

**The impact of antiretroviral therapy used in  
pregnancy on the health of HIV-positive women**

**Thesis presented for the degree of  
Doctor of Philosophy**

**UCL**

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## Declaration

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

Signed ..... Date.....

## **Abstract**

In the UK, antiretroviral therapy (ART) is used during the vast majority of pregnancies among women living with HIV. This thesis aims to examine some of the consequences of antenatal ART use on women's health during and after pregnancy.

Initially, a linkage was developed between two well established studies, the UK Collaborative HIV Cohort (UK CHIC) Study and the UK and Ireland's National Study of HIV in Pregnancy and Childhood (NSHPC). The resultant dataset was used to assess pregnancy incidence in women attending HIV clinical care at UK CHIC sites in 2000-2009. The overall pregnancy incidence increased. The rate of increase did not significantly differ between ethnic groups, age groups or according to ART use.

In women starting life-long cART at least one year after HIV diagnosis, those who had previously used short-course cART in pregnancy were more likely to experience viral rebound and interrupt their treatment compared to those who had never previously used ART.

Levels of the liver enzyme alanine transaminase (ALT) were assessed in women on combination ART (cART). The risk of liver enzyme elevation (LEE) was higher during pregnancy than at other times in women who started ART during pregnancy and in women who conceived on ART.

The risk of viral rebound (HIV-RNA >200 copies/ml) whilst on cART was higher in women who had recently had a pregnancy than in similar women who had not recently been pregnant. In post-pregnant women remaining on cART, the risk of viral rebound was higher in women who had started cART during their pregnancy than in women who had conceived on cART.

The findings presented in this thesis contribute to the evidence-base for the management of pregnant women living with HIV and highlight the need for close monitoring of toxicity in pregnancy and additional drug adherence support following pregnancy.

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## Abbreviations

aHR	Adjusted hazard ratio
AIDS	Acquired Immune Deficiency Syndrome
ALT	Alanine transaminase
aOR	Adjusted odds ratio
ART	Antiretroviral therapy
AST	Aspartate aminotransferase
AZT	Zidovudine (also abbreviated to ZDV)
BHIVA	British HIV Association
BMI	Body mass index
cART	Combination antiretroviral therapy
CI	Confidence interval
DNA	Deoxyribonucleic acid
EDC	Estimated date of conception
EDD	Expected date of delivery
EFV	Efavirenz
ELISA	Enzyme-linked immunosorbent assay
EU	European Union
FDA	US Food and Drug Administration
FDC	Fixed-dose combination
GGT	$\gamma$ -glutamyl transferase
HAART	Highly active antiretroviral therapy
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HDRD	UK HIV Drug Resistance Database
HIV	Human immunodeficiency virus
HPA	Health Protection Agency
HR	Hazard ratio
ICH	UCL Institute of Child Health
INI	Integrase inhibitor
IQR	Inter-quartile range
IU	International Unit
LFT	Liver function test
MRC	Medical Research Council
MSM	Men who have sex with men
MTCT	Mother-to-child transmission

NFV	Nelfinavir
NHS	National Health Service
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NRTI	Nucleoside reverse transcriptase inhibitor
NSHPC	National Study of HIV in Pregnancy and Childhood
NtRTI	Nucleotide reverse transcription inhibitor
NVP	Nevirapine
OR	Odds ratio
PCP	<i>Pneumocystis pneumonia</i>
PCR	Polymerase chain reaction
PEP	Post-exposure prophylaxis
PHE	Public Health England
PI	Protease inhibitor
PLCS	Pre-labour caesarean section
PMTCT	Prevention of mother-to-child transmission
PrEP	Pre-exposure prophylaxis
PWID	People who inject drugs
PY	Person years
RNA	Ribonucleic acid
RT	Reverse transcriptase
RTV	Ritonavir
SAS	Statistical Analysis Software
SIV	Simian immunodeficiency virus
SSA	Sub-Saharan Africa
SOPHID	Survey of Prevalent HIV Infections Diagnosed
START	Short-term antiretroviral therapy
STI	Sexually transmitted infection
TDR	Transmitted drug resistance
UCL	University College London
UK	United Kingdom
UK CHIC	UK Collaborative HIV Cohort
ULN	Upper limit of normal
US	United States (of America)
VL	Viral load
WHO	World Health Organization
ZDV	Zidovudine (also abbreviated to AZT)

## Publications arising from this research

Five peer reviewed papers were published based on the research presented in this thesis (Appendix IIa-Appendix IIe).

- a. Huntington *et al.* Using two on-going HIV studies to obtain clinical data from before, during and after pregnancy for HIV-positive women. *BMC Medical Research Methodology* 2012; **12**:110.
- b. Huntington *et al.* Predictors of pregnancy and changes in pregnancy incidence among HIV-positive women accessing HIV clinical care. *AIDS* 2013; **27**:95-103
- c. Huntington *et al.* Response to antiretroviral therapy (ART): comparing women with previous use of zidovudine monotherapy (ZDVm) in pregnancy with ART naive women. *BMC Infectious Diseases* 2014; **14**:127.
- d. Huntington *et al.* Pregnancy is associated with elevation of liver enzymes in HIV-positive women on antiretroviral therapy. *AIDS* 2015; **29**:801-9.
- e. Huntington *et al.* The risk of viral rebound in the year after delivery in women remaining on antiretroviral therapy. *AIDS* 2015; **29**: 2269-78.

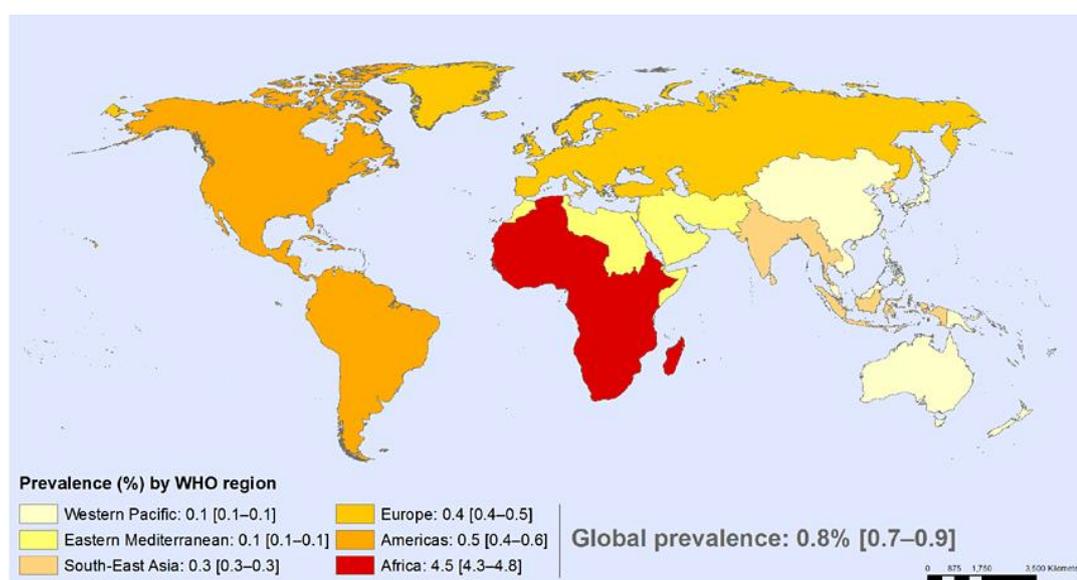
# Chapter 1 Introduction

## 1.1 An overview of HIV

### 1.1.1 Global epidemiology

When starting this work, the most up-to-date estimates of the number of people living with HIV were from 2008. At that time there were an estimated 33.4 (95% confidence interval [CI] 31.1-35.8) million people living with HIV worldwide of whom 15.7 (CI 14.2-17.2) million were women [1]. More recent data indicate that in 2015, there were 36.7 (CI 34.0-39.8) million people living with HIV globally, of whom 17.8 (CI 16.4-19.5) million were women [1, 2]. The highest burden continues to be in Sub-Saharan Africa (Figure 1.1). In 2015, there were an estimated 19.1 (CI 17.7-20.5) million people living with HIV in Eastern and Southern Africa and 6.5 (CI 5.3-7.8) million in Western and Central Africa compared to 2.4 (CI 2.2-2.7) million in Western and Central Europe and North America [2].

Figure 1.1. The number of people estimated to be living with HIV, 2014 by World Health Organization (WHO) region



The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

Data Source: World Health Organization  
Map Production: Information Evidence and Research (IER)  
World Health Organization

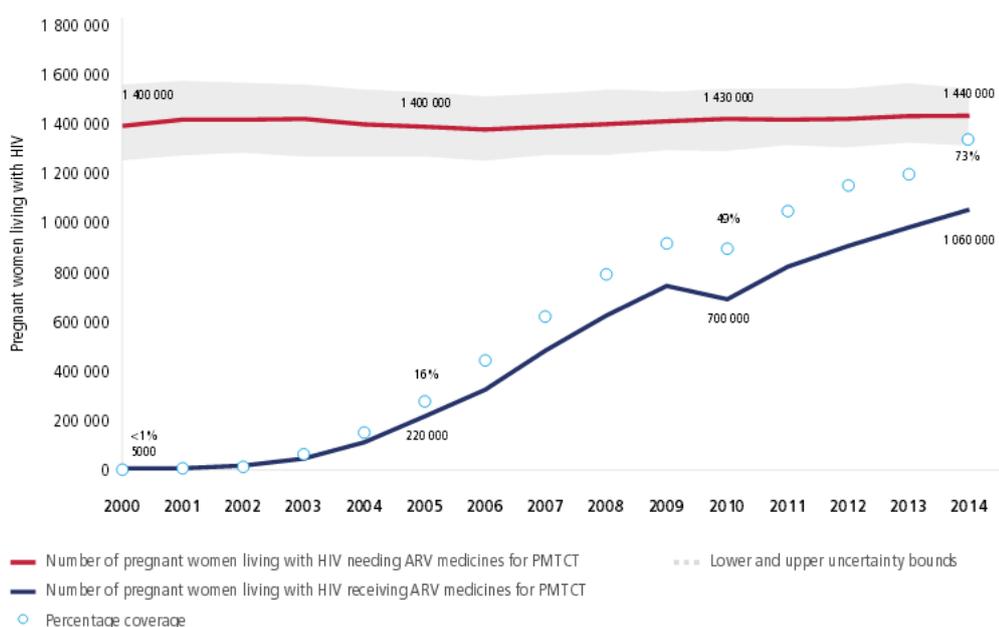


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Globally, the number of new infections has decreased, with an estimated 2.1 (CI 1.8-2.4) million new infections in 2015 [2, 3]. The number of deaths due to acquired immunodeficiency syndrome (AIDS) has also fallen, with an estimated 1.1 million (CI 940,000-1.3 million) deaths in 2015, compared to 2.0 (CI 1.7-2.4) million in 2008. However, as transmission continues to occur, the number of individuals living with HIV worldwide continues to increase and as such HIV continues to have a huge impact on global health and economic systems [1]. Although the number of deaths from HIV/AIDS is likely to continue to fall, the WHO predicts that HIV/AIDS will remain one of the world's leading causes of death by 2030 [4].

Women and young people are disproportionately affected by HIV. In 2008, there were an estimated 370,000 new infections in children younger than 15 years, the majority due to mother-to-child transmission (MTCT), and most (90%) in sub-Saharan Africa [1]. This was less than in previous years [5] and, due to the successes of prevention programmes, the number of new infections among children has continued to fall, with an estimated 150,000 (CI 110,000-190,000) infections among children in 2015 [2]. Access to antiretroviral therapy (ART) in pregnancy for women living in low- and middle-income countries remains insufficient but has increased steadily since 2008 from 40% to 73% in 2014, when the most recent data are available [2, 6] (Figure 1.2).

Figure 1.2. Number of pregnant women living with HIV in low- and middle-income countries and the number and percentage of them receiving ART drugs for prevention of mother-to-child transmission (PMTCT) of HIV, 2000-2014



Sources: Global AIDS Response Progress Reporting (UNAIDS/UNICEF/WHO); validation process for the number of pregnant women living with HIV receiving ARV medicines for preventing the mother-to-child transmission of HIV; and UNAIDS 2014 estimates for the number of pregnant women living with HIV.  
 \*Based on the use of different ARV medicines according to recommendations that have changed over time. Notably, single-dose nevirapine is included in the data for 2000–2009.

### 1.1.2 HIV epidemiology in the UK

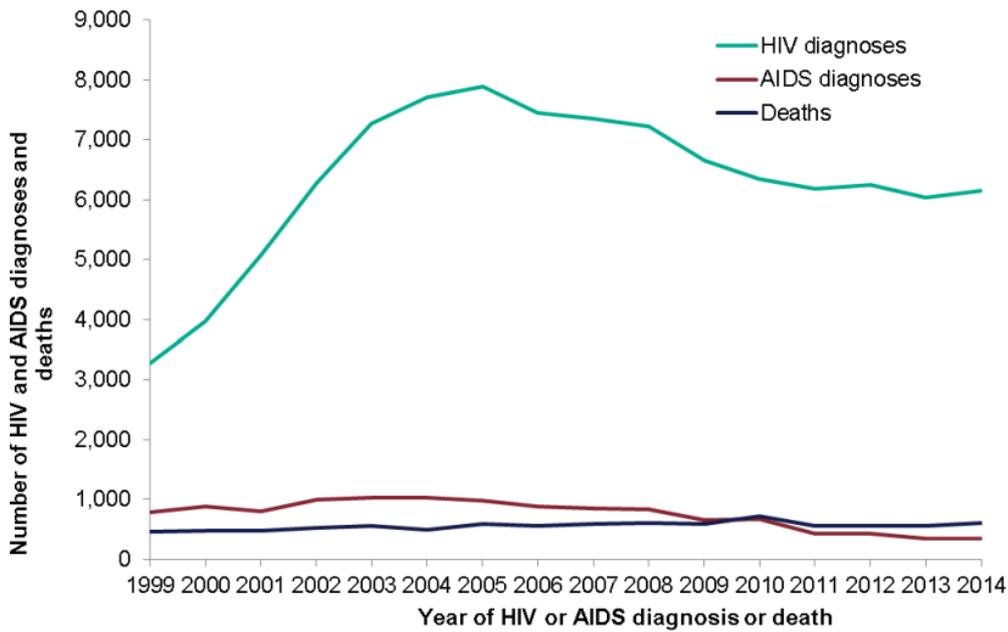
In the UK, the number of people living with HIV has continued to increase during the last decade. When starting this research, the most recent estimate available, from 2008, was that there were 83,000 people living with HIV in the UK, 27% of whom were unaware of their infection [7, 8].

More recent data from Public Health England (PHE) estimated that in 2014 there were 103,700 (95% credible interval [CrI] 65,000-75,100) people living with HIV in the UK, 17% of whom were unaware of their HIV status [9, 10]. In the UK (in people aged 15-44 years old), the prevalence of HIV is estimated to be 2.3 (CrI 2.1-2.5) per 1000 population overall, 1.7 per 1000 in women and 2.8 per 1000 in men (2014 estimate) [9]. The number of new HIV diagnoses in the UK has fallen from a peak in 2005 (n=7892), with 6151 people newly diagnosed in 2014 (Figure 1.3) [9], slightly higher than the number diagnosed in the previous year.

The number of AIDS diagnoses and deaths among people living with HIV has remained low during the past decade, having greatly fallen since the mid-1990s when effective ART became available (Figure 1.3). Late diagnosis (a CD4 count of  $\leq 350$  cells/mm<sup>3</sup> at diagnosis) increases the risk of AIDS [11, 12] and the majority of deaths among individuals living with HIV are among people already immunocompromised at diagnosis [10].

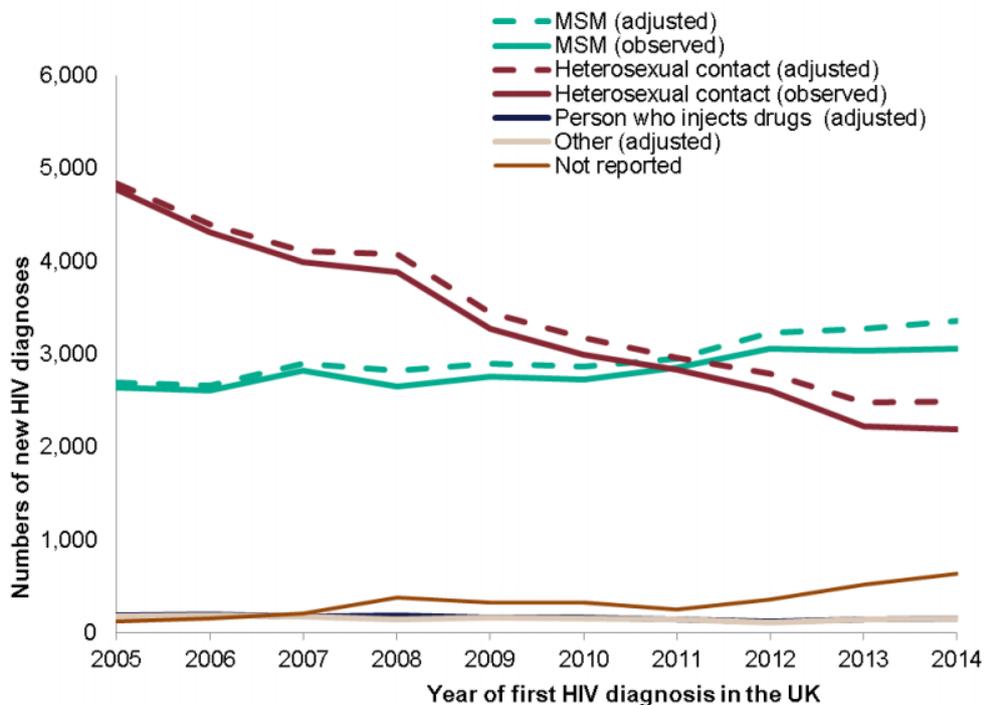
The majority of HIV-positive individuals receiving HIV clinical care in the UK are on life-long ART; 75% (45,953/60,805) in 2009, when this research was started, and 91% (76,462/85,489) in 2014, when the latest data were available. Among people on life-long ART, 95% were virally suppressed [9].

Figure 1.3. New HIV diagnoses, AIDS and deaths over time, 1999-2014



Source: PHE, HIV New Diagnoses, Treatment and Care in the UK 2015 Report [9].

Figure 1.4. New HIV diagnoses in the UK by exposure group, 2005-2014



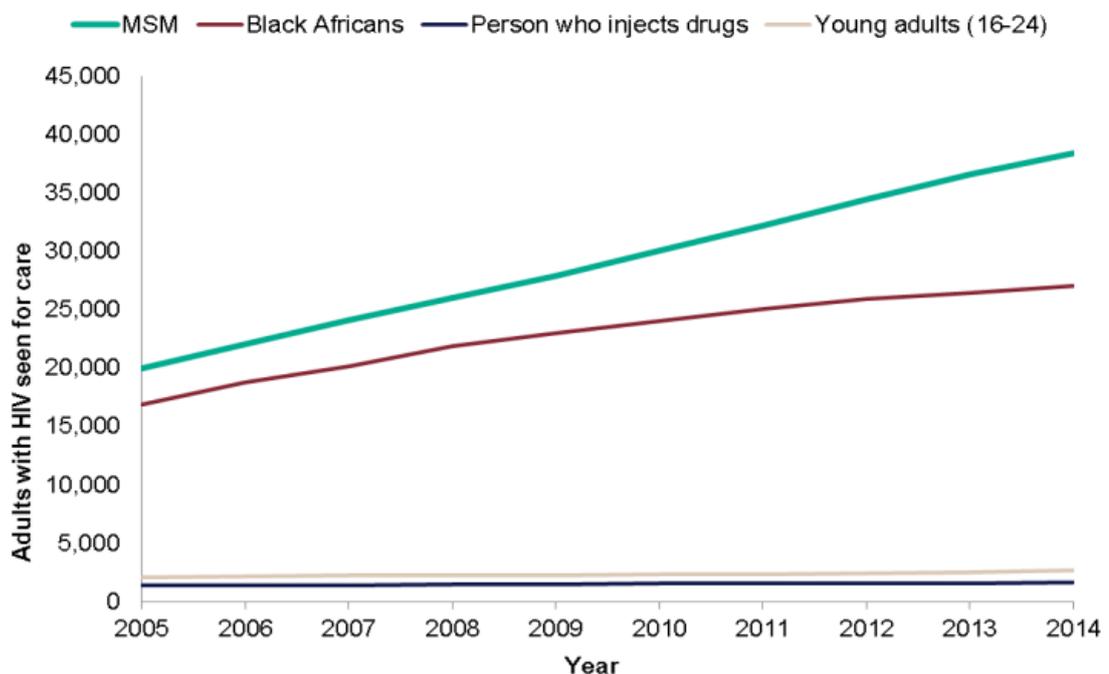
Source: PHE, HIV New Diagnoses, Treatment and Care in the UK 2015 Report [9].

Adjustments are for missing information in case reporting.

In 2014, 40% (2490/6151) of people newly diagnosed with HIV had acquired their infection through heterosexual contact and 55% (n=3360) through sex between men. In the UK, in contrast to many other European countries, the number of people who are infected through sharing injecting drug equipment is very low (Figure 1.4). In 2014, there were 131 diagnoses in people thought to have acquired HIV through shared use of injecting drug equipment, representing 2% of diagnoses in that year [10].

The number of people accessing HIV-related clinical care has steadily increased during the past decade. In 2014, 85,489 adults accessed HIV-related care: 57,347 men and 28,142 women. Of these, 45% (n=38,432) were men infected via sex with other men; 30% (n=25,459) were women infected heterosexually; 18% (n=15,383) were men infected heterosexually, 2% (n=1654) were people infected through shared use of injecting drug equipment and 2% (n=1709) were infected via MTCT (Figure 1.5) [9].

Figure 1.5. Number of adults accessing HIV care in the UK by key prevention groups, 2005-2014



Source: PHE, HIV New Diagnoses, Treatment and Care in the UK 2015 Report [9].

MSM: men who have sex with men. Groups are not mutually exclusive, Black African and Young adults include all exposure categories, MSM and PWID include all ethnicities

### 1.1.3 The history of HIV and AIDS

#### **The first recognised AIDS cases**

HIV is thought to have entered the human population at some point between 1915 and 1941 [13] but was not identified until the 1980s. Initially, the disease, which in 1982 became known as AIDS, [14] was discovered after investigations into a number of rare illnesses in the US. Reports of *Pneumocystis pneumonia* (PCP) and Kaposi's sarcoma, among MSM in New York and California [15, 16] led epidemiologists to identify a new illness which impaired T-cell function, weakening the immune system. Further AIDS cases were soon identified in other groups including women, injecting drug users, haemophiliacs and infants, indicating that transmission could occur via a number of routes [14, 16-20].

In 1983 and 1984 the causative virus was isolated and named by two groups independently [21-23] and in 1986 the decision was made to call the virus the human immunodeficiency virus [24-26]. It later became called 'HIV-1' when, in 1986, a distinct strain of the virus, which was named 'HIV-2', was isolated in West Africa [27]. HIV-2 infection results in a similar, but somewhat slower, disease progression than HIV-1 infection [28].

#### **The origin of HIV**

Both HIV-1 and HIV-2 are thought to have originated from simian immunodeficiency viruses (SIVs). The HIV-1 genome is most closely related to that of the SIVcpz genome, which infects the chimpanzee species, *Pan troglodytes troglodytes* [29, 30]. There are three principal groups of HIV-1 identified through phylogenetic analysis: M, the main group which is found globally; O, an outlier group found mostly in Cameroon, Gabon and Equatorial Guinea; and N, a newer group found mostly in Cameroon. Each group is thought to have independently entered the human population via cross-species transfer of a recombinant form of SIV probably from human contact with primate blood during hunting or butchering of chimpanzee meat [30-33].

HIV-2, which is less widespread than HIV-1, is thought to have originated from SIVsmm which infects the West African sooty mangabey monkey (scientific name *Cercocebus atys*). HIV-2 is mostly found in West Africa but has spread to some parts of Europe and India [29].

#### 1.1.4 HIV transmission

HIV can be transmitted via a number of routes. In HIV-positive individuals, the virus is present in bodily fluids including blood, semen, vaginal fluids and breast milk. Transmission occurs when these fluids come into contact with a mucus membrane, damaged tissue or direct contact with the bloodstream. Globally, the most common routes of transmission are through sex, use of contaminated drug injecting paraphernalia, and from mother to child (vertical transmission). HIV can also be transmitted via contaminated blood, blood products, organs or tissues and through needle stick injuries.

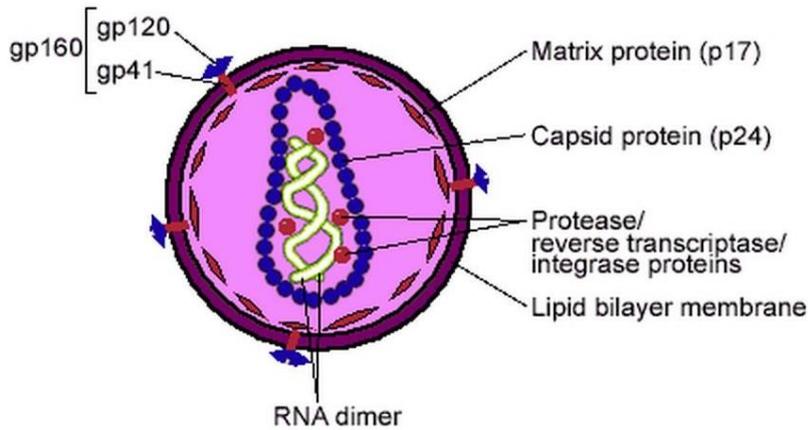
The risk of HIV transmission is dependent on numerous factors but primarily on the amount of circulating virus (the viral load) in the infected person. It is estimated that for every 1-log decrease in plasma viral load there is a 2.5 fold reduction in the risk of onward transmission [34]. The risk of transmission is higher for anal sex than for vaginal sex and is higher for receptive than for insertive anal sex [35-37]. Co-infection with a sexually transmitted infection (STI) increases the risk of sexual transmission [38].

#### 1.1.5 The molecular structure of HIV

##### **Virus structure and genome**

HIV is a type of retrovirus. The virion, the virus when it is outside a host cell, is approximately 100nm in diameter and spherical. Within the virus core are two copies of the single stranded ribonucleic acid (RNA) and the viral enzymes; reverse transcriptase (RT), integrase and protease (Figure 1.6) [29, 39].

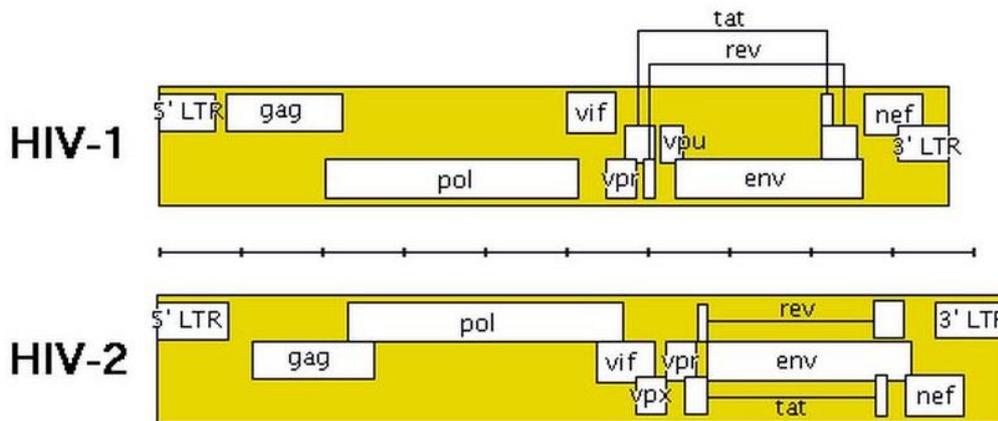
Figure 1.6. The structure of the HIV virion



Source: The Molecules of HIV – A Hypertextbook. Available at [www.mclcd.co.uk/hiv](http://www.mclcd.co.uk/hiv) (Accessed May 2015).

The HIV-1 genome contains at least ten overlapping genes (*env*, *pol*, *gag*, *vif*, *vpr*, *tat*, *rev*, *vpu*, and *nef*). The same area of the DNA codes for different proteins using staggered reading frames [29] (Figure 1.7).

Figure 1.7. HIV-1 and HIV-2 genomes.



Genes are shown in their respective reading frames and are flanked by long-terminal repeats

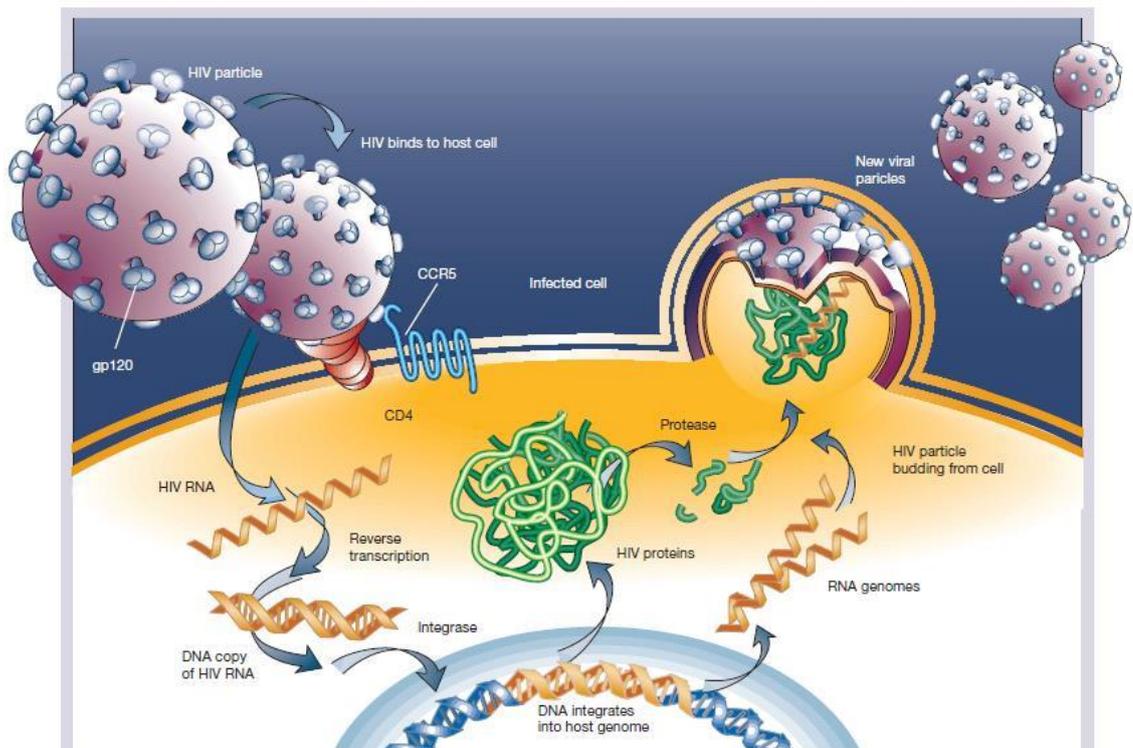
Source: The Molecules of HIV – A Hypertextbook. Available at [www.mclcd.co.uk/hiv](http://www.mclcd.co.uk/hiv) (accessed May 2015).

## Infection of host cells

The main host cell of HIV is the CD4+ helper T-lymphocyte. These cells, referred to as CD4 cells, form an important part of the immune system helping CD8+ T-lymphocytes destroy cells expressing foreign antigens and stimulating the production of antibodies [29]. Other cells which express CD4 antigens on their surface, including macrophages and dendritic cells, can also be infected by (and act as host cells to) HIV.

Fusion of the virus with the host cell's membrane allows the contents of the virus to enter the cell's cytosol. The viral enzyme RT then transcribes the viral RNA into DNA which the integrase enzyme incorporates at random into the host cell's genome. When the host cell transcribes its own DNA into messenger RNA (mRNA) it also transcribes the viral DNA. New virions bud off from the cell membrane eventually destroying the host cell (Figure 1.8).

Figure 1.8. Overview of HIV virus replication cycle; binding to and entering the host cell; reverse transcription of viral RNA; integration of viral DNA into the host genome; and production and release of new virions



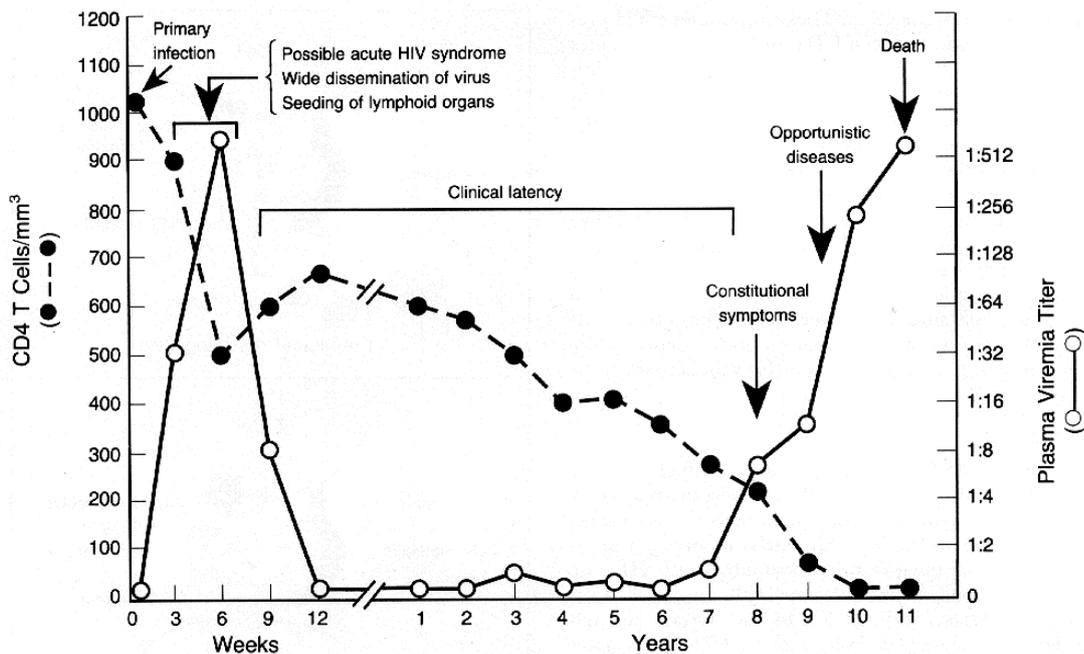
Source: Wiess, 2001 [40].

## 1.1.6 The impact of HIV on the human immune system

### Immune response to HIV infection

A typical pattern of HIV infection starts with an acute or primary phase followed by a longer asymptomatic phase and finally a symptomatic phase. During the acute phase of infection, which lasts 2 to 12 weeks, there is initially a short period of around 10 days when the viral RNA is not detectable. Plasma viral load rapidly increases reaching a peak at 21-28 days after infection [41] before declining to a viral set point after 3-6 months [41-44]. The number of CD4 cells in the blood falls by as much as half, returning to around normal levels (540-1120 cells/mm<sup>3</sup>) in the following months [45, 46] (Figure 1.9).

Figure 1.9. The typical immune response to HIV infection

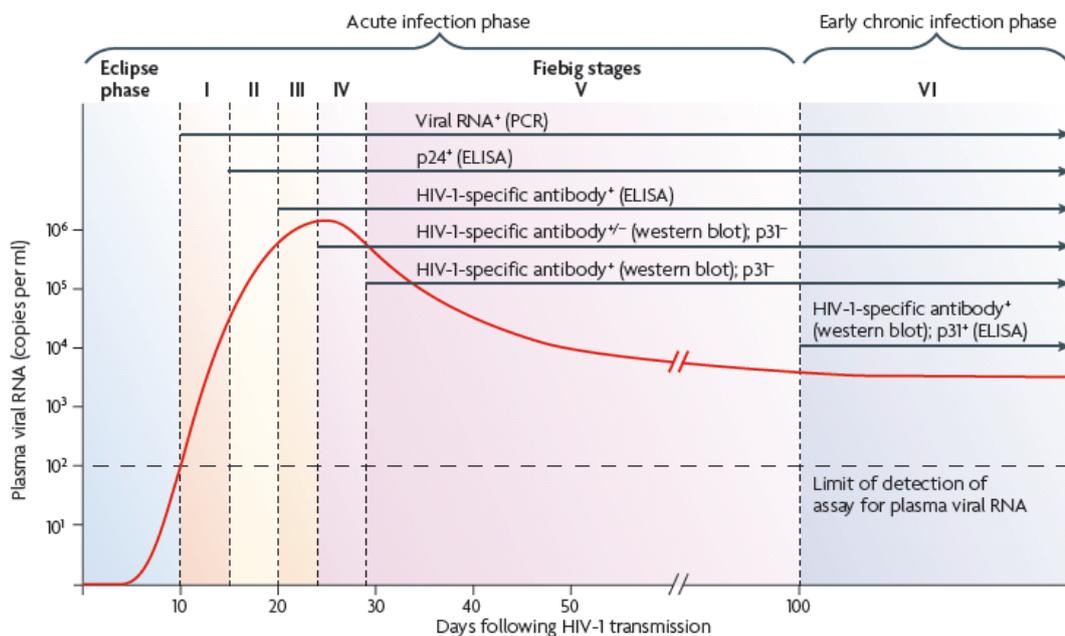


Source: Pantaleo *et al.* 1993 [47]

Seroconversion occurs within 1-3 months of infection with the body starting to produce detectable levels of antibodies and T-cells in response to the virus [42]. Many individuals experience seroconversion illness, acute 'flu-like' symptoms which can include fever, nausea, skin rashes and diarrhoea [48].

Enzyme-linked immunosorbent assays (ELISAs) that detect the presence of HIV specific antibodies can be used to detect HIV infection from around 20 days after exposure. ELISAs that detect viral antigens such as p24 can be effective from around 15 days after infection and polymerase chain reaction (PCR) can be used to detect viral RNA from around 10 days after infection (Figure 1.10) [41].

Figure 1.10. Assays used for detection of HIV infection



Source: McMichael *et al.* 2010 [41]

The term ‘viral load’ refers to the number of copies of HIV-RNA per millilitre (ml). A baseline viral load measurement is normally performed shortly after HIV diagnosis. If ART is not started straight away, viral load is also measured before starting ART, in order to inform decisions about which regimen to use, and is also monitored closely after ART initiation or if the regimen is changed, to assess how effective the regimen is. Among people who are stable on ART, viral load monitoring is performed at regular intervals, typically every 3-6 months.

There are three main techniques used for measuring viral load. These are: branched-chain DNA technique, nucleic sequence-based amplification (NASBA) and reverse transcriptase-PCR [49, 50]. For each technique, there are multiple commercially available assays on the market. Commercial RNA assays include, Roche COBAS®, Abbott RealTime, Seimens Versant™ and bioMerieux Nuclisens®. Although there is a

high correlation between the results produced by different assays on the same sample, there are small differences, since each assay has slightly different performance characteristics [51]. The correlation between assays is lower in blood/serum samples with lower levels of viral load. All commercially available assays can detect virus levels as low as 1000 copies/ml, many to as low as 40 copies/ml and some to as low as 20 copies/ml [52, 53]

## **AIDS**

The symptomless chronic phase of infection can last many years. During this time the number of CD4 cells are slowly depleted (Figure 1.9.). The immune system is gradually weakened until the body becomes vulnerable to common infections such as Candidiasis, and more serious opportunistic infections such as PCP. This is known as the symptomatic phase of infection. There are a number of infections and illnesses classified as AIDS defining, that is, if an HIV-positive individual is diagnosed with one or more, they are classified as having an AIDS event (Table 1.1). In the UK, the European AIDS case definition is used for adults aged 15 years and older [54, 55], and for children of less than 15 years old [56]. These are based on the uniform AIDS case definition published in 1982 [17]. In the absence of treatment, the median time from initial infection with HIV to AIDS is 10-11 years [46, 47, 57]. If untreated, many of these infections/illnesses can eventually be fatal [58].

**Table 1.1. 1993 European AIDS surveillance case definition - list of indicator diseases [54, 55]**

- Bacterial infections, multiple or recurrent in a child under 13 years of age
- Candidiasis of bronchi, trachea, or lungs
- Candidiasis, oesophageal
- Cervical cancer, invasive
- Coccidioidomycosis, disseminated or extrapulmonary
- Cryptococcosis, extrapulmonary
- Cryptosporidiosis, intestinal with diarrhoea (> 1 month's duration)
- Cytomegalovirus disease (other than liver, spleen, or nodes) in a patient over one month of age
- Cytomegalovirus retinitis (with loss of vision)
- Encephalopathy, HIV-related
- Herpes simplex: chronic ulcer(s) (>1 month's duration); or bronchitis, pneumonitis, or oesophagitis in a patient over one month of age

- Histoplasmosis, disseminated or extrapulmonary
- Isosporiasis, intestinal with diarrhoea (>1 month's duration)
- Kaposi's sarcoma
- Lymphoid interstitial pneumonia in a child under 13 years of age
- Lymphoma, Burkitt's (or equivalent term)
- Lymphoma, immunoblastic (or equivalent term)
- Lymphoma, primary, of brain
- *Mycobacterium avium* complex, or *M. kansasii*, disseminated or extrapulmonary
- *Mycobacterium tuberculosis*, pulmonary in an adult or adolescent ( $\geq 13$  years)
- *Mycobacterium tuberculosis*, extrapulmonary
- Mycobacterium, other species or unidentified species, disseminated or extrapulmonary
- Pneumocystis carinii pneumonia (PCP)
- Pneumonia, recurrent
- Progressive multifocal leukoencephalopathy
- *Salmonella* (non-typhoid) septicaemia, recurrent
- Toxoplasmosis of brain in a patient over one month of age
- Wasting syndrome due to HIV

### 1.1.7 ART

There is currently no cure for HIV. The use of combination ART, first introduced in 1995-1996, is now the main treatment strategy for HIV [59-64]. ART is very effective – to such an extent that in developed countries the life expectancy of individuals who are asymptomatic at diagnosis is now approaching that of non-infected individuals [65, 66].

The aim of ART is to suppress viral replication for as long as possible in order to prevent damage to the immune system. The different classes of ART drugs target different stages of the HIV replication cycle. Drugs from different classes are used together, with regimens typically including a combination of three drugs from at least two drug classes. In 2014, there were 28 ART drugs (including fixed-dose combinations [FDC]) used in the European Union (EU) (Table 1.2) [67]. In addition to these, there are a number of drugs which were previously but no longer licensed for use.

### **Nucleoside reverse transcriptase inhibitors (NRTIs)**

Nucleotides form the building blocks of DNA. NRTIs and nucleotide reverse transcription inhibitors (NtRTIs) act as nucleoside/nucleotide analogues. The enzyme RT incorporates NRTIs into the new viral DNA chain instead of nucleotides resulting in chain termination, in other words, the construction of the viral DNA is halted [68, 69].

### **Non-nucleoside reverse transcriptase inhibitors (NNRTIs)**

NNRTIs inhibits the action of RT by binding to the enzyme near its active site. This changes the shape of the active site, decreasing the action of the enzyme [70, 71].

### **Protease inhibitors (PIs)**

HIV-1 protease is an enzyme involved in processing of HIV polyproteins, precursors to the structural proteins and enzymes of the mature virion. PIs bind to the active site of the protease enzyme inhibiting its action [72].

Use of a PI co-administered with low dose ritonavir, termed a 'boosted PI', can improve the effectiveness of the treatment and is frequently used in combination therapy. The first PI, saquinavir, was approved for use in 1995. There are now 6 PIs licensed for use in the EU (Table 1.2).

### **Newer classes of ART drugs**

There are newer ART drug classes which target other parts of the viral replication cycle [71]. Integrase inhibitors (INIs) prevent insertion of the viral DNA into the host's DNA by inhibiting the viral enzyme, integrase [71]. Raltegravir was the first INI licensed for use in the EU in 2008. Since then, two further drugs have been licenced (Table 1.2).

Fusion inhibitors prevent the virus binding to host cells. Enfuvirtide (T-20) was the only drug of this type used in the EU. Due to its high cost and the need for it to be administered by injection it is no longer used in Europe and is used in the US only as a salvage therapy for people with multi-drug resistance.

Drugs have been developed which bind to the CCR5 and CXCR4 co-receptors which are required for entry of the virus into the host cell. The only CCR5 inhibitor currently used is maraviroc, licensed in 2007.

### **Fixed-dose combinations (FDCs)**

FDCs are single tablets which contain two or more co-formulated drugs. Some FDCs need to be used in combination with an additional drug or drugs to make the full regimen. Others, referred to as single tablet regimens, contain the full regimen required.

### **Adverse consequences of ART use**

Many ART drugs cause adverse side effects, either short-term or long term. These can vary from minor to life threatening and are either caused by a response of the body to the drug (allergic reaction or hypersensitivity) or as a direct effect of the drug on the body. Some side effects can be successfully treated with other drugs, such as anti-nausea drugs or painkillers, and others with behavioural change, such as taking drugs just before sleep or with food. Some side effects cannot be treated and may require a change in regimen. Documented long-term side effects include diabetes, lipodystrophy, lipoatrophy (loss or gain of fat) [73], osteopenia (thinning bones), cardiovascular disease and myocardial infarction, [74] kidney problems and liver disease [75].

Table 1.2. ART drugs licensed for treatment of HIV in the EU - October 2014

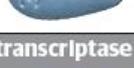
Generic name	Trade name	Formulation	Standard adult dose	Pills/day	
<b>Single-tablet regimens</b>					
<b>Dolutegravir / abacavir / lamivudine</b>	<i>Triumeq</i>		Tablet comprising 50mg dolutegravir, 600mg abacavir and 300mg lamivudine	One tablet once a day	1
<b>Efavirenz / emtricitabine / tenofovir</b>	<i>Atripla</i>		Tablet comprising 600mg efavirenz, 200mg emtricitabine and 245mg tenofovir	One tablet once a day	1
<b>Elvitegravir / cobicistat / emtricitabine / tenofovir</b>	<i>Stribild</i>		Tablet comprising 150mg elvitegravir, 150mg cobicistat, 200mg emtricitabine, 245mg tenofovir	One tablet once a day	1
<b>Rilpivirine / emtricitabine / tenofovir</b>	<i>Eviplera</i>		Tablet comprising 25mg rilpivirine, 200mg emtricitabine and 245mg tenofovir	One tablet once a day	1
<b>Fixed-dose combinations</b>					
<b>Abacavir / lamivudine</b>	<i>Kivexa</i>		Tablet comprising 600mg abacavir and 300mg lamivudine	One tablet once a day	1
<b>Abacavir / lamivudine / zidovudine</b>	<i>Trizivir</i>		Tablet comprising 300mg abacavir, 150mg lamivudine and 300mg zidovudine	One tablet twice a day	2
<b>Emtricitabine / tenofovir</b>	<i>Truvada</i>		Tablet comprising 200mg emtricitabine and 245mg tenofovir	One tablet once a day	1
<b>Lamivudine / zidovudine</b>	<i>Combivir</i>		Tablet comprising 150mg lamivudine and 300mg zidovudine	One tablet twice a day	2
<b>Nucleoside reverse transcriptase Inhibitors (NRTIs)</b>					
<b>Abacavir</b>	<i>Ziagen</i>		300mg tablet	300mg twice a day or 600mg once a day	2
<b>Emtricitabine</b>	<i>Emtriva</i>		200mg capsule	200mg once a day	1
<b>Lamivudine</b>	<i>Epivir</i>		150* and 300mg tablets	150mg twice a day or 300mg once a day	2 1
<b>Zidovudine</b>	<i>Retrovir</i>		100 and 250mg* capsules	250mg twice a day	2
<b>Nucleotide reverse transcriptase Inhibitor (NtRTI)</b>					
<b>Tenofovir</b>	<i>Viread</i>		245mg tablet	245mg once a day	1
<b>Non-nucleoside reverse transcriptase Inhibitors (NNRTIs)</b>					
<b>Efavirenz</b>	<i>Sustiva</i> <i>Stocrin</i>		600mg tablet* and 200mg capsule	600mg once a day	1 or 3
<b>Etravirine</b>	<i>Intence</i>		100 and 200mg* tablet	200mg twice daily	2 or 4
<b>Nevirapine</b>	<i>Viramune</i>		200mg tablet	200mg once a day for two weeks then 200mg twice a day	2
<b>Nevirapine</b>	<i>Viramune prolonged-release</i>		400mg tablet	400mg once a day after introductory period on non-extended-release nevirapine	1
<b>Rilpivirine</b>	<i>Edurant</i>		25mg tablet	25mg once a day	1

Table 1.2 continued. ART drugs licensed for treatment of HIV in the EU - October 2014

Generic name	Trade name	Formulation	Standard adult dose	Pills/day
<b>Protease Inhibitors</b>				
<b>Atazanavir</b>	<i>Reyataz</i>	 150, 200 and 300mg* capsule	300mg with 100mg ritonavir once a day	2 or 3 §
<b>Darunavir</b>	<i>Prezista</i>	 600, and 800mg* tablet	800mg with 100mg ritonavir once a day or 600mg with 100mg ritonavir twice a day	2 to 4 §
<b>Fosamprenavir</b>	<i>Telzir</i>	 700mg tablet	700mg with 100mg ritonavir twice a day	4 §
<b>Lopinavir / ritonavir</b>	<i>Kaletra</i>	 Tablet comprising 200mg lopinavir and 50mg ritonavir	Two tablets twice a day or four tablets once a day	4
<b>Ritonavir</b>	<i>Norvir</i>	 100mg tablet	Full dose: 600mg twice a day To 'boost' other PIs: 100 - 200mg once or twice a day	12 1 to 4
<b>Tipranavir</b>	<i>Aptivus</i>	 250mg capsule	500mg with 200mg ritonavir twice a day	8 §
<b>CCR5 Inhibitor</b>				
<b>Maraviroc</b>	<i>Celsentri</i>	 150* and 300mg tablets	300mg twice a day or 150mg twice a day with ritonavir-boosted PI except tipranavir and fosamprenavir or 600mg twice a day with efavirenz or etravirine without a ritonavir-boosted PI	2 to 4
<b>Integrase Inhibitors</b>				
<b>Dolutegravir</b>	<i>Tivicay</i>	 50mg tablet	50mg once a day or 50mg twice a day if taken with efavirenz, nevirapine or tipranavir, or for HIV known to be resistant to Integrase Inhibitors	1 or 2
<b>Elvitegravir</b>	<i>Vitekta</i>	 85, 150mg* tablet	85mg once a day with atazanavir/ritonavir or lopinavir/ritonavir 150mg once a day with darunavir/ritonavir or fosamprenavir/ritonavir	1
<b>Raltegravir</b>	<i>Isentress</i>	 400mg tablet	400mg twice a day	2
*Formulation(s) shown. § Includes ritonavir tablet(s).				

Source: NAM website [67].

## 1.1.8 Clinical care of people living with HIV in the UK

### **HIV treatment clinics**

The majority of HIV clinical care in the UK is provided by the National Health Service (NHS) specialist HIV services. NHS HIV services are open access; patients can choose where they attend care and can transfer between services or use multiple services. There are currently around 220 specialist NHS HIV services in the UK. Some hospitals and clinics which do not provide routine HIV clinical care provide antenatal care for pregnant women living with HIV and their infants.

### **Starting life-long ART**

High viral load and low CD4 count are associated with increased risk of disease progression [76, 77] and are therefore used as surrogate markers for clinical progression of HIV. Both are traditionally measured as part of HIV clinical care. In the UK, in the absence of HIV-related illnesses, CD4 count has routinely been used as a guide for when to start life-long ART. In most circumstances, once treatment has been initiated it is then continued even when a high CD4 is achieved [78]. As the evidence has grown on the benefits of starting ART earlier i.e. with a higher CD4 count, the cut off at which ART is recommended has increased. Early BHIVA guidelines, published prior to 2008, recommended that treatment be started when the CD4 count was 200-350 cells/mm<sup>3</sup> and before it reached 200 cells/mm<sup>3</sup> [79-83]. The guidelines published in 2008 emphasised starting at 350 cells/mm<sup>3</sup> (in asymptomatic patients without additional comorbidities) [78]. Guidelines, published in 2012, emphasised the importance of not delaying initiation if the CD4 count was approaching 350 cells/mm<sup>3</sup> [84] and the 2014 guidelines, recommended ART use for patients with a CD4 count >350 cells/mm<sup>3</sup> who wanted to start treatment to minimise the risk of onward transmission [85]. The most recent BHIVA guidelines, when submitting this thesis, were the 2015 guidelines [86], and the 2015 European HIV Guidelines [87], published in October 2015. Both recommend that all adults living with HIV start ART irrespective of their CD4 count. These changes to the guidance were made in response to strong evidence that starting ART at a higher CD4 count benefits the health of the individual as well as reduces the risk of onward transmission [88-90], and even at CD4 counts above 500 cells/mm<sup>3</sup>, a lower CD4 count is associated with an increased risk of AIDS and death [91, 92]. This brought the UK and European guidance in line with the US (DHHS) [93] and WHO guidelines [94] which also recommend universal use of ART by people living with HIV.

## ART use

When starting this research, the first line treatment in the UK was typically a combination of one NNRTI with two NRTIs. An alternative to this was the use of NRTIs plus a ritonavir boosted PI (PI/r) or an NRTI only regimen. The 2015 British HIV Association (BHIVA) treatment guidelines [86], recommend the first line treatment for ART-naïve people living with HIV be two NRTIs plus either a PI/r, an NNRTI or an INI (Table 1.3).

Table 1.3. Summary recommendations for choice of ART according to 2015 BHIVA treatment guidelines

	Preferred	Alternative
<b>NRTI backbone</b>	Tenofovir and emtricitabine	Abacavir and lamivudine <sup>a,b</sup>
<b>Third agent (alphabetical order)</b>	Atazanavir/r Darunavir/r Dolutegravir Elvitegravir/c <sup>c</sup> Raltegravir Rilpivirine <sup>d</sup>	Efavirenz

/r: boosted with ritonavir; /c: boosted with cobicistat

<sup>a</sup> Abacavir is contraindicated if an individual is HLA-B\*57:01 positive

<sup>b</sup> Use recommended only if baseline viral load is <100,000 copies/mL except when initiated in combination with dolutegravir in which case abacavir/lamivudine can be used at any baseline viral load.

<sup>c</sup> Tenofovir/emtricitabine/elvitegravir/c fixed-dose combination should not be initiated in individuals with creatinine clearance <70 mL/min

<sup>d</sup> Use recommended only if baseline viral load is <100,000 copies/mL

**NB.** The viral load advice for abacavir/lamivudine and rilpivirine applies only to initiating these agents in individuals with a detectable viral load – when these agents are used as a switch option in the context of viral load suppression the baseline viral load can be disregarded.

Source: BHIVA 2015 Treatment Guidelines [86]

As well as the effectiveness of ART drugs, the choice of regimen is dependent on a number of other factors. These include clinical factors such as drug resistance (baseline resistance testing is undertaken before ART initiation), the presence of factors that may place individuals at higher risk of drug specific toxicities and the cost of the drugs. If adherence might be a problem then combinations that are more forgiving to poor adherence (such as PI-based regimens) or available as a single tablet regimen may be preferable. Drugs taken at night, such as efavirenz, might not be suitable for people who work at night.

### 1.1.9 HIV drug resistance

Phenotypic resistance is the ability of a virus (or bacteria) to replicate in the presence of a drug which normally kills it. This can lead to drug failure and an increase in the viral load which puts the individual at risk of HIV-related disease and death [95-98]. Drug resistance develops due to mutations; random errors in the virus's genetic code which occur during viral replication and which result in different amino acids being used in the viral proteins. HIV has a high replication rate and a high mutation rate – with approximately one mutation per virion [44, 99] as well as a high capacity for its proteins to function after multiple amino acid changes [71, 100]. Over time an HIV-positive individual will have many different viral variants (quasi species) which differ by one or more bases [101].

### 1.1.10 Genetic barrier to resistance

Different drugs have different genetic barriers to resistance. This is dependent on the number of mutations required to confer drug resistance. Some drugs require only a single mutation for the virus to have high-level resistance. This is the case for NVP [102] and EFV which both have a low genetic barrier [102, 103]. Other drugs require multiple mutations, and therefore have a higher genetic barrier [102, 104].

Mutations can be classified as either primary or secondary. Primary mutations are inhibitor specific and may have an effect on the susceptibility to a drug/s. Secondary mutations occur after one or more primary mutations are already present - they may not change the susceptibility to a drug but instead affect viral 'fitness' [105], its ability to create successive generations [106].

### 1.1.11 Changes in viral profiles

Whereas many mutations have no effect on the virus or reduce its fitness, mutations which affect the proteins which are drug targets namely, RT, integrase, protease, and the glycoprotein gp41, can result in drug resistance. Mutations which confer resistance can result in a lower enzymatic efficiency and reduced viral fitness. The wild-type virus is therefore normally 'fitter' than a mutant strain and thus the predominant strain [106].

However, in the presence of ART, the drug is less effective against the drug resistant strain which then has an advantage over the wild-type strain and can become the dominant strain [107]. The virus profile can change quickly following cessation of ART with the wild-type strain reverting back to become the main circulating strain as the resistant strain no longer has any advantage over the wild-type strain [108-111]. At this point the resistant strain may not be detectable using PCR. However, when ART is subsequently restarted, the resistant strain, which if it persists at low/undetectable levels in tissues, can again become the dominant strain [112].

Because drugs within the same class all target the same part of the virus replication cycle, drug resistance to one ART drug can result in resistance to other drugs in the same class [113, 114].

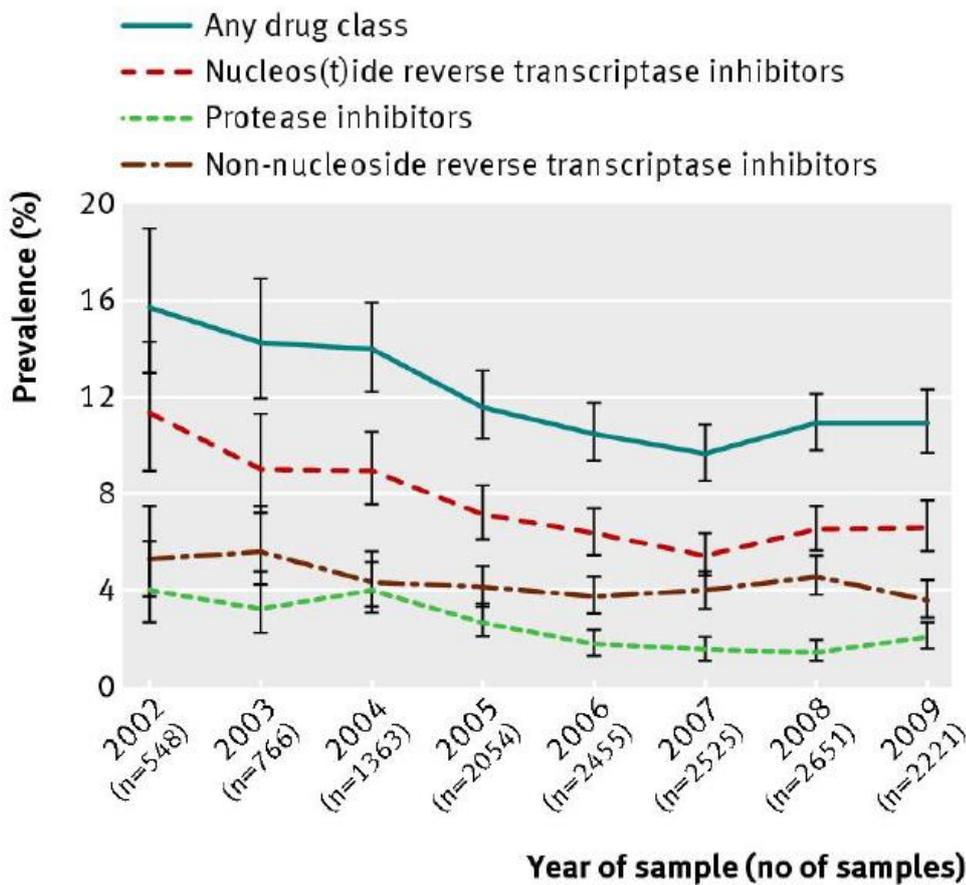
#### 1.1.12 Transmitted drug resistance (TDR) in the UK

Drug resistance strains of the virus can be passed on to an individual when they become infected including infants infected via MTCT [115, 116]. This is referred to as transmitted drug resistance (TDR) and means that people starting ART with no previous exposure to ART (ART naïve) still require a resistance test in order to select the most appropriate regimen [78].

There is some evidence that there has been a decrease in the prevalence of TDR in the UK [117]. A study which used linked data from the UK HIV Drug Resistance Database (HDRD), the UK Collaborative HIV Cohort (UK CHIC) study and the UK Register of HIV Seroconverters showed that among ART naïve adults the prevalence of TDR peaked in 2002 when 16% of patients had resistance to any drug class (i.e. at least one mutation associated with TDR), 11% to an NRTI, 6% to an NNRTI and 5% to a PI. In 2004, prevalence had fallen to 9%, 4.6%, 4.4% and 2.1% for any drug class, NRTI, NNRTI and PIs respectively. The prevalence of resistance also decreased over time among recently infected individuals (who had seroconverted in the last 18 months) [117]. A study which linked data from the UK HDRD, UK CHIC and the Survey of Prevalent HIV Infections Diagnosed (SOPHID) found that 11% of people tested before starting ART in 2002-2009 had TDR. The prevalence of TDR declined from 16% in 2002 to 10% in 2007 after which it plateaued (11% in 2009) (Figure 1.11). The extent to

which ART experienced and ART naïve individuals contribute to the onward transmission of drug resistant strains is unclear [118].

Figure 1.11. Prevalence of TDR in the UK over time by ART drug class, 2002-2009



Bars show the 95% confidence intervals

Source: UK Collaborative Group on HIV Drug Resistance, 2012 [119].

## 1.2 HIV and pregnancy

### 1.2.1 Vertical transmission

Vertical transmission, from mother to child, can occur during pregnancy (*in utero*), during labour and delivery (*intrapartum*) and during breastfeeding via breast milk or blood (*postpartum*) [120]. It is thought that around 15-20% of vertical transmissions occur during pregnancy, half during labour/delivery, and 30-40% during breastfeeding [121-123]. With no interventions to minimise the transmission risk, the rate of vertical transmission is approximately 25% to 48% in lower income settings and 13% to 32% in

high income settings [124]. Maternal HIV viral load is strongly associated with MTCT risk [125-128]. A UK study found that women with a viral load  $\geq 10,000$  copies/ml had a transmission rate of 9.2% compared to a rate of 0.05% in women with a viral load  $< 50$  copies/ml [129]. There are a number of additional factors which increase the risk of MTCT including a low maternal CD4 count and younger gestational age of the baby at birth [130-133]. Factors which increase the risk of transmission via breast feeding include high viral load [134], low CD4 count [134], mastitis [135, 136], the presence of an abscess [135] and mixed feeding [137-139]. The risk of transmission is related to the length of exposure, but there is a higher risk in the first 3-6 months after birth [140].

### 1.2.2 Antenatal screening

The routine offer and recommendation of antenatal HIV testing was introduced in England in 1999-2000 with a target of 90% uptake and 80% of infections identified by the end of 2002 [141]. Similar policies were implemented in the rest of the UK in the following years. Following introduction of the policy, the uptake of testing swiftly increased [142] and is now over 97% [143].

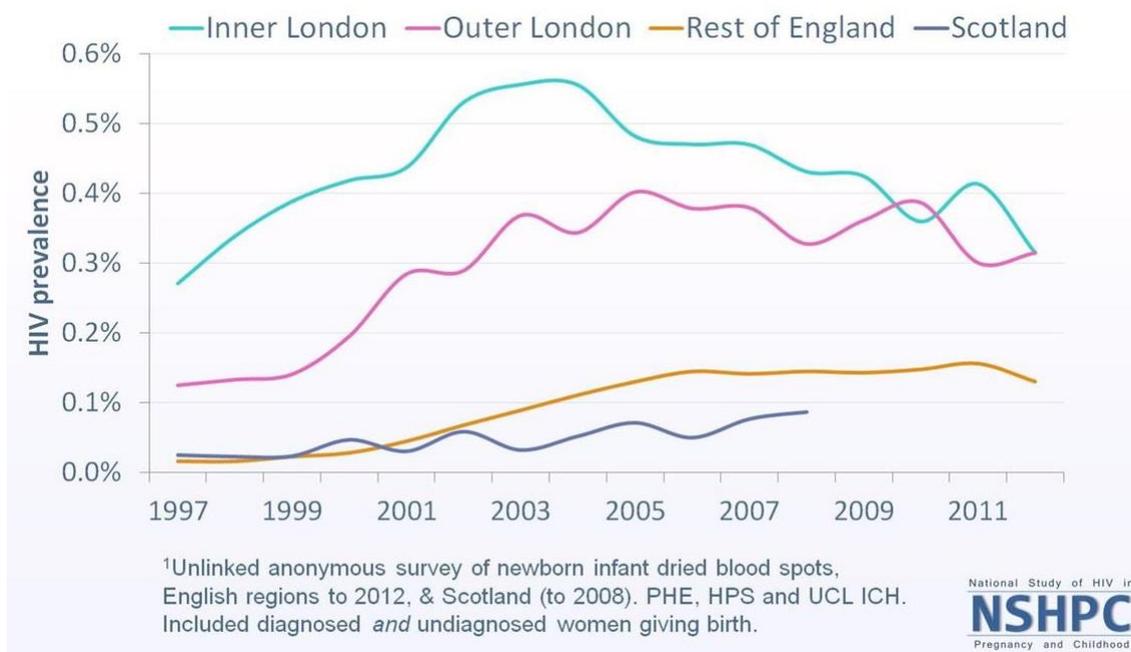
Current testing policy states that women should be offered an HIV test early on in their pregnancy or as soon as possible after they first attend antenatal care. Women who are initially negative but have a high risk of infection or women who initially decline a test should be offered testing later on in their pregnancy. The children of women who are diagnosed either before or during antenatal care and whose children are not known to be infected should also be tested [144].

HIV testing is also recommended for all patients attending termination of pregnancy (TOP) services, genitourinary medicine (GUM) clinics, drug dependency services and services treating patients with tuberculosis, hepatitis B, hepatitis C and lymphoma as well as in primary care where the diagnosed prevalence of HIV is higher than 0.2% [8]. Self-test kits can now be purchased online (since April 2015).

### 1.2.3 HIV prevalence in pregnant women in the UK

Unlinked anonymous testing of neonatal dried blood spots indicates that the overall prevalence of HIV (diagnosed and not diagnosed) among women giving birth in England and Scotland has gradually increased over time. In the areas covered by the study (64% of women giving birth in England and Scotland), 2.1 per 1000 women were living with HIV in 2008, the most recent data available when starting this research. As would be expected, the prevalence was higher in London than outside London (3.7 per 1000 women vs. 1.5 per 1000 women, respectively) [8]. However, the prevalence among women living in London had fallen since 2003 and the prevalence among women living elsewhere in England and in Scotland had increased (Figure 1.12).

Figure 1.12. HIV prevalence in pregnant women in England and Scotland



Source: PHE, Health Protection Scotland (HPS) and the Institute for Child Health (ICH) [145]

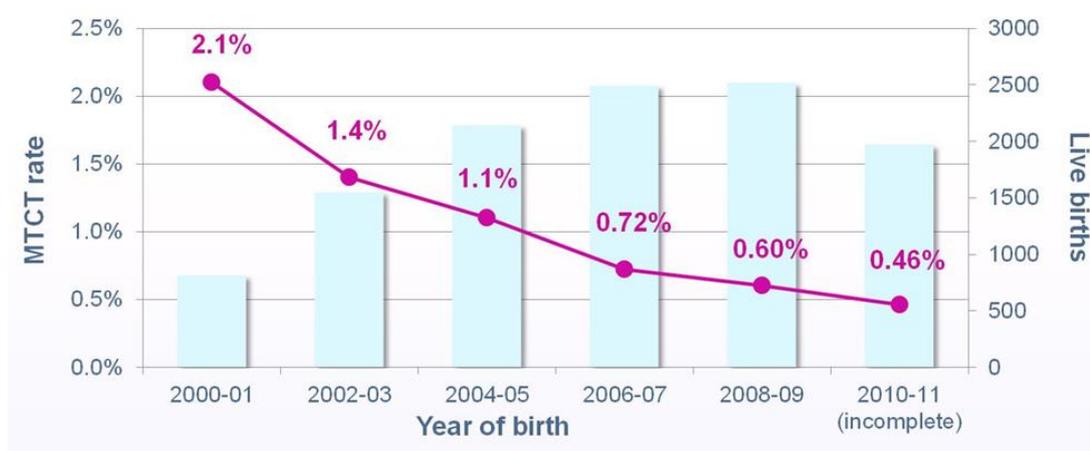
Available from: [www.ucl.ac.uk/nshpc/slides](http://www.ucl.ac.uk/nshpc/slides) (Accessed January 2016).

### 1.2.4 MTCT rates in the UK

The most recent data available (from March 2015) suggest that there have been in total at least 18,417 children born to HIV-positive mothers in the UK. The number of infants

known to have become infected with HIV is 222 (representing 1.3% of the 17,637 infants born to women diagnosed with HIV before they delivered) [145]. The overall MTCT rate among HIV-positive women giving birth in the UK was 19.6% (8-33%) in 1993, has fallen to around 0.3% (17/5946) (CI 0.2-0.4%) in 2010-14 [145] (Figure 1.13).

Figure 1.13. MTCT rates in diagnosed women, UK and Ireland 2000-2011



Approximately 12,500 singleton births; decline in MTCT rate over time ( $p < 0.001$ ).

Source: NSHPC website [145] (Accessed August 2015), derived from Townsend *et al.* 2014 [129].

### 1.2.5 Preventing MTCT

#### Antenatal ART use

There are a number of interventions used in the UK to minimise the risk of MTCT. ART use in pregnancy, and when breastfeeding, dramatically reduces the risk of MTCT by reducing the mother's viral load [130, 131, 146, 147]. ART drugs have been used in pregnancy since 1994 when ZDV, administered during pregnancy, labour and to the infant for six weeks after birth, was found to reduce MTCT risk by 68% (there was an 8% transmission rate in the intervention group compared to a 25% transmission rate in the placebo group) [148]. Later studies found that the use of combination ART reduced the MTCT rate further [127, 149] and in resource rich countries, such as the UK, the use of ZDV monotherapy (ZDVm) became restricted to women with a low viral load

who had not yet reached the CD4 threshold for life-long ART initiation [144]. Despite the effectiveness of ART at reducing the risk of MTCT, there is some evidence that vertical transmission can still occur even if the mother has an undetectable plasma viral load [129, 132, 147] since although there is correlation between the viral load in the plasma and in the genital tract, women can be infectious due to genital tract shedding despite viral suppression in the plasma [150].

Because of its history of use in pregnancy, ZDV has typically been included in the short-term combination therapy regimen recommended for use in pregnancy. However, a study using the UK and Ireland National Study of HIV in Pregnancy and Childhood (NSHPC) data found that ZDV-sparing regimens are as effective at reducing vertical transmission as ZDV-containing regimens [151]. The ART regimens previously recommended for use in pregnancy are discussed in Section 1.2.8.

### **Avoidance of breastfeeding**

In breast milk, the HIV virus is found in both the liquid phase and within white blood cells [139]. In the UK where formula feeding is safe and socially acceptable and practised by many mothers, avoidance of breastfeeding is recommended for all HIV-positive women. Transmission rates are lower in infants exclusively breast fed than in infants mixed fed i.e. with breast milk and formula or solids [137-139], therefore exclusive breastfeeding (and the use of ART) plus weaning at 6 months is recommended in settings where exclusive formula feeding is not possible or well adhered to [152] and for women in the UK who choose to breastfeed.

### **Caesarean section**

Studies indicate that pre-labour caesarean section (PLCS) is associated with a reduced risk of MTCT compared with vaginal delivery [153, 154]. In some studies this association was also seen in women with an undetectable viral load [131]. However, in a French cohort, PLCS was not associated with a reduced risk of transmission among women with a viral load <400 copies/mL who delivered at term [155]. Similarly, observational data in the UK indicates that PLCS is not associated with reduced transmission rates among women on HAART [129].

### 1.2.6 HIV and fertility rates

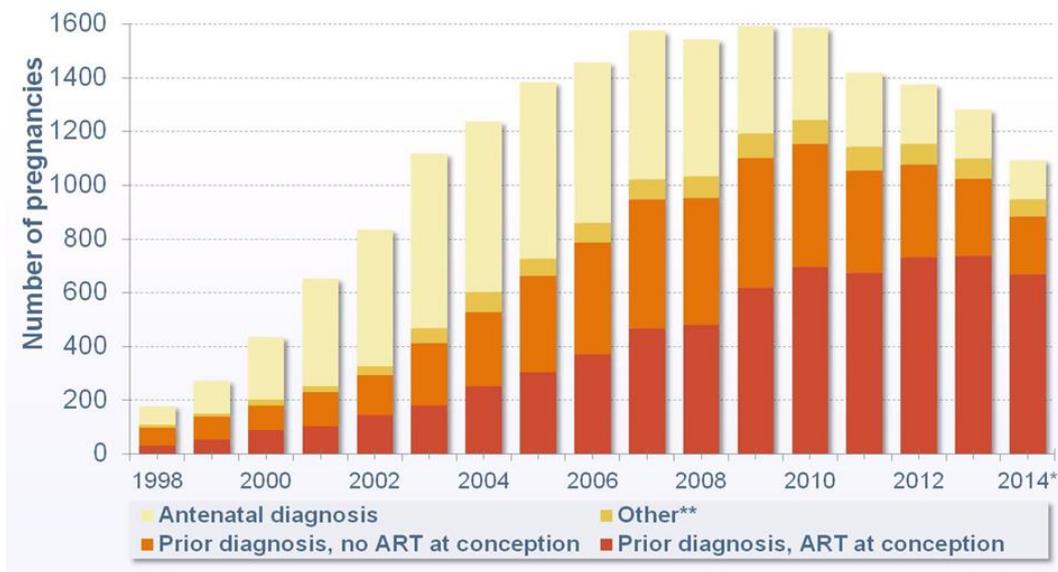
In Europe, HIV diagnosis was previously associated with a reduced live-birth rate and an increased termination rate [156, 157]. However, with the introduction of ART leading to reduced rates of vertical transmission and improved prognosis for adults and children living with HIV, [59, 158] (including pregnant women [159]), the number of pregnancies among HIV-positive women has increased in Europe and elsewhere [157, 160, 161]. A European study of HIV-positive women published in 2008 concluded that HIV infection did not influence women's desire to have children [162]. A study of women living with HIV in the UK found that more than half said that their HIV diagnosis affected their fertility intentions, with 11% wanting children sooner [163].

As well as possibly influencing people's decisions whether and when to have children, HIV affects some biological mechanisms related to fertility. In men, HIV can reduce the quality and quantity of semen [164] and in women it may increase the risk of menstrual disorders [165]. There is some evidence that either the virus or the use of ART increases the risk of early menopause [166].

### 1.2.7 HIV diagnosis prior to pregnancy

Since 2005, pregnancies in women already aware of their HIV infection (whether diagnosed in or outside the antenatal setting) have outnumbered pregnancies in women not yet diagnosed (Figure 1.14). At the same time, pregnancies in women already on ART began to outnumber pregnancies in women diagnosed but not yet on life-long ART. In recent years, three-quarters of diagnosed women were already on ART at conception [145].

Figure 1.14. Timing of maternal HIV diagnosis among HIV-positive pregnant women in UK and Ireland



\*All pregnancies reported by March 2015, regardless of outcome; reporting delay for recent years. \*\*Other category is pregnancies lacking information on precise timing of diagnosis and/or ART use. Source: NSHPC website (Accessed January 2016) [145].

### 1.2.8 Clinical management of pregnant women living with HIV in the UK

The clinical management of HIV-positive pregnant women in the UK has changed since the time when ZDVm was first recommended [167]. When starting this research the most recent BHIVA guidelines for the clinical management of HIV-positive pregnant women were published in 2008 [144]. Updated guidelines were subsequently published in 2012 [168] and in 2014 [169]. Current recommendations for antenatal ART, mode of delivery, infant treatment and feeding and drug resistance testing are summarised below. At the time of submission of the thesis, the BHIVA's pregnancy specific guidelines had not yet been updated in line with changes to the general guidelines [86], however, the recommendation of universal ART use now eradicates the need for short-term ART use in pregnancy.

## **ART use**

Women already receiving ART at time of conception are recommended to continue on therapy during and after the pregnancy. If they have an undetectable viral load and are tolerating the therapy well then they would normally continue on the same regimen, even if it contains efavirenz, which was previously not recommended for use in pregnancy. If the current regimen is failing then the regimen should be changed to an appropriate alternative. Women who conceive on ART are likely to be on drug combinations similar to those recommended for women starting therapeutic ART in pregnancy [85].

Pregnant women not yet on ART are now advised to start cART and remain on therapy after delivery. Until the September 2015 update to the BHIVA guidelines [86], only pregnant women with a CD4 count  $<350$  cells/mm<sup>3</sup> or co-morbidities were recommended to initiate therapy [78] (Table 1.4 and Table 1.5). Women with no HIV-related symptoms and whose CD4 count was above 350 cells/mm<sup>3</sup> were recommended a short-course of cART during the pregnancy to prevent MTCT. In order to reduce the risk of resistance it was important that when therapy was stopped after delivery, consideration was given to the half-life of each drug to avoid inadvertent monotherapy of the drug with the longest half-life [85].

