are readily available, affordable, safe and acceptable (Taylor *et al*, 2012; World Health Organization, 2010a). Although the risk of post-natal transmission by this route is significantly reduced in women receiving cART during the breastfeeding period, some risk still remains (de Vincenzi, 2011; Shapiro *et al*, 2010). In the UK additional support to formula feed should be provided where necessary (Taylor *et al*, 2012)[9].

Effectiveness of interventions

PMTCT is, on the whole, the great success story in HIV prevention. The use of antiretroviral prophylaxis or treatment during the antenatal and intra-partum periods, and prophylaxis for the neonate, combined with elective caesarean section delivery and the avoidance of breastfeeding (Taylor *et al*, 2012) has reduced the MTCT rate in the UK and Ireland to very low levels in recent years, with current rates being just 0.5% (based on data for 2010-11) (Townsend *et al*, 2014). Dramatic declines, and currently low MTCT rates, have also been documented in other resource-rich settings (Nesheim *et al*, 2013; Thorne *et al*, 2005; von Linstow *et al*, 2010; Warszawski *et al*, 2008). Globally, there is a target set by the Joint United Nations Programme on HIV/AIDS (UNAIDS), for the 'virtual elimination' of MTCT worldwide by

[9] The UK guideline does state that in exceptional circumstances women on cART with repeated undetectable viral loads who choose to breastfeed should be closely monitored (e.g. regular viral load monitoring) and should cease breastfeeding at six months (Taylor *et al*, 2012).

2015 (an MTCT rate of <5% in breastfeeding settings and <2% in non-breastfeeding settings) (World Health Organization and UNICEF, 2012). Though much remains to be done, significant progress has been made with antiretroviral coverage among pregnant women living with HIV reaching 62% in 2012, while the number of children newly infected with HIV in 2012 was 35% lower than in 2009 (UNAIDS, 2013).

It should, however, be remembered that even in resource-rich settings with highly effective interventions, some transmissions do still occur, including in utero transmissions prior to diagnosis or cART initiation. Furthermore, as has been noted, even in treated women, the effectiveness of ART in reducing viral load to undetectable levels may vary (e.g. due to variations in drug absorption). Women who have received sub-optimal care during pregnancy, for example, insufficient antenatal ART are at particular risk of transmission (Bailey *et al*, 2011). In some cases this stems from women's complex social circumstances (Modestini *et al*, 2013; National Study of HIV in Pregnancy and Childhood *et al*, 2007). Finally, it should be noted that vertical transmission is multifactorial and there is no viral load level under which it does not occur (Townsend *et al*, 2014; Warszawski *et al*, 2008).

1.2.5 Summary

Women account for over half of people living with HIV worldwide, and most of these (around 80% in the UK) are of childbearing age. With effective treatment HIV is now a chronic, manageable, life-long condition. Over the last two decades dramatic improvements in the health, quality of life and life expectancy of people living with HIV have given HIV-positive women a greater opportunity for childbearing. There are now over 1500 pregnancies to diagnosed women in the UK and Ireland annually, with over 16,000 reported since surveillance began. Widespread antenatal screening, together with effective PMTCT interventions, have resulted in MTCT rates of just 0.5% in recent years. However, questions remain regarding the optimal management of diagnosed women of childbearing age, not only during pregnancy, but more broadly, and within the context of potential future pregnancies. Indeed, a substantial and increasing proportion of conceptions are occurring in diagnosed women, many of whom were diagnosed antenatally during a previous pregnancy. Yet, UK guidelines offer little guidance on the optimal strategies for the therapeutic and obstetric management of women experiencing repeat pregnancies following their diagnosis, and it is not currently known how these women are being managed or what their pregnancy outcomes are.

Chapter 2 Literature review

This narrative review considers some key contemporary issues related to the health, management and pregnancy outcomes of HIV-positive women of childbearing age, with an emphasis on those of particular relevance to women who have had, or may in the future experience, repeat pregnancies following their HIV diagnosis. The review focuses largely on studies from resource-rich settings, although the broader literature, including data from resource-limited settings, is cited where pertinent.

2.1 Methods

Literature searches were conducted in PubMed (http://www.ncbi.nlm.nih.gov/pubmed/). All searches were restricted to English language papers published between 1990 and 2014. Reference lists of key papers were hand-searched. Regular content alerts from key journals (The Lancet, The Lancet Infectious Diseases, New England Journal of Medicine, AIDS, Journal of Acquired Immunodeficiency Syndromes, Current Opinion in HIV and AIDS, and HIV Medicine), were subscribed to, and a broad monthly content alert from Scopus (http://www.scopus.com/) for any papers related to HIV was used to help identify any relevant papers not identified through the more specific searches. Proceedings of the following key conferences were searched: International AIDS Society, AIDS, Conference on Retroviruses and Opportunistic Infections, BHIVA annual conferences. Organisation websites and internet searches were used to identify relevant guidelines and data sources data (e.g. Office for National Statistics, WHO, National Institute for Health and Clinical Excellence (NICE), Royal College of Obstetricians and Gynaecologists (RCOG)). BHIVA guidelines for the management of HIV, both in adults and in pregnant women specifically, published between 2000 and 2012 were all obtained and reviewed.

2.2 Fertility of HIV-positive women

There is quite a substantial international literature on childbearing desires and fertility among women living with HIV. Both Western and African studies are considered here given that the majority of diagnosed women in the UK are migrants from sub-Saharan Africa and "motherhood is personally, culturally, and historically rooted" (Kennedy *et al*, 2014). The potential impact of HIV on fertility is outlined, and factors influencing childbearing desires and fertility among people living with HIV explored[10]. The narrative then focuses on what is known about the frequency and predictors of repeat pregnancies among diagnosed women in resource-rich settings.

Impact of HIV on fertility

In the early years of the epidemic, HIV was associated with a poor prognosis, and in the absence of interventions for PMTCT, declines in pregnancy rates and increases in terminations were documented (Stephenson *et al*, 1996; van Benthem *et al*, 2000). The introduction of cART is generally considered to have led to an increased pregnancy rate, and a reduction in terminations in resource-rich settings (Blair *et al*, 2004; Sharma *et al*, 2007; Townsend *et al*, 2008b; van Benthem *et al*, 2000). Further to this, it is likely that low rates of MTCT (Thorne *et al*, 2005; Townsend *et al*, 2014; von Linstow *et al*, 2010; Warszawski *et al*, 2008) combined with greatly improved AIDS-free survival in more recent years (May *et al*, 2011b; Nakagawa *et al*, 2012; Samji *et al*, 2013; van Sighem *et al*, 2010), have had an impact on HIV-positive women's fertility. Nonetheless, even in the cART era, there is evidence to suggest that the fertility of HIV-positive women may differ to that of the general population. An analysis of the US Women's Interagency HIV Study data for 2002-2009 provided a pregnancy rate ratio of 0.60 (0.46–0.78) in HIV-positive compared with HIV-negative women, after adjusting for age, parity and other relevant factors, while those with low CD4 counts had a significantly longer time to first pregnancy than those with stronger immune systems (Linas *et al*, 2011). Similar findings were reported in an earlier analysis (data for 1994-2002) of the same cohort, with overall pregnancy rates among HIV-positive and HIV-negative women of 7.4 and 15.2 per 100 person-years respectively, and a significant difference being apparent during all time periods studied. Interestingly, this earlier analysis revealed no difference in pregnancy rate before and after the introduction of cART (Massad *et al*, 2004).

[10] The main focus here is on HIV-positive women. However, some studies discussed included both men and women.

The biological mechanisms through which HIV may affect fertility are not well defined, and are difficult to disentangle from the influence of social and cultural factors. Some studies have found low CD4 counts and high HIV viral loads to be associated with amenorrhea and irregular menstrual cycles (Cejtin *et al*, 2006; Chirgwin *et al*, 1996), while others have not found a difference after adjusting for potential confounders of the association such as illicit drug use (Ellerbrock *et al*, 1996). There has also been research into whether HIV may cause premature ovarian ageing but the evidence is inconclusive (Kushnir *et al*, 2011). Meanwhile, HIV infection in men has been associated with reduced semen quantity and quality (Nicopoullos *et al*, 2004), which may impact on the fertility of women in seroconcordant partnerships. As well as these possible direct effects on biological fertility, HIV may also have indirect effects, for example, through co-morbidities such as sexually transmitted infections (STIs) (Kushnir *et al*, 2011).

Fertility among people living with HIV

There are a wide range of biological, social and cultural factors that influence reproductive decision-making and fertility regardless of HIV. These may include existing family size, the outcome of any previous pregnancies, social and cultural factors, age, childbearing desires, partner's views and family expectations. Among people living with HIV additional factors also come into play including health status, issues of disclosure, concerns regarding their future health, perceived risk of MTCT and information provided by health care providers (Bedimo-Rung *et al*, 2005; Blair *et al*, 2004; Craft *et al*, 2007; Finocchario-Kessler *et al*, 2010; Fiore *et al*, 2008; Kirshenbaum *et al*, 2004; Loutfy *et al*, 2009; Nattabi *et al*, 2009; Ogilvie *et al*, 2007; Wilcher *et al*, 2009). However, childbearing desires, intentions and actual childbearing, though clearly inter-related, are distinct concepts. The link between them is complex, and will be moderated by a range of factors (Finocchario-Kessler *et al*, 2010; Loutfy *et al*, 2009). For example, there is evidence that a high proportion of pregnancies among HIV-positive women are unplanned or unintended[11]. Just over half of pregnancies to diagnosed women in Europe (Fiore *et al*, 2008), and 56% in Canada (Loutfy *et al*, 2011) were unplanned or unintended. Similarly, in a study in one UK city only 53% of women reported that their pregnancy was planned, although only half of were aware of their HIV status at the time of that pregnancy (Moses *et al*, 2012). Meanwhile, in a recent US study, 19% of diagnosed women had planned their pregnancy, with the remainder either reporting ambivalence (58%) or that it was unplanned (23%) (Rahangdale *et al*, 2014). On the other hand, those who desire children may

[11] A wide range of terms are used to describe pregnancies (e.g. 'planned', 'unplanned', 'wanted', 'unwanted', 'intended', 'unintended'). These terms are understood, interpreted and used by women in many ways (Barrett *et al*, 2002; Fischer *et al*, 1999).

experience difficulties conceiving, or make a conscious decision not to become pregnant for a variety of reasons including their HIV status (Bedimo-Rung *et al*, 2005; Kushnir *et al*, 2011).

In the simplest terms, a prevailing message of published literature is that substantial proportions people living with HIV desire, and intend, to have (more) children[12] (Berhan *et al*, 2013; Cliffe *et al*, 2011; Cooper *et al*, 2009; Fiore *et al*, 2008; Gingelmaier *et al*, 2011; Heard *et al*, 2007; Kaida *et al*, 2010; Kennedy *et al*, 2014; Loutfy *et al*, 2009; Myer *et al*, 2007; Nostlinger *et al*, 2013), with levels of childbearing desires being similar to those of the general population (Finocchario-Kessler *et al*, 2010; Ogilvie *et al*, 2007; Stanwood *et al*, 2007; Wesley, 2003). Indeed, in a UK questionnaire-based survey of 450 women attending HIV clinics during 2003-2004 three-quarters stated that they desired (more) children (Cliffe *et al*, 2011). With regard to factors influencing childbearing desires, a recently published systematic review and meta-analysis of 20 international studies among people living with HIV (three-quarters of which were carried out in Africa) revealed that the most important predictors of childbearing desires were being childless (pooled odds ratio (OR) compared with those who already had children: 2.96, 95% confidence interval (CI): 1.77-4.95) and younger age (pooled OR comparing those aged <30 *vs*. ≥30 years: 2.31, 95% CI: 1.87-2.84) (Berhan *et al*, 2013). Number of living children also has an influence, with fewer living children being associated with increased childbearing desires (Chen *et al*, 2001; Myer *et al*, 2007; Nakayiwa *et al*, 2006). Having a partner has also been found to be a predictor of desiring children in a number of studies (Cliffe *et al*, 2011; Cooper *et al*, 2009; Heard *et al*, 2007; Laursen *et al*, 2013; Ogilvie *et al*, 2007), as has shorter relationship duration (Myer *et al*, 2007; Stanwood *et al*, 2007). Meanwhile, studies in Western settings have tended to report higher childbearing desires among those originating from Africa (Bungener *et al*, 2000; Heard *et al*, 2007; Loutfy *et al*, 2009). Health concerns have been found to be important in mitigating childbearing desires, with women reporting concerns about the impact of pregnancy on their health, as well as worries about vertical transmission and the risk of infecting their partners (Nattabi *et al*, 2009), with the availability of ART and PMTCT interventions positively associated with fertility desires and intentions in some studies (Cliffe *et al*, 2011; Cooper *et al*, 2009). For example, in the UK study by Cliffe *et al*, although a third of women said they initially did not want children following their HIV diagnosis, 41% reported that they had changed their mind following improvements in HIV treatment (Cliffe *et al*, 2011).

[12] The definitions of childbearing desires and intent, and the way they were assessed varied widely between studies. For example, in a Canadian study women who agreed with the statement "I expect to give birth to children in the future" were classed as intending to have children (Ogilvie *et al*, 2007), while in the UK study women responding "yes" to the question ''Would you like any (more) children?'' were defined as having fertility intentions (Cliffe *et al*, 2011).

Other studies have focused on factors associated with actual childbearing (or pregnancy), which of course involves not only childbearing desires and intent but also biological factors and practical considerations. However, predictors were similar to those of desiring children, as shown in Box 2.1.

Box 2.1 Key predictors of pregnancy among HIV-positive women

Predictor	Study reference
Younger maternal age	(Bedimo-Rung *et al*, 2005; Blair *et al*, 2004; Huntington *et al*, 2013; Kaida *et al*, 2013; Linas *et al*, 2011; Massad *et al*, 2004; Myer *et al*, 2010)
Null parity or lower parity	(Fiore *et al*, 2008; Linas *et al*, 2011)
Black African ethnicity*	(Huntington *et al*, 2013)
Higher maternal health status (actual or perceived)	(Bedimo-Rung *et al*, 2005; Blair *et al*, 2004; Fiore *et al*, 2008; Huntington *et al*, 2013; Linas *et al*, 2011; Massad *et al*, 2004; Myer *et al*, 2010)

*Among those living in a Western setting

Frequency and predictors of repeat pregnancies among HIV-positive women

As shown in Chapter 1, there have been significant increases in the number of pregnancies to diagnosed women in the UK, with similar trends observed elsewhere. However, despite a wealth of literature on HIV in pregnancy, little to date has been published specifically on the frequency, trends or predictors of repeat pregnancies among diagnosed women in resource-rich settings. The European Collaborative Study (ECS) enrols HIV-positive women during pregnancy and prospectively follows their infants (European Collaborative Study, 2001). An analysis of ECS data from nine European countries was conducted to investigate the frequency and predictors of having a live birth reported during 1986-2003. Overall, 5.6% (218/3911) of women had more than one live birth (37 of whom had three or more). The time to subsequent birth decreased over time; during the latest period (2000-2003) 14% of women had a subsequent delivery within two years of their first. Factors predictive of repeat live births in adjusted analyses included black African ethnicity (OR compared with white women: 2.45, 95% CI: 1.75-3.43) and younger age (OR for women aged >30 years *vs*. <25 years: 0.54, 95% CI: 0.37-0.80). In analyses restricted to the cART era there was no difference in terms of ART

receipt in the index pregnancies of those who experienced subsequent pregnancies and those who did not. Maternal health, as indicated by CD4 count, was not associated with the probability of having a repeat birth (Agangi *et al*, 2005). There are, however, several methodological limitations of this study. The ECS only includes live births, and thus the probability or rate of repeat pregnancies overall could not be estimated. It is also a consented cohort and some women may choose not to participate. Furthermore, the ECS operates in selected sites within each country and does not therefore have national coverage; women who present with a subsequent pregnancy at a non-participating centre would not have their repeat birth incorporated into the dataset. The number of women experiencing a repeat pregnancy, or indeed live birth, will thus be underestimated. Finally, the analysis was limited by the small sample size and has limited generalisability to the contemporary population of HIV-positive women in Europe due to the time period covered. Since this study no detailed analyses of sequential pregnancies (or births) among diagnosed women in a European setting have been published.

The US Women and Infants Transmission Study (WITS) is an ongoing prospective cohort study of HIV-positive pregnant women. An analysis of data from six sites in the US and Puerto Rico during 1989-2004 revealed that 22% (492/2246) of women had more than one pregnancy reported. A range of socio-demographic and clinical factors were identified as being associated with repeat pregnancy including being younger, healthier (and, linked with this, not being on ART), having fewer previous live births, and a lower educational attainment, though these were unadjusted analyses (Bryant *et al*, 2007). Unlike the European study, there was no association between ethnicity and repeat pregnancy in the US study by Bryant *et al*, perhaps reflecting broader differences in the characteristics of ethnic minority groups in Europe and the US (Newell *et al*, 2007). For example, black African HIV-positive women in Europe are predominantly migrants which is not the case in the US (Nesheim *et al*, 2013). An advantage of this study over the earlier European study was that all pregnancies, rather than only live births, were included. However, WITS shares the major limitation of the ECS for investigating the occurrence of repeat pregnancies (or births) in that it is not a national study. Although the authors state that most women are re-enrolled in subsequent pregnancies, since women may move to a different geographical location between pregnancies under-ascertainment of their repeat pregnancies is a possibility.

Summary

Prior to the work carried out for this PhD, no national level analyses on the frequency, time trends or predictors of repeat pregnancies in the UK and Ireland had been performed, and no European study had estimated the rate of repeat pregnancies among diagnosed women. Indeed, international data were sparse, and the few previous studies that had been conducted were outdated (conducted on data collected up to the early to mid-2000's), with the previous European study, in particular, having been limited by the relatively small number of repeat deliveries as well as some important methodological weaknesses.

2.3 Women's engagement with antenatal care

The optimal management of HIV in pregnancy is reliant on women booking for antenatal care in good time, regardless of whether they have diagnosed or undiagnosed HIV. Booking thus presents a crucial step in the care pathway. The importance of booking for antenatal care early in pregnancy, irrespective of HIV status, as well as the additional importance for women living with HIV, is outlined here. Socio-demographic risk factors for late booking are reviewed among the general UK population (in recognition of international variations in healthcare systems and antenatal care pathways), and then among HIV-positive women specifically, also drawing on the literature from other resource-rich settings owing to a paucity of UK studies.

Importance of timely booking for antenatal care

UK guidelines recommend that pregnant women should book for antenatal care by 10-13 weeks gestation (National Institute for Health and Clinical Excellence, 2008; Royal College of Obstetricians and Gynaecologists, 2008). This enables the timely offer of screening for infections including HIV and other STIs, conditions such as sickle cell disease, as well as fetal anomalies and Downs Syndrome (National Institute for Health and Clinical Excellence, 2008)[13]. It also allows adequate time for pregnant women to make informed decisions regarding their care. For HIV-positive women a sexual health assessment is also recommended (Taylor *et al*, 2012), particularly for those newly diagnosed, since genital tract infections could potentially influence the risk of MTCT (King *et al*, 2013). After a woman has booked for care, her pregnancy 'risk status' can be assessed (Cantwell *et al*, 2011), enabling early intervention and appropriate management of both pre-existing and pregnancy-related conditions such as diabetes and pre-eclampsia. Women's obstetric histories can also be reviewed and taken into

[13] Also see NHS antenatal and newborn screening timeline: http://cpd.screening.nhs.uk/timeline (Accessed January 2014).

consideration in the management of their current pregnancy. Poor engagement with antenatal care, as indicated by late or never booking and/or poor attendance for appointments, has been associated with adverse maternal and perinatal outcomes in the general population (Blondel *et al*, 1993; Blondel *et al*, 1998; Raatikainen *et al*, 2007; Tucker *et al*, 2010). The 2011 Confidential Enquiry into Maternal Deaths in the UK noted a high rate of late booking among women who died (Cantwell *et al*, 2011), though causality cannot be presumed.

For women living with HIV, early booking is of additional importance to ensure that they receive the HIV-specific care they require in a timely manner including assessment of their clinical status and initiation of ART. Early booking for antenatal care is of increasing importance for the optimal management of HIV in pregnancy in light of the move towards earlier initiation of antenatal ART, as described in Chapter 1, Section 1.2.4. Indeed, a UK audit found late booking to be a key reason for women receiving insufficient antenatal ART (Modestini *et al*, 2013). Inadequate antenatal care has also been reported to be a risk factor for non-receipt of antenatal ART in the US (Abatemarco *et al*, 2008; Wilson *et al*, 2004), and an increased risk for the vertical transmission of HIV (Peters *et al*, 2003; Warszawski *et al*, 2008).

Antenatal care booking among the general UK population

National Health Service (NHS) maternity statistics for England show that during 2009-2010, 37% of women booked at 13 gestational weeks or later (Health and Social Care Information Centre, 2010). Several studies have explored the reasons for late booking in the UK general population though definitions of 'late booking' vary. A national survey of women's experience of maternity care in England, involving a random sample of over 5000 women receiving care during 2010, reported that parous women booked later than nulliparous women (with 59% and 66% respectively having booked by 10 completed weeks) (Redshaw *et al*, 2010). An association between higher parity and later booking was also reported by two retrospective London-based studies one of which classified late booking as ≥13 weeks (Cresswell *et al*, 2013), and the other as >18 weeks (Baker *et al*, 2012). Both studies adjusted for confounding factors and reported that although there was no significant difference in timing of booking between nulliparous women and those with only one previous birth, women with a higher number of previous births (two or more in the study by Creswell *et al*, and four or more in the Baker *et al* study) were at significantly increased risk. Both were reasonably large studies consisting of 20,135 women and 5629 women respectively. The national survey by Redshaw *et al* did not report on maternal age in relation to antenatal booking but the two London-based studies, as well as an earlier study which analysed data from nine UK maternity units, all

reported that younger women were more likely to book late (Baker *et al*, 2012; Cresswell *et al*, 2013; Kupek *et al*, 2002).

With regard to socio-cultural factors, not being in a relationship (Redshaw *et al*, 2010; Rowe *et al*, 2008) and having unstable accommodation (Cresswell *et al*, 2013), the latter a possible marker of social marginalisation, have been associated with later booking. However, there was no significant association with an area-level deprivation measure in the study by Redshaw *et al*, nor in a study of social and ethnic variations in antenatal care usage, though the latter was a postal survey subject to selection bias (for example, only 5% of those responding to the survey had booked late) (Rowe *et al*, 2008). Meanwhile, being born outside the UK and/or being of non-white ethnicity has been quite consistently reported as a risk factor for late booking (Cresswell *et al*, 2013; Kupek *et al*, 2002; Redshaw *et al*, 2010; Rowe *et al*, 2008), particularly noteworthy given that most HIV-positive women in the UK are black African. In the national survey, women belonging to black and minority ethnic groups who were born outside the UK had an adjusted OR for booking by 10 weeks of 0.59 (95% CI: 0.48-0.72) compared with white UK born women (Redshaw *et al*, 2010). Linked to this, an inability to speak English has been identified as a risk for late booking (Cresswell *et al*, 2013). A recently published systematic review of the international literature on antenatal care usage among migrants and their descendants living in the Western world identified a lack of knowledge about the healthcare system and language difficulties as the most important barriers to accessing antenatal care, other barriers included cultural factors e.g. religious practices, as well as practical concerns e.g. lack of transport and childcare (Boerleider *et al*, 2013). However, the review excluded certain groups such as undocumented migrants, refugees and asylum seekers who may potentially face even greater difficulties accessing healthcare (Rechel *et al*, 2013).

Engagement with antenatal care among HIV-positive women

There is a paucity of published data from Europe, including the UK, on the engagement of HIV-positive women with antenatal care. A small study in one London centre reported that HIV-positive women tended to book later than the general clinic population (a median of 16 gestational weeks compared with 11 weeks) (Parisaei *et al*, 2007). The limited data that has been published on factors associated with antenatal care engagement among HIV-positive women originates largely from the US. These data are only briefly considered here as it may be difficult to translate to the UK situation, not only due to differences between the UK and US populations of HIV-positive women (Newell *et al*, 2007), but also because of the inherent differences in healthcare systems. For example, the UK healthcare system is funded through

general taxation and provides universal access[14]. Meanwhile, in the US healthcare is provided largely by the private sector which may favour those who can afford good healthcare, leaving the poor with limited access[15]. Despite this, the US studies identified similar risk factors to those noted among the general UK population, with both higher parity and being single (Abatemarco *et al*, 2008) being risk factors for receiving limited antenatal care (defined as less than five visits). Additionally, drug use was negatively associated with antenatal care engagement (Abatemarco *et al*, 2008; Peters *et al*, 2003; Turner *et al*, 1995). Women of black ethnicity experienced poorer antenatal care usage (Abatemarco *et al*, 2008; Peters *et al*, 2003), a finding also reported in an analysis of data from the French Perinatal Cohort with 14% of black Africans and 10% of white women initiating antenatal care during the third trimester (p<0.001), though the association was attenuated after adjusting for late HIV diagnosis (Jasseron *et al*, 2008)[16].

Summary

Timely booking for antenatal care is a vital step in the care pathway for the optimal management of HIV during pregnancy, as well as being important for a healthy pregnancy, yet there is a notable lack of literature on HIV-positive women's engagement with care. The population sub-groups that emerge as being at risk of poorer engagement, for example, migrant women, suggest that many HIV-positive women may be at heightened risk of late booking as compared with the general population. Furthermore, being parous, particularly having had several previous births, has been quite consistently identified as a significant risk factor for poorer engagement both in the UK general population, and among HIV-positive women in other settings. This suggests that diagnosed women experiencing repeat pregnancies may be a group at potentially heightened risk.

[14] Although primary care (i.e. access to a GP) is available to everyone, secondary care may be chargeable for some population groups (see: http://www.nhs.uk/NHSEngland/AboutNHSservices/uk-visitors/Pages/accessing-nhs-services.aspx, Accessed September 2014).

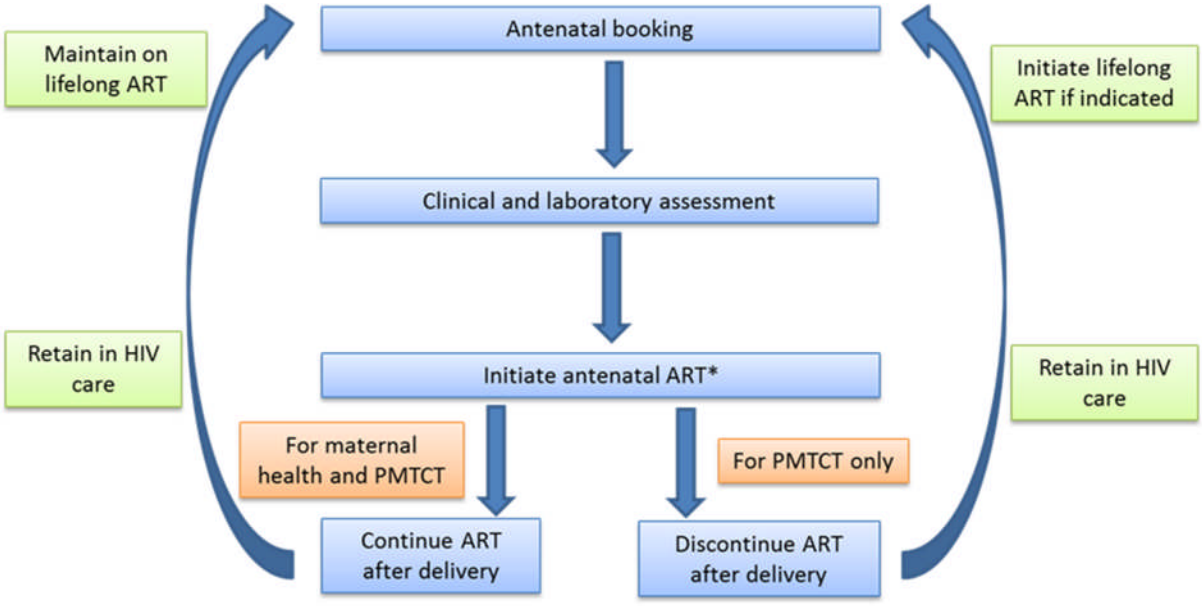
[15] For further information on differences between the UK and US healthcare systems see: http://news.bbc.co.uk/1/hi/health/8201711.stm, Accessed September 2014.

[16] An association between black African ethnicity and later booking has also been recently reported in an analysis of the NSHPC data by Tariq *et al* (2012). The work was conducted concurrently to the analyses presented in this thesis and is discussed further in Chapter 5 in relation to analyses on antenatal care booking.

2.4 Engagement with HIV care, and the health and management of women in the context of pregnancy and beyond

Figure 2.1 provides a simplified overview of the 'loop' of care for diagnosed women experiencing repeat pregnancies, linking together the various elements discussed in this section (as well as antenatal booking, as discussed in the previous section). Specific details of UK recommendations regarding timing of ART initiation and indications for treatment were provided in Chapter 1 (Sections 1.1.5 and 1.2.4) and have been omitted from the figure for clarity.

Figure 2.1 Simplified loop of care for women experiencing repeat pregnancies



*For women not already on ART

After providing a brief overview of the potential impact of pregnancy on HIV disease, the literature on the following aspects of women's health and management are reviewed: i) timely initiation of antenatal ART, ii) potential discontinuation of antenatal ART after delivery when received for PMTCT only (which may impact on maternal health in future pregnancies), iii) retention in HIV care after pregnancy (thus facilitating the timely ART initiation outside pregnancy, and completing the 'loop').

Influence of pregnancy on HIV disease progression

Since the process of pregnancy itself is associated with physiological alterations e.g. suppression of immune function (Kuhnert *et al*, 1998), it has the potential to alter the course of HIV disease, or modify the impact of treatment on disease progression. Although an early review of the literature tentatively concluded that pregnancy may slightly increase the risk of HIV disease progression (French *et al*, 1998), the expanding evidence-base in the ART era points towards no significantly increased risk (Heffron *et al*, 2014; MacCarthy *et al*, 2009; Saada *et al*, 2000; van Benthem *et al*, 2002; Westreich *et al*, 2013). There are, however, some contrasting findings. In one US observational cohort pregnancy was associated with a significantly decreased risk of disease progression (Tai *et al*, 2007), though this could perhaps partly be explained by healthier women becoming pregnant (Le Moing *et al*, 2008). Furthermore, some important methodological limitations of the study have been noted (Westreich *et al*, 2008). However, a French cohort study of women conceiving on ART found that CD4 counts were stable with no increase after delivery, as may have been expected (Le Moing *et al*, 2008). A detailed assessment of the evidence-base is beyond the scope of this review. Of note with regard to repeat pregnancies, a US study specifically compared disease trajectories among women with a single pregnancy and those with two pregnancies, and reported that having more than one pregnancy did not result in any adverse consequences in terms of CD4 count and viral load (Minkoff *et al*, 2003).

Timing of antenatal ART initiation

Women presenting in pregnancy and not yet in receipt of ART will comprise those who require ART for their own health (CD4 <350 cells/µl and/or symptomatic) (Williams *et al*, 2012), and those with higher CD4 counts who need ART for PMTCT only. A number of studies have explored reasons for non-uptake, or delayed initiation of antenatal ART. Late HIV diagnosis (Bailey *et al*, 2011; von Linstow *et al*, 2010), illicit drug use (Abatemarco *et al*, 2008; Bailey *et al*, 2011; Orloff *et al*, 2001), being asymptomatic and/or less immunosuppressed (Abatemarco *et al*, 2008; Bailey *et al*, 2011; Orloff *et al*, 2001) and being single (Bailey *et al*, 2011) have all

been found to be important risk factors. With regard to ethnicity, the findings appear to differ according to setting with no association between ethnicity and uptake of antenatal ART in Western Europe (Bailey *et al*, 2011), but women of black ethnicity had a decreased odds of ART receipt in the US (Abatemarco *et al*, 2008). This may reflect differences in the populations studied (Newell *et al*, 2007), the time periods (the US study having been conducted during the late 1990s), as well as potential differences between the US and Europe in terms of disparities in access to healthcare according to ethnic group. Some women may also choose to decline ART (Mayaux *et al*, 2003; Modestini *et al*, 2013; von Linstow *et al*, 2010).

Discontinuation of ART after pregnancy

Pregnant women who do not require treatment for their own health may receive short-course ART, stopped after delivery (Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission, 2012; Taylor *et al*, 2012). Current policy for HIV treatment outside the context of pregnancy is that once initiated, patients should remain on ART for life (Panel on Antiretroviral Guidelines for Adults and Adolescents, 2013; Williams *et al*, 2012; World Health Organization, 2013). This is in light of some important randomised trials that have raised concerns about the impact of HIV treatment interruptions (investigated as a potential strategy to optimise lifelong HIV treatment). The Strategies for Management of Antiretroviral Therapy (SMART) Study, the largest to date, reported that among people with CD4 counts of >350 cells/μl, those randomised to episodic rather than continuous treatment experienced a significantly increased risk of opportunistic disease and death (El-Sadr *et al*, 2006). Similar findings were reported from the Trivacan trial which reported a 2.5-fold higher risk of severe morbidity among those on CD4 guided treatment interruption (Danel *et al*, 2006). Both trials were consequently halted early, and call into question the risks, in terms of maternal health, of short-course ART for PMTCT. Pregnant women are the only population group recommended to take short-course therapy. This is because, for those with no indication for treatment themselves, the purpose of antenatal ART is for the prevention of vertical transmission of HIV. As discussed in Chapter 1, Section 1.1.5, the risk-benefit ratio of initiating lifelong ART in adults with high CD4 counts (e.g. >350 cells/μl) is uncertain.

Several studies have explored disease progression after the discontinuation of antenatal ART. A cohort study in Brazil which followed up women presenting with a CD4 count of >300 cells/μl and receiving short-course ART during pregnancy, reported that CD4 counts fell to <300 cells/μl in a mean of 3.5 years after delivery (Palacios *et al*, 2009), though the study was relatively small consisting of only 75 women. In a multi-country African study 28% of women

with an initial CD4 count of ≥400 cells/μl had declined to <350 cells/μl at 24 months post-partum (Ekouevi *et al*, 2012), while follow-up data from a randomised trial in Botswana found that among women with CD4 counts ≥200 cells/μl discontinuing ART after the breastfeeding period, 15% of women (*n*=84) re-initiated cART for their own health (except in one woman who initiated ART for PMTCT in a subsequent pregnancy) at a median of 12 months post-partum (Shapiro *et al*, 2013). Meanwhile, a study in Haiti revealed that women with a delivery CD4 count of 350-499 cells/μl experienced decline to 350 cells/μl in an average of 19 months (compared with 71 months among those with delivery counts of ≥500 cells/μl) (Coria *et al*, 2012). Indeed, some other studies on this topic have highlighted that women's starting CD4 count is important for subsequent disease progression. For example, an analysis of trial data (investigating an extended nevirapine regimen for infants to prevent HIV transmission via breastfeeding in four African countries) found that during one year post-partum follow-up of the mothers, 37% of those with a delivery CD4 count of 400-549 cells/μl had dropped to <350 cells/μl compared with just 7% of those with a delivery CD4 count of >550 cells/μl. Based on these findings the authors suggest that continuation of ART after delivery may be advisable only for those women with lower delivery CD4 counts (in this case <550 cells/μl) (Watts *et al*, 2013). In the multi-country African study by Ekouevi *et al*, when women were grouped into those with enrolment CD4 counts of 400-499 cells/μl and those with counts of ≥500 cells/μl, 46% and 19% respectively had declined to <350 cells/μl by 24 months (Ekouevi *et al*, 2012).

Other studies have compared levels of disease progression in women who continue *vs*. discontinue ART post-partum. A retrospective cohort study in one US state followed 158 women (49 who continued, and 109 who discontinued ART post-partum) for a median of 33 months; opportunistic infections occurred in two (4%) women who continued ART and 10 (9%) who discontinued (*p*=0.26), and there were two deaths, both among discontinuers who developed opportunistic infections. However, this was a small study and the results were likely influenced by the fact that there were some important differences between those who continued *vs*. discontinued ART with greater parity, the absence of a partner, and having no indication for treatment all being independently associated with ART discontinuation (Onen *et al*, 2008). Among women enrolled in the US WITS with a CD4 count of >350 cells/μl, a comparison of those who chose to stop and those continuing ART post-partum found no significant difference in either clinical or immunological disease progression between groups although the study was relatively short with a 12 month follow-up period (Watts *et al*, 2009). Of course these observational data are subject to bias and confounding that cannot always be completely adjusted for in the analyses. The Kesho Bora trial, a multi-centre African study designed to assess the effectiveness of ART during pregnancy, randomised 824 women to

receive either triple therapy continued throughout the breastfeeding period or zidovudine plus sdNVP with no post-partum ART. Women continuing ART after delivery had a significantly lower risk of disease progression (a combined endpoint of death, WHO clinical stage 4 disease, or CD4 <200/µl) during the post-partum period indicating a potential benefit, in terms of maternal health, of the continuation of ART post-partum in this African setting[17] (Kesho Bora Study Group, 2012). Such randomised trial data can provide strong, high-quality evidence for associations because confounding and selection bias should be minimal and standardised procedures can be applied. On the other hand, trial data might have limited generalisability since the characteristics of participants may differ from those of the broader population of interest, and trials tend not to be carried out under 'real life' conditions.

In 2012 the WHO introduced 'Option B+' whereby pregnant women initiate lifelong ART irrespective of their CD4 count (World Health Organization, 2012, 2013). The benefits of such an approach have been cited as enabling the simplification of PMTCT programmes, potential health benefits from the earlier initiation of lifelong ART, MTCT prevention in future pregnancies, reducing the risk of HIV transmission to sexual partners, and avoiding stopping and starting of ART (World Health Organization, 2012). In resource-rich settings this recommendation needs to be considered in the context of changing guidelines towards earlier initiation of ART among the general HIV-positive population, with some now recommending treatment for all, irrespective of CD4 count (Panel on Antiretroviral Guidelines for Adults and Adolescents, 2013; Thompson *et al*, 2012). It should, however, be noted that as discussed in Chapter 1, the evidence-base on the optimal timing of ART initiation is inconclusive (Sabin *et al*, 2013). Current UK guidelines do allow for the continuation of antenatal ART in women who have not yet reached the treatment threshold, but have a CD4 count of 350-500 cells/µl and wish to continue therapy (Taylor *et al*, 2012). The potential benefits and risks of the Option B+ strategy are wide-ranging, and the evidence-base is lacking, as highlighted in a recent review (Ahmed *et al*, 2013). Further research is required, not only internationally, but also with regard to the applicability of such an approach to resource-rich settings.

Retention in HIV care after pregnancy

Irrespective of whether ART is continued or discontinued after delivery, ensuring that women remain engaged in HIV care after their pregnancy ends is key to their optimal health and

[17] A key aim of the analysis was to assess whether triple ART taken during pregnancy and breastfeeding was associated with an increased risk of disease progression after discontinuation, as compared with antenatal zidovudine plus sdNVP (which was not expected to impact on the course of HIV disease). In this regard there was no significant difference in disease progression between the two groups 18 months after ART was stopped.

management. HIV-related services encompass a broad spectrum of care for people living with HIV including regular monitoring of CD4 counts to enable the timely initiation of ART, monitoring of treatment side effects and sub-optimal response to therapy, adherence support, regular sexual health assessments, and monitoring of general physical and psychological health thus enabling appropriate referrals (Asboe *et al*, 2012; Fakoya *et al*, 2008). For women of childbearing age, and their partners, attendance at HIV services also provides the opportunity for advice on contraception, as well as pre-conception counselling (Fakoya *et al*, 2008).

In a study of loss to follow-up from HIV care in England, Wales and Northern Ireland during 1998-2007, following attendance for care in a given year, 10% of diagnosed adults did not attend during the subsequent calendar year, and cumulatively nearly two-fifths of those attending during 1998-2006 were lost to follow-up by the end of 2007 (Rice *et al*, 2011). The study revealed that being female and of childbearing age were both associated with an increased risk of loss to follow-up (Rice *et al*, 2011). Furthermore, there is a body of international evidence to suggest that post-partum women are at particular risk of loss to follow-up (Clouse *et al*, 2013; Lemly *et al*, 2007; Myer *et al*, 2012; Rana *et al*, 2010; Wang *et al*, 2011), as well as poorer adherence to ART, as highlighted in a large, international systematic review (Nachega *et al*, 2012). For example, in a French study of HIV care attendance over a 24 month period after giving birth, although the proportion with no attendance (11%) was very similar to the 10% one year loss to follow-up rate documented by Rice *et al*, attendance was reported to be irregular (less than four visits during the 24 month follow-up) in a further 14% of women. This meant that only 75% of these post-partum women attended care regularly (Lemly *et al*, 2007). Meanwhile data from the US found that only 37% of women attended the recommended number of HIV care visits during the year after delivery (Rana *et al*, 2010). Again, the differing healthcare systems and standards of HIV care in the UK and the US should be borne in mind here. In the UK, of all adults attending HIV care during 2011, 95% were retained in care the following year (Aghaizu *et al*, 2013). The comparable figure for the US was much lower at around 50% (Centers for Disease Control and Prevention, 2011). Childcare responsibilities are a potential barrier to regular care attendance (Boehme *et al*, 2014), and have also been linked to poorer adherence to ART in post-partum women (Merenstein *et al*, 2009; Merenstein *et al*, 2008; Turner *et al*, 2000). Psychological factors such as post-partum depression may also play a role (Nachega *et al*, 2012). Since the NSHPC does not collect information on the HIV-related care of women after delivery, it is not possible to explore the level of lost to follow-up after pregnancy among diagnosed women in the UK using this data source alone.

Summary

There are gaps in knowledge regarding the optimal management of diagnosed women of childbearing age. In particular, that many diagnosed women may have more than one pregnancy raises the question as to whether lifelong ART (WHO Option B+) should be initiated in all pregnant women, rather than short-term antenatal ART for PMTCT, discontinued after delivery, as per current UK recommendations for women not needing treatment. The evidence-base for such an approach is currently lacking.

2.5 Impact of short-course antenatal ART on subsequent response to therapy

As discussed in Chapter 1, short-course ART has been an extremely effective cornerstone of PMTCT interventions. However, aside from the potential detrimental impact of short-course ART on women's health in the short or longer-term, there is concern that the discontinuation of therapy after delivery may limit future therapy options, either in subsequent pregnancies, or when HIV treatment is later required for women's own health.

Development of drug resistance following exposure to single dose nevirapine (sdNVP) for PMTCT

Until 2006 sdNVP was recommended by the WHO for the prevention of vertical transmission in resource-limited settings due to its relative effectiveness (reducing the risk of MTCT by around 40-50% (Guay *et al*, 1999; Jackson *et al*, 2003)), simplicity and low cost (World Health Organization, 2004, 2006). There is, however, a substantial and growing evidence-base demonstrating high levels of resistance mutations following sdNVP exposure, including those which confer cross-resistance to other NNRTIs (Cunningham *et al*, 2002; Eshleman *et al*, 2001; Jourdain *et al*, 2004; Lockman *et al*, 2010; Wind-Rotolo *et al*, 2009). In a systematic review and meta-analysis the pooled estimate of the prevalence of nevirapine resistance in women exposed to sdNVP, with or without other antenatal ART, was 35.7% (95% CI: 23.0-50.6) at 4-8 weeks post-partum (Arrive *et al*, 2007). Even when women receive nevirapine in combination with other drugs, due to its long half-life 'functional monotherapy' may result if drug stoppages are not staggered (Mackie *et al*, 2004). By providing a 'tail' of other drugs while nevirapine levels decline, the risk of resistance mutations can be lowered as highlighted in a recent review (Paredes *et al*, 2013). sdNVP continues to be used in many resource-limited

settings (UNAIDS, 2011a), and there will be many women with a history of exposure to this regimen in pregnancy.

Subsequent response to NNRTI-based therapy following exposure to sdNVP

NNRTI resistance mutations may be archived in the latent viral reservoir (Wind-Rotolo *et al*, 2009) and can therefore potentially hamper subsequent response to NNRTI-based therapy. Studies from resource-limited settings have reported that women with sdNVP exposure may be at increased risk of virological failure when they subsequently initiate nevirapine (or other NNRTI)-containing regimes (Paredes *et al*, 2013). In a Thai trial, 1844 women who received antenatal zidovudine were randomised to either receive sdNVP or placebo at delivery. Among 269 women who subsequently initiated nevirapine-containing cART regimens post-partum, virological suppression after six months was less frequent among those exposed to sdNVP (49% *vs*. 68%, *p*=0.03) (Jourdain *et al*, 2004). The Optimal Combination Therapy after Nevirapine Exposure (OCTANE) study, conducted in seven African countries, demonstrated that among women previously exposed to sdNVP, 8% of those on ritonavir-boosted lopinavir-containing regimens experienced virological failure or death versus 26% of those on a nevirapine-containing regimen (*p*=0.001) (Lockman *et al*, 2010). Data on women receiving NNRTI-based ART (either nevirapine- or efavirenz-containing) in Zambia were also consistent with an increased risk of virological failure in the six months after sdNVP exposure (compared with those without prior sdNVP), though the adjusted HR was not significant (1.6, 95% CI: 0.9–2.7) (Chi *et al*, 2007). All three were large-scale, high-quality studies and the findings have important, far-reaching implications for PMTCT interventions in resource-limited settings.

However, several studies have demonstrated that the risks of subsequent virological failure may decline with a longer interval between sdNVP and subsequent treatment, which fits with the concept of fading resistance over time (Eshleman *et al*, 2001). Two studies (an observational study nested within the Mashi randomised trial in which women receiving antenatal zidovudine were randomised to receive either sdNVP or placebo, and a multi-country study with no randomisation) reported inferior virological responses when NNTRI-based regimens were commenced within six or twelve months of sdNVP exposure but not when the interval was greater than this (Lockman *et al*, 2007) and (Stringer *et al*, 2010) respectively. Since there was no randomisation in the latter study there may have been some systematic differences between those who received sdNVP and those who did not, though women were matched according to health status to help address this. Meanwhile, a South African observational study showed no evidence of poorer virological suppression when NNRTI-based

therapy was initiated 18-36 months after sdNVP but documented that presence of the K103N mutation was strongly associated with virological failure (Coovadia *et al*, 2009).

Development of drug resistance following exposure to short-course cART for PMTCT

Some studies have evaluated the emergence of resistance resulting from receipt of cART for PMTCT, though most were relatively small-scale. Selected studies are detailed in Table 2.1. In general, these studies point towards the development of quite significant levels of NNRTI resistance mutations in women exposed to nevirapine-containing regimens, but tend to report much lower levels of resistance following exposure to PIs. For example, resistance mutations were identified in 13% of women in the Irish analysis by Lyons *et al*, all of whom received a nevirapine-containing regimen (Lyons *et al*, 2005b). Similar levels of resistance mutations were subsequently reported in a small, single site study from the US; four of 21 (19%) women with exposure to ART in a previous pregnancy (three of whom had received nevirapine) developed resistance (Overton *et al*, 2005). Notably high levels of NNRTI resistance mutations were detected in another US study in which two of eight women (25%) receiving nevirapine developed an NNRTI resistance mutation. However, the study highlights that the estimated prevalence of resistance mutations differs depending on the specific mutations tested for, and also the resistance testing methodology employed (Paredes *et al*, 2010).

Meanwhile, no PI resistance mutations were detected in the US study by Overton *et al* and rates were very low (1%) in the study by Paredes *et al*. In the small German study restricted to women who had received PI-based cART the authors concluded that there were no clinically significant resistance mutations (Gingelmaier *et al*, 2010). Likewise, in the Mma Bana study in Botswana (a trial of ART-naive women randomised to either triple NRTI or PI-based regimens for PMTCT) no clinically significant mutations were detected among 54 samples genotyped one month after the discontinuation of ART (Souda *et al*, 2013). However, high levels of resistance to nelfinavir were reported in the small sub-study of women enrolled in a randomised trial (Ellis *et al*, 2011).

Table 2.1 Selected studies investigating development of drug resistance following exposure to short-course cART for PMTCT

Study reference	Setting	*n**	Type of cART regimen	Duration of cART received	Timing of post-partum resistance testing	Frequency of resistance mutations	Notes/ additional details
(Lyons *et al*, 2005b)	Ireland	39	NNRTI (nevirapine)-based in 29 (74%) and PI (nelfinavir)-based in 10 (26%)	Median: 70 days	Median of 42 days post-partum	7 resistance mutations in 5 (13%) women	All mutations were in women who were ART-naive and received nevirapine
(Overton *et al*, 2005)	US	21	Nevirapine-based in 13 (62%)	Not reported	Conducted when women presented with a subsequent pregnancy	19% (4/21 women)	3 of the 4 mutations were in women exposed to nevirapine. No PI resistance mutations were detected
(Pilotto *et al*, 2009)	Brazil	139	NNRTI-based (22%) or PI-based (78%)	Median: 84 days	Not reported	14% overall	Conference abstract (limited data available)
(Paredes *et al*, 2010)	US and Puerto Rico	114	82% received cART (NNRTI (nevirapine)-based in 8 women and PI (nelfinavir)-based in 87). 18% received dual therapy	Mean: 68 days for NNRTI-based cART and 110 days for PI-based	Median of 70 days post-partum	Overall, 49 women (43%) had at least 1 resistance mutation	Mutations were detected in 25%** (2/8) of those who received nevirapine, and 1% of those who received PI-based cART

Continued overleaf

Table 2.1 *Continued:* Selected studies investigating development of drug resistance following exposure to short-course cART for PMTCT

Study reference	Setting	*n**	Type of cART regimen	Duration of cART received	Timing of post-partum resistance testing	Frequency of resistance mutations	Notes/ additional details
(Gingelmaier *et al*, 2010)	Germany	36	All PI-based	Median: 59 days	Median of 44 days post-partum	None	The authors state that there were no "clinically significant" mutations
(Souda *et al*, 2013)	Botswana	54	NRTI-based in 29 (69%) and PI-based in 25 (58%)	Median: 266 days	One month after cART discontinuation (7 months post-partum)	None	The authors state there were no "clinically significant" mutations - only mutations present among ART-naive adults in Botswana)
(Ellis *et al*, 2011)	US	16	Half were randomised to nelfinavir and half to nevirapine-based therapy	Mean: 88 days before delivery plus 236 days after (nelfinavir), and 125 days before plus 372 days after (nevirapine)	Median of 88 days after ART discontinuation	Detected in 75% of those who received nelfinavir and 50% of those who received nevirapine	

*Number of participants with post-partum resistance testing results
**Based on the K103N mutation (the proportion was 12.5% for the Y188C mutation)

Response to antenatal ART among women with exposure to short-course cART

There are relatively few data on the subsequent response to antenatal ART among women with prior exposure to short-course cART for PMTCT. In a small Irish study during 1998-2005 the authors reported no increased risk of MTCT in repeat compared with index pregnancies, and a higher proportion of women achieved virological control in their repeat pregnancies (Lyons *et al*, 2005a). However, this was an initial descriptive analysis, and the type of ART received in women's current and previous pregnancies was not detailed. The most relevant study on this topic is an analysis of the French Perinatal Cohort that included 869 ART-naive women and 247 who had previously received ART for PMTCT during a previous pregnancy (various regimens, 52% had received cART and this was largely PI-based). The multivariable analysis was restricted to women receiving PI-based cART in their current pregnancy and revealed that previous exposure to cART was not associated with detectable viral load at delivery (adjusted OR (aOR): 0.60, 95% CI: 0.33-1.10). The association between previous cART and MTCT was not, however, explored (Briand *et al*, 2011).

Conversely, in a US study, pre-pregnancy cART exposure (based on self-report and not limited to use for PMTCT) was found to be a significant risk factor for detectable viral load at delivery in unadjusted analyses (Katz *et al*, 2010). However, as the analysis was not restricted to women who had received previous short-course cART during a pregnancy, the results are less relevant to the question as to whether short-course ART for PMTCT hampers subsequent response to therapy. For example, some of the women will have previously initiated cART for their own health and stopped for some reason, possibly an unscheduled stoppage. The multivariable analyses were conducted separately on cART-naive and cART-experienced women so adjusted comparisons between the two groups could not be drawn. Furthermore, information on the type of cART received previously was not provided, which may be important in light of the resistance studies suggesting that the risks may be largely confined to those with previous NNRTI exposure.

Meanwhile, a study in three US centres provided inconclusive results. The authors assessed the time to virological suppression during pregnancy, defined as either <400 copies/ml or <1000 copies/ml, among 62 ART-experienced women (not necessarily during a previous pregnancy) and 76 ART-naive women. Most (79%) received a PI-based regimen and the proportion achieving virological suppression (<400 copies/ml) during pregnancy was similar in the two groups: 92% in ART-experienced and 93% in ART naive (p=0.82), although the median time to viral suppression was longer in the ART-experienced group (27 days (IQR: 18.5–54.3) *vs*. 25 days (IQR: 16-34), p=0.02). A similar pattern was

observed when the <1000 copies/ml virological failure cut-off was used. However, the associations did not hold in adjusted analyses (Aziz *et al*, 2013). It should be borne in mind that all these are observational studies and some demographic and clinical differences between women with prior exposure to short-course cART and ART-naive women were noted. Though some of these differences could be adjusted for in the analyses, unmeasured or residual confounding may remain.

Summary

In the UK and Ireland, as in many resource-rich settings, the majority of women receive cART for PMTCT, with most now recommended to receive PI-based cART (Taylor *et al*, 2012). While inferior virological responses to ART have been documented in women with prior exposure to sdNVP, little is known about the impact of short-course cART for PMTCT on response to cART in subsequent pregnancies. This information is important not only to ensure women are managed effectively in their current pregnancy, but also to inform the evidence-base on the potential benefits and risks of discontinuing ART after delivery.

2.6 Adverse perinatal outcomes among HIV-positive women

With an increasing proportion of women conceiving on treatment, more fetuses are being exposed to ART throughout the gestational period. Adverse perinatal outcomes are thus a high priority for pregnancy-related HIV research. When considering the risk of adverse perinatal outcomes among diagnosed women one needs to keep in mind that in addition to the biologic, obstetric, demographic and behavioural factors that influence risks among the general population, the role of HIV disease and ART also require consideration. This section provides a brief overview of the frequency of selected adverse perinatal outcomes (namely preterm birth, low birthweight, congenital abnormalities and stillbirths) among diagnosed women, and then explores some key risk factors for adverse outcomes, with an emphasis on those of relevance to women experiencing repeat pregnancies. The narrative then focuses on preterm delivery as an outcome of particular interest in view of the growing but conflicting evidence-base on the risk of preterm delivery among diagnosed women, particularly in relation to antenatal cART exposure.

Brief overview of the occurrence of adverse perinatal outcomes (see Box 2.2)

Preterm delivery, defined as <37 gestational weeks (Steer, 2005), affects around 7% of pregnancies in England and Wales (Office for National Statistics, 2011a), and 6% across Europe (Beck *et al*, 2010). Rates in the US are even higher at 12-13% (Goldenberg *et al*, 2008). Infants born preterm are at increased risk of mortality as well as a range of

neurological and developmental conditions that continue into adulthood (Riley *et al*, 2008; Saigal *et al*, 2008). In England and Wales the overall infant mortality rate in 2009 was 4.4 per 1000 live births but 27.5 per 1000 among those born at 24-36 weeks gestation (Office for National Statistics, 2011a). A number of studies have reported higher rates of preterm delivery among HIV-positive women than the general population, or in some cases an HIV-negative control group (Boer *et al*, 2007; European Collaborative Study and Swiss Mother and Child HIV Cohort Study, 2000; Lopez *et al*, 2012; Rudin *et al*, 2011; Sibiude *et al*, 2012; Townsend *et al*, 2007), with both HIV infection itself, as well as ART received during pregnancy, appearing to play a role. The risk among HIV-positive women receiving antenatal cART is a particularly active area of research, as will be discussed.

With any drug received during pregnancy the potential risk to the fetus needs careful consideration. Internationally, the ongoing safety of ART in pregnancy, in terms of teratogenic effects, is monitored through the Antiretroviral Pregnancy Registry (APR). This passive surveillance scheme, introduced in 1989, is designed to detect any major teratogenic effects of antiretrovirals to which women are exposed during pregnancy. Data on potential teratogenic effects of antenatal ART from the APR and other studies are largely reassuring, rates of congenital abnormalities among infants with in utero exposure being consistent with those in the general population (Antiretroviral Pregnancy Registry Steering Committee, 2013; Gibb *et al*, 2012; Townsend *et al*, 2009; Watts *et al*, 2007). There have been concerns around first trimester exposure to ART, efavirenz in particular, which originated from animal studies (Nightingale, 1998), and some clinical case reports (De Santis *et al*, 2002; Fundaro *et al*, 2002). However, a recent systematic review and the APR have both found no evidence of an increased risk of overall birth defects associated with first trimester efavirenz exposure (Antiretroviral Pregnancy Registry Steering Committee, 2013; Ford *et al*, 2011). Current UK guidelines recommend that efavirenz may be prescribed during pregnancy, and may be continued throughout pregnancy in women conceiving on it (Taylor *et al*, 2012). The frequency of congenital abnormalities in infants born to diagnosed women reported to the NSHPC during 1990-2007 was 2.8% overall (including major and minor abnormalities), consistent with rates in the general population (around 2%) – see Box 2.2. There was no significant increase in risk for infants exposed to ART, or by timing of ART exposure (2.8% in unexposed infants, 3.1% in those with first trimester exposure, and 2.7% following second or third trimester exposure, p=0.69) (Townsend *et al*, 2009).

Low birthweight (defined by the WHO as <2.5kg), which is of course correlated with gestational age at delivery, is a risk for neonatal morbidity and mortality (Malin *et al*, 2014). Earlier NSHPC analyses reported that around 14% of infants were of low birthweight

(Townsend *et al*, 2008b) compared with around 6% in the general population (Moser *et al*, 2008). Meanwhile, around 1 in 200 pregnancies in the UK results in a stillbirth (Centre for Maternal and Child Enquiries, 2011; Smith *et al*, 2007). Among births to diagnosed women reported to the NSHPC the rate of stillbirths was notably higher at 11 per 1000 births overall during 1990-2006 (Townsend *et al*, 2008b), and has been documented to be higher in women on cART (12.7 per 1000) compared with those on mono or dual therapy (5.7 per 1000) (Townsend *et al*, 2007). It is thus clear that HIV-positive women may be at potentially increased risk of some adverse perinatal outcomes as compared with the general population (see Box 2.2, but note that data are not directly comparable), the reasons for which are likely to be multifactorial including socio-demographic differences as well as the potential impact of HIV and antenatal exposure to ART.

Box 2.2 Overview of the risk of selected adverse outcomes in HIV-positive women compared with the general population, UK and Ireland*

Outcome	Risk in HIV-positive women	Risk in the general population	
		All women	Black African women
Pre-term delivery (<37 gestational weeks)	14.2% during 1990-2006 (Townsend *et al*, 2008b)	7.0% in 2009 (Office for National Statistics, 2011a)	7.7% in 2009 (Office for National Statistics, 2011a)
Congenital abnormalities	2.8% of births during 1990-2007 (Townsend *et al*, 2009)	2.2% of births during 2011** (Springett *et al*, 2013)	Comparable data not available
Low birthweight (<2.5 kg)	14.1% among deliveries during 1990-2006 (Townsend *et al*, 2008b)	6.1% among singleton live births in 2005 (Moser *et al*, 2008)	7.4% among singleton live births in 2005 (Moser *et al*, 2008)
Stillbirth	1.1% of deliveries during 1990-2006 (Townsend *et al*, 2008b)	0.5% of deliveries in 2009 (Centre for Maternal and Child Enquiries, 2011)	0.9% of deliveries among black women (*not* black African women specifically) in 2009 (Centre for Maternal and Child Enquiries, 2011)

*Estimates of the frequency of adverse outcomes among HIV-positive women are based on analyses of NSHPC data for the UK and Ireland. Estimates for the general population are based either on data for the UK (stillbirths) or for England and Wales only (preterm delivery, congenital abnormalities, low birthweight).

**Prevalence is the number of cases of congenital abnormality (live births, stillbirths, late miscarriages and terminations of pregnancy for fetal abnormality) as a proportion of the total number of live and stillbirths. Data is for more recent years are likely to be incomplete (e.g. the prevalence was 2.6% in 2007) (Springett *et al*, 2013).

Note: Data are intended to provide a broad, national-level picture of the frequency of the selected adverse outcomes. Data for HIV-positive women and the general population are not directly comparable due to differing methodologies, definitions and time periods for which data are available.

Factors influencing perinatal outcomes

This section provides background on some key risk factors for adverse perinatal outcomes that are of particular relevance to women experiencing repeat pregnancies. It does not aim to elucidate reasons for the differing rates of adverse outcomes among HIV-positive women as compared with the general population but rather draw on available data from both in order to identify potential risk factors.

Parity itself has been associated with perinatal outcomes among the general population, though the direction of the association differs depending on the outcome of interest. Women who are parous appear to have lower risks of stillbirth; in a large systematic review and meta-analysis nulliparous women had a 42% increased odds of stillbirth compared with parous women (Flenady *et al*, 2011). Parous women also have a lower risk of having low birthweight or small for gestational age infants with a pooled odds ratio for low birthweight among nulliparous compared with parous women of 1.41, 95% CI: 1.26-1.58 based on a meta-analysis of 41 studies (Shah, 2010), though the analyses were unadjusted for confounding factors. The risk of congenital abnormalities according to parity is complex, varying by type of abnormality (Duong *et al*, 2012). Finally, in the aforementioned meta-analysis by Shah *et al* there was no association between parity and the probability of preterm delivery (OR comparing nulliparous to parous women: 1.13, 95% CI: 0.96-1.34). Elucidating the relationship between parity and adverse outcomes is, however, complicated, likely encompassing both biological and psychosocial influences. For example, the higher rate of adverse outcomes documented among nulliparous women may in part be explained by higher risk women being less likely to have subsequent pregnancies (Miranda *et al*, 2011).

In Western settings substantial proportions of pregnancies to diagnosed women are occurring in those of older age (Aebi-Popp *et al*, 2010; Brown *et al*, 2012; Liuzzi *et al*, 2013; Townsend *et al*, 2008b), and of course women will be older at their repeat pregnancies. In the general population, advanced maternal age is a well-documented obstetric risk factor and has been linked with an increased risk of a range of adverse outcomes. Some examples are provided in Box 2.3. Older women are also at increased risk of pregnancy complications such as pre-eclampsia and gestational diabetes (Jacobsson *et al*, 2004).

Box 2.3 Examples of studies reporting an association between advanced maternal age and an increased risk of adverse perinatal outcomes

Outcome	Study reference
Stillbirth	(Flenady *et al*, 2011; Fretts, 2010; Huang *et al*, 2008; Nybo Andersen *et al*, 2000; Smith *et al*, 2007)
Miscarriage/fetal death	(Fretts *et al*, 1995; Jacobsson *et al*, 2004; Nybo Andersen *et al*, 2000)
Ectopic pregnancy	(Nybo Andersen *et al*, 2000)
Low birthweight	(Aldous *et al*, 1993; Cleary-Goldman *et al*, 2005; Nabukera *et al*, 2008)
Preterm delivery	(Aldous *et al*, 1993; Astolfi *et al*, 1999; Cleary-Goldman *et al*, 2005; Jacobsson *et al*, 2004; Nabukera *et al*, 2008)
Congenital abnormalities	(Cleary-Goldman *et al*, 2005)

HIV-positive women of older ages may also face additional risks such as poorer health due to more advanced HIV disease, and more complex treatment histories. Furthermore, HIV may cause premature ageing, even among those with well controlled infection (Capeau, 2011). Therefore, the risks of childbearing at older ages may potentially be even more pronounced in HIV-positive women. There are limited studies examining the association between maternal age and perinatal outcomes among diagnosed women, but some evidence of an increased risk of preterm delivery in older women is apparent. A Dutch cohort study of 143 women delivering under a policy of vaginal delivery reported that women aged ≥35 years had a five-fold increased risk of preterm delivery compared with those aged ≤25 years although this was not significant after adjusting for parity, CD4 count, first trimester cART use and mode of delivery (Boer *et al*, 2007). Meanwhile, an analysis of data from the Swiss Mother and Child HIV Cohort Study for 2003-2008 revealed a statistically significant increased odds of a combined 'pregnancy complications' variable (mainly pre-term delivery) per one year increase in maternal age (aOR: 1.06, 95% CI: 1.01-1.12), after adjusting for confounders including co-infections, body mass index, smoking, and alcohol or drug use (Aebi-Popp *et al*, 2010). A recent Italian analysis of national observational data on over 1500 pregnancies found that miscarriage, preterm delivery and low birthweight were more common among women aged ≥35 years, though only miscarriage remained significantly associated in the multivariable analyses (Liuzzi *et al*, 2013). The lack of an association in the adjusted analyses of both Boer *et al* and Liuzzi *et al* may reflect the important role of confounding factors that are potentially correlated with

age such as maternal health. HIV-positive women in poorer health have been documented to be at increased risk of preterm delivery (Aebi-Popp *et al*, 2010; Schulte *et al*, 2007; Sibiude *et al*, 2012; Thorne *et al*, 2004; Townsend *et al*, 2007; Townsend *et al*, 2010a; van der Merwe *et al*, 2011).

There is some debate regarding the optimal inter-pregnancy interval in the general population (World Health Organization, 2005). Short, as well as very long, intervals have been identified as a risk for adverse infant and maternal outcomes in both resource-limited and resource–rich settings, as reported in two large meta-analyses (Conde-Agudelo *et al*, 2006; Wendt *et al*, 2012). The adjusted pooled estimates produced in the meta-analysis exploring the influence of short inter-pregnancy intervals by Wendt *et al* revealed a significant association between an interval of less than six months and preterm birth (aOR: 1.41, 95% CI: 1.20-1.65), low birthweight (aOR: 1.44, 95% CI: 1.30-1.61), stillbirth (aOR: 1.35, 95% CI: 1.07-1.71) and early neonatal death (aOR: 1.29, 95% CI: 1.02-1.64). The associations with preterm delivery and low birthweight were also significant among the group with an inter-pregnancy interval of six to 11 months. The earlier meta-analysis by Conde-Agudelo *et al* also reported significant associations between intervals of less than six months and preterm delivery, low birthweight and, additionally, small for gestational age. Long intervals (of more than 59 months) were also significantly associated with all three outcomes. Reflecting these risks, the WHO recommends that following a live birth couples should wait at least 24 months before trying to conceive again (World Health Organization, 2005). Inter-pregnancy intervals, and the associated probability of adverse pregnancy outcomes, have not been explored among diagnosed women at the national level in the UK and Ireland.

Factors associated with preterm delivery

This review now focuses on preterm delivery. Multiple pathways, which are incompletely understood, are believed to lead to the onset of preterm labour including inflammation, infection, placental abruption and maternal-fetal stress (Goldenberg *et al*, 2008; Short *et al*, 2014). Preterm deliveries may occur spontaneously, or may be delivered early, either by induction of labour or caesarean section, for reasons such as obstetric or fetal complications. These are termed ‘iatrogenic’ or ‘indicated’ preterm deliveries. Goldenberg *et al* estimate that in the general population around 30–35% of preterm births are indicated, and the remaining 65-70% are spontaneous, composed of 40–45% following spontaneous preterm labour, and 25–30% following preterm premature rupture of membranes (Goldenberg *et al*, 2008). Though spontaneous preterm delivery is more common, some recent studies have suggested that iatrogenic preterm delivery may be of particular concern for HIV-positive women (Lopez *et al*, 2012; Sibiude *et al*, 2012). Aside from the potential

risk factors for preterm delivery already discussed in the context of adverse perinatal outcomes more generally (parity, advanced maternal age and inter-pregnancy intervals), other risk factors among the general population include obstetric history (e.g. history of preterm delivery), maternal factors (e.g. lower socio-economic status, black ethnicity), pregnancy characteristics (e.g. multiple pregnancy, poorer maternal nutritional and health status), pregnancy complications (e.g. pre-eclampsia), stress and smoking (Goldenberg *et al*, 2008; Slattery *et al*, 2002). Similar predictors, and additionally illicit drug use, have been reported among HIV-positive women as outlined in a recent comprehensive review on HIV and preterm delivery (Short *et al*, 2014).

Antenatal cART use and the risk of preterm delivery

In 1998 Swiss data raised concerns about the high rates (33%) of preterm delivery among a small group (*n*=37) of women receiving cART (Lorenzi *et al*, 1998). This was followed by a larger analysis of data from 10 European countries which found that compared with women who did not receive antenatal ART those who received either PI-based cART or non-PI-based cART during pregnancy had 2.60 (95% CI: 1.43-4.75) and 1.82 (95% CI: 1.13-2.92) times the odds of delivering preterm respectively, including adjustment for maternal CD4 count (European Collaborative Study and Swiss Mother and Child HIV Cohort Study, 2000). Since then antenatal cART use has been linked with an increased risk of preterm delivery in a number of other European studies (Boer *et al*, 2007; Grosch-Woerner *et al*, 2008; Lopez *et al*, 2012; Ravizza *et al*, 2007; Rudin *et al*, 2011; Thorne *et al*, 2004). In the UK and Ireland specifically, women receiving cART had 1.5 (95% CI: 1.19-1.93) times the odds of delivering preterm compared with those on mono or dual therapy (Townsend *et al*, 2007). An increased risk has also been reported in a more recent single-centre UK study (Short *et al*, 2013). These observational European data have been supported by findings from the Mma Bana randomised controlled trial (Powis *et al*, 2011), as well as observational data (van der Merwe *et al*, 2011) from African settings, though the Kesho Bora trial reported no increased risk (de Vincenzi, 2011). Conversely, some US-based studies have failed to demonstrate an overall association between ART exposure and preterm delivery (Dola *et al*, 2011; Patel *et al*, 2010; Tuomala *et al*, 2002; Tuomala *et al*, 2005), although a pooled analysis of data from the UK and Ireland, Europe, and the US did find a significant 1.5 increased odds of preterm delivery with cART as compared with dual therapy (Townsend *et al*, 2010a).

Evidence is emerging that both type and timing of ART are important with respect to preterm delivery risk. Several studies have explored the effect of the type of ART received, many revealing an association among women receiving PI-based cART specifically, or that the association was strongest among this group. A meta-analysis published in 2007 found

no overall association between cART and preterm delivery but did report a pooled OR for preterm delivery of 1.35, 95% CI: 1.08–1.70 among those receiving PI-based regimens compared with other (non-PI) combination regimens (Kourtis *et al*, 2007). The growing evidence-base, including data from the US, continues to link PI-based cART in particular with an increased risk of preterm delivery (Cotter *et al*, 2006; Grosch-Woerner *et al*, 2008; Ravizza *et al*, 2007; Schulte *et al*, 2007). Furthermore, a recent French study implicated ritonavir boosted PI-based cART specifically (Sibiude *et al*, 2012), though it is not clear whether this is due to the main PI received (lopinavir), the ritonavir booster, or the effectiveness of the boosted regimen. These observational data have also been supported by an analysis of data from the Mma Bana trial in Botswana in which women were randomised to receive either PI- or NNRTI-based cART. Those in the PI group had a two-fold increased odds of preterm delivery compared with those who received NNRTI-based cART (Powis *et al*, 2011).

Meanwhile, a number of studies have reported an increased risk of preterm delivery in women who conceived on ART or had first trimester exposure. For example, the ECS/Swiss cohort study found that women on cART from prior to conception had over twice the odds of delivering preterm compared with those initiating it during the third trimester (OR: 2.17, 95% CI: 1.03-4.58) (European Collaborative Study and Swiss Mother and Child HIV Cohort Study, 2000). Similarly, in a subsequent analysis of European data for 2000-2004, compared with those receiving mono or dual therapy there was a particularly high odds of preterm delivery among those who were on cART from prior to pregnancy (OR: 2.05, 95% CI: 1.43-2.95) (Thorne *et al*, 2004). A recent US study reported that women exposed to PI-based cART during the first trimester had a preterm delivery odds of 1.55 (95% CI: 1.16-2.07) compared with those who had no first trimester ART exposure (Watts *et al*, 2013). A Brazilian study found that women receiving cART from prior to conception had a five-fold increased odds of preterm delivery compared with those starting during pregnancy, although the analysis was not adjusted for CD4 count (Machado *et al*, 2009). Finally, in the previously mentioned French Perinatal Cohort analysis the adjusted odds of preterm delivery among those conceiving on cART (any type) was 1.31 (95% CI: 1.11-1.55) compared with those starting during pregnancy (Sibiude *et al*, 2012). When considering these findings it should be borne in mind that women already on treatment at conception may represent those in poorer health, which as has been mentioned, may in itself may be a risk for preterm delivery thus creating confounding by indication. Although most studies adjusted for maternal CD4 count some residual confounding may remain. Indeed, the evidence-base is inconclusive. An analysis of the NSHPC data by Townsend *et al* found no significant difference in risk among those initiating cART at <13 *vs*. ≥13 weeks (Townsend *et al*, 2007). Swiss cohort data also

showed no significant difference in preterm delivery risk between those starting cART before rather than during pregnancy (Rudin *et al*, 2011). Meanwhile, a single centre UK study reported a five-fold higher odds of preterm delivery among those initiating cART during pregnancy (Short *et al*, 2013), with similar findings documented in a Spanish cohort (Lopez *et al*, 2012), though the risk appears to vary depending on timing of initiation during pregnancy. It has been suggested that an increased risk associated with cART initiation during pregnancy may be due to immune reconstitution, whereby an increase in CD4 count following ART initiation results in an increased inflammatory response to opportunistic infections (Short *et al*, 2013; Short *et al*, 2014).

This is an area of ongoing research continuing to yield inconclusive results, in particular with regard to the influence of the timing of ART initiation on preterm delivery risk. The reasons for these disparate findings are a matter of discussion and debate but likely include heterogeneity in the populations studied, variations in study designs, bias by indication for treatment, and confounding (Kourtis *et al*, 2011; Short *et al*, 2014; Thorne *et al*, 2012; Watts *et al*, 2012). The evidence for a link between PI-based cART and preterm delivery is of concern since this is the recommended regimen for short-course antenatal ART in the UK (Taylor *et al*, 2012). Meanwhile, the possible higher risk in women conceiving on ART is worrying in light of the increasing proportion of women conceiving on ART, as documented in Chapter 1. Furthermore, these data are pertinent to both the WHO option of lifelong ART for pregnant women (Option B+) (World Health Organization, 2013), which would further increase the number of women conceiving (any subsequent pregnancies) on therapy, and international guidelines which are shifting towards recommending the earlier initiation treatment among people living with HIV (Sabin *et al*, 2013).

Summary

HIV-positive women may be at increased risk of adverse pregnancy outcomes. Although it appears that being parous *per se* may provide some protective effect, women experiencing repeat pregnancies have other risk factors such as increased maternal age (as compared with index pregnancies), the fact that they will have been living with HIV for longer, and are potentially more likely to conceive (their subsequent pregnancies) on ART. Indeed, there is a need for more data on perinatal outcomes, preterm delivery in particular, among pregnancies to diagnosed women in the contemporary context of widespread cART use and an increasing proportion of women conceiving on treatment.

2.7 Obstetric management of sequential pregnancies

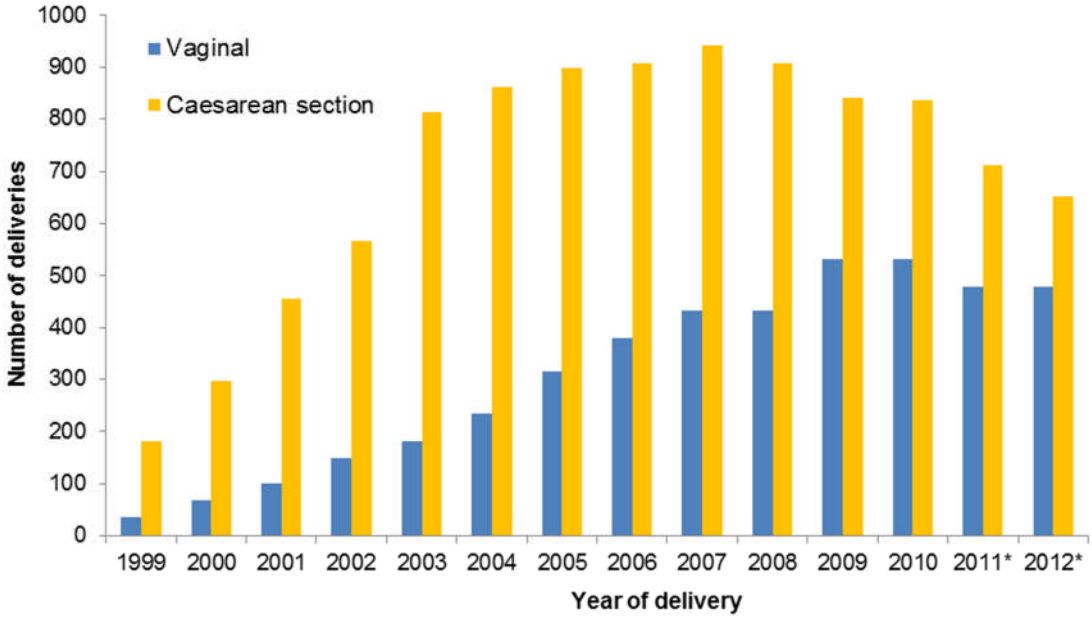
Caesarean section deliveries among HIV-positive women

Elective caesarean section has been widely used for PMTCT in resource-rich settings since the 1990's (Boer *et al*, 2010; Briand *et al*, 2013; Dominguez *et al*, 2003; Livingston *et al*, 2010; Mark *et al*, 2012; Townsend *et al*, 2008b). Since 2005, UK guidelines have allowed for the option of a planned vaginal delivery in women on cART with an undetectable viral load at 36 weeks (de Ruiter *et al*, 2008; Hawkins *et al*, 2005), with the most recent guideline specifically recommending a vaginal delivery in these women (Taylor *et al*, 2012). Guidelines for many other European countries now also allow for vaginal deliveries in women on suppressive therapy (Aebi-Popp *et al*, 2013b). Data reported to the NSHPC revealed that during 1999-2004 around 80% of deliveries were by caesarean section (composed of 60% elective and 20% emergency), with a subsequent decline to 60% (35% elective plus 25% emergency) in 2010-2012 (NSHPC, unpublished data[18]). Declines were also reported in a recent analysis of data from 10 European countries with elective caesarean sections accounting for 65% of deliveries before the change in guidelines and 27% afterwards (Aebi-Popp *et al*, 2013a). Despite these declines, as is clear from Figure 2.2, there is a large pool of diagnosed women in the UK and Ireland who have previously delivered by caesarean section. During 1999-2012 there were a total of 9870 caesarean section deliveries, accounting for 69% of all births. Furthermore, as evidenced here, and highlighted in the recent European analysis by Abei-Popp *et al*, many women are continuing to deliver by this route.

UK guidelines for the general obstetric population allow for vaginal birth after caesarean (VBAC) in women with no contraindications[19], with the decision made jointly between the woman and obstetrician (Royal College of Obstetricians and Gynaecologists, 2007). However, guidelines for the management of HIV in pregnancy offer few recommendations in this regard (Taylor *et al*, 2012).

[18] Data extracted from the NSHPC database, based on reports received by end of September 2013.
[19] One such contraindication relates to the number of previous caesarean sections; repeat caesarean section is recommended for women with a history of three or more caesarean sections (Royal College of Obstetricians and Gynaecologists, 2007).

Figure 2.2 Trends in mode of delivery among HIV-positive women in the UK and Ireland, 1999-2012



*Incomplete data due to reporting delays

Source: NSHPC, unpublished data (reported by end September 2013).

Risks associated with caesarean section deliveries

Caesarean section is a major operation, and is not without risks and potential complications. Caesarean section deliveries have been associated with some adverse post-natal outcomes including surgical site infection, a longer recovery period, and an increased risk of hysterectomy caused by postpartum haemorrhage (Bernstein, 2005; Goer, 2001; National Institute for Health and Clinical Excellence, 2011). Furthermore, a number of studies have reported that the risk of complications following caesarean section deliveries may be higher among HIV-positive women than HIV-negative controls (Calvert *et al*, 2013b; Fiore *et al*, 2004; Grubert *et al*, 2002; Maiques-Montesinos *et al*, 1999)[20]. However, others have found no difference (European Mode of Delivery Collaboration, 1999; Panburana *et al*, 2003). Maternal health may be important here. For example, in the study by Semprini *et al* women who were severely immunosuppressed were found to be at higher risk than healthier HIV-positive women (Semprini *et al*, 1995), and Maiques-Montesinos *et al* reported a lower risk of complications in women with CD4 >500 cells/µl

[20] Of note, the systematic review by Calvert *et al* and the study by Fiore *et al* both reported higher rates of post-delivery complications in HIV-positive women irrespective of mode of delivery.

compared with those with lower CD4 counts (Maiques-Montesinos *et al*, 1999). An increased risk among those with more advanced disease was also noted in a Cochrane review of caesarean section for PMTCT (Read *et al*, 2005). A recent analysis of diagnosed women enrolled in the French Perinatal Cohort reported post-partum complications (occurring immediately after delivery) in 6.5% of women delivering by caesarean section, either elective or emergency, compared with 2.9% among those delivering vaginally (p<0.01), with infection and haemorrhage being the most frequent. Complications, as well as prolonged hospitalisation, were more common among women with low CD4 counts both overall, and for all modes of delivery (Briand *et al*, 2013). Furthermore, women who have experienced a previous caesarean section may be at increased risk of a range of complications and adverse outcomes in subsequent pregnancies. These include abnormal placentation, scar dehiscence, uterine rupture, hysterectomy and stillbirth, as well as perinatal morbidity and mortality (Gilliam, 2006; Goer, 2001; O'Neill *et al*, 2013; Silver, 2012; Smith *et al*, 2003). A systematic review of 11 studies in the general obstetric population found that the rate of a range of adverse outcomes including hysterectomy, blood transfusions, surgical injury and placenta previa increased with the number of caesarean sections (Marshall *et al*, 2011). Whether or not HIV-positive women are at increased risk of complications compared with the general population, the risk of potential post-operative complications following caesarean section delivery cannot be overlooked. These risks should inform the mode of delivery decision-making process, particularly if there is not a strong indication for a caesarean section e.g. maternal preference in those with undetectable viral loads.

Risks of repeat caesarean section vs. vaginal birth after caesarean section (VBAC)

Several systematic reviews and meta-analyses have been conducted to assess the evidence around the risks of VBAC compared with repeat caesarean section. However, the evidence to date is inconclusive, perhaps reflecting the wide range of outcomes that require consideration, many of which are rare. In a large systematic review published in 2010, pooled data provided no evidence of a significantly increased risk of hysterectomy, haemorrhage, or blood transfusions in women delivering by VBAC compared with repeat caesarean section, but there was an increased risk of uterine rupture (0.47% *vs*. 0.03% respectively, p<0.001) and perinatal mortality (0.13% *vs*. 0.05%, p=0.002). Meanwhile, maternal mortality was higher in those delivering by repeat caesarean section (0.013% *vs*. 0.004%, p=0.027) (Guise *et al*, 2010). It should be noted that there was some heterogeneity in the findings of the studies in the review, as well as variations in the definitions and classifications used. Furthermore, all studies reported on the actual rather than intended mode of delivery, and there were no randomised trials eligible for conclusion.

The authors concluded that adverse outcomes were rare following both VBAC and repeat caesarean section, and that VBAC is a reasonable option for most women.

In light of the limitations of the available data highlighted in the review by Guise *et al*, a recently published Cochrane review sought to identify randomised trial data, published subsequent to the review, assessing the benefits and harms of VBAC *vs*. planned repeat caesarean section (Dodd *et al*, 2013). Only one study assessing clinical outcomes was identified - a trial nested in a prospective cohort study, although only 1% of women actually agreed to be randomised with others assigned mode of delivery according to their preference. The risk of serious adverse infant outcomes (a composite measure) was lower in the repeat elective caesarean section group (0.9% *vs*. 2.4%, *p*=0.011), as were serious adverse outcomes for the mother (3.1% *vs*. 4.5%, though this was not statistically significant: *p*=0.08) (Crowther *et al*, 2012). Despite randomisation to mode of delivery being largely unfeasible, an advantage of the study was that women were analysed according to planned, rather than actual, mode of delivery.

With regard to uterine rupture specifically, a major potential risk of VBAC, a national UK-based case-control study has been conducted which included all 159 women who had experienced a uterine rupture during a 13 month study period (2009-2010), and 448 control women with a previous caesarean section delivery, regardless of current mode of delivery. Although uterine rupture was rare (0.2 per 1000 maternities overall), among those with a previous caesarean section, the rate was higher in women planning a vaginal delivery (2.1 per 1000) than in those planning a repeat caesarean section (0.3 per 1000) (Fitzpatrick *et al*, 2012). Similarly, a large national study of 18,794 births registered in Norway to women who had previously delivered by caesarean section found the risk of uterine rupture to be significantly higher in women having a subsequent spontaneous (OR: 6.65, 95% CI: 2.4-18.6) or induced (12.60, 95% CI: 4.4-36.4) trial of labour rather than a repeat caesarean, though again the absolute risks were low (5 per 1000 overall) (Al-Zirqi *et al*, 2010). The results of these two large studies are consistent with those of the review by *Guise et al*.

Summary

A large proportion of births to diagnosed women in the UK and Ireland have been delivered by caesarean section. Many of these women may, under current guidelines, be eligible for a vaginal delivery in subsequent pregnancies. Little is known about how HIV-positive women experiencing repeat pregnancies are being managed obstetrically in the UK and Ireland. The risks and benefits of vaginal delivery after previous caesarean section(s) are uncertain among the general population and have been little explored among women living with HIV.

2.8 Rationale for this PhD

The aim of this thesis is to investigate the epidemiology of sequential pregnancies among HIV-positive women in the UK and Ireland, and to explore the health, therapeutic and obstetric management, and pregnancy outcomes of women experiencing them.

There are now a large number of pregnancies to HIV-positive women in the UK and Ireland, with over 1500 currently reported each year. An increasing number of these women will have experienced a previous pregnancy for which they received HIV-related care, and may have further pregnancies. An understanding of the epidemiology of repeat pregnancies is required to inform appropriate management strategies and service provision. However, the few studies that have been conducted on this topic had some important methodological limitations, were conducted some years ago, and included relatively small numbers of pregnancies thus limiting their generalisability to the contemporary population. The NSHPC is a well-established, active, national surveillance system providing an ideal dataset with which to examine, on a large and national scale, the epidemiology of repeat pregnancies among diagnosed women. This thesis examines patterns of repeat pregnancies among HIV-positive women in the UK and Ireland, estimates the rate of these pregnancies, and investigates the demographic and clinical characteristics of women experiencing them (Chapter 4).

In the contemporary context of widespread cART use and PMTCT interventions, diagnosed women are potentially presenting in pregnancy with increasingly complex treatment and management histories, as well as the possibility of future pregnancies. Chapter 5 explores several inter-related issues regarding women's engagement with HIV and pregnancy-related care, and the health and management of women experiencing sequential pregnancies. Timely booking for antenatal care and initiation of antenatal ART, are fundamental to ensure both maternal and infant health, and are thus explored here, including assessment of predictors of late booking and ART initiation, in order to identify potential inequalities in access to or uptake of care. Meanwhile, that many diagnosed women may have more than one pregnancy raises the question of whether lifelong ART should be initiated in all pregnant women, rather than short-term antenatal ART for PMTCT, discontinued after delivery. This issue is explored by investigating the immunological status and virological outcomes of a sub-group of women who were not on ART at conception of their repeat pregnancy. Finally, women's good engagement with HIV care is crucial to maintain their optimal health, and the literature suggests that women may be at heightened risk of loss to follow-up from HIV care after pregnancy. This has been little explored in the

UK and Ireland and is therefore investigated the last part of Chapter 5 using NSHPC data matched with the Survey of Prevalent HIV Infections Diagnosed (SOPHID).

For women not yet requiring treatment for their own health, short-course antenatal ART has been the cornerstone of PMTCT interventions. However, there is a lack of data on the impact of previous short-course cART for PMTCT on response to cART in subsequent pregnancies. This information is important not only to ensure women are managed effectively in their current pregnancy, but also to inform clinical decisions around the potential future benefits and risks of discontinuing ART after delivery. Here, the risk of detectable viral load at delivery, and of MTCT, in women who experienced short-course cART for PMTCT in a previous pregnancy, is investigated (Chapter 6).

HIV-positive women are a complex group to manage obstetrically for a variety of reasons that may be compounded in sequential pregnancies. For example, at their repeat pregnancies women will be older, a well-documented risk factor for adverse pregnancy outcomes in the general population, and will have been living with HIV for longer. As has been highlighted, current rates of vertical transmission in the UK and Ireland are very low, bringing other pregnancy and perinatal outcomes to the forefront. There is a need for more data on the perinatal outcomes of pregnancies to diagnosed women in the contemporary context. In particular, preterm delivery has become an outcome of concern in relation to antenatal exposure to cART. Chapter 7 examines the frequency of adverse pregnancy and perinatal outcomes (stillbirth, miscarriage, preterm delivery, low birthweight and congenital abnormalities), and investigates whether women experiencing repeat pregnancies are at increased risk of these. Risk factors for preterm delivery are explored among those experiencing repeat pregnancies. Data on repeat pregnancies enables the exploration of the influence of factors such as previous preterm delivery and inter-pregnancy interval on preterm delivery risk, which are often not assessed or accounted for in studies of preterm delivery among HIV-positive women.

Finally, over two-thirds of women reported to the NSHPC during the last decade or so delivered by caesarean section, many of whom may, under the current guidelines, be eligible for a vaginal delivery in subsequent pregnancies (if they are on suppressive therapy and have no obstetric contraindications). The risks and benefits of vaginal delivery after previous caesarean section(s) are, however, uncertain, and there is an absence of specific recommendations for the management of HIV-positive women in this regard. It has not been assessed, at the national level, how women with a history of caesarean section are being obstetrically managed. The second part of Chapter 7 explores mode of delivery among diagnosed women with repeat births, including temporal trends and patterns within

women (VBAC, for example), and assesses the frequency of adverse outcomes likely related to the mode of delivery.