The timing of antenatal ART initiation is a balance between limiting the ART exposure of the foetus, especially in the early stages of foetal development, with the urgency to start ART for the health of the mother and/or to ensure viral suppression is achieved as soon as possible and definitely before delivery.

The latest available data on ART use in pregnancy when starting this thesis were from 2006. At that time, the majority of diagnosed pregnant women used ART at some point during pregnancy (98%), most using combination therapy (95%) and only 4.4% using ZDVm [170]. Around half the women were prescribed a short-course of ART for PMTCT only [170].

Table 1.4. BHIVA 2012 guidelines for ART combinations used in pregnant and non-pregnant people starting ART treatment for therapeutic and PMTCT reasons [84, 168].

Reason for ART use	Status	Recommended combinations	Criteria
Therapeutic	Not pregnant	First line regimens:	
		Efavirenz + nucleoside backbone <sup>1</sup>	-
		Nevirapine + nucleoside backbone <sup>1</sup>	CD4 <250 cells/mm <sup>3</sup>
		PI/r <sup>3</sup> + nucleoside backbone <sup>1</sup>	-
Therapeutic	Pregnant	In the absence of contraindications:	
		Efavirenz + nucleoside backbone <sup>2</sup>	-
		Nevirapine + nucleoside backbone <sup>2</sup>	CD4 <250 cells/mm <sup>3</sup>
		PI/r <sup>3</sup> + nucleoside backbone <sup>2</sup>	-
PMTCT only	Pregnant	PI/r <sup>3</sup> + nucleoside backbone <sup>2</sup>	-
		Abacavir + lamivudine + ZDV	VL <100,000 copies/ml
		ZDV monotherapy <sup>4</sup>	VL <10,000 copies/ml

Therapeutic ART use refers here to life-long ART and PMTCT refers to the use of short-course ART  
 PI/r: ritonavir boosted protease inhibitor; ZDV: zidovudine; VL: viral load.

<sup>1</sup>Nucleoside backbone combinations: tenofovir + emtricitabine; abacavir + lamivudine

<sup>2</sup>Nucleoside backbone combinations: tenofovir + emtricitabine; abacavir + lamivudine; or ZDV + lamivudine

<sup>3</sup>Typically lopinavir or atazanavir

<sup>4</sup>Women on ZDVm are also given a ZDV infusion starting four hours before the caesarean [144]

Table 1.5. Changes over time in BHIVA guidance on when and which ART drugs to start in pregnancy

	Year	Recommendation
<b>Women not needing ART treatment for their own health</b>		
When to start	2001	Not specified
	2005	Start in the 2 <sup>nd</sup> trimester
	2008	Start by 28 weeks Start at 20-24 weeks for women with high VL wanting a vaginal delivery
	2012	Start by 24 weeks Start at the beginning of 2 <sup>nd</sup> trimester if VL >30,000 copies/ml or earlier if VL >100,000 copies/ml
	2014	No change from 2012 guidelines
What to start	2001	ZDVm in women with VL <20,000 copies/ml Short-course cART considered as an alternative (no regimen is specified but there is a suggestion that a PI-based regimen such as nelfinavir could be used)
	2005	PI-based cART ZDVm is alternative for women with VL <10,000 copies/ml willing to deliver by PLCS
	2008	PI/r cART with ZDV + lamivudine nucleoside backbone if no contraindications ZDVm is alternative for women with VL <10,000 copies/ml willing to deliver by PLCS
	2012	No change from 2008 guidelines
	2014	No change from 2008 guidelines

Table 1.5 continued. Changes over time in BHIVA guidance on when and which ART drugs to start in pregnancy

Women needing treatment for their own health		
When to start	2001	Not specified
	2005	Not specified
	2008	As soon as possible but preferably waiting until the 2 <sup>nd</sup> trimester unless the woman has an opportunistic infection
	2012	No change from 2008 guidelines
	2014	No change from 2008 guidelines
What to start		
	2001	As per adult treatment guidelines [80]  The guidelines note that there are more data on the safety and effectiveness of ZDV than other drugs but that ritonavir and nevirapine have also been found to reduce vertical transmission risk
	2005	As per adult treatment guidelines [82]  Notes that stavudine plus didanosine should be avoided
	2008	As per adult treatment guidelines [82, 171]
	2012	As per adult treatment guidelines [84]  The guidelines note that the first line therapy combinations typically used outside pregnancy (tenofovir/emtricitabine or abacavir/lamivudine) can be used as the nucleoside backbone in pregnancy instead of ZDV/lamivudine (for which there is most evidence)  This is in combination with efavirenz or nevirapine (if low CD4 count) or a PI/r such as lopinavir, atazanavir or saquinavir
	2014	As per 2012 guidelines

PLCS: pre-labour caesarean section; VL: viral load

Source: BHIVA guidelines for the management of pregnant women living with HIV published in 2001, 2005, 2008, 2012 and 2014 [144, 168, 169, 172, 173].

### **Mode of delivery**

Women on either life-long or short-course combination therapy with a viral load of <50 copies/mL at 36 weeks can opt for a vaginal birth. Women on ZDVm are recommended to have a PLCS at 38 weeks. Women with a viral load >50 copies/mL at 36 weeks should have their treatment changed and are recommended a PLCS at 38 weeks. They should also be given intravenous ZDV starting four hours before the caesarean. In some cases the mother will also be given a single dose of NVP [144]. Women presenting in labour who are either known to be HIV-positive or are diagnosed in labour are given a combination containing NVP and intravenous ZDV [144].

### **ART given to the infant**

Infants should be given ZDVm twice daily for 4 weeks or, an alternative monotherapy if the mother's regimen does not include ZDV. If the mother has a detectable viral load or did not use ART in pregnancy then the infant is given triple therapy (PEP) for 4 weeks.

### **Infant feeding**

It is recommended that in the UK where alternatives to breast feeding are accessible, all HIV-positive mothers avoid breastfeeding irrespective of their viral load, CD4 count or ART use. Formula-feeding is recommended as the alternative to breastfeeding. If women choose to breastfeed they should continue to use cART until one week after cessation. Infants should be exclusively breastfed until the weaning period and breastfeeding should be stopped by the end of 6 months.

### **Resistance testing**

Women should have a baseline resistance test before their ART regimen is decided. When treatment is failing resistance testing should also be carried out to help identify a suitable alternative regimen [144].

Current treatment guidelines state that women starting ART in pregnancy should have a resistance test prior to starting unless they present in late pregnancy - when ART should be started swiftly before the resistance results are returned. Women using short-course ART during pregnancy should also have a resistance test after ART is stopped [144].

## **Pregnancy outcome**

Use of cART, particularly during the start of pregnancy has, in some settings, been found to be associated with pre-term delivery [174] and pre-eclampsia [175]. The use of cART, and more specifically the use of protease inhibitor (PI)-containing regimens, have been associated with a lower birth weight [176, 177]. Use of NRTIs, including ZDV, have been associated with mitochondrial toxicity in infants exposed *in utero* [178, 179], the risk being higher in infants exposed to NRTI combinations than ZDV monotherapy [179]. *In utero* exposure to triple therapy increased the risk of neutropenia in infants up to one month old [180] and cART can increase the risk of mothers developing anaemia [181].

## Chapter 2 Literature review

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Whilst in Chapter 1 I gave an overall introduction to HIV and HIV within the context of pregnancy, the aim of this chapter is to give a more detailed account of our current understanding of the areas addressed in this research. These include the impact of pregnancy and ART use in pregnancy on disease progression, drug resistance, toxicity within pregnancy and the associations between pregnancy and HIV viral load.

### 2.1 Methods

This is a narrative review of topics addressed in the research. Literature searches were conducted primarily using PubMed<sup>1</sup>. The search terms used can be found in Appendix Ia. Key papers were searched for relevant references. Most of the relevant papers found were in English, since the majority of research with international relevance is published in English and since the search terms I used were in English. However, I also read a handful of relevant papers in Spanish. I was alerted to relevant papers being published via emails from Scopus<sup>2</sup>. Searches in Google<sup>3</sup> were used to find grey literature and conference proceedings. Google scholar<sup>4</sup> was used to find peer reviewed articles which were missed or could not be found in PubMed. Specific websites were searched for relevant grey literature including published statistics, reports and national and international treatment guidelines. These included the websites for the UK and Ireland National Study of HIV in Pregnancy and Childhood (NSHPC)<sup>5</sup>, the Health Protection Agency (HPA) (which became part of Public Health England [PHE] in 2010)<sup>6</sup>, the Office for National Statistics (ONS)<sup>7</sup>, the World Health Organization (WHO)<sup>8</sup>, the British HIV Association (BHIVA)<sup>9</sup>, and the Royal College of Midwives<sup>10</sup>. I also read a number of PhD theses written by colleagues at UCL in order to find further references of relevance.

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<sup>1</sup> [www.ncbi.nlm.nih.gov/pubmed](http://www.ncbi.nlm.nih.gov/pubmed)

<sup>2</sup> [www.scopus.com](http://www.scopus.com)

<sup>3</sup> [www.google.co.uk](http://www.google.co.uk)

<sup>4</sup> [www.google.co.uk/scholar](http://www.google.co.uk/scholar)

<sup>5</sup> [www.ucl.ac.uk/nshpc](http://www.ucl.ac.uk/nshpc)

<sup>6</sup> [www.gov.uk/government/collections/hiv-surveillance-data-and-management](http://www.gov.uk/government/collections/hiv-surveillance-data-and-management)

<sup>7</sup> [www.ons.gov.uk/ons/index.html](http://www.ons.gov.uk/ons/index.html)

<sup>8</sup> [www.who.int/en/](http://www.who.int/en/)

<sup>9</sup> [www.BHIVA.org](http://www.BHIVA.org)

<sup>10</sup> [www.rcm.org.uk](http://www.rcm.org.uk)

## 2.2 Pregnancy and disease progression

Some early studies indicated that pregnancy may have a deleterious effect on HIV progression [182-185]. A meta-analysis of 7 studies published in 1983-1996 found a weak association between pregnancy and disease progression [186]. However, numerous studies have found no such association [187-193] (Appendix Ib: Table 1 and Table 2). Many of the studies which examined disease progression after pregnancy, including those which found an association and those which did not, had limited statistical power due to the small number of women included in the analysis. For example, a Swiss study which found no association between pregnancy and time to AIDS or death included only 32 pregnant women [182]. Since most were observational studies they were subject to the methodological limitations of observational studies i.e. they could not adjust for unmeasured confounders. This is particularly important within the context of pregnancy because women who have a pregnancy may have different demographic and clinical characteristics from women who do not. Many of the studies assessed outcomes which, certainly within the UK, are now relatively rare events among women living with HIV such as death, AIDS, symptomatic disease or a CD4 count <200 cells/mm<sup>3</sup>.

More recent studies have either found no association between pregnancy and disease progression [147] or a lower risk of progression to AIDS or death (hazard ratio [HR] 0.40, 95% confidence interval [CI] 0.2-0.79) [194] in women with a pregnancy than in women without. Again, these differences are likely to be a result of existing differences in the health and immune status of women in the two groups rather than a consequence of the pregnancy itself. In the UK, women attending HIV related clinical care who are pregnant have a higher average CD4 count and lower viral load and are more likely to be asymptomatic than non-pregnant women [162]. Although they may indicate some benefit to the woman's health in using short-course ART intended for PMTCT.

## 2.3 Pregnancy and CD4 count

There is evidence that pregnancy affects cell-mediated immunity [195] but its impact on the immune system is not fully understood. Some studies have found that the CD4 cell count declines during pregnancy, returning to baseline afterwards perhaps as a consequence of hemodilution [147, 192, 196]. Others have reported an increase in CD4 count at delivery [147, 185] including a study in the late 1990s in Côte d'Ivoire which found that the placebo group (women who did not use ART in pregnancy) had a stable CD4 cell count throughout pregnancy and a raised CD4 count at delivery. In this study the average CD4 count fell after delivery but remained above the baseline level at six months postpartum [197].

## 2.4 Zidovudine (ZDV)

ZDV, also called Azidothymidine (AZT), is a nucleoside reverse transcriptase inhibitor (NRTI). It was the first antiretroviral therapy licensed for the treatment of AIDS (in 1987) and HIV (in 1990) and remains the only ART drug licensed for use in pregnancy (in the third trimester). In 1994, the Paediatric AIDS Clinical Trials Group (PACTG) 076 clinical trial found that ZDV was safe and effective at reducing HIV mother-to-child transmission (MTCT) [148]. This proof of concept study found a 68% reduction in the transmission rate, from 23% in the placebo group to 8% in the treatment group who started ZDV between 14 and 34 weeks gestation, and were given intravenous ZDV at delivery and whose infants were given oral ZDV for 6 weeks and formula fed [198]. Further studies in the late 1990s found further evidence that ZDV monotherapy (ZDVm) started in late pregnancy was effective at reducing MTCT among breastfeeding [199, 200] and non-breastfeeding populations [201]. Several studies found that ZDVm used for the prevention of MTCT (PMTCT) did not cause toxicity [148, 193, 199-201] or accelerate disease progression [193]; prospective reporting to the Antiretroviral Pregnancy Register (APR) indicates that *in utero* exposure to ZDVm does not increase the risk of teratogenicity (congenital malformations). [202].

With the increased evidence regarding the effectiveness of ZDV at preventing MTCT, it became widely used during pregnancy both as a monotherapy then as a dual therapy and later as part of combination antiretroviral therapy (cART) [128, 203-205]. Although ZDV is commonly chosen as part of the antenatal cART regimen, this choice is primarily related to the history of its use in pregnancy.

British HIV Association (BHIVA) treatment guidelines for the use of ART for PMTCT have changed over time with the emphasis moving towards the use of cART and away from ZDVm (Table 2.1). Until September 2015, when ART was recommended for everyone living with HIV irrespective of their CD4 count [86], the use of short-term ZDVm in pregnancy was reserved for women not wishing to use cART who were willing to deliver by pre-labour Caesarean section (PLCS) and who had repeatedly low viral load (HIV RNA <10,000 copies/mL), and wild-type virus [144]. Its antenatal use in resource rich settings, such as the UK, was viewed by some as substandard compared to the use of cART [206]. Some studies found that use of cART reduces the risk of MTCT to a greater extent than ZDVm [127, 207]. However, when used in women with a high CD4 count and low viral load, and in combination with pre-labour caesarean section [149], ZDVm is effective at preventing MTCT [153] and had some advantages over cART. Not without its own risks [208], the use of ZDVm may have avoided some of the risks associated with antenatal use of cART such as the increased risk of pre-term delivery [209-213], hepatotoxicity and the development of drug and drug class resistance associated with the use of non-nucleoside reverse transcriptase inhibitors (NNRTIs). It also minimised the exposure of the developing fetus to potentially harmful drugs. Use of NRTIs, including ZDV, have been associated with mitochondrial toxicity in infants exposed *in utero* [178, 179], the risk being higher in infants exposed to NRTI combinations than ZDVm [179]. In a study in Botswana, *in utero* exposure to cART increased the risk of neutropenia in infants up to one month old, compared to the use of ZDVm [180].

Table 2.1. Summary of the changing BHIVA guidelines on the use of ZDVm during pregnancy for PMTCT

Year of publication	Summary of Recommendations
1999 [214]	<p>ZDVm is recommended for women:</p> <ul style="list-style-type: none"> <li>• Not requiring treatment for their own health</li> <li>• With a high CD4 count (suggested cut off &gt;200 cells/mm<sup>3</sup>)</li> <li>• Low viral load, &lt;30,000 copies/ml</li> <li>• Delivery by elective caesarean section</li> </ul>
2001 [172]	<p>cART is offered as an alternative to ZDVm</p> <p>ZDVm is recommended for women:</p> <ul style="list-style-type: none"> <li>• Not requiring treatment for their own health</li> <li>• With a high CD4 count (suggested cut off &gt;200 cells/mm<sup>3</sup>)</li> <li>• Low viral load, &lt;20,000 copies/ml</li> <li>• Delivery by elective caesarean section</li> </ul>
2005, 2008 & 2012 [144, 168, 173]	<p>ZDVm is offered as a 'valid option' for women not wishing to use cART</p> <p>ZDVm can be used by women:</p> <ul style="list-style-type: none"> <li>• Not requiring treatment for their own health (i.e. with CD4 count &gt;350 cells/mm<sup>3</sup>)</li> <li>• Low viral load, &lt;10,000 copies/ml</li> <li>• Delivery by elective caesarean section</li> <li>• With the wild-type virus</li> </ul>
2015 [86]	<p>Although the pregnancy guidelines have not yet been updated, the recommendation for cART use by all adults living with HIV means that the use of ZDVm in pregnancy is no longer appropriate</p>

In many countries, including the UK, few women used ZDVm for PMTCT in recent years [215]. This was a result of an increasing proportion of women conceiving on ART, and an increase in the use of short-course cART among women not on ART at conception who had not yet reached the CD4 threshold for starting life-long ART [151].

In many resource-limited settings single-dose nevirapine (sd-NVP) has been widely used for PMTCT due to its effectiveness, low cost and ease of administration [216, 217]. However, a combination of sd-NVP with two NRTIs such as ZDV and lamivudine (3TC) is more effective at reducing the risk of MTCT and NNRTI-resistance compared to sd-NVP alone [218, 219]. Therefore, in 2006 the WHO recommended that, where cART was not available, that ZDVm be used from 28 weeks of pregnancy until seven days after delivery, with the addition of 3TC plus sd-NVP at delivery (WHO Option A). The availability of ZDV in settings where cART was not available means that some women who required treatment for their own health or who would have been better suited to using short-course cART used ZDV instead [220, 221].

When undertaking the analysis of outcomes after use of ZDVm, the latest WHO guidelines, published in 2010, [152] recommended ZDVm as an alternative to cART for women not requiring treatment for their own health (i.e. with CD4 count  $\geq 350$  cells/mm<sup>3</sup> and no clinical symptoms, WHO stage 3 or 4). Those guidelines stated that ZDVm should be started as early as 14/40 weeks, as there is increasing evidence that starting ART earlier in the pregnancy decreases the risk of vertical transmission [148, 149]. As with the earlier guidelines, sd-NVP was recommended at delivery and with the addition of lamivudine (3TC) to ZDV from the time of delivery and for the next 7 days, although the 2010 guidelines also state that sd-NVP can be omitted if ZDV is used for at least 4 weeks before delivery. At that time, US guidelines also offered ZDVm as an option for women not requiring treatment for their own health with low viral load (<1000 copies/mL) [222]. The equivalent European treatment guidelines did not mention ZDVm as an alternative to cART for PTMCT [223].

## 2.5 Antenatal ART use

Due to the ethical and logistical constraints of undertaking clinical trials among pregnant women, observational studies and prospective reporting to the Antiretroviral Pregnancy Register (APR) [202] are used to assess the safety of antenatal ART use for the infant and mother. Prospective reporting (to the APR) of congenital birth defects in babies with first-trimester exposure to ART is used to identify ART drugs which might be teratogenic. The

congenital malformation rate is calculated once 200 first-trimester exposures have been reported. Thus it is not possible to quickly assess newer ART drugs used by few women.

When starting this research, efavirenz was not recommended for use in pregnancy or among women likely to conceive as it was associated with birth defects in one animal study [224] and a small number of case studies had reported neural tube defects following first trimester exposure [225-227]. As such, treatment guidelines recommended that women planning a pregnancy avoid using efavirenz [144]. Efavirenz together with a nucleoside backbone is now the recommended first-line ART regimen in the UK and is therefore widely used by women. There has been little further evidence to indicate that efavirenz has any teratogenic effect [228] and as such it is now recommended for use by women starting therapeutic ART in pregnancy without additional precautions [169]. At no point were women who conceived whilst on efavirenz recommended to switch to an alternative regimen for reasons of safety [172].

There are a number of other ART drugs which are not recommended for use during pregnancy due to their adverse side effects on the mother or foetus. Since 2005 the BHIVA guidelines have noted that stavudine and didanosine should not be used in pregnancy [173, 229]. The US Food and Drug Administration (FDA) issued a warning against these drugs in 2001 after a number of deaths from lactic acidosis were reported among pregnant women using these drugs in triple therapy [230-233]. These drugs are no longer in use [67].

NVP is not recommended for pregnant women with a CD4 count >250 cells/ $\mu$ l [144, 229] due to the risk of hepatotoxicity [234, 235]. Raised liver enzymes have been observed in women on NVP-containing regimens, with Grade 3-4 liver enzyme elevation (LEE) occurring in 0.5-9% [236-241] with 3-29% requiring a treatment change as a result of toxicity [236, 242, 243] (Appendix Ib: Table 5). A number of deaths among pregnant women have been reported as a result of Stevens-Johnson syndrome, a hypersensitivity reaction to NVP [237].

## 2.6 Antenatal ART use and disease progression

Studies in non-pregnant people living with HIV assessing the merits of structured ART interruption and re-initiation, based on specific CD4 thresholds, have found that ART treatment interruptions significantly increased the risk of morbidity and mortality. As such, this strategy is not recommended [244-246]. Postpartum cessation of short-course ART used during pregnancy for PMTCT could be seen as a type of treatment interruption, since women who stop ART postpartum will subsequently restart ART, either for their own health or for PMTCT in a subsequent pregnancy.

Few studies have assessed the impact of short-course ART use in pregnancy on the mother's health (Appendix 1b: Table 2). However, randomised control trials (RCTs) comparing the effectiveness of two short-course regimens used in pregnancy have generally observed low rates of disease progression following pregnancy [247, 248]. An early study which randomised HIV-positive women (with CD4 >200 cells/mm<sup>3</sup> and low viral load) to receive either ZDVm or placebo treatment in pregnancy found that CD4 count and viral load did not significantly differ between the groups at 6 months post-partum. Neither was there a significant difference in the rate of disease progression (from asymptomatic to symptomatic disease) or in the time to AIDS/death between the groups [193] indicating that the use of short-course ZDVm during pregnancy was neither beneficial nor detrimental to the women's health compared to no ART use. A number of studies have found that women who remained on treatment after pregnancy have better outcomes [249-253], lower rates of loss to follow-up [254] and better infant survival [253] than women who used short-course ART (Appendix 1b: Table 2). However, these were small observational studies and some included women in the short-course ART group with CD4 counts below 350 cells/mm<sup>3</sup> [254, 255]. As yet, there are no results from RCTs assessing the benefits remaining on ART after pregnancy in women with a high CD4 count.

## 2.7 Drug resistance among women with a pregnancy

ART drug resistance in pregnant women could increase the risk of vertical transmission [256, 257] as well as compromise the woman's future treatment options. One study linked

data from the NSHPC, the Survey of Prevalent HIV Infections Diagnosed (SOPHID) and the UK HDRD to examine the prevalence of transmitted drug resistance (TDR) in ART naïve women diagnosed with HIV in pregnancy. They found that in 2000-2013 5.2% had TDR increasing to 10.1% in 2012-2013 (when the most recent data were available) (Figure 2.1). However, only half the women in the NSHPC had a resistance test result in the UK HDRD. Factors associated with having a resistance test were having had at least one pregnancy, being diagnosed more recently (in 2010-2013 compared to earlier years), attending antenatal care in London and being born in the UK/rest of Europe compared to elsewhere [258].

Figure 2.1. TDR in women diagnosed with HIV during pregnancy in the UK

TDR by drug class	Woman's year of HIV diagnosis (n=1032)						Total	P value
	2000-03	2004-05	2006-07	2008-09	2010-2011	2012-2013		
Any resistance	3.4%	7.3%	2.4%	5.2%	5.4%	10.1%	<b>5.2%</b>	<0.01
Any NRTI resistance	1.1%	2.6%	0.8%	2.1%	2.0%	4.5%	<b>1.9%</b>	0.18
Any NNRTI resistance	1.1%	3.9%	1.3%	1.7%	4.4%	6.3%	<b>2.8%</b>	0.02
Any PI resistance	1.1%	1.7%	0.8%	1.7%	0.5%	1.8%	<b>1.2%</b>	0.65
Number of women with a RT	88	234	375	291	203	111	<b>1302</b>	

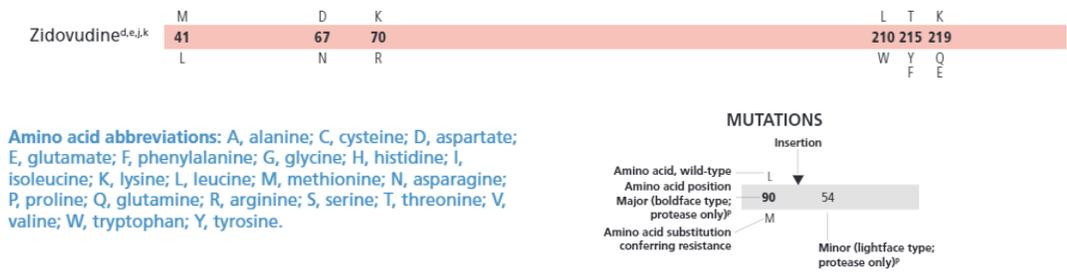
This table includes women diagnosed during their index pregnancy, classified as 'ART naïve' on the resistance test request, with a resistance test performed during pregnancy. RT: resistance test; TDR: transmitted drug resistance. Adapted from : Byrne *et al.* 2015 [258].

### ZDV resistance

Several point mutations in *pol*, the gene which codes for reverse transcriptase (RT), confer resistance to ZDV (Figure 2.2). Shortly after ZDV was first used for the treatment of AIDS and HIV infection, resistance to the drug was identified in individuals with AIDS. Four amino acid substitutions in the RT protein were initially identified as important for conferring ZDV resistance at codons 67, 70, 215 and 219 [103, 259] (Figure 2.2). Other important mutations have since been identified at codons 41 and 210 [260-262]. A single mutation at codon 70 or 215 confers some resistance, but single mutations at either codon 67 or 219 do not [263]. Development of a mutation at codon 70 alone does not have a great impact on phenotypic resistance, although it may be associated with a rise in viral

load. Development of a mutation at codon 215 then at 41 is associated with high level resistance and increased viral load. Mutation at codon 215 is the most common mutation leading to ZDV resistance and occurs prior to mutations at the other codons (although mutation at codon 70 appears first it quickly reverts to wild-type) [264].

Figure 2.2. Mutations in the RT gene associated with resistance to ZDV



Source: Johnson *et al.* 2008 [265].

Unlike resistance to NVP or 3TC which requires a single mutation, resistance to ZDV requires multiple sequential mutations. As such, the development of resistance to ZDV following short-term ZDVm for PMTCT is uncommon [193, 197, 266, 267]. However use of ZDV does not completely suppress viral replication and so there were initially concerns that used as a monotherapy it might result in ZDV resistance. Some early studies found that this was the case in 9.6% (6/62) [268], 17% (38/220) [269], 24% (34/142) [256] and 25% (4/16) [270] of women who used short-course ZDVm in pregnancy. However, in these studies many women had advanced disease and would therefore not meet clinical criteria for ZDVm use in other settings in more recent years [169, 214]. A postpartum follow-up study to an RCT of ZDVm use in pregnancy (among HIV-positive women with CD4>200 cells/ $\mu$ L and with a low viral load), found no significant difference in the proportion of women with ZDV resistance between the treatment and placebo groups [193]. Since 1998, cART has been recommended for women with advanced disease and current treatment guidelines recommend the use of ZDVm only for pregnant asymptomatic women with CD4 count >350 cells/mm<sup>3</sup> and repeated viral RNA <10,000 copies/mL [144]. A comparison of women given ZDVm in pregnancy before and after 1998 found that a higher proportion of women treated before 1998 developed genotypic resistance than women treated after 1998 (10.5% [2/19] vs. 0% [0/21] respectively, p=0.22) [267]. In a further analysis of this

cohort, no ZDV resistant minority strains were detected [266]. In studies of pregnant women with CD4 counts >200 cells/ $\mu$ l who used ZDVm, no women developed genotypic resistance [197, 266, 271] but a small proportion (2.5%; 1/39) had low-level resistance (K70R mutation) after delivery [271].

## **ART drug resistance following short-course ART in pregnancy**

The use of sd-NVP administered at labour results in NVP resistance in 15-65% of women [109, 272-274]. The HIVNET 012 study found that among drug naïve women given sd-NVP for PMTCT, 19% (21/111) developed NVP resistance [109]. Although sd-NVP is not used in pregnancy in the UK, a large proportion of HIV-positive pregnant women attending antenatal care in the UK were born elsewhere, so could have received sd-NVP as part of antenatal care received outside the UK.

Genotypic resistance to NVP has been also reported following the use of short-course NVP-containing cART in pregnancy [275, 276]. A study in Ireland found that 5/39 (13%) women given short-course NVP-containing triple ART in pregnancy had drug resistant mutations shortly after cessation of ART. Four of the five women had also been tested for resistance prior to the pregnancy and had no evidence of resistance at that time [275]. A study in the US reported resistance mutations in 4/21 (19%) pregnant women who had used NVP-based short-course cART in a previous pregnancy [276]. Although it is possible this was TDR since these women were not tested for resistance prior to their first pregnancy.

Contrary to the findings of these studies an Argentinian study of 20 women who used short-course ART in pregnancy found that when NVP was used in combination with ZDV and 3TC it did not select for resistant mutations (at 1-15 months after ART cessation) among NVP naïve women [277]. A study in Brazil of asymptomatic or mildly symptomatic women with a CD4 count  $>250$  cells/mm<sup>3</sup> who took short-course cART in pregnancy found that none of the six women who used a NVP-containing regimen developed NVP resistance mutations but 24% (4/17) of the women who had taken a nelfinavir (NFV)-containing regimen had NFV resistant mutations at 24 weeks after ART cessation [278].

## **2.8 Treatment outcomes following short-course ART in pregnancy**

A number of studies have looked at response to ART treatment following exposure to sd-NVP in pregnancy (Appendix Ib: Table 3). A Thai study found that women who used sd-NVP in pregnancy were more likely to have detectable viral load after 6 months on treatment (subsequently started) than women who used ZDVm in pregnancy [274]. In

other studies, the use of sd-NVP at delivery was not associated with CD4 response once therapy was subsequently started [274, 279]. A Zambian study published in 2010, found that in women on therapeutic ART, those with previous exposure to sd-NVP had better survival rates than women with no previous ART use.

The interval between sd-NVP exposure and treatment initiation is important; there appears to be an association between sd-NVP exposure and virological failure if the interval is <12 months but not if the interval is >12 months [279-283]. These differences are a result of the decline in the resistant strains during the 6 to 12 months after NVP exposure [109, 284] although resistant strains may persist in minority viral populations [285].

Fewer studies have examined response to treatment following antenatal use of short-course cART. A study from the US, Brazil and Peru looked at the outcomes of women starting therapeutic ART (efavirenz plus tenofovir and emtricitabine) at least 24 weeks after using cART in pregnancy. None of the factors examined were associated with virological response and only poor drug adherence was associated with viral rebound [286] (Appendix Ib: Table 4).

## 2.9 Hepatotoxicity and pregnancy

Drug-related hepatotoxicity can be defined as 'injury to the liver that is associated with impaired liver function caused by exposure to a drug' [287]. The severity of hepatotoxicity varies. Severe ART induced hepatotoxicity is rare, but it can be fatal [236, 288, 289]. Liver related conditions are now one of the most common reasons for non-AIDS related deaths among individuals living with HIV in Europe [290]. Unlike some other side-effects of using ART there are no medications which can be taken to alleviate toxicity. If it is severe then the drug regimen must be switched to an alternative regimen, something which could have implications on the woman's future treatment options and, if the woman is pregnant, on the risk of MTCT [291].

Although all ART drugs have been associated with hepatotoxicity [69, 292] the mechanisms by which they cause toxicity are not clear and vary according to drug type. NRTIs can cause mitochondrial toxicity, this is particularly the case with zalcitabine, didanosine and stavudine, which are no longer used, but less so with abacavir and

tenofovir, which are still used [293]. Although mild lactate elevation is common with these drugs, occurring in 10-40% of patients, severe liver damage is rare [294]. NNRTIs can cause a hypersensitivity reaction, a consequence of the immune system over-reacting to the presence of the drug, resulting in LEE. Around 10-15% of patients using NVP develop any LEE and 1-5% develop severe LEE [295]. The risk of NVP-induced hepatotoxicity is higher in women and at higher CD4 counts, most notably  $>250$  cells/mm<sup>3</sup> in women and  $>400$  cells/mm<sup>3</sup> in men [236]. Efavirenz can also cause liver toxicity, but it occurs less frequently than in those receiving NVP [296, 297].

Although PIs do not cause liver toxicity to the same extent as NNRTIs they can reduce the clearance of other hepatotoxic drugs. Among patients taking Kaletra (ritonavir-boosted lopinavir) rates of severe liver toxicity are around 2-10% [298-300].

There are a number of factors predictive of ART-induced hepatotoxicity. Studies have identified female gender as an independent predictor of hepatotoxicity [301-305]. A study in Uganda found that male gender predicted hepatotoxicity, but this could be due to confounders such as alcohol consumption [306]. Whereas some studies have seen older age associated with an increased risk [305, 307] a study of patients using ritonavir-boosted lopinavir found that there was a decreased risk with older age [299]. Other factors associated with hepatotoxicity include: ethnicity [308]; concurrent drug treatment, for example for TB [309] or hepatitis C (HCV) [310]; certain types of human leucocyte antigens (HLA) [311, 312]; higher baseline viral load ( $>100,000$  copies/mL) [300, 313]; a higher CD4 count [288, 314, 315]; pregnancy [316, 317]; increased duration of ART exposure [295]; and recent ART initiation [302].

Some studies have found that higher baseline levels of hepatic markers, such as alanine transaminase (ALT) and aspartate transaminase (AST), are associated with a higher risk of hepatotoxicity [305], including studies which measured hepatotoxicity based on a rise from baseline ALT [295, 299]. This is presumably because raised levels of these enzymes at baseline indicate some pre-existing hepatopathy.

The interaction between these risk factors is not fully understood and their impact on ART-induced hepatotoxicity may differ greatly according to which ART drugs are being used. There are many other factors which, in the absence of ART, can affect hepatic function (and therefore levels of liver enzymes in the blood) including pregnancy (as discussed in a

later section), alcohol consumption [313], body mass index (BMI) [313] and the use of other medicinal or recreational drugs. Hepatitis B (HBV) and hepatitis C (HCV) are important risk factors for hepatopathy among the HIV-positive population. In many cases of ART-induced hepatotoxicity the person also has additional risk factors for liver disease as well as ART use [237, 302, 303, 307, 314, 318].

HIV may itself be harmful to the liver [319], since the replication of virus in Kupffer cells and other liver cells could cause inflammation. This may explain why toxicity biomarkers can fall after ART initiation [306].

The level of ART induced hepatotoxicity varies between settings and appears higher in resource rich compared to resource limited settings [239, 241, 243, 275, 306, 320, 321]. This probably reflects the different characteristics of HIV-positive individuals in these settings including ethnicity, the prevalence of HBV/HCV co-infection, average CD4 count as well as the different types of ART drugs being used [321].

### **Measuring hepatotoxicity**

There are a number of tests used to assess the health of the liver. The least costly and least intrusive method is liver function tests (LFTs) which measure the concentration of liver enzymes in the blood serum including bilirubin, albumin, GGT ( $\gamma$ -glutamyl transferase) and transferases such as ALT and AST. ALT is an enzyme found in liver cells and is an important catalyst in the alanine cycle. Injury to the liver as a result of disease, infection or toxicity can result in the release of this protein into the blood stream, raising serum levels to above the normal range. Abnormal levels of ALT, as well as other liver enzymes are therefore used in clinical practice as clinical markers to indicate hepatopathy [305] including hepatotoxicity but are not a direct test for toxicity. Fibroscan, ultrasound scans and liver biopsy are also used to assess liver disease. These are useful tools for assessing more advanced hepatopathy but since biopsy is invasive and scans more expensive, they are not used for routine monitoring of liver function. Fibroscan, a type of ultrasound, is contraindicated during pregnancy [169].

At present there is no standard used for assessing hepatotoxicity. Most studies investigating ART-induced hepatotoxicity use the AIDS Clinical Trial Group criteria [322] which grades adverse events on a scale of 1-4, where 1 is mild and 4 is life-threatening. LEE is graded according to ALT or AST levels (Table 2.2). Some hepatotoxicity studies

consider ALT levels above a grade 3 as their cut off [288, 316, 318, 323], while others use grades 1-4 to indicate ‘any LEE’ and grades 3-4 to indicate ‘severe LEE’ [324, 325]. Increasingly, studies adapt these grades and measure an increase in ALT from baseline [305, 326]. The upper limit of normal (ULN) also varies between settings and laboratories [327], as does how the ULN is derived. Few articles state the ULN, but where the ULN is stated it is typically between 30 and 45 International Units (IU) [302, 303, 307, 318, 326]. The US National Institute of Diabetes and Digestive and Kidney Diseases suggest that the use of a common reference is reasonable, particularly when using data from multiple centres; they state 40 U/L as the default ULN for ALT [328]. A rule of thumb used in clinical drug safety tests, referred to as Hy’s law, classifies a drug as high risk for fatal drug-induced liver injury if, in the subjects being tested, it results in a 3-fold increase in ALT or AST above the ULN compared to the placebo or control drug and, among people with a 3-fold increase and no pre-existing liver disease or hepatitis A, B or C infection, some also have a 2-fold increase above the ULN in serum total bilirubin [329].

Table 2.2. Grading for severity of liver test abnormalities (ALT levels only) using multiples of the upper limit of normal (ULN), as specified by the AIDS Clinical Trials Group, and converted to ALT ranges if 40 IU/L is used for the ULN [322]

	Grade 1	Grade 2	Grade 3	Grade 4
Description	Mild	Moderate	Severe	Life threatening
Criteria	1.25-2.5 x ULN	>2.5-5.0 x ULN	>5.0-10 x ULN	>10 x ULN
ALT (IU/L) if ULN is 40 IU/L	50-100	>100-200	>200-400	>400

ULN: upper limit of normal

It is important to remember that although LEE is often used to assess ART-induced hepatotoxicity, it is a surrogate marker and there are many factors unrelated to toxicity which can also affect ALT levels including obstetric complications, auto-immune liver diseases, viral infections, alcohol induced liver disease and liver steatosis (referred to as non-alcoholic fatty liver disease [NAFLD]) [330].

## **Monitoring hepatotoxicity in people living with HIV**

People living with HIV who are on ART have regular LFTs performed as part of their clinical care. The level of monitoring depends on their risk factors, how recently they started ART and their pregnancy status and can vary somewhat between HIV clinics. BHIVA guidelines for the management of HIV-positive pregnant women [169] recommend that women commencing cART in pregnancy have LFTs as per routine initiation of cART, i.e. two weeks after initiation, and at every antenatal visit. Women have a minimum of three LFTs during pregnancy irrespective of the type of ART used. Typically, these are performed at booking (i.e. when they first present), at 20 weeks and 36 weeks gestation. Women are monitored more closely during pregnancy in part due to their risk of obstetric complications, particularly in the final trimester [169]. Women with HIV/HBV or HIV/HCV co-infection are also recommended to have a liver function test at 2 weeks after commencing cART with subsequent monitoring of ALT throughout pregnancy and postpartum [169].

## **Pregnancy and the liver**

Pregnancy can increase the risk of some liver disorders, such as hepatic vein thrombosis, and in some cases increase the risk of liver dysfunction, such as hepatitis E [331] whilst other liver disorders only occur in pregnancy. Two such life threatening examples are, HELLP syndrome (haemolysis, elevated liver enzymes, low platelets) and acute fatty liver of pregnancy. Other examples are hyperemesis gravidarum, the liver dysfunction associated with pre-eclampsia, and obstetric cholestasis. The mechanisms causing these dysfunctions are distinct and not fully understood. They are a result of immunological, metabolic and hormonal changes. Pregnancy greatly increases the risk of fulminant hepatic failure in women with hepatitis E [331], possibly due to changes in the Th1-Th2 balance or impaired cellular immunity as a result of hormonal changes [332]. In parts of Asia, African and Latin America, there can be large hepatitis E epidemics and hepatitis E contributes to a significant number of pregnancy complications [333]. However, in the UK, the incidence of hepatitis E is very low. In the last quarter of 2015, there were 218 cases of hepatitis E reported in England and Wales, less than 42 of which were in women younger than 59 years old [334]. Hyperemesis gravidarum may be an adverse reaction to the placental hormone, human chorionic gonadotropin, whilst HELLP syndrome is thought to be a result of activation of the coagulation cascade. Acute fatty liver of pregnancy is

caused by a deficiency in LCHAD (3-hydroxyacyl-CoA dehydrogenase, an enzyme used to breakdown fatty acids) by the fetus resulting in an accumulation of unmetabolised fatty acids, in the fetus and then the mother. Hormonal changes affecting bile secretion and mutations in the genes coding for bile transporter proteins are thought to cause obstetric cholestasis [335].

A 15 month prospective study of >4000 HIV-negative women in antenatal care in Wales found that 3% had some form of LEE; two-thirds of these were due to pre-eclampsia and only <2% due to drug toxicity [336].

Even in the absence of disease, some markers of hepatic function change during pregnancy. Although at least one study observed an increase in ALT levels in pregnancy [337], the general consensus is that ALT levels fall during normal pregnancy but remain within the normal range [338-340]. This fall is due to the effect of plasma volume expansion (PVE), also referred to as 'hemodilution': an increase in plasma volume during pregnancy due to the increased circulatory needs of the maternal organs and placenta. The average plasma increase is 45% but the increase varies hugely between individuals ranging from a minimal change to a doubling of plasma volume. It is not clear why there is such variation but positive predictors of PVE include parity, multiple births and pre-pregnancy maternal BMI. Plasma volume typically starts to increase at 6-10 weeks gestation, increasing rapidly in the second trimester and plateauing at around 32 weeks [341, 342]. PVE has a significant effect on biomarker concentrations including ALT, which is lower during each trimester than outside pregnancy [343]. As such, the reference range for liver enzymes during pregnancy differs from the reference range outside pregnancy (Table 2.3).

Table 2.3. Typical UK reference ranges for liver enzymes by pregnancy trimester

Liver enzyme	Not pregnant	Pregnant	Pregnancy trimester		
			1 <sup>st</sup>	2 <sup>nd</sup>	3 <sup>rd</sup>
ALT (IU/L)	0-40	-	6-32	6-32	6-32
AST (IU/L)	7-40	-	10-28	11-29	11-30
Bilirubin (µmol/L)	0-17	-	4-16	3-13	3-14
GGT (IU/L)	11-50	-	5-37	5-43	3-41
Alkaline phosphatase (IU/L)	30-130	-	32-100	43-135	133-418
Albumin (g/L)	35-46	28-37	-	-	-
Bile acids (µmol/L)	0-14	0-14	-	-	-

Source: Walker *et al.* [339], originally adapted from other sources [338, 344, 345].

Whilst other published reference ranges are similar [346], one Nigerian study provides a range for each trimester (1<sup>st</sup> trimester 3-30 IU/L; 2<sup>nd</sup> trimester 2-33 IU/L; 3<sup>rd</sup> trimester 2-25 IU/L) [347]. It is not clear how quickly ALT levels return to pre-pregnancy levels after pregnancy, and this is likely to vary according to the level of PVE and the amount of blood loss at delivery [348]. A temporary post-partum increase in ALT above normal levels has been reported [343, 346, 349]. A study of 94 women delivering at a London hospital found that ALT peaked at 5 days post-partum by 147% on average compared to pre-pregnancy levels. At 5 days post-partum, 8% of ALT results were above the non-pregnant range, and by 10 days post-partum, 1% remained above the non-pregnant range [349]. A Swedish study, which looked at concentrations of biomarkers during and after normal pregnancy, found that ALT levels at 45-202 days post-delivery were higher than at any point during pregnancy and higher than the reference range used for healthy non-pregnant women [343]. A Danish study of Caucasian women with non-complicated pregnancy measured ALT in pregnancy, at labour and at 1 and 2 days post-partum. Although ALT fell during pregnancy the average ALT was always within the non-pregnant reference range. However, at delivery and in the 2 days post-partum it increased above the ULN for non-pregnant women. Their non-pregnant ALT reference interval was 10.2-44.9 IU/L. They

suggested a reference interval for pregnancy of 8.4-35.9 IU/L, for the labour and postpartum day 1, 4.8-41.9 IU/L and for postpartum day 2, 7.8-58.1 IU/L [346].

### **ART-related hepatotoxicity in pregnancy**

The physiological and hormonal changes that occur during pregnancy affect the distribution, absorption, and metabolism of drugs [350, 351]. These pharmacokinetic changes may result in an increased susceptibility to ART-related hepatotoxicity. High rates of hepatotoxicity have been observed among pregnant women on ART, mostly women using NVP. However, the effect of pregnancy on hepatotoxicity is not clear and is likely to vary according to ART drug.

NVP-induced hepatotoxicity in pregnancy has been well documented [236, 288, 316, 317, 352, 353] (Appendix Ib: Table 5 and Table 6) with the proportion of women who develop NVP-hepatotoxicity in pregnancy ranging from 5-34% depending on the setting and how hepatotoxicity is defined [243, 354, 355]. A single or double dose of NVP given at delivery for PMTCT does not appear to cause hepatotoxicity [217, 356, 357]. Some studies comparing the risk of NVP-induced hepatotoxicity in pregnant and non-pregnant women, found that pregnant women were at increased risk [236, 316, 317, 320] (Appendix Ib: Table 7). In studies, where analyses are not adjusted [316, 320], this increase in risk may reflect the characteristics of pregnant women, for example their ethnicity or higher CD4 count when starting ART. However, pregnancy was independently associated with an increased risk of any LEE (grade 1-4) among women using NVP in multivariable analysis [317]. Other studies have either found that pregnancy is not associated with NVP-induced hepatotoxicity [358, 359] [220, 318] or have found a comparable rate in pregnant women as would be expected in non-pregnant women [237, 239, 321, 360, 361]. A systematic review of adverse events in pregnant women on NVP found that overall 3.2% [CI 2.1-4.3%] of women experienced a severe hepatotoxic event, comparable with the level in the general population. Pregnant women with a CD4 count  $>200$  cells/mm<sup>3</sup> had a higher risk than non-pregnant women (OR 1.5 [0.9-2.3]) but this did not reach statistical significance [362]. Therefore the relationship between NVP-induced hepatotoxicity and pregnancy is unclear. The relationship between pregnancy and ART-induced hepatotoxicity and factors predictive of pregnancy, such as gender, black ethnicity and higher CD4 counts, are likely to be complex.

Given recent guidelines for ART use in pregnancy [169], women starting ART in the first half of pregnancy are likely to have a lower CD4 count and be starting treatment for their own health, compared to women starting ART in the second half of pregnancy. After accounting for this, the timing of NVP initiation in pregnancy could also have an impact on the risk of hepatotoxicity. In many studies which noted hepatotoxicity among pregnant women, NVP was started late in the second trimester or in the third trimester [236, 288, 325]. In one study which found that pregnant women were less likely to experience toxicity compared to non-pregnant women (in unadjusted analysis), NVP was started in the first trimester or early in the second trimester [359]. A study of patients at HIV clinics in London found that 5% of women who started ART in pregnancy experienced LEE compared to 0% of women who were already on ART [321] (Appendix Ib: Table 8).

There are few studies which assess the risk of hepatotoxicity among pregnant women using antiretroviral drugs other than NVP (Appendix Ib: Table 6). One such study found a similar rate of LEE in pregnant women on NVP-containing regimens and pregnant women on non-NVP-containing regimens [324]. Toxicity has also been reported in pregnant women using nelfinavir (in combination with zidovudine and lamivudine) [236, 289, 316], and efavirenz (also in combination with zidovudine and lamivudine) [289] (Appendix Ib: Table 6). However, pregnancy does not appear to increase the risk of nelfinavir-related hepatotoxicity [316] or hepatotoxicity associated with the use of other ART drugs [359]. In a study of pregnant and non-pregnant women with HIV in the Netherlands, in which half the women were on a PI-based regimen, pregnancy was not independently associated with risk of hepatotoxicity (grade 3 LEE) [318].

Some studies investigating hepatotoxicity among patients starting therapy only include treatment-naive patients [243]. Temporary exposure to ART in pregnancy for PMTCT may affect the risk of hepatotoxicity once ART is subsequently started for the woman's own health. There is limited evidence from studies which include both ART naive and ART-experienced individuals that previous ART exposure is protective against hepatotoxicity when ART is started [302].

## 2.10 Postpartum viral rebound

### **The impact of ART on HIV viral load and viral replication**

HIV-1 RNA levels in the blood fall rapidly following ART initiation. It takes around 12 weeks for levels to fall below 50 copies/mL [363, 364]. They continue to fall for several months reaching a plateau (constant phase) of around 3-10 copies/ml in the majority of individuals [363-368], a level which is only detectable using RT-PCR assays. A viral load of <50 copies/ml can be categorised as 'undetectable' since RNA 40/50 copies/ml is typically the lower limit of detection for standard viral load assays, although some more sensitive tests can test below 20 copies/ml. Viral replication can be suppressed for many years, but even the most effective antiretroviral drugs cannot eradicate the virus from the body. The mechanisms through which the body maintains this residual viraemia are not fully understood, but may be due to the presence of cellular reservoirs and/or residual ongoing viral replication [369, 370]. The consequence of this residual viraemia is that when ART is stopped, or the patient is unable to maintain high levels of adherence, the viral load swiftly returns to detectable levels. Viral rebound is associated with higher viral load at treatment initiation, poor drug adherence, the use of certain ART drugs and previous treatment interruptions [371-373]. A study using the UK Collaborative HIV Cohort (UK CHIC) data found that in people who previously interrupted treatment those who had interrupted with a detectable viral load were at greater risk of viral rebound when they subsequently started ART than those who interrupted with an undetectable viral load [371].

### **Viral rebound and viral blip definitions**

Viral rebound is an increase in HIV RNA above a specific threshold, following a period of viral suppression. Different studies have used different approaches to measure changes in viral load after pregnancy. Whilst some studies have measured the change in median viral load from baseline (either before pregnancy or at delivery), others have defined viral rebound as either HIV-RNA >400 copies/ml [374], a >0.5 log<sub>10</sub> increase in viral RNA from baseline [375], or ≥0.7 log<sub>10</sub> (5-fold) increase from baseline, or if viral load was undetectable in pregnancy, then an increase to >500 copies/mL postpartum [376]. In Chapter 6 and Chapter 8, viral rebound is defined as a single measure of HIV-RNA >200

copies/ml and in Chapter 8, which examines viral rebound in post-pregnant women and controls, it is also defined as a single measure >1000 copies/ml in the sensitivity analysis.

A viral blip is a transient increase in viral load to around 50-1000 copies/ml. Viral blips are thought to occur in 20-60% of people on ART including when people are fully adherent to their ART regimen. It is unclear whether they are caused by changes in the immune system, for example due to illness, or temporary fluctuations in ART concentrations. The BHIVA treatment guidelines suggest that a single viral load of 50-200 copies/ml is not a cause for concern but a viral load above 200 copies/ml or repeated blips should be investigated further [77].

### **Viral rebound following cessation of ART**

Viral rebound is almost inevitable when therapeutic ART is interrupted [377]. Studies measuring viral load after ART cessation have observed an overshoot in viral load, which peaked within the first 3 weeks after discontinuation [378, 379]. The overshoot may be due to a temporary increase in target cells (CD4 cells) as a result of the treatment and could be similar to the viraemia observed during initial HIV infection [380].

As is the case outside the context of pregnancy, viral rebound is generally observed following cessation of short-course ART after pregnancy [132, 193, 197, 381, 382] (Appendix: Table 9, Page 337) although not always [383]. Where this was observed some years after pregnancy [384] it is likely a consequence of disease progression which would have occurred irrespective of the pregnancy. Increases in viral load shortly after pregnancy have also been observed among women who did not use ART in pregnancy [132, 193, 197, 385] (in the pre-HAART era) and in women who remained on either ZDVm [132, 382, 385] or on cART [374, 376, 381, 382, 385] (Appendix Ib: Table 10) including in women who achieved viral suppression in pregnancy. Viral rebound (measured at anywhere between 6 and 24 weeks after delivery) occurs in around 48%-85% [374, 375, 381] of women using short-course cART in pregnancy and around 15%-29% [375, 376, 381] of women remaining on cART after delivery. This suggests that changes occurring after pregnancy or at delivery can also cause or influence postpartum viral rebound. A temporary increase in HIV has also been observed in breast milk following cessation of ZDV used for PMTCT [386].

A number of immunological changes are known to occur in the postpartum period - there are changes in inflammatory and coagulation biomarkers, including D-dimer [387], and an increase in CD4 T-cells and  $\beta$ 2-microglobulin, irrespective of ART use or HIV-infection [385]. Physiological changes also occur such as the disappearance of PVE and raised levels of oestrogen and progesterone. Some studies have found that drug adherence deteriorates after pregnancy [376, 388, 389]. Treatment interruptions and changes to medication are also more likely to occur in the postpartum period than at other times [376]. The extent to which each of these factors affects the risk of postpartum viral rebound is not clear.

## 2.11 Role of the researcher

I came to the PhD from a background in HIV surveillance and epidemiology, having previously worked on a number of regional and national surveillance systems at the Health Protection Agency and on secondment to the Centre for Epidemiological Studies in HIV/AIDS and STIs in Catalonia. During my PhD, I was based at the Royal Free Hospital within UCL's HIV Epidemiology and Biostatistics Group. This group is part of the Research Department of Infection and Population Health within the Institute of Epidemiology and Health Care. I was linked to the UCL Institute of Child Health, where the NSHPC is coordinated and where Dr Claire Thorne, my secondary supervisor, is based.

The areas of research were loosely defined in an initial funding application for the project, made by Professor Caroline Sabin and Dr Claire Thorne. On starting the PhD, I undertook a literature search and, following this, developed the research questions responding to the gaps in knowledge.

The collaboration between NSHPC and UK CHIC allowed the study of areas which could not be addressed using either dataset independently. From the start of the collaboration, it was mutually agreed that the combined dataset would only be used for research which could not be undertaken using either dataset independently. For example, there is evidence that ART use in pregnancy is associated with an increased risk of pre-term delivery. This is a question which could be (and has been) investigated using the NSHPC dataset, so was not looked at as part of this PhD. Other clinical complications of pregnancy, such as antepartum haemorrhage, intrauterine infections and hypertension

disorders of pregnancy, could also be investigated using only the NSHPC dataset and use of the combined dataset would not provide any additional benefit. Hepatotoxicity is one potential side-effect of ART use for which there were some data available and the analysis could only be performed using the linked dataset, since the ALT data came only from UK CHIC, and the obstetric data from the NSHPC.

The initial matching strategy was devised by Professor Caroline Sabin, Dr Claire Thorne and Dr Loveleen Bansal-Matharu in 2009. It was my role to improve and develop the strategy, as well as document the matching process and assess its completeness. From 2010 onwards I repeated the matching annually using the most up-to-date datasets available. This process involved liaison with colleagues at ICH and the Royal Free Hospital, cleaning and preparing the separate datasets in preparation for the linkage and running the linkage. Once the combined dataset was complete, I created a number of new variables required for the analyses. I also produced a condensed database for researchers and clinicians analysing the UK CHIC data who wanted to exclude pregnant women or women with a previous pregnancy. I designed and conducted all analyses outlined in this thesis with advice from Professor Caroline Sabin. I have presented parts of the work at national and international conferences as well as producing peer reviewed papers (Appendix IIa-e).

## 2.12 Research objectives

Globally the use of ART in pregnancy is vital for minimising the risk of MTCT as well as improving the health of women living with HIV. In the UK, ART is used by the vast majority of the HIV-positive women who are pregnant. Until recently, there have been a considerable number of women who use short-course ART during pregnancy for the PMTCT, although increasingly ART was being used throughout pregnancy as many women were already on life-long ART when they conceived. The consequences for the woman of ART use during and after pregnancy and when she subsequently starts life-long ART for her own health are not fully understood. This research focuses on the associations between ART use in pregnancy and the health of the women during and after pregnancy.

The main research objectives were to:

1. Create a dataset containing detailed clinical data for HIV-positive women which included antenatal data for women with a pregnancy.
2. Describe ART use in pregnancy among HIV-positive women.
3. Estimate the incidence of pregnancy among HIV diagnosed women attending HIV-clinical care and identify predictors of pregnancy among this group.
4. Compare the response to treatment once started for the woman's health in women who previously used short-course ZDVm or short-course combination therapy in pregnancy and compare these with the response to treatment in women with no previous ART use.
5. Investigate whether pregnancy is associated with liver enzyme elevation (LEE) in women using ART in pregnancy.
6. Assess whether, in women on ART, the risk of viral rebound is higher during the postnatal period than at other times outside pregnancy.

## 2.13 Ethical and research governance

All the studies used for the analyses in this thesis have ethics approval from the London Multi-Centre Research Ethics Committee. The references are as follows:

- NSHPC: Data protection registration number Z6364106 Section 19.  
London MREC ref: MREC/04/2/009.  
Reviewed 28 January 2004, and approved. Amendment (1), Perinatal HIV Audit 2002-2005, reviewed 2 February 2006, and approved. Amendment (2), Perinatal HIV Audit Protocol reviewed 8 November 2012, and approved.
- UK CHIC: MREC/00/7/47.
- UK HIV drug resistance database (HDRD) (described in the methods section of Chapter 6): MREC/01/2/1.

Where data are collected which support the “treatment or prevention” of sexually transmitted disease, individual patient consent for data collection and retention is not required under the exemption specified in the Department of Health's STD Regulations

2000 [390]. The Department of Health have confirmed that the NSHPC, and similar studies, such as UK CHIC, come under this remit<sup>11</sup>.

## 2.14 Data security and integrity

The NSHPC and UK CHIC do not collect unique identifiers, such as National Insurance Number, but they do collect some patient identifiers such as date of birth, sex, ethnicity and soundex. To maintain patient confidentiality, it is crucial that all data are stored securely. Forms containing patient data which are sent to the NSHPC are stored in locked cupboards at the ICH. Access to these cupboards is limited to UCL students and staff working on the study. Where possible all electronic data are stored as password protected files or databases on secure drives where access is limited to UCL students or staff working on the study. I was sent only the NSHPC data needed for the linkage and analyses. The files were transferred to me via a secure document gateway. Files can only be downloaded from the gateway using an encryption key (a password) which was sent to me via an encrypted email. To enhance security, the encryption key was only valid for one day.

The NSHPC data are archived quarterly and the UK CHIC data are archived annually. I stored only one copy of the linked dataset as a SAS file on a secure network drive. No backup was needed as the SAS code used to create the dataset was saved as a separate file, so a replica linked dataset could be created if required. Linked datasets from previous years were kept in case analyses needed rerunning or something needed to be checked.

When analysing data in SAS, temporary subsets of the data are created. These are deleted when the file is closed but can be recreated using the code file. This means that data integrity is preserved since the data in the original file is not easily altered.

When visiting King's and North Middlesex hospitals, I was not given access to patient records. The clinician or research nurse working at the clinics looked through patient's electronic notes to try to find out why they had been included in the clinics' list of people

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<sup>11</sup> Further information on the NSHPC ethics approval is available on the NSHPC website, [www.ucl.ac.uk/nshpc/ethics](http://www.ucl.ac.uk/nshpc/ethics) (Accessed May 2015).

seen for antenatal care, but not included in the linked dataset or in the UK CHIC dataset. The lists provided by the sites for the assessment of the linkage were anonymised and were a subset of the data normally sent to UK CHIC.

# Chapter 3 Developing a strategy for record linkage between UK CHIC and the NSHPC

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## 3.1 Introduction

The UK and Ireland's National Study of HIV in Pregnancy and Childhood (NSHPC) collects data on HIV-positive pregnant women. The data collected refer to the perinatal period only and it is therefore not possible, using only this data, to assess women's health after pregnancy or to compare the clinical outcomes of pregnant and non-pregnant women. An additional limitation of using the NSHPC data in isolation is that it collects few clinical data during pregnancy, namely the first and last CD4 counts and viral loads. No data are collected on co-infections, toxicity, or comorbidity and it is therefore of limited use when investigating the health of women in pregnancy. In contrast, the UK Collaborative HIV Cohort (UK CHIC) study, also referred to simply as 'UK CHIC', collates extensive clinical and laboratory data collated from patients' medical records. However, the UK CHIC dataset cannot be used in isolation to assess the health of women during or after pregnancy because no obstetric data are collected. It is therefore not possible to tell whether a woman has previously had a pregnancy, whether she has used short-course antiretroviral therapy ART in pregnancy or whether clinical tests such as viral loads and CD4 counts were performed during pregnancy.

Collaboration was established between the NSHPC and UK CHIC in order to assess the health of HIV-positive women during and after pregnancy. This required finding and linking individual patient records from both datasets for women who attended HIV clinical care at a UK CHIC site and who had a pregnancy. There was no unique identifier (such as national insurance (NI) number or NHS number) which could be used to find records for the same woman reported to both studies since UK CHIC, and until recently, the NSHPC, collect only pseudonymised data. Therefore, a strategy was developed to find records for the same woman in both datasets using a combination of demographic and clinical variables. This strategy (referred to as 'matching') was initially developed in 2009 by Dr Claire Thorne and Dr Loveleen Bansil-Matharu. As part of this PhD, I developed the

matching strategy, assessed its completeness and representativeness and created new variables using data from both datasets. This chapter also describes the two studies, outlines their data collection methods, and summarises the variables in each dataset. From 2010 onwards, I repeated the matching annually using the most up-to-date datasets available. The number of records matched at each stage of the matching process is presented in Appendix V . The datasets created were used for all analyses in this thesis and a condensed version of that dataset was used by researchers and clinicians analysing the UK CHIC data.

A paper summarising the matching strategy was published in 2012 (Appendix IIa) [391].

## 3.2 The UK CHIC study

The UK CHIC study is an ongoing observational study collating HIV-related clinical data on adults and adolescents aged 16 years and older accessing HIV clinical care in the UK (Table 3.1). The study began in 2001 and includes data from 1996 onwards where available [392]. Details of the UK CHIC steering committee and collaborating sites are included in Appendix VII. The number of sites providing data has increased over time, to 19 in the latest dataset used in this research. New sites entering the cohort provide data from 2000 or 1996 onwards depending on whether the older data were stored in an electronic format. The analyses in this thesis concentrate on data from 2000 onwards when combination antiretroviral therapy (cART) and the use of short-course ART in pregnancy were well established.

Extensive clinical data, recorded as part of a patient's medical record, are collated annually. Each November a request is made for all data up to 31<sup>st</sup> December of that year to be submitted by the following January. There is a delay of approximately 9-12 months from the end of the calendar year to the completion of that years dataset. This is due to the complexity of collating data from all the collaborating sites and the subsequent data cleaning and deduplication of records required.

The data fields collated include demographic and clinical data such as: the Soundex code<sup>12</sup> (a four digit code which is the first letter of the surname followed by a three number

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<sup>12</sup> The NSHPC website provides a Soundex calculator for reporting sites to use [www.ucl.ac.uk/nshpc/reporting/soundex](http://www.ucl.ac.uk/nshpc/reporting/soundex) these can also be found elsewhere online.

code derived from the surname); first name initial; date of birth (DOB); country of birth (COB); gender; ethnicity; probable route of HIV infection; date of first HIV-diagnosis; all CD4 cell counts and dates; all CD8 cell counts and dates; all HIV-RNA (viral load) assessments and dates; ART drugs prescribed and the dates of starting and stopping ART; AIDS events; hepatitis test results and dates; and liver function test (LFT) results and dates. UK CHIC does not collect obstetric data or pregnancy status. The UK CHIC data collection form contains the full list of fields collated. The form used for data to 31<sup>st</sup> December 2012 is included in Appendix IV . Each year the updated form, specifying the required data formats and coding, is circulated to participating centres. Sites then upload an electronic version of their data, which has been collected as part of the patient's clinical care record, to a secure website. HIV-positive adults of 16 years and older attending HIV clinical care at any time since 1996 are included. The datasets are named chronologically; the dataset containing data to 31<sup>st</sup> December 2010 (i.e. data requested in November 2010) is called 'UK CHIC 2010'. In some cases, clinics provide data up to the date they submit and beyond the deadline for submission. These are included in the dataset but not in the analysis.

Data received from each centre are checked for accuracy and discrepancies by the UK CHIC data manager (Dr Teresa Hill). The reporting site is asked to correct any errors identified before their data are incorporated into the final UK CHIC dataset.

Each individual reported to UK CHIC has one record in the UK CHIC dataset. When a new patient enters the cohort they are added to the dataset. If a patient attends multiple sites during the same or different years their data are combined into a single UK CHIC record in a process referred to as de-duplication. A computerised algorithm uses clinical and demographic data including Soundex and DOB to categorise pairs of records as a definite match, definite non-match or indeterminate match. Indeterminate matches are then manually checked by two independent investigators. A third investigator then manually checks records where consensus was not found. If it is unclear whether the records refer to the same individual they are left as separate records in the final dataset (typically ~100 records). These records often contain very little clinical data, hence why it is difficult to determine whether or not they refer to the same individual.

After de-duplication the clinic ID, patient's initial and Soundex are removed from the dataset but remain on an archived dataset stored at the Medical Research Council (MRC)

Clinical Trials Unit (CTU). Each individual in the dataset is assigned a unique UK CHIC identifying number, referred to as the *Patnum*. Each year de-duplication is repeated for all records. If individuals were seen at multiple sites they are given a *DupPatnum*. The same method is used each year to de-duplicate records. However, an individual identified as a non-duplicate in one year might be identified as a duplicate in another year depending on the data reported for them. This means that their *Patnum* may not be consistent across years.

Table 3.1. HIV clinical sites participating in UK CHIC and the number of women attending care at each site (n=12,970)

Name of hospital, site or NHS trust <sup>1</sup>	UK CHIC site code	Year of entry into study	Women in UK CHIC (% of total female sample)
Brighton and Sussex University Hospitals NHS Trust	101	2001	374 3%
St. Mary's Hospital, Imperial College Healthcare NHS Trust, London	102	2001	1189 9%
Chelsea & Westminster Healthcare NHS Trust, London	103	2001	1151 9%
Mortimer Market Centre, London	104	2001	1159 9%
Kings College Hospital NHS Foundation Trust, London	105	2001	1478 11%
Royal Free NHS Trust and Royal Free University College Medical School, London	106	2001	1112 9%
Barts and The London NHS Trust, London	107	2004	985 8%
The Lothian University Hospitals NHS Trust, Edinburgh	108	2005	374 3%
North Middlesex University Hospital NHS Trust	109	2005	847 7%
Homerton University Hospital NHS Trust, London	110	2005	689 5%
North Bristol NHS Trust	111	2006	425 3%
University Hospitals of Leicester NHS Trust	112	2008	707 6%
South Tees Hospitals NHS Foundation Trust	113	2009	203 2%
South London Healthcare NHS Trust, Woolwich	114	2010	826 6%
St. George's Healthcare NHS Trust, London	115	2010	799 6%
York Teaching Hospitals NHS Foundation Trust	116	2011	77 1%
Coventry & Warwickshire NHS Trust	117	2012	104 1%
Ashford & St. Peter's Hospitals NHS Foundation Trust	118	2012	257 2%
The Royal Wolverhampton NHS Trust	119	2012	214 2%

<sup>1</sup> This refers to the first UK CHIC site at which the woman attended HIV clinical care according to the UK CHIC 2012 dataset

After the creation of the new dataset, additional fields are derived from the reported data. These include the first and last date an individual attended care and the dates when ART drugs were either started or stopped with variables indicating how many drugs were prescribed on each of the dates. ART data are cleaned, removing errors, for example where a new regimen is started and a previous regimen overlaps with this period. Data on deaths are updated from data received from Public Health England (PHE) and the Office for National Statistics (ONS) and the dataset is linked to the latest UK HIV drug resistance database (HDRD)<sup>13</sup>. Much of this data cleaning is undertaken by Sophie Jose, the UK CHIC statistician.

Each year, for the analyses included in this thesis, an extract of the UK CHIC dataset was created containing only records for women. Women typically represent just over one-quarter (28% in recent years) of the individuals reported to the study.

Each year the new dataset is archived as a SAS file. All statistical analyses are undertaken in SAS (SAS Institute, Cary, North Carolina, USA) with the most up-to-date version of the software available being used throughout.

UK CHIC is part of numerous research collaborations. As well as linkage with the UK HIV drug resistance database (HDRD) and with the National Study of HIV in Pregnancy and Childhood (NSHPC) described in this thesis, it is also linked to the Collaborative HIV Paediatric study (CHIPS)<sup>14</sup> a longitudinal study of children in the UK and Ireland, to provide longitudinal data in adolescents transitioning from paediatric to adult care. UK CHIC provides follow-up data to the UK Register of HIV Seroconverters<sup>15</sup>, a national cohort of patients with a known date of HIV seroconversion, and provides an independent dataset used to validate findings from the ART Cohort Collaboration (ARTCC)<sup>16</sup>. UK CHIC has also been part of a large collaborative study of 33 HIV cohorts in Europe, The Collaboration of Observational HIV Epidemiological Research Europe (COHERE)<sup>17</sup>, and has collaborated with the Canadian HIV Observational Cohort (CANOC)<sup>18</sup>. More recently UK CHIC has been linked with the Pharmacokinetic and clinical observations in people

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<sup>13</sup> Further details on the UK CHIC study are available at [www.ukchic.org.uk](http://www.ukchic.org.uk)

<sup>14</sup> [www.chipscohort.ac.uk](http://www.chipscohort.ac.uk)

<sup>15</sup> The UK Register of HIV Seroconverters is part of the Concerted Action on SeroConversion to AIDS and Death in Europe (CASCADE) collaboration [www.cascade-collaboration.org](http://www.cascade-collaboration.org)

<sup>16</sup> [www.art-cohort-collaboration.org](http://www.art-cohort-collaboration.org)

<sup>17</sup> [www.cphiv.dk/COHERE\\_org](http://www.cphiv.dk/COHERE_org)

<sup>18</sup> [www.canoc.ca](http://www.canoc.ca)

over fifty (POPPY)<sup>19</sup> study, an observational study examining clinical outcomes and co-morbidities in older adults living with HIV, and to the UK CHIC Bio-resource, a consented HIV sub-study of the National NIHR BioResource<sup>20</sup>. These collaborations allow the comparison of outcomes across different settings and provide sufficiently large numbers to analyse rare outcomes for which there would be insufficient data from any single cohort.

### 3.3 The NSHPC

In the UK, antenatal data on HIV-positive women are collected as part of the NSHPC, overseen at the UCL Institute of Child Health. The NSHPC has ongoing obstetric and paediatric reporting schemes which run in parallel. The study aims to collate data on all HIV-positive women with a pregnancy, all infants born to HIV-positive mothers and all children living with HIV in the UK and Ireland. In this thesis only data from the obstetric scheme is used and therefore only that part of the study is described in detail.<sup>21</sup> Details of the NSHPC steering committee and funders are included in Appendix VIII.

The obstetric scheme was started in 1989 and is administered under the auspices of the Royal College of Obstetricians and Gynaecologists. All maternity units in the UK (currently 228) report pseudonymised data through active quarterly reporting. A named respondent at each site, typically a specialist midwife, is asked to return a reporting card every quarter indicating the number of cases seen during that quarter, including a null form if no cases were seen. Cases include all pregnancies in HIV-positive women irrespective of pregnancy outcome (including termination or miscarriage) and irrespective of when HIV was diagnosed (before or during the pregnancy). A standardised notification form (now mauve in colour) is completed for each reported pregnancy (Appendix IIIa). For pregnancies expected to reach full term, an outcome form (now yellow in colour) is sent for completion at the time of the expected date of delivery (EDD) (Appendix IIIb). The data collected in these forms has changed somewhat over time to reflect changes in the management of pregnancies among women living with HIV and to address new research questions resulting from these changes. The forms included in the appendix were the current forms

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<sup>19</sup> <https://clinicaltrials.gov/ct2/show/NCT01737047>

<sup>20</sup> <https://bioresource.nihr.ac.uk/>

<sup>21</sup> Further details on the NSHPC are available at [www.ucl.ac.uk/nshpc](http://www.ucl.ac.uk/nshpc)

when the matching strategy was developed and the data collected are presented in Table 3.2 and Table 3.3.

On receipt of a form, the information is entered into the NSHPC database, managed in Microsoft Access (Microsoft Corp., Redmond, Washington, USA). A new pregnancy report is linked to any previous reports for the same woman with matching of women based on DOB and other information such as COB and date of HIV diagnosis. Paediatric reports pertaining to the woman's children, including the child's HIV infection status, are also linked to the record. Increasingly, women with a pregnancy reported to NSHPC are linked to their own paediatric report if they themselves acquired HIV vertically as an infant. The site providing antenatal care and the site of delivery, which were often, but not always, the same site, were both recorded and may differ from the site at which the woman received ongoing HIV clinical care. Non-response from maternity units was followed up to ensure a high reporting rate. The NSHPC dataset is archived each calendar quarter using R (R Development Core Team). It is then imported into STATA (Stata Corporation, College Station, Texas, USA) and routine checks carried out.

An extract of the NSHPC dataset was provided on request for the purpose of matching with the UK CHIC dataset. These were sent as password protected Excel files (Microsoft Corp., Redmond, Washington, USA) via a secure document gateway. Only variables used for the matching and variables used in the analyses in this thesis were included in the extracted dataset.

Table 3.2. Data collected on the 2008/2009 NSHPC notification form

Demographic	<p>DOB</p> <p>Hospital number (or other reference)</p> <p>Soundex</p> <p>Postcode (minus last letter)</p> <p>Ethnic origin</p> <p>Country of birth (COB)</p> <p>Date of arrival if COB is not UK/Ireland</p>
Pregnancy history	<p>Previous live births</p> <p>Previous stillbirths</p> <p>Miscarriages/terminations</p>
HIV history	<p>Exposure group</p> <p>HIV infection probably acquired in the UK/abroad</p> <p>Date of HIV diagnosis</p> <p>Diagnosis in relation to the pregnancy (before/during)</p> <p>Seroconversion during the pregnancy (yes/no/NK)</p> <p>Setting of HIV diagnosis (GUM/antenatal/other)</p>
Pregnancy	<p>Booking date and expected date of delivery (EDD)</p> <p>Pregnancy outcome (continuing to term/miscarriage/termination)</p> <p>Dates of pregnancy outcome</p> <p>If continuing to term: planned mode of delivery</p>
ART use	<p>Was ART used when the woman became pregnant?</p> <p>Was ART used during the pregnancy?</p> <p>ART drugs used in pregnancy (name, start &amp; stop dates, use before pregnancy)</p>
Maternal health	<p>Status during the pregnancy (CDC stage C disease/ asymptomatic/ symptomatic not stage C)</p> <p>Concurrent infection (none/HBV/HCV/syphilis/other)</p> <p>First viral load during pregnancy (and date)</p> <p>First CD4 cell count during pregnancy (and date)</p>

COB: country of birth; DOB: date of birth; GUM: genitourinary medicine clinic; HBV: hepatitis B virus; HCV: hepatitis C virus; NK: not known.

Table 3.3. Data collected on the 2008/2009 NSHPC outcome form

Demographic	Postcode at delivery (minus last letter) Hospital of delivery and paediatrician
Pregnancy	Pregnancy outcome (live/stillbirth) EDD Date of delivery Gestation at delivery (weeks)
Infant	Gender Twin (yes/no) Birth weight (kg) Hospital number NHS number
Delivery	Mode of delivery (ECS /emergency CS/planned VD/unplanned VD, reason) Planned mode of delivery (VD/ECS/NK) Instrumental delivery (yes/no) Rupture of membranes and duration Complications in pregnancy (no/yes and details) Congenital abnormalities (no/yes and details)
ART use in pregnancy	Ante-partum treatment (no/yes) Reason for ART (PMTCT only/maternal health and PMTCT) Details of all ART drugs used in pregnancy (including start/stop dates) Details of other drugs used in pregnancy (including start/stop dates) Intra-partum treatment (none/IV ZDV/sd NVP/other oral antiretrovirals)
Maternal health	Status at delivery (CDC stage C/asymptomatic/symptomatic not stage C/date of death) Viral load (and date) near delivery (just before delivery if possible) CD4 cell count (and date) near delivery (just before delivery if possible) Resistance testing done this pregnancy (yes/no/NK/clade of virus)

CS: caesarean section; ECS: elective caesarean section; EDD: expected date of delivery; IV ZDV: intravenous zidovudine; HBV: hepatitis B virus; HCV: hepatitis C virus; PMTCT: prevention of mother-to-child transmission; sd NVP: single-dose nevirapine; VD: vaginal delivery.

## 3.4 Finding women reported to UK CHIC and the NSHPC

### 3.4.1 The basic matching strategy

The process of finding records for women reported to both NSHPC and UK CHIC is referred to here as 'matching'. Initial attempts were made to match the datasets using demographic variables only (DOB, COB, and ethnicity). Although it is difficult to determine the level of false matching, the level was thought unacceptably high as 10% (156/1575) of the women that were matched were matched with more than one record from the other dataset. In an attempt to maximise the number of true matches and minimise the number of false matches, a strategy was devised using deterministic decision criteria based on a combination of demographic and clinical fields. The strategy, developed in 2009, is described below and outlined in Figure 3.1.

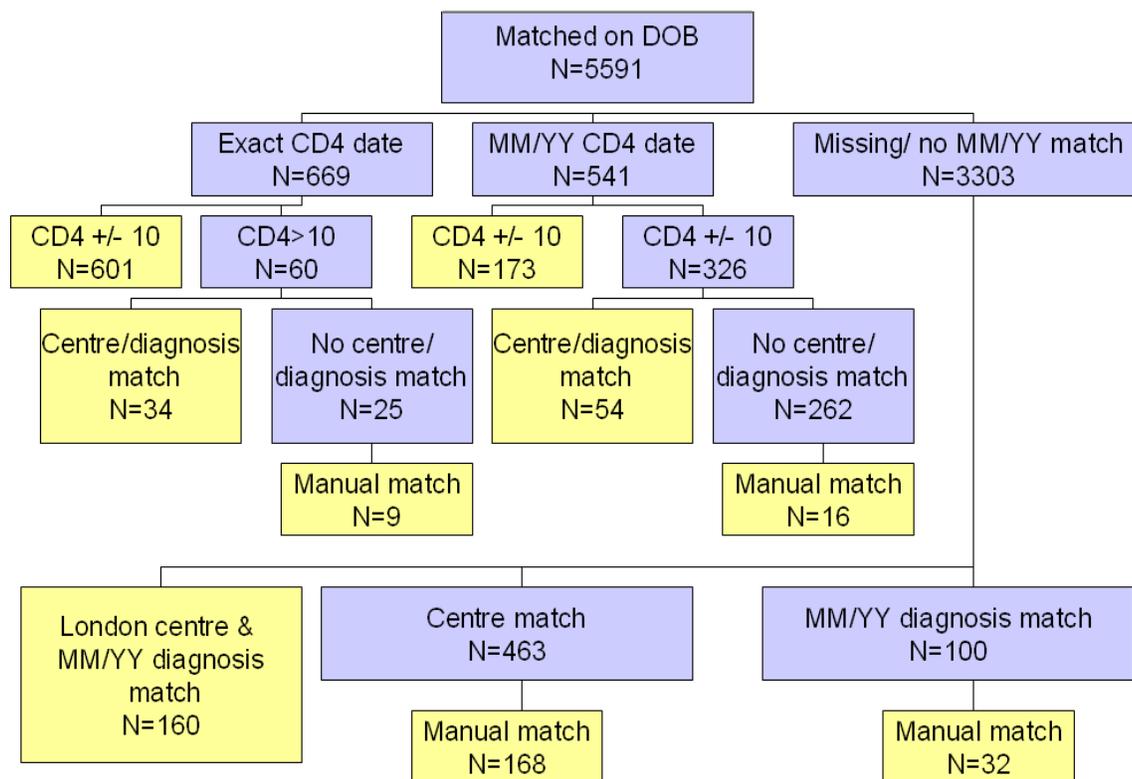
1. Initially, records in UK CHIC were paired with records in NSHPC if they had the same DOB. This created a temporary dataset, referred to as the 'linked dataset', containing pairs of records which were potential matches (i.e. the NSHPC and UK CHIC records for the same woman). Each woman's UK CHIC record could appear multiple times in the linked dataset if her DOB was the same as multiple women in NSHPC and vice versa. A series of criteria, based on demographic and clinical variables (described in points 2-5), were then used in turn to assess whether the linked records were a genuine match (i.e. referred to the same woman). If a woman was part of multiple pairings which met the criteria for being a match, the pairings were manually reviewed to assess which appeared genuine. In some cases this appeared to be a result of incomplete deduplication which was reported to the appropriate data manager. As pairs were confirmed as a genuine match, they were moved from the linked dataset to the matched dataset and subsequently removed from the linked dataset so they were no longer eligible to be a genuine match with another record. Records remaining in the linked dataset, which had not yet been confirmed as a genuine match, were then assessed according to the next criteria.
2. The first criterion used to assess whether paired records were a match was the date of CD4 cell counts where the CD4 counts were  $\leq 10$  cells/mm<sup>3</sup> different (on that date).

Further, if the date of the CD4 cell counts in both records were the same but the CD4 counts were  $>10$  cells/mm<sup>3</sup> different, the pair was considered to be a genuine match if the NSHPC and UK CHIC records came from the same site (i.e. the woman had delivered and had ever received HIV clinical care at the same site) or the date of HIV-diagnosis was the same in the NSHPC and UK CHIC.

Remaining records which had an exact CD4 date match but were not matched using this criterion were then manually reviewed, to determine if matching was possible based on further CD4 dates or viral load dates, COB etc.

3. The second criterion used to assess records remaining in the linked dataset (without a matching CD4 date) was month and year of CD4 count. As with the first criterion, records were thought to be a genuine match if the NSHPC and UK CHIC records had a CD4 count  $\leq 10$  cells/mm<sup>3</sup> different (on that date), were reported from the same site or had the same HIV-diagnosis date. Records not matched using these criteria but which had identical month and year of CD4 count were manually reviewed.
4. Any records remaining in the linked dataset were matched if they had the same month and year of HIV-diagnosis and were seen at a London site in both UK CHIC and NSHPC.
5. Finally, records remaining in the linked dataset with either a matching site or month and year of HIV-diagnosis (but not seen at a London site) were manually reviewed using other fields to assess whether any were genuine matches.

Figure 3.1. Diagram showing matching of UK CHIC with NSHPC



Source: Bansi *et al.* Abstract P56. BHIVA Conference, Liverpool, 2009 [393], with permission.

### 3.4.2 Datasets used for developing the matching strategy

The matching strategy was developed using the UK CHIC 2009 dataset (Figure 3.2). It contained records for 8286 women, aged 16-49, who attended HIV-related care at any point in the period 1996-2009.

A restricted NSHPC dataset, containing data until 31<sup>st</sup> December 2010 was used. This contained records for 8932 women with a total of 11,771 pregnancies conceived after 1995 and reported by 31<sup>st</sup> December 2010. Women diagnosed with HIV after their only reported pregnancy were excluded as were women who only attended care in Ireland (since none of the UK CHIC sites were located in Ireland). In this dataset, the highest number of pregnancies reported per woman was six (after HIV-diagnosis or where HIV was diagnosed during the first reported pregnancy).

In order to minimise any reporting delay, the most recent datasets were used. This meant that the NSHPC dataset, which is updated as and when reports are received and archived quarterly, contained data until up to one year after the UK CHIC data, which is collated annually with a 12-18 month delay before the dataset is finalised. Only data to the end of the UK CHIC period were analysed.

### 3.4.3 Developments to the matching strategy

The following additional variables were considered in the development of the matching strategy.

CD4 count/ HIV viral load:

In the initial matching strategy, only the earliest viral load and CD4 count in pregnancy were considered. This was changed to include the latest CD4 count and viral load date and measurement in pregnancy. Although these fields were not reported for all women, their inclusion increased the likelihood that women could be matched based on exact CD4 date and CD4 count  $\pm 10$  cells/mm<sup>3</sup>.

Soundex:

Soundex was not considered in the basic matching. It is a non-unique code derived from the patient's surname and can change over time, if, for example, the woman marries and changes her surname. Soundex is provided for the majority of UK CHIC records. The NSHPC has requested Soundex on the reporting forms since 2008 and the reporting of Soundex has increased over time. However, in the NSHPC dataset used here, only 3.4% (n=306) of women had Soundex reported.

Clinic/site:

In the initial matching strategy, only site of delivery was considered. This was changed to also consider the site of notification, as in some cases no site of delivery was reported or the site of notification and delivery differed.

Approximate dates:

In the initial matching strategy, month/year was used for the CD4 count and HIV diagnosis date comparisons. This was compared with using  $\pm 30$  days, since two dates could be one

day apart but if one fell on the last day of the month and the other on the first day of the next month they would not be matched. It was decided that  $\pm 30$  days was more appropriate.

Changes to the NSHPC data format:

Previously, the NSHPC data was provided in a single spreadsheet. With developments in the matching process, more NSHPC data fields were used in the matching process and so the data format was changed, three spreadsheets were extracted from the NSHPC database to be used for the matching;

1. Pregnancy data – one line per pregnancy
2. ART drug data - one line per ART drug
3. CD4 and viral load data - one line per test date (either CD4, viral load or both)

These datasets were transposed and merged to create an NSHPC dataset containing one row (referred to as a ‘record’) per woman which included all data for each of her pregnancies.

### Discrepancy checking

Discrepancy checking was introduced as part of the matching strategy. Where paired records, thought to be a genuine match had a discrepancy in another field, they were manually reviewed to see if the other fields supported or refuted their matched status.

The discrepancies are categorised in Table 3.4 and Table 3.5. All pairs that were thought to be a genuine match but had a strong discrepancy for COB (category 0) or ethnicity (category 3) were manually reviewed.

Table 3.4. Categorising strength of discrepancy for COB reported by NSHPC and UK CHIC

Category	Type of match/discrepancy
0	Not a match
1	Exact match
7	One dataset has ‘UK’ the other has a different country
8	One dataset has ‘Africa’ the other has a specific African country
9	One or both datasets have missing COB

Table 3.5. Categorising strength of match/discrepancy for ethnicity reported by NSHPC and UK CHIC

Category	Type of match/discrepancy
1	Exact match
2	Weak discrepancy e.g. black-African vs. black-other
3	Strong discrepancy e.g. black vs. white
9	One or both datasets has missing ethnicity

Other discrepancies which led to records being manually reviewed were: drug naivety after pregnancy according to UK CHIC; a date of death reported to UK CHIC which predated a delivery date or clinical data in NSHPC; a date of UK arrival reported in NSHPC later than a CD4 count or viral load measurement reported in UK CHIC; CD4 counts  $>100$  cells/mm<sup>3</sup> different in NSHPC and UK CHIC (where matching was based on having the same CD4 dates or CD4 dates  $<30$  days apart in both studies and the same HIV diagnosis date or clinic site). If manual review of records revealed that one of the records had an obvious mistake in a field, such as ethnicity, this was reported to the relevant data manager for checking.

#### Viral load:

Viral load measurements and the dates on which they were performed were used in an attempt to identify additional matches. Linked records with the same viral load date and HIV-RNA  $\pm 10$  copies/ml (on that date) were matched. This resulted in 32 additional pairs being matched, more than half of these pairings (n=17) then had to be checked because they had discrepant COB in NSHPC and UK CHIC. Therefore, this step was not used in the final matching strategy. Instead, viral load date was used as a variable to identify potential genuine matches in the manual matching stage (described below).

#### Fuzzy DOB:

Not all women have their full DOB recorded in their clinic notes. Where DOB is not known a proxy date is normally used. If only the month and year of birth are known, the proxy date is either the 1<sup>st</sup> or the 15<sup>th</sup> of that month. If only the year of birth is known, the proxy date is either the 1<sup>st</sup> January or 30<sup>th</sup> June (i.e. the start or middle of the year). In the UK

CHIC 2009 dataset, 5% (443/8929) of women had a DOB on the first of the month, higher than the 3% (12/365) we would anticipate. There were 120 (1.3%) women with their DOB on 1<sup>st</sup> January, almost four-times as many as on the following day (n=31) and higher than the 0.3% (1/365) we would anticipate. Dates of significance, such as national independence days or Christmas day, and dates that are easy to recall, such as 1<sup>st</sup> January, 2<sup>nd</sup> February, 3<sup>rd</sup> March and so on, were also more common than we would anticipate, presumably because they are chosen by women who did not know their actual DOB.

If the same proxy date was reported to NSHPC as to UK CHIC (i.e. in antenatal care and in HIV clinics), then the use of a proxy date should not introduce any selection bias, as matching should not be affected by the number of women with a DOB on a particular date, if other variables such as CD4 date and CD4 count are available. If however, the full DOB was reported in only one clinic and the proxy date was used in the other, this would mean the records would not be paired during the first step of the matching strategy.

To assess the extent to which this might be a problem, all records with a DOB on the 1<sup>st</sup> or 15<sup>th</sup> of the month in UK CHIC or NSHPC were linked to records with a DOB in the same month in the other dataset. The same matching strategy was then used as described for records with identical DOB.

Overall, 25 additional pairs were found to be matches, but when they were manually reviewed, all had discrepancies which indicated that they were not genuine matches. This step was therefore not incorporated into the matching strategy.

#### 3.4.4 Manual review and matching

Paired records remaining in the linked dataset, i.e. which had identical DOB in UK CHIC and the NSHPC but which were not matched based on any of the matching criteria, were reviewed to identify any further matches. In the 2009 dataset, at this stage there were more than 5000 pairs remaining in the linked dataset and it was not practical to review them all. Instead, records were selected for review. In the initial matching strategy pairs were reviewed if they were reported from the same site or if they had a matching month and year of HIV diagnosis date. In the final matching strategy the following criteria were

used to select pairs (with the same DOB) for manual review: records were from the same reporting site, the HIV diagnosis dates were <30 days apart, there were drug start/stop dates <7 days apart; they had identical Soundex, or the pattern of ART use indicated that ART had been used in pregnancy (described in further detail below). The variables used to judge whether paired records were a genuine match included, from UK CHIC: date of death; from NSHPC: date of UK arrival; and from both studies: COB, ethnicity, HIV diagnosis date, viral load and date, CD4 count and date, ART drug dates and site. No discrepancy checks were run on the records matched in this step since the variables used in the discrepancy checking had already been reviewed.

Although many of the variables used in the manual review were the same as the variables used in the earlier stages, some further matches were made. In some cases this was because whilst reviewing the records I could spot typos or uncommonly occurring characteristics which indicated a match. For example, two records with an identical CD4 date but with discrepant CD4 counts 345 vs. 34 cells/mm<sup>3</sup> would not be matched at an earlier stage unless the records also had a matching site or HIV diagnosis date. However, if there were any other variables which matched, such as COB or ethnicity the reviewer would assume that one of the CD4 counts had been recorded incorrectly.

#### Soundex:

At the stage where records with identical Soundex were reviewed, the linked dataset contained 152 NSHPC records linked to at least one UK CHIC record where both records had Soundex reported. However, only 5% (n=7) of these pairs had matching Soundex in NSHPC and UK CHIC. Although few records were matched using the manual review of Soundex it was retained in the matching strategy since it was anticipated that the reporting of Soundex to the NSHPC would increase over time so it might be more useful in future years.

#### ART use:

Pairs of records were reviewed if the pattern of ART use in UK CHIC indicated that ART might have been used during pregnancy. Of the 5019 pairs remaining in the linked dataset at this stage, 6% (n=309) had an ART start date in UK CHIC which was during a pregnancy (indicated in NSHPC), (303 NSHPC records were linked to only one UK CHIC record and 6 NSHPC records were linked to multiple UK CHIC records) (Table 3.6).

Table 3.6. Criteria used to select pairs for manual review from pairs remaining in the linked dataset but not having been matched according to the main matching criteria

Criteria								n <sup>4</sup>	M
Started ART in pregnancy <sup>1</sup>	x	x	x	x	x	x		257	-
Started ART in pregnancy with CD4 >350 cells/μl	x			x		x		243	16
Started zidovudine monotherapy in pregnancy <sup>2</sup>	x	x	x					29	19
'Pregnancy' reported as reason for stopping ART <sup>3</sup>			x	x	x		x	70	4
Number of pairs meeting criteria (indicated by x)	23	5	1	9	8	211	52	309	39

n: number of pairs; M: number of pairs accepted as a genuine match

<sup>1</sup> ART start dates from UK CHIC and delivery date from NSHPC

<sup>2</sup> Second pregnancy trimester onwards

<sup>3</sup> The reason for ART stop is an under reported field in UK CHIC

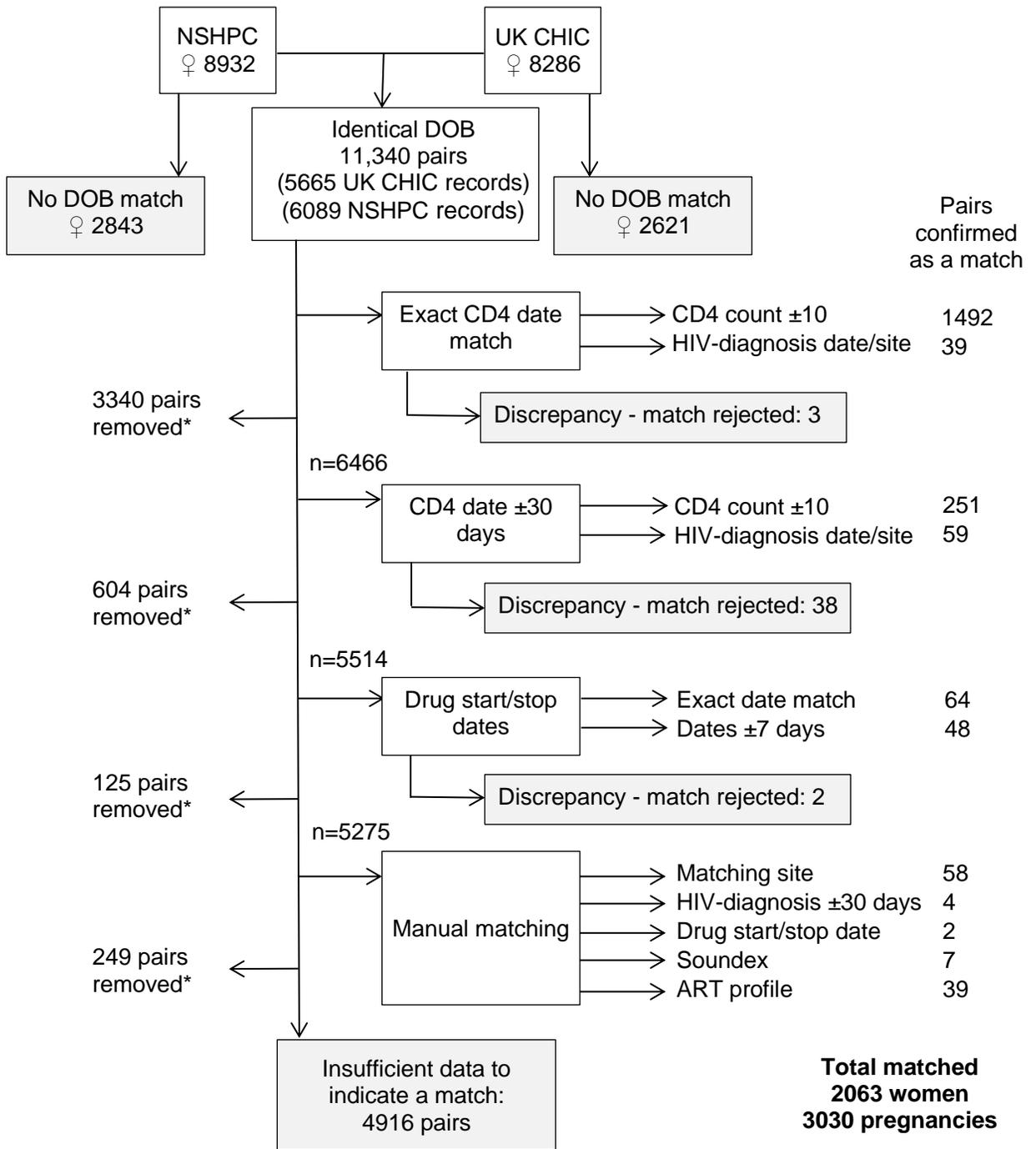
<sup>4</sup> Women could contribute data to multiple rows therefore the total number of linked pairs is less than the sum of this column.

### 3.4.5 Matching overview

Using the updated matching strategy, the NSHPC and UK CHIC records for 2063 women were matched, representing one-quarter (25%) of the women in UK CHIC (Figure 3.2). Of the 1996 records which were matched prior to the manual matching stage, 296 (15%) had to be reviewed because they had a discrepancy in at least one field. Of these, 253 (85%) had sufficient matching data in other fields to indicate that they were a genuine match, whilst 43 (15%) did not appear to be a genuine match and were not included in the final dataset (Table 3.7).

The majority of records that were matched met either the first or third matching criteria i.e. they either had the same CD4 cell count date (72% of matched records) or a CD4 cell count date within 30 days (12% of matched records) plus a CD4 cell count within 10 cells/mm<sup>3</sup>. The matching made at other stages of the matching strategy each accounted for <5% of the total matches (Table 3.8).

Figure 3.2. Criteria used to match records for women reported to NSHPC and UK CHIC



\* Pairs were removed as one or both records in the pair were confirmed as a match in a different pair  
Using UK CHIC data to end 2009 and NSHPC data to end 2010

Table 3.7. The number and type of discrepancies at each stage of the matching strategy and the number of discrepant pairs accepted and rejected as a genuine match (UK CHIC 2009 dataset)

Stage of matching	Discrepancy reason <sup>1</sup>	Accepted	Rejected <sup>2</sup>	
Exact CD4 date match + CD4 count $\pm 10$	Total	139/1494 (9%)	137	2 (1%)
	COB	42	41	1
	Ethnicity	6	6	-
	Drug naïve	74	73	1
	Date of UK arrival	17	17	-
Exact CD4 date match + HIV diagnosis date/site	Total	3/40 (8%)	2	1 (50%)
	COB	1	-	1
	Ethnicity	1	1	-
	Drug naïve	1	1	-
	Date of UK arrival	0	-	-
CD4 date $\pm 30$ days + CD4 count $\pm 10$	Total	51/270 (19%)	32	19 (37%)
	COB	12	2	10
	Ethnicity	13	4	9
	Drug naïve	19	19	-
	Date of UK arrival	7	7	-
CD4 date $\pm 30$ days + HIV diagnosis date/site	Total	38/78 (49%)	19	19 (50%)
	COB	35	16	19
	Ethnicity	1	1	-
	Drug naïve	2	2	-
	Date of UK arrival	0	-	-
Drug start/stop dates Exact dates	Total	21/65 (32%)	20	1 (5%)
	COB	18	18	-
	Ethnicity	3	2	1
	Drug naïve	0	-	-
	Date of UK arrival	0	-	-
Drug start/stop dates $\pm 7$ days	Total	44/49 (90%)	43	1 (2%)
	COB	23	23	-
	Ethnicity	21	20	1
	Drug naïve	0	-	-
	Date of UK arrival	0	-	-
Total		296/1996	253	43

<sup>1</sup>The first row shows the number with a discrepancy/matched during that stage of matching (%).

<sup>2</sup>percentage of those with a discrepancy who are rejected as a match.

No women had a date of death earlier than a delivery date or CD4/viral load test date.

Table 3.8. Number and percentage of women matched at each stage of the matching process (UK CHIC 2009 dataset)

Criteria used to match records (All pairs have matching DOB)	Matched pairs (n=2063)	%	% Cumulative
Exact CD4 date + CD4 $\pm$ 10	1492	72	72
Exact CD4 date + diagnosis date/site	39	2	74
CD4 date $\pm$ 30 days + CD4 $\pm$ 10	251	12	86
CD4 date $\pm$ 30 days + diagnosis date/site	59	3	89
Drug start and stop dates	64	3	92
Drug start and stop dates $\pm$ 7 days	48	2	94
Manual match – site	58	3	97
Manual match – diagnosis date	4	0.2	98
Manual match – drug start and stop dates	2	0.1	98
Manual match – Soundex	7	0.3	98
Manual match – likely to have had pregnancy	39	2	100

## 3.5 Characterising women found in both studies

### 3.5.1 Women in UK CHIC with a pregnancy

Of the 8286 women in the UK CHIC 2009 dataset, 25% (n=2063) were also found in the NSHPC dataset, indicating that they had ever had a pregnancy in the UK during which they were known to be HIV-positive. Among women in the combined dataset, 74% were of black-African ethnicity, 74% were born in the African WHO region and 87% were infected with HIV via heterosexual sex (Table 3.9). There were 3030 pregnancies in total, 87% of which resulted in a live birth. Women had between one and six pregnancies, with the median number being one. The average age was 30 years at the start of the first reported pregnancy and 55% of women were already diagnosed with HIV prior to this pregnancy.

Table 3.9. Characteristics of women in the UK CHIC-NSHPC 2009 combined dataset (n=2063)

		n	%
Ethnicity	Black-African	1535	74.4
	White	243	11.8
	Black-Caribbean	104	5.0
	Other	173	8.4
	Not known	8	0.4
Region of birth <sup>1</sup>	African	1527	74.0
	European	347	16.8
	Region of the Americas	87	4.2
	Eastern Mediterranean	53	2.6
	South-East Asia	25	1.2
	Western Pacific	16	0.8
	Not known	8	0.4
Probable route of infection <sup>2</sup>	Heterosexual sex	1798	87.2
	Injecting drug use	40	1.9
	Other	135	6.5
	Not known	90	4.4
Age at start of first pregnancy	Median [interquartile range (IQR)] (years)	30	[27-34]
HIV-diagnosis in relation to first reported pregnancy	Before	1131	54.8
	During	911	44.2
	At delivery	21	1.0
Pregnancy outcome (n=3030)	Live birth	2632	86.9
	Miscarriage	178	5.9
	Termination	113	3.7
	Stillbirth	33	1.1
	Ectopic	4	0.1
	Continuing to term	70	2.3

<sup>1</sup> WHO World Regions

<sup>2</sup> Using UK CHIC categories and data

### 3.5.2 Availability of pre and post-pregnancy clinical data

Half (49.6%, n=1024) the women in the UK CHIC-NSHPC combined dataset had some clinical data in UK CHIC prior to their first reported pregnancy, for a median of 2.8 (IQR 1.2-5.4) years before the pregnancy. The majority of the pregnancies which started prior to 2009 had some clinical data in UK CHIC following the pregnancy (92.0%, 2471/2685), for a median of 3.8 (IQR 1.8-6.4) years. The median time between delivery and the next viral load or CD4 assessment was 1.8 (IQR 1.1-3.5) months. The majority of pregnancies with no data in UK CHIC after the delivery had resulted in a live-birth (92.5%, 198/214) and 36% (77/214) had data in UK CHIC before the pregnancy. In some cases this was because they had delivered in the last few months before the end of follow-up (i.e. when data was reported to). As no data on departure from the UK were available it was not possible to determine whether women with no post-delivery data had left the UK, transferred care to a non-UK CHIC site or remained in the UK but stopped attending HIV clinical care. The percentage with a UK date of arrival was the same for women with and without post-delivery data (61% [1523/2496] vs. 61% [115/189], Chi-squared test p=0.96). The median time between UK arrival and delivery were also similar (4.1 [IQR 2.0-7.3] vs. 3.0 [IQR 1.0-5.8] years respectively, Mann-Whitney test p<0.20).

### 3.6 Representativeness of pregnant women in UK CHIC

Women in the NSHPC whose record was found in UK CHIC (n=2063), referred to as 'matched', were compared with women in the NSHPC whose record was not found in UK CHIC (n=6869), referred to as 'non-matched' (i.e. women with a pregnancy who did not attend HIV clinical care at a UK CHIC collaborating site). Using logistic regression, matched women were more likely to have attended antenatal care in London than non-matched women (83% [n=1717] vs. 37% [n=2530] respectively, odds ratio [OR] 8.5 [7.5-9.6], p<0.001) and were slightly older at the start of their first pregnancy (median age: matched women 30.4 [IQR 26.5-34.3] years; non-matched women 29.6 [IQR 25.8-33.6] years, p<0.001). Using HIV diagnosis date from NSHPC, a greater proportion of matched women were diagnosed with HIV before their index pregnancy compared to non-matched women; 55% (n=1131) vs. 48% (n=3278) respectively (OR 1.34 [1.21-1.48], p<0.001).

A smaller proportion of matched compared to non-matched women had an index pregnancy with an outcome not yet reported to NSHPC (i.e. the outcome was reported as 'continuing to term') (2% [n=30] vs 5% [n=342] respectively, OR 0.28 [0.19-0.41],  $p < 0.001$ ), most of which were conceived in 2009/10 (73%, 273/372). When first pregnancies with an 'other/missing' outcome (i.e. women who left the UK or who were lost to follow-up, 6 non-matched records and 0 matched) and pregnancies where outcome was not yet reported were excluded, the outcomes for first pregnancies were similar for matched and non-matched women (Chi-squared test  $p = 0.15$ ), with 90% (1834/2033) vs. 89% (5782/6521) resulting in a live birth respectively.

A higher proportion of matched than non-matched women had at least one repeat pregnancy; 34% (n=709) vs. 20% (n=1394) (OR 2.00 [1.80-2.23],  $p < 0.001$ ). The likelihood of being matched was greater for women with sequential pregnancies than for women with a single pregnancy (OR 2.08 [1.86-2.31],  $p < 0.001$ ).

Ethnicity varied somewhat; a smaller proportion of matched women were black-African compared to non-matched women (74% [n=1535] vs. 78% [n=5362], OR 0.82 [0.73-0.92],  $p < 0.001$ ). This difference remained significant when 'ever seen for antenatal care in London' was included in the model (adjusted OR [aOR] 0.67 [0.58-0.76],  $p < 0.001$ ). A higher proportion of matched women were black-Caribbean compared to non-matched women (5% [n=104] vs. 3% [n=230] respectively, OR 1.53 [1.21-1.94],  $p < 0.001$ ), but this difference was attenuated after adjustment for antenatal care in London (aOR 1.00 [0.78-1.29],  $p = 0.99$ ). The proportion of women who were of white ethnicity was similar among matched and non-matched women (12% [n=243] vs. 13% [n=919] respectively, OR 0.86 [0.74-1.01],  $p = 0.06$  and aOR 1.40 [1.18-1.65],  $p < 0.001$ , adjusted for antenatal care in London.)

A higher proportion of matched than non-matched women were using ART around the time of conception (30.4% [n=628] vs. 20.6% [n=1424], respectively,  $p < 0.001$ ). This was also the case after excluding women who were not diagnosed with HIV prior to their pregnancy.

In the NSHPC dataset, women of black-African ethnicity were more likely to have a DOB where the date matched the month (i.e. 1<sup>st</sup> January, 2<sup>nd</sup> February etc.) compared to women of white ethnicity (7% [474/6897] vs. 3.9% [45/1162], OR 1.83 (1.34-2.50)

$p < 0.001$ ). Records where DOB date matched the month were less likely to be matched (aOR 0.78 (0.64-0.95),  $p = 0.01$ , adjusted for ethnicity).

### 3.6.1 Geographical representativeness of the UK CHIC dataset

Some of the differences in characteristics between matched and non-matched women may be due to differences in women attending care at UK CHIC sites and women attending care elsewhere. As a large number of UK CHIC centres are in London (Table 3.1), in the UK CHIC dataset, 85% (7014/8286) of women ever attended a HIV clinic in London and of those attending care in 2009, 82% (3906/4755) attended a London site. This is higher than seen in the whole UK HIV-positive population (Table 3.10). In the NSHPC dataset, 48%, (4247/8932) of women had ever received antenatal care (whilst HIV diagnosed) in London. Women in NSHPC who ever attended antenatal care in London differed somewhat from women who only attended for care elsewhere, for example, they were older at the start of their first pregnancy (31.1 and 29.6 years respectively,  $p < 0.001$ ), they were more likely to be of black-African or black-Caribbean ethnicity and less likely to be of white ethnicity compared to women seen outside London (black-African: 79.8% [3390/4247] vs. 74.9% [3507/4685], OR 1.33 [1.20-1.47],  $p < 0.001$ ; black-Caribbean: 5.7% [n=240] vs 2.0% [n=94], OR 2.93 [2.30-3.73],  $p < 0.001$ ; and white: 8.1% [n=346] vs. 17.4% [n=816], OR 0.42 [0.37-0.48],  $p < 0.001$  respectively). The proportion of women diagnosed with HIV before their first reported pregnancy was similar for women seen in London and seen elsewhere, (49% [2061/4247] and 50.5% [2366/4685] respectively, Chi-squared test,  $p = 0.06$ ).

Table 3.10. The number and percentage of women accessing HIV clinical care in London of those accessing care in the UK, according to The Survey of Prevalent HIV Infections Diagnosed (SOPHID)<sup>22</sup> (2000-2009) [394].

Year	UK	London	% (London/UK total)
2000	4871	2829	58
2001	6231	3716	60
2002	8248	4543	55
2003	10,413	5189	50
2004	12,309	5680	46
2005	14,324	6336	44
2006	15,921	6798	43
2007	17,149	7080	41
2008	18,489	7505	41
2009	19,312	7696	40
<b>Total</b>	<b>127,267</b>	<b>57,372</b>	<b>45</b>

### 3.7 Completeness of the matching

There was no 'gold standard' which could be used to determine whether all women in UK CHIC with a pregnancy were found in NSHPC or whether all paired records genuinely referred to the same woman.

After completion of the matching strategy there were 4916 pairs (3014 UK CHIC records and 3285 NSHPC records) remaining in the linked dataset i.e. records linked because they had the same DOB, which had not been confirmed as genuine matches according to the matching criteria. Of these, 137 (2.8%) pairs had records from NSHPC and UK CHIC reported from the same site but could not be confirmed as a genuine match due to insufficient data in other fields (47% [n=64] had no CD4 count reported to the NSHPC).

<sup>22</sup> Further details on SOPHID are available at [www.gov.uk/hiv-surveillance-systems](http://www.gov.uk/hiv-surveillance-systems)

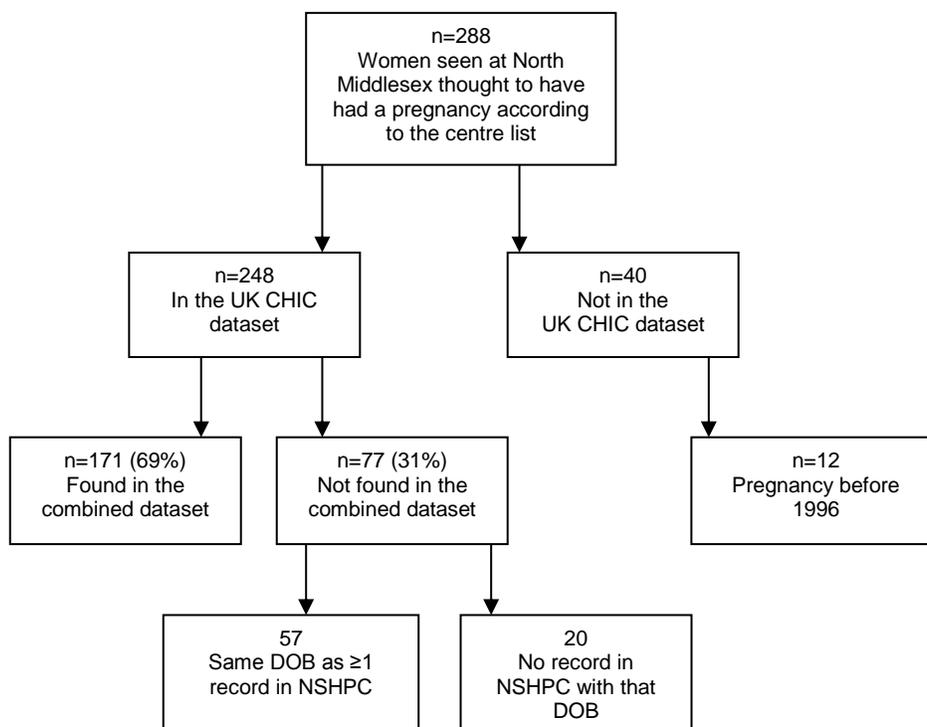
### 3.7.1 Comparing records from sites which record pregnancy

In order to assess the completeness of the matching, two clinics which collaborate in the UK CHIC study and which record pregnancy status in women's clinical records offered to generate a list of women (DOB or clinic ID only) attending their clinics who had had a pregnancy.

#### North Middlesex University Hospital

North Middlesex University Hospital sent a list of women's clinic IDs, DOB and their delivery date for 288 HIV-positive women known to have had a pregnancy. Although clinic ID is reported to UK CHIC by clinics, it is not included in the final UK CHIC dataset. Therefore, Dr Teresa Hill, the UK CHIC data manager, provided me with the UK CHIC unique IDs (Patnum) for these women. I assessed how many women in the North Middlesex list appeared in the combined dataset (Figure 3.3). If women were not found in the combined dataset, the NSHPC dataset was searched for any records with the DOB to see if the women had ever had a pregnancy reported to the NSHPC.

Figure 3.3. Assessing whether women with a pregnancy at North Middlesex are included in the UK CHIC-NSHPC 2009 combined dataset to assess completeness of the matching



Of the 288 women in the North Middlesex list, 40 were not found in the UK CHIC dataset (12 of whom had a pregnancy before 1996) (Figure 3.3). Of the 248 women in the UK CHIC dataset, 171 (69%) were in the UK CHIC-NSHPC 2009 combined dataset (Table 3.11). Of the 77 women who were not in the combined dataset, 20 had a DOB which did not match any DOB in the NSHPC dataset indicating that these women did not have a pregnancy reported to NSHPC (12 had a fuzzy DOB match to a record with 1<sup>st</sup> or 15<sup>th</sup> of the same month and year but no CD4 date match). Of the 57 records not found in the combined dataset, but with a DOB matching at least one record in the NSHPC dataset, 7 had a pregnancy reported to NSHPC by North Middlesex but the paired records had insufficient data to confirm that they were a genuine match.

I visited North Middlesex and spoke with the data manager, midwife and clinician to try to understand why some of the women on the list they had produced for me were not found in the UK CHIC or NSHPC datasets. The midwife informed me that there was some reporting delay of pregnancies to NSHPC, with older records still being reported as and when time permitted. However, she could not tell me which pregnancies had or had not been reported. When reviewed by the clinician, it was clear that some patients included in their list, had not received sufficient HIV clinical care to be included in the UK CHIC reporting, for example they had been seen once, but had not received any clinical assessments.

Of the records which were linked to at least one record in NSHPC, but not confirmed as a match, it is difficult to know how many were genuine matches. It is probable that the 7 pairs with data reported from North Middlesex to UK CHIC and the NSHPC were genuine matches, but there was no further data to confirm or refute this. This exercise indicated that there was likely to be some incomplete matching due to insufficient data, such as CD4 dates, as well as underreporting or reporting delay. It was not possible to determine the level of under-matching. It is further complicated by the fact that women can choose where they access antenatal care and where they access HIV clinical care and these might not be at the same site.

Table 3.11. Comparison of records from North Middlesex University Hospital for women living with HIV known to have had a pregnancy and records in matched dataset over time

Year	North Middlesex dataset		UK CHIC - NSHPC combined dataset <sup>1</sup>		% of North Middlesex records found in the combined dataset	
	Pregnancies	Women	Pregnancies	Women	Pregnancies	Women
1996	4	4	1	1	25	25
1997	3	3	0	0	0	0
1998	9	9	4	4	44	44
1999	11	9	7	6	64	67
2000	21	20	17	16	81	80
2001	20	18	17	15	85	83
2002	16	15	8	7	50	47
2003	38	29	19	12	50	41
2004	37	30	22	20	59	67
2005	27	20	20	14	74	70
2006	32	23	25	18	78	78
2007	45	27	40	22	89	81
2008	37	22	36	21	97	95
2009	28	14	24	11	86	79
2010	19	5	14	4	74	80
Total	347	248	254	171	73	69

<sup>1</sup> Of the women in the North Middlesex dataset

### King's College Hospital

At King's College Hospital all appointments with a midwife or doctor regarding pregnancy or antenatal care are recorded in the patient's clinical record. The HIV research nurse provided me with a list of the DOB and attendance date of 272 women who had attended an antenatal appointment and accessed HIV clinical care at King's College Hospital. Of these, 32 were recent patients who had not yet been reported to UK CHIC, 6 were not recent patients and were not in UK CHIC. Of the 234 women in UK CHIC, 80.8% (n=189) were in the UK CHIC-NSHPC combined dataset (Figure 3.4).

Of the 44 women not in the combined dataset, 7 women did not have a record in NSHPC with their DOB (3 from 2005, 3 from 2008 and one from 2009), two did have a record in NSHPC with their DOB but the NSHPC record had been matched to a different UK CHIC record and was therefore probably not their record. It is therefore probable that these 9 women did not have a pregnancy reported to NSHPC.

I visited the research nurse at King's College Hospital. The research nurse examined the records for the women who had been included in the list but who were not in the UK CHIC-NSHPC combined dataset. In some cases, individuals who had attended an antenatal appointment were not pregnant (or were not recorded as being pregnant in their clinic record). This included women (and men) who had received fertility advice. In one case a woman had received two ultrasound scans despite not being pregnant.

The number of women receiving antenatal care each year was higher, according to the King's College Hospital records, than the number of women in the combined dataset (Table 3.12). This indicates some level of under-matching. However, it is difficult to assess the extent of this and it was clear that not all women who received antenatal care at King's had a pregnancy.

Figure 3.4. Assessing whether women who attended antenatal care at King’s College Hospital were included in the UK CHIC-NSHPC combined dataset

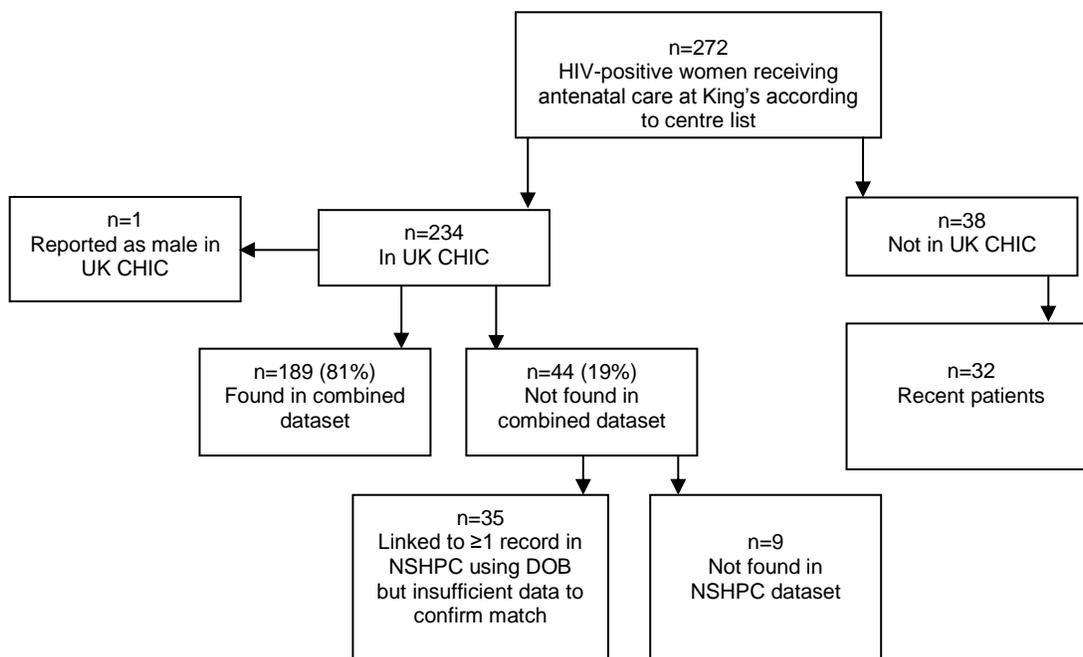


Table 3.12. Comparison of records from King’s College Hospital for HIV-positive women known to have had a pregnancy and records in the combined dataset

Year	Women seen for antenatal care at King’s	UK CHIC-NSHPC combined dataset <sup>1</sup>	%
2004	18	17	94.4
2005	61	52	85.2
2006	54	47	87.0
2007	44	39	88.6
2008	37	24	64.9
2009	19	10	52.6
<b>Total</b>	<b>233</b>	<b>189</b>	<b>81.1</b>

<sup>1</sup> Of the women seen for antenatal care at King’s

Note that an additional record from 2010 was not included in the table

### 3.7.2 Estimating completeness of the matching using national surveillance data

National HIV surveillance data from the Health Protection Agency (HPA) (now Public Health England [PHE]) were used to assess the completeness of the matching between the NSHPC and UK CHIC.

The Survey of Prevalent HIV Diagnosed (SOPHID) collects data on all adults diagnosed with HIV who attend clinical care at HIV clinics in the UK and is thought to have near-complete coverage. The most up-to-date annual report published by the HPA included data for adults aged 15-49 years [394], therefore I made a request for data specifically relating to adults aged 16-49 years old.

The number of women (aged 16–49 years) who attended HIV-related care in the 2009 UK CHIC dataset increased yearly; from 2036 in 1996 to 4755 in 2009, totalling 45,768 person years and representing approximately 29.5% (37,577/127,267 person years) of HIV-positive women (aged 16–49) attending HIV care in the UK in 2000–2009.

In 2009, there were 19,312 women (aged 16–49 years) seen for HIV-clinical care in the UK (SOPHID data) and 1198 women living with HIV who had a pregnancy (1211 pregnancies) starting in that year (according to the NSHPC dataset used in this study), indicating that approximately 6.2% (1198/19,312) of women living with HIV who attended HIV-care in 2009 had a pregnancy starting that year. We would therefore anticipate that 6.2% of the 4755 women in UK CHIC would have a pregnancy in 2009 equating to 295 women (95% confidence interval 279–311 women). The UK CHIC-NSHPC combined dataset actually contained 275 women with at least one pregnancy in 2009, 4 fewer than the lower limit of the anticipated range.

However, there are a number of limitations to this analysis. Despite good coverage by SOPHID and NSHPC, we know from a matching exercise between SOPHID and NSHPC and between UK CHIC and SOPHID that there is incomplete matching of records between these datasets, so not all women reported to UK CHIC or reported to NSHPC are in fact reported to SOPHID. This analysis also assumes that there is no difference in the pregnancy rate across the country. Many of the UK CHIC sites are based in London where the number of pregnancies among women living with HIV is likely to differ compared to elsewhere in England and Wales, as is the case in the general population [395].

### 3.8 Discussion

A strategy was developed to identify women reported to both NSHPC and UK CHIC, i.e. women who attended HIV-related clinical care at a site participating in UK CHIC and who had a pregnancy. Since it was not possible to use a single unique identifier to find records for the same woman in both studies, a deterministic decision criteria based on demographic and clinical data common to both NSHPC and UK CHIC was used. Using this strategy we were able to determine that almost one-quarter of HIV-positive women in UK CHIC had a pregnancy, as a minimum estimate. This method combined the use of automated matching with manual review of selected records, as has been used elsewhere [396-400]. It was undertaken within the software used for analysis of data (SAS) allowing it to be repeated in subsequent years with the use of minimal resources or programming expertise. A number of records were scrutinised as part of the matching process, for example where two records from one study were matched to a single record from the other study or where two matched records had a discrepancy. This resulted in small improvements to both datasets with mistakes being corrected or two records for the same woman in the same dataset being merged.

There was no 'gold-standard' available to calculate the completeness of the matching. Instead, national HIV surveillance data of individuals attending HIV-related care (SOPHID), provided by PHE, were used to estimate the expected number of women with a pregnancy in the UK CHIC dataset. The number of women with a pregnancy in the UK CHIC-NSHPC combined dataset was lower than the anticipated number for this period, indicating that there was incomplete matching. However, this needs to be interpreted with care, as there are many limitations to this way of estimating completeness. In reality the level of matching may be higher since this estimate assumes that all women in the NSHPC are reported to SOPHID, which previous matching studies indicate is not the case [401]. It also assumes that the fertility rate is uniform throughout the UK. At the time of the linkage, in the general population, the fertility rate of women living in London was lower than in any other region in England or Wales (with the exception of the North East of England) [402].

A large number of records were paired because they had the same DOB but were not thought to be a genuine match according to the other criteria used. It is unlikely that many of these were genuine matches as we would expect some women to share birth dates given the number of women in both datasets, particularly as women who do not know their

DOB sometimes use proxy dates, which are therefore more common in the dataset [403]. UK CHIC and NSHPC records with identical DOB reported from the same site but no other matching variables (137 pairs) may have been genuine matches; however, in this instance under-matching was preferable to incorrect matching. The analyses in this thesis focus on the period of pregnancy or post-pregnancy, and as such it was preferable to potentially not include all pregnancies in the analysis rather than include a period of time which was thought to be during pregnancy but was not. Many of these records were not matched because they had limited clinical data which could be compared. It is therefore likely that, even if they were matched, they would have been excluded from analyses due to lack of clinical data such as CD4 counts.

There are a number of limitations to the methods used, including the use of blocking to select records, in this instance DOB. This method is effective at limiting the records in the matching process to those likely to be matches and is frequently used in matching large datasets [398, 404, 405]. However, it means that incorrect or inconsistent reporting of DOB results in a record being excluded; this may be more common among some groups than others, potentially introducing selection bias [403, 406]. Use of demographic data for record matching, such as age, ethnicity, and COB, within any matching algorithm is likely to create some false positive matches. Given our study population of pregnant women, multiple women had the same ethnicity, COB, and age, therefore the additional use of clinical data was vital for matching. However, this resulted in some selection bias, as women with more clinical data (either because they had been diagnosed prior to pregnancy, were receiving ART when they conceived or had repeat pregnancies) were more likely to be matched than women with less data. This difference also indicates that the matching was somewhat incomplete. Since women in the NSHPC had 8.5 times the odds of being matched if they attended care in London than if they attended care elsewhere (because many of the UK CHIC sites were located in London), other differences between the matched and non-matched women could be attributed to differences between HIV-positive women living in London and elsewhere. For example, in the general population the average age of women giving birth in London is higher than elsewhere in England and Wales [407]. This could explain why the matched women were somewhat older at the start of their index pregnancy compared to the non-matched women. The differences in ethnicity between matched and non-matched women could also be explained by differences in ethnicity between women attending care in and outside

London. However, when taking location into account, black-African women were still less likely to be matched than women of other ethnicities.

Data discrepancies in fields common to both studies were harmonised where possible, or else categorized as 'not known' (as described in the following chapter). These discrepancies were unlikely to be a result of incorrect matching, as matched records with strong discrepancies were manually checked for additional matching variables. A woman's antenatal data, used for completing the NSHPC reporting form, and HIV clinical data extracted for inclusion in UK CHIC, are typically stored separately, even within the same hospital (although more hospitals are moving to integrated software systems across clinics). Reasons why these databases might be discrepant include incorrect or incomplete recording of data and inconsistent or inaccurate reporting by patients, for example where language is a problem, if they do not know or do not want to disclose their DOB to maintain anonymity [403].

The UK CHIC-NSHPC dataset has a number of applications. As well as helping to improve the data quality of both datasets, it allows analyses which could not be performed using either dataset in isolation. Used in combination with all records for women in UK CHIC it is possible to compare the health of pregnant women with the health of non-pregnant women and to assess pregnancy incidence among women accessing HIV clinical care. The matching of datasets also allows the exclusion of pregnant women from the UK CHIC dataset if required for specific analyses.

## Chapter 4 Methods

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### 4.1 Introduction

The matching strategy, described in the previous chapter, resulted in the creation of a dataset, referred to as the matched dataset, containing data from the UK Collaborative HIV Cohort (UK CHIC) study and the UK and Ireland's National Study of HIV in Pregnancy and Childhood (NSHPC) for women found in both studies. In this chapter I describe the creation of new variables using data from one or both studies including the start date for life-long ART and the variable which categorises the type of ART used in pregnancy. I also describe how I dealt with discrepancies in variables reported to both studies and I define commonly used variables.

### 4.2 Using data from both sources to create variables and dealing with discrepancies

#### **HIV diagnosis date discrepancies**

Of the 2063 women in the matched dataset, 24% (n=503) had identical HIV diagnosis dates in their UK CHIC and NSHPC records, 37% (n=756) had diagnosis dates  $\leq 30$  days apart and 33% (n=652) had dates  $>30$  days apart (Table 4.1). Similar proportions were seen for the women with UK CHIC and NSHPC reports from the same site (86% of women in the matched dataset). In women for whom UK CHIC and NSHPC reports were from different sites, only 10% (29/296) had identical HIV diagnosis dates and 51% (151/296) had dates  $>30$  days apart (Table 4.1). It is not clear whether this is a result of incorrect matching of UK CHIC and NSHPC records. However, much of the inaccuracy of HIV diagnosis dates is likely to be due to non-disclosure or recall bias, i.e. people recall a different date when asked at different times, which would result in a higher rate of discrepancies when reports come from two different sites.

Table 4.1. Summary of discrepancies in HIV diagnosis date between NSHPC and UK CHIC records for the same woman

HIV diagnosis dates match/discrepancy	Overall (n=2063)		No site match (n=296)		Site match <sup>1</sup> (n=1767)	
	N	%	n	%	n	%
Identical dates	503	24	29	10	474	27
1-30 days apart	756	37	89	30	667	38
31-365 days apart	429	21	83	28	346	20
>365 days apart	223	11	68	23	155	9
One or both had missing dates	152	7	27	9	125	7

<sup>1</sup>At any point they received care from the same site

Of the 652 women with HIV diagnosis dates >30 days apart, 45% (n=290) had a date in NSHPC later than the date in UK CHIC. Of these, 27% (n=79) were diagnosed with HIV during their first reported pregnancy according to NSHPC but before their first reported pregnancy according to UK CHIC. This discrepancy was not limited to specific sites; at least one instance of such a discrepancy occurred in data from each of the UK CHIC sites. It is not clear whether this discrepancy was a result of women being retested for HIV whilst pregnant (as part of routine antenatal screening), despite already being aware of their HIV-positive status, or whether their first attendance in antenatal care was reported by NSHPC as their HIV diagnosis date despite their diagnosis occurring before the pregnancy. Alternatively, women may have been aware of their HIV diagnosis and received HIV-clinical care at one site whilst attending a different site for antenatal care where they did not disclose their HIV status.

As is the case with DOB, proxy dates are used by some clinics and in the NSHPC database if only the month or year of HIV diagnosis is known. In the matched dataset there were 303 records with HIV diagnosis date reported as 30<sup>th</sup> June in one study but not the other (NSHPC n=299, UK CHIC n=4). Of these, 58% (n=175) had a diagnosis date reported by the other study which was in the same year, either before (n=114) or after (n=61) 30<sup>th</sup> June, suggesting that one clinic reported the actual date of diagnosis whilst the other reported only the year or a proxy date.

### **HIV diagnosis date combined variable**

Where the HIV diagnosis dates reported by NSHPC and UK CHIC were not identical, the earliest HIV diagnosis date from either study was used (n=1865) unless one date appeared to be a proxy date (i.e. either 1<sup>st</sup> January or 30<sup>th</sup> June) and the later date (believed to be the genuine date) was during the same year, in which case the later date was used (n=116). The earliest CD4 cell count, viral load measurement or ART start date was used if no HIV diagnosis date was available (n=4), or if that date preceded the earliest HIV diagnosis date (n=78).

Using the HIV diagnosis dates reported, a variable was created which categorised the timing of HIV diagnosis in relation to each pregnancy i.e. before or during the pregnancy. Although an equivalent variable was reported in NSHPC, it was underreported and in some cases was discrepant with the HIV diagnosis date reported. If no HIV diagnosis date was reported to the NSHPC but it was reported that the woman was diagnosed prior to the pregnancy then diagnosis was categorised as occurring before the pregnancy even if the HIV diagnosis date in UK CHIC was after the start of the pregnancy (n=7). If no HIV diagnosis date was reported to NSHPC but it was reported that the woman was diagnosed during the pregnancy then the woman was categorised as being diagnosed during the pregnancy even if the HIV diagnosis date in UK CHIC was after the delivery date (n=2).

Only if the woman was diagnosed with HIV before or during a pregnancy was the pregnancy included in the final dataset, since women who were not diagnosed until delivery or later could not have used ART during the pregnancy. Overall, 21 women were diagnosed with HIV after their first reported pregnancy, 8 were diagnosed on the day they delivered, 8 within a week of delivery and 5, more than a week after delivery. Of these, 9 women had no further pregnancies and were therefore excluded from the dataset. The remaining 12 women had at least one subsequent pregnancy. Their first reported pregnancy was excluded, their second pregnancy was re-categorised as their first, their third as their second, and so on.

### **Country of birth**

Table 4.2 summarises the number of discrepancies in COB for matched records. Overall, 58% of women had the same COB in their NSHPC and UK CHIC records and 34% had COB missing from at least one of the study datasets. The majority of records with

discrepant COB had 'UK' (or in a handful of cases 'Scotland') reported as the COB in one study but not in the other (with 37 different countries reported overall as the non-UK country).

Table 4.2. Summary of discrepancies in COB between matched records

Category of match/discrepancy	n	%
Exact match	1205	58
UK vs. non-UK	106	
UK in UK CHIC record	89	5
UK in NSHPC record	17	
Africa vs. named country in Africa <sup>1</sup>	6	0.3
Missing COB	694	34
Missing in UK CHIC only	673	
Missing in NSHPC only	14	
Missing in both	7	
Other discrepancy	52	3

<sup>1</sup>In all cases it was in the NSHPC record that COB was recorded as 'Africa'

In most of the analyses in this thesis, ethnicity rather than COB is considered, since so many COB were represented in the dataset. Where region of birth (ROB) was used, this was categorised using the WHO regions [408]. Records with discrepant ROB (n=98) were categorised as 'not known' (n=2) or as the non-European region if the region was European in one dataset and non-European in the other (n=96) (94 had UK as the COB in one study but not in the other).

## Ethnicity

The two studies categorise ethnicity slightly differently. The studies use four common categories: White; Black-African; Black-Caribbean; Other Asian/Oriental; and Other/mixed. However, the UK CHIC uses a further four categories: Black-unspecified/black-other; Indian/Pakistani/Bangladeshi; Other; and Not known, while the NSHPC uses a further two: black-other; Asian/Indian/Subcontinental. The NSHPC form also has a text field for ethnicity to be entered where ethnicity is 'other or mixed'.

The strength of the match/discrepancy between data in the matched pairs was categorised into four categories (Table 4.3). Where ethnicity was not an exact match (n=161), for example 'black-African' versus 'black-other', the ethnicity reported to UK CHIC was used since some analyses included women reported to UK CHIC but not to the NSHPC. There were 17 pairs with a strong discrepancy, for example, 'black-African' vs. 'white'. These records had been checked at the discrepancy checking stage of the matching and had sufficient data in common from other fields, including COB, to indicate that they referred to the same woman. Where there was a strong discrepancy, this was assumed to be due to an error in one dataset and the COB was used to indicate which ethnicity was more likely to be correct. For example, a woman reported as being 'white' in UK CHIC and 'black-Caribbean' in NSHPC had her COB reported as Trinidad in both datasets and was therefore categorised as being of 'black-Caribbean' ethnicity in the final dataset. Where the COB could not be used, the child's ethnicity was checked (as this is reported to NSHPC) to indicate if there was an obvious mistake in the reporting of the mother's ethnicity. Where ethnicity could not be determined it was coded as 'not known' in the combined dataset (n=8).

Table 4.3. Summary of discrepancies/matching in ethnicity between matched records

Category of match/discrepancy	n	%
Exact match	1808	88
One or more have missing ethnicity	77	4
Missing in UK CHIC	(74)	
Missing in NSHPC	(3)	
Discrepancy	17	0.8
Matched using CD4 date	(7)	
Matched using CD4±30 days	(5)	
Matched using ART start/stop dates	(3)	
Manually matched	(2)	
Not exact match - weaker discrepancy	161	8

## **Soundex**

Soundex was not used in the analysis, but discrepancies in soundex were examined. This was to identify any false matches and to gauge how many apparently genuine matches had different soundex, indicating to what extent soundex might be useful in the matching strategy. Of the 2063 women in the matched dataset, only 1% (n=24) had soundex recorded in UK CHIC and the NSHPC due to underreporting of this variable to the NSHPC. Of these women, 7 had been matched at the manual matching stage because they had matching soundex (as well as similarities in other variables). For the remaining 17 women with records matched using other criteria, 65% (n=11) had the same soundex in the NSHPC and UK CHIC and 35% (n=6) did not. These were all reviewed and appeared to be genuine matches indicating that although soundex could be used to confirm a match (in combination with other variables) we would anticipate that around one-third of genuine matches would have discrepant soundex in the NSHPC and UK CHIC. There are numerous possible reasons for these discrepancies: chance; women changing their surname when they marry or divorce; incorrect spelling of surname; or multiple names used by the same individual. The use of Soundex as a variable for record linkage is particularly problematic within this population, since many of the women will be married or get married whilst under HIV care and may therefore change their surname and because of the stigma still associated with HIV, some patients attending HIV clinics may not disclose their real name.

## **Site**

At many hospitals a pregnant woman with HIV would receive antenatal care in a different department to where she receives routine HIV clinical care. Especially in London, women may choose to access antenatal care at a different hospital from where they receive HIV clinical care since different sites offer different antenatal facilities and there may be other practical reasons such as proximity to home or work. Women may also change the site at which they receive HIV clinical care, for example if they move, their clinician moves or for numerous other reasons. Although the UK CHIC dataset includes a list of all sites which have ever reported data for an individual (i.e. sites they have ever attended for HIV clinical care), it does not contain all the dates of attendance at each of the sites. It was therefore difficult, for women who had attended more than one site, to assess whether they attended antenatal care at the same site where they attended HIV clinical care. This is also

complicated by differences in the division of care between hospital sites, with some sites managing antenatal care within the HIV clinic and others having two separate clinics within the same trust. Overall, 92% of women had NSHPC and UK CHIC data reported from the same site (Table 4.4).

Table 4.4. The number and percentage of records in the matched dataset with NSHPC and UK CHIC data for the same woman from the same or from different sites

Sites reporting NSHPC and UK CHIC data for the same woman	Number (n=2063)	%
Match	1899	92
Not a match - both London sites	62	3
Not a match - not both London sites	101	5
Site data missing	1	0.1

### HIV viral load

It was important for a number of analyses to establish the woman's viral load at delivery, and more specifically whether the viral load was undetectable. Viral load measurements are collated by both studies; the UK CHIC study collates all viral load measurements performed in HIV clinical care and the NSHPC requests the first and last viral load measurements performed during pregnancy. In order to create a dichotomous variable categorising viral load at delivery as either detectable (HIV-RNA >50 copies/ml) or undetectable (HIV-RNA ≤50 copies/ml) using all the available data, all viral load measurements ≤30 days before delivery were assessed.

Of the 3030 pregnancies in the matched dataset, 69% (n=2090) had a viral load measurement ≤30 days before delivery reported by at least one study; 41% (n=1257) had data from both studies, 16% (n=480) from NSHPC only and 12% (n=353) from UK CHIC only. When viral load was categorised as either detectable or undetectable, there were 94 pregnancies with a discrepancy in the data from UK CHIC and NSHPC (Table 4.5).

Table 4.5. Comparison of viral load at delivery reported by NSHPC and UK CHIC for pregnancies in the combined dataset (n=3030)

Viral load at delivery <sup>1</sup>		UK CHIC		
		Undetectable	Detectable	No VL <sup>1</sup>
NSHPC	Undetectable	805	62 <sup>2</sup>	352
	Detectable	32 <sup>3</sup>	358	128
	No VL <sup>1</sup>	219	134	940

VL: viral load

<sup>1</sup> ≤30 days before delivery

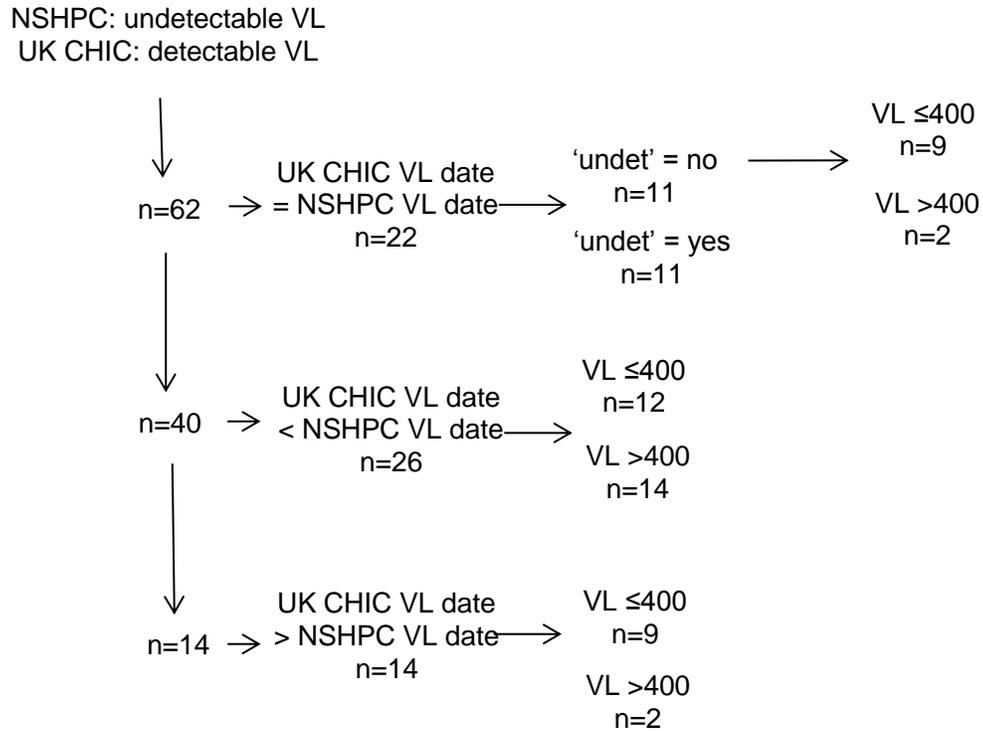
<sup>2</sup> 22 of these were reported on the same day

<sup>3</sup> 2 of these were reported on the same day

The accuracy of assays used to measure viral load has improved over time. For some of the older viral load assays, 400 copies/ml was the cut off for detecting viral load. Therefore, UK CHIC collected an additional dichotomous variable ‘undet’ which indicates whether a viral load was undetectable/detectable according to the assay used at the time.

Of the 62 discrepancies where viral load was reported as >50 copies/ml in UK CHIC and ≤50 copies/ml in NSHPC, 22 were reported on the same date. Of these, 11 were reported as undetectable according to the UK CHIC undet variable.

Figure 4.1. Discrepancies in viral load at delivery: UK CHIC >50 copies/ml and NSHPC ≤50 copies/ml

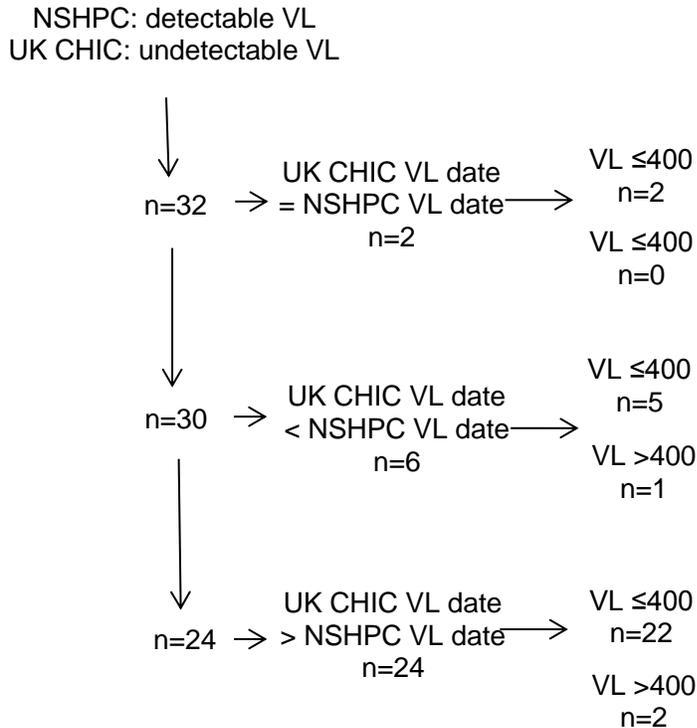


VL: viral load (copies/ml)

For the 26 women with a viral load date in UK CHIC 3-29 days before the date in NSHPC, 12 had a viral load ≤400 copies/ml. It is possible that some of these women had not achieved undetectable levels when the viral load was reported to UK CHIC but had an additional viral load measurement taken closer to the time of delivery, by which point they had achieved viral suppression.

For the 14 women with a viral load date in UK CHIC after the NSHPC date, two were categorised as undetectable in the undet field. Viral load varied from 54 to 730 and although it is feasible that the viral load increased from <50 copies/ml to >50 copies/ml in the period between tests, it is very unlikely, since all these women were on ART at this point.

Figure 4.2. Discrepancies in viral load at delivery: UK CHIC  $\leq 50$  copies/ml and NSHPC  $> 50$  copies/ml



VL: viral load (copies/ml)

For the 32 records where viral load was  $\leq 50$  copies/ml in UK CHIC and  $> 50$  copies/ml in NSHPC, the dates of viral load were the same for 2 records and in both cases the viral loads reported to NSHPC were close to 50 copies/ml (82 and 60 copies/ml). The majority of viral loads reported were  $\leq 400$  copies/ml. It is possible that in some cases the viral load fell from the time of the NSHPC viral load measurement to the UK CHIC viral load measurement.

One option would be to only use data from UK CHIC for analysis of viral load at delivery. This would mean not utilising all the available data; there were 353 records with viral load data only available in NSHPC. It is difficult to know whether discrepancies between datasets are due to changes in viral load in the time between tests, inaccurate reporting of dates or viral loads (particularly in the NSHPC data, for which forms are manually completed), different assays being used in the different laboratories or incorrect matching

of records (i.e. the UK CHIC and NSHPC records do not refer to the same woman). UK CHIC collects data on which viral load assay is used for each viral load assessment. Not all sites used the same viral load assay but this field was not examined in detail.

It was decided that the most appropriate way to categorise viral load at delivery was to use the viral load taken closest to the date of delivery from either dataset. Where viral load measurements were on the same date in NSHPC and UK CHIC the viral load was categorised as undetectable if both viral loads were reported as <100 copies/ml. They were also categorised as undetectable if the viral loads were both <400 copies/ml and UK CHIC reported that the viral load was undetectable in the undet field. Otherwise, if one study reported viral load >100 copies/ml and the other <100 copies/ml, the viral load was categorised as not known (NK).

Using this criteria, of the 62 women with viral load  $\leq 50$  copies/ml in NSHPC and >50 copies/ml in UK CHIC, 14 were recoded as detectable, 40 as undetectable and 8 as NK. For the 32 women with viral load >50 copies/ml in NSHPC and  $\leq 50$  copies/ml in UK CHIC, 6 were categorised as detectable and 26 as undetectable.

Assessing the latest viral load within the 30 days before delivery meant that no viral load data were available for 31% of pregnancies. In order to increase the number of pregnancies with data available, the period was extended to 91 days (three months) before delivery. It is likely that most of the women with undetectable viral load during this three month period also had undetectable viral load at delivery. The Women and Infants Transmission Study (WITS), in the US, found that approximately 87% of women who achieved viral suppression in pregnancy remained virally suppressed at delivery [409].

### 4.3 Defining commonly used variables

Women:

The WHO defines an adult as someone older than 19 years and an adolescent as someone aged 10-19 years inclusive [410]. Throughout the thesis I refer to people in the datasets as 'women'.

#### Childbearing age:

Childbearing age was defined as 16-49 years. Although childbearing age could extend to women younger than 16, the UK CHIC study only collects data for women aged 16 years and older. The oldest age at conception in the NSHPC dataset was 49 years.

#### Estimated date of conception:

The estimated date of conception (EDC) was calculated as 266 days (38 weeks) before the expected date of delivery (EDD). The EDD is an estimate of 40 weeks gestation which includes approximately 14 days between the first day of the last menstrual period and conception and is therefore typically calculated using the date of the woman's last menstrual period or the dating ultrasound scan. The EDC was primarily used to establish whether the woman was on ART prior to becoming pregnant. Since very few women started ART close to the time of conception it was not felt necessary to account for the woman's ethnicity when calculating this variable, although there is evidence that the length of gestation differs by a few days according to ethnicity [411].

The EDD was used as the reference point from which to calculate the EDC rather than the actual delivery date since not all pregnancies had a delivery date reported (for example, where the pregnancy was ongoing when reported), some pregnancies ended early (due to miscarriage or termination) and because, for pregnancies resulting in a live birth, the duration of gestation varied greatly. Although 40 weeks (280 days) is the average duration of pregnancy, this includes approximately two weeks prior to conception [412]; thus, I used a duration of 266 days to back calculate the EDC.

#### Delivery date:

The EDD was used to indicate the end of the pregnancy if the delivery date had not been reported, for example if the pregnancy was on-going when the NSHPC report was completed or the woman had moved abroad before delivery.

#### Pregnancy trimesters:

The first, second and third trimesters of pregnancy were defined (using the EDC as the reference date) as: 0 to <14 weeks gestation; 14 to <28 weeks gestation (or the delivery date if this was prior to 28 weeks); and 28 weeks until the delivery date respectively.

#### Index pregnancy:

The index pregnancy was the first pregnancy reported to NSHPC following HIV diagnosis or during which HIV diagnosis occurred.

#### Postpartum:

The postpartum period refers to the period after childbirth. It typically refers to a period from immediately after delivery to around 6-12 weeks after delivery, however, it can refer to a longer period of time, up to a year, for example in reference to illnesses which can occur within that longer period, such as postpartum depression. In this thesis, the postpartum period being referred to is specified in the relevant methods section.

#### Infant HIV infection status:

Infants born to HIV-positive mothers are tested for HIV infection in the first 48 hours after delivery, when they are 6 weeks old and 3 months old (using PCR [polymerase chain reaction] test). They also have an HIV antibody test at 18 months old and may be tested on other occasions if there are additional risks such as breast feeding. Infants were categorised as HIV-positive if they were reported (to NSHPC) as 'presumed HIV-positive' or 'confirmed HIV-positive' since it is rare that the later test does not confirm the first test result [149].

#### Attendance in HIV clinical care:

For some analyses it was important to include only women who attended HIV clinical care in a given period. A dichotomous variable (yes/no) was created for each year to indicate whether each woman had received HIV clinical care at a UK CHIC site. Since no marker of attendance was available in the dataset, for most analyses a CD4/CD8 cell count, viral load, drug start/stop date, or date of an AIDS event were used as a proxy for attendance.

Although a CD4 cell count or viral load measurement are not necessarily performed at every clinic attendance it was assumed that patients receiving regular care would have them measured at least once every six months. In analyses which used only CD4 cell count and viral load to indicate clinical care, this is specified in the relevant methods section.

Earliest and latest date of HIV clinic attendance:

The earliest date on which HIV clinical care was received was estimated using the earliest of: CD4 cell count; CD8 cell count; viral load measurement; ART start date; or AIDS event. The latest clinical date was the latest of: CD4 cell count; CD8 cell count; viral load measurement; ART start date, ART stop date; or AIDS event.

Hepatitis B virus (HBV) and Hepatitis C virus (HCV) co-infection:

Since all women in the UK CHIC-NSHPC dataset are HIV-positive, 'HBV/HCV co-infection' is used throughout to refer to HIV co-infection with either HBV, HCV or both HBV and HCV. As part of the routine data collection, the UK CHIC study collates data on hepatitis testing and test results. Few data were available on the timing of hepatitis infection, whether an individual received treatment for HCV infection or whether the treatment was effective. Women were categorised as having HBV/HCV co-infection if they had ever received a positive result for hepatitis C antibody or hepatitis B surface antigen. For analyses performed on the UK CHIC 2009 and UK CHIC 2010 datasets (Table 4.16), hepatitis status of women was determined using only data from UK CHIC.

In 2013, data on hepatitis status among patients attending HIV-related care at UK CHIC sites since 2004 was obtained from clinic notes at 11 of the 16 UK CHIC centres. The data collected included hepatitis test results, biopsy results and any use of hepatitis treatment. It was undertaken as part of Alicia Thornton's PhD project focusing on hepatitis co-infection within the UK CHIC cohort [413]. The 'enhanced' hepatitis data were available from the start of 2014. They were used to determine hepatitis status for the analyses undertaken on the UK CHIC 2011 and UK CHIC 2012 datasets. The existing UK CHIC dataset, provided by the centres as part of their routine annual data reporting, was used to determine hepatitis status for women who only attended HIV care prior to 2004 or who attended one of the five UK CHIC centres which did not provide enhanced hepatitis data.

With regard to HBV/HCV co-infection status, there were a small number of women with a discrepancy in the data available from their clinic notes (enhanced hepatitis data) and the existing data in UK CHIC. In these cases the clinic notes were taken as being correct. The UK CHIC data were only used if no data were available from the clinic notes.

#### 4.4 Categorising ART use in pregnancy

The UK CHIC and NSHPC datasets both contain data relating to ART use which could be used to categorise previous ART experience, ART use at conception and ART use in pregnancy. Combining the data from both studies was problematic, for example where there was a discrepancy. However, this was necessary in order to utilise all the available data pertaining to ART use.

All variables (reported and derived) relating to ART use are listed in Table 4.6 and Table 4.7. The numbers presented throughout this chapter refer to the UK CHIC-NSHPC 2009 dataset, and only pregnancies conceived in 2000-2009 where HIV was diagnosed before or during the pregnancy were included (n=2620). In the dataset, the maximum number of pregnancies any woman had was six. For this reason there are six variables for each of the variables which refer to a specific pregnancy, such as estimated date of conception or delivery date. If, for example, a woman only had one pregnancy then the variables 2-6 were left null.

Initially, ART status was assessed using the NSHPC and the UK CHIC data separately. Where the ART status was in agreement or where one study had any data, the final ART status was categorised accordingly. Where there was a discrepancy: one study indicating that the woman was using ART and the other indicating that she was not, data were examined and a series of criteria were developed to categorise ART use.