2.9 Aim and objectives

The overarching aim of this thesis is to investigate the epidemiology of repeat pregnancies among diagnosed HIV-positive women in the UK and Ireland. The objectives are to:

1. Estimate the rate of repeat pregnancies, document temporal trends, and model birth-spacing intervals

2. Characterise the group of women experiencing repeat pregnancies and identify factors associated with having more than one pregnancy as a diagnosed woman

3. Investigate engagement with HIV and pregnancy-related care, and the health and management of women experiencing sequential pregnancies. Specifically to:

    a) Describe timing of antenatal booking for repeat compared with index pregnancies, investigate factors associated with late booking, and explore delays from booking to initiation of HIV-related antenatal care

    b) Investigate immunological status, timing of ART initiation, and virological outcomes among repeat pregnancies in women not on ART at conception

    c) Assess the completeness of matching of the NSHPC dataset with SOPHID, and use the matched data to explore attendance for HIV care after pregnancy

4. Investigate the probability of detectable viral load at delivery and MTCT in women who experienced short-course cART for PMTCT in a previous pregnancy

5. Explore the probability of adverse pregnancy and perinatal outcomes (stillbirth, miscarriage, preterm delivery, low birthweight and congenital abnormalities) among women's repeat pregnancies, and investigate risk factors for preterm delivery in this group

6. Describe mode of delivery for women's repeat births, explore patterns within women, and document serious adverse outcomes that may be related to mode of delivery

Chapter 3 Data sources and methods

3.1 National Study of HIV in Pregnancy and Childhood (NSHPC)

The UK and Ireland's NSHPC is based at the University College London (UCL) Institute of Child Health (ICH). The study comprises two active confidential reporting schemes: an obstetric and a paediatric scheme. Together these aim to capture all pregnancies to HIV-positive pregnant women living in the UK or Ireland, all infants born to HIV-positive women, and all children living with HIV infection[21]. A schematic representation of the structure of the NSHPC data collection systems is provided in Figure 3.1 and the standardised data collection forms are provided in Appendix III.

3.1.1 Obstetric scheme

The obstetric scheme began in 1989. The system is administered under the auspices of the Royal College of Obstetricians and Gynaecologists (RCOG). All (currently 228) maternity units in the UK and Ireland have a named respondent, an obstetrician originally but now often a specialist midwife or other specialist as appropriate to that unit, who is responsible for notifying all pregnancies in HIV-positive women, regardless of timing of diagnosis (before or during pregnancy) to the NSHPC. This is an active scheme. Respondents are requested to return a reporting card quarterly indicating the number of cases seen during the previous quarter, including null returns. All pregnancies should be reported, including those that have ended in a termination or miscarriage. 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. New pregnancy reports are linked to previous reports for the same woman based on maternal date of birth together with the geographic location of the report and other relevant information such as country of birth and timing of HIV diagnosis, and in more recent years, NHS number. All stages of the reporting process are closely monitored by the NSHPC team at ICH with non-response at any stage of the process followed up in order to ensure high reporting rates.

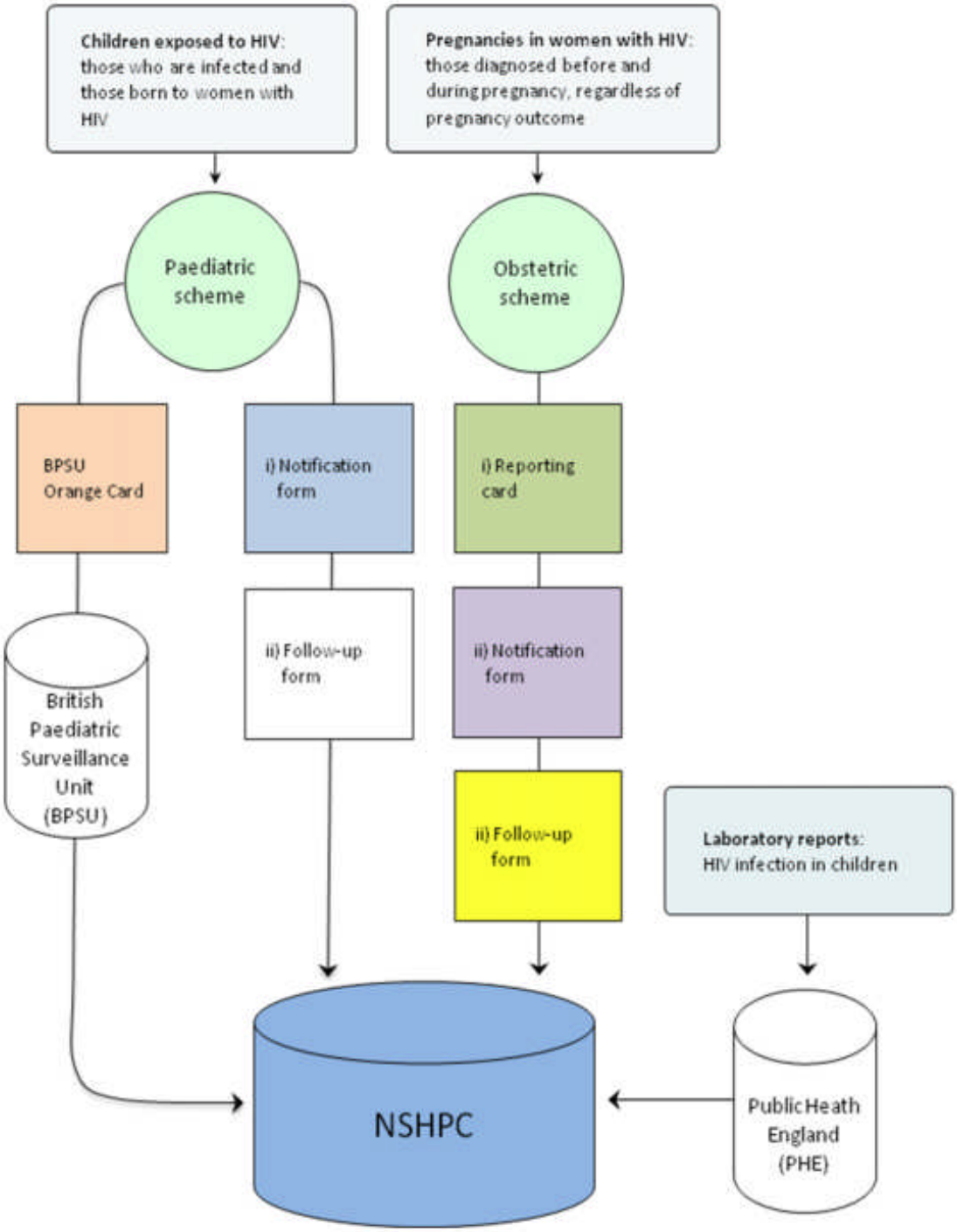
[21] The NSHPC also receives a small number of reports from the Channel Islands which are included in the analyses presented in this thesis.

3.1.2 Paediatric scheme

Paediatric cases of HIV and children born to HIV-positive mothers are mainly notified through the British Paediatric Surveillance Unit (BPSU) of the Royal College of Paediatrics and Child Health (RCPCH). The paediatric reporting scheme began in 1986 (reporting of AIDS diagnoses only), and was extended to include HIV-exposed and HIV-positive children 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. The card contains a list of rare diseases and conditions in childhood, which includes paediatric HIV/AIDS, as well as children born to HIV-positive women. Paediatricians are asked to return the card indicating whether or not they have seen a child with any of the listed conditions during the past month. The BPSU notifies the NSHPC of any paediatric cases of HIV/AIDS or exposed infants, and the paediatrician is then requested to complete an NSHPC paediatric notification form. Paediatric units seeing large numbers 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. As per the obstetric reporting, this is an active scheme with monitoring and follow-up of non-response 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. Infants born to HIV-positive mothers should be independently reported through both the obstetric and paediatric schemes. HIV-positive children born abroad and those born to women who remained undiagnosed during pregnancy will only be reported through the paediatric scheme. However, the majority of exposed infants (born in the UK or Ireland) were reported through both schemes (>90% for births during 2000-2010). Finally, a very small number of reports of HIV in children come from laboratories via Public Health England (PHE), formerly the Health Protection Agency (HPA), though these contain minimal information. Such reports are checked against children already in the NSHPC database to try to avoid duplicates.

Figure 3.1 NSHPC reporting structure



Source: (Tariq, 2013), with permission.

3.1.3 Data items

All data are collected using standardised data collection forms (Appendix III). Forms are periodically reviewed and new variables may be added. The scheme is anonymous, no names or addresses, aside from residential postcodes excluding the last digit, are collected. Some data items are collected through both schemes while others are collected through just one as is appropriate[22].

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 source of exposure (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 details include 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 gestational weeks). Information on ART, including whether the woman was on treatment at conception, and whether she received antiretrovirals in pregnancy, together with drugs received and timing of antenatal ART (whether or not the woman conceived on ART and ART start dates) is requested. Maternal clinical status comprises whether the woman has ever had CDC Stage C disease (AIDS), whether she has had HIV/AIDS symptoms during the pregnancy and concurrent infections. The earliest antenatal CD4 count and viral load measurement are also collected.

The obstetric outcome form includes the date of delivery, pregnancy outcome, gestational age, planned and actual mode of delivery, whether membranes ruptured prior to delivery and, if so, the duration of rupture. Information on pregnancy complications such as pre-eclampsia and gestational diabetes is also sought. Details of ante-partum and intra-partum ART, as well as any other non-HIV drugs such as tuberculosis treatment or methadone taken during pregnancy are requested. Maternal clinical status (HIV/AIDS symptoms) at delivery, together with CD4 count and viral load closest to delivery are also collected.

[22] Furthermore, some questions appear on both notification and outcome forms as a means of helping ensure completeness of key data items and to update data reported on the notification form (e.g. in relation to drugs received during pregnancy which may have not yet been initiated at the time the notification form was completed, or may have changed during the course of pregnancy).

Information on the infant includes birthweight, the presence of perinatal infections and congenital abnormalities, as well as details of post-partum prophylaxis.

Independently, the paediatric notification form requests information on the child's demographic details, 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 relevant paediatric respondent.

3.1.4 Data management, checking and cleaning

The data are held and managed in a Microsoft Access database (version 2003 for the data analysed in this thesis) (Microsoft Corp., Redmond, Washington, USA). All new reports are checked against the current dataset to identify duplicates. Pregnancies from the same woman are linked, as are obstetric and paediatric reports pertaining to the same live birth. Routine checks and cleaning are conducted on the NSHPC dataset during data entry and also through a series of Access queries performed quarterly by the NSHPC team which help identify inconsistencies and unlikely values. Where appropriate, these are checked with the relevant NSHPC respondent and corrected. At the end of each calendar quarter a set of standard queries is run to extract paediatric and obstetric data for analysis from the main dataset. The outputs of these queries are then compiled into a single analysis dataset via R (R Development Core Team), with the analysis dataset subsequently imported into Stata (Stata Corporation, College Station, Texas, USA) where further routine data checks are carried out[23]. To ensure the quality of the data prior to the 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 as appropriate e.g. by referring back to the original hard copy of the report, or in some cases where there was no appropriate alternative, recoding them as missing. Through the generation of a new 'conception date' variable (see Section 3.1.5 below), and the cross-checking dates of conception, expected dates of delivery and pregnancy outcomes for subsequent pregnancies in the same woman it was possible to detect a small number (<10) of duplicate reports not previously identified through the standard data cleaning procedures.

[23] These checks are supplementary to the routine quarterly data checks carried out within the Access database.

The NSHPC Stata dataset is structured as one row per pregnancy, with a unique identifier for each pregnancy and also for each woman, thus pregnancies for the same woman can be identified. In order to analyse repeat pregnancies in the NSHPC dataset the inbuilt _n and _N variables for creating group identifiers were utilised (_n assigning a consecutive number to each pregnancy occurring within the same woman, and _N indicating the total number of pregnancies per woman).

3.1.5 Definitions and categorisation of variables

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.

Repeat pregnancies

A woman's first reported, or 'index' pregnancy (the terms are used interchangeably throughout this thesis), refers to their first pregnancy as a diagnosed woman, whether their HIV diagnosis was made prior to that pregnancy, for example in a GUM clinic, or through antenatal screening. It is important to note that a proportion of women will already be parous at the time of their first pregnancy reported to the NSHPC. Therefore, women's first reported pregnancy is not necessarily their first ever pregnancy. 'Repeat', 'sequential' or 'subsequent' pregnancies (terms are used interchangeably throughout this thesis) refer to second and subsequent pregnancies since HIV diagnosis, reported to the NSHPC. The way the variable was constructed, the inclusion criteria, and whether analyses were conducted at the woman level or the pregnancy level, differ according to the specific analyses being carried out. For example, some analyses include all repeat (second and subsequent pregnancies), others only second reported pregnancies, and others the last reported pregnancy according the question being addressed. The study population used for individual analyses is therefore clearly defined within each chapter.

Maternal demographic characteristics

Maternal age at conception (used in Chapter 4) was defined as women's age at the start of their pregnancy (last menstrual period), derived using women's date of birth and the estimated date of conception. Maternal age at delivery (used in Chapters 5, 6 and 7) 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) (Royal College of Obstetricians and Gynaecologists). Up to 2001 only information on previous live births was requested; previous stillbirths are thus only included for women with a pregnancy reported from 2002 onwards. 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 ethnic group is defined as white, black African, black Caribbean, black other, Asian/Indian Subcontinent, Asian other/Oriental and other/mixed. Maternal ethnic group was subsequently categorised as white, black African and other. World region of birth was largely grouped as UK or Ireland, sub-Saharan Africa and Elsewhere. For some analyses (Chapter 4) the following more detailed breakdown was used: UK or Ireland, 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 (United Nations, 2010).

Likely source of maternal HIV infection was categorised as either 'injecting drug use' or 'other', representing two quite distinct populations of women. The injecting drug use group consists of women with a history of injecting drug use. The latter group comprises largely women with a likely heterosexual route of acquisition and/or those originating from a high HIV prevalence area of the world. There is substantial overlap between these two groups, and this, combined with changes in the way information has been collected over time, means that it was not appropriate to attempt to distinguish between them. The small groups of women with other exposure risks, for example, transfusion-associated infection, and young women who themselves acquired HIV vertically were also included in the 'other' risk group.

Estimated date of conception and gestational age

Date of conception was estimated by taking 280 days (40 weeks) away from the expected date of delivery for all pregnancies[24] which is a widely used estimation of the average duration of pregnancy (American College of Obstetricians and Gynecologists, 2013).

[24] For the purposes of calculating date of conception, if only a paediatric report had been received for the pregnancy (the paediatric form does not collect the expected date of delivery), date of conception was approximated as the date of delivery minus gestational age, if gestational age was missing (~1% of all reports) this was inputted as 280 days. This imputed variable was used solely for purpose of estimating date of conception.

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.

Timing of antenatal booking

Gestation at antenatal booking was estimated by calculating the number of days from estimated date of conception to reported date of booking for antenatal care. Details of the categorisation of this variable are provided in the relevant chapter (Chapter 5).

Maternal clinical and immunological characteristics

Information on presence of maternal HIV/AIDS symptoms included those occurring at any time during pregnancy; based on this, women were coded as either symptomatic or asymptomatic during pregnancy. The NSHPC requests two antenatal CD4 count and viral load measurements (earliest and last during pregnancy). These variables are therefore pregnancy-specific e.g. the variable 'earliest CD4 count' refers to the earliest antenatal measurement during the pregnancy of interest. Earliest measurements were restricted to those taken during pregnancy, including those up to 14 days prior to the estimated date of conception to allow for potential inaccuracies in estimated conception date. For some analyses measurements were further restricted to those taken prior to (and up to 14 days after) antenatal ART initiation. CD4 counts were grouped as: <200, 200-349, 350-499 and ≥500 cells/μl. A binary grouping of <350 and ≥350 cells/μl was also used because guidelines recommend that CD4 count <350 cells/μl be used as the threshold for initiation of ART (Gazzard *et al*, 2008; Williams *et al*, 2012). Viral load measurements defined as 'closest to delivery' were restricted to those taken within 28 days prior to and seven days after delivery[25]. An undetectable viral load was defined as <50 copies/ml. The detectability limit of assays has changed over time. Where viral load was analysed as a continuous variable those reported as being below a certain detection limit (e.g. '<200 copies/ml') were recoded as the mid-point thus the example given was recoded as 100 copies/ml (Townsend *et al*, 2008a). This continuous variable was used for descriptive analyses only; for most analyses viral load was treated either as a binary variable (detectable and undetectable), or occasionally as a categorical variable classified as <50, 50-999, 1000-9999 and ≥10,000 copies/ml.

Antiretroviral therapy

Type 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

[25] See Section 3.4 for information on the imputation of viral loads missing within this restricted time period.

cART was further classified as PI-based (either ritonavir boosted or unboosted), NNRTI-based, PI- and NNRTI-based (triple class therapy) and NRTI only. With regards to the timing of ART initiation, pregnancies were grouped according to whether they were conceived on ART or not. Where ART was started antenatally the start date is collected through the obstetric scheme only. For some analyses timing (e.g. trimester or gestational week) of start of antenatal ART was used, while for others duration of antenatal ART received (i.e. ART start date to date of delivery) was utilised, as appropriate.

Mode of delivery and pregnancy outcomes

Deliveries were classified as vaginal (planned or unplanned), elective caesarean section (pre-planned and conducted before the onset of labour or the rupture of membranes), or emergency caesarean section (conducted after rupture of membranes or onset of labour). 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 (fetal deaths occurring before 24 weeks gestation) (Royal College of Obstetricians and Gynaecologists, 2013), or terminations. At any given point in time a proportion of pregnancies will be continuing to term. For others, the woman may be reported to have gone abroad during pregnancy, or to have died. In some cases the outcome had simply not been reported (i.e. no obstetric outcome form or paediatric form had been returned). Finally, a small number of live births subsequently result in a neonatal death, defined as deaths occurring during the first 28 days of life (Perinatal Institute, 2011).

Infant HIV status

Infants were categorised as being ‘presumed HIV-positive’ if they had a positive 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*, 2008a).

3.1.6 Datasets for analysis

Two extracts of the NSHPC dataset were used in this thesis. The first included pregnancies conceived between January 1990 and December 2009, and reported by the end of

December 2010 (analysed in Chapter 4). The second included pregnancies ending between January 1990 and December 2010, reported by the end of June 2011[26] (analysed in Chapters 5, 6 and 7). The same exclusion criteria were applied to both datasets (see Figures 3.2 and 3.3), but exclusions based on 'pregnancy year' were made according to the year of conception for the first dataset since the analyses of this dataset were concerned with the occurrence (conception) of pregnancies. For the second dataset, 'pregnancy year' was based on the year of delivery, or expected year of delivery for pregnancies ending in outcomes other than a live or stillbirth.

The following standard exclusions were made to the datasets prior to all analyses presented in this thesis (see Figures 3.2 and 3.3). Further exclusion criteria required for specific analyses are detailed in the relevant chapters.

- 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. Although the NSHPC receives some reports (largely through the paediatric scheme) that relate to such pregnancies, these women would not have been able to receive any HIV-specific care during pregnancy and are not explored in this thesis

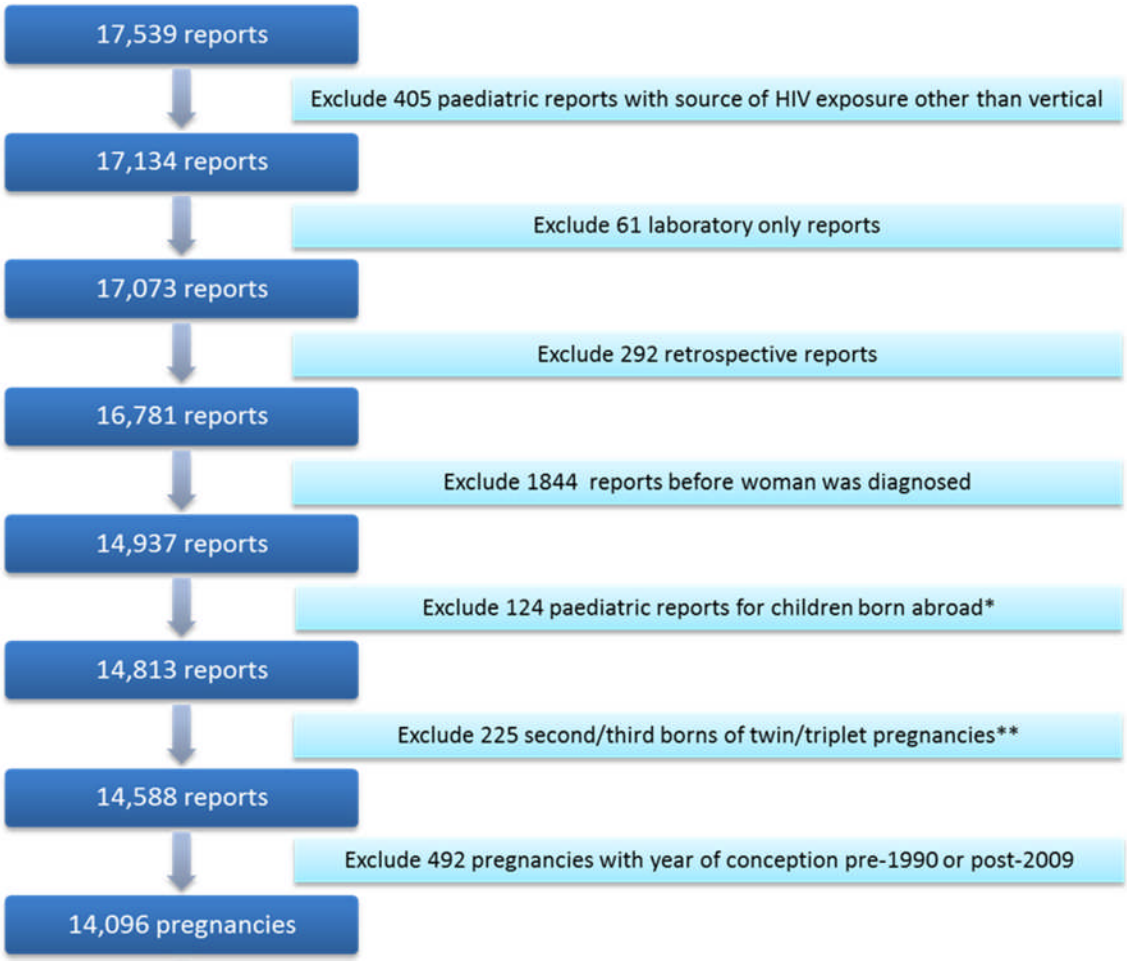
- Children who were born abroad and subsequently came to the UK (unless the mother was also reported to the NSHPC i.e. she was in the UK or Ireland at some point during pregnancy)

[26] To ensure the final year of data in each extract was as complete as possible pregnancies occurring post-2009 were excluded from the first extract, and those delivered post-2010 excluded from the second extract. Such pregnancies were largely ongoing at the time of analysis thus data were incomplete.

- The second and third born infants of multiple pregnancies - their information was retained and could be referred to as required, but due to the structure of the data this was necessary to avoid each infant being counted as a separate pregnancy

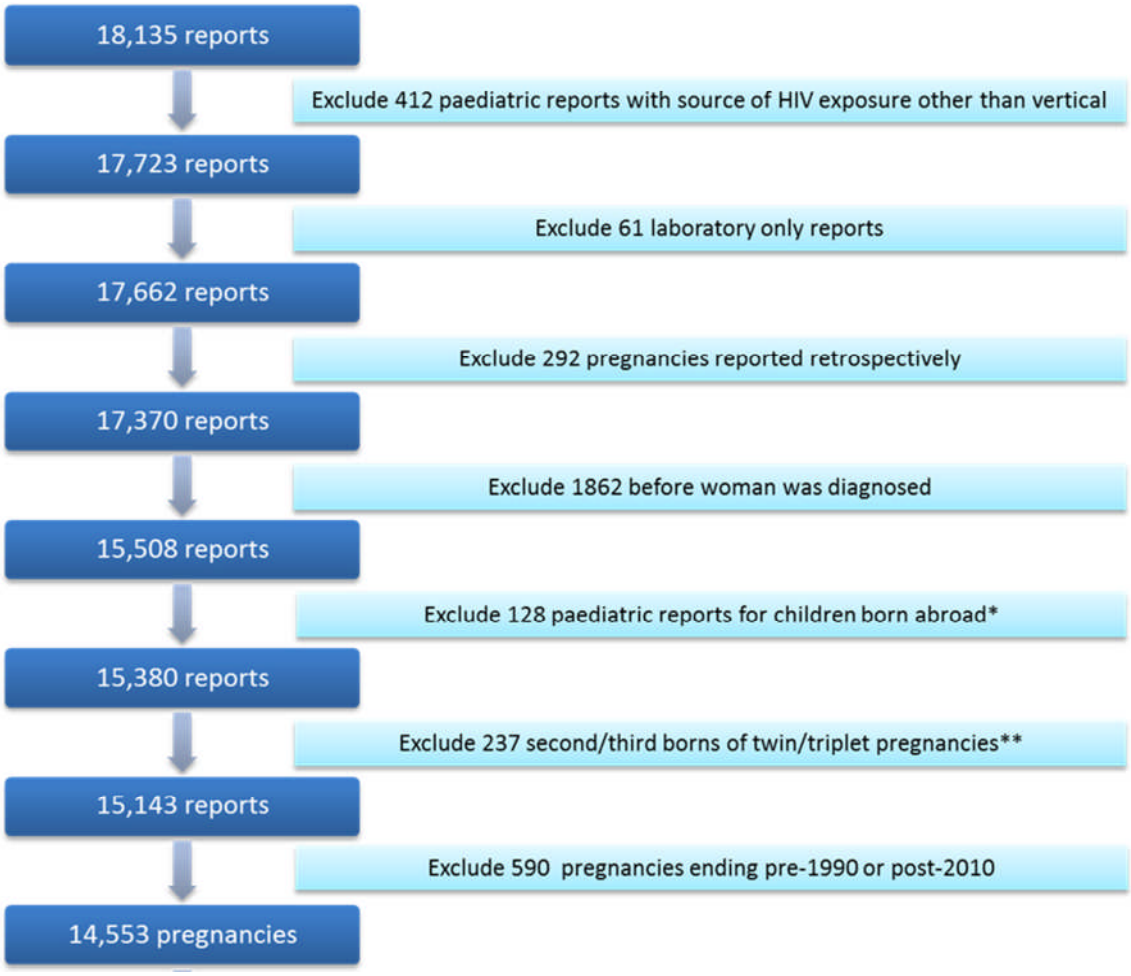
Temporal trends in sequential pregnancies, presented in Chapter 4, were assessed using all years of data (i.e. from 1990 onwards). However, subsequent analyses were restricted to the year 2000 onwards to ensure that findings were reflective of the more recent epidemiological situation (i.e. widespread antenatal HIV testing, availability of cART and low MTCT rates) (Public Health England, 2013a; Townsend *et al*, 2014). The epidemiology of HIV among pregnant women in the UK and Ireland has also changed significantly since the early years of the epidemic (Townsend *et al*, 2014; Townsend *et al*, 2008b). The period from 2000 onwards covers the majority of pregnancies reported to the NSHPC (almost 90% of pregnancies occurred during 2000-2009, based on data presented in Chapter 4). Some analyses were conducted on further restricted time periods as described in the relevant chapters.

Figure 3.2 NSHPC study population, pregnancies occurring during 1990-2009



*Unless the woman was also reported to the NSHPC (i.e. she was in the UK or Ireland during pregnancy)
**Thus two/three births are counted as one pregnancy only

Figure 3.3 NSHPC study population, pregnancies ending during 1990-2010



*Unless the woman was also reported to the NSHPC (i.e. she was in the UK or Ireland during pregnancy)
**Thus two/three births are counted as one pregnancy only

3.2 Survey of Prevalent HIV Infections Diagnosed (SOPHID)

SOPHID is a cross-sectional survey of all HIV-positive people attending for HIV-related care at NHS sites in England, Wales and Northern Ireland. During the period of data collection pertaining to the analyses presented in this thesis the survey was run by the HPA (now PHE), with Scottish data collected separately by Health Protection Scotland. The survey ran twice a year in London and annually outside London. In each survey, providers of HIV treatment or care collated a list of all individuals who had attended for HIV-related care. Anonymised epidemiological and demographic data collected on each patient were provided to PHE where the data was collated, de-duplicated and cleaned. Data collected included demographic information (e.g. sex, age and ethnicity) and clinical details such as CD4 count and treatment status (Public Health England, 2013c). These data enable annual estimates of all people attending care in each calendar year to be produced. Since individuals are 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. Information on deaths was routinely incorporated into SOPHID by matching with the HIV and AIDS New Diagnoses and Deaths (HANDD) database. HANDD, also run by PHE, collates information on all new HIV diagnoses, AIDS and death reports from clinicians and laboratories in England, Wales and Northern Ireland (Scottish data are collected separately by Health Protection Scotland). The HANDD dataset is also linked to the Office for National Statistics deaths register (Public Health England, 2013b).

SOPHID data were used to investigate the retention of women in HIV care following delivery and pertain to Chapter 5 only. Further details, including procedures used to link the NSHPC and SOPHID datasets are therefore detailed in that chapter.

3.3 Ethical approval and governance

The NSHPC has been approved by the London Multi-Centre Research Ethics Committee approval (MREC/04/2/009). This work was a secondary analysis of routinely collected surveillance data for which individual patient consent was not required[27]. SOPHID is exempt from ethical approval as it fulfils a surveillance purpose. The HPA was registered under the Data Protection Act 1998 to handle data for diagnostic, public health and other purposes, and is registered under Section 251 of the Health and Social Care Act 2001.

[27] Further details of NSHPC ethical approval and governance are available here: http://www.ucl.ac.uk/nshpc/ethics (Accessed March 2014).

During the period of SOPHID data collection presented in this thesis (data to 2010), the HPA had approval from the Patient Information Advisory Group to handle data for purposes that include surveillance and the control of disease, even where specific patient consent has not been given.

3.4 Missing data

As has been described, in the process of NSHPC data collection, and the cleaning and preparation of the dataset for analysis, the amount of missing data was minimised as far as possible. 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). Other potential options for dealing with missing data include methods such as multiple imputation which involves generating a number of different imputed datasets, based on the distribution of the available data, the results of which are then combined (Rubin, 1987; Sterne *et al*, 2009). The application of such an approach to dealing with missing data in the NSHPC dataset was assessed. It was, however, deemed largely inappropriate, and was therefore not utilised. The main reasons for this are as follows: 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 (Sterne *et al*, 2009). While for some NSHPC variables this 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.

One key outcome variable with substantial missing data was viral load at delivery. This was missing for around 45% of deliveries during 2000-2010 (based on data presented in Chapter 6). That many of these women had an earlier undetectable viral load reported earlier in the pregnancy is a potential reason in itself for a later (undetectable) viral load not

to have been reported. Since the majority of women in the UK and Ireland receive ART during pregnancy (Townsend *et al*, 2014), with most receiving cART, it is reasonable to assume that most of those with an undetectable viral load earlier in that pregnancy will remain undetectable at delivery. The method devised to address this is outlined here since it pertains to several analyses presented in this thesis. Essentially, if delivery viral load (as measured during the 28 days before and up to seven days after delivery) was missing but the woman's last available viral load measurement at any time during that pregnancy was undetectable, delivery viral load was imputed as undetectable. Supporting this approach, an analysis of data from the US WITS study demonstrated that 87% of women with an initial undetectable viral load remained undetectable at delivery (Katz *et al*, 2010). Furthermore, among women in the NSHPC (during 2000-2010) for whom both an 'earliest' and 'closest to delivery' viral load was reported only 8% with an initially undetectable viral load were reported to be detectable at the time of delivery. Where the imputed variable was used as the main outcome variable, sensitivity analyses were conducted based on the original non-imputed variable, to confirm that imputation did not significantly alter the findings or the conclusions drawn.

3.5 Statistical analyses

Data were analysed using Stata versions 11.0-12.1 (Stata Corp., College Station, Texas, USA). Where names of commands in the Stata language are provided these appear in courier font.

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 the size of any cells was less than five), with trends in proportions assessed using the χ^2 test for trend (Kirkwood *et al*, 2003). A Bonferroni correction for multiple comparisons was used were applicable (Bland *et al*, 1995). For non-normally distributed variables medians were compared using the Wilcoxon-Mann-Whitney test ('`ranksum`') (Kirkwood *et al*, 2003; Mann, 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). Statistical tests were considered significant if the *p*-value was <0.05, unless otherwise stated.

Construction of multivariable models

The general approach to multivariable model construction is provided here, in the context of a logistic regression analysis (a methodology which was used for a number of analyses of binary outcome variables presented in this thesis[28]). The same approach was applied to analyses conducted using other statistical methods, namely Cox proportional hazards and ordinal logistic regression modelling. Further details of specific analyses are provided in the relevant chapters.

Univariable analyses were carried out to obtain crude ORs with 95% CIs. Corresponding *p*-values were obtained using the Wald test for binary variables and the likelihood ratio (LR) test for categorical variables. Multivariable models were developed using a forward-fitting approach. For analyses examining the association between a defined exposure and outcome, potential confounders were identified in bivariate analyses; 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). Variables were kept in the model if they improved the fit (based on extent of change in the crude OR, and the *p*-value from the LR test comparing the model including the variable to the model excluding it). 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.

Meanwhile, for risk factor analyses, conducted to identify all relevant factors independently associated with a defined outcome, variables significantly associated with the outcome in the univariable analysis were included in the multivariable model. Remaining variables that were significantly associated with the outcome at the more conservative $p<0.1$ level were then added to the model in turn; goodness-of-fit was assessed using LR tests.

Selection of the baseline group for categorical variables

For categorical variables the most appropriate baseline group was selected, generally the lowest value of the variable (e.g. earliest time period), but the decision took into account what was most logical and relevant in terms of interpreting the analyses, the size of each group (avoiding the use of very small groups as the baseline where possible), and the desirability of ensuring consistency between analyses as far as was reasonable.

[28] 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 *et al*, 2000; McNutt *et al*, 2003). However, it remains a valid measure of association.

Adjustment for clustering

For some analyses, women with repeat pregnancies contributed more than one pregnancy to the dataset, which may therefore be described as being clustered at the woman level. If these clustered observations (pregnancies) are treated as being independent, as is the case with standard statistical approaches, the resulting standard errors are likely to be biased and will be too narrow due to intracluster correlation (i.e. pregnancies in the same woman are likely be more similar to each other than pregnancies in different women). Clustering was adjusted for using robust standard errors. 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 number of clusters is large ≥30 (Kirkwood *et al*, 2003). This adjustment was applied using the '`cluster`' option in Stata (Rogers, 1993). Since the LR test does not take account of clustering, in analyses conducted using robust standard errors the Wald test was used in place of the LR test (Kirkwood *et al*, 2003). For analyses which included only one pregnancy per woman, for example, those restricted to second reported pregnancies, no adjustment for clustering was required.

3.6 Role of the researcher

During the course of this PhD research I was based within the NSHPC team at the UCL Institute of Child Health. The NSHPC dataset has not previously been analysed in the context of exploring repeat pregnancies to diagnosed women (most prior NSHPC analyses have been carried out at either the pregnancy or woman level only). I therefore generated new identifiers for pregnancies within the same woman and established appropriate analytic methods for data of this form. I cleaned and prepared the NSHPC datasets prior to analysis, including making appropriate exclusions, and the generation of new variables as required. The NSHPC and SOPHID datasets have not been previously been matched. I liaised with colleagues at PHE (where matching was conducted) regarding the matching procedures, and was responsible for integrating the matched dataset into the main NSHPC Stata dataset, making the appropriate exclusions, and preparing this matched dataset for analysis[29]. I designed and conducted all analyses presented in this thesis.

[29] Preparation of the matched dataset was carried out in collaboration with my colleague Shema Tariq.

Chapter 4 Incidence, patterns and predictors of repeat pregnancies

Alongside the year-on-year increase in the overall number of pregnancies to HIV-positive women in the UK and Ireland has been an increase in the proportion occurring in previously diagnosed women. Though this is due in part to increasing uptake of HIV testing in a range of settings, a substantial proportion are in women who were diagnosed antenatally during a previous pregnancy. However, little is known about the incidence, temporal trends or predictors of repeat pregnancies among diagnosed women in the UK and Ireland, or indeed internationally. Reliable national data on the number and rate of repeat pregnancies is important to inform HIV and reproductive health service provision. The objectives of this chapter are firstly to estimate the rate of repeat pregnancies in HIV-positive women in the UK and Ireland during 1990-2009, document temporal trends, and explore birth-spacing intervals (Objective 1), and then to characterise the group of women with repeat pregnancies and identify factors associated with having a sequential pregnancy during 2000-2010 (Objective 2).

4.1 Incidence and patterns of repeat pregnancies

4.1.1 Methods

Dataset

The following analyses were conducted on pregnancies that occurred during 1990-2009, and were reported by the end of December 2010. For this reason data for 2009 are incomplete. However, the proportion of repeat pregnancies and characteristics of women reported were considered to be representative of the full year. Reported pregnancies were included in the analysis regardless of outcome: live births, stillbirths, terminations, miscarriages (including ectopic pregnancies), and those that were ongoing or had unknown outcomes (e.g. because the woman had gone abroad during pregnancy). Analyses were conducted on women's pregnancies reported to the NSHPC, rather than exploring their total reproductive histories in depth[30]. However, it should be noted that a proportion of women are already parous at the time of their first pregnancy reported to the NSHPC.

[30] Information requested by the NSHPC on women's reproductive histories prior to their HIV diagnosis is limited simply to the number of previous births they have had. No other details, such as the dates of these previous births, are collected.

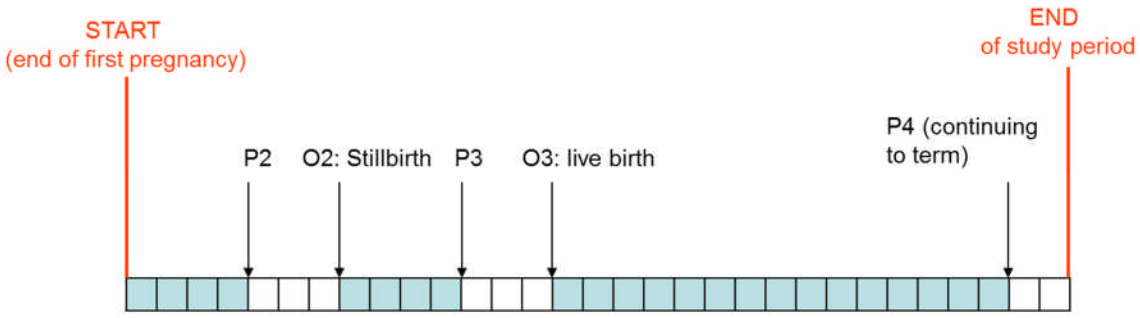
Rate calculations

The rate of repeat pregnancies was estimated per 100 woman-years. For calculation of the rate of all repeat pregnancies (i.e. second, third, fourth etc), the numerator was the number of all repeat pregnancies reported. The denominator 'time at risk of repeat pregnancies' was defined as the sum of the time from the end of women's first reported pregnancy to the end of the study period (31st December 2009), the end of their reproductive life which was defined as turning age 50, or their date of death (if reported to have died), whichever occurred first. Women were not 'at risk' of becoming pregnant and therefore did not contribute to the denominator, whilst pregnant. There is no consensus definition regarding the age at which a woman reaches the end of her childbearing years. Turning either age 45 or age 50 are commonly used definitions and since there are a number of pregnancies reported to the NSHPC among women aged 45 years and over (*n*=126 during 1990-2009), a cut-off of turning age 50 was deemed most appropriate. Figure 4.1 provides an example of the reproductive history of a woman in the NSHPC dataset. This woman had three repeat pregnancies and contributed a total of 5.75 years at risk of repeat pregnancy.

For calculation of the rate of second pregnancies only (i.e. excluding third and subsequent pregnancies), the numerator consisted of second pregnancies, and time at risk ended at the start of the second pregnancy, the end of the study period, the end of women's reproductive life, or date of death – whichever occurred first. Figure 4.2 provides an example of a woman who had a second pregnancy, and contributed a total of 2.75 years at risk.

The rate of second pregnancies during each calendar year was estimated (the numerator was the number of second pregnancies occurring in a given calendar year). Trends in the rate of repeat pregnancies were assessed fitting Poisson regression models.

Figure 4.1 Time at risk of repeat pregnancies – an example



Key:

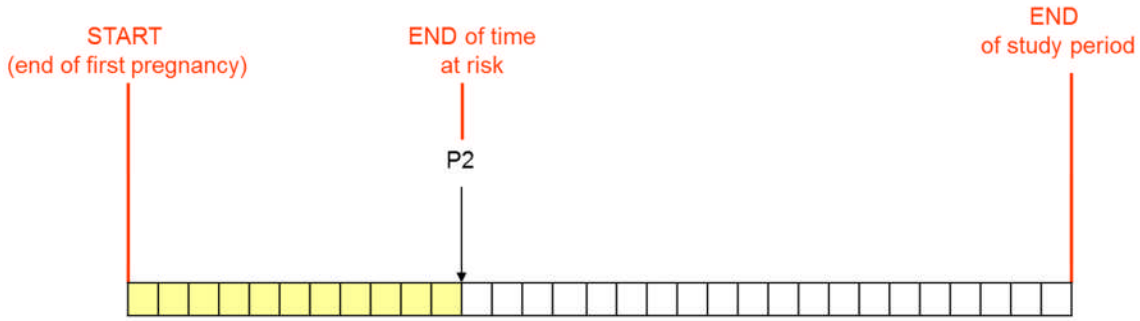
P - Pregnancy initiation date
O - Pregnancy outcome date

Time at risk of repeat pregnancy

Time *not* at risk of repeat pregnancy

Each block represents a quarter of a year

Figure 4.2 Time at risk of a second pregnancy – an example



Key:

P - Pregnancy initiation date
O - Pregnancy outcome date

Time at risk of second pregnancy

Time *not* at risk of second pregnancy

Each block represents a quarter of a year

Kaplan–Meier analyses

To further explore the pattern of repeat pregnancies, Kaplan–Meier analyses were used to estimate the probability of having a second pregnancy among all women in the NSHPC (i.e. all women with one pregnancy already reported to the study). As for analyses of the rate of second pregnancies, time at risk started at the end of women's first pregnancy, and women were censored at the end of the study period, or their date of death – whichever occurred first. The Kaplan–Meier approach assumes that censoring is non-informative (i.e. that it is independent of the event of interest) (Bland *et al*, 1998). To ensure that this assumption was met, women were not censored at the end of their reproductive lives[31]. The proportional hazards assumption was checked by comparing the Kaplan–Meier plots with the predicted plots by time period (Therneau *et al*, 2000).

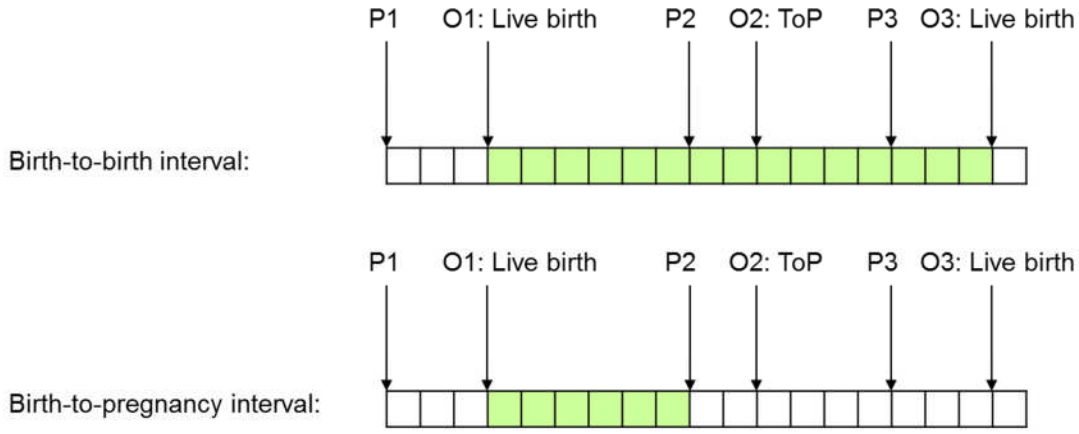
The probability of having a second pregnancy according to the time period in which women's first reported pregnancy occurred was also explored. For this analysis women were censored at four years after the end of their first pregnancy, rather than the end of the study period, since women who had their first pregnancy during the most recent time period (2005-2009) could not contribute more than four years at risk. Differences between time periods were assessed using the log rank test for trend.

Estimating birth spacing intervals

Birth spacing intervals were estimated among women with more than one pregnancy reported. There are various methods for estimating birth spacing intervals. Two of the WHO methods were used. Firstly, birth-to-birth intervals were estimated among live births only, defined as the time in years between the dates of delivery of women's first and second live births, and between each subsequent live birth. Secondly, birth-to-pregnancy intervals – defined as the time in years between the date of delivery of a live birth and the start of the subsequent pregnancy, irrespective of the outcome (World Health Organization, 2005). Figure 4.3 illustrates these two different methods. Using the first method, the woman depicted has a 3.75 year interval between her first and second live birth, while using the second method, the same woman has a 1.5 year interval between her first live birth and the start of her subsequent pregnancy.

[31] Since reaching the end of reproductive life is associated with the probability of experiencing the outcome of interest (pregnancy), right censoring women in this way would constitute 'informative censoring'. In practical terms it made very little difference to the results whether or not women were censored at the end of their reproductive lives.

Figure 4.3 Birth spacing interval definitions



Key:

P - Pregnancy initiation date
O - Pregnancy outcome date
ToP - Termination of Pregnancy

Birth spacing interval

Each block represents a quarter of a year

Source: Based on definitions provided by: (World Health Organization, 2005).

4.1.2 Study population

There were a total of 14,096 pregnancies during 1990-2009. Of the 13,355 pregnancies with a recorded outcome, 11,915 (89.2%) resulted in a live birth, 121 (0.9%) in a stillbirth, 1317 (9.9%) in either a miscarriage or termination, and for two (0.01%) the woman was reported to have died. Of those remaining, 146 were continuing to term, 183 women had gone abroad, and for 412 the outcome was not reported. Of the 12,036 live and stillbirths, there were 11,818 singletons, 214 sets of twins and four sets of triplets.

The number of pregnancies reported to the NSHPC between 1990 and 2009, according to year of conception, increased dramatically (by 1546%) from 89 to 1465 (p<0.001) (Figure 4.4). The number of pregnancies was below 200 each year until 1997 and then rapidly increased. Since 2006 the number of pregnancies reported each year has been relatively stable with a slightly lower number in 2009 most likely due to reporting delay.

Figure 4.4 Number of pregnancies by year, 1990-2009

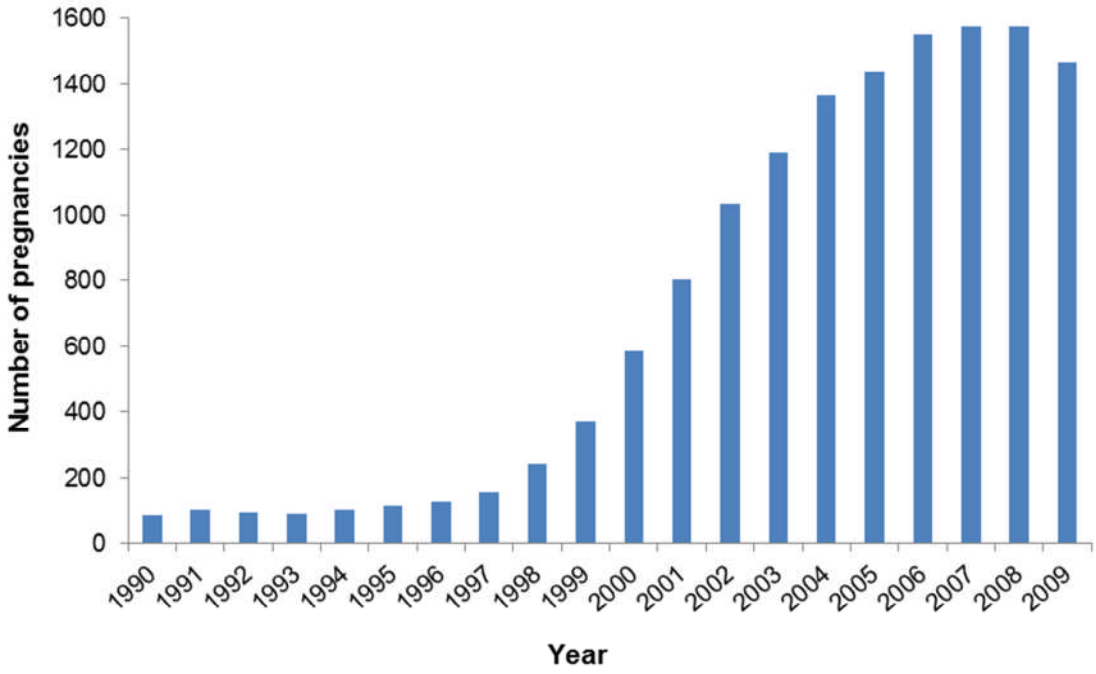


Table 4.1 describes some key maternal characteristics for all pregnancies reported during 1990-2009, overall and by time period. Almost 90% of all pregnancies reported occurred during 2000-2009. The median age of women at conception of their pregnancy was 29.8 years (IQR: 26.0-33.8). Over three quarters of pregnancies were to black African women, and just under a third were in nulliparous women. To briefly summarise key changes over time, average maternal age increased (p<0.001), and the proportion of pregnancies occurring in white women declined (p<0.001) with a corresponding increase the proportion occurring in black African women (p<0.001). In line with this, the proportion of pregnancies to women who were born in the UK or Ireland declined (p<0.001), while an increasing proportion of pregnancies occurred in women from Western and Southern Africa in particular (both p<0.001). The proportion in women with a history of injecting drug use declined substantially. There was an increase in the proportion of pregnancies occurring in nulliparous women between 1990-1994 and 2000-2004, with some decline in 2005-2009.

As discussed in Chapter 1, the demographics of the population of HIV-positive women in the UK and Ireland have changed dramatically over the last two decades, and the changes documented in Table 4.1 largely reflect this. However, some diagnosed HIV-positive women will experience more than one pregnancy, and it may be hypothesised that some of the observed changes could be partly explained by this.

Table 4.1 Maternal characteristics for pregnancies reported to the NSHPC, overall and by time period, 1990-2009

Characteristic	TOTAL	Time period*				*p*-value**
		1990-1994	1995-1999	2000-2004	2005-2009	
	n (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	
Total	14096	484	1022	4985	7605	-
Age at conception, yrs (*n*=14,010)						
Median (IQR)	29.8 (26.0-33.8)	27.1 (24.2-29.9)	28.9 (25.6-32.4)	29.0 (25.4-32.9)	30.7 (26.8-34.6)	<0.001
Ethnic group (*n*=13,963)						
White	2124 (15.2)	212 (49.2)	274 (26.9)	648 (13.1)	990 (13.1)	<0.001
Black African	10748 (77.0)	206 (47.8)	684 (67.1)	3913 (79.1)	5945 (78.6)	<0.001
Other	1091 (7.8)	13 (3.0)	62 (6.1)	389 (7.9)	627 (8.3)	<0.001
World region of origin (*n*=13,749)						
UK/Ireland	2035 (14.8)	146 (47.1)	253 (25.0)	683 (13.9)	953 (12.8)	<0.001
Europe	427 (3.1)	14 (4.0)	43 (4.3)	116 (2.4)	254 (3.4)	0.76
Eastern Africa	5957 (43.3)	145 (41.4)	422 (41.7)	2111 (42.8)	3279 (44.0)	0.07
Middle Africa	1064 (7.7)	21 (6.0)	78 (7.7)	421 (8.5)	544 (7.3)	0.37
Western Africa	2335 (17.0)	9 (2.6)	129 (12.8)	857 (17.4)	1340 (18.0)	<0.001
Southern Africa	1018 (7.4)	2 (0.6)	32 (3.2)	397 (8.1)	587 (7.9)	<0.001
Africa (unspecified)	160 (1.2)	4 (1.1)	13 (1.3)	56 (1.1)	87 (1.2)	0.93
Elsewhere	753 (5.5)	9 (2.6)	42 (4.2)	288 (5.8)	414 (5.6)	0.05
HIV risk factor (*n*=13,274)						
Other***	12743 (96.0)	323 (68.7)	886 (89.2)	4620 (96.8)	6914 (98.2)	<0.001
Injecting drug use	531 (4.0)	147 (31.3)	107 (10.8)	153 (3.2)	124 (1.8)	<0.001
Parity (*n*=12,365)						
Nulliparous	3913 (31.7)	22 (13.6)	225 (24.0)	1529 (35.3)	2137 (30.8)	0.04
1	4523 (36.6)	64 (39.5)	379 (40.5)	1528 (35.2)	2552 (36.8)	0.44
2	2404 (19.4)	42 (25.9)	179 (19.1)	788 (18.2)	1395 (20.1)	0.33
≥3	1525 (12.3)	34 (21.0)	153 (16.4)	493 (11.4)	845 (12.2)	0.003

Continued overleaf

Table 4.1 *Continued*: Maternal characteristics for pregnancies reported to the NSHPC, overall and by time period, 1990-2009

Characteristic	TOTAL	Time period*				*p*-value**
		1990-1994	1995-1999	2000-2004	2005-2009	
	n (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	
Timing of HIV diagnosis (*n*=13,969)						
Before this pregnancy	8223 (58.9)	335 (72.5)	596 (58.8)	2194 (44.2)	5098 (67.7)	<0.001
During this pregnancy	5746 (41.1)	127 (27.5)	417 (41.2)	2765 (55.8)	2437 (32.3)	<0.001

*Based on year of conception

***p*-values for trends over time comparing each category with all others combined with a Bonferroni correction to take account of multiple comparisons

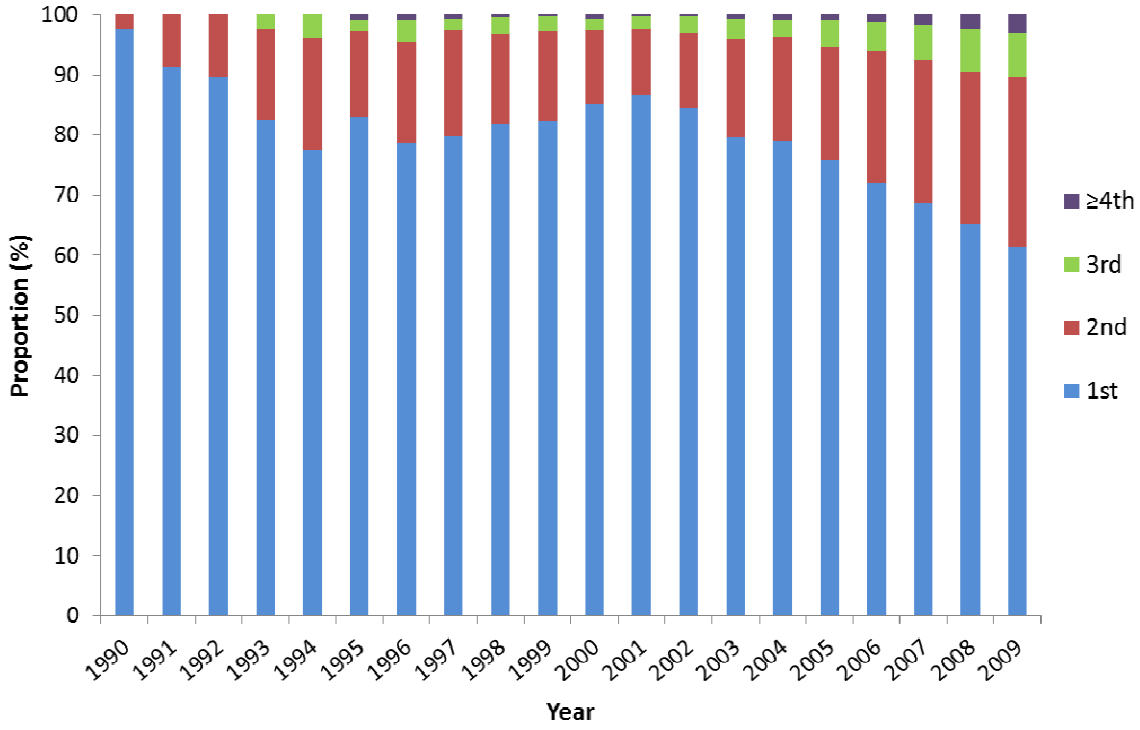
***Other comprises largely those originating from a high HIV prevalence area and/or with heterosexual exposure to HIV

4.1.3 Number and proportion of repeat pregnancies

The 14,096 reported pregnancies occurred among 10,568 diagnosed HIV-positive women, totalling 3528 repeat pregnancies in all. There were 2737 (25.9%) women who experienced repeat pregnancies (2117 women had two pregnancies, 475 had three and 145 had four or more). The maximum number of pregnancies was six (three women each had six pregnancies). Of the 3528 repeat pregnancies an outcome was recorded for 3404. Of these, 3013 (88.5%) resulted in a live birth, 30 (0.9%) in a stillbirth, 360 (10.6%) in either a miscarriage or termination, and for one (0.03%) the woman was reported to have died. Of the remaining 124 pregnancies, 38 were continuing to term, for 22 the woman had gone abroad, and for 64 the outcome was not reported.

Both the number and proportion of repeat pregnancies (i.e. pregnancies to women who already had at least one pregnancy reported) increased. The proportion increased between 1990 and 1994 with some levelling off during the remainder of the 1990's. During the next decade the proportion increased substantially from 14.9% (87/585) in 2000 to 38.6% (565/1465) in 2009 (p<0.001). In 2009, 28.2% of all pregnancies were second pregnancies, 7.4% were third, and 2.9% were fourth or subsequent (Figure 4.5).

Figure 4.5 Proportion of first and subsequent pregnancies by year, 1990-2009



4.1.4 Rate of repeat pregnancies

The analysis of the rate of repeat pregnancies included 9916 women (652 were excluded because their first pregnancy was ongoing thus they did not contribute any time at risk). There were a total of 52,676 woman-years at risk and 3528 repeat (second, third, fourth etc) pregnancies. The median time at risk was 4.6 years. The overall rate of repeat pregnancies was 6.7 (95% CI: 6.5-6.9) per 100 woman-years (i.e. among 100 women followed for one year it would be anticipated that seven would become pregnant).

For the analysis of second pregnancies, the number of women was the same (9916) and the 2737 second pregnancies were included. The total duration of time at risk was 40,760 woman-years. The median time at risk was 3.2 years. The overall rate of second pregnancies was also 6.7 (95% CI: 6.5-7.0) per 100 woman-years. Subsequent analyses focus on second pregnancies.

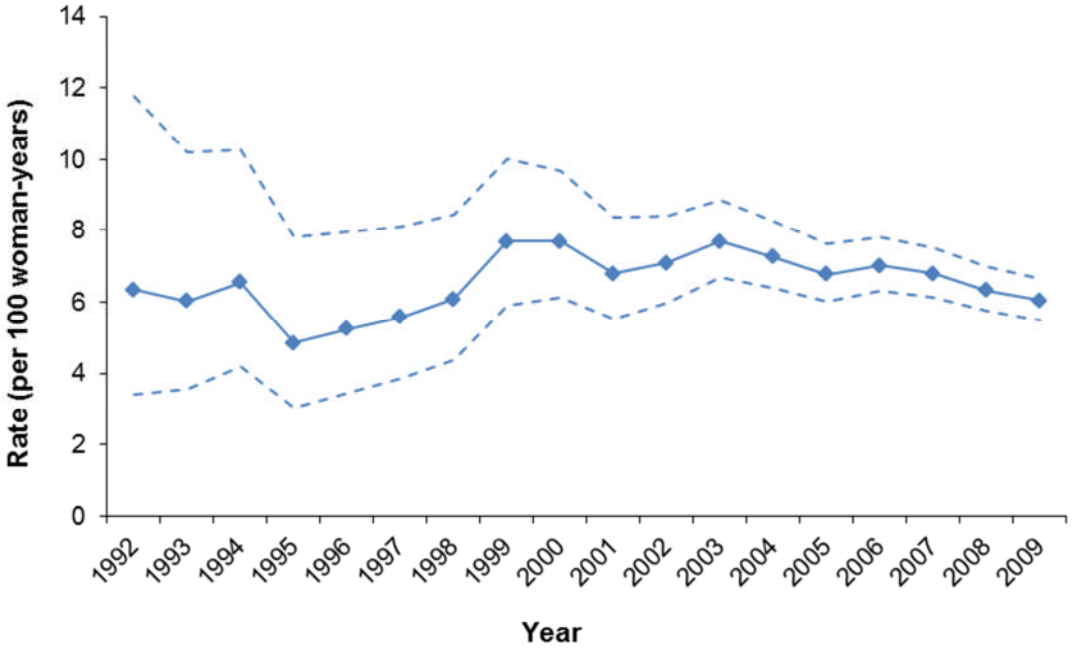
The rate of second pregnancies was 7.0 per 100 woman-years during 1990-1994, 6.1 during 1995-1999, 7.3 during 2000-2004 and 6.5 during 2005-2009 (Table 4.2).

Table 4.2 Number and rate of second pregnancies by time period, 1990-2009

Time period	Number of second pregnancies	Woman-years at risk	Rate (95% CI) per 100 woman-years
1990-1994	54	766	7.0 (5.4-9.2)
1995-1999	159	2590	6.1 (5.3-7.2)
2000-2004	726	9920	7.3 (6.8-7.9)
2005-2009	1798	27,484	6.5 (6.2-6.9)

When trends in the rate of second pregnancies were examined by single calendar year (Figure 4.6), the rate was stable overall (p=0.167). There was, however, some increase between 1995 and 1999, after which the rate stabilised with some decline in the most recent years. This will likely be due to the large number of women having a first pregnancy during the most recent years who have had little time to go on and have a second pregnancy. The wider confidence intervals in the earlier years of the study reflect the relatively small number of pregnancies during that period.

Figure 4.6 Rate of second pregnancies per 100 woman years, by year, 1992-2009



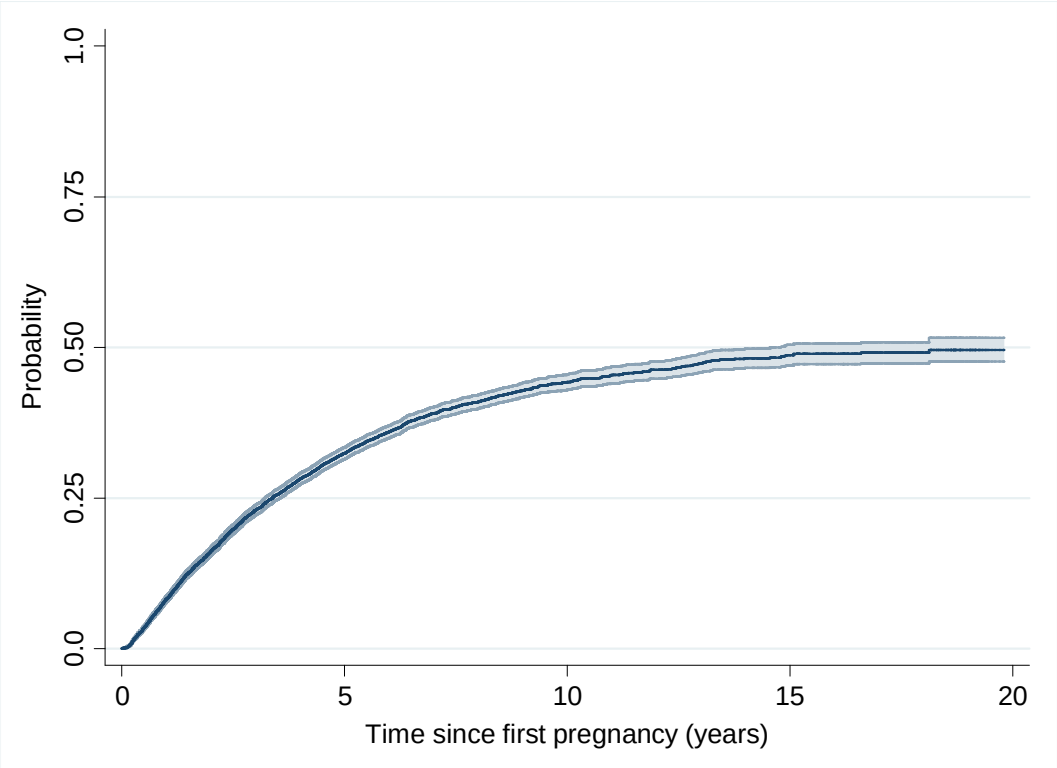
*For clarity this figure excludes data for 1990 and 1991 due to the very small number of second pregnancies in each of those years (<10)

Note: Lower and upper confidence limits are denoted by the dashed lines.

4.1.5 Probability of repeat pregnancies

In the initial Kaplan–Meier analysis an estimated 25% of women had a second pregnancy after 3.2 years of follow-up, and an estimated 50% of women had a second pregnancy after 20 years of follow-up (Figure 4.7). As can be seen in the figure, most women who experienced a repeat pregnancy did so within 10 years of their first; over 40% of women were an estimated to have had a second pregnancy after 10 years of follow-up.

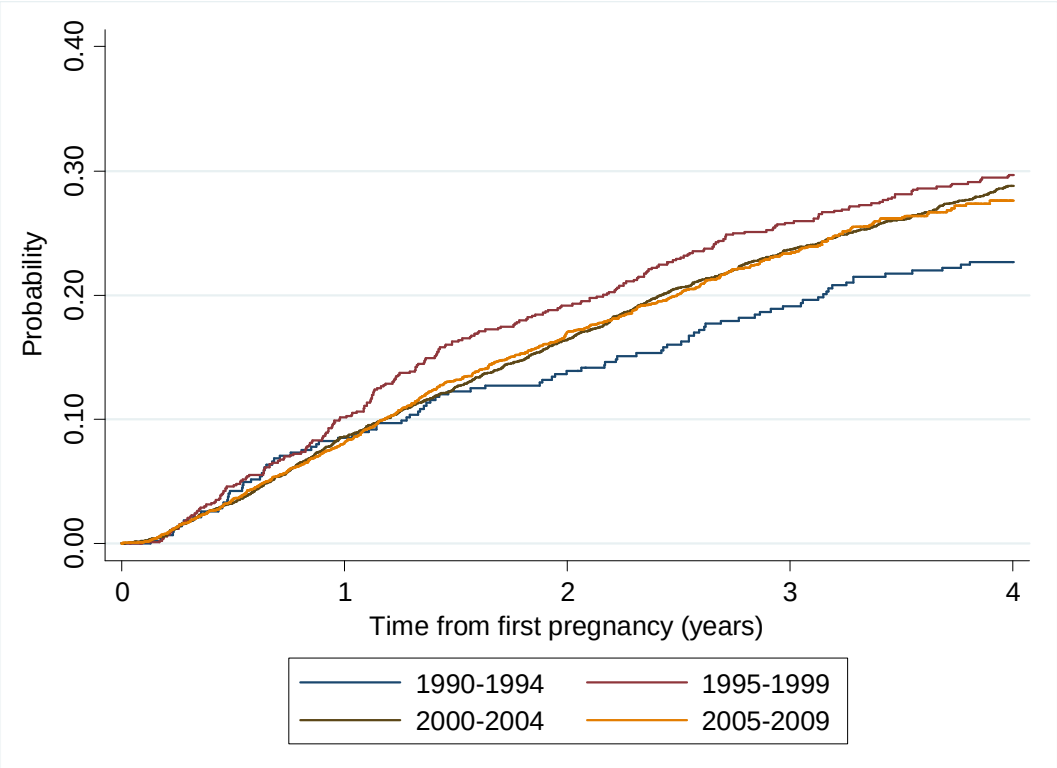
Figure 4.7 Cumulative probability of having a second pregnancy during 1990-2009



Note: Probability is represented by the dark blue line and the 95% CIs by the lines above and below.

Kaplan–Meier analysis of time to second pregnancy showed differences in the probability of having a second pregnancy according to the time period in which women's first pregnancy occurred (log rank test: p=0.06) (Figure 4.8). Women having their first pregnancy during the earliest time period (1990-1994) were least likely to have a second pregnancy while those whose first pregnancy occurred during 1995-1999 were most likely to, and to do so more quickly. The probability of second pregnancies was very similar among women whose first pregnancy occurred during the periods 2000-2004 and 2005-2009.

Figure 4.8 Cumulative probability of second pregnancy by time period of first reported pregnancy



4.1.6 Birth spacing intervals

The median birth-to-birth interval among live births during 1990-2009 was 2.7 years (IQR: 1.7-4.1) between first and second deliveries, with a range of 0.7 years (257 days) to 18.6 years. However, very few women had an interval of more than 10 years (Figure 4.9) Very short intervals occurred in a few women who conceived quickly after their first delivery, some of whom delivered their second infant preterm (hence the very short gap). The interval between second and third deliveries was 2.3 years (IQR: 1.5-3.9), it was also 2.3 years (1.5-3.7) between third and fourth deliveries (Figure 4.10). The pattern was similar when live birth-to-pregnancy intervals were examined; the median interval between first live birth and the subsequent pregnancy was 1.9 years (IQR: 1.0-3.3). The interval between the second live birth and subsequent pregnancy was 1.6 years (IQR: 0.7-3.0), as was the interval between the third live birth and subsequent pregnancy (1.6 years (IQR: 0.7-3.0) (Figure 4.11). When the analyses were restricted to women whose first birth occurred during 2000 or later, the findings were similar; the median birth-to-birth interval between first and second delivery was 2.6 years (IQR: 1.7-3.9), and the birth-to-pregnancy interval was 1.8 years (IQR: 0.9-3.1).

Figure 4.9 Interval between first and second live birth (birth-to-birth interval)

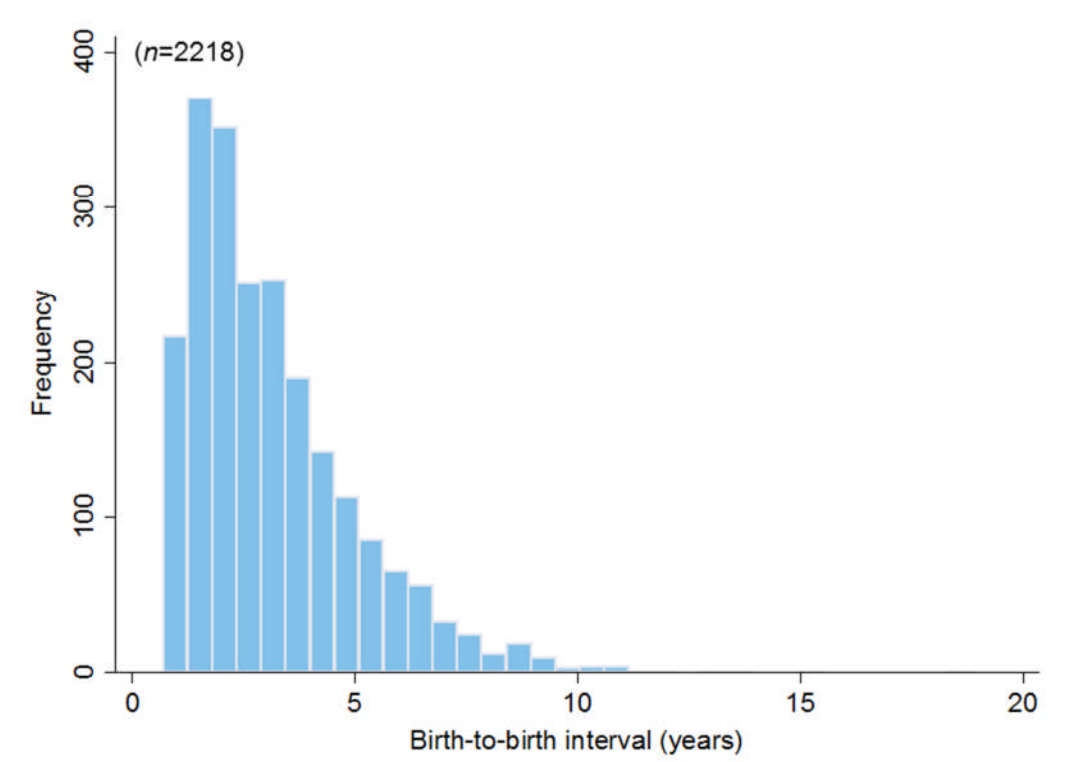
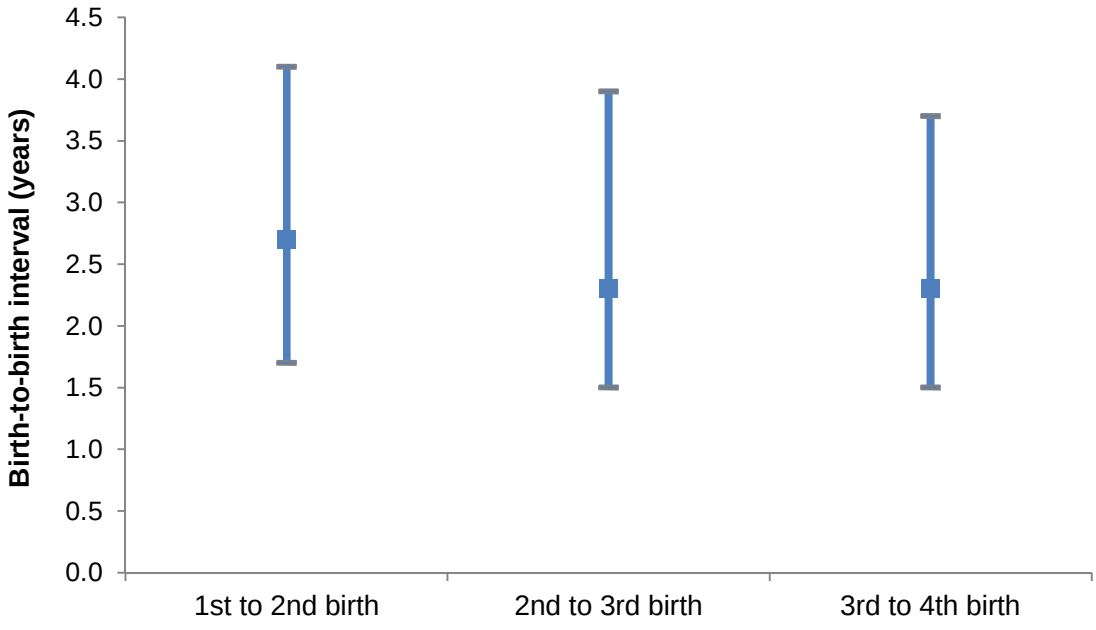
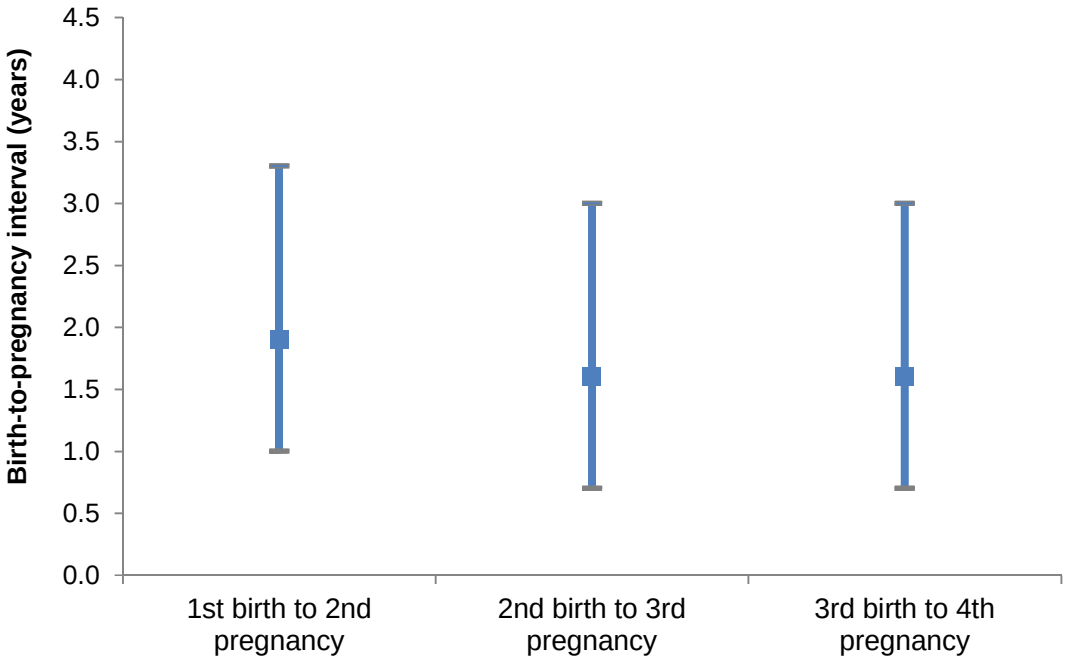


Figure 4.10 Quartiles of birth-to-birth intervals



Note: Squares represent the median interval and lines represent the first and third quartiles.

Figure 4.11 Quartiles of birth-to-pregnancy intervals



Note: Squares represent the median interval and lines represent the first and third quartiles.

4.2 Predictors of repeat pregnancies

4.2.1 Methods

Dataset

The following analyses were restricted to women whose first pregnancy occurred during 2000-2009 to ensure that findings were reflective of the more recent epidemiological situation. Reported pregnancies were included in the analysis regardless of pregnancy outcome. Only the first born of twin and triplet pregnancies were included in the analyses, with one exception in the analyses addressing stillbirth and neonatal death (see below).

Since not all women were at risk of a subsequent pregnancy during the study period, for the comparisons of characteristics of women with repeat pregnancies and those with a single pregnancy only, the following women were excluded: i) those whose first reported pregnancy ended on or after 31st December 2009, and ii) those who were reported to have died during their first pregnancy. As for the first part of this chapter, women were not censored at the end of their reproductive life to ensure that the assumption of non-informative censoring was met (Bland *et al*, 1998) since reaching the end of reproductive life is clearly associated with the probability of becoming pregnant.

For analyses investigating the occurrence of a stillbirth or neonatal death in women's first pregnancy as a predictor of repeat pregnancy, the dataset was restricted to women whose first pregnancy ended in either a stillbirth/neonatal death or a live birth (as the comparison group). One first born twin (a stillbirth) was excluded from this specific analysis because the second twin was a live birth. There were no other twin or triplet pregnancies with discordant outcomes. The analysis of having an HIV-positive infant in first pregnancy as a predictor of repeat pregnancy was restricted to live births with known information on infant HIV status.

Kaplan–Meier analyses

Kaplan–Meier analyses were used to explore the probability of repeat pregnancies and time to repeat pregnancies according to demographic, clinical and immunological characteristics, and previous adverse pregnancy outcomes. Differences between groups were assessed with the log rank test or the log rank test for trend for ordered categorical variables. The *y*-axes of Kaplan–Meier graphs examining differences between groups are truncated at 0.6 for clarity.

Cox proportional hazards modelling

Demographic, clinical and immunological characteristics associated with having a second pregnancy during 2000-2009 were explored in separate risk factor analyses. For the analysis of clinical and immunological factors associated with repeat pregnancies two variables were used: earliest CD4 count and HIV/AIDS symptoms during first reported pregnancy.

For risk factor analyses univariable and multivariable analyses were conducted using Cox proportional hazards models to calculate crude and adjusted hazard ratios (HR and aHR respectively). Multivariable models were built using a forward-fitting approach as described in Chapter 3, Section 3.5. Year of first pregnancy was included in the multivariable models *a priori* to take account of changes, for example in the management of women, over the study period. The proportional hazards assumption (i.e. that the HR is constant over time) was assessed by examining log-log plots to ensure plots for the different strata of a given variable, adjusted for all other variables included in the model, were approximately parallel. The model's Schoenfeld residuals were also analysed, both for each covariate and globally (Therneau *et al*, 2000). The association between adverse pregnancy outcomes in women' first reported pregnancy and the probability of repeat pregnancy were also analysed fitting Cox proportional hazards models.

4.2.2 Study population

The analysis of women whose first pregnancy occurred during 2000-2009 excluded 651 women with a single pregnancy who were not 'at risk' of having a repeat pregnancy during the study period because their first pregnancy was ongoing (no women were reported to have died during their first pregnancy). A total of 11,426 pregnancies among 8661 women (2238 (25.8%) of whom had repeat pregnancies) were thus included in the subsequent analyses. Of these, 1798 had two pregnancies, 364 had three, 65 women had four, and 11 women had five. Of all 11,426 pregnancies an outcome was recorded for 10,858 (95.0%) of which 9826 (90.5%) resulted in a live birth, 100 (0.9%) in a stillbirth, and 932 (8.6%) in a miscarriage or termination. Outcome was not known for 568 pregnancies, including 36 continuing to term and 167 where the woman had gone abroad before delivery.

To briefly characterise the study population, the median age of women at conception of their first pregnancy was 29.4 years (IQR: 25.6-33.4) and 56.7% of women were parous (58.6% among women from sub-Saharan Africa and 48.3% among those born in the UK or Ireland). The majority of women (87.2%, *n*=7402) were born abroad, and 78.8% (*n*=6773) were of black African ethnicity. Nearly all (97.7%, *n*=7873) had acquired HIV through a non-injecting drug use route (largely composed of those with heterosexual exposure and/or originating from a high HIV prevalence area of the world).

4.2.3 Demographic predictors

The demographic characteristics of women with and without repeat pregnancies are compared in Table 4.3. Women with repeat pregnancies were more likely to have had their first pregnancy earlier in the study period. They were also younger (at their first pregnancy) than those with a single pregnancy, and a significantly higher proportion originated from the UK or Ireland (14.1% *vs*. 12.3%). Half of the women with repeat pregnancies were nulliparous at time of their first reported pregnancy, a significantly higher proportion than among those with a single pregnancy.

Information on key demographic variables was generally well reported: maternal date of birth (from which age at first pregnancy is derived) was missing for 43 (0.5%) women, ethnicity for 70 (0.8%), world region of origin for 173 (2.0%), likely route of HIV acquisition for 601 (6.9%), and parity for 1009 (11.7%). Table 4.4 compares the characteristics of women who had missing information on one or more of the key demographic variables (*n*=1577) and those with complete information. Women with missing information on any demographic variable were younger, more likely to be white, born in the UK or Ireland, and less likely to have repeat pregnancies than those with complete information.

Table 4.3 Comparison of the demographic characteristics of women with a single pregnancy and those with repeat pregnancies

Characteristic	Number of women with a single pregnancy (%)	Number of women with repeat pregnancies (%)	*p*-value
Total	6423 (100)	2238 (100)	-
Year of conception* (*n*=8661)			
2000-2002	1254 (19.5)	815 (36.4)	<0.001
2003-2005	2208 (34.4)	912 (40.8)	
2006-2009	2961 (46.1)	511 (22.8)	
Age at conception, yrs* (*n*=8618)			
<25	1206 (18.9)	654 (29.3)	<0.001
25-29	2014 (31.6)	815 (36.5)	
30-34	1898 (29.7)	571 (25.5)	
≥35	1264 (19.8)	196 (8.8)	
Ethnic group (*n*=8591)			
White	819 (12.9)	287 (12.8)	0.590
Black African	5019 (79.0)	1754 (78.4)	
Other	515 (8.1)	197 (8.8)	
World region of origin (*n*=8488)			
UK/Ireland	771 (12.3)	315 (14.1)	<0.001
Europe	209 (3.3)	52 (2.3)	
Eastern Africa	2878 (46.0)	895 (40.0)	
Middle Africa	396 (6.3)	217 (9.7)	
Western Africa	954 (15.3)	458 (20.5)	
Southern Africa	576 (9.2)	161 (7.2)	
Africa (unspecified)	105 (1.7)	10 (0.5)	
Elsewhere	362 (5.8)	129 (5.8)	
HIV risk factor (*n*=8060)			
Injecting drug use	138 (2.4)	49 (2.3)	0.793
Other**	5742 (97.7)	2131 (97.8)	
Parity* (*n*=7652)			
Nulliparous	2326 (40.7)	987 (50.9)	<0.001
1	2921 (33.6)	596 (30.7)	
2	916 (16.0)	244 (12.6)	
≥3	547 (9.6)	115 (5.9)	

*At first reported pregnancy
**Other comprises largely those originating from a high HIV prevalence area and/or with heterosexual exposure to HIV

Table 4.4 Comparison of women with complete information on key demographic variables and those with missing information (on one or more variable)

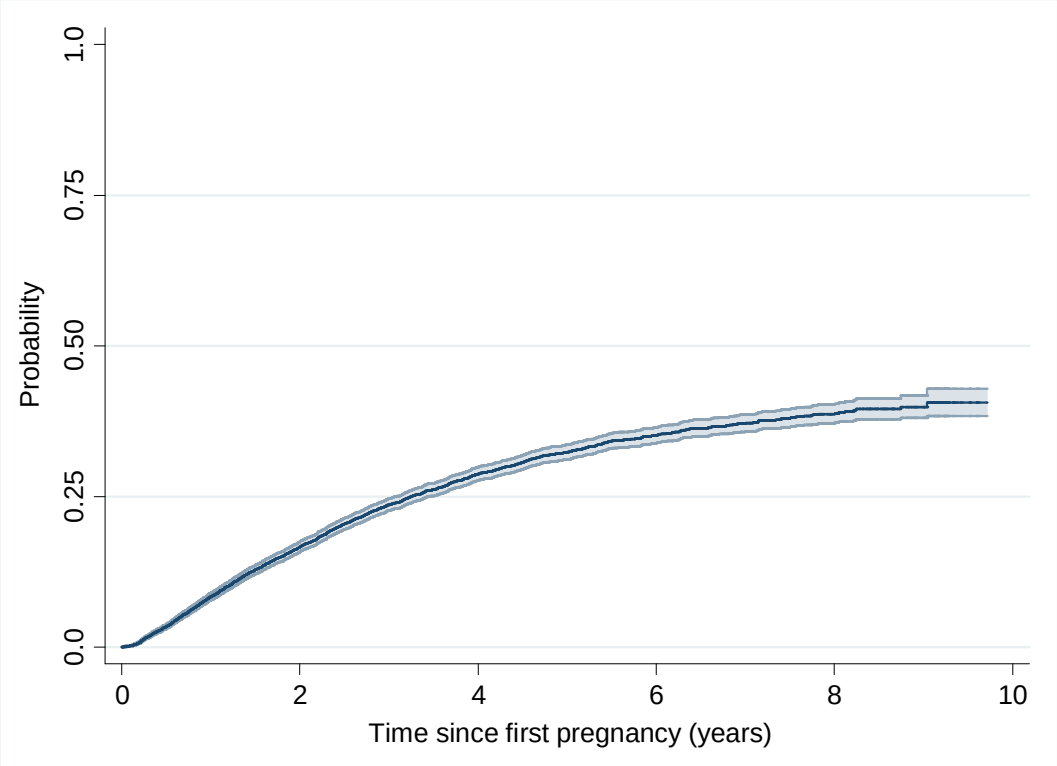
Characteristic	Number of women with complete information (%)	Number of women with missing information (%)	*p*-value
Total	7084 (100)	1577 (100)	-
Age at conception, yrs* (*n*=8618)			
<25	1480 (20.9)	380 (24.8)	0.002
25-29	2318 (32.7)	511 (33.3)	
30-34	2074 (29.3)	395 (25.8)	
≥35	1212 (17.1)	248 (16.2)	
Ethnic group (*n*=8591)			
White	802 (11.3)	304 (20.2)	<0.001
Black African	5702 (80.5)	1071 (71.1)	
Other	580 (8.2)	132 (8.8)	
World region of origin (*n*=8488)			
UK/Ireland	791 (11.2)	295 (21.0)	<0.001
Europe	205 (2.9)	56 (4.0)	
Eastern Africa	3268 (46.1)	505 (36.0)	
Middle Africa	511 (7.2)	102 (7.3)	
Western Africa	1202 (17.0)	210 (15.0)	
Southern Africa	608 (8.6)	129 (9.2)	
Africa (unspecified)	78 (1.1)	37 (2.6)	
Elsewhere	421 (5.9)	70 (5.0)	
HIV risk factor (*n*=8060)			
Injecting drug use	1158 (2.2)	29 (3.0)	0.149
Other**	6926 (97.8)	947 (97.0)	
Parity* (*n*=7652)			
Nulliparous	3065 (43.3)	248 (43.7)	0.778
1	2340 (33.0)	177 (31.2)	
2	1070 (15.1)	90 (15.8)	
≥3	609 (8.6)	53 (9.3)	
Timing of HIV diagnosis (*n*=8587)*			
Before pregnancy	2986 (42.3)	629 (41.3)	0.487
During pregnancy	4078 (57.7)	894 (58.7)	
Repeat pregnancy (*n*=8661)			
Yes	1893 (26.7)	345 (21.9)	<0.001
No	5191 (73.3)	1232 (78.1)	

*At first reported pregnancy

**Other comprises largely those originating from a high HIV prevalence area and/or with heterosexual exposure to HIV

In the time to event Kaplan–Meier analysis there were a total of 29,306 woman-years at risk. The median time at risk was 2.9 years. Figure 4.12 shows the Kaplan–Meier curve of the probability of second pregnancy; at 10 years of follow-up 40% of women had a second pregnancy. The 25% survival time was 3.3 years (i.e. after 3.3 years of follow-up an estimated 25% of women would have had a second pregnancy). The subsequent three graphs show Kaplan–Meier curves stratified by the key demographic characteristics that were found to be associated with having a repeat pregnancy in the descriptive analyses.