Table 4.6. NSHPC variables used to categorise antenatal ART use

Variable name	n	Variable type/categories	Reported/ Created	Description
EDC	6	Date	Created	Estimated date of conception (266 days before EDD)
DELIVERY	6	Date	Reported	Delivery date (or EDD if delivery date was missing)
QRT	6	Numeric	Reported	Calendar quarter - allowing cross reference to the ART data
PRETRT	6	Yes/No/NK	Reported	On ART at conception?
TRT	6	Yes/No/NK/Declined/Not yet	Reported	Received ART during pregnancy?
ART_REASON	6	Maternal health/PMTCT	Reported	Reason for ART use i.e. PMTCT or maternal health and PMTCT
NSHPC_START_ART	6	Yes/No/NK	Created	Yes if TRT = 'Yes' No if TRT = 'Declined' or 'No' NK if TRT = 'NK' or 'Not yet'
P_DRUGSTART	16	Date	Reported	Date that ART drug was started (either before or during the pregnancy)
P_DRUGSTOP	16	Date	Reported	Date that ART drug was stopped
P_DRUG	16	Text	Reported	ART drug name
P_DRUG_CON	16	Yes/No	Reported	Were they on the ART drug at conception?
P_QRT	16	Numeric	Reported	Calendar quarter - allowing cross reference to the pregnancy

EDD: expected date of delivery; NK: not known; PMTCT: prevention of mother-to-child transmission

Table 4.7. UK CHIC variables used to establish ART use

Variable name	n	Variable type/code	Created/ Reported	Description
DSTART	78	Date	Created <sup>1</sup>	Date started ART drug
DSTOP	78	Date	Created <sup>1</sup>	Date stopped ART drug
DRUG	78	Coded	Reported	ART drug
EARLIEST_DATE	1	Date	Created	Earliest date in UK CHIC (i.e. earliest viral load/CD4 count/DSTART)
SEEN_PREG	6	Yes/No	Created	Attended care at a UK CHIC site during the pregnancy <sup>2</sup>
SEEN_12MB4	6	Yes/No	Created	Attended care at a UK CHIC site in the year before conception <sup>2</sup>
SEEN_6MB4	6	Yes/No	Created	Attended care at a UK CHIC site in the 6 months before conception <sup>2</sup>
FIRST_IN_CHIC	6	Before/During/After/NK <sup>3</sup>	Created	Timing of earliest attendance in UK CHIC in relation to the pregnancy <sup>4</sup>

<sup>1</sup>Drug dates are either reported or derived by the UK CHIC statistician Sophie Jose from drug data submitted in a different format

<sup>2</sup>A woman was categorised as having attended HIV care if she had a CD4 cell count, viral load measurement or DSTART

<sup>3</sup>This variable is categorised as NK if the EARLIEST\_DATE was null, i.e. no clinical data were reported for the woman in UK CHIC

<sup>4</sup>According to the EARLIEST\_DATE

## 4.5 Using NSHPC and UK CHIC variables to assess ART use

A hypothetical example is shown in Figure 4.3 and Table 4.8. In this example, the woman had two pregnancies, the first in 2006 and the second in 2009. During her first pregnancy she was diagnosed with HIV and at that point received HIV clinical care for the first time. This meant that her EARLIEST\_DATE was during her first reported pregnancy, so the variable FIRST\_IN\_CHIC\_1 was categorised as 'during'. She used a short-course triple ART regimen during her first pregnancy, stopping ART use within a week of delivery. Some years later, she started life-long ART and was still on this triple regimen when she conceived her second pregnancy. She remained on that regimen throughout the pregnancy and after delivery. As such, at the end of follow-up, the variables DSTOP 4-6 were null as were the variables EDC3-EDC6 and DELIVERY3-DELIVERY6 (as she only had two pregnancies).

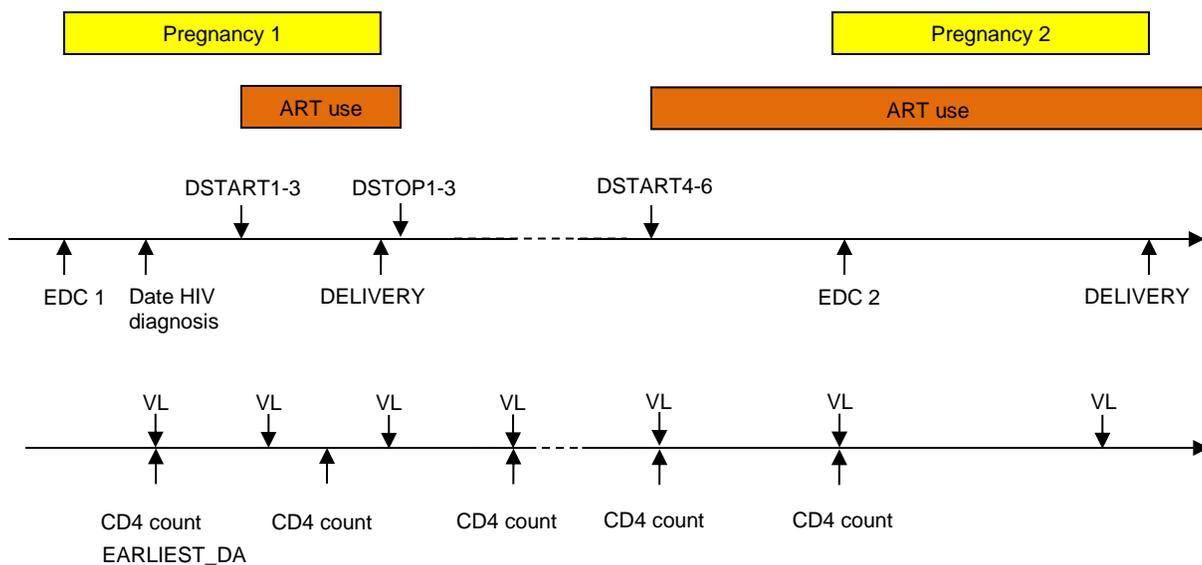
Table 4.8. UK CHIC and NSHPC variables and dates used to assess the timing of ART use in relation to pregnancies (from the hypothetical example in Figure 4.3)

NSHPC	UK CHIC	Date (dd/mm/yy)
EDC1		01/02/06
	HIV Diagnosis	01/04/06
	EARLIEST_DATE	04/04/06
P_DRUGSTART1-3	DSTART1-3	14/06/06
DELIVERY1		25/10/06
P_DRUGSTOP1-3	DSTOP1-3	31/10/06
P_DRUGSTART4-6 <sup>1</sup>	DSTART4-6	20/02/08
EDC2		01/04/09
DELIVERY2		25/12/09

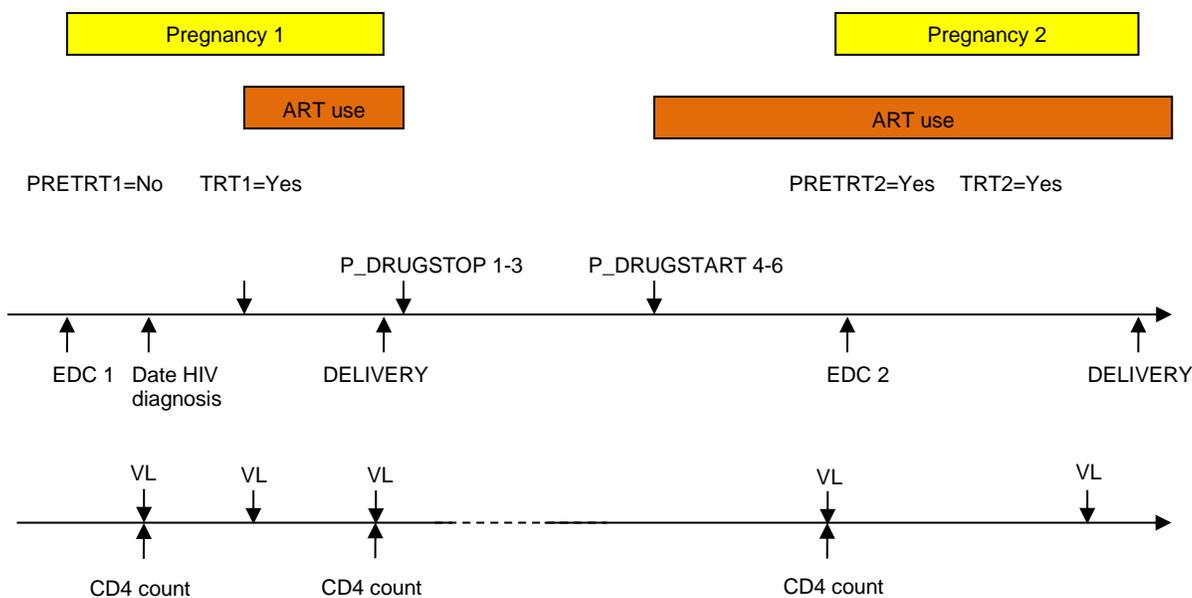
<sup>1</sup>These dates are reported when the pregnancy is reported to the NSHPC in 2009

Figure 4.3. Diagram showing UK CHIC and NSHPC variables used to assess the timing of ART use (orange boxes) in relation to pregnancies (yellow boxes) (where the x axis represents time)

a.) UK CHIC variables



b.) NSHPC variables



#### 4.5.1 ART use at conception

ART use at conception was categorised using UK CHIC and NSHPC data (the criteria used are outlined in Appendix VI : Table 1). There was agreement (between UK CHIC and NSHPC data) in the categorisation of ART use at conception for 2188 pregnancies (887 on ART, 1296 not on ART, 5 NK), a further 1080 pregnancies had data on ART use at conception available in only one study (93 on ART, 989 not on ART) and 185 pregnancies had discrepant data (Table 4.9).

Table 4.9. ART use according to UK CHIC and the NSHPC

	NSHPC		
	On ART	Not on ART	NK
UK CHIC	6 months before conception		
On ART	336	7	560
Not on ART	18	14	453
NK	35	814	383
	Conception		
On ART	887	100	9
Not on ART	85	1296	7
NK	84	982	5
	During pregnancy		
On ART	2210	15	23
Not on ART	144	39	32
NK	99	32	26

There were 85 pregnancies where the UK CHIC data indicated that ART was not being used at the estimated time of conception but the NSHPC data indicated that it was. These records were manually reviewed to determine the possible reasons for the discrepancies and how best to categorise ART use (Table 4.10). Following review, 60 pregnancies were re-categorised as being on ART at conception, 20 pregnancies as not being on ART and 5 as ART use not known.

There were a further 100 pregnancies where the UK CHIC data indicated that ART was being used at conception but the NSHPC data indicated that it was not. These were reviewed and the reasons for the discrepancies are summarised in Table 4.11. Following review, 35 pregnancies were re-categorised as on ART at conception, 61 as not on ART and 4 as ART status not known.

Pregnancies with a discrepancy in ART use at conception were compared to those without a discrepancy. The chance of having a discrepancy increased slightly over time (odds ratio [OR] 1.06 [95% confidence interval CI 1.0-1.3]  $p=0.04$ ). Having a discrepancy was not associated with ethnicity or with the HIV clinic that was attended.

Overall, 1049 (40%) pregnancies were categorised as having ART use at the time of conception, 1559 (60%) as no ART use, and 12 (0.5%) as ART status not known (3 with no data in either dataset and 9 due to an unresolved discrepancy).

Table 4.10. Discrepancies between ART status at conception (UK CHIC not on ART vs. NSHPC on ART) (n=85)

Reason for discrepancy	n	ART status
No clinical data reported in UK CHIC (CD4, ART or VL) for the woman in the 12 months before pregnancy	20	On ART
No clinical data in UK CHIC (CD4, ART or VL) for the woman in the 6 months before and during pregnancy	10	On ART
ART was started (according to UK CHIC) within 7 days of the EDC	1	On ART
Short treatment interruption (according to UK CHIC) around the time of the EDC	5	On ART
Viral load at conception <1000 copies/ml indicating ART was being used but not recorded in UK CHIC	20	On ART
≥1000 copies/ml indicating ART was not being used	11	Not on ART
Viral load at conception and in 12 weeks before pregnancy was null and viral load at 12 weeks gestation was ≥1000 copies/ml	1	Not on ART
Women started ART (according to UK CHIC) after the pregnancy but had viral load ≤50 copies/ml at that time indicating that they were probably already on ART	2	On ART
Conflicting data on ART status in the NSHPC data	2	Not on ART
Limited data in ART status in NSHPC record (ie. no date or drug information provided)	6	Not on ART
	2	On ART
Not known	0	Not on ART
	5	Not known

ART: antiretroviral therapy; EDC: Estimated date of conception; VL: viral load

Table 4.11. Discrepancies between ART status at conception (UK CHIC on ART vs. NSHPC not on ART) (n=100)

Reason for discrepancy	n	ART status	
ART use was ZDVm (in UK CHIC) started in previous pregnancy – indicating that drug stop dates were missing	6	Not on ART	
Previous use of combination ART (in UK CHIC) started in pregnancy with CD4 count >350 cells/mm <sup>3</sup> indicating that drug stop dates were missing	11	Not on ART	
No drug start or stop dates reported by NSHPC	6	On ART	
Viral load at conception	<1000 copies/ml indicating ART use at that time	18	On ART
	≥1000 copies/ml indicating no ART use at that time	26	Not on ART
Viral load 6 months before conception <sup>1</sup>	<1000 copies/ml indicating ART use at that time	10	On ART
	≥1000 copies/ml indicating no ART use at that time	5	Not on ART
Viral load at 12 weeks gestation	≥1000 copies/ml indicating no ART use <sup>1</sup>	8	Not on ART
Not known		1	On ART
		5	Not on ART
		4	Not known

<sup>1</sup> No viral load data from the time of conception was reported. ZDVm: Zidovudine monotherapy.

#### 4.5.2 ART use at 6 months before conception

As with ART status at conception, ART status at six months before pregnancy was established for NSHPC and UK CHIC separately, and then both were used to create a combined variable. The criteria used are outlined in Appendix VI : Table 2.

ART status at 6 months before conception was in agreement for 733 pregnancies (336 on ART, 14 not on ART, 383 NK), a further 1862 records had ART status available from only one study (595 on ART, 1267 not on ART) and 25 pregnancies had a discrepant ART status in UK CHIC and NSHPC (Table 4.9). The reasons for these discrepancies were investigated and summarised in Table 4.12. In the final dataset, 906 (35%) pregnancies were categorised as being on ART at 6 months before conception, 1557 (59%) as not being on ART and 157 (6%) as ART use not known (Table 4.13).

Table 4.12. Discrepancies between ART status in UK CHIC and NSHPC datasets at 6 months before conception

Reason for discrepancy	n	ART status
<b>UK CHIC not on ART vs. NSHPC on ART</b>	<b>18</b>	
Viral load at 6 months before conception <1000 copies/ml indicating ART use at that time	7	On ART
≥1000 copies/ml indicating no ART use at that time	4	Not on ART
Short treatment interruption due to treatment switch (according to UK CHIC) around this time	1	On ART
Started ART 5 months before conception according to UK CHIC and 6-12 months before according to NSHPC	3	On ART
Other	3	Not known
<b>UK CHIC on ART vs. NSHPC not on ART</b>	<b>7</b>	
Viral load at 6 months before conception <1000 copies/ml indicating ART use at that time	4	On ART
≥1000 copies/ml indicating no ART use at that time	1	Not on ART
Other	2	Not known

Table 4.13. Summary of ART use at six months before conception according to UK CHIC, NSHPC and in the final dataset (n=2060)

UK CHIC	NSHPC	Final dataset	n	Drug data used <sup>1</sup>
Yes	Yes	Yes	336	UK CHIC
Yes	NK	Yes	520	UK CHIC
		NK	40 <sup>2</sup>	-
NK	Yes	Yes	35	NSHPC
No	No	No	14	-
No	NK	No	439	-
		NK	14 <sup>3</sup>	-
NK	No	No	814	-
NK	NK	NK	98	-
		No	285 <sup>4</sup>	-
		Yes	11	NSHPC
No	Yes	No	4	-
		NK	3	-
		Yes	4	NSHPC
Yes	No	No	1	-
		NK	2	-

<sup>1</sup>Drug regimen, number of drugs and drug start and stop dates.

<sup>2</sup>NSHPC data indicated that ART was not being used at the time of conception.

<sup>3</sup>NSHPC data indicated that ART was being used at the time of conception.

<sup>4</sup>HIV diagnosis date was after 6 months before conception (n=77). ART was not being used at conception (n=208).

#### 4.5.3 ART use at 6 and 12 months after delivery

As limited data were available from NSHPC on drug use after pregnancy, only UK CHIC data were used to categorise ART use at 6 and 12 months after delivery (Appendix VI : Table 3).

#### 4.5.4 ART use during pregnancy

As with ART use at conception, ART use during pregnancy was categorised using NSHPC and UK CHIC data separately and then a combined variable was created (Appendix VI : Table 4).

UK CHIC and NSHPC were in agreement for the majority of pregnancies (n=2371, 90.5%) (ART status was: n=2332 on ART; n=39 not on ART), 195 (9.5%) pregnancies had ART status only available from one study (ART status was: n=122 on ART; n=64 not on ART) and a further 26 pregnancies did not have ART status available from either. There were 159 pregnancies with discrepant ART status (Table 4.9).

Where data from the NSHPC indicated that the woman was on ART at some point during the pregnancy and UK CHIC indicated that they were not (n=144) they were categorised as being on ART in the final dataset. It could be that the ART drugs prescribed during pregnancy were not noted in their medical notes at the site where they received their ongoing HIV clinical care.

There were 15 pregnancies in which the UK CHIC data indicated that ART was used but the NSHPC data indicated that it was not. This could be because the NSHPC reporting form was completed prior to ART initiation. UK CHIC drug start dates indicate that some of these women took ART for only a short time during the pregnancy (close to the end), indicating that they may have declined treatment initially and accepted treatment at a later time during the pregnancy or delayed ART start for some other reason. If, according to UK CHIC, they had not conceived on ART, but started ART during pregnancy the woman was re-coded as being on ART. This gave a total of 2457 (94%) that were categorised as being on ART, 103 (4%) as not on ART and a further 60 (2%) pregnancies where ART status was not known (Table 4.14).

Table 4.14. Summary of ART use during pregnancy according to UK CHIC and NSHPC and its final categorisation in the combined dataset (n=2060 pregnancies)

UK CHIC	NSHPC	Final dataset	n	Drug data used <sup>1</sup>
Yes	Yes	Yes	2210	NSHPC
Yes	NK	Yes	23	UK CHIC
NK	Yes	Yes	99	NSHPC
No	No	No	39	-
No	NK	No	32	-
NK	No	No	32	-
NK	NK	NK	26	-
No	Yes	Yes	118	NSHPC
		No	0	-
		NK	26	-
Yes	No	Yes	7	UK CHIC
		No	0	-
		NK	8	-

<sup>1</sup>Drug regimen, number of drugs and drug start and stop dates.

#### 4.5.5 Categorising ART use during pregnancy

ART status at 6 months before conception, at conception, during pregnancy and at 6 and 12 months after pregnancy (the variables previously described) were used to categorise ART use during pregnancy into broad categories (Appendix VI : Table 5).

1. ART use limited to pregnancy and post-pregnancy.

This refers to women who started ART in pregnancy and stopped ART within six months of delivery. It includes women with a CD4 count above 350 cells/mm<sup>3</sup> who used short-course ART in pregnancy for PMTCT and stopped ART at delivery. It also includes a smaller number of women who, according to treatment guidelines, should have started life-long ART but stopped ART within 6 months of delivery.

2. Long term treatment used for the woman's own health continued after delivery.

Additional variables were created to indicate whether the woman was also pregnant at 6 months before or at 6 or 12 months after the pregnancy of interest, and if they were pregnant at that time, whether there had been a gap in treatment between pregnancies.

In some cases categorising ART use was straightforward, for example if the woman was using ART before, during and after the pregnancy. However, the data were more complex for many pregnancies due to treatment interruptions either before, during or after pregnancy.

Overall, ART use was limited to the time of pregnancy and post-pregnancy in 31% (n=823) of pregnancies. For 39% (n=1023) of the pregnancies, ART was being used at the time of conception (18 of these conceived during a short treatment break/interruption), and life-long ART was started during 19% (n=493) of pregnancies. ART was not used (or at least no ART use was reported) during 4% (n=103) of the pregnancies in the dataset, 35 of these went to full term (30 resulting in a live birth), 45 resulted in a miscarriage and 23 were terminated. ART category was not available for 7% (n=178) of pregnancies.

The way that ART use was categorised was simplified for the analysis of response to treatment following short-course ART use in pregnancy (Chapter 6). The simplified criteria were outlined in the relevant methods section.

## 4.6 Start date for life-long ART

A series of criteria were developed to pinpoint the date on which each woman started life-long ART. Previously, the first date on which any ART drug was started (the DSTART1 variable in the UK CHIC dataset) was used as the ART start date. However, it was not appropriate to use this date since women could have used short-course ART in one or more pregnancies for PMTCT before subsequently starting ART for therapeutic reasons.

Initially, a dataset was created including all women reported to UK CHIC and antenatal data from NSHPC for those with a pregnancy (i.e. the UK CHIC-NSHPC 2009 dataset was merged with the UK CHIC 2009 dataset). The dataset contained 9726 women, 7898 of whom were aged 16-49 years when they attended care, 2063/7898 of whom had a pregnancy reported to NSHPC. Since only women with a pregnancy had data in both datasets, only ART dates and CD4 cell counts from UK CHIC were considered (i.e. the NSHPC data for these variables were ignored).

Using ART start and stop dates, each period of ART use was measured and variables were created characterising the woman at the start of each period. These variables included: CD4 cell count, pregnancy status, AIDS diagnosis and HBV diagnosis. Each period of non-ART use was also measured.

The start of the earliest period of ART use which met any of the criteria outlined in Table 4.15 was used as the start date for life-long ART. This was typically the first period of any ART use but in some cases followed one or multiple short periods of ART use (in pregnancy). Some women had a short period of ART use outside pregnancy, not meeting the criteria. This was not considered as the start date of life-long ART.

Table 4.15. Criteria used to indicate if and when life-long ART was started among women who attended HIV clinical care at a UK CHIC site in 2000-2009 aged 16-49 (n=7898).

Criteria <sup>1</sup>	Started life-long ART <sup>2</sup>	n	%	
ART use ≥12 months	Yes	4286	54	
ART use ≥12 months with interruptions <3 months	Yes	233	3	
ART started within 3 months of AIDS diagnosis	Yes	111	1	
ART started with CD4 count <200 cells/mm <sup>3</sup>	Yes	475	6	
ART started with CD4 count <350 cells/mm <sup>3</sup>	a. Not during pregnancy	Yes	338	4
	b. During pregnancy (year ≥2008)	Yes	36	<1
ART started following diagnosis of HBV <sup>3</sup> (year ≥2008)	Yes	3	<1	
ART started with CD4 % <14 (year ≥2008)	Yes	39	<1	
ART started outside pregnancy <9 months before end of follow-up and still on ART at end of follow-up	Yes	171	2	
No evidence of ART use	No	1625	21	
Not on ART at end of follow-up but short period/s of ART use (<12 months) were started during pregnancy or with CD4 count >350 cells/mm <sup>3</sup>	No	496	6	
Inconclusive treatment patterns or limited follow up period <sup>4</sup>	Yes	18	1	
	No	5	<1	
	NK	62	<1	

<sup>1</sup> The start of the earliest period meeting any criteria was used as the start date for life-long ART

<sup>2</sup> By end of follow-up

<sup>3</sup> Defined as a positive result for hepatitis B surface antigen test in the 3 months before starting ART

<sup>4</sup> Assigned after manual review

On the last day of follow-up, of the 7898 women (aged 16-49) who accessed HIV clinical care at a UK CHIC site at some point during 2000-2009, 5710 (72%) had already started life-long ART, 2126 (27%) had not started life-long ART and 62 (1%) had not started life-long ART but had previously been on ART. Among the women who started life-long ART, 93% (5281/5710) had no previous ART experience when starting.

#### 4.7 Summary data for UK CHIC-NSHPC combined datasets used in 2009-2012

The linkage between the NSHPC and UK CHIC datasets was repeated annually using the most up-to-date datasets available. The number of women included in each dataset is summarised in Table 4.16. Over the four years for which the datasets were linked, the UK CHIC-NSHPC combined dataset included 21%-26% of the women in UK CHIC and 23%-30% of the women in the NSHPC dataset. There was an increase in the percentage of women linked in the 2010 compared to in 2009 (from 21% to 25% of UK CHIC and from 23% to 30% of NSHPC). After this, the percentage of women included was fairly consistent across the 2010, 2011 and 2012 datasets. The increase in percentage of women included from the 2009 to the 2010 dataset might, in part, be due to improved competence in the linkage process, although this would probably only have a small impact, since the same coding was used and updated. It is more likely that the improvement was due to improvements in the data quality since this was a time when the HIV commissioners started using patient outcomes data and when national HIV reporting to Public Health England was altered to collect more detailed and data more regularly.

Each year it took around nine months for the UK CHIC data to be collated, validated, de-duplicated and then linked to the NSHPC data. The last two analyses were performed in 2014 using the 2012 dataset, since the 2013 dataset was not yet finalised. These two analyses were then published in early 2015 [414, 415] and the PhD submitted later that year.

Table 4.16. Summary of the matching between UK CHIC and NSHPC and the creation of combined datasets: 2009-2012

UK CHIC-NSHPC combined dataset	2009	2010	2011	2012
<b>UK CHIC</b>				
Data to end (year)	2009	2010	2011	2012
Number of HIV clinics contributing data	13	15	16	19
Number of women in dataset <sup>1</sup>	9726	11,305	11,971	12,970
Percentage found in NSHPC	21%	25%	26%	26%
<b>NSHPC</b>				
Date of archive	Sept 2010	Sept 2011	June 2013	March 2014
Number of women in dataset <sup>2</sup>	8929	9501	10,556	11,033
% found in UK CHIC	23%	30%	30%	30%
<b>UK CHIC-NSHPC combined dataset</b>				
Total number of women	2063	2823	3150	3317
Total number of women after exclusions <sup>3</sup>	2048	2793	3070	3283
Pregnancies conceived in the period of interest <sup>4</sup>	2634	3733	4291	4732
Pregnancies conceived in 2000-2009 <sup>5</sup>	2634	3475	3584	3652

<sup>1</sup> This includes women with CD4 cell count/viral load measurements at any point since 1995. In each dataset <5 women were excluded because they had no DOB reported

<sup>2</sup> This excludes women who only attended antenatal care in Ireland/Isle of Man/Channel Islands and women diagnosed with HIV after delivery of their only/last reported pregnancy

<sup>3</sup> Women were excluded if they only had a pregnancy starting after the period for which UK CHIC data was available

<sup>4</sup> 2000 to end 2009/2010/2011/2012

<sup>5</sup> In this row each column contains data for to the same period of time thereby allowing comparison between the datasets

# Chapter 5 Predictors of pregnancy and trends in ART use and pregnancy incidence among women accessing HIV clinical care

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## 5.1 Introduction

Diagnosed HIV-positive women accessing HIV clinical care in the UK include women of different ethnicities, ages and levels of morbidity [416]. The characteristics of this diverse group have continued to change over time such that current clinic populations now include an increasing proportion of older women and women on antiretroviral therapy (ART) [417]. With advances in ART and developments in prescribing practice [78, 418, 419] leading to the improved wellbeing and longevity of HIV-positive women [59, 420], coupled with effective prevention of mother-to-child-transmission (PMTCT) [131, 149] many women living with HIV choose to have children [163, 170]. In many cases, women have consecutive pregnancies [160, 421]. This increased pregnancy rate is occurring both in women who are already on life-long ART as well as diagnosed women with no current indication to start treatment i.e. those without symptoms who have a high CD4 count [171].

In the UK and Ireland, almost three-quarters of pregnancies in HIV-positive women are now in women already diagnosed [422]. The changing demographic and clinical characteristics of pregnant women living with HIV are likely to reflect, to some extent, the changing characteristics of all women living with HIV in the UK. However, there may also be changes in the pregnancy rate among specific subgroups. For example, as the proportion of diagnosed women receiving ART has increased, so we would expect the proportion of pregnant women who conceive on ART to also increase. We would also expect an increase in the average age of women conceiving due to an increase in the number of repeat pregnancies and an increase in the median age of women having children seen in the general population [402].

A paper summarising the data presented in the latter half of this chapter was published in 2013 and is included in Appendix IIb [423].

## 5.2 Methods

The main objectives of this chapter were, in HIV-positive diagnosed women, to identify factors predictive of having a pregnancy and changes in the pregnancy incidence. The analysis was split into two sections:

### 1) All women in UK CHIC with a pregnancy

Using the UK CHIC-NSHPC 2009 dataset, the number of pregnancies conceived each year and the use of ART at conception and during each pregnancy were assessed using generalized estimating equations (SAS command PROC GENMOD) accounting for repeat measures.

### 2) Women attending HIV clinical care at a UK CHIC site

- Characteristics of women attending clinical care
- Characteristics of women with a pregnancy
- Factors predictive of having a pregnancy
- Pregnancy incidence over time

For the second part of the analyses, the UK CHIC 2009 and UK CHIC-NSHPC 2009 datasets were combined to produce a dataset containing data for all women reported to UK CHIC at any point during 2000-2009 plus NSHPC data for women with a pregnancy during that period. The dataset was reformatted so that it contained one row per woman per year. It only included data for years in which some clinical data were available and when the woman was of childbearing age (16-49 years). This meant that pregnancies conceived during a calendar year in which the woman did not access care at a UK CHIC site were excluded.

Variables included in the dataset were: ethnicity, probable route of HIV infection, age at start of year, ART status at start of year, earliest CD4 count in the year (determined using UK CHIC data) and whether the women became pregnant during that year. For women with a pregnancy, data were also included on the estimated date of conception (EDC), pregnancy outcome and whether the pregnancy was an index or repeat pregnancy. Index pregnancy referred to the first pregnancy after HIV-diagnosis in the UK or the pregnancy during which HIV-diagnosis occurred, whereas repeat pregnancy referred to any subsequent pregnancy (even if it was their first pregnancy during the study period). As pregnancies could overlap two calendar years, the year of pregnancy referred to the year of the EDC.

Pregnancies resulting in a live or stillbirth were categorised as ending at delivery and pregnancies resulting in miscarriage or termination, and ectopic pregnancies, were categorised as ending early. Where pregnancy outcome was not known (n=23), the pregnancy was excluded from the analysis of factors predictive of pregnancy outcome.

As only women with a pregnancy had any data in the NSHPC dataset, UK CHIC data alone were used to determine ethnicity, route of infection, HIV diagnosis date, ART status and CD4 count.

If a woman was diagnosed with HIV during her index pregnancy and attended care for the first time during that year (463 pregnancies), the attendance and pregnancy for that year were excluded (i.e. removed from the numerator and denominator for that calendar year). However, all future years during which the woman attended care (and any subsequent pregnancies) were included. If a woman had more than one pregnancy starting in the same calendar year, only the first was considered (only 5 women conceived two pregnancies in the same year which both resulted in a live or stillbirth). In a separate analysis, in order to assess trends in index pregnancies, women with an index pregnancy before 2000 were excluded as were data for all years following an index pregnancy (among women who had an index pregnancy in 2000-2009). Data were manipulated in this way because once a woman had an index pregnancy she was no longer 'at risk' of having a further index pregnancy.

The characteristics of women under follow-up and with a pregnancy in each year were first described. The pregnancy rate was described for each calendar year using the number of women (aged 16-49 years) with clinical data in UK CHIC as the denominator and the number with a pregnancy (all outcomes) starting during that year as the numerator.

Predictors of pregnancy were identified using generalised estimating equations (Poisson regression), unadjusted and adjusted for year, age, CD4, ethnicity and ART use (Yes/No binary variable), and accounting for repeat measures. I also considered the addition of interaction terms between calendar year and each covariate in the model in order to investigate whether there was evidence that calendar year trends varied in some subgroups of the population. The model parameters were centred so that the intercept provided the predicted pregnancy rate in 2005 for a woman aged 30 years. Trends in index pregnancies were assessed in a similar way, although as women could only have one index pregnancy, this assessment did not take account of repeat measures.

## 5.3 Results

### 5.3.1 Overall number of pregnancies and ART use in pregnancy

A total of 2620 pregnancies were conceived in the 1888 women attending care in 2000-2009; 1306 women (69%) had a single pregnancy, 459 (24%) had two pregnancies, 102 (5%) had three, and 21 (1.1%) had four or five pregnancies. The total number of pregnancies conceived each year increased in the period 2000-2006 (from 159 to 321) but decreased subsequently to 280 in 2009 (Table 5.1). A small number of women had two pregnancies starting in the same calendar year. This meant that the number of pregnancies in some years was slightly higher than the number of women with a pregnancy in that year. In most cases, the first of the two pregnancies resulted in a miscarriage (21/28).

Information on the use of ART at the time of conception was available for 2339 (89%) pregnancies. Where ART status was known, the percentage of women on ART when they conceived increased over time (22.6% [124/548] in the period 2000-2003 compared to 45.0% [399/886] in the period 2007-2009) (Figure 5.1 and Table 5.1). These denominators included pregnancies among women who were not diagnosed with HIV when they conceived.

Among women who were on ART when they conceived, non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimens were the most commonly used (53% [474/901]). The use of protease inhibitor (PI)-based regimens increased during the decade (29% [10/35] in 2000 and 46% [62/136] in 2009), whilst the use of regimens which contained only nucleoside reverse transcriptase inhibitors (NRTIs) fell from a peak of around 15% in 2002 to 1.5% (2/136) by 2009 (Figure 5.2 and Table 5.1).

Over the decade, the use of short-course ART (including combination ART [cART] and zidovudine monotherapy [ZDVm]) in pregnancy declined among women not on ART when they conceived (from 64% in 2000 to 59% in 2009). At the same time, there was an increase in women starting life-long ART during pregnancy (Table 5.2 and Figure 5.3).

Table 5.1. ART use among HIV-positive women with a pregnancy starting in 2000-2009 that resulted in a live or stillbirth

Year of conception	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	Total	OR/Coefficient (95% CI)	p-value (trend)
Number of women with a pregnancy	156	185	202	270	299	288	316	310	290	275	2591	-	-
Number of pregnancies	159	187	202	271	299	295	321	313	293	280	2620	-	-
Number of pregnancies where ART status at conception was known <sup>1</sup>	131	168	184	250	270	272	292	290	253	229	2339	-	-
Pregnancies conceived on ART	35	42	47	84	87	101	106	125	138	136	901		
% (of those with known ART status)	26.7	25.0	25.5	33.6	32.2	37.1	36.3	43.1	54.5	59.4	38.5	1.21 (1.17-1.25)	<0.001
Median time since HIV-diagnosis (years)	2.7	4.2	4.3	3.3	4.2	4.8	3.7	5.0	4.9	5.9	4.6	1.07 (1.04-1.09)	<0.001
Type of ART regimen used (%)													
NNRTI-based	51.4	69.0	42.6	51.2	60.9	56.4	55.7	47.2	48.6	50.7	52.6	1.10 (0.41-2.97)	0.85
PI-based	28.6	14.3	27.7	31.0	21.8	35.6	34.0	48.0	47.1	45.6	37.0	1.17 (1.11-1.24)	<0.001
NRTIs-only	0.0	11.9	14.9	11.9	13.8	5.9	3.8	2.4	1.4	1.5	5.7	0.74 (0.74-0.90)	<0.001
Other/not specified	20.0	4.8	14.9	6.0	3.4	2.0	6.6	2.4	2.9	2.2	4.8	0.79 (0.70-0.89)	<0.001

<sup>1</sup>ART use during pregnancy was other/not known for 80 pregnancies: this included 29 pregnancies where ART data was incomplete, 35 pregnancies where the woman was on ART before and after the pregnancy but not on the EDC and 16 pregnancies where the woman was receiving ART before the pregnancy but was not on treatment at 6 and 12 months after delivery. OR: Odds ratio – per additional year - calculated using logistic regression for variables which outcomes are percentages. Coefficient – per additional year - calculated using linear regression for time since diagnosis.

Figure 5.1. ART experience at the time of conception among pregnancies conceived from 2000 to 2009 (before or during which HIV was diagnosed)

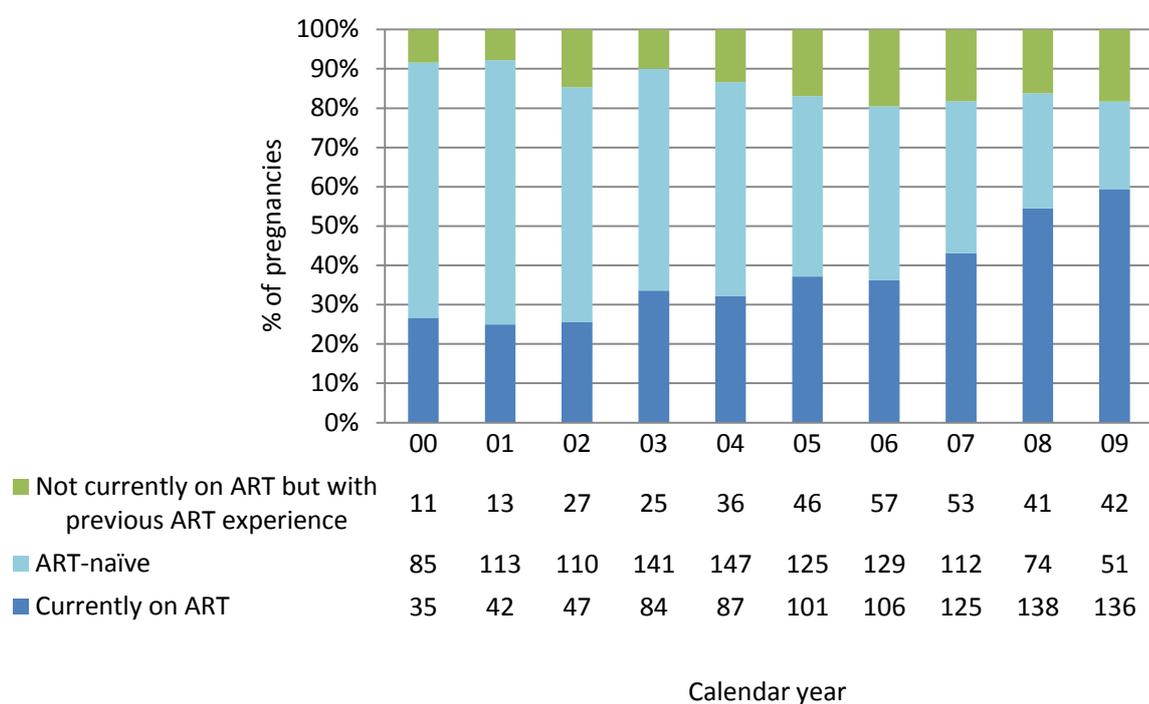


Figure 5.2. The type of regimen used by women on ART at conception

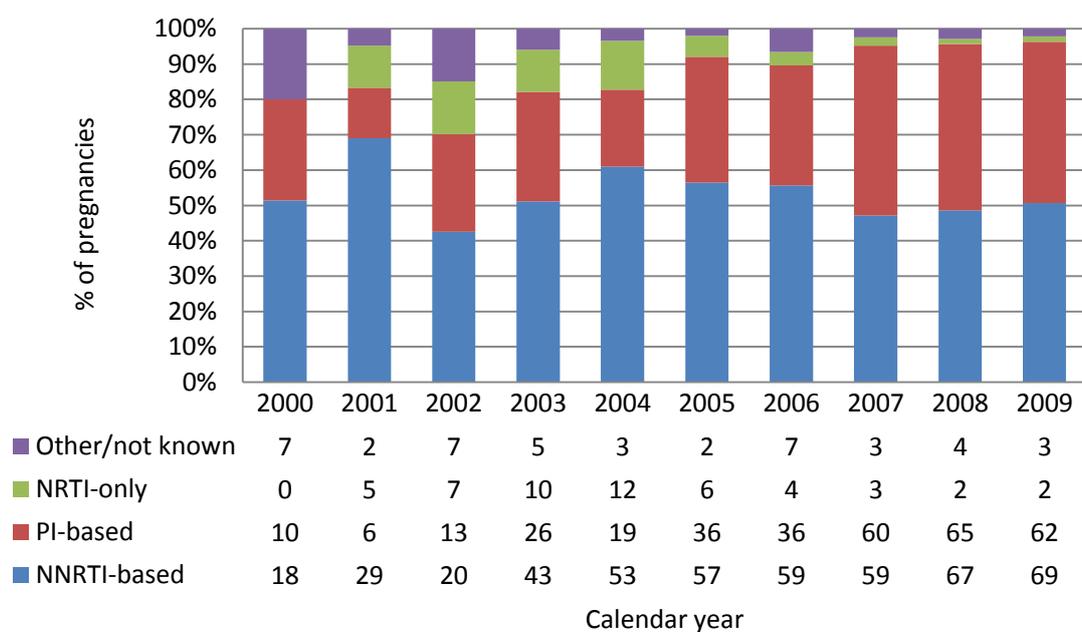


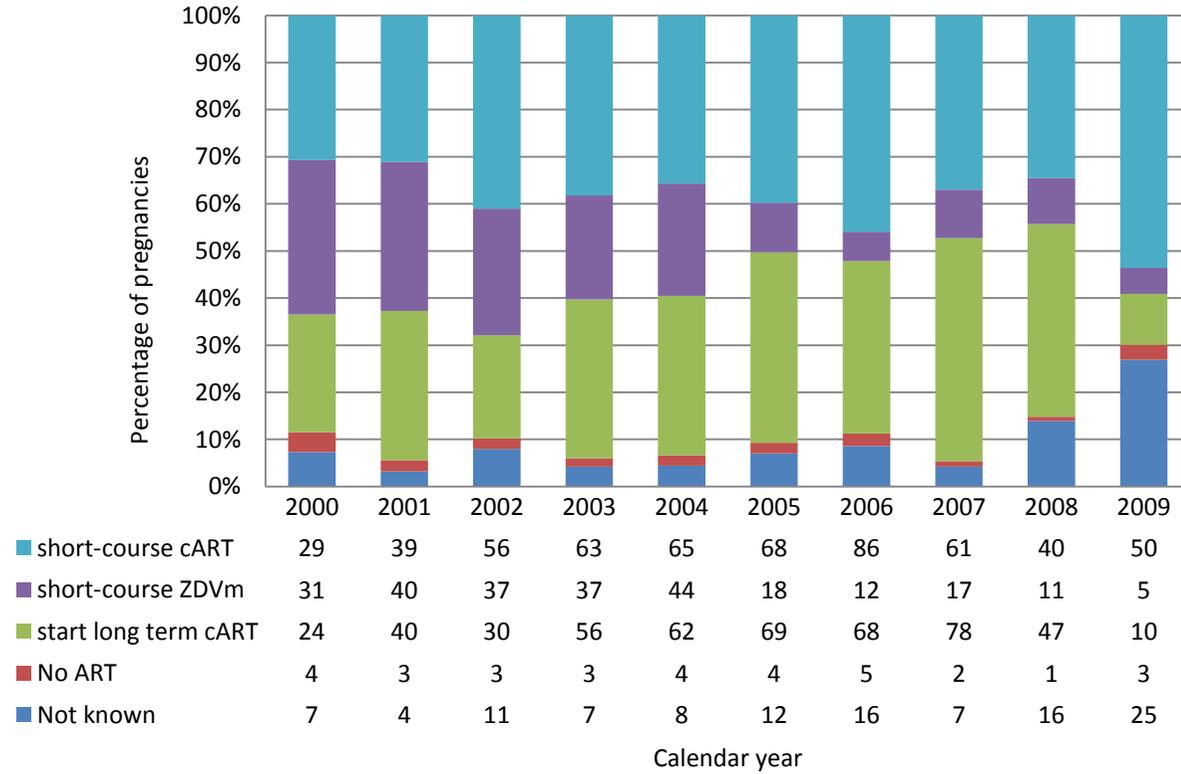
Table 5.2. ART use during pregnancy among HIV-positive women not on ART at conception with a pregnancy starting in 2000-2009 which resulted in a live or stillbirth

Year of start of pregnancy	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	Total	OR/Coefficient (95% CI)	p- value (trend)
Not on ART at time of conception	96	126	137	166	183	171	186	165	115	93	1438		
% (of those with known ART status)	73.3	75.0	74.5	66.4	67.8	62.9	63.7	56.9	45.5	40.6	61.5		
ART use in pregnancy (%)													
All short-course ART	63.5	62.7	67.9	60.2	59.6	50.3	52.2	47.3	44.3	59.1 <sup>1</sup>	56.3	0.90 (0.87-0.94)	<0.001
ZDVm (of those on short-course ART)	32.8	31.6	26.9	22.0	23.9	10.5	6.2	10.3	9.8	5.5	18.4	0.79 (0.73-0.85)	<0.001
Start life-long ART	25.0	31.7	21.9	33.7	33.9	40.4	36.6	47.3	40.9	10.8 <sup>1</sup>	33.7	1.05 (1.00-1.09)	0.03
No ART used	4.2	2.4	2.2	1.8	2.2	2.3	2.7	1.2	0.9	3.2	2.2	0.97 (0.77-1.22)	0.81
Other/not known	7.3	3.2	8.0	4.2	4.4	7.0	8.6	4.2	13.9	26.9 <sup>1</sup>	7.9	1.36 (1.20-1.54)	<0.001
Diagnosed prior to that pregnancy	34	43	56	61	80	80	115	97	66	65	697		
% (of those not on ART)	35.4	34.1	40.9	36.7	43.7	46.8	61.8	58.8	57.4	69.9	48.5	1.27 (1.12-1.22)	<0.001
Previous ART experience (n)	11	13	27	25	36	46	57	53	41	42	351		
% (of those not on ART at conception)	11.5	10.3	19.7	15.1	19.7	26.9	30.6	32.1	35.7	45.2	24.4	1.21 (1.15-1.27)	<0.001
% (of those not on ART at conception and diagnosed before that pregnancy)	32.4	30.2	48.2	41.0	45.0	57.5	49.6	54.6	62.1	64.6	50.4	1.16 (1.09-1.23)	<0.001
Median time since HIV diagnosis (years)	1.9	2.3	2.1	2.0	2.5	2.5	2.9	3.0	3.6	3.2	2.7	1.06 (1.03-1.10)	<0.001

Footnote for Table 5.2.

<sup>1</sup>The number of women starting life-long ART is likely to be underestimated and the number using short-course ART overestimated in 2009 due to limited follow-up time. OR: Odds ratio – per additional year - calculated using logistic regression for variables which outcomes are percentages. Coefficient – per additional year - calculated using linear regression for time since HIV-diagnosis.

Figure 5.3. ART use during pregnancies where the woman was not on ART at conception



NB: The number of women starting life-long ART is likely to be underestimated and the number using short-course ART overestimated in 2009 due to the limited follow-up time.

### 5.3.2 Pregnancies among women already attending HIV clinical care

#### **Characteristics of women attending clinical care at UK CHIC sites**

In total, 7853 women aged 16-49 years accessed HIV care at a UK CHIC site at some point during the period 2000-2009. During this time, the number of women accessing care more than doubled from 2074 in 2000 to 4876 in 2009 (Table 5.3). The majority of women accessing HIV care were of black-African ethnicity and most were infected via heterosexual sex (Table 5.3). The characteristics of women accessing care changed somewhat during the period of interest; the proportion of women of black-African, black-Caribbean or black-other ethnicity increased whilst the proportion of women of white ethnicity decreased. The proportion whose probable route of HIV infection was heterosexual sex increased whilst the proportion whose probable route of infection was injecting drug use (IDU) or contaminated blood/blood products decreased. The median age of women attending care increased from 33 to 37 years and the number of women in the oldest age group (36-49 years) almost quadrupled (Table 5.3 and Figure 5.4a).

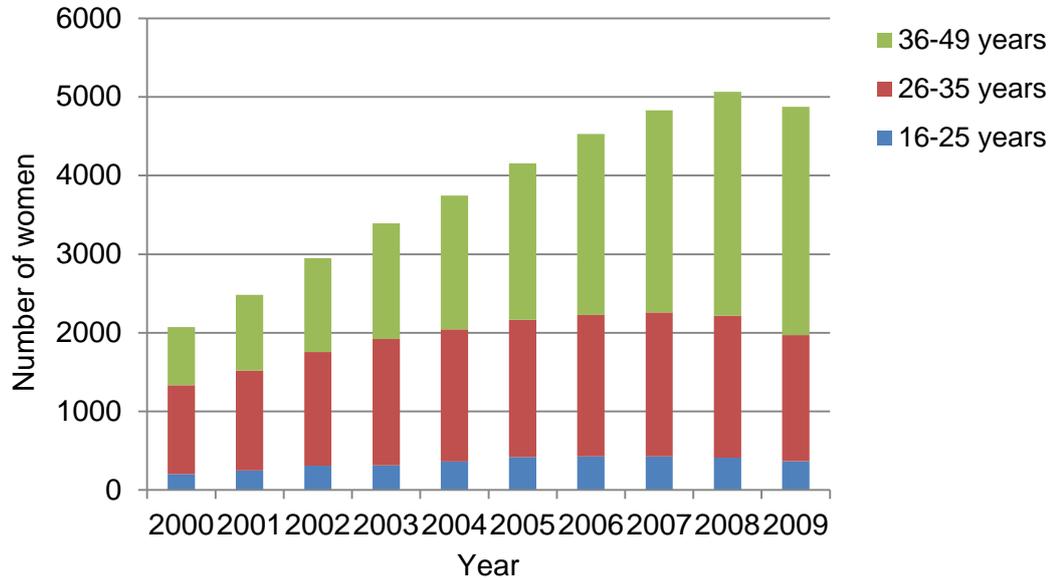
Age varied according to ethnicity; compared with black-African women, women of black-Caribbean, black-other or 'other' ethnicity were more likely to be in the youngest age group (16-25 years) whilst women of white ethnicity were less likely to be in this age group ( $p < 0.001$  in logistic regression) (data not shown). The proportion of women born in the UK varied by ethnicity (white, 64.3%, 594/924; black-African, 7.3%, 231/2284; black-Caribbean, 38.3%, 88/230, where country of birth was reported).

Table 5.3. Characteristics of all HIV-positive women of childbearing age receiving HIV clinical care at UK CHIC sites in 2000-2009

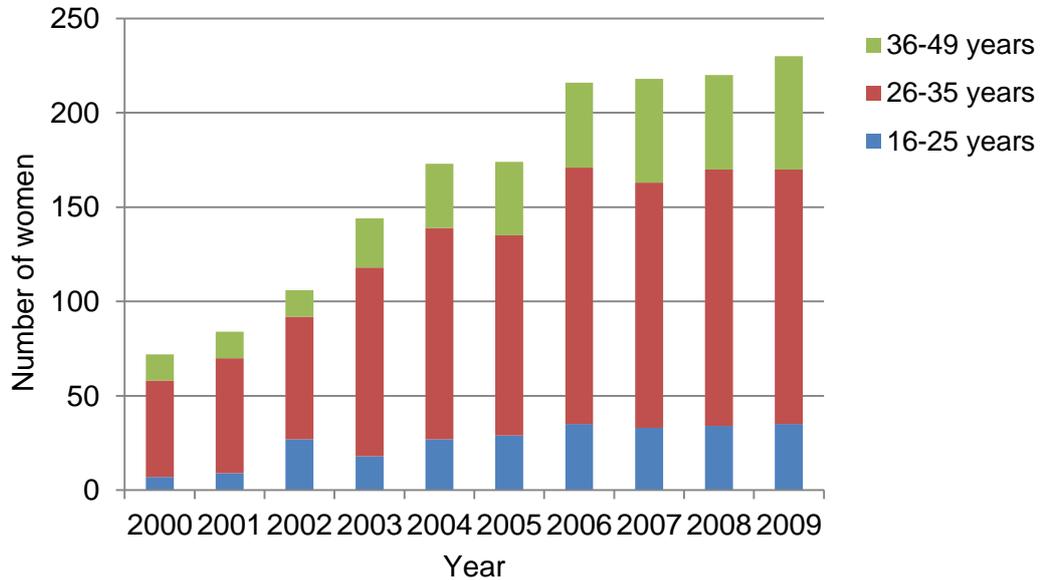
		2000/1	%	2002/3	%	2004/5	%	2006/7	%	2008/9	%
Number of women receiving HIV clinical care		4555		6340		7901		9359		9942	
Median age (years) [IQR]		33	[29-38]	34	[29-39]	35	[30-40]	36	[31-41]	37	[32-42]
Age group (years)	16-25	450	9.9	621	9.8	782	9.9	855	9.1	778	7.8
	26-35	2401	52.7	3059	48.2	3426	43.4	3631	38.8	3410	34.3
	36-49	1704	37.4	2660	42.0	3693	46.7	4873	52.1	5754	57.9
ART use	On ART	2220	48.7	3278	51.7	4371	55.3	5863	62.7	6780	68.2
	Not on ART	2335	51.3	3062	48.3	3530	44.7	3496	37.3	3162	31.8
CD4 count (cells/mm <sup>3</sup> )	≤200	1140	25.0	1336	21.1	1326	16.8	1226	13.1	1045	10.5
	201-350	1146	25.2	1602	25.3	2045	25.9	2121	22.7	1927	19.4
	>350	1849	40.6	2979	47.0	4131	52.3	5542	59.2	6654	66.9
	NK	420	9.2	423	6.7	399	5.0	470	5.0	316	3.2
Median CD4 (cells/mm <sup>3</sup> ) [IQR]		338	[220-532]	353	[217-520]	380	[247-543]	420	[280-583]	463	[319-640]
Probable route of infection	Heterosexual sex	3606	79.2	5238	82.6	6703	84.8	7883	84.2	8297	83.5
	IDU	355	7.8	373	5.9	367	4.6	378	4.0	332	3.3
	Blood products	27	0.6	35	0.6	40	0.5	47	0.5	32	0.3
	Other/NK	567	12.4	694	10.9	791	10.0	1051	11.2	1281	12.9
Ethnicity	White	1147	25.2	1275	20.1	1408	17.8	1547	16.5	1616	16.3
	Black-Caribbean	134	2.9	221	3.5	306	3.9	374	4.0	448	4.5
	Black-African	2749	60.4	4113	64.9	5238	66.3	6214	66.4	6523	65.6
	Black-other	100	2.2	143	2.3	189	2.4	268	2.9	304	3.1
	Other	216	4.7	305	4.8	427	5.4	540	5.8	581	5.8
	Not reported	209	4.6	283	4.5	333	4.2	416	4.4	470	4.7

Figure 5.4. Women attending for HIV clinical care at UK CHIC sites stratified by age group

a. All women



b. Women with a pregnancy



### **Pregnancies among diagnosed women accessing HIV clinical care**

Of the 7853 women who accessed HIV care over the period 2000-2009, 1291 women had at least one pregnancy: 1000 (77.5%) women had a single pregnancy, 245 (19.0%) had two pregnancies and 46 (3.6%) women had three or more pregnancies. There were 1637 pregnancies in total. The number of pregnancies increased each year from 72 in 2000 to 230 in 2009.

The number of pregnancies and the characteristics of pregnant women under follow-up are presented in Table 5.4. The proportion of pregnancies which were repeat pregnancies (sequential pregnancy after HIV diagnosis) increased from 30.1% (47/156) in 2000/01 to 52.2% (235/450) in 2008/09 ( $p < 0.001$  using generalized estimating equation accounting for repeat measures), with 735 (44.9%) of the pregnancies being repeat pregnancies overall. The majority of women with a pregnancy were aged 26-35 years and this remained the case over time, the percentage of women in the older age group increased from 17.9% in 2000/1 to 24.4% in 2008/9 and there was an increase in the median age of pregnant women from 31 to 32 years respectively (Figure 5.4b). The proportion of pregnancies which were repeat pregnancies increased among all age groups (16-25 years, 25.0% (4/16) in 2000/01 to 46.4% (32/69) in 2008/09,  $p < 0.001$ ; 26-35 years, 33.0% (37/112) to 51.3% (139/271),  $p < 0.001$  and 36-49 years, 21.4% (6/28) to 58.2% (64/110),  $p < 0.001$ ).

The proportion of pregnant women on ART (at the start of the year in which they conceived) increased ( $p < 0.001$ ). In line with this, among women with a pregnancy, the median CD4 cell count (at the start of the year) gradually increased over time and the proportion with CD4  $< 350$  cells/mm<sup>3</sup> decreased ( $p < 0.001$ ). The proportion of pregnancies among women of black-African or black-Caribbean ethnicity increased ( $p < 0.001$ ) and that among white women decreased ( $p < 0.001$ ) (Table 5.4). Most pregnancies were in women infected via heterosexual sex (97.0%, 1432/1477, where probable route of exposure was reported), with 1.9% ( $n=28$ ) in women infected via injecting drug use, 0.7% ( $n=11$ ) in women infected via MTCT and six pregnancies in women infected via other routes.

Table 5.4. Characteristics of HIV-positive pregnant women who were already accessing HIV clinical care at UK CHIC sites in 2000-2009 before their pregnancy

	2000/1	%	2002/3	%	2004/5	%	2006/7	%	2008/9	%
Women with a pregnancy accessing HIV clinical care [95% CI]	156	3.4 [2.9-4.0]	250	3.9 [3.5-4.4]	347	4.4 [3.9-4.8]	434	4.6 [4.2-5.1]	450	4.5 [4.1-4.9]
Repeat pregnancies	47	30.1	90	36.0	156	45.0	207	47.7	235	52.2
Median age (years) [IQR]	31	[27-34]	31	[27-34]	31	[27-35]	32	[27-35]	32	[28-35]
Age group (years)										
16-25	16	10.3	45	18.0	56	16.1	68	15.7	69	15.3
26-35	112	71.8	165	66.0	218	62.8	266	61.3	271	60.2
36-49	28	17.9	40	16.0	73	21.0	100	23.0	110	24.4
ART use										
On ART	72	46.2	127	50.8	179	51.6	225	51.8	287	63.8
CD4 count (cells/mm <sup>3</sup> )										
≤200	31	19.9	35	14.0	36	10.4	44	10.1	37	8.2
201-350	49	31.4	65	26.0	98	28.2	106	24.4	103	22.9
>350	74	47.4	137	54.8	204	58.8	264	60.8	302	67.1
NK	2	1.3	13	5.2	9	2.6	20	4.6	8	1.8
Median CD4 count (cells/mm <sup>3</sup> ) (IQR)	338	[220-532]	389	[257-544]	401	[283-564]	425	[287-597]	458	[321-630]
Ethnicity										
White	35	22.4	30	12.0	48	13.8	42	9.7	48	10.7
Black-Caribbean	3	1.9	6	2.4	14	4.0	18	4.1	18	4.0
Black-African	104	66.7	182	72.8	236	68.0	322	74.2	329	73.1
Black-other	5	3.2	12	4.8	10	2.9	11	2.5	11	2.4
Other	4	2.6	7	2.8	26	7.5	18	4.1	20	4.4
Not reported	5	3.2	13	5.2	13	3.7	23	5.3	24	5.3

## **Pregnancy incidence and predictors of pregnancy**

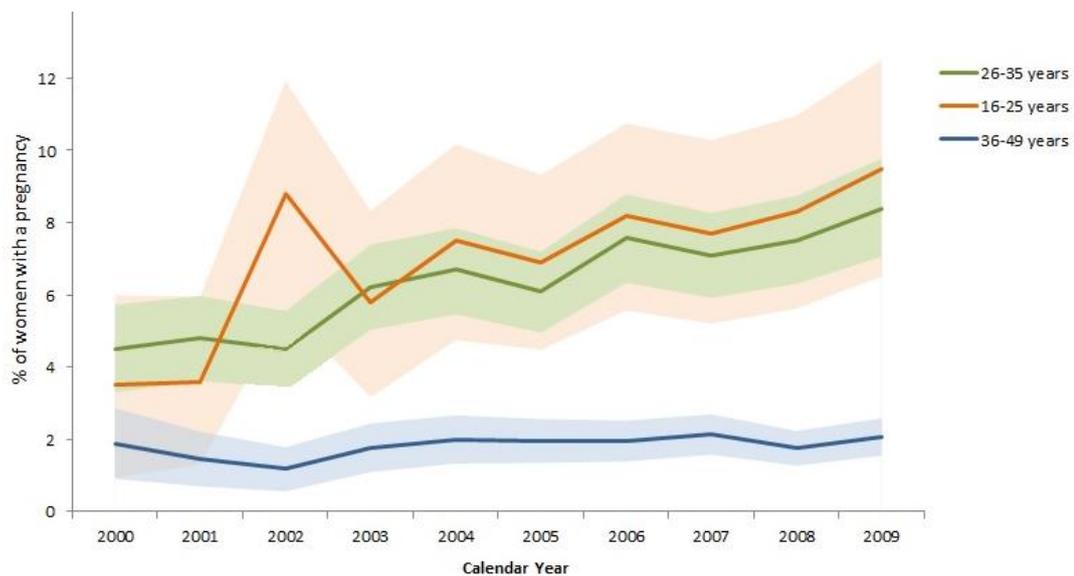
Pregnancy incidence among women accessing HIV care was 3.5% (72/2074, 95% confidence interval (CI) 2.7-4.3) in 2000 and 4.7% (230/4876, 95% CI 4.1-5.3) in 2009, with the highest incidence in 2006 (4.8%, 216/4528, 95% CI 4.1-5.4). The likelihood that women had a pregnancy increased over the study period (relative rate [RR] per later year: 1.03 [1.01-1.05],  $p < 0.001$ ), even after controlling for other factors (adjusted RR (aRR) per later year: 1.05 [1.03-1.07],  $p < 0.001$ ) (Table 5.5).

There were a number of independent predictors of pregnancy: older women were less likely to have a pregnancy than younger women (aRR 0.44 per 10 year increment in age [95% CI 0.41-0.46],  $p < 0.001$ ) as were women with CD4  $< 200$  cells/mm<sup>3</sup> compared with women with CD4 200-350 cells/mm<sup>3</sup> (aRR 0.65 [0.55-0.77],  $p < 0.001$ ). Women of white ethnicity were less likely to have a pregnancy compared with women of black-African ethnicity (aRR 0.67 [0.57-0.80],  $p < 0.001$ ) as were women of black-Caribbean ethnicity after controlling for differences in age, ART use and CD4 count (aRR 0.75 [0.58-0.97],  $p = 0.03$ ). Women infected via injecting drug use were less likely to have a pregnancy than women infected via heterosexual sex (aRR 0.58 [0.35-0.97],  $p = 0.04$ ). In unadjusted analyses, women on ART were less likely to have a pregnancy than women not on ART (RR 0.82 [0.74-0.91],  $p < 0.001$ ) but this was not the case after adjusting for other factors.

The pregnancy rate increased for women in all age groups over the study period (16-25 years, aRR 1.07 per later calendar year [1.02-1.12],  $p = 0.004$ ; 26-35 years, aRR 1.06 [1.04-1.09],  $p < 0.001$ ; 36-49 years, aRR 1.05 [1.00-1.09],  $p = 0.03$ ) (Figure 5.5). The rate of increase in pregnancy incidence was not significantly different for the three age groups ( $p$ -value for interaction=0.15). Similarly, there was an increase in pregnancy rate for all CD4 groups with little evidence that the rate of increase was significantly different for any of these groups ( $p$ -value for interaction=0.07). Pregnancy incidence increased among women of black-African ethnicity (aRR 1.06 [1.03-1.08],  $p < 0.001$ ). There was no evidence that the rate of change of pregnancy incidence differed for any ethnic group relative to that of women of black-African ethnicity, apart from women categorised as 'black-other', who experienced a somewhat slower increase in pregnancy rate ( $p = 0.02$ ). As only a small proportion of women with a pregnancy acquired HIV via routes other than heterosexual sex, it was not possible to assess trends over time in pregnancy rate for different routes of infection. The rate of increase in pregnancy incidence over this period did not significantly differ between women on

ART and women not on ART (p-value for interaction=0.14), with predictors of pregnancy being the same regardless of treatment.

Figure 5.5. Pregnancy incidence in 2000-2009 among women accessing HIV clinical care – by age group (the shaded areas show the 95% confidence intervals)



### Pregnancy outcome

The majority of pregnancies resulted in a delivery (86.8%, 1421/1637; 1401 live births and 20 stillbirths) and 193 (11.8%) pregnancies ended early (126 miscarriages, 63 terminations and 4 ectopic pregnancies). Information on pregnancy outcome was unavailable for 8 (0.5%) pregnancies, with a further 15 (0.9%) ongoing at the time of data submission. Among women with a pregnancy, older women were less likely than younger women to have a pregnancy resulting in delivery (aRR 0.95 [0.92-0.99], p=0.02, adjusted for calendar year, CD4 count and ethnicity) and women infected via contaminated blood/blood products were more likely to have a pregnancy resulting in a delivery than women infected via heterosexual sex (aRR 1.22 [1.10-1.34], p=0.001). Ethnicity, ART use and CD4 count were not predictive of whether pregnancies resulted in a delivery. The proportion of pregnancies resulting in delivery increased over time (aRR 1.01 [1.00-1.02], p=0.05) and there was a fall in the proportion of pregnancies resulting in a termination, from 12.8% (20/156) in 2000/01 to 2.9% (13/450) in 2008/09, p<0.001.

Table 5.5. Characteristics associated with having a pregnancy among HIV-positive women already accessing HIV clinical care at UK CHIC sites in 2000-2009

	Person-years (PY)	Pregnancies	Pregnancy rate (per 100 PY)	95% CI	Relative Rate	95% CI	p-value	Adjusted Relative Rate <sup>1</sup>	95% CI	p-value	
Year of conception <sup>2</sup>	38,097	1637	4.3	4.1 - 4.5	1.03	1.01-1.05	<0.001	1.05	1.03-1.07	<0.001	
Age group	16-25 years	3486	254	7.3	6.4 - 8.1	1.12	0.98-1.29	0.10	1.12	0.98-1.29	0.11
	26-35 years	15,927	1032	6.5	6.1 - 6.9	1.00	-	-	1.00	-	-
	36-49 years	18,684	351	1.9	1.7 - 2.1	0.30	0.26-0.34	<0.001	0.29	0.25-0.33	<0.001
ART use	On ART	22,512	890	4.0	3.7 - 4.2	0.82	0.74-0.91	<0.001	0.95	0.85-1.05	0.32
CD4 count (cells/mm <sup>3</sup> )	≤200	6073	183	3.0	2.6 - 3.4	0.64	0.54-0.76	<0.001	0.65	0.55-0.77	<0.001
	201-350	8841	421	4.8	4.3 - 5.2	1.00	-	-	1.00	-	-
	>350	21,155	981	4.6	4.4 - 4.9	0.98	0.87-1.10	0.71	0.99	0.88-1.11	0.83
	NK	2028	52	2.6	1.9 - 3.3	0.54	0.41-0.72	<0.001	0.52	0.39-0.68	<0.001
Ethnicity	White	6993	203	2.9	2.5 - 3.3	0.62	0.52-0.73	<0.001	0.67	0.57-0.80	<0.001
	Black-Caribbean	1483	59	4.0	3.0 - 5.0	0.85	0.65-1.11	0.23	0.75	0.58-0.97	0.03
	Black-African	24,837	1173	4.7	4.5 - 5.0	1.00	-	-	1.00	-	-
	Black-other	1004	49	4.9	3.5 - 6.2	1.04	0.77-1.39	0.81	0.94	0.71-1.25	0.68
	Other	2069	75	3.6	2.8 - 4.4	0.77	0.59-0.99	0.04	0.71	0.56-0.91	0.01
	Not reported	1711	78	4.6	3.6 - 5.5	0.96	0.75-1.23	0.76	0.95	0.75-1.20	0.66

<sup>1</sup> Where all variables in the table were included in the model.

<sup>2</sup> Estimated year of conception is a continuous variable. RRs refer to an increase of one year

## Index pregnancies

A separate analysis was undertaken looking only at index pregnancies. The number of index pregnancies increased each year from 46 in 2000 to 98 in 2009, with 902 in total. Overall there were 153 index pregnancies in women aged 16-25 years, 571 in women aged 26-35 years and 178 in women aged 36-49 years. Among all women of child bearing age accessing care the index pregnancy rate increased (aRR 1.03 [1.01-1.06],  $p=0.007$ ). The rate increased among women aged 26-35 years (aRR 1.06 [1.03-1.10],  $p<0.001$ ) but the increase in rate in women aged 16-25 years and those aged over 35 years were not statistically significant (aRR 1.05 [0.99-1.11],  $p=0.12$  and aRR 1.02 [0.96-1.07],  $p=0.61$  respectively). There was no evidence that the rate of increase in women aged 16-25 differed from the rate in women aged 26-35 years ( $p$ -value for interaction= $0.58$ ). There was evidence that the rate of increase differed in women aged 26-35 years compared to women aged 36-49 years ( $p$ -value for interaction= $0.004$ ). There was no statistically significant difference in the rate of increase in index pregnancies between women on ART and women not on ART ( $p$ -value for interaction= $0.26$ ), between women with different CD4 counts ( $p$ -value for interaction= $0.15$ ) or between different ethnic groups (interactions: white vs. black-African  $p=0.31$ , black-Caribbean vs. black-African  $p=0.08$ ).

As was the case with all pregnancies, younger age was predictive of having an index pregnancy (aRR 0.37 per 10 year increment in age [95% CI 0.34-0.41],  $p<0.001$ , adjusted for CD4, ART use, ethnicity, exposure group and year). Women with CD4  $<200$  cells/mm<sup>3</sup> were less likely to have a pregnancy compared with women with CD4 200-350 cells/mm<sup>3</sup> (aRR 0.63 [0.51-0.79],  $p<0.001$ ) and when adjusted for other factors the chance of women on ART having an index pregnancy did not significantly differ from that of women not on ART (aRR 1.04 [0.90-1.12],  $p=0.57$ ). With regard to ethnicity, only women of white ethnicity had less chance of having an index pregnancy compared to women of black-African ethnicity (aRR 0.67 [0.54-0.82],  $p<0.001$ ). There was no statistically significant difference in the chance of having an index pregnancy between women of black-Caribbean ethnicity and women of white ethnicity (aRR 0.82 [0.59-1.15],  $p=0.26$ ). With regard to exposure group, only women infected via vertical transmission had significantly less chance of having an index pregnancy compared to women infected via heterosexual sex when other factors were considered (aRR 0.29 [0.14-0.62],  $p=0.001$ ). The difference in chance of having an index pregnancy was not statistically significant when women infected via injecting drug use were compared with women infected via heterosexual sex (aRR 0.67 [0.40-1.08],  $p=0.10$ ).

## 5.4 Discussion

Among women attending care at a UK CHIC site with a pregnancy, there was an increase in the number (and proportion) of women already on ART at conception, as has been reported from the UK and Ireland (using the NSHPC data) [422] and elsewhere [131]. This increase in number is due to the cumulative effect of additional women starting treatment each year whilst those who previously started remain on treatment. In the future, the vast majority of HIV diagnosed women will be on ART when they conceive since they will be recommended life-long ART at diagnosis [9][86]. In pregnancies conceived on ART, the fetus is exposed to cART for the full duration of its development including the early weeks of pregnancy when neural development occurs. The short and long-term implications of this in utero exposure, are not clear. The Antiretroviral Pregnancy Register (APR)<sup>23</sup> collates data on pregnancy outcome in women who use ART in pregnancy. Each year it enrolls around 1300 women from the US and 200 from elsewhere. The latest estimated prevalence of birth defects in women with first trimester use of ART was 2.9 [95% CI 2.5-3.3] per 100 live births [202], not significantly higher than the estimated prevalence in the general US population [424]. The data collated by the registry is limited for a number of reasons. For some ART drugs, particularly newer drugs, the number of women using them in pregnancy is very small - making it difficult to identify rare events. Data refer to the duration of pregnancy and shortly after and there is no long-term follow up. In addition, there is likely to be bias in which pregnancies are reported - with birth defects or adverse events likely to be reported than uneventful pregnancies resulting in an overestimation of the teratogenic effect of a drug.

As well as the possible risks posed by ART use throughout pregnancy, there are also some benefits. The risk of toxicity is highest when ART is first started. Therefore, toxicity is less likely to occur in women already on ART at conception than in women starting ART in pregnancy – an area which I explore in a Chapter 7. Use of ART throughout pregnancy also minimises the risk of vertical transmission [129] since women who conceive and remain on ART throughout pregnancy are more likely to be virally suppressed in pregnancy and at delivery than women who use short-course ART during pregnancy [131].

The increasing number of repeat pregnancies in combination with an increasing number of women on ART at the time of conception also meant that by 2009 only 1 in 5

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<sup>23</sup> Information on the Antiretroviral Pregnancy Register can be found at [www.apregistry.com](http://www.apregistry.com)

pregnancies were among women naïve to ART. The majority of women not on ART at conception (around 39% overall), used ART during pregnancy with only a small proportion not using any ART (2.4% overall, trend  $p=0.44$ ) either because they declined it, were diagnosed close to the time of delivery and/or delivered early i.e. before ART could be started. Among women who did not conceive on ART, the proportion who started life-long ART increased over the decade, reflecting a move towards starting treatment at a higher CD4 count, [78] even before the 2008 BHIVA guidelines recommended starting at or before a CD4 count of 350 cells/mm<sup>3</sup>. For some women, pregnancy provided them with an opportunity to start life-long ART because they were diagnosed in pregnancy and already had a CD4 count at which life-long ART was recommended. For women who are lost-to-follow up or disengaged with clinical care, pregnancy can provide an opportunity and the motivation to re-engage with clinical care.

The pregnancy incidence among women attending HIV care was more than double the incidence in the general population at the time. In 2000, the pregnancy incidence among women aged 15-44 in England and Wales was 1.4% compared to 3.5% among women in this study. In 2009, the pregnancy incidence in England and Wales was 1.7% compared to 4.7% in this study [425]. Whether the differences in pregnancy incidence between women attending HIV care and the general population are due only to the differences in the age and ethnic breakdown of the two groups is not clear as the national data for this period were not available by ethnicity or age group. There was an increase in the overall pregnancy rate among HIV-positive women accessing clinical care over the period 2000-2009. The increased pregnancy rate in later years remained after adjusting for the changing characteristics of women under HIV care in these clinics over the decade, such as increased average age - changes which also occurred elsewhere in Europe [426]. Of note, there was no evidence that the pregnancy rate increased more among women on ART than among women not on ART or among women of a particular age, ethnicity or CD4 category.

The increase in pregnancy rate across this diverse group is likely to reflect improvements in HIV treatment and management which have led to reduced morbidity [59, 420] and MTCT rates [131, 149]. During this period there was also an increase in the pregnancy rate in the general population in England and Wales [425]. An increasing number of pregnancies were repeat pregnancies, as has previously been reported in the UK and Ireland (using the NSHPC data) [427] and elsewhere [160]. However, the increase in pregnancy rate also occurred in index pregnancies and was

therefore not only because of an increase in the rate of repeat pregnancies. Changing attitudes towards childbearing following improvements in ART treatment and a fall in the risk of vertical transmission have been reported [163, 428, 429]. These changes include an increased desire to have children and may have contributed to the fall in the number of terminations among women living with HIV, also reported elsewhere [428]. Whilst in the general population in England and Wales, in women aged 15-44 years, the number of pregnancies which were terminated increased from 174,198 to 187,637 over this period, and the percentage of pregnancies which were terminated remained stable at around 22% [425]. The fall in the number of terminations among women living with HIV could also be due to a reduction in the number of unplanned pregnancies, thought to be high among this population [162, 430, 431]. However, no data were available on the use of contraception or pregnancy intention. It should also be noted that the number of terminations reported to the NSHPC is an underestimation because only HIV-positive women accessing antenatal care are reported to the study. As such, diagnosed HIV-positive women who seek a termination would not normally be reported to the NSHPC.

There were a number of characteristics predictive of having a pregnancy among women receiving HIV clinical care. Younger women were more likely to have a pregnancy than older women as we see in the general population [402] and as has been reported from studies of pregnancy rate [428, 432] and pregnancy intention [433-436] among HIV-positive women. Women infected via injecting drug use were less likely to have a pregnancy than women infected via heterosexual sex, after accounting for age, CD4 count and ethnicity. This has been found elsewhere [161, 436] and may reflect differences in health, lifestyle, desire for children [436] or menstrual changes associated with methadone maintenance and illicit drug use [437]. These could not be assessed as no data on these variables were collected by either dataset. Women of black-African ethnicity were more likely to have a pregnancy than women of white ethnicity or women of black-Caribbean ethnicity reflecting cultural differences in attitudes to childbearing and family size. African ethnicity was predictive of fertility intention among HIV-positive women in Canada [432]. In France, HIV-positive women born in Africa were more likely to want children than women born in Europe [436]. Differences in the pregnancy rate between women of black-African and black-Caribbean ethnicity likely reflect cultural differences and differences in the proportion that were UK born.

When other factors were considered, ART use did not remain an independent predictor of pregnancy, although it has been found to be in some studies [428, 435]. However,

analyses that consider the impact of ART on pregnancy rate may suffer from the problems of time-varying confounding, and may be biased as a result.

Predictors of pregnancy were similar for index pregnancies as they were for all pregnancies although some of the associations did not reach statistical significance. This may be a result of insufficient statistical power due to small numbers.

In UK CHIC the number of pregnancies increased from 156 in 2000/01 to 450 in 2008/09, due to an increase in the number of women accessing and remaining in care [417], and an increase in the likelihood that women became pregnant. Among all diagnosed HIV-positive women in the UK and Ireland, including those diagnosed during pregnancy, the number of pregnancies stabilised in 2006 at around 1500 pregnancies per year [145], when pregnancy incidence in our study was highest (4.8%). This plateau could be a result of reporting delay, but could also be due to the increasing number of older women accessing care, women who, in general, are less likely to have a pregnancy. Recently, the number of sequential pregnancies in the UK and Ireland has also plateaued as an increasing number of women may have completed their family [145].

As the number of pregnancies has risen, so has the use of specialist antenatal services. All HIV-positive women who are pregnant or planning a pregnancy require a high level of clinical care from a multidisciplinary team including specialist midwives, obstetricians, HIV specialists, GPs, paediatricians and health workers. Many women may also require additional support in areas such as ART adherence support, advice regarding HIV disclosure and social/immigration issues [439] and assisted reproduction. Demand for these services is likely to remain or increase further, particularly as an increasing number of older women have pregnancies (as is the case in the UK as a whole [440, 441]). Older women may require additional support, particularly those aged over 40, as they are at increased risk of experiencing fertility problems [442] and pregnancy complications [443-445], some of which are also associated with ART use in pregnancy [175, 210, 426, 446]. Infants born to older women also have an increased risk of neural tube defects [447] and Down's Syndrome [448]. Older maternal age and HIV have both also been associated with an increased risk of stillbirth [449] and miscarriage [450-452]. An updated analysis, using more recent data would help inform those planning and commissioning HIV services in estimating the number of women attending HIV clinical care likely to have a pregnancy.

There were a number of limitations to the data available for analysis. Some variables which might be predictive of pregnancy, such as parity, were available in NSHPC but

not in UK CHIC. Since I examined characteristics predictive of pregnancy among women in UK CHIC it was not possible to assess parity – since only women with a pregnancy since HIV diagnosis (and were therefore reported to NSHPC) had any data on parity.

The analyses focused on HIV diagnosed women already attending care and pregnancies during which HIV was diagnosed were not included in the analysis. Factors predictive of pregnancy in women not aware of their HIV status may differ from those of diagnosed women.

Another limitation of the analysis was that instead of considering CD4 count and ART use as time-dependent variables, only the first CD4 count and ART status at start of each year were considered. This strategy was used to simplify the analysis and although CD4 counts are likely to be stable and ART status consistent throughout the year they may have changed by the time the woman conceived. ART status did not take into account whether the woman was on ART for her own health or for PMTCT during an earlier pregnancy. Women whose pregnancies ended in termination or first trimester miscarriage may not have accessed antenatal care, and therefore not been reported to the NSHPC. As such, the proportion of pregnancies ending early is likely to be a minimum estimate and despite there being no significant change in the rate of miscarriages among reported pregnancies there may have been changes in the rate during this period.

The incomplete linkage between records in UK CHIC and NSHPC for women reported to both could result in an underestimation of pregnancy incidence. However, any such underestimation is unlikely to affect our assessment of the predictors of pregnancy or the trends over time. A higher proportion of women in the UK CHIC dataset accessed care in London than is the case nationally. The characteristics of pregnant women accessing care in London may differ from those accessing care outside London. However, changes in pregnancy incidence at UK CHIC sites are likely to be similar to changes in pregnancy incidence elsewhere.

In conclusion, an increasing number of pregnancies among women accessing HIV clinical care reflect increases in the pregnancy rate among this group as well as increases in the total number of women accessing care. HIV-positive women who are pregnant or planning a pregnancy require a high level of clinical care. The care needed by this population as a whole may increase as more older women have pregnancies.

## Key points

- An increasing number of pregnancies were among women already on life-long ART (27% in 2000 and 59% in 2009).
- In women who conceived whilst not already on ART, the percentage with previous exposure to ART rose (from 12% in 2000 to 45% in 2009).
- In women who were not on ART when they conceived, the percentage that started life-long ART in pregnancy rose (from 25% in 2000 to 41% in 2008) while the percentage that used short-course ART in pregnancy fell (from 64% in 2000 to 59% in 2009).
- Independent predictors of pregnancy among women attending HIV clinical care included: younger age, having a CD4 count 200-350 cells/mm<sup>3</sup> (compared to a lower CD4 count) and black-African ethnicity (compared to white ethnicity). After adjusting for other factors, women on ART were no more likely to have a pregnancy than women not on ART.
- The overall pregnancy rate increased over time as did the index pregnancy rate. This increase was not focused in any one particular group.

# Chapter 6 Short-course ART use in pregnancy and the response to ART once therapy is subsequently started

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## 6.1 Introduction

The results of the previous chapter indicate that in recent years around 20% of pregnant women in UK CHIC used short-course combination antiretroviral therapy (cART) and 5% used short-course zidovudine monotherapy (ZDVm) for PMTCT. It is not clear whether this short-term use of ART in pregnancy has any impact on treatment outcomes once women subsequently start life-long ART for their own health.

In this chapter I assess, in women starting life-long ART, how many had previously used short-course ART in pregnancy. Then, in two separate analyses, I examine treatment outcomes in women starting life-long ART who have been diagnosed with HIV for at least one year. Firstly I compare the outcomes of women who previously used short-course ZDVm in pregnancy with women who had never previously used ART (ART-naïve) and secondly, I compare the outcomes of women who previously used short-course cART in pregnancy with the outcomes of ART-naïve women. Parts of this analysis were published in 2014 [453] (Appendix IIc).

## 6.2 Methods

### **Categorising ART use in pregnancy**

The type of ART used in each pregnancy was determined using a combination of ART data from NSHPC and UK CHIC. For each pregnancy, ART use was categorised as ZDVm if this drug was reported by both studies or by one study if the other had missing data. If data were contradictory, i.e. one study reported the use of cART and the other reported the use of ZDVm, this was categorised as ART type not known. Short-course cART was defined as the use of three or more ART drugs started during pregnancy and stopped within six months of delivery. This definition, which extends into the postnatal period, was used because although the vast majority of women who used

short-course cART stopped at delivery, some stopped ART several months after delivery. This postnatal use of ART could have been because they were breastfeeding. However, it is more likely to be a result of inaccurate reporting of the ART stop date or the delivered date, if for example the expected date of delivery was reported as a proxy for the actual date of delivery.

I examine ZDVm use in pregnancy in the period 1997-2010. This period was selected since it includes most of the pregnancies during which ZDVm was used in women included in the later analyses. Data from all years prior to 1997 were examined when assessing ART experience in women in the later analyses.

The date on which a woman started life-long ART (considered the baseline date) was determined (using UK CHIC data) using the earliest of: cART use for  $\geq 12$  months (this could include treatment changes or interruptions of  $< 3$  months), cART started with a CD4 count  $< 200$  cells/mm<sup>3</sup>; cART started with a CD4 count  $< 350$  cells/mm<sup>3</sup> outside pregnancy; cART started with a CD4 count  $< 350$  cells/mm<sup>3</sup> in pregnancy after 2008; or cART started within 6 months of an AIDS event.

When starting life-long ART (sometimes referred to in this chapter as starting 'treatment'), women were categorised as 'ZDVm-experienced' if they had used short-course ZDVm in pregnancy but had never used cART, as 'cART-experienced' if they had used short-course cART in pregnancy (irrespective of whether they had used ZDVm in any other pregnancy) or as 'ART-naïve' if they had no evidence of any prior ART use. Women with one or more previous pregnancies, but with no evidence of ART use were excluded from the ART-naïve group since ART use in pregnancy could not be ruled out. Women were excluded from the ART-experienced group if they had used ART at times outside pregnancy and the 6 months postpartum. In some cases, the pattern of ART use (in UK CHIC) suggested that short-course cART had been used in pregnancy but this could not be confirmed because no pregnancy was recorded in NSHPC for that period. Alternatively, the pregnancy may have been reported to NSHPC but the UK CHIC record was not matched to the NSHPC record in the dataset linkage.

Throughout the analyses I continue to refer to women as either 'ZDVm-experienced', 'cART-experienced' or 'ART-naïve'. This refers to their ART status at the point of starting life-long ART (baseline) since no women were ART-naïve and all were cART-experienced once they had started life-long ART.

Baseline CD4 cell count and viral load were established using the latest measurement available in UK CHIC within the 3 months before initiation of life-long ART. The CD4 count and viral load measurements closest to 6, 12 and 24 months after initiation were identified as long as they were measured within 3 months of the date of interest (i.e. within the 3-9, 9-15 and 21-27 month windows respectively).

### **Inclusion and exclusion criteria**

Women were included in the analysis if they were aged  $\geq 16$  years and had been diagnosed with HIV for at least one year when starting life-long ART, thereby excluding late diagnosed women who would likely have worse outcomes. Only women aged 49 years or younger at diagnosis were included, thereby including only women who could have used short-course cART or ZDVm in pregnancy before starting long-term treatment.

### **Statistical analysis**

The characteristics of women who had previously used ART and women who were ART-naïve, including their clinical characteristics at baseline, were compared using t-test (for comparing mean CD4 counts), the Kruskal-Wallis test for non-Normally distributed continuous variables and the Chi-squared test for categorical variables, unless expected values in any group were  $< 5$ , when Fisher's exact test was used. The availability of viral load and CD4 data were compared in the same way.

In women on ART, the outcomes examined were: time to death/AIDS, change in CD4 count from baseline at 6 and 24 months; time to viral suppression (viral load  $\leq 50$  copies/ml) within 6 months; time to viral rebound (a single measure of HIV-RNA  $> 200$  copies/ml) 0-6 months after suppression in women with viral suppression by 6 months; time to viral rebound  $> 6$ -24 months after viral suppression among women who had suppressed within 6 months and were still under follow-up (i.e. had not experienced a rebound within 6 months of suppression), time to any regimen change within 24 months (not including treatment interruptions) and time to a treatment interruption of at least 30 days within 24 months.

The Kaplan-Meier method was used to produce figures showing the cumulative incidence of viral suppression within 6 months and the cumulative incidence of viral rebound 0-6 months and  $> 6$ -24 months after suppression in women who virally suppressed within 6 months. Outcomes were compared using Cox proportional

hazards regression (time to AIDs/death, viral suppression, viral rebound, regimen change and regimen interruption) or linear regression (change in CD4 count).

For the time to AIDS/death analysis, follow-up was right-censored at the last clinic visit or on 31<sup>st</sup> December 2012, whichever occurred first. For the time to virological suppression analysis, only women with a viral load measurement in the first six months on ART were included and follow-up was right-censored at six months after starting treatment or when ART was interrupted for any period of time. Then in sensitivity analysis, any treatment interruption was ignored. For the analysis of time to viral rebound, follow-up started at the point of viral suppression and was right-censored if the woman died or interrupted treatment, six months after the last viral load measurement within 2 years of starting treatment, or on 31<sup>st</sup> December 2012, whichever occurred first. For the time to treatment switch and treatment interruption analyses, follow-up was right-censored after two years, if the woman died or at her last clinic visit, whichever occurred first.

For both analyses (1: ZDVm-experienced vs. ART-naïve; 2: cART-experienced vs. ART-naïve) the UK CHIC dataset containing data to end 2012 was used. Due to the small number of women in the ZDVm-experienced group, variables were categorised slightly differently in the two analyses and slightly different inclusion criteria were used (described below).

### **Analysis 1: ZDVm-experienced vs. ART-naïve women**

Women were included in the analysis if they started long-term cART in the period 2003-2010, allowing at least two years of follow-up. Women not attending care at a UK CHIC site (i.e. those with no viral load or CD4 measurements reported) in the first two years on ART were excluded.

In adjusted analyses the variables included in the model were: age at baseline; pregnancy status at baseline (pregnant/not pregnant); ethnicity (black-African/other); HIV risk/exposure group (heterosexual sex v other); years since HIV diagnosis; year starting treatment; type of ART regimen started (non-nucleoside reverse transcriptase inhibitor [NNRTI]-based/protease inhibitor [PI]-based [including ritonavir boosted and non-boosted]/nucleoside/nucleotide reverse transcriptase inhibitor [NRTI] only and other regimens); baseline viral load (categorised as either  $\leq 10,000$ / $> 10,000$  copies/ml/not known or as a continuous variable [ $\log_{10}$  copies/ml]); baseline CD4 (categorised as either  $\leq 200$ / $201-350$ / $> 350$  cells/mm<sup>3</sup>/not known or as a continuous

variable); hepatitis B or hepatitis C (HBV/HCV) co-infection and previous AIDS event at baseline (yes/no).

Women with no baseline viral load were categorised as having viral load  $\leq 10,000$  copies/ml (n=241) but were excluded in sensitivity analysis and in the analysis of time to viral suppression/rebound. Due to the immunological and physiological changes that occur during pregnancy, and potential differences in drug adherence rates, women starting life-long ART whilst pregnant may experience different treatment outcomes from women starting whilst not pregnant. A sensitivity analysis was therefore also performed excluding women who were pregnant when starting life-long ART.

### **Analysis 2: cART-experienced vs. ART-naïve women**

Women were included in the analysis if they started life-long cART in the period 2006-2010, allowing at least two years of follow-up. Women not attending care at a UK CHIC site (i.e. those with no viral load or CD4 measurements reported) in the first two years on ART were excluded.

In addition to the outcomes already listed, time to severe liver enzyme elevation (LEE) of ALT (alanine transaminase) ( $\geq$  grade 3 according to the Division of AIDS toxicity guidelines [322]) was also examined using Cox proportional hazards regression. Follow-up was right censored at the last clinic visit, on 31<sup>st</sup> December 2012 or if the woman died.

In adjusted analyses the variables included in the model were the same as in the ZDVm analysis however, since the number of women included in analyses was larger, ethnicity was categorised into more categories (black-African/black-Caribbean/white/other or not known) as was exposure group (heterosexual sex/injecting drug use [IDU]/other or not known), CD4 count ( $\leq 200/201-350/351-500/>500$  cells/mm<sup>3</sup>/not known) and ART regimen type (NNRTI-based/PI-based/NRTI only/other and not known).

A sensitivity analysis was performed excluding women with no baseline viral load and/or no CD4 cell count. An additional viral rebound sensitivity analysis was performed in which follow-up was censored at the start of any subsequent pregnancy.

Viral suppression and viral rebound could be associated with whether or not viral suppression was achieved during the pregnancy in which ART was previously used. Therefore an additional analysis was undertaken including only women with previous

cART experience and including in the model a variable categorising viral suppression (HIV-RNA  $\leq 50$  copies/ml) in the final trimester of the previous pregnancy (categorised as yes/no/not known).

Drug resistance was assessed using data from the UK HIV Drug Resistance Database (UK HDRD). This dataset, established in 2011, aims to collate the results of all genotypic resistance tests performed in routine HIV clinical care in the UK [454]<sup>24</sup>. Data from the UK CHIC study are linked annually to the UK HDRD using common pseudonymised identifiers. The dataset used in this analysis was the most up-to-date dataset available at the time and contained resistance data to the end of 2010. It included approximately 85% of all HIV drug-resistance tests performed in the UK until that point.

Women were defined as having resistance to a class of ART drug if they had least one major resistance-associated mutation which gave reduced susceptibility to that class (Appendix X) [102]. The four main drug classes were examined: non-nucleoside reverse-transcriptase inhibitors (NNRTIs), nucleoside reverse-transcriptase inhibitors (NRTIs), protease inhibitors (PIs) and integrase inhibitors (INI).

In ART-naïve and cART experienced women drug resistance data were examined from before initiation of life-long ART and in the month following viral rebound. In cART-experienced women, drug resistance data prior to any short-course cART use was also assessed. The prevalence of genotypic resistance to  $\geq 1$  drug class when starting treatment was compared in ART-naïve and cART-experienced women using logistic regression. Further statistical analysis of the resistance data was not undertaken because few of the women had any data available.

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<sup>24</sup> Being initially funded by the Department of Health, the UK HDRD is now funded by the UK Medical Research Council (MRC) (grant G0900274) and is coordinated at UCL's MRC Clinical Trials Unit (CTU). Further information is available from the website [www.ctu.mrc.ac.uk/hivrd/public/drug\\_resistance.asp](http://www.ctu.mrc.ac.uk/hivrd/public/drug_resistance.asp) (Accessed June 2016).

## 6.3 Results

### **Antenatal ART experience among women starting life-long ART**

In the period 2003-2012, 6207 women (aged 16 years and older and HIV-diagnosed at age 49 years or younger) in UK CHIC started life-long ART, representing 55.8% of the 11,114 women in UK CHIC during this period. Among women starting life-long ART, the percentage who had previously had a pregnancy (after or during which HIV was diagnosed) rose from 6.2% (39/627) in women starting life-long ART in 2003 to 13.9% (35/251) in women starting life-long ART in 2012 (Table 6.1). The median time between being diagnosed with HIV and starting life-long ART was shorter in the earlier years of this period than in the later years (3.6 [inter-quartile range (IQR) 1.4-26.1] months compared to 15.6 [IQR 1.3-72.6] months for women starting ART in 2003 and 2012 respectively) (Table 6.1). The percentage of women who had been diagnosed for at least one year when starting life-long ART rose from 35.4% (222/627) to 52.2% (131/251) for women starting treatment in 2003 and 2012 respectively (Table 6.1).

The majority of women who started life-long ART during the period 2003-2012 had never previously used ART (90.3%, 5579/6175) (Table 6.2). However, the proportion that had previously used ART increased over time from 4.0% (25/627) in 2003 to 12.0% (30/251) in 2012. Among all the 596 women with previous ART experience when starting life-long ART, 75.2% (n=448) had used short-course cART, whilst 19.3% (n=115) had used only ZDVm only and 5.5% (n=33) had used both ZDVm and cART during different pregnancies (Table 6.2).

Table 6.1. Time since HIV diagnosis and previous pregnancies in women starting life-long ART in 2003-2012

Year	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
Women attending HIV care at a UK CHIC site	4315	4823	5453	5924	6171	6586	6927	7399	7574	6207
Already started life-long ART (% of those attending care)	2771 (64.1)	3232 (66.9)	3728 (68.2)	4411 (74.3)	4766 (77.1)	5285 (80.1)	5828 (84.0)	6464 (87.3)	6867 (90.6)	5947 (95.7)
Started life-long ART (% of those attending care)	627 (14.5)	584 (12.1)	800 (14.7)	659 (11.1)	664 (10.8)	701 (10.6)	658 (9.5)	641 (8.6)	590 (7.8)	251 (4.0)
(% of those attending care yet to start ART)	(40.6)	(36.7)	(46.4)	(43.6)	(47.3)	(53.9)	(59.9)	(68.6)	(83.5)	(96.5)
<b>Women starting life-long ART</b>										
Any previous pregnancy reported to NSHPC n (% of those starting ART)	39 (6.2)	61 (10.4)	98 (12.3)	73 (11.3)	75 (11.3)	99 (14.1)	97 (14.7)	92 (14.4)	76 (12.9)	35 (13.9)
Median time since HIV-diagnosis [IQR] (months)	3.6 [1.4-26.1]	8.5 [1.6-37.5]	10.7 [1.6-40.9]	9.4 [1.7-45.6]	18.6 [2.0-54.9]	18.3 [2.0-56.0]	13.6 [1.4-59.7]	16.5 [1.2-67.9]	16.3 [1.2-74.5]	15.6 [1.3-72.6]
Diagnosed $\geq$ 1 year before starting ART n (% of those starting ART)	222 (35.4)	268 (45.9)	390 (48.8)	312 (47.3)	373 (56.2)	390 (55.6)	338 (51.4)	341 (53.2)	309 (52.4)	131 (52.2)

This table includes data for women aged  $\geq$ 16 years when attending care who were aged  $\leq$ 49 years at HIV diagnosis

Table 6.2. Previous use of cART and ZDVm in pregnancy among women in UK CHIC starting life-long ART in 2003-2012

<b>Year</b>	<b>2003</b>	<b>2004</b>	<b>2005</b>	<b>2006</b>	<b>2007</b>	<b>2008</b>	<b>2009</b>	<b>2010</b>	<b>2011</b>	<b>2012</b>	<b>Total</b>
Women starting life-long ART	627	584	800	659	664	701	658	641	590	251	6175
ART-naïve when starting ART (% of women starting ART)	602 (96.0)	540 (92.5)	736 (92.0)	597 (90.6)	603 (90.8)	618 (88.2)	578 (87.8)	563 (87.8)	521 (88.3)	221 (88.0)	5579 (90.3)
ART-experienced when starting ART (% of women starting ART)	25 (4.0)	44 (7.5)	64 (8.0)	62 (9.4)	61 (9.2)	83 (11.8)	80 (12.2)	78 (12.2)	69 (11.7)	30 (12.0)	596 (9.7)
short-term ZDVm only (% of ART-experienced women)	9 (36.0)	13 (29.5)	12 (18.8)	8 (12.9)	14 (23.0)	16 (19.3)	13 (16.3)	14 (17.9)	15 (21.7)	1 (3.3)	115 (19.3)
short-term cART only (% of ART-experienced women)	16 (64.0)	30 (68.2)	49 (76.6)	50 (80.6)	45 (73.8)	65 (78.3)	62 (77.5)	59 (75.6)	46 (66.7)	26 (86.7)	448 (75.2)
short-term cART and ZDVm used (% of ART-experienced women)	0 (0.0)	1 (2.3)	3 (4.7)	4 (6.5)	2 (3.3)	2 (2.4)	5 (6.3)	5 (6.4)	8 (11.6)	3 (10.0)	33 (5.5)

This table includes data for women aged ≥16 years when attending care who were aged ≤49 years at HIV diagnosis

## **ZDVm use in pregnancy among women in UK CHIC**

During the period 1997-2010 there were a total of 234 pregnancies during which ZDVm was used (and ART data were available); one pregnancy resulted in a stillbirth and 233 in a live birth. The median time between conceiving and starting ZDVm was 26 (IQR 23-29) weeks. The median duration of pregnancy was 36 (IQR 35-37) weeks, and the median duration of ZDVm use in pregnancy was 10 (IQR 8-13) weeks or 13 (IQR 10-21) weeks including postnatal use. In most cases, ZDVm was stopped at/after delivery (n=160) or during the final trimester (n=28). This latter group appeared to stop ZDVm whilst still being pregnant but may have stopped at delivery as there may be some inaccuracy in the reporting of drug stop dates or the delivery date, if for example the expected date of delivery was used as a proxy for the actual date of delivery. A small number of women switched from ZDVm to cART either during their final trimester (n=3) or after delivery (n=39). All these women had had a CD4 count >350 cells/mm<sup>3</sup> when they started ZDVm. In some pregnancies it was not clear from the data when ZDVm was started or stopped (n=4).

Most pregnancies during which ZDVm was used were index pregnancies (91.0%, n=213), with a smaller number being second (n=19) or third (n=2) pregnancies since HIV-diagnosis. For the non-index pregnancies, ART use in any previous pregnancy had been either cART (n=18), ZDVm (n=1) or not known (n=4).

Among the 213 women using ZDVm in their index pregnancy, 97 women had at least one subsequent pregnancy during which they used short-course cART (n=43), started life-long ART (n=19), no ART data were available (n=22) or they had already started life-long ART in the interval between pregnancies (n=13).

### **6.4 Analysis 1: Treatment outcomes in ZDVm-experienced and ART-naïve women**

Overall, 93 ZDVm-experienced and 1667 ART-naïve women who started life-long cART in 2003–2010 were included in the analysis. Five of the ZDVm-experienced women included in Table 6.2 were excluded from the analysis as there was evidence from the NSHPC data that they had started therapy at an earlier date than indicated in the UK CHIC data. One additional woman was excluded as she had no viral load or CD4 count data in the first two years on treatment. ZDVm-experienced women had used ZDVm in either one (n=86) or two pregnancies (n=7). None of the infants

acquired HIV. In pregnancy, ZDVm was used for a median of 12 (IQR 8–16) weeks and was typically started at 26 (IQR 23–28) weeks gestation. The median duration between delivery (of the latest pregnancy) and starting life-long ART was 61 (IQR 41–77) months; three women started within 12 months of delivery.

The baseline demographic and clinical characteristics of ZDVm-experienced and ART-naïve women at the time of starting life-long ART are summarised in Table 6.3. ZDVm-experienced women had been diagnosed for longer than ART-naïve women (ZDVm-experienced: median 6 [4-9] years since HIV diagnosis; ART-naïve: 4 [2-7] years,  $p < 0.001$ ). ZDVm-experienced women were on average younger than ART-naïve women (ZDVm-experienced: median age 33 [30–38] vs. ART-naïve: 35 [30–41] years,  $p = 0.04$ ), more likely to have been infected via heterosexual sex (ZDVm-experienced: 96.8% vs. ART-naïve: 89.8%,  $p = 0.03$ ) and more likely to be pregnant when starting life-long ART (ZDVm-experienced: 20.4% vs. ART-naïve: 8.0%,  $p < 0.001$ ). A similar proportion of women were of black-African ethnicity (ZDVm-experienced: 63.4%; ART-naïve: 64.5%,  $p = 0.84$ ). Overall, 31.5% ( $n = 555$ ) used a PI-based regimen (ritonavir-boosted or non-boosted), 62.8% ( $n = 1106$ ) an NNRTI-based regimen and 5.6% ( $n = 99$ ) an NRTI-only or other regimen. The regimens used were similar regardless of prior ZDVm experience ( $p = 0.32$ ).

ZDVm-experienced women were more likely to have at least one viral load measurement recorded in the first 6 months on treatment (ZDVm-experienced: 98.9% [92/93]; ART-naïve: 91.4% [1523/1667],  $p = 0.01$ ). In women with at least one viral load measurement in this period, the median number of measurements was the same for ZDVm-experienced and ART-naïve women (median 3 [IQR 2–4],  $p = 0.10$ ). There was weak evidence that ZDVm-experienced women were more likely to have at least one CD4 count in the first 6 months on treatment (any CD4 measurement: ZDVm-experienced: 95.7% [89/93]; ART-naïve: 90.0% [1501/1667],  $p = 0.07$ ).

ZDVm-experienced and ART-naïve women started therapeutic ART at similar mean CD4 counts (ZDVm-experienced: 290 [standard deviation (SD) 190] cells/mm<sup>3</sup>; ART-naïve: 271 [167] cells/mm<sup>3</sup>,  $p = 0.65$ ) and viral load (ZDVm-experienced: 4.1 [3.4-4.5] log<sub>10</sub> copies/ml; ART-naïve: 4.2 [2.8-4.9] log<sub>10</sub> copies/ml,  $p = 0.81$ ). Few women in either group were known to have HBV and/or HCV (ZDVm-experienced: 5.4%; ART-naïve: 9.3%,  $p = 0.20$ ) and few had previously had an AIDS event (ZDVm-experienced: 7.5%; ART-naïve: 13.6%,  $p = 0.09$ ).

Table 6.3. Characteristics of ZDVm-experienced and ART-naïve women starting life-long ART in 2003-2010 at least one year after HIV-diagnosis

Characteristics at start of treatment		ZDVm-experienced (n=93)		ART-naïve (n=1667)		p-value
Year, n (%)	2003-2005	28	(30.1)	571	(34.3)	0.59
	2006-2008	38	(40.9)	681	(40.9)	
	2009-2010	27	(29.0)	415	(24.9)	
Median age (years) [IQR]		33	[30-38]	35	[30-41]	0.04
Ethnicity, n (%)	Black-African	59	(63.4)	1075	(64.5)	0.84
	Non-black-African/not known	34	(36.6)	592	(35.5)	
Exposure group, n (%)	Heterosexual sex	90	(96.8)	1497	(89.8)	0.03
	Other	3	(3.2)	170	(10.2)	
HBV/HCV, n (%)		5	(5.4)	155	(9.3)	0.20
CD4 count (cells/mm <sup>3</sup> ), n (%) (n=91 and n=1461)	≤200	60	(25.9)	203	(27.7)	0.81
	201-350	129	(55.6)	408	(55.7)	
	>350	43	(18.5)	121	(16.5)	
	Mean [SD]	290	[190]	271	[167]	
Viral load >10,000 copies/ml, n (%) (n=86, n=1433)		39	(45.4)	652	(45.5)	0.97
Median viral load [IQR] (log <sub>10</sub> copies/ml)		4.1	[3.4-4.5]	4.2	[2.8-4.9]	0.81
Years since HIV diagnosis, median [IQR]		6	[4-9]	4	[2-7]	<0.001
Previous AIDS event, n (%)		7	(7.5)	226	(13.6)	0.09
Pregnant, n (%)		19	(20.4)	134	(8.0)	<0.001
Type of ART regimen, n (%)						
PI-based (boosted and non-boosted)		25	(26.9)	530	(31.8)	0.32
NNRTI-based		60	(64.5)	1046	(62.8)	
NRTI/Other		8	(8.6)	91	(5.5)	
Number of drugs in regimen <sup>1</sup> , n (%)	3	62	(72.1)	1119	(68.7)	0.50
	≥4	24	(27.9)	511	(31.4)	

<sup>1</sup> A ritonavir boosted PI in combination with two nucleosides was counted at 3 drugs in total.

## **AIDS/death**

Whilst on treatment, 1.1% (n=1) of ZDVm-experienced and 5.1% (n=85) of ART-naïve women developed an AIDS defining illness. None of the ZDVm-experienced women died but 32 (1.9%) ART-naïve women died. The specific cause of death was not reported for 23 of these women. Where the cause of death was reported, it was reported as: sepsis (n=2), 'brain' (n=1), heart failure and acute myocarditis (n=1), malnutrition (n=1), cervical cancer (n=1), obesity (n=1), thrombocytopenia 2 gastroenteritis (n=1) and toxic shock (n=1).

The risk of AIDS/death was low in both groups and the AIDS/death event rate was 2.9 [0-8.7] per 100 person-years of follow-up (PY) in ZDVm-experienced women and 13.7 [10.7-16.6]/100 PY in ART-naïve women. In crude analysis there was weak evidence that the risk of AIDS/death was lower in ZDVm-experienced women than in ART-naïve women (hazard ratio [HR] 0.16 [95% confidence interval (CI) 0.02-1.14], p=0.07). However, the difference in risk was not statistically significant in adjusted analysis (adjusted hazard ratio [aHR] 0.21 [0.03-1.51], p=0.12). In the adjusted model the other factors with a statistically significant association with AIDS/death were: having previously had an AIDS event (aHR 1.82 [1.19-2.79], p=0.006), having a baseline CD4 count  $\leq 200$  cells/mm<sup>3</sup> compared to 201-350 cells/mm<sup>3</sup> (aHR 2.30 [1.41-3.75], p<0.001), and starting a PI-based regimen compared to starting an NNRTI-based regimen (aHR 1.75 [1.17-2.61], p=0.006) (Table 6.4).

Table 6.4. Cox proportional hazards model for time to AIDS/death among ART-naive and ZDVm-experienced women on life-long ART

Variable		aHR	95% confidence interval	p-value
ZDVm-experience		0.21	0.03 - 1.51	0.12
Age (per 10 additional years)		1.17	0.92 - 1.49	0.20
Pregnant when starting ART		0.48	0.17 - 1.33	0.16
Ethnicity	Black-African	Reference		
	Other/not known	1.02	0.68 - 1.54	0.91
Exposure	Heterosexual sex	Reference		
	Other/not known	0.95	0.48 - 1.85	0.87
Year of HIV diagnosis		1.01	0.97 - 1.06	0.56
Year of starting treatment		0.99	0.90 - 1.10	0.90
ART regimen	NNRTI-based	Reference		0.01
	PI-based	1.75	1.17 - 2.61	
	NRTI/other	1.90	0.98 - 3.65	
Baseline viral load >10,000 copies/ml		1.11	0.74 - 1.69	0.61
Baseline CD4 count (cells/mm <sup>3</sup> )	≤200	2.30	1.41 - 3.75	<0.001
	201-350	Reference		
	>350	1.14	0.57 - 2.25	
	Not known	3.19	1.76 - 5.80	
HBV/HCV		1.31	0.73 - 2.37	0.37
Previous AIDS event		1.82	1.19 - 2.79	0.01

## CD4 count increase

Figure 6.1 and Table 6.5 present the mean CD4 count and mean CD4 increase from baseline at each 2 month interval throughout the first 24 months on treatment. These appear similar in ART-naïve and ZDVm-experienced women although the line of the ZDVm-experienced women has more 'noise' due to the smaller number of women in this group.

Figure 6.1. Mean CD4 count and CD4 change from baseline within 2 month periods since starting long-term ART in ART-naïve and ZDVm-experienced women

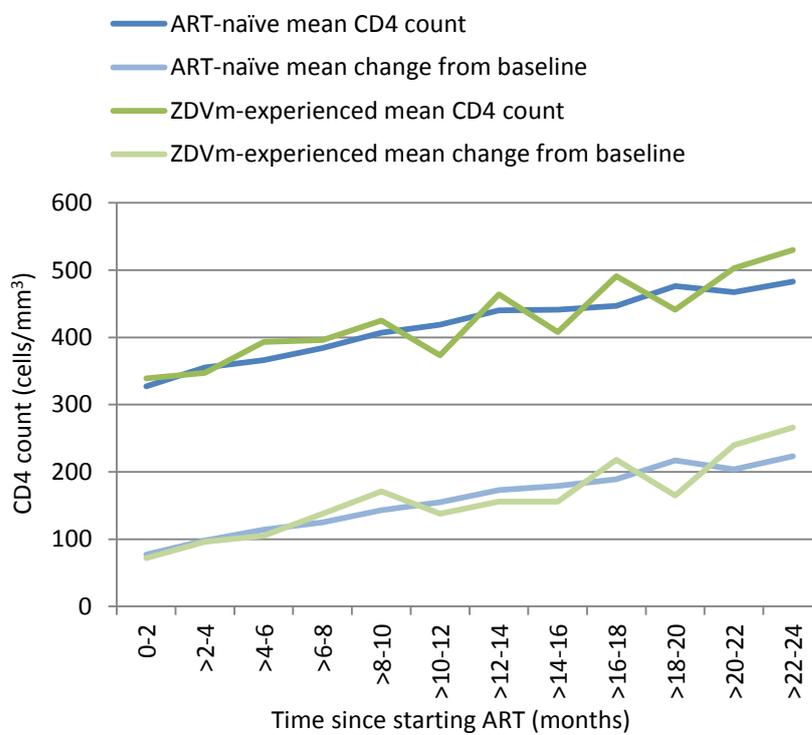


Table 6.5. Mean CD4 count and CD4 change from baseline within 2 month periods since starting long-term ART in ART-naive and ZDVm-experienced women

Months since ART start	0-2	>2-4	>4-6	>6-8	>8-10	>10-12	>12-14	>14-16	>16-18	>18-20	>20-22	>22-24
<b>ZDVm-experienced</b>												
Mean CD4 count	339	347	393	396	425	373	464	408	491	441	503	530
n	66	59	49	46	40	40	40	32	34	41	25	34
Mean change in CD4	72	96	105	138	171	138	156	156	218	165	240	266
n (also with baseline CD4)	65	58	48	44	39	38	39	31	33	41	24	33
<b>ART-naïve</b>												
Mean CD4 count	327	355	366	384	407	419	440	441	447	476	467	483
n	1056	1028	895	806	831	806	746	725	718	697	623	671
Mean change in CD4	77	98	114	125	143	155	173	179	189	217	204	223
n (also with baseline CD4)	997	954	820	739	744	723	671	646	630	621	554	587

After 6 months on treatment the mean CD4 count was 393 cells/mm<sup>3</sup> in ZDVm-experienced women and 388 cells/mm<sup>3</sup> in ART-naïve women. At that time there was no statistically significant association between ZDVm experience and mean change in CD4 count from baseline in crude or adjusted analysis (difference in mean: -7.2 [95% CI -40.1, 25.7] cells/mm<sup>3</sup>, p=0.67; adjusted difference in mean -10.2 [95% CI -42.4, 21.9] cells/mm<sup>3</sup>, p=0.53) (Table 6.6). There were, however, a number of other variables associated with CD4 count change (Table 6.6). After 6 months on ART, women who had been pregnant when starting treatment had on average a greater increase in CD4 count than women who were not pregnant when starting treatment (adjusted difference in mean 45.2 [95% CI 18.2, 72.2] cells/mm<sup>3</sup>, p=0.001).

After 24 months on treatment the mean CD4 count was 526 cells/mm<sup>3</sup> in ZDVm-experienced women and 490 cells/mm<sup>3</sup> in ART-naïve women. Again there was no statistically significant association between ZDVm experience and change in CD4 count from baseline in crude or adjusted analysis (difference in mean: 23.1 [95% CI -25.2, 71.4] cells/mm<sup>3</sup>, p=0.35; adjusted difference in mean 16.4 [95% CI -30.9, 63.6] cells/mm<sup>3</sup>, p=0.50). At 24 months, having a higher baseline CD4 count was associated with a smaller increase in CD4 count (adjusted difference in mean -13.8 [95% CI -20.9, -6.7] cells/mm<sup>3</sup> per additional 100 cells/mm<sup>3</sup> at baseline, p<0.001). Other variables associated with change in CD4 count were: black-African ethnicity compared to ethnicity 'other/not known' (adjusted difference in mean -31.0 [95% CI -53.8, -8.1] cells/mm<sup>3</sup>, p=0.008), year of starting treatment (adjusted difference in mean per additional year 7.0 [95% CI 1.6, 12.3] cells/mm<sup>3</sup>, p=0.01), and starting an NRTI/other type regimen compared to an NNRTI-based regimen (adjusted difference in mean -51.9 [95% CI -99.2, -4.6] cells/mm<sup>3</sup>, p=0.03). Women with a baseline viral load >10,000 copies/ml had a greater increase in CD4 count (adjusted difference in mean 74.1 [95% CI 51.6, 96.8] cells/mm<sup>3</sup>, p<0.001). Viral load remained associated with CD4 count change when log<sub>10</sub> viral load was included in the model instead of the binary variable (≤/ >10,000 copies/ml) which resulted in the exclusion of an additional 204 women with no baseline viral load (adjusted difference in mean 38.6 [95% CI 28.9, 48.4] cells/mm<sup>3</sup>, p<0.001).

After 24 months on ART, women with HBV/HCV had on average a smaller increase in CD4 count than women without HBV/HCV (adjusted difference in mean -55.9 [95% CI -96.8, -14.9] cells/mm<sup>3</sup>, p=0.01). This difference was much smaller and did not reach statistical significance after only 6 months on ART (adjusted difference in mean -5.0 [95% CI -31.5, -21.4] cells/mm<sup>3</sup>, p=0.71).

After 24 months on ART the association between pregnancy status when starting life-long ART and CD4 count was not statistically significant (adjusted difference in mean 24.7 [95% CI -16.2, 65.6] cells/mm<sup>3</sup>, p=0.24).

### **Viral suppression**

More than three-quarters of women in both groups achieved viral suppression within 6 months on ART (ZDVm-experienced: 88.4% [76/86]; ART-naïve: 77.2% [1059/1371] among women with baseline viral load and a viral load measurement during the first 6 months on ART). The median time to viral suppression (Kaplan Meier estimate) was 2.8 (95% CI 2.3-3.2, IQR 1.4-4.4) months for ZDVm-experienced women and 3.2 (95% CI 3.0-3.3, IQR 1.8-5.3) months for ART-naïve women.

In Cox proportional hazards analysis, women with no baseline viral load measurement were excluded (ZDVm-experienced n=7 and ART-naïve n=234) as were women with no viral load measurement in the first six months of ART use (n=0 ZDVm-experienced and n=62 ART-naïve). ZDVm-experienced women were more likely to achieve viral suppression within the first 6 months on treatment compared to women who were ART-naïve (HR 1.32 [1.04-1.66], p=0.02) (Figure 6.2 and Table 6.7). This was also true in the adjusted model (aHR 1.31 [1.03-1.66], p=0.03). Women who were pregnant when starting life-long ART were more likely to achieve viral suppression (aHR 1.47 [1.19-1.81], p<0.001). Women starting a PI-based regimen or an NTRI/other regimen were less likely to achieve viral suppression compared to women starting an NNRTI-based regimen (PI-based: aHR 0.77 [0.67-0.88], p<0.001; NRTI/other: aHR 0.67 [0.51-0.88], p=0.004) and women starting ART with a CD4 count >350 cells/mm<sup>3</sup> were less likely to achieve viral suppression compared to women starting with CD4 201-350 cells/mm<sup>3</sup> (aHR 0.83 [0.70-0.98], p=0.03). Compared to women with a low baseline viral load, women with a higher baseline viral load were less likely to achieve viral suppression (baseline viral load [ $\log_{10}$  copies/ml] aHR 0.78 [0.75-0.82], p<0.001) (Table 6.7).

Table 6.6. Mean change in CD4 count after 6 and 24 months on ART in women who were ZDVm-experienced or ART-naïve when starting life-long ART

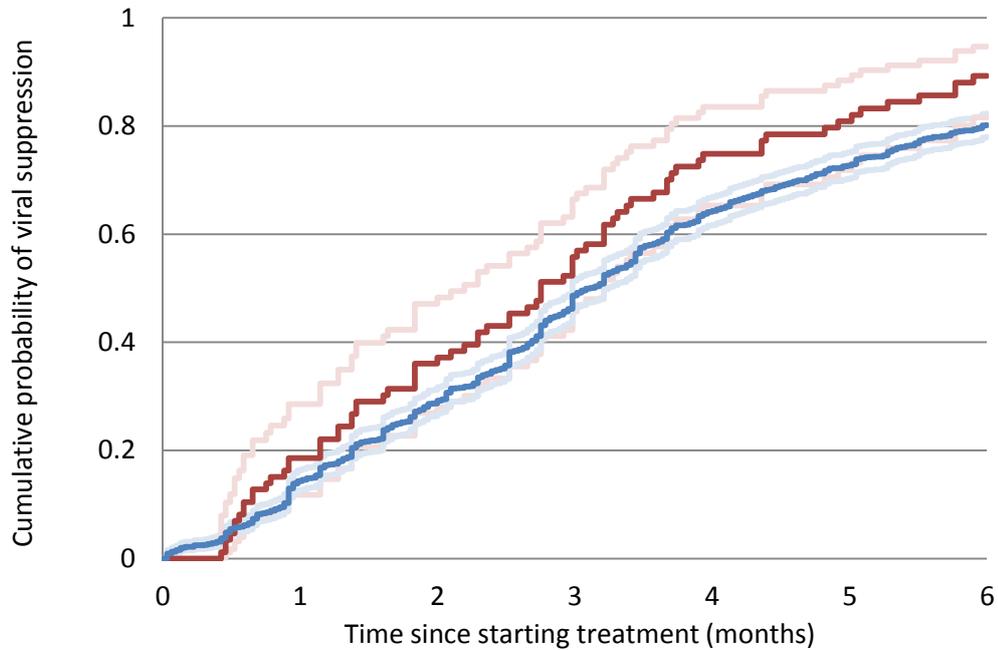
Variable	6 months on ART			24 months on ART					
	Adjusted difference in means	95% confidence interval		p-value	Adjusted difference in means	95% confidence interval		p-value	
ZDVm-experience	-10.2	-42.4,	21.9	0.53	16.4	-30.9,	63.6	0.50	
Age (per 10 additional years)	1.5	-7.9,	11.0	0.75	6.3	-7.6,	20.3	0.37	
Pregnant when starting ART	45.2	18.2,	72.2	0.001	24.7	-16.2,	65.6	0.24	
Ethnicity	Black-African	Reference			Reference				
	Other/not known	-16.8	-32.2,	-1.4	0.03	-31.0	-53.8,	-8.1	0.01
Exposure	Heterosexual sex	Reference			Reference				
	Other/not known	9.2	-17.9,	36.4	0.50	5.5	-36.8,	47.8	0.80
Year of HIV diagnosis	-2.0	-3.9,	-0.1	0.04	-2.2	-5.0,	0.6	0.12	
Year of starting treatment	5.7	2.2,	9.2	0.001	7.0	1.6,	12.3	0.01	
ART regimen	NNRTI-based	Reference			Reference				
	PI-based	8.3	-8.3,	24.8	0.33	-11.2	-36.0,	13.7	0.38
	NRTI/other	-33.8	-65.3,	-2.3	0.04	-51.9	-99.2,	-4.6	0.03
Baseline viral load >10,000 copies/ml	44.0	28.6,	59.4	<0.001	74.2	51.6,	96.8	<0.001	
Baseline CD4 count (per additional 100 cells/mm <sup>3</sup> )	-14.0	-18.8,	-9.3	<0.001	-13.8	-20.9,	-6.7	<0.001	
HBV/HCV	-5.0	-31.5,	21.4	0.71	-55.9	-96.8,	-14.9	0.01	
Previous AIDS event	-5.2	-27.0,	16.6	0.64	19.0	-12.8,	50.8	0.24	

Denominators: 6 months: ZDVm-experienced: n=78; ART-naïve: n=1445; 24 months: ZDVm-experienced: n=65; ART-naïve: n=1236.

Table 6.7. Cox proportional hazards model for time to viral suppression within 6 months on treatment in ZDVm-experienced (n=86) and ART-naive women (n=1371)

Variable		aHR	95% confidence interval	p-value
ZDVm-experience		1.31	1.03 - 1.66	0.03
Age (per additional 10 years)		1.06	0.98 - 1.14	0.16
Pregnant when starting ART		1.47	1.19 - 1.81	<0.001
Ethnicity	Black-African	Reference		
	Other/not known	1.05	0.92 - 1.19	0.48
Exposure	Heterosexual sex	Reference		
	Other/not known	0.92	0.73 - 1.15	0.45
Year of HIV diagnosis		1.01	0.99 - 1.02	0.28
Year of starting treatment		1.07	1.04 - 1.10	<0.001
ART regimen	NNRTI-based	Reference		<0.001
	PI-based	0.77	0.67 - 0.88	
	NRTI/other	0.67	0.51 - 0.88	
Baseline viral load (log <sub>10</sub> copies/ml)		0.78	0.75 - 0.82	<0.001
Baseline CD4 count (cells/mm <sup>3</sup> )	≤200	0.93	0.81 - 1.08	0.18
	201-350	Reference		
	>350	0.83	0.70 - 0.98	
	Not known	0.97	0.68 - 1.39	
HBV/HCV		0.96	0.77 - 1.21	0.75
Previous AIDS event		1.03	0.86 - 1.23	0.78

Figure 6.2. Cumulative incidence of virological suppression within 6 months on treatment: ZDVm-experienced women (red line with 95% CIs in light red) compared to ART-naïve women (blue line with 95% CIs in light blue) – where women with no baseline viral load or viral load measurement within the 6 months on ART were excluded



ART-naïve	1371	1162	948	675	460	348	251
ZDVm-experienced	86	70	54	38	21	16	9

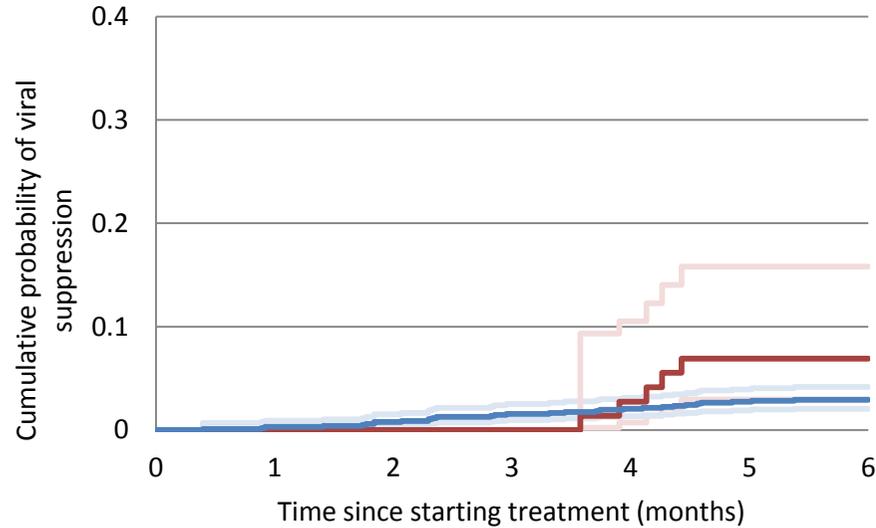
## **Viral rebound**

Among women who achieved viral suppression within 6 months on ART (n=1135) the risk of viral rebound was examined within the periods 0-6 and 6-24 months after suppression. Few women experienced viral rebound in the first 6 months after suppression (ZDVm-experienced 6.6% [5/76]; ART-naïve 2.8% [30/1059] (Figure 6.3a). In crude analysis there was weak evidence that ZDVm-experienced women were more likely to experience viral rebound (aHR 2.37 [0.92-6.07], p=0.07) but in the adjusted analysis there was no statistically significant association between ZDVm experience and the risk of viral rebound (aHR 1.65 [0.60-4.56], p=0.33) (Table 6.8). During this period, women who had started treatment whilst pregnant were more likely to experience viral rebound compared to women who were not pregnant when starting treatment (aHR 6.34 [2.86-14.07], p<0.001). The risk of viral rebound was lower in older women than in younger women (aHR per additional 10 years 0.47 [0.27-0.80], p=0.01). Women who started an NRTI/other regimen were more likely to experience viral rebound compared to women who started an NNRTI-based regimen (aHR 4.84 [1.47-15.88], p=value 0.01).

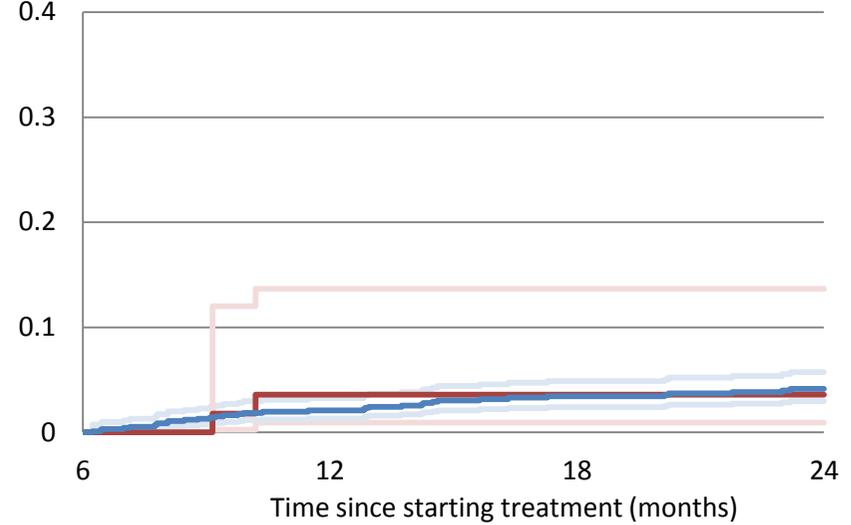
In the period 6-24 months after suppression, among women who were yet to experience viral rebound, few women experienced viral rebound (ZDVm-experienced 3.0% [2/66]; ART-naïve 3.6% [35/969] (Figure 6.3b). None of the variables included in the adjusted model had a statistically significant association with the risk of viral rebound in the 6-24 months after viral suppression including previous use of ZDVm (HR 0.91 [0.22-3.79], p=0.90; aHR 0.88 [0.21-3.72], p=0.86).

Figure 6.3. Cumulative incidence of viral rebound among women achieving viral suppression within six months of starting ART: women with ZDVm experience (red line with 95% CIs in light red) compared to ART-naïve women (blue line with 95% CIs in light blue)

a.) 0-6 months after viral suppression



b.) 6-24 months after viral suppression



At risk											
ART-naïve	1059	1041	1025	1008	993	977	969	969	836	739	628
ZDVm-experienced	76	73	73	73	70	67	66	66	52	48	43

Both figures include only women with viral suppression within 6 months on ART and b) includes only women still at risk of viral rebound

Table 6.8. Time to viral rebound 0-6 months and 6-24 months after viral suppression (within 6 months) in ZDVm-experienced and ART-naive women on life-long ART

Variable	0-6 months after suppression			6-24 months after suppression			
	aHR	95% confidence interval	p-value	aHR	95% confidence interval	p-value	
ZDVm-experience	1.65	0.60 - 4.56	0.33	0.88	0.21 - 3.72	0.86	
Age (per additional 10 years)	0.47	0.27 - 0.80	0.01	0.94	0.61 - 1.46	0.79	
Pregnant when starting ART	6.34	2.86 - 14.07	<0.001	2.21	0.82 - 5.91	0.12	
Ethnicity	Black-African	Reference		Reference			
	Other/not known	1.13	0.51 - 2.51	0.77	1.40	0.66 - 2.95	0.38
Exposure	Heterosexual sex	Reference		Reference			
	Other/not known	1.01	0.25 - 4.11	0.99	1.20	0.34 - 4.20	0.78
Year of HIV diagnosis	0.98	0.88 - 1.09	0.73	1.06	0.99 - 1.15	0.11	
Year of starting treatment	0.97	0.81 - 1.15	0.71	0.91	0.78 - 1.07	0.25	
ART regimen	NNRTI-based	Reference		Reference		0.57	
	PI-based	2.03	0.91 - 4.54		1.46	0.72 - 2.96	
	NRTI/other	4.84	1.47 - 15.88		-		
Baseline viral load (log <sub>10</sub> copies/ml)	1.23	0.88 - 1.71	0.22	1.22	0.90 - 1.64	0.20	
Baseline CD4 count (cells/mm <sup>3</sup> )	≤200	1.41	0.57 - 3.50	0.56	1.23	0.57 - 2.65	0.90
	201-350	Reference		Reference			
	>350	1.85	0.76 - 4.47		1.04	0.38 - 2.87	
	Not known	1.78	0.38 - 8.27		1.64	0.37 - 7.30	
HBV/HCV	1.00	0.28 - 3.48	0.99	2.32	0.95 - 5.71	0.07	
Previous AIDS event	1.15	0.33 - 4.07	0.82	0.91	0.36 - 2.26	0.83	

### **Regimen change or interruption whilst on treatment**

Within the first 24 months on treatment, 41.5% (730/1760) of women changed their regimen (ZDVm-experienced: 37.6% (35/93); ART-naïve 41.7% [695/1667]) either by increasing the number of drugs by one (29.9%, n=218 overall) or more (11.1%, n=81), replacing drugs in the regimen whilst maintaining the overall number (36.3%, n=265) or reducing the number of drugs by one (13.0%, n=95) or more (4.8%, n=35). There was no statistically significant association between ZDVm experience and changing regimen (aHR 0.91 [0.65-1.29], p=0.60) (Table 6.9). However, women who were pregnant when starting treatment were more likely to change their regimen compared to women who were not pregnant when starting treatment (aHR 1.39 [1.08-1.79], p=0.01). Changing regimen was also associated with having HBV/HCV co-infection (aHR 1.38 [1.08-1.77], p=0.01), starting treatment with a CD4 count >350 cells/mm<sup>3</sup> compared to 201-350 cells/mm<sup>3</sup> (aHR 0.78 [0.62-0.98], p=0.03), starting an NRTI/other regimen compared to starting an NNRTI-based regimen (aHR 1.69 [1.27-2.24], p<0.001) and the year in which treatment was started (aHR 0.93 [0.90-0.96] per additional year, p<0.001) (Table 6.9).

An interruption of ART for at least 30 days occurred in 14.0% (13/93) of ZDVm-experienced women and 18.3% (305/1667) of ART-naïve women. In women who interrupted treatment, the interruption occurred after a median of 7.9 (IQR 3.0-15.0) months on ART and the median time to restarting treatment was 3.7 (IQR 1.9-13.2) months from the date of interruption. There was no statistically significant association between ZDVm experience and interrupting treatment (aHR 0.73 [0.41-1.28], p=0.26) (Table 6.9). As with treatment changes, women who were pregnant when starting treatment were more likely to interrupt their regimen (aHR 1.47 [1.03-2.10], p=0.03) (Table 6.9). Interrupting ART was also associated with younger age (aHR 0.86 [0.75-1.00], p=0.05 per 10 additional years), and the year in which treatment was started (aHR 0.91 [0.86-0.96] per additional year, p=0.001).

Table 6.9. Time to switching or interrupting ART regimen in ZDVm-experienced and ART-naive women starting life-long ART

Variable	Time to any change in regimen			Time to ART interruption			
	aHR	95% confidence interval	p-value	aHR	95% confidence interval	p-value	
ZDVm-experience	0.91	0.65 - 1.29	0.60	0.73	0.41 - 1.28	0.26	
Age (per 10 additional years)	0.96	0.87 - 1.06	0.37	0.86	0.75 - 1.00	0.05	
Pregnant when starting ART	1.39	1.08 - 1.79	0.01	1.47	1.03 - 2.10	0.03	
Ethnicity	Black-African	Reference		Reference			
	Other/not known	1.18	1.00 - 1.38	0.05	1.01	0.79 - 1.29	0.92
Exposure	Heterosexual sex	Reference		Reference			
		1.18	0.88 - 1.57	0.27	0.82	0.55 - 1.22	0.32
Year of HIV diagnosis	1.01	0.99 - 1.03	0.36	1.00	0.97 - 1.03	0.96	
Year of starting treatment	0.93	0.90 - 0.96	<0.001	0.91	0.86 - 0.96	0.001	
ART regimen	NNRTI-based	Reference		Reference			
	PI-based	1.16	0.99 - 1.37	<0.001	1.60	1.26 - 2.04	<0.001
	NRTI/other	1.69	1.27 - 2.24		1.02	0.62 - 1.70	
Baseline viral load (log <sub>10</sub> copies/ml)	1.00	0.85 - 1.17	0.99	1.22	0.96 - 1.54	0.10	
Baseline CD4 count (cells/mm <sup>3</sup> )	≤200	1.07	0.89 - 1.29	0.005	1.29	0.99 - 1.68	<0.001
	201-350	Reference		Reference			
	>350	0.78	0.62 - 0.98		0.84	0.60 - 1.16	
	Not known	1.26	1.00 - 1.59		0.50	0.31 - 0.80	
HBV/HCV	1.38	1.08 - 1.77	0.01	1.45	1.02 - 2.05	0.04	
Previous AIDS event	1.11	0.89 - 1.39	0.35	0.78	0.58 - 1.05	0.11	

## **Sensitivity analyses**

In sensitivity analyses, when the 153 women who were pregnant when starting life-long ART were excluded, the main findings were unaltered. There was no statistically significant association between ZDVm experience and AIDS/death (aHR 0.23 [0.03-1.66], p=0.14), mean change in CD4 count after 6 months (adjusted difference in means 6.1 [-29.4, 41.5], p=0.74) or 24 months on ART (adjusted difference in means 39.3 [-11.4, 90.0], p=0.13), switching treatment (aHR 0.81 [0.53-1.24], p=0.33) or interrupting treatment (aHR 0.71 [0.36-1.39], p=0.32). As with the main analysis, ZDVm-experienced women were more likely to achieve viral suppression within 6 months (aHR 1.45 [1.12-1.88], p=0.005) but there was no statistically significant association between ZDVm experience and viral rebound at 0-6 months (aHR 1.51 [0.19-12.0], p=0.70) or at >6-24 months (aHR 0.95 [0.22-4.05], p=0.94) after viral suppression.

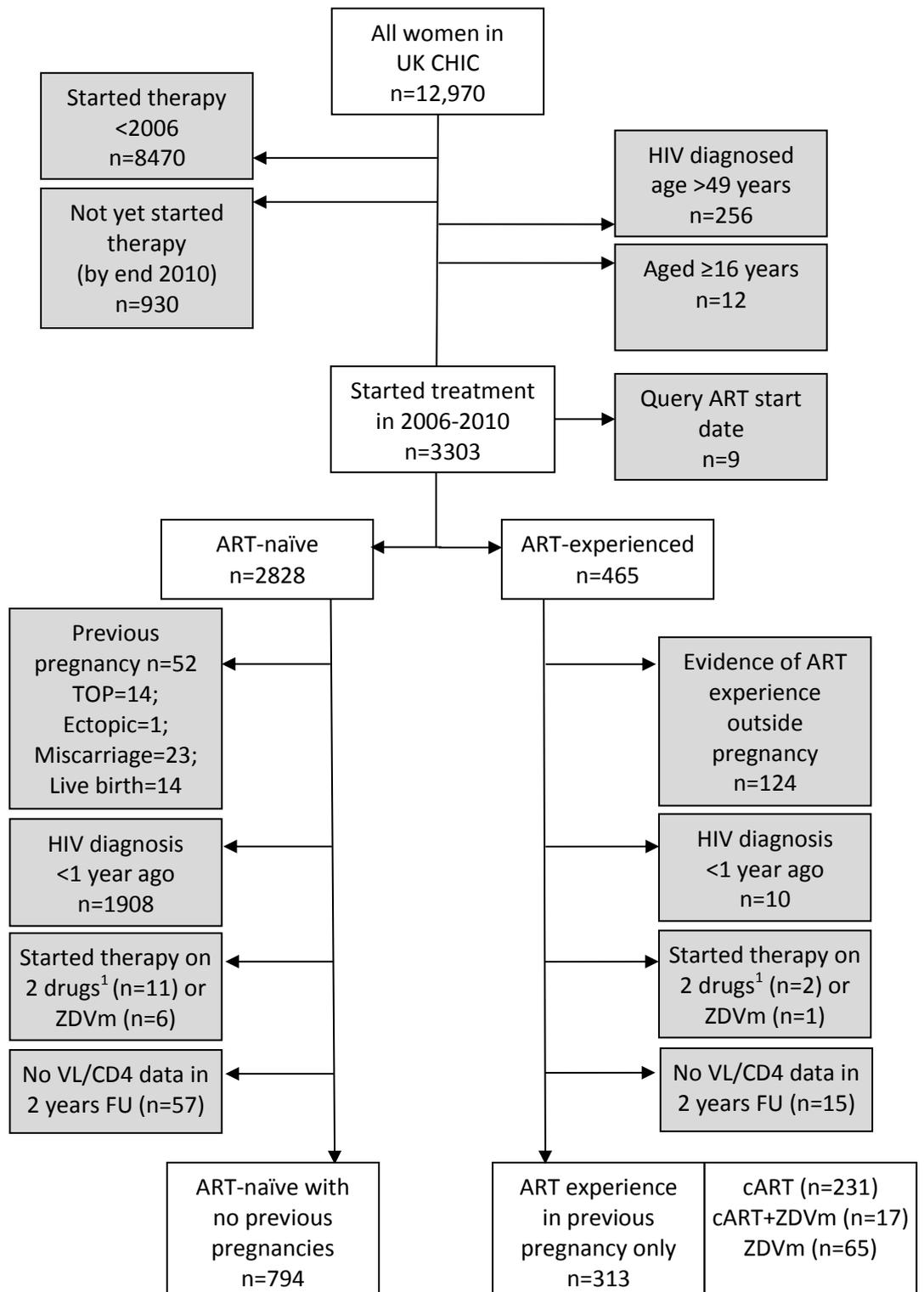
## **6.5 Analysis 2: Treatment outcomes in cART-experienced and ART-naïve women**

### **ART use in pregnancy**

There were 248 women who started life-long ART and who had previously used short-course cART in one (n=208), two (n=20) or three (n=3) pregnancies or who had used cART in at least one pregnancy and ZDVm in at least one pregnancy (n=17) (Figure 6.4).

In cART-experienced women starting treatment, where the duration of ART use was known (281/297 pregnancies), the median duration of use in a pregnancy (including any postpartum use) was 15 (10-20) weeks. The median cumulative duration of previous ART use was 16 (IQR 11-23) weeks. Where the regimen used in pregnancy was reported (290 pregnancies) the regimen was: PI-based (60.7%, n=176); NNRTI-based (26.9%, n=78), (77 of which contained nevirapine (NVP); or another type of regimen (8.9%, n=26). The median interval between the end of their last pregnancy in which short-course ART was used and the date on which they started treatment was 31 (IQR 21-52) months; 10.9% (n=27) of women had an interval of less than one year.

Figure 6.4. Diagram showing inclusion in and exclusion from Analysis 2



Shaded boxes indicate groups excluded from the analysis

<sup>1</sup> In some cases these were clinical trials of drugs where the number of drugs was not reported

### **Duration of follow-up and availability of CD4 count and viral load measurements**

The 1042 women included in the analysis were followed for a total of 3877 PY from the date they started life-long ART (ART-experienced women: 897 PY and ART-naïve women: 2980 PY).

The percentage of women with at least one viral load measurement within the first six months on ART was similar in both groups (cART-experienced: 91.9% [228/248]; ART-naïve 93.0% [738/794],  $p=0.59$ ). The median number of viral load measurements in this period was the same for both groups (3 [IQR 2-4],  $p=0.41$ ), this was also the case in the first 24 months of treatment (cART-experienced women: 7 [IQR 5-10]; ART-naïve women: 7 [IQR 6-10],  $p=0.23$ ).

The percentage of women with at least one CD4 cell count within the first six months on ART was similar in cART-experienced and ART-naïve women (88.3% [219/248] vs. 90.7% [720/794] respectively,  $p=0.27$ ). However, cART-experienced women had, on average, fewer CD4 counts in the first 6 months on treatment (cART-experienced: 2 [IQR 1-3]; ART-naïve: 2 [IQR 1-3]),  $p$ -value for distribution  $<0.001$  and in the first 24 months on treatment (cART-experienced: 5 [IQR 4-7]; ART-naïve: 6 [IQR 4-8],  $p<0.001$ ).

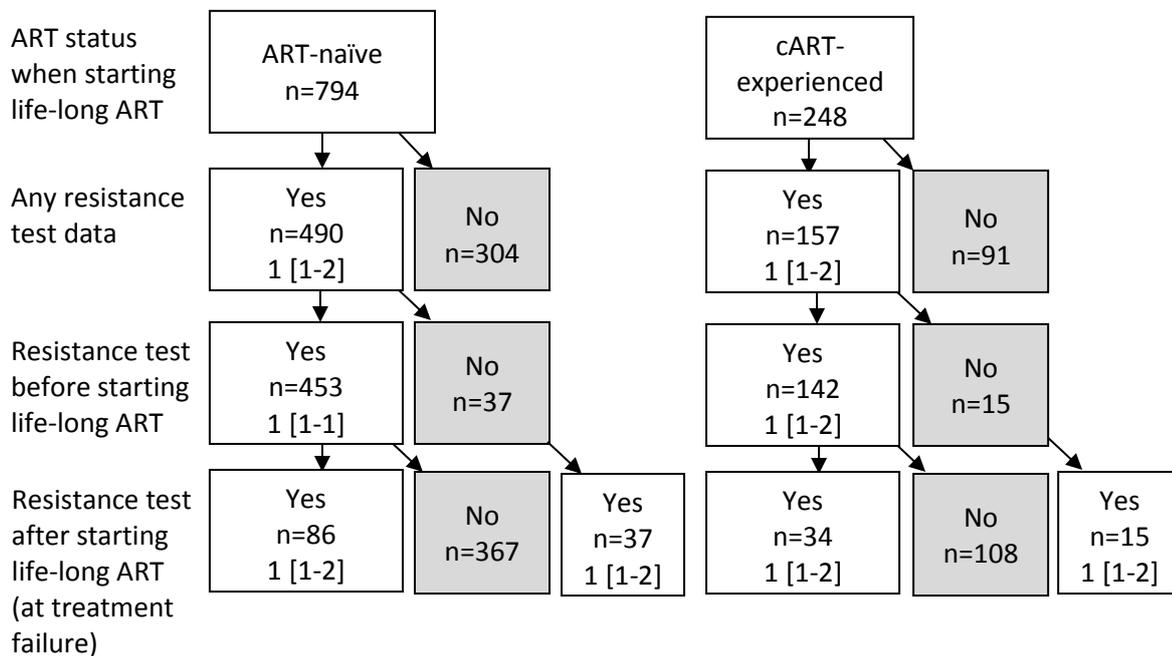
### **Availability of drug resistance data**

Prior to starting treatment, 57.3% ( $n=142$ ) of cART-experienced women had at least one resistance test performed (Figure 6.5). The percentage of cART-experienced women with a resistance test prior to starting treatment increased over time from 36.6% (15/41) of women starting therapy in 2006 to 63.0% (34/54) of women starting life-long ART in 2010 (Chi-square  $p$ -value 0.02). Of women with a resistance test, 69 women had the test prior to any ART use and 69 women had a test following ART use and in the year before starting treatment (22 women had a test at both these times). A further 26 women had a resistance test prior to starting treatment but not when ART-naïve or in the year before starting treatment.

Prior to starting treatment, 57.1% (453/794) of ART-naïve women had at least one resistance test performed (Figure 6.5), with the percentage increasing over time from 44.7% (67/150) of women starting treatment in 2006 to 61.3% (84/137) of women starting treatment in 2010 (Chi-square  $p<0.001$ ). Of these, 155 (34.2%) women had a test within 6 months of their HIV diagnosis, 171 (37.7%) women in the 6 months before starting treatment (36 women had a test within 6 months of diagnosis and another test

6 months prior to starting treatment) and 91 (20.1%) women had a test at another time prior to starting treatment.

Figure 6.5. Resistance test data for ART-naïve and cART-experienced women included in the analysis



Median number of tests is shown with IQR in square brackets

### Baseline characteristics when starting treatment

The characteristics of cART-experienced and ART-naïve women starting treatment are presented in Table 6.10. Compared to ART-naïve women, cART-experienced women were more likely to be of black-African ethnicity (75.4% vs. 61.5% respectively), infected with HIV via heterosexual sex (98.0% vs. 90.8%) and be pregnant when starting life-long ART (17.3% vs. 10.8%). cART-experienced women were less likely to have had an AIDS event (cART-experienced: 6.9%; ART-naïve: 13.7%). When starting treatment there was no statistically significant difference in mean CD4 count (cART-experienced CD4 283 cells/mm<sup>3</sup> vs. ART-naïve 269 cells/mm<sup>3</sup>, p=0.18). A larger percentage of cART-experienced women had viral load >10,000 copies/ml than ART-naïve women (69.0% vs. 59.6%). In both groups, most women started an NNRTI-based regimen (ART-naïve 54.0%; cART-experienced 61.3%) and most women started on a combination of three drugs (57.3% and 64.0% respectively). Baseline ALT data were available for only 31.1% (n=77) of cART-experienced and 37.0% (n=294) of ART-naïve women.

Table 6.10. Characteristics of women starting treatment in 2006-2010 (n=1042)

Baseline characteristics		cART-experienced n=248		ART-naïve n=794		p=
Year, n (%)	2006-2007	79	(31.9)	318	(40.1)	0.05
	2008-2009	115	(46.4)	339	(42.7)	
	2010	54	(21.8)	137	(17.3)	
Age, n (%)	16-29 years	75	(30.2)	194	(24.4)	<0.001
	30-39 years	138	(55.7)	356	(44.8)	
	40-49 years	35	(14.1)	244	(30.7)	
	Median [IQR] years	33	[28-37]	35	[30-41]	
Ethnicity, n (%)	Black African	187	(75.4)	488	(61.5)	<0.001
	White	25	(10.1)	166	(20.9)	
	Black Caribbean	19	(7.7)	45	(5.7)	
	Other/NK	17	(6.9)	95	(12.0)	
Exposure category, n (%)	Heterosexual sex	243	(98.0)	721	(90.8)	0.001
	IDU	3	(1.2)	39	(4.3)	
	Other/NK	2	(0.8)	34	(4.9)	
HBV/HCV, n (%)		17	(6.9)	78	(9.8)	0.16
<sup>1</sup> CD4 count (cells/mm <sup>3</sup> ), n (%) n=232,n=732	≤200	60	(25.9)	203	(27.7)	0.81
	201-350	129	(55.6)	408	(55.7)	
	351-500	30	(12.9)	79	(10.8)	
	>500	13	(5.6)	42	(5.7)	
	Mean [SD]	283	[139]	269	[145]	
<sup>1</sup> Viral load >10,000 (copies/ml), n (%) n=229,n=726		158	(69.0)	433	(59.6)	0.01
Median [IQR] (log <sub>10</sub> copies/ml)		4.5	[3.8-4.9]	4.3	[3.5-4.9]	0.02
Years since diagnosis, median [IQR]		4.4	[2.6-6.9]	3.7	[2.1-6.2]	<0.001
Previous AIDS event, n (%)		17	(6.9)	109	(13.7)	0.004
Pregnant, n (%)		43	(17.3)	86	(10.8)	0.007
Type of ART regimen, n (%)	PI-based	108	(43.6)	302	(35.8)	0.18
	NNRTI-based	134	(54.0)	522	(61.3)	
	NRTI-based	2	(0.8)	12	(1.1)	
	Other	4	(1.6)	15	(1.8)	
Drugs in regimen, n (%)	3	142	(57.3)	508	(64.0)	0.07
	≥4	106	(42.7)	286	(36.0)	

<sup>1</sup>Latest measurement within the 6 months before starting treatment

### **Drug resistance before starting life-long ART**

In cART-experienced women with a resistance test at any point before starting life-long ART, 11.3% (16/142) had resistance to  $\geq 1$  drug class (to either one [n=15] or two [n=1] drug classes). In women tested prior to using short-course ART in pregnancy, 7.3% (5/69) had resistance to a single drug class (Table 6.11). Of the 453 ART-naïve women with a resistance test at any point before starting treatment, 12.6% (n=57) had resistance to at least one drug class; 46 women had resistance to a single drug class and 11 women had resistance to two drug classes.

When starting treatment, cART-experienced women were no more likely to have resistance to  $\geq 1$  drug class than ART-naïve women (odds ratio [OR] 0.88 [CI 0.49-1.59], p=0.68).

Table 6.11. Drug resistance prior to starting treatment in ART-naïve and cART-experienced women with ≥1 resistance test prior to starting treatment

Women with ≥1 resistance test prior to starting treatment		Resistance to ≥1 drug class		Type of drug class resistance [total]		
ART-naïve (n=453)		No	396 (87.4%)			
		Yes	57 (12.6%)			
			Single drug class	n=46		
			PI	3		
			NRTI	1		
			NNRTI	42		
			Two drug classes	n=11		
		PI+NRTI	2			
		PI+NNRTI	3			
		NRTI+NNRTI	6			
cART-experienced	When ART-naïve (n=69)	No	64 (92.8%)			
		Yes	5 (7.3%)			
			Single drug class	n=5		
			PI	1		
			NRTI	1		
			NNRTI	3		
	In 12 months before starting life-long ART (n=69)		No	66 (95.7%)		
			Yes	3 (4.3%) <sup>1</sup>		
			Single drug class	n=2		
			NNRTI	2		
			Two drug classes	n=1		
			NRTI+NNRTI	1		
	Any time prior to starting life-long ART <sup>2</sup> (n=142)		No	126 (88.7%)		
		Yes	16 (11.3%)			
		Single drug class	n=15			
		PI	2			
		NRTI	3			
		NNRTI	10			
		Two drug classes	n=1			
		NRTI+NNRT	1			

<sup>1</sup> These women did not have a resistance test when they were ART-naïve

<sup>2</sup> There were 22 women tested when they were ART-naïve and also tested during the 12 months prior to starting life-long ART. The three cART-experienced women with ≥1 drug class resistance prior to starting treatment did not have a resistance test when they were ART-naïve

The major drug resistance mutations identified in these women are shown in Appendix IX

## **AIDS/death**

Whilst on treatment, 4.4% (n=11) of cART-experienced women and 5.9% (n=47) of ART-naïve women developed AIDS or died. The AIDS/death event rate was 14.7 (95% CI 6.0 – 23.4)/100 PY in cART-experienced women and 18.9 (13.5 – 24.3)/100 PY in ART-naïve women. The cause of death was reported for only 7 of the 20 women who died (18 ART-naïve women and 2 cART-experienced women died). The cause of deaths were reported as: 'brain'; 'HIV disease'; 'malnutrition due to bowel obstruction'; 'thrombocytopenia 2 gastroenteritis'; 'murder'; 'cerebral toxoplasmosis' and 'metastatic cervical cancer HIV diabetes mellitus'. Only two of the deaths were preceded by an AIDS event. One woman was diagnosed with cerebral toxoplasmosis having started ART two months before and died within two months of the AIDS event. Another woman was diagnosed with 'Lymphoma, Burkitt's, immunoblastic or equivalent'. She died 6 months after the AIDS diagnosis but the cause of death was not reported.

There was no statistically significant association between cART experience and AIDS/death in crude or adjusted analysis (HR 0.76 [95% CI 0.39-1.46], p=0.41; aHR 0.82 [0.41-1.65], p=0.58). In the adjusted model, factors with a statistically significant association with AIDS/death were: older age (aHR 1.45 [1.01-2.09] per 10 additional years, p=0.04); baseline CD4 count  $\leq 200$  cells/mm<sup>3</sup> compared to 201-350 cells/mm<sup>3</sup> (aHR 2.77 [1.50-5.13], global p<0.001); a baseline viral load >10,000 copies/ml (aHR 1.92 [1.00-3.71], p=0.05); and starting a PI-based regimen compared to starting an NNRTI-based regimen (aHR 1.90 [1.10-3.28], p=0.02) (Table 6.12).