Figure 4.12 Cumulative probability of having a second pregnancy by time since first pregnancy, 2000-2009



Note: Probability is represented by the dark blue line and the 95% CIs by the lines above and below.

Figure 4.13 shows both a strong association and a clear pattern between maternal age at first pregnancy and repeat pregnancy (log rank test for trend: p<0.001). Women aged <25 years at their first pregnancy were most likely to have a second pregnancy, with over 50% having one by 10 years of follow-up. During the first year of follow-up the estimated probability of having a second pregnancy was around 10% among all age groups (except those aged ≥35 years) but subsequently diverged. Women aged ≥35 years at the time of

their first pregnancy took longest to conceive their second pregnancy, and had the lowest probability of having one. After approximately six years of follow-up there were no further second pregnancies among this group of women.

Figure 4.13 Cumulative probability of having a second pregnancy by age group at first pregnancy

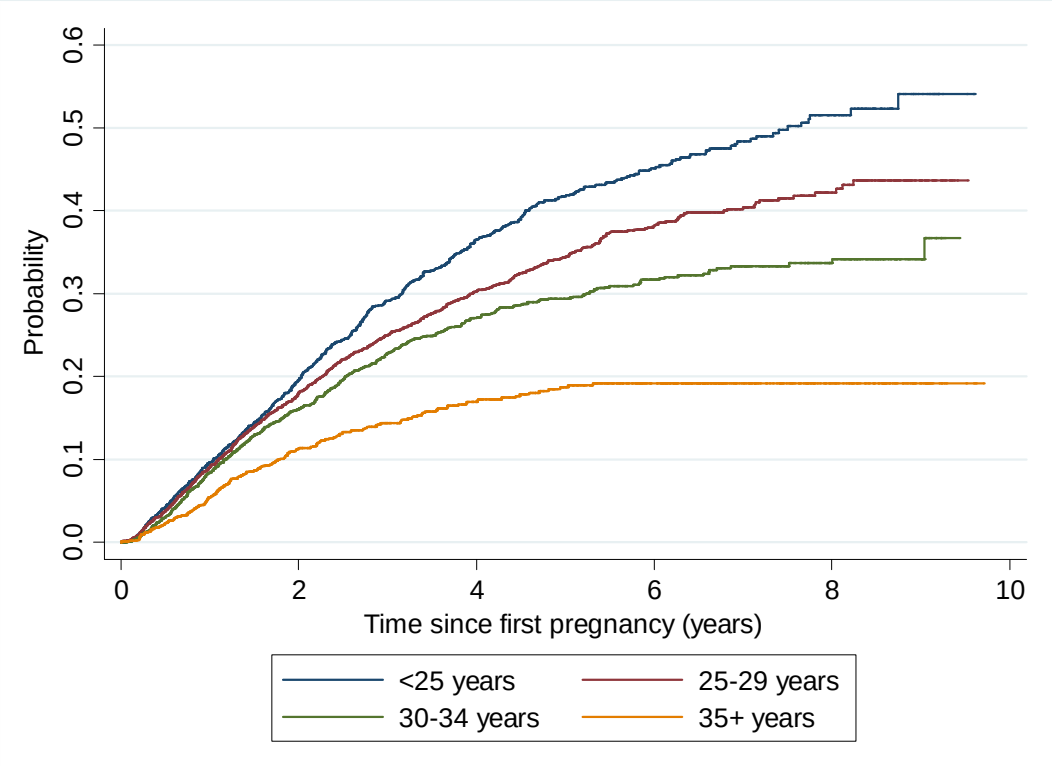


Figure 4.14 shows a clear trend between women's parity at their first pregnancy (i.e. the number of births women had experienced prior to their first pregnancy reported to the NSHPC) and the probability of having a second pregnancy (log rank test for trend: $p<0.001$). Women who were nulliparous at their first reported pregnancy were most likely to have a second pregnancy, with over 45% having one by the end of follow-up. The probability of second pregnancy was inversely associated with women's parity at first reported pregnancy.

Figure 4.14 Cumulative probability of having a second pregnancy by parity at first pregnancy

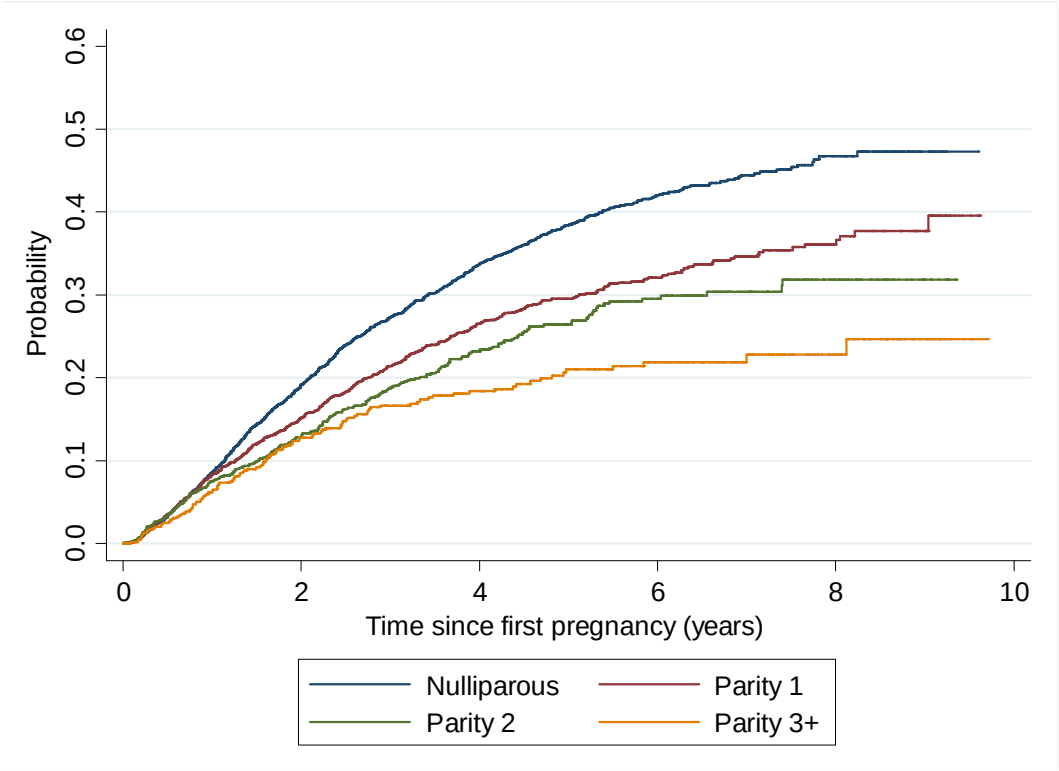


Figure 4.15 shows that the probability of repeat pregnancy varies by maternal world region of origin (log rank test: $p<0.001$). Women from Middle and Western Africa, followed by those born in the UK or Ireland were most likely to have a second pregnancy and to do so more quickly. The number of women from the rest of Europe was relatively small.

Figure 4.15 Cumulative probability of having a second pregnancy by world region of origin

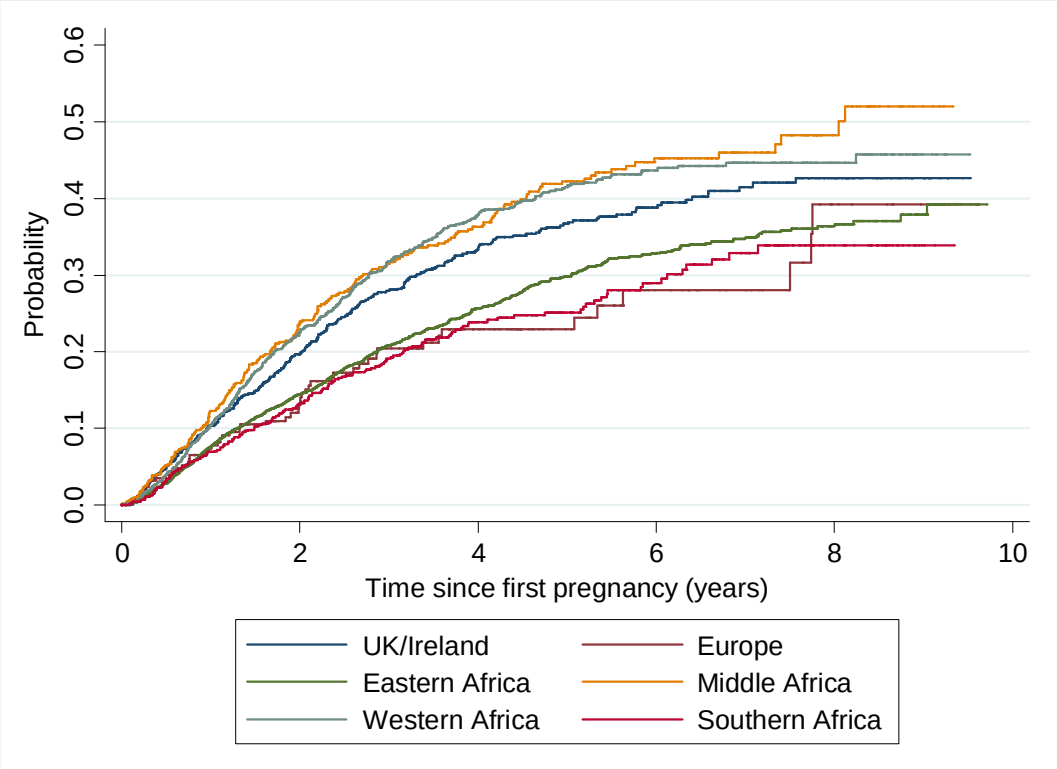


Table 4.5 shows the results of univariable and multivariable Cox proportional hazards analysis of demographic factors associated with having a second pregnancy. As seen in the preceding Kaplan–Meier analyses, the univariable Cox proportional hazards analysis showed that older women and parous women were less likely to have a repeat pregnancy. There were also variations by maternal world region of origin. The final multivariable model included maternal region of origin, year of pregnancy, maternal age and parity at first pregnancy, with 7525 women included. There was no association between the year in which women's first pregnancy occurred and the probability of repeat pregnancy in this model. The probability of a repeat pregnancy declined with increasing age at first pregnancy (p<0.001), and women who were parous at first reported pregnancy were less likely to conceive again. Compared with women born in the UK or Ireland, those from the rest of Europe, Eastern Africa, Southern Africa and Africa (unspecified) were less likely to have a repeat pregnancy, while women from Middle Africa and Western Africa were more likely to. The global Therneau-Grambsch test[32] for the final model was significant suggesting that the assumption of proportional hazards may not be met. Inspection of the individual Schoenfeld residuals for each variable in the model indicated that maternal age group and parity were the variables contributing to this non-proportionality. However, the

[32] The Therneau and Grambsch test was run in Stata using the `estat phtest` command.

global test for proportionality might be over sensitive to small deviations from the proportional hazards assumption. This means that observing a significant value of the test statistic often makes no difference to the overall conclusions and estimates, particularly with large datasets (Therneau *et al*, 2000). Examination of the log-log plots (i.e. the plot of the probability of having a second pregnancy against time since first pregnancy on log-log scale) revealed that the lines were reasonably parallel, satisfying the proportional hazards assumption to an acceptable degree. Plots stratified by maternal age group and parity together with a brief description and interpretation of these are provided in Appendix IV. The model was therefore accepted in its current form[33].

[33] An alternative, where there is only one exposure of interest is to present stratified analyses. However, as this was a risk factor analysis with several exposure variables, stratification was not appropriate and would result in an overly complex and difficult to interpret model.

Table 4.5 Univariable and multivariable analyses of demographic characteristics associated with having a second pregnancy

	n (%)**	Univariable analyses		Multivariable analysis (*n*=7525)	
		HR (95% CI)	*p*-value	aHR (95% CI)	*p*-value
Year of conception*					
Change per year	-	1.00 (0.98-1.02)	0.929	1.02 (1.00-1.04)	0.134
Age at conception, yrs*					
<25	1860 (35.2)	1	<0.001	1	<0.001
25-29	2829 (28.8)	0.82 (0.74-0.90)		0.86 (0.77-0.97)	
30-34	2469 (23.1)	0.68 (0.61-0.76)		0.73 (0.64-0.83)	
≥35	196 (13.4)	0.40 (0.34-0.47)		0.44 (0.37-0.53)	
World region of origin					
UK/Ireland	1086 (29.0)	1	<0.001	1	<0.001
Europe	261 (19.9)	0.69 (0.51-0.92)		0.73 (0.54-0.98)	
Eastern Africa	3773 (23.7)	0.76 (0.67-0.86)		0.83 (0.72-0.95)	
Middle Africa	613 (35.4)	1.18 (0.99-1.40)		1.29 (1.07-1.55)	
Western Africa	1412 (32.4)	1.13 (0.98-1.31)		1.16 (1.00-1.36)	
Southern Africa	737 (21.9)	0.68 (0.56-0.82)		0.62 (0.51-0.77)	
Africa (unspecified)	115 (8.7)	0.24 (0.13-0.46)		0.24 (0.11-0.51)	
Elsewhere	491 (26.3)	0.80 (0.65-0.98)		0.85 (0.69-1.06)	
Parity*					
Nulliparous	3313 (30.0)	1	<0.001	1	<0.001
1	2517 (23.7)	0.75 (0.68-0.83)		0.83 (0.75-0.93)	
2	1160 (21.0)	0.65 (0.56-0.75)		0.79 (0.68-0.91)	
≥3	115 (17.4)	0.50 (0.41-0.60)		0.65 (0.53-0.80)	

*At first reported pregnancy
***n* is the total of number women, and the proportion of those women who had repeat pregnancies is shown in brackets

4.2.4 Clinical and immunological predictors

The clinical and immunological characteristics (at first reported pregnancy) of women with and without a repeat pregnancy are compared in Table 4.6. Women with a repeat pregnancy were less likely to have been diagnosed prior to their first pregnancy. There was no significant difference between the two groups with respect to reported HIV/AIDS symptoms. Neither was there any significant different in earliest antenatal CD4 counts; around 45% in both groups had CD4 counts <350 cells/μl in their first pregnancy, with a median count of 370 cells/μl in both groups (and IQRs of 250-520 cells/μl in those with a repeat pregnancy and 250-520 cells/μl in those with a single pregnancy reported, p=0.642). However, some treatment differences were apparent with a lower proportion of women with repeat pregnancies conceiving their first pregnancy on treatment (among those diagnosed before pregnancy), and a higher proportion having not received antenatal ART in their first pregnancy. That 7.3% of those in the repeat pregnancy group did not receive antenatal ART is concerning, although it should be noted that only 3.8% (81/2130) of women did not receive ART during their second pregnancy.

Information on earliest CD4 count was missing for 1488 (17.2%) women and information on the presence of HIV/AIDS symptoms at any time during pregnancy for 1131 (13.1%) women. In total 1831 (21.1%) women were missing information on either of these variables. Women with missing information were younger, more likely to be white, to be from the UK or Ireland, or from Middle, Western or Southern Africa, to have an injecting drug use-associated mode of HIV acquisition, and to have been diagnosed during pregnancy. They were less likely to have a repeat pregnancy compared with those who had complete information (Table 4.7).

Table 4.6 Comparison of clinical and immunological characteristics of women with a single pregnancy and those with repeat pregnancies

Characteristic	Number of women with a single pregnancy (%)	Number of women with repeat pregnancies (%)	*p*-value
Earliest CD4 count, cells/µl* (*n*=7173)			
≥500	1529 (28.9)	532 (28.3)	0.953
350-499	1398 (26.4)	493 (26.3)	
200-349	1568 (29.6)	562 (29.9)	
<200	800 (15.1)	291 (15.5)	
HIV/AIDS symptoms* (*n*=7530)			
No	5358 (97.2)	1957 (97.1)	0.822
Yes	156 (2.8)	59 (2.9)	
Timing of HIV diagnosis* (*n*=8337)			
Prior to first reported pregnancy	2760 (43.4)	855 (38.4)	<0.001
During first reported pregnancy	3599 (56.6)	1373 (61.6)	
Antenatal ART* **(*n*=3473)			
From before conception	1320 (49.6)	374 (46.0)	0.031
Started during pregnancy	1202 (45.2)	381 (46.8)	
None	137 (5.2)	59 (7.3)	

*At first reported pregnancy
**Among women diagnosed prior to their first reported pregnancy only

Table 4.7 Comparison of women with complete information on key clinical and immunological factors (CD4 count or HIV/AIDS symptoms) and those with missing information on these variables

Characteristic	Number of women with complete information (%)	Number of women with missing information (%)	*p*-value
Age at conception, yrs* (*n*=8618)			
<25	1378 (21.1)	482 (23.2)	0.021
25-29	2127 (32.5)	702 (33.8)	
30-34	1924 (29.4)	545 (26.3)	
≥35	1113 (17.0)	347 (16.7)	
Ethnic group (*n*=8591)			
White	853 (12.5)	253 (14.3)	<0.001
Black African	5364 (78.6)	1409 (79.7)	
Other	606 (8.9)	106 (6.0)	
World region of origin (*n*=8488)			
UK/Ireland	838 (12.4)	248 (14.4)	<0.001
Europe	213 (3.2)	48 (2.8)	
Eastern Africa	3143 (46.5)	630 (36.5)	
Middle Africa	473 (7.0)	140 (8.1)	
Western Africa	1076 (15.9)	336 (19.5)	
Southern Africa	536 (7.9)	201 (11.7)	
Africa (unspecified)	67 (1.0)	48 (2.8)	
Elsewhere	417 (6.2)	74 (4.3)	
HIV risk factor (*n*=8060)			
Injecting drug use	131 (2.0)	56 (3.6)	<0.001
Other**	6392 (98.0)	1481 (96.4)	
Timing of HIV diagnosis* (*n*=8587)			
Before pregnancy	2922 (42.8)	693 (39.3)	0.008
During pregnancy	3902 (57.2)	1070 (60.7)	
Repeat pregnancy (*n*=8661)			
Yes	1823 (26.7)	415 (22.7)	<0.001
No	5007 (73.3)	1416 (77.3)	

*At first reported pregnancy

**Other comprises largely those originating from a high HIV prevalence area and/or with heterosexual exposure to HIV

The Kaplan–Meier analysis showed no association between earliest antenatal CD4 count in first pregnancy and the probability of repeat pregnancy (log rank test for trend: *p*=0.665) (Figure 4.16). There was also no association between having HIV/AIDS symptoms at any time during first pregnancy and the probability of repeat pregnancy (log rank test: *p*=0.658) (Figure 4.17).

Figure 4.16 Cumulative probability of having a second pregnancy by earliest CD4 count (cells/µl) during first pregnancy

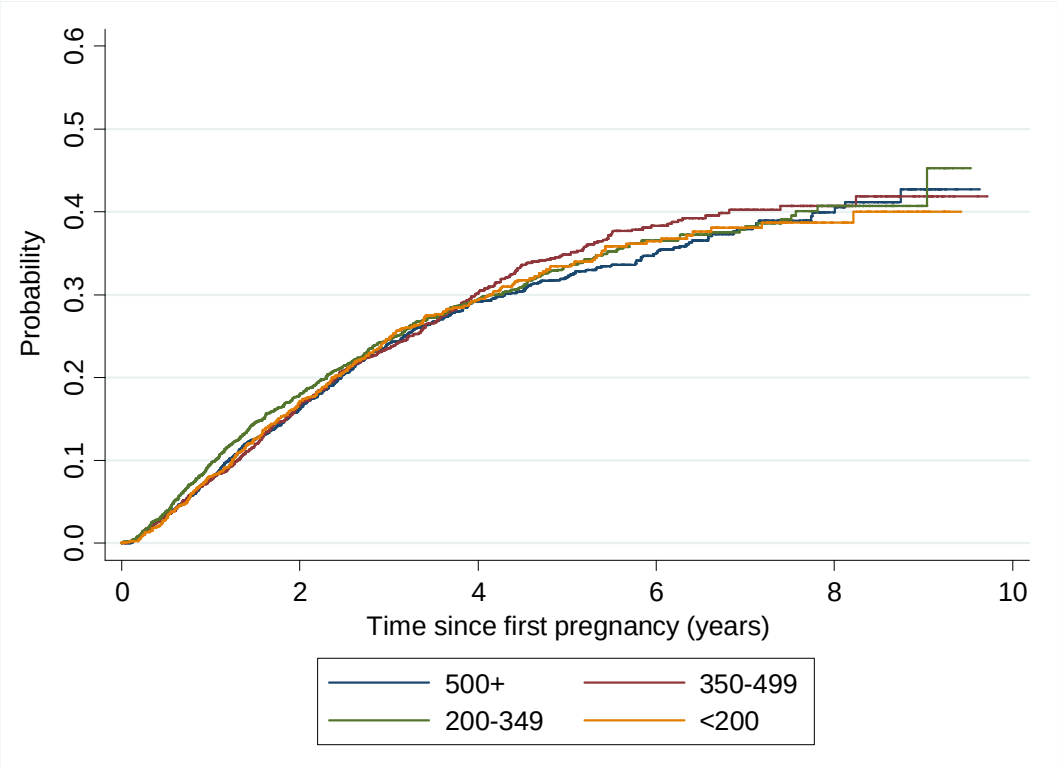
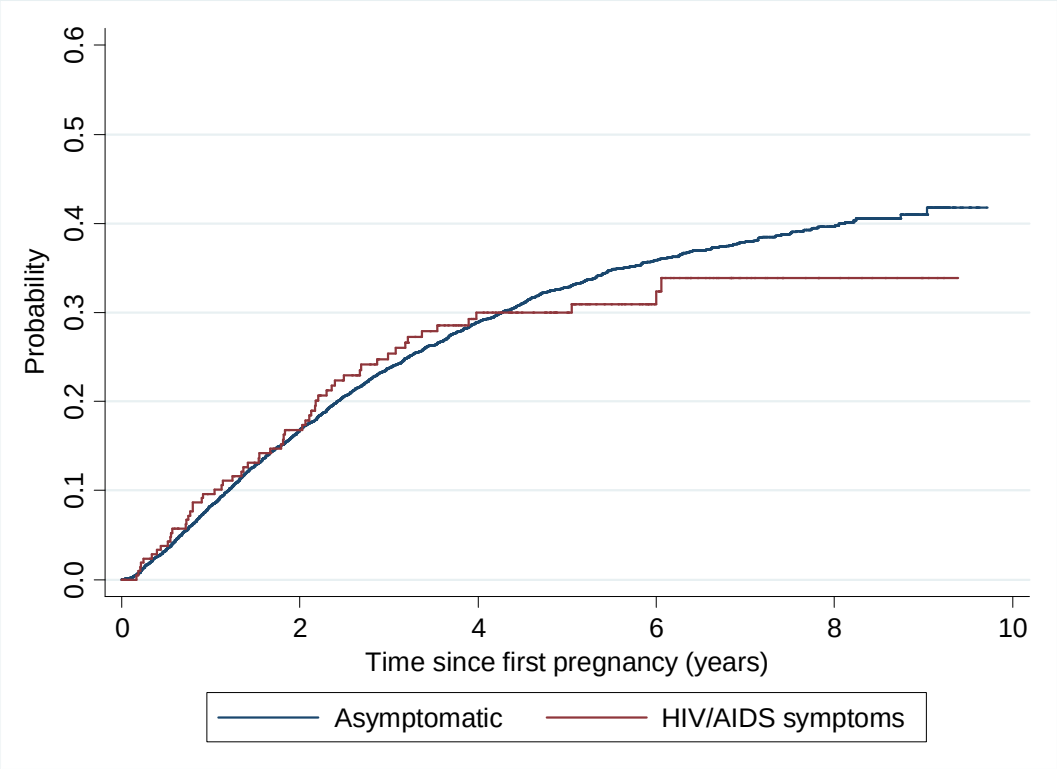


Figure 4.17 Cumulative probability of having a second pregnancy according to presence of HIV/AIDS symptoms during first pregnancy



Cox proportional hazards modelling showed no univariable association between maternal health and the probability of repeat pregnancy (Table 4.8)[34]. There remained no association between CD4 count and repeat pregnancy (p=0.619) after adjusting for the demographic variables that had previously been shown to be associated with the probability of repeat pregnancy (year (adjusted for *a priori*), maternal age and parity at first pregnancy, and maternal region of origin). Similarly, there remained no association between having HIV/AIDS symptoms at first pregnancy and the probability of repeat pregnancy (p=0.895) after adjustment for the demographic variables (data not shown).

[34] The findings were very similar, with no evidence of an association, if the earliest antenatal CD4 count measurements were restricted to those taken prior to ART initiation (overall p-value for the association between CD4 count and probability of repeat pregnancy based on the univariable Cox proportional hazards model: p=0.772).

Table 4.8 Univariable analyses of clinical and immunological factors associated with having a second pregnancy

	n (%)**	Univariable analyses	
		HR (95% CI)	*p*-value
Earliest CD4 count, cells/µl*			
≥500	2061 (25.8)	1	0.860
350-499	1891 (26.1)	1.04 (0.92-1.18)	
200-349	2130 (26.4)	1.05 (0.93-1.18)	
<200	1091 (26.7)	1.02 (0.88-1.17)	
HIV/AIDS symptoms*			
No	7315 (26.8)	1	0.657
Yes	215 (27.4)	0.94 (0.73-1.22)	

*At first reported pregnancy
***n* is the total of number women, and the proportion of those women who had repeat pregnancies is shown in brackets

4.2.5 Previous adverse pregnancy outcomes

The analysis of stillbirth or neonatal death in first pregnancy as a predictor of repeat pregnancy included 7496 women (1970 of whom had a second pregnancy) with a total of 25,496 woman-years of follow-up. The analysis investigating whether having an HIV-positive infant in first pregnancy was a predictor of repeat pregnancy included 6471 women with 22,969 years of follow-up.

Table 4.9 describes the association between adverse outcomes in women's first pregnancy and their probability of having a second pregnancy. Women whose first pregnancy ended in either stillbirth or neonatal death were significantly more likely to have a second pregnancy than those ending in a live birth. The interval between having a first birth which resulted in either a stillbirth or neonatal death and conceiving again was just 0.67 years (IQR: 0.26-1.23)[35]. There was no evidence of an association between MTCT having occurred the first pregnancy and the probability of having further pregnancies, although the number of transmissions that occurred may have been too small to detect such an association.

Table 4.9 Comparison of the outcomes of first pregnancies among women with a single pregnancy and those with repeat pregnancies

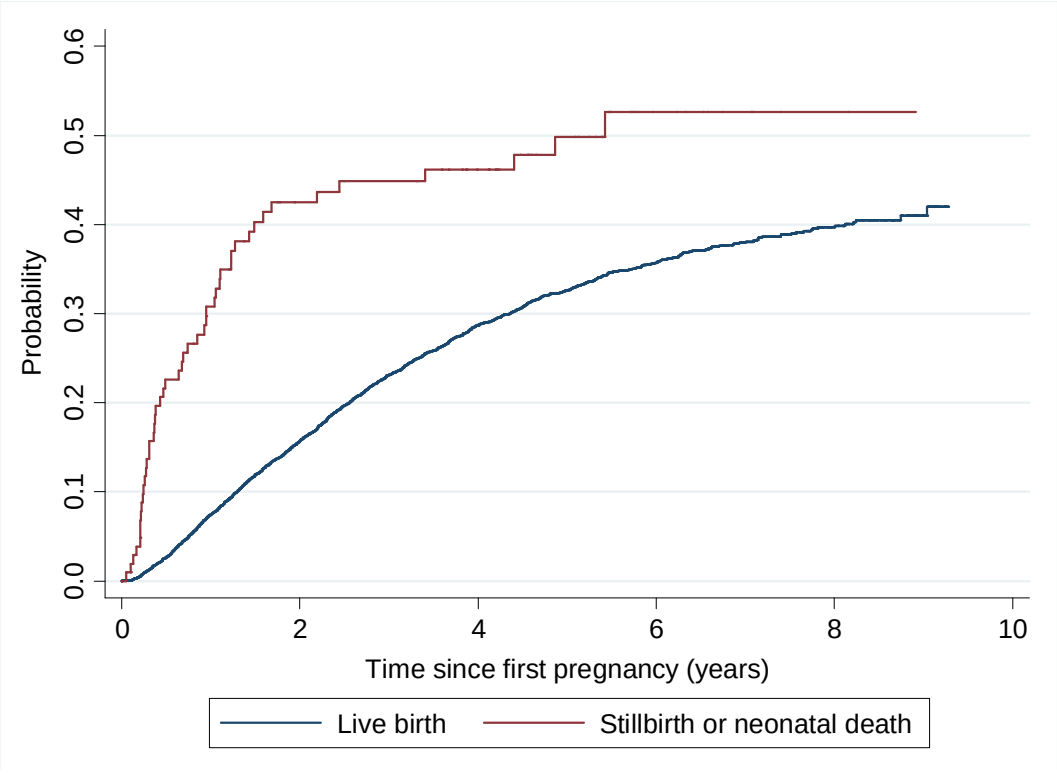
Outcome of first reported pregnancy	Number of women with a single pregnancy (%)	Number of women with repeat pregnancies (%)	*p*-value
Stillbirth or neonatal death (*n*=7496)			
Yes	57 (1.0)	48 (2.4)	<0.001
No*	5469 (99.0)	1922 (97.6)	
HIV-positive infant (*n*=6471)			
Yes	54 (1.2)	22 (1.2)	0.777
No	4637 (98.9)	1758 (98.8)	

*Live birth

[35] As compared with a live birth-to-pregnancy interval of 1.8 years (IQR: 0.9-3.1) as documented in the first part of this chapter.

That women whose first pregnancy ended in a stillbirth or neonatal death were more likely to have a repeat pregnancy, and to do so more quickly than those whose first pregnancy ended in a live birth (log rank test: $p<0.001$), can be seen clearly in the Kaplan–Meier analysis (Figure 4.18). For example, after two years of follow-up an estimated 43% of women who had previously experienced a stillbirth or neonatal death had become pregnant again compared with 16% of those with a prior live birth.

Figure 4.18 Cumulative probability of having a second pregnancy according to the outcome of women's first reported pregnancy

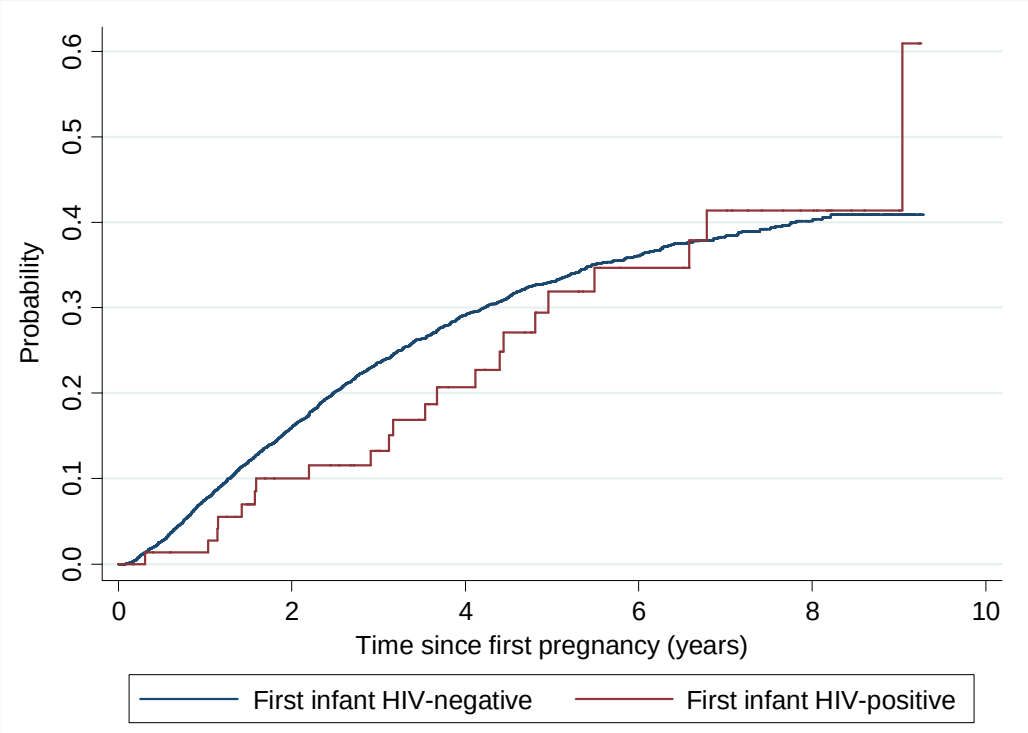


Using Cox proportional hazards modelling the crude HR for the association between stillbirth or neonatal death in first pregnancy and the probability of repeat pregnancy was 2.2 (95% CI: 1.66-2.94), $p<0.001$. There was no evidence of significant confounding of this association by year of first pregnancy, maternal age, maternal world region of origin, or parity in the bivariable analyses, and the association remained when a multivariable model was constructed adjusting for the aforementioned demographic variables (aOR: 2.37, 95% CI: 1.76-3.20, $p<0.001$).

In the Kaplan–Meier analysis of the association between HIV status of women's first infant and the probability of further pregnancy, there was no association (log rank test: *p*=0.604) (Figure 4.19). This figure should, however, be interpreted with some caution due to the small number of vertical transmissions (*n*=22); the seemingly large increase in the probability of repeat pregnancy among these women at around nine years of follow-up represents the occurrence of just one repeat pregnancy.

The crude HR for the association between having an HIV-positive infant in first pregnancy and the probability of repeat pregnancy was 0.89 (95% CI: 0.59-1.36), *p*=0.604. There was no evidence of significant confounding of this association by year of first pregnancy, maternal age, maternal world region of origin, or parity in the bivariable analyses, and there remained no evidence of an association when a multivariable model was constructed (adjusting for the aforementioned demographic variables); aOR: 0.98, 95% CI: 0.63-1.50, *p*=0.916).

Figure 4.19 Cumulative probability of having a second pregnancy according to HIV status of fist infant



4.3 Discussion

Frequency of pregnancies and trends over time

There has been a significant increase in the number of pregnancies among diagnosed women in the UK and Ireland over the last two decades (though the annual number of pregnancies reported to the NSHPC has plateaued at around 1500 per year since 2006), with a growing proportion accounted for by repeat pregnancies (39% in 2009). This increase largely reflects changing migration patterns, with increases in migration from sub-Saharan Africa[36] where HIV prevalence is high (UNAIDS, 2013), together with the introduction of routine antenatal screening for HIV in the late 1990's (Townsend *et al*, 2006). However, reproductive decision-making and fertility which, as discussed in Chapter 2, Section 2.2, are likely to be influenced by a wide range of biological, social and cultural factors, have also played a role. It is pertinent that women who had their first pregnancy during 1995-1999 were most likely to have a second pregnancy, and to do so most quickly, possibly reflecting the advent of cART which had a significant impact on the quality of life and life expectancy of people living with HIV (Gange *et al*, 2002; May *et al*, 2011b; Nakagawa *et al*, 2012; Samji *et al*, 2013; van Sighem *et al*, 2010). There may well have been an accumulation of women of child-bearing age who had either avoided starting a family, or were unable to conceive due to poor health in the pre-cART era. Improvements in women's health, together with reductions in MTCT risk (Duong *et al*, 1999; Townsend *et al*, 2008a), may have had both biological and psychological effects on women's fertility (Blair *et al*, 2004; Sharma *et al*, 2007). This pool of women may thus have been quick to initiate and complete their childbearing after the introduction of cART. This overall increase in pregnancies will have resulted in an accumulation of diagnosed HIV-positive women who have already had a pregnancy and are therefore 'at risk' of further (repeat) pregnancies.

The aim of the analyses presented in this chapter was to estimate the incidence of repeat pregnancies occurring in diagnosed HIV-positive women in the UK and Ireland. This may not, however, accurately reflect women's full reproductive history since becoming infected with HIV. Women's first pregnancy reported to the NSHPC is, for the purposes of this thesis, classified as their first pregnancy as a diagnosed woman (whether her diagnosis was made before or during that pregnancy). Since uptake of antenatal HIV testing is high in the UK (>95%) (Public Health England, 2013a), as is reporting of pregnancies to the

[36] An analysis of the 2001 UK Census data, conducted by the Institute for Public Policy Research and Sheffield University Social and Spatial Inequalities Research Group is available on the BBC News website (http://news.bbc.co.uk/1/shared/spl/hi/uk/05/born_abroad/html/overview.stm). Additionally, 2011 Census data are available here: Estimated Overseas born Population resident in the UK tab 1.3 (both websites Accessed October 2013).

NSHPC, very few diagnosed women will have had a pregnancy in the UK or Ireland that was not reported to the study. In addition, during the study period, a large proportion of women (around 60%) were not aware of their HIV status until antenatal screening during their first reported pregnancy. However, the majority of HIV-positive pregnant women in the UK and Ireland originate from abroad. A substantial proportion of migrants are likely to have been infected with HIV prior to arriving in the UK or Ireland (Rice *et al*, 2012), many of whom will be part way through their childbearing when they arrive (for example, 59% of women from sub-Saharan Africa were parous at their first reported pregnancy). Although it is therefore reasonable to assume that some women will have experienced a pregnancy as an HIV-positive woman prior to their arrival into the UK or Ireland, the vast majority originate from sub-Saharan Africa where availability of HIV testing is often low. Data compiled through Demographic and Health Surveys and AIDS Indicator Surveys in 29 African countries during 2003-2011 revealed that on average, 71% of women had never been tested for HIV (Staveteig *et al*, 2013), thus many of these women will have remained undiagnosed prior to arrival. Although the NSHPC collects information on women's overall parity, irrespective of their HIV status at the time of any previous pregnancies, neither the date of any previous unreported pregnancy nor whether the woman had diagnosed HIV at the time is available.

Meanwhile, women may return to their country of origin or move elsewhere outside the UK and Ireland, either temporarily or permanently, at some stage during their reproductive lives; any further pregnancies that they then have would not be eligible to be reported to the NSHPC[37]. In these analyses only 1% of women were documented to have 'gone abroad' during pregnancy, but others may travel after their pregnancy ends and this information would not be captured though the NSHPC. Some of those who do travel home may of course subsequently return to the UK or Ireland; among women with a first pregnancy during 2000-2009 who were reported to have gone abroad during that pregnancy, 5% (8/152) had a subsequent pregnancy reported to the NSHPC. In a cross-sectional survey of African migrants living in London, 46% of women had visited their home country in the last five years (Fenton *et al*, 2001). Though all those participating in the study by Fenton *et al* had subsequently returned to the UK, this data demonstrates that many migrants from sub-Saharan Africa are able to visit their country of origin, a proportion of whom may remain there.

It is probable that some women who experience an early termination or miscarriage will not be reported to the NSHPC as they did not access antenatal care (an issue which is explored in more detail in Chapter 7). Therefore, such pregnancies are likely to be under-

[37] Assuming they do not return to the UK or Ireland during their subsequent pregnancy.

ascertained through the NSHPC which would result in an under-estimation of the number and rate of pregnancies, and an over-estimation of pregnancy spacing intervals. However, other ongoing studies of HIV in pregnancy, for example, the ECS only collect information on pregnancies ending in a live birth (Thorne *et al*, 2005). A further issue is that the probability of repeat pregnancy among women whose first pregnancy occurred towards the end of the study period may be an underestimation due to lack of time for a subsequent pregnancy, as well as delays in the reporting of pregnancies. The rate of repeat pregnancies was 6.5 per 100 woman years during 2005-2009, lower than the rate of 7.3 per 100 woman years during 2000-2004. One might expect the true rate for the latest period to be similar to that for the preceding period.

This was the first European study to estimate the rate of repeat pregnancies among diagnosed HIV-positive women, and there is no study with which to make a direct comparison of the rate. Previous studies from the US and Europe have provided estimates of the overall pregnancy rate among HIV-positive women; a rate of 5.5 (95% CI: 5.2-5.8) per 100 woman-years in the US during 1992-2001 was estimated using data from the Adult and Adolescent Spectrum of Disease Project (Blair *et al*, 2004), while slightly higher rates have been reported among women enrolled in the US Women's Interagency HIV Study; 7.4 per 100 woman-years during 1994-2002 (Massad *et al*, 2004), and 6.8 (95% CI: 6.1-7.5) per 100 woman-years in more recent years (2002-2009) (Linas *et al*, 2011). Similar rates, 6.0-8.2 per 100 woman-years (depending on time since HIV diagnosis), have been reported from Europe (van Benthem *et al*, 2000). The rate of repeat pregnancies reported here (6.7, 95% CI: 6.5-6.9) per 100 woman-years is thus consistent with the range observed in similar settings. A recent UK study, published subsequent to this work, conducted on an extract of the NSHPC dataset linked with women enrolled in the UK Collaborative HIV Cohort (UK CHIC) study[38], reported a pregnancy incidence of 3.5% (95% CI: 2.7-4.3) in 2000 and 4.7% (95% CI: 4.1-5.3) in 2009 among women attending care in 13 HIV Centres (Huntington *et al*, 2013). Again, these are overall pregnancy rates (i.e. including first pregnancies to diagnosed women) so are not directly comparable with repeat pregnancy rates presented in this chapter. Furthermore, as UK CHIC is not a national cohort, only 23% of HIV-positive women with a pregnancy in the UK were matched with UK CHIC (Huntington *et al*, 2012).

Birth spacing

The birth-to-birth interval of 2.6 years between first and second live births during 2000-2009 is in line with the interval among the general UK population (2.9 years in 2008). It is not

[38] The UK Collaborative HIV Cohort (UK CHIC) study collects clinical data on diagnosed HIV-positive people attending a sample of large HIV Clinics. The study does not collect information on pregnancy (Huntington *et al*, 2012; UK Collaborative HIV Cohort Steering Committee, 2004).

surprising that they are not exactly the same since the demographics of the population of HIV-positive women are very different to those of the general UK population. A much larger proportion of women reported to the NSHPC are black African (>75%) compared with the proportion of black Africans in the general population (approximately 1.5%)[39] (Office for National Statistics, 2011b). The earlier European study of repeat pregnancies reported a longer interval of 3.5 years between live births (Agangi *et al*, 2005). This could be due to cultural factors and/or policies that influence the advice given to women by healthcare professionals, as well as the availability of, and attitudes towards, contraception. Differences in population structures may also contribute e.g. the proportion of women of black African ethnicity was much lower (19%) in the study by Agangi *et al*.

Demographic predictors of repeat pregnancies

Aside from variations in the probability of repeat pregnancies by time period, Cox proportional hazards modelling demonstrated that younger age at first pregnancy was associated with an increased probability of further pregnancies. This is both logical and consistent with other studies of repeat pregnancies among diagnosed women in similar settings (Agangi *et al*, 2005; Blair *et al*, 2004; Bryant *et al*, 2007). Studies of the overall pregnancy rate among diagnosed women have also found younger age to be a predictor of pregnancy (Blair *et al*, 2004; Huntington *et al*, 2013; Linas *et al*, 2011; Massad *et al*, 2004), and of childbearing desires and intentions (Berhan *et al*, 2013). Women who were parous at their first reported pregnancy were less likely to conceive again, and the probability declined with increasing number of previous births at first (HIV-positive) pregnancy. An association between fewer previous births and an increased probability of repeat pregnancy was also observed in the US (Bryant *et al*, 2007). In the previous European study, restricted to live births only, although a similar trend was observed, the finding was non-significant (Agangi *et al*, 2005). Since the NSHPC does not collect information on the number of living children, this could not be explored as a predictor of pregnancy, nor adjusted for in the analyses. Some of the parous women in the study may have children that are no longer living, thus potentially increasing their childbearing desires (see Chapter 2, Section 2.2).

The lower probability of repeat pregnancies among women born elsewhere in Europe compared with those born in the UK or Ireland may reflect the low fertility rates in some European countries (Billari *et al*, 2004). European women could also potentially be more likely, than those born in Africa for example, to move between the UK or Ireland and their home country during their reproductive lives. Any subsequent pregnancies that they experienced would hence not be reported to the NSHPC. There were marked variations in

[39] Based on the 2009 mid-year population estimates for England and Wales stratified by ethnic group.

the probability of repeat pregnancy among women from different regions of sub-Saharan Africa even after adjusting for maternal age, parity and year of first pregnancy; the probability was higher among those from Middle and Western Africa though the latter was borderline significant, and lower among those from Eastern and Southern Africa. This pattern is likely to reflect a complex range of cultural, behavioural and migratory factors such as fertility patterns in women's countries of origin, the demographics of women who migrate from different regions, and cultural beliefs and attitudes regarding HIV and childbearing. For example, in many African countries, and indeed elsewhere, HIV unfortunately remains a significant source of stigma (Grossman *et al*, 2013; Rankin *et al*, 2005). However, in some cultures the stigma of not having children can be greater than the stigma of being HIV-positive since child bearing is often a central component of social status and identity for both men and women (Ibisomi *et al*, 2014; Nabukera *et al*, 2008; Nattabi *et al*, 2009). These stigmas can thus influence the fertility of HIV-positive people in various ways. For example, in South Africa it has been documented that it is socially unacceptable for people who had disclosed their HIV status to have more children (Cooper *et al*, 2007). On the other hand, HIV-positive women have reported that in order to avoid stigmatisation by the community they continued to have children to conceal their HIV status (Aka-Dago-Akribi *et al*, 1999; Cooper *et al*, 2007), to be seen as leading 'normal' lives (Smith *et al*, 2010). Such influences, the direction in which they act, and their strength, may differ by African region/country. Similarly, there are variations in fertility across Africa; for example, the average number of children per woman is 5.7 in Nigeria (National Population Commission (NPC) [Nigeria] and ICF Macro, 2009), compared with 2.1 in South Africa (Department of Health/ Medical Research Council/ OrcMacro, 2007). Such differences may be borne out in women's fertility patterns after arrival into the UK and Ireland.

Clinical predictors of repeat pregnancies

Women with repeat pregnancies were less likely to have been diagnosed prior to their first pregnancy, which may reflect the fact that these women were more likely to have their first pregnancy earlier in the study period when HIV testing was less widespread (British HIV Association *et al*, 2008). Maternal health, indicated by CD4 count and presence of HIV/AIDS symptoms at first pregnancy, was not associated with the probability of repeat pregnancy. In interpreting this finding it should be borne in mind that a woman's health status could change considerably between her first pregnancy and the time that she conceives again, for example, if she initiates treatment for her own health during the intervening period. Some treatment differences were, however, apparent. Among women diagnosed prior to their first reported pregnancy, those who went on to have a repeat pregnancy were less likely to have conceived their first pregnancy whilst on ART. However, given that there was no association between CD4 count and repeat pregnancy (and this

remained the case when women's earliest antenatal CD4 measurements were restricted to those taken prior to ART initiation), this difference may reflect issues such as access to treatment rather than women's health status. Furthermore, both this finding, and the fact that a higher proportion of women who went on to have a repeat pregnancy did not receive ART in their index pregnancy (7% compared with 5%), are likely, in part at least, due to changes in treatment policies and practice over time. Over a third (36%) of index pregnancies to those who subsequently experienced a repeat pregnancy occurred during the earliest time period (2000-2002) compared with 19% of those to women with a single pregnancy reported. The overall proportion of women in the NSHPC conceiving on treatment has increased over time, while the proportion not receiving antenatal ART has declined considerably (Townsend *et al*, 2014; Townsend *et al*, 2008b). It is reassuring that there were fewer (3.8%) women who did not receive ART during their second pregnancy, tying in with the temporal change in antenatal ART uptake.

Data from the US has shown that healthier women, indicated by higher CD4 percentages and lower viral loads, were more likely to have repeat pregnancies (Bryant *et al*, 2007; Minkoff *et al*, 2003), with a 10% increased probability of repeat pregnancy per 10% increase in CD4 percentage reported by Bryant *et al* during 1989-2004. Meanwhile, no association was observed in Europe (Agangi *et al*, 2005). The two US studies both used data from the US WITS so one would expect their findings to concur. In these studies CD4 measurements were taken post-partum (after women's first pregnancy), whereas in the analyses presented here the earliest CD4 measurement in women's first pregnancies were used. The US studies also measured CD4 percentages, rather than counts. The recent analysis of linked NSHPC and UK CHIC data reported that compared with women who had CD4 counts of 200-350 cells/µl, those with CD4 <200 cells/µl had a significantly lower overall pregnancy rate (not only repeat pregnancies) (adjusted relative rate: 0.65, 95% CI: 0.55-0.77), though CD4 measurements were the earliest taken during the year in which women became pregnant (Huntington *et al*, 2013).

Previous adverse pregnancy outcomes and the probability of repeat pregnancy

Data from the general population indicates that women who have experienced a previous adverse pregnancy outcome such as a stillbirth frequently become pregnant again, with around 50% of women conceiving again within 12 months (Hughes *et al*, 1999; Lee *et al*, 2013). Among HIV-positive women specifically, studies in African settings have reported increased pregnancy desire and intentions among those who have experienced adverse pregnancy outcomes (Moyo *et al*, 2004; Smee *et al*, 2011). In the present analyses, the increased probability and rapidity of repeat pregnancy among women whose first pregnancy resulted in a stillbirth or neonatal death was marked. The birth-to-pregnancy

interval among this group of women was just 0.67 years (eight months). Similarly short intervals among women who have experienced a stillbirth have been documented previously in the general population (Hughes *et al*, 1999). There was, however, little evidence for an association between vertical transmission of HIV occurring in the first pregnancy and having a repeat pregnancy. Although this could be due to a lack of power to detect an association, other studies from the UK and the US also found no association between having an HIV-positive infant and the desire for further children (Cliffe, 2005; Sowell *et al*, 2002). If having an HIV-positive child does influence the desire for further children its impact may be complex. For example, women may not want to risk having further children for fear of transmitting HIV again; alternatively they may be more likely to desire further, possibly HIV-negative, children. Any potential association may also have changed over time; prior to the introduction of DNA PCR methods for HIV diagnosis in children (Dunn *et al*, 1995), diagnosing a child took around 18 months[40] thus a woman could have become pregnant again before knowing whether or not her first child was HIV-positive.

Limitations

Though the NSHPC provides an excellent data source for estimating the incidence of repeat pregnancies (the strengths of the system in this regard are discussed further in Chapter 8), some limitations require consideration. The study collects little information on social factors such as socio-economic status, relationship status or level of education, which could be important predictors of repeat pregnancy. Also, information on contraceptive use is not available, and the system does not collect information on whether or not pregnancies were planned. Studies among HIV-positive women in Europe and Canada have reported that around half of pregnancies were unplanned (Fiore *et al*, 2008; Loutfy *et al*, 2011). Meanwhile, data from the third National Survey of Sexual Attitudes and Lifestyles (Natsal-3) in Britain revealed that 16% of pregnancies to all women aged 16-44 years were unplanned with a further 29% being classified as ambivalent (Wellings *et al*, 2013). As noted in Chapter 2, defining a pregnancy as 'planned' *vs*. 'unplanned' or 'unintended' or 'unwanted' is not clear cut, and the terms may be interpreted differently by different people (Barrett *et al*, 2002; Fischer *et al*, 1999). It is feasible that where the distinction can be made, the characteristics of women experiencing 'planned' pregnancies may be quite different to those experiencing 'unplanned' pregnancies. For example, the Natsal-3 survey reported that characteristics such as young age, smoking, drug use, and

[40] The delay is necessary with antibody detection methods to ensure that the presence of an infant's own antibodies can be distinguished from passively transferred maternal antibodies. Current UK guidelines do, however, still recommend that all children born to HIV-positive mothers have a confirmatory antibody test at 18 months in order to detect any late transmissions via breastfeeding (Taylor *et al*, 2012).

lower educational level were strongly associated with the risk of having an unplanned pregnancy (Wellings *et al*, 2013).

With regards to missing data, there were some differences between individuals missing key demographic variables and those with complete data. It was therefore not appropriate to entirely exclude cases with missing data from the analyses. Any bias that would be introduced by excluding these cases was minimised by only excluding them where necessary (i.e. from the bivariable and multivariable analyses as appropriate). Women with missing demographic and/or clinical and immunological information were younger, much more likely to be white and to be born in the UK or Ireland. It is possible that this may represent a sub-group of women who are less engaged with HIV services and antenatal care. That repeat pregnancies were less frequent in those with missing information will largely reflect the fact that for women who have experienced repeat pregnancies there will have been more than one opportunity for the NSHPC to collect demographic information on the woman. Self-reported information is subject to recall bias (Coughlin, 1990). Most variables explored as predictors of repeat pregnancy in these analyses were not self-reported. However, in many cases parity (at first reported pregnancy) will be self-reported (to the care provider who subsequently reported data to the NSHPC), and could therefore be reported differentially. For example, women who have experienced the loss of a child, or who have left children in their country of origin, may be less likely to report these children when asked about their childbearing history (United Nations Statistics Division, 2013).

4.4 Key findings

- The annual number of pregnancies among HIV-positive women in the UK and Ireland has increased dramatically since the NSHPC began (from 89 pregnancies in 1990 to 1465 in 2009, $p<0.001$)

- During 1990-2009, 14,096 pregnancies were reported in 10,568 diagnosed HIV-positive women; 2737 (25.9%) women had repeat pregnancies (2117 women had two pregnancies, 475 had three and 145 had four or more)

- The proportion of pregnancies that were repeat increased substantially over time ($p<0.001$), reaching 38.6% (565/1465) in 2009

- The overall rate of repeat pregnancies was 6.7 (95% CI: 6.5-6.9) per 100 woman-years during 1990-2009

- The median birth-to-birth interval between first and second deliveries was 2.7 years (IQR: 1.7-4.1) and the birth-to-pregnancy interval was 1.9 years (IQR: 1.0-3.3)

- There were a total of 11,426 pregnancies among 8661 women whose first pregnancy occurred during 2000-2009, 2238 (25.8%) of whom had repeat pregnancies

- Cox proportional hazards modelling of predictors of repeat pregnancy revealed that during 2000-2009:

    - The probability of having a repeat pregnancy declined significantly with increasing age at first pregnancy

- Women who were parous at their first reported pregnancy since HIV diagnosis were less likely to conceive again, and the probability declined with increasing number of previous births at first pregnancy

- Compared with women born in the UK or Ireland, those from the rest of Europe, Eastern Africa, Southern Africa and Africa (unspecified) were less likely to have a repeat pregnancy, while women from Middle Africa and Western Africa were more likely to

- In this study population, few women had HIV/AIDS symptoms during their index pregnancy and the overall median CD4 count was 370 cells/µl. Maternal health status during first pregnancy (CD4 count and presence of HIV/AIDS symptoms) was not associated with the probability of repeat pregnancy

- Women whose first pregnancy ended in a stillbirth or neonatal death were more likely to have a repeat pregnancy, and did much more rapidly than those whose initial pregnancy resulted in a live birth

- There was no evidence of an association between having a previously had an HIV-positive infant and the probability of having a second pregnancy though numbers were small, with MTCT rates of <1.5%

- These findings highlight that diagnosed women experiencing repeat pregnancies are a substantial and growing group; it is important that the epidemiology of repeat pregnancies in this population is thoroughly understood

Chapter 5 Engagement with care, and the health and management of women experiencing sequential pregnancies

This chapter investigates engagement with HIV and pregnancy-related care, and the health and management of women experiencing sequential pregnancies (Objective 3). It aims to inform the optimal management of HIV-positive women of childbearing age in the context of current and potential future pregnancies, as well as identifying variations in access to or uptake of care.

5.1 Timing of presentation for antenatal care

Booking for antenatal care in good time not only helps ensure a healthy pregnancy but, for women living with HIV, it is also important in order to enable timely PMTCT interventions. There is a paucity of literature on HIV-positive women's engagement with antenatal care, as highlighted in Chapter 2, Section 2.3. The objective of this first part of the chapter is to describe timing of antenatal booking for repeat pregnancies compared with index pregnancies, explore factors associated with late booking among the repeat pregnancies, and delays from booking to initiation of HIV-related antenatal care (Objective 3a).

5.1.1 Methods

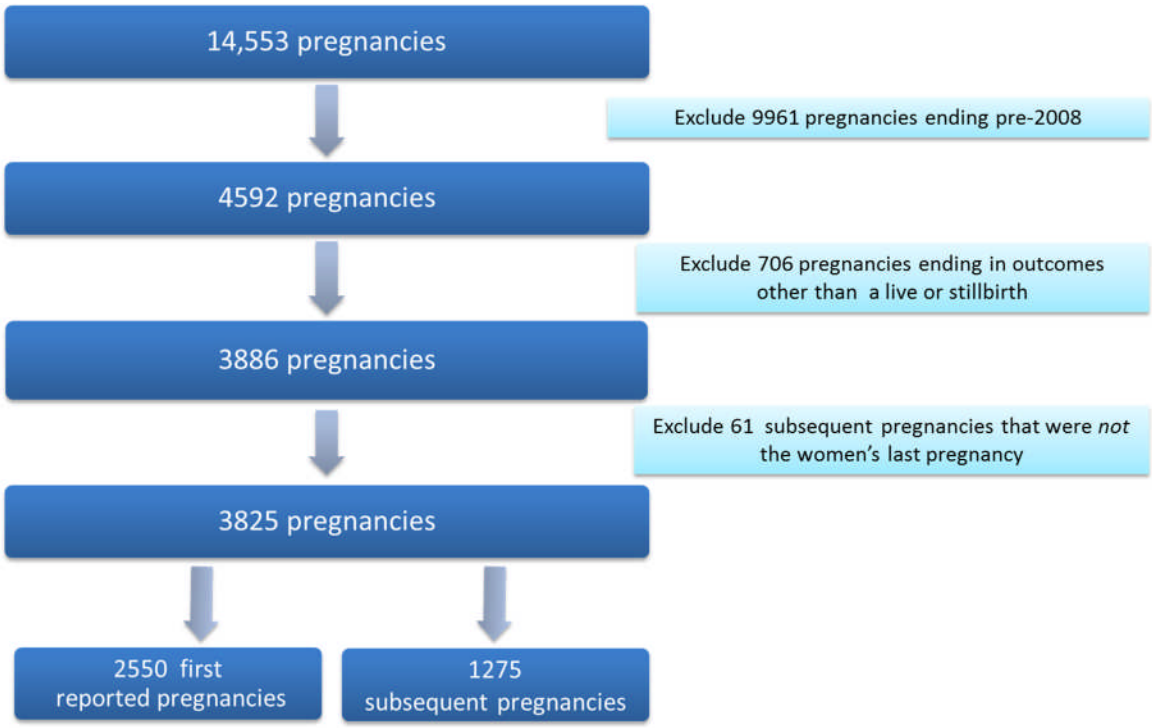
Dataset

These analyses were based on NSHPC pregnancies delivered during 2008-2010 as antenatal booking data were not collected by the NSHPC prior to 2008. The main group for analysis consisted of pregnancies ending in a live or stillbirth to diagnosed HIV-positive women who had already had a previous birth reported to the NSHPC (irrespective of when their first delivery occurred). A comparison group consisting of first reported live and stillbirths was also utilised in initial descriptive analyses (Figure 5.1).

Women who had had a previous pregnancy with an outcome other than a live or stillbirth, e.g. miscarriage or termination, were excluded since the aim was to explore booking among women who had experienced a previous complete pregnancy. Women with a previous birth would have experienced the various aspects of general and HIV-specific management and care that completing a pregnancy entails including booking for antenatal care, antenatal HIV testing (if appropriate), laboratory monitoring of HIV disease and

complications, receiving or being offered ART, and caregiving to other children. Those with outcomes other than a live or stillbirth in their subsequent pregnancy were excluded since women experiencing outcomes such as termination of pregnancy or miscarriage may not have had sufficient time to book for antenatal care before the pregnancy ended, and the group who did so would be biased towards women who booked for care early. If a woman had more than two births reported to the NSHPC only her last was included in the 'subsequent pregnancy' group. There were, however, some women appearing in the full dataset (*n*=3825) more than once, for example, having had a first pregnancy in 2008 and a second in 2010.

Figure 5.1 Study population flow chart – antenatal care booking analyses



Classifications and definitions

Timing of antenatal booking was categorised as follows: <13 completed weeks gestation, 13-17 weeks, 18-23 weeks, ≥24 weeks. The <13 weeks cut-off was based on UK recommendations that women should book by around 10-13 gestational weeks (National Institute for Health and Clinical Excellence, 2008; Royal College of Obstetricians and Gynaecologists, 2008). Booking after 13 completed weeks was thus considered 'late'. However, in order to further explore late booking, this group was divided into three categories. A ≥24 weeks group was chosen based on the 2008 BHIVA guideline which recommended ART initiation by 20-28 weeks (de Ruiter *et al*, 2008), and the current guideline recommending starting by 24 weeks (Taylor *et al*, 2012). The remaining group (13-23 weeks) was split at 17 weeks as a pragmatic cut-off. Earliest antenatal CD4 counts were restricted to those prior to ART initiation. As a high proportion of women had no delivery viral load reported (with 28 days before and up to seven days after delivery), an imputed variable was also used as described in Chapter 3 (if viral load in the last 28 days of pregnancy was missing but an undetectable viral load was last reported earlier in that pregnancy, delivery viral load was imputed as undetectable).

Statistical analyses

Univariable and multivariable ordinal logistic regression models were fitted to analyse factors associated with timing of booking for antenatal care in women's subsequent pregnancies. Ordinal logistic regression allows modelling of outcomes with more than two naturally ordered categories (Dupont, 2009). It was used to explore the four antenatal booking groups in a more appropriate way than simply dichotomising the outcome variable. The Brant test was used to check that the proportional odds assumption that underlies ordinal logistic regression was not violated (i.e. that the log odds between successive outcome categories can be expressed as parallel lines) (Brant, 1990). This means, for example, that the change in log-odds for the lowest (<13 weeks) category compared with the remaining three groups combined is equal to that for the highest (≥24 weeks) group compared with all three lower groups combined. Therefore, only one model is required to describe the relationships between each outcome group *vs*. the other three groups combined (UCLA: Statistical Consulting Group).

Regression analyses were restricted to women's last reported pregnancy during 2008-2010, and did not include first reported pregnancies, thus each woman only contributed one pregnancy to the dataset. It was therefore not necessary to use statistical methods to adjust for clustering of pregnancies within women. Although first pregnancies were included as a comparison group in some of the initial descriptive analyses there were only 85 women who contributed both a first and subsequent pregnancy to the dataset. Ordinal

logistic regression models are fitted using a likelihood-based method thus models were constructed using the same procedures as for a standard risk factor analysis logistic regression model (as described in Chapter 3, Section 3.5).

5.1.2 Study population

The study population consisted of 3825 deliveries during 2008-2010. There were 1275 subsequent deliveries (1266 live and 9 stillbirths) to women who already had at least one birth reported to the NSHPC; 1002 were second deliveries, 236 third, 33 fourth, and four were fifth deliveries. There were 1255 singleton and 20 twin pregnancies in the subsequent pregnancy group. Meanwhile, the comparison group of first reported births during 2008-2010 consisted of 2550 deliveries; 2529 live births and 21 stillbirths. There were 2487 singleton pregnancies and 63 sets of twins.

The characteristics of the first and subsequent pregnancy groups are compared in Table 5.1. Subsequent pregnancies were less likely to have occurred earlier in the study period (p<0.001), more likely to be in women aged ≥35 years (p<0.001), more likely to have been reported in London or Ireland (p<0.001), and the women experiencing them were more likely to be on ART at conception (p<0.001). There was little difference in maternal HIV risk factor (p=0.702). Subsequent pregnancies were slightly, though not significantly, more likely to be in women from sub-Saharan Africa (p=0.093), and less likely to be twin or triplet pregnancies (p=0.071).

Information on antenatal booking date was reported for just under three quarters of all pregnancies (73.9%, 2827/3825), and this proportion was similar among the subsequent (74.8%, 953/1275) and first pregnancy groups (73.5%, 1874/2550) (p=0.405). Compared with women for whom date of antenatal booking was reported to the NSHPC, those with missing booking date were more likely to be reported earlier in the study period; over half (53.8%) of those with missing information were reported in 2008 compared with 26.9% of those with known information (p<0.001), less likely to have been reported in London (26.0% *vs*. 42.9%, p<0.001), and less likely to have conceived on ART (33.5% *vs*. 40.7%). There were no significant differences in maternal age (p=0.403), HIV risk factor (p=0.211), world region of origin (p=0.426), parity (p=0.119), or whether the woman was diagnosed prior to or during (her first reported) pregnancy (p=0.295).

Table 5.1 Antenatal care booking analyses – characteristics of first and subsequent pregnancies

Characteristic	First pregnancies		Subsequent pregnancies		*p*-value
	n	%	*n*	%	
Parity* (*n*=3504)					
Nulliparous	1007	43.1	0	0.0	-
1	780	33.4	533	44.3	
2	376	16.1	413	34.3	
≥3	137	7.4	258	21.4	
Year of delivery (*n*=3825)					
2008	939	36.8	359	28.2	<0.001
2009	841	33.0	474	37.2	
2010	770	30.2	442	34.7	
Age at delivery, yrs (*n*=3811)					
<25	354	14.0	102	8.0	<0.001
25-34	1507	59.4	771	60.5	
≥35	675	26.6	402	31.5	
HIV risk factor (*n*=3496)					
Other**	2221	98.7	1228	98.6	0.702
Injecting drug use	29	1.3	18	1.4	
World region of origin (*n*=3759)					
UK/Ireland	344	13.8	163	12.8	0.093
Sub-Saharan Africa	1898	76.4	1010	79.3	
Elsewhere	243	9.8	101	7.9	
Pregnancy type (*n*=3825)					
Singleton	2487	97.5	1255	98.4	0.071
Twin/triplet	63	2.5	20	1.6	
Conception interval, yrs* (*n*=1275)**					
<2	-	-	366	28.7	-
2-3	-	-	498	39.1	
4-5	-	-	263	20.6	
≥6	-	-	148	11.6	
Reporting region (*n*=3816)					
London	925	36.4	543	42.6	<0.001
Elsewhere in England	1282	50.4	530	41.6	
Wales, Scotland, N Ireland	175	6.9	54	4.2	
Ireland	160	6.3	147	11.5	
Earliest CD4 count, cells/µl (*n*=3239)					
≥500	649	29.8	400	37.6	<0.001
350-499	598	27.5	326	30.7	
200-349	627	28.8	253	23.8	
<200	302	13.9	84	7.9	

Continued overleaf

Table 5.1 *Continued:* Antenatal care booking analyses – characteristics of first and subsequent pregnancies

Characteristic	First pregnancies		Subsequent pregnancies		*p*-value
	n	**%**	***n***	**%**	
On ART at conception (*n*=3577)					
No	1652	68.1	526	45.7	<0.001
Yes	775	31.9	624	54.3	
Timing of HIV diagnosis (*n*=2526)					
Before first reported pregnancy	1481	58.6	-	-	-
During first reported pregnancy	1045	41.4	-	-	

*Number of previous live or stillbirths irrespective of whether woman had diagnosed HIV at the time of these previous pregnancies
**Other comprises largely those originating from a high HIV prevalence area and/or with heterosexual exposure to HIV
***Interval between conception date of current pregnancy and previous pregnancy reported to the NSHPC

5.1.3 Timing of antenatal booking

The median gestational age at antenatal booking was 13.0 weeks (IQR: 10.6-17.0) overall, thus half of women (50.1%, 1416/2827) booked at 13 completed weeks gestation or later. The medians were similar among the first and subsequent pregnancy groups: 12.9 weeks (IQR: 10.5-17.4) *vs*. 13.0 weeks (IQR: 10.6-16.4) respectively (p=0.268), and the corresponding proportions booking at ≥13 weeks were 49.8% and 50.7% (p=0.653). When the first pregnancies were restricted to those in nulliparous women the median was 12.6 weeks (IQR: 10.3-17.0) and there remained no statistically significant difference in timing of booking between the first and repeat pregnancies (p=0.673). Figures 5.2 and 5.3 show the distribution of gestational weeks at antenatal booking among the first and subsequent pregnancy groups respectively. Both have a right-skewed distribution. The number of women booking after 28 completed weeks gestation is relatively low in both groups, though there is a tail of women booking late, and right up to the time of delivery. When the group of first pregnancies was split into those in women who were diagnosed with HIV prior to and during pregnancy the medians were 12.3 weeks (IQR: 10.1-15.6) and 14.3 weeks (IQR: 11.1-20.1) respectively (p<0.001).

Figure 5.2 Distribution of gestational weeks at antenatal booking among first reported pregnancies

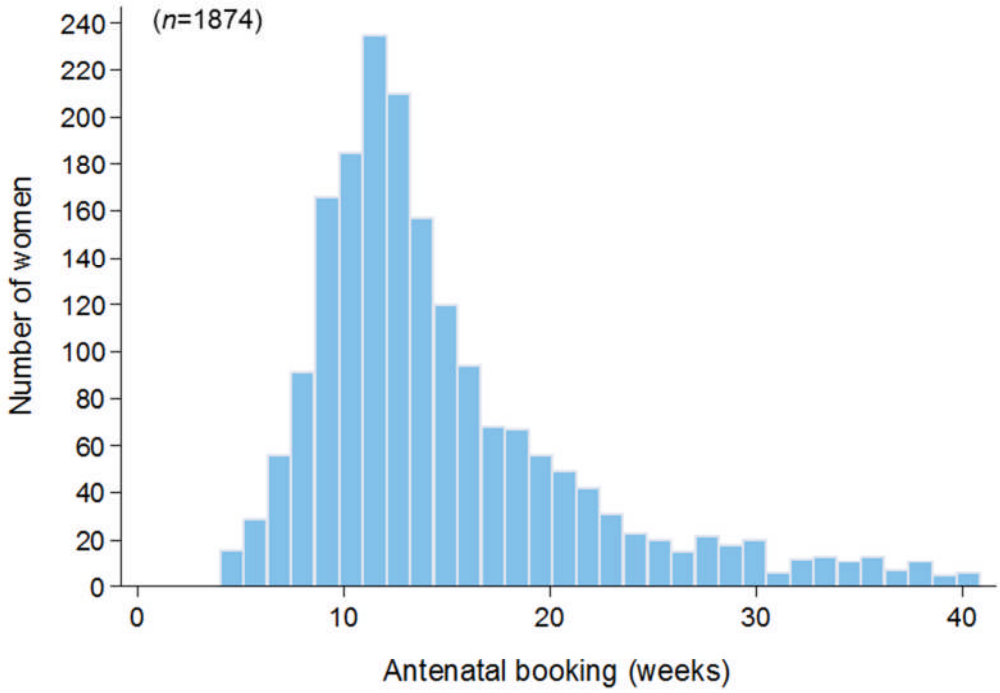
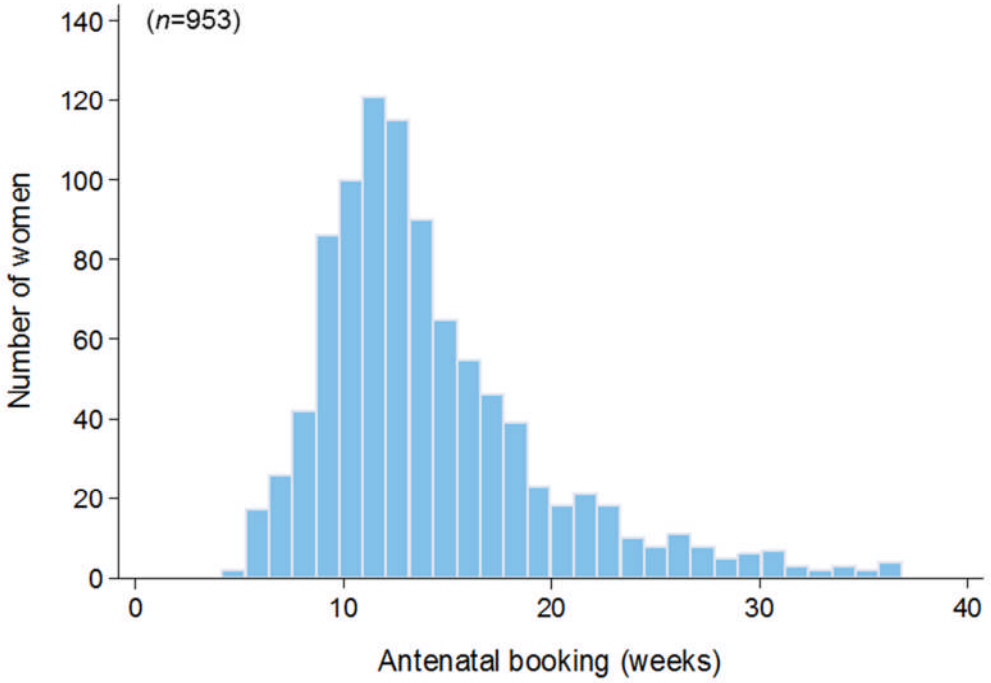


Figure 5.3 Distribution of gestational weeks at antenatal booking among subsequent pregnancies



Among the subsequent pregnancy group, the majority of women booked before 24 completed weeks; 49.3% before 13 weeks, 32.0% between 13 and 17 weeks, 11.9% at 18-23 weeks, and the remaining 6.8% at 24 weeks or later. The proportion booking before 13 completed weeks increased from 38.5% in 2008 to 59.7% in 2010.

With little evidence of any overall difference in the proportion of women booking late (≥13 weeks) in first compared with subsequent pregnancies, further analyses focused on subsequent pregnancies in order to identify factors associated with late booking in this group specifically. This also enabled risk factors that were only available for the subsequent pregnancy group to be included in the analyses e.g. inter-pregnancy conception interval.

There were 85 women with more than one pregnancy during 2008-2010 who had information available on timing of antenatal booking (i.e. both their first and last reported pregnancies occurred during the three year study period). Table 5.2 explores patterns in timing of antenatal booking in first and subsequent pregnancies among this small sub-population of women. Among the 40 women who booked at <13 weeks for their subsequent pregnancy, over half (52.5%) had also booked at <13 weeks for their previous pregnancy, although 10.0% had booked for their first pregnancy very late (≥24 weeks). Looking at the table the other way around, of the 22 women who booked at ≥18 weeks for their first pregnancy, over three quarters (77.3%) booked before 18 weeks for their subsequent pregnancy (with 40.9% having booked before 13 weeks). There were only four women who booked at ≥24 weeks in their subsequent pregnancy, all of whom had booked at 13-17 weeks in their first. Due to the relatively small number of women with more than one pregnancy during 2008-2010, these findings should be interpreted with some caution. It was also therefore not appropriate to consider timing of booking at previous pregnancy in the analyses of factors associated with timing of booking in women's repeat pregnancies.

Table 5.2 Patterns in timing of booking for antenatal care in women's first and subsequent pregnancies

Timing of antenatal booking for subsequent pregnancy	Timing of antenatal booking for first reported pregnancy									
	<13 wks		13-17 wks		18-24 wks		≥24 wks		Total	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%
<13 wks	21	52.5	10	25.0	5	12.5	4	10.0	40	100
13-17 wks	15	50.0	7	23.3	6	20.0	2	6.7	30	100
18-24 wks	3	27.3	3	27.3	5	45.5	0	0.0	11	100
≥24 wks	0	0.0	4	100.0	0	0.0	0	0.0	4	100
Total	39	45.9	24	28.2	16	18.8	6	7.1	85	100

5.1.4 Factors associated with late booking for antenatal care

Table 5.3 shows the characteristics of women in the subsequent pregnancy group according to timing of antenatal booking (*n*=953). There were variations in timing of booking according to year of delivery (p<0.001), conception interval (*p*=0.003), region of reporting (*p*<0.001) and whether or not the woman was on ART at conception (*p*<0.001), as well as some weaker evidence of a difference by parity (*p*=0.065). Specifically, women delivering earlier in the study period were more likely to book later (33.8% of those booking at ≥24 weeks were delivered in 2008 compared with 17.0% of those booking at <13 weeks). Women with a very short inter-pregnancy conception interval also booked later (46.2% of those booking at ≥24 weeks had an interval of <2 years compared with 24.3% of those booking at <13 weeks), as did those who were not on ART at conception (accounting for 60.9% of those booking at ≥24 weeks *vs*. 37.3% of those booking at <13 weeks). The relationship between region of reporting and timing of booking appears a little more complex with both early and very late bookers being more common in London. Finally, women with ≥3 previous births (irrespective of whether they had diagnosed HIV at the time of these previous births) were more likely to book very late (accounting for 33.9% of women booking at ≥24 weeks and 18.7% of those booking at <13 weeks).

Although overall there were no significant differences in timing of booking according to maternal age (*p*=0.604), world region of origin (*p*=0.115), HIV risk factor (*p*=0.954), or earliest antenatal CD4 count in that pregnancy (*p*=0.246), some patterns are apparent. Women booking late tended to be older (38.5% of those booking at ≥24 weeks were aged ≥35 years compared with 30.6% of those booking at <13 weeks), which may well be associated with the fact that women of higher parity (who were more likely to book later) may be older. The late booking women were somewhat more likely to originate from sub-Saharan Africa (89.2% of very late bookers (≥24 weeks) compared with 78.3% of early bookers). Finally, of some concern, 15.9% of the very late bookers had a CD4 count of <200 cells/µl though numbers were small (*n*=10).

Table 5.3 Characteristics of women according to timing of antenatal booking for subsequent pregnancies

Characteristic	Gestation at booking for antenatal care								*p*-value
	<13 wks		13-17 wks		18-23 wks		≥24 wks		
	n	%	*n*	%	*n*	%	*n*	%	
Parity (*n*=923)*									
1	212	46.6	121	41.0	44	40.7	24	36.9	0.065
2	158	34.7	96	32.5	40	37.0	19	29.2	
≥3	85	18.7	78	26.4	24	22.2	22	33.9	
Year of delivery (*n*=953)									
2008	80	17.0	73	23.9	33	29.2	22	33.8	<0.001
2009	178	37.9	131	43.0	49	43.4	32	49.2	
2010	212	45.1	101	33.1	31	27.4	11	16.9	
Age at delivery, yrs (*n*=953)									
<25	42	8.9	22	7.2	13	11.5	3	4.6	0.604
25-34	284	60.4	185	60.7	64	56.6	37	56.9	
≥35	144	30.6	98	32.1	36	31.9	25	38.5	
World region of origin (*n*=953)									
UK/Ireland	59	12.6	41	13.4	12	10.6	5	7.7	0.115
Sub-Saharan Africa	368	78.3	240	78.7	98	86.7	58	89.2	
Elsewhere	43	9.1	24	7.9	3	2.7	2	3.1	
HIV risk factor (*n*=935)									
Other**	453	98.5	295	98.3	110	99.1	63	98.4	0.954
Injecting drug use	7	1.5	5	1.7	1	0.9	1	1.6	

Continued overleaf

Table 5.3 *Continued*: Characteristics of women according to timing of antenatal booking for subsequent pregnancies

Characteristic	Gestation at booking for antenatal care								*p*-value
	<13 wks		13-17 wks		18-23 wks		≥24 wks		
	n	%	*n*	%	*n*	%	*n*	%	
Conception interval, yrs* (*n*=953)**									
<2	114	24.3	93	30.5	27	23.9	30	46.2	0.003
2-3	197	41.9	120	39.3	53	46.9	15	23.1	
4-5	96	20.4	58	19.0	26	23.0	9	13.8	
≥6	63	13.4	34	11.1	7	6.2	11	16.9	
Reporting region (*n*=952)									
London	253	53.8	123	40.5	40	35.4	32	49.2	<0.001
Elsewhere in England	163	34.7	124	40.8	38	33.6	23	35.4	
Wales, Scotland, N Ireland	17	3.6	18	5.9	5	4.4	0	0.0	
Ireland	37	7.9	39	12.8	30	26.5	10	15.4	
Earliest CD4 count, cells/µl (*n*=870)									
≥500	169	39.4	100	35.8	37	37.4	25	39.7	0.246
350-499	128	29.8	96	34.4	28	28.3	16	25.4	
200-349	106	24.7	61	21.9	24	24.2	12	19.0	
<200	26	6.1	22	7.9	10	10.1	10	15.9	
On ART at conception (*n*=938)									
No	172	37.3	150	49.5	59	53.6	39	60.9	<0.001
Yes	289	62.7	153	50.5	51	46.4	25	39.1	

*Number of previous live or stillbirths irrespective of whether woman had diagnosed HIV at the time of these previous pregnancies
**Other comprises largely those originating from a high HIV prevalence area and/or with heterosexual exposure to HIV
***Interval between conception date of current pregnancy and previous pregnancy reported to the NSHPC

The results of the univariable ordinal logistic regression analyses (Table 5.4) showed that the following variables were significantly associated with timing of booking for antenatal care: parity (p=0.016), year of delivery (p<0.001), world region of origin (p=0.040) and region of pregnancy report (p<0.001). There was weak evidence of an association between timing of booking and inter-pregnancy conception interval (p=0.074), and also earliest antenatal CD4 count (p=0.091). Meanwhile, there was very little evidence of an association with maternal age (p=0.620) or maternal HIV risk factor (p=0.858). After including all variables that were significant in the univariable analyses in the multivariable model, there was reasonable evidence that adding conception interval and earliest antenatal CD4 count each improved the fit of the model (LR test: p=0.117 and p=0.055 respectively). There was little support for the inclusion of either maternal age (LR test: p=0.386) or HIV risk factor (LR test: p=0.140).

Table 5.4 shows the results of the multivariable ordinal logistic regressions. The result from the Brant test was not significant (p=0.282) confirming that the proportional odds assumption for the ordinal logistic regression model was met. The multivariable model demonstrated that higher parity (≥3), earlier year of delivery, being reported in England (excluding London) or Ireland, and not being on ART at conception were independently associated with later booking for antenatal care. In the multivariable model the association between a very short conception interval (<2 years) and later booking was attenuated and no longer significant at the p<0.05 level, however, the pattern remained. This may be due to the reduction in power in the multivariable model (there were 849 observations in the final model whereas 953 women had information available on conception interval). There was also some (non-significant) suggestion that women from sub-Saharan Africa were more likely than those born in the UK or Ireland to book late (aOR: 1.36, 95% CI: 0.90-2.04), and that women with the lowest CD4 counts were more likely to book later (aOR: 1.56, 95% CI: 0.93-2.60 among those with <200 cells/μl compared with women with ≥500 cells/μl).

Table 5.4 Univariable and multivariable analyses of factors associated with later booking for antenatal care among subsequent pregnancies

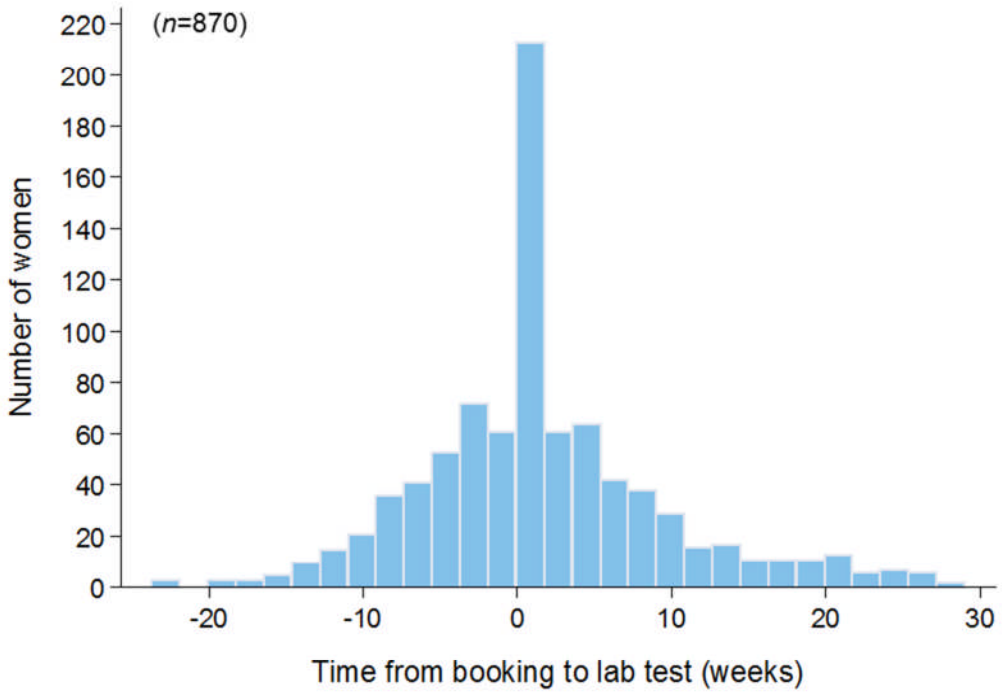
	Univariable analyses			Multivariable analysis (*n*=849)		
	OR	95% CI	*p*-value	aOR	95% CI	*p*-value
Parity*						
1	1		0.016	1		0.023
2	1.11	(0.84-1.47)		0.99	(0.73-1.35)	
≥3	1.57	(1.15-2.15)		1.54	(1.10-2.17)	
Year of delivery						
2008	1		<0.001	1		<0.001
2009	0.74	(0.54-1.01)		0.75	(0.53-1.06)	
2010	0.41	(0.29-0.56)		0.44	(0.30-0.63)	
Age at delivery, yrs						
<25	1		0.620			
25-34	1.06	(0.68-1.66)				
≥35	1.19	(0.74-1.90)				
World region of origin						
UK/Ireland	1		0.040	1		0.104
Sub-Saharan Africa	1.19	(0.83-1.72)		1.36	(0.90-2.04)	
Elsewhere	0.67	(0.38-1.18)		0.86	(0.46-1.63)	
Maternal HIV risk factor						
Other**	1		0.858			
Injecting drug use	0.91	(0.34-2.46)				
Conception interval, yrs***						
<2	1		0.074	1		0.178
2-3	0.71	(0.53-0.96)		0.72	(0.52-0.99)	
4-5	0.73	(0.52-1.04)		0.71	(0.48-1.04)	
≥6	0.64	(0.42-0.98)		0.75	(0.47-1.20)	
Reporting region						
London	1		<0.001	1		<0.001
Elsewhere in England	1.36	(1.04-1.78)		1.47	(1.10-1.97)	
Wales, Scotland, N Ireland	1.36	(0.76-2.44)		1.31	(0.67-2.56)	
Ireland	2.70	(1.85-3.94)		2.50	(1.65-3.77)	
Earliest CD4 count, cells/µl						
≥500	1		0.091	1		0.067
350-499	1.05	(0.78-1.42)		0.87	(0.63-1.20)	
200-349	0.94	(0.67-1.31)		0.77	(0.54-1.10)	
<200	1.80	(1.10-2.94)		1.56	(0.93-2.60)	
On ART at conception						
No	1		<0.001	1		<0.001
Yes	0.55	(0.43-0.70)		0.59	(0.46-0.78)	

*Number of previous live or stillbirths irrespective of whether woman had diagnosed HIV at the time
**Other comprises largely those originating from a high HIV prevalence area and/or with heterosexual exposure to HIV
***Interval between conception date of current and previous pregnancy reported to the NSHPC

5.1.5 Time lag between antenatal booking and laboratory testing

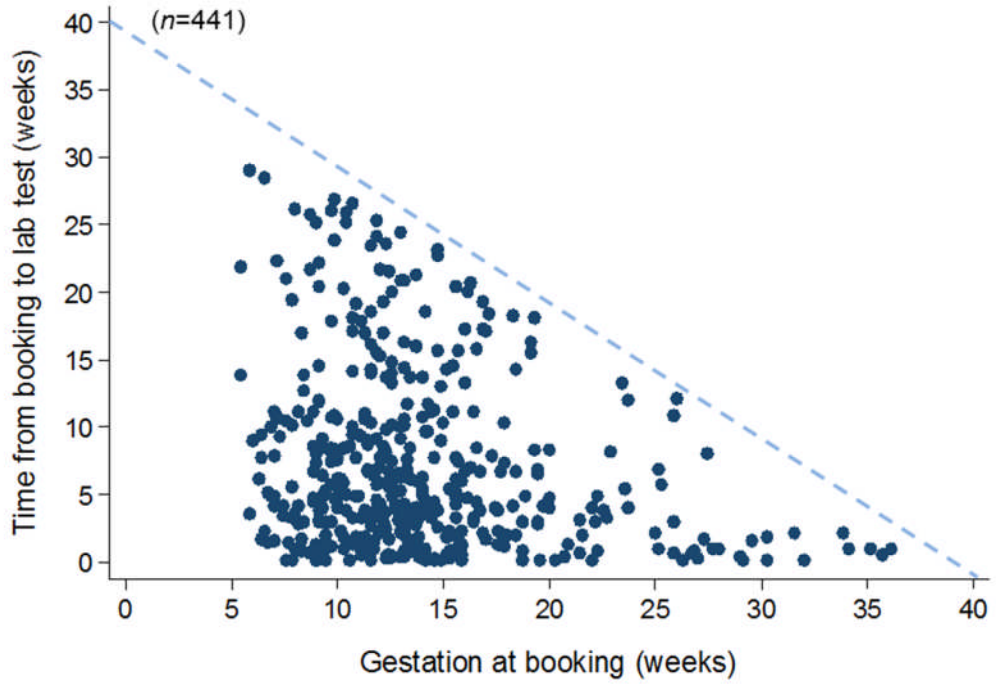
Among the 870 subsequent pregnancies with information available, the median time lag from antenatal booking to date of first laboratory test (e.g. CD4 count, viral load) during that pregnancy was zero weeks (i.e. the blood sample was taken on the same day as antenatal booking) (IQR: -3.1 to 4.9 weeks). As shown in Figure 5.4, there is thus a large spike at zero weeks. Since this analysis included subsequent pregnancies only, all women had been diagnosed with HIV before the pregnancy under consideration, and around half had had their laboratory test prior to their antenatal care booking appointment. However, 29.8% (259/870) did not have an HIV-related laboratory test until four or more weeks after booking, accounting for 58.7% (259/441) of those women whose laboratory test was carried out after they booked for care. Among the sub-group of women who were not on ART at conception and had their first laboratory test after their date of booking (*n*=216), the median lag between booking and laboratory test was 4.2 weeks (IQR: 1.7-9.4).