Table 6.12. Cox proportional hazards model for time to AIDS/death among ART-naive and cART-experienced women on life-long ART

Variable		aHR	95% confidence interval	p-value
cART-experienced		0.82	0.41 - 1.65	0.58
Age (per 10 additional years)		1.45	1.01 - 2.09	0.04
Pregnant when starting ART		0.82	0.30 - 2.21	0.69
Ethnicity	Black-African	Reference		0.48
	White	0.78	0.36 - 1.70	
	Black-Caribbean	0.93	0.33 - 2.63	
	Other/not known	0.33	0.08 - 1.39	
Exposure group	Heterosexual sex	Reference		0.81
	PWID	1.08	0.28 - 4.09	
	Other/not known	0.52	0.07 - 3.84	
Year of HIV diagnosis		0.97	0.90 - 1.05	0.51
Year of starting treatment		1.06	0.86 - 1.30	0.60
ART regimen	PI-based	1.90	1.10 - 3.28	0.05
	NNRTI-based	Reference		
	NRTI only	-		
	Other	4.07	0.94 - 17.63	
Baseline viral load >10,000 copies/ml		1.92	1.00 - 3.71	0.05
Baseline CD4 count (cells/mm <sup>3</sup> )	≤200	2.77	1.50 - 5.13	<0.001
	201-350	Reference		
	351-500	0.30	0.04 - 2.22	
	>500	1.43	0.32 - 6.42	
	Not known	4.50	1.81 - 11.24	
HBV/HCV		1.61	0.69 - 3.77	0.27
Previous AIDS event		1.44	0.75 - 2.79	0.28

PWID: People who inject drugs

### **Liver enzyme elevation**

Whilst on treatment, few women in either group experienced severe LEE (cART-experienced: 2.8% [7/248]; ART-naïve: 2.1% [17/794]). There was no statistically significant association between ART experience and severe LEE in crude or adjusted analysis (HR 1.24 [0.48-3.17],  $p=0.65$ ; aHR 0.93 [0.34-2.53],  $p=0.88$ ). None of the variables included in the adjusted model had a statistically significant association with LEE (data not presented).

### **CD4 count increase at 6 and 24 months**

The mean CD4 cell count and mean increase from baseline CD4 count at each 2 month interval following initiation of treatment are presented in Figure 6.6 and Table 6.13. Throughout the first 24 months on treatment the mean CD4 count and the mean increase in CD4 count from baseline appear slightly higher in cART-experienced women than in ART-naïve women. However, there was no statistically significant difference between the two groups with regard to their increase in CD4 count after 6 months or after 24 months on treatment (Table 6.14). After 6 months, the difference in mean was 19.8 [95% CI -3.6, 43.2],  $p=0.10$ , and the adjusted difference in mean was 15.0 [-9.2, 39.1] cells/mm<sup>3</sup>,  $p=0.22$ . After 24 months, the difference in mean was -1.7 [-35.5, 32.1],  $p=0.92$ , and the adjusted difference in mean was 4.2 [-31.0, 39.4] cells/mm<sup>3</sup>,  $p=0.82$ . At this time the mean CD4 count was 525 cells/mm<sup>3</sup> and 516 cells/mm<sup>3</sup> in cART-experienced and ART-naïve women respectively.

Figure 6.6. Mean CD4 count and CD4 change from baseline within 2 month periods since starting long-term ART in ART-naïve and cART-experienced women

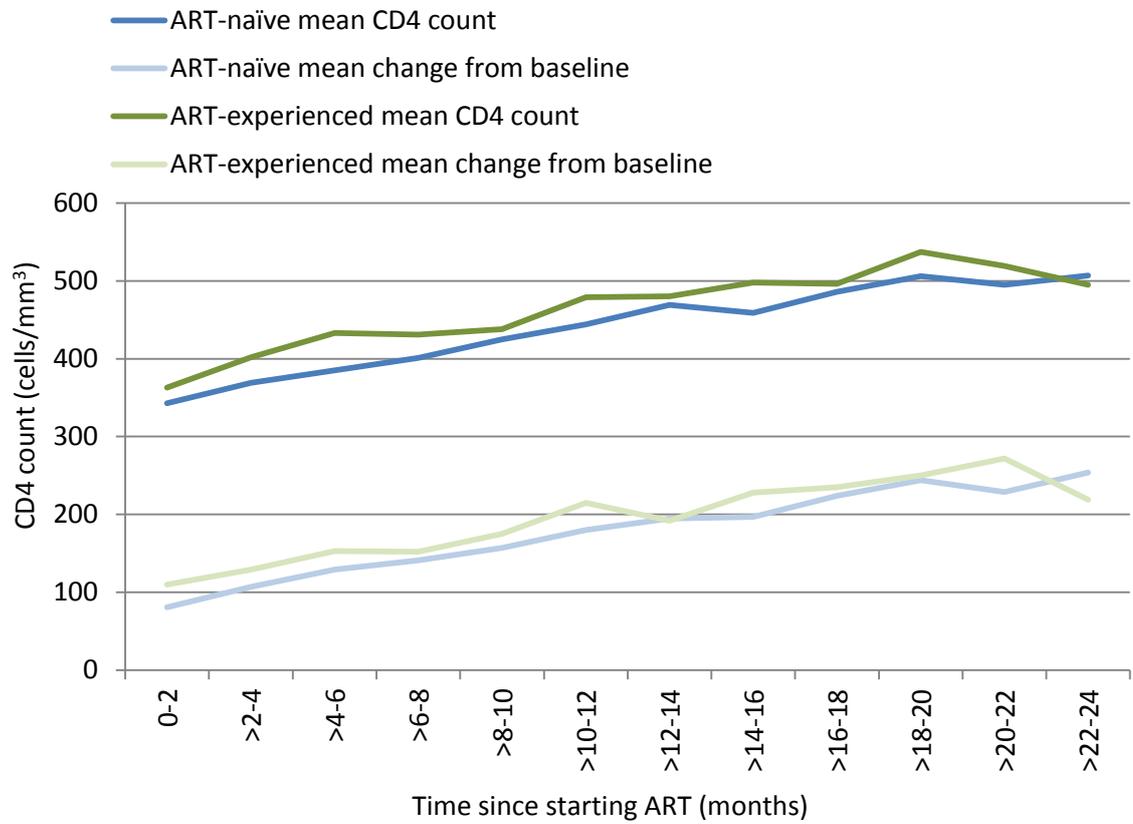


Table 6.13. Mean CD4 count and CD4 change from baseline within 2 month periods since starting long-term ART in ART-naïve and cART-experienced women

Months since ART start	0-2	>2-4	>4-6	>6-8	>8-10	>10-12	>12-14	>14-16	>16-18	>18-20	>20-22	>22-24
<b>ART-naïve</b>												
Mean CD4 count	339	357	370	390	411	420	445	437	475	485	490	470
n	526	494	416	376	386	364	317	327	315	310	277	289
Mean change in CD4	74	97	120	120	150	174	180	184	220	228	217	230
n (also with baseline CD4)	507	473	400	359	360	348	292	301	290	292	257	268
<b>ZDVm-experienced</b>												
Mean CD4 count	359	388	410	422	433	486	475	513	505	530	490	504
n	155	128	122	104	116	89	96	89	98	97	79	82
Mean change in CD4	94	121	140	129	160	219	187	206	210	250	226	230
n (also with baseline CD4)	150	123	119	102	109	84	92	86	89	91	71	78

Table 6.14. Adjusted difference in mean CD4 cell count after 6 and 24 months on treatment in cART-experienced and ART-naïve women

Variable	6 months on ART			24 months on ART			
	Adjusted difference in mean	95% CI	p-value	Adjusted difference in mean	95% CI	p-value	
cART-experienced	15.0	-9.2, 39.1	0.22	4.2	-31.0, 39.4	0.82	
Age (per 10 additional years)	2.0	-11.4, 15.3	0.77	8.9	-10.7, 28.5	0.37	
Pregnant when starting treatment	37.2	4.3, 70.1	0.03	29.4	-19.0, 77.8	0.23	
Ethnicity							
	Black-African	Reference		Reference			
	White	9.5	-18.1, 37.1	0.50	68.8	28.3, 109.4	<0.001
	Black Caribbean	-17.0	-56.8, 22.8	0.40	11.6	-47.4, 70.6	0.70
	Other/not known	8.1	-24.0, 40.3	0.62	36.2	-11.6, 84.1	0.14
Exposure group							
	Heterosexual sex	Reference		Reference			
	IDU	-69.0	-129.1, -8.9	0.02	-45.8	-134.5, 42.9	0.31
	Other/not known	-17.8	-71.0, 35.4	0.51	-10.7	-84.2, 62.7	0.77
Year of HIV diagnosis							
		-1.3	-4.4, 1.7	0.39	1.4	-3.1, 5.8	0.54
Year starting ART							
		4.2	-3.1, 11.4	0.26	-5.1	-16.3, 6.1	0.37
Regimen							
	NNRTI-based	Reference		Reference			
	PI-based	0.1	-21.3, 21.5	0.99	-13.4	-45.4, 18.6	0.41
	NRTI only	-21.8	-117.5, 73.8	0.65	-74.8	-222.1, 72.5	0.32
	Other	20.3	-54.1, 94.7	0.59	18.0	-93.7, 129.6	0.75
Baseline viral load >10,000 copies/ml							
		50.5	29.5, 71.5	<0.001	59.6	28.6, 90.7	<0.001
CD4 count (per additional 100 cells/mm <sup>3</sup> )							
		-17.4	-24.5, 10.2	<0.001	-16.0	-27.4, -4.7	0.01
HBV/HCV							
		26.1	-12.6, 64.9	0.19	-69.8	-128.1, -11.5	0.02
Previous AIDS event							
		-2.4	-34.0, 29.1	0.88	-3.0	-50.1, 44.0	0.90

The adjusted model included only women with a baseline CD4 count (cART-experienced n=232; ART-naïve n=732). Women who were pregnant when starting treatment had a higher mean CD4 cell count at baseline and a greater increase in CD4 cell count compared to women who were not pregnant when starting treatment (mean CD4 cell count at baseline 343 cells/mm<sup>3</sup> and 263 cells/mm<sup>3</sup> respectively, adjusted difference in mean at 6 months: 37.2 [95% CI -4.3, 39.1] cells/mm<sup>3</sup>, p=0.22) (Table 6.14).

Other variables associated with CD4 cell count increase at 6 months were exposure group, baseline viral load and baseline CD4 count. On average, women thought to have acquired HIV through sharing injecting drug equipment had a smaller increase in CD4 cell count compared to women who acquired HIV via heterosexual sex (adjusted difference in mean: -69.0 [95% CI -129.1, -8.9] cells/mm<sup>3</sup>, p=0.02). Women with a baseline viral load >10,000 copies/ml had a greater increase in CD4 cell count (at 6 months and at 24 months) than women with a lower baseline viral load (adjusted difference in mean 6 months: 50.5 [95% CI 29.5, 71.5] cells/mm<sup>3</sup>, p<0.001). This was also the case after excluding the 87 women with no baseline viral load measurement, who were assumed to have a viral load ≤10,000 copies/ml in the main analysis (adjusted difference in mean 52.5 [95% CI 30.8, 74.1] cells/mm<sup>3</sup>, p<0.001). When the binary variable (viral load ≤/ >10,000 copies/ml) was replaced by a continuous variable (log<sub>10</sub> viral load) there was a statistically significant association between log<sub>10</sub> viral load and CD4 count change (adjusted difference in mean: 27.5. [95% CI 17.9, 37.1] cells/mm<sup>3</sup>, p<0.001) despite no obvious correlation when these data were presented as a scatter plot (Figure 6.7).

Women starting ART with a higher CD4 count had a slightly smaller increase in CD4 count compared to women starting ART with a lower CD4 count (adjusted difference in mean per additional 100 cells/mm<sup>3</sup>: -17.4 [95% CI -24.5, -10.2], p<0.001) (Figure 6.8). Women starting ART with a CD4 count within the categories: ≤200, 201-350, 351-500 and >500 cells/mm<sup>3</sup> had a mean CD4 increase after 6 months of: 142, 153, 120 and 39 cells/mm<sup>3</sup> respectively.

After 24 months on ART, baseline CD4 count was associated with CD4 cell count increase (adjusted difference in mean per additional 100 cells/mm<sup>3</sup>: -16.0 [95% CI -27.4, -4.7], p=0.01). Baseline viral load was also associated with CD4 cell count increase (adjusted difference in mean viral load >10,000 copies/ml vs. ≤10,000 copies/ml: 59.6 [95% CI 28.6, 90.7], p<0.001). In addition, white ethnicity was associated with a greater increase in CD4 count compared to black-African ethnicity

(adjusted difference in mean: 68.8 [95% 28.3, 109.4],  $p < 0.001$ ) and HBV/HCV co-infection was associated with a smaller increase in CD4 cell count (adjusted difference in mean: -69.8 [95% -128.1, -11.5],  $p = 0.02$ ) (Table 6.14).

Figure 6.7. Scatter plot showing baseline viral load and CD4 cell count change from baseline after 6 months on ART

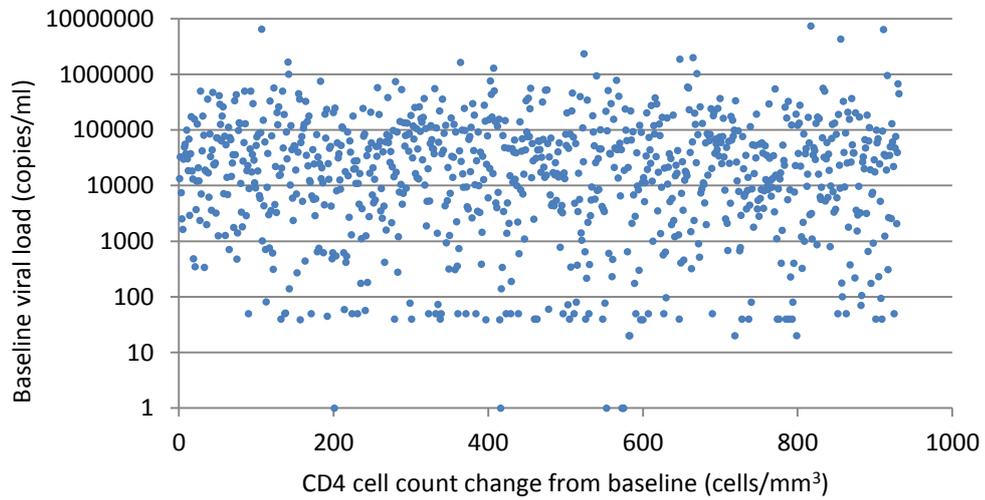
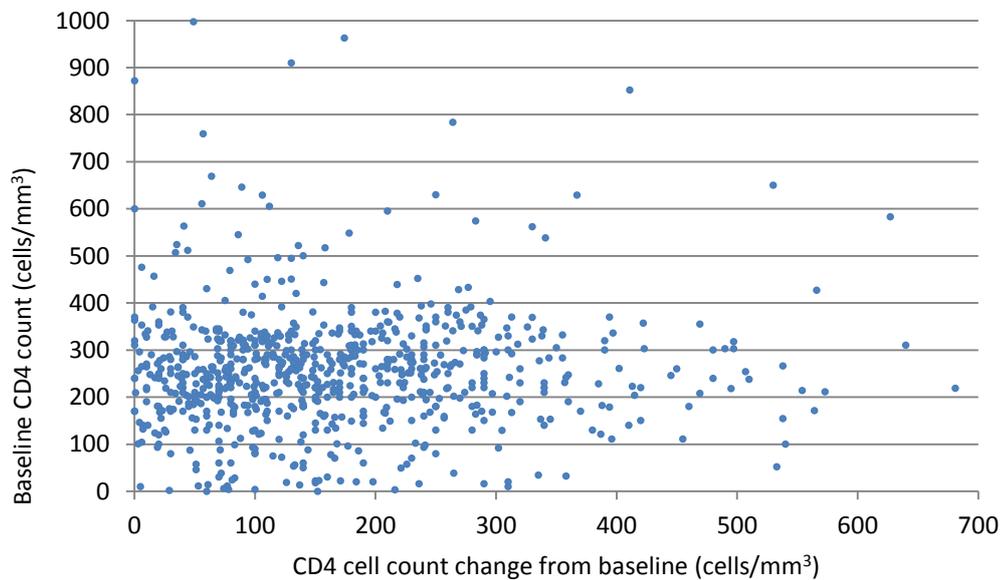


Figure 6.8. Scatter plot showing baseline CD4 count and CD4 cell count change from baseline after 6 months on ART



## **Viral suppression within six months**

Overall, 79.9% of women achieved viral suppression within six months of being on ART (cART-experienced: 76.8%; ART-naïve: 80.9%) and 92.9% within 2 years (cART-experienced: 90.7%; ART-naïve: 93.6%). The median time to viral suppression (Kaplan Meier estimate) was 3.44 (95% CI 3.02-3.70) months for cART-experienced women and 2.98 (2.79-3.18) months for ART-naïve women. In Cox proportional hazards analysis, 76 women were excluded because they had no viral load measurement in the first six months on ART. In unadjusted analysis there was weak evidence of an association between cART experience and viral suppression (HR 0.85 [95% CI 0.72-1.01],  $p=0.06$ ) (Figure 6.9). However, the association was not statistically significant when only baseline viral load was taken into account ( $p=0.24$ ) and there was no statistically significant association between cART experience and viral suppression in the final adjusted model (aHR 0.86 [95% CI 0.72-1.03],  $p=0.10$ ) (Table 6.15). In sensitivity analysis, when ART interruptions were ignored, there was weak evidence that women with ART experience were less likely to achieve viral suppression (aHR 0.84 [0.71-1.01],  $p=0.058$ ).

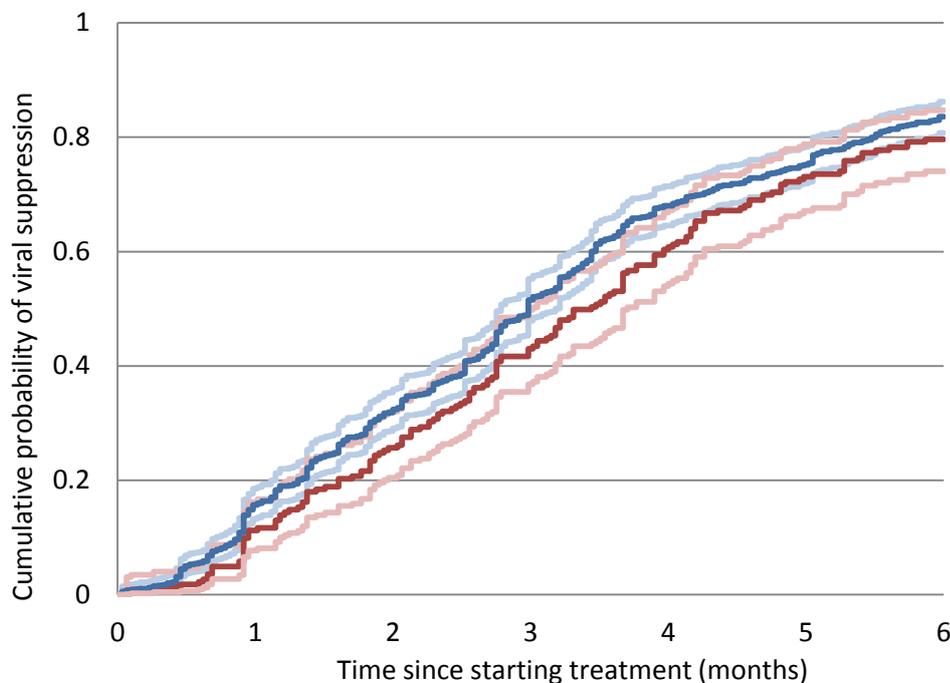
Baseline viral load was negatively associated with viral suppression within 6 months on ART; women with a viral load  $>10,000$  copies/ml were less likely to achieve viral suppression compared to women with a lower viral load (aHR 0.54 [0.46-0.63],  $p<0.001$  or aHR 0.70 [0.65-0.75],  $p<0.001$  when  $\log_{10}$  viral load was included in the model as a continuous variable resulting in the exclusion of a further 52 women with no baseline viral load measurement). In the main model, baseline CD4 count, drug regimen and pregnancy status when starting ART were also associated with viral suppression (Table 6.15). Women who were pregnant when starting treatment were more likely to achieve viral suppression compared to women who were not pregnant (aHR 1.77 [1.41-2.21],  $p<0.001$ ). Women with a higher baseline CD4 count were more likely to achieve viral suppression (CD4 count 351-500 cells/mm<sup>3</sup> vs. 201-350 cells/mm<sup>3</sup> aHR 1.29 [1.03-1.63],  $p=0.03$ ) and women starting a PI-based regimen were less likely to achieve viral suppression than women starting an NNRTI-based regimen (aHR 0.64 [0.55-0.75],  $p<0.001$ ).

In cART-experienced women, the interval between ART use in pregnancy and starting treatment was not associated with time to viral suppression (aHR 0.99 [0.99-1.01],  $p=0.67$  when the interval was a continuous variable and aHR 0.98 [0.59-1.61],  $p=0.93$  when the interval was categorised as  $</\geq 1$  year).

Table 6.15. Adjusted hazard ratio for achieving viral suppression within 6 months on treatment in cART-experienced and ART-naïve women

Variable		aHR	95% CI	p-value
cART-experienced		0.86	0.72 - 1.03	0.10
Age (per 10 additional years)		1.04	0.95 - 1.15	0.38
Pregnant when starting treatment		1.77	1.41 - 2.21	<0.001
Ethnicity	Black-African	Reference		0.33
	White	0.92	0.75 - 1.13	
	Black-Caribbean	1.04	0.77 - 1.39	
	Other/not known	0.81	0.64 - 1.03	
Exposure group	Heterosexual	Reference		0.83
	IDU	0.86	0.53 - 1.40	
	Other/not known	1.00	0.67 - 1.51	
Year of HIV diagnosis		1.01	0.99 - 1.04	0.21
Year starting ART		0.97	0.92 - 1.02	0.20
Regimen	NNRTI-based	Reference		<0.001
	PI-based	0.64	0.55 - 0.75	
	NRTI only	0.59	0.30 - 1.16	
	Other/not known	0.85	0.49 - 1.49	
Baseline viral load >10,000 copies/ml		0.54	0.46 - 0.63	<0.001
CD4 count category (cells/mm <sup>3</sup> )	≤200	0.85	0.71 - 1.02	0.006
	201-350	Reference		
	351-500	1.29	1.03 - 1.63	
	>500	0.89	0.64 - 1.22	
	Not known	0.70	0.49 - 0.99	
HBV/HCV		0.94	0.70 - 1.27	0.69
Previous AIDS event		0.94	0.74 - 1.18	0.57

Figure 6.9. Kaplan-Meier plot showing cumulative probability of viral suppression during the first six months on ART among ART-naïve women (blue line with 95% CIs in light blue) and women with cART-experience (red line with 95% CIs in light blue) at baseline



At risk							
ART-naïve	738	615	487	345	224	171	113
cART-experienced	228	197	163	125	86	59	43

Few of the women who did not achieve viral suppression within 6 months had a resistance test in this period (cART-experienced: 11.3% [6/53] and ART-naïve: 12.8% [18/141] had a test). Of those tested, one cART-experienced woman had resistance to  $\geq 1$  drug class (representing 16.7% of the 6 women tested). She had resistance to NNRTI and NRTI drug classes (Appendix IX). She had also been tested prior to starting treatment and had no evidence of resistance at that time. In the ART-naïve group, 5 women (representing 27.8% of the 18 women tested) had resistance to either one (NNRTI n=1; NRTI n=1), two (NNRTI and NRTI n=2) or three (NNRTI and NRTI and PI n=1) drug classes. Two of these women had evidence of the same type of drug resistance prior to starting treatment whilst two did not and one was not tested for resistance prior to starting treatment.

## Viral rebound

Among women who achieved viral suppression within 6 months on ART (n=772) the risk of viral rebound was examined within the periods 0-6 and 6-24 months after suppression. In both periods and for both cART-experienced and ART-naïve women, less than 10% of women experienced viral rebound, among those who remained on ART.

Within the 0-6 months after suppression there was no statistically significant association between ART experience and viral rebound (HR 1.73 [95% CI 0.78-3.86], p=0.18; aHR 1.03 [0.42-2.50], p=0.96) (Figure 6.10a). The risk of viral rebound decreased with increasing age (aHR 0.54 [0.30-1.00], p=0.05 per 10 additional years) and women who were pregnant when starting treatment were six times more likely to experience viral rebound than women who were not pregnant when starting treatment (aHR 6.24 [2.24-17.34], p<0.001) (Table 6.16).

There was weak evidence that in women who did not experience a rebound within 6 months of suppression, the risk of rebound in the 6-24 months after suppression was higher in cART-experienced women than in ART-naïve women (HR 2.19 [1.04-4.60], p=0.03; aHR 2.14 [0.96-4.77], p=0.06) (Figure 6.10b). The risk of viral rebound was associated with year of HIV diagnosis (aHR 1.11 [1.01-1.22], p=0.03) and women who started a PI-based regimen were more likely to experience viral rebound than women who started an NNRTI-based regimen (aHR 2.98 [1.32-6.73], p=0.01) (Table 6.16).

The findings were not altered when, in sensitivity analysis, follow-up was censored if a woman became pregnant. In a sub-analysis including only women with previous use of ART, viral suppression in the final trimester of the previous pregnancy was not associated with viral suppression in the first six months on life-long ART (not achieving viral suppression vs. achieving viral suppression: aHR 0.78 [0.56-1.23], p=0.20) or with viral rebound 0-6 months after suppression (aHR 2.16 [0.31-14.96], p=0.44) or 6-24 months after suppression (aHR 0.87 [0.14-5.65], p=0.88). The interval between ART use in pregnancy and starting life-long ART was not associated with the risk of viral rebound (either as a continuous or binary variable).

Table 6.16. Time to viral rebound 0-6 months and 6-24 months after viral suppression (within 6 months) in cART-experienced and ART-naive women on life-long ART

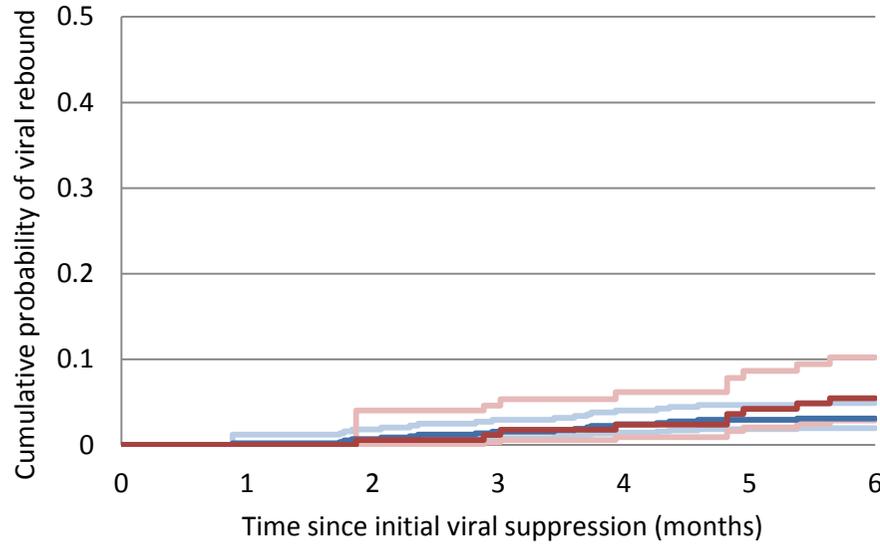
Variable	0-6 months after suppression			6-24 months after suppression		
	aHR	95% CI	p-value	aHR	95% CI	p-value
cART-experienced	1.03	0.42 - 2.50	0.96	2.14	0.96 - 4.77	0.06
Age (per 10 additional years)	0.54	0.30 - 1.00	0.05	0.82	0.48 - 1.42	0.49
Pregnant when starting treatment	6.24	2.24 - 17.34	<0.001	1.88	0.71 - 4.98	0.20
Ethnicity						
Black-African	Reference		0.57	Reference		0.79
White	1.24	0.41 - 3.77		1.19	0.39 - 3.64	
Black Caribbean	1.37	0.36 - 5.24		1.81	0.52 - 6.37	
Other/not known	2.50	0.68 - 9.24		1.39	0.38 - 5.07	
Exposure group			0.87			0.39
Heterosexual	Reference			Reference		
IDU	-			2.10	0.36 - 12.43	
Other/not known	1.63	0.26 - 10.33		2.57	0.52 - 12.74	
Year of HIV diagnosis	0.93	0.80 - 1.09	0.37	1.11	1.01 - 1.22	0.03
Year starting ART	1.06	0.78 - 1.44	0.69	0.96	0.72 - 1.26	0.75
Regimen			0.07			0.08
NNRTI-based	Reference			Reference		
PI-based	2.73	0.98 - 7.63		2.98	1.32 - 6.73	
NRTI-based	8.83	0.95 - 81.72		-		
Other	6.52	0.73 - 58.47		-		
Baseline viral load >10,000 copies/ml	2.52	0.96 - 6.61	0.06	1.32	0.59 - 2.93	0.50
CD4 count (cells/mm <sup>3</sup> )			0.16			0.77
≤200	2.26	0.83 - 6.20		1.61	0.64 - 4.05	
201-350	Reference			Reference		
351-500	1.06	0.27 - 4.12		1.67	0.55 - 5.12	
>500	3.81	1.04 - 14.02		-		
Not known	0.72	0.08 - 6.11		2.01	0.51 - 7.91	

Table 6.16 continued.

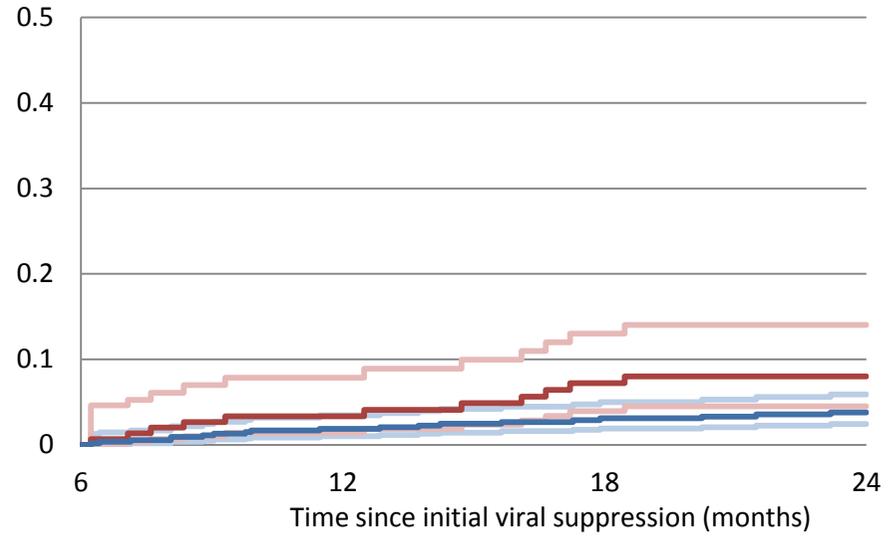
	0-6 months after suppression			6-24 months after suppression		
	aHR	95% CI	p-value	aHR	95% CI	p-value
HBV/HCV	1.24	0.28 - 5.54	0.78	1.41	0.40 - 4.96	0.59
Previous AIDS event	1.70	0.35 - 8.28	0.51	2.22	0.79 - 6.23	0.13

Figure 6.10. Kaplan-Meier plots showing cumulative probability of viral rebound within 6 months of viral suppression among ART-naïve (blue line with 95% CIs in light blue) and cART-experienced women (red line with 95% CIs in light red) with viral suppression within 6 months on ART

a.) 0-6 months after viral suppression



b.) 6-24 months after viral suppression



At risk											
ART-naïve	597	590	583	574	562	556	553	553	499	452	391
cART-experienced	175	175	173	167	160	155	153	153	130	116	101

Both figures include only women with viral suppression within 6 months on ART and b) includes only women still at risk of viral rebound

The association between having genotypic resistance to  $\geq 1$  drug class prior to starting life-long ART and the risk of viral rebound was not statistically significant in the 0-6 months period after suppression (aHR 2.31 [0.75-7.14],  $p=0.15$ ) but was statistically significant in the >6-24 month period (aHR 5.87 [1.30-26.4],  $p=0.02$ ). These adjusted models included resistance prior to ART as a dichotomous variable (yes/no) and were restricted to women with a resistance test prior to starting life-long ART and who had achieved viral suppression within 6 months. There was no statistically significant association between cART experience and viral rebound at 0-6 months after suppression (aHR 0.84 [0.27-2.66],  $p=0.77$ ) but there was at 6-24 months after suppression (aHR 11.03 [2.75-46.27],  $p<0.001$ ).

Of the 57 women who experienced viral rebound within 24 months of viral suppression, only a third had a resistance test within one month of the rebound (cART-experienced: 30.0% [6/20]; ART-naïve: 35.1% [13/37]). In the cART-experienced group, 2/6 women tested had resistance to one (NNRTI, Y181C mutation  $n=1$ ) or two drug classes (NNRTI and NRTI, mutations Y181C, G190A, K103N, L74V and M184V  $n=1$ ). Both women were tested prior to starting ART and had no evidence of drug resistance at that time. In the ART-naïve group, 4/13 women tested had resistance to either one (PI  $n=1$ ; NRTI,  $n=2$ ) or two drug classes (NNRTI and NRTI  $n=1$ ). One of the women with NRTI resistance had no test prior to starting treatment, the other two women with NRTI resistance (including one woman who also had NNRTI resistance) had evidence of NRTI resistance prior to starting treatment. The woman with PI resistance had evidence of PI resistance prior to starting treatment. The mutations identified in each group are listed in Appendix IX. There were no mutations identified which are associated with resistance to integrase inhibitors.

### **Regimen change or interruption having started life-long ART**

Within the first 24 months of starting treatment, 39.0% (406/1042) of women changed their regimen either by increasing the number of drugs in the regimen by one (31.5%,  $n=128$  overall) or more (16.5%,  $n=67$ ) drugs, replacing drugs in the regimen whilst maintaining the overall number of drugs (30.5%,  $n=124$ ) or reducing the number of drugs by one (17.2%,  $n=70$ ) or more (4.2%,  $n=17$ ). The percentage of women who changed regimen was 42.3% (105/248) in cART-experienced women and 37.9% (301/794) in ART-naïve women. There was no statistically significant association between ART experience and changing regimen (aHR 1.02 [0.81-1.29],  $p=0.85$ ) (Table 6.17). In the adjusted model, women who were pregnant when starting treatment were more likely to change their regimen than women who were not pregnant (aHR 1.75

[1.31-2.33],  $p > 0.001$ ). Changing regimen was also associated with the year in which life-long ART was started and with age, with the risk decreasing over time (aHR 0.90 [0.84-0.97] per additional year,  $p = 0.01$ ) and decreasing with older age (aHR 0.82 [0.71-0.95],  $p = 0.01$ ). Women starting an NRTI only regimen were more likely to change their regimen than women starting an NNRTI-based regimen (aHR 2.62 [1.20-5.69], global  $p = 0.007$ ).

The percentage of women who interrupted treatment for any period of time was 25.0% ( $n = 62$ ) in cART-experienced women and 17.4% ( $n = 138$ ) in ART-naïve women. In those who interrupted treatment, the interruption occurred after a median of 8.9 (IQR 3.4-16.1) months on ART and the median time to restarting treatment was 3.3 (IQR 1.7-10.7) months from the date of interruption. CART-experienced women were more likely to interrupt treatment compared to ART-naïve women (HR 1.48 [1.10-2.00],  $p = 0.01$ ; aHR 1.48 [1.07-2.04],  $p = 0.02$ ) (Table 6.17). Women starting a PI-based regimen were more likely to interrupt their regimen than women starting an NNRTI-based regimen (aHR 1.77 [1.32-2.39], global  $p = 0.002$ ), this remained the case after excluding 129 women who started treatment whilst pregnant (aHR 1.97 [1.45-2.67],  $p < 0.001$ ).

There was no statistically significant association between baseline pregnancy status and interrupting ART (aHR 0.81 [0.51-1.27],  $p = 0.35$ ). The association between ART experience and interrupting treatment remained when women who started treatment whilst pregnant were excluded (aHR 1.46 [1.02-2.08],  $p = 0.04$ ).

Table 6.17. Time to switching or interrupting ART regimen in cART-experienced and ART-naive women starting life-long ART

	Time to any change in regimen			Time to treatment interruption		
	aHR	95% confidence interval	p-value	aHR	95% confidence interval	p-value
cART-experienced	1.02	0.81 - 1.29	0.85	1.48	1.07 - 2.04	0.02
Age (per 10 additional years)	0.82	0.71 - 0.95	0.01	0.90	0.74 - 1.10	0.31
Pregnant when starting treatment	1.75	1.31 - 2.33	>0.001	0.81	0.51 - 1.27	0.35
Ethnicity						
	Black-African	Reference	0.21	Reference		0.19
	White	1.03	0.78 - 1.36	0.61	0.39 - 0.97	
	Black-Caribbean	0.92	0.60 - 1.42	1.00	0.57 - 1.73	
	Other/not known	0.68	0.47 - 0.99	0.79	0.48 - 1.31	
Exposure group			0.19			0.45
	Heterosexual sex	Reference				
	People who inject drugs	1.25	0.72 - 2.16	1.63	0.76 - 3.51	
	Other/not known	0.60	0.31 - 1.14	0.98	0.43 - 2.25	
Year of HIV diagnosis		1.03	1.00 - 1.06	0.98	0.94 - 1.03	0.26
Year starting ART		0.90	0.84 - 0.97	0.96	0.86 - 1.06	0.39
Regimen			0.007			<0.001
	NNRTI-based	Reference				
	PI-based	1.23	0.99 - 1.52	1.77	1.32 - 2.39	
	NRTI only	2.62	1.20 - 5.69	1.84	0.57 - 5.90	
	Other	2.11	1.11 - 4.00	-		
Baseline viral load >10,000 copies/ml		1.04	0.84 - 1.30	0.79	0.59 - 1.07	0.13
CD4 count (cells/mm <sup>3</sup> )			0.10			0.12
	≤200	1.13	0.89 - 1.44	1.18	0.84 - 1.66	
	201-350	Reference				
	351-500	0.69	0.48 - 1.00	0.71	0.42 - 1.20	
	>500	0.83	0.51 - 1.33	0.79	0.40 - 1.57	
	Not known	1.23	0.85 - 1.79	0.51	0.26 - 1.00	
HBV/HCV		1.14	0.79 - 1.66	1.43	0.86 - 2.37	0.17
Previous AIDS event		0.86	0.63 - 1.19	1.30	0.86 - 1.97	0.22

## 6.6 Discussion

Of the women in UK CHIC who started life-long ART in 2003-2012, almost one in ten had previously used ART, a smaller proportion than in many settings [220]. The majority (81%) of these women had used a combination of ART drugs, whilst 19% had used only ZDVm (Table 6.2). The observed decline in the use of ZDVm in pregnancy has previously been reported in the UK [170] and elsewhere [127], including in resource limited settings [455]. It reflected the increasing number of women who conceived whilst already on cART and the shift towards the use of cART in women who used short-term ART for PMTCT, reflecting the growing evidence that antenatal use of cART was both safe and effective [127, 131, 149, 361, 456-458].

The recent changes to the UK treatment guidelines [86]. mean that in the UK, as well as elsewhere, women will no longer use short-course ART in pregnancy. This means that the vast majority of women living with HIV who become pregnant will either already be on ART, if they are already diagnosed, or will start life-long ART, if they are diagnosed whilst pregnant. In each of the final five years of data presented in this chapter (2008-2012), 12% of women starting life-long ART had some previous ART experience (Table 6.2). Assuming this was also true in more recent years, we can estimate that approximately 12% of women who have recently started life-long ART, since the changes to the guidance, will have some previous exposure to ART from short-course antenatal use. It is important for clinicians to be able to anticipate the treatment outcomes of these women.

In this chapter I compared the response to ART in women starting treatment for their own health who had used either short-course ZDVm (Analysis 1) or cART (Analysis 2) in pregnancy for PMTCT with the response in women who had never previously used ART. As we would anticipate, the treatment outcomes of women in this study were similar or better than the outcomes for women starting ART in 1998-2006, observed in a previous UK CHIC study [459] which included recently diagnosed women. The risk of AIDS/death was low in all the groups assessed in this study. Since the outcome assessed was AIDS or death it did not allow for direct comparison with the risk of death in the general population. There was limited information on the cause of death for the small number of women who died. The data that were available indicate that few women died of HIV related causes, although in some cases it was not clear, since the reported cause of death was non-specific. Women starting treatment who had previously used cART were at no greater risk of AIDS/death compared to ART-naïve

women (Table 6.12). There was weak evidence that ZDVm-experienced women starting treatment had a lower risk of AIDS/death compared to ART-naïve women starting treatment (Table 6.3). The association was not statistically significant when other factors were considered in adjusted analysis. The other variables associated with the risk of AIDS/death - a previous AIDS event, having a lower CD4 count when starting treatment, older age, and higher baseline viral load - have also been reported elsewhere [460-462].

All the groups assessed showed a good immunological response to treatment with an increase of  $>200$  cells/mm<sup>3</sup> from the pre-treatment CD4 count at 24 months. The average CD4 counts after 6, 12 and 24 months on ART were similar to those previously reported from men and women starting treatment at the Royal Free Hospital which included people who were recently diagnosed (Figure 6.1 and Figure 6.6) [463]. The previous use of cART or ZDVm did not predict CD4 count increase after 6 or 24 months on ART (Table 6.5 and Table 6.13). The only previous study which compared response to treatment in ART-naïve and cART-experienced women did not examine CD4 response [286]. In studies which compared response to treatment in ART-naïve and single dose NVP exposed women, immunological response was not associated with previous ART use in women starting therapy [220, 274, 279]. Larger increases in CD4 cell counts were seen among women who started treatment when pregnant. The reasons for this are unclear as no data were collected on possible confounders such as drug adherence, diet, exercise and weight.

HBV or HCV co-infection was negatively associated with CD4 cell count increase. Previous studies have found such an association between HCV and CD4 cell changes once ART is initiated [464], whereas studies assessing the association between HBV infection and CD4 cell count provide conflicting results [465, 466]. Few of the women in this study had HBV or HCV; only 5% of ZDVm-experienced women and 7% of cART-experienced had either HBV, HCV or both HBV and HCV coinfection. It was therefore not possible to separate these into smaller categories as this would create very small groups and therefore reduce statistical power.

Women with a higher baseline CD4 count had a slightly smaller increase in CD4 count compared to women with a lower baseline CD4 count; the average increase in CD4 at 24 months was 14-16 cells/mm<sup>3</sup> less with each additional 100 cells/mm<sup>3</sup> at baseline (Table 6.6 and Table 6.14). This is probably because women with a lower CD4 count at baseline had a greater scope for improvement. Although these differences were statistically significant they were small and may not have clinical importance particularly

as the average CD4 count after 24 months on ART was around 500 cells/mm<sup>3</sup> in all the groups.

An undetectable viral load, the main aim of treatment, was achieved by the majority of women within 6 months on ART and by around half within 3 months. In women with a viral load measurement within the first six months on ART, ZDVm-experienced women were 31% more likely to achieve viral suppression than ART-naïve women. It is possible that women who had used ZDVm in pregnancy had better engagement with clinical services, particularly as more of them were pregnant when starting life-long ART or would have become pregnant during follow-up. However, if this were the case then we would also anticipate an association between cART experience and viral suppression, but there was no such association in Analysis 2. Therefore, it is unclear why ZDVm-experienced women were more likely to achieve viral suppression.

Women starting a PI-based regimen were less likely to achieve viral suppression within 6 months compared to women starting an NNRTI-based regimen (aHR 0.77 in analysis 1 and aHR 0.64 in analysis 2) and the use of PI-based regimen was associated with a two-fold increased risk of AIDS/death in both analyses. These differences are probably due to unmeasured confounders since, at the time, the recommended first line treatment was efavirenz with PI-based regimens only recommended for people with NNRTI or NRTI resistance, women planning to become pregnant and patients with psychiatric problems [78].

As we might anticipate, baseline viral load was negatively associated with viral suppression, since women with a higher baseline viral load had a larger gap between their starting point and viral load  $\leq 50$  copies/ml. In this group of women who had been diagnosed for at least one year, having very high viremia at baseline could indicate a greater length of infection and therefore we would anticipate a slower immune response as has previously been observed in a large European HIV cohort [467].

In both analyses, women who started treatment whilst pregnant were more likely to achieve viral suppression (Table 6.7) and (Table 6.15). Women starting ART during pregnancy have increased contact with health care professionals regarding antenatal care as well as ongoing HIV clinical care. They will therefore be more regularly monitored and receive adherence support as well as being highly motivated to achieve viral suppression in order to minimise the risk of MTCT.

Although only women with a viral load measurement within the period of interest were included in the time to viral suppression analysis, differences in the frequency and

timing of viral load measurements will impact on the outcome and it is important to bear in mind that the Kaplan-Meier plots (Figure 6.2 and Figure 6.9) do not depict viral response but rather the first viral load assay performed where the viral load is undetectable.

Viral rebound was more likely to occur in cART-experienced women than in ART-naïve women (Table 6.16). This association was only seen in the 6-24 months period after viral suppression, not in the first six months after suppression, when very few of the women developed viral rebound. There was no statistically significant association between ZDVm experience and viral rebound.

Viral rebound can be the result of drug resistance. Drug resistance is however unlikely to be the reason that cART-experienced women were more likely to develop viral rebound. A smaller proportion of cART-experienced women had drug resistance prior to starting life-long ART compared to the ART-naïve women (11% vs. 13% respectively) and the association between cART experience and viral rebound remained and was statistically significant when baseline drug resistance was taken into account. Although drug resistant HIV strains have been identified in women following the use of short-course ART in pregnancy [278, 468] there is little evidence to suggest that the use of short-course cART or ZDVm (among those meeting the strict clinical criteria for its use) in pregnancy increases the prevalence of drug resistance [193, 469]. The prevalence of drug resistance was considerably higher than the prevalence of transmitted drug resistance (TDR) in HIV-positive women in the UK for this period (4-7%) [470] and higher than the prevalence in women diagnosed in pregnancy in 2000-2013 (5.2%) [258]. Although this latter analysis of NSHPC data found an increasing prevalence over time with 10.1% prevalence in 2012-2013. The high prevalence observed here could be because women with a 'positive' result for drug resistance were more likely to have data reported, because women with more complete data were more likely to have their UK CHIC and NSHPC records linked and therefore be included in the dataset or because of selective testing in areas of higher TDR prevalence.

Resistance data were not available for all women. In ART-naïve and cART-experienced women, 57% had at least one resistance test before starting ART. Over the period of the study there have been technical improvements in resistance testing. The percentage of women who had a resistance test performed increased over the study period to >60% in the latest year. In a direct linkage between the NSHPC and the UK HDRD (undertaken by Dr Laura Byrne at ICH), 50% of the women in the NSHPC

had at least one resistance test in the UK HDRD [258]. Resistance tests are normally performed prior to starting ART [84]. It is not clear whether lack of resistance data for some women was the result of reporting delay, incomplete linkage between the UK HDRD and UK CHIC or no test being performed.

Viral rebound can also be the result of poor drug adherence [389, 471, 472]. Previous studies have found that pregnancy impacts drug adherence and retention in care – and these can also be altered in the postnatal period [473]. A study from the US, Brazil and Peru which examined the outcomes of women starting therapeutic ART at least 24 weeks after using cART in pregnancy found that poor drug adherence was associated with viral rebound [286]. Although some of the differences between ART-naïve and ART-experienced women were accounted for in adjusted analysis, there are likely to be other important confounders which were not measured including parental responsibilities, family size, and socioeconomic status [474].

Having ZDVm or cART experience was not predictive of changing drug regimen within 24 months of starting life-long ART (Table 6.9 and Table 6.17). Observational studies show that regimen changes are more often due to toxicity than to immunological or virological failure [475, 476]. In both analyses, regimen switching decreased over time but was more common in women who were pregnant when starting treatment than in women who were not pregnant. In earlier years, this could be due to women switching away from regimens not recommended for use in pregnancy such as didanosine (no longer prescribed) or efavirenz (no longer contraindicated in pregnancy) [477]. In this analysis, pregnancy was not associated with severe LEE, however, the results of the next chapter indicate that there is an association between pregnancy status and toxicity which could explain the association between pregnancy and switching observed here.

Compared to ART-naïve women, women with previous cART experience were 1.5 times more likely to interrupt ART (Table 6.9 and Table 6.17). It is possible that some of the women were misclassified as starting life-long ART and were actually starting short-course cART in pregnancy which they later stopped. This might also explain why starting a PI-based regimen, the typical regimen prescribed for short-course ART in pregnancy, was associated with treatment interruption. However, there was no statistically significant association between pregnancy status when starting ART and interrupting ART and when women who were pregnant at baseline were excluded in sensitivity analysis, the association between ART experience and treatment interruption remained. The association between cART experience and treatment interruption might be due to difficulties in maintaining ART adherence among women

with a previous pregnancy i.e. mothers with parental responsibilities. In analysis 1 there was no statistical association between ZDVm experience and interrupting ART.

The women included in these analyses are not representative of all women starting life-long ART in the UK. The analyses did not include women diagnosed within the past year or women older than 49 years. Women with no clinical data who might have transferred to a clinic not part of UK CHIC or who may have been lost to follow-up were excluded, as they had no clinical data to analyse.

The use of ART data from both UK CHIC and NSHPC for the same women meant that analysing the timing of ART use and whether it was used in pregnancy or not was at times problematic. This was a result of contradictory data in the two datasets or differences in the dates of ART use reported to the two studies. In women starting life-long ART with some evidence of previous ART use it was not clear for about 30% whether this had been cART or ZDVm used in pregnancy or some other type of ART use such as starting long-term ART but then interrupting for an extended period. This was a result of underreporting of ART stop dates, inconsistencies in NSHPC and UK CHIC data and the reporting to NSHPC of antenatal ART use but no drug use dates. It is not clear whether the women reported as being on a drug regimen containing 4 drugs were genuinely on a non-standard regimen or whether this was a result of under-reporting of drug stop dates.

The need to use drug data from UK CHIC to assess drugs started before pregnancy and stopped afterwards meant that some women who used ZDVm (according to their NSHPC record) were not included in the analysis of ZDVm use, as there were no drug data in UK CHIC at that time i.e. they did not attend care at a UK CHIC site at the time of their pregnancy. Analysis 1 suffered from lack of statistical power since only 93 women had only ZDVm experience. Although 213 women used ZDVm in their index pregnancy 43 then went on to use short-course cART in a subsequent pregnancy and other women were excluded from the analysis for other reasons. Using a larger dataset, for example a European HIV cohort, would increase the number of women in a similar analysis.

At baseline, more than one-quarter of women had no baseline viral load measurement and more than one-quarter had no baseline CD4 cell count. All women should all have had their viral load and CD4 counts monitored at the time of starting ART as part of their clinical care [78]. Missing data may be due to incomplete reporting to the UK CHIC study and/or transfer of care around the time of starting treatment to clinic not participating in the UK CHIC study. Exclusion of these women in sensitivity analysis did

not change the main findings. However, in future analyses baseline CD4 count and viral load could be imputed for women with missing data by assessing measurements of similar women or by using earlier CD4 counts/viral load data. Some women could have used sd-NVP during a pregnancy abroad, which, if used in the past 12 months, could impact their response to life-long ART. This could not be assessed as there were no data on ART regimens used prior to arrival in the UK.

## **Conclusion**

The findings of these analyses add support to the limited number of studies which indicate that short-term use of ART for PMTCT is not detrimental to women's long-term outcomes [193, 382, 478, 479]. Whilst we may expect slightly higher rates of viral rebound and treatment interruption in women who have previously used ART in pregnancy for PMTCT, the differences are small and are likely to be a consequence of unmeasured confounders or differences in adherence. It is therefore important that these women are supported in their drug adherence. This might be most effective if given by peers with similar experiences of ART use. If the differences between women with and without prior use of ART in pregnancy are due to differences in adherence this warrants further studies to identify interventions which promote adherence in women with children.

## **Key points from this chapter**

- Among women in UK CHIC who started life-long ART in 2003-2012, 9.7% had previously used ART.
- Once life-long ART was started, compared to ART-naïve women, women who had previously used ART in pregnancy:
  - had similar increases in CD4 count
  - had a similar low risk of AIDS/death
  - had a higher (ZDVm-experienced) or similar (cART-experienced) chance of achieving viral suppression
  - were more likely to develop viral rebound during the 6-24 months after viral suppression (cART-experienced women)
  - were more likely to interrupt ART (cART-experienced)
- In the analysis of cART-experienced vs ART naïve women starting life-long ART, 57% of women had a resistance test prior to starting life-long ART; at this time 11% of cART-experienced and 13% of ART-naïve women had resistance to at least one drug class.

# Chapter 7 The impact of pregnancy and ART use in pregnancy on hepatotoxicity in women living with HIV

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## 7.1 Introduction

High rates of hepatotoxicity (chemical-driven liver damage) have been observed among pregnant women on antiretroviral therapy (ART), mostly women on nevirapine (NVP). Whether pregnancy increases the risk of hepatotoxicity among women on ART is not clear. Cross-sectional studies that compare the rate of liver enzyme elevation (LEE) in pregnant and non-pregnant women on ART have produced conflicting results, with some finding that pregnancy increases the risk of LEE and others finding no such association.

In the UK, the vast majority of women living with HIV use ART in pregnancy. The characteristics of women starting ART in pregnancy may mean that they are more susceptible to LEE than non-pregnant women, since they are more likely to start with a higher CD4 count, a factor which, at least in the case of NVP, is associated with an increased risk of hepatotoxicity [480]. As was observed in Chapter 5, women are increasingly conceiving on life-long ART and therefore use ART for the full duration of pregnancy. Few studies have examined hepatotoxicity rates in women already on ART at conception. The linkage of the NSHPC and UK CHIC datasets allows the analysis of ALT levels before, during and after pregnancy as well as comparison with non-pregnant women, something not possible using either dataset independently.

In this chapter I aim to examine the impact of pregnancy on average alanine transaminase (ALT), identify characteristics predictive of LEE and examine whether pregnancy increases the risk of LEE in pregnancies during which ART is started and in pregnancies conceived on ART. Findings from this chapter were published in 2015 (Appendix IIId) [414].

## 7.2 Methods

The analysis is divided into three sections:

1. Preliminary descriptive analyses
  - Assessing the availability of ALT data in the UK CHIC dataset and identifying characteristics predictive of having  $\geq 1$  ALT measurement
  - Descriptive analysis taking each ALT measurement as a separate observation
2. The impact of pregnancy on median ALT levels
  - Comparing median ALT before, during and after pregnancy with median ALT in non-pregnant controls
  - Identifying factors predictive of ALT
  - Comparing median ALT before, during and after pregnancy in women already on ART and in women starting ART in pregnancy
3. The impact of pregnancy on the risk of LEE
  - Identifying factors independently associated with LEE and severe LEE including pregnancy status
  - Examining changes/interruptions of ART following LEE/severe LEE

### 7.2.1 Methods Section 1: preliminary descriptive analyses

Liver function tests (LFTs), including the test for alanine transaminase (ALT), are performed in all HIV clinics in the UK. However, LFTs are not performed routinely in all women. Testing occurs more regularly in some groups of women and at particular periods of time. Also, some clinics participating in the UK CHIC study do not store LFT data in an electronic format which can easily be reported to UK CHIC and therefore do not report ALT data to the study. Therefore, as a first step, I assessed the availability of ALT data in the dataset and the demographic and clinical characteristics associated with having any ALT data.

#### **Dataset**

For the first two analyses of this chapter, the UK CHIC 2011 dataset was used (women only). In order to obtain pregnancy information for women with a pregnancy during this period, the UK CHIC dataset was linked to NSHPC dataset (archived in June 2013). Only data to 31<sup>st</sup> December 2011 were analysed. For this analysis, therefore the

dataset contained all women in UK CHIC irrespective of whether or not they had a pregnancy. The use of short-course ART in pregnancy or life-long treatment was determined using a combination of data from UK CHIC and NSHPC, as described in Chapter 4.

### **Descriptive analysis taking each ALT measurement as a separate observation**

Each ALT measurement in the UK CHIC dataset within the period 2000-2011 was taken as a separate observation. Repeat measures from the same woman were included in the analyses and as this was a preliminary analysis, no adjustment was made to take this into account. Time updated variables were created at the time of each ALT measurement. These included: current pregnancy status, whether the woman had a previous pregnancy whilst HIV-positive, ART use, duration of ART use and latest CD4 count within the previous 3 months.

#### **7.2.2 Methods Section 2: the impact of pregnancy on median ALT**

In the second section, which examines the impact of pregnancy on median ALT, non-pregnant women in UK CHIC with similar characteristics to pregnant women were used as controls in order to minimise the confounding effect of differences between pregnant and non-pregnant women. The median ALT before, during and after pregnancy was calculated for women who conceived on ART. These three values were compared to the median ALT in non-pregnant women on ART for equivalent periods of time. In the same way, median CD4 count was compared in pregnant and non-pregnant women.

In order to assess the impact of the timing of ART initiation on ALT levels in pregnancy, ALT measurements before, during and after pregnancy were compared in three groups: women on ART at conception; women starting ART in the first half of pregnancy (women likely to require ART for their own health); and women starting ART in the second half of pregnancy (women likely to require ART for PMTCT only).

### **Developing a selection process to find non-pregnant controls in the dataset**

I devised a simple selection strategy to identify and match pregnant women with controls i.e. non-pregnant women with characteristics similar to those of the pregnant women.

## Selecting pregnancies

For each pregnancy in the dataset conceived in 2000-2011, the woman was characterised on the estimated date of conception (EDC) for example, her age, ART status, latest CD4 count and so on. A single variable was then created summarising the woman's characteristics. This variable was then used to find a suitable control. Table 7.1 shows an example. The summary variable (a concatenated variable) was formed by combining the code for the following variables: calendar year; ART status; age group; previous pregnancy (whilst HIV positive); CD4 count; and previous ART experience. If, for example, a woman conceived in the year 2009 (code: 2009), was not on ART (code: 0), was 20-24 years old (code: 2), had previously been pregnant (code: 1), had a CD4 count  $>500$  cells/mm<sup>3</sup> (code: 4) and had ART experience (code: 1) the summary variable would be '200902141' – created by combining the codes 2009, 0, 2, 1, 4 and 1.

## Finding controls

In order to find suitable controls, time updated variables were created to characterise each woman in the dataset on 48 different reference dates (four dates per year at three month intervals) throughout the period 2000-2011. This included characteristics which were to be used to create the summary variable and characteristics which were used to assess whether the woman was eligible to be a control at that particular time, such as pregnancy status. A summary variable, with the same format as the variable used to characterise women at the start of each pregnancy, was then created for each woman at each of the 48 reference dates.

Table 7.1. Example variables used to find non-pregnant controls for pregnant women in UK CHIC

Variable	Category	Code
Calendar year	2000	2000
	2001	2001
	etc.	etc.
ART status <sup>1</sup>	On ART	1
	Not on ART	0
Age group (years)	16-19	1
	20-24	2
	25-29	3
	35-39	4
	40-44	5
	45-49	6
Previous pregnancy	Yes	1
	No	0
CD4 count (cells/mm <sup>3</sup> )	0-200	1
	201-350	2
	351-500	3
	>500	4
Previous ART use <sup>2</sup>	Experienced	1
	Naive	0

A summary variable was created for each woman for each time point by combining the codes for each variable listed in the table.

<sup>1</sup>NSHPC data were used to assess ART use at the time of conception, unless no data were provided, in which case UK CHIC data were used.

<sup>2</sup>NSHPC and UK CHIC data were used to assess previous ART use.

## Selecting controls

Two separate tables were then created.

1. Table of pregnant women

This table contained the variables: woman's unique ID, summary variable, EDC. A woman was only included when the pregnancy resulted in a live birth, there was  $\geq 1$  ALT measurement in the 9 months following the EDC and a recent CD4 count (within the 6 months before the EDC). Each woman's first pregnancy during the period 2000-2011 that met the criteria was included.

2. Table of controls

This contained the variables: woman's unique ID, summary variable, reference date, random number (generated in SAS – used to select the control if there was more than one appropriate control available). A woman could only be included in this table when she was not pregnant, did not have a pregnancy in the subsequent 18 months, had at least 3 ALT measurements in the following year, and had a recent CD4 count (within the previous 6 months). If a woman's summary variable was the same on multiple reference dates in the same year, only the earliest was included. Each woman could be used as a control multiple times but for non-overlapping periods of time.

Multiple pregnant women had the same summary variable which complicated the merging of tables. In this example, the same summary variable occurred up to nine times i.e. there were a maximum of nine pregnant women seen in the same year with the same characteristics. To get round this problem, separate tables containing only one woman with each summary variable were created. The first table contained the first instance of each summary variable, the second table contained the second instance of each summary variable, and so on, with the ninth table containing data for only one woman. In this example, nine separate tables were created. The first table was then merged with the list of all potential controls (merged using the summary variable), thereby matching pregnancies and controls with the same status. Since the list of controls was ordered using the random number, if there were multiple controls with the same status, it was random as to which was selected. As controls were matched to pregnant women, that period of follow-up was removed from the list of potential controls. This process was then repeated for each of the remaining 8 tables. For these analyses, two controls were sought for each pregnant woman. Therefore, the

whole process was repeated using the original 9 tables of pregnant women and the list of remaining controls.

The reference date was used as a pseudo date of conception for the controls. The duration from the EDC to delivery was measured for each pregnancy. This duration was used to create a pseudo delivery date for each of the controls. Dates 3, 6, and 9 months before and after pregnancy, and equivalent time points for the controls were then calculated.

### **Statistical analyses**

The characteristics of pregnant women were compared to those of the controls using Chi-squared test for categorical variables and Kruskal-Wallis test for continuous variables (not Normally distributed). If a woman had more than one ALT measurement within any three month period, the mean of her ALT values was used for that woman for that period. The median value for each group for each 3 month period was then calculated (not Normally distributed data). The median values for the two groups were then compared using Kruskal-Wallis test. The proportion of women with at least one ALT measurement above the upper limit of normal (ULN) (40 IU/L) were calculated for each period of interest. Median CD4 counts for pregnant and non-pregnant women were calculated and summarised in the same way.

### **Random effects mixed regression model**

A random effects mixed regression model with unstructured covariance matrix was constructed to confirm whether pregnancy was independently associated with ALT. This approach takes into account the within-individual correlations between repeated measures within each woman's data (SAS function: proc mixed). The unstructured covariance matrix was chosen (instead of autoregressive, compound symmetry or toeplitz structures) because it gave the smallest values for AICC and BIC (fit statistics). Age (more specifically,  $(\text{age}-35)/10$ , i.e. a unit of 10 years where age 35 was considered as the reference value) was used as the 'time' covariate. Each ART drug was initially assessed as a dichotomous variable (used/not used) in unadjusted analysis and included in the final model if it had p value  $<0.10$  in unadjusted analysis and was statistically significant in the adjusted model.

Women were included in the analysis if they attended care at any point during 2000-2011 and had  $\geq 1$  ALT measurement from that period. Data were included from the start of 2000 to the end of 2011, unless a woman entered or left UK CHIC during that period,

in which case data from her earliest to her latest attendance were used. The period 2000-2011 was split into 3 month intervals, creating 48 reference dates. Time-dependent covariates were created for each woman for each reference date including: age; pregnancy status (pregnant/not pregnant); previous pregnancy whilst HIV-positive (yes/no); pregnancy trimester (1<sup>st</sup>, 2<sup>nd</sup>, 3<sup>rd</sup>); ART use (yes/no); current ART regimen; previous ART status (yes/no); and most recent CD4 count, ALT and viral load (within the previous 6 months). For each woman, data at each time point were only included if  $\geq 1$  ALT measurement was reported in the past 6 months, if the woman was aged 16-49 and had some clinical data in UK CHIC during that calendar year.

### **Assessing median ALT before, during and after pregnancy among women starting ART before or during pregnancy**

Index pregnancies in 2000-2011 resulting in a live or still birth and where  $\geq 1$  ALT measurement was available were included. For each group, a median ALT value was calculated for each pregnancy trimester and each 3 month period from 9 months before to 18 months after pregnancy. The three groups were: women already on ART before the pregnancy; women who started ART in the first 20 weeks of pregnancy (women likely to be starting long-term therapeutic ART); and women who started ART at or after 20 weeks of pregnancy (women likely to be starting short-course ART for PMTCT). ART status at the start of pregnancy and, in women not yet on ART, the timing of ART initiation during pregnancy were assessed using the NSHPC data unless no data were available, when UK CHIC data were used (if available). If data were not available from either study regarding ART use in pregnancy, the pregnancy was excluded from the analysis (n=20). When categorising the women into the three groups, ART use following pregnancy was not considered.

The analysis was undertaken among women without hepatitis B or hepatitis C (HBV/HCV) co-infection. A separate analysis was undertaken including only women with HBV/HCV co-infection.

### 7.2.3 Methods Section 3: the impact of pregnancy on the risk of LEE

#### **Dataset**

In the third section, which examines the impact of pregnancy on LEE risk, the dataset used was created by linking the UK CHIC dataset containing data until 31<sup>st</sup> December 2012 to the NSHPC dataset archived in March 2014.

#### **Inclusion criteria**

The analyses were limited to women not on any ART on 31<sup>st</sup> December 1999 and who started ART at any point during 2000-2012 whilst aged 16-49 years. The date of ART initiation was considered the baseline date. Women with  $\geq 1$  ALT measurement while on ART and CD4 count and viral load data available were included. When assessing incident LEE, only the first initiation of ART over the study period was considered for each woman, i.e. if she temporarily stopped ART and restarted at a later point, only the first period of use was considered. Women with severe LEE (i.e.  $>5$  times the ULN) at baseline, indicating liver dysfunction, were excluded (n=10). Women were included irrespective of pregnancy status or previous ART experience at baseline as these characteristics were taken into account in adjusted analyses. All pregnancy outcomes were included.

#### **Outcomes**

The UK CHIC dataset was previously used to assess ALT levels among HIV-positive men and women not on ART in order to establish a robust definition of an 'ALT flare'. The recommendation from this previous publication was that an ALT flare should be defined on the basis of two consecutive measurements  $>200$  IU/L  $>14$  days apart, since many patients not on ART had a single increase in ALT [481]. However, this is not an appropriate measure to use in the context of pregnancy since the follow-up time is short and many of the women in UK CHIC only had one ALT measurement during pregnancy. Therefore, ALT levels were graded according to the Division of AIDS toxicity guidelines [322]. The primary outcomes were incidence of any LEE (grade 1-4) and incidence of severe LEE (grade 3-4). LEE was defined as  $\geq 1.25$  times the ULN among women with no evidence of LEE at baseline or  $\geq 1.25$  times the baseline ALT among women with ALT  $>ULN$  at baseline. Severe LEE was defined in the same way, but using  $>5$  times the ULN. The secondary outcomes were regimen changes (any

addition or discontinuation of at least one drug in the regimen) and interruptions within three months of incident LEE.

It was assumed that women with no ALT data before starting ART (n=1856) did not have ALT above the ULN. A sensitivity analysis was undertaken excluding women with no baseline ALT. An additional sensitivity analysis was undertaken to account for the fall in median ALT during pregnancy. This was done by adding 8 IU/L to all ALT measurements taken during pregnancy since the upper limit of the typical ALT ranges in pregnancy is 8 IU/L lower than at other times, summarised in Table 2.3 [339]).

As the risk of LEE may be higher in the first few months of ART use, an increase in the risk of LEE in pregnant women may be a consequence of women starting ART antenatally. A sensitivity analysis was therefore undertaken excluding women who were pregnant when starting ART.

Although women could act as their own controls, contributing data when pregnant and when not pregnant, some women did not have a pregnancy during follow-up. Analyses were adjusted in order to account for any differences between women who had a pregnancy and those who did not. However, since there could be residual confounding and no data were collected on possible confounders such as alcohol consumption, diet and weight, a sensitivity analysis was undertaken including only women who had a pregnancy at some point during follow-up.

## **Analysis**

Initially the baseline characteristics of women with and without a pregnancy at any point during follow-up were compared using Chi-squared and Kruskal-Wallis tests. Follow-up was started on the date of first ART use and was censored at ART discontinuation, at last clinic visit or at 31<sup>st</sup> December 2012, whichever occurred first. Kaplan-Meier analyses were used to describe the probability of LEE and severe LEE. Cox proportional hazards models were used to calculate crude and adjusted hazard ratios for the associations between factors and incident LEE/severe LEE (SAS command PROC PHREG). The counting process style of input was used and covariates were either considered as fixed or time-dependent [482]. Fixed characteristics at baseline considered for inclusion were: calendar year; previous antenatal use of short-course ART; pre-ART CD4 count (not known (NK)/ $\leq$ 250/251-350/351-500/ $>$ 500 cells/mm<sup>3</sup>); pre-ART viral load ( $\leq$ / $>$ 100,000 copies/ml); pre-ART ALT; route of exposure; ethnicity and HBV/HCV co-infection. For pre-ART CD4 count, viral load and ALT, the latest measurement in the six months prior to baseline was

used. Time-dependent covariates considered, assessed at one month intervals, were age, pregnancy status, cumulative use of ART, latest CD4 count category, latest viral load category and current drug regimen (dichotomised as used/not used for each drug). Any covariates that were associated with the outcome ( $p < 0.10$ ) in the univariate models were considered for inclusion in the multivariable models; covariates with a  $p$ -value  $\leq 0.05$  were retained in the final model, as were age, route of exposure, ethnicity and HBV/HCV co-infection, as these were of interest for our research question.

Finally, I examined changes in ART regimen and interruption of ART in women who experienced LEE.

## 7.3 Results

### 7.3.1 Results Section 1: preliminary descriptive analyses

#### **ALT data among women in UK CHIC**

The UK CHIC dataset contained clinical data for 11,439 women who attended HIV-related clinical care (i.e. had a CD4 count or viral load reported in UK CHIC) at any point during the period 2000-2011. The dataset contained 100,105 ALT measurements in total; more than half the women had at least one ALT measurement (54.1%,  $n=6188$ ) and just under half had multiple ALT measurements (49.6%,  $n=5677$ ). The number of ALT measurements per woman ranged from 0 to 238. Among women with  $\geq 1$  ALT measurement, the median number of measurements was 11 (interquartile range [IQR] 5-22).

Of the 8658 women who started life-long ART, i.e. not including short-course ART use in pregnancy, 22.0% ( $n=1908$ ) had  $\geq 1$  ALT measurement prior to starting ART and 51.9% ( $n=4497$ ) had  $\geq 1$  ALT measurement after starting, although they were not necessarily still on ART when these measurements were taken. In women with  $\geq 1$  ALT measurement, the median number of measurements was 3 [IQR 1-6] prior to starting ART, 10 [IQR 5-23] after starting ART and 5 (IQR 3-7) within one year of starting ART. Overall, 19.9% ( $n=1725$ ) of women had  $\geq 1$  ALT measurement before and  $\geq 1$  ALT measurement after starting ART.

### **ALT data during pregnancy in UK CHIC**

Of the 11,439 women of any age who attended HIV-related clinical care in 2000-2011, one-quarter (25.1%, n=2872) had at least one pregnancy starting in that period; 1817 women had a single pregnancy, 770 women had two pregnancies, 221 women had three pregnancies and 62 women had four or five pregnancies. Just over half the women with a pregnancy had  $\geq 1$  ALT measurement (51.3%, n=1473) and just under half had multiple ALT measurements (48.0%, n=1378) at any point during 2000-2011. At least one ALT measurement was taken during 27.4% (1175/4288) of pregnancies conceived in 2000-2011; 26.7% (724/2711) of index pregnancies and 28.6% (451/1557) of subsequent pregnancies. There were a total of 4582 ALT measurements taken during the pregnancies conceived in 2000-2011. The median number of ALT measurements during pregnancies with  $\geq 1$  ALT measurement, was 4 (IQR 2-5) during index pregnancies and 3 (IQR 2-5) during subsequent pregnancies.

### **Hepatitis co-infection among women in UK CHIC**

Overall, 83.7% (9574/11,439) of women had evidence that they had received a test for HBV and 86.8% (9934/11,439) for HCV. There were 870 women with HBV, HCV or HBV and HCV co-infection, representing 7.6% of women who received HIV care in 2000-2011. This makes the assumption that women with no evidence of having been tested for hepatitis were not infected. There were 363 women who were HBV co-infected and 528 women who were HCV co-infected, representing 3.2% and 4.6% of women in UK CHIC in 2000-2011 respectively. Of these, 21 were co-infected with HIV, HBV and HCV.

Of the 870 women with HIV-HBV/HCV co-infection, more than two-thirds (68.9%, n=599) had  $\geq 1$  ALT measurement in the dataset and 62.2% (n=541) had multiple ALT measurements. Within this group, among women with  $\geq 1$  ALT measurement, the median number of ALT measurements was 14 (IQR 5-32).

### **Characteristics predictive of having $\geq 1$ ALT measurement in the UK CHIC database**

There were a number of characteristics predictive of having  $\geq 1$  ALT measurement in the UK CHIC dataset (Table 7.2). Women with HBV/HCV co-infection were more likely to have  $\geq 1$  ALT measurement (69% vs. 53%, aOR 1.46, 95% confidence intervals (CI) [1.23-1.74]), as were women of white ethnicity compared to women of black-African ethnicity (73% vs. 50%, aOR 2.55 [2.24-2.90]). Women whose probable route of HIV

infection was injecting drug use (IDU) were more likely to have  $\geq 1$  ALT measurement than women infected via heterosexual sex in unadjusted analysis (71% vs. 53%, OR 2.12 [1.70-2.64]) but were less likely to have  $\geq 1$  ALT measurement when HBV/HCV co-infection and ethnicity were taken into account (aOR 0.78 [0.60-1.01], p-value 0.06 in a model including only those three variables, and aOR 0.75 [0.58-0.98], p-value 0.03 in the overall model). More than two-thirds of women who had been infected with HIV through sharing injecting drug equipment had HBV/HCV co-infection (69.4%, 281/405, compared to 7.6%, n=870 overall), and 85.4% (346/405) were of white ethnicity, (compared to 15.6%, n=1785 overall). The longer a woman had been attending HIV-care the more likely she was to have  $\geq 1$  ALT measurement and the more measurements she had (Table 7.3). Women who had ever used ART were more likely to have  $\geq 1$  ALT measurement than women who had not (57% vs. 42%, OR 1.81) but to a lesser extent when duration of HIV-care was taken into account (aOR 1.14 in the overall model).

Women who had a pregnancy (conceived in 2000-2011) were less likely to have  $\geq 1$  ALT measurement than women who did not have a pregnancy in this period (51% vs. 55%, aOR 0.73 [0.66-0.80]). The median number of ALT measurements was 1 [IQR 0-12] in women who had a pregnancy and 2 [IQR 0-12] in women who had not (p-value 0.09). In women with  $\geq 1$  ALT measurement, the median number of ALT measurements was 12 [IQR 6-23] in women who had a pregnancy and 11 [IQR 4-22] in women who had not (p<0.001) (Table 7.3). In unadjusted analysis, the likelihood of having  $\geq 1$  ALT measurement increased with age (OR 1.09 per additional 10 years), but the opposite was true when other factors were taken into account (aOR 0.91 per additional 10 years). Women aged  $\leq 49$  at the start of 2000 were more likely to have  $\geq 1$  ALT measurement than women aged >49 years (aOR 1.52 [1.21-1.91], p-value <0.001).

Table 7.2. Characteristics predictive of having  $\geq 1$  ALT measurement in the UK CHIC database

		Total	n	%	OR	p-value	aOR	p-value
All women		11,439	6188	54.1	-	-	-	-
Ever pregnant	No	8567	4715	55.0	Baseline		Baseline	
	Yes	2872	1473	51.3	0.86 (0.79-0.94)	<0.001	0.73 (0.66-0.80)	<0.001
HBV/HCV co-infection	No/not tested	10,569	5589	52.9	Baseline			
	Yes	870	599	68.9	1.97 (1.70-2.28)	<0.001	1.46 (1.23-1.74)	<0.001
Route of infection	Heterosexual sex	10,099	5396	53.4	Baseline		Baseline	
	IDU	405	287	70.9	2.12 (1.70-2.64)	<0.001	0.75 (0.58-0.98)	0.03
	Other/NK	935	505	54.0	1.02 (0.90-1.17)	0.73	1.24 (1.07-1.48)	0.004
Ethnicity	Black-African	7582	3802	50.2	Baseline		Baseline	
	White	1785	1305	73.1	2.70 (2.41-3.03)	<0.001	2.55 (2.24-2.90)	<0.001
	Black-Caribbean	505	239	47.3	0.89 (0.75-1.07)	0.22	0.94 (0.78-1.12)	0.48
	Other/NK	1567	842	53.7	1.16 (1.04-1.29)	0.01	1.27 (1.13-1.43)	<0.001
Duration in UK CHIC (years)	0-1	1639	500	30.5	Baseline		Baseline	
	2-5	4258	2101	49.3	2.22 (1.97-2.51)	<0.001	2.24 (1.97-2.56)	<0.001
	6-10	3453	2087	60.4	3.48 (3.07-3.95)	<0.001	3.81 (3.30-4.39)	<0.001
	>10	2089	1500	71.8	5.80 (5.03-6.69)	<0.001	5.96 (5.07-7.01)	<0.001
Any ART use	No	2076	874	42.1	Baseline		Baseline	
	Yes	9363	5314	56.8	1.81 (1.64-2.00)	<0.001	1.14 (1.02-1.28)	0.03
Median age at start 2000 (years) [IQR]		29		[23-35]	1.09 (1.04-1.13)	<0.001	0.91 (0.87-0.95)	<0.001

Footnote for Table 7.2.

This table includes data for women who attended care at any point in 2000-2011. aOR: adjusted odds ratio - multivariable logistic regression includes all variables listed in the model. The odds ratio for age refers to an increase of 10 years.

Table 7.3. Median number of ALT measurements in UK CHIC among all women and among women with  $\geq 1$  ALT measurement in 2000-2011

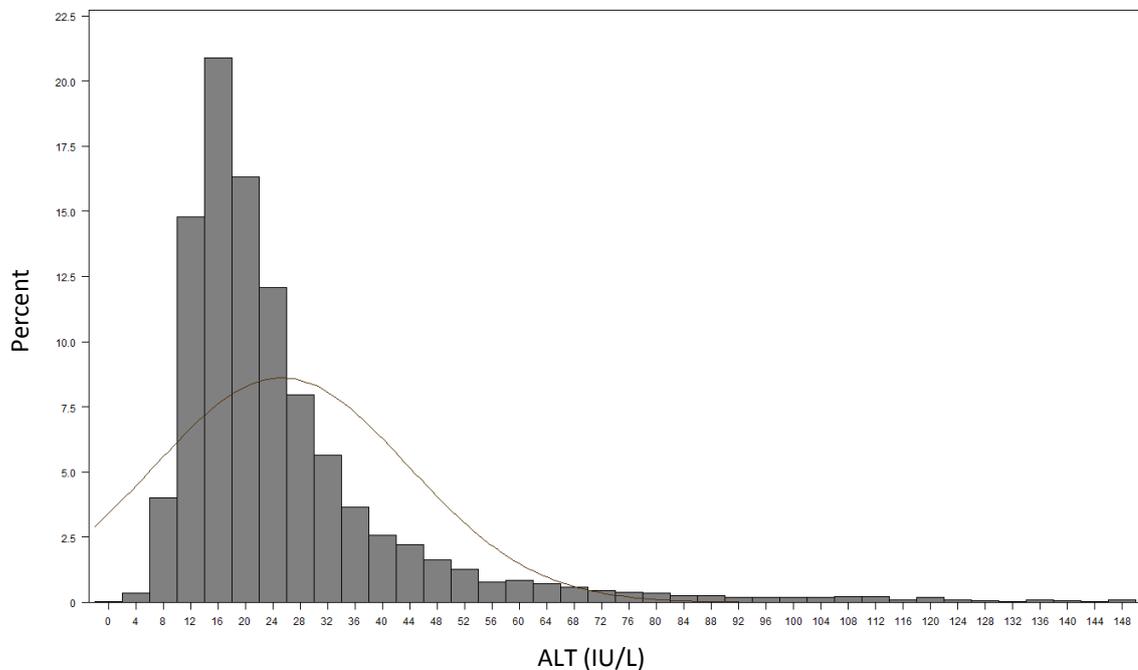
Characteristic	All women			Women with $\geq 1$ ALT measurement			
	Median	IQR	p-value	Median	IQR	p-value	
All women	1	0-12		11	5-22		
Ever pregnant	No	2	0-12	0.09	11	4-22	<0.001
	Yes	1	0-12		12	6-23	
HBV/HCV co-infection	No/not tested	1	0-11	<0.001	11	5-22	0.002
	Yes	6	0-20		14	5-32	
Exposure group	Heterosexual sex	1	0-12	<0.001	11	5-23	<0.001
	IDU	6	0-27		15	5-40	
	Other/NK	1	0-8		7	3-15	
Ethnicity	Black-African	1	0-11	<0.001	11	4-21	<0.001
	White	7	0-21		13	6-30	
	Black-Caribbean	0	0-9		10	4-17	
	Other/NK	1	0-11		11	4-21	
Duration in UK CHIC (years)	0-1	0	0-1	<0.001	2	1-4	<0.001
	2-5	0	0-7		7	4-12	
	6-10	5	0-17		14	8-24	
	>10	13	0-38		29	11-42	
Any ART use	No	0	0-2	<0.001	3	1-6	<0.001
	Yes	3	0-14		12	6-25	

IQR: inter quartile range. Overall p-values were calculated using Kruskal-Wallis Test

### Upper limit of normal (ULN) among ART naïve women in UK CHIC

All ALT measurements among women who were not known to have HBV/HCV co-infection and who were ART naïve at the time of the measurement were included (2717 women, 13,096 ALT measurements). The median ALT was 20 (IQR 15-29) IU/L, the 95<sup>th</sup> percentile was 73 IU/L and the 97.5<sup>th</sup> percentile was 115 IU/L. ALT data were highly skewed (Figure 7.1).

Figure 7.1. Distribution of ALT results (within the range 0-150 IU/L) among ART naïve women not diagnosed with HBV/HCV co-infection attending HIV care in at a UK CHIC site in 2000-2011 (n=2717)



### Preliminary descriptive analysis of ALT data

Among the 5589 women with  $\geq 1$  ALT measurement, there were a total of 100,105 ALT measurements in the period 2000-2011 (Table 7.4).

The median ALT overall was 22 (IQR 16-32) IU/L and among women without HBV/HCV co-infection it was 21 (IQR 15-30) IU/L. Among all women on ART, the median ALT was 21 (IQR 15-29) IU/L, there was some evidence that this was higher than the level among women not on ART (median ALT 20 [IQR 15-30] IU/L,  $p=0.06$ ).

Table 7.4. Preliminary descriptive analysis of ALT data among 5589 women in UK CHIC with  $\geq 1$  ALT measurement: each ALT measurement was taken as a separate observation and pregnancy status and ART use was determined at each ALT measurement

Status at time of ALT measurement	Number of ALT measurements	Median ALT (IU/L) [IQR]	p-value
Total	100,105	22 [16-32]	-
HBV/HCV co-infected <sup>1</sup>	13,701	34 [22-56]	<0.001
Non-HBV/HCV co-infected	86,404	21 [15-30]	
On ART	69,357	21 [15-29]	0.06
Not on ART	17,047	20 [15-30]	
Women on ART			
0-3 months since ART start	7719	22 [15-33]	<0.001
3-6 months since ART start	3835	21 [15-31]	
6-12 months since ART start	5595	20 [15-29]	
Pregnant	4372	15 [11-22]	<0.001
Not pregnant	82,032	21 [15-30]	
All pregnant women			
1st trimester	1133	17 [12-24]	<0.001
2nd trimester	1790	14 [10-20]	
3rd trimester	1449	15 [11-24]	
Women on ART at conception			
1st trimester	767	17 [13-25]	<0.001
2nd trimester	1395	14 [10-19]	
3rd trimester	1363	15 [11-24]	
Women on ART post-partum			
0-3 months post-partum	738	19 [13-28]	<0.001
3-6 months post-partum	659	21 [15-30]	
6-12 months post-partum	1327	19 [14-28]	

<sup>1</sup>Women with HBV/HCV co-infection are excluded from all subsequent rows.

The median ALT during pregnancy was 15 (IQR 11-22) IU/L, this was lower than in non-pregnant women (21 [IQR 15-30] IU/L,  $p < 0.001$ ). In pregnant women, the median ALT was 17, 14 and 15 IU/L during the 1<sup>st</sup>, 2<sup>nd</sup> and 3<sup>rd</sup> trimesters respectively. Median ALT measurements among post-partum women remaining on ART were 19, 21 and 19 IU/L respectively at 0-3 months, 3-6 months and 6-12 months after pregnancy.

This preliminary analysis indicates that median ALT levels may be lower during pregnancy than outside pregnancy, quickly returning to pre-pregnancy levels following delivery.

### 7.3.2 Results Section 2: the impact of pregnancy on median ALT

#### **Comparing pregnant women with controls to assess the impact of pregnancy on ALT**

There were 760 pregnancies meeting the inclusion criteria for the first part of this section, i.e. a woman's first pregnancy with  $\geq 1$  ALT measurement conceived on ART in 2000-2011. Of these, 643 were matched with at least one control; two controls were found for 435, with only one control found for the remaining 208. This gave a total of 1078 controls. There were 894 women used as a control: 739 women were used as a control once; 129 women were used twice, and 26 women were used three or four times. The median pregnancy duration was 37 weeks (IQR 37-38 weeks) and pregnancy duration ranged from 26-42 weeks.

The characteristics of women who were pregnant were compared to the characteristics of those who were not (controls) (Table 7.5).

Table 7.5. Comparison of pregnant women and controls – characteristics at the start of pregnancy (pregnancy group) or reference date (controls)

Characteristic		Pregnancy group (n=643)		Controls (n=1078)		p-value
Year*, n (%)	2000-2002	96	(14.9)	158	(14.7)	-
	2003-2005	143	(22.2)	235	(21.8)	
	2006-2008	174	(27.1)	308	(28.6)	
	2009-2011	230	(35.8)	377	(35.0)	
Age*, n (%)	16-24 years	81	(12.6)	117	(10.9)	-
	25-29 years	135	(21.0)	213	(19.8)	
	30-34 years	229	(35.6)	381	(35.3)	
	35-49 years	198	(30.8)	367	(34.0)	
	Median (IQR) years	32	(28-36)	32	(29-36)	
Ethnicity, n (%)	Black African	448	(69.7)	691	(64.1)	0.01
	White	92	(14.3)	210	(19.5)	
	Black Caribbean	26	(4.0)	30	(2.8)	
	Other/NK	77	(12.0)	147	(13.6)	
Exposure category, n (%)	Heterosexual sex	617	(96.0)	1007	(93.4)	0.07
	Injecting drug use	4	(0.6)	7	(0.7)	
	Other/NK	22	(3.4)	64	(5.9)	
Previous pregnancy* (whilst HIV-positive)		135	(21.0)	225	(20.9)	-
CD4 count* (cells/mm <sup>3</sup> ), n (%)	≤200	89	(13.8)	161	(14.9)	-
	201-350	158	(24.6)	274	(25.4)	
	351-500	173	(26.9)	270	(25.1)	
	>500	223	(34.7)	373	(34.6)	
	Median (IQR)	420	(280-580)	405	(257-571)	
Viral load (copies/ml), n (%)	≤50	245	(38.1)	473	(43.9)	<0.001
	51-1000	40	(6.2)	98	(9.1)	
	1001-10,000	43	(6.7)	81	(7.5)	
	>10,000	49	(7.6)	109	(10.1)	
	No VL reported	266	(41.4)	317	(29.4)	
Years since diagnosis, n (%)	<2	255	(39.7)	356	(33.0)	0.01
	2 to <5	133	(20.7)	284	(26.4)	
	5 to <10	184	(28.6)	263	(24.4)	
	10+	71	(11.0)	175	(16.2)	
	Median [IQR]	3.6	[0.4-7.2]	3.8	[1.2-7.8]	

\* Variables used to select suitable controls.

All women were on ART and therefore had previous ART exposure.

The time since HIV diagnosis was slightly shorter for the pregnant women than for the controls (3.6 vs. 3.8 years, p-value 0.01). A larger percentage of pregnant women were of black-African ethnicity than of the controls (69.7% vs. 64.1%, global p-value 0.01). In both groups, more than one-third of women were virally suppressed (HIV RNA  $\leq$ 50 copies/ml), however, the percentage with viral suppression was lower in pregnant women than in the controls (58.6% vs. 70.6%, global p-value  $<$ 0.001 where viral load was known).

The availability of ALT data was compared during the pre-pregnancy, pregnancy and postpartum periods (Table 7.6). The controls were more likely to have ALT data compared to the pregnancy group.

Table 7.6. Availability of ALT data among pregnant women and controls

Period in relation to pregnancy <sup>1</sup>		Pregnancy group n=643		Controls n=1078		p-value
Before <sup>2</sup>	$\geq$ 1 ALT measurement, n (%)	346	(53.8)	734	(68.1)	$<$ 0.001
	median count [IQR]	1	[0-2]	1	[0-2]	
During	$\geq$ 1 ALT measurement, n (%)	636	(99.0)	1076	(99.8)	0.01
	median count [IQR]	4	[3-5]	3	[3-4]	
After <sup>3</sup>	$\geq$ 1 ALT measurement, n (%)	501	(77.9)	972	(90.2)	0.001
	median count [IQR]	1	[1-2]	2	[1-2]	

<sup>1</sup>Equivalent periods for controls where the reference date is used as the pseudo-date of conception

<sup>2</sup>0-6 months before pregnancy

<sup>3</sup>0-6 months after pregnancy

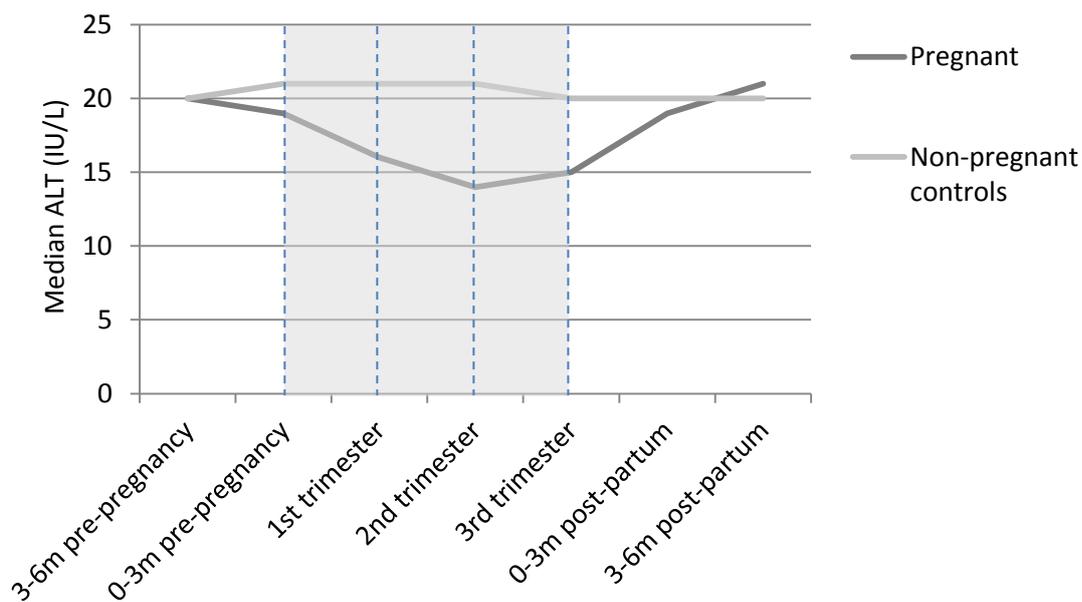
Median ALT levels for pregnant women and controls are presented in Table 7.7 and Figure 7.2. Prior to pregnancy, the median ALT was similar in both groups. Whilst all median ALT values remained within the normal range, ALT levels fell during the first and second pregnancy trimester, plateauing during the third. In the third trimester the median ALT was 15 IU/L, 5 IU/L less than the median ALT among the control group at the equivalent time. During all three pregnancy trimesters the median ALT was lower than in the controls. Shortly after pregnancy, ALT returned to pre-pregnancy levels and the median ALT at 3-6 months postpartum was similar for both groups (p-value 0.60).

Table 7.7. Median ALT levels during defined periods before, during and after pregnancy – and in equivalent periods for controls

Period of interest <sup>1</sup>		Pregnancy group Median (IQR)		Controls Median (IQR)		p-value
Before pregnancy	3-6 months (n=265, n=579)	20	(15-26)	20	(14-29)	0.68
	0-3 months (n=269, n=602)	19	(14-27)	21	(15-29)	0.10
During pregnancy	1 <sup>st</sup> trimester (n=426, n=809)	16	(13-24)	21	(15-30)	<0.001
	2 <sup>nd</sup> trimester (n=552, n=1002)	14	(11-20)	21	(16-30)	<0.001
	3 <sup>rd</sup> trimester (n=496, n=717)	15	(11-22)	20	(15-28)	<0.001
After pregnancy	0-3 months (n=395, n=827)	19	(14-28)	20	(15-29)	0.04
	3-6 months (n=371, n=747)	21	(14-30)	20	(15-29)	0.60

<sup>1</sup>Equivalent periods for controls where the reference date is used as the pseudo-date of conception

Figure 7.2. Median ALT levels among women on ART: pregnant women and controls (the shaded areas indicate the three pregnancy trimesters)



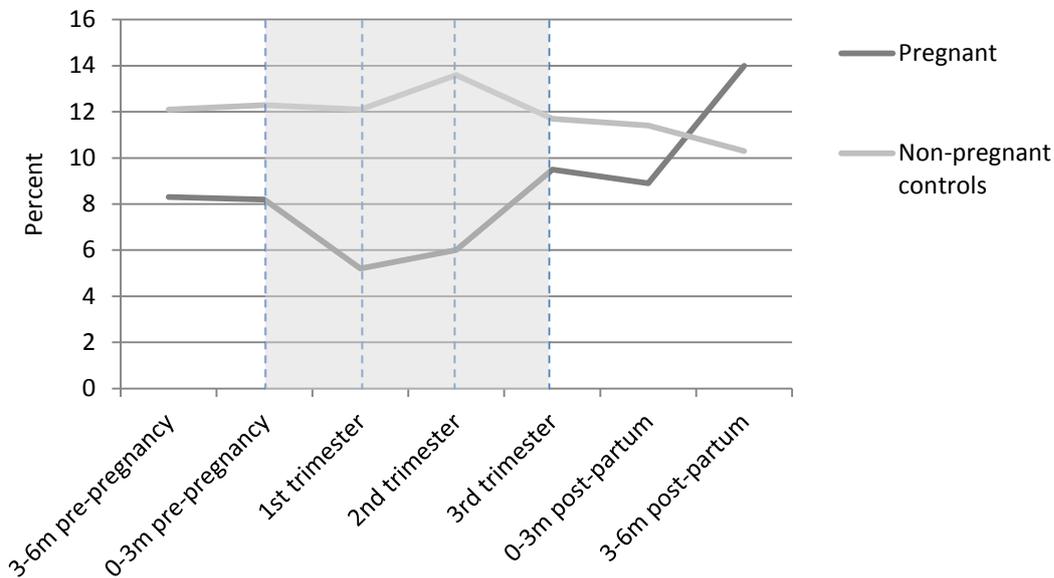
The proportion of women with ALT above ULN during each perinatal period is presented in Table 7.8 and Figure 7.3. Prior to pregnancy, the percentage of women with ALT above ULN was higher in the control group than in the pregnancy group, but this difference was not statistically significant. Among the pregnant women, the percentage with ALT above ULN fell during the first trimester, but increased during the second and third trimesters, increasing to above pre-pregnancy levels after delivery. A smaller percentage of pregnant women had ALT above ULN in the first and second trimester than in the controls.

Table 7.8. Proportion of women with mean ALT above ULN during each perinatal period

Period of interest <sup>1</sup>		Pregnancy group		Control group		p-value (Chi-squared)
		%	(n/N)	%	(n/N)	
Before pregnancy	3-6 months	8.3	(22/265)	12.1	(70/579)	0.10
	0-3 months	8.2	(22/269)	12.3	(74/602)	0.07
During pregnancy	1 <sup>st</sup> trimester	5.2	(22/426)	12.1	(98/809)	<0.001
	2 <sup>nd</sup> trimester	6.0	(33/552)	13.6	(136/1002)	<0.001
	3 <sup>rd</sup> trimester	9.5	(47/496)	11.7	(84/717)	0.22
After pregnancy	0-3 months	8.9	(35/395)	11.4	(94/827)	0.18
	3-6 months	14.0	(52/371)	10.3	(77/747)	0.07

<sup>1</sup>Equivalent periods for controls where the reference date is used as the pseudo-date of conception

Figure 7.3. Proportion of women with mean ALT above ULN during each perinatal period or equivalent periods for controls (shaded areas indicate the three pregnancy trimesters)



The analysis was repeated using a stricter matching criterion; this included the addition of ethnicity, exposure group and type of ART regimen, categorised as PI-based, NNRTI-based, NRTI-based or other drug regimen. The outcome was unchanged and the results are not included.

### Median CD4 count before, during and after pregnancy

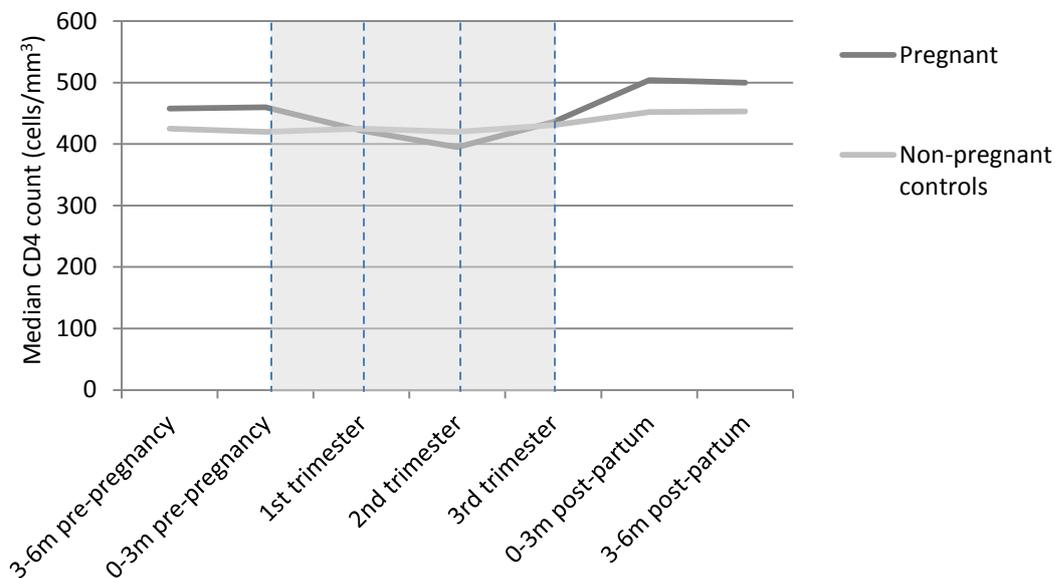
Median CD4 count was assessed for the periods before, during and after pregnancy (Table 7.9 and Figure 7.4). Although the median CD4 count appeared to dip during pregnancy, there was only a significant difference in the second trimester (395 vs. 420 cells/mm<sup>3</sup> respectively in the pregnancy and control groups) with median CD4 counts being similar for pregnant women and controls in the first and third trimesters. Before and after pregnancy, the median CD4 count was higher in the pregnancy group than in the controls.

Table 7.9. Median CD4 count during defined perinatal periods among the pregnancy group and controls

Period of interest <sup>1</sup>		Pregnancy group		Controls		p-value
		Median CD4 count (cell/mm <sup>3</sup> ) [IQR]				
Before pregnancy	3-6 months (n=298, n=600)	458	[310-600]	425	[297-609]	0.31
	0-3 months (n=291, n=610)	460	[330-615]	420	[280-581]	0.04
During pregnancy	1 <sup>st</sup> trimester (n=442, n=765)	422	[270-584]	425	[297-600]	0.18
	2 <sup>nd</sup> trimester (n=569, n=677)	395	[274-548]	420	[280-604]	0.05
	3 <sup>rd</sup> trimester (n=488, n=456)	436	[309-576]	431	[287-597]	0.85
After pregnancy	0-3 months (n=424, n=803)	504	[360-668]	452	[320-630]	0.01
	3-6 months (n=381, n=733)	500	[360-640]	453	[322-635]	0.04

<sup>1</sup>Equivalent periods for controls where the reference date is used as the pseudo-date of conception. IQR: interquartile range.

Figure 7.4. Median CD4 counts among women on ART: pregnant and matched non-pregnant women (the shaded areas indicate the three pregnancy trimesters)



### Variables independently associated with ALT

A mixed effect regression model was developed to identify variables independently associated with ALT, whilst taking into account repeated measures (i.e. multiple ALT measurements for the same woman). In total, 5394 women contributed 19,397 person-years (PY) of follow-up to the analysis. The characteristics of women at the start of follow-up are summarised in Table 7.10.

At the start of follow-up, 14.5% (n=783) of women had previously had a pregnancy. In total, 598 PY of follow-up were contributed by women when pregnant and 18,799 PY when not pregnant. Overall, 16.5% (n=888) of women were pregnant at some point during follow-up, including 6.5% (n=353) who were pregnant at the start of follow-up. During follow-up there were a total of 1390 pregnancies with 510 women having one pregnancy; 276 having two pregnancies and 102 having three or more pregnancies. The majority of pregnancies resulted in a live birth (88.1%, n=1225), with 6.4% (n=89) resulting in a miscarriage, 3.0% (n=42) being terminated, and the remaining 34 having other outcomes (including unknown outcome because the woman was lost to follow-up). The majority of women with a pregnancy had been infected with HIV via heterosexual sex (94.8%, n=842) and two-thirds of women were of black-African ethnicity (67.7%, n=601).

Table 7.10. Demographic and clinical characteristics of women in the longitudinal analysis

Baseline characteristics		All women (n=5394)		Pregnancy during follow-up			
				Yes (n=888)		No (n=4506)	
Age, n (%)	16-24 years	530	(9.8)	149	(16.8)	381	(8.5)
	25-29 years	837	(15.5)	260	(29.3)	577	(12.8)
	30-34 years	1228	(22.8)	303	(34.7)	925	(20.5)
	35-39 years	1290	(23.9)	153	(17.2)	1137	(25.2)
	40-49 years	1509	(28.0)	18	(2.0)	1491	(33.1)
	Median [IQR] years	35	[29-40]	30	[26-34]	36	[31-41]
Ethnicity, n (%)	Black African	3373	(62.5)	601	(67.7)	2772	(61.5)
	White	1120	(20.8)	140	(15.8)	980	(21.7)
	Black Caribbean	186	(3.5)	45	(5.1)	141	(3.1)
	Other/NK	715	(13.3)	102	(11.5)	613	(13.6)
Exposure category, n (%)	Heterosexual sex	4717	(87.5)	842	(94.8)	3875	(86.0)
	IDU	260	(4.8)	15	(1.7)	245	(5.4)
	Other/NK	417	(7.7)	31	(3.5)	386	(8.6)
HBV/HCV infection		538	(10.0)	58	(6.5)	480	(10.7)
CD4 count (cells/mm <sup>3</sup> ), n (%)	≤200	1101	(20.4)	158	(17.8)	943	(20.9)
	201-350	1217	(22.6)	225	(25.3)	992	(22.0)
	351-500	1139	(21.1)	208	(23.4)	931	(20.7)
	>500	1554	(28.8)	249	(28.0)	1305	(29.0)
	NK	383	(7.1)	48	(5.4)	335	(7.4)
	Median [IQR]	373	[221-554]	376	[245-540]	371	[220-557]
Viral load (copies/ml), n (%)	≤50	2131	(39.5)	270	(30.4)	1861	(41.3)
	51-1000	806	(14.9)	166	(18.7)	640	(14.2)
	1001-10,000	809	(15.0)	170	(19.1)	639	(14.2)
	>10,000	1313	(24.3)	224	(25.2)	1089	(24.2)
	NK	335	(6.2)	58	(6.5)	277	(6.1)
ALT (IU/L), n (%)	<40	4592	(85.1)	795	(89.5)	3797	(84.3)
	40 - ≤100	673	(12.5)	82	(9.2)	591	(13.1)
	>100	129	(2.4)	11	(1.2)	118	(2.6)
	Median [IQR]	20	[15-30]	18	[13-25]	21	[15-31]
ART use	ART experienced	3572	(66.2)	553	(62.3)	3019	(67.0)
	On ART	3204	(59.4)	487	(54.8)	2717	(60.3)
Current type of ART regimen	PI-based	1199	(37.4)	221	(45.4)	978	(21.7)
	NNRTI-based	1517	(47.4)	199	(40.9)	1318	(29.2)
	NRTI-based	86	(2.7)	12	(2.5)	74	(1.6)
	Other	402	(12.6)	55	(11.3)	347	(7.7)
ART drug in regimen	Zidovudine	972	(18.0)	235	(26.5)	742	(16.5)
	Tenofovir	1393	(25.8)	237	(26.7)	1246	(27.7)
	Ritonavir	1192	(22.1)	275	(31.0)	995	(22.1)
	Darunavir	150	(2.8)	23	(2.6)	141	(3.1)
	Saquinavir	148	(2.8)	37	(4.2)	114	(2.5)

IQR: interquartile range; NNRTI: non-nucleoside reverse transcriptase inhibitor; PI: protease inhibitor; NRTI: nucleoside/nucleotide reverse transcriptase inhibitor.

Table 7.11. Results from mixed effects regression model to describe associations between each factor and the ALT value

Predictor		Univariate Estimate	p-value	Multivariable Estimate	p-value
Constant				22.7	<0.001
Pregnant		-4.5	<0.001	-3.3	<0.001
Previous pregnancy (whilst HIV-positive)		-2.2	<0.001	-1.0	<0.001
Hepatitis co-infected		20.3	<0.001	17.1	<0.001
Ethnicity	Black-African	Reference	<0.001	Reference	<0.001
	White	9.0		4.2	
	Black-Caribbean	0.2		-0.03	
	Other/NK	3.0		1.7	
Exposure group	Heterosexual sex	Reference	<0.001	Reference	<0.001
	IDU	20.5		4.7	
	Other/NK	1.0		-0.4	
CD4 count (cells/mm <sup>3</sup> )	≤200	4.0	<0.001	2.6	<0.001
	201-350	0.6		-0.06	
	351-500	-0.1		-0.3	
	>500	Reference		Reference	
	NK	0.1		0.2	
Viral load (copies/ml)	≤50	Reference	<0.001	Reference	0.01
	51-1000	0.7		0.6	
	1001-10,000	0.3		0.4	
	>10,000	1.9		1.0	
	NK	1.5		1.4	
Drug regimen	No ART	Reference	<0.001	Reference	<0.001
	PI-based	-2.3		0.7	
	NRTI-based	1.2		0.9	
	NNRTI-based	-0.2		3.0	
	Other	0.2		2.6	
Duration on ART (per additional year)		-0.2	<0.001	-0.05	0.27
ART drug	Zidovudine	-2.1	<0.001	-2.2	<0.001
	Tenofovir	0.7	0.002	1.2	<0.001
	Ritonavir	-3.2	<0.001	-2.7	<0.001
	Darunavir	-3.0	<0.001	-2.2	<0.001
	Saquinavir	0.6	0.27	1.4	0.01

The model identifies a number of factors which are independently associated with ALT (Table 7.11). The mean ALT for a person who, at any time over the study, is 35 years old, is not pregnant, has not previously been pregnant, is of black-African ethnicity, acquired HIV via heterosexual sex, has a CD4 count  $>500$  cells/mm<sup>3</sup>, has an undetectable viral load and is not on ART is 25.6 IU/L. ALT increases by, on average, 22.7 IU/L per 10 year increase in age. Pregnancy decreased ALT by, on average, 3.3 IU/L. Women who had previously been pregnant (when HIV-positive) had ALT, on average, 1.0 IU/L lower than women with no previous pregnancy (since HIV diagnosis).

Factors predictive of higher ALT were: HBV/HCV co-infection; white or 'other/NK' ethnicity (compared to black-African ethnicity); probable route of infection through sharing injecting drug equipment (compared to heterosexual sex); CD4 count  $\leq 200$  cells/mm<sup>3</sup> (compared to CD4 count  $>500$  cells/mm<sup>3</sup>); having detectable viral load or having no viral load reported in the previous 6 months (compared to having undetectable viral load); the use of an NNRTI-based regimen (compared to not using any ART); and the use of the ART drugs tenofovir or saquinavir. Use of zidovudine, ritonavir and darunavir were associated with lower ALT.

The association between cumulative time on ART and ALT was not statistically significant (p-value 0.27). Having had a pregnancy in the past 6 months was not associated with ALT in univariate analysis (estimate -0.6, p-value 0.30).

### **Median ALT before, during and after pregnancy according to ART use**

Median ALT during pregnancy and in the 9 months before and 18 months after pregnancy was examined in three groups: women who were already on ART when they conceived; women who started ART in the first half of pregnancy; and women who started ART in the second half of pregnancy. The data are presented in Table 7.12 and Figure 7.5. Data were available for 793 women in total; 646 had  $\geq 1$  ALT measurement during pregnancy and 275 had  $\geq 1$  ALT measurement in the periods before, during and after pregnancy. Among women already on ART when they conceived, ALT levels fell during pregnancy, plateauing in the final trimester and returning to pre-pregnancy levels by 0-3 months post-partum (Table 7.12 and Figure 7.5). A similar pattern was seen in women who started ART during the first 20 weeks of pregnancy; the median ALT fell during the first half of pregnancy, increasing during the 6 months following pregnancy, returning to pre-pregnancy levels by 6-9 months postpartum with a temporary peak above pre-pregnancy levels at 3-6 months post-partum, (79.5% [89/112] of these women were still on ART at 3 months post-partum). Women starting

ART after 20 gestational weeks had a somewhat lower median ALT prior to pregnancy (17 IU/L), the fall in ALT was not as marked during pregnancy which meant that all groups had similar median ALT at the end of pregnancy. Median ALT peaked at 3-6 months post-partum and returned to pre-pregnancy levels by 9-12 months postpartum. In this group, 58.1% (126/217) were on ART at 3 months post-partum.

Figure 7.5. Trends in median ALT (IU/L) before, during and after pregnancy according to ART status among HIV-positive women with an index pregnancy in 2000-2011 (the shaded areas indicate the three pregnancy trimesters)

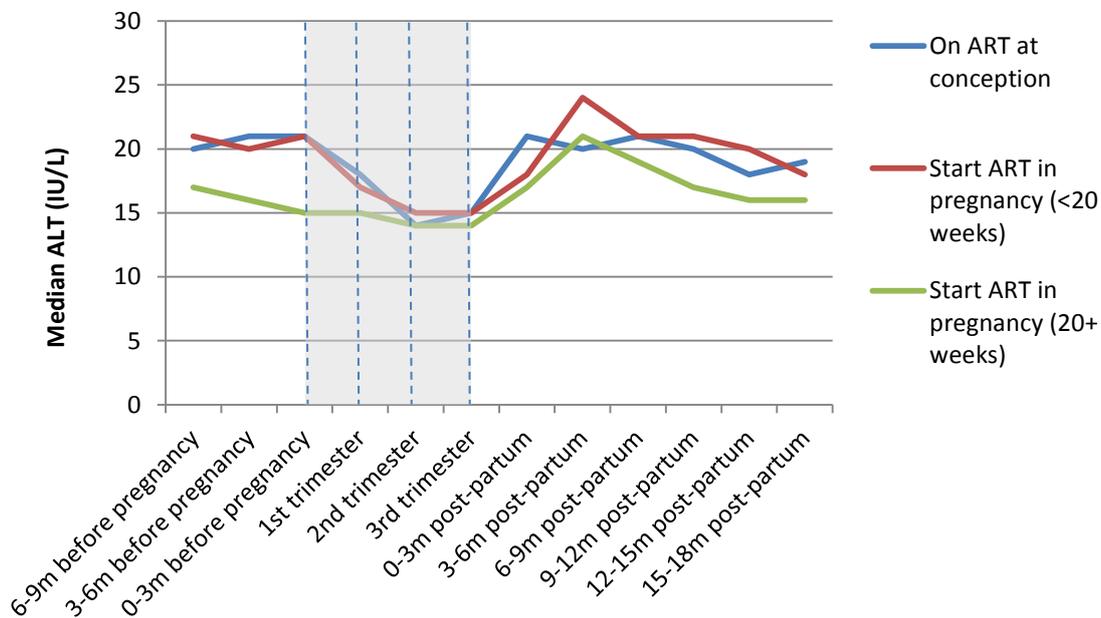


Table 7.12. Median ALT measurements before, during and after index pregnancies resulting in a live or still birth where ALT data was available in 2000-2011

Perinatal Period <sup>1</sup>		Initiation of ART					
		Before conception		<20 weeks		≥20 weeks	
		n (n=318)	Median [IQR] (IU/L)	n (n=142)	Median [IQR] (IU/L)	n (n=288)	Median [IQR] (IU/L)
Before pregnancy	6-9 months	160	20 [15-28]	17	21 [17-29]	32	17 [13-21]
	3-6 months	167	21 [16-29]	25	20 [15-23]	39	16 [14-26]
	0-3 months	170	21 [15-28]	24	21 [15-32]	37	15 [13-24]
During pregnancy	1 <sup>st</sup> trimester	212	18 [14-25]	72	17 [13-24]	88	15 [12-19]
	2 <sup>nd</sup> trimester	221	14 [11-20]	99	15 [11-27]	200	14 [11-20]
	3 <sup>rd</sup> trimester	194	15 [12-22]	84	15 [11-27]	198	14 [10-23]
After pregnancy	0-3 months	174	21 [15-30]	85	18 [13-26]	151	17 [13-23]
	3-6 months	182	20 [15-29]	57	24 [17-34]	123	21 [14-32]
	6-9 months	160	21 [15-30]	65	21 [14-36]	116	19 [14-27]
	9-12 months	163	20 [15-27]	64	21 [14-32]	103	17 [13-22]
	12-15 months	164	18 [14-26]	54	20 [15-28]	110	16 [13-23]
	15-18 months	156	19 [14-28]	64	18 [15-24]	121	16 [14-22]

<sup>1</sup>Equivalent periods for controls where the reference date is used as the pseudo-date of conception

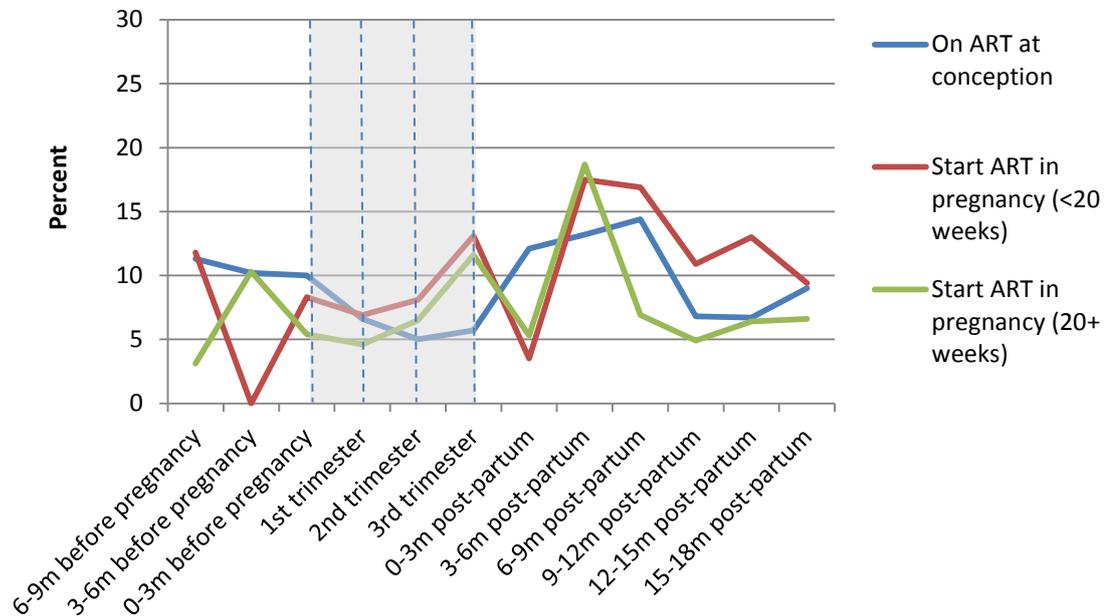
For all groups, the median ALT remained within the normal range throughout. The percentage of women with a mean ALT above the ULN was assessed in each three month period of interest (Table 7.13 and Figure 7.6). The overall pattern showed a fall in the percentage of women with ALT above ULN during pregnancy with an increase following pregnancy. However, due to the small number of ALT measurements available for each group there was a lot of fluctuation in the proportion of women with ALT above ULN and comparison between groups was not possible.

Table 7.13. The proportion of women with mean ALT above ULN (40 IU/L) during each period before, during and after index pregnancy in 2000-2011

Perinatal Period		On ART at conception (n=318)		Start ART at <20 weeks (n=142)		Start ART at ≥20 weeks (n=288)	
		%	n/N	%	n/N	%	n/N
Pre-pregnancy	6-9m	11.3	18/160	11.8	2/17	3.1	1/32
	3-6m	10.2	17/167	0.0	0/25	10.3	4/39
	0-3m	10.0	17/170	8.3	2/24	5.4	2/37
Trimester	1 <sup>st</sup>	6.6	14/212	6.9	5/72	4.6	4/88
	2 <sup>nd</sup>	5.0	11/221	8.1	8/99	6.5	13/200
	3 <sup>rd</sup>	5.7	11/194	13.1	11/84	11.6	23/198
Post-partum	0-3m	12.1	21/174	3.5	3/85	5.3	8/151
	3-6m	13.2	24/182	17.5	10/57	18.7	23/123
	6-9m	14.4	23/160	16.9	11/65	6.9	8/116
	9-12m	6.8	11/163	10.9	7/64	4.9	5/103
	2-15m	6.7	11/164	13.0	7/54	6.4	7/110
	5-18m	9.0	14/156	9.4	6/64	6.6	8/121

m: months

Figure 7.6. The proportion of women with mean ALT above ULN (40 IU/L) during each period before, during and after their index pregnancy in 2000-2011 (the shaded areas indicate the pregnancy trimesters)



The analysis was repeated for women with HBV/HCV co-infection, of whom 57 had perinatal ALT data from their index pregnancy. Due to small numbers comparison between groups was not possible but the overall pattern of ALT in women with HBV/HCV co-infection was similar to that in non-co-infected women although with, on average, higher pre-pregnancy ALT. The results are not presented here.

### 7.3.3 Results Section 3: the impact of pregnancy on the risk of LEE

#### Baseline characteristics

The 3815 women included in the analysis contributed 17,753 PY of follow-up. The median duration of follow-up was 4.1 (IQR 1.6-7.2) years. When starting ART, the median age was 34 years, 66.0% of women were of black-African ethnicity, 90.6% acquired HIV via heterosexual sex and 8.3% had HBV/HCV co-infection (Table 7.14). Overall, 38.3% of women were HIV diagnosed within the three months before starting

ART and 46.5% had a CD4 count  $\leq 250$  cells/mm<sup>3</sup>. Over half the women were on a non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimen; 19.2% (n=732) used an NVP-containing drug regimen. At baseline, 304 women had an ALT above ULN, representing 8.0% of the total or 15.5% of the 1959 women with baseline ALT data.

When starting ART, 14.2% (n=541) of women were pregnant; 25.7% (n=982) were pregnant at some time during follow-up (including the 541 pregnant at baseline): 742 women had one pregnancy and 240 women had more than one pregnancy. Women with a pregnancy during follow-up differed from women without: they were less likely to be of white ethnicity (12.7% (n=125) vs. 18.6% (n=526), p-value <0.001), to have acquired HIV through sharing injecting drug equipment (0.9% (n=9) vs. 4.0% (n=113), p-value <0.001) and be HBV/HCV co-infected (5.7% (n=56) vs. 9.2% (n=261), p-value <0.001). Women with a pregnancy were less likely to start ART with CD4  $\leq 250$  cells/mm<sup>3</sup> and more likely to start with CD4  $> 500$  cells/mm<sup>3</sup> (49.6% (391/789) vs. 65.7% (1383/2105), and 12.3% (97/789) vs. 6.7% (140/2105) respectively, p-value <0.001) and more likely to use an NVP-containing drug regimen (25.3% (n=248) vs. 17.1% (n=484), p-value <0.001). Women with a pregnancy were less likely to have ALT  $> 40$  IU/L at baseline (4.2% (n=41) vs. 9.3% (n=263), p-value <0.001).

In the first 6 months on ART, the proportion of women with at least one ALT measurement was similar in both groups (63.4% (n=623) vs. 65.4% (n=1852), p-value 0.27) and the median number of ALT measurements during this period was the same (2 [IQR 0-4], p-value 0.72). The median number of ALT measurements undertaken in the first 6 months on ART remained stable over time (three or four for each year). ALT monitoring, in general, did not increase over time.

Table 7.14. Baseline characteristics of 3815 HIV-positive women starting ART in 2000-2012

Characteristic	n	(%)
Age, median [IQR]	34	[29-39]
Exposure group	Heterosexual sex	3456 (90.6)
	IDU	122 (3.2)
	Other/Not known	237 (6.2)
Ethnicity	Black-African	2517 (66.0)
	White	651 (17.1)
	Black-Caribbean	133 (3.5)
	Other/Not known	514 (13.5)
HIV-HBV/HCV co-infection	317	(8.3)
Year of starting ART	2000-2002	793 (20.8)
	2003-2005	1020 (26.7)
	2006-2008	1062 (27.8)
	2009-2014	940 (24.6)
Time since HIV-diagnosis	<3 months	1460 (38.3)
	3-<12 months	651 (17.1)
	1-<5 years	928 (24.3)
	≥5 years	776 (20.3)
	Median months [IQR]	7.5 [1.5-46]
CD4 count (cells/mm <sup>3</sup> )	≤250	1774 (46.5)
	251-350	564 (14.8)
	351-500	319 (8.4)
	>500	237 (6.2)
	Not known	921 (24.1)
Viral load (copies/ml)	≤400	463 (12.1)
	400-≤10,000	605 (15.9)
	10,000-≤100,000	1074 (28.2)
	≥100,000	779 (20.4)
	Not known	894 (23.4)
ALT >ULN at baseline	304	(8.0)
Previous ART use	218	(5.7)
Pregnancy status	Non-pregnant	3274 (85.8)
	Pregnant <20 weeks gestation	208 (5.5)
	Pregnant ≥20 weeks gestation	333 (8.7)
Type of ART regimen	NNRTI	2134 (55.9)
	PI <sup>a</sup>	1176 (30.8)
	NRTI <sup>b</sup>	130 (3.4)
	Other	375 (9.8)

ALT: alanine transaminase; HBV: hepatitis B; HCV: hepatitis C; IDU: injecting drug use; IQR: interquartile range; NNRTI: non-nucleoside reverse transcriptase inhibitor; NRTI: nucleoside/nucleotide reverse transcriptase inhibitor; PI: protease inhibitor; ULN: upper limit of normal.

<sup>a</sup> 1036 women were on a ritonavir-boosted PI and 140 were on a non-boosted PI.

<sup>b</sup> This includes 68 women on zidovudine monotherapy.

## Incidence of LEE

Overall, 1080 (28.3%) women developed LEE. After one year on treatment the cumulative incidence of LEE was 15% (95% CI 14%-17%), increasing to 30% (95% CI 28%-31%) by five years. The overall estimated rate of LEE was 6.3 (95% CI 5.9-6.7)/100 PY. The rate of LEE was 14.5 (11.4-17.5)/100 PY in pregnancy and 6.0 (5.6-6.4)/100 PY outside pregnancy. In women with HBV/HCV co-infection, 149 (47%) developed LEE, with LEE rates being 14.4 (12.1-16.7)/100 PY in women with HBV/HCV co-infection and 5.8 (5.4-6.1)/100 PY in women without co-infection.

In the first six months on ART, the rate of LEE was 21.8 (19.7-23.8)/100 PY. For this period, the rate was higher in women who were pregnant than in women who were not pregnant (32.2 [23.9-40.5]/100 PY vs. 20.8 [18.7-22.8]/100 PY, respectively). In women who had been on ART for more than six months, the rate of LEE was 4.2 (3.9-4.6)/100 PY. The rate was higher in women who were pregnant than in women who were not pregnant (7.0 [4.5-9.5]/100 PY vs. 4.2 [3.8-4.5]/100 PY, respectively) (Table 7.15).

Table 7.15. Rates of LEE and severe LEE per 100 person-years, with 95% confidence intervals (CIs), according to pregnancy status and duration on ART

	All women, CI		Pregnant, CI		Not pregnant, CI	
<b>LEE</b>						
Overall	6.3	5.9-6.7	14.5	11.4-17.5	6.0	5.6-6.4
≤6 months on ART	21.8	19.7-23.8	32.2	23.9-40.5	20.8	18.7-22.8
>6 months on ART	4.2	3.9-4.6	7.0	4.5-9.5	4.2	3.8-4.5
<b>Severe LEE</b>						
Overall	0.7	0.6-0.8	3.9	2.4-5.3	0.6	0.5-0.7
≤6 months on ART	2.9	2.2-3.7	9.0	4.7-13.3	2.4	1.7-3.0
>6 months on ART	0.5	0.4-0.6	2.0	0.7-3.2	0.4	0.3-0.5

LEE occurred during 11.6% (63/541) of pregnancies in which ART was started. In women who developed LEE during such a pregnancy, it occurred at a median of 30 (IQR 25-33) weeks gestation and 8 (IQR 4-12) weeks after ART initiation. In pregnancies conceived on ART during which LEE occurred, it occurred at median of 16 (IQR 9-28) weeks gestation.

### **Incidence of severe LEE**

Overall, 151 (4.0%) women developed severe LEE. The cumulative incidence of severe LEE at one and 5 years after treatment initiation was 2.2% (1.7%-2.7%) and 4.3% (3.5%-5.0%), respectively. The overall estimated rate of severe LEE was 0.7 (0.6-0.8)/100 PY. The rate of severe LEE was 3.9 (2.4-5.3)/100 PY in pregnancy and 0.6 (0.5-0.7)/100 PY outside pregnancy. In women with HBV/HCV co-infection (both pregnant and non-pregnant), 18 (5.7%) developed severe LEE; the rates were 1.2 (0.6-1.8) in women with HBV/HCV co-infection and 0.7 (0.6-0.8)/100 PY in women without co-infection.

In the first six months on ART the rate of severe LEE was 2.9 (2.2-3.7)/100 PY. For this period, the rate was higher in women who were pregnant than in women who were not pregnant (9.0 [4.7-13.3]/100 PY vs. 2.4 [1.7-3.0]/100 PY, respectively). In women who had been on ART for more than 6 months, the rate of severe LEE was 0.5 (0.4-0.6)/100 PY. The rate was higher in women who were pregnant than in women who were not pregnant (2.0 [0.7-3.2]/100 PY vs. 0.4 [0.3-0.5]/100 PY, respectively) (Table 7.15).

Severe LEE occurred during 3.3% (18/541) of pregnancies during which ART was started. In women who developed severe LEE during such a pregnancy, it occurred at a median of 30 (IQR 27-31) weeks gestation and 9 (IQR 3-12) weeks after ART initiation. In pregnancies conceived on ART with severe LEE, this occurred at a median of 24 (IQR 11-29) weeks gestation.

### **Factors associated with LEE**

Being pregnant was independently associated with an increased risk of LEE (Table 7.16). This remained the case in further analyses limited to women conceiving on ART (aHR 1.91 [1.28-2.84], p=0.001). The recent CD4 count, but not the CD4 count at ART initiation, was associated with LEE with women who attained a CD4 count >500 cells/mm<sup>3</sup> having a decreased risk of LEE. Women receiving zidovudine (ZDV)-containing regimens had a lower risk of LEE than women on ZDV-sparing regimens. Whilst women receiving NVP or efavirenz were at increased risk of LEE (Table 7.16), this risk dropped with longer exposure to the NNRTI drug class. Other factors independently associated with LEE were HBV/HCV co-infection and having acquired HIV via IDU. There was a small, but significant, increase in the risk of developing LEE in later calendar years.

### **Factors associated with severe LEE**

Factors associated with developing severe LEE were similar to those associated with developing any LEE (Table 7.17). Being pregnant was associated with an increased risk; this was also the case when women who started ART whilst pregnant were excluded (aHR 4.99 [2.55-9.80],  $p < 0.001$ ). Calendar year, age, and CD4 count were all associated with the risk of severe LEE, but there were no specific antiretroviral drugs which were significantly associated with severe LEE in univariate analyses. There were no deaths related to severe LEE.

Table 7.16. Results from unadjusted and adjusted Cox proportional hazards regression analyses to identify factors associated with the incidence of any LEE

		Unadjusted		Adjusted	
		HR (95% CI)	p-value	HR (95% CI)	p-value
Pregnant		1.38 (1.11-1.73)	0.004	1.66 (1.31-2.09)	<0.001
Age (per 10 year increase)		1.00 (0.92-1.08)	0.98	1.05 (0.96-1.14)	0.31
Route of exposure	Heterosexual sex	Reference	<0.001	Reference	0.02
	IDU	2.60 (2.00-3.37)		1.55 (1.12-2.15)	
	Other/Not known	1.02 (0.78-1.33)		0.93 (0.71-1.22)	
Ethnicity	Black-African	Reference	0.001	Reference	0.35
	White	1.37 (1.18-1.60)		1.17 (0.98-1.38)	
	Black-Caribbean	1.08 (0.76-1.52)		1.03 (0.73-1.46)	
	Other/Not known	1.09 (0.91-1.31)		1.08 (0.90-1.30)	
Calendar year		1.06 (1.03-1.08)	<0.001	1.05 (1.03-1.08)	<0.001
HBV/HCV co-infection		2.22 (1.87-2.64)	<0.001	1.85 (1.52-2.27)	<0.001
LEE at baseline		1.56 (1.21-2.01)	<0.001	-	
Latest CD4 count (cells/mm <sup>3</sup> )	≤250	Reference	<0.001	Reference	0.05
	251-350	0.85 (0.70-1.04)		0.82 (0.67-0.99)	
	351-500	0.88 (0.73-1.06)		0.83 (0.68-1.00)	
	>500	0.77 (0.63-0.93)		0.72 (0.59-0.87)	
	Not known	0.62 (0.52-0.76)		0.62 (0.51-0.75)	

Table 7.16 is continued on the next page

Table 7.16 continued. Results from unadjusted and adjusted Cox proportional hazards regression analyses to identify factors associated with the incidence of any LEE

		Unadjusted		Adjusted	
		HR (95% CI)	p-value	HR (95% CI)	p-value
CD4 count at ART start (cells/mm <sup>3</sup> )	≤250	Reference	0.004	-	
	251-350	0.74 (0.57-0.96)			
	351-500	0.73 (0.58-0.92)			
	>500	0.66 (0.53-0.82)			
	Not known	0.81 (0.65-1.01)			
Latest viral load (copies/ml)	≤50	Reference		-	
	>50	0.88 (0.74-1.04)	0.13		
Viral load at ART start (copies/ml)	≤100,000	Reference		-	
	>100,000	0.88 (0.70-1.10)	0.25		
ART drug in regimen	Zidovudine	0.68 (0.59-0.79)	<0.001	0.73 (0.62-0.85)	<0.001
	Efavirenz	1.00 (0.88-1.14)	0.52	1.26 (1.07-1.48)	0.005
	Nevirapine	1.02 (0.88-1.18)	0.77	1.54 (1.27-1.87)	<0.001
	Raltegravir	1.88 (1.14-3.08)	0.01	-	
Duration on ART (per additional year)		1.03 (0.95-1.12)	0.43	-	
Duration on PI regimen		1.07 (1.03-1.11)	0.001	-	
Duration on NNRTI regimen		0.94 (0.91-0.98)	0.004	0.90 (0.86-0.95)	<0.001
Duration on NRTI regimen		1.10 (0.98-1.24)	0.11	-	

ALT: alanine transaminase; HBV: hepatitis B; HCV: hepatitis C; HR: hazard ratio; IDU: injecting drug use; IQR: interquartile range; LEE: liver enzyme elevation; NNRTI: non-nucleoside reverse transcriptase inhibitor; NRTI: nucleoside/nucleotide reverse transcriptase inhibitor; PI: protease inhibitor; ULN: upper limit of normal. Adjusted by covariates in the table with aHR presented.

Table 7.17. Results from unadjusted and adjusted Cox proportional hazards regression analyses to identify factors associated with the incidence of severe LEE

		Unadjusted		Adjusted	
		HR (95% CI)	p-value	HR (95% CI)	p-value
Pregnant		3.68 (2.40-5.64)	<0.001	3.57 (2.30-5.54)	<0.001
Age (per 10 year increase)		0.74 (0.60-0.91)	0.005	0.77 (0.61-0.98)	0.04
Route of exposure	Heterosexual sex	Reference	0.09	Reference	0.16
	IDU	1.70 (0.79-3.63)		1.16 (0.46-2.93)	
	Other/Not known	0.37 (0.12-1.16)		0.33 (0.10-1.06)	
Ethnicity	Black-African	Reference	0.60	Reference	0.58
	White	1.26 (0.84-1.90)		1.31 (0.84-2.04)	
	Black-Caribbean	0.86 (0.32-2.34)		0.84 (0.31-2.28)	
	Other/Not known	0.89 (0.53-1.48)		0.91 (0.54-1.53)	
Calendar year at baseline		1.04 (0.99-1.10)	0.13	1.06 (1.00-1.12)	0.05
HBV/HCV co-infection		1.64 (1.00-2.68)	0.05	1.55 (0.88-2.73)	0.13
LEE at baseline		1.19 (0.59-2.43)	0.63	-	
Latest CD4 count (cells/mm <sup>3</sup> )	≤250	Reference	0.14	Reference	
	251-350	0.61 (0.34-1.09)		0.51 (0.29-0.91)	0.02
	351-500	1.01 (0.63-1.62)		0.77 (0.48-1.24)	0.28
	>500	0.66 (0.39-1.12)		0.30 (0.30-0.84)	0.01
	Not known	0.65 (0.39-1.08)		0.57 (0.35-0.95)	0.03

Table 7.17 is continued on the next page.

Table 7.17 continued. Results from unadjusted and adjusted Cox proportional hazards regression analyses to identify factors associated with the incidence of severe LEE

		Unadjusted		Adjusted	
		HR (95% CI)	p-value	HR (95% CI)	p-value
CD4 count at ART start (cells/mm <sup>3</sup> )	≤250	Reference	0.97	-	
	251-350	1.11 (0.69-1.78)			
	351-500	1.19 (0.63-2.25)			
	>500	0.91 (0.40-2.10)			
	Not known	1.02 (0.69-1.51)			
Latest viral load (copies/ml)	≤50	Reference		-	
	>50	0.94 (0.60-1.47)	0.79		
Viral load at ART start (copies/ml)	≤100,000	Reference		-	
	>100,000	1.01 (0.67-1.51)	0.96		
ART drug in regimen	Zidovudine	0.84 (0.59-1.20)	0.33	-	
	Efavirenz	0.75 (0.53-1.07)	0.12	-	
	Nevirapine	0.91 (0.61-1.36)	0.63	-	
	Raltegravir	2.42 (0.78-7.60)	0.13	-	
Duration on ART (per 1 year increase)		0.92 (0.76-1.11)	0.38	-	
Duration on PI regimen		1.10 (0.98-1.24)	0.10	-	
Duration on NNRTI regimen		0.89 (0.80-1.00)	0.05	-	
Duration on NRTI regimen		0.95 (0.69-1.31)	0.75	-	

ALT: alanine transaminase; HBV: hepatitis B; HCV: hepatitis C; HR: hazard ratio; IDU: injecting drug use; IQR: interquartile range; LEE: liver enzyme elevation; NNRTI: non-nucleoside reverse transcriptase inhibitor; NK: not known; NRTI: nucleoside/nucleotide reverse transcriptase inhibitor; PI: protease inhibitor; ULN: upper limit of normal.

Adjusted by covariates in the table with adjusted HR presented.

## Sensitivity analyses

Pregnancy remained associated with an increased risk of LEE and severe LEE when the analyses included only the 982 women who had a pregnancy during follow-up. Pregnancy was independently associated with an increased risk of LEE (aHR 2.03 [1.52-2.72], p-value <0.001) and with an increased risk of severe LEE (aHR 5.97 [3.12-11.42], p-value <0.001). Overall, 271 (27.6%) women developed LEE and 49 (5.0%) women developed severe LEE.

The main findings were not changed when only the 3274 women who were not pregnant when they started ART were included. Pregnancy (as a time-updated variable) was independently associated with an increased risk of LEE (aHR 1.91 [1.28-2.84], p-value 0.001) and with an increased risk of severe LEE (aHR 4.37 [2.15-8.88], p-value <0.001).

Taking into account the fall in ALT which occurs during pregnancy did not change the main findings of the analysis. Pregnancy (as a time-dependent variable) was independently associated with an increased risk of LEE (aHR 2.01 [1.62-2.50], p-value <0.001) and with an increased risk of severe LEE (aHR 3.86 [2.44-6.12], p-value <0.001). Overall, 1095 (28.7%) women developed LEE and 152 (4.0%) women developed severe LEE.

The main findings were unaltered when women with no baseline ALT measurement were excluded. In the main analyses these women (n=1856) were categorised as having no evidence of LEE at baseline.

I undertook an additional analysis comparing the risk of LEE in pregnant women who conceived on ART (n=280) with the risk in non-pregnant controls on ART (n=474). For this I used a Cox proportional hazards model to calculate crude hazard ratios (aHRs). The pregnant women were similar to controls with regard to: calendar year; age; ethnicity; exposure group; previous pregnancy (dichotomised as yes/no); CD4 count category and type of ART regimen used. The full results of the analysis are not presented. In brief, where LEE was defined as ALT  $\geq$ 50 IU/L (40 IU/L x1.25) outside pregnancy and ALT  $\geq$ 40 IU/L (32 IU/L x1.25) in pregnancy, the risk of LEE was similar in both groups (hazard ratio (HR) 0.82 [0.54-1.25], p-value 0.36). The risk of severe LEE (defined as ALT >200 IU/L (40 IU/L x5) outside pregnancy and ALT >160 IU/L (32 IU/L x5) in pregnancy), was higher in the pregnant women than in the controls (HR 3.09 [1.03-9.21], p-value 0.04). The analysis was limited to the duration of pregnancy,

to women who conceived on ART and, despite using controls similar to the pregnant women, not all differences between the groups could be accounted for.

### **Treatment switches and interruptions among women with LEE**

Among women who developed LEE, 5.9% (64/1080) stopped/interrupted ART and 12.0% (n=130) switched regimen at a median of 44 (15-69) and 24 (9-50) days after LEE diagnosis respectively. The percentage who altered their regimen was 14.8% (122/826) among women with ALT 50-100 IU/L, 21.0% (34/162) among women with ALT 101-200 IU/L and 41.3% (38/92) among women with ALT >200 IU/L (global  $p < 0.001$ ).

Women who developed LEE in pregnancy were more likely to stop/interrupt their regimen or switch their regimen than women who were not pregnant when they developed LEE (stop/interrupt regimen: 23.9% [21/88] vs. 4.3% [43/992] respectively, odds ratio [OR] 6.92 [3.88-12.33],  $p < 0.001$ ; switch regimen: 21.6% [19/88] vs. 11.2% [111/992], respectively, OR 2.19 [1.27-3.78],  $p = 0.005$ ).

Among the 21 women who developed LEE in pregnancy and then stopped/interrupted ART, 20 stopped at delivery or postpartum and one interrupted ART during pregnancy. This woman conceived on an efavirenz-containing regimen, interrupted ART in the first trimester and started a ZDV-containing regimen in the second trimester. Among the 19 women who developed LEE in pregnancy and then switched regimen, 17 switched during pregnancy, in the first (n=4), second (n=7) or third trimester (n=6), and 2 switched postpartum.

Among women who developed severe LEE, 13.3% (20/151) stopped/interrupted ART and 25.2% (n=38) switched regimen within 90 days at a median of 41 (17-50) days and 23 (6-51) days, respectively, after the elevated ALT measurement. The difference in the percentage of women who altered their regimen among women who developed severe LEE in pregnancy and women who developed severe LEE whilst not pregnant was not statistically significant (stop/interrupt regimen: 22.2% [6/27] vs. 11.3% [14/124] respectively, OR 2.25 [0.78-5.41]; switch regimen: 25.9% [7/27] vs. 25.0% [31/124], respectively, OR 1.05 [0.41-2.72]).

## 7.4 Discussion

### **The availability of ALT data in UK CHIC**

The number of women included in each ALT analysis was limited by the fact that almost half the women in UK CHIC had no ALT data in the dataset. This was also true for one-quarter of women with a pregnancy. This meant that, for some analyses, there was insufficient statistical power to measure differences between groups due to small numbers.

White ethnicity, having hepatitis B or C, and acquiring HIV through sharing injecting drug equipment were all characteristics predictive of having any ALT data in the dataset and therefore predictive of inclusion in ALT analyses. These characteristics were also associated with having a higher ALT in the mixed effects regression model. This is a consequence of the UK CHIC study being an observational study; LFTs are performed as part of routine monitoring but they are also performed where indicated. Therefore, women at greater risk of, or with clinical indication for, hepatic dysfunction have more regular monitoring of ALT. An increase in the frequency of ALT monitoring is likely to increase the detection rate of raised ALT. Closer monitoring of higher risk groups is likely to result in an overestimation of the median ALT and in the incidence of LEE and severe LEE (in the final analysis) in groups which are monitored more closely. Increased monitoring in higher risk groups is the likely explanation for why women with a pregnancy during follow-up were less likely to have any ALT data compared to women without a pregnancy, since the characteristics associated with having a higher ALT (HBV/HCV co-infection, white ethnicity and HIV infection via IDU) are characteristics negatively associated with having a pregnancy among women living with HIV (Chapter 5).

During antenatal care, liver enzymes are closely monitored, even among women with a low risk of liver dysfunction, because a rise in some liver enzymes can indicate obstetric complications such as pre-eclampsia and obstetric cholestasis. In pregnancy, women typically have a minimum of three LFTs (at first antenatal visit, 20 weeks and 36 weeks gestation) compared to one every 6 months outside pregnancy (in women stable on treatment) [169]. This is probably why, among women with any ALT data, women who were pregnant had, on average, more ALT measurements than their non-pregnant counterparts (Table 7.6, Page 257).

### **Median ALT during pregnancy**

In preliminary analysis, where each ALT measurement was taken as an independent observation, the median ALT was 6 IU/L lower in pregnancy than at other times (15 vs. 21 IU/L). In the mixed effect regression model, pregnancy decreased ALT by 3.3 IU/L in the adjusted analysis, or 4.5 IU/L in crude analysis (Table 7.11, Page 264). These values are lower than the 8 IU/L difference between the upper limit of the reference ranges used in clinical practice inside and outside of pregnancy (ALT 32 IU/L vs. 40 IU/L, respectively) [339]. This would suggest that the creation of a reference range inside and outside of pregnancy specific to individuals living with HIV in the UK would be beneficial to clinicians and their patients.

The comparison of ALT levels in pregnant and non-pregnant women was achieved by developing a repeatable method which allowed non-pregnant controls to be found and selected at random from the dataset using SAS. The variables used to find controls could be specified according to the requirements of the analysis, and as such the strategy was later adapted for use in the analysis of postpartum viral rebound (Chapter 8).

Whilst small variations in median ALT were observed over time in the non-pregnant controls, there was an obvious drop in ALT during the first two trimesters of pregnancy, with ALT plateauing in the third trimester and returning to pre-pregnancy levels by 3-6 months after delivery (Figure 7.2, Page 258). A similar pattern was observed in pregnancy among women with HBV/HCV co-infection, who had, on average, higher ALT levels. This drop in ALT during pregnancy is thought to be a consequence of plasma volume expansion (PVE) rather than liver pathology [342, 348] and has previously been documented among HIV-negative pregnant women [339, 343, 346]. A change in CD4 count was also observed among women during pregnancy (Figure 7.4, Page 262), although to a lesser extent. This too has previously been reported [483]. Since the fall in ALT in pregnancy is thought to be a consequence of physiological rather than pathological changes it is unlikely to have any implications for the woman's health. However, ignoring changes in ALT which occur during normal pregnancy could mean that LEE and severe LEE are underestimated or overlooked in pregnancy. Clinicians should be mindful that a lower ALT threshold is more appropriate during pregnancy and further work is needed to examine normal changes in ALT during pregnancy among HIV-positive women.

### **Characteristics associated with ALT**

Women with a prior pregnancy had ALT levels, on average 1 IU/L lower than women who had not previously had a pregnancy. This small difference in ALT was statistically significant (p-value <0.001) but not clinically relevant. Women infected with HIV through sharing injecting drug equipment had a higher mean ALT than women infected via heterosexual sex, (whilst adjusting for HBV/HCV co-infection) perhaps due to undiagnosed HBV/HCV infection among women who had injected drugs.

### **ALT after delivery**

There was some evidence of a temporary peak in ALT, above pre-pregnancy levels, following delivery (Figure 7.5, Page 266). This post-partum overshoot in ALT, may be due to a temporary increase in serum ALT immediately after delivery, has been observed in other studies [343, 346, 349] and was also seen, to a lesser extent, in the postpartum CD4 count (Figure 7.4, Page 262). However, in women who conceived on ART (and remained on ART after delivery), ALT swiftly returned to pre-pregnancy levels with little or no peak in ALT after delivery (Figure 7.2, Page 258 and Figure 7.5, Page 266). This indicates that the temporary peak in ALT is not only a result of physiological changes occurring after delivery, since these would affect all postpartum women. The number of women with postpartum ALT data was small (only 174 women who conceived their index pregnancy whilst on ART had ALT data for 0-3 months postpartum). Further analysis with a larger sample size and where LFTs are performed according to a schedule is required to gain a clearer understanding of postpartum ALT changes and the clinical implications of such changes.

### **LEE in pregnancy**

When the proportion of women with ALT above the ULN, i.e. raised liver enzymes, was compared in pregnant women and non-pregnant controls, a smaller proportion of pregnant women had raised liver enzymes than non-pregnant women (Figure 7.3 Page 260 and Table 7.8, Page 259). This reflects the small drop in ALT during pregnancy previously discussed. When the Cox proportional hazards models were used, pregnancy was found to be independently associated with an increased risk of LEE and severe LEE. The overall rates of LEE and severe LEE in HIV-positive women on ART were 6.3/100 and 0.7/100 PY respectively. The rate of severe LEE was lower than in a study of pregnant and non-pregnant women in Côte d'Ivoire who started NVP-containing regimens (2.2 [1.1-4.0]/100 PY) [220], but Côte d'Ivoire is a very different setting from the UK. No other studies have reported LEE rates. In our study, LEE and

severe LEE developed during 11.6% and 3.3% of pregnancies during which ART had been initiated, lower than percentages reported among pregnant women starting NVP-containing regimens [316, 321] but similar to pregnant women starting nelfinavir-containing regimens [316] or when only a small proportion of women start NVP-containing regimens [318].

The initial period on ART is a time of increased toxicity risk. This was supported by the results here, where half of the 30% of women who developed LEE within 5 years did so within the first year. Therefore, it is to be expected that some of the women who were pregnant when starting ART would develop LEE. However, the results suggest that pregnancy itself confers an additional risk of 70% for LEE (a 1.7-fold increase in risk) and 260% (a 3.6-fold increase in risk) for severe LEE. The increase in risk was apparent both in women who had recently started ART and women who had been on treatment for more than six months (Table 7.15, Page 272).

Some previous cross-sectional studies also adjusting for factors associated with LEE, failed to observe an association between LEE and pregnancy [318, 320, 358]. These only assessed pregnancies during which ART was started and had a short follow-up. In my study and in a US study [317], which also observed an association between pregnancy and LEE, pregnancies conceived on ART were included. In my study women acted as their own controls by contributing data when pregnant and when not pregnant. Pregnancy remained associated with LEE and severe LEE in sensitivity analysis when women with no pregnancy during follow-up were excluded supporting the idea that it is being pregnant which increases the risk of LEE rather than any differences between women who had a pregnancy and women who did not.

In sensitivity analysis, when the fall in ALT due to PVE in pregnancy was taken into account, pregnancy remained associated with LEE and severe LEE. No previous studies assessing the association between pregnancy and LEE accounted for the fall in median ALT during pregnancy. Previous studies which did not observe an association between pregnancy and LEE may have had a different outcome if the ALT threshold for defining LEE differed according to pregnancy status [220, 318, 320, 358]. In studies which found an increased risk of LEE in pregnancy, but which ignored pregnancy status when defining LEE, the risk of LEE in pregnancy may have been underestimated [317].

### **Reasons for the increased risk of LEE in pregnancy**

The mechanism by which pregnancy could increase susceptibility to ART-induced hepatotoxicity is not clear and may differ by ART drug [326]. The biological mechanisms which increase susceptibility to liver dysfunction during pregnancy in other diseases, such as hepatitis E or hepatic vein thrombosis, including those unique to pregnancy, such as obstetric cholestasis, are diverse and poorly understood.

As ALT is a biomarker used to indicate hepatocellular injury, LEE does not equate to ART-induced hepatotoxicity. In pregnancy, LEE could be a result of obstetric complications. However, obstetric complications, such as pre-eclampsia, typically occur in late pregnancy, whereas in this study, LEE occurred in the first half of pregnancy among women already on ART. Also, the rate of LEE was higher than would be anticipated due to obstetric complications; a study of non-HIV-positive pregnant women observed liver dysfunction in 3% of pregnancies [336] which is thought to be similar in HIV-positive pregnant women [355].

### **Other factors associated with LEE**

HBV/HCV infection can lead to LEE and is associated with an increased risk of ART-induced hepatotoxicity [326]. In our setting, HBV/HCV co-infection increased the risk of LEE 1.9-fold and severe LEE 1.6 fold. The latter association was not statistically significant; probably due to insufficient statistical power, since only 18 women with HBV/HCV co-infection developed severe LEE.

There was a small but statistically significant increase in risk of LEE and severe LEE with increasing calendar year. This is unlikely to be due to changes in ALT monitoring since monitoring did not increase overall or in women starting treatment. It could be due to changes in variables not measured by UK CHIC but known to affect ALT such as BMI, alcohol consumption, co-medication or use of illicit drugs [313].

To minimize hepatotoxicity risk, NVP-containing regimens are not recommended for individuals starting ART with CD4 >250 cells/mm<sup>3</sup> [84]. In our study, where one-fifth of women were receiving an NVP-containing regimen, higher CD4 count category, as a time-dependent variable, was associated with a lower risk of LEE and severe LEE, which counters the evidence that starting ART with CD4 count >250 cells/mm<sup>3</sup> increases the risk of NVP-induced hepatotoxicity [240, 320], although other studies have not found such an association [239, 358].

## **Treatment switches and interruptions after LEE**

As anticipated, the proportion of women who altered their ART regimen following LEE was higher the more severe the elevation was. It is not surprising that women who experienced LEE in pregnancy were more likely to stop/interrupt treatment than women who experienced LEE outside pregnancy, since many of the pregnant women would have planned to stop ART at delivery irrespective of LEE. The woman who interrupted ART during pregnancy probably did so to avoid using efavirenz [477]. Switching regimens can cause disruption and increased the risk of viral rebound and therefore vertical transmission. It is concerning that pregnant women with LEE had twice the odds of switching regimen compared to women with LEE outside pregnancy.

## **Limitations**

No data were collected by either study on body mass index (BMI) or body fat distribution, variables which are strongly predictive of ALT levels [484]. This was also true for alcohol consumption, the use of hormonal contraceptives, other medications (other than ART) or illicit/recreational drug use. These variables are important confounders when studying toxicity and should be included in any future studies assessing ALT levels in pregnancy.

The characteristics of women more closely monitored were negatively associated with having a pregnancy, so if anything, this would increase the detection rate of LEE in non-pregnant women. On the other hand, there may be an increased detection rate of LEE in pregnancy due to more regular monitoring of liver enzymes. This was not the case for women who recently started ART - the median number of ALT measurements was the same in and outside pregnancy. This is because all women starting ART are recommended to have LFTs performed at 2-4 weeks and 3 months after starting ART, irrespective of pregnancy status (women starting an NVP-containing regimen are recommended more regular LFTs; every fortnight during the first 2 months and then at 3 months after starting ART) [84].

For the analysis of median ALT in women who conceived on ART and in women who started ART in pregnancy (Table 7.12, Page 267 and Figure 7.5, Page 266) it was important to categorise the reason for ART use in pregnancy (i.e. PMTCT or mother's health). This categorisation is not straightforward and in an attempt to simplify the method described in Chapter 4 a 20 week cut-off was used reflecting treatment guidelines at the time [169]. ART use was categorised as starting life-long ART for the woman's health if it was started at <20 weeks gestation or as short-course ART for

PMTCT if it was started at  $\geq 20$  weeks gestation. However, examining ART use among the women who were categorised into each group showed that using this cut-off was somewhat flawed. One-fifth of women categorised as starting life-long ART, actually stopped ART in the first three months after delivery and more than half the women thought to have used short-course ART remained on ART for at least 3 months after delivery. In some cases there was also a discrepancy in the timing of ART use in the NSHPC and UK CHIC data.

### **The clinical consequences of LEE in pregnancy**

The clinical consequences of LEE are not clear; few women developed severe LEE (2% of pregnancies and 0.7% of women) and none experienced liver failure. Women experiencing LEE may have symptoms including rash, nausea, vomiting, pain or diarrhoea or have no symptoms. Due to the risk of viral rebound, treatment changes are not recommended where toxicity is mild but there is currently no agreement on how to manage pregnant women who develop LEE whilst on ART. Close monitoring of liver biomarkers and any symptoms of toxicity, including rashes is important during antenatal care [168]. Particularly with severe LEE, further tests are required since LEE could indicate obstetric complications. Clearer guidance is required for clinicians caring for pregnant women on ART as to the best course of action when LEE occurs.

### **Key points from this chapter**

- Approximately half the women in the UK CHIC study had some ALT data reported for the period 2000-2011.
- Factors predicative of women having ALT data in UK CHIC were dissimilar to those predictive of having a pregnancy. Even after accounting for these differences, women who had a pregnancy were less likely to have any ALT data in UK CHIC compared to women who did not have a pregnancy.
- Within the study population, the median ALT fell by 3-5 IU/L during pregnancy, returning to the pre-pregnancy level within a few months of delivery. This fall occurred in the first two trimesters.
- The risk of LEE and severe LEE was raised in pregnancies conceived on ART and in pregnancies during which ART was started even when the temporary drop in ALT during pregnancy was taken into account.
- Pregnant women who experienced LEE had two times the odds of switching regimen than women who experienced LEE outside pregnancy.

# Chapter 8 Post-pregnancy viral rebound in women on suppressive antiretroviral therapy at delivery

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## 8.1 Introduction

Viral rebound generally occurs rapidly following cessation of antiretroviral therapy (ART) including discontinuation of short-course ART after delivery [132, 197, 381, 382]. Postpartum increases in viral load have also been observed in women who remain on ART, even when viral suppression was achieved in pregnancy [374, 376, 382].