Figure 5.4 Time lag from date of antenatal booking to first laboratory test during that pregnancy, among subsequent pregnancies



A plot of the time lag between antenatal booking and first laboratory test against gestational weeks at booking (restricted to women whose first laboratory test was carried after their date of booking) is provided in Figure 5.5. This shows that although many were carried out close to the time of booking there were substantial delays for some women. Women booking late in pregnancy would be expected to have laboratory testing carried out as soon as possible, yet delays were apparent even among some women booking at ≥18 weeks as can be seen in the figure. For example, of the 162 women booking at ≥18 weeks for whom date of first laboratory test was known (and was after the date of booking) the median lag to laboratory test of 8.2 weeks (IQR: 6.9-14.3) and 19 had a delay of more than five weeks.

Figure 5.5 Time lag from antenatal booking to first laboratory test during that pregnancy by gestation at booking, among subsequent pregnancies



Notes:

The line of equality (dashed line) represents the border for admissible points on the scatter plot assuming a 40 week pregnancy gestation. For example, a woman booking at 10 gestational weeks is unlikely to have a time lag of more than 30 weeks from booking to laboratory test.

Analyses restricted to those with a first laboratory test *after* date of antenatal booking.

5.1.6 Time lag between antenatal booking and ART initiation

Analyses were conducted on 358 pregnancies in women who were not on treatment at conception and started ART after booking (46 of the available 404 pregnancies were excluded because the woman had already started ART by the time of booking, or did no antenatal ART was received). The median time lag between antenatal booking and start of ART was 8.7 weeks (IQR: 4.6-12.6 weeks) overall. There was no evidence that this lag changed during the three year study period; 8.3 weeks (IQR: 5.1-12.7) in 2008 and 8.6 weeks (IQR: 3.8-12.4) in 2010, p=0.980). The distribution is shown in Figure 5.6, with reasonably uniform numbers starting ART over the period of 1-15 weeks after booking, and relatively few (though some, n=40), not starting until 15 weeks after booking. When this association was examined separately for women with an earliest antenatal CD4 count of <350 cells/μl and those with a count of ≥350 cells/μl, the medians were 7.1 weeks (IQR: 3.3-10.4) and 10.0 weeks (IQR: 5.7-13.6) respectively (p<0.001).

Figure 5.6 Time lag from antenatal booking to ART initiation, among subsequent pregnancies

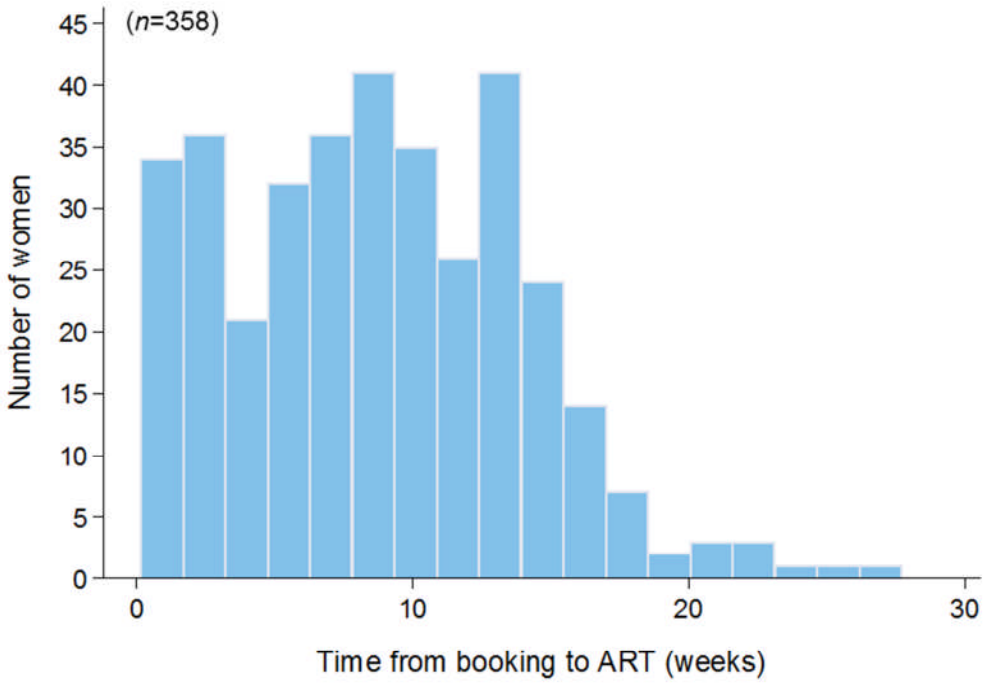
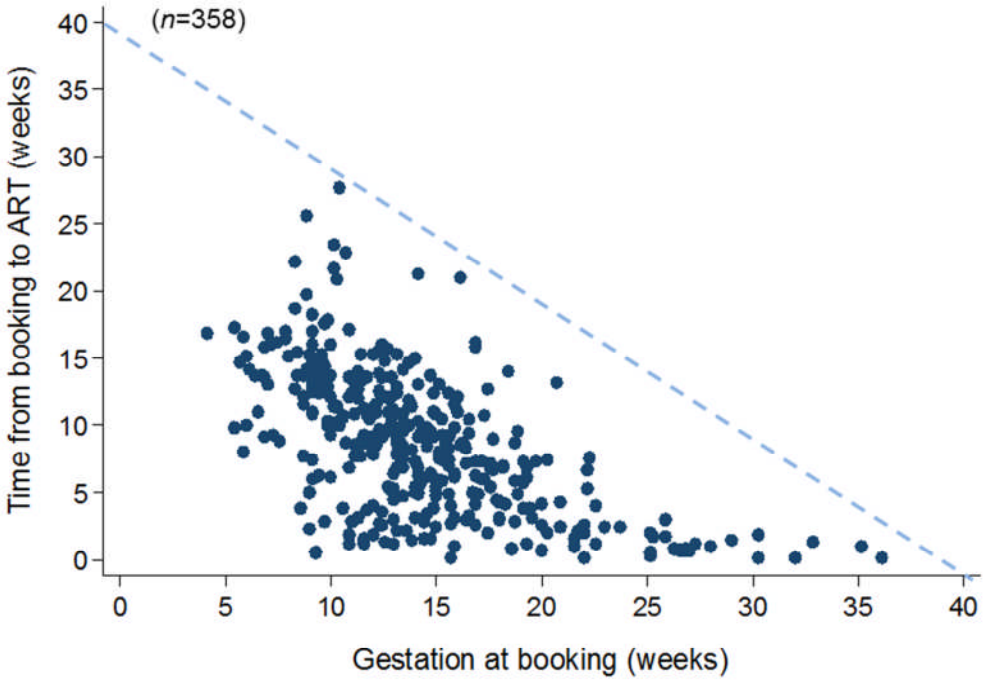


Figure 5.7 shows that the time lag between antenatal booking and start of ART declined with increasing gestational weeks at booking. There were however, 130 women who had a delay of more than 10 weeks, nine of whom had a lag of more than 20 weeks. Of the 121 women with a lag of between 10 and 20 weeks, 30.4% had a detectable viral load at delivery and one infant was known to have acquired HIV. Almost one quarter (28/118) had an earliest antenatal CD4 count of <350 cells/µl, five of which were <200 cells/µl. Meanwhile, of the nine women with a lag greater than 20 weeks, viral load close to delivery was reported for eight, three of which were detectable. There were no HIV-positive infants although information was missing for two women, one with a detectable viral load and one whose viral load was undetectable. Six women had an earliest antenatal CD4 count of ≥500 cells/µl, but two had counts <350 cells/µl (one of which was <200 cells/µl), and CD4 count was not reported for the one remaining woman.

A restricted analysis was carried out to explore the time lag between antenatal booking and ART by gestational weeks at booking among 110 women with an earliest antenatal CD4 count of <350 cells/µl (Figure 5.8). These women should be initiated on ART promptly for their own health (de Ruiter *et al*, 2008; Taylor *et al*, 2012). Quite substantial delays were apparent among some women, for example, as can be seen, 30 women had a lag of greater than 10 weeks, five of whom had not booked for antenatal care until ≥13 weeks. These delays are of particular concern for the health of these women, as well as for MTCT risks.

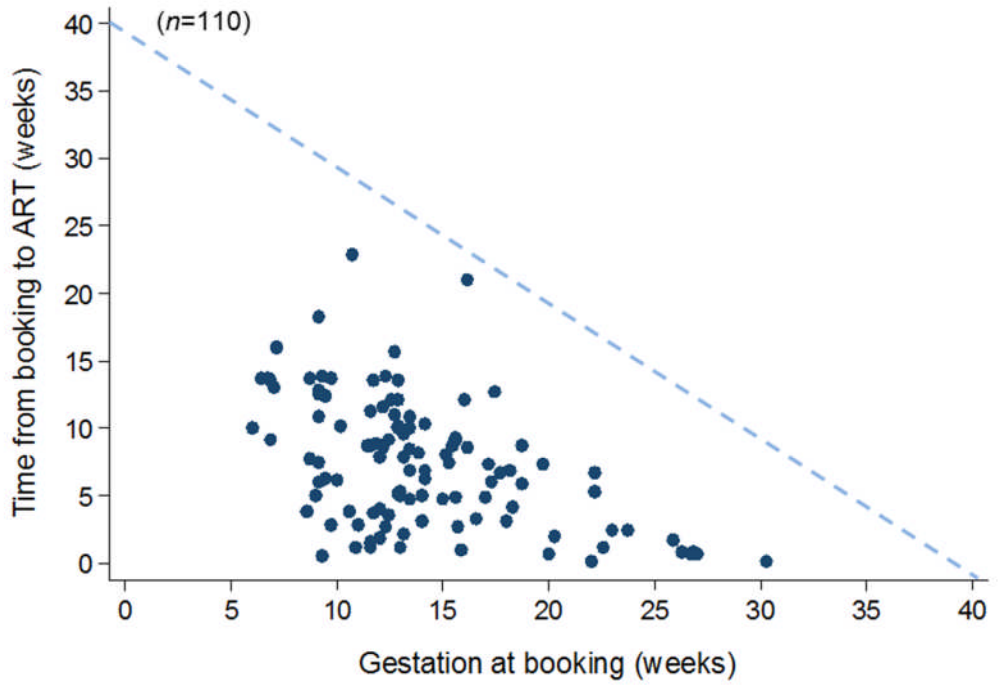
A more detailed adjusted analysis of demographic, clinical and immunological factors associated with timing of ART initiation are presented in the second part of this chapter, enabling the analyses to be conducted on the larger dataset of subsequent pregnancies during 2000-2010 rather than the sub-group of pregnancies with information available on timing of antenatal booking.

Figure 5.7 Association between gestation at antenatal booking and time lag from booking to ART initiation, among subsequent pregnancies



Note: The line of equality (dashed line) represents the border for admissible points on the scatter plot assuming a 40 week pregnancy gestation. For example, a woman booking at 10 gestational weeks is unlikely to have a time lag of more than 30 weeks from booking to starting ART.

Figure 5.8 Association between gestation at antenatal booking and time lag from booking to ART initiation among subsequent pregnancies to women with an earliest antenatal CD4 count of <350 cells/μl



Note: The line of equality (dashed line) represents the border for admissible points on the scatter plot assuming a 40 week pregnancy gestation. For example, a woman booking at 10 gestational weeks is unlikely to have a time lag of more than 30 weeks from booking to starting ART.

5.2 Immunological status, timing of antenatal ART, and virological outcomes among women not on ART at conception

HIV-positive pregnant women not requiring treatment for their own health are recommended to take short-course ART to prevent vertical transmission (de Ruiter *et al*, 2008; Taylor *et al*, 2012). Although this is a highly effective prevention measure (Townsend *et al*, 2014), increased morbidity and mortality among people randomised to CD4 count guided HIV treatment interruptions have been reported in non-pregnant populations (Danel *et al*, 2006; El-Sadr *et al*, 2006), which may have implications for optimal management of HIV in childbearing women. Current WHO guidelines provide the option of lifelong ART for pregnant women irrespective of health status (Option B+) (World Health Organization, 2013)[41]. To help address the question of whether it would be beneficial to initiate lifelong ART in all pregnant women, the immunological status and virological outcomes of second pregnancies to women not on ART at conception are investigated here. Timing of antenatal ART initiation is also explored among this group of women (Objective 3b).

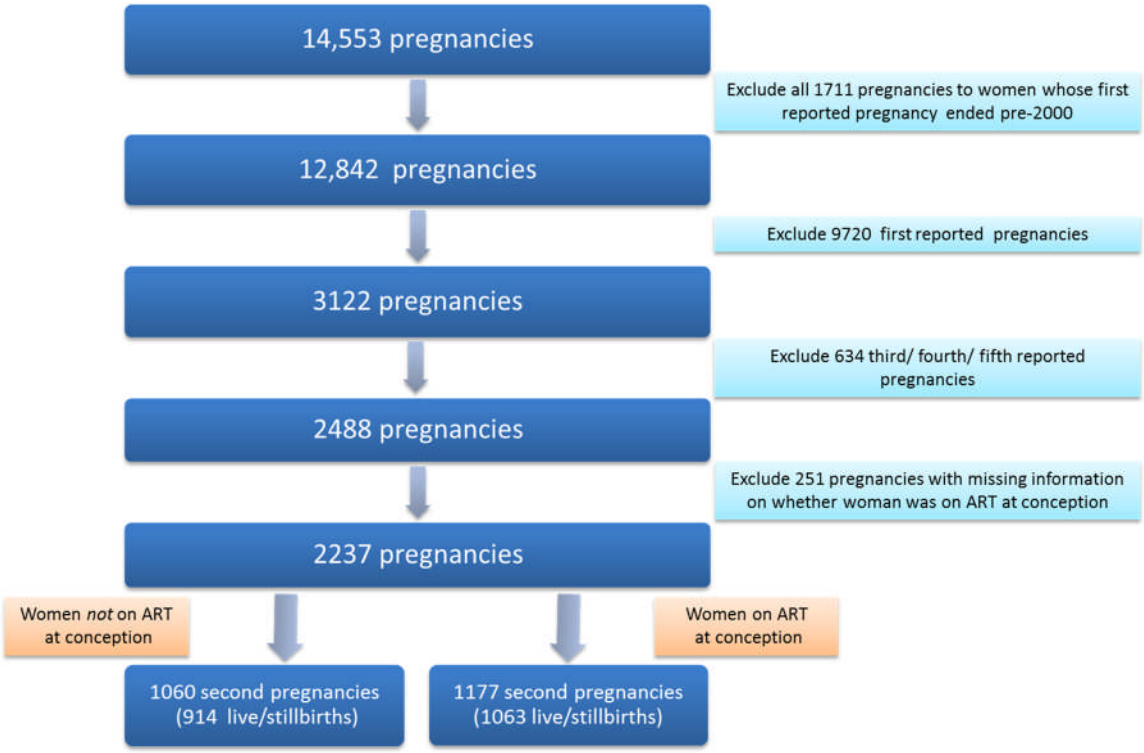
5.2.1 Methods

Dataset

The main study population included second pregnancies reported during 2000-2010 to women whose first reported pregnancy occurred from 2000 onwards and who were not on ART at conception of their second pregnancy (Figure 5.9). Further subsequent pregnancies (i.e. third, fourth etc) were not included as few women were not on treatment by such time and these pregnancies are likely to represent a very specific, small, sub-population. For analyses exploring maternal viral load at delivery a comparison group consisting of second pregnancies (resulting in a live or stillbirth) to women who conceived their second pregnancy on ART was used. These analyses were restricted to pregnancies in which the woman received ART during pregnancy as the aim was to compare the risk of detectable viral load at delivery in women who conceived on treatment with those starting ART during pregnancy.

[41] The WHO states that the advantages of Option B+ are "further simplification of regimen and service delivery and harmonization with ART programmes, protection against mother-to-child transmission in future pregnancies, a continuing prevention benefit against sexual transmission to serodiscordant partners, and avoiding stopping and starting of ARV drugs".

Figure 5.9 Study population flow chart – second pregnancies according to women's ART status at conception



Classifications and definitions

CD4 counts were the earliest reported measurements in the relevant pregnancy. Measurements were restricted those taken prior to ART initiation (except where CD4 count was included as a covariate in the analyses of detectable viral load at delivery). An immunological indication for treatment was defined as a CD4 count of <350 cells/µl (Williams *et al*, 2012). Delivery viral load measurements taken prior to or within the first seven days after ART initiation were excluded except those taken within seven days of delivery, since the probability of achieving an undetectable viral load within this short period of time is likely to be low (Patel *et al*, 2007). The imputed viral load variable described in Chapter 3, Section 3.4, was utilised (i.e. if viral load in the last 28 days of pregnancy was missing but an undetectable viral load was last reported earlier in that pregnancy, delivery viral load was imputed as undetectable). As a sensitivity analysis the multivariable analyses were re-run using the original non-imputed variable.

Statistical analyses

Analyses of factors associated with having a CD4 count of <350 cells/μl were conducted using standard risk factor analysis logistic regression methods as described in Chapter 3, Section 3.5. As only second pregnancies were included in the analyses, each woman only contributed one pregnancy to the dataset thus no adjustment for clustering of pregnancies within women was required.

Kaplan–Meier analysis was used to graphically describe the time to ART initiation. Analyses of factors associated with the time to antenatal ART initiation were conducted using Cox proportional hazards modelling. These analyses were restricted to pregnancies resulting in a live or stillbirth since initiation of antenatal ART is unlikely in pregnancies resulting in other outcomes (e.g. a termination). Even where treatment is required for the woman's own health, information on ART start dates are tend to be poorly reported to the NSHPC if the pregnancy has not resulted in a birth. Crude and adjusted HRs were estimated. The proportional hazards assumption (i.e. that the HR is constant over time, with constant differences over strata) was assessed by examining log-log plots to ensure plots for the different strata of a given variable, adjusted for all other variables included in the model, were approximately parallel. The model's Schoenfeld residuals were also analysed, both for each covariate and globally (Therneau *et al*, 2000).

Logistic regression models were fitted to analyse the association between timing of ART initiation and the risk of detectable viral load at delivery. As above, no adjustment for clustering at the woman level was required.

5.2.2 Study population

The main study population consisted of 1177 second pregnancies to women who were not on treatment at conception, 1063 of which resulted in a live or stillbirth. Among the 1177 pregnancies, 76.0% were in women from sub-Saharan Africa, and the median maternal age at delivery (or end of pregnancy for outcomes other than a live or stillbirth) was 30.3 years (IQR: 26.9-34.0). Most pregnancies (74.1%) occurred during the more recent (2006-2010) time period, with 43.4% occurring during 2008-2010, and only 4.1% during 2000-2002. The median interval between conception of women's first and second pregnancies was 2.3 years (IQR: 2.2-2.5).

5.2.3 Immunological status

Earliest antenatal CD4 count was available for 71.2% (838/1177) of pregnancies, this was measured at a median of 15.0 gestational weeks (IQR: 9.6-20.6). When pregnancies with missing information on CD4 count were compared with those with known CD4 count, they were more likely to have occurred during the earlier time periods (p<0.001). There was, however, little difference in median maternal age (30.0 years, IQR: 26.7-33.3 *vs*. 30.4 years, IQR: 27.0-34.2, p=0.133), the proportion originating from sub-Saharan Africa (79.4% *vs*. 74.6%, p=0.082), with a history of injecting drug use (4.0% *vs*. 2.2%, p=0.10), or with a short (<2 year) inter-pregnancy conception interval (43.7% *vs*. 39.4%, p=0.153).

The median earliest antenatal CD4 count was 390 cells/µl (IQR: 271-534, range: 20-1644[42]) (Figure 5.10). Forty-one percent (340/838) of women had immunological indication for treatment a quarter (n=85) of whom were severely immunosuppressed (<200 cells/µl), representing 10.1% of all 838 women. The remaining approximately 60% of women, who were not yet requiring treatment, were composed of 29.2% (n=245) with CD4 counts of 350-499 cells/µl and 30.2% (n=253) with ≥500 cells/µl. The findings did not change when the analysis was restricted to the most recent time period (2008-2010), 39.8% (160/402) of women had an indication for treatment with 10.0% (40/402) being severely immunosuppressed[43]. The distribution of CD4 counts that were <350 cells/µl are shown in more detail in Figure 5.11. The cluster of women with CD4 counts <100 cells/µl are a group of particular concern requiring rapid initiation of ART. Some of the large spikes, for example, at around 200 cells/µl, are likely due to rounded values being reported to the NSHPC.

[42] The small number of high CD4 count measurements (>1200 cells/µl, including the outlier at 1644 cells/µl) were double-checked on the original report submitted to the NSHPC, and cross-checked with the CD4 counts reported for the women's previous pregnancies which were found to be similarly high suggesting that the high values were not due to data entry errors. Although high, these values are approximately within the range of possible CD4 count values (http://namlife.org/cms1254931.aspx, Accessed December 2013), and were therefore retained in the dataset.

[43] Since 2008 UK guidelines have recommended that people living with HIV initiate treatment before their CD4 count falls below 350 cells/µl (Gazzard *et al*, 2008; Williams *et al*, 2012). Prior to this treatment initiation was recommended at CD4 counts of 200-350 cells/µl (Gazzard, 2005; Pozniak *et al*, 2003).

Figure 5.10 Distribution of earliest antenatal CD4 counts among women not on ART at conception

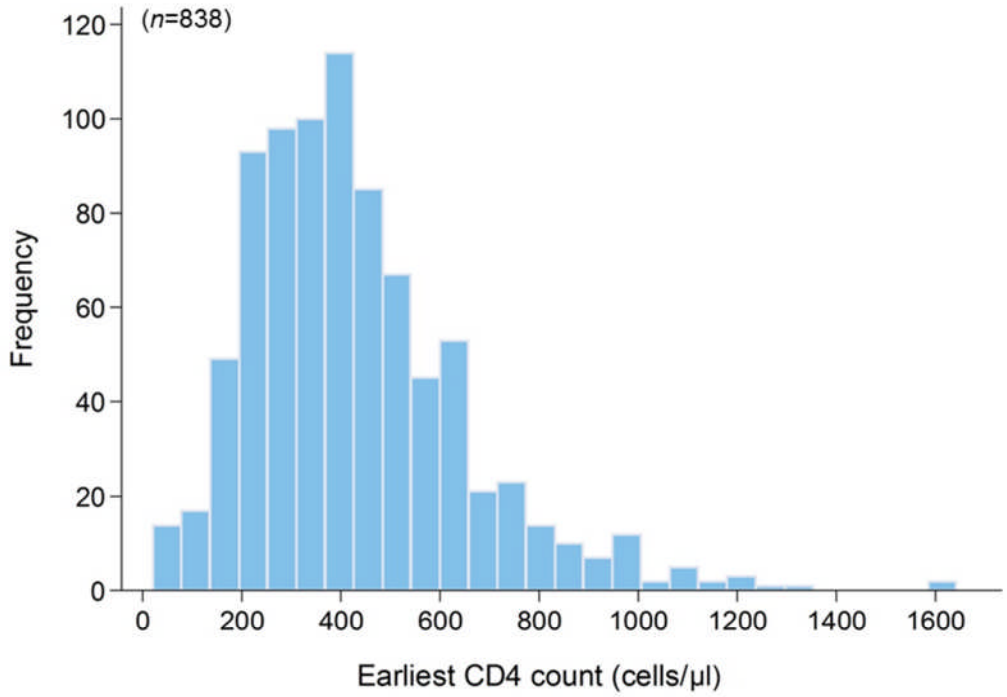
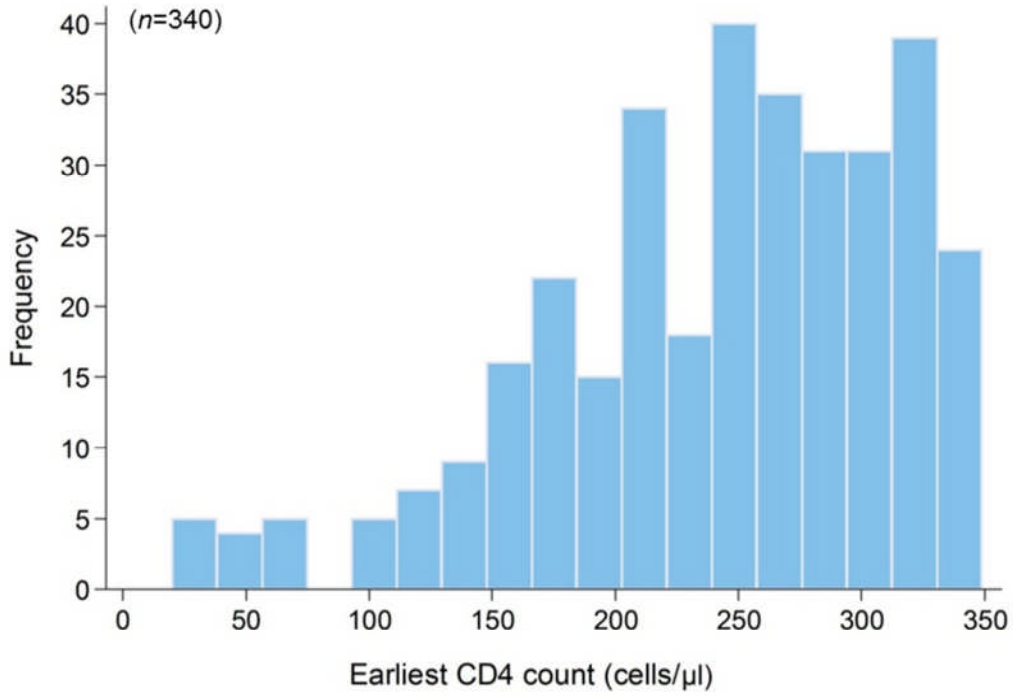


Figure 5.11 Distribution of earliest antenatal CD4 counts among women with a CD4 count <350 cells/µl who were not on ART at conception



Of those women with an immunological indication for treatment at their second pregnancy, 44.3% (93/210) had had an earliest antenatal CD4 count of ≥350 cells/μl at their first. Looking at this the other way around, 25.9% (93/359) of women with CD4 count of ≥350 cells/μl at their first pregnancy had declined to CD4 <350 cells/μl at their second. These findings demonstrate that HIV disease can progress quite markedly between a woman's first and subsequent pregnancy and should be considered when recommending whether women remain on lifelong ART after their first pregnancy ends. Of the 359 women with CD4 count of ≥350 cells/μl at their first pregnancy, 169 had 350-499 cells/μl of whom 40.2% (*n*=68) had declined to <350 cells/μl at their second pregnancy, compared with 13.2% (*n*=25) of those starting with CD4 ≥500 cells/μl. Also noteworthy is that of the 340 women with an earliest antenatal CD4 count of <350 cells/μl in their second pregnancy, 55.7% (117/210) had also had an indication for treatment at the time of their first reported pregnancy (CD4 <350 cells/μl) and yet were not on ART at conception of their subsequent pregnancy. This may at least in part be due to disengagement from HIV care between pregnancies. The third part of this chapter explores women's attendance for HIV care after pregnancy.

5.2.4 Factors associated with an immunological indication for treatment among women not on ART at conception

Table 5.5 shows factors associated with presenting with a CD4 count of <350 cells/μl at second pregnancy. Firstly, the influences of women's demographic and clinical characteristics at the time of their second pregnancy were explored. The most important factor was the inter-pregnancy conception interval; compared with women who had a very short conception interval (<2 years) those with longer intervals tended to be more likely to have an earliest antenatal CD4 count of <350 cells/μl (p=0.054) though this was only significant at the p<0.05 level for the group with an interval of 4-5 years. There was also some weaker evidence that women who were diagnosed with HIV during (rather than prior to) their first reported pregnancy were less likely to have a CD4 count of <350 cells/μl (OR: 0.79, 95% CI: 0.58-1.07). Although a slightly higher proportion of those from sub-Saharan Africa compared with women born in the UK or Ireland had a CD4 count of <350 cells/μl at their second pregnancy (42.1% *vs*. 35.5%) the difference was not significant (OR: 1.32, 95% CI: 0.90-1.94). Similarly, women aged ≥35 years had a higher risk compared with those aged <25 years (46.4% *vs*. 38.8%) but this was not significant (OR: 1.37, 95% CI: 0.85-2.20). There was no difference according to time period (p=0.879).

Secondly, key clinical and immunological characteristics at women's preceding pregnancy (i.e. first reported) were explored (also shown in Table 5.5). Women with lower earliest antenatal CD4 counts during their first pregnancy were, not surprisingly, more likely to have

an earliest antenatal CD4 count of <350 cells/µl at their second pregnancy (p<0.001). This association held when last CD4 count measurements taken during their first pregnancy were examined (also p<0.001). It should be noted that while earliest antenatal CD4 counts were restricted to those taken prior to ART initiation, no such restriction was applied to the last antenatal CD4 count measurements thus the majority of women would have been on ART at the time of their last antenatal CD4 count. When the proportion of women with a CD4 count <350 cells/µl at their second pregnancy was compared among those who had missing information on CD4 count during their first pregnancy and those with a known CD4 count there was little difference (40.8% *vs*. 40.6% based on earliest CD4 count in first pregnancy, and 42.9% *vs*. 40.0% based on last CD4 count in first pregnancy, data not shown in Table 5.5). In relation to the duration of ART received during their first pregnancy, women who received less than two weeks ART were more likely than those who received 12-40 weeks ART to present with a CD4 count of <350 cells/µl at their second pregnancy (OR: 2.58, 95% CI: 1.09-6.08), as were women who did not receive ART during their first pregnancy (OR: 2.13, 95% CI: 1.36-3.33).

The multivariable model included latest CD4 count in first reported pregnancy and conception interval only. Earliest CD4 count and duration of ART received during first pregnancy were excluded due to co-linearity. For example, latest antenatal CD4 counts will be highly dependent on duration of ART received, and also influenced by earliest antenatal CD4 count. Meanwhile, there was no evidence from the LR test that adding maternal age group (p=0.818), world region of origin (p=0.382), HIV risk factor (p=0.312), time period (p=0.935), or timing of HIV diagnosis (p=0.234) improved the fit of the model. It is thus clear that the key predictors of women having a CD4 count of <350 cells/µl at their second pregnancy were having a lower CD4 count in their first pregnancy and having a longer inter-pregnancy conception interval.

Table 5.5 Univariable and multivariable analyses of factors associated with having a CD4 count of <350 cells/μl at second pregnancy among women not on ART at conception

	CD4 count <350 cells/μl/ Total (%)	Univariable analyses			Multivariable analysis (*n*=606)		
		OR	95% CI	*p*-value	aOR	95% CI	*p*-value
Age at delivery, yrs							
<25	51/131 (38.9)	1		0.155			
25-34	211/541 (39.0)	1.00	(0.68-1.48)				
≥35	78/165 (47.3)	1.41	(0.88-2.24)				
World region of origin							
UK/Ireland	49/138 (35.5)	1		0.292			
Sub-Saharan Africa	263/624 (42.1)	1.32	(0.90-1.94)				
Elsewhere	28/75 (37.3)	1.08	(0.60-1.94)				
HIV risk factor							
Other*	328/804 (40.8)	1		0.213			
Injecting drug use	10/18 (55.6)	1.81	(0.71-4.65)				
Time period of delivery**							
2000-2002	10/23 (43.5)	1.20	(0.51-2.84)				
2003-2005	65/164 (39.6)	1.03	(0.69-1.53)				
2006-2008	160/382 (41.9)	1.13	(0.82-1.55)				
2009-2010	105/269 (39.0)	1		0.879			
Timing of HIV diagnosis							
Before first reported pregnancy	109/244 (44.7)	1		0.125			
During first reported pregnancy	230/591 (38.9)	0.79	(0.58-1.07)				
Conception interval, yrs***							
<2	123/330 (37.3)	1		0.054	1		0.003
2-3	137/344 (39.8)	1.11	(0.82-1.52)		1.52	(0.98-2.35)	
4-5	63/122 (51.6)	1.80	(1.18-2.73)		3.16	(1.71-5.84)	
≥6	17/42 (40.5)	1.14	(0.59-2.20)		2.23	(0.90-5.55)	
Earliest CD4 count, cells/μl†							
≥500	25/190 (13.2)	1		<0.001			
350-499	68/169 (40.2)	4.44	(2.64-7.48)				
200-349	96/132 (72.7)	17.60	(9.96-31.09)				
<200	21/28 (75.0)	19.80	(7.63-51.36)				
Last CD4 count, cells/μl†							
≥500	54/318 (17.0)	1		<0.001	1		<0.001
350-499	88/190 (46.3)	4.22	(2.80-6.35)		4.73	(3.04-7.34)	
200-349	109/138 (79.0)	18.38	(11.11-30.40)		24.50	(13.91-43.16)	
<200	16/22 (72.7)	13.04	(4.88-34.84)		13.23	(4.44-39.47)	
Duration of ART, wks***							
<2	15/24 (62.5)	2.58	(1.09-6.08)				
2-12	100/305 (32.8)	0.75	(0.54-1.05)				
13-40	119/303 (39.3)	1		<0.001			
Unknown duration	25/60 (41.7)	1.10	(0.63-1.94)				
None received	62/107 (57.9)	2.13	(1.36-3.33)				

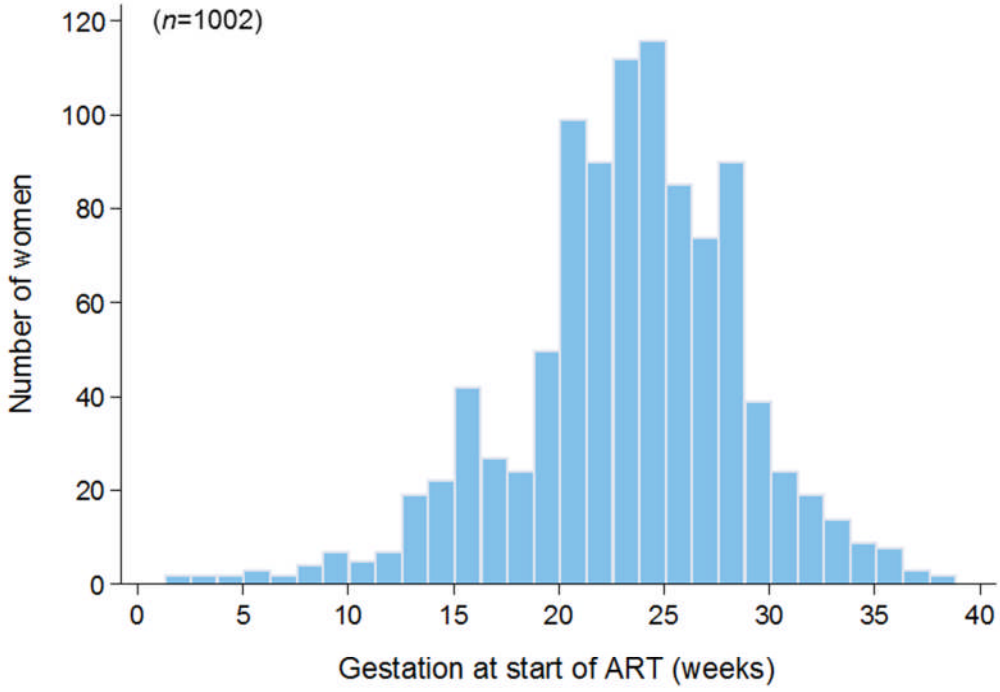
*Other comprises largely those originating from a high HIV prevalence area and/or with heterosexual exposure to HIV
**Expected year of delivery for outcomes other than a live or stillbirth
***Interval from conception of first pregnancy to conception of second pregnancy
†During first reported pregnancy

Overall, 4.7% (45/951) of women had HIV/AIDS symptoms during their second pregnancy, of whom most (81.1%, 36/44) were asymptomatic at the time of their first reported pregnancy. As per the definition of the study population, none of these symptomatic women had commenced ART for their own health in the interval between their first and second pregnancies. Or if they had, they discontinued treatment at some point prior to conception of their second pregnancy, which is of concern.

5.2.5 Timing of antenatal ART initiation

Of the 1063 women who had a live or stillbirth and did not conceive on treatment, 97.2% (1028/1058) were reported to have received antenatal ART during their second pregnancy, with information on date of ART initiation available for 1002. Figure 5.12 shows the distribution of gestational weeks at ART initiation. ART commenced at a median gestation of 23.7 weeks (IQR: 20.4-27.0); 24.1 weeks (IQR: 21.6-27.5) among those with CD4 ≥350 cells/µl and 22.7 weeks (IQR: 18.6-26.0) among those with CD4 <350 cells/µl. The cluster of values at around 14 weeks links in with the median time of booking for antenatal care being 13 weeks; those requiring ART for their own health should start ART without delay. It also ties in with some women waiting until the start of their second trimester to commence ART. Meanwhile, the second cluster at around 24 weeks reflects the approximate gestation for ART initiation as per UK recommendations (de Ruiter *et al*, 2008; Hawkins *et al*, 2005). The majority (70.2%) started during the second trimester, 4.4% during the first trimester, while the remaining quarter did not start ART until their third trimester. Among women starting during the first trimester this ranged from week one onwards. Of course women starting ART in the first few weeks after conception are unlikely to have been aware of their pregnancy and would have simply started ART as part of their routine non-pregnancy related HIV care. Of the 256 women who did not start ART until the third trimester of their pregnancy, seven received less than two weeks of ART prior to delivery. Of those seven women, six were of black African ethnicity (all born abroad) and one was white; six received cART and one received dual therapy; one had CDC stage C disease (AIDS) at delivery while the rest were asymptomatic. One had an infant who was known to have acquired HIV (delivered vaginally at 38 weeks).

Figure 5.12 Timing of antenatal ART initiation



In line with shifting UK recommendations for the earlier initiation of ART during pregnancy, there was a significant decrease in the median gestational age at ART initiation over time (test for trend: $p<0.001$) (Table 5.6).

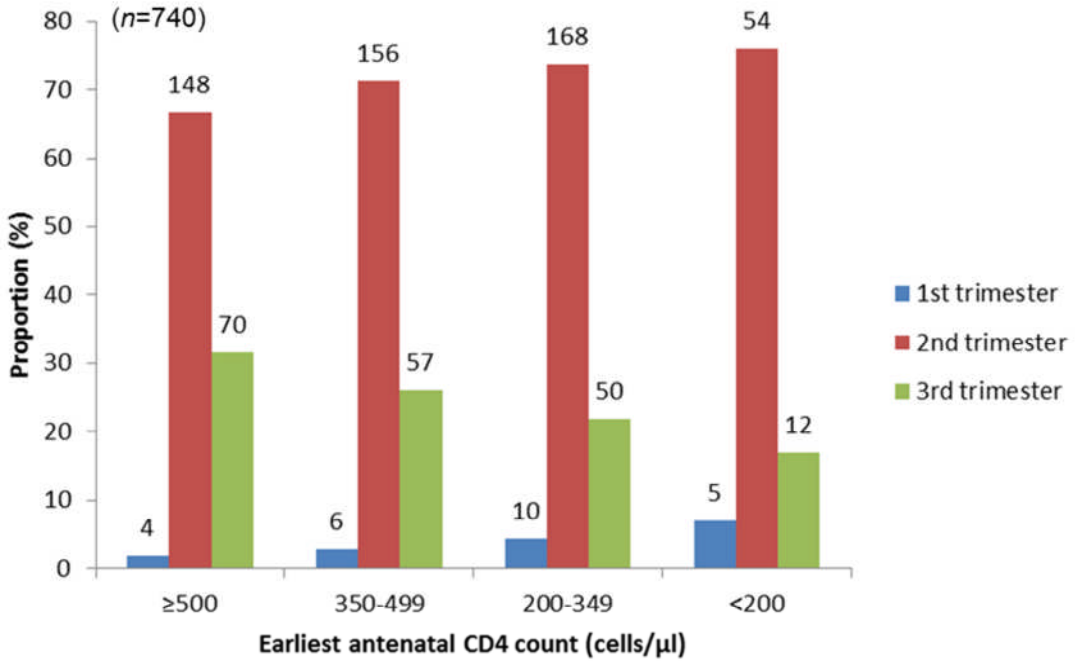
Table 5.6 Median gestation at antenatal ART initiation, by time period

Time period*	*n*	Gestation, wks	IQR, wks	*p*-value**
2000-2002	34	25.6	23.4-29.5	<0.001
2003-2005	252	26.0	22.4-28.5	
2006-2008	246	23.7	20.9-26.5	
2009-2010	293	21.5	18.6-24.5	

*Based on year of delivery
**Test for trend

When timing of ART initiation was explored according to earliest antenatal CD4 count, among all CD4 groups the majority of women started ART during the second trimester (Figure 5.13). The proportion starting ART during the first trimester was small in all CD4 groups but did increase with decreasing CD4 count. Of those with a CD4 count of <200 cells/µl, 83.1% had started ART by the end of the second trimester compared with 68.5% of those with a CD4 count of ≥500 cells/µl. However, it is of note that even among the lowest CD4 count group (<200 cells/µl) 16.9% of women did not start ART until the third trimester. As mentioned, disengagement from HIV care after pregnancy is explored in the third part of this chapter.

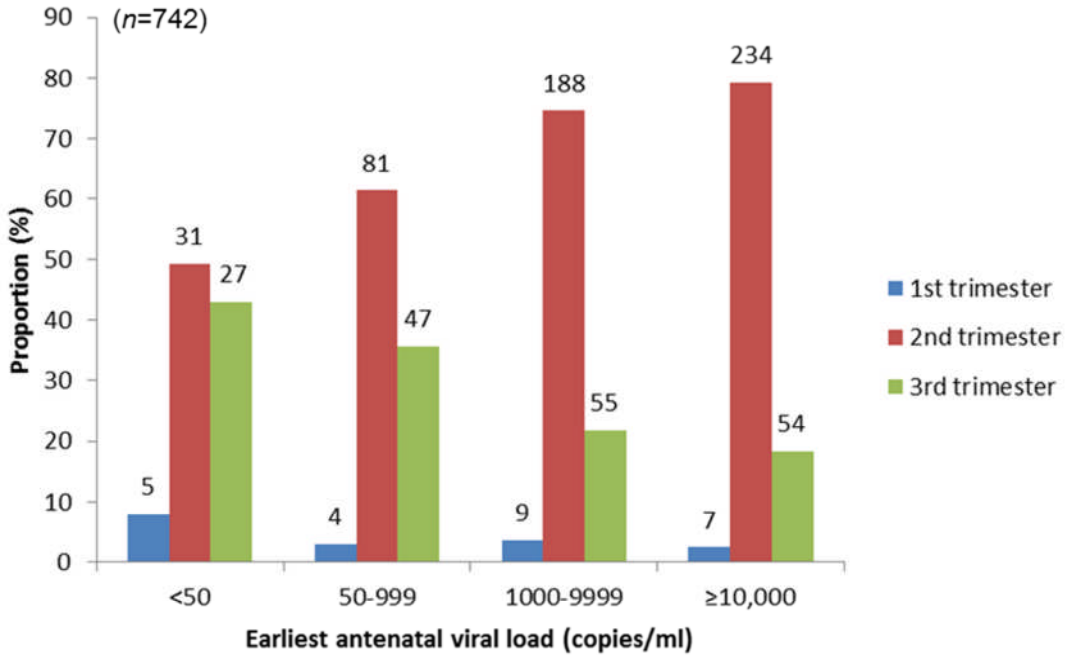
Figure 5.13 Timing of antenatal ART initiation according to earliest antenatal CD4 count



Note: Number of pregnancies shown above bars.

Women with higher earliest pre-ART antenatal viral loads were more likely to have initiated ART by the end of the second trimester than those with lower viral loads (Figure 5.14). However, 18.3% of those in the highest viral load group (≥10,00 copies/ml) did not start ART until the third trimester. The 63 women with undetectable earliest antenatal viral loads in their second pregnancy will likely be a combination of those who had been on ART prior to pregnancy, and perhaps stopped when they decided to conceive or discovered they were pregnant (e.g. to avoid taking ART during the first trimester of pregnancy), those who already had a low viral load at conception that rapidly declined to undetectable after ART initiation[44], and elite controllers[45]. Information on ART taken outside of pregnancy is not collected by the NSHPC.

Figure 5.14 Timing of antenatal ART initiation according to earliest antenatal viral load



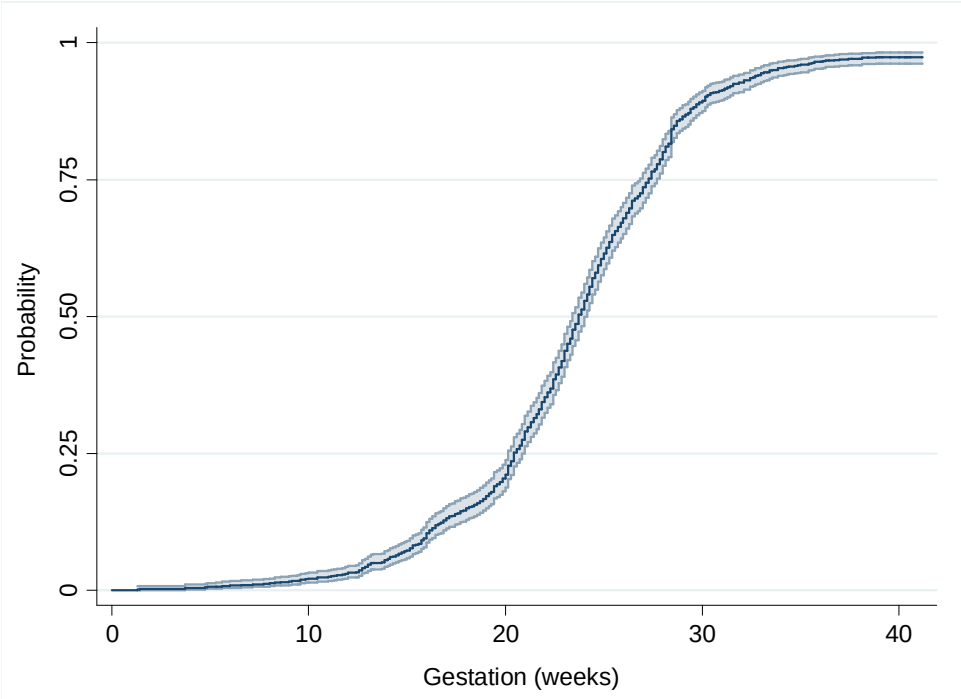
Note: Number of pregnancies shown above bars.

[44] Pre-ART measurements included those taken up to 14 days after ART initiation (though most women would have their viral load and CD4 count assessed prior to ART initiation).
[45] A small proportion of people living with HIV are able to maintain a low viral load in the absence of ART (Lambotte *et al*, 2005).

5.2.6 Factors associated with timing of antenatal ART initiation

A time-to-event analysis was conducted to explore factors independently associated with the timing of antenatal ART. The analysis was based on 1032 of the total 1063 live and stillbirths: 1002 with information available on timing of ART initiation (as described in Section 5.2.5 above), and 30 in women who did not receive ART and were thus censored at their date of delivery. The remaining 31 women were excluded from the analyses as they either had missing information of antenatal ART receipt (*n*=5) or did receive antenatal ART but the start date was missing (*n*=26). The 50% survival time was 23.7 weeks; i.e. after 23.7 weeks of follow-up an estimated 50% of women had initiated ART (as documented in the earlier descriptive analyses) (Figure 5.15).

Figure 5.15 Cumulative probability of initiating antenatal ART by gestational week



Note: Probability is represented by the dark blue line and the 95% CIs by the lines above and below.

In the Cox model a HR of less than one indicates a longer time from conception to start of antenatal ART compared with the baseline group for that variable. The univariable Cox proportional hazards models (Table 5.7) showed that the following factors were associated with timing of ART initiation: world region of origin (p=0.015), time period (p<0.001), region of report (p<0.001), earliest antenatal CD4 count (p=0.005) and viral load (p<0.001). Specifically, women originating from sub-Saharan Africa had a slightly longer time from

conception to start of ART, though this was not significantly different to those born in the UK or Ireland (HR: 0.89, 95% CI: 0.75-1.05). In line with changing guidelines towards earlier antenatal ART initiation, ART started earlier in the later years. Women in Ireland had a significantly longer time to ART than those reported in London (HR: 0.80, 95% CI: 0.65-0.97), while those in Wales, Scotland or Northern Ireland had a shorter time (HR: 1.95, 95% CI: 1.41-2.71). As would be expected, both lower CD4 counts and higher viral loads were associated with a shorter time to ART. Women with a history of injecting drug use showed a longer time to ART initiation though this was not significant, possibly due to small numbers in this group. There was no significant evidence that timing of ART initiation varied according to maternal age (p=0.502).

All variables that were significantly associated with timing of ART initiation in the univariable analysis were included in the initial multivariable model (world region of origin, time period, region of report, earliest antenatal CD4 count and viral load). Adding maternal age did not further improve the fit (LR test: p=0.400) and it was therefore dropped. Although decisions regarding when to start ART in the non-pregnant HIV-positive population are based mainly on CD4 counts (or other clinical indicators) (Williams *et al*, 2012), in pregnant women timing will depend more heavily on both viral load (the main aim of ART during pregnancy being to achieve an undetectable viral load by the time of delivery), and CD4 counts. It therefore makes sense to investigate the influence of both CD4 count and viral load in the model despite potential co-linearity. There was also reasonable evidence for including both variables in the model: LR test p=0.128 for including CD4 count after accounting for viral load, and p=0.013 for including viral load after accounting for CD4 count.

In the final multivariable model (Table 5.7) women with a high viral load (≥10,000 copies/ml) or low CD4 count (<200 cells/µl) started ART significantly earlier than those with lower viral load or higher CD4 counts respectively, while women from sub-Saharan Africa started later than those from the UK or Ireland. There remained a strong trend of earlier ART initiation over time period (p<0.001). However, there was no longer a significant association between region of report and time to ART initiation (p=0.315).

Table 5.7 Univariable and multivariable analyses of time to antenatal ART initiation

	n	Univariable analyses			Multivariable analysis (*n*=714)		
		HR*	95% CI	*p*-value	aHR*	95% CI	*p*-value
Age at delivery, yrs							
<25	163	1		0.502			
25-34	686	1.10	(0.92-1.31)				
≥35	182	1.12	(0.91-1.39)				
World region of origin							
UK/Ireland	162	1		0.015	1		0.029
Sub-Saharan Africa	788	0.89	(0.75-1.05)		0.78	(0.63-0.97)	
Elsewhere	81	1.23	(0.94-1.61)		0.99	(0.73-1.35)	
HIV risk factor							
Other**	981	1		0.214			
Injecting drug use	28	0.78	(0.52-1.16)				
Time period of delivery							
2000-2002	40	1		<0.001	1		<0.001
2003-2005	259	1.43	(1.00-2.04)		1.01	(0.61-1.66)	
2006-2008	433	2.03	(1.43-2.88)		1.52	(0.94-2.45)	
2009-2010	300	2.74	(1.92-3.92)		2.26	(1.38-3.68)	
Reporting region							
London	482	1		<0.001	1		0.315
Elsewhere in England	385	1.19	(1.04-1.36)		1.05	(0.89-1.23)	
Wales, Scotland, N Ireland	39	1.95	(1.41-2.71)		1.39	(0.91-2.13)	
Ireland	125	0.80	(0.65-0.97)		0.88	(0.67-1.16)	

Continued overleaf

Table 5.7 *Continued*: Univariable and multivariable analyses of time to antenatal ART initiation

	n	Univariable analyses			Multivariable analysis (*n*=714)		
		HR*	95% CI	*p*-value	aHR*	95% CI	*p*-value
Earliest CD4 count, cells/µl* **							
≥500	224	1		0.005	1		0.128
350-499	221	1.11	(0.92-1.34)		1.08	(0.88-1.32)	
200-349	233	1.25	(1.04-1.51)		1.21	(0.98-1.48)	
<200	72	1.59	(1.22-2.08)		1.35	(1.01-1.80)	
Earliest viral load, copies/ml* **							
<50	64	1		<0.001	1		0.013
50-999	133	1.00	(0.74-1.35)		1.14	(0.83-1.58)	
1000-9999	255	1.34	(1.02-1.77)		1.31	(0.97-1.78)	
≥10,000	297	1.55	(1.18-2.03)		1.52	(1.12-2.08)	

*HR of <1 indicates a longer time to ART initiation
**Other comprises largely those originating from a high HIV prevalence area and/or with heterosexual exposure to HIV
***Restricted to measurements taken prior to ART initiation

The global Therneau-Grambsch statistic[46] for the final model was significant suggesting that the assumption of proportional hazards may not be met. Inspection of the individual Schoenfeld residuals for each variable in the model indicated that time period and earliest antenatal CD4 count were the variables contributing to this non-proportionality. As discussed in Chapter 4, the global test for proportionality might be over sensitive to small deviations from the proportional hazards assumption. This means that observing significant value of the test statistic often makes no difference to the overall conclusions and estimates, particularly with large datasets (Therneau *et al*, 2000). Examination of the log-log plots (i.e. the plot of the probability of not initiating ART against time to treatment initiation in log-log scale) revealed the lines to be reasonably parallel in line with satisfying the proportional hazards assumption to an acceptable degree. Plots stratified by time period and by CD4 count and a brief description and interpretation of these are provided in Appendix V.

Sensitivity analyses

In light of the significant changes in timing of ART initiation over the study period, and the possible non-proportionality of time period in the main model, a sub-analysis was conducted in which the multivariable model was re-run restricted to 341 pregnancies during 2008-2010 (Table 5.8). This cut-off was chosen to represent the most recent time period and also because 2008 was the year of the last BHIVA guideline published during the study period. This three-year period was thus homogeneous with respect to UK guidelines for the management of HIV in pregnant women. The findings were similar to those of the main model, and the only variable with some evidence of non-proportionality was CD4 count. Even within this short time period there was a clear trend of shorter time to ART initiation by year. Women from sub-Saharan Africa had a longer time to ART initiation than white women. Although the difference was no longer significant at the $p<0.05$ level, this was likely due to a reduction in power as the point estimate (aOR 0.78) was unchanged. There remained a trend towards a shorter time to ART in women with lower CD4 counts and with high viral loads. In fact, the influence of CD4 count was even stronger, likely due to changing guidelines for the management of adults living with HIV towards initiation of ART at higher CD4 counts. The 2008 guideline recommended ART initiation in all those with CD4 counts of <350 cells/μl (Gazzard *et al*, 2008). Meanwhile, ART initiation was significantly quicker in the rest of England compared with London. Although the direction of association was observed in the full model (2000-2010) it was non-significant.

[46] The Therneau and Grambsch test was run in Stata using the `estat phtest` command.

Table 5.8 Multivariable analysis of time to ART initiation, restricted to 2008-2010

	n	Multivariable analysis (*n*=341)		
		aHR*	**95% CI**	***p*-value**
World region of origin				
UK/Ireland	51	1		0.136
Sub-Saharan Africa	255	0.78	(0.57-1.09)	
Elsewhere	35	1.08	(0.69-1.69)	
Year of delivery				
2008	113	1		<0.001
2009	127	1.01	(0.77-1.32)	
2010	101	1.68	(1.26-2.23)	
Reporting region				
London	141	1		0.011
Elsewhere in England	155	1.45	(1.14-1.85)	
Wales, Scotland, N Ireland	17	1.71	(0.99-2.96)	
Ireland	28	1.05	(0.69-1.61)	
Earliest CD4 count, cells/µl**				
≥500	106	1		0.002
350-499	102	0.96	(0.72-1.29)	
200-349	102	1.49	(1.10-2.01)	
<200	31	1.71	(1.10-2.65)	
Earliest viral load, copies/ml**				
<50	26	1		0.057
50-999	50	1.74	(1.06-2.87)	
1000-9999	121	1.45	(0.92-2.27)	
≥10,000	144	1.73	(1.10-2.72)	

*HR of <1 indicates a longer time to ART initiation
**Restricted to measurements taken prior to ART initiation

5.2.7 Virological outcomes

For this part of the analysis, alongside the 1063 live and stillbirths to women not on ART at conception, a comparison group consisting of 914 second pregnancies resulting in a birth to women who conceived on treatment was used. The characteristics of the two groups are compared in Table 5.9. Compared with women conceiving on treatment, women not on ART at conception of their second pregnancy were younger, more likely to have delivered during an earlier time period, to be reported in Ireland, and more likely to have received a PI-based cART regimen during pregnancy. There was no significant difference in maternal health status between the two groups (p=0.162). Of the women who were not on ART at conception but received antenatal ART, most (70.1%) received more than 12 weeks of ART, 29.2% received 2-12 weeks and the remaining 0.7% received less than two weeks.

Table 5.9 Characteristics of second pregnancies ending in a live or stillbirth according to whether the woman was on ART at conception

Characteristic	Women not on ART at conception (*n*=1063)		Women on ART at conception (*n*=914)		*p*-value
	n	%	*n*	%	
Age at delivery, yrs (*n*=1976)					
<25	168	15.8	61	6.7	<0.001
25-34	706	66.5	544	59.5	
≥35	188	17.7	309	33.8	
World region of origin (*n*=1976)					
UK/Ireland	169	15.9	114	12.5	0.082
Sub-Saharan Africa	812	76.5	733	80.2	
Elsewhere	81	7.6	67	7.3	
HIV risk factor (*n*=1929)					
Other*	1009	97.2	875	98.2	0.148
Injecting drug use	29	2.8	16	1.8	
Time period of delivery (*n*=1977)					
2000-2002	43	4.0	33	3.6	<0.001
2003-2005	262	24.6	165	18.1	
2006-2008	452	42.5	371	40.6	
2009-2010	306	28.8	345	37.7	
Reporting region (*n*=1976)					
London	489	46.0	448	49.0	0.016
Elsewhere in England	400	37.7	355	38.8	
Wales, Scotland, N Ireland	40	3.8	37	4.0	
Ireland	133	12.5	74	8.1	
Type of antenatal ART (*n*=1942)					
Mono/dual	98	9.5	6	0.7	<0.001
cART - PI-based	738	71.8	401	43.9	
cART - NNRTI-based	156	15.2	438	47.9	
cART - PI and NNRTI	23	2.2	56	6.1	
cART - NRTI only	13	1.3	13	1.4	
Earliest CD4 count, cells/µl (*n*=1790)**					
≥500	302	31.6	285	34.2	0.162
350-499	278	29.0	262	31.5	
200-349	285	29.8	221	26.5	
<200	92	9.6	65	7.8	

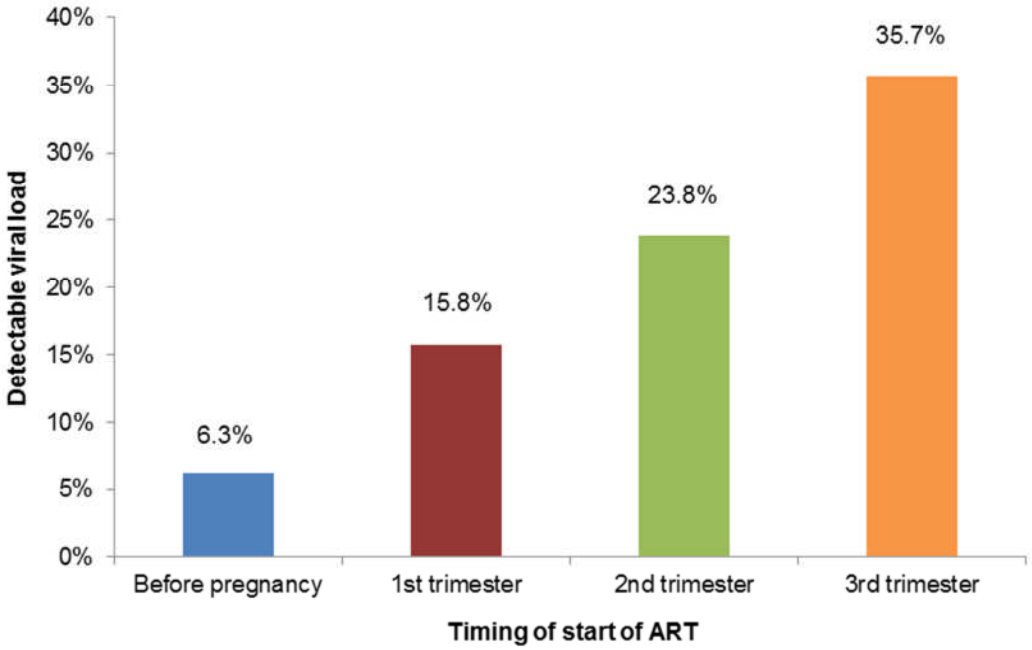
*Other comprises largely those originating from a high HIV prevalence area and/or with heterosexual exposure to HIV

**Not restricted to measurements taken prior to ART initiation

Among women not on ART at conception, 30 were reported to have not received ART during pregnancy. Of these, information on viral load at delivery was only reported for five; one of which was undetectable and four were detectable. Three women with detectable HIV RNA had particularly high viral load (all >17,000 copies/ml). Further analyses exploring viral suppression by delivery were restricted to the 1942 pregnancies in which the woman received ART during pregnancy; 1028 in women not on ART at conception (but were known to have received antenatal ART) and 914 in women conceiving on treatment. Viral load at delivery was reported for 57.1% of all pregnancies, and was available for a similar proportion of women in the two groups (59.6% and 54.2% respectively). Imputation of missing viral load as undetectable if there was an undetectable viral load earlier during the pregnancy increased available data to 86.8% of all pregnancies; 81.7% among those not on ART at conception and 92.6% among those who were.

Overall 16.2% (273/1686) of women's second pregnancies ending in a live or stillbirth had a detectable viral load at delivery, although among these the actual value was reasonably low (median: 188 copies/ml, IQR: 90-590, range: 51-412,000). The proportion of women with detectable viral load at delivery was 26.2% (220/840) in women starting ART in pregnancy compared with 6.3% (53/846) in women who conceived their second pregnancy on ART. Among those starting ART during pregnancy the risk of detectable viral load increased the later ART was started; from 15.8% (6/38) among those starting in the first trimester to 35.7% (71/199) among those not starting until the third trimester (Figure 5.16). The risk of MTCT in women not on ART at conception was 0.91% (8/878) compared with 0.27% (2/740) among those who were (p=0.121). No further analyses were conducted on this outcome due to the small number of vertical transmissions.

Figure 5.16 Timing of ART initiation and risk of detectable viral load at delivery



For the univariable and multivariable analyses of factors associated with detectable maternal viral load at delivery it was not appropriate to consider duration of antenatal ART since all women conceiving on ART will have received ≥12 weeks of ART. Similarly, earliest viral load was not considered since the vast majority of women who were on ART at conception had an undetectable viral load, which is simply a product of already being on treatment.

In the univariable analyses, factors associated with having a detectable viral load at delivery of second pregnancy were: not being on ART at conception, delivering during an earlier time period, being reported in London (or elsewhere in England), receiving mono or dual ART compared with PI-based cART (while those receiving NNRTI-based cART had a lower odds), lower earliest antenatal CD4 count, and younger maternal age. There was little evidence of a difference according to world region of origin (although women born abroad did have a slightly increased odds) and no difference according to HIV risk factor (Table 5.10).

In the multivariable analysis, compared with women conceiving on treatment, those not on ART at conception (but who received it during pregnancy) had a 4.3-fold increased odds of detectable viral load at delivery after adjusting for time period, place of report, type of ART received, and earliest CD4 count (Table 5.10). The following factors also remained associated with a detectable viral load at delivery in the final multivariable model: delivering during an earlier time period, receiving mono or dual therapy (while those receiving NNRTI-

based cART had a lower risk compared with the baseline PI-based cART group), and having a lower CD4 count. The odds were lower among those reported in Ireland, and higher (though not significantly so) among those reported in England (outside London) compared with those reported in London. There was little evidence the fit of the model was improved by the addition of maternal age (LR test p=0.519), world region of origin (LR test p=0.472), or HIV risk factor (LR test p=0.301).

Sensitivity analyses

Several sensitivity analyses were conducted on the main multivariable model to assess the robustness of the findings. When the main multivariable model (as shown in Table 5.10) was re-run using the non-imputed viral load variable the aOR was similar though slightly lower at 3.85, 95% CI: 2.65-5.59, p<0.001 (n=1048), compared with aOR: 4.34, 95% CI: 3.03-6.20 obtained from the main model (n=1590). Next, to check whether the observed association was driven by the small group of 'high risk' women who received a very short (<14 days) duration of ART (n=7), the main model (based on the imputed viral load variable) was re-run excluding this sub-group of pregnancies. The findings were very similar to those of the model fitted to the full dataset (aOR: 4.31, 95% CI: 3.01-6.18, p<0.001).

Table 5.10 Univariable and multivariable analyses of the association between timing of ART and detectable viral load at delivery

	Detectable/Total (%)	Univariable analyses			Multivariable analysis (*n*=1590)		
		OR	95% CI	*p*-value	aOR	95% CI	*p*-value
Timing of ART							
After conception	220/840 (26.2)	5.31	(3.86-7.30)		4.34	(3.03-6.20)	
Prior to conception	53/846 (6.3)	1		<0.001	1		<0.001
Age at delivery, yrs							
<25	33/184 (17.9)	1		0.046			
25-34	183/1049 (17.4)	0.97	(0.64-1.46)				
≥35	57/452 (12.6)	0.66	(0.41-1.05)				
World region of origin							
UK/Ireland	30/234 (12.8)	1		0.288			
Sub-Saharan Africa	218/1317 (16.6)	1.35	(0.90-2.03)				
Elsewhere	24/134 (17.9)	1.48	(0.83-2.66)				
HIV risk factor							
Other*	260/1612 (16.1)	1		0.499			
Injecting drug use	7/34 (20.6)	1.35	(0.58-3.13)				
Time period of delivery							
2000-2002	12/47 (25.5)	2.34	(1.16-4.70)		3.32	(1.38-8.00)	
2003-2005	76/338 (22.5)	1.98	(1.39-2.81)		1.90	(1.24-2.90)	
2006-2008	110/715 (15.4)	1.24	(0.90-1.70)		1.05	(0.74-1.49)	
2009-2010	75/586 (12.8)	1		<0.001	1		0.002
Reporting region							
London	141/830 (17.0)	1		0.001	1		<0.001
Elsewhere in England	116/647 (17.9)	1.07	(0.81-1.40)		1.34	(0.98-1.83)	
Wales, Scotland, N Ireland	3/63 (4.8)	0.24	(0.08-0.79)		0.31	(0.09-1.06)	
Ireland	13/145 (9.0)	0.48	(0.26-0.88)		0.42	(0.22-0.80)	

Continued overleaf

Table 5.10 *Continued*: Univariable and multivariable analyses of the association between timing of ART and detectable viral load at delivery

	Detectable/Total (%)	Univariable analyses			Multivariable analysis (*n*=1590)		
		OR	95% CI	*p*-value	OR	95% CI	*p*-value
Type of antenatal ART							
Mono/dual	33/71 (46.5)	3.96	(2.42-6.50)		2.89	(1.65-5.06)	
cART - PI-based**	177/985 (18.0)	1		<0.001	1		<0.001
cART - NNRTI-based	45/536 (8.4)	0.41	(0.29-0.58)		0.48	(0.32-0.74)	
cART - Other***	18/94 (19.1)	1.13	(0.66-1.91)		1.16	(0.62-2.18)	
Earliest CD4 count, cells/μl†							
≥500	60/534 (11.2)	1		<0.001	1		<0.001
350-499	82/486 (16.9)	1.60	(1.12-2.29)		1.94	(1.31-2.87)	
200-349	77/442 (17.4)	1.67	(1.16-2.40)		2.00	(1.34-2.97)	
<200	38/128 (29.7)	3.34	(2.10-5.31)		4.50	(2.69-7.51)	

*Other comprises largely those originating from a high HIV prevalence area and/or with heterosexual exposure to HIV
**Of the 985 women who received PI-based cART it was ritonavir boosted in 89.4% (*n*=881)
***Includes NNRTI and PI, and NRTI only – groups combined due to small numbers
†Not restricted to measurements taken prior to ART initiation

5.3 Attendance for HIV care after pregnancy

Current UK guidelines on the routine monitoring of people living with HIV recommend between two and four visits to HIV services per year (Asboe *et al*, 2012). Pregnancy provides an opportunity to engage women in long-term HIV care. Retention in HIV care after pregnancy ends is important for the continuation of HIV treatment in women requiring ART for their own health, and the monitoring of those discontinuing ART after delivery so that treatment can be initiated when indicated. For those not already on ART, it may also facilitate early initiation for PMTCT in any subsequent pregnancies. The NSHPC only collects information on women during their pregnancy and the immediate post-partum period, so it is not possible to investigate attendance for HIV care after pregnancy using NSHPC data alone. Therefore, to obtain this information the NSHPC dataset was linked with SOPHID data for England, Wales and Northern Ireland. SOPHID is described in Chapter 3, Section 3.2. This final part of the chapter assesses the completeness of matching of the NSHPC dataset with the SOPHID dataset, describes representativeness of the women in the matched dataset, and uses the matched data to explore attendance for HIV care after pregnancy (Objective 3c).

5.3.1 Methods

Matching procedure

An extract of the NSHPC dataset consisting of women reported to the obstetric reporting scheme who were known to have been pregnant during 2000-2010 was provided to the HPA (PHE since April 2013). The dataset included various demographic and clinical identifiers on which to match the dataset with SOPHID, including postcode minus the last letter (full postcode is not collected by the NSHPC). Women who attend care during their pregnancy should be independently reported to both the NSHPC and SOPHID.

Data linkage procedures were carried out by the HIV and STI Department of the HPA[47]. Matching was conducted on a range of identifiers collected by both the NSHPC and SOPHID. Initial matches were identified using date of birth (and female sex), and a hierarchical matching procedure was then applied utilising full/part postcode, country of birth and clinical information as detailed in the matching algorithm (provided in Appendix VI). Where potential duplicates were identified, for example, one NSHPC record matching to more than one SOPHID record, these were excluded if it was not possible to manually

[47] Matching was conducted by Cuong Chau.

assign a best match. Women who were reported to the NSHPC as having gone abroad during pregnancy were excluded based on the assumption that the majority of these women do not subsequently return to the UK[48]. SOPHID does not cover Ireland, and data from Scotland (pregnancies reported to the NSHPC and HIV care attendances in Scotland reported to SOPHID) were excluded because prior to 2008 Scottish reports to SOPHID for the same person were not reliably linked over time. The analyses were thus based on pregnancies reported in England, Wales and Northern Ireland.

The analyses presented here were restricted to women with one or more pregnancies during 2000-2009 whose first pregnancy reported to the NSHPC occurred from 2000 onwards. The 2009 cut-off was applied in order that there was a minimum of one calendar year of follow-up (opportunity to be reported to SOPHID) for each pregnancy reported to the NSHPC.

Definitions

Women present in the NSHPC dataset were coded as being 'matched' with SOPHID if they appeared in the SOPHID dataset at any point during 2000-2009. Since women attending care during pregnancy should be reported to both the NSHPC and SOPHID, it should be possible to match them (dependent on the availability and accurate recording of variables used to match on), even if they never attended care outside of pregnancy. However, some women in the NSHPC may not be matched to SOPHID because they never attended HIV care, for example, a woman who received no HIV-related antenatal care during pregnancy and presented to hospital in labour. The coding of these women as 'not matched' and subsequently estimating the proportion that were lost to follow-up only among those that were matched may lead to an under-estimation of loss to follow-up. Therefore, a sensitivity analysis was also carried out in which women who were not matched were, instead of being excluded from the analyses, coded as being lost to follow-up (a worst-case scenario). However, there are also other reasons for non-matches such as a lack of information or incorrect information on the identifiers used for matching. For example, if women move and change their postcode this may result in a non-match.

Attendance for HIV care during the calendar year following delivery was coded as a binary ('yes' or 'no') variable. Women in the NSHPC who were successfully matched with SOPHID were coded as attending care during the calendar year following delivery if they had an attendance for HIV care reported to SOPHID (during the relevant calendar year). For example, a woman delivering at any point during 2006 would be coded as attending HIV

[48] In Chapter 4 it was noted that among women with a first pregnancy during 2000-2009 who were reported to have gone abroad during that pregnancy, 5% had a subsequent pregnancy reported to the NSHPC.

care during the subsequent calendar year if she was had at least one SOPHID HIV care attendance reported at any time during 2007.

5.3.2 Study population

The NSHPC dataset for matching consisted of 7253 women with a total of 9338 pregnancies ending during 2000-2009 (based on date of birth or expected date of delivery for outcomes other than live or stillbirths). At their first reported pregnancy the median age of women in the dataset was 30.3 years (IQR: 26.6-34.3), 78.9% originated from sub-Saharan Africa, and 42.2% were diagnosed with HIV prior to pregnancy.

5.3.3 Completeness of matching of the NSHPC and SOPHID

Of the 7253 women in the NSHPC dataset, 6218 (85.7%) were matched with a woman in SOPHID. Looking at this at the pregnancy, rather than the woman level, of the 9338 pregnancies in the NSHPC dataset, 8224 (88.1%) were matched with a woman in SOPHID.

5.3.4 Characteristics of matched and unmatched women

The demographic characteristics of the 7253 women in the NSHPC dataset according to whether they had been matched to a SOPHID record are shown in Table 5.11. A significantly larger proportion of matched than unmatched women had more than one pregnancy reported to the NSHPC (26.3% *vs*. 6.9%, $p<0.001$). This is likely because each pregnancy a woman has reported to the NSHPC provides an additional opportunity for the demographic information which was utilised in the matching process to have been collected. Since attending for antenatal HIV care should also be recorded as an attendance for HIV care in SOPHID it provides an additional opportunity for her information to be collected by SOPHID too. There was also an association between matching and time period ($p=0.026$); matched women were less likely to have delivered their first pregnancy early in the study period (17.1% of matched women had their first pregnancy during 2000-2002 *vs*. 20.3% of unmatched women) and also later in the study period (10.8% *vs*. 12.1% respectively during 2009-2010). A smaller proportion of matched than unmatched women had a history of injecting drug use (1.3% *vs*. 3.1%, $p<0.001$). There were differences according to reporting region of women's first pregnancy ($p<0.001$) with a larger proportion of unmatched women being reported in London (49.5% *vs*. 42.0%), and maternal age ($p=0.041$) with a smaller proportion of matched than unmatched women being aged ≥35 years (21.0% *vs*. 24.1%). There was little difference according to world region of origin ($p=0.416$).

Information on the majority of the demographic variables provided in Table 5.11 was missing for ≤2% of women. Therefore, missingness of general demographic information (not necessarily variables specifically matched on) is unlikely to be strongly associated with the probability of matching.

Table 5.11 Demographic characteristics of women reported to the NSHPC according to whether they were matched to SOPHID

Characteristic	Matched		Unmatched		*p*-value
	n	%	*n*	%	
Number of pregnancies reported* (*n*=7253)					
1	4583	73.7	964	93.1	<0.001
>1	1635	26.3	71	6.9	
Time period of delivery (*n*=7253)**					
2000-2002	1062	17.1	210	20.3	0.026
2003-2005	2128	34.2	338	32.7	
2006-2008	2357	37.9	362	35.0	
2009-2010	671	10.8	125	12.1	
Age at delivery, yrs (*n*=7248)					
<25	1060	17.1	182	17.6	0.041
25-34	3854	62.0	601	58.2	
≥35	1302	21.0	249	24.1	
World region of origin (*n*=7154)					
UK/Ireland	735	11.9	105	10.5	0.416
Sub-Saharan Africa	4846	78.7	800	80.3	
Elsewhere	577	9.4	91	9.1	
HIV risk factor (*n*=6890)					
Other***	5845	98.7	941	96.9	<0.001
Injecting drug use	74	1.3	30	3.1	
Reporting region (*n*=6407)					
London	2773	49.5	340	42.0	<0.001
Elsewhere in England	2733	48.8	440	54.4	
Wales and N Ireland	92	1.6	29	3.6	

*Includes only pregnancies reported to the NSHPC (i.e. to diagnosed HIV-positive women)
**Expected year of delivery for outcomes other than a live or stillbirth
***Other comprises largely those originating from a high HIV prevalence area and/or with heterosexual exposure to HIV

5.3.5 Attendance for HIV care after pregnancy

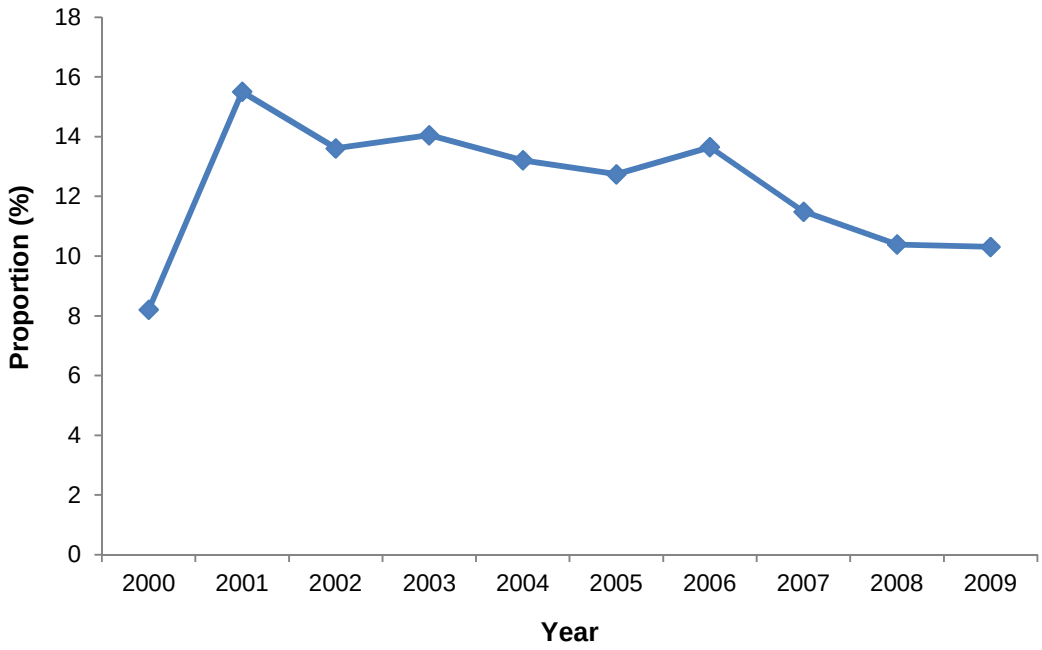
Overall, among the 8224 NSHPC pregnancies that had been matched to SOPHID, 12.2% (1005/8216) of the women did not access HIV care during the calendar year after delivery, after excluding eight women who, based on the matched data, were identified as having died during the same year, or the calendar year after, their pregnancy ended[49]. Five of the eight women had HIV, AIDS or an AIDS-defining illness (e.g. Kaposi's sarcoma) listed as a cause of death (up to four causes of death are documented), three of whom died within 42 days of the date of delivery[50]. Other causes of death included septicaemia (in two women, both of whom also had AIDS reported as a cause of death), bronchopneumonia and liver failure.

Some women will become pregnant again during the calendar year after delivery and will be coded in the matched dataset as attending care *and* being pregnant. However, we cannot be sure whether they are simply attending HIV-related antenatal care or whether they would have attended HIV care regardless of their subsequent pregnancy. Meanwhile, if all unmatched pregnancies (*n*=1114) were, instead of being excluded from the analyses, coded as being lost to follow-up (i.e. the assumption being that they could not be matched because they had never attended HIV care either before, during or after pregnancy and were therefore not present in the SOPHID dataset), the proportion not attending care was 22.7% (2119/9338) – the worst case scenario. All subsequent analyses are based on the initial estimate of the proportion of pregnancies for which the woman did not attend HIV care during the year after delivery (12.2%).

The proportion of women not attending care during the year after delivery decreased over the study period; from 15.5% among women whose pregnancy ended in 2001 to 10.3% among those whose pregnancy ended in 2009 (test for trend 2000-2009: $p<0.001$) (Figure 5.17). The low proportion among women whose pregnancy ended in 2000 may be a spurious result as there were relatively few pregnancies in this year compared with the later years and the number of women not attending care the following year was also small (*n*=20).

[49] Although a further seven women died during the calendar year following delivery, all of these women did attend care that year so it was not appropriate to exclude them.
[50] The WHO defines a maternal death as “the death of a woman while pregnant or within 42 days of termination of pregnancy, irrespective of the duration and site of the pregnancy, from any cause related to or aggravated by the pregnancy or its management but not from accidental or incidental causes” (see: http://www.who.int/healthinfo/statistics/indmaternalmortality/en/, Accessed September 2014).

Figure 5.17 Proportion of women who did not attend HIV care during the calendar year after pregnancy, by year, 2000-2009



The proportion of women not attending care during the year after their pregnancy ended was 12.5% (777/6210) after first reported pregnancies, and 11.4% (228/2006) after subsequent pregnancies (i.e. including all second, third etc pregnancies) (p=0.173). When only women's last reported pregnancies (among those with more than one pregnancy reported) were examined the proportion was 12.2% (199/1635) in comparison with the aforementioned 12.5% among first pregnancies (p=0.710).

When the potential impact of parity *per se* (regardless of whether the woman had diagnosed HIV at the time of any previous births) was examined, 12.5% of nulliparous women did not attend care the year following delivery, and the proportion was 12.0% among those with one previous birth, 11.7% among those with two and 11.8% among those with three or more previous births (test for trend: p=0.451).

5.4 Discussion

Engagement with antenatal care

Entering the antenatal care pathway early in pregnancy is crucial to enable effective interventions for PMTCT, as well as helping to ensure a healthy pregnancy. Among women experiencing a repeat pregnancy, the median gestational age at antenatal booking was 13 weeks. In the present analyses half of women booked at ≥13 weeks. It thus appears that HIV-positive women may be at risk of booking later than the general population in which 37% booked at ≥13 weeks (data for 2009-2010) (Health and Social Care Information Centre, 2010), although a clear trend towards earlier booking over time was apparent among women in the NSHPC. The potential later booking among women living with HIV likely reflects the socio-demographic characteristics of this population. A large proportion of HIV-positive women live in London (43% of those presenting with a sequential pregnancy in this analysis), and in an earlier London-based study HIV-positive women booked later than a general population (Parisaei *et al*, 2007). In the present analyses, although women in London tended to book earlier based on the multivariable analyses, the descriptive analyses revealed a more complex pattern with both early and very late bookers being more common in London.

Other important factors may include socio-economic status and maternal ethnicity or region of origin. Being born outside the UK and/or being of non-white ethnicity has been quite consistently reported as a risk factor for later booking (Cresswell *et al*, 2013; Kupek *et al*, 2002; Redshaw *et al*, 2010; Rowe *et al*, 2008). Although being of lower socio-economic status has not been clearly linked with later booking in the few studies that have examined this among the general UK population (Redshaw *et al*, 2010; Rowe *et al*, 2008), its potential role should not be overlooked. It was not possible to assess the influence of socio-economic status here because this information is not collected by the NSHPC, although being born abroad, which is collected by the NSHPC, does form a component of socio-economic status. The majority of HIV-positive women in the NSHPC originate from sub-Saharan Africa and may, even at their repeat pregnancies, book later for reasons such as language barriers or concerns about their immigration status. Migrants, particularly groups such as asylum seekers and undocumented migrants, may have transient lifestyles which could lead to disengagement from care (Dartnall *et al*, 2005), and some may return to their home country in between pregnancies. Furthermore, disparities in antenatal care usage may be influenced by variations in health literacy[51]. Poorer health literacy has been

[51] There is no universally accepted definition of health literacy. It is defined by the US Centres for Disease Control as “The capacity to obtain, process, and understand basic health information and services to make appropriate health decisions”. See: http://www.cdc.gov/healthliteracy/ (Accessed January 2014).

associated with lower levels of health care service utilisation, and a range of adverse health outcomes (Berkman *et al*, 2011). Although in the current analysis women from sub-Saharan Africa were not significantly more likely to book late compared with women born in the UK or Ireland, the direction of the association was compatible with this (aOR: 1.36, 95% CI: 0.90-2.04). A separate analysis of the NSHPC data focusing on the association between ethnicity and late presentation to antenatal care revealed that African ethnicity was a significant predictor of late booking among women diagnosed with HIV prior to that pregnancy (aOR: 1.80, 95% CI: 1.14-2.82) compared with white women (Tariq *et al*, 2012). The non-significant association in the present analysis may be a combination of the different grouping of the outcome variable (a binary <13 weeks *vs.* ≥13 weeks was used in the analysis by Tariq *et al* rather than the four categories used here), together with the present analysis being restricted to women who had already experienced a pregnancy since their diagnosis. Though the analysis by Tariq *et al* was restricted to women with a prior HIV diagnosis, only a portion (~40%) of these will have had a previous pregnancy, with some diagnosed in other settings (Byrne *et al*, 2013).

A higher number of previous births was correlated with later booking. Similar findings have been observed in the general UK population (Baker *et al*, 2012; Cresswell *et al*, 2013; Redshaw *et al*, 2010), and also among HIV-positive women in the US (Abatemarco *et al*, 2008), as discussed in Chapter 2, Section 2.3. The reason for this is not entirely clear but may reflect a combination of factors such as women feeling less anxious about subsequent pregnancies, combined with being busy looking after their other children. It was, however, reassuring that over three quarters of those who booked at ≥18 weeks for their first pregnancy booked before 18 weeks for their subsequent pregnancy (and 40% had booked before 13 weeks). That women not on ART at conception booked significantly later than those conceiving on treatment is of concern since timely booking and prompt referral to HIV services for prescription of ART is needed for this group. Higher levels of loss to follow-up from HIV care have been reported among people not receiving treatment (Gerver *et al*, 2010); disengagement from services may thus be important among this group. This assertion is further supported by the finding in the present analyses that 16% of very late bookers (≥24 weeks) had a CD4 count of <200 cells/μl. It is also noteworthy that 7% of women didn't book until ≥24 weeks, with those from sub-Saharan Africa at disproportionate risk. Booking this late may leave insufficient time for antenatal ART to be initiated early enough to reduce viral load to undetectable levels prior to delivery, as well as meaning that women may miss out on other aspects of routine antenatal care.

Timing of antenatal ART initiation

The timing of antenatal ART initiation among women's subsequent pregnancies since their HIV diagnosis was investigated in two parts of this chapter. Delays from antenatal booking to initiation of ART during 2008-2010 were explored in the first part. Meanwhile, predictors of timing of antenatal ART initiation (regardless of antenatal care booking) during 2000-2010 were investigated in the second part[52]. When considering the timing of antenatal ART initiation it should be remembered that women not conceiving on ART may include those who need ART for their own health, and those with higher CD4 counts who require ART for PMTCT only.

In the main analysis (2000-2010) the vast majority of women received ART prior to delivery with only 3% receiving none. This is within the range reported across Europe (Bailey *et al*, 2011; Keiser *et al*, 2008; von Linstow *et al*, 2010). Among those not conceiving on treatment, antenatal ART was commenced at a median of 23.7 gestational weeks; this declined over time reflecting evolving practice towards earlier initiation of ART in pregnancy (de Ruiter *et al*, 2008; Hawkins *et al*, 2005; Taylor *et al*, 2012). However, almost a quarter of women did not start ART until the third trimester. Delays in both laboratory assessment and ART initiation were further explored among sequential pregnancies in women who had booked for antenatal care, and were thus known to have at least some engagement with services. The median time lag from antenatal booking to first laboratory test during that pregnancy was zero weeks (i.e. blood sample was taken on the same day as booking), with half of women having their earliest antenatal laboratory test prior to the date of booking (presumably in many cases these were routine monitoring tests since all women were previously diagnosed). This prompt laboratory assessment in the bulk of women is reassuring. However, delays were noted, with 30% of women having a delay of four or more weeks suggesting that this is an area of practice that needs improving. It is possible that some of the delays in laboratory testing may be explained by tests being conducted in other parts of the healthcare system, not captured by the NSHPC. For example, if a woman has a routine laboratory assessment in the few weeks before she becomes pregnant, this would not necessarily be reported to the NSHPC (which only requests the results of tests conducted during pregnancy) but may influence the decision about when to conduct baseline laboratory testing in pregnancy (with testing potentially being deemed as less urgent in women with a recently documented undetectable viral load, for example).

Delays from antenatal booking to ART initiation were apparent (8.7 weeks overall). Such delays may have consequences on pregnancy outcomes. For example, nearly a third of

[52] Thus enabling analyses to be conducted on all (second) pregnancies to women not on ART at conception rather than restricted to the sub-group for whom timing of antenatal care booking was available.

women who experienced a delay of 10-20 weeks between booking and starting ART had detectable viral load at delivery, and there was one vertical transmission among this group. Among women with CD4 counts <350 cells/µl who had not initiated ART prior to booking, there was an average lag of seven weeks from booking (the point at which, on average, women's first antenatal CD4 count measurements were taken) to ART initiation. Women with an immunological indication for treatment are recommended to initiate ART as soon as possible, though this may be deferred until the start of the second trimester (de Ruiter *et al*, 2008; Taylor *et al*, 2012).

It is not clear to what extent delays in ART initiation are health system or provider-related, structural (e.g. the socio-economic environment of HIV-positive women), or related to women's individual circumstances, beliefs and choices. The analysis of antenatal ART initiation among all second pregnancies indicated that timing of treatment initiation was largely influenced by women's viral loads and CD4 counts as one would expect. Several non-clinical predictors also emerged in these analyses. There was evidence that women from sub-Saharan Africa were more likely to start ART later in pregnancy. Variations in uptake of antenatal ART among women reported to the NSHPC according to African region of origin have been documented, with those from Western Africa being at greatest risk of non-receipt of antenatal ART (Tariq, 2013). It is difficult to draw conclusions about the potentially increased risk of delays in ART initiation among women with a history of injecting drug use due to small numbers which may have limited power to detect an association, but this observation does tie in with data from Europe and the US (Abatemarco *et al*, 2008; Bailey *et al*, 2011; Orloff *et al*, 2001). Meanwhile, in the analysis restricted to 2008-2010 there was evidence of later ART initiation in London though this could reflect more complex case loads in London rather than differences in practice.