In this chapter I assess the risk of viral rebound following pregnancy in women who are virally suppressed at delivery by comparing the risk of viral rebound in post-pregnant women with the risk in non-pregnant women who have not recently had a pregnancy (controls). One of my initial intentions was to assess viral rebound immediately after delivery. However, if women did experience a short-term peak in viral load immediately after pregnancy it was unlikely to be captured in the data, since the median time to first viral load assessment was 49 days after delivery. Therefore, since the availability of viral load data in the first 3 months postpartum was insufficient for such an analysis, the analysis was revised to consider the risk of viral rebound in the 12 months after pregnancy. The findings from this chapter were published in 2015 (Appendix IIe) [415].

## 8.2 Methods

The aims of this chapter were:

- 1) To assess the availability of HIV-RNA data during pregnancy and post-pregnancy in women in UK CHIC and in the UK CHIC-NSHPC combined dataset.
- 2) To identify factors associated with viral rebound in the post-pregnancy year in women virally suppressed at delivery.
- 3) To compare the risk of viral rebound during the post-pregnancy year with the risk at other times outside pregnancy, stratified by when ART was started.

### 8.2.1 Assessing the availability of viral load data

The dataset contained UK CHIC data for all women reported to UK CHIC and NSHPC data for those with a pregnancy. Data to 31<sup>st</sup> December 2012 were analysed.

Both studies collect viral load data. The NSHPC aims to collect two viral load measurements per pregnancy, the first measurement taken during pregnancy and the second measurement '*near delivery – just before delivery if possible*' (Appendix IIIa and Appendix IIIb). UK CHIC collects date and outcome of all viral load measurements performed as part of HIV clinical care (Appendix IV). Viral load data from both studies were examined. When assessing the number of viral load measurements for a given period, if a viral load measurement was reported to both studies on the same day it was only counted once.

### 8.2.2 Identifying factors associated with viral rebound in the post-pregnancy year

#### **Inclusion criteria**

Pregnancies in women aged 16 and older, resulting in a live birth in 2006-2011 were included in the analysis, allowing at least one year of post-pregnancy follow-up. Women with repeat pregnancies during this period were included in the analysis multiple times. If, during the 12 months following delivery, a woman became pregnant again, the data were censored on the estimated date of conception (EDC) of the second pregnancy. Pregnancies were only included in the analysis if at least one viral load measurement was available in the UK CHIC data in the post-pregnancy year, indicating that the woman had received HIV-clinical care at a UK CHIC site during that period.

Since the outcomes might differ according to the type of pregnancy (i.e. index or non-index), in sensitivity analysis, only a woman's first pregnancy meeting the criteria was included. In a second sensitivity analysis, only a woman's last pregnancy meeting the criteria was included.

## **Categorising the type of ART used in pregnancy**

The NSHPC and UK CHIC data were used to assess whether each woman was on ART at conception, during pregnancy, at delivery and in the six months following pregnancy. Data relating to ART use in UK CHIC were compared with data in the NSHPC. This comparison is included in the results section. There were some discrepancies between whether women were on ART or not according to UK CHIC and the NSHPC (82 pregnancies had a discrepancy at conception and 53 at delivery). Where there was a discrepancy, a woman was categorised as being on ART if data from only one study indicated that she was on ART but the other did not.

The type of ART use was categorised according to ART use at conception, delivery and 6 months post-pregnancy and was categorised as follows:

- Continuing use of life-long ART – the woman conceived on ART and was still on ART 6 months after delivery.
- Short-course ART for the prevention of mother-to-child-transmission (PMTCT) – the woman started ART during her pregnancy and stopped (for at least 30 days) within 6 months of delivery.
- Starting life-long ART in pregnancy – the woman did not conceive on ART, but started ART during pregnancy and was still on ART 6 months after delivery.

This strategy was used rather than the more complex strategy described in Chapter 4 or the simplified strategy of using 20 weeks gestation as a cut-off to indicate life-long or short-course ART use, as was used in Chapter 7. The method used in Chapter 7 was not used here because although women starting ART in the second half of pregnancy could be assumed to be starting short-course ART, closer examination of the data showed that this was not always the case. The NSHPC also captures data on the reason for ART use in pregnancy (i.e. for PMTCT only or for the mother's health), a variable which is underreported. Where it was reported, the results were compared with the ART categorisation using the ART data in UK CHIC and the NSHPC.

## **Statistical analysis**

Kaplan-Meier analyses were used to assess the cumulative probability of viral rebound within 12 months of delivery. Due to the limited number of viral load measurements in this period, viral rebound was defined as a single measure of HIV-RNA >200 copies/ml. The analysis started on the first day after delivery. Follow-up was censored if the woman died, became pregnant again or at 12 months after delivery, whichever

occurred first. Cox proportional hazards models were used to calculate the crude and adjusted hazard ratios viral rebound (aHRs) of viral rebound (SAS command PROC PHREG). In unadjusted analysis the baseline characteristics assessed included: CD4 at conception and delivery, type of ART regimen and type of ART use (as described above). Other variables assessed included age, hepatitis B virus (HBV)/hepatitis C virus (HCV) infection, ethnicity and exposure group. All variables were included in the adjusted model.

In a secondary analysis, Kaplan-Meier analysis was used to assess the cumulative probability of viral rebound only when ART was being used. For this analysis, follow-up was also censored at the point that ART was interrupted.

### 8.2.3 Comparing the risk of viral rebound in post-pregnant women and controls

The risk of viral rebound in the post-pregnancy year was compared with the risk at other times outside pregnancy among women on ART. This was done by comparing the risk of viral rebound in post-pregnant women (women with a pregnancy in the previous year) with the risk in controls (women who had not been pregnant in the previous year). Post-pregnant women were stratified by when they had started life-long ART (before or during the pregnancy) and controls were selected who had been on ART for a similar duration.

#### **Selecting cases**

Women were included in the analysis if they had a pregnancy resulting in a live birth in 2006-2011, an HIV-RNA  $\leq 50$  copies/ml at latest viral load  $\leq 3$  months before delivery and they remained on cART (use of  $\geq 3$  ART drugs) for  $\geq 6$  months after delivery. Women with at least one viral load measurement in the year after delivery were included and only a woman's earliest pregnancy meeting the criteria was included.

## **Analysis-specific criteria for selecting controls**

The criteria used to select suitable controls were:

Analysis 1: Women continuing on life-long ART throughout pregnancy and after delivery:

Pregnant women and controls were matched using age (year), calendar year and the number of years since starting their most recent period of ART use.

Analysis 2: Women starting life-long ART in pregnancy:

Pregnant women and controls were matched using age (grouped as: 16-19; 20-24; 25-29; 30-34; 35-39; 40-44; 45-49 years), two year calendar period (grouped as: 2006-2007; 2008-2009; 2010-2011), number of months since starting treatment (grouped as: 0 -<3; 3-<6; 6-<9 months) and CD4 count when starting treatment (grouped as:  $\leq 200$ ; 201-350; 351-500;  $> 500$  cells/ $\mu$ l).

For Analysis 2, age and year intervals were used rather than the exact age or year. This was to maximise the number of controls available for this analysis, where controls must recently have started life-long ART.

Differences in other characteristics were accounted for in adjusted analyses.

## **Selecting controls**

Two controls were sought for each post-pregnant woman using a strategy adapted from that described in Chapter 7.

Analysis 1: In order to find controls for women who were already on life-long ART when they conceived, the period 2006-2011 was split into 3 month intervals creating 24 reference dates. The same woman could be used as a control multiple times, but only for non-overlapping periods of time.

Analysis 2: In order to find controls for women who started life-long ART during their pregnancy, the period 2006-2011 was split into 1 month intervals creating 72 reference dates. Women could only be used as a control once, since women could only be used as a control when they had recently started treatment.

On each of the reference dates the characteristics of each woman in UK CHIC were assessed. The characteristics that were considered were: previous and current

pregnancy status; latest CD4 count (in the previous 6 months); latest viral load (in the previous 6 months); as well as the variables used for selecting controls. Women were only eligible to act as a control when they were not pregnant and had not been pregnant in the previous year. The pregnancy status in the subsequent year was not considered. Women acting as a control also had to have undetectable viral load (HIV-RNA  $\leq 50$  copies/ml) at their latest viral load measurement, remain on ART for at least 6 months, and have at least one viral load measurement in the year following the reference date, indicating that they attended HIV-clinical care. For controls, the reference date was used as the pseudo delivery date.

### **Statistical analysis**

Initially, the number of viral load measurements in the 12 month follow-up was assessed. Characteristics of post-pregnancy women and controls were compared using the Chi-squared test for categorical variables and Kruskal-Wallis test for continuous (non-Normally distributed) variables.

The primary outcome was viral rebound (defined as a single measure of HIV-RNA  $>200$  copies/ml) within 12 months of the delivery (post-pregnant women) or pseudo-delivery (controls). In sensitivity analysis, viral rebound was defined as a single measure of HIV-RNA  $>1000$  copies/ml. Kaplan-Meier analysis was used to assess the cumulative probability of viral rebound and Cox proportional hazards models to calculate crude and adjusted hazard ratios (HRs). As the Kaplan-Meier analyses suggested that hazards were likely to diverge after 3 months, separate models are presented for the periods  $<3$  months and 3-12 months post-delivery/pseudo-delivery, with the latter model including only women who had not experienced viral rebound and whose follow-up had not been censored during the first three month period. In unadjusted analyses, the baseline characteristics assessed were: post-pregnancy status (post-pregnancy/control), CD4 count category, type, duration and number of drugs in the ART regimen (where ritonavir was not counted as an additional drug when it was used to boost a protease inhibitor (PI) regimen), parity (the number of live births since HIV diagnosis), HBV/HCV co-infection, ethnicity and exposure group. Follow-up was censored at 12 months post-delivery/pseudo-delivery, if a woman died, interrupted ART, or became pregnant again, whichever occurred first.

## 8.3 Results

### 8.3.1 Availability of viral load data

#### **Availability of viral load data among women in UK CHIC**

There were a total of 247,496 viral load measurements in the UK CHIC 2012 dataset for the period 2000-2012 (women only). Of the women who attended HIV care during that period, 96% (12,001/12,458) had  $\geq 1$  viral load measurement during that time. For women with  $\geq 1$  viral load measurement, the median number of measurements per woman was 15 (interquartile range [IQR] 5-30, range 1-118) and the median interval between measurements was 3.0 (IQR 1.8-4.1) months.

#### **Availability of viral load data in pregnancy**

In the UK CHIC-NSHPC 2012 combined dataset, there were 4100 pregnancies resulting in a live birth in 2000-2012 among 2889 women; 1910 women had a single pregnancy and 979 had two or more (up to five) pregnancies. The majority of these pregnancies (98%, n=4028) had  $\geq 1$  viral load measurement during the pregnancy in either the NSHPC or UK CHIC; 95% (n=3911) had  $\geq 1$  measurement reported to the NSHPC and 86% (n=3534) had  $\geq 1$  measurement in the UK CHIC dataset. The median number of viral load measurements in pregnancy was 4 (IQR 3-6) among women with  $\geq 1$  viral load measurement (Table 8.1). The percentage of pregnancies with a viral load measurement from the third trimester was high (89%, n=3638 overall). This is of interest because the latest viral load measurement from the third trimester was used in later analyses to assess whether women had undetectable viral load at delivery.

The period of time prior to pregnancy of the same duration as the pregnancy was examined (the median duration of pregnancy being 37 (IQR 36-38) weeks). For pregnancies in which at least one viral load measurement was performed (and reported), just over half (55% 1953/3534) had at least one viral load measurement performed in the period before the pregnancy. In other words, these women attended HIV clinical care before and during pregnancy. When only women who were already diagnosed with HIV prior to their pregnancy were included, 80% [1935/2428] had at least one viral load measurement performed in the (roughly) nine months prior to the pregnancy. In pregnancies during which at least one viral load measurement was performed, 83% (n=3534) had at least one viral load measurement during the same duration of time after the pregnancy. Among pregnancies in which at least one viral

load measurement was available, the median number of viral load measurements was 2 (IQR 2-3), 4 (3-6) and 2 (1-3), in the periods (of the same duration) before, during and after pregnancy.

### **Availability of post-pregnancy viral load data**

Viral load measurements reported to UK CHIC and the NSHPC were examined in the 12 months post-pregnancy. Although many of the viral load measurements reported to the NSHPC were also found in the UK CHIC dataset, the percentage of women with  $\geq 1$  viral load measurement in the 12 months post-pregnancy was slightly higher when data from both datasets were considered than when only UK CHIC data was considered (UK CHIC-NSHPC dataset: 80% vs. UK CHIC: 78%) (Table 8.1).

Overall, 15% (n=625) of women had a viral load measurement in the first month post-pregnancy. The percentage of women with  $\geq 1$  viral load measurement by 3, 6, 9 and 12 months post-pregnancy was 58%, 72%, 77% and 80% respectively, with most of this data coming from UK CHIC (Table 8.1).

Among women with  $\geq 1$  viral load measurement within 6 months of delivery, the median time between delivery and the first viral load measurement was 50 (IQR 35-81) days in UK CHIC, 18 (2-54) days in the NSHPC and 49 (33-79) days if data from both studies were considered.

For this preliminary analysis, the pregnancy status of women was not considered when assessing post-pregnancy viral load data. However, it is likely that a small number of viral load measurements performed in the 12 months post-pregnancy were obtained during a subsequent pregnancy.

Table 8.1. Availability of viral load data during and after pregnancy in the NSHPC, UK CHIC and the combined dataset (n=4100 pregnancies)

Period of interest	UK CHIC				NSHPC				Combined dataset			
	≥1 VL measurement (%)		Median VL [IQR]		≥1 VL measurement (%)		Median VL [IQR]		≥1 VL measurement (%)		Median VL [IQR]	
			All	≥1 VL <sup>1</sup>			All	≥1 VL <sup>1</sup>			All	≥1 VL <sup>1</sup>
<b>In pregnancy</b>												
Pregnancy	3534	(86.2)	4 [2-5]	4 [3-6]	3911	(95.4)	2 [1-2]	2 [1-2]	4028	(98.2)	4 [3-6]	4 [3-6]
1 <sup>st</sup> trimester	2201	(53.7)	1 [0-1]	1 [1-2]	1706	(41.6)	0 [0-1]	1 [1-1]	2481	(60.5)	1 [0-1]	1 [1-2]
2 <sup>nd</sup> trimester	3064	(74.7)	1 [0-2]	2 [1-3]	1634	(39.9)	0 [0-1]	1 [1-1]	3369	(82.2)	2 [1-3]	2 [1-3]
3 <sup>rd</sup> trimester	2984	(72.8)	1 [0-2]	2 [1-3]	3205	(78.2)	1 [1-1]	1 [1-1]	3638	(88.7)	2 [1-2]	2 [1-3]
<b>After pregnancy</b>												
0-1 month post-pregnancy	546	(13.3)	0 [0-0]	1 [1-1]	193	(4.7)	0 [0-0]	1 [1-1]	625	(15.2)	0 [0-0]	1 [1-1]
0-3 months post-pregnancy	2290	(55.8)	1 [0-1]	1 [1-1]	266	(6.5)	0 [0-0]	1 [1-1]	2364	(57.7)	1 [0-1]	1 [1-1]
0-6 months post-pregnancy	2892	(70.5)	1 [0-2]	2 [1-2]	324	(7.9)	0 [0-0]	1 [1-1]	2963	(72.3)	1 [0-2]	2 [1-2]
0-9 months post-pregnancy	3086	(75.3)	2 [1-3]	2 [2-3]	420	(10.2)	0 [0-0]	1 [1-1]	3161	(77.1)	2 [1-3]	3 [2-4]
0-12 months post-pregnancy	3189	(77.8)	2 [1-4]	3 [2-4]	534	(13.0)	0 [0-0]	1 [1-1]	3275	(79.9)	2 [1-3]	3 [2-4]

<sup>1</sup> Refers to the median number of viral load (VL) measurements among women with at least one VL measurement during the period of interest.

If a VL measurement is reported to UK CHIC and the NSHPC (with the same date) it is only counted as 1 VL measurement in the combined dataset.

### 8.3.2 Identifying factors associated with viral rebound in the 12 months post-pregnancy

#### **Overall number of pregnancies**

In the period 2006-2011, there were 1512 deliveries among 1301 women that resulted in a live birth; 1108 women had one delivery, 176 women had two and 17 women had three or four such deliveries during this period. An additional 756 pregnancies were not included in the analysis for the following reasons: the woman did not attend a UK CHIC site in the year following delivery (n=431); the latest viral load measurement in pregnancy was detectable (n=309); no viral load data were available in the third trimester (n=9); it was not clear whether viral load was detectable or undetectable at delivery due to discrepant data in the NSHPC and UK CHIC (n=7).

#### **Categorising ART use**

At conception more than half of the women were already on ART (57%) (Table 8.2). Of the 645 women not on ART, 40% started ART during the first 20 weeks of pregnancy and 59% during or after 20 weeks gestation. Three women had no evidence of ART use during pregnancy and one woman was reported as using ART but with no further information available. The ART data indicated that 15 women were not on ART at delivery, although this could be a consequence of inaccurate reporting/estimation of the delivery date.

For the pregnancies included in the analysis, 802 women were categorised as being on life-long ART, 179 as using short-course ART in pregnancy and 424 as starting life-long ART during the pregnancy. There were a further 107 pregnancies which did not fit within these three categories of ART use and were therefore categorised as 'other'; 15 were not on ART at delivery; 52 interrupted treatment after delivery despite conceiving on ART; and 40 had no post-pregnancy ART data (Table 8.2).

Overall, for the women included in the analysis, the NSHPC reported variable 'reason for ART use in pregnancy' categorised 51% (n=768) as using ART in pregnancy for maternal health, 24% (n=356) as using ART for PMTCT and 26% (n=388) had no reason reported. There were some discrepancies between the categorisation of ART use according to the reported variable in NSHPC and according to the ART data from both studies. Among the 802 women categorised as already on life-long ART according to the ART data, 5% (n=40) were reported to the NSHPC as using ART for PMTCT.

Among women categorised as using short-course ART according to the ART data, 15% (n=27) were reported to the NSHPC as using ART for maternal health. Among women categorised as starting life-long therapy according to the ART data, 43% (n=183) were reported as using ART for PMTCT, 31% (130) were reported as using ART for maternal health, and no reason was reported for the remaining 26% (n=111) (26%).

Table 8.2. Summary of ART use at conception, during pregnancy, at delivery and during the first 6 months after delivery (n=1512 pregnancies)

On ART at conception n (%)		Start ART during pregnancy n (%)		ART use at delivery n		Post-pregnancy ART use <sup>1</sup> n (%)		
Yes	867 (57.3%)	-	-	No	7	-		
				Yes	860	Stop 0-3 m	29	(3.4)
						Stop 3-6 m	23	(2.7)
						Continue >6 m	802	(93.3)
				NK	6	(0.7)		
No	645 (42.7%)	At <20 weeks	259 (40.2%)	No	1	-		
				Yes	258	Stop 0-3 m	40	(15.5)
						Stop 3-6 m	6	(2.3)
						Continue >6 m	202	(78.3)
						NK	10	(3.9)
		At ≥20 weeks	382 (59.2%)	No	3	-		
				Yes	379	Stop 0-3 m	119	(31.4)
						Stop 3-6 m	14	(3.7)
						Continue >6 m	222	(58.6)
						NK	24	(6.3)
No/NK	4 (0.6%)	No	4	-				

<sup>1</sup> m refers to months after delivery. NK: not known.

### Baseline characteristics

The characteristics of women included in the analysis at delivery are presented in Table 8.3. In brief, median age at delivery was 33 years, 76% of women were of black-African ethnicity and 97% had acquired HIV via heterosexual sex. This was the first pregnancy since HIV-diagnosis for 59% of the women and 21% of women were diagnosed during the pregnancy. At delivery, median CD4 count was 450 cells/μl and 61% of women were on a PI-based regimen. The deliveries were evenly distributed across the study period (2006-2011).

Table 8.3. Characteristics of women at the time of delivery in 2006-2011 stratified by ART use in pregnancy

		All		On life-long ART		Short-course ART		Start life-long ART	
		n	%	n	%	n	%	n	%
Total number		1512		802		179		424	
Year of delivery	2006-2007	497	32.9	222	27.7	101	56.4	139	32.8
	2008-2009	499	33.0	268	33.4	54	30.2	138	32.6
	2010-2011	516	34.1	312	38.9	24	13.4	147	34.7
Age	16-29 years	461	30.5	160	20.0	83	46.4	174	41.0
	30-34 years	527	34.9	272	33.9	65	36.3	154	36.3
	35-39 years	398	26.3	280	34.9	23	12.9	76	17.9
	40-49 years	126	8.3	90	11.2	8	4.5	20	4.7
	Median [IQR] years	33	[28-36]	34	[31-37]	30	[25-33]	31	[27-34]
Ethnicity	Black African	1152	76.2	624	77.8	129	72.1	318	75.0
	White	154	10.2	78	9.7	20	11.2	46	10.9
	Black Caribbean	55	3.6	17	2.1	11	6.2	20	4.7
	Other/NK	151	10.0	83	10.4	19	10.6	40	9.4
Exposure category	Heterosexual sex	1472	97.4	781	97.4	179	100	408	96.2
	Injecting drug use	12	0.8	8	1.0	0	-	4	0.9
	Other/NK	28	1.9	13	1.6	0	-	12	2.8
Previous deliveries	0	884	58.5	377	47.0	131	73.2	320	75.5
	1	442	29.2	281	35.0	38	21.2	90	21.2
	≥2	186	12.3	144	18.0	10	5.6	14	3.3
HBV/HCV co-infection		77	5.1	43	5.4	12	6.7	15	3.5
CD4 count (cells/μl) (n=1494, n=789, n=178)	≤200	186	12.3	93	11.8	13	7.3	76	18.0
	201-350	264	17.5	142	18.0	32	18.0	75	17.8
	351-500	460	30.4	255	32.3	60	33.7	109	25.8
	>500	584	38.6	299	37.9	73	41.0	162	38.4
	Median [IQR]	450	[330-590]	450	[330-580]	472	[350-590]	430	[290-610]

Table 8.3 continued

		All		On life-long ART		Short-course ART		Start life-long ART	
		n	%	n	%	n	%	n	%
HIV diagnosed during this pregnancy		322	21.3	0	-	92	51.4	207	48.8
Pregnancy duration	Median [IQR] (weeks)	37	[36-38]	37	[36-38]	37	[36-38]	37	[36-38]
Type of ART regimen	No ART	15	1.0	-	-	-	-	-	-
	PI	916	60.5	391	48.8	155	86.6	315	74.3
	NRTI	63	4.2	18	2.2	11	6.2	64	15.1
	NNRTI	483	31.9	378	47.1	9	5.0	29	6.8
	Other	35	2.3	15	1.9	4	2.2	16	3.8
Number of drugs in regimen	0	15	1.0	-	-	-	-	-	-
	1-2	48	3.2	15	1.9	8	4.5	18	4.3
	3	1356	89.7	718	89.5	164	91.6	392	92.5
	≥4	93	6.2	69	8.6	7	3.9	14	3.3

NNRTI: non-nucleoside reverse-transcriptase inhibitor; NRTI: nucleoside reverse-transcriptase inhibitor; PI: protease inhibitor. There were an additional 107 pregnancies with ART use categorised as 'other'. These are included in the total column (All) but not as a separate column.

The median follow-up time was 12 (IQR 12-12) months, with a median number of viral load measurements of 3 (IQR 2-4). There were 131 (9%) women who became pregnant again within a year of delivery.

Two women died, both within 3 months of delivery. The causes of the death were not reported. Three infants (0.2%) were known to have become infected with HIV.

### **Number of women experiencing viral rebound**

Overall, one-third (33%, n=497) of women experienced viral rebound in the year following pregnancy. The cumulative incidence of viral rebound at 3 months post-pregnancy was 19% (95% CI 17%-21%); by 6 months post-pregnancy this had increased to 27% (25%-29%). The median time to viral rebound was 2.6 (IQR 1.5-4.8) months after delivery. The cumulative incidence of viral rebound at 3 and 6 months post-pregnancy was: for women already on life-long ART, 4.3% (2.9%-5.7%) and 6.6% (4.8%-8.3%); for women who started life-long ART, 32% (27%-36%) and 42% (37%-47%); and for women who used short-course ART in pregnancy, 50% (43%-58%) and 76% (73%-83%) (Figure 8.1a).

A similar pattern was observed when follow-up was censored if/when ART was stopped or interrupted (Figure 8.1b). Censoring data in this way meant that follow-up on all women who used short-course ART was censored by 5 months post-pregnancy (the red line). Women who started life-long ART during pregnancy had a lower cumulative probability of viral rebound when follow-up was censored at any ART interruption than when follow-up was not censored in this way.

### **The availability of post-pregnancy viral load data**

The availability of viral load data and the percentage of women with detectable viral load were assessed for each post-pregnancy month (Table 8.4). For each group, the first month after pregnancy had the fewest women with any HIV-RNA measurement and the second month had the highest.

Figure 8.1a. Kaplan-Meier plot showing cumulative probability of viral rebound in the year after pregnancy stratified by type of ART used in pregnancy

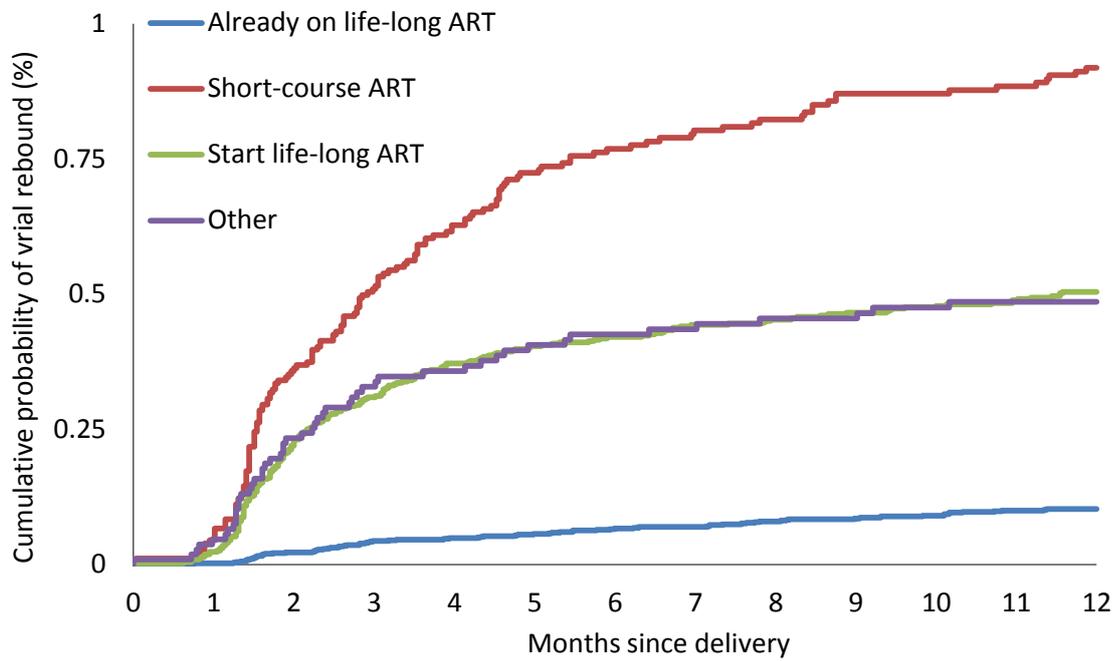


Figure 8.1b. Where follow-up was censored if ART was stopped

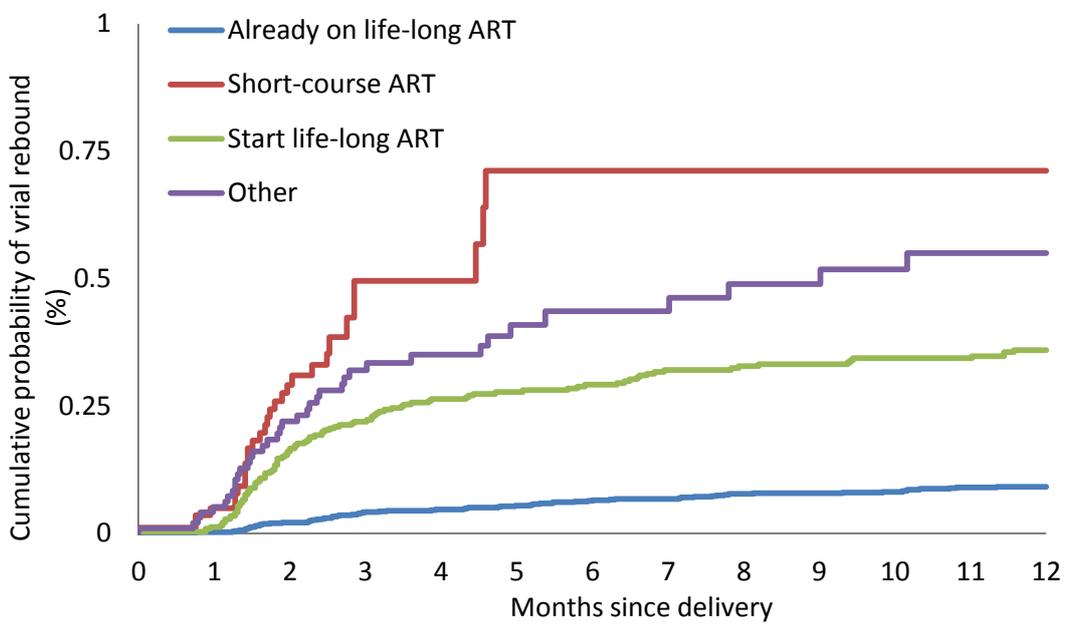
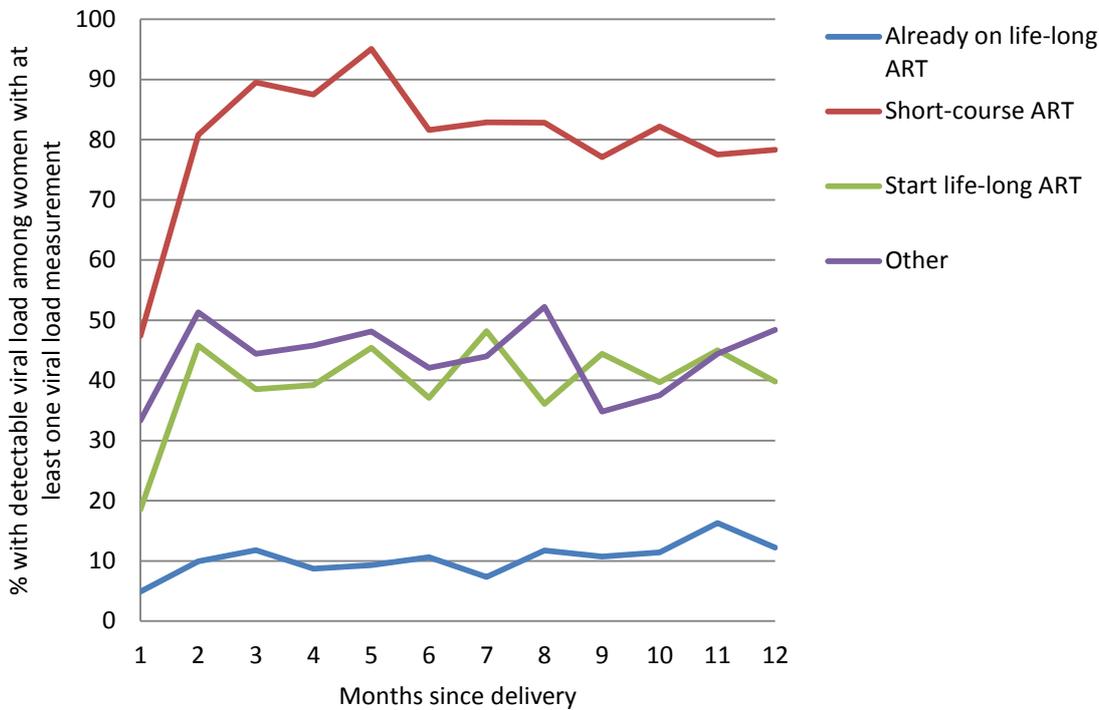


Table 8.4. Percentage of women with detectable viral load among women with  $\geq 1$  viral load measurement during each month in the year following delivery according to type of ART use

Type of ART use in pregnancy		Months since delivery											
		1	2	3	4	5	6	7	8	9	10	11	12
Already on life-long ART	% with VL data	10.1	40.4	26.4	22.8	25.6	25.8	23.8	25.6	22.2	27.3	23.7	21.4
	% with detectable VL <sup>1</sup>	4.9	9.9	11.8	8.7	9.3	10.6	7.3	11.7	10.7	11.4	16.3	12.2
Short-course ART	% with VL data	10.6	43.6	21.2	22.3	22.9	21.2	22.9	16.2	26.8	25.1	22.3	25.7
	% with detectable VL <sup>1</sup>	47.4	80.8	89.5	87.5	95.1	81.6	82.9	82.8	77.1	82.2	77.5	78.3
Start life-long ART	% with VL data	12.7	50.5	28.8	22.9	22.9	21.0	19.6	19.6	23.3	18.4	18.9	21.9
	% with detectable VL <sup>1</sup>	18.5	45.8	38.5	39.2	45.4	37.1	48.2	36.1	44.4	39.7	45.0	39.8
Other	% with VL data	14.0	36.4	25.2	22.4	25.2	17.8	23.4	21.5	21.5	29.9	16.8	29.0
	% with detectable VL <sup>1</sup>	33.3	51.3	44.4	45.8	48.1	42.1	44.0	52.2	34.8	37.5	44.4	48.4

VL: viral load; <sup>1</sup> % with detectable VL (HIV RNA >50 copies/ml) of women with VL data i.e. women with  $\geq 1$  viral load measurement during that month.

Figure 8.2. Percentage of women with detectable viral load among women with at least one viral load measurement during each month in the year following delivery according to ART use category



### Factors associated with viral rebound

In adjusted analysis including all the variables in Table 8.5, women who had used short-course ART in pregnancy had 16 times the risk of viral rebound in the year following pregnancy compared to women who were on life-long ART when they conceived. Women who did not conceive on ART but who started life-long ART during pregnancy had 7 times the risk of experiencing viral rebound in the year following pregnancy compared to women who had conceived on ART. Women in the group categorised as ‘other’ (aHR 6.2) also had a higher risk of viral rebound in the year following pregnancy than women who conceived and remained on ART.

In the year after pregnancy, age and calendar year were both associated with risk of viral rebound. The risk decreased with increasing age (aHR 0.75 per 10 year increase in age) and over time (aHR 0.95 per additional year). Women with at least one pregnancy (since HIV-diagnosis) prior to the pregnancy being considered had a higher risk of viral rebound (aHR 1.2) than women with no pregnancy prior to the one being considered in this analysis. Women with a higher CD4 count also had a higher risk of

viral rebound compared to women with a CD4 count  $\leq 250$  cells/ $\mu$ l (aHR 2.17 for women with a CD4 count  $> 500$  cells/ $\mu$ l) (Table 8.5).

Women with HBV/HCV co-infection had less risk of viral rebound (aHR 0.61) compared to women without hepatitis (26% [20/77] of women with HBV/HCV co-infection experienced viral rebound compared to 33% [477/1435] of women without co-infection).

### **Sensitivity analysis**

In sensitivity analysis, only a woman's first pregnancy meeting the inclusion criteria during the period of interest was included in the analysis (1301 pregnancies). The results were similar to the results of the primary analysis. Women who used short-course ART were at increased risk of viral rebound (aHR 16.2 [11.8-22.4],  $p < 0.001$ ) compared to women on life-long ART when they conceived, as were women who started life-long ART in pregnancy (aHR 7.0 [5.2-9.4],  $p < 0.001$ ). As in the main analysis, risk of viral rebound was higher in women with a previous pregnancy, although this lost statistical significance probably due to lack of power (aHR 1.18 [0.95-1.47],  $p$ -value 0.14). In the sensitivity analysis fewer women had a prior pregnancy than in the primary analysis (32% [417/1301] vs. 42%).

In an additional sensitivity analysis, only a woman's last pregnancy meeting the inclusion criteria during the period of interest was included (1301 pregnancies). Again, the results were similar to primary analysis results. Use of short-course ART was associated with an increased risk of viral rebound (aHR 15.8 [11.5-21.8],  $p < 0.001$ ) as was starting life-long ART (aHR 7.3 [5.5-9.6],  $p < 0.001$ ) compared to the group already on life-long ART. More than three-fifths of the women (42%, [546/1301]) had previously had a pregnancy; as in the main analysis, these women had an increased risk of viral rebound compared to women without a prior pregnancy (aHR 1.28 [1.04-1.57],  $p$ -value 0.02).

In adjusted analysis, ethnicity and route of exposure were not associated with the risk of viral rebound.

Table 8.5. Unadjusted and adjusted Cox proportional hazards regression analyses to identify factors associated with the incidence of post-pregnancy viral rebound

		Unadjusted		Adjusted	
		HR (95% CI)	p-value	HR (95% CI)	p-value
Type of ART use	Already on life-long ART	Reference	<0.001	Reference	<0.001
	Short-course ART	18.3 (13.9-24.1)		16.0 (11.9-21.6)	
	Start life-long ART	6.9 (5.3-8.9)		7.23 (5.52-9.47)	
	Other	6.7 (4.7-9.5)		6.18 (4.33-8.81)	
Previous pregnancy	0.73 (0.61-0.88)	<0.001	1.21 (1.00-1.47)	0.05	
Age (per 10 year increase)	0.47 (0.40-0.55)	<0.001	0.75 (0.63-0.89)	0.001	
Calendar year (per 1 year increase)	0.87 (0.82-0.91)	<0.001	0.95 (0.89-1.00)	0.05	
Route of exposure	Heterosexual sex	Reference	0.53	Reference	0.77
	IDU	0.66 (0.21-2.06)		1.03 (0.31-3.40)	
	Other/NK	0.72 (0.34-1.51)		0.76 (0.36-1.61)	
Ethnicity	Black-African	Reference	0.06	Reference	0.61
	White	1.17 (0.88-1.56)		0.97 (0.72-1.32)	
	Black-Caribbean	1.67 (1.12-2.49)		0.92 (0.61-1.38)	
	Other/NK	1.15 (0.86-1.53)		1.20 (0.61-1.38)	
HBV/HCV co-infection	0.71 (0.46-1.14)	0.14	0.61 (0.38-0.96)	0.03	
CD4 count (cells/ $\mu$ l)	$\leq$ 250	Reference	<0.001	Reference	<0.001
	251-350	1.34 (0.92-1.95)		1.47 (1.01-2.16)	
	351-500	1.61 (1.14-2.27)		2.00 (1.41-2.85)	
	>500	1.93 (1.39-2.69)		2.17 (1.54-3.06)	
	NK	0.75 (0.23-2.42)		1.40 (0.43-4.53)	

Separate models were created after stratifying by type of ART (Table 8.6). The results were similar for each group, although many associations were not statistically significant in the short-course ART and starting life-long ART groups, which contained small numbers. The notable difference between groups was the association between CD4 count and viral rebound. Among women already on life-long ART, women with a CD4 count  $\leq 250$  cells/ $\mu$ l had the highest risk of viral rebound. This was not the case for women who started life-long ART during their pregnancy. In this group, women with CD4  $\leq 250$  cells/ $\mu$ l had a lower risk of viral rebound than women with CD4 251-350 cells/ $\mu$ l, CD4 351-500 cells/ $\mu$ l, or CD4  $>500$  cells/ $\mu$ l (Table 8.6).

Table 8.6. Adjusted Cox proportional hazards regression analyses to identify factors associated with the incidence of post-pregnancy viral rebound stratified by type of ART use

		Already on life-long ART (n=802)		Short-course ART (n=179)		Start life-long ART (n=424)	
		aHR (95% CI)	p-value	aHR (95% CI)	p-value	aHR (95% CI)	p-value
Previous pregnancy		1.94 (1.2-3.1)	0.006	1.01 (0.7-1.5)	0.9	1.19 (0.9-1.6)	0.26
Age (per 10 year increase)		0.65 (0.4-1.0)	0.05	1.06 (0.8-1.4)	0.7	0.80 (0.6-1.0)	0.10
Calendar year (per 1 year increase)		0.93 (0.8-1.1)	0.26	1.00 (0.9-1.1)	0.9	0.95 (0.9-1.0)	0.26
Route of exposure	Heterosexual sex	-	-	-	-	Reference	0.79
	IDU					1.41 (0.4-5.2)	
	Other/NK					0.83 (0.4-2.0)	
Ethnicity	Black-African	Reference	0.44	Reference	0.2	Reference	0.61
	White	0.38 (0.1-1.2)		1.73 (1.0-3.0)		0.81 (0.5-1.3)	
	Black-Caribbean	-		0.83 (0.4-1.6)		0.98 (0.5-1.8)	
	Other/NK	1.05 (0.5-2.1)		1.10 (0.7-1.9)		1.23 (0.8-2.0)	
HBV/HCV co-infection		1.31 (0.5-3.3)	0.56	0.52 (0.3-1.1)	0.1	0.49 (0.2-1.2)	0.11
CD4 count (cells/μl)	≤250	Reference	0.11	Reference	0.01	Reference	<0.001
	251-350	0.40 (0.2-0.8)		1.35 (0.6-2.8)		2.25 (1.2-4.2)	
	351-500	0.51 (0.3-1.0)		1.62 (0.8-3.2)		3.05 (1.7-5.5)	
	>500	0.47 (0.3-0.9)		0.81 (0.4-1.6)		5.90 (3.4-10.3)	
	NK	0.40 (0.1-3.0)		-		9.38 (2.1-41.4)	

No model was created for the ART use group categorised as 'other'.

### 8.3.3 Comparing the risk of viral rebound in post-pregnant women and controls

#### **Analysis 1: Post-pregnant women conceiving on cART and controls**

There were 623 post-pregnant women who conceived on cART, with two controls identified for 607, only one for 11 and none for five women, giving a total of 1225 controls, this included 174 who were controls for multiple women.

The post-pregnant women and controls were similar with regard to age, year and duration on cART (the matching characteristics) (Table 8.7). They were also similar with regard to time since HIV-diagnosis (median 5.9 years), type of regimen used (overall, 55% used an NNRTI-based regimen), the proportion with HBV/HCV co-infection (7% overall), and ethnic group (73% black-African overall). The two groups differed with regard to HIV exposure category, latest CD4 count and parity (Table 8.7).

In the month following delivery/pseudo-delivery, 10% (64/618) of post-pregnant women had a viral load measurement and 26% (320/1225) of controls ( $p < 0.001$ ). After 3 months, 70% (435/618) of post-pregnant women and 70% (862/1225) of controls had had at least one viral load measurement ( $p$ -value 0.99). The median number of viral load measurements overall was 3 (2-4) for both the groups ( $p$ -value 0.11).

#### **Viral rebound in post-pregnant women conceiving on cART and controls**

A larger percentage of post-pregnant than control women experienced viral rebound (post-pregnant: 10.7% [66/618]; controls: 7.4% [91/1225]). The cumulative probability of viral rebound at one, three and six months post-delivery/pseudo-delivery was 1.1% (95% CI 0.3%-2.0%), 5.9% (4.0%-7.7%) and 8.6% (6.3%-10.8%), respectively in post-pregnant women, and 0.9% (0.0%-1.4%), 2.2% (1.4%-3.0%) and 4.5% (3.3%-5.6%) in controls (Figure 8.3a).

In adjusted analysis, risk of viral rebound in the first three months after delivery/pseudo-delivery was significantly associated with post-pregnant status, calendar year and CD4 count (Table 8.8). Post-pregnant women were more likely to experience viral rebound over this period than controls (aHR 2.63) although the risk of viral rebound itself decreased in later calendar years (aHR 0.81 per later year). A CD4 count  $\leq 200$  cells/ $\mu$ l at delivery/pseudo-delivery was also significantly associated with viral rebound (aHR 2.89).

The risk of viral rebound in the 3-12 month period after delivery/pseudo-delivery was associated with years since HIV diagnosis, type of drug regimen and number of drugs. There was no statistically significant association between viral rebound and post-pregnant status after restricting to this subgroup who had maintained viral suppression for at least 3 months. Women who were diagnosed with HIV more than 10 years ago were more likely to experience viral rebound than women diagnosed 2-10 years ago (aHR 1.83). Women on a  $\geq 4$  drug regimen were more likely to experience viral rebound than women on a triple drug regimen (aHR 2.41) as were women on a PI-based regimen compared to women on an NNRTI-based regimen (aHR 1.89).

Table 8.7. Baseline characteristics of post-pregnant women and controls

Baseline characteristic <sup>3</sup>		On ART at conception <sup>1</sup>				Started ART during the pregnancy <sup>2</sup>					
		Post-pregnant n=618		Controls n=1225		p-value	Post-pregnant n=321		Controls n=568		p-value
		N	%	n	(%)		n	%	n	(%)	
Year <sup>4</sup>	2006 – 2007	206	(33.4)	407	(33.3)	-	114	(35.5)	207	(36.4)	-
	2008 – 2009	207	(33.6)	413	(33.7)		99	(30.8)	176	(31.0)	
	2010 – 2011	205	(33.2)	405	(33.1)		108	(33.6)	185	(32.6)	
Age <sup>4</sup>	Median [IQR] years	34	[31-37]	34	[31-37]	-	31	[28-35]	32	[28-35]	-
Ethnicity	Black African	479	(77.5)	882	(72.0)	0.07	251	(78.2)	375	(66.0)	0.002
	White	61	(9.9)	163	(13.3)		25	(7.8)	78	(13.7)	
	Black Caribbean	14	(2.3)	36	(2.9)		14	(4.4)	30	(5.3)	
	Other/NK	64	(10.4)	139	(11.8)		31	(9.7)	85	(15.0)	
Exposure category	Heterosexual sex	604	(97.7)	1140	(93.1)	0.001	309	(96.3)	520	(91.6)	0.01
	Injecting drug use	6	(1.0)	31	(2.5)		0	-	10	(1.8)	
	Other/NK	8	(1.3)	54	(4.4)		12	(3.7)	38	(6.7)	
Parity <sup>5</sup>	0	353	(57.1)	855	(69.8)	<0.001	280	(87.2)	470	(82.8)	<0.01
	1	196	(31.7)	252	(20.6)		37	(11.5)	68	(12.0)	
	≥2	69	(11.2)	118	(9.6)		4	(1.3)	30	(5.3)	
Latest CD4 count (cells/μl)	≤200	39	(6.3)	58	(4.7)	<0.001	51	(15.9)	113	(19.9)	0.05
	201 – 350	153	(24.8)	201	(16.4)		93	(29.0)	172	(30.3)	
	351 – 500	191	(31.0)	315	(25.7)		81	(25.2)	159	(28.0)	
	>500	234	(37.9)	651	(53.1)		96	(29.9)	124	(21.8)	

Table 8.7 continued

Baseline characteristic <sup>3</sup>		On ART at conception <sup>1</sup>				Started ART during the pregnancy <sup>2</sup>					
		Post-pregnant n=618		Controls n=1225		p-value	Post-pregnant n=321		Controls n=568		p-value
		n	%	n	(%)		n	%	n	(%)	
HBV/HCV co-infection		37	(6.0)	93	(7.6)	0.20	8	(2.5)	46	(8.1)	0.001
Median time since HIV diagnosis [IQR] (years)		5.9	[3.7-8.3]	5.9	[3.6-8.7]	0.33	0.6	[0.5-3.8]	2.8	[0.7-6.5]	<0.001
Duration of current period of ART use <sup>4</sup>	0 – 2 months	-	-	-	-	-	65	(20.3)	106	(18.7)	-
	3 – 5 months	-	-	-	-	-	233	(72.8)	416	(73.2)	-
	6 – 8 months	-	-	-	-	-	22	(6.9)	46	(8.1)	-
	8 – 12 months	39	(6.3)	78	(6.4)	-	-	-	-	-	-
	1 – 4 years	394	(63.8)	785	(64.1)	-	-	-	-	-	-
	≥5 years	185	(29.9)	362	(29.6)	-	-	-	-	-	-
Type of ART regimen	PI	221	(35.8)	404	(33.0)	0.49	84	(26.2)	160	(28.2)	0.68
	NRTI	7	(1.1)	22	(1.8)	-	3	(0.9)	3	(0.5)	-
	NNRTI	332	(53.7)	676	(55.2)	-	221	(68.9)	388	(68.3)	-
	Other	58	(9.4)	123	(10.0)	-	13	(4.1)	17	(3.0)	-
Number of drugs in regimen	2	12	(1.9)	43	(3.5)	0.26	-	-	-	-	0.06
	3	552	(89.3)	1064	(86.9)	-	308	(96.0)	557	(98.1)	-
	≥4	54	(8.7)	118	(9.6)	-	13	(4.1)	11	(1.9)	-

<sup>1</sup> Or 9 months prior to pseudo-delivery for controls; <sup>2</sup> Or in the 8 months prior to pseudo-delivery for controls; <sup>3</sup> At delivery (post-pregnant women) or pseudo-delivery (controls);

<sup>4</sup> Characteristics used to identify suitable controls for post-pregnant women. In addition, post-pregnant women who started ART during pregnancy were also matched to controls using CD4 count at ART start. <sup>5</sup> Previous live births reported to NSHPC not including live births delivered prior to HIV diagnosis.

Figure 8.3. Kaplan-Meier plot showing cumulative probability of viral rebound among women on ART: post-partum women (black line) and controls (grey line)

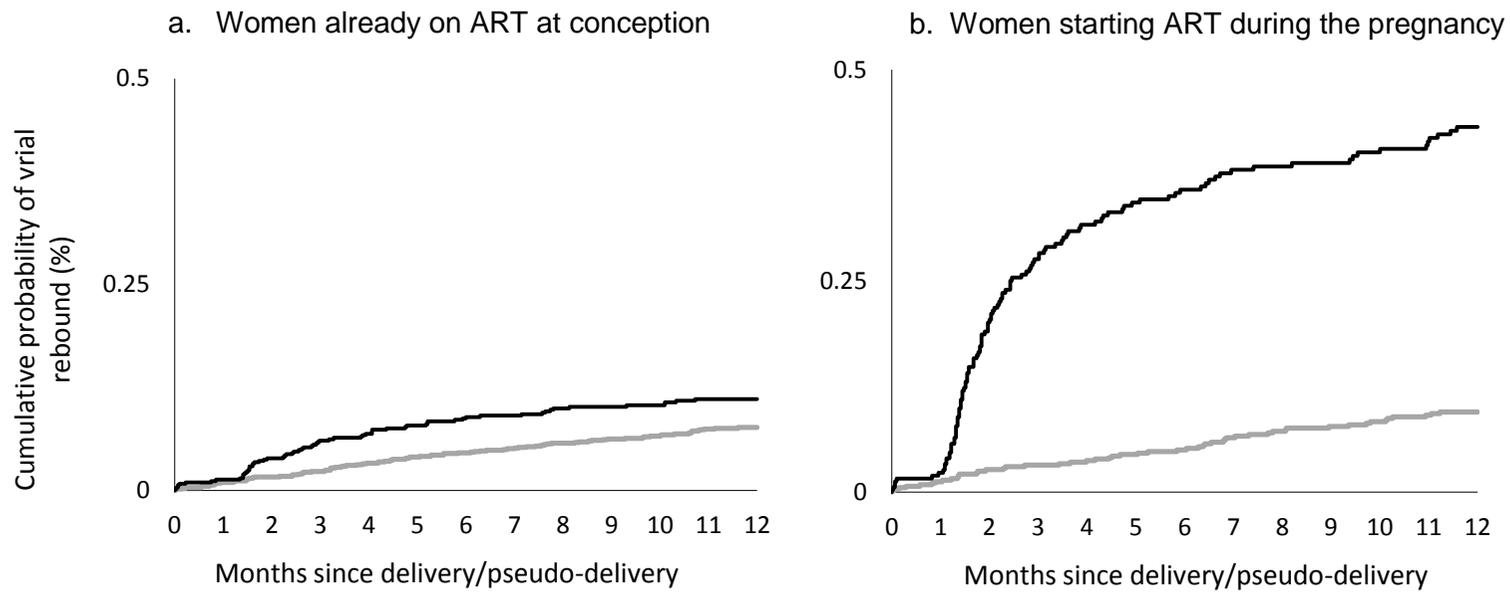


Table 8.8. Adjusted hazard ratios for viral rebound in post-pregnant women who conceived on ART and controls stratified by time since delivery

Baseline characteristic at delivery/pseudo-delivery		<3 months since delivery/pseudo-delivery		3-12 months since delivery/pseudo-delivery	
		aHR (95% CI)	p- value	aHR (95% CI)	p- value
Group	Control	Reference	<0.001	Reference	0.76
	Post-pregnant	2.63 (1.58-4.39)		0.93 (0.59-1.47)	
Calendar year (per additional year)		0.81 (0.70-0.95)	0.01	0.96 (0.84-1.09)	0.50
Age (per 10 additional years)		0.93 (0.55-1.55)	0.77	0.84 (0.55-1.28)	0.42
Ethnicity	Black African	Reference	0.41	Reference	0.59
	White	1.79 (0.87-3.71)		0.75 (0.36-1.57)	
	Black Caribbean	1.52 (0.36-6.35)		0.45 (0.06-3.28)	
	Other/NK	1.34 (0.62-2.91)		0.69 (0.33-1.45)	
Exposure category	Heterosexual sex	Reference	0.63	Reference	0.87
	Injecting drug use	0.41 (0.05-3.72)		0.73 (0.14-3.84)	
	Other/NK	0.56 (0.08-4.17)		1.21 (0.45-3.25)	
Previous live birth		1.31 (0.79-2.20)	0.10	1.37 (0.89-2.11)	0.16
HBV/HCV co-infected		1.43 (0.58-3.55)	0.44	1.25 (0.59-2.65)	0.57
Latest CD4 count (cells/ $\mu$ l)	$\leq$ 200	2.89 (1.14-7.31)	0.10	2.05 (0.96-4.34)	0.05
	201-350	1.74 (0.88-3.46)		1.12 (0.65-1.95)	
	351-500	1.79 (0.96-3.36)		0.64 (0.36-1.13)	
	>500	Reference		Reference	
Duration of ART use	8-12 months	1.34 (0.56-3.25)	0.19	0.98 (0.41-2.34)	0.77
	1-4 years	Reference		Reference	
	$\geq$ 5 years	0.57 (0.29-1.13)		0.83 (0.50-1.37)	
Time since HIV diagnosis	8-23 months	0.66 (0.25-1.74)	0.69	1.66 (0.82-3.37)	0.04
	2-9 years	Reference		Reference	
	$\geq$ 10 years	1.04 (0.49-2.21)		1.83 (1.08-3.09)	
Type of ART regimen	PI	1.13 (0.66-1.93)	0.96	1.89 (1.19-3.00)	0.06
	NRTI	-		0.92 (0.12-6.87)	
	NNRTI	Reference		Reference	
	Other	0.95 (0.38-2.34)		1.39 (0.66-2.95)	
Number of drugs in regimen	2	2.36 (0.51-11.0)	0.17	2.17 (0.73-6.50)	0.01
	3	Reference		Reference	
	$\geq$ 4	1.86 (0.91-3.81)		2.41 (1.36-4.25)	

## **Analysis 2: Post-pregnant women starting cART in pregnancy and controls**

There were 363 post-pregnant women who started cART during pregnancy, with two controls identified for 247, only one for 74 and none for 42 women, giving a total of 568 controls.

Post-pregnant women and controls were similar with regard to age, year, duration on cART and CD4 count when starting cART (the matching characteristics) (Table 8.7). They were also similar regarding type of drug regimen (overall, 69% used an NNRTI-based regimen) but differed with regard to ethnicity, exposure category, parity, HBV/HCV co-infection, duration since HIV diagnosis and latest CD4 count. On average, post-pregnant women had been diagnosed more recently, had a higher median CD4 count (391 vs. 350 cells/ $\mu$ l), and were less likely to have had a previous live birth (since HIV diagnosis).

More than half (53% [171/321]) of post-pregnant women were diagnosed with HIV during the recent pregnancy, of whom 65% (111/171) had a CD4 count <350 cells/ $\mu$ l when starting cART, with 47% (81/171) having a CD4 count <200 cells/ $\mu$ l. In women already diagnosed when they became pregnant, 59% (89/150) had a CD4 count <350 cells/ $\mu$ l when starting cART, with 32% (48/150) having a CD4 count <200 cells/ $\mu$ l; of these almost two-thirds (65% [98/150]) attended care at a UK CHIC site in the year prior to the pregnancy, of whom 53% (52/98) started cART with a CD4 count <350 cells/ $\mu$ l. Of the remaining 46 women not attending a UK CHIC site in the year prior to pregnancy, 22 had no evidence that they had ever attended care at a UK CHIC site prior to their pregnancy and 24 had attended care at a UK CHIC site more than one year before the pregnancy. In this latter group, the median time between their latest attendance before the pregnancy and their first attendance in pregnancy was 22 (IQR 18-32) months and two-thirds (67% [16/24]) started cART with a CD4 count <350 cells/ $\mu$ l.

In the month following delivery/pseudo-delivery, 14% (44/321) of post-pregnant and 27% (152/568) of controls ( $p < 0.001$ ) had a viral load measurement. At 3 months post-delivery/pseudo-delivery, 80% (256/321) of post-pregnant women and 79% (450/568) of controls had had at least one viral load measurement ( $p$ -value 0.85). The median number of viral load measurements in the first year after delivery/pseudo-delivery was 3 (2-4) for the post-pregnant women and 3 (3-4) for the controls ( $p$ -value <0.001).

### **Viral rebound in post-pregnant women starting cART in pregnancy and controls**

A larger percentage of post-pregnant women experienced viral rebound than controls (post-pregnant: 37.1% [119/321]; controls: 9.2% [52/568]). The cumulative probability of viral rebound at one, three and six months after delivery/pseudo-delivery was 1.9% (95% CI 0.4%-3.5%), 27% (22%-32%) and 35% (30%-41%) respectively in post-pregnant women, and 1.1% (0%-1.9%), 3.0% (1.6%-4.4%) and 4.8% (3.0%-6.6%) respectively in controls (Figure 8.3b).

In the adjusted analysis, the risk of viral rebound in the first three months post-delivery/pseudo-delivery was associated with post-pregnant status (aHR 11.7 for post-pregnant women) and CD4 count (aHR 0.18 CD4 count <200 vs. >500 cells/ $\mu$ l) (Table 8.9).

The risk of viral rebound in the 3-12 months post-delivery/pseudo-delivery was associated with post-pregnant status (aHR 3.94 for post-pregnant women), calendar year (aHR 0.82 per later year), ethnicity (aHR 2.44 for women of black-Caribbean ethnicity) and parity (aHR 2.92 for women with a previous live birth) (Table 8.9).

In sensitivity analysis, when viral rebound was defined as HIV RNA >1000 copies/ml, similar associations were observed although some lost statistical significance. The association between age and viral rebound became statistically significant for women who had started cART in pregnancy and controls (0-3 months post-delivery/pseudo-delivery: aHR 0.63 [0.40-0.98]; 3-12 months post-delivery/pseudo-delivery aHR 0.55 [0.32-0.93] per 10 additional years). Post-pregnant status remained associated with viral rebound when 143 women (46 post-pregnant and 97 controls) with previous cART experience were excluded.

Table 8.9. Adjusted hazard ratios for viral rebound in post-pregnant women starting ART during pregnancy and controls stratified by time since delivery

Baseline characteristic at delivery/pseudo-delivery		<3 months since delivery/pseudo-delivery		3-12 months since delivery/pseudo-delivery	
		aHR (95% CI)	p-value	aHR (95% CI)	p-value
Group	Control	Reference	<0.001	Reference	<0.001
	Post-pregnant	11.7 (6.69-20.5)		3.94 (2.43-6.40)	
Calendar year (per additional year)		0.99 (0.87-1.12)	0.88	0.82 (0.70-0.95)	0.01
Age (per 10 additional years)		0.75 (0.50-1.11)	0.14	0.69 (0.44-1.08)	0.10
Ethnicity	Black African	Reference	0.83	Reference	0.10
	White	0.68 (0.29-1.62)		0.72 (0.31-1.71)	
	Black Caribbean	1.12 (0.48-2.64)		2.44 (1.10-5.45)	
	Other/NK	0.95 (0.48-1.87)		0.86 (0.38-1.92)	
Exposure category	Heterosexual sex	Reference	0.32	Reference	0.42
	Injecting drug use	5.63 (0.59-53.4)		3.59 (0.38-33.9)	
	Other/NK	1.03 (0.36-2.95)		1.50 (0.53-4.26)	
Previous live birth		1.51 (0.82-2.77)	0.19	2.92 (1.53-5.57)	0.001
HBV/HCV co-infected		0.70 (0.21-2.34)	0.56	0.67 (0.19-2.32)	0.53
Latest CD4 count (cells/ $\mu$ l)	$\leq$ 200	0.18 (0.07-0.46)	<0.001	0.79 (0.39-1.59)	0.21
	201-350	0.40 (0.22-0.71)		0.61 (0.33-1.13)	
	351-500	0.88 (0.54-1.43)		0.50 (0.24-1.03)	
	>500	Reference		Reference	
Duration of ART use	0-2 months	0.77 (0.46-1.30)	0.63	0.73 (0.39-1.38)	0.35
	3-5 months	Reference		Reference	
	6-8 months	-		0.54 (0.19-1.52)	
Time since HIV diagnosis	8-23 months	0.85 (0.52-1.38)	0.78	0.98 (0.54-1.78)	0.95
	2-9 years	Reference		Reference	
	$\geq$ 10 years	1.04 (0.36-2.99)		0.84 (0.30-2.35)	
Type of ART regimen	PI	1.02 (0.64-1.65)	0.99	1.52 (0.93-2.49)	0.34
	NRTI	-		1.99 (0.38-10.45)	
	NNRTI	Reference		Reference	
	Other	1.11 (0.40-3.12)		0.68 (0.09-5.05)	
Number of drugs in regimen	3	Reference	0.91	Reference	0.78
	$\geq$ 4	1.07 (0.33-3.50)		1.18 (0.36-3.95)	

## 8.4 Discussion

Initially, I examined the availability of viral load data in the dataset. The large majority of women had at least one viral load measurement reported, but it was surprising that not all women had one. In pregnancy too, most, but not all, women had at least one viral load measurement in UK CHIC and/or NSHPC. Viral load is routinely tested in clinical HIV care. Lack of any viral load data in the dataset is probably not a result of non-attendance - since only women with some clinical data in the dataset, such as CD4 count, had their data examined. Although there may be some circumstances under which women attending care do not have a blood sample taken/tested, absence of viral load data is more likely to be a consequence of non-reporting of data or a technical failure in the laboratory to obtain a viral load measurement from the sample. Among women with viral load data, the median interval between viral load measurements was 3 months. This interval will probably increase as clinics move toward less frequent monitoring of patients who are stable on treatment [485] and may be affected by the short interval between viral load measurements during pregnancy. There was a median of 4 viral load measurements reported in pregnancy, double the number reported in the period of the same duration before or after pregnancy. This reflects the increase in viral load monitoring during pregnancy [169] due to the importance of achieving or maintaining viral suppression to minimize vertical transmission.

The availability of viral load data following pregnancy was also examined. There was some evidence of loss-to-follow-up (LTFU) for one in five pregnancies; 20% of pregnancies in the combined dataset had no viral load measurement reported in the post-pregnancy year, higher than in a UK study of post-pregnancy LTFU which estimated that 12% of women did not access care in the post-pregnancy year [486, 487]. It is likely that some of the women with no viral load data stopped attending HIV clinical care for that period of time. However, there are other reasons why women might not have any viral load (and CD4) measurement reported from that period. Some may have moved abroad or returned to their country of origin and continued to access HIV care abroad. Some women may have moved within the UK. It is not uncommon for families to move areas after the birth of a child and some women may have transferred to another HIV clinic within the UK, not part of UK CHIC. Women who did not attend care after pregnancy, and were therefore not included in analyses, are likely to have higher rates of viral rebound than the women who attended care. This selection bias may therefore result in an underestimation of post-pregnancy viral rebound. The pregnancies included in both of the post-pregnancy analyses were only those of

women who had achieved viral suppression during pregnancy. Women with a detectable viral load at delivery, are also likely to have detectable viral loads for at least some of the period after delivery, particularly as these women may have been having adherence problems during pregnancy or entered care late, leaving insufficient time to achieve viral suppression by delivery. In addition, only live births were assessed. The risk of viral rebound may differ according to pregnancy outcome, something which would be difficult to assess using the NSHPC data due to small numbers and underreporting of miscarriages and terminations of pregnancy.

In the first analysis of the post-partum year, viral rebound was examined in four groups: women who conceived on life-long ART; women who started life-long ART in the pregnancy; women who used short-course ART in the pregnancy; and women who did not fit into any of these groups. As anticipated, the risk of post-pregnancy viral rebound was highest in women who stopped ART at delivery or shortly after (the short-course ART group). When interpreting Figure 8.1 it is important to bear in mind that follow-up started at delivery, not when ART was stopped. Women were included in the short-course ART group if they started ART in pregnancy and stopped ART within 6 months of delivery. Although many of the women in this group stopped ART at delivery, some remained on ART for a number of weeks or even months after delivery. For some, this was a temporary switch (of 4 weeks) to a PI-based regimen – recommended for women stopping an NNRTI-containing regimen [84]. For others it may have been an unplanned treatment interruption. Whatever the reason, it delayed the viral rebound until weeks/months after delivery. It is also important to bear in mind that the data do not show the actual timing of when viral rebound occurred. Although a woman's viral load may have rapidly reached detectable levels, this would not be captured in the data until the next viral load measurement. Although three-quarters of women who used short-course ART had experienced viral rebound by six months post-pregnancy, some women had not yet had a viral load measurement by this point, so the actual percentage of women who experienced viral rebound was probably higher, closer to 100%. In view of this limitation, I also examined the percentage of women with detectable viral load among women with a viral load measurement reported in any given month (Table 8.4 and the same data presented as a graph in Figure 8.2).

Examining viral rebound in this way showed a steep increase in the percentage of women with a detectable viral load in the first 2 months after delivery (to around 80%). Again, this percentage would probably be higher, if follow-up was started when ART was stopped rather than at delivery.

Although the rapid increase in viral load after cessation of cART is expected, it might be something best avoided (by remaining on cART), particularly if there is an overshoot (a temporary peak) in viral load, as some studies suggest [197, 378, 380] as this would increase the risk of onward transmission. This is an additional benefit of the recent changes to ART guidance [86], since all women, whether they start ART in pregnancy or conceive on ART, will be advised to remain on ART after pregnancy. For a number of reasons it is unlikely that the high viral load post pregnancy resulted in a large number of transmissions, as is the case in newly infected individuals who contribute to a disproportionate number of transmission events due to a temporary peak in their viraemia shortly after HIV infection [488]. Women are unlikely to re-initiate sexual activity until around 2-3 months after delivery [489]. Sexually active HIV-positive women are strongly advised to have protected sex. Postnatal women living with HIV are encouraged to bottle feed rather than breastfeed their infant [169]. Although bottle feeding is socially acceptable and is fairly common in the wider population within the UK, some women may have chosen to breast feed for social, financial or cultural reasons. Cessation of short-course ART after pregnancy does not appear to lead to increased morbidity or mortality among women with high CD4 counts i.e. women eligible for short-course ART in pregnancy [249]. However, it may have implications for the women's health and future treatment, as examined in Chapter 6. Remaining on treatment after pregnancy will likely be beneficial for the woman's health as well as minimising HIV transmission risk in subsequent pregnancies [89, 490]. The PROMISE study is currently assessing the benefits, in resource limited settings, of women with higher CD4 counts remaining on cART after delivery (Trial reference: NCT01061151).

In women who remained on ART after delivery, risk of viral rebound was not as high as in those who stopped. However, women who started life-long ART in pregnancy had 7 times the risk of viral rebound compared to women already on life-long ART (aHR 7.2) - by six months post-pregnancy, 42% of women who started life-long ART during their pregnancy experienced viral rebound compared to only 7% of women who had conceived on ART. For the former, the cumulative probability of viral rebound was not as high when follow-up was censored if ART was stopped, even for a short time. This indicates that some, but not all, of the viral rebounds were a consequence of a short treatment interruption (if the interruption had been longer than 30 days then they would not have been included in this ART group).

The analysis comparing women who started life-long ART during pregnancy and women who remained on life-long ART (analysis 3) found that the risk of viral rebound in the post-pregnancy year was higher than in matched controls – women who had

been on ART for a similar duration but who had not recently had a pregnancy. Among women who conceived on cART, the risk of viral rebound was 2.6-fold higher in the first three months after delivery than among matched controls, but similar in the 3-12 months after delivery. In contrast, among women who started life-long ART during pregnancy, viral rebound risk was 11.7-fold higher than among matched controls during the first three months and 3.9-fold higher 3-12 months after delivery. Previous studies have reported a high prevalence of viral rebound in post-pregnant women remaining on therapy [375, 376, 381], but this is the first to compare the risk of viral rebound in post-pregnant women with rates seen in a demographically matched group of non-post-pregnant women.

Overall, 9% of women who conceived on life-long ART experienced viral rebound within six months of delivery, less than in a Brazilian study in which 15% (9/52) of post-pregnant women, who conceived on and remained on cART after pregnancy, developed viral rebound (0.5 log<sub>10</sub> increase) at six months post-pregnant [375]. This difference may be because women in the Brazilian study had more advanced disease and not all had achieved viral suppression during pregnancy. Two further studies [376, 381] reported that 18% and 19% (respectively) of post-pregnant women who remained on cART experienced viral rebound (defined as ≥0.7 log<sub>10</sub> increase at 24 weeks post-pregnant and ≥0.5 log<sub>10</sub> increase at 6-12 weeks post-pregnant respectively). However, neither of these studies stratified by timing of cART initiation (before or during the pregnancy), which limits comparison here. Further analysis is needed to determine the proportion of women with viral rebound who subsequently regained virological control and whether that was achieved without a regimen change.

Although physiological changes during pregnancy and at delivery might have contributed to the increased incidence of viral rebound in the first three months after delivery, this would not explain the ongoing increased risk of viral rebound after three months among women who started life-long ART in pregnancy, or the much higher incidence in women who started life-long ART in pregnancy than in women conceiving on cART. The more likely explanation is reduced adherence to cART following pregnancy. Studies have observed a fall in adherence following pregnancy [376, 388, 389], when the risk of vertical transmission has passed (if breastfeeding is avoided) and the demands of looking after the baby are high. Treatment interruptions and changes to medication are also more likely in this period [376]. Treatment interruptions and regimen alterations are common in the first year of treatment, particularly for women [476, 491]. Reduced adherence could also explain, in part, the almost three-

fold increase in viral rebound observed in the 3-12 months after delivery/pseudo-delivery in women with a previous live birth at baseline, i.e. women with the additional burden of looking after children as well as their new baby. Other studies have found that both drug adherence and access to antenatal HIV services fall with an increasing number of children in the household [492-494]. Post-pregnancy treatment interruptions could be examined further in a future analysis of the combined dataset.

Adherence is defined by the WHO as ‘the extent to which a person’s behaviour – taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider’ [495]. Adherence is difficult to accurately measure and adherence data is not collected by UK CHIC or the NSHPC. There are numerous factors known to be associated with adherence. These include regimen-related factors such as pill burden [496, 497], dose burden [497, 498], dietary restrictions [499] and side-effects [500]. Factors relating to the individual are also important predictors of adherence including: age [501, 501, 502, 502, 503, 503]; belief systems; forgetfulness [504]; understanding of the importance of adherence [504]; disclosure of HIV status [503]; depression [497]; stress; and social support [497]. In both analyses of viral load in the postpartum year, a number of factors which are known to be predictive of adherence were found to be associated with viral rebound. Whereas older age is commonly associated with poorer health, risk of viral rebound decreased with increasing age in the first, but not the second analysis. This association is likely to be due to behavioural differences and better drug adherence in older women. The lack of association between age and viral rebound in the second analysis might be because few adolescents and young adults were included.

In this observational study, data were collected as part of patients’ clinical records and can therefore be used as a proxy for HIV clinic attendance. For all groups, the median number of viral loads was three in the year following delivery/pseudo-delivery. However, for women who recently started cART, there was evidence that post-pregnant women attended care less often than controls. Previous studies have noted low attendance rates in clinical care in the three months following childbirth [505] and a delay in seeking HIV care [492] or inability to complete post-pregnant follow-up [506] among women with children in the household.

CD4 count was also associated with viral rebound. In women who started life-long ART in pregnancy and their controls, risk of viral rebound in the first three months after delivery/pseudo-delivery was lower in women with a low CD4 count than in women with a high CD4 count. Despite only including women who, according to the data, remained

on cART for at least six months after delivery, some discontinuations may not have been recorded in the clinical notes. A woman's CD4 count at cART initiation could indirectly affect adherence; for example, women with a high CD4 count may not perceive the need for perfect adherence as much as women starting cART with a low CD4 count. A Ugandan study found that a high CD4 count at ART start was not associated with adherence (measured using MEMSCap pill bottles) but was associated with more treatment interruptions and persistent detectable viraemia [507]. In some settings where WHO Option B+ has been implemented, high rates of loss-to-follow-up have been observed among pregnant women starting life-long cART with a high CD4 cell count [508, 509]. We do not know if a similar incidence of post-pregnant viral rebound would occur if all pregnant women not yet on ART started life-long treatment in pregnancy, as is now the recommendation [510]. There may be a similar reason for the association between HBV/HCV co-infection and viral rebound seen in the first, but not the second analysis. Women with HBV/HCV were less likely to experience viral rebound in adjusted analyses than women without hepatitis, perhaps due to the increased contact with their HIV clinician resulting in a better understanding of the importance of ART adherence.

Among women already on life-long ART, women with a lower CD4 count were at increased risk of viral rebound in the 3-12 months post-delivery/pseudo-delivery. Although all these women were virally suppressed at baseline, a low CD4 count indicates that they were having adherence problems or that the regimen was failing due to resistance.

Assessing the CD4 count at which ART was started was not an intended outcome of the study. However, it is of interest to note that 62% of the women who started ART during pregnancy had a CD4 count below the threshold at the time for treatment initiation in the UK (350 cells/ $\mu$ l) [85]. Most of these women were diagnosed with HIV during the pregnancy, highlighting the importance of antenatal screening for HIV, routine in the UK since 2002 [142].

For women who started cART in pregnancy and their controls, a quadruple regimen was associated with increased risk of viral rebound in the 3-12 months after delivery/pseudo-delivery compared to a triple regimen. Since the standard first line treatment in the UK during the study period was a triple regimen (where ritonavir use as a pharmacological booster is not counted as a component of the regimen) [84], use of a quadruple regimen suggests that they were on a subsequent regimen due to development of resistance or problems with a previous regimen/s. Adherence could be

more of an issue for women on a quadruple regimen, since adherence is negatively associated with pill burden [63].

As previously mentioned increased viral load following pregnancy could have a detrimental impact on women's health and future treatment options and increase the risk of HIV transmission. Therefore, these findings indicate a need for additional support for ART adherence and for maintained engagement with HIV clinical care for this group. This could include support from clinicians, specialist nurses and peer support (via charities) from women with experience of taking ART during and after pregnancy. As the incidence of viral rebound was higher in women who started therapy in pregnancy than in women already on therapy, adherence support is particularly needed for women starting life-long treatment during pregnancy, especially those who already have children. It is encouraging that the risk of viral rebound was lower in later years. This may reflect improvements in clinical management of people living with HIV including the management of side effects as well as the increased use of fixed-dose regimens (FDRs) over the study period. Different ART combinations have different thresholds of adherence needed to ensure viral suppression. In other words, some are more forgiving to suboptimal adherence than others. Regimens have become more forgiving to lapses in adherence; older regimens required very high rates of adherence (of around 95%), whilst newer NNRTI combinations require about 85% adherence [511]. The UK CHIC study does not collect data on pill burden or use of FDRs, so these could not be assessed as potential factors associated with viral rebound. However, other studies have found that use of a single-pill regimen can improve adherence [512]. For pregnant women starting life-long cART in pregnancy, a once a day FDR may promote good adherence. Regimens which are more forgiving to poor adherence could also be considered as the initial regimen. Further studies are required to identify the most effective strategies for improving post-pregnant ART adherence.

There are a number of important limitations to bear in mind when interpreting the results of these analyses. Whilst several relevant variables were included in the adjusted models, not all confounders could be accounted for. Resistance cannot be ruled out as the reason for viral rebound. However, in sensitivity analysis excluding women with known previous exposure to ART, post-pregnant status remained significantly associated with an increased risk of viral rebound.

To avoid detecting viral blips, viral rebound is often defined on the basis of two consecutive HIV-RNA >200/400/1000 copies/ml; I was not able to take this approach due to the limited number of viral load measurements reported in this group. This

should not have an impact on the outcome when the risk of viral rebound was compared between groups.

ART use in pregnancy was categorised as either 'conceived on life-long', 'started life-long ART', or 'short-course ART' using data from both studies. The categorisation of ART use was not straightforward and there were a sizable number of women whose ART use did not fit within the three categories. For the purposes of the first analysis, these pregnancies were grouped together as 'other'. It is difficult to interpret the results of this group which included women whose ART use was not known or who, according to the data, stopped ART after delivery despite conceiving on ART. This