Women's motivations for taking antenatal ART require some consideration here. The main aim of ART during pregnancy is to reduce the risk of vertical transmission, as well as having health benefits for women with low CD4 counts. A qualitative study of African HIV-positive women's engagement with HIV care in the UK revealed that women are strongly motivated to take ART for the health of their babies (Tariq, 2013). Meanwhile, in interviews conducted with pregnant women in Australia, even those who had reservations about taking ART for their own health were prepared to adhere to therapy during pregnancy for the sake of their babies (McDonald *et al*, 2011). However, some women do have concerns and reservations about taking ART during pregnancy (McDonald *et al*, 2011; Tariq, 2013). An audit of women in the NSHPC who received either no antenatal ART or a short duration reported that, among women diagnosed prior to conception, declining treatment was the most common reason (11/15, 73%) (Modestini *et al*, 2013). This has also been shown to be an important reason for non-receipt of antenatal ART elsewhere. In the French Perinatal

Cohort, although the overall proportion of women who did not receive antenatal ART was low (4%), a third of these had declined ART (Mayaux *et al*, 2003), and in Denmark two of the seven women who did not receive ART had declined it (von Linstow *et al*, 2010). These data are not only of relevance to the 3% of women who received no antenatal ART in their second pregnancy, but may also be pertinent to some of the delays noted. For example, some women may delay ART initiation for fear of causing harm to their unborn baby. Women's experience of ART in previous pregnancies may also have an influence – those who have had negative experiences such as drug side-effects or adverse pregnancy outcomes may have concerns that these will re-occur. Finally, it should be remembered that some HIV-positive women have very difficult personal and social circumstances with issues around housing, immigration status and intimate partner violence (Anderson, 2008; Dhairyawan *et al*, 2013; Tariq, 2013) to name but a few, potentially leading to delays in receiving the pregnancy-related HIV care that they require, even for those experiencing sequential pregnancies.

Maternal health among those not on ART at conception

The analyses revealed that two-fifths of women not on ART at conception had an immunological indication for treatment. In itself, this finding suggests that there may have been potential health benefits for these women of remaining on (lifelong) ART after their first pregnancy ended. With regards to the management of these women, guidelines in place during the study period stated that diagnosed adults with CD4 counts of <350 cells/µl were eligible for treatment (Gazzard, 2005; Gazzard *et al*, 2008), with the pre-2008 guidelines allowing for individualised decisions for patients with CD4 counts of 200-350 cells/µl. However, 10% of women in this analysis had advanced disease (CD4 count of <200 cells/µl) and should therefore have been on treatment irrespective of time period. It is also of note that the proportion of women with an indication for treatment was little altered when data were restricted to 2008-2010. Delays in HIV treatment outside the context of pregnancy have been reported in the UK. For example, data from UK CHIC showed that during 1997-2003, a third of adults diagnosed with CD4 counts of >500 cells//µl did not start ART until their CD4 count had fallen to <200 cells/µl (Stohr *et al*, 2007), contrary to national guidelines. A more recent analysis of the same dataset revealed that although the majority (>90%) of people with low CD4 counts do receive treatment (a finding also supported by national level data (Delpech *et al*, 2013)), there was an approximate three month lag from having a low (<350 cells/µl) CD4 count measurement to ART initiation (Kober *et al*, 2012).

Late diagnosis has been identified as a key reason for people starting treatment at low CD4 counts more generally (47% of people in the UK and Ireland were diagnosed late in 2012 (Aghaizu *et al*, 2013), though of course this would not apply to a population of previously

diagnosed women presenting with repeat pregnancies. In US and UK settings socio-demographic factors that have been associated with non-receipt of ART among people requiring treatment include injecting drug use (Cohen *et al*, 2004; Fleishman *et al*, 2012; Gebo *et al*, 2005; Kober *et al*, 2012) and younger age (Fleishman *et al*, 2012; Gebo *et al*, 2005; Kober *et al*, 2012). Some studies have also found female gender to be a risk factor (Fleishman *et al*, 2012; Gebo *et al*, 2005), though this was not the case in two UK studies (Elford *et al*, 2008b; Kober *et al*, 2012). In the US individuals of black ethnicity were at increased risk of not receiving ART (Fleishman *et al*, 2012; Gebo *et al*, 2005), but in the UK this does not appear to apply. One study reported that only those for whom ethnicity was unknown were at increased risk (Kober *et al*, 2012), while Elford *et al* reported no differences by ethnicity (Elford *et al*, 2008b).

In the current analyses there were no clear demographic predictors of having an indication for treatment among women not on ART at conception of their subsequent pregnancy. It is not entirely clear whether this is due to a lack of power, simply reflects equality in access to care, or the greater homogeneity of the population of HIV-positive pregnant women compared with the broader population of people living with HIV. However, social marginalisation may also be relevant here. Although information on women's social situation and psychological status is not collected by the NSHPC, an audit of perinatal transmissions in England revealed psychosocial issues to be important (National Study of HIV in Pregnancy and Childhood *et al*, 2007). Indicators of marginalisation such as homelessness, a lack of social support and mental health issues have been linked with delayed access to HIV care (Aidala *et al*, 2004; Maisels *et al*, 2001; Tegger *et al*, 2008). Meanwhile, that women with a longer conception interval between their pregnancies were more likely to present with a low CD4 count at their second pregnancy will partly reflect the natural course of HIV disease (characterised by declining CD4 counts over time) but also suggests a potential lack of consistent engagement with care in between pregnancies. Although all women in the present study have had a prior pregnancy and most likely therefore had at least some level of engagement with HIV care, it cannot be assumed that all will engage well with HIV services after their pregnancy ends. Good engagement with HIV care is no doubt fundamental to the timely initiation of ART.

Attendance for HIV care after pregnancy and HIV treatment initiation

That a significant proportion of women not on ART at conception of their second pregnancy had an indication for treatment raises the question as to women's engagement with routine HIV care after their pregnancy ends. In order to help address this, the NSHPC was, for the first time, matched with the SOPHID dataset of people attending HIV care in England, Wales and Northern Ireland. The proportion of women in the NSHPC dataset for 2000-2009

who were successfully matched was high (86%), demonstrating the feasibility of this methodology, particularly among women with more than one pregnancy reported. Most women, 88%, attended HIV care during the calendar year following pregnancy (12% were classed as lost to follow-up), similar to the findings of a French study in which 11% of women were lost to follow-up post-partum (Lemly *et al*, 2007). The proportion is also consistent with that reported in a SOPHID analysis of diagnosed adults attending care during 1998-2007 in which 10% did not access care during the following year (Rice *et al*, 2011).

That only 12% of women did not attend HIV care after their pregnancy ended suggests that a lack of engagement with HIV services following pregnancy may not be the main, or certainly not the only, reason for women presenting with low CD4 counts (and not being on treatment) in their subsequent pregnancy. The reasons for CD4 counts falling to low levels before treatment begins (or never starting treatment) among those already diagnosed may include missed appointments or inconsistent care (Dombrowski *et al*, 2013; Wolbers *et al*, 2008) and patients declining treatment (Horne *et al*, 2007; Maisels *et al*, 2001). In the UK study by Horne *et al*, 28% of patients initially declined the offer to start treatment (Horne *et al*, 2007). People's motives for being unwilling to initiate ART are likely to be wide-ranging and complex, encompassing social, behavioural and psychological factors, interlaced with their beliefs about, and understanding of, both HIV and ART. In a South African study 'feeling healthy' was cited by over a third of those who did not wish to initiate ART (Katz *et al*, 2011). Perceived necessity of treatment has also been associated with uptake of ART in the UK (Horne *et al*, 2007) and other Western settings (Gold *et al*, 2001; Maisels *et al*, 2001). Fear of side effects emerges as another salient explanation in the published literature (Bassetti *et al*, 1999; Gold *et al*, 2000; Gold *et al*, 2001; Horne *et al*, 2007; Katz *et al*, 2011; Kremer *et al*, 2004; Maisels *et al*, 2001; Misener *et al*, 1998). Other factors include concerns around disclosure of HIV status (Katz *et al*, 2011), and concepts around embarking on, and adhering to, complex lifelong treatment regimens and the perceived impact of this on people's lives (Bassetti *et al*, 1999; Gold *et al*, 2001; Horne *et al*, 2007; Maisels *et al*, 2001). In some cases clinicians may make a decision to delay treatment, for example, where they have serious concerns regarding a patient's likely level of adherence (Bassetti *et al*, 1999; Bogart *et al*, 2000). Of note to the UK setting specifically, during the period studied undocumented migrants were charged for their ART which may well have put some off trying to access treatment. Since 2012, in England treatment has been provided free regardless of migration status (Department of Health, 2012).

Reasons for loss to follow-up from HIV care

Reasons for non-attendance for HIV care after pregnancy are likely to be multifactorial. Emigration is an important consideration. A recent UK audit reported that one quarter of people living with HIV who appeared not to be in care were no longer in resident in the UK (Clay, 2013), while a case note review in a London clinic revealed that for over half of those lost to follow-up there was some indication that they may have left the UK, either voluntarily or involuntarily (Gerver *et al*, 2010). However, this information is not routinely collected by SOPHID. Deaths are likely to have been under-estimated since this information is incorporated into SOPHID via matching with the HIV and AIDS New Diagnoses Database; as with any such procedure there will be some under-matching. Eight women were reported to have died during the calendar year that their pregnancy ended or the year after. In the context of the total number of pregnancies this number in itself is relatively small, and Gerver *et al* reported that in a London clinic only 2% of those lost to follow-up were known to have died (Gerver *et al*, 2010). Therefore, death is unlikely to be a significant reason for non-matches. However, further investigation into the specific circumstances of these deaths may help inform strategies or policies to help prevent future deaths among HIV-positive women. In sub-Saharan Africa, HIV is a major contributor to maternal mortality with HIV-positive pregnant and post-natal women being an estimated eight times more likely to die compared with HIV-negative women (Calvert *et al*, 2013a; Zaba *et al*, 2013). Exploring the contribution of HIV to maternal mortality in the UK is an important area for investigation. The most recent report of the Confidential Enquiries into Maternal Deaths in the United Kingdom documented 11 deaths for which HIV was the cause of death (out of 817 deaths overall) during 2000-2008 (Cantwell *et al*, 2011).

Disengagement from care may be intentional or unintentional (Ware *et al*, 2013), and in relation to HIV care, may involve issues such as stigma and fear of disclosure as well as practical difficulties e.g. transportation (Boehme *et al*, 2014; Coleman *et al*, 2007; Horstmann *et al*, 2010). In childbearing women, psychological factors such as post-partum depression may be relevant (Nachega *et al*, 2012). A small UK study reported depression in 21% (*n*=62) of HIV-positive post-partum women (Loftus *et al*, 2014). Also of relevance to this population group, childcare responsibilities[53] may be a barrier to regular HIV care attendance (Boehme *et al*, 2014), and have also been linked to poorer adherence to ART in post-partum women (Merenstein *et al*, 2009; Merenstein *et al*, 2008; Turner *et al*, 2000).

[53] The majority of pregnancies reported to the NSHPC result in a live birth (>90% during 2000-2009, based on data presented in Chapter 4, Section 4.2).

Disease progression following pregnancy

It was not feasible to assess detailed trajectories of women's HIV disease progression over time using the NSHPC dataset, since only measurements taken during pregnancy are requested. It is, however, salient that a quarter of women with a CD4 count of ≥350 cells/μl at their first pregnancy had fallen below the treatment threshold by their second pregnancy, particularly as second pregnancies occurred relatively soon, on average 2.3 years after the first. Significant levels of disease progression after the discontinuation of antenatal ART in post-partum women have also been reported elsewhere (Coria *et al*, 2012; Ekouevi *et al*, 2012; Watts *et al*, 2013), as detailed in Chapter 2, Section 2.4. Not surprisingly, initial CD4 count is important – in the present analysis 40% of women with a CD4 count of 350-499 cells/μl at their first pregnancy had declined to <350 cells/μl by their second, compared with 13% of those with initial CD4 counts of ≥500 cells/μl. More data are needed on differences in disease progression in women who continue and discontinue ART post-partum (among those not yet requiring treatment for their own health). The ongoing Promoting Maternal and Infant Survival Everywhere (PROMISE) Study, a trial in which women are randomised to either continue or stop ART post-partum with follow-up to compare morbidity and mortality among the two groups (International Maternal Pediatric Adolescent AIDS Clinical Trials Group, 2009) is due for completion in 2016 and should provide an important contribution to the evidence-base.

With regards to disease progression among untreated HIV-positive people more generally, the largest study to date was based on data from Concerted Action on Seroconversion to AIDS and Death in Europe (CASCADE), a collaboration of 25 European HIV cohorts involving over 18,000 individuals with reliable information on the date of seroconversion. The median time from HIV seroconversion to CD4 count falling to <350 cell/μl was 4.18 years (95% CI: 4.09–4.28) with just over one quarter of people requiring treatment (at the CD4 count <350 cell/μl threshold) within one year of seroconverting (Lodi *et al*, 2011). The findings of all these aforementioned studies on HIV disease progression are clearly pertinent to the question as to whether, with regards to maternal health, it may be beneficial for all pregnant women to initiate lifelong ART.

Virological outcomes according to timing of ART initiation (before or during pregnancy)

That longer duration of antenatal ART decreases the risk of detectable viral load at delivery, and hence MTCT, has been well documented in a wide range of settings (Chibwesha *et al*, 2011; Denoeud-Ndam *et al*, 2013; Hoffman *et al*, 2010; Patel *et al*, 2007; Rachas *et al*, 2013; Read *et al*, 2012; Warszawski *et al*, 2008), including a recent analysis of the NSHPC data (Townsend *et al*, 2014). However, the analyses presented in the second part of this chapter revealed that women starting ART antenatally had over four

times the odds of a detectable viral load at delivery in their second pregnancy compared with those conceiving on treatment, adjusting for confounders including CD4 count. Although with appropriate interventions the risk of MTCT is now very low (Townsend *et al*, 2014), some transmissions do still occur, and the rate was three times higher among those not on ART at conception in the present analyses. These findings suggest that in terms of MTCT risk there appears to be a clear benefit of being on ART prior to conception, which may avert in utero transmissions as well as those occurring around the time of delivery. A lower risk of MTCT in women conceiving on treatment compared with those starting cART during pregnancy has been reported from South Africa (0.7% vs. 5.7%, p=0.01) (Hoffman *et al*, 2010).

Only 6% of women conceiving on ART had a detectable viral load at delivery indicating that the vast majority are being well managed prior to and during pregnancy, and suggesting high levels of adherence among this population. However, poor adherence, viral load 'blips' (transient increases in viral load levels) (Havlir *et al*, 2001), or treatment failure may be contributing to the detectable levels in the remaining small proportion of women. Recent data from Western Europe also documented very low rates (3%) of virological failure (defined as >200 copies/ml after ≥24 weeks of ART) among women conceiving on treatment (Bailey *et al*, 2013).

Limitations

Information on timing of antenatal care booking was only available for 2008-2010, precluding detailed analyses of patterns in the timing of booking for women's previous and subsequent pregnancies as only 85 had date of booking reported for more than one pregnancy, though some informative descriptive analyses were possible. Furthermore, booking date was missing for around a quarter of pregnancies, though this appeared to be largely related to time period (as well as being more common in London centres), with reporting improving significantly between 2008 and 2010. This likely reflects the fact that this 'new' piece of information has only been collected by the NSHPC since 2008. However, a proportion of those with missing booking date may be accounted for by women who did not receive antenatal care (e.g. presented in labour). Such women may represent a particularly high risk group requiring targeted interventions to help them engage with services. As noted, assessments of variations in access to and uptake of care are limited by the absence of information on some potentially important socio-demographic characteristics of women. This broader limitation of the NSHPC is discussed further in Chapter 8, including possible future work to help elucidate reasons for delays.

Earliest antenatal CD4 count was missing for around 30% of pregnancies (Section 5.2). Though this proportion is quite high, there was little difference in the characteristics of pregnancies with and without missing CD4 counts suggesting that this is unlikely to have substantially biased the findings. As mentioned, limited data are available on disease trajectories as the NSHPC does not routinely collect clinical measurements on women outside of their pregnancies and this precluded detailed follow-up of women's health status after pregnancy. Examination of changes in women's CD4 counts between their first and second pregnancies did, however, provide the opportunity to make some assessment of the change in women's immunological status between their first and second pregnancies since their diagnosis. It should be borne in mind that immune function is lowered during pregnancy (Kuhnert *et al*, 1998), thus women's immunological status in pregnancy may not be an accurate reflection of their 'non-pregnant' state of health.

Although a high proportion of women reported to the NSHPC were successfully matched to a SOPHID record, there were some notable differences between women who were matched and those who were not which could have biased the findings. Unmatched women could represent a group particularly poorly engaged with services. These women may be more likely to be lost to follow-up after pregnancy than matched women, thus resulting in an over-estimation of women's attendance for HIV care after pregnancy. The lack of data on emigration which, as discussed, may be an important exploratory factor for non-attendance after pregnancy, is an important limitation. Assuming, as seems likely, that a proportion of those who do not attend care (whether or not matched) have left the country, then the true rate of loss to follow-up among women in the UK and Ireland may be lower than the estimated 12%. Furthermore, analyses of attendance for care after pregnancy only examined the calendar year after delivery. It is recognised that a proportion of women not attending HIV services during this single year will attend at some point in the future. However, since women are recommended to attend care several times per year (Asboe *et al*, 2012), non-attendance during one complete calendar year represents a good indicator of at least some extent of loss to follow-up whether permanent or temporary. Meanwhile, a proportion of those who did attend during the calendar year after delivery may be lost to follow-up at some point in the future. Indeed, women's motivation to attend care may be heightened during the post-partum period.

5.5 Key findings

Timing of antenatal booking

- Information on antenatal booking date was reported for 73.9% (*n*=2827) of all pregnancies during 2008-2010. The proportion was similar for repeat (74.8%, *n*=953) and first pregnancies (73.5%, *n*=1874)

- Median gestational age at antenatal booking among women presenting with a repeat pregnancy was 13.0 weeks (IQR: 10.6-16.4), similar to that among first reported pregnancies. At women's repeat pregnancies, 49.3% booked at <13 weeks, 32.0% at 13-17 weeks, 11.9% at 18-23 weeks, and the remaining 6.8% at ≥24 weeks

- Higher parity (≥3), earlier year of delivery, being reported in England (outside London) or Ireland, and not being on ART at conception were independently associated with later booking for antenatal care

- Median time lag from booking to antenatal ART initiation among those not on ART prior to pregnancy was 8.7 weeks (IQR: 4.6-12.6 weeks), and was significantly shorter in women requiring ART for their own health (<350 cells/μl) than those requiring it for PMTCT only (CD4 ≥350 cells/μl); 7.1 weeks (IQR: 3.3-10.4) *vs*. 10.0 weeks (IQR: 5.7-13.6) respectively *(p*<0.001)

Immunological status, timing of ART, and virological outcomes among women not on ART at conception

- There were 1177 second pregnancies to women not on treatment at conception during 2000-2010 (accounting for 53% of second pregnancies)

- Two-fifths had an immunological indication for ART (CD4 <350 cells/μl), of whom nearly half had a CD4 count of ≥350 cells/μl at their first pregnancy

- 3% of women did not receive antenatal ART and the remainder commenced treatment at a median of 23.7 weeks, with a quarter not starting until their third trimester

- In a multivariable analysis women with a high viral load or low CD4 count started ART significantly earlier. There was a strong trend of earlier ART initiation over

calendar time, while women from sub-Saharan Africa started later than those from the UK or Ireland

- Compared with women conceiving on ART, those who initiated it during pregnancy had over four times the odds of having a detectable viral load at delivery

Attendance for HIV care after pregnancy

- 88% of 9338 pregnancies in the NSHPC dataset for England, Wales and Northern Ireland during 2000-2009 were matched with a SOPHID record

- Based on the matched data, 12.2% of women did not access HIV care during the calendar year after delivery

- The proportion of women not attending care during the calendar year after delivery was similar for first reported and subsequent pregnancies

Chapter 6 Influence of short-course antenatal cART on response to therapy in subsequent pregnancies

Many pregnant women not yet requiring treatment for their own health will receive short-course ART for PMTCT (Taylor *et al*, 2012). As discussed in Chapter 2, Section 2.5, inferior virological responses to NNRTI-based treatment have been well documented among women with prior exposure to sdNVP. However, the influence of previous short-course cART for PMTCT on response to therapy in subsequent pregnancies has been little investigated. Such information will help inform clinical decision-making around the use of short-course cART in pregnancy given the high probability of future pregnancies (as shown in Chapter 4). Therefore, the objective of this chapter is to investigate the probability of detectable viral load at delivery and MTCT in women who experienced short-course cART for PMTCT in a previous pregnancy (Objective 4).

6.1 Methods

Dataset

Pregnancies to women whose first reported pregnancy occurred during 2000-2010 were included in these analyses. The dataset included both index (first reported) and subsequent (second) pregnancies in this group of women. Analyses were performed on the following two groups: i) 'ART-naive' - consisting of pregnancies in women with no known ART use prior to pregnancy (based on the fact that they were not on ART at conception of their first reported pregnancy) which provided the baseline group, and ii) 'previous short-term cART for PMTCT' (hereafter referred to as the 'cART-experienced' group) - consisting of pregnancies in women who had received at least seven days of cART during their previous (index) pregnancy, regardless of that pregnancy outcome, but were not on ART at the time of conception of their subsequent pregnancy. The two analysis groups were constructed independently and although some women will contribute their first reported pregnancy to the ART-naive group and their subsequent pregnancy to the cART-experienced group, others will only contribute one pregnancy to the dataset e.g. those women who only had one pregnancy reported to the NSHPC can only possibly contribute a pregnancy to the ART-naive group. Further eligibility criteria for both the analysis groups were that pregnancy outcome was a live birth to a woman who did not conceive on treatment but received antenatal cART (Figure 6.1). Pregnancies resulting in an outcome other than a live birth (e.g. stillbirth, miscarriage) were excluded as information on infant HIV status is

only obtained for live born infants. Pregnancies among women with exposure to mono or dual therapy in a previous pregnancy, and in those who had taken short-course cART in more than one previous pregnancy, were excluded to ensure the dataset for analysis was as 'clean' and homogeneous as possible.

Figure 6.1 Study population inclusion criteria – influence of short-course antenatal cART on response to therapy in subsequent pregnancies

ART-naive group	cART-experienced group
Index pregnancy	Second reported pregnancy
Live birth	Live birth
Woman was *not* on ART at conception but received cART (any duration) during that pregnancy	Woman was *not* on ART at conception but received cART (any duration) during that pregnancy
	Woman was *not* on ART at conception of her first reported pregnancy but had received at least seven days of cART during that previous pregnancy

Definitions

Detectable viral load at delivery was analysed. Viral load measurements taken prior to, or within the first seven days after cART initiation, were excluded, except those within seven days of delivery[54], since the probability of achieving an undetectable viral load within this short period of time is likely to be low (Patel *et al*, 2007). As a high proportion of women had no viral load data reported, an imputed variable was also constructed as described in Chapter 3, Section 3.4 (if viral load within 28 days before and seven days after delivery was missing but the last reported viral load measurement in that pregnancy was undetectable then delivery viral load was imputed as undetectable). Multivariable analyses were also carried out with the original non-imputed variable as sensitivity analyses.

[54] Although it is possible that some women with a detectable viral load within the seven days after delivery actually had an undetectable viral load at delivery (which was not reported to the NSHPC) and discontinued cART at delivery resulting in an increase in their viral load to detectable levels, this is likely to apply to few women. Of the 53 women with detectable viral loads measured during the seven days after delivery, most (*n*=42) were taken within the first three days. Furthermore, not all women discontinue cART after delivery.

Statistical analyses

The proportion of pregnancies with viral load <50 copies/ml at delivery was compared between the cART-experienced group and the ART-naive group. Logistic regression models were fitted in univariable and multivariable analyses to investigate the probability of detectable maternal viral load at delivery and MTCT in the cART-experienced group compared with the ART-naive group. Robust standard errors were used to account for the contribution some women made to both analysis groups (i.e. a pregnancy in the ART-naive group and a subsequent pregnancy in the cART-experienced group) (Kirkwood *et al*, 2003). This may lead to clustering of outcomes at the woman level (see Chapter 3, Section 3.5). Time period of delivery was included in the models *a priori* to take account of changes over time in the management of HIV in pregnancy. Further logistic regression models in which type of cART (PI-based or NNRTI-based) was specified were constructed using the same variables as were included in the overall model to ensure comparability. These further models were constructed to examine in more detail the range of potential patterns of antenatal ART use that women with sequential pregnancies may have experienced. PI-based and NNRTI-based regimens were the main focus of these analyses, being the most common. As will be shown, other regimens e.g. triple NRTI-based cART are relatively rare, therefore the numbers eligible for inclusion in multivariable analyses would be small and the findings of less relevance to the current clinical situation.

6.2 Probability of detectable viral load at delivery

6.2.1 Study population

The study population consisted of 5977 pregnancies; 5372 in ART-naive women, and 605 in women who had received at least seven days of cART for PMTCT during their previous pregnancy[55]. Among the cART-experienced group, the median interval from the end of their previous pregnancy to the start of their current pregnancy was 1.7 years (IQR: 0.9-2.7). The median maternal age at delivery was 29.5 years (IQR: 25.9-33.3), and the age distribution was similar in the cART-experienced and ART-naive groups; the majority of women in both groups being aged 25-34 years (66.3% and 63.3% respectively) (Table 6.1). Among the ART-naive group, 27.7% (1487/5365) of pregnancies were in women diagnosed before pregnancy. The median duration of antenatal cART was 14.1 weeks (IQR: 10.7-17.6) overall. The cART-experienced group was more likely to have received >12 weeks of antenatal cART (74.8% *vs*. 62.3%), and more likely to deliver vaginally (33.5% *vs*. 28.5%).

[55] If women who were missing information on cART duration during their previous pregnancy but had achieved an undetectable viral load at delivery of that previous pregnancy were re-coded as having received at least seven days of cART this only added one additional pregnancy to the cART-experienced group so was deemed unnecessary.

The proportion of preterm deliveries (<37 weeks gestation) was similar in the two groups (10.9% and 12.9% respectively), as was the median earliest antenatal viral load measurement (4600, IQR: 374-20,587 copies/ml and 4565, IQR: 479-22,000 copies/ml), *p*=0.371.

Maternal immune function (earliest antenatal CD4 count in that pregnancy), was better in the cART-experienced group (median: 400 cells/μl, IQR: 277-533) compared with the ART-naive group (median: 348 cells/μl, IQR: 230-498). The cART-experienced group was more likely to receive PI-based cART than the ART-naive group (80.9% *vs*. 65.1%), and a higher proportion received a boosted PI (92.0% *vs*. 79.1%). NNRTI-based cART was received by 15.5% of the cART experienced group and 30.3% of the ART-naive group.

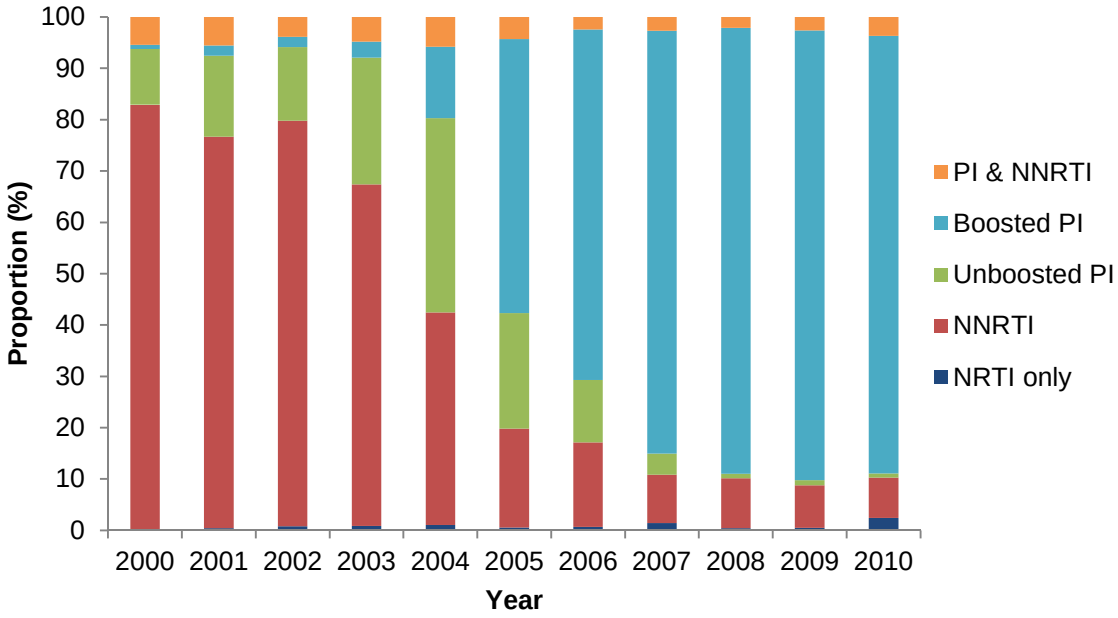
Table 6.1 Demographic, clinical and obstetric characteristics of pregnancies in ART-naive and cART-experienced women

Characteristic	Pregnancies to ART-naive women (*n*=5372)		Pregnancies to cART-experienced women (*n*=605)		*p*-value
	n	%	*n*	%	
Age at delivery, yrs (*n*=5958)					
<25	1094	20.4	102	16.9	0.114
25-34	3391	63.3	401	66.3	
≥35	868	16.2	102	16.9	
World region of origin (*n*=5922)					
UK/Ireland	691	13.0	91	15.1	0.362
Sub-Saharan Africa	4110	77.3	456	75.5	
Elsewhere	517	9.7	57	9.4	
Time period of delivery (*n*=5977)					
2000-2002	760	14.1	13	2.1	<0.001
2003-2005	1757	32.7	106	17.5	
2006-2008	1951	36.3	287	47.4	
2009-2010	904	16.8	199	32.9	
Timing of antenatal booking* (*n*=1395)					
First trimester	538	46.8	100	40.8	0.014
Second trimester	521	45.3	134	54.7	
Third trimester	91	7.9	11	4.5	
Earliest CD4 count, cells/µl (*n*=5261)					
≥500	1169	24.9	174	30.9	<0.001
350-499	1172	24.9	170	30.2	
200-349	1477	31.4	165	29.3	
<200	880	18.7	54	9.6	
Type of cART (*n*=5964)					
PI-based	3490	65.1	487	80.9	<0.001
Of which were ritonavir-boosted	*2759*	*79.1*	*448*	*92.0*	
Of which were unboosted	*730*	*20.9*	*39*	*8.0*	
NNRTI-based	1626	30.3	93	15.5	
PI and NNRTI	200	3.7	15	2.5	
Of which were ritonavir-boosted	*110*	*55.0*	*14*	*93.3*	
Of which were unboosted	*90*	*45.0*	*1*	*6.7*	
NRTI only	46	0.9	7	1.2	
cART duration, wks (*n*=5572)					
<2	155	3.1	1	0.2	<0.001
2-12	1720	34.5	148	25.0	
13-40	3105	62.3	443	74.8	
Mode of delivery (*n*=5962)					
Elective caesarean section	2895	48.6	286	47.4	0.006
Emergency caesarean section	1366	22.9	115	19.1	
Vaginal	1701	28.5	202	33.5	
Gestational age, wks (*n*=5935)					
≥37	5171	87.1	539	89.1	0.128
<37	764	12.9	66	10.9	

*Available from 2008

There were changes over time in the type of cART that women received. NNRTI-based regimens predominated during 2000-2003. There was then an increase in PI-based regimens – initially these were mainly unboosted PIs but from 2005/06 ritonavir-boosted PI-based cART became the most common regimen (Figure 6.2). Among those women receiving NNRTI-based cART, almost all in both the cART-experienced and ART-naive groups took regimens containing nevirapine (95.7% and 98.0% respectively).

Figure 6.2 Type of antenatal cART received, by year, 2000-2010



6.2.2 Patterns of cART use among cART-experienced women

Among the 605 pregnancies in cART-experienced women, type of cART received in both current and previous pregnancy was reported for 600 (Table 6.2). Overall, 58.8% (*n*=353) of women received the same type of cART regimen in their current and previous pregnancy. Looking at the patterns of cART use in a little more detail, in conjunction with Table 6.2 there were 385 pregnancies in women who had received PI-based cART in a previous pregnancy, and 194 in those with previous NNRTI-based cART exposure. Among current pregnancies in which the woman received NNRTI-based cART (*n*=92), most (82.6%) had also received NNRTI-based cART in their previous pregnancy (all of whom had received a regimen containing nevirapine). Among those receiving PI-based cART in their current pregnancy (*n*=487) almost three-quarters (74.1%) had received PI-based cART in their previous pregnancy. Of women receiving boosted PI-based cART in their current pregnancy, over half also received a boosted PI in their previous pregnancy, with most others receiving either an NNRTI (21.0%) or an unboosted PI (18.5%). Among all 194 pregnancies in women with previous NNRTI-based cART exposure, over half received PI-based cART in their current pregnancy (*n*=110, composed of *n*=94 boosted + *n*=16 unboosted).

Table 6.2 Type of cART received in current and previous pregnancy among cART-experienced women

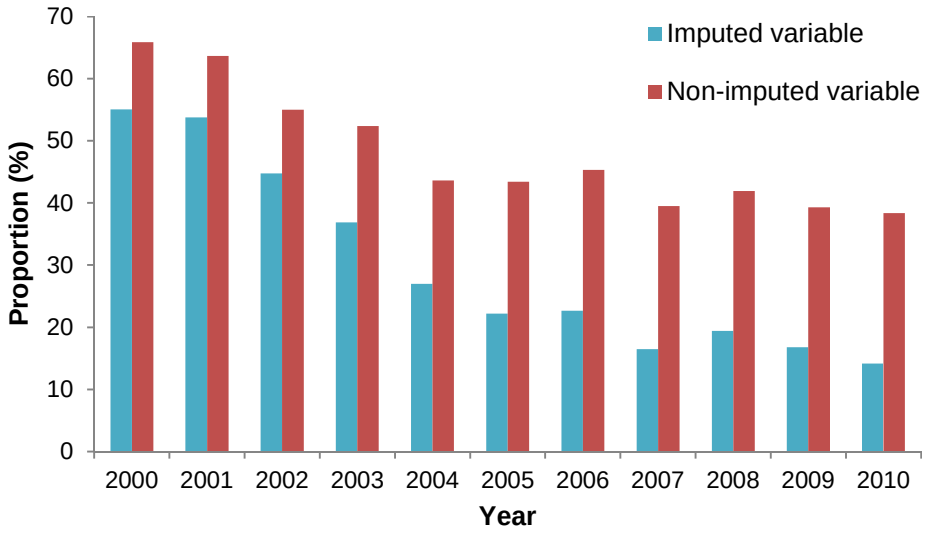
Type of cART in current pregnancy	Type of cART in previous pregnancy											
	NRTI only		NNRTI		Unboosted PI		Boosted PI		PI & NNRTI		Total	
	n	*%*	*n*	*%*	*n*	*%*	*n*	*%*	*n*	*%*	*n*	*%*
NRTI only	2	28.6	0	0.0	1	14.3	2	28.6	2	28.6	7	100
NNRTI	1	1.1	76	82.6	11	12.0	4	4.4	0	0.0	92	100
Unboosted PI	0	0.0	16	41.0	18	46.2	3	7.7	2	5.1	39	100
Boosted PI	4	0.9	94	21.0	83	18.5	257	57.4	10	2.2	448	100
PI & NNRTI	0	0.0	8	57.1	0	0.0	6	42.9	0	0.0	14	100
Total	7		194		113		272		14		600	

Note: The type of ART recommended by the British HIV Association varied over the study period (see Appendix II).

6.2.3 Availability of data on viral load at delivery

Viral load at delivery was reported for 54.9% (3281/5977) of all pregnancies, and was available for a greater proportion of the cART-experienced than ART-naive group (62.3% *vs*. 54.1%, *p*<0.001). Imputation of missing viral load as undetectable if there was an undetectable viral load earlier in that pregnancy increased available data to 74.7% for all pregnancies (4462/5977): 85.1% (515/605) among cART-experienced and 73.5% (3947/5372) among ART-naive. These differences reflect the declining frequency of missing viral load over time, from 55.0% in 2000 to 14.1% in 2010 (*p*<0.001) based on the imputed viral load variable, and from 65.9% to 38.4% (*p*<0.001) based on the non-imputed variable (Figure 6.3).

Figure 6.3 Proportion of pregnancies with missing viral load (imputed and non-imputed variable), by year, 2000-2010



Further analyses were conducted on the imputed viral load variable (with concurrent sensitivity analyses to confirm that the models did not differ significantly from those conducted using the non-imputed variable). Women with missing viral load were younger (22.7% *vs*. 19.2% being aged <25 years *p*=0.003), more likely to have received less than two weeks of antenatal cART (7.1% *vs*. 1.6%, *p*<0.001), and to have a low CD4 count (<350 cells/µl) (56.2% *vs*. 47.3%, *p*<0.001). There was no difference in maternal world region of origin (*p*=0.331) (Table 6.3).

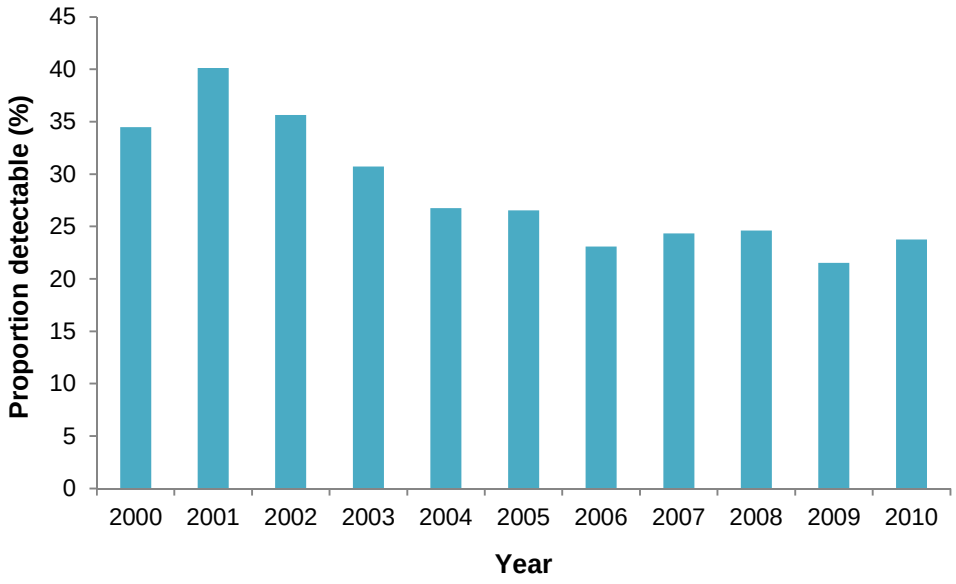
Table 6.3 Key characteristics of women with and without information on viral load at delivery (based on imputed viral load variable)

Characteristic	Women with viral load at delivery		Women missing viral load at delivery		*p*-value
	n	**%**	***n***	**%**	
Age at delivery, yrs (*n*=5958)					
<25	856	19.2	340	22.7	0.003
25-34	2849	63.9	943	63.0	
≥35	756	16.9	214	14.3	
World region of origin (*n*=5922)					
UK/Ireland	576	13.0	206	13.8	0.331
Sub-Saharan Africa	3413	77.0	1154	77.4	
Elsewhere	442	10.0	131	8.8	
cART duration, wks (*n*=5572)					
<2	71	1.6	85	7.1	<0.001
2-12	1328	30.4	540	45.0	
13-40	2973	68.0	575	47.9	
Earliest CD4 count, cells/µl (*n*=5261)					
≥500	1104	25.8	239	24.5	<0.001
350-499	1154	26.9	188	19.3	
200-349	1303	30.4	339	34.8	
<200	726	16.9	208	21.4	

6.2.4 Detectable viral load among ART-naive and cART-experienced women

Among those women with data on viral load at delivery, it was detectable for 26.0% of deliveries, although among these the actual level was generally low (median: 192 copies/ml, IQR: 89-696), with only 7.4% at ≥10,000 copies/ml. The proportion of pregnancies in which the woman had a detectable viral load at delivery peaked at 40.2% in 2001 and then declined year-on-year to 23.1% in 2006, thereafter remaining stable (Figure 6.4).

Figure 6.4 Proportion of pregnancies with a detectable viral load at delivery, by year, 2000-2010



The probability of detectable viral load was 26.2% in the ART-naive and 24.3% in the cART-experienced groups giving an unadjusted OR of 0.90 (95% CI: 0.73-1.11). Among those with a detectable viral load, the median measurement was similar in the two groups (ART-naive: 196 copies/ml, IQR: 89-703, and cART-experienced: 184, IQR: 88-510). In univariable analyses, younger age, earlier time period, receiving less than two weeks of cART, receiving a triple class regimen, and having a lower antenatal CD4 count were significantly associated with detectable viral load. After adjusting for these factors there was a slightly, but only weakly significant, increased odds of detectable viral load (aOR: 1.27, 95% CI: 1.01-1.60, *p*=0.043) associated with prior cART exposure in pregnancy (Table 6.4). When the analysis was repeated using the original (non-imputed) viral load variable, the aOR was similar at 1.21 (95% CI: 0.95-1.54, *p*=0.127), with the lack of statistical

significance most likely a result of loss of power in the model. Although a woman's earliest antenatal viral load may be associated with her viral load at the time of delivery, it was not considered appropriate to adjust for earliest viral load in the multivariable models since earlier undetectable viral loads were used to impute viral load at delivery where this was missing. There was no difference in the median earliest viral load between the two analysis groups (p=0.371). There is also substantial overlap between earliest viral load and viral load at delivery since the vast majority of women with an undetectable earliest viral load will remain undetectable at the time of delivery.

Table 6.4 Univariable and multivariable analyses of the association between previous antenatal cART and detectable viral load at delivery in a subsequent pregnancy

	Detectable/ Total (%)	Univariable analyses			Multivariable analysis (*n*=4208)		
		OR	95% CI	*p*-value	aOR	95% CI	*p*-value
Group							
ART-naive	1033/3947 (26.2)	1		0.342	1		0.043
Previous cART	125/515 (24.3)	0.90	(0.73-1.11)		1.27	(1.01-1.60)	
Age at delivery, yrs							
<25	255/856 (29.8)	1		0.016	1		0.009
25-34	719/2849 (25.2)	0.80	(0.67-0.94)		0.76	(0.63-0.92)	
≥35	183/756 (24.2)	0.75	(0.60-0.94)		0.72	(0.57-0.93)	
World region of origin							
UK/Ireland	140/576 (24.3)	1		0.640			
Sub-Saharan Africa	889/3413 (26.0)	1.10	(0.89-1.36)				
Elsewhere	118/442 (26.7)	1.13	(0.85-1.52)				
Time period of delivery							
2000-2002	144/391 (36.8)	1		<0.001	1		
2003-2005	371/1338 (27.7)	0.66	(0.52-0.84)		0.61	(0.46-0.80)	<0.001
2006-2008	433/1802 (24.0)	0.54	(0.43-0.69)		0.55	(0.41-0.74)	
2009-2010	210/931 (22.6)	0.50	(0.39-0.65)		0.62	(0.45-0.86)	
cART duration, wks							
<2	62/71 (87.3)	1		<0.001	1		<0.001
2-12	555/1328 (41.8)	0.10	(0.05-0.21)		0.11	(0.06-0.23)	
13-40	514/2973 (17.3)	0.03	(0.01-0.06)		0.03	(0.01-0.06)	
Type of cART							
PI	803/3134 (25.6)	1		<0.001	1		<0.001
NNRTI	282/1108 (25.5)	0.99	(0.85-1.16)		0.62	(0.50-0.76)	
NRTI	6/44 (13.6)	0.46	(0.19-1.09)		0.48	(0.17-1.35)	
PI & NNRTI	66/173 (38.2)	1.79	(1.30-2.46)		1.20	(0.82-1.74)	
Earliest CD4 count, cells/µl							
≥500	214/1104 (19.4)	1		<0.001	1		<0.001
350-499	276/1154 (23.9)	1.31	(1.07-1.60)		1.50	(1.20-1.88)	
200-349	353/1303 (27.1)	1.55	(1.27-1.88)		1.94	(1.56-2.41)	
<200	253/726 (34.8)	2.22	(1.79-2.76)		3.40	(2.64-4.38)	

Note: All pregnancy-specific characteristics relate to current pregnancy.

All further models were adjusted for the same factors as the initial model (as shown in Table 6.4) namely maternal age, time period, duration of cART, CD4 count and type of cART received in current pregnancy. Firstly a logistic regression model was fitted including type of cART previously received (Table 6.5). Only pregnancies in women who had prior exposure to either PI- or NNRTI-based cART were included (excluding those who had taken both PIs and NNTRIs). Comparing pregnancies in those who had previously received a PI-based cART regimen with all ART-naive pregnancies, there was no difference in the odds of detectable viral load (aOR: 1.08, 95% CI: 0.81-1.45, p=0.580). Meanwhile, among pregnancies in women who had previously received an NNRTI-based cART regimen, there was an increased odds of detectable viral load compared with the ART-naive group (aOR: 1.81, 95% CI: 1.25-2.63, p=0.002). Younger maternal age, earlier time period, receiving less than two weeks of cART, type of cART, and lower antenatal CD4 count all remained associated with a detectable viral load in the multivariable model. Receipt of an NNRTI-based cART regimen in the current pregnancy was associated with a decreased odds of detectable viral load compared with PI-based regimens, a difference which remained when only boosted PI-based regimens were included (aOR: 0.52, 95% CI: 0.42-0.66, p<0.001).

Table 6.5 Univariable and multivariable analyses of the association between type of previous antenatal cART received and detectable viral load at delivery in a subsequent pregnancy

	Detectable/ Total (%)	Univariable analyses			Multivariable analysis (*n*=4188)		
		OR	95% CI	*p*-value*	aOR	95% CI	*p*-value*
Group							
ART-naive	1033/3947 (26.2)	1			1		
Previous PI cART	73/332 (22.0)	0.80	(0.61-1.04)	0.088	1.08	(0.81-1.45)	0.580
Previous NNRTI cART	47/162 (29.0)	1.15	(0.82-1.63)	0.419	1.81	(1.25-2.63)	0.002
Age at delivery, yrs							
<25	254/853 (29.8)	1		0.017	1		0.007
25-34	716/2836 (25.2)	0.80	(0.67-0.95)		0.76	(0.63-0.92)	
≥35	182/751 (24.2)	0.75	(0.60-0.94)		0.72	(0.56-0.92)	
World region of origin							
UK/Ireland	140/574 (24.4)	1		0.652			
Sub-Saharan Africa	884/3396 (26.0)	1.09	(0.88-1.35)				
Elsewhere	118/440 (26.8)	1.14	(0.85-1.52)				
Time period of delivery							
2000-2002	144/390 (36.9)	1		<0.001	1		<0.001
2003-2005	371/1336 (27.8)	0.66	(0.52-0.83)		0.60	(0.45-0.79)	
2006-2008	429/1792 (23.9)	0.54	(0.43-0.68)		0.55	(0.41-0.73)	
2009-2010	209/923 (22.6)	0.50	(0.39-0.65)		0.64	(0.46-0.88)	
cART duration, wks							
<2	62/71 (87.3)	1		<0.001	1		<0.001
2-12	554/1322 (41.9)	0.10	(0.05-0.21)		0.11	(0.06-0.23)	
13-40	510/2958 (17.2)	0.03	(0.01-0.06)		0.03	(0.01-0.06)	
Type of cART							
PI	800/3120 (25.6)	1		0.002	1		<0.001
NNRTI	282/1106 (25.5)	0.99	(0.85-1.16)		0.60	(0.49-0.74)	
NRTI	6/41 (14.6)	0.50	(0.21-1.19)		0.56	(0.20-1.57)	
PI & NNRTI	65/172 (37.8)	1.76	(1.28-2.42)		1.17	(0.80-1.70)	
Earliest CD4 count, cells/µl							
≥500	214/1097 (19.5)	1		<0.001	1		<0.001
350-499	275/1149 (23.9)	1.30	(1.06-1.59)		1.50	(1.20-1.87)	
200-349	352/1297 (27.1)	1.54	(1.27-1.87)		1.95	(1.57-2.42)	
<200	252/725 (34.8)	2.20	(1.77-2.73)		3.40	(2.64-4.38)	

*Individual *p*-values provided for the exposure of interest

Note: All pregnancy-specific characteristics relate to current pregnancy.

Further analyses were conducted to explore the association between type of previous cART exposure and probability of detectable viral load. When the model was restricted to pregnancies in women who received PI-based (boosted or unboosted) cART in their current pregnancy (and the cART-experienced group included only pregnancies in women who had received PI-based cART in both their previous and current pregnancy), there was no increased probability of detectable viral load in the PI-experienced compared with the ART-naive group (aOR: 1.09, 95% CI: 0.81-1.47, *p*=0.571) (Table 6.6).

Table 6.6 Univariable and multivariable analyses of the association between previous PI-based antenatal cART receipt and detectable viral load at delivery in a subsequent pregnancy (among those who received PI-based cART in their current pregnancy)

	Detectable/ Total (%)	Univariable analyses			Multivariable analysis (*n*=2868)		
		OR	95% CI	*p*-value	aOR	95% CI	*p*-value
Group							
ART-naive	703/2717 (25.9)	1		0.114	1		0.571
Previous PI cART	68/311 (21.9)	0.80	(0.61-1.05)		1.09	(0.81-1.47)	
Age at delivery, yrs							
<25	183/596 (30.7)	1		0.005	1		0.002
25-34	462/1904 (24.3)	0.72	(0.59-0.89)		0.69	(0.55-0.86)	
≥35	125/527 (23.7)	0.70	(0.54-0.92)		0.65	(0.49-0.87)	
World region of origin							
UK/Ireland	100/412 (24.3)	1		0.338			
Sub-Saharan Africa	573/2278 (25.2)	1.05	(0.82-1.35)				
Elsewhere	89/309 (28.8)	1.26	(0.90-1.77)				
Time period of delivery							
2000-2002	33/78 (42.3)	1		<0.001	1		0.169
2003-2005	211/688 (30.7)	0.60	(0.37-0.97)		0.69	(0.41-1.15)	
2006-2008	349/1465 (23.8)	0.43	(0.27-0.68)		0.60	(0.37-1.00)	
2009-2010	178/797 (22.3)	0.39	(0.24-0.64)		0.69	(0.41-1.16)	
cART duration, wks							
<2	37/42 (88.1)	1		<0.001	1		<0.001
2-12	359/871 (41.2)	0.09	(0.04-0.24)		0.11	(0.05-0.29)	
13-40	357/2056 (17.4)	0.03	(0.01-0.07)		0.03	(0.01-0.08)	
Earliest CD4 count, cells/µl							
≥500	161/853 (18.9)	1		<0.001	1		<0.001
350-499	199/860 (23.1)	1.29	(1.02-1.64)		1.42	(1.10-1.84)	
200-349	249/901 (27.6)	1.64	(1.31-2.06)		1.99	(1.55-2.54)	
<200	128/309 (41.4)	3.04	(2.28-4.05)		3.97	(2.90-5.43)	

Note: All pregnancy-specific characteristics relate to current pregnancy.

When the model was restricted to pregnancies in women who received NNRTI-based cART in their current pregnancy (and the cART-experienced group included only pregnancies in women who had received NNRTI-based cART in both their previous and current pregnancy), there was no increased probability of detectable viral load in the NNRTI-experienced compared with the ART-naive group (aOR: 0.93, 95% CI: 0.47-1.83, *p*=0.828) (Table 6.7).

Table 6.7 Univariable and multivariable analyses of the association between previous NNRTI-based antenatal cART receipt and detectable viral load at delivery in a subsequent pregnancy (among those who received NNRTI-based cART in their current pregnancy)

	Detectable/ Total (%)	Univariable analyses			Multivariable analysis (*n*=1023)		
		OR	95% CI	*p*-value	aOR	95% CI	*p*-value
Group							
ART-naive	265/1031 (25.7)	1		0.367	1		0.828
Previous NNRTI cART	13/63 (20.6)	0.75	(0.40-1.40)		0.93	(0.47-1.83)	
Age at delivery, yrs							
<25	51/203 (25.1)	1		0.499	1		0.861
25-34	192/730 (26.3)	1.06	(0.74-1.52)		0.99	(0.66-1.49)	
≥35	35/161 (21.7)	0.83	(0.50-1.36)		0.86	(0.48-1.56)	
World region of origin							
UK/Ireland	28/123 (22.8)	1		0.655			
Sub-Saharan Africa	227/877 (25.9)	1.18	(0.75-1.87)				
Elsewhere	21/92 (22.8)	1.00	(0.52-1.93)				
Time period of delivery							
2000-2002	103/283 (36.4)	1		<0.001	1		0.004
2003-2005	120/531 (22.6)	0.51	(0.37-0.70)		0.55	(0.38-0.80)	
2006-2008	39/209 (18.7)	0.40	(0.26-0.62)		0.49	(0.29-0.82)	
2009-2010	16/71 (22.5)	0.51	(0.28-0.93)		0.95	(0.48-1.88)	
cART duration, wks							
<2	16/18 (88.9)	1		<0.001	1		<0.001
2-12	163/374 (43.6)	0.10	(0.02-0.43)		0.09	(0.02-0.42)	
13-40	91/673 (13.5)	0.02	(0.00-0.09)		0.02	(0.03-0.08)	
Earliest CD4 count, cells/µl							
≥500	38/174 (21.8)	1		0.484	1		0.003
350-499	49/219 (22.4)	1.03	(0.63-1.68)		1.43	(0.82-2.48)	
200-349	79/313 (25.2)	1.21	(0.78-1.88)		1.78	(1.05-3.01)	
<200	92/340 (27.1)	1.33	(0.86-2.05)		2.63	(1.54-4.50)	

Note: All pregnancy-specific characteristics relate to current pregnancy.

However, in a final model which included women who received PI-based cART (boosted or unboosted) in their current pregnancy and NNRTI-based cART in their previous pregnancy, there was a significantly increased odds of detectable viral load in the NNRTI-experienced compared with the ART-naive group (aOR: 2.12, 95% CI: 1.30-3.47, *p*=0.003) (Table 6.8). This association remained when the analysis was restricted to the 2309 women who received a boosted PI in their current pregnancy (2231 women in the ART-naive group received a boosted PI and 78 cART-experienced women); aOR: 2.18, 95% CI: 1.28-3.74, *p*=0.004 with 2183 observations in the multivariable model (details not shown as very similar to Table 6.8).

Table 6.8 Univariable and multivariable analyses of the association between previous antenatal NNRTI-based cART receipt and detectable viral load at delivery in a subsequent pregnancy (among those who received PI-based cART in their current pregnancy)

	Detectable/ Total (%)	Univariable analyses			Multivariable analysis (*n*=2659)		
		OR	95% CI	*p*-value	aOR	95% CI	*p*-value
Group							
ART-naive	703/2717 (25.9)	1		0.226	1		0.003
Previous NNRTI cART	29/92 (31.5)	1.32	(0.84-2.06)		2.12	(1.30-3.47)	
Age at delivery, yrs							
<25	171/558 (30.6)	1		0.019	1		0.004
25-34	441/1753 (25.2)	0.76	(0.62-0.94)		0.71	(0.56-0.89)	
≥35	119/497 (23.9)	0.71	(0.54-0.94)		0.65	(0.48-0.87)	
World region of origin							
UK/Ireland	97/374 (25.9)	1		0.644			
Sub-Saharan Africa	543/2110 (25.7)	0.99	(0.77-1.27)				
Elsewhere	84/297 (28.3)	1.13	(0.80-1.59)				
Time period of delivery							
2000-2002	33/77 (42.9)	1		<0.001	1		0.323
2003-2005	210/697 (30.1)	0.57	(0.36-0.93)		0.65	(0.39-1.09)	
2006-2008	342/1371 (24.9)	0.44	(0.28-0.71)		0.62	(0.38-1.03)	
2009-2010	147/664 (22.1)	0.38	(0.23-0.62)		0.64	(0.38-1.08)	
cART duration, wks							
<2	36/41 (87.8)	1		<0.001	1		<0.001
2-12	341/823 (41.4)	0.10	(0.04-0.25)		0.12	0.05-0.30)	
13-40	337/1889 (17.8)	0.03	(0.01-0.08)		0.03	(0.01-0.08)	
Earliest CD4 count, cells/µl							
≥500	155/783 (19.8)	1		<0.001	1		<0.001
350-499	186/795 (23.4)	1.24	(0.97-1.57)		1.37	(1.06-1.78)	
200-349	239/834 (28.7)	1.63	(1.29-2.05)		1.98	(1.54-2.55)	
<200	120/299 (40.1)	2.72	(2.03-3.63)		3.55	(2.59-4.87)	

Note: All pregnancy-specific characteristics relate to current pregnancy.

6.3 Risk of MTCT

Information on infant HIV status was available for 87.8% of births (5248/5977). Missing HIV status was more common in recent years due to delays in the reporting of this. However, the proportion was similar for the ART-naive and cART-experienced groups (12.1% *vs*. 13.4% respectively, *p*=0.345). The overall risk of MTCT was 1.1% (60/5248, 95% CI: 0.9-1.4). Of these 60 transmissions, 69.7% occurred in pregnancies among women who received <13 weeks antenatal cART, and 86.5% were in women with a detectable viral load at delivery (based on the imputed viral load variable). The risk was 1.2% (58/4724) among the ART-naive, and 0.4% (2/542) among the cART-experienced groups (OR: 0.31, 95% CI: 0.08-1.27, *p*=0.103).

In univariable analyses, factors associated with an increased MTCT risk were preterm delivery, earlier time period, shorter duration of antenatal cART, and emergency caesarean section delivery (Table 6.9). The final model investigating the association between previous cART exposure and MTCT included time period and duration of cART received; no other explanatory variables were included as none significantly improved the fit of the model (Wald test *p*-values: preterm delivery *p*=0.383, type of cART *p*=0.801, mode of delivery *p*=0.215, CD4 count: *p*=0.188). Delivery viral load was not considered for inclusion in the multivariable model since it is on the causal pathway. There remained no association between previous cART for PMTCT and the probability of transmission in the final model (aOR: 0.42, 95% CI: 0.10-1.78, *p*=0.241, Table 6.9). However, the number of transmissions was low, precluding investigation according to type of cART previously received.

Table 6.9 Univariable and multivariable analyses of the association between previous antenatal cART and MTCT occurring in a subsequent pregnancy

	HIV-positive infants/Total (%)	Univariable analyses			Multivariable analysis (*n*=4867)		
		OR	95% CI	*p*-value	aOR	95% CI	*p*-value
Group							
ART-naive	58/4724 (1.2)	1		0.103	1		0.241
Previous HAART	2/524 (0.4)	0.31	(0.08-1.27)		0.42	(0.10-1.78)	
Age at delivery, yrs							
<25	13/1064 (1.2)	1		0.913			
25-34	36/3330 (1.1)	0.88	(0.47-1.67)				
≥35	10/837 (1.2)	0.98	(0.43-2.24)				
World region of origin							
UK/Ireland	7/700 (1.0)	1		0.429			
Sub-Saharan Africa	50/4008 (1.3)	1.25	(0.56-2.77)				
Elsewhere	3/496 (0.6)	0.60	(0.16-2.34)				
Time period of delivery							
2000-2002	16/714 (2.2)	1		0.039	1		0.184
2003-2005	18/1773 (1.0)	0.45	(0.23-0.88)		0.46	(0.23-0.93)	
2006-2008	19/2043 (0.9)	0.41	(0.21-0.80)		0.58	(0.28-1.21)	
2009-2010	7/718 (1.0)	0.43	(0.18-1.05)		0.69	(0.26-1.80)	
cART duration, wks							
<2	9/130 (6.9)	1		<0.001	1		<0.001
2-12	30/1689 (1.8)	0.24	(0.11-0.52)		0.25	(0.12-0.55)	
13-40	17/3048 (0.6)	0.08	(0.03-0.17)		0.08	(0.03-0.19)	
Type of cART							
PI	35/3404 (1.0)	1		0.069			
NNRTI	21/1586 (1.3)	1.29	(0.75-2.23)				
NRTI	1/48 (2.1)	2.05	(0.27-15.29)				
PI & NNRTI	3/198 (1.5)	1.48	(0.45-4.86)				
Mode of delivery							
Elective caesarean	26/2584 (1.0)	1		0.037			
Emergency caesarean	22/1196 (1.8)	1.84	(1.04-3.27)				
Vaginal	12/1454 (0.8)	0.82	(0.41-1.63)				
Gestational age, wks							
≥37	46/4543 (1.0)	1		0.035			
<37	13/664 (2.0)	1.95	(1.04-3.63)				
Last CD4 count, cells/µl							
≥500	12/1597 (0.8)	1		0.085			
350-499	10/1222 (0.8)	1.09	(0.47-2.53)				
200-349	16/1250 (1.3)	1.71	(0.81-3.63)				
<200	11/565 (2.0)	2.62	(1.15-5.97)				

Note: All pregnancy-specific characteristics relate to current pregnancy.

6.4 Discussion

ART prophylaxis for PMTCT needs to be effective in reducing viral load to undetectable levels by the time of delivery, safe and well tolerated during pregnancy, and should not limit future therapy options for the woman, or indeed any HIV-positive infants. Although antenatal cART has shown to be highly effective in reducing viral loads to undetectable levels, and consequently preventing MTCT (Townsend *et al*, 2014), few studies have examined the effect of short-course therapy on response to ART in subsequent pregnancies (see Chapter 2, Section 2.5). This chapter investigated whether previous exposure to short-term cART for PMTCT was associated with the probability of detectable viral load at delivery and/or the risk of MTCT in subsequent pregnancies.

Overall probability of detectable viral load at delivery

Overall, around a quarter of women had a detectable viral load at delivery (≥50 copies/ml). This is consistent with data from other European countries and the US. For example, the proportion was 27% among women enrolled in the ECS during 1997-2004 (Patel *et al*, 2007) and 21% in the Swiss Mother and Child HIV Cohort Study during 2003-2008 (Aebi-Popp *et al*, 2010). Meanwhile, 32% of women enrolled in the US WITS during 1998-2002 had a detectable delivery viral load, defined as >400 copies/ml (Katz *et al*, 2010). In these studies, all or the vast majority of women received antenatal ART. Given that maternal viral load is the pre-eminent risk factor for MTCT (see Chapter 1, Section 1.2.3), and that all women included in the current analyses received antenatal cART, the finding that one in four women did not achieve virological suppression by delivery is of concern. Receipt of a sufficient duration of ART during pregnancy is key to the achievement of full viral suppression by delivery and thus the avoidance of MTCT (Aziz *et al*, 2013; Thorne *et al*, 2005; Townsend *et al*, 2014; Tubiana *et al*, 2010), particularly among those with high baseline viral loads (Read *et al*, 2012). Women included in the current analysis received on average 14 weeks of cART. As has been mentioned, UK guidelines have brought forward the recommended gestation by which women not requiring treatment for their own health should start antenatal ART (Taylor *et al*, 2012), similar to WHO guidelines (World Health Organization, 2013). This move is pertinent given the findings presented here. This allows more time for women to achieve an undetectable viral load, particularly those with high baseline levels. It should be borne in mind that, as shown in Chapter 5, compared with women conceiving on ART, those who initiated it during pregnancy had over four times the odds of having a detectable viral load at delivery.

Aside from duration of antenatal ART, adherence is likely a key mediator of viral suppression (Aziz *et al*, 2013; Weinberg *et al*, 2009). Though adherence tends to be better in pregnant than post-partum women, levels are still frequently below those required to achieve viral suppression. In a systematic review meta-analysis of the international literature the pooled estimate showed that 24% of pregnant women had inadequate adherence (<80% adherence) (Nachega *et al*, 2012). There is little data on adherence among HIV-positive pregnant women in the UK specifically. A small study in one centre reported that five of the 32 women eligible for inclusion were non-adherent (though the term was not defined) during pregnancy (Kingston *et al*, 2007). Meanwhile, a review of 73 women in receipt of boosted lopinavir-based cART noted poor adherence in 14% of them (Caswell *et al*, 2011). These data suggest that poor adherence may well be an important contributor to the lack of viral suppression by delivery documented in a quarter of women in the present analysis.

Type of cART received in current pregnancy and probability of detectable viral load at delivery

The analyses presented here demonstrate that NNRTI-based cART appears more effective than PI-based regimens in reducing viral load to undetectable levels during pregnancy[56]. Almost all women receiving NNRTI-based cART took a nevirapine-containing regimen. The evidence on the relative effectiveness of PIs and NNRTIs varies. A comprehensive review and meta-analysis conducted by Chou *et al* in 2006 reported that in a direct meta-analysis of 'head-to-head' trials comparing PI-based and NNRTI-based regimens found NNRTI-based regimens to be more effective in viral suppression (OR 1.60, 95% CI: 1.31−1.96). By contrast, indirect comparisons drawn between studies showed NNRTIs to be less effective than PIs. The authors suggest that indirect comparisons may be unreliable in the context of HARRT due to the complex nature of the regimens used, variations between studies and changes over time (Chou *et al*, 2006). A recent meta-analysis including four studies which examined the effectiveness, in terms of viral suppression by 48 weeks, of nevirapine-based cART compared with ritonavir-boosted PI regimens reported no significant difference (risk ratio: 0.90; 95% CI: 0.77-1.06), and the findings of the four individual studies were homogeneous in this respect (Kawalec *et al*, 2013). Among pregnant women specifically, the evidence is also inconclusive. The ECS reported a shorter time to achieving undetectable viral load among pregnant women starting nevirapine-based cART compared with PI-based cART, adjusting for baseline viral load and other factors (Patel *et al*, 2007). However, most women received nelfinavir which, as an unboosted PI, has been shown to be inferior to ritonavir-boosted regimens (Walmsley *et al*, 2002). An analysis of the US

[56] A finding also demonstrated in the analyses of the association between timing of ART initiation and the risk of detectable viral load at delivery (Chapter 5), though neither analysis was specifically designed to compare the effectiveness of NNTRI and PI based regimens *per se.*

WITS data for 1998-2005 reported no significant association between the type of ART received and the risk of detectable viral load, though the numbers in each group were relatively small (Katz *et al*, 2010). However, data from three US centres revealed that pregnant women receiving NNTRI-based therapy achieved a viral load of <400 copies/ml more rapidly than those receiving PIs (aHR: 2.48, IQR: 1.33–4.63) (Aziz *et al*, 2013). Meanwhile, an analysis of data from five UK centres reported a shorter time to undetectable viral load for PI compared with NNRTI-based regimens (nevirapine-based in all but one woman) with a HR of 0.70 (95% CI: 0.52–0.94) (Read *et al*, 2012).

When comparing the findings of such studies it should be remembered that there are variations between studies in the specific drugs used, the populations studied, and the confounders adjusted for. Indications for treatment, which often cannot be accounted for, may also have a significant impact. In the present analysis, two-thirds of PI regimens were boosted and the increased risk of detectable virus among those receiving PIs remained when comparing boosted PIs with NNRTI-based regimens. This could in part relate to the fact that higher adherence may be required for PI-based regimens in order to achieve virological suppression (Maggiolo *et al*, 2005), while less than 95% adherence to NNRTI-based regimens can be sufficient (Bangsberg, 2006). Of course, the type, frequency and severity with which side effects are experienced may impact on adherence. For example, lopinavir/ritonavir (Kaletra®) is the most commonly used boosted PI in this population; of the women in these analyses who received a boosted PI-based regimen, most (81%, 2605/3207) took Kaletra®. Though this is generally a well-tolerated drug, the most common side-effects are those of a gastrointestinal nature including nausea and vomiting (Croxtall *et al*, 2010) which may exacerbate common symptoms of pregnancy. Another relevant issue is that nevirapine-based cART is only recommended for those with low CD4 counts (<250 cells/µl) (de Ruiter *et al*, 2008; Taylor *et al*, 2012) because of the potential risk of hepatotoxicity in those with better functioning immune systems (Dieterich *et al*, 2004; Lyons *et al*, 2006; Sanne *et al*, 2005). This may also introduce some confounding by indication with regard to the type of ART received, because women with low CD4 counts may have high baseline viral loads, which are associated with an increased time to viral suppression. Furthermore, there is some evidence that higher CD4 counts may be independently associated with a more rapid reduction in viral load after ART initiation (Aziz *et al*, 2013; Read *et al*, 2012). In the present analyses this was taken into account by adjusting for CD4 counts in the multivariable models.

Influence of previous short-course cART on the probability of detectable viral load at delivery

Overall, there was weak evidence of an increased risk of detectable viral load at delivery among the cART-experienced group in the multivariable analysis (aOR: 1.27, 95% CI: 1.01-1.60). In the US, Katz *et al* reported an overall increased risk of detectable viral load at delivery among cART-experienced women (37% among the cART experienced compared with 24% among the cART-naive), though the cART-experienced group was not restricted to those previously exposed solely for PMTCT (Katz *et al*, 2010). Meanwhile, no overall difference was observed in an Irish study (Lyons *et al*, 2005a) (details of previous studies on this topic are provided in Chapter 2, Section 2.5). However, when the association in the present analysis was explored according to type of cART previously received an increased risk was apparent only among women who had received NNRTI-based cART (aOR: 1.81, 95% CI: 1.25-2.63), and not among those with prior PI-based cART exposure (aOR: 1.08, 95% CI: 0.81-1.45).

The presence of resistance mutations, and an increased risk of subsequent virological failure, has been documented in women exposed to ART for PMTCT, particularly nevirapine-containing regimens (Arrive *et al*, 2007; Paredes *et al*, 2013). In the present study, all women who received NNRTI-based cART in their previous pregnancy had taken a regimen containing nevirapine. Resistance data is not collected by the NSHPC but the fact that women with previous NNRTI-based cART exposure were at increased risk of not achieving virological suppression compared with ART-naive women could reasonably be considered to be due to the development of resistance to nevirapine. However, interestingly, when the association was investigated further, it emerged that the increased risk only applied to women who were exposed to NNTRI-based cART during their first pregnancy and subsequently received PI-based regimens, but not those receiving repeat NNRTI-based therapy. This may reflect differences in indication for the type of cART received. Drug resistance testing is recommended for all women discontinuing ART after delivery (Taylor *et al*, 2012), and type of ART given in any subsequent pregnancy should depend on the results. Women receiving NNRTIs in more than one pregnancy may therefore represent a group who were relatively straightforward to manage e.g. presented early and had no adherence issues thus increasing their probability of achieving viral suppression. Meanwhile, women who had adherence problems in their first pregnancy, or were more complex cases to manage for a variety of social and behavioural reasons, may have been more likely to be prescribed a PI in their subsequent pregnancy, particularly since boosted PIs are now the regimen of choice for short-course antenatal ART in the UK (Taylor *et al*, 2012). Furthermore, as mentioned, those starting nevirapine-based regimens during pregnancy should have only been those with low CD4 counts who required

treatment for their own health (de Ruiter *et al*, 2008; Hawkins *et al*, 2005; Taylor *et al*, 2012). It would therefore likely have been planned that they would continue treatment after delivery. The women who did stop at some point after delivery may well have decided to do so themselves rather than having a structured treatment interruption overseen by their clinician. Again, this ties in with such women being initiated on PI-based regimens in their subsequent pregnancies.

Meanwhile, that there was no increased risk of detectable viral load among women who received PI-based cART in both their previous and current pregnancy is consistent with the findings of the French Perinatal Cohort. The authors reported no evidence of an increased risk of detectable viral load among women receiving antenatal PI-based cART who had been exposed to cART (mostly, 93%, PI-based) for PMTCT during a previous pregnancy (Briand *et al*, 2011). This is also consistent with the lack of genotypic resistance to PI-based cART following short-course therapy for PMTCT observed in Germany (Gingelmaier *et al*, 2010) and in the Mma Bana study in Botswana (Souda *et al*, 2013). However, some studies have reported the development of PI resistance mutations, to nelfinavir in particular, following the use of PI-based cART for PMTCT (see Chapter 2, Section 2.5).

There has been a significant shift towards the use of boosted PI-based regimens for pregnant women in the UK and Ireland, and this regimen has predominated since 2005. Since the majority of women are therefore now receiving boosted PI-based cART (85% of the study population in 2010), these findings are reassuring in terms of potential future pregnancies for women whose index pregnancy occurred in recent years. Meanwhile, although the use of NNRTI-based cART declined significantly between 2000 and 2006, it has been quite stable since then; in 2010 16% of women received this regimen (consistent with the low proportion of women with severe immunosuppression). It is important that any ART discontinuations among this group are structured as outlined in UK guidelines (Taylor *et al*, 2012).

Influence of previous short-course cART on the risk of MTCT

The risk of vertical transmission was 1.2% among ART-naive women and 0.4% among those with previous cART exposure. There was no association in the multivariable analysis (p=0.241), though the number of transmissions was low and power was therefore limited. Previous studies have not specifically assessed the association between prior exposure to cART for PMTCT and MTCT in subsequent pregnancies, although Lyons *et al* reported no increased risk of HIV transmission in repeat compared with index pregnancies (Lyons *et al*, 2005a). However, the study also had limited power. The lack of an association is consistent

with there being little increased risk of detectable viral load overall, and the fact that even where delivery viral load was detectable, levels were generally low.

Limitations

A limitation of the NSHPC data for these analyses is that only information on ART received in relation to pregnancy is collected. Therefore it has been assumed that if a woman did not conceive her first pregnancy on ART then she has not previously received cART (i.e. is ART-naive). It is possible that some women may have previously received ART for their own health and subsequently stopped. However, this is likely to only apply to a small proportion of women and any such misclassification is likely non-differential so will only have attenuated the associations between previous cART exposure and the outcomes. Some women who were born abroad may also have been exposed to ART during previous pregnancies prior to arriving in the UK or Ireland.

That no information was available on the presence of resistance mutations hinders the interpretation of the findings. The lack of evidence of an increased risk of detectable viral load at delivery among women who received either repeat NNRTI-based cART or repeat PI-based cART suggests that resistance may not be a significant issue in this population. However, this assertion would need to be verified by obtaining drug resistance profiles for the women reported to the NSHPC. Indeed, as mentioned, women in whom resistance mutations were detected may have consequently received a different drug combination from the same class in their subsequent pregnancy. Some measure of women's level of adherence to ART during pregnancy would also aid interpretation of the findings.

Reported viral load close to delivery was missing for 45% of women, a potentially important limitation. However, the use of an imputed variable increased available data thus providing greater power to detect associations. Sensitivity analyses supported the use of the imputed variable. It was not felt appropriate to adjust baseline viral load in these analyses (notwithstanding that this is an important predictor of delivery viral load) because earlier undetectable viral loads were used to impute viral load at delivery where this was missing. Since baseline viral loads were not significantly different in the ART-naive and cART-experienced groups (p=0.371) this was unlikely to have been an important confounder overall.

6.5 Key findings

- There were 5372 pregnancies in ART-naive women who started cART after conception, and 605 in women who had received short-term cART in their previous pregnancy

- cART was received for a median of 14.1 weeks (IQR: 10.7-17.6) and in around a quarter of pregnancies there was a detectable viral load at delivery

- The risk of detectable viral load at delivery was 26.2% among ART-naive women and 24.3% among the cART-experienced

- Overall, there was weak evidence of an increased risk of detectable viral load at delivery in the cART-experienced group compared with the ART-naive group in adjusted analyses (aOR: 1.27, 95% CI: 1.01-1.60)

- In stratified analyses an increased risk of detectable viral load at delivery was apparent only among women who previously received NNRTI-based cART (aOR:1.81, 95% CI: 1.25-2.63), and not among those with PI-based cART exposure (aOR:1.08, 95% CI: 0.81-1.45)

- The risk of MTCT was 1.2% (58/4724) among the ART-naive, and 0.4% (2/542) among the cART-experienced groups (OR: 0.31, 95% CI: 0.08-1.27, p=0.103)

- In multivariable analyses there was no association between previous cART for PMTCT and the probability of MTCT (aOR: 0.42, 95% CI: 0.10-1.78, p=0.241) though the number of transmissions was low with only two transmissions in the cART experienced group

Chapter 7 Adverse pregnancy and perinatal outcomes, and mode of delivery

This chapter focuses largely on the perinatal period, firstly exploring adverse pregnancy and perinatal outcomes in HIV-positive women's sequential pregnancies, and then investigating trends and patterns in mode of delivery.

7.1 Adverse pregnancy and perinatal outcomes

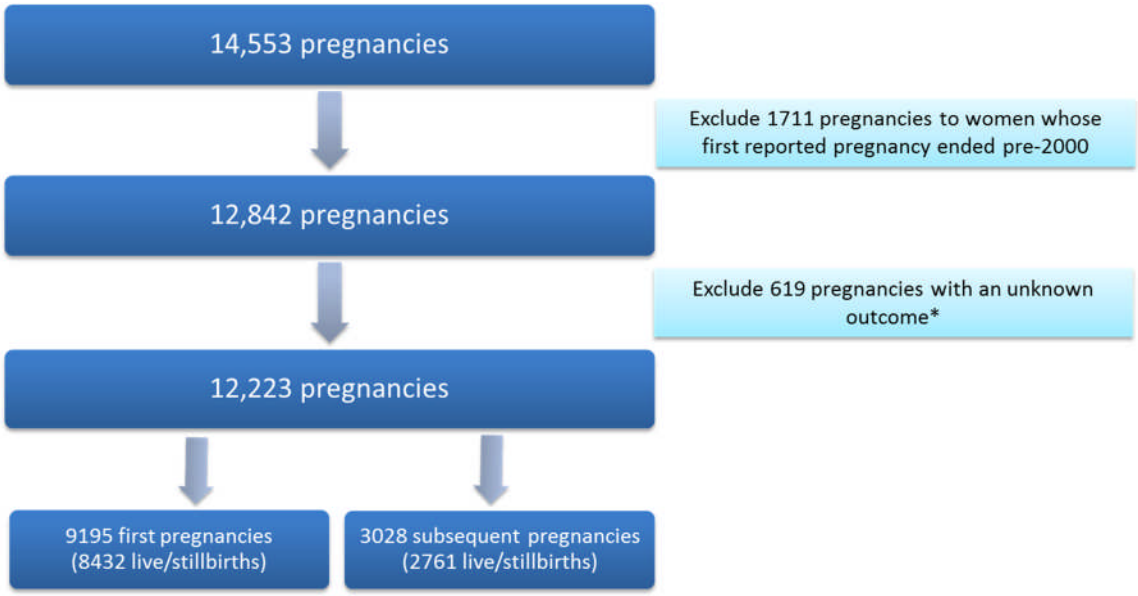
As discussed in Chapter 2, Section 2.6, there is evidence to suggest that HIV-positive women may be at greater risk of adverse perinatal outcomes such as preterm delivery, low birthweight and stillbirth compared with the general population. Furthermore, these women may be at additional risk at their repeat pregnancies compared with index pregnancies. For example, they will be older, have been living with HIV for longer, and may be more likely to conceive on ART. The first part of this chapter explores the probability of adverse pregnancy and perinatal outcomes (stillbirth, miscarriage, preterm delivery, low birthweight, congenital abnormalities) among women's repeat pregnancies. Risk factors for preterm delivery are also investigated in this group (Objective 5). Utilising data on these repeat pregnancies also enables the exploration of the influence of factors such as previous preterm delivery and inter-pregnancy interval on preterm delivery risk, which are often not assessed or accounted for in studies of preterm delivery among HIV-positive women.

7.1.1 Methods

Dataset

All repeat (second and subsequent) pregnancies during 2000-2010 to women whose first reported pregnancy ended in 2000 or later were included. A comparison group of index pregnancies reported during the same period was also utilised (Figure 7.1). Women's pregnancies were assigned a 'pregnancy number' (i.e. first, second, third, among all reported pregnancies for each woman irrespective of outcome), even for analyses that were subsequently restricted to live and stillbirths. Women classed as being of 'older' or 'advanced' maternal age were those aged ≥35 years at delivery (or end of pregnancy for outcomes other than a live or stillbirth), a commonly used cut-off (Brown *et al*, 2012; Cleary-Goldman *et al*, 2005; Fretts *et al*, 1995; Liuzzi *et al*, 2013; Nabukera *et al*, 2008).

Figure 7.1 Study population flow chart – adverse pregnancy and perinatal outcomes analyses



*Excludes pregnancies where the outcome was not reported to be either a live birth, stillbirth, miscarriage (including ectopic pregnancy), or termination

Pregnancy outcomes

Descriptive analyses of pregnancy outcomes (live birth, stillbirth, miscarriage, termination) included all repeat pregnancies with a known pregnancy outcome, and a comparison group of first reported pregnancies with known outcomes. Definitions of pregnancy outcomes, including stillbirth and miscarriage, are provided in Chapter 3, Section 3.1.5.

Preterm delivery

These analyses included pregnancies resulting in a live or stillbirth. Preterm delivery was defined as a delivery at <37 gestational weeks. For some sub-analyses preterm was further restricted to include only infants born at <35 weeks and at <32 weeks. 'Previous preterm delivery' was coded as 'yes' if the woman had had one or more previous preterm deliveries (<37 weeks) ever reported to the NSHPC. Information on whether any previous unreported deliveries (e.g. those that occurred before the woman was diagnosed with HIV or prior to her arrival into the UK or Ireland) were preterm is not collected by the NSHPC. Since UK guidelines state that elective caesarean sections for PMTCT should be scheduled for 38-39 weeks (Taylor *et al*, 2012), elective caesarean sections carried out solely for PMTCT should not influence the rate of preterm deliveries.

Low birthweight

Birthweight has been collected through the NSHPC paediatric scheme since its inception, and began to also be collected through the obstetric scheme in 2002. Low birthweight was defined as <2.5kg, and very low birthweight as <1.5kg (World Health Organization, 2010b). Birthweight *z*-scores[57] by sex and gestational age were calculated for the study population using the British 1990 growth reference population as the standard. This standard population was created using the LMS method which uses three curves; the median (M), coefficient of variation (S) and skewness (L) to summarise the changing distribution of a measurement, in this case birthweight, by age (Cole *et al*, 1992). The software is freely available including the reference population (Pan *et al*, 2012). A *z*-score of zero indicates that the baby's birthweight is the mean, for that gestation and gender, of the birthweight in the British standard population. Infants with a negative *z*-score have a lower birthweight than the standard population mean.

Congenital abnormalities

Abnormalities were categorised using WHO International Classification of Diseases (World Health Organization, 2010b). The following abnormalities were classified as minor: polydactyly, malformed ear, abnormalities of the feet, minor mouth abnormalities, undescended testes, accessory nipple, spinal hairy patch, strawberry nevi, skin tag, and subclinical sub-ependymal cysts, in line with previous analyses of the NSHPC dataset (Townsend *et al*, 2009). For infants with more than one abnormality only the most major was included in the analysis. Information is presented at the pregnancy, rather than infant, level for consistency with other analyses in this chapter. For multiple pregnancies, an abnormality was coded as being present if either twin was recorded as having an abnormality.

Statistical analyses

The main aim of the analyses was to explore adverse outcomes, preterm delivery in particular, among repeat pregnancies. Some important exposures of interest, such as birth-to-pregnancy intervals and history of previous adverse outcomes, are only available for repeat pregnancies. Therefore, although a comparison group of first reported pregnancies was used for some descriptive analyses, detailed univariable and multivariable analyses focused on repeat pregnancies. This was so that the associations between such exposures and pregnancy outcomes could be fully explored. Logistic regression models were used to identify demographic, clinical and immunological predictors of preterm delivery. Robust

[57] These are standard deviation scores, which indicate the distance, in standard deviations, of an individual's birthweight from the mean birthweight of a specified reference population.

standard errors were used to adjust for clustering since women may contribute more than one repeat pregnancy to the dataset (Kirkwood *et al*, 2003) (see Chapter 3, Section 3.5).

It is well documented that women who have multiple pregnancies are at higher risk of preterm delivery (Goldenberg *et al*, 2008; Steer, 2005). However, they were included here as an exposure of interest because there is little current data on the magnitude of increased risk of outcomes such as preterm delivery among multiple pregnancies in HIV-positive women since they are often excluded from analyses from the outset (Lopez *et al*, 2012; Sibiude *et al*, 2012; Townsend *et al*, 2007). Where the time elapsed between pregnancies was explored as an exposure, the birth-to-pregnancy rather than birth-to-birth interval was used to avoid overestimation of the association between the birth interval and adverse pregnancy outcomes. For example, if a second pregnancy results in a preterm delivery, then the interval between the previous and current birth will be shorter than if the second delivery had been at term (Conde-Agudelo *et al*, 2006; Shachar *et al*, 2013). The birth-to-pregnancy interval was categorised as <6, 6-17, 18-35, 36-59, and ≥60 months. In the study population there was a right-skewed distribution of birth-to-pregnancy intervals hence the smaller groupings for the more common, shorter intervals. The association between the birth-to-pregnancy interval and adverse pregnancy outcomes is commonly represented by a J-shaped curve (Conde-Agudelo *et al*, 2006). Therefore, one of the lowest risk middle categories of birth-to-pregnancy interval (36-59 months) was used as the baseline for univariable and multivariable analyses. Viral load at delivery was not considered as a potential predictor of preterm delivery in these analyses due to the potential for reverse causality (i.e. women delivering early may not have had the opportunity to receive a sufficient duration of antenatal ART to reduce viral load to undetectable levels) (Bailey *et al*, 2011).

7.1.2 Study population

These analyses included 3028 repeat pregnancies (97.0% of all repeat pregnancies – the remaining 3% were those for which the outcome of the pregnancy was unknown e.g. the pregnancy was continuing to term, or the woman had gone abroad). Of these, 2737 (90.4%) resulted in a live birth, 24 (0.8%) in a stillbirth, 199 (6.6%) a miscarriage, and 68 (2.2%) in a termination. Of the 2761 live and stillbirths, there were 2713 singletons and 48 sets of twins (all twin pregnancies resulted in a live birth). In addition to the repeat pregnancies, there were 9195 index pregnancies with a known outcome including 8432 live and stillbirths.

7.1.3 Characteristics of first and repeat pregnancies

Table 7.1 shows the key characteristics of the first and repeat pregnancies. At their repeat pregnancies, women were significantly older than in their index pregnancies (31.9 years, IQR: 28.2-35.4 *vs*. 30.3 years, IQR: 26.5-34.3, $p<0.001$), and over a quarter (27.6%) were aged ≥35 years, with 5.0% being aged ≥40 years. There was a significant secular increase in the proportion of pregnancies that were in women aged ≥35 years (e.g. from 15.9% in 2003 to 33.9% in 2010, $p<0.001$). At their index pregnancy 42.7% of women were nulliparous. Women were significantly more likely to conceive their repeat pregnancies while on ART (48.8% *vs*. 21.9%, $p<0.001$), and less likely to be immunosuppressed (8.5% had a CD4 <200 cells/μl compared with 15.7% at their first pregnancy, $p<0.001$). They were also more likely to have suppressed viral load by the time of delivery in their repeat pregnancies (83.5% *vs*. 73.7%, $p<0.001$). Of note, the proportion of repeat pregnancies conceived on treatment increased significantly in more recent years (from 40.7% in 2005 to 61.5% in 2010, test for trend: $p<0.001$).

Information on the interval between the date of delivery of women's previous live birth (reported to the NSHPC) and the start of their subsequent pregnancy was available for 2561 repeat pregnancies. The median interval was 1.8 years (IQR: 0.9-3.1 years), 43.2% were conceived in less than 18 months, and 10.7% in less than six months.

Table 7.1 Adverse pregnancy and perinatal outcomes analyses - characteristics of women in their first and subsequent pregnancies

Characteristic	First pregnancies		Subsequent pregnancies		*p*-value
	n	**%**	***n***	**%**	
Age at delivery, yrs (*n*=12,175)					
<25	1602	17.5	314	10.4	<0.001
25-29	2793	30.5	796	26.3	
30-34	2794	30.5	1081	35.7	
35-39	1589	17.4	684	22.6	
≥40	371	4.1	151	5.0	
Ethnic group (*n*=12,049)					
White	1205	13.4	429	14.2	0.585
Black African	6998	77.6	2368	78.2	
Other	819	9.1	230	7.6	
Time period of delivery* (*n*=12,223)					
2000-2002	1549	16.8	102	3.4	<0.001
2003-2005	2883	31.4	622	20.5	
2006-2008	3066	33.3	1224	40.4	
2009-2010	1697	18.5	1080	35.7	
HIV risk factor (*n*=11,517)					
Other**	8349	97.6	2896	97.8	0.489
Injecting drug use	207	2.4	65	2.2	
Pregnancy type (*n*=12,223)					
Singleton	9039	98.3	2980	98.4	0.678
Twin/triplet	156	1.7	48	1.6	
On ART at conception (*n*=11,562)					
No	6909	78.1	1392	51.2	<0.001
Yes	1935	21.9	1326	48.8	
Parity (*n*=8194)					
Nulliparous	3496	42.7	-	-	-
Parous	4698	57.3	-	-	
Earliest CD4 count, cells/µl (*n*=9770)					
≥500	2106	28.6	827	34.5	<0.001
350-499	1909	25.9	720	30.0	
200-349	2202	29.9	648	27.0	
<200	1154	15.7	204	8.5	
Viral load at delivery, copies/ml (*n*=8619)* **					
<50	4664	73.3	1885	83.5	<0.001
≥50	1697	26.7	373	16.5	

*Expected year of delivery for outcomes other than a live or stillbirth

**Other comprises largely those originating from a high HIV prevalence area and/or with heterosexual exposure to HIV

***Based on the imputed viral load variable (see Chapter 3, Section 3.4)

7.1.4 Pregnancy outcomes among first and repeat pregnancies

Table 7.2 shows pregnancy outcomes according to pregnancy number, including first reported pregnancies as a comparison group. The live birth rate was very similar at around 90%, irrespective of pregnancy number, except for fifth and sixth births for which it was much lower at 78.6%. The probability of stillbirth was 0.9% overall, and was slightly, but not significantly, lower among repeat compared with first pregnancies (0.8% *vs*. 1.0%, p=0.440), perhaps because miscarriages were more common among repeat pregnancies (6.6% *vs*. 4.7%, p<0.001). However, this increased risk of reported miscarriage needs to be interpreted with caution as ascertainment may be an issue. At their repeat pregnancies women are, by definition, previously diagnosed and miscarriages among this group may be more likely to be reported to the NSHPC, an issue which is discussed in more depth in the discussion section of this chapter. The increased risk among repeat pregnancies remained after adjusting for maternal age (p=0.002), but was attenuated (p=0.282) after adjusting for the fact that women were more likely to be on ART at conception of their repeat pregnancy (which could simply reflect the better reporting of miscarriages among women already on ART at conception). The probability of reported miscarriage was particularly high for the fourth pregnancies (8.9%) and fifth pregnancies (14.3%) (p=0.065 and p=0.092 respectively when compared with first reported pregnancies), although the numbers were small. Only one woman had a sixth pregnancy reported and this ended in a miscarriage. Terminations were less common among repeat than first reported pregnancies (2.2% *vs*. 3.6%, p<0.001).

When the group for analysis was restricted to women who were known to be nulliparous at the time of their first reported pregnancy, the live birth rate was slightly lower among the repeat pregnancies (90.9% *vs*. 92.7%, p=0.042), there remained no significant difference in the stillbirth rate (1.0% *vs*. 1.1%, p=0.605) and miscarriage remained more common among the repeat pregnancies (5.7% *vs*. 4.0%, p=0.012). Women were still slightly less likely to have termination at their repeat pregnancy although the difference was no longer significant (2.2% *vs*. 2.5%, p=0.585).

Table 7.2 Pregnancy outcomes according to pregnancy number

Outcome	Pregnancy												Total among repeat pregnancies	
	1st		2nd		3rd		4th		5th		6th			
	n	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
Live birth	8345	90.8	2175	90.3	470	91.4	81	90.0	11	78.6	0	0.0	2737	90.4
Stillbirth	87	1.0	22	0.9	2	0.4	0	0.0	0	0.0	0	0.0	24	0.8
Miscarriage*	434	4.7	155	6.4	33	6.4	8	8.9	2	14.3	1	100.0	199	6.6
Termination	329	3.6	57	2.4	9	1.8	1	1.1	1	7.1	0	0	68	2.2
Total	9195	100	2409	100	514	100	90	100	14	100	1	100	3028	100

*Includes ectopic pregnancies

Focusing on the repeat pregnancy group, the 24 stillbirths occurred at a median gestational age of 31.5 weeks (IQR: 29.0-38.0 weeks). One woman had two stillbirths reported. Those aged ≥35 years appeared to be at slightly higher risk than younger women (1.0% *vs*. 0.8%) though this was not statistically significant (p=0.784). There were also seven reported neonatal deaths among the live born infants (a rate of 2.6 per 1000). Of these, five were born very preterm (<32 weeks), one was 32-34 weeks, and the remaining infant was born at term but had a major congenital abnormality.

Of the 199 miscarriages four were ectopic pregnancies. The median gestational age at miscarriage was 12.0 weeks (IQR: 9.0-14.0 weeks). There were 20 late miscarriages (≥20 completed weeks gestation). A total of 33 women had more than one miscarriage reported (one woman had four, two women had three, and 30 women had two). Having a miscarriage, rather than a live birth, was significantly more common among those aged ≥35 years compared with those <35 years (10.2% (83/813) *vs*. 5.4% (115/2121), p<0.001), and was particularly prevalent among those aged ≥40 years (13.9%).

Among the 68 terminations the median gestational age was 10.0 weeks (IQR: 9.0-14.5). There were four terminations carried out at 24 weeks, all had major congenital abnormalities; two had severe chromosomal abnormalities, and the remaining two had multiple abnormalities, the most significant being a cleft lip/palate in one and a digestive abnormality in the other. There were no terminations carried out after 24 weeks.

Infant HIV status was reported for 84.3% of live births (2306/2737) in the repeat pregnancy group; 13 infants (0.47%) were known to have acquired HIV. None of these women were reported to have had more than one HIV-positive infant.

7.1.5 Preterm delivery

Information on gestational age was available for 98.3% (2715/2761) of the repeat pregnancies ending in a live or stillbirth. The median gestational age at delivery was 38 weeks (IQR: 37-39). The proportion of preterm deliveries (<37 weeks) was 13.1% (355/2715), including 82 (3.0%) very preterm (<32 weeks). The proportion of singleton repeat pregnancies that were preterm was 12.4%. Among those deliveries that were preterm, the median gestational age was 34 weeks (IQR: 32-36). The risk of preterm delivery was similar though slightly but not significantly (p=0.240) lower among repeat than first reported pregnancies (1161/8311, 14.0%). The findings were similar if restricted to women who were nulliparous at their first reported pregnancy (12.9% in repeat and 14.0% in first pregnancies, p=0.280). Subsequent analyses are based on repeat pregnancies only.

As shown in Table 7.3, 40.8% of preterm deliveries were in women who had a history of preterm delivery. Pregnancies in women belonging to the white ethnic group accounted for 18.9% of preterm deliveries but only 11.7% of term deliveries and, likely related to this, women with a history of injecting drug use accounted for 4.6% of preterm deliveries and only 1.9% of those that were at term. Not surprisingly, multiple pregnancies accounted for a much larger proportion of preterm than term deliveries (6.8% *vs*. 1.0%). Women who were severely immunosuppressed accounted for 12.2% of preterm and 5.2% of term deliveries and, tying in with this, 5.3% of preterm deliveries were in symptomatic women compared with 2.0% of those delivered at term.

Table 7.3 Comparison of the characteristics of women with preterm and term deliveries

Characteristic	Preterm		Term		*p*-value
	n	%	*n*	%	
History of preterm delivery (*n*=2429)					
No	173	59.2	1885	88.2	<0.001
Yes	119	40.8	252	11.8	
Age at delivery, yrs (*n*=2714)					
<25	39	11.0	245	10.4	0.576
25-29	97	27.3	620	26.3	
30-34	120	33.8	871	36.9	
35-39	78	22.0	522	22.1	
≥40	21	5.9	101	4.3	
Birth-to-pregnancy interval, mths* (*n*=2311)					
<6	39	14.3	202	9.9	0.201
6-17	84	30.8	663	32.5	
18-35	87	31.9	629	30.9	
36-59	43	15.8	386	18.9	
≥60	20	7.3	158	7.8	
Ethnic group (*n*=2715)					
White	67	18.9	276	11.7	0.001
Black African	263	74.1	1885	79.9	
Other	25	7.0	199	8.4	
Time period of delivery (*n*=2715)					
2000-2002	14	3.9	73	3.1	0.214
2003-2005	84	23.7	459	19.4	
2006-2008	138	38.9	975	41.3	
2009-2010	119	33.5	853	36.1	
HIV risk factor (*n*=2653)					
Other**	332	95.4	2262	98.1	0.001
Injecting drug use	16	4.6	43	1.9	
Pregnancy type (*n*=2715)					
Singleton	331	93.2	2337	99.0	<0.001
Twin/triplet	24	6.8	23	1.0	
HIV/AIDS symptoms (*n*=1950)					
No	248	94.7	1655	98.0	0.001
Yes	14	5.3	33	2.0	
On ART at conception (*n*=2488)					
No	161	49.2	1137	52.6	0.254
Yes	166	50.8	1024	47.4	
Earliest CD4 count, cells/µl (*n*=2342)					
≥500	99	32.7	796	39.0	<0.001
350-499	82	27.1	650	31.9	
200-349	85	28.1	487	23.9	
<200	37	12.2	106	5.2	
Type of ART (*n*=2654)					
None	6	1.7	31	1.3	0.366
Mono/dual	14	4.0	118	5.1	
cART - PI-based	202	58.2	1343	58.2	
cART - NNRTI-based	99	28.5	696	30.2	
cART - other***	26	7.5	119	5.2	

*Only includes pregnancies to women whose previous pregnancy resulted in a live birth

**Other comprises largely those originating from a high HIV prevalence area and/or with heterosexual exposure to HIV

***Includes PI and NNRTI, NRTI only and unspecified

In the univariable analyses (Table 7.4) a history of preterm delivery was strongly associated with the preterm delivery in current pregnancy; the probability of preterm delivery was 8.4% in those who had not had a previous preterm delivery reported, and 32.1% in those who had, giving an unadjusted odds ratio for the association between previous preterm delivery and subsequent preterm delivery of: 5.15, 95% CI: 3.90-6.79. Other factors associated with preterm delivery were white ethnicity, multiple pregnancy, a history of injecting drug use, maternal HIV/AIDS symptoms, and a low CD4 count. Although overall there was no evidence of an association between birth-to-pregnancy interval and preterm delivery, those with an interval of <6 months were at significantly increased risk compared with the baseline group (with an interval of 36-59 months): OR: 1.73, 95% CI: 1.09-2.76. There was little evidence of an association between preterm delivery and maternal age although there was an indication of a higher odds among those aged ≥40 years (unadjusted OR compared with the 30-34 year age group: 1.51, 95% CI: 0.92-2.48). Time period of delivery was not significantly associated with preterm delivery, and there was little evidence of an association between being on ART at conception and preterm delivery (p=0.253). Antenatal exposure to cART (compared with mono/dual therapy) has been previously linked with preterm delivery in the UK, including previous analyses of the NSHPC data (Martin *et al*, 2007; Short *et al*, 2013; Townsend *et al*, 2007). In this analysis, although there was a trend towards an increased probability among those on cART, this was not significant, likely due to the fact that there were only 14 preterm deliveries in the mono/dual baseline group.

The multivariable model (Table 7.4) included previous preterm delivery, maternal ethnic group, HIV risk factor, pregnancy type and antenatal CD4 count closest to delivery. Although the presence of HIV/AIDS symptoms was associated with preterm delivery in the univariable analysis, this variable was not included in the multivariable model since it is correlated with CD4 count and was also missing for 28.2% of pregnancies. Previous preterm delivery was strongly associated with preterm delivery in the multivariable model (aOR: 5.60, 95% CI: 4.13-7.59). Compared with white women, black African women had a lower odds of preterm delivery, as did those belonging to other ethnic groups. Multiple pregnancies remained strongly associated with an increased probability of preterm delivery (aOR: 9.63, 95% CI: 5.05-18.35), as did having a CD4 count of <200 cells/ɱl (aOR: 2.80, 95% CI: 1.72-4.55). After adjusting for the other variables in the model, the association between having a history of injecting drug use and preterm delivery was attenuated, though numbers were small. There was little evidence from the Wald test that any of the remaining variables improved the fit of the model; time period (p=0.333), whether the woman was on ART at conception (p=0.657), maternal age at delivery (p=0.398) or type of antenatal ART received (p=0.621). There was also no evidence to include birth-to-pregnancy interval in the model (p=0.854), and, if this variable was included in the multivariable model, there was no longer any evidence that intervals of <6 months were associated with an increased risk

of preterm delivery compared with intervals of 36-59 months (aOR: 1.25, 95% CI: 0.72-2.18).

When the model was re-run with the outcome defined as preterm delivery at <35 completed gestational weeks (rather than <37 weeks) but keeping all other variables constant (including previous preterm delivery being defined as a previous delivery at <37 weeks), the association between previous and subsequent preterm delivery was even stronger (aOR: 6.94, 95% CI: 4.73-10.19, $p<0.001$), and stronger still when the outcome was defined as <32 weeks (aOR: 7.73, 95% CI: 4.40-13.58, $p<0.001$).

Table 7.4 Univariable and multivariable analyses of factors associated with preterm delivery among repeat pregnancies

	Preterm/Total (%)	Univariable analyses			Multivariable analysis (*n*=2057)		
		OR	95% CI	*p*-value	aOR	95% CI	*p*-value
History of preterm delivery							
No	173/2058 (8.4)	1		<0.001	1		<0.001
Yes	119/371 (32.1)	5.15	(3.90-6.79)		5.60	(4.13-7.59)	
Age at delivery, yrs							
<25	39/284 (13.7)	1.16	(0.77-1.73)				
25-29	97/717 (13.5)	1.14	(0.85-1.52)				
30-34	120/991 (12.1)	1		0.579			
35-39	78/600 (13.0)	1.08	(0.79-1.48)				
≥40	21/122 (17.2)	1.51	(0.92-2.48)				
Birth-to-pregnancy interval, mths*							
<6	39/241 (16.2)	1.73	(1.09-2.76)				
6-17	84/747 (11.2)	1.14	(0.77-1.67)				
18-35	87/716 (12.2)	1.24	(0.85-1.82)				
36-59	43/429 (10.0)	1		0.198			
≥60	20/178 (11.2)	1.14	(0.65-1.99)				
Ethnic group							
White	67/343 (19.5)	1		0.002	1		<0.001
Black African	263/2148 (12.2)	0.57	(0.42-0.79)		0.46	(0.30-0.69)	
Other	25/224 (11.2)	0.52	(0.31-0.85)		0.38	(0.20-0.71)	
Time period of delivery							
2000-2002	14/87 (16.1)	1		0.224			
2003-2005	84/543 (15.5)	0.95	(0.52-1.75)				
2006-2008	138/1113 (12.4)	0.74	(0.41-1.33)				
2009-2010	119/972 (12.2)	0.73	(0.40-1.31)				

Continued overleaf

Table 7.4 *Continued*: Univariable and multivariable analyses of factors associated with preterm delivery among repeat pregnancies

	Preterm/total (%)	Univariable analyses			Multivariable analysis (*n*=2057)		
		OR	95% CI	*p*-value	aOR	95% CI	*p*-value
HIV risk factor							
Other**	332/2594 (12.8)	1		0.002	1		0.566
Injecting drug use	16/59 (27.1)	2.54	(1.41-4.55)		1.27	(0.56-2.86)	
Pregnancy type							
Singleton	331/2668 (12.4)	1		<0.001	1		<0.001
Twin/triplet	24/47 (51.1)	7.37	(4.11-13.20)		9.63	(5.05-18.35)	
HIV/AIDS symptoms							
No	248/1903 (13.0)	1		0.001			
Yes	14/47 (29.8)	2.83	(1.50-5.34)				
On ART at conception							
No	161/1298 (12.4)	1		0.253			
Yes	166/1190 (13.9)	1.14	(0.91-1.44)				
Last antenatal CD4 count, cells/µl							
≥500	99/895 (11.1)	1		<0.001	1		<0.001
350-499	82/732 (11.2)	1.01	(0.74-1.39)		1.07	(0.75-1.53)	
200-349	85/572 (14.9)	1.40	(1.03-1.92)		1.34	(0.92-1.94)	
<200	37/143 (25.9)	2.81	(1.83-4.31)		2.80	(1.72-4.55)	
Type of ART							
None	6/37 (16.2)	1.63	(0.59-4.54)				
Mono/dual	14/132 (10.6)	1		0.765			
cART - PI-based	202/1545 (13.1)	1.27	(0.71-2.25)				
cART - NNRTI-based	99/795 (12.5)	1.20	(0.66-2.18)				
cART - other***	26/145 (17.9)	1.84	(0.91-3.72)				

*Only includes pregnancies to women whose previous pregnancy resulted in a live birth
**Other comprises largely those originating from a high HIV prevalence area and/or with heterosexual exposure to HIV
***Includes PI and NNRTI, NRTI only and unspecified

To assess the potential influence of missing data on the model, when women with missing information on any of the variables included in the main multivariable model were compared with those with complete information, they were at increased risk of preterm delivery (17.2% (113/658) *vs*. 11.8% (242/2057), $p<0.001$). This difference remained even when missing CD4 count was ignored ($p<0.001$), but was mainly due to missing information on history of preterm delivery; the risk was 22.0% (63/286) in those with missing information on history of preterm delivery compared with 12.0% (292/2429) with known information ($p<0.001$).

Sensitivity analyses: Association between previous preterm delivery and subsequent preterm delivery

Since multiple pregnancies were included in the model, if a woman's previous preterm delivery was a multiple pregnancy then the association between previous preterm delivery and subsequent preterm delivery could potentially be underestimated (i.e. if the previous preterm delivery was solely due to it being a multiple pregnancy). Therefore, as a sensitivity analysis the model was re-run after excluding all multiple pregnancies (i.e. both current and previous) (Table 7.5). The resulting aOR for the association between previous preterm delivery and current preterm delivery was very similar (aOR: 5.79).

As outlined earlier in this chapter, repeat pregnancies were coded as such if the woman had one or more previous pregnancies reported to the NSHPC. However, women may be parous at the time of their first reported pregnancy, and some of these women may have experienced a preterm delivery prior to their entry into the NSHPC. To explore this potential source of misclassification the main model was re-run excluding all repeat pregnancies to women who were parous at their first reported pregnancy. The strong association between previous and subsequent preterm delivery remained (aOR: 4.39), although the aOR was slightly lower (Table 7.5).

Table 7.5 Sensitivity analyses of the association between previous and subsequent preterm delivery

Restrictions to study population	Multivariable analysis*			
	n	**aOR**	**95% CI**	***p*-value**
Singletons	2002	5.79	4.23-7.92	<0.001
Women nulliparous at their first reported pregnancy	1198	4.39	2.90-6.64	<0.001

*Odds of preterm delivery among women with a previous preterm delivery compared with those without (model adjusted for maternal ethnic group, HIV risk factor, multiple pregnancy, and last antenatal CD4 count)

Sub-analyses: Conceiving on ART as a predictor of preterm delivery

Several analyses presented in Chapter 5 of this thesis explored issues regarding the potential benefits of the initiation of lifelong ART for all pregnant women. Related to this, any associations between conceiving on ART and adverse pregnancy outcomes need to be considered. Therefore, the association between conceiving on ART and the risk of preterm delivery was explored in more detail (Table 7.6), particularly given that, although possible in the present analyses, most previous studies on ART and preterm delivery have not adjusted for previous preterm delivery (Boer *et al*, 2007; European Collaborative Study and Swiss Mother and Child HIV Cohort Study, 2000; Grosch-Woerner *et al*, 2008; Lopez *et al*, 2012; Martin *et al*, 2007; Ravizza *et al*, 2007; Rudin *et al*, 2011; Short *et al*, 2013; Thorne *et al*, 2004; Townsend *et al*, 2007). As was shown in Table 7.4, overall there was no significant association between being on ART at conception and the probability of preterm delivery. However, the analysis was based on all women thus the group who were not on ART at conception will include some women who never received ART during pregnancy (*n*=42). When the univariable analysis was restricted to women who received at least 14 days of ART (any type) during pregnancy the odds of preterm delivery among women on ART at conception compared with those initiating ART during pregnancy was 1.19 (95% CI: 0.94-1.50) (Table 7.6). When the analysis group was further restricted to include only those who received ≥14 days of PI-based cART during pregnancy, the association was stronger (OR: 1.36, 95% CI: 1.00-1.87). However, this association was nullified when the other variables included in the main multivariable analysis (previous preterm delivery, ethnic group, HIV risk factor, multiple pregnancy, and last antenatal CD4 count) were adjusted for (aOR: 1.05, 95% CI: 0.70-1.57).

Given current CD4 count thresholds of <350 cells/μl for initiation of lifelong ART (Taylor *et al*, 2012), it is among women who present in pregnancy with a CD4 count of ≥350 cells/μl where the balance of risks and benefits of initiating lifelong ART (in terms of future pregnancy outcomes) need careful consideration. When the probability of preterm delivery in those conceiving on PI-based cART was compared with those not on ART at conception but who received ≥14 days of PI-based antenatal cART, and restricted to those with a pre-ART antenatal CD4 count of ≥350 cells/μl, the OR was 1.77 (95% CI: 1.23-2.54). Although the association became non-significant after adjusting for the other variables in the main multivariable model (excluding CD4 count), the direction of the aOR was the same (1.37, 95% CI: 0.90-2.10).

Table 7.6 Sub-analyses: conceiving on ART as a predictor of preterm delivery

Restrictions to study population*	Univariable analyses 1***				Univariable analyses 2 ***†				Multivariable analyses***			
	n	OR	95% CI	*p*-value	*n*	OR	95% CI	*p*-value	*n*	aOR	95% CI	*p*-value
Women who received ≥14 days of antenatal ART (any type)	2440	1.19	0.94-1.50	0.150	2039	1.04	0.79-1.36	0.778	2039	0.95	0.71-1.27	0.726
Women who received ≥14 days of antenatal PI-based cART	1434	1.36	1.00-1.87	0.053	1203	1.21	0.84-1.74	0.302	1203	1.05	0.70-1.57	0.810
Women who received ≥14 days of antenatal PI-based cART and had a pre-ART CD4 count of ≥350 cells/µl**	1164	1.77	1.23-2.54	0.002	1030	1.73	1.20-2.49	0.003	1030	1.37††	0.90-2.10	0.145

*Restrictions detailed in the table were applied to both women on ART at conception and those who were not (see ** below for the exception to this rule)
**Pre-ART CD4 counts for women on ART at conception are not routinely collected by the NSHPC. This specific restriction was therefore only applied to women not on ART at conception
***Odds of preterm delivery among women on ART at conception compared with those starting ART during pregnancy. Multivariable model adjusted for previous preterm delivery, ethnic group, HIV risk factor, multiple pregnancy, and last antenatal CD4 count
†Models restricted to those with complete information on all variables included in the multivariable model
††Not adjusted for CD4 count since the analyses were restricted to those with a CD4 count of ≥350 cell/µl

7.1.6 Low birthweight and small for gestational age

Analyses of low birthweight and small for gestational age were restricted to live born infants. Among repeat pregnancies the median birthweight was 3.1kg (IQR: 2.8-3.4), and 12.6% (2232/2553) of infants were of low birthweight (<2.5kg), including 53 infants (2.1%) of very low birthweight (<1.5kg). The median birthweight among repeat pregnancies was significantly (p<0.001) higher compared with first reported pregnancies (3.0kg, IQR: 2.7-3.4). In line with this, the proportion of low birthweight infants was significantly (p=0.009) lower among the repeat pregnancies compared with first reported pregnancies (14.7%, 1099/7491). This difference remained when the analysis was restricted to infants born at term: 5.0% (112/2230) among repeat pregnancies and 6.2% (404/6486) for first reported pregnancies (p=0.037). When the analysis was restricted to women who were nulliparous at their first reported pregnancy a similar pattern was observed; the proportion of low birthweight infants was 13.5% among the repeat pregnancies and 15.4% among the first reported (p=0.131). Similarly, mean z-scores of birthweight (accounting for gestational age and gender) were higher among repeat than first reported pregnancies (-0.009 and -0.179 respectively, p<0.001), and a significant difference remained when the analysis was restricted to infants born at term (-0.020 *vs*. -0.175, p<0.001).

7.1.7 Congenital abnormalities

Information on the presence of congenital abnormalities was reported for 96.7% (2648/2737) of pregnancies resulting in a live birth and 83.3% (20/24) of those resulting in a stillbirth. Overall, 2.9% (78/2668) of pregnancies resulted in the birth of an infant with an abnormality; 2.8% (n=75) of live born infants and 15.0% (n=3) of stillborns. The probability of abnormality among the repeat pregnancies was very similar to that among first reported pregnancies (also 2.9%, 235/8159, p=0.908). There was also no significant difference if the study population was restricted to women who were nulliparous at their first reported pregnancy (p=0.943).

Among the repeat pregnancies there were 34 infants with minor abnormalities and 46 with major abnormalities, the latter thus accounting for 57.5% of all 80 abnormalities reported. The most common types of abnormalities were those affecting the limbs, the majority of which were having extra digits (17/20), followed by heart and circulatory abnormalities (n=15) all of which were considered major abnormalities (Table 7.7). Of the three stillborn infants with an abnormality one had a heart defect, one had a bowel obstruction, and the remaining infant had a chromosomal abnormality.

The probability of having an infant with an abnormality was similar in women aged ≥35 years and <35 years (2.7% (19/713) *vs*. 3.0% (1895/1954), *p*=0.630, but there was evidence of an increased risk among those aged ≥40 years compared with <40 years (5.8% (7/120) *vs*. 2.8% (71/2547), *p*=0.053). There was no evidence to suggest that infants born to women on ART at conception were at an increased risk of abnormalities compared with those starting during pregnancy (2.7% *vs*. 3.0% respectively, *p*=0.615).

Table 7.7 Congenital abnormalities among live and stillbirths

Congenital abnormality	Minor	Major	Total*	
			n	%
Limbs	17	3	20	25.0
Heart & circulatory	0	15	15	18.8
Integument	9	0	9	11.3
Urinary	1	5	6	7.5
Musculoskeletal	0	6	6	7.5
Chromosomal	0	6	6	7.5
Genital organs	3	2	5	6.3
Digestive	0	3	3	3.8
Eye, ear, face, neck	2	0	2	2.5
Respiratory	1	1	2	2.5
Cleft palate/lip	0	2	2	2.5
Nervous system	0	1	1	1.3
Type not specified	0	1	1	1.3
Total	34	46	80	100

*Includes two second born twins (where the first born did not have an abnormality but the second born twin did)

Among the 62 repeat pregnancies that ended in a termination at <24 completed gestational weeks, two abnormalities were reported, both of which were major (one was anencephaly and the other chromosomal). Abnormalities among the four terminations carried out at 24 gestational weeks (there were none later than this) were described earlier in this chapter in relation to pregnancy outcomes (Section 7.1.4).

7.2 Mode of delivery

As shown in Chapter 2, Section 2.7, there is a large pool of diagnosed women in the UK and Ireland with a history of caesarean section delivery. UK guidelines allow for, and more recently specifically recommend, vaginal deliveries for women on cART with undetectable viral loads (de Ruiter *et al*, 2008; Hawkins *et al*, 2005; Taylor *et al*, 2012). The risks and benefits of vaginal delivery after previous caesarean section(s) are, however, uncertain among the general population and have been little explored among women living with HIV. The objective of the second part of this chapter is to describe mode of delivery among repeat pregnancies, explore patterns within women (VBAC for example), and document serious adverse outcomes that may be related to mode of delivery (Objective 6).

7.2.1 Methods

Analyses were restricted to deliveries during 2005-2010 to women who had already experienced at least one live or stillbirth since their HIV diagnosis (Figure 7.2) since UK guidelines on the obstetric management of HIV in pregnancy have changed quite substantially over the last decade, as discussed in Chapter 2, Section 2.7. If a woman had more than one repeat delivery during the study period only her last was included (hereafter referred to as her 'subsequent' or 'current' delivery'). Where a woman's 'previous' delivery is referred to this was her immediately preceding birth. The dataset was based on deliveries, and for the purpose of these analyses multiple pregnancies were considered as one delivery (based on information reported for the first born twin) in line with the way such data are routinely recorded by the NSHPC. Some sub-analyses were restricted to women who were nulliparous at the time of their first pregnancy reported to the NSHPC. Reasons for emergency caesarean sections are collected via the obstetric scheme only. Viral load was the reported measurement closest to delivery (within 28 days prior and up to seven days after)[58].

[58] For most analyses in this thesis, an imputed viral load variable was used whereby if no viral load was reported within 28 days prior and up to seven days after delivery but the woman had an undetectable viral load reported earlier in that pregnancy then her delivery viral load was imputed as undetectable (as described in Chapter 3, Section 3.4). It was not felt appropriate to use the imputed variable in these analyses since actual viral load closest to the point of delivery (whether or not reported to the NSHPC) could substantially influence the mode of delivery undertaken.

Figure 7.2 Study population flow chart – mode of delivery analyses

*Information on these previous pregnancies was retained in the dataset for exploration of patterns in mode of delivery within women

7.2.2 Study population

There were 1996 subsequent deliveries (1981 live and 15 stillbirths) eligible for inclusion in the analysis; 1598 were second deliveries, 346 third, 46 fourth and six fifth (Table 7.8). There were 1960 singletons and 36 pairs of twins. The majority of deliveries (86.2%) were to women who were born abroad, with most of these originating from sub-Saharan Africa. Women's median age at delivery of their last reported infant was 32.5 years (IQR: 28.7-36.0); most women were aged 25-34 years although almost one third were ≥35 years. The median birth-to-birth interval between women's last birth and their previous birth was 2.2 years (IQR: 1.1-3.6). The last antenatal CD4 count measurement during that pregnancy was <350 cells/µl in 29.0% of pregnancies, and viral load at delivery was undetectable in 77.4%.

Table 7.8 Mode of delivery analyses - characteristics of subsequent pregnancies

Characteristic	*n*	%
Pregnancy (*n*=1996)		
Second	1598	80.1
Third	346	17.3
Fourth	46	2.3
Fifth	6	0.3
Year of delivery (*n*=1996)		
2005	179	9.0
2006	220	11.0
2007	322	16.1
2008	359	18.0
2009	474	23.7
2010	442	22.1
Age at delivery, yrs (*n*=1995)		
<25	182	9.1
25-34	1179	59.1
≥35	634	31.8
World region of origin (*n*=1995)		
UK/Ireland	276	13.8
Sub-Saharan Africa	1559	78.1
Elsewhere	160	8.0
Pregnancy outcome (*n*=1996)		
Live birth	1981	99.2
Stillbirth	15	0.8
Pregnancy type (*n*=1996)		
Singleton	1960	98.2
Twin/triplet	36	1.8
Gestational age, wks (*n*=1963)		
≥37	1718	87.5
<37	245	12.5
Last CD4 count, cells/µl (*n*=1712)		
≥500	677	39.5
350-499	540	31.5
200-349	393	23.0
<200	102	6.0
Viral load at delivery, copies/ml (*n*=1071)		
≤50	829	77.4
>50	242	22.6

Time trends in mode of delivery

Mode of delivery was reported for 98.7% (1970/1996) of live and stillbirths in this dataset. Overall 47.0% (925/1970) were delivered by elective caesarean section, 31.2% (*n*=615) vaginally, and 21.8% (*n*=430) by emergency caesarean section. Of note, the rate of elective caesarean section among the last reported births was higher than that among women having their first delivery during the same period (41.2% (2257/5480))[59]. Mode of delivery was reported for 12 of the 15 stillbirths; there were five emergency caesarean sections and seven vaginal deliveries (five planned and two unplanned). Figures 7.3 and 7.4 show trends in mode of delivery over time; the overall proportion of vaginal deliveries increased significantly between 2005 and 2010 (from 21.0% to 39.3%, $p<0.001$). The proportion of women who had a planned vaginal delivery more than doubled over the six year study period (from 13.1% in 2005 to 29.0% in 2010 $p<0.001$). There was no significant change in the proportion of unplanned vaginal deliveries ($p=0.565$). In line with the overall increase in vaginal deliveries, the proportion of caesarean sections declined (from 79.0% to 60.7% $p<0.001$) driven by a decline in elective caesarean sections (from 58.5% to 39.5%, $p<0.001$), while the proportion of emergency caesarean sections was stable; 20.5% in 2005 and 21.2% in 2010 ($p=0.140$).

[59] This group of first reported pregnancies during 2005-2010 did not form part of the study population but data is provided here for context.

Figure 7.3 Mode of delivery for subsequent births, by year, 2005-2010

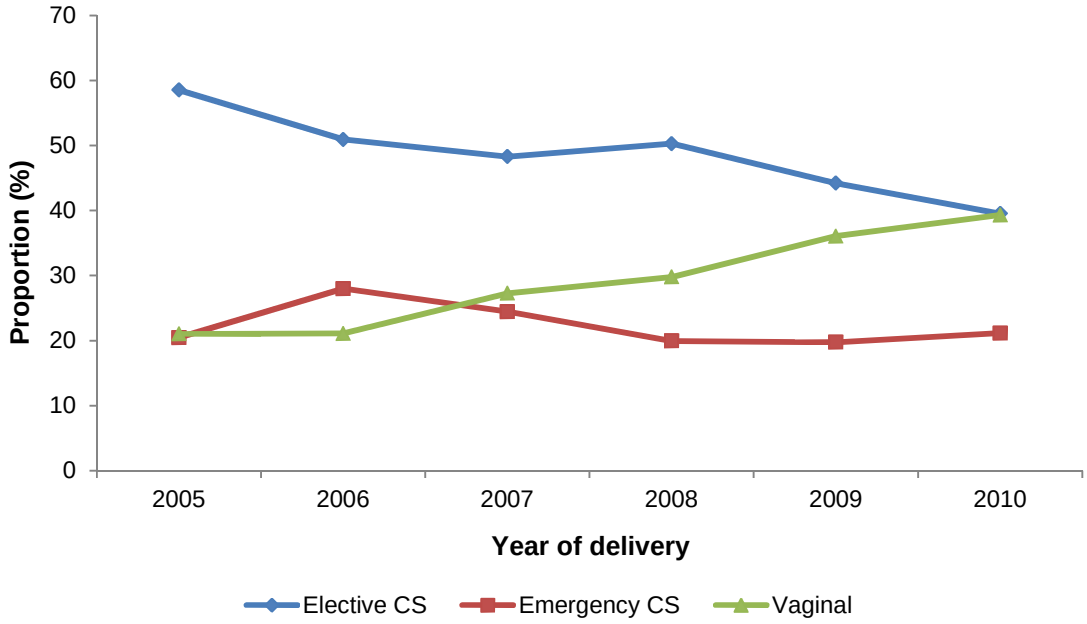
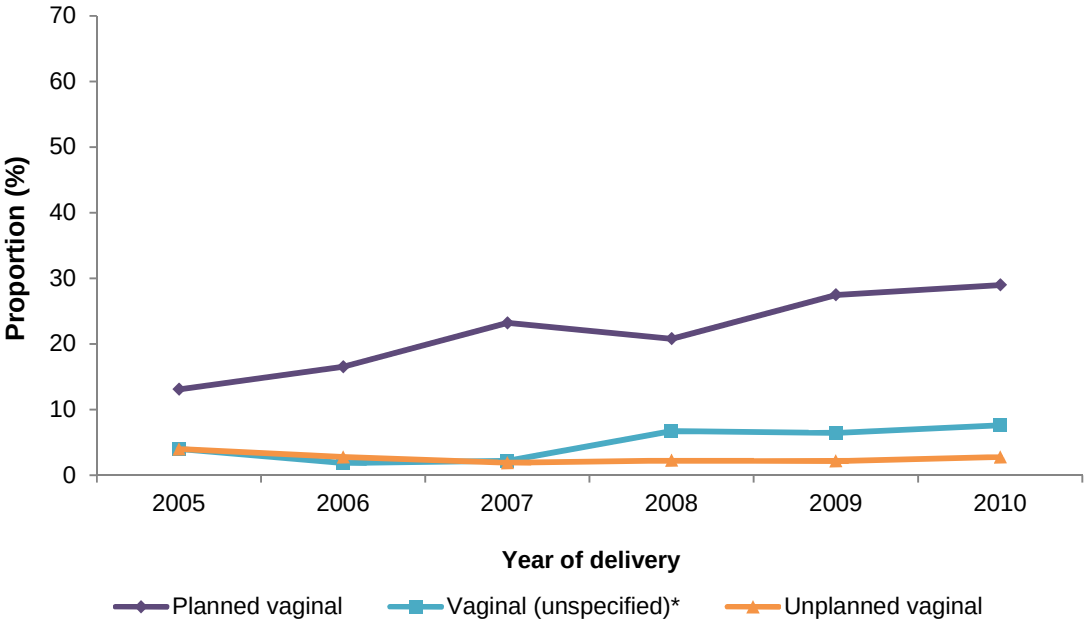


Figure 7.4 Subsequent births delivered vaginally according to whether they were reported to have been planned, by year, 2005-2010



*Not specified whether planned or unplanned

Note: Figure 7.4 provides a breakdown of the vaginal deliveries shown in Figure 7.3.

7.2.3 Planned and actual mode of delivery

Emergency caesarean sections

Among the 430 women delivering by emergency caesarean section during 2005-2010 the planned mode of delivery was reported for 243, around half (51.4%) of whom had planned for an elective caesarean section, and half for a vaginal delivery. Over a third (36.9%, 158/428) of emergency caesarean sections were delivered preterm. Information on the reason for emergency caesarean section was reported for 208 women. The most common reason was rupture of membranes (either 'spontaneous' or 'premature') accounting for a quarter of cases (*n*=51, 24.5%), followed by fetal distress (*n*=42, 20.2%), labour (*n*=36, 17.3%), and failure to progress (*n*=25, 12.0%). All other reasons given each accounted for <5% of the remaining deliveries.

Vaginal deliveries

Of those delivering vaginally this was reported as being the planned mode of delivery for 95.4% (477/500). Looking at this the other way around, of the 607 women who planned to deliver vaginally 78.6% did deliver vaginally, 19.4% by emergency caesarean section. The remaining small proportion (2.0%) were reported to have delivered by elective caesarean section likely due to a change in the planned mode close to the time of delivery e.g. due to an unsuppressed viral load late in pregnancy or emergent obstetric indications. Overall, 10.8% (66/609) of vaginal deliveries were preterm. The majority of women delivering vaginally who had a viral load delivery measurement, reported had an undetectable viral load (88.9%, 279/314); the proportion was 91.0% among the planned vaginal deliveries. Although the NSHPC requests the viral load measurement closest to delivery, it is possible that this is not always what is actually reported. Among the vaginal deliveries, viral load measurements were taken at a median of 25 days (IQR: 14-44.5) prior to delivery, and of those with a detectable viral load, the majority (85.7%, 30/35) were <400 copies/ml. It is thus feasible that some of the women reported as having a detectable viral load may in fact have become undetectable at the point of delivery. Furthermore, maternal choice may play a role, particularly for women with a very low, but detectable, viral load.

Elective caesarean sections

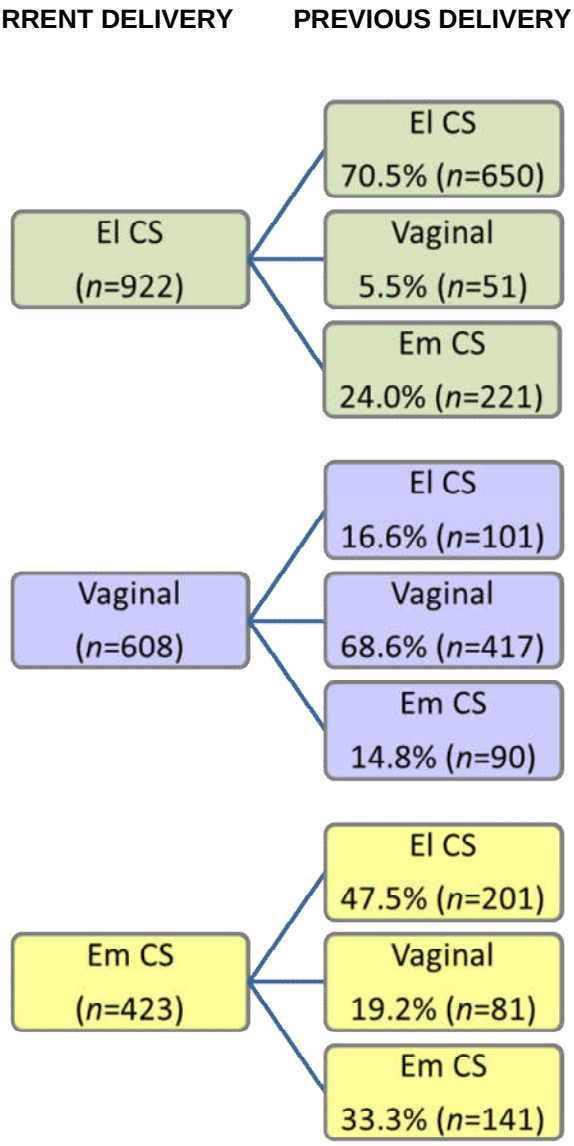
Of the 499 women who had an elective caesarean section planned 70.3% delivered by this route, 25.1% by emergency caesarean section (half of which were preterm deliveries), and 4.6% delivered vaginally. Among those who had an elective caesarean section, 73.4% had an undetectable viral load (for context, the corresponding proportion among first reported pregnancies was 60.6% (783/1292)). Among the last reported pregnancies, the proportion

of those delivered by elective caesarean section with an undetectable viral load did not decrease over the study period (it was 78.6% in 2010), though this largely reflects improvements in viral suppression by delivery over time. Viral load measurements were taken at a median of 21 days (IQR: 9.0-41.5) prior to delivery.

7.2.4 Mode of delivery patterns within women

There were 1953 women with information available on the mode of delivery for both their current (last reported) and previous birth. Figure 7.5 shows that among women delivering vaginally 31.4% had delivered their previous infant by caesarean section (either elective or emergency). Of the 1404 women who had delivered their previous infant by caesarean section, 13.6% (*n*=191) subsequently had a VBAC, and this proportion increased significantly from 8.3% in 2005 to 17.3% in 2010 (test for trend: $p<0.001$). Meanwhile, of women delivering by elective caesarean section 94.5% had delivered their previous infant by caesarean section (either elective or emergency). Among women delivering by emergency caesarean section 33.3% delivered their previous infant by emergency caesarean section.

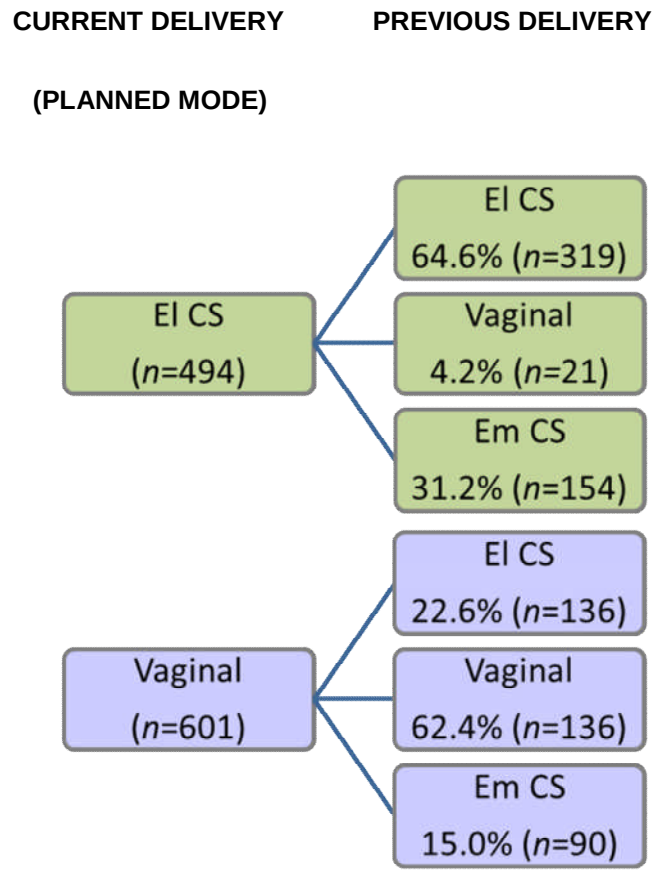
Figure 7.5 Mode of delivery for current and previous birth



El CS – Elective caesarean section, Em CS – Emergency caesarean section

Figure 7.6 shows patterns in women's planned mode of delivery for their current pregnancy according to the mode of delivery of their previous pregnancy. Of the 601 women who had planned a vaginal delivery for their current pregnancy, over a third (37.6%) had delivered their previous pregnancy by a caesarean section. Meanwhile, of the 494 women planning to deliver their subsequent pregnancy by elective caesarean section, the vast majority had previously delivered by a caesarean section with only 4.2% having previously delivered vaginally. With regard to the success rate of VBAC, of the 226 women who had previously delivered by caesarean section and planned to have a subsequent VBAC, 61.6% (*n*=138) successfully delivered by this route (data not shown).

Figure 7.6 Planned mode of delivery for current birth and actual mode of delivery for previous birth

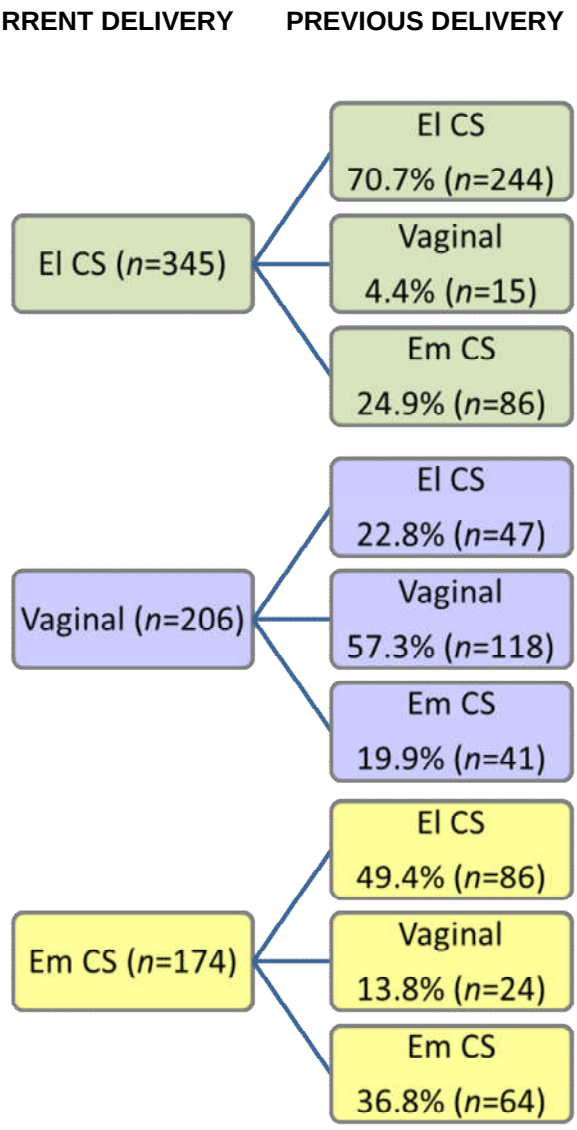


El CS – Elective caesarean section, Em CS – Emergency caesarean section

Sensitivity analyses: Patterns in mode of delivery within nulliparous women

Analyses restricted to women who were nulliparous at their first reported pregnancy included 742 women, 725 (97.7%) of whom had known mode of delivery for both their previous (first) reported pregnancy and current (second) pregnancy. Figure 7.7 shows that the patterns in mode of delivery among this sub-group were similar to those among all women. Among those delivering vaginally, 42.7% had delivered their previous infant by caesarean section (either elective or emergency), this proportion remained stable between 2005 and 2010 (test for trend: p=0.619). Looking at this the other way around, of the 568 women who had delivered their previous infant by caesarean section, 15.5% (n=88) subsequently had a VBAC, and this proportion increased significantly from 6.8% in 2005 to 18.0% in 2010 (test for trend: p=0.022). Of women delivering by elective caesarean section the vast majority (95.6%) had delivered their previous infant by caesarean section (either elective or emergency).

Figure 7.7 Mode of delivery for current and previous birth, among women who were reported to be nulliparous at their first reported pregnancy



El CS – Elective caesarean section, Em CS – Emergency caesarean section

7.2.5 Women with two or more caesarean sections

After their last reported delivery, 1235 women had experienced two or more caesarean sections (1018 women had two, 197 had three, 19 had four, and one woman had five)[60]. Only five women had had more than one previous caesarean section and then delivered an infant vaginally during 2005-2010, of whom two were nulliparous at their first reported pregnancy, and the remaining three were parous. An additional three women had more than one previous caesarean section and then planned to deliver their last infant vaginally (but actually delivered by emergency caesarean section), all of whom were parous at their first reported pregnancy.

7.2.6 Adverse obstetric outcomes that may be related to mode of delivery

Uterine rupture

Among all 1996 deliveries four uterine ruptures were reported to have occurred representing a risk of 0.20% (95% CI: 0.004-0.40), all resulting in an emergency caesarean section. The risk was 0.28% (95% CI: 0.006-0.56) among the 1404 women who had previously delivered by caesarean section. Three of these women had experienced one previous caesarean section, and one woman had experienced two. Elective caesarean section had been planned for two of the women, a vaginal delivery for one, and for the remaining woman the planned mode of delivery was not reported. None of the four women were reported to have died. Of the four infants two were stillborn; one at 32 weeks gestation, and one at 41 weeks gestation, the latter was born to the one woman who was planning to have a vaginal delivery. The remaining two deliveries were live births; one at 32 weeks and one at 39 weeks. Neither of the live born infants was known to have acquired HIV.

MTCT

There were 10 HIV-positive infants delivered during the study period, of whom five were delivered by elective caesarean section, two by emergency caesarean section, and the remaining three vaginally, giving transmission rates of 0.65% (95% CI: 0.08-1.21, *n*=5/774), 0.58% (95% CI: -0.02-1.38, *n*=2/345) and 0.62% (95% CI: -0.08-1.31, *n*=3/487) respectively. The very small number of HIV-positive infants in each of these three groups makes it difficult to draw valid comparisons.

Table 7.9 shows the current and previous modes of delivery for the women whose infants vertically acquired HIV together with relevant clinical and obstetric details for their current

[60] Based on all their deliveries reported to the NSHPC during 1990-2010.

pregnancy. Of the five women who delivered HIV-positive infants by elective caesarean section, all had delivered their previous infant by caesarean section, three had a detectable viral load at delivery (of the remaining two, one was undetectable (<50 copies/ml) and one was missing), and three were reported to have been parous at the time of their first pregnancy reported to the NSHPC. Of the two women who delivered an HIV-positive infant by emergency caesarean section, both had delivered previously by caesarean section and both had detectable viral loads. Finally, of the three women who delivered vaginally one had planned for a caesarean section but planned mode of delivery was missing for the remaining two (one of whom had a detectable viral load at delivery). Two of the women had previous vaginal deliveries and one a previous elective caesarean section. None of the women reported here had more than one HIV-positive infant.

Table 7.9 Current and previous mode of delivery among women who had HIV-positive infants in their last reported pregnancy

Woman	Actual mode of delivery*	Planned mode of delivery*	Preterm delivery	Viral load, copies/ml**	Mode of delivery for previous pregnancies***	Parity at first reported pregnancy
1	Elective CS	n/a	No	≥10,000	2x elective CS	Not reported
2	Elective CS	n/a	Not reported	Not reported	1x elective CS	2
3	Elective CS	n/a	No	<50	1x elective CS	1
4	Elective CS	n/a	No	50-999	1x elective CS	Nulliparous
5	Elective CS	n/a	No	≥10,000	1x emergency CS	1
6	Emergency CS	Not reported	No	≥10,000	1x emergency CS	Nulliparous
7	Emergency CS	Not reported	No	50-999	1x elective CS	Not reported
8	Vaginal	Elective CS	No	Not reported	3 x vaginal	Nulliparous
9	Vaginal	Not reported	Yes	≥10,000	1x emergency CS	2
10	Vaginal	Not reported	No	<50	1x vaginal	2

CS - caesarean section
*For current (last reported) pregnancy
**Closest to delivery (in current pregnancy), restricted to measurements taken between 28 days before and seven days after delivery
***Previous pregnancies reported to the NSHPC

7.3 Discussion

7.3.1 Adverse pregnancy and perinatal outcomes

Risk of adverse outcomes among HIV-positive women

Among the repeat pregnancies the overall risk of preterm delivery was 13%, which is consistent with previous analyses of UK data on HIV-positive women (Cheshire *et al*, 2012; Short *et al*, 2013; Townsend *et al*, 2007), but higher than the 7% recorded among the general population in England and Wales (Office for National Statistics, 2011a), and across Europe (6%) (Beck *et al*, 2010). Similarly, the risk of low birthweight, at 13%, was notably higher than among the UK general population (6%) (Moser *et al*, 2008). Comparisons between HIV-positive women and the general population should be made with caution. For example, the socio-economic characteristics of HIV-positive women, who are largely migrants from sub-Saharan Africa, will differ to those of the general population. However, it is of note that among the general population of black African women living in the UK the risk of pre-term delivery (8%) (Office for National Statistics, 2011a) and low birthweight (7%) (Moser *et al*, 2008) were still considerably lower than among HIV-positive women. The role of HIV-related factors cannot, therefore, be ruled out. The rate of congenital abnormalities, at 2.9% during 2000-2010, was not dissimilar to the prevalence among the general population (2.6% in 2007), though comparisons are difficult due to the differing definitions, methodologies, and time periods for which data is available (see Chapter 2, Section 2.6).

Adverse outcomes among repeat compared with index pregnancies

At their repeat pregnancies HIV-positive women did not appear to be at increased risk of stillbirth, preterm delivery, having an infant with a low birthweight or congenital abnormalities compared with index pregnancies. This largely allays concerns about a potentially increased risk of adverse pregnancy outcomes in repeat pregnancies (see Chapter 2, Section 2.6). The probability of having a low birthweight infant was in fact significantly lower among the repeat pregnancies, tying in with the reduced risk of low birthweight infants among parous women in the general population (Shah, 2010). Indeed, being parous *per se* has been associated with a lower risk of a range of adverse outcomes in the general population as detailed in Chapter 2, Section 2.6. Furthermore, the lack of increased risk of adverse outcomes among the repeat pregnancies may reflect a combination of factors which could be balancing out the risks among the two groups. For example, although median maternal age was greater among the repeat pregnancies, the

proportion aged ≥40 years was similar (5% *vs*. 4%) thus the impact of increased maternal age may not be substantial. Maternal health was actually better among the repeat than first pregnancy groups, likely because a higher proportion were on ART at conception (49% *vs*. 22%). However, associations are complex, with, for example, interactions between the influence of parity and correlated exposures such as maternal age (Kozuki *et al*, 2013; Lisonkova *et al*, 2010). These were not explored in detail here as the analyses largely aimed to explore adverse outcomes among the repeat pregnancies specifically rather than elucidate the mechanisms through which parity may influence pregnancy and perinatal outcomes more generally.

In contrast to findings with respect to stillbirth, preterm birth, low birthweight and birth defects, women were at significantly increased risk of reported miscarriage at their repeat pregnancies (7% *vs*. 5%, $p<0.001$). As has been mentioned, this finding should be interpreted with caution. Although reporting of late miscarriages (≥20 weeks) is likely to be reasonably complete, since over 80% of women book for antenatal care before 18 weeks gestation (as shown in Chapter 5), early miscarriages are likely to be under-reported to the NSHPC since information is generally collected at the time that women first book for antenatal care, which in this population was at an average of around 13 weeks gestation (also shown in Chapter 5). Furthermore, there may be some differential reporting of miscarriage which could bias the findings; miscarriages might be more likely to be reported among women who have already experienced a pregnancy as a diagnosed woman. Of course another explanation that needs to be considered is toxicities of early pregnancy exposure to ART. After adjusting for whether women were on ART at conception there was no longer a significant difference in the risk of miscarriage, suggesting that this may play a role. However, reporting (or selection) bias may also be relevant here with women on ART from prior to conception potentially being more likely to have a miscarriage reported. Relatively few studies have explored miscarriage as a potential adverse pregnancy outcome in the cART era. An analysis of HIV-positive women enrolled in the US Women's Interagency HIV Study during 1994-2002 found no evidence of an increased risk among those who were already on ART at their last study visit prior to conception (Massad *et al*, 2004). However, data from a single UK centre during 1997-2012, (which will thus also be present in the national NSHPC dataset) showed that the odds of miscarriage among those on cART prior to pregnancy was 9.75 (95% CI: 2.13-44.62) times that in women starting cART during pregnancy. These findings should, however, be interpreted with caution; the OR was not adjusted for confounding factors, and the number of miscarriages was small,

with only 15 reported during the study period, hence the very wide confidence intervals. Also, as per the NSHPC analyses, reporting bias is probable (Dale, 2013)[61].

That women's repeat pregnancies since diagnosis were less likely to result in a termination than first pregnancies ties in with the decline in terminations among HIV-positive women over time (Townsend *et al*, 2008b). It may also reflect the fact that these women have already experienced a pregnancy as an HIV-positive woman in the era of very low rates of MTCT (the study population was restricted to women whose first reported pregnancy was from 2000 onwards), thus potentially allaying women's fears around MTCT. Women's better health at their repeat pregnancies may also have had an impact. Other studies have reported declining rates of termination in the cART era (Massad *et al*, 2004; van Benthem *et al*, 2000). Furthermore, aside from the influence of an HIV diagnosis on decision-making, already having children may influence decisions regarding the termination of subsequent unintended pregnancies in the general population (Skjeldestad *et al*, 1994).

Risk factors for preterm delivery among repeat pregnancies

The following factors were associated with an increased risk of preterm delivery among repeat pregnancies in adjusted analyses: previous preterm delivery, white ethnicity, multiple pregnancy, and low antenatal CD4 count. In the multivariable model, women with a previous preterm delivery reported to the NSHPC had over five times the odds of having a subsequent preterm delivery. Although studies on the association between previous and subsequent preterm delivery among HIV-positive women specifically are lacking in the published literature, in the general population prior preterm delivery has been found to be a strong predictor of subsequent preterm delivery, as highlighted in two large reviews (Goldenberg *et al*, 2008; Slattery *et al*, 2002). In a recent Italian study among HIV-positive women, a significant association was also detected, though the adjusted OR was lower than in the present study (aOR: 2.22, 95% CI: 1.23–4.01) (Liuzzi *et al*, 2013). This could in part reflect the higher overall risk of preterm delivery in the Italian study population (21%) compared with HIV-positive women in the UK and Ireland. In the current analyses the association was even stronger for women who had previously delivered very preterm infants (<34 weeks or <32 weeks), a pattern that has also been noted in the general population (Goldenberg *et al*, 2008; Mercer *et al*, 1999). The robustness of these findings was assessed in several sensitivity analyses and remained after excluding multiple pregnancies and women who were parous at their first reported pregnancy. This data underscores the important influence of obstetric history. Such histories need to be borne in

[61] Noteworthy, but of less relevance to the interpretation of the findings presented here, the Development of AntiRetroviral Therapy in Africa (DART) trial reported no increased risk of miscarriage/termination (a combined outcome) in women on long-term tenofovir-containing cART compared with without tenofovir exposure during pregnancy (Gibb *et al*, 2012). As noted in Chapter 1, tenofovir is one of the WHO recommended first-line drugs for adults.

mind not only for the obstetric, but also for the therapeutic management of diagnosed women. For example, prior preterm delivery may be an important indicator for the earlier initiation of antenatal ART to ensure viral suppression by delivery.

Compared with white women, those of black African or 'other' ethnicity were at lower risk of preterm delivery. A review of the international evidence-base pointed towards an increased risk among black women living in the western world (Goldenberg *et al*, 2008), though disentangling the influence of ethnicity from socio-economic factors is difficult. The findings of other UK-based studies have varied. For example, a large cohort study of live singleton births among 122,415 nulliparous women reported a preterm delivery odds ratio of 1.33 (95% CI: 1.15-1.56) for black compared with white women, after adjusting for deprivation (Patel *et al*, 2004). Meanwhile, a study of over 36,000 live births in Birmingham did not find an increased risk among black women, although there was some evidence of an increased risk of very preterm delivery (both <34 weeks and <28 weeks), even after adjusting for factors such as maternal deprivation. However, the number of black women included in the study was relatively small (*n*=213) (Aveyard *et al*, 2002). Among HIV-positive women specifically, studies from other European countries have suggested lower risks among black women, though the difference was not always significant (Boer *et al*, 2007; Rudin *et al*, 2011; Thorne *et al*, 2004). In the UK and Ireland, white HIV-positive women may have other risks, for example over 90% of women with a history of injecting drug use belonged to the white ethnic group. Smoking is another potential risk factor for preterm delivery (Goldenberg *et al*, 2008), and is much more prevalent among white than black African women (Karlsen *et al*, 2012). Meanwhile, the finding that women who were immunocompromised had an increased risk of preterm delivery is consistent with other studies both in African settings and the Western world (Ezechi *et al*, 2013; Thorne *et al*, 2004; Townsend *et al*, 2010a; Turner *et al*, 2013). This emphasises the need for good clinical management of these women from early in pregnancy, as this may have benefits beyond PMTCT, and indeed maternal health, by also influencing perinatal outcomes.

As outlined in Chapter 2, Section 2.6, there has been much discussion and debate regarding the association between antenatal ART receipt, particularly cART, and preterm delivery. The current analysis was not specifically designed to investigate this association in detail and focused on the specific group of women experiencing repeat pregnancies. However, although overall there was no significant association between the type of ART received and the risk of preterm delivery (*p*=0.765), the direction of the odds ratios did suggest that women who received cART (PI- or NNRTI-based) may be at increased risk, consistent with previous studies from Europe and elsewhere (Short *et al*, 2014). Assessing the association in more recent years is difficult as the majority of women reported to the NSHPC are receiving cART (95% of treated women in this analysis), resulting in the lack of

a valid comparison group. An important source of confounding, when considering the association between PI-based cART and preterm delivery, is indication for treatment, as a range of factors will influence the type of antenatal ART a woman receives. For example, it is possible that women who have already experienced a preterm delivery may be less likely to be put on a PI-based regimen in a subsequent pregnancy due to concerns that a PI-based regimen might increase her already heightened risk of a preterm delivery. Although there was little evidence of this in the NSHPC (58% of those with a previous preterm delivery took PI-based cART in their subsequent pregnancy compared with 59% of those with no history of preterm delivery), it cannot be ruled out in other settings.

Of course, the benefits of early initiation of ART need to be balanced with the potential risks. In the present analysis although there was some evidence of an increased odds of preterm delivery among those conceiving on PI-based cART compared with those starting PI-based cART during pregnancy, this was nullified after adjusting for confounding factors. This adds to the evidence-base in support of the early initiation of ART, or indeed lifelong ART initiation, among pregnant women (i.e. suggesting that this would not lead to an increased risk of preterm delivery in any future pregnancies which would consequently be conceived on ART). However, these findings need to be corroborated by other studies, and in other settings. Indeed, it is of concern that a number of previous studies have reported an increased risk of preterm delivery among women on ART from before or early in pregnancy, as detailed in Chapter 2, Section 2.6. More research is clearly required to elucidate the relationship between timing of ART initiation and preterm delivery risk.

Since these analyses focused on repeat pregnancies it was possible to explore the association between birth-to-pregnancy intervals and preterm delivery. This is an exposure of interest since short, as well as very long, intervals have been associated with adverse pregnancy outcomes, as documented in systematic reviews by Conde-Agudelo *et al* 2006 and Wednt *et al* 2012. Regarding the increased risk among those with very short intervals, a potential biological mechanism is the “maternal nutritional depletion hypothesis” (i.e. it takes some time for a woman’s nutrient stores to replenish post-natally), thus if she becomes pregnant again during this time she may lack essential nutrients which are important for a healthy pregnancy (King, 2003). Although in the univariable analyses women with a short (<6 months) interval had an increased risk of preterm delivery, this was no longer significant in adjusted analyses. Another European study also reported a lack of an association (Di Renzo *et al*, 2011). It may be difficult to draw comparisons with data from the general population since the characteristics of HIV-positive women with short intervals may well differ to those of the broader population. The ability to capture birth-to-pregnancy intervals also warrants some discussion here. Inevitably, shorter intervals are more likely to be included in the analyses because women having a pregnancy in more

recent years, but leaving several years before conceiving again, will not yet have had their repeat pregnancy. Longer intervals will thus only be available for women who had a previous pregnancy early in the study period while short intervals should be more evenly distributed among the early and later pregnancies. Furthermore, migrant women with longer intervals may potentially be more likely to have returned home by the time of their subsequent pregnancy.

Limitations

In interpreting the descriptive analyses of the risk of adverse pregnancy and perinatal outcomes in women's first and repeat pregnancies, it should be noted that around half of women were parous prior to their first pregnancy reported to the NSHPC. The analyses were designed to document the frequency of adverse outcomes among women's repeat pregnancies since their diagnosis, and draw comparisons with the risk in their first pregnancies as a diagnosed woman, rather than explore the association between parity and pregnancy outcomes more broadly i.e. outside the context of HIV. However, the potential influence of overall parity on the findings should not be overlooked. To consider the impact that parity may have had, sensitivity analyses were carried out on women known to be nulliparous at the time of their first pregnancy reported to the NSHPC, and the results were generally comparable, as has been described.

An important limitation of the preterm delivery analyses is that because the NSHPC does not collect information on some well-known important risk factors for preterm delivery such as socio-economic status and smoking (Goldenberg *et al*, 2008; Slattery *et al*, 2002), these could not be investigated or adjusted for in the analyses. The presence of other infections has also been implicated in preterm deliveries (Slattery *et al*, 2002). However, this information was only added to the NSHPC data collection form in mid-2008 and thus could not be included as a covariate in the analyses without vastly reducing the power of the analyses. It is not known whether women's previous unreported pregnancies (e.g. those occurring prior to diagnosis) were delivered preterm and this could be important in predicting future preterm delivery risk given the strong associations reported here. Furthermore, it was not possible to reliably distinguish idiopathic preterm deliveries from those delivered early for reasons such as obstetric or fetal complications (indicated deliveries), and this information is not specifically requested by the NSHPC. However, there is likely to be some overlap between risk factors for idiopathic and 'indicated' preterm delivery, and it has been suggested that some women who are delivered early for obstetric reasons may also have been at increased risk of an idiopathic preterm delivery (Ananth *et al*, 2006; Mazaki-Tovi *et al*, 2007).

With regard to missing data, although gestational age at delivery was available for 98% of births, information on potential predictors of preterm delivery was missing for some women. Women with missing data on any explanatory variable had a higher probability of preterm delivery, the reasons for which are likely to be multifactorial. For example, women arriving at hospital in preterm labour may not have sufficient time for laboratory testing and are thus more likely to have missing delivery CD4 counts. Meanwhile, history of previous preterm delivery was missing if the women's previous reported pregnancy did not result in a live or stillbirth. Some studies have reported an increased risk of preterm delivery in women with a history of adverse outcomes such as miscarriage and termination of pregnancy (Di Renzo *et al*, 2011; Goldenberg *et al*, 1993; Swingle *et al*, 2009), though this was not investigated here in light of the probable under-reporting of both miscarriages and terminations.

7.3.2 Mode of delivery

Temporal trends in mode of delivery

During 2005-2010 nearly half (47%) of sequential (last reported) deliveries were planned caesarean sections (compared with 41% of first reported pregnancies during the same period). However, the proportion of vaginal deliveries almost doubled (from 21% to 39%), reflecting the move towards the normalisation of vaginal delivery among women living with HIV. Similar trends have been observed across Europe following similar changes to recommendations on mode of delivery (Aebi-Popp *et al*, 2013a). Nevertheless, the proportion of caesarean section deliveries remained relatively high in 2010 (61%, composed of 40% elective and 21% emergency). This needs to be considered in the context of background rates of caesarean section deliveries in the general population. In England during 2009-2010 one quarter of deliveries were by caesarean section (composed of 10% elective and 15% emergency) (Health and Social Care Information Centre, 2010). Similarly, the rate of caesarean section deliveries among HIV-positive women in France during 2005-2010, at 53%, was reported to be twice that of the general population (Briand *et al*, 2013).

Reasons for the higher rate of caesarean sections (both elective and emergency) among HIV-positive women are likely to be complex and multifactorial. Although, as shown in the first part of this chapter, at their repeat (compared with first reported) pregnancies women were significantly more likely to achieve an undetectable viral load by delivery, still one quarter of those delivering by elective caesarean section had unsuppressed virus at delivery and were therefore not eligible for a vaginal delivery. Meanwhile, elective caesarean section was the strongly recommended mode of delivery for those living with HIV for over a decade and thus some women may still feel this is the safest choice, as may

some obstetricians. This analysis focused on women's repeat pregnancies which adds another dimension to decisions around mode of delivery; many of these women will have previously successfully delivered an HIV-negative infant by caesarean section which may reinforce this as the 'safest choice' for the health of their baby. Indeed, of those women delivering by elective caesarean section the vast majority (95%) had also delivered their previous infant by caesarean section. Maternal request and prior obstetric history, particularly having previously delivered by caesarean section, have been shown to be important (Aebi-Popp *et al*, 2013a; Briand *et al*, 2013; Livingston *et al*, 2010; Mark *et al*, 2012; Suy *et al*, 2008), and data for the general UK population revealed that previous caesarean section was the most common reason for delivering a subsequent baby by the same route (Thomas *et al*, 2001). Furthermore, some studies have reported HIV-positive women on cART to be at increased risk of pregnancy complications such as pre-eclampsia (Suy *et al*, 2008; Wimalasundera *et al*, 2002) which may be an indication for an early (caesarean section) delivery. Counselling women with repeat pregnancies about the very low risk of vertical transmission associated with vaginal deliveries among those on suppressive therapy, as well as options such as VBAC, will help enable them, together with their obstetrician, to make an informed choice. It should also be borne in mind that mode of delivery in the current pregnancy will impact on future obstetric management; for example, in the general population VBAC is not recommended for women with more than three previous caesarean section deliveries (Royal College of Obstetricians and Gynaecologists, 2007).

Mode of delivery patterns for women's previous and subsequent births

Although the majority of women in this study population had a history of caesarean section delivery in previous pregnancies, VBAC is now considered a safe option for most women (Royal College of Obstetricians and Gynaecologists, 2007). Of those who had previously delivered by caesarean section 14% had a VBAC. The success rate of VBAC was 62% (i.e. the proportion of women planning a VBAC who successfully delivered by the route). This is towards the lower end of success rates among the general population – a systematic review and meta-analysis reported a range of 60-82% (Guise *et al*, 2004), with the RCOG guideline quoting a narrower but not inconsistent range of 72-76% based on three key studies (Royal College of Obstetricians and Gynaecologists, 2007). The potential risks of VBAC among this population, uterine rupture for example, do however need consideration. There were four uterine ruptures reported overall, a rate of 2.0 per 1000 (95% CI: 0.04-4.0), and 2.8 (95% CI: 0.06-5.6) among those who delivered their previous infant by caesarean section, although a vaginal delivery was only known to have been planned for one of these four women. A national-level UK study reported a uterine rupture rate of 1.1 (95% CI: 0.9-1.3) per 1000 maternities among women with a previous caesarean section delivery

(Fitzpatrick *et al*, 2012). Although the rate appears to be higher in the NSHPC population, the confidence intervals do overlap, and it is difficult to draw conclusions due to the small number of events. The study by Fitzpatrick *et al* also reported that the risk of rupture increased with number of previous caesarean sections, and was higher in those planning a vaginal delivery rather than an elective caesarean section. Looking forwards, these are factors relevant to HIV-positive women in the UK and Ireland in light of current guidelines. However, the risk of uterine rupture is low and needs to be balanced against the risks of having a repeat caesarean section.

Missed opportunities for vaginal deliveries

Of the women who delivered by elective caesarean section, nearly three quarters had an undetectable viral load and were thus eligible for a vaginal delivery in the absence of obstetric indications for caesarean section. The recent European pooled analysis (including data from the UK and Ireland) highlighted the missed opportunities for vaginal delivery with 55% of those with an undetectable viral load delivering by caesarean section during 2000-2010 (Aebi-Popp *et al*, 2013a). Possible reasons for the high rate of caesarean sections in the current study population have been discussed above. However, that a quarter of women delivering their repeat pregnancy by elective caesarean section were not eligible for vaginal delivery also needs to be addressed. The most important factors influencing the achievement of an undetectable viral load by delivery include baseline viral load and duration of ART (see Chapter 1, Section 1.2.4). As shown in Chapter 5, women on ART at conception had over five times the odds of having undetectable viral load at delivery than those initiating ART during pregnancy. Implementation of more recent guidelines recommending earlier initiation of antenatal ART (Taylor *et al*, 2012), together with efforts to encourage and enable women to book earlier for antenatal care thus providing the opportunity for earlier initiation of ART, should enable more women to be eligible for a normal delivery.

Risk of emergency caesarean section delivery

One concern regarding the recommendation for vaginal delivery among eligible HIV-positive women is the potential for the rate of emergency caesarean sections to increase. An earlier analysis of the NSHPC data for 1999-2006 reported an increase in the rate of emergency caesarean sections from 17% to 23%. At the time it was suggested this may be attributable to the increasing number of women eligible to attempt a vaginal delivery in which unforeseen complications may arise (Townsend *et al*, 2008b). Reassuringly, among the repeat pregnancies there was no increase in the proportion of emergency caesarean sections during 2005-2010 despite a significant increase in vaginal deliveries. The previously observed increase might be explained by obstetricians being particularly

cautious, and hence more frequently resorting to an emergency caesarean if complications arose in women attempting a normal delivery, as the option of planned vaginal birth had only been recently introduced (see Appendix II). As noted in Chapter 1, Section 1.2.4, there is now increasing evidence that the risk of transmission is very low among women with an undetectable viral load suggesting little additional benefit of caesarean section among these women, which may impact on clinical decision-making.

Limitations of mode of delivery analyses

The classification of caesarean sections as elective or emergency is carried out by the healthcare professional reporting to the NSHPC, with some data cleaning by the NSHPC team. For example, an elective caesarean section reported to have been carried out after the rupture of membranes will be reclassified as emergency. Definitions have not been entirely consistent over time and this may lead to some misclassification, though it is not clear how this may have influenced the findings. Limited data is currently available on adverse outcomes associated with different modes of delivery as this is not specifically requested on the NSHPC reporting forms. However, since uterine rupture is a very serious outcome, associated with maternal and perinatal severe morbidity as well as mortality (Ofir *et al*, 2003; Ronel *et al*, 2012), it was possible to search the free-text notes field of the NSHPC database to identify occurrences with reasonable confidence that this outcome was likely to be documented. This approach was not deemed appropriate for other less serious adverse events which are less likely to be consistently reported. Also, although the number of deliveries in the dataset was sufficiently large for most analyses, uterine rupture is a rare event, reflected in the wide confidence intervals around the estimated rate. Meanwhile, though information on the duration of rupture of membranes may be of relevance to analyses of mode of delivery, this has only been collected by the NSHPC since 2007 and insufficient data was available at the time of analysis.

As shown in the first part of this chapter, over half (57%) of women were parous at the time of their first pregnancy reported to the NSHPC. The inclusion of such women, rather than restricting the analysis to only those women who were nulliparous, could potentially influence the findings. Details of these women's prior obstetric history are not collected by the NSHPC. However, most women in the NSHPC originate from Africa, many of whom will have acquired their HIV infection in their country of origin (Health Protection Agency, 2011a). Therefore, any deliveries they had prior to their arrival in the UK are likely to have been vaginal deliveries even if they had diagnosed HIV, since elective caesarean sections have been little used for PMTCT in Africa (Aizire *et al*, 2013). To confirm that the inclusion of these women did not substantially affect the findings on patterns of mode of delivery within women, sensitivity analyses were conducted among those nulliparous at their first

reported pregnancy and the findings were very similar. Related to this, the analyses were restricted to women's last reported live or stillbirth only, and consideration of their obstetric history largely utilised only information on their immediately preceding delivery. Nevertheless, it is women's preceding delivery that is likely to have most bearing on the subsequent delivery.

7.4 Key findings

Adverse pregnancy and perinatal outcomes

- Of the 3028 repeat pregnancies during 2000-2010 most (90.4%) resulted in a live birth, 0.8% in a stillbirth, 6.6% a miscarriage, 2.2% in a termination

- Few women had repeated adverse outcomes; only one woman had two stillbirths, 33 had more than one miscarriage, and none had more than one HIV-positive infant

- Women were significantly more likely to conceive their repeat (as compared with index) pregnancies on ART (48.8% *vs*. 21.9%, $p<0.001$), and the proportion of repeat pregnancies conceived on ART increased significantly in more recent years (from 40.7% in 2005 to 61.5% in 2010, test for trend: $p<0.001$).

- Overall, 13.1% of repeat births were preterm, 12.6% of infants were of low birthweight, and 2.9% had a congenital abnormality

- Compared with first reported pregnancies, at their repeat pregnancies women did not appear to be at increased risk of stillbirth ($p=0.440$), preterm delivery ($p=0.240$), or having an infant with congenital abnormalities ($p=0.908$). They had a lower risk of having a low birthweight infant ($p=0.009$), but an increased risk of reported miscarriage ($p<0.001$)

- On multivariable analysis factors associated with preterm delivery among repeat pregnancies were a previous preterm delivery, being white, having a multiple pregnancy, and being immunosuppressed

- In a sub-analysis there was little evidence of an increased probability of preterm delivery among women conceiving on cART

Mode of delivery

- Almost half (47.0%) of the 2761 repeat live/stillbirths during 2005-2010 were delivered by elective caesarean section, 31.2% vaginally, and 21.8% by emergency caesarean section

- There was a significant increase in infants delivered vaginally between 2005 and 2010, from 21.0% to 39.3%, $p<0.001$, although, overall, 19.4% of women planning to deliver vaginally actually delivered by emergency caesarean section

- Despite the increase in women planning vaginal deliveries there was no evidence of an increase in emergency caesarean section deliveries ($p=0.140$)

- Almost a third (31.4%) of women delivering vaginally had delivered their previous infant by caesarean section. Looking at this the other way around, 13.6% of women who had delivered their previous infant by caesarean section subsequently had a VBAC, and this proportion increased significantly, from 8.3% in 2005 to 17.3% in 2010 (test for trend: $p<0.001$)

- Among women delivering by elective caesarean section the vast majority (94.5%) had delivered their previous infant via caesarean section

- Nearly three quarters (73.4%) of women delivering by elective caesarean section had an undetectable viral load and were thus eligible for a vaginal delivery

- MTCT rates were 0.65% (95% CI: 0.08-1.21 $n=5$) for elective caesarean section deliveries, 0.58% (95% CI: -0.02-1.38, $n=2$) for emergency caesarean section and 0.62% (95% CI:-0.08-1.31, $n=3$) for vaginal deliveries

Chapter 8 Discussion

The overarching aim of this thesis was to investigate the epidemiology of sequential pregnancies among HIV-positive women in the UK and Ireland, and to explore the health, therapeutic and obstetric management, and pregnancy outcomes of the women experiencing them. Such information will inform the care of HIV-positive women in the UK and Ireland and other similar settings, in the context of current and potential future pregnancies. The four results chapters of the thesis explored the frequency and predictors of repeat pregnancies (Chapter 4), women's engagement with HIV and pregnancy-related care and the health and management of those experiencing sequential pregnancies (Chapter 5), the influence of short-course cART for PMTCT on response to therapy in subsequent pregnancies (Chapter 6), and pregnancy and perinatal outcomes, together with mode of delivery (Chapter 7). A detailed discussion of the findings of these chapters, contextualised within the published literature, is provided within each chapter. This final chapter draws together key findings of the thesis under some broad themes, within the context of contemporary issues around the management of HIV-positive women of childbearing age. The implications of the findings for policy and practice are discussed. The broader strengths and limitations of the NSHPC are reviewed, and areas for future work highlighted.

8.1 Key findings and implications for policy and practice

8.1.1 High and increasing occurrence of repeat pregnancies

This thesis provides the first estimates of the rate of repeat pregnancies to diagnosed women in a European setting, and the first detailed exploration of repeat pregnancies among HIV-positive women in the UK and Ireland. The data clearly show that a substantial and increasingly large proportion of pregnancies to diagnosed women in the UK and Ireland are second and subsequent (accounting for 39% of pregnancies reported in 2009). This proportion now appears to be levelling off, with repeat pregnancies accounting for just under half of all pregnancies reported annually since 2011 (National Study of HIV in Pregnancy and Childhood, 2014). These data underscore the need for clinicians to take into account the high probability of future pregnancies among HIV-positive women who have already experienced a pregnancy as a diagnosed woman. It is important that demographic and clinical characteristics of these women, and the challenges that they present for therapeutic and obstetric management in current and potential future

pregnancies, are thoroughly understood. The analyses revealed clear variations in the probability of repeat pregnancies according to demographic characteristics. Repeat pregnancies were more likely in women who were younger, had fewer previous births, and in women from Middle and Western Africa compared with women born in the UK or Ireland, though there was no apparent association with clinical or immunological status. Such variations are an important consideration when planning reproductive health services and HIV care for people living with HIV.

The provision of on-going reproductive health care for HIV-positive women of childbearing age is undoubtedly important. This needs to encompass contraceptive advice, the avoidance of unintended pregnancies and pre-conception counselling including advice on conception strategies for serodiscordant couples (Hoyt *et al*, 2012; Steiner *et al*, 2013). Optimising maternal and infant health is of course an integral element, particularly for women living with HIV. Women may also need advice regarding unplanned pregnancies and access to termination of pregnancy services. Though information on contraceptive use and/or whether pregnancies were planned is not collected by the NSHPC, it is likely that a high proportion of pregnancies to HIV-positive women are unintended, as is the case among the general UK population (see Chapter 4, Section 4.3). Unintended and mistimed pregnancies are associated with adverse maternal and infant outcomes (Gipson *et al*, 2008; Shah *et al*, 2011), and the avoidance of these among HIV-positive women is one of the four components of the WHO's comprehensive approach for PMTCT (World Health Organization, 2003). The provision of accessible and effective family planning, and supporting women to make adequate use of such services, is therefore essential. Since HIV-positive women appear to be at higher risk of several adverse perinatal outcomes than the general population (see Chapter 2, Section 2.6 and Chapter 7, Section 7.1), identifying and addressing modifiable risk factors for adverse outcomes among these women is especially important. Two in five women conceived their repeat pregnancy less than 18 months after their previous delivery, with 11% conceiving in under six months. Short inter-pregnancy intervals have been associated with a range of adverse outcomes among the general population including preterm birth, low birthweight and stillbirth (Conde-Agudelo *et al*, 2006; Wendt *et al*, 2012). Although not significant in adjusted analyses presented in this thesis, there was an association between an inter-pregnancy interval of less than six months and an increased preterm delivery risk. Supporting HIV-positive women to achieve adequate birth spacing may thus be beneficial.

8.1.2 Women's engagement with HIV and pregnancy-related care

Several analyses presented in this thesis explored women's engagement with HIV and pregnancy-related care, and sought to identify variations in access to and uptake of care according to demographic or clinical characteristics. Although the data demonstrated good engagement with care overall (the majority of women received antenatal ART and MTCT rates were low), they do raise some areas of concern (Chapter 5). For example, almost half of women booked late for antenatal care at their repeat pregnancy. It is important that care providers understand the high probability of pregnancy (particularly in some groups), and ensure that women know how to access local antenatal services should they become pregnant (again). Women also need to be counselled on the benefits of booking for antenatal care early, even if they have safely delivered before. Close links between HIV and reproductive care services are crucial.

Potential missed opportunities for the timely initiation of ART among this population of previously diagnosed women were also apparent, during both pregnant and non-pregnant periods. Antenatal ART commenced at a median of 24 weeks among those with CD4 counts of ≥350 cells/μl, and only one week earlier if CD4 was <350 cells/μl. The latter group raise some concern since they require prompt treatment initiation for their own health (though may be deferred until after the first trimester) (Taylor *et al*, 2012), and are also a group at greater risk of MTCT (e.g. see Chapter 6). Of course ART initiation during pregnancy is to some extent dependent on timing of antenatal booking, but notable delays were apparent even after women had booked (a median lag of 10 and seven weeks from booking to starting ART in women with CD4 ≥350 cells/μl and <350 cells/μl respectively). These delays appear to be at least partly health service or provider-related; laboratory testing delays were noted, with 30% of women having a delay of four or more weeks from booking to laboratory testing. This is a potential area in which to improve practice. Guidelines should recommend that all HIV-positive women who are not on treatment have blood samples taken on the day that they book for antenatal care[62]. Education and efforts to raise awareness in primary care, antenatal and HIV services may also be needed. The benefits of earlier ART initiation in terms of PMTCT have been recently highlighted within the NSHPC as a whole (Townsend *et al*, 2014). Although there was a trend towards earlier antenatal ART initiation over time among women's sequential pregnancies, booking delays and the long interval between booking and starting ART in some women need to be addressed. Recommendations for future research on this topic are outlined in Section 8.3 below.

[62] UK National Screening Committee Programme Standards for the Infectious Diseases in Pregnancy Screening Programme do indicate that pregnant women already known to be HIV-positive should have prompt clinical evaluation (UK National Screening Committee, 2010).

Analyses of the health of women presenting with a second pregnancy who were not on ART at conception revealed that two-fifths had a CD4 count of <350 cells/µl, and 10% were severely immunosuppressed. This underscores the need for careful monitoring of CD4 counts and emergence of HIV/AIDS symptoms in all women after pregnancy, particularly those who discontinue ART after delivery. The data also raise concern as to the extent of loss to follow-up of women from care after their pregnancy ends. Linked NSHPC-SOPHID data revealed that 12% of women did not access HIV care during the calendar year after delivery. It is reassuring that the majority of women engaged with HIV care after pregnancy, though their motivation to continue this could wane over time. The reasons that these women presenting with low CD4 counts have not yet started treatment need further exploration. This should include an assessment of the contribution of disengagement from care in both the short and longer-term, and an exploration of the underlying reasons for delays in treatment initiation among those who are engaged in care (see Section 8.3 below). The healthcare sector has a vital role in ensuring HIV-positive women are maintained in care. It is essential that healthcare providers make HIV care as accessible as possible for women with children to care for. Important considerations include the provision of appointments at convenient times and locations, as well as having mechanisms in place to maintain women in care (e.g. follow-up of those who miss appointments). Patients in care should be provided with appropriate and accessible information, and engaged in a dialogue that takes into consideration their individual circumstances, beliefs, concerns and level of health literacy, to help them to make informed decisions about their care (Nunes *et al*, 2009). Patient organisations may have an important part to play here. It is essential that patients have a good understanding of the benefits of ART, and HIV care more broadly, even if they feel well. Prior exposure to short-course ART for PMTCT may potentially create confusion around the need to initiate lifelong treatment in the future. This needs to be clearly explained from the outset.

Analyses revealed that women with repeat pregnancies are a heterogeneous group. Investigation of demographic characteristics associated with poorer engagement with care (late booking for antenatal care, later initiation of antenatal ART, or having an indication for treatment among those not on ART at conception of their second pregnancy) largely demonstrated equality in the timeliness of care, consistent with the equity in care seen among the UK HIV-positive population more generally (Delpech *et al*, 2013). However, some variations were apparent, as highlighted in Chapter 5. For example, women originating from sub-Saharan Africa started antenatal ART significantly later than those born in the UK or Ireland, and there was also some indication of later booking for antenatal care among this group. Migrants from sub-Saharan Africa face a multitude of potential

barriers to accessing healthcare including stigma, discrimination and poverty (Elford *et al*, 2008a; Ibrahim *et al*, 2008; Prost, 2005). The provision of culturally appropriate, accessible services is essential, though clearly a comprehensive approach is needed to reduce social and economic disparities which may impact on many aspects of the lives of migrants. It is important to note that only relatively broad socio-demographic categories can be explored using the NSHPC data which may have concealed important variations between sub-groups (see 'strengths and limitations' below). Treatment and health status were also associated with women's level of engagement with care. For example, women not on ART at conception of their repeat pregnancies booked for antenatal care significantly later than those conceiving on treatment. Meanwhile, women who received insufficient ART (none or short duration) during their first pregnancy were at increased risk of presenting in a subsequent pregnancy with a low CD4 count. Such groups may require particularly close follow-up to ensure good engagement with care. Identifying women who are engaging poorly with services in their first pregnancy, and providing additional support not only during but also after pregnancy, may have benefits for their future pregnancies, as well as for their health more generally. Although women with a history of injecting drug use now only account for a small proportion of women reported to the NSHPC (the small sample size potentially resulting in a lack of power to detect associations), studies in other settings have found these women to be at increased risk of adverse outcomes such as insufficient antenatal ART (Bailey et al, 2011). These women may require specialised outreach services to help engage them with HIV and pregnancy care. The findings presented in this thesis highlight the need for further research to help identify modifiable structural or individual-level barriers to timely ART initiation among diagnosed women, both within and outside the context of pregnancy (see Section 8.3 below).

8.1.3 Optimising management

Though the benefits of antenatal ART far outweigh the risks (Newell *et al*, 2013), the optimisation of the care of HIV-positive childbearing women is a priority for both women and their infants. Good maternal health likely has benefits for the outcomes of their current and any future pregnancies. For example, women in poorer health (indicated by lower CD4 counts) had an increased probability of preterm delivery in their repeat pregnancies (Chapter 7). Meanwhile, ensuring that HIV-positive women live as long and healthy lives as possible, throughout and beyond their childbearing years, benefits both themselves and their children. Since the first trials carried out in the 1990's demonstrated the effectiveness of ART taken during pregnancy for PMTCT (see Chapter 1, Section 1.2.4), short-course antenatal ART for women not in need of treatment for their own heath has been a mainstay of PMTCT interventions, recommended in both resource-rich and resource-limited settings

(Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission, 2012; Taylor *et al*, 2012; World Health Organization, 2013). However, the landscape has changed dramatically since the early years of the epidemic, and during the course of this PhD the WHO introduced 'Option B+' for HIV-positive pregnant women (see Chapter 2, Section 2.4). The possibility of lifelong ART for all women is thus an emerging theme in the management of HIV in pregnancy. The evidence-base for such an approach is, however, lacking, with issues such as operational challenges, cost, equity in access, retention in care, adherence, maternal health, drug resistance, and women's views and preferences requiring more research (Ahmed *et al*, 2013; Shaffer *et al*, 2014). Several analyses presented in this thesis contribute new information to the evolving evidence-base.

In support of an argument for recommending lifelong ART for all pregnant women, analyses revealed that a quarter of women with a CD4 count of ≥350 cells/μl at their first pregnancy had counts of <350 cells/μl at their second pregnancy (Chapter 5). These data indicate that for many women there may be health benefits of initiating lifelong ART in their first pregnancy, whether or not they experience future pregnancies. UK guidelines allow for, rather than recommend, lifelong ART for pregnant women presenting with CD4 counts of 350-500 cells/μl (in the absence of other indications e.g. certain co-infections) (Taylor *et al*, 2012). A recommendation could be considered for this group in particular, as the probability of having an indication for treatment at their second pregnancy was especially high (40% had <350 cells/μl at their second pregnancy). Similar findings have been reported in other settings (Coria *et al*, 2012; Ekouevi *et al*, 2012; Watts *et al*, 2013). Furthermore, the high probability of repeat pregnancies in the contemporary population of HIV-positive women, often within a relatively short time period (the median birth-to-pregnancy interval was less than two years), calls into question the use of short-course therapy from a practical perspective.

Data presented in this thesis also demonstrate that the initiation of lifelong ART may have benefits for women's future pregnancy outcomes. Women starting ART during their second pregnancy had over four times the odds of having a detectable viral load at delivery compared with those conceiving on treatment. Although the risk of MTCT is now very low in appropriately managed women, it still exists and the unadjusted rate was three times higher among those not on ART at conception compared with those conceiving on treatment (Chapter 5). A further possible benefit of women conceiving their repeat pregnancies on ART is that more women might then achieve an undetectable viral load by delivery, thus enabling them to plan for a normal delivery (in the absence of other contraindications) (see Chapter 7). Finally, around half of women presenting with a repeat pregnancy were not yet on treatment. As noted in Chapter 1, viral load is highly correlated with the risk of onward

transmission of HIV, not only for MTCT but also transmission to sexual partners. The role of the treatment of HIV-positive women of childbearing age as an HIV prevention strategy in the UK setting is difficult to assess as we do not know what proportion of HIV-positive pregnant women in the UK are in serodiscordant partnerships or the contribution of this group to the overall rate of HIV transmission in the UK. However, 45% of new infections in the UK in 2012 were heterosexually acquired (Aghaizu *et al*, 2013), and an increasing proportion are believed to have been acquired in the UK (it is estimated that over two-fifths of infections in people born abroad were acquired in the UK, based on data for 2010) (Rice *et al*, 2012). Since women with (repeat) pregnancies are a group who are likely to be having unprotected sex, there is clearly potential for onward transmission which could be reduced with effective treatment (Cohen *et al*, 2011).

These potential benefits of lifelong ART are, however, based on the assumption that women adhere to treatment once initiated, and conceive any subsequent pregnancies on suppressive therapy. Disengagement from HIV care is therefore of particular concern. Early data from Malawi, where the Option B+ approach has been championed, indicate that retention in care presents a challenge, particularly among women initiating ART during pregnancy (i.e. those not yet needing treatment for their own health) (Tenthani *et al*, 2014). Further to this, sub-optimal ART adherence has been noted in post-partum women (Nachega *et al*, 2012), which can result in poor virological suppression thus creating an environment in which drug resistance can develop (Clavel *et al*, 2004; Tang *et al*, 2012). This may impact on women's response to therapy and future treatment options. Nonetheless, the analyses in Chapter 5 revealed that women conceiving their subsequent pregnancies on treatment booked significantly earlier for antenatal care, suggesting potentially higher levels of engagement with care among this group compared with those not receiving ART prior to pregnancy. Supporting this assertion, not being on ART has been associated with a greater risk of loss to follow-up from HIV care among the broader UK HIV-positive population (Gerver *et al*, 2010; Rice *et al*, 2011), and among post-partum women in other settings (Coria *et al*, 2012; Tenthani *et al*, 2014).

Around half of repeat pregnancies were conceived on ART (and the proportion increased from 41% in 2005 to 62% in 2010). Should the Option B+ approach be adopted, theoretically all women would eventually be conceiving their repeat pregnancies on ART. Though there was no significant association between conceiving on ART and preterm delivery risk (Chapter 7), the results should be interpreted with some caution as this was a sub-analysis which may have been limited by small numbers. The situation needs ongoing monitoring. Furthermore, with most women now receiving PI-based HAART during pregnancy (Chapter 6), there is the potential for increasing preterm delivery rates among

HIV-positive women in years to come as the current evidence-base points towards PI-based cART as a particular risk for preterm delivery (see Chapter 2, Section 2.6). Meanwhile, the potential adverse impact of earlier initiation of lifelong ART on women's longer-term health also needs consideration. As has been recently highlighted, though new formulations of antiretrovirals have improved safety profiles, drug toxicities are still a concern and need to be carefully balanced against the benefits of starting ART earlier in women not needing treatment for their own health (Sabin *et al*, 2013). Finally, women's opinions and choices are an important consideration, and the HIV-positive community has voiced concerns and reservations about lifelong ART for all women (Ngarina *et al*, 2014; Welbourn, 2012).

Analyses revealed no evidence of an association between previous short-course PI-based cART exposure and response to therapy in a subsequent pregnancy (Chapter 6). Looking towards women's future pregnancies, this finding is reassuring, indicating that short-course PI-based therapy continues to be a viable option, thus supporting current recommendations (Taylor *et al*, 2012). There was, however, some evidence that women previously exposed to NNRTI-based regimens may have an increased probability of not adequately suppressing the virus in future pregnancies. Women in receipt of these regimens during pregnancy may require particularly careful monitoring after their pregnancy ends in order to support them to continue to adhere to their treatment and ensure that any treatment discontinuations are carefully managed.

In summary, analyses presented in this thesis suggest that lifelong ART may have benefits for many women of childbearing age and their future pregnancy outcomes, but do also support short-course therapy as an effective PMTCT intervention, even with future pregnancies in mind. These findings add to the evidence-base to inform policy and clinical decision-making in the UK and Ireland, and other resource-rich countries. It may be hard to extrapolate the findings to resource-limited settings where the situation is very different and the challenges presented by the epidemic are far greater. Equity in access to care is a particular issue in settings such as sub-Saharan Africa where many people still do not have access to the live-saving treatment that they require (UNAIDS, 2013)[63]. However, for example, the clear association between conceiving subsequent pregnancies on ART and a decreased risk of detectable viral load at delivery (Chapter 5) has broader applicability. MTCT rates are still high in some low and middle-income countries with 260,000 new infections in children during 2012 and, despite significant improvements in recent years, nearly two-fifths of women are still not receiving effective antenatal ART (UNAIDS, 2013).

[63] In 2012, HIV treatment coverage was 61% in low and middle-income countries (UNAIDS, 2013).

Lifelong ART in this population has a potentially important role in reducing the risk of MTCT in future pregnancies.

The data also need to be considered in light of the changing global situation with regards to HIV treatment. The WHO now provides a programmatic recommendation for the treatment of people with CD4 counts of ≤500 cells/μl, and all those with serodiscordant partners regardless of CD4 count (World Health Organization, 2013)[64]. Some other international guidelines recommend that treatment is offered to all HIV-positive people (Panel on Antiretroviral Guidelines for Adults and Adolescents, 2013; Thompson *et al*, 2012). Although the UK remains more conservative in its recommendations (Williams *et al*, 2012)[65], it seems likely that the current global move towards more HIV-positive people being on treatment at higher CD4 counts will continue. In the UK and Ireland, and other resource-rich settings, an individualised approach to the management of HIV in pregnancy may be most appropriate, with all women starting ART in pregnancy enabled to make an informed decision about whether to continue treatment for life on the basis of their CD4 count and viral load (without a specified minimum CD4 count at which lifelong treatment can begin), plans for future pregnancies, the HIV status of their partner, and their personal preference. It remains imperative that the risks and benefits of lifelong ART are carefully assessed, with respect to both childbearing women and their infants, and the broader HIV-positive population.

8.2 Strengths and limitations

Limitations relevant to specific analyses have been discussed within each results chapter of this thesis. Here, some of the broader strengths and limitations of the NSHPC are highlighted.

The NSHPC is a large, well established, active surveillance system which has been running for over two decades, and reporting of pregnancies in women with diagnosed HIV is comprehensive (Townsend *et al*, 2008b). It is a national study and all analyses in this thesis were restricted to women diagnosed prior to delivery. Due to the routine offer and high uptake of antenatal HIV screening since 2000, the number of pregnant women with undiagnosed HIV by the time of delivery is low (Townsend *et al*, 2006). Findings are thus highly generalisable to the population of HIV-positive women living in the UK and Ireland.

[64] The WHO provides this as a programmatic recommendation (for resource-limited settings, typically in the context of high HIV prevalence). It indicates that priority should be given to those with CD4 counts of ≤350 cells/μl.

[65] UK guidelines recommend treatment initiation in those with an AIDS-defining illness and/or CD4 counts of ≤350 cells/μl (or at higher CD4 counts for those meeting certain criteria e.g. hepatitis B or C co-infection) (Williams *et al*, 2012).

The major strength of the NSHPC for examining repeat pregnancies in HIV-positive women compared with other similar data sources such as the ECS (sites in 10 European countries) (Thorne *et al*, 2005) and the US WITS (six clinical consortia across the US) (Sheon *et al*, 1996), is that it has national coverage. This, together with high reporting rates, means that the NSHPC provides reliable denominators for estimating the rate of repeat pregnancies. Families with young children may be quite a mobile population in general, and migrants particularly so (Creighton *et al*, 2004). Women who move to a different geographic location in the UK or Ireland between pregnancies should still be reported to the NSHPC and can be linked with their previously reported pregnancies. The NSHPC also seeks to collect information on all pregnancies, not only live births, although there is likely to be under-ascertainment of early miscarriages and terminations (as discussed in Chapter 7). Furthermore, since it is an active surveillance study, rather than a consented cohort, there is not an issue of under ascertainment of pregnancies due to women declining to participate. As evidenced in this thesis, the NSHPC provides a rich source of data on the health, management and pregnancy outcomes of women in the context of sequential pregnancies.

The NSHPC is a voluntary and national scheme. It is therefore necessary to prioritise the information requested in order to limit the number of data items collected, thus ensuring reporting rates remain high and that data are as complete and high quality as possible. This does, however, mean that it is not feasible to collect some specific data items that would have been informative in the analyses and for the interpretation of the results. Although around half of women were parous prior to their first pregnancy reported to the NSHPC, detailed information on women's previous pregnancies not reported to the NSHPC is not collected. For example, no information is collected on the timing of previous pregnancies, women's total number of living children, mode of delivery or gestational age. This presents a limitation for the analyses conducted in this thesis and may have resulted in some confounding that could not be adjusted for in the analyses, as has been highlighted in the relevant results chapters (in particular, Chapters 4 and 7). Meanwhile, factors related to women's social circumstances (e.g. socio-economic status, relationship status and migration status) would be useful. For example, the vast majority of diagnosed women in the UK and Ireland are migrants from sub-Saharan Africa who represent a very diverse population. In the context of comprehensive reporting, it is difficult to request additional highly sensitive information which could depress reporting rates or respondents' ability to provide timely information. Therefore, the NSHPC does not allow specific investigation of groups such as undocumented migrants and asylum seekers who may experience particular difficulties in accessing healthcare (Rechel *et al*, 2013). Other behavioural characteristics, such as smoking during pregnancy, would be helpful for analyses of

perinatal outcomes, though potentially difficult to collect as the information would be self-reported and desirability bias[66] may be an issue. Indeed, unmeasured factors that could not be either explored as predictors of outcomes of interest in their own right, or adjusted for as confounding factors, present a limitation for the analyses.

By its nature, the NSHPC only requests information during the antenatal (and immediate post-partum) period which makes it difficult to explore the longer-term health of childbearing women. However, unique to those women with more than one pregnancy reported to the study, the dataset allows the assessment of some clinical and immunological trajectories between women's pregnancies. This could be utilised further in the future given the large number of repeat pregnancies now being reported. Furthermore, the feasibility and utility of linking the NSHPC with SOPHID, enabling the attainment of additional information on women after their pregnancy ends (and hence prior to any future pregnancies), has been demonstrated here with >85% of women matched to SOPHID.

Finally, missing data is an issue for any study and can potentially lead to biased findings if missingness is not random. The extent of missing data on key exposure and outcome variables was assessed within each chapter. Any bias that may have been introduced by missing data was explored by comparing the characteristics of those with and without missing data on the outcome of interest. On the whole, the proportion of missing data on key variables was low, except for some clinical and immunological variables. For example, viral load at delivery was missing for around 45% of pregnancies. However, the use of an imputed variable (see Chapter 3, Section 3.4) proved effective in increasing available data. The robustness of analyses conducted on the imputed variable was confirmed by running concurrent sensitivity analyses on the non-imputed variable. Furthermore, an advantage of focusing on women with repeat pregnancies reported is that there is more than one opportunity for woman-specific (though not pregnancy-specific) characteristics to be collected, thus further reducing the amount of missing data. This could, however, also potentially introduce some bias when drawing comparisons with women who have only had one pregnancy reported.

8.3 Conclusions and recommendations for future research

This thesis informs the evidence-base for the effective management of HIV-positive women in the context of current and potential future pregnancies. It also identifies several areas for further work on sequential pregnancies, as well as the broader health and management of women of childbearing age.

[66] Desirability bias results from people's responses being biased towards those that are considered more socially acceptable (Fisher, 1993).

The high probability of repeat pregnancies among HIV-positive women emphasises the importance of ongoing reproductive care which needs to take account of demographic variations in the likelihood of future pregnancies. With regard to future NSHPC analyses, the findings highlight that women experiencing repeat pregnancies since their HIV diagnosis are no longer simply a 'sub-group' that require investigation in their own right but a large, integral part of the NSHPC population. The impact of these repeat pregnancies e.g. the clustering of pregnancies within women which requires statistical adjustment, need consideration with respect to all future analyses of the dataset. Meanwhile, information on whether or not pregnancies were planned would be informative on a range of issues relevant to the contemporary population of HIV-positive women. For example, understanding whether the high probability of repeat pregnancies among women originating from Middle and Western Africa is related to a higher prevalence of unplanned pregnancy among these groups would help inform the provision of family planning services tailored to women most in need. However, attempting to collect such information through an ongoing national study such as the NSHPC could be problematic, not least because of the range of ways in which a 'planned' or 'unplanned' pregnancy may be understood and interpreted, as noted in Chapter 4, Section 4.3. Information on pregnancy planning may therefore be best collected by means of a specific survey, for example a short questionnaire left in clinics for women to complete.

Late booking for antenatal care and delays in antenatal ART initiation, particularly among those requiring treatment, are an issue for some women. In order to address these delays, further research is required to elucidate the reasons behind them including potential structural barriers (e.g. the socio-economic environment of HIV-positive women) and those related to women's individual circumstances, beliefs and choices. Assessment of the contribution of disengagement from HIV care after pregnancy, as well as any inequalities in access to or uptake of care that cannot be explored using the NSHPC data alone (e.g. in relation to immigration status), will be important. Mixed methods research including interviews or focus groups with women could help draw out some of the more nuanced differences between sub-groups and identify common themes around women's reasons for delaying ART initiation. Reasons such as concerns about side-effects of ART or safety for the unborn baby, for example, might be targeted via interventions such as patient information leaflets addressing women's key concerns. A questionnaire-based survey and/or interviews with clinicians could also help to identify any health system or provider-related barriers to timely laboratory assessment and ART initiation.

Pregnancies reported to the NSHPC are predominantly in black African women with a likely heterosexual route of HIV exposure. Notwithstanding the heterogeneity within this

population, it should also be remembered that the small numbers of pregnancies in some other population sub-groups precluded detailed analyses. One emerging sub-group is that of young women who acquired HIV vertically from their own mothers (Kenny *et al*, 2012; Thorne *et al*, 2007b). Recent analyses have shown that 45 of these women have had pregnancies, a third of whom have had more than one (NSHPC, unpublished data reported by end of June 2013). These women may have particularly complex treatment histories, and (repeat) pregnancies in this group will need assessing as numbers increase.

As has been highlighted, there are many unanswered questions around the Option B+ approach for the management of HIV in pregnancy. Analyses presented in this thesis add to the evidence-base for such an approach, indicating potential benefits of lifelong ART for both maternal health and future pregnancy outcomes. The NSHPC dataset, especially when linked to other data sources such as SOPHID, can continue to contribute to the evidence-base for the UK and other similar settings. For example, though analyses showed high levels of attendance for HIV care during the year after delivery, monitoring longer-term retention in care will be important, including how retention differs between those who remain on ART and those who discontinue after delivery. This could be carried out by means of ongoing linkage with SOPHID. The linked data could also provide information on diagnosed women's use of HIV care prior to conception. Adherence to ART, both during and outside of pregnancy, is likely to be difficult to collect through an ongoing national-level study. However, longer-term viral suppression in post-partum women could be assessed through the linkage with SOPHID which collects information on a range of indicators among those attending HIV care, including viral loads and CD4 counts. Again, monitoring differences between women who remain on ART after pregnancy and discontinuers would be helpful. It would also be informative to examine whether women who start and stop ART with each pregnancy have a faster rate of CD4 count decline than those who have never received ART (potentially utilising a 'control' group of as-yet untreated women present in SOPHID). Additionally, the UK CHIC study, which has now been successfully linked with the NSHPC, provides a rich source of data on patterns of ART use and clinical and immunological trajectories during and outside of women's pregnancies (Huntington *et al*, 2012). However, only a proportion of women reported to the NSHPC are captured by UK CHIC, which is not a national study. Recent US data demonstrated that women who maintained viral suppression between pregnancies had improved health at delivery of their sequential pregnancies, as well as reduced rates of vertical transmission (Stewart *et al*, 2014). It would be interesting to explore this in the UK setting.

Given expanded access to ART in resource-limited settings and the global shift towards earlier initiation of HIV treatment, together with the findings of this thesis, it seems

inevitable that women will present in pregnancy with increasingly complex treatment histories (either in the context of previous pregnancies or prior treatment for their own health). There was no evidence that the use of short-course PI-based cART impacted on response to therapy in subsequent pregnancies, supporting current UK recommendations for the management of HIV in pregnancy. However, the lack of drug resistance data hampered interpretation of the findings. There are currently no data on the prevalence of drug resistance among HIV-positive pregnant women in the UK and Ireland, or the contribution of short-course therapy for PMTCT to the development of resistance. This thesis highlights the utility of data linkage; the high level of matching achieved between the NSHPC and SOPHID paves the way for future linkages, particularly with other national level datasets. Linkage with the UK Drug Resistance Database (currently underway) will enable assessment of the prevalence of antiretroviral drug resistance in women's index pregnancies, and emergence of resistance in subsequent pregnancies. Investigation and ongoing monitoring of drug resistance will be important to inform best clinical management of women, with a view to the impact of current treatment decisions on future pregnancies as well as women's longer-term health and management.

Repeat pregnancies were more likely to be conceived on ART than index pregnancies, and the proportion of all pregnancies conceived on treatment may increase given the move towards earlier initiation of HIV treatment. Although the analyses showed that women were not at increased risk of adverse perinatal outcomes at their repeat, as compared with index, pregnancies, the risk of outcomes such as preterm delivery was high (13%). There is a need for careful monitoring of perinatal outcomes, particularly for pregnancies conceived on cART, in light of the uncertainties in the evidence-base for preterm delivery risk. This should include assessment of the outcomes of antenatal exposure to newer antiretrovirals and those used in third-line regimens. Information on co-infections (e.g. hepatitis B, hepatitis C, syphilis) has been collected by the NSHPC since 2008 and future analyses should explore how such co-infections may impact on pregnancy outcomes. The analyses on preterm delivery risk also demonstrated the importance of women's obstetric histories; previous preterm delivery emerged as a very strong risk factor for preterm delivery in subsequent pregnancies. This finding has implications for future analyses of preterm delivery, an area of ongoing interest and research, which should be adjusted for prior obstetric history. Such adjustments may also be an important consideration for analyses of other adverse perinatal outcomes such as low birthweight. With respect to future NSHPC data collection, requesting information on whether or not women's previous unreported pregnancies (e.g. those occurring prior to HIV diagnosis) were delivered preterm would aid future analyses.

Finally, there are complexities in the obstetric management of women's repeat pregnancies. This thesis provides the first national-level exploration of patterns in mode of delivery in women's sequential pregnancies. Almost a third of women delivering vaginally had delivered their previous infant by caesarean section. The large pool of women with a history of caesarean section birth(s), together with more recent guidelines specifically recommending a vaginal delivery among eligible women (Taylor *et al*, 2012), means the rate of vaginal deliveries in women with a history of caesarean section is likely to increase in the coming years. Adverse outcomes such as uterine rupture, and the potential impact on the risk of MTCT, should be closely monitored.

References

Abatemarco DJ, Catov JM, Cross H, Delnevo C, and Hausman A (2008). Factors associated with zidovudine receipt and prenatal care among HIV-infected pregnant women in New Jersey. *J Health Care Poor Underserved,* 19(3), 814-828.

Abduljalil K, Furness P, Johnson TN, Rostami-Hodjegan A, and Soltani H (2012). Anatomical, physiological and metabolic changes with gestational age during normal pregnancy: a database for parameters required in physiologically based pharmacokinetic modelling. *Clin Pharmacokinet,* 51(6), 365-396.

Adler MW (2001). ABC of AIDS: Development of the epidemic. *BMJ,* 322(7296), 1226-1229.

Aebi-Popp K, Lapaire O, Glass TR, Vilen L, Rudin C, Elzi L, Battegay M, Keiser O, de Tejada BM, and Hoesli IM (2010). Pregnancy and delivery outcomes of HIV infected women in Switzerland 2003-2008. *Journal of Perinatal Medicine,* 38(4), 353-358.

Aebi-Popp K, Mulcahy F, Glass TR, Rudin C, Martinez de Tejada B, Bertisch B, Fehr J, Grawe C, Scheibner K, Rickenbach M, Hoesli I, and Thorne C (2013a). Missed opportunities among HIV-positive women to control viral replication during pregnancy and to have a vaginal delivery. *J Acquir Immune Defic Syndr,* 64(1), 58-65.

Aebi-Popp K, Mulcahy F, Rudin C, Hoesli I, Gingelmaier A, Lyons F, and Thorne C (2013b). National Guidelines for the prevention of mother-to-child transmission of HIV across Europe - how do countries differ? *Eur J Public Health,* 23(6), 1053-1058.

Agangi A, Thorne C, and Newell ML (2005). Increasing likelihood of further live births in HIV-infected women in recent years. *BJOG,* 112(7), 881-888.

Aghaizu A, Brown AE, Nardone A, Gill ON, Delpech VC, and Contributors (2013). HIV in the United Kingdom 2013 Report: data to end 2012. London, UK: Public Health England.

Ahmed S, Kim MH, and Abrams EJ (2013). Risks and benefits of lifelong antiretroviral treatment for pregnant and breastfeeding women: a review of the evidence for the Option B+ approach. *Curr Opin HIV AIDS,* 8(5), 473-488.

Aidala A, Needham Waddell E, and Sotheran J (2004). The Delayers Report: Factors associated with delayed care seeking among HIV-infected individuals in New York city. New York, US: Mailman School of Public Health of Columbia University and HIV Health and Human Services Planning Council of New York.

Aizire J, Fowler MG, and Coovadia HM (2013). Operational issues and barriers to implementation of prevention of mother-to-child transmission of HIV (PMTCT) interventions in Sub-Saharan Africa. *Curr HIV Res,* 11(2), 144-159.

Al-Zirqi I, Stray-Pedersen B, Forsen L, and Vangen S (2010). Uterine rupture after previous caesarean section. *BJOG,* 117(7), 809-820.

Aldous MB and Edmonson MB (1993). Maternal age at first childbirth and risk of low birth weight and preterm delivery in Washington State. *JAMA,* 270(21), 2574-2577.

American College of Obstetricians and Gynecologists (2013). ACOG Committee Opinion No. 579: Definition of term pregnancy. *Obstetrics and Gynecology,* 122(5), 1139-1140.

Ananth CV, Getahun D, Peltier MR, Salihu HM, and Vintzileos AM (2006). Recurrence of spontaneous versus medically indicated preterm birth. *Am J Obstet Gynecol,* 195(3), 643-650.

Anderson J (2008). Coming and going: some aspects of care for migrants with HIV in the UK. *J Infect,* 57(1), 11-15.

Antiretroviral Pregnancy Registry Steering Committee (2013). Antiretroviral Pregnancy Registry International interim report: 1 January 1989 through 31 July 2013. Wilmington, US: Registry Coordinating Center.

Arrive E, Newell ML, Ekouevi DK, Chaix ML, Thiebaut R, Masquelier B, Leroy V, Perre PV, Rouzioux C, and Dabis F (2007). Prevalence of resistance to nevirapine in mothers and children after single-dose exposure to prevent vertical transmission of HIV-1: a meta-analysis. *International Journal of Epidemiology,* 36(5), 1009-1021.

Asboe D, Aitken C, Boffito M, Booth C, Cane P, Fakoya A, Geretti AM, Kelleher P, Mackie N, Muir D, Murphy G, Orkin C, Post F, Rooney G, Sabin C, Sherr L, Smit E, Tong W, Ustianowski A, Valappil M, Walsh J, Williams M, and Yirrell D (2012). British HIV Association guidelines for the routine investigation and monitoring of adult HIV-1-infected individuals 2011. *HIV Med,* 13(1), 1-44.

Astolfi P and Zonta LA (1999). Risks of preterm delivery and association with maternal age, birth order, and fetal gender. *Human Reproduction,* 14(11), 2891-2894.

Aveyard P, Cheng KK, Manaseki S, and Gardosi J (2002). The risk of preterm delivery in women from different ethnic groups. *BJOG,* 109(8), 894-899.

Aziz N, Sokoloff A, Kornak J, Leva NV, Mendiola ML, Levison J, Feakins C, Shannon M, and Cohan D (2013). Time to viral load suppression in antiretroviral-naive and -experienced HIV-infected pregnant women on highly active antiretroviral therapy: implications for pregnant women presenting late in gestation. *BJOG,* 120(12), 1534-1547.

Babiker AG, Emery S, Fatkenheuer G, Gordin FM, Grund B, Lundgren JD, Neaton JD, Pett SL, Phillips A, Touloumi G, and Vjechaj MJ (2013). Considerations in the rationale, design and methods of the Strategic Timing of AntiRetroviral Treatment (START) study. *Clin Trials,* 10 Suppl 1 S5-S36.

Bailey H, Townsend C, Cortina-Borja M, and Thorne C (2011). Insufficient antiretroviral therapy in pregnancy: missed opportunities for prevention of mother-to-child transmission of HIV in Europe. *Antivir Ther,* 16(6), 895-903.

Bailey H, Townsend CL, Cortina-Borja M, and Thorne C (2013). Improvements in virological control among women conceiving on combination antiretroviral therapy in Western Europe. *AIDS,* 27(14), 2312-2315.

Baker EC and Rajasingam D (2012). Using Trust databases to identify predictors of late booking for antenatal care within the UK. *Public Health,* 126(2), 112-116.

Bangsberg DR (2006). Less than 95% adherence to nonnucleoside reverse-transcriptase inhibitor therapy can lead to viral suppression. *Clin Infect Dis,* 43(7), 939-941.

Barrett G and Wellings K (2002). What is a 'planned' pregnancy? Empirical data from a British study. *Soc Sci Med,* 55(4), 545-557.

Bassetti S, Battegay M, Furrer H, Rickenbach M, Flepp M, Kaiser L, Telenti A, Vernazza PL, Bernasconi E, and Sudre P (1999). Why is highly active antiretroviral therapy (HAART) not prescribed or discontinued? Swiss HIV Cohort Study. *J Acquir Immune Defic Syndr,* 21(2), 114-119.

Beck S, Wojdyla D, Say L, Betran AP, Merialdi M, Requejo JH, Rubens C, Menon R, and Van Look PF (2010). The worldwide incidence of preterm birth: a systematic review of maternal mortality and morbidity. *Bull World Health Organ,* 88(1), 31-38.

Bedimo-Rung AL, Clark AR, Dumestre J, Rice J, and Kissinger P (2005). Reproductive decision-making among HIV-Infected women. *J Natl Med Assoc,* 97(10), 1403-1410.

Berhan Y and Berhan A (2013). Meta-analyses of fertility desires of people living with HIV. *BMC Public Health,* 13(1), 409.

Berkman ND, Sheridan SL, Donahue KE, Halpern DJ, and Crotty K (2011). Low health literacy and health outcomes: an updated systematic review. *Ann Intern Med,* 155(2), 97-107.

Bernstein PS (2005). Risks associated with cesarean delivery. Available at: http://www.medscape.org/viewarticle/512946_4 (Accessed February 2014).

BHIVA Writing Committee on behalf of the BHIVA Executive Committee (2001). British HIV Association (BHIVA) guidelines for the treatment of HIV-infected adults with antiretroviral therapy. *HIV Med,* 2(4), 276-313.

Billari FC and Kohler HP (2004). Patterns of low and lowest-low fertility in Europe. *Popul Stud (Camb),* 58(2), 161-176.

Blair JM, Hanson DL, Jones JL, and Dworkin MS (2004). Trends in pregnancy rates among women with human immunodeficiency virus. *Obstetrics and Gynecology,* 103(4), 663-668.

Bland JM and Altman DG (1995). Multiple significance tests: the Bonferroni method. *BMJ,* 310(6973), 170.

Bland JM and Altman DG (1998). Survival probabilities (the Kaplan-Meier method). *BMJ,* 317(7172), 1572.

Bland JM and Altman DG (2000). Statistics notes. The odds ratio. *BMJ,* 320(7247), 1468.

Blondel B, Dutilh P, Delour M, and Uzan S (1993). Poor antenatal care and pregnancy outcome. *Eur J Obstet Gynecol Reprod Biol,* 50(3), 191-196.

Blondel B and Marshall B (1998). Poor antenatal care in 20 French districts: risk factors and pregnancy outcome. *J Epidemiol Community Health,* 52(8), 501-506.

Boehme AK, Davies SL, Moneyham L, Shrestha S, Schumacher J, and Kempf MC (2014). A qualitative study on factors impacting HIV care adherence among postpartum HIV-infected women in the rural southeastern USA. *AIDS Care,* 26(5), 574-581.

Boer K, England K, Godfried MH, and Thorne C (2010). Mode of delivery in HIV-infected pregnant women and prevention of mother-to-child transmission: changing practices in Western Europe. *HIV Med,* 11(6), 368-378.

Boer K, Nellen JF, Patel D, Timmermans S, Tempelman C, Wibaut M, Sluman MA, van der Ende ME, and Godfried MH (2007). The AmRo study: pregnancy outcome in HIV-1-infected women under effective highly active antiretroviral therapy and a policy of vaginal delivery. *BJOG,* 114(2), 148-155.

Boerleider AW, Wiegers TA, Mannien J, Francke AL, and Deville WL (2013). Factors affecting the use of prenatal care by non-western women in industrialized western countries: a systematic review. *BMC Pregnancy Childbirth,* 13, 81.

Bogart LM, Kelly JA, Catz SL, and Sosman JM (2000). Impact of medical and nonmedical factors on physician decision making for HIV/AIDS antiretroviral treatment. *J Acquir Immune Defic Syndr,* 23(5), 396-404.

Brant R (1990). Assessing proportionality in the proportional odds model for ordinal logistic regression. *Biometrics,* 46(4), 1171-1178.

Briand N, Jasseron C, Sibiude J, Azria E, Pollet J, Hammou Y, Warszawski J, and Mandelbrot L (2013). Cesarean section for HIV-infected women in the combination antiretroviral therapies era, 2000-2010. *Am J Obstet Gynecol,* 209(4), 335 e331-312.

Briand N, Mandelbrot L, Blanche S, Tubiana R, Faye A, Dollfus C, Chenadec JL, Benhammou V, Rouzioux C, and Warszawski J (2011). Previous antiretroviral therapy for prevention of mother-to-child transmission of HIV does not hamper the initial response to PI-based multitherapy during subsequent pregnancy. *J Acquir Immune Defic Syndr,* 57(2), 126-135.

British HIV Association, British Association of Sexual Health and HIV, and British Infection Society (2008). UK National Guidelines for HIV Testing.

Brown K, Holland B, Mosquera C, Calilap C, and Bardeguez A (2012). Human immunodeficiency virus infection in advanced maternal age gravidas. *AIDS Res Hum Retroviruses,* 28(3), 265-269.

Bryant AS, Leighty RM, Shen X, Read JS, Brouwers P, Turpin DB, LaRussa PS, Pacheco-Acosta E, Paul ME, Vajaranant M, and Tuomala RE (2007). Predictors of repeat pregnancy among HIV-1-infected women. *J Acquir Immune Defic Syndr,* 44(1), 87-92.

Bungener C, Marchand-Gonod N, and Jouvent R (2000). African and European HIV-positive women: psychological and psychosocial differences. *AIDS Care,* 12(5), 541-548.

Byrne L, Townsend CL, Thorne C, and Tookey P (2013). Place of diagnosis and CD4 count in pregnant HIV-positive women diagnosed before conception in the UK & Ireland: 2007-2012. Paper presented at the 19th Annual Conference of the British HIV Association, Manchester, UK.

Calvert C and Ronsmans C (2013a). The contribution of HIV to pregnancy-related mortality: a systematic review and meta-analysis. *AIDS,* 27(10), 1631-1639.

Calvert C and Ronsmans C (2013b). HIV and the risk of direct obstetric complications: a systematic review and meta-analysis. *PLoS One,* 8(10), e74848.

Cantwell R, Clutton-Brock T, Cooper G, Dawson A, Drife J, Garrod D, Harper A, Hulbert D, Lucas S, McClure J, Millward-Sadler H, Neilson J, Nelson-Piercy C, Norman J, O'Herlihy C, Oates M, Shakespeare J, de Swiet M, Williamson C, Beale V, Knight M, Lennox C, Miller A, Parmar D, Rogers J, and Springett A (2011). Saving Mothers' Lives: Reviewing maternal deaths to make motherhood safer: 2006-2008. The Eighth Report of the Confidential Enquiries into Maternal Deaths in the United Kingdom. *BJOG,* 118 Suppl 1, 1-203.

Capeau J (2011). Premature Aging and Premature Age-Related Comorbidities in HIV-Infected Patients: Facts and Hypotheses. *Clin Infect Dis,* 53(11), 1127-1129.

Caswell RJ, Phillips D, Chaponda M, Khoo SH, Taylor GP, Ghanem M, Poulton M, Welch J, Gibbons S, Jackson V, and Lambert JS (2011). Utility of therapeutic drug monitoring in the management of HIV-infected pregnant women in receipt of lopinavir. *Int J STD AIDS,* 22(1), 11-14.

Cejtin HE, Kalinowski A, Bacchetti P, Taylor RN, Watts DH, Kim S, Massad LS, Preston-Martin S, Anastos K, Moxley M, and Minkoff HL (2006). Effects of human immunodeficiency virus on protracted amenorrhea and ovarian dysfunction. *Obstetrics and Gynecology,* 108(6), 1423-1431.

Centers for Disease Control and Prevention (2011). Vital signs: HIV prevention through care and treatment--United States. *MMWR Morb Mortal Wkly Rep,* 60(47), 1618-1623.

Centers for Disease Control and Prevention (2012). Estimated HIV incidence in the United States, 2007–2010. HIV Surveillance Supplemental Report 2012;17(No. 4). Atlanta, US: Centers for Disease Control and Prevention.

Centre for Maternal and Child Enquiries (2011). Perinatal Mortality 2009: United Kingdom. London: CMACE.

Chadborn TR, Delpech VC, Sabin CA, Sinka K, and Evans BG (2006). The late diagnosis and consequent short-term mortality of HIV-infected heterosexuals (England and Wales, 2000-2004). *AIDS,* 20(18), 2371-2379.

Chen JL, Philips KA, Kanouse DE, Collins RL, and Miu A (2001). Fertility desires and intentions of HIV-positive men and women. *Fam Plann Perspect,* 33(4), 144-152, 165.

Cheshire M, Kingston M, McQuillan O, and Gittins M (2012). Are HIV-related factors associated with pre-term delivery in a UK inner city setting? *Journal of the International AIDS Society,* 15 Suppl 4, 18223.

Chi BH, Sinkala M, Stringer EM, Cantrell RA, Mtonga V, Bulterys M, Zulu I, Kankasa C, Wilfert C, Weidle PJ, Vermund SH, and Stringer JS (2007). Early clinical and immune response to NNRTI-based antiretroviral therapy among women with prior exposure to single-dose nevirapine. *AIDS,* 21(8), 957-964.

Chibwesha CJ, Giganti MJ, Putta N, Chintu N, Mulindwa J, Dorton BJ, Chi BH, Stringer JS, and Stringer EM (2011). Optimal time on HAART for prevention of mother-to-child transmission of HIV. *J Acquir Immune Defic Syndr,* 58(2), 224-228.

Chirgwin KD, Feldman J, Muneyyirci-Delale O, Landesman S, and Minkoff H (1996). Menstrual function in human immunodeficiency virus-infected women without acquired immunodeficiency syndrome. *J Acquir Immune Defic Syndr Hum Retrovirol,* 12(5), 489-494.

Chou R, Fu R, Huffman LH, and Korthuis PT (2006). Initial highly-active antiretroviral therapy with a protease inhibitor versus a non-nucleoside reverse transcriptase inhibitor: discrepancies between direct and indirect meta-analyses. *Lancet,* 368(9546), 1503-1515.

Clavel F and Hance AJ (2004). HIV drug resistance. *New England Journal of Medicine,* 350(10), 1023-1035.

Clay K (2013). Audit of people with diagnosed HIV infection not attending for care. Paper presented at the 19th Annual Conference of the British HIV Association, Manchester, UK.

Cleary-Goldman J, Malone FD, Vidaver J, Ball RH, Nyberg DA, Comstock CH, Saade GR, Eddleman KA, Klugman S, Dugoff L, Timor-Tritsch IE, Craigo SD, Carr SR, Wolfe HM, Bianchi DW, and D'Alton M (2005). Impact of maternal age on obstetric outcome. *Obstetrics and Gynecology,* 105(5 Pt 1), 983-990.

Cliffe S (2005). Estimating HIV prevalence in the general female population in Great Britain using data from pregnant women having live births. PhD Thesis, Univerisity College London, London, UK.

Cliffe S, Townsend CL, Cortina-Borja M, and Newell ML (2011). Fertility intentions of HIV-infected women in the United Kingdom. *AIDS Care,* 23(9), 1093-1101.

Clouse K, Pettifor A, Shearer K, Maskew M, Bassett J, Larson B, Van Rie A, Sanne I, and Fox MP (2013). Loss to follow-up before and after delivery among women testing HIV positive during pregnancy in Johannesburg, South Africa. *Tropical Medicine & International Health,* 18(4), 451-460.

Cohen MH, Cook JA, Grey D, Young M, Hanau LH, Tien P, Levine AM, and Wilson TE (2004). Medically eligible women who do not use HAART: the importance of abuse, drug use, and race. *Am J Public Health,* 94(7), 1147-1151.

Cohen MS, Chen YQ, McCauley M, Gamble T, Hosseinipour MC, Kumarasamy N, Hakim JG, Kumwenda J, Grinsztejn B, Pilotto JH, Godbole SV, Mehendale S, Chariyalertsak S, Santos BR, Mayer KH, Hoffman IF, Eshleman SH, Piwowar-Manning E, Wang L, Makhema J, Mills LA, de Bruyn G, Sanne I, Eron J, Gallant J, Havlir D, Swindells S, Ribaudo H, Elharrar V, Burns D, Taha TE, Nielsen-Saines K, Celentano D, Essex M, and Fleming TR (2011). Prevention of HIV-1 infection with early antiretroviral therapy. *New England Journal of Medicine,* 365(6), 493-505.

Cohen MS, Gay C, Kashuba AD, Blower S, and Paxton L (2007). Narrative review: antiretroviral therapy to prevent the sexual transmission of HIV-1. *Ann Intern Med,* 146(8), 591-601.

Cole TJ and Green PJ (1992). Smoothing reference centile curves: the LMS method and penalized likelihood. *Stat Med,* 11(10), 1305-1319.

Coleman S, Boehmer U, Kanaya F, Grasso C, Tan J, and Bradford J (2007). Retention challenges for a community-based HIV primary care clinic and implications for intervention. *AIDS Patient Care STDS,* 21(9), 691-701.

Conde-Agudelo A, Rosas-Bermudez A, and Kafury-Goeta AC (2006). Birth spacing and risk of adverse perinatal outcomes: a meta-analysis. *JAMA,* 295(15), 1809-1823.

Connor EM, Sperling RS, Gelber R, Kiselev P, Scott G, O'Sullivan MJ, VanDyke R, Bey M, Shearer W, Jacobson RL, and et al. (1994). Reduction of maternal-infant transmission of human immunodeficiency virus type 1 with zidovudine treatment. Pediatric AIDS Clinical Trials Group Protocol 076 Study Group. *New England Journal of Medicine,* 331(18), 1173-1180.

Cooper D, Harries J, Myer L, Orner P, Bracken H, and Zweigenthal V (2007). "Life is still going on": reproductive intentions among HIV-positive women and men in South Africa. *Soc Sci Med,* 65(2), 274-283.

Cooper D, Moodley J, Zweigenthal V, Bekker LG, Shah I, and Myer L (2009). Fertility intentions and reproductive health care needs of people living with HIV in Cape Town, South Africa: implications for integrating reproductive health and HIV care services. *AIDS Behav,* 13 Suppl 1, 38-46.

Cooper ER, Charurat M, Mofenson L, Hanson IC, Pitt J, Diaz C, Hayani K, Handelsman E, Smeriglio V, Hoff R, and Blattner W (2002). Combination antiretroviral strategies for the treatment of pregnant HIV-1-infected women and prevention of perinatal HIV-1 transmission. *J Acquir Immune Defic Syndr,* 29(5), 484-494.

Coovadia A, Hunt G, Abrams EJ, Sherman G, Meyers T, Barry G, Malan E, Marais B, Stehlau R, Ledwaba J, Hammer SM, Morris L, and Kuhn L (2009). Persistent minority K103N mutations among women exposed to single-dose nevirapine and virologic response to nonnucleoside reverse-transcriptase inhibitor-based therapy. *Clin Infect Dis,* 48(4), 462-472.

Coria A, Noel F, Bonhomme J, Rouzier V, Perodin C, Marcelin A, Li Z, Tosteson TD, Deschamps MM, Wright PF, and Pape JW (2012). Consideration of postpartum management in HIV-positive Haitian women: an analysis of CD4 decline, mortality, and follow-up after delivery. *J Acquir Immune Defic Syndr,* 61(5), 636-643.

Cotter AM, Garcia AG, Duthely ML, Luke B, and O'Sullivan MJ (2006). Is antiretroviral therapy during pregnancy associated with an increased risk of preterm delivery, low birth weight, or stillbirth? *J Infect Dis,* 193(9), 1195-1201.

Coughlin SS (1990). Recall bias in epidemiologic studies. *J Clin Epidemiol,* 43(1), 87-91.

Craft SM, Delaney RO, Bautista DT, and Serovich JM (2007). Pregnancy decisions among women with HIV. *AIDS Behav,* 11(6), 927-935.

Creighton S, Sethi G, Edwards SG, and Miller R (2004). Dispersal of HIV positive asylum seekers: national survey of UK healthcare providers. *BMJ,* 329(7461), 322-323.

Cresswell JA, Yu G, Hatherall B, Morris J, Jamal F, Harden A, and Renton A (2013). Predictors of the timing of initiation of antenatal care in an ethnically diverse urban cohort in the UK. *BMC Pregnancy Childbirth,* 13, 103.

Crowther CA, Dodd JM, Hiller JE, Haslam RR, and Robinson JS (2012). Planned vaginal birth or elective repeat caesarean: patient preference restricted cohort with nested randomised trial. *PLoS Med,* 9(3), e1001192.

Croxtall JD and Perry CM (2010). Lopinavir/Ritonavir: a review of its use in the management of HIV-1 infection. *Drugs,* 70(14), 1885-1915.

Cunningham CK, Chaix ML, Rekacewicz C, Britto P, Rouzioux C, Gelber RD, Dorenbaum A, Delfraissy JF, Bazin B, Mofenson L, and Sullivan JL (2002). Development of resistance mutations in women receiving standard antiretroviral therapy who received intrapartum nevirapine to prevent perinatal human immunodeficiency virus type 1 transmission: a substudy of pediatric AIDS clinical trials group protocol 316. *J Infect Dis,* 186(2), 181-188.

Cuzick J (1985). A Wilcoxon-type test for trend. *Stat Med,* 4(1), 87-90.

Dale H (2013). Does initiation of highly active antiretroviral therapy (HAART) before pregnancy increase risk of adverse outcomes: miscarriage, prematurity, stillbirth? Paper presented at the 19th Annual Conference of the British HIV Association, Manchester, UK.

Danel C, Moh R, Minga A, Anzian A, Ba-Gomis O, Kanga C, Nzunetu G, Gabillard D, Rouet F, Sorho S, Chaix ML, Eholie S, Menan H, Sauvageot D, Bissagnene E, Salamon R, and Anglaret X (2006). CD4-guided structured antiretroviral treatment interruption strategy in HIV-infected adults in west Africa (Trivacan ANRS 1269 trial): a randomised trial. *Lancet,* 367(9527), 1981-1989.

Dartnall L, Ganguly N, and Batterham J (2005). Access to Maternity Services Research Report. London, UK: COI and Department of Health.

de Mendoza C and Soriano V (2004). Resistance to HIV protease inhibitors: mechanisms and clinical consequences. *Curr Drug Metab,* 5(4), 321-328.

de Ruiter A, Mercey D, Anderson J, Chakraborty R, Clayden P, Foster G, Gilling-Smith C, Hawkins D, Low-Beer N, Lyall H, O'Shea S, Penn Z, Short J, Smith R, Sonecha S, Tookey P, Wood C, and Taylor G (2008). British HIV Association and Children's HIV Association guidelines for the management of HIV infection in pregnant women 2008. *HIV Med,* 9(7), 452-502.

De Santis M, Carducci B, De Santis L, Cavaliere AF, and Straface G (2002). Periconceptional exposure to efavirenz and neural tube defects. *Arch Intern Med,* 162(3), 355.

de Vincenzi I (2011). Triple antiretroviral compared with zidovudine and single-dose nevirapine prophylaxis during pregnancy and breastfeeding for prevention of mother-to-child transmission of HIV-1 (Kesho Bora study): a randomised controlled trial. *Lancet Infect Dis,* 11(3), 171-180.

Delpech V, Brown AE, Croxford S, Chau C, Polavarapu V, Cooper N, Rooney G, and Yin Z (2013). Quality of HIV care in the United Kingdom: key indicators for the first 12 months from HIV diagnosis. *HIV Med,* 14 Suppl 3, 19-24.

Denoeud-Ndam L, Fourcade C, Ogouyemi-Hounto A, Azon-Kouanou A, d'Almeida M, Azondekon A, Alao MJ, Dossou-Gbete V, Afangnihoun A, Girard PM, Cot M, and Zannou DM (2013). Predictive factors of plasma HIV suppression during pregnancy: a prospective cohort study in Benin. *PLoS One,* 8(3), e59446.

Department of Health (2012). HIV treatment for overseas visitors: Guidance for the NHS: Department of Health.

Department of Health/ Medical Research Council/ OrcMacro (2007). South Africa Demographic and Health Survey 2003. Pretoria, South Africa: Department of Health.

Dhairyawan R, Tariq S, Scourse R, and Coyne KM (2013). Intimate partner violence in women living with HIV attending an inner city clinic in the UK: prevalence and associated factors. *HIV Med,* 14(5), 303-310.

Di Renzo GC, Giardina I, Rosati A, Clerici G, Torricelli M, and Petraglia F (2011). Maternal risk factors for preterm birth: a country-based population analysis. *European Journal of Obstetrics Gynecology and Reproductive Biology,* 159(2), 342-346.

Dieterich DT, Robinson PA, Love J, and Stern JO (2004). Drug-induced liver injury associated with the use of nonnucleoside reverse-transcriptase inhibitors. *Clin Infect Dis,* 38 Suppl 2, S80-89.

Dodd JM, Crowther CA, Huertas E, Guise JM, and Horey D (2013). Planned elective repeat caesarean section versus planned vaginal birth for women with a previous caesarean birth. *Cochrane Database Syst Rev,* 12, CD004224.

Dola CP, Khan R, DeNicola N, Amirgholami M, Benjamin T, Bhuiyan A, and Longo S (2011). Combination antiretroviral therapy with protease inhibitors in HIV-infected pregnancy. *J Perinat Med,* 40(1), 51-55.

Dolling D, Sabin C, Delpech V, Smit E, Pozniak A, Asboe D, Brown AL, Churchill D, Williams I, Geretti AM, Phillips A, Mackie N, Murphy G, Castro H, Pillay D, Cane P, and Dunn D (2012). Time trends in drug resistant HIV-1 infections in the United Kingdom up to 2009: multicentre observational study. *BMJ,* 345, e5253.

Dombrowski JC, Kitahata MM, Van Rompaey SE, Crane HM, Mugavero MJ, Eron JJ, Boswell SL, Rodriguez B, Mathews WC, Martin JN, Moore RD, and Golden MR (2013). High levels of antiretroviral use and viral suppression among persons in HIV care in the United States, 2010. *J Acquir Immune Defic Syndr,* 63(3), 299-306.

Dominguez KL, Lindegren ML, D'Almada PJ, Peters VB, Frederick T, Rakusan TA, Ortiz IR, Hsu HW, Melville SK, Sadek R, and Fowler MG (2003). Increasing trend of Cesarean deliveries in HIV-infected women in the United States from 1994 to 2000. *J Acquir Immune Defic Syndr,* 33(2), 232-238.

Dumond JB, Yeh RF, Patterson KB, Corbett AH, Jung BH, Rezk NL, Bridges AS, Stewart PW, Cohen MS, and Kashuba AD (2007). Antiretroviral drug exposure in the female genital tract: implications for oral pre- and post-exposure prophylaxis. *AIDS,* 21(14), 1899-1907.

Dunn DT, Brandt CD, Krivine A, Cassol SA, Roques P, Borkowsky W, De Rossi A, Denamur E, Ehrnst A, and Loveday C (1995). The sensitivity of HIV-1 DNA polymerase chain reaction in the neonatal period and the relative contributions of intra-uterine and intra-partum transmission. *AIDS,* 9(9), F7-11.

Dunn DT, Newell ML, Ades AE, and Peckham CS (1992). Risk of human immunodeficiency virus type 1 transmission through breastfeeding. *Lancet,* 340(8819), 585-588.

Duong HT, Hoyt AT, Carmichael SL, Gilboa SM, Canfield MA, Case A, McNeese ML, and Waller DK (2012). Is maternal parity an independent risk factor for birth defects? *Birth Defects Res A Clin Mol Teratol,* 94(4), 230-236.

Duong T, Ades AE, Gibb DM, Tookey PA, and Masters J (1999). Vertical transmission rates for HIV in the British Isles: estimates based on surveillance data. *BMJ,* 319(7219), 1227-1229.

Dupont WD (2009). Statistical Modelling for Biomedical Researchers - A Simple Introduction to the Analysis of Complex Data (2nd ed.). Cambridge, UK: Cambridge University Press.

Eaton JW, Johnson LF, Salomon JA, Barnighausen T, Bendavid E, Bershteyn A, Bloom DE, Cambiano V, Fraser C, Hontelez JA, Humair S, Klein DJ, Long EF, Phillips AN, Pretorius C, Stover J, Wenger EA, Williams BG, and Hallett TB (2012). HIV treatment as prevention: systematic comparison of mathematical models of the potential impact of antiretroviral therapy on HIV incidence in South Africa. *PLoS Med,* 9(7), e1001245.

Ekouevi D, Abrams EJ, Schlesinger M, Myer L, Phanuphak N, and Carter RJ (2012). Maternal CD4+ cell count decline after interruption of antiretroviral prophylaxis for the prevention of mother-to-child transmission of HIV. *PLoS One,* 7(8), e43750.

Ekouevi DK, Coffie PA, Becquet R, Tonwe-Gold B, Horo A, Thiebaut R, Leroy V, Blanche S, Dabis F, and Abrams EJ (2008). Antiretroviral therapy in pregnant women with advanced HIV disease and pregnancy outcomes in Abidjan, Cote d'Ivoire. *AIDS,* 22(14), 1815-1820.

El-Sadr WM, Lundgren JD, Neaton JD, Gordin F, Abrams D, Arduino RC, Babiker A, Burman W, Clumeck N, Cohen CJ, Cohn D, Cooper D, Darbyshire J, Emery S, Fatkenheuer G, Gazzard B, Grund B, Hoy J, Klingman K, Losso M, Markowitz N, Neuhaus J, Phillips A, and Rappoport C (2006). CD4+ count-guided interruption of antiretroviral treatment. *New England Journal of Medicine,* 355(22), 2283-2296.

El Beitune P and Duarte G (2006). Antiretroviral agents during pregnancy: consequences on hematologic parameters in HIV-exposed, uninfected newborn infant. *Eur J Obstet Gynecol Reprod Biol,* 128(1-2), 59-63.

Elford J, Ibrahim F, Bukutu C, and Anderson J (2008a). HIV-related discrimination reported by people living with HIV in London, UK. *AIDS Behav,* 12(2), 255-264.

Elford J, Ibrahim F, Bukutu C, and Anderson J (2008b). Uptake of antiretroviral treatment among people living with HIV in London: ethnicity, gender and sexual orientation. *Sex Transm Infect,* 84(3), 176-178.

Ellerbrock TV, Wright TC, Bush TJ, Dole P, Brudney K, and Chiasson MA (1996). Characteristics of menstruation in women infected with human immunodeficiency virus. *Obstetrics and Gynecology,* 87(6), 1030-1034.

Ellis GM, Huang S, Hitti J, and Frenkel LM (2011). Selection of HIV Resistance associated with Antiretroviral Therapy (ART) Initiated due to Pregnancy and Suspended Postpartum. *J Acquir Immune Defic Syndr,* 58(3), 241-247.

Eshleman SH, Mracna M, Guay LA, Deseyve M, Cunningham S, Mirochnick M, Musoke P, Fleming T, Glenn Fowler M, Mofenson LM, Mmiro F, and Jackson JB (2001). Selection and fading of resistance mutations in women and infants receiving nevirapine to prevent HIV-1 vertical transmission (HIVNET 012). *AIDS,* 15(15), 1951-1957.

European AIDS Cinical Society (2013). Guidelines, Version 7.0, October 2013.

European Centre for Disease Prevention and Control/ WHO Regional Office for Europe (2013). HIV/AIDS surveillance in Europe 2012. Stockholm, Sweden: European Centre for Disease Prevention and Control.

European Collaborative Study (1994). Caesarean section and risk of vertical transmission of HIV-1 infection. *Lancet,* 343(8911), 1464-1467.

European Collaborative Study (1999). Maternal viral load and vertical transmission of HIV-1: an important factor but not the only one. *AIDS,* 13(11), 1377-1385.

European Collaborative Study (2001). HIV-infected pregnant women and vertical transmission in Europe since 1986. *AIDS,* 15(6), 761-770.

European Collaborative Study and Swiss Mother and Child HIV Cohort Study (2000). Combination antiretroviral therapy and duration of pregnancy. *AIDS,* 14(18), 2913-2920.

European Mode of Delivery Collaboration (1999). Elective caesarean-section versus vaginal delivery in prevention of vertical HIV-1 transmission: a randomised clinical trial. *Lancet,* 353(9158), 1035-1039.

Ezechi OC, Gab-Okafor CV, Oladele DA, Kalejaiye OO, Oke BO, Ohwodo HO, Adu RA, Ekama SO, Musa Z, Onwujekwe DI, David AN, and Ujah IA (2013). Pregnancy, obstetric and neonatal outcomes in HIV positive Nigerian women. *Afr J Reprod Health,* 17(3), 160-168.

Fakoya A, Lamba H, Mackie N, Nandwani R, Brown A, Bernard E, Gilling-Smith C, Lacey C, Sherr L, Claydon P, Wallage S, and Gazzard B (2008). British HIV Association, BASHH and FSRH guidelines for the management of the sexual and reproductive health of people living with HIV infection 2008. *HIV Med,* 9(9), 681-720.

Fearon M (2005). The laboratory diagnosis of HIV infections. *Can J Infect Dis Med Microbiol,* 16(1), 26-30.

Fenton KA, Chinouya M, Davidson O, and Copas A (2001). HIV transmission risk among sub-Saharan Africans in London travelling to their countries of origin. *AIDS,* 15(11), 1442-1445.

Fidler S, Anderson J, Azad Y, Delpech V, Evans C, Fisher M, Gazzard B, Gill N, Lazarus L, Lowbury R, Orton K, Osoro B, Radcliffe K, Smith B, Churchill D, Rogstad K, and Cairns G (2013). Position statement on the use of antiretroviral therapy to reduce HIV transmission, January 2013: the British HIV Association (BHIVA) and the Expert Advisory Group on AIDS (EAGA). *HIV Med,* 14(5), 259-262.

Finocchario-Kessler S, Sweat MD, Dariotis JK, Trent ME, Kerrigan DL, Keller JM, and Anderson JR (2010). Understanding High Fertility Desires and Intentions Among a Sample of Urban Women Living with HIV in the United States. *AIDS Behav,* 14(5), 1106-1114.

Fiore S, Heard I, Thorne C, Savasi V, Coll O, Malyuta R, Niemiec T, Martinelli P, Tibaldi C, and Newell ML (2008). Reproductive experience of HIV-infected women living in Europe. *Hum Reprod,* 23(9), 2140-2144.

Fiore S, Newell ML, and Thorne C (2004). Higher rates of post-partum complications in HIV-infected than in uninfected women irrespective of mode of delivery. *AIDS,* 18(6), 933-938.

Fischer RC, Stanford JB, Jameson P, and DeWitt MJ (1999). Exploring the concepts of intended, planned, and wanted pregnancy. *J Fam Pract,* 48(2), 117-122.

Fischl MA, Richman DD, Grieco MH, Gottlieb MS, Volberding PA, Laskin OL, Leedom JM, Groopman JE, Mildvan D, and Schooley RT (1987). The efficacy of azidothymidine (AZT) in the treatment of patients with AIDS and AIDS-related complex. A double-blind, placebo-controlled trial. *New England Journal of Medicine,* 317(4), 185-191.

Fisher RJ (1993). Social Desirability Bias and the Validity of Indirect Questioning. *Journal of Consumer Research,* 20(2), 303-315.

Fitzpatrick KE, Kurinczuk JJ, Alfirevic Z, Spark P, Brocklehurst P, and Knight M (2012). Uterine rupture by intended mode of delivery in the UK: a national case-control study. *PLoS Med,* 9(3), e1001184.

Fleishman JA, Yehia BR, Moore RD, Gebo KA, and Agwu AL (2012). Disparities in receipt of antiretroviral therapy among HIV-infected adults (2002-2008). *Med Care,* 50(5), 419-427.

Flenady V, Koopmans L, Middleton P, Froen JF, Smith GC, Gibbons K, Coory M, Gordon A, Ellwood D, McIntyre HD, Fretts R, and Ezzati M (2011). Major risk factors for stillbirth in high-income countries: a systematic review and meta-analysis. *Lancet,* 377(9774), 1331-1340.

Floridia M, Tamburrini E, Ravizza M, Anzidei G, Tibaldi C, Bucceri A, Maccabruni A, Guaraldi G, Meloni A, Ravagni Probizer MF, Guerrao B, and Martinelli P (2006). Antiretroviral therapy at conception in pregnant women with HIV in Italy: wide range of variability and frequent exposure to contraindicated drugs. *Antivir Ther,* 11(7), 941-946.

Ford N, Calmy A, and Mofensen L (2011). Safety of efavirenz in first-trimester of pregnancy: an updated systematic review and meta-analysis. *AIDS,* 25(18), 2301-2304.

French R and Brocklehurst P (1998). The effect of pregnancy on survival in women infected with HIV: a systematic review of the literature and meta-analysis. *BJOG,* 105(8), 827-835.

Fretts R (2010). Stillbirth epidemiology, risk factors, and opportunities for stillbirth prevention. *Clinical Obstetrics and Gynecology,* 53(3), 588-596.

Fretts RC, Schmittdiel J, McLean FH, Usher RH, and Goldman MB (1995). Increased maternal age and the risk of fetal death. *New England Journal of Medicine,* 333(15), 953-957.

Fundaro C, Genovese O, Rendeli C, Tamburrini E, and Salvaggio E (2002). Myelomeningocele in a child with intrauterine exposure to efavirenz. *AIDS,* 16(2), 299-300.

Galli L, Puliti D, Chiappini E, Gabiano C, Ferraris G, Mignone F, Vigano A, Giaquinto C, Genovese O, Anzidei G, Badolato R, Buffolano W, Maccabruni A, Salvini F, Cellini M, Ruggeri M, Manzionna M, Bernardi S, Tovo P, and de Martino M (2009). Is the interruption of antiretroviral treatment during pregnancy an additional major risk factor for mother-to-child transmission of HIV type 1? *Clin Infect Dis,* 48(9), 1310-1317.

Gange SJ, Barron Y, Greenblatt RM, Anastos K, Minkoff H, Young M, Kovacs A, Cohen M, Meyer WA, and Munoz A (2002). Effectiveness of highly active antiretroviral therapy among HIV-1 infected women. *J Epidemiol Community Health,* 56(2), 153-159.

Garcia PM, Kalish LA, Pitt J, Minkoff H, Quinn TC, Burchett SK, Kornegay J, Jackson B, Moye J, Hanson C, Zorrilla C, and Lew JF (1999). Maternal levels of plasma human immunodeficiency virus type 1 RNA and the risk of perinatal transmission. Women and Infants Transmission Study Group. *New England Journal of Medicine,* 341(6), 394-402.

Gazzard B (2005). British HIV Association (BHIVA) guidelines for the treatment of HIV-infected adults with antiretroviral therapy (2005). *HIV Med,* 6 Suppl 2, 1-61.

Gazzard BG, Anderson J, Babiker A, Boffito M, Brook G, Brough G, Churchill D, Cromarty B, Das S, Fisher M, Freedman A, Geretti AM, Johnson M, Khoo S, Leen C, Nair D, Peters B, Phillips A, Pillay D, Pozniak A, Walsh J, Wilkins E, Williams I, Williams M, and Youle M (2008). British HIV Association Guidelines for the treatment of HIV-1-infected adults with antiretroviral therapy 2008. *HIV Med,* 9(8), 563-608.

Gebo KA, Fleishman JA, Conviser R, Reilly ED, Korthuis PT, Moore RD, Hellinger J, Keiser P, Rubin HR, Crane L, Hellinger FJ, and Mathews WC (2005). Racial and gender disparities in receipt of highly active antiretroviral therapy persist in a multistate sample of HIV patients in 2001. *J Acquir Immune Defic Syndr,* 38(1), 96-103.

Gerver SM, Chadborn TR, Ibrahim F, Vatsa B, Delpech VC, and Easterbrook PJ (2010). High rate of loss to clinical follow up among African HIV-infected patients attending a London clinic: a retrospective analysis of a clinical cohort. *J Int AIDS Soc,* 13, 29.

Gibb DM (2000). Antenatal screening for HIV infection. *AIDS Patient Care STDS,* 14(3), 125-131.

Gibb DM, Kizito H, Russell EC, Chidziva E, Zalwango E, Nalumenya R, Spyer M, Tumukunde D, Nathoo K, Munderi P, Kyomugisha H, Hakim J, Grosskurth H, Gilks CF, Walker AS, and Musoke P (2012). Pregnancy and infant outcomes among HIV-infected women taking long-term ART with and without tenofovir in the DART trial. *PLoS Med,* 9(5), e1001217.

Gilliam M (2006). Cesarean delivery on request: reproductive consequences. *Semin Perinatol,* 30(5), 257-260.

Gingelmaier A, Eberle J, Kost BP, Bogner JR, Hofmann J, Weissenbacher T, Kastner R, Friese K, and Weizsaecker K (2010). Protease inhibitor-based antiretroviral prophylaxis during pregnancy and the development of drug resistance. *Clin Infect Dis,* 50(6), 890-894.

Gingelmaier A, Wiedenmann K, Sovric M, Mueller M, Kupka MS, Sonnenberg-Schwan U, Mylonas I, Friese K, and Weizsaecker K (2011). Consultations of HIV-infected women who wish to become pregnant. *Arch Gynecol Obstet,* 283(4), 893-898.

Gipson JD, Koenig MA, and Hindin MJ (2008). The effects of unintended pregnancy on infant, child, and parental health: a review of the literature. *Stud Fam Plann,* 39(1), 18-38.

Goer H (2001). The case against elective cesarean section. *J Perinat Neonatal Nurs,* 15(3), 23-38; quiz 89.

Gold RS, Hinchy J, and Batrouney CG (2000). The reasoning behind decisions not to take up antiretroviral therapy in Australians infected with HIV. *Int J STD AIDS,* 11(6), 361-370.

Gold RS and Ridge DT (2001). "I will start treatment when I think the time is right": HIV-positive gay men talk about their decision not to access antiretroviral therapy. *AIDS Care,* 13(6), 693-708.

Goldenberg RL, Culhane JF, Iams JD, and Romero R (2008). Epidemiology and causes of preterm birth. *Lancet,* 371(9606), 75-84.

Goldenberg RL, Mayberry SK, Copper RL, Dubard MB, and Hauth JC (1993). Pregnancy outcome following a second-trimester loss. *Obstetrics and Gynecology,* 81(3), 444-446.

Granich RM, Gilks CF, Dye C, De Cock KM, and Williams BG (2009). Universal voluntary HIV testing with immediate antiretroviral therapy as a strategy for elimination of HIV transmission: a mathematical model. *Lancet,* 373(9657), 48-57.

Grosch-Woerner I, Puch K, Maier RF, Niehues T, Notheis G, Patel D, Casteleyn S, Feiterna-Sperling C, Groeger S, and Zaknun D (2008). Increased rate of prematurity associated with antenatal antiretroviral therapy in a German/Austrian cohort of HIV-1-infected women. *HIV Med,* 9(1), 6-13.

Grossman CI and Stangl AL (2013). Editorial: Global action to reduce HIV stigma and discrimination. *J Int AIDS Soc,* 16(3 Suppl 2), 18881.

Grubert TA, Reindell D, Kastner R, Belohradsky BH, Gurtler L, Stauber M, and Dathe O (2002). Rates of postoperative complications among human immunodeficiency virus-infected women who have undergone obstetric and gynecologic surgical procedures. *Clin Infect Dis,* 34(6), 822-830.

Guay LA, Musoke P, Fleming T, Bagenda D, Allen M, Nakabiito C, Sherman J, Bakaki P, Ducar C, Deseyve M, Emel L, Mirochnick M, Fowler MG, Mofenson L, Miotti P, Dransfield K, Bray D, Mmiro F, and Jackson JB (1999). Intrapartum and neonatal single-dose nevirapine compared with zidovudine for prevention of mother-to-child transmission of HIV-1 in Kampala, Uganda: HIVNET 012 randomised trial. *Lancet,* 354(9181), 795-802.

Guise JM, Berlin M, McDonagh M, Osterweil P, Chan B, and Helfand M (2004). Safety of vaginal birth after cesarean: a systematic review. *Obstetrics and Gynecology,* 103(3), 420-429.

Guise JM, Denman MA, Emeis C, Marshall N, Walker M, Fu R, Janik R, Nygren P, Eden KB, and McDonagh M (2010). Vaginal birth after cesarean: new insights on maternal and neonatal outcomes. *Obstetrics and Gynecology,* 115(6), 1267-1278.

Hammer SM, Katzenstein DA, Hughes MD, Gundacker H, Schooley RT, Haubrich RH, Henry WK, Lederman MM, Phair JP, Niu M, Hirsch MS, and Merigan TC (1996). A trial comparing nucleoside monotherapy with combination therapy in HIV-infected adults with CD4 cell counts from 200 to 500 per cubic millimeter. AIDS Clinical Trials Group Study 175 Study Team. *New England Journal of Medicine,* 335(15), 1081-1090.

Havlir DV, Bassett R, Levitan D, Gilbert P, Tebas P, Collier AC, Hirsch MS, Ignacio C, Condra J, Gunthard HF, Richman DD, and Wong JK (2001). Prevalence and predictive value of intermittent viremia with combination hiv therapy. *JAMA,* 286(2), 171-179.

Hawkins D, Blott M, Clayden P, de Ruiter A, Foster G, Gilling-Smith C, Gosrani B, Lyall H, Mercey D, Newell ML, O'Shea S, Smith R, Sunderland J, Wood C, and Taylor G (2005). Guidelines for the management of HIV infection in pregnant women and the prevention of mother-to-child transmission of HIV. *HIV Med,* 6 Suppl 2, 107-148.

Health and Social Care Information Centre (2010). NHS Maternity Statistics - England, 2009-2010. Available at: http://www.hscic.gov.uk/catalogue/PUB02111 (Accessed October 2013).

Health Protection Agency (2011a). HIV in the United Kingdom: 2011 Report. London, UK: Health Protection Agency.

Health Protection Agency (2011b). Time to test for HIV: Expanded healthcare and community HIV testing in England. Interim report. London, UK: Health Protection Agency.

Heard I, Sitta R, and Lert F (2007). Reproductive choice in men and women living with HIV: evidence from a large representative sample of outpatients attending French hospitals (ANRS-EN12-VESPA Study). *AIDS,* 21 Suppl 1, S77-82.

Heffron R, Donnell D, Kiarie J, Rees H, Ngure K, Mugo N, Were E, Celum C, and Baeten JM (2014). A Prospective Study of the Effect of Pregnancy on CD4 Counts and Plasma HIV-1 RNA Concentrations of Antiretroviral-Naive HIV-1-Infected Women. *J Acquir Immune Defic Syndr,* 65(2), 231-236.

Hoffman RM, Black V, Technau K, van der Merwe KJ, Currier J, Coovadia A, and Chersich M (2010). Effects of highly active antiretroviral therapy duration and regimen on risk for mother-to-child transmission of HIV in Johannesburg, South Africa. *J Acquir Immune Defic Syndr,* 54(1), 35-41.

Horne R, Cooper V, Gellaitry G, Date HL, and Fisher M (2007). Patients' perceptions of highly active antiretroviral therapy in relation to treatment uptake and adherence: the utility of the necessity-concerns framework. *J Acquir Immune Defic Syndr,* 45(3), 334-341.

Horstmann E, Brown J, Islam F, Buck J, and Agins BD (2010). Retaining HIV-infected patients in care: Where are we? Where do we go from here? *Clin Infect Dis,* 50(5), 752-761.

Hosseinipour M, Cohen MS, Vernazza PL, and Kashuba AD (2002). Can antiretroviral therapy be used to prevent sexual transmission of human immunodeficiency virus type 1? *Clin Infect Dis,* 34(10), 1391-1395.

Hoyt MJ, Storm DS, Aaron E, and Anderson J (2012). Preconception and contraceptive care for women living with HIV. *Infect Dis Obstet Gynecol,* 2012, 604183.

Huang L, Sauve R, Birkett N, Fergusson D, and van Walraven C (2008). Maternal age and risk of stillbirth: a systematic review. *Canadian Medical Association Journal,* 178(2), 165-172.

Hughes PM, Turton P, and Evans CDH (1999). Stillbirth as risk factor for depression and anxiety in the subsequent pregnancy: cohort study. *BMJ,* 318(7200), 1721-1724.

Huntington SE, Bansi LK, Thorne C, Anderson J, Newell ML, Taylor GP, Pillay D, Hill T, Tookey PA, and Sabin CA (2012). Using two on-going HIV studies to obtain clinical data from before, during and after pregnancy for HIV-positive women. *BMC Med Res Methodol,* 12, 110.

Huntington SE, Thorne C, Bansi LK, Anderson J, Newell ML, Taylor GP, Pillay D, Hill T, Tookey PA, and Sabin CA (2013). Predictors of pregnancy and changes in pregnancy incidence among HIV-positive women accessing HIV clinical care. *AIDS,* 27(1), 95-103.

Ibisomi L and Mudege NN (2014). Childlessness in Nigeria: perceptions and acceptability. *Cult Health Sex,* 16(1), 61-75.

Ibrahim F, Anderson J, Bukutu C, and Elford J (2008). Social and economic hardship among people living with HIV in London. *HIV Med,* 9(8), 616-624.

International Maternal Pediatric Adolescent AIDS Clinical Trials Group (2009). HAART Standard Version of the Promoting Maternal and Infant Survival Everywhere (PROMISE) Study. Available at: http://clinicaltrials.gov/show/NCT00955968 (Accessed December 2013).

Ioannidis JP, Abrams EJ, Ammann A, Bulterys M, Goedert JJ, Gray L, Korber BT, Mayaux MJ, Mofenson LM, Newell ML, Shapiro DE, Teglas JP, and Wilfert CM (2001). Perinatal transmission of human immunodeficiency virus type 1 by pregnant women with RNA virus loads <1000 copies/ml. *J Infect Dis,* 183(4), 539-545.

Jackson JB, Musoke P, Fleming T, Guay LA, Bagenda D, Allen M, Nakabiito C, Sherman J, Bakaki P, Owor M, Ducar C, Deseyve M, Mwatha A, Emel L, Duefield C, Mirochnick M, Fowler MG, Mofenson L, Miotti P, Gigliotti M, Bray D, and Mmiro F (2003). Intrapartum and neonatal single-dose nevirapine compared with zidovudine for prevention of mother-to-child transmission of HIV-1 in Kampala, Uganda: 18-month follow-up of the HIVNET 012 randomised trial. *Lancet,* 362(9387), 859-868.

Jacobsson B, Ladfors L, and Milsom I (2004). Advanced maternal age and adverse perinatal outcome. *Obstetrics and Gynecology,* 104(4), 727-733.

Jasseron C, Mandelbrot L, Tubiana R, Teglas JP, Faye A, Dollfus C, Le Chenadec J, Rouzioux C, Blanche S, and Warszawski J (2008). Prevention of mother-to-child HIV transmission: similar access for sub-Sahara African immigrants and for French women? *AIDS,* 22(12), 1503-1511.

Jourdain G, Ngo-Giang-Huong N, Le Coeur S, Bowonwatanuwong C, Kantipong P, Leechanachai P, Ariyadej S, Leenasirimakul P, Hammer S, and Lallemant M (2004). Intrapartum exposure to nevirapine and subsequent maternal responses to nevirapine-based antiretroviral therapy. *New England Journal of Medicine,* 351(3), 229-240.

Kaida A, Laher F, Strathdee SA, Janssen PA, Money D, Hogg RS, and Gray G (2010). Childbearing Intentions of HIV-Positive Women of Reproductive Age in Soweto, South Africa: The Influence of Expanding Access to HAART in an HIV Hyperendemic Setting. *Am J Public Health,* 101(2), 350-358.

Kaida A, Matthews LT, Kanters S, Kabakyenga J, Muzoora C, Mocello AR, Martin JN, Hunt P, Haberer J, Hogg RS, and Bangsberg DR (2013). Incidence and Predictors of Pregnancy among a Cohort of HIV-Positive Women Initiating Antiretroviral Therapy in Mbarara, Uganda. *PLoS One,* 8(5), e63411.

Karlsen S, Millward D, and Sandford A (2012). Investigating ethnic differences in current cigarette smoking over time using the health surveys for England. *Eur J Public Health,* 22(2), 254-256.

Katz IT, Essien T, Marinda ET, Gray GE, Bangsberg DR, Martinson NA, and De Bruyn G (2011). Antiretroviral therapy refusal among newly diagnosed HIV-infected adults. *AIDS,* 25(17), 2177-2181.

Katz IT, Shapiro R, Li D, Govindarajulu U, Thompson B, Watts DH, Hughes MD, and Tuomala R (2010). Risk factors for detectable HIV-1 RNA at delivery among women receiving highly active antiretroviral therapy in the women and infants transmission study. *J Acquir Immune Defic Syndr,* 54(1), 27-34.

Kawalec P, Kryst J, Mikrut A, and Pilc A (2013). Nevirapine-Based Regimens in HIV-Infected Antiretroviral-Naive Patients: Systematic Review and Meta-Analysis of Randomized Controlled Trials. *PLoS One,* 8(10), e76587.

Keiser O, Gayet-Ageron A, Rudin C, Brinkhof MW, Gremlich E, Wunder D, Drack G, Hirschel B, and de Tejada BM (2008). Antiretroviral treatment during pregnancy. *AIDS,* 22(17), 2323-2330.

Kennedy VL, Serghides L, Raboud JM, Su D, Blitz S, Hart TA, Walmsley SL, Angel JB, Smaill FM, Ralph ED, Tharao WE, and Loutfy MR (2014). The importance of motherhood in HIV-positive women of reproductive age in Ontario, Canada. *AIDS Care,* 26(6), 777-784.

Kenny J, Williams B, Prime K, Tookey P, and Foster C (2012). Pregnancy outcomes in adolescents in the UK and Ireland growing up with HIV. *HIV Med,* 13(5), 304-308.

Kesho Bora Study Group (2012). Maternal HIV-1 disease progression 18-24 months postdelivery according to antiretroviral prophylaxis regimen (triple-antiretroviral prophylaxis during pregnancy and breastfeeding vs zidovudine/single-dose nevirapine prophylaxis): The Kesho Bora randomized controlled trial. *Clin Infect Dis,* 55(3), 449-460.

Kind C, Rudin C, Siegrist CA, Wyler CA, Biedermann K, Lauper U, Irion O, Schupbach J, and Nadal D (1998). Prevention of vertical HIV transmission: additive protective effect of elective Cesarean section and zidovudine prophylaxis. Swiss Neonatal HIV Study Group. *AIDS,* 12(2), 205-210.

King CC, Ellington SR, and Kourtis AP (2013). The role of co-infections in mother-to-child transmission of HIV. *Curr HIV Res,* 11(1), 10-23.

King JC (2003). The risk of maternal nutritional depletion and poor outcomes increases in early or closely spaced pregnancies. *J Nutr,* 133(5 Suppl 2), 1732S-1736S.

Kingston MA, Letham CJ, and McQuillan O (2007). Adherence to antiretroviral therapy in pregnancy. *Int J STD AIDS,* 18(11), 787-789.

Kirkwood BR and Sterene JAC (2003). Essential Medical Statistics (2nd ed.). Oxford, UK: Blackwell.

Kirshenbaum SB, Hirky AE, Correale J, Goldstein RB, Johnson MO, Rotheram-Borus MJ, and Ehrhardt AA (2004). "Throwing the dice": pregnancy decision-making among HIV-positive women in four U.S. cities. *Perspect Sex Reprod Health,* 36(3), 106-113.

Kober C, Johnson M, Fisher M, Hill T, Anderson J, Bansi L, Gompels M, Palfreeman A, Dunn D, Gazzard B, Gilson R, Post F, Phillips AN, Walsh J, Orkin C, Delpech V, Ainsworth J, Leen C, and Sabin CA (2012). Non-uptake of highly active antiretroviral therapy among patients with a CD4 count < 350 cells/muL in the UK. *HIV Med,* 13(1), 73-78.

Kourtis AP and Bulterys M (2010). Mother-to-child transmission of HIV: pathogenesis, mechanisms and pathways. *Clin Perinatol,* 37(4), 721-737.

Kourtis AP, Bulterys M, Nesheim SR, and Lee FK (2001). Understanding the timing of HIV transmission from mother to infant. *JAMA,* 285(6), 709-712.

Kourtis AP and Fowler MG (2011). Antiretroviral use during pregnancy and risk of preterm delivery: more questions than answers. *J Infect Dis,* 204(4), 493-494.

Kourtis AP, Schmid CH, Jamieson DJ, and Lau J (2007). Use of antiretroviral therapy in pregnant HIV-infected women and the risk of premature delivery: a meta-analysis. *AIDS,* 21(5), 607-615.

Kozuki N, Lee AC, Silveira MF, Sania A, Vogel JP, Adair L, Barros F, Caulfield LE, Christian P, Fawzi W, Humphrey J, Huybregts L, Mongkolchati A, Ntozini R, Osrin D, Roberfroid D, Tielsch J, Vaidya A, Black RE, and Katz J (2013). The associations of parity and maternal age with small-for-gestational-age, preterm, and neonatal and infant mortality: a meta-analysis. *BMC Public Health,* 13(Suppl 3), S2.

Kremer H, Bader A, O'Cleirigh C, Bierhoff HW, and Brockmeyer NH (2004). The decision to forgo antiretroviral therapy in people living with HIV compliance as paternalism or partnership? *Eur J Med Res,* 9(2), 61-70.

Kuhnert M, Strohmeier R, Stegmuller M, and Halberstadt E (1998). Changes in lymphocyte subsets during normal pregnancy. *Eur J Obstet Gynecol Reprod Biol,* 76(2), 147-151.

Kupek E, Petrou S, Vause S, and Maresh M (2002). Clinical, provider and sociodemographic predictors of late initiation of antenatal care in England and Wales. *BJOG,* 109(3), 265-273.

Kushnir VA and Lewis W (2011). Human immunodeficiency virus/acquired immunodeficiency syndrome and infertility: emerging problems in the era of highly active antiretrovirals. *Fertil Steril,* 96(3), 546-553.

Lallemant M, Jourdain G, Le Coeur S, Mary JY, Ngo-Giang-Huong N, Koetsawang S, Kanshana S, McIntosh K, and Thaineua V (2004). Single-dose perinatal nevirapine plus standard zidovudine to prevent mother-to-child transmission of HIV-1 in Thailand. *New England Journal of Medicine,* 351(3), 217-228.

Lambotte O, Boufassa F, Madec Y, Nguyen A, Goujard C, Meyer L, Rouzioux C, Venet A, and Delfraissy JF (2005). HIV controllers: a homogeneous group of HIV-1-infected patients with spontaneous control of viral replication. *Clin Infect Dis,* 41(7), 1053-1056.

Laursen T, Kesmodel US, Hojgaard A, Ostergaard L, Ingerslev HJ, and Wejse C (2013). Reproductive patterns and fertility wishes among HIV-infected patients: survey from six outpatient clinics in Denmark. *Int J Infect Dis,* 17(10), e851-856.

Le Moing V, Taieb A, Longuet P, Lewden C, Delcey V, Drobacheff MCT, Chene G, and Leport C (2008). Pregnancy may be followed by an inflexion of the immune reconstitution in HIV-infected women who receive antiretroviral drugs before conception. *HIV Med,* 9(10), 897-900.

Lee L, McKenzie-McHarg K, and Horsch A (2013). Women's Decision Making and Experience of Subsequent Pregnancy Following Stillbirth. *Journal of Midwifery & Womens Health,* 58(4), 431-439.

Lemey P, Pybus OG, Wang B, Saksena NK, Salemi M, and Vandamme AM (2003). Tracing the origin and history of the HIV-2 epidemic. *Proc Natl Acad Sci USA,* 100(11), 6588-6592.

Lemly D, Mandelbrot L, Meier F, Firtion G, Matheron S, Jeantils V, and Scott TA (2007). Factors related to medical appointment attendance after childbirth among HIV-infected women in the Paris region. *AIDS Care,* 19(3), 346-354.

Lemp GF, Payne SF, Neal D, Temelso T, and Rutherford GW (1990). Survival trends for patients with AIDS. *JAMA,* 263(3), 402-406.

Linas BS, Minkoff H, Cohen MH, Karim R, Cohan D, Wright RL, Young M, Watts DH, and Golub ET (2011). Relative time to pregnancy among HIV-infected and uninfected women in the Women's Interagency HIV Study, 2002-2009. *AIDS,* 25(5), 707-711.

Lisonkova S, Janssen PA, Sheps SB, Lee SK, and Dahlgren L (2010). The effect of maternal age on adverse birth outcomes: does parity matter? *Journal of Obstetrics and Gynaecology Canada,* 32(6), 541-548.

Liuzzi G, Pinnetti C, Floridia M, Tamburrini E, Masuelli G, Dalzero S, Sansone M, Giacomet V, Degli Antoni AM, Guaraldi G, Meloni A, Maccabruni A, Alberico S, Portelli V, Ravizza M, and The Italian Group On Surveillance On Antiretroviral Treatment In Pregnancy (2013). Pregnancy Outcomes in HIV-Infected Women of Advanced Maternal Age. *HIV Clin Trials,* 14(3), 110-119.

Livingston EG, Huo Y, Patel K, Brogly SB, Tuomala R, Scott GB, Bardeguez A, Stek A, and Read JS (2010). Mode of delivery and infant respiratory morbidity among infants born to HIV-1-infected women. *Obstetrics and Gynecology,* 116(2 Pt 1), 335-343.

Lockman S, Hughes MD, McIntyre J, Zheng Y, Chipato T, Conradie F, Sawe F, Asmelash A, Hosseinipour MC, Mohapi L, Stringer E, Mngqibisa R, Siika A, Atwine D, Hakim J, Shaffer D, Kanyama C, Wools-Kaloustian K, Salata RA, Hogg E, Alston-Smith B, Walawander A, Purcelle-Smith E, Eshleman S, Rooney J, Rahim S, Mellors JW, Schooley RT, and Currier JS (2010). Antiretroviral therapies in women after single-dose nevirapine exposure. *New England Journal of Medicine,* 363(16), 1499-1509.

Lockman S, Shapiro RL, Smeaton LM, Wester C, Thior I, Stevens L, Chand F, Makhema J, Moffat C, Asmelash A, Ndase P, Arimi P, van Widenfelt E, Mazhani L, Novitsky V, Lagakos S, and Essex M (2007). Response to antiretroviral therapy after a single, peripartum dose of nevirapine. *New England Journal of Medicine,* 356(2), 135-147.

Lodi S, Phillips A, Touloumi G, Geskus R, Meyer L, Thiebaut R, Pantazis N, Amo JD, Johnson AM, Babiker A, and Porter K (2011). Time from human immunodeficiency virus seroconversion to reaching CD4+ cell count thresholds <200, <350, and <500 Cells/mm(3): assessment of need following changes in treatment guidelines. *Clin Infect Dis,* 53(8), 817-825.

Loftus H, Burnett A, Greig J, Naylor S, and Bates S (2014). HIV control in post-partum mothers; a turbulent time. Paper presented at the Third Joint Conference of the British HIV Association (BHIVA) with the British Association for Sexual Health and HIV (BASHH), Liverpool, UK.

Lopez M, Figueras F, Hernandez S, Lonca M, Garcia R, Palacio M, and Coll O (2012). Association of HIV infection with spontaneous and iatrogenic preterm delivery: effect of HAART. *AIDS,* 26(1), 37-43.

Lorenzi P, Spicher VM, Laubereau B, Hirschel B, Kind C, Rudin C, Irion O, and Kaiser L (1998). Antiretroviral therapies in pregnancy: maternal, fetal and neonatal effects. Swiss HIV Cohort Study, the Swiss Collaborative HIV and Pregnancy Study, and the Swiss Neonatal HIV Study. *AIDS,* 12(18), F241-247.

Loutfy M, Raboud J, Wong J, Yudin M, Diong C, Blitz S, Margolese S, Hart T, Ogilvie G, Masinde K, Tharao W, Linklater G, Salam K, Ongoiba F, Angel J, Smaill F, Rachlis A, Ralph E, and Walmsley S (2011). High prevalence of unintended pregnancies in HIV-positive women of reproductive age in Ontario, Canada: a retrospective study. *HIV Med,* 13(2), 107-117.

Loutfy MR, Hart TA, Mohammed SS, Su D, Ralph ED, Walmsley SL, Soje LC, Muchenje M, Rachlis AR, Smaill FM, Angel JB, Raboud JM, Silverman MS, Tharao WE, Gough K, and Yudin MH (2009). Fertility desires and intentions of HIV-positive women of reproductive age in Ontario, Canada: a cross-sectional study. *PLoS One,* 4(12), e7925.

Lyall EG, Blott M, de Ruiter A, Hawkins D, Mercy D, Mitchla Z, Newell ML, O'Shea S, Smith JR, Sunderland J, Webb R, and Taylor GP (2001). Guidelines for the management of HIV infection in pregnant women and the prevention of mother-to-child transmission. *HIV Med,* 2(4), 314-334.

Lyons F, Hopkins S, Kelleher B, McGeary A, Sheehan G, Geoghegan J, Bergin C, Mulcahy FM, and McCormick PA (2006). Maternal hepatotoxicity with nevirapine as part of combination antiretroviral therapy in pregnancy. *HIV Med,* 7(4), 255-260.

Lyons F, O'Dea S, Holmes A, Butler K, Bergin C, and Mulcahy F (2005a). Management of sequential pregnancies in HIV infected women. Paper presented at the 18th Conference on Retroviruses and Opportunistic Infections, Boston, US.

Lyons FE, Coughlan S, Byrne CM, Hopkins SM, Hall WW, and Mulcahy FM (2005b). Emergence of antiretroviral resistance in HIV-positive women receiving combination antiretroviral therapy in pregnancy. *AIDS,* 19(1), 63-67.

MacCarthy S, Laher F, Nduna M, Farlane L, and Kaida A (2009). Responding to her question: a review of the influence of pregnancy on HIV disease progression in the context of expanded access to HAART in sub-Saharan Africa. *AIDS Behav,* 13 Suppl 1, 66-71.

Machado ES, Hofer CB, Costa TT, Nogueira SA, Oliveira RH, Abreu TF, Evangelista LA, Farias IF, Mercadante RT, Garcia MF, Neves RC, Costa VM, and Lambert JS (2009). Pregnancy outcome in women infected with HIV-1 receiving combination antiretroviral therapy before versus after conception. *Sex Transm Infect,* 85(2), 82-87.

Mackie NE, Fidler S, Tamm N, Clarke JR, Back D, Weber JN, and Taylor GP (2004). Clinical implications of stopping nevirapine-based antiretroviral therapy: relative pharmacokinetics and avoidance of drug resistance. *HIV Med,* 5(3), 180-184.

Maggiolo F, Airoldi M, Kleinloog HD, Callegaro A, Ravasio V, Arici C, Bombana E, and Suter F (2007). Effect of adherence to HAART on virologic outcome and on the selection of resistance-conferring mutations in NNRTI- or PI-treated patients. *HIV Clin Trials,* 8(5), 282-292.

Maggiolo F, Ravasio L, Ripamonti D, Gregis G, Quinzan G, Arici C, Airoldi M, and Suter F (2005). Similar adherence rates favor different virologic outcomes for patients treated with nonnucleoside analogues or protease inhibitors. *Clin Infect Dis,* 40(1), 158-163.

Maguire A, Sanchez E, Fortuny C, and Casabona J (1997). Potential risk factors for vertical HIV-1 transmission in Catalonia, Spain: the protective role of cesarean section. The Working Group on HIV-1 Vertical Transmission in Catalonia. *AIDS,* 11(15), 1851-1857.

Maiques-Montesinos V, Cervera-Sanchez J, Bellver-Pradas J, Abad-Carrascosa A, and Serra-Serra V (1999). Post-cesarean section morbidity in HIV-positive women. *Acta Obstet Gynecol Scand,* 78(9), 789-792.

Maisels L, Steinberg J, and Tobias C (2001). An investigation of why eligible patients do not receive HAART. *AIDS Patient Care STDS,* 15(4), 185-191.

Malin G, Morris R, Riley R, Teune M, and Khan K (2014). When is birthweight at term abnormally low? A systematic review and meta-analysis of the association and predictive ability of current birthweight standards for neonatal outcomes. *BJOG,* 121(5), 515-526.

Mandelbrot L, Le Chenadec J, Berrebi A, Bongain A, Benifla JL, Delfraissy JF, Blanche S, and Mayaux MJ (1998). Perinatal HIV-1 transmission: interaction between zidovudine prophylaxis and mode of delivery in the French Perinatal Cohort. *JAMA,* 280(1), 55-60.

Mann HBW, D. R., (1947). On a test whether one of two random variables is stochastically larger than the other. *Annals of Mathematical Statistics,* 18, 50-60.

Mark S, Murphy KE, Read S, Bitnun A, and Yudin MH (2012). HIV mother-to-child transmission, mode of delivery, and duration of rupture of membranes: experience in the current era. *Infect Dis Obstet Gynecol,* 2012, 267969.

Marks G, Crepaz N, and Janssen RS (2006). Estimating sexual transmission of HIV from persons aware and unaware that they are infected with the virus in the USA. *AIDS,* 20(10), 1447-1450.

Marshall NE, Fu R, and Guise JM (2011). Impact of multiple cesarean deliveries on maternal morbidity: a systematic review. *Am J Obstet Gynecol,* 205(3), 262 e261-268.

Martin F and Taylor GP (2007). Increased rates of preterm delivery are associated with the initiation of highly active antiretrovial therapy during pregnancy: a single-center cohort study. *J Infect Dis,* 196(4), 558-561.

Massad LS, Springer G, Jacobson L, Watts H, Anastos K, Korn A, Cejtin H, Stek A, Young M, Schmidt J, and Minkoff H (2004). Pregnancy rates and predictors of conception, miscarriage and abortion in US women with HIV. *AIDS,* 18(2), 281-286.

May M, Gompels M, Delpech V, Porter K, Post F, Johnson M, Dunn D, Palfreeman A, Gilson R, Gazzard B, Hill T, Walsh J, Fisher M, Orkin C, Ainsworth J, Bansi L, Phillips A, Leen C, Nelson M, Anderson J, and Sabin C (2011a). Impact of late diagnosis and treatment on life expectancy in people with HIV-1: UK Collaborative HIV Cohort (UK CHIC) Study. *BMJ,* 343, d6016.

May MT and Ingle SM (2011b). Life expectancy of HIV-positive adults: a review. *Sexual Health,* 8(4), 526-533.

Mayaux MJ, Dussaix E, Isopet J, Rekacewicz C, Mandelbrot L, Ciraru-Vigneron N, Allemon MC, Chambrin V, Katlama C, Delfraissy JF, and Puel J (1997). Maternal virus load during pregnancy and mother-to-child transmission of human immunodeficiency virus type 1: the French perinatal cohort studies. SEROGEST Cohort Group. *J Infect Dis,* 175(1), 172-175.

Mayaux MJ, Teglas JP, and Blanche S (2003). Characteristics of HIV-infected women who do not receive preventive antiretroviral therapy in the French Perinatal Cohort. *J Acquir Immune Defic Syndr,* 34(3), 338-343.

Mazaki-Tovi S, Romero R, Kusanovic JP, Erez O, Pineles BL, Gotsch F, Mittal P, Than NG, Espinoza J, and Hassan SS (2007). Recurrent preterm birth. *Semin Perinatol,* 31(3), 142-158.

McDonald K and Kirkman M (2011). HIV-positive women in Australia explain their use and non-use of antiretroviral therapy in preventing mother-to-child transmission. *AIDS Care,* 23(5), 578-584.

McNutt LA, Wu C, Xue X, and Hafner JP (2003). Estimating the relative risk in cohort studies and clinical trials of common outcomes. *Am J Epidemiol,* 157(10), 940-943.

Mercer BM, Goldenberg RL, Moawad AH, Meis PJ, Iams JD, Das AF, Caritis SN, Miodovnik M, Menard MK, Thurnau GR, Dombrowski MP, Roberts JM, and McNellis D (1999). The preterm prediction study: effect of gestational age and cause of preterm birth on subsequent obstetric outcome. National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. *Am J Obstet Gynecol,* 181(5 Pt 1), 1216-1221.

Merenstein D, Schneider MF, Cox C, Schwartz R, Weber K, Robison E, Gandhi M, Richardson J, and Plankey MW (2009). Association of child care burden and household composition with adherence to highly active antiretroviral therapy in the Women's Interagency HIV Study. *AIDS Patient Care STDS,* 23(4), 289-296.

Merenstein DJ, Schneider MF, Cox C, Schwartz R, Weber K, Robison E, Gandhi M, Richardson J, and Plankey MW (2008). Association between living with children and adherence to highly active antiretroviral therapy in the Women's Interagency HIV Study. *Pediatrics,* 121(4), e787-793.

Minkoff H, Hershow R, Watts DH, Frederick M, Cheng I, Tuomala R, Pitt J, Zorrilla CD, Hammill H, Adeniyi-Jones SK, and Thompson B (2003). The relationship of pregnancy to human immunodeficiency virus disease progression. *Am J Obstet Gynecol,* 189(2), 552-559.

Miranda ML, Edwards SE, and Myers ER (2011). Adverse birth outcomes among nulliparous vs. multiparous women. *Public Health Rep,* 126(6), 797-805.

Mirochnick M, Best BM, and Clarke DF (2010). Antiretroviral pharmacology: special issues regarding pregnant women and neonates. *Clin Perinatol,* 37(4), 907-927, xi.

Misener TR and Sowell RL (1998). HIV-infected women's decisions to take antiretrovirals. *West J Nurs Res,* 20(4), 431-447.

Mocroft A, Youle M, Morcinek J, Sabin CA, Gazzard B, Johnson MA, and Phillips AN (1997). Survival after diagnosis of AIDS: a prospective observational study of 2625 patients. Royal Free/Chelsea and Westminster Hospitals Collaborative Group. *BMJ,* 314(7078), 409-413.

Modestini C, Rodling S, French CE, Martin N, Tookey P, and Burns F (2013). HIV positive pregnant women who receive less than two weeks of ART before delivery: why does it occur? Paper presented at the 19th Annual Conference of the British HIV Association, Manchester, UK.

Mofenson LM, Lambert JS, Stiehm ER, Bethel J, Meyer WA, 3rd, Whitehouse J, Moye J, Jr., Reichelderfer P, Harris DR, Fowler MG, Mathieson BJ, and Nemo GJ (1999). Risk factors for perinatal transmission of human immunodeficiency virus type 1 in women treated with zidovudine. Pediatric AIDS Clinical Trials Group Study 185 Team. *New England Journal of Medicine,* 341(6), 385-393.

Montaner JS, Hogg R, Wood E, Kerr T, Tyndall M, Levy AR, and Harrigan PR (2006). The case for expanding access to highly active antiretroviral therapy to curb the growth of the HIV epidemic. *Lancet,* 368(9534), 531-536.

Montaner JS, Lima VD, Barrios R, Yip B, Wood E, Kerr T, Shannon K, Harrigan PR, Hogg RS, Daly P, and Kendall P (2010). Association of highly active antiretroviral therapy coverage, population viral load, and yearly new HIV diagnoses in British Columbia, Canada: a population-based study. *Lancet,* 376(9740), 532-539.

Mortimer PP and Loveday C. (2001). The virus and the tests. In M. W. Adler (Ed.), *ABC of HIV and AIDS* (eBook. 5th ed., pp. 6-11): Wiley-Blackwell: BMJ Books.

Moser K, Stanfield KM, and Leon DA (2008). Birthweight and gestational age by ethnic group, England and Wales 2005: introducing new data on births. *Health Stat Q*(39), 22-31, 34-55.

Moses SH and Dhar J (2012). A survey of the sexual and reproductive health of HIV-positive women in Leicester. *Int J STD AIDS,* 23(4), 282-284.

Moyo W and Mbizvo MT (2004). Desire for a future pregnancy among women in Zimbabwe in relation to their self-perceived risk of HIV infection, child mortality, and spontaneous abortion. *AIDS Behav,* 8(1), 9-15.

Myer L, Carter RJ, Katyal M, Toro P, El-Sadr WM, and Abrams EJ (2010). Impact of antiretroviral therapy on incidence of pregnancy among HIV-infected women in Sub-Saharan Africa: a cohort study. *PLoS Med,* 7(2), e1000229.

Myer L, Cornell M, Fox MP, Garone D, Wood R, and Prozesky HW (2012). Loss to Follow-up and Mortality among Pregnant and Non-pregnant Women Initiating ART: South Africa. Paper presented at the 19th Conference on Retroviruses and Opportunistic Infections, Seattle, US.

Myer L, Morroni C, and Rebe K (2007). Prevalence and determinants of fertility intentions of HIV-infected women and men receiving antiretroviral therapy in South Africa. *AIDS Patient Care STDS,* 21(4), 278-285.

Nabukera SK, Wingate MS, Kirby RS, Owen J, Swaminathan S, Alexander GR, and Salihu HM (2008). Interpregnancy interval and subsequent perinatal outcomes among women delaying initiation of childbearing. *Journal of Obstetrics and Gynaecology Research,* 34(6), 941-947.

Nachega JB, Hislop M, Dowdy DW, Chaisson RE, Regensberg L, and Maartens G (2007). Adherence to nonnucleoside reverse transcriptase inhibitor-based HIV therapy and virologic outcomes. *Ann Intern Med,* 146(8), 564-573.

Nachega JB, Uthman OA, Anderson J, Peltzer K, Wampold S, Cotton MF, Mills EJ, Ho YS, Stringer JS, McIntyre JA, and Mofenson LM (2012). Adherence to antiretroviral therapy during and after pregnancy in low-income, middle-income, and high-income countries: a systematic review and meta-analysis. *AIDS,* 26(16), 2039-2052.

Nakagawa F, Lodwick RK, Smith CJ, Smith R, Cambiano V, Lundgren JD, Delpech V, and Phillips AN (2012). Projected life expectancy of people with HIV according to timing of diagnosis. *AIDS,* 26(3), 335-343.

Nakayiwa S, Abang B, Packel L, Lifshay J, Purcell DW, King R, Ezati E, Mermin J, Coutinho A, and Bunnell R (2006). Desire for children and pregnancy risk behavior among HIV-infected men and women in Uganda. *AIDS Behav,* 10(4 Suppl), S95-104.

Nardone A, Delpech V, Gill ON, Fenton KA, and Anderson J (2013). HIV in the UK: test, test, and test again. *Lancet,* 382(9906), 1687-1688.

National Institute for Health and Clinical Excellence (2008). Routine antenatal care for the healthy pregnant woman London, UK: National Institute for Clinical Excellence.

National Institute for Health and Clinical Excellence (2011). NICE clinical guideline 132: Caesarean section. London, UK.

National Population Commission (NPC) [Nigeria] and ICF Macro (2009). Nigeria Demographic and Health Survey 2008. Abuja, Nigeria: National Population Commission and ICF Macro.

National Study of HIV in Pregnancy and Childhood (2013). Quarterly slide set (data up to end of December 2012). Available at: http://www.ucl.ac.uk/nshpc/slides (Accessed March 2014).

National Study of HIV in Pregnancy and Childhood (2014). Quarterly slide set (data up to end of March 2014). Available at: http://www.ucl.ac.uk/nshpc/slides (Accessed May 2014).

National Study of HIV in Pregnancy and Childhood, Children's HIV Association, and NHS Audit and Information Analysis Unit (2007). Perinatal transmission of HIV in England 2002-2005: Executive summary.

Nattabi B, Li J, Thompson SC, Orach CG, and Earnest J (2009). A systematic review of factors influencing fertility desires and intentions among people living with HIV/AIDS: implications for policy and service delivery. *AIDS Behav,* 13(5), 949-968.

Nesheim S, Harris LF, and Lampe M (2013). Elimination of perinatal HIV infection in the USA and other high-income countries: achievements and challenges. *Curr Opin HIV AIDS,* 8(5), 446-455.

Newell ML (1998). Mechanisms and timing of mother-to-child transmission of HIV-1. *AIDS,* 12(8), 831-837.

Newell ML and Bunders MJ (2013). Safety of antiretroviral drugs in pregnancy and breastfeeding for mother and child. *Curr Opin HIV AIDS,* 8(5), 503-509.

Newell ML, Huang S, Fiore S, Thorne C, Mandelbrot L, Sullivan JL, Maupin R, Delke I, Watts DH, Gelber RD, Cunningham CK; PACTG 316 Study Team (2007). Characteristics and management of HIV-1-infected pregnant women enrolled in a randomised trial: differences between Europe and the USA. *BMC Infectious Diseases,* 7, 60.

Ngarina M, Tarimo EA, Naburi H, Kilewo C, Mwanyika-Sando M, Chalamilla G, Biberfeld G, and Ekstrom AM (2014). Women's preferences regarding infant or maternal antiretroviral prophylaxis for prevention of mother-to-child transmission of HIV during breastfeeding and their views on Option B+ in Dar es Salaam, Tanzania. *PLoS One,* 9(1), e85310.

NHS Executive (1999). Reducing mother to baby transmission of HIV. London, UK: Department of Health.

Nicopoullos JD, Almeida PA, Ramsay JW, and Gilling-Smith C (2004). The effect of human immunodeficiency virus on sperm parameters and the outcome of intrauterine insemination following sperm washing. *Hum Reprod,* 19(10), 2289-2297.

Nightingale SL (1998). From the Food and Drug Administration. *JAMA,* 280(17), 1472.

Nostlinger C, Desjardins F, Dec J, Platteau T, and Hasker E (2013). Child desire in women and men living with HIV attending HIV outpatient clinics: evidence from a European multicentre study. *Eur J Contracept Reprod Health Care,* 18(4), 251-263.

Nunes V, Neilson J, O'Flynn N, Calvert N, Kuntze S, Smithson H, Benson J, Blair J, Bowser A, Clyne W, Crome P, Haddad P, Hemingway S, Horne R, Johnson S, Kelly S, Packham B, Patel M, and Steel J (2009). Medicines concordance and adherence: involving adults and carers in decisions about prescribed medicines. National Clinical Practice Guideline Number 76. London.

Nybo Andersen AM, Wohlfahrt J, Christens P, Olsen J, and Melbye M (2000). Maternal age and fetal loss: population based register linkage study. *BMJ,* 320(7251), 1708-1712.

O'Neill SM, Kearney PM, Kenny LC, Khashan AS, Henriksen TB, Lutomski JE, and Greene RA (2013). Caesarean delivery and subsequent stillbirth or miscarriage: systematic review and meta-analysis. *PLoS One,* 8(1), e54588.

Office for National Statistics (2011a). Statistical Bulletin. Gestation-specific Infant Mortality in England and Wales, 2009.

Office for National Statistics (2011b). Statistical Bulletin. Population Estimates by Ethnic Group 2002 – 2009.

Ofir K, Sheiner E, Levy A, Katz M, and Mazor M (2003). Uterine rupture: risk factors and pregnancy outcome. *Am J Obstet Gynecol,* 189(4), 1042-1046.

Ogilvie GS, Palepu A, Remple VP, Maan E, Heath K, MacDonald G, Christilaw J, Berkowitz J, Fisher WA, and Burdge DR (2007). Fertility intentions of women of reproductive age living with HIV in British Columbia, Canada. *AIDS,* 21, S83-S88.

Onen NF, Nurutdinova D, Sungkanuparph S, Gase D, Mondy K, and Overton ET (2008). Effect of postpartum HIV treatment discontinuation on long-term maternal outcome. *Journal of the International Association of Physicians in AIDS Care,* 7(5), 245-251.

Orloff SL, Bulterys M, Vink P, Nesheim S, Abrams EJ, Schoenbaum E, Palumbo P, Steketee RW, and Simonds RJ (2001). Maternal characteristics associated with antenatal, intrapartum, and neonatal zidovudine use in four US cities, 1994-1998. *J Acquir Immune Defic Syndr,* 28(1), 65-72.

Overton ET, Sungkanuparph S, Nurutdinova D, and Powderly WG (2005). Antiretroviral resistance among HIV-positive pregnant women who have antiretroviral experience from previous pregnancy. *AIDS,* 19(13), 1439.

Pacheco SE, McIntosh K, Lu M, Mofenson LM, Diaz C, Foca M, Frederick M, Handelsman E, Hayani K, and Shearer WT (2006). Effect of perinatal antiretroviral drug exposure on hematologic values in HIV-uninfected children: An analysis of the women and infants transmission study. *J Infect Dis,* 194(8), 1089-1097.

Palacios R, Senise J, Vaz M, Diaz R, and Castelo A (2009). Short-term antiretroviral therapy to prevent mother-to-child transmission is safe and results in a sustained increase in CD4 T-cell counts in HIV-1-infected mothers. *HIV Med,* 10(3), 157-162.

Pan H and Cole TJ (2012). LMSgrowth, a Microsoft Excel add-in to access growth references based on the LMS method. Version 2.77 Available at: http://www.healthforallchildren.co.uk/ (Accessed October 2013).

Panburana P, Phaupradit W, Tantisirin O, Sriintravanit N, and Buamuenvai J (2003). Maternal complications after Caesarean section in HIV-infected pregnant women. *Aust N Z J Obstet Gynaecol,* 43(2), 160-163.

Panel on Antiretroviral Guidelines for Adults and Adolescents (2013). Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Available at: http://aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf (Accessed January 2014).

Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission (2012). Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States. Available at: http://aidsinfo.nih.gov/contentfiles/PerinatalGL.pdf (Accessed February 2014).

Pantaleo G, Graziosi C, and Fauci AS (1993). New concepts in the immunopathogenesis of human immunodeficiency virus infection. *New England Journal of Medicine,* 328(5), 327-335.

Paredes R, Cheng I, Kuritzkes DR, and Tuomala RE (2010). Postpartum antiretroviral drug resistance in HIV-1-infected women receiving pregnancy-limited antiretroviral therapy. *AIDS,* 24(1), 45-53.

Paredes R, Marconi VC, Lockman S, Abrams EJ, and Kuhn L (2013). Impact of antiretroviral drugs in pregnant women and their children in Africa: HIV resistance and treatment outcomes. *J Infect Dis,* 207 Suppl 2, S93-100.

Parisaei M, Anderson J, Erskine KJ, and Gann S (2007). Experience of delivering women with HIV in an inner city London hospital 1994-2004. *Int J STD AIDS,* 18(8), 527-530.

Patel D, Cortina-Borja M, Thorne C, and Newell ML (2007). Time to undetectable viral load after highly active antiretroviral therapy initiation among HIV-infected pregnant women. *Clin Infect Dis,* 44(12), 1647-1656.

Patel K, Shapiro DE, Brogly SB, Livingston EG, Stek AM, Bardeguez AD, and Tuomala RE (2010). Prenatal protease inhibitor use and risk of preterm birth among HIV-infected women initiating antiretroviral drugs during pregnancy. *J Infect Dis,* 201(7), 1035-1044.

Patel RR, Steer P, Doyle P, Little MP, and Elliott P (2004). Does gestation vary by ethnic group? A London-based study of over 122,000 pregnancies with spontaneous onset of labour. *International Journal of Epidemiology,* 33(1), 107-113.

Paterson DL, Swindells S, Mohr J, Brester M, Vergis EN, Squier C, Wagener MM, and Singh N (2000). Adherence to protease inhibitor therapy and outcomes in patients with HIV infection. *Ann Intern Med,* 133(1), 21-30.

Peeters M, Jung M, and Ayouba A (2013). The origin and molecular epidemiology of HIV. *Expert Rev Anti Infect Ther,* 11(9), 885-896.

Perinatal Institute (2011). Perinatal Mortality Definitions. Available at: http://www.perinatal.nhs.uk/pnm/definitions.htm (Accessed October 2013).

Peters V, Liu KL, Dominguez K, Frederick T, Melville S, Hsu HW, Ortiz I, Rakusan T, Gill B, and Thomas P (2003). Missed opportunities for perinatal HIV prevention among HIV-exposed infants born 1996-2000, pediatric spectrum of HIV disease cohort. *Pediatrics,* 111(5 Pt 2), 1186-1191.

Phillips AN, Dunn D, Sabin C, Pozniak A, Matthias R, Geretti AM, Clarke J, Churchill D, Williams I, Hill T, Green H, Porter K, Scullard G, Johnson M, Easterbrook P, Gilson R, Fisher M, Loveday C, Gazzard B, and Pillay D (2005). Long term probability of detection of HIV-1 drug resistance after starting antiretroviral therapy in routine clinical practice. *AIDS,* 19(5), 487-494.

Pilotto JH, Grinsztejn B, Veloso V, Couto-Fernandez JC, Rodrigues-Pedro A, Velasco-De-Castro CA, Ribeiro JE, Khalili R, Muri S, Ismerio R, Hoffman R, Currier J, and Morgado MG (2009). HIV drug resistance after HAART discontinuation among treatment-naive women who initiate antiretroviral therapy for the prevention of mother-to-child transmission in Rio de Janeiro, Brazil. *Antiviral Therapy,* 14(4), A167-A167.

Powis KM, Kitch D, Ogwu A, Hughes MD, Lockman S, Leidner J, van Widenfelt E, Moffat C, Moyo S, Makhema J, Essex M, and Shapiro RL (2011). Increased Risk of Preterm Delivery Among HIV-Infected Women Randomized to Protease Versus Nucleoside Reverse Transcriptase Inhibitor-Based HAART During Pregnancy. *J Infect Dis,* 204(4), 506-514.

Pozniak A, Gazzard B, Anderson J, Babiker A, Churchill D, Collins S, Fisher M, Johnson M, Khoo S, Leen C, Loveday C, Moyle G, Nelson M, Peter B, Phillips A, Pillay D, Wilkins E, Williams I, and Youle M (2003). British HIV Association (BHIVA) guidelines for the treatment of HIV-infected adults with antiretroviral therapy. *HIV Med,* 4 Suppl 1, 1-41.

Prost A (2005). A review of research among black African communities affected by HIV in the UK and Europe. Glasgow, UK: Medical Research Council

Public Health England (2013a). Antenatal screening for infectious diseases in England: summary report for 2012. London, UK: Public Health England.

Public Health England (2013b). HIV & AIDS New Diagnoses & Deaths (HANDD) metafiles. Available at: http://www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1317139917763 (Accessed January 2014).

Public Health England (2013c). Survey of Prevalent HIV Infections Diagnosed (SOPHID) metadata files. Available at: http://www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1317139918001 (Accessed December 2013).

Quinn TC, Wawer MJ, Sewankambo N, Serwadda D, Li C, Wabwire-Mangen F, Meehan MO, Lutalo T, and Gray RH (2000). Viral load and heterosexual transmission of human immunodeficiency virus type 1. Rakai Project Study Group. *New England Journal of Medicine,* 342(13), 921-929.

Raatikainen K, Heiskanen N, and Heinonen S (2007). Under-attending free antenatal care is associated with adverse pregnancy outcomes. *BMC Public Health,* 7, 268.

Rachas A, Warszawski J, Le Chenadec J, Legeai C, Teglas JP, Goujard C, Rouzioux C, Mandelbrot L, Tubiana R, and Meyer L (2013). Does pregnancy affect the early response to cART? *AIDS,* 27(3), 357-367.

Rahangdale L, Stewart A, Stewart RD, Badell M, Levison J, Ellis P, Cohn SE, Kempf MC, Lazenby GB, Tandon R, Rana A, Nguyen ML, Sturdevant MS, and Cohan D (2014). Pregnancy intentions among women living with HIV in the United States. *J Acquir Immune Defic Syndr,* 65(3), 306-311.

Rana AI, Gillani FS, Flanigan TP, Nash BT, and Beckwith CG (2010). Follow-up care among HIV-infected pregnant women in Mississippi. *J Womens Health,* 19(10), 1863-1867.

Rankin WW, Brennan S, Schell E, Laviwa J, and Rankin SH (2005). The stigma of being HIV-positive in Africa. *PLoS Med,* 2(8), e247.

Ravizza M, Martinelli P, Bucceri A, Fiore S, Alberico S, Tamburrini E, Tibaldi C, Guaraldi G, Anzidei G, Maccabruni A, Crisalli MP, and Floridia M (2007). Treatment with protease inhibitors and coinfection with hepatitis C virus are independent predictors of preterm delivery in HIV-infected pregnant women. *J Infect Dis,* 195(6), 913-914.

Read JS and Newell MK (2005). Efficacy and safety of cesarean delivery for prevention of mother-to-child transmission of HIV-1. *Cochrane Database Syst Rev,* 4, CD005479.

Read PJ, Mandalia S, Khan P, Harrisson U, Naftalin C, Gilleece Y, Anderson J, Hawkins DA, Taylor GP, and de Ruiter A (2012). When should HAART be initiated in pregnancy to achieve an undetectable HIV viral load by delivery? *AIDS,* 26(9), 1095-1103.

Rechel B, Mladovsky P, Ingleby D, Mackenbach JP, and McKee M (2013). Migration and health in an increasingly diverse Europe. *Lancet,* 381(9873), 1235-1245.

Redshaw M and Heikkila K (2010). Delivered with care: A national survey of women's experience of maternity care 2010. Oxford, UK: National Perinatal Epidemiology Unit, University of Oxford.

Rice BD, Delpech VC, Chadborn TR, and Elford J (2011). Loss to follow-up among adults attending human immunodeficiency virus services in England, Wales, and Northern Ireland. *Sex Transm Dis,* 38(8), 685-690.

Rice BD, Elford J, Yin Z, and Delpech VC (2012). A new method to assign country of HIV infection among heterosexuals born abroad and diagnosed with HIV. *AIDS,* 26(15), 1961-1966.

Riley K, Roth S, Sellwood M, and Wyatt JS (2008). Survival and neurodevelopmental morbidity at 1 year of age following extremely preterm delivery over a 20-year period: a single centre cohort study. *Acta Paediatr,* 97(2), 159-165.

Rogers WH (1993). Regression standard errors in clustered samples. *Stata Technical Bulletin Reprints,* 13, 19-23.

Ronel D, Wiznitzer A, Sergienko R, Zlotnik A, and Sheiner E (2012). Trends, risk factors and pregnancy outcome in women with uterine rupture. *Arch Gynecol Obstet,* 285(2), 317-321.

Ross AC, Leong T, Avery A, Castillo-Duran M, Bonilla H, Lebrecht D, Walker UA, Storer N, Labbato D, Khaitan A, Tomanova-Soltys I, and McComsey GA (2012). Effects of in utero antiretroviral exposure on mitochondrial DNA levels, mitochondrial function and oxidative stress. *HIV Med,* 13(2), 98-106.

Rowe RE, Magee H, Quigley MA, Heron P, Askham J, and Brocklehurst P (2008). Social and ethnic differences in attendance for antenatal care in England. *Public Health,* 122(12), 1363-1372.

Royal College of Obstetricians and Gynaecologists (2007). Green Top Guideline No.45 - Birth after previous caesarean birth. London, UK: Royal College of Obstetricians and Gynaecologists.

Royal College of Obstetricians and Gynaecologists (2008). Standards for Maternity Care. Report of a Working Party. London, UK: Royal College of Obstetricians and Gynaecologists.

Royal College of Obstetricians and Gynaecologists (2013). Medical terms explained. Available at: http://www.rcog.org.uk/womens-health/patient-information/medical-terms-explained (Accessed January 2014).

Rubin DB (1987). Multiple imputation for nonresponse in surveys. New York, US: Wiley.

Rudin C, Spaenhauer A, Keiser O, Rickenbach M, Kind C, Aebi-Popp K, and Brinkhof MW (2011). Antiretroviral therapy during pregnancy and premature birth: analysis of Swiss data. *HIV Med,* 12(4), 228-235.

Saada M, Le Chenadec J, Berrebi A, Bongain A, Delfraissy JF, Mayaux MJ, and Meyer L (2000). Pregnancy and progression to AIDS: results of the French prospective cohorts. SEROGEST and SEROCO Study Groups. *AIDS,* 14(15), 2355-2360.

Sabin CA, Cooper DA, Collins S, and Schechter M (2013). Rating evidence in treatment guidelines: a case example of when to initiate combination antiretroviral therapy (cART) in HIV-positive asymptomatic persons. *AIDS,* 27(12), 1839-1846.

Saigal S and Doyle LW (2008). An overview of mortality and sequelae of preterm birth from infancy to adulthood. *Lancet,* 371(9608), 261-269.

Samji H, Cescon A, Hogg RS, Modur SP, Althoff KN, Buchacz K, Burchell AN, Cohen M, Gebo KA, Gill MJ, Justice A, Kirk G, Klein MB, Korthuis PT, Martin J, Napravnik S, Rourke SB, Sterling TR, Silverberg MJ, Deeks S, Jacobson LP, Bosch RJ, Kitahata MM, Goedert JJ, Moore R, Gange SJ; North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) of IeDEA (2013). Closing the Gap: Increases in Life Expectancy among Treated HIV-Positive Individuals in the United States and Canada. *PLoS One,* 8(12).

Sanne I, Mommeja-Marin H, Hinkle J, Bartlett JA, Lederman MM, Maartens G, Wakeford C, Shaw A, Quinn J, Gish RG, and Rousseau F (2005). Severe hepatotoxicity associated with nevirapine use in HIV-infected subjects. *J Infect Dis,* 191(6), 825-829.

Schulte J, Dominguez K, Sukalac T, Bohannon B, and Fowler MG (2007). Declines in low birth weight and preterm birth among infants who were born to HIV-infected women during an era of increased use of maternal antiretroviral drugs: Pediatric Spectrum of HIV Disease, 1989-2004. *Pediatrics,* 119(4), e900-906.

Semprini AE, Castagna C, Ravizza M, Fiore S, Savasi V, Muggiasca ML, Grossi E, Guerra B, Tibaldi C, and Scaravelli G (1995). The incidence of complications after caesarean section in 156 HIV-positive women. *AIDS,* 9(8), 913-917.

Shachar BZ and Lyell DJ (2013). Interpregnancy interval and obstetrical complications. UpToDate, Available at: http://www.uptodate.com/contents/interpregnancy-interval-and-obstetrical-complications (Accessed 22 September 2013).

Shaffer N, Abrams EJ, and Becquet R (2014). Option B+ for prevention of mother-to-child transmission of HIV in resource-constrained settings: great promise but some early caution. *AIDS,* 28(4), 599-601.

Shah PS (2010). Parity and low birth weight and preterm birth: a systematic review and meta-analyses. *Acta Obstet Gynecol Scand,* 89(7), 862-875.

Shah PS, Balkhair T, Ohlsson A, Beyene J, Scott F, and Frick C (2011). Intention to become pregnant and low birth weight and preterm birth: a systematic review. *Matern Child Health J,* 15(2), 205-216.

Shapiro RL, Hughes MD, Ogwu A, Kitch D, Lockman S, Moffat C, Makhema J, Moyo S, Thior I, McIntosh K, van Widenfelt E, Leidner J, Powis K, Asmelash A, Tumbare E, Zwerski S, Sharma U, Handelsman E, Mburu K, Jayeoba O, Moko E, Souda S, Lubega E, Akhtar M, Wester C, Tuomola R, Snowden W, Martinez-Tristani M, Mazhani L, and Essex M (2010). Antiretroviral regimens in pregnancy and breast-feeding in Botswana. *New England Journal of Medicine,* 362(24), 2282-2294.

Shapiro RL, Kitch D, Ogwu A, Hughes MD, Lockman S, Powis K, Souda S, Moffat C, Moyo S, McIntosh K, van Widenfelt E, Zwerski S, Mazhani L, Makhema J, and Essex M (2013). HIV transmission and 24-month survival in a randomized trial of HAART to prevent MTCT during pregnancy and breastfeeding in Botswana. *AIDS,* 27(12), 1911-1920.

Sharma A, Feldman JG, Golub ET, Schmidt J, Silver S, Robison E, and Minkoff H (2007). Live birth patterns among human immunodeficiency virus-infected women before and after the availability of highly active antiretroviral therapy. *Am J Obstet Gynecol,* 196(6), 541 e541-546.

Sheon AR, Fox HE, Rich KC, Stratton P, Diaz C, Tuomala R, Mendez H, Carrington J, and Alexander G (1996). The women and infants transmission study (WITS) of maternal-infant HIV transmission: study design, methods and baseline data. *J Womens Health,* 5, 69-78.

Short CE, Douglas M, Smith J, and Taylor G (2013). Preterm delivery risk in women initiating antiretroviral therapy to prevent HIV mother-to-child transmission. *HIV Med,* 15(4), 233-238.

Short CE and Taylor GP (2014). Antiretroviral therapy and preterm birth in HIV-infected women. *Expert Rev Anti Infect Ther,* 12(3), 293-306.

Shuter J (2008). Forgiveness of non-adherence to HIV-1 antiretroviral therapy. *J Antimicrob Chemother,* 61(4), 769-773.

Sibiude J, Warszawski J, Tubiana R, Dollfus C, Faye A, Rouzioux C, Teglas JP, Ekoukou D, Blanche S, and Mandelbrot L (2012). Premature delivery in HIV-infected women starting protease inhibitor therapy during pregnancy: role of the ritonavir boost? *Clin Infect Dis,* 54(9), 1348-1360.

Siegfried N, van der Merwe L, Brocklehurst P, and Sint TT (2011). Antiretrovirals for reducing the risk of mother-to-child transmission of HIV infection. *Cochrane Database Syst Rev,* 7, CD003510.

Silver RM (2012). Implications of the first cesarean: perinatal and future reproductive health and subsequent cesareans, placentation issues, uterine rupture risk, morbidity, and mortality. *Semin Perinatol,* 36(5), 315-323.

Skjeldestad FE, Borgan JK, Daltveit AK, and Nymoen EH (1994). Induced abortion. Effects of marital status, age and parity on choice of pregnancy termination. *Acta Obstet Gynecol Scand,* 73(3), 255-260.

Slattery MM and Morrison JJ (2002). Preterm delivery. *Lancet,* 360(9344), 1489-1497.

Smee N, Shetty AK, Stranix-Chibanda L, Chirenje M, Chipato T, Maldonado Y, and Portillo C (2011). Factors Associated With Repeat Pregnancy Among Women in an Area of High HIV Prevalence in Zimbabwe. *Womens Health Issues,* 21(3), 222-229.

Smith DJ and Mbakwem BC (2010). Antiretroviral therapy and reproductive life projects: mitigating the stigma of AIDS in Nigeria. *Soc Sci Med,* 71(2), 345-352.

Smith GC and Fretts RC (2007). Stillbirth. *Lancet,* 370(9600), 1715-1725.

Smith GC, Pell JP, and Dobbie R (2003). Caesarean section and risk of unexplained stillbirth in subsequent pregnancy. *Lancet,* 362(9398), 1779-1784.

Souda S, Gaseitsiwe S, Georgette N, Powis K, Moremedi D, Iketleng T, Leidner J, Moffat C, Ogwu A, Lockman S, Moyo S, Mmalane M, Musonda R, Makhema J, Essex M, and Shapiro R (2013). No clinically significant drug-resistance mutations in HIV-1 subtype C-infected women after discontinuation of NRTI-based or PI-based HAART for PMTCT in Botswana. *J Acquir Immune Defic Syndr,* 63(5), 572-577.

Sowell RL, Murdaugh CL, Addy CL, Moneyham L, and Tavokoli A (2002). Factors influencing intent to get pregnant in HIV-infected women living in the southern USA. *AIDS Care,* 14(2), 181-191.

Springett A, Budd J, Draper ES, Fitzsimons K, Kurinczuk J, Rankin J, Rounding C, Stoianova S, Tonks A, Tucker D, Wellesley D, Wreyford B, and Morris JK (2013). Congenital Anomaly Statistics 2011: England and Wales. London, UK: British Isles Network of Congenital Anomaly Registers.

Stanwood NL, Cohn SE, Heiser JR, and Pugliese M (2007). Contraception and fertility plans in a cohort of HIV-positive women in care. *Contraception,* 75(4), 294-298.

Staveteig S, Wang S, Head SK, Bradley SEK, and Nybro E (2013). Demographic Patterns of HIV Testing Uptake in Sub-Saharan Africa. DHS Comparative Reports No. 30. Calverton, Maryland, US.

Steer P (2005). The epidemiology of preterm labour. *BJOG,* 112 Suppl 1, 1-3.

Steiner RJ, Dariotis JK, Anderson JR, and Finocchario-Kessler S (2013). Preconception care for people living with HIV: recommendations for advancing implementation. *AIDS,* 27 Suppl 1, S113-119.

Stephenson JM and Griffioen A (1996). The effect of HIV diagnosis on reproductive experience. Study Group for the Medical Research Council Collaborative Study of Women with HIV. *AIDS,* 10(14), 1683-1687.

Sterne JA, White IR, Carlin JB, Spratt M, Royston P, Kenward MG, Wood AM, and Carpenter JR (2009). Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. *BMJ,* 338, b2393.

Stewart R, Wells CE, Roberts S, Rogers V, McElwee B, McIntire D, and Sheffield J (2014). Benefit of inter-pregnancy HIV viral load suppression on subsequent maternal and infant outcomes. *Am J Obstet Gynecol,* 210(1 Supp 1).

Stohr W, Dunn D, Porter K, Hill T, Gazzard B, Walsh J, Gilson R, Easterbrook P, Fisher M, Johnson M, Delpech V, Phillips A, and Sabin C (2007). CD4 cell count and initiation of antiretroviral therapy: trends in seven UK centres, 1997-2003. *HIV Med,* 8(3), 135-141.

Stringer JS, McConnell MS, Kiarie J, Bolu O, Anekthananon T, Jariyasethpong T, Potter D, Mutsotso W, Borkowf CB, Mbori-Ngacha D, Muiruri P, Ong'ech JO, Zulu I, Njobvu L, Jetsawang B, Pathak S, Bulterys M, Shaffer N, and Weidle PJ (2010). Effectiveness of non-nucleoside reverse-transcriptase inhibitor-based antiretroviral therapy in women previously exposed to a single intrapartum dose of nevirapine: a multi-country, prospective cohort study. *PLoS Med,* 7(2), e1000233.

Suy A, Hernandez S, Thorne C, Lonca M, Lopez M, and Coll O (2008). Current guidelines on management of HIV-infected pregnant women: Impact on mode of delivery. *European Journal of Obstetrics Gynecology and Reproductive Biology,* 139(2), 127-132.

Suy A, Martinez E, Coll O, Lonca M, Palacio M, de Lazzari E, Larrousse M, Milinkovic A, Hernandez S, Blanco JL, Mallolas J, Leon A, Vanrell JA, and Gatell JM (2006). Increased risk of pre-eclampsia and fetal death in HIV-infected pregnant women receiving highly active antiretroviral therapy. *AIDS,* 20(1), 59-66.

Swingle HM, Colaizy TT, Zimmerman MB, and Morriss FH Jr. (2009). Abortion and the risk of subsequent preterm birth: a systematic review with meta-analyses. *J Reprod Med,* 54(2), 95-108.

Tai JH, Udoji MA, Barkanic G, Byrne DW, Rebeiro PF, Byram BR, Kheshti A, Carter JD, Graves CR, Raffanti SP, and Sterling TR (2007). Pregnancy and HIV disease progression during the era of highly active antiretroviral therapy. *J Infect Dis,* 196(7), 1044-1052.

Tang MW and Shafer RW (2012). HIV-1 antiretroviral resistance: scientific principles and clinical applications. *Drugs,* 72(9), e1-25.

Tariq S (2013). HIV-positive African women's engagement with HIV care in the UK during and after pregnancy. PhD Thesis, City University London, London, UK.

Tariq S, Elford J, Cortina-Borja M, and Tookey PA (2012). The association between ethnicity and late presentation to antenatal care among pregnant women living with HIV in the UK and Ireland. *AIDS Care,* 24(8), 978-985.

Taylor GP, Clayden P, Dhar J, Gandhi K, Gilleece Y, Harding K, Hay P, Kennedy J, Low-Beer N, Lyall H, Palfreeman A, Tookey P, Welch S, Wilkins E, and de Ruiter A (2012). British HIV Association guidelines for the management of HIV infection in pregnant women 2012. *HIV Med,* 13 Suppl 2, 87-157.

Tegger MK, Crane HM, Tapia KA, Uldall KK, Holte SE, and Kitahata MM (2008). The effect of mental illness, substance use, and treatment for depression on the initiation of highly active antiretroviral therapy among HIV-infected individuals. *AIDS Patient Care STDS,* 22(3), 233-243.

Tenthani L, Haas AD, Tweya H, Jahn A, van Oosterhout JJ, Chimbwandira F, Chirwa Z, Ng'ambi W, Bakali A, Phiri S, Myer L, Valeri F, Zwahlen M, Wandeler G, and Keiser O (2014). Retention in care under universal antiretroviral therapy for HIV-infected pregnant and breastfeeding women ('Option B+') in Malawi. *AIDS,* 28(4), 589-598.

The International Perinatal HIV Group (1999). The mode of delivery and the risk of vertical transmission of human immunodeficiency virus type 1--a meta-analysis of 15 prospective cohort studies *New England Journal of Medicine,* 340(13), 977-987.

The Working Group on Mother-To-Child Transmission of HIV (1995). Rates of mother-to-child transmission of HIV-1 in Africa, America, and Europe: results from 13 perinatal studies. *J Acquir Immune Defic Syndr Hum Retrovirol,* 8(5), 506-510.

Therneau TM and Grambsch PM. (2000). Modeling Survival Data: Extending the Cox Model. New York, US: Springer.

Thomas J and Paranjoth S (2001). The National Sentinel Caesarean Section Audit Report: Royal College of Obstetricians and Gynaecologists Clinical Effectiveness Support Unit.

Thompson MA, Aberg JA, Hoy JF, Telenti A, Benson C, Cahn P, Eron JJ, Gunthard HF, Hammer SM, Reiss P, Richman DD, Rizzardini G, Thomas DL, Jacobsen DM, and Volberding PA (2012). Antiretroviral treatment of adult HIV infection: 2012 recommendations of the International Antiviral Society-USA panel. *JAMA,* 308(4), 387-402.

Thorne C and Newell ML (2007a). Safety of agents used to prevent mother-to-child transmission of HIV: is there any cause for concern? *Drug Saf,* 30(3), 203-213.

Thorne C, Patel D, Fiore S, Peckham C, and Newell M (2005). Mother-to-child transmission of HIV infection in the era of highly active antiretroviral therapy. *Clin Infect Dis,* 40(3), 458-465.

Thorne C, Patel D, and Newell ML (2004). Increased risk of adverse pregnancy outcomes in HIV-infected women treated with highly active antiretroviral therapy in Europe. *AIDS,* 18(17), 2337-2339.

Thorne C and Townsend CL (2012). A new piece in the puzzle of antiretroviral therapy in pregnancy and preterm delivery risk. *Clin Infect Dis,* 54(9), 1361-1363.

Thorne C, Townsend CL, Peckham CS, Newell ML, and Tookey PA (2007b). Pregnancies in young women with vertically acquired HIV infection in Europe. *AIDS,* 21(18), 2552-2556.

Tookey PA, Gibb DM, Ades AE, Duong T, Masters J, Sherr L, Peckham CS, and Hudson CN (1998). Performance of antenatal HIV screening strategies in the United Kingdom. *J Med Screen,* 5(3), 133-136.

Tovanabutra S, Robison V, Wongtrakul J, Sennum S, Suriyanon V, Kingkeow D, Kawichai S, Tanan P, Duerr A, and Nelson KE (2002). Male viral load and heterosexual transmission of HIV-1 subtype E in northern Thailand. *J Acquir Immune Defic Syndr,* 29(3), 275-283.

Tovo PA, Newell ML, Mandelbrot L, Semprini A, and Giaquinto C (1999). Recommendations for the management of HIV infected women and their infants. A European Consensus. Luxembourg: European Commission.

Townsend CL, Byrne L, Cortina-Borja M, Thorne C, de Ruiter A, Lyall H, Taylor GP, Peckham CS, and Tookey PA (2014). Earlier initiation of ART and further decline in mother-to-child HIV transmission rates, 2000-2011. *AIDS,* 28(7), 1049-1057.

Townsend CL, Cliffe S, and Tookey PA (2006). Uptake of antenatal HIV testing in the United Kingdom: 2000-2003. *J Public Health (Oxf),* 28(3), 248-252.

Townsend CL, Cortina-Borja M, Peckham CS, de Ruiter A, Lyall H, and Tookey PA (2008a). Low rates of mother-to-child transmission of HIV following effective pregnancy interventions in the United Kingdom and Ireland, 2000-2006. *AIDS,* 22(8), 973-981.

Townsend CL, Cortina-Borja M, Peckham CS, and Tookey PA (2007). Antiretroviral therapy and premature delivery in diagnosed HIV-infected women in the United Kingdom and Ireland. *AIDS,* 21(8), 1019-1026.

Townsend CL, Cortina-Borja M, Peckham CS, and Tookey PA (2008b). Trends in management and outcome of pregnancies in HIV-infected women in the UK and Ireland, 1990-2006. *BJOG,* 115(9), 1078-1086.

Townsend CL, Schulte J, Thorne C, Dominguez KI, Tookey PA, Cortina-Borja M, Peckham CS, Bohannon B, and Newell ML (2010a). Antiretroviral therapy and preterm delivery-a pooled analysis of data from the United States and Europe. *BJOG,* 117(11), 1399-1410.

Townsend CL, Tookey PA, Newell ML, and Cortina-Borja M (2010b). Antiretroviral therapy in pregnancy: balancing the risk of preterm delivery with prevention of mother-to-child HIV transmission. *Antivir Ther,* 15(5), 775-783.

Townsend CL, Willey BA, Cortina-Borja M, Peckham CS, and Tookey PA (2009). Antiretroviral therapy and congenital abnormalities in infants born to HIV-infected women in the UK and Ireland, 1990-2007. *AIDS,* 23(4), 519-524.

Tubiana R, Le Chenadec J, Rouzioux C, Mandelbrot L, Hamrene K, Dollfus C, Faye A, Delaugerre C, Blanche S, and Warszawski J (2010). Factors associated with mother-to-child transmission of HIV-1 despite a maternal viral load <500 copies/ml at delivery: a case-control study nested in the French perinatal cohort (EPF-ANRS CO1). *Clin Infect Dis,* 50(4), 585-596.

Tucker A, Ogutu D, Yoong W, Nauta M, and Fakokunde A (2010). The unbooked mother: a cohort study of maternal and foetal outcomes in a North London Hospital. *Arch Gynecol Obstet,* 281(4), 613-616.

Tuomala RE, Shapiro DE, Mofenson LM, Bryson Y, Culnane M, Hughes MD, O'Sullivan MJ, Scott G, Stek AM, Wara D, and Bulterys M (2002). Antiretroviral therapy during pregnancy and the risk of an adverse outcome. *New England Journal of Medicine,* 346(24), 1863-1870.

Tuomala RE, Watts DH, Li D, Vajaranant M, Pitt J, Hammill H, Landesman S, Zorrilla C, and Thompson B (2005). Improved obstetric outcomes and few maternal toxicities are associated with antiretroviral therapy, including highly active antiretroviral therapy during pregnancy. *J Acquir Immune Defic Syndr,* 38(4), 449-473.

Turner AN, Tabbah S, Mwapasa V, Rogerson SJ, Meshnick SR, Ackerman WE, and Kwiek JJ (2013). Severity of Maternal HIV-1 Disease Is Associated With Adverse Birth Outcomes in Malawian Women: A Cohort Study. *J Acquir Immune Defic Syndr,* 64(4), 392-399.

Turner BJ, Markson L, Hauck W, Cocroft J, and Fanning T (1995). Prenatal care of HIV-infected women: analysis of a large New York State cohort. *J Acquir Immune Defic Syndr Hum Retrovirol,* 9(4), 371-378.

Turner BJ, Newschaffer CJ, Zhang D, Cosler L, and Hauck WW (2000). Antiretroviral use and pharmacy-based measurement of adherence in postpartum HIV-infected women. *Med Care,* 38(9), 911-925.

UCLA: Statistical Consulting Group ([no date]). Stata Data Analysis Examples: Ordered Logistic Regression. Available at: http://www.ats.ucla.edu/stat/stata/dae/ologit.htm (Accessed Novemeber 2013).

UK Collaborative HIV Cohort Steering Committee (2004). The creation of a large UK-based multicentre cohort of HIV-infected individuals: The UK Collaborative HIV Cohort (UK CHIC) Study. *HIV Med,* 5(2), 115-124.

UK National Screening Committee (2010). Infectious Diseases in Pregnancy Screening Programme: Programme Standards.

UNAIDS (2011a). Global plan towards the elimination of new HIV infections among children by 2015 and keeping their mothers alive.

UNAIDS (2011b). HIV/AIDS in Europe and central Asia: 2011 progress report.

UNAIDS (2013). Global Report: UNAIDS report on the global AIDS epidemic 2013.

United Nations (2010). Composition of macro geographical (continental) regions, geographical sub-regions, and selected economic and other groupings. Available at: http://unstats.un.org/unsd/methods/m49/m49regin.htm (Accessed March 2011).

United Nations Statistics Division. (2013). *Evaluation of Fertility Data Collected from Population Censuses.* Paper presented at the United Nations Workshop on Census Evaluation, Hanoi, Viet Nam.

van Benthem BH, de Vincenzi I, Delmas MC, Larsen C, van den Hoek A, and Prins M (2000). Pregnancies before and after HIV diagnosis in a european cohort of HIV-infected women. European Study on the Natural History of HIV Infection in Women. *AIDS,* 14(14), 2171-2178.

van Benthem BH, Vernazza P, Coutinho RA, and Prins M (2002). The impact of pregnancy and menopause on CD4 lymphocyte counts in HIV-infected women. *AIDS,* 16(6), 919-924.

van der Merwe K, Hoffman R, Black V, Chersich M, Coovadia A, and Rees H (2011). Birth outcomes in South African women receiving highly active antiretroviral therapy: a retrospective observational study. *J Int AIDS Soc,* 14, 42.

van Sighem A, Gras L, Reiss P, Brinkman K, de Wolf F; ATHENA national observational cohort study (2010). Life expectancy of recently diagnosed asymptomatic HIV-infected patients approaches that of uninfected individuals. *AIDS,* 24(10), 1527-1535.

von Linstow ML, Rosenfeldt V, Lebech AM, Storgaard M, Hornstrup T, Katzenstein TL, Pedersen G, Herlin T, Valerius NH, and Weis N (2010). Prevention of mother-to-child transmission of HIV in Denmark, 1994-2008. *HIV Med,* 11(7), 448-456.

Walmsley S, Bernstein B, King M, Arribas J, Beall G, Ruane P, Johnson M, Johnson D, Lalonde R, Japour A, Brun S, and Sun E (2002). Lopinavir-ritonavir versus nelfinavir for the initial treatment of HIV infection. *New England Journal of Medicine,* 346(26), 2039-2046.

Wang B, Losina E, Stark R, Munro A, Walensky RP, Wilke M, Martin D, Lu Z, Freedberg KA, and Wood R (2011). Loss to follow-up in a community clinic in South Africa--roles of gender, pregnancy and CD4 count. *S Afr Med J,* 101(4), 253-257.

Ware NC, Wyatt MA, Geng EH, Kaaya SF, Agbaji OO, Muyindike WR, Chalamilla G, and Agaba PA (2013). Toward an understanding of disengagement from HIV treatment and care in sub-Saharan Africa: a qualitative study. *PLoS Med,* 10(1), e1001369.

Warszawski J, Tubiana R, Le Chenadec J, Blanche S, Teglas JP, Dollfus C, Faye A, Burgard M, Rouzioux C, and Mandelbrot L (2008). Mother-to-child HIV transmission despite antiretroviral therapy in the ANRS French Perinatal Cohort. *AIDS,* 22(2), 289-299.

Watts DH, Balasubramanian R, Maupin RT, Jr., Delke I, Dorenbaum A, Fiore S, Newell ML, Delfraissy JF, Gelber RD, Mofenson LM, Culnane M, and Cunningham CK (2004). Maternal toxicity and pregnancy complications in human immunodeficiency virus-infected women receiving antiretroviral therapy: PACTG 316. *Am J Obstet Gynecol,* 190(2), 506-516.

Watts DH, Brown ER, Maldonado Y, Herron C, Chipato T, Reddy L, Moodley D, Nakabiito C, Manji K, Fawzi W, George K, Richardson P, Zwerski S, Coovadia H, and Fowler M (2013). HIV disease progression in the first year after delivery among African women followed in the HPTN 046 clinical trial. *J Acquir Immune Defic Syndr,* 64(3), 299-306.

Watts DH, Li D, Handelsman E, Tilson H, Paul M, Foca M, Vajaranant M, Diaz C, Tuomala R, and Thompson B (2007). Assessment of birth defects according to maternal therapy among infants in the Women and Infants Transmission Study. *J Acquir Immune Defic Syndr,* 44(3), 299-305.

Watts DH, Lu M, Thompson B, Tuomala RE, Meyer WA, 3rd, Mendez H, Rich K, Hanson C, LaRussa P, Diaz C, and Mofenson LM (2009). Treatment interruption after pregnancy: effects on disease progression and laboratory findings. *Infect Dis Obstet Gynecol,* 2009, 456717.

Watts DH and Mofenson LM (2012). Antiretrovirals in pregnancy: a note of caution. *J Infect Dis,* 206(11), 1639-1641.

Weinberg A, Harwood JE, McFarland EJ, Pappas J, Davies J, Kinzie K, Barr E, Paul S, Salbenblatt C, Soda E, Vazquez A, Peloquin CA, and Levin MJ (2009). Kinetics and determining factors of the virologic response to antiretrovirals during pregnancy. *Infect Dis Obstet Gynecol,* 2009, 621780.

Welbourn A (2012). An HIV-free generation: human sciences vs plumbing Available at: http://www.opendemocracy.net/5050/alice-welbourn/hiv-free-generation-human-sciences-vs-plumbing (Accessed March 2014).

Wellings K, Jones KG, Mercer CH, Tanton C, Clifton S, Datta J, Copas AJ, Erens B, Gibson LJ, Macdowall W, Sonnenberg P, Phelps A, and Johnson AM (2013). The prevalence of unplanned pregnancy and associated factors in Britain: findings from the third National Survey of Sexual Attitudes and Lifestyles (Natsal-3). *Lancet,* 382(9907), 1807-1816.

Wendt A, Gibbs CM, Peters S, and Hogue CJ (2012). Impact of increasing inter-pregnancy interval on maternal and infant health. *Paediatr Perinat Epidemiol,* 26 Suppl 1, 239-258.

Wesley Y (2003). Desire for children among black women with and without HIV infection. *J Nurs Scholarsh,* 35(1), 37-43.

Westreich D and Kipp A (2008). Pregnancy and HIV disease progression: methodological concerns. *J Infect Dis,* 197(7), 1074-1075.

Westreich D, Maskew M, Evans D, Firnhaber C, Majuba P, and Sanne I (2013). Incident pregnancy and time to death or AIDS among HIV-positive women receiving antiretroviral therapy. *PLoS One,* 8(3), e58117.

Wilcher R and Cates W (2009). Reproductive choices for women with HIV. *Bull World Health Organ,* 87(11), 833-839.

Williams I, Churchill D, Anderson J, Boffito M, Bower M, Cairns G, Cwynarski K, Edwards S, Fidler S, Fisher M, Freedman A, Geretti AM, Gilleece Y, Horne R, Johnson M, Khoo S, Leen C, Marshall N, Nelson M, Orkin C, Paton N, Phillips A, Post F, Pozniak A, Sabin C, Trevelion R, Ustianowski A, Walsh J, Waters L, Wilkins E, Winston A, and Youle M (2012). British HIV Association guidelines for the treatment of HIV-1-positive adults with antiretroviral therapy 2012. *HIV Med,* 13 Suppl 2, 1-85.

Wilson TE, Ickovics JR, Royce R, Fernandez MI, Lampe M, and Koenig LJ (2004). Prenatal care utilization and the implementation of prophylaxis to prevent perinatal HIV-1 transmission. *Matern Child Health J,* 8(1), 13-18.

Wimalasundera RC, Larbalestier N, Smith JH, de Ruiter A, Mc GTSA, Hughes AD, Poulter N, Regan L, and Taylor GP (2002). Pre-eclampsia, antiretroviral therapy, and immune reconstitution. *Lancet,* 360(9340), 1152-1154.

Wind-Rotolo M, Durand C, Cranmer L, Reid A, Martinson N, Doherty M, Jilek BL, Kagaayi J, Kizza A, Pillay V, Laeyendecker O, Reynolds SJ, Eshleman SH, Lau B, Ray SC, Siliciano JD, Quinn TC, and Siliciano RF (2009). Identification of nevirapine-resistant HIV-1 in the latent reservoir after single-dose nevirapine to prevent mother-to-child transmission of HIV-1. *J Infect Dis,* 199(9), 1301-1309.

Wolbers M, Bucher HC, Furrer H, Rickenbach M, Cavassini M, Weber R, Schmid P, Bernasconi E, Hirschel B, and Battegay M (2008). Delayed diagnosis of HIV infection and late initiation of antiretroviral therapy in the Swiss HIV Cohort Study. *HIV Med,* 9(6), 397-405.

World Health Organization (2003). Strategic approaches to the prevention of HIV infection in infants: report of a WHO meeting, Morges, Switzerland, 20-22 March 2002.

World Health Organization (2004). Antiretroviral drugs for treating pregnant women and prevention HIV infection in infants : guidelines on care, treatment and support for women living with HIV/AIDS and their children in resource-constrained settings. Geneva, Switzerland: World Health Organization.

World Health Organization (2005). Report of a WHO Technical Consultation on Birth Spacing. Geneva, Switzerland: World Health Organization.

World Health Organization (2006). Antiretroviral drugs for treating pregnant women and preventing HIV infection in infants: towards universal access: recommendations for a public health approach. Geneva, Switzerland: World Health Organization.

World Health Organization (2007). WHO case definitions of HIV for surveillance and revised clinical staging and immunological classification of HIV-related disease in adults and children. Geneva, Switzerland: World Health Organization.

World Health Organization (2010a). Guidelines on HIV and infant feeding: Principles and recommendations for infant feeding in the context of HIV and a summary of evidence. Geneva, Switzerland: World Health Organization.

World Health Organization (2010b). International Statistical Classification of Diseases and Related Health Problems 10th Revision. ICD-10 Version: 2010. Available at: http://apps.who.int/classifications/icd10/browse/2010/en#/P05 (Accessed October 2011).

World Health Organization (2012). Use of antiretroviral drugs for treating pregnant women and preventing HIV infection in infants. Programmatic update. Geneva, Switzerland: World Health Organization.

World Health Organization (2013). Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. Geneva, Switzerland: World Health Organization.

World Health Organization and UNICEF (2012). Global monitoring framework and strategy for the global plan towards the elimination of new HIV infections among children by 2015 and keeping their mothers alive (EMTCT). Geneva, Switzerland: World Health Organization.

Zaba B, Calvert C, Marston M, Isingo R, Nakiyingi-Miiro J, Lutalo T, Crampin A, Robertson L, Herbst K, Newell ML, Todd J, Byass P, Boerma T, and Ronsmans C (2013). Effect of HIV infection on pregnancy-related mortality in sub-Saharan Africa: secondary analyses of pooled community-based data from the network for Analysing Longitudinal Population-based HIV/AIDS data on Africa (ALPHA). *Lancet,* 381(9879), 1763-1771.

Appendices

Appendix I Peer reviewed publication reprints

i) French CE, Thorne C, Tariq S, Cortina-Borja M, Tookey PA. Immunologic status and virologic outcomes in repeat pregnancies to HIV-positive women not on antiretroviral therapy at conception: a case for lifelong antiretroviral therapy? *AIDS* 2014; 28:1369-1372 (Page 335).

ii) French CE, Tookey PA, Cortina-Borja M, de Ruiter A, Townsend CL, Thorne C. Influence of short-course antenatal antiretroviral therapy on viral load and mother-to-child transmission in subsequent pregnancies among HIV-infected women. *Antivir Ther* 2013;18(2):183-92 (Page 339).

iii) French CE, Cortina-Borja M, Thorne C, Tookey PA. Incidence, patterns, and predictors of repeat pregnancies among HIV-infected women in the United Kingdom and Ireland, 1990-2009. *JAIDS* 2012;59(3):287-93 (Page 349).

Appendix II British HIV Association guidelines – key recommendations

Guidelines for the management of HIV in adults				
	2001 guideline	**2005 guideline**	**2008 guideline**	**2012 guideline**
CD4 count threshold at which to start lifelong ART (in patients with chronic infection and no other indication for treatment)	Before CD4 count falls to <200 cells/µl	Before CD4 count falls to <200 cells/µl	In patients with a CD4 count of <350 cells/µl	In patients with a CD4 count of ≤350 cells/µl (note: ART initiation should not be delayed if CD4 count is close to the threshold)
Guidelines for the management of HIV in pregnancy				
	2001 guideline	**2005 guideline**	**2008 guideline**	**2012 guideline**
When to start ART in pregnancy i) Women not requiring treatment for their own health	No specific recommendation regarding timing	Short-term ART starting in the second trimester with standard cART regimens	Aim to start by 28 weeks, with a possible earlier start between 20 and 24 weeks for women with high baseline viral loads wanting a vaginal delivery	All women should start by week 24 of pregnancy. Start at the beginning of the second trimester if baseline viral load is >30,000 copies/ml, and consider starting earlier if >100,000 copies/ml

Continued overleaf

Guidelines for the management of HIV in pregnancy				
	2001 guideline	**2005 guideline**	**2008 guideline**	**2012 guideline**
ii) Women needing treatment for their own health (according to adult guidelines)	No specific recommendation regarding timing. It is noted that women should be managed as if they were not pregnant	No specific recommendation regarding timing	Start ART early, although can usually be deferred until after the first trimester	Start ART as soon as possible as per adult guidelines, but may be delayed until after the first trimester unless patient has an opportunistic infection
What to start (in women not needing treatment for their own health)	Zidovudine monotherapy (assuming low viral load of <10,000-20,000 copies/ml). Alternatively, short-course cART may be considered	A protease inhibitor based combination is recommended. Alternatively, zidovudine monotherapy in women with viral loads of <10,000 copies/ml willing to deliver by elective caesarean section	Standard cART regimens; to contain zidovudine and lamivudine if no contraindications. Regimen should also contain a boosted protease inhibitor	Boosted protease inhibitor-based cART. Alternatively, zidovudine monotherapy in women with viral loads of <10,000 copies/ml willing to deliver by elective caesarean section
Mode of delivery (assuming no contraindication)	Pre-labour caesarean section for all women*	Elective caesarean section for all women on zidovudine monotherapy, and women on cART with a detectable (≥50 copies/ml) viral load	Elective caesarean section for all women on zidovudine monotherapy, and women on cART with a detectable (≥50 copies/ml) viral load	Vaginal delivery for women on cART with a viral load <50 copies/ml plasma at 36 weeks. Elective caesarean section for all women on zidovudine monotherapy

*The guideline allows for consideration of vaginal delivery in women on ART with an undetectable viral load, but notes that there is insufficient evidence for a recommendation.

Notes: This table provides an overview of changes over time in key recommendations that are of relevance to issues explored within this thesis. The guidelines themselves are comprehensive and include contain further details, including specific recommendations for a range of clinical scenarios.

List of references to British HIV Association guidelines:
Adult guidelines: (BHIVA Writing Committee on behalf of the BHIVA Executive Committee, 2001; Gazzard, 2005; Gazzard *et al*, 2008; Williams *et al*, 2012)
Pregnancy guidelines: (de Ruiter *et al*, 2008; Hawkins *et al*, 2005; Lyall *et al*, 2001; Taylor *et al*, 2012)

Appendix III NSHPC data collection forms

NSHPC confidential pregnancy notification

MREC approval ref: MREC/04/2/009 *Form date: 01/10* **www.nshpc.ucl.ac.uk**

CONFIDENTIAL

Woman's date of birth: ___/___/___ Hospital number (or other ref): …… Soundex ……

Postcode (leave off last letter) ☐☐☐☐ ☐☐■ Previous livebirths ..... stillbirths ..... miscs/terms ……

Ethnic origin ☐ White ☐ Black African ☐ Black Caribbean ☐ Black Other
☐ Asian, Indian Subcontinent ☐ Asian, other / Oriental ☐ Other or mixed, specify .....

Country of birth …….. If not UK/Ireland, date arrived ___/___/____

PROBABLE SOURCE OF MATERNAL INFECTION

Maternal infection probably acquired: ☐ In UK/Ireland ☐ Abroad, specify ..... ☐ NK where

Likely exposure: ☐ Heterosexual - specify partner's likely risk factor, if known .....
☐ Injecting drug use ☐ Vertical transmission ☐ Other, specify .....

TIMING OF DIAGNOSIS Date of first positive test: ___/___/____ If type 2 only, please tick here ☐

Diagnosed **when**: ☐ During this pregnancy ☐ Before this pregnancy

Diagnosed **where**: ☐ Antenatal ☐ GUM clinic ☐ Other .....

Any evidence of **seroconversion** in this pregnancy? ☐ No ☐ Yes, specify details overleaf ☐ Not known

PREGNANCY Booking date: ___/___/___ EDD ___/___/___ (*and/or* LMP ___/___/___)

☐ Continuing to term - if continuing, planned mode of delivery: ☐ Vaginal ☐ CS ☐ Not yet decided

☐ Miscarriage ☐ Termination } Date of misc/TOP: ___/___/___ at ..... weeks gestation
Any congenital abnormality? ☐ No ☐ Yes, please specify.....

DRUG TREATMENT *DURING THIS PREGNANCY*

Was this woman on antiretroviral drugs when she became pregnant? ☐ Yes ☐ No

Did she receive antiretroviral drugs in pregnancy? ☐ Not yet ☐ Yes ☐ No ☐ Declined

Please provide details of antiretrovirals:	Before preg? (please circle)	Date started (or gest week) (if in pregnancy)		Date stopped (or gest week)	
Drug 1	Yes / No	___/___/___	_____	___/___/___	_____
Drug 2	Yes / No	___/___/___	_____	___/___/___	_____
Drug 3	Yes / No	___/___/___	_____	___/___/___	_____
Drug 4	Yes / No	___/___/___	_____	___/___/___	_____

MATERNAL CLINICAL STATUS

CDC Stage C disease ever: ☐ No ☐ Yes* if yes, date of onset: _____/_____/_____

Symptomatic in this pregnancy: ☐ No ☐ Yes* **Please provide details overleaf*

Concurrent infection(s)? ☐ None ☐ HBV ☐ HCV ☐ Syphilis ☐ Other, specify ……..

MATERNAL TEST RESULTS *first test results available this pregnancy*

Viral load ..... copies/ml Date ___/___/___ **CD4** no._____ (_____%) Date ___/___/___

Form completed by: Name _____ Date ___/___/___

Position _____ Telephone _____ Email _____

Thank you for your help. Please return this form to: Dr Pat Tookey, RCOG, 27 Sussex Place, Regent's Park, London NW1 4RG.
Telephone NSHPC on 020 7905 2815 if you have any queries or email nshpc@ich.ucl.ac.uk

NSHPC outcome of notified pregnancy

MREC approval ref: MREC/04/2/009 *form date: 01/10* **www.nshpc.ucl.ac.uk**

CONFIDENTIAL

Your ref: ..... EDD: Hospital of delivery .....

PREGNANCY OUTCOME: ☐ Livebirth *or* ☐ Stillbirth Date ___/___/___ Gestation ..... (wks)

☐ Male ☐ Female Birthweight ..... (kg) Hospital no ..... NHS no .....

Postcode at delivery (leave off last letter) ☐☐☐☐ ☐☐■ Paediatrician .....

Mode of delivery: *If twins, please tick here* ☐ *and write details of second twin overleaf*

☐ Elective CS, reason: ☐ Prevention of mother-to-child transmission ☐ Other, specify .....

☐ Planned vaginal delivery ☐ Unplanned vaginal delivery, reason: .....

☐ Emergency CS, specify reason: .....

What was *planned* mode of delivery? ☐ Vaginal ☐ Elective CS ☐ Not known

Instrumental delivery: ☐ No ☐ Yes, details .....

Rupture of membranes: ☐ Yes, duration ..... hours ..... minutes ***or*** ☐ Ruptured only at delivery

Complications in pregnancy:

☐ No ☐ Pre-eclampsia* ☐ Gestational diabetes ☐ Other* **Please provide details overleaf*

Perinatal infections: ☐ No ☐ Yes, specify .....

Congenital abnormalities: ☐ No ☐ Yes, specify .....

DRUG TREATMENT DURING PREGNANCY (continue overleaf if necessary)

Ante-partum treatment: ☐ No ☐ Yes, reason (if known): ☐ Prevention of mother-to-child transmission ***only*** ☐ Maternal health ***and*** prevention of transmission

Antiretrovirals:	Date started (or gest week)	Date stopped (or gest week)
Drug 1	___/___/___ _____	___/___/___ _____
Drug 2	___/___/___ _____	___/___/___ _____
Drug 3	___/___/___ _____	___/___/___ _____
Drug 4	___/___/___ _____	___/___/___ _____
Drug 5	___/___/___ _____	___/___/___ _____

Any other significant drugs (eg. PCP prophylaxis, TB treatment, methadone, illicit drugs):

Drug 1 ..... date ___/___/___ Drug 2 ..... date ___/___/___

Intra-partum treatment:

☐ None ☐ IV AZT ☐ Single dose nevirapine ☐ Other oral antiretrovirals: .....

Post-partum treatment for **infant**: ☐ Yes, drug(s)..... ☐ No ☐ Not known

MATERNAL CLINICAL STATUS If woman has died date of death ___/___/___

Symptomatic at delivery: ☐ No ☐ Yes, details.....

MATERNAL TEST RESULTS *NEAR DELIVERY* *just before delivery if possible*

Viral load ..... copies/ml Date ___/___/___ **CD4** no. _____ (_____%) Date ___/___/___

Resistance testing done this pregnancy? ☐ Yes ☐ No ☐ Not known Clade of virus if known .....

Form completed by: Name _____ Date ___/___/___

Position _____ Telephone _____ Email _____

Thank you for your help. Please return this form to: Dr Pat Tookey, RCOG, 27 Sussex Place, Regent's Park, London NW1 4RG.
Telephone NSHPC on 020 7905 2815 if you have any queries, or email nshpc@ich.ucl.ac.uk

NSHPC confidential paediatric notification

LONDON MREC/04/2/009 www.nshpc.ucl.ac.uk

Office use only: *Form date: 01/08*

CSTU	MSTU	SU	PAED	HOSP

Paediatrician

CONFIDENTIAL Please complete this form as far as you can, even if you do not have all details requested

A. CHILD DETAILS

NHS no ..... Hospital no ..... Initials ..... Soundex .....

Date of birth ___/___/___ ☐ Male ☐ Female Home postcode *(leave off last letter)* ☐☐☐☐ ☐☐■

Ethnic origin ☐ White ☐ Black African ☐ Black Caribbean ☐ Black Other

☐ Asian, Indian Subcontinent ☐ Other Asian / Oriental ☐ Other or mixed, specify .....

Born in ☐ UK/Ireland: Hospital of birth ..... Home postcode at birth *(leave off last letter)* ☐☐☐☐ ☐☐■

or ☐ Abroad: Country of birth ..... and date arrived in UK/Ireland ___/___/___

B. HOW WAS THIS CHILD IDENTIFIED AS INFECTED OR AT RISK OF INFECTION?

☐ Mother known to be infected in pregnancy ☐ Child symptomatic

☐ Mother/other family member found to be infected (specify relationship) .....

☐ Other, specify .....

Date of child's first lab investigation ___/___/___

If you are aware of *siblings* reported to us, please give dates of birth or other ref: .....

C. PERINATAL DETAILS

Gestation ..... Birthweight .....

Mode of delivery ☐ Vaginal ☐ Elective CS ☐ Emergency CS ☐ Not known

Any perinatal infections? ☐ No ☐ Yes, specify .....

Any congenital abnormalities? ☐ No ☐ Yes, specify .....

Any other problems? ☐ No ☐ Yes, specify .....

Antiretroviral treatment for mother and/or baby to reduce risk of vertical transmission? ☐ No ☐ Yes, specify below

Antenatally? ☐ No ☐ Yes, specify ..... ☐ NK

Intrapartum? ☐ No ☐ Yes, IV AZT ☐ Yes, other, specify..... ☐ NK

Post-partum (baby)? ☐ No ☐ Yes, specify ..... ☐ NK

Was the child breastfed? ☐ No ☐ Yes, breastfed for how long? (wks) ..... ☐ NK if breastfed

D. PROBABLE SOURCE OF INFECTION

1. Exposed to maternal infection? ☐ Yes, please give ***mother's*** details below ☐ No, go to question 2 below ☐ NK

a) Mother's date of birth ___/___/___ b) No. of *previous* livebirths..... stillbirths..... miscarriages/terms.....

c) Mother's country of birth ..... if not UK/Ireland, date arrived ___/___/___

d) Mother diagnosed ☐ After the birth of this child ☐ While pregnant with this child ☐ Before this pregnancy

e) Any evidence of **seroconversion** in this pregnancy? ☐ No ☐ Yes, specify..... ☐ Not known

f) Maternal infection probably acquired: ☐ In UK/Ireland ☐ Abroad, specify ..... ☐ NK where

g) Mother's likely source of infection:

☐ Heterosexual exposure, specify partner's likely risk factor(s) if known .....

☐ Injecting drug use ☐ Other, specify..... ☐ No information on mother's exposure

2. Other exposure risk for child? ☐ No ☐ Yes, please give details.....

.....

NSHPC follow-up to establish infection status

LONDON MREC04/2/009 www.nshpc.ucl.ac.uk

office use only *Form date: 01.08*

CSTU	MSTU	SU	PAED	HOSP

Paediatrician …….. Hospital ……..

CONFIDENTIAL Please complete this form as far as you can, even if you do not have all details requested

Please complete or amend these child details

Date of birth ____/____/____ ☐ Male ☐ Female Initials ……. soundex if available ……

Hospital no …… NHS no ……..

Current home postcode (**leave off last letter**) ☐☐☐☐ ☐☐■

The last report we had on this child related to examination on ___/___/___ when his/her **infection status had not yet been confirmed**. If you have more recent information, please complete all sections of this form.

If you have not seen this child since the last report please tick here ☐, complete the section on **INFECTION STATUS**, provide any test results *not previously reported* and complete the section on **FOLLOW UP STATUS.**

INFECTION STATUS & LABORATORY INVESTIGATIONS

Do you consider this child to be ☐ infected ☐ not infected ☐ indeterminate (definitions overleaf)

Please provide date of sample and ring type of test and result for all diagnostic tests since ___/___/___

	sample date	type of test	result		sample date	type of test	result
1.	___/___/___	antibody / PCR	+ / -	4.	___/___/___	antibody / PCR	+ / -
2.	___/___/___	antibody / PCR	+ / -	5.	___/___/___	antibody / PCR	+ / -
3.	___/___/___	antibody / PCR	+ / -	6.	___/___/___	antibody / PCR	+ / -

THERAPY & CLINICAL DETAILS

PCP prophylaxis? ☐ No ☐ Yes, specify …… date started ___/___/___

Any other serious infections or conditions? ☐ No ☐ Yes, specify ……

FOLLOW UP STATUS

Date of last contact ___/___/___ ☐ Still in follow-up at this unit ☐ Discharged (uninfected)

☐ Follow-up elsewhere, please give details ……

……

☐ Lost to follow up ☐ Known to have left UK/Eire ☐ Dead, date of death ___/___/___

Details of death: Certified cause a) disease or condition directly leading to death ……

b) secondary cause(s) ……

Post-mortem? ☐ Not done ☐ Done (please attach a copy if possible)

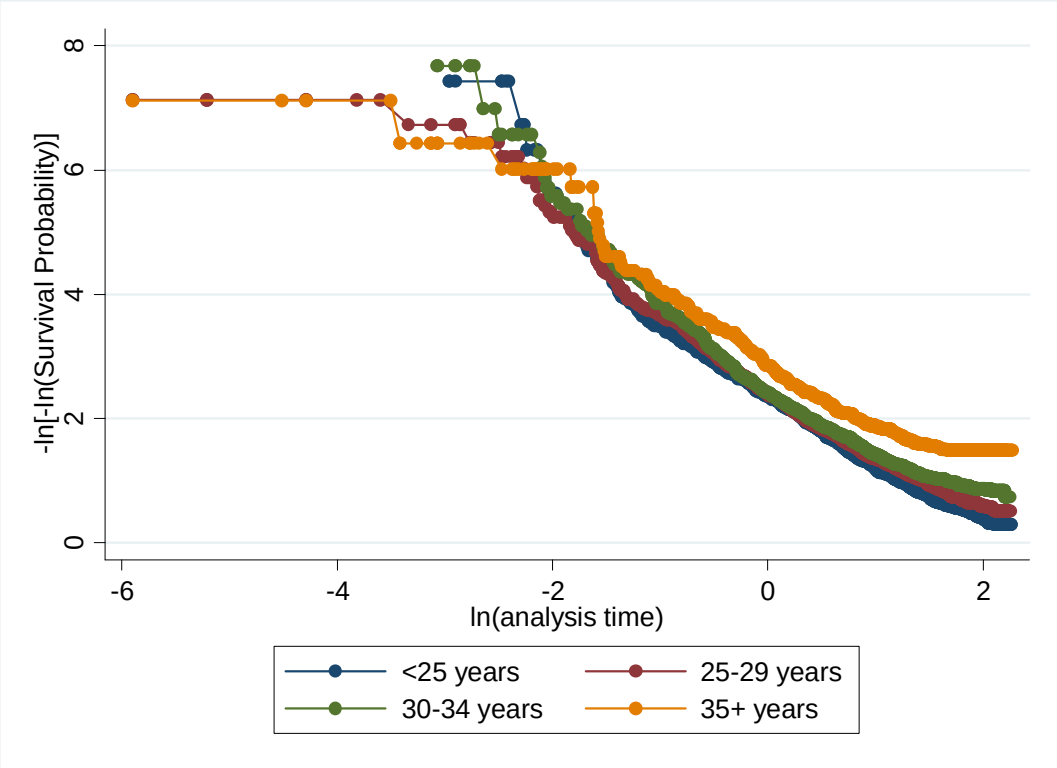
Completed by: Name _____ Position_____ Date ___/___/___

Tel no _____ Email_____

Thank you for completing this form. Please return it to: Surveillance Studies Group, MRC Centre of Epidemiology for Child Health, Institute of Child Health, 30 Guilford Street, London WC1N 1BR. Call us with any queries on 020 7905 2815 or email nshpc@ich.ucl.ac.uk

Appendix IV Log-log plots of time to second pregnancy

Figure A.1 Log-log plot of time to second pregnancy stratified by age group at first reported pregnancy



Notes:

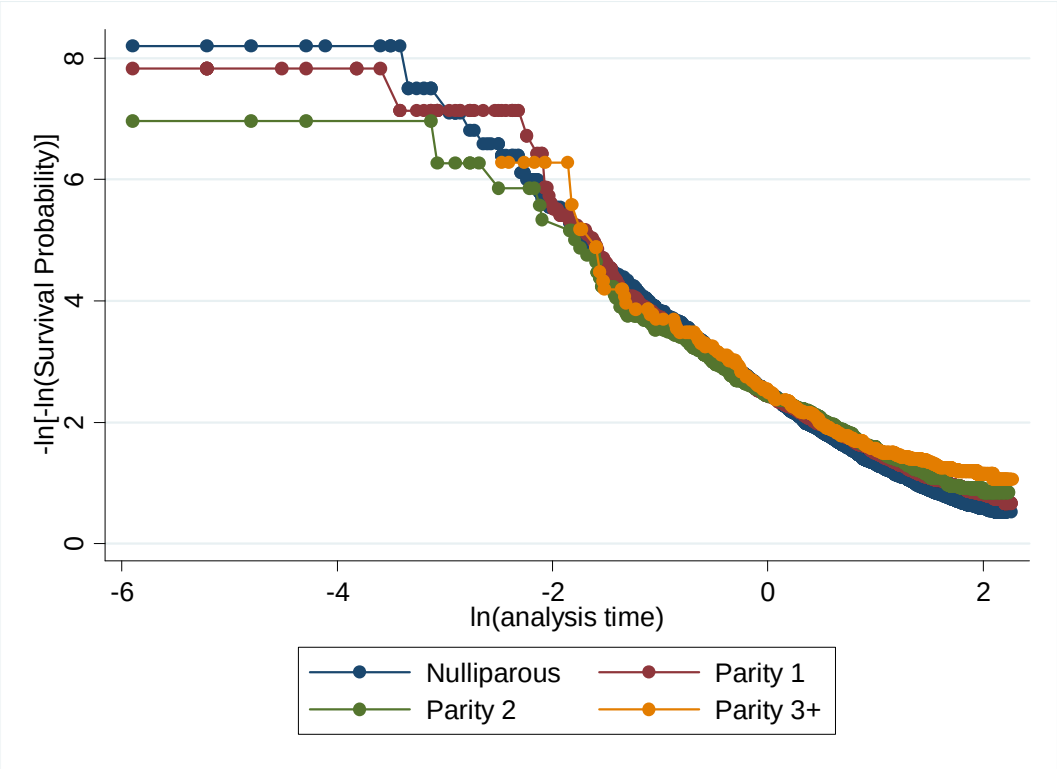
Log-log plot shows the probability of experiencing a repeat pregnancy against time since first pregnancy on the log-log scale.

Analyses adjusted for the other variables in the multivariable model, namely year, region of origin and parity (see Chapter 4, Table 4.5).

Comment on parallelism

Broadly speaking, the four lines in Figure A.1 may be considered to be reasonably parallel, though overlapping. It should be remembered that the number of repeat pregnancies experienced by women who were aged ≥35 years at their first reported pregnancy (the main contributor to the crossing of lines) was small (*n*=26).

Figure A.2 Log-log plot of time to second pregnancy stratified by parity at first reported pregnancy



Notes:

Log-log plot shows the probability of experiencing a repeat pregnancy against time since first pregnancy on the log-log scale.

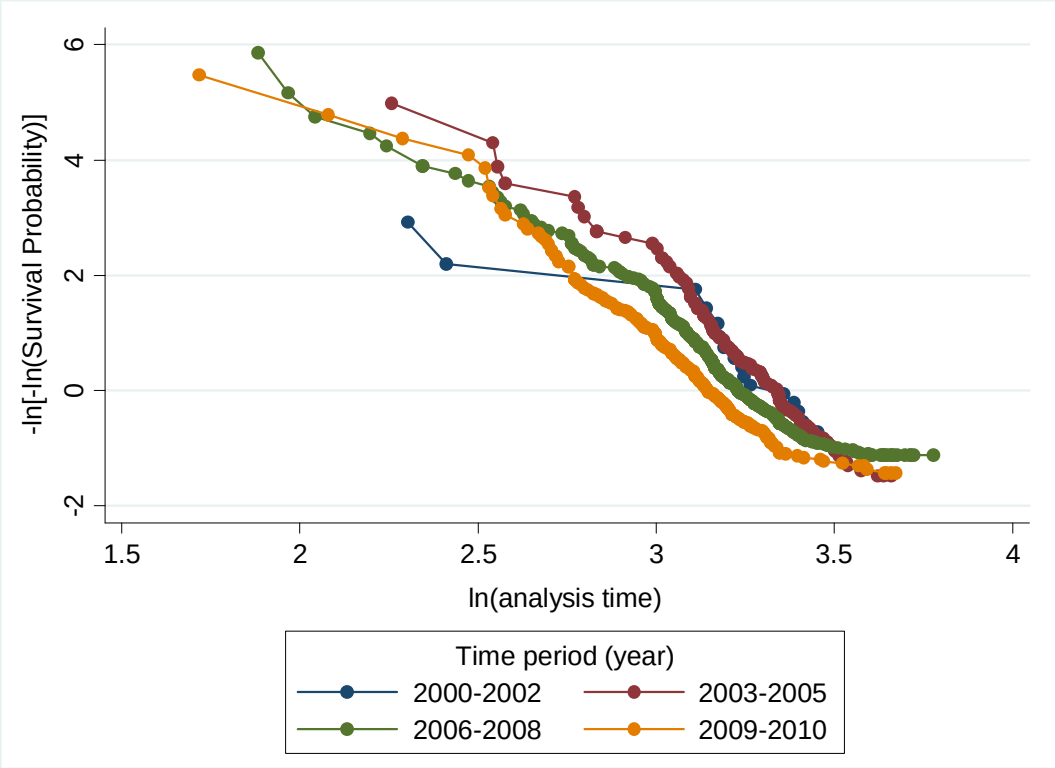
Analyses adjusted for the other variables in the multivariable model, namely year, maternal age, and maternal world region of origin (see Chapter 4, Table 4.5).

Comment on parallelism

The four lines in Figure A.2 may be considered to be reasonably parallel, though overlapping. The crossing of lines early in the analysis time occurs in the presence of relatively few data points.

Appendix V Log-log plots of time to initiation of antenatal ART

Figure A.3 Log-log plot of time to initiation of antenatal ART stratified by time period



Notes:

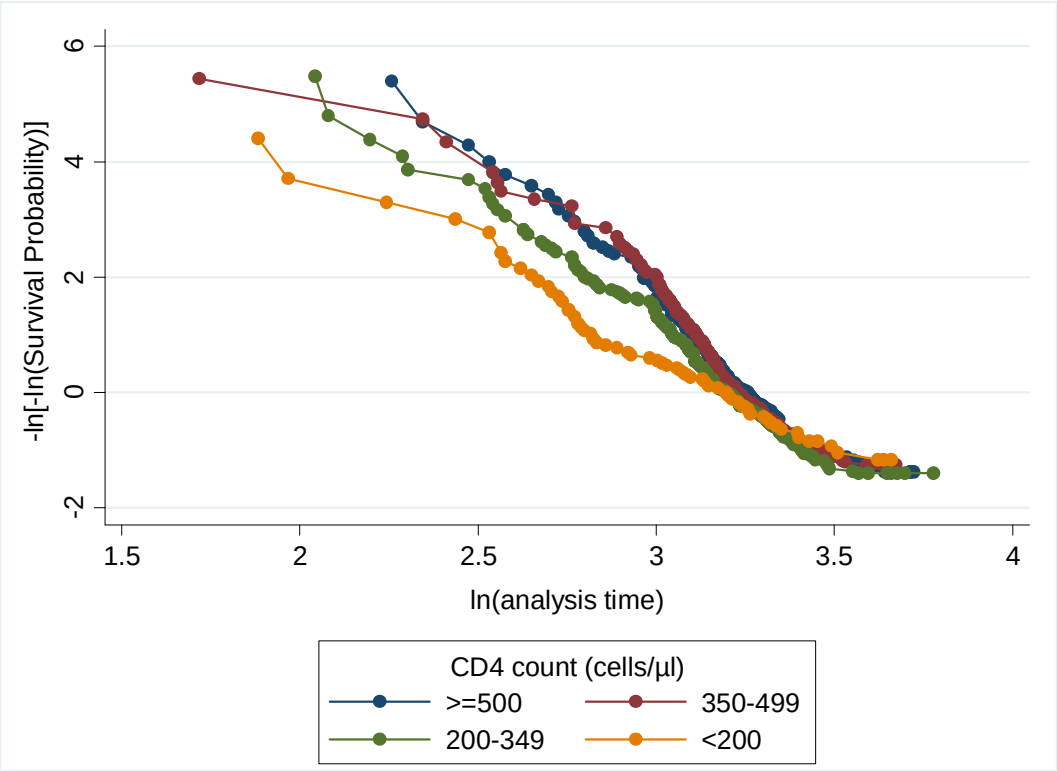
Log-log plot shows the probability of not initiating ART against time to treatment initiation on the log-log scale.

Analyses adjusted for the other variables in the multivariable model, namely earliest antenatal CD4 count, region of report, and earliest antenatal viral load (Chapter 5, Table 5.7).

Comment on parallelism

The four lines in Figure A.3 may be considered to be parallel. There are however some crossing of lines, likely reflecting changes in guidelines and clinical practice over time in the timing of ART initiation. It should be remembered that relative to later years, the number of pregnancies during the earliest time period (2000-2002), which is the main contributor to the crossing of lines, is small (*n*=40), with just two data points causing this data line to cross the other three. Similarly, where the lines for 2006-2008 and 2009-2010 cross the number of data points are small, after this, the lines consist of a much larger number of data points and the two lines run parallel to each other.

Figure A.4 Log-log plot of time to initiation of antenatal ART stratified by earliest antenatal CD4 count



Notes:

Log-log plot shows the probability of not initiating ART against time to treatment initiation on the log-log scale.

Analyses adjusted for the other variables in the multivariable model, namely time period, region of report, and earliest antenatal viral load (see Chapter 5, Table 5.7).

Comment on parallelism

Similar to the previous figure, in Figure A.4, the early crossing of the lines for CD4 count ≥500 cells/µl and 350-499 cells/µl groups occurs in the presence of relatively few data points in both categories. That all lines appear to converge late in the analysis time should be considered in context of the fact that only a very small proportion of women did not receive antenatal ART (3% overall). The differences between groups at the end of the analysis time will therefore be small (i.e. a matter of a percentage point or two).

Appendix VI 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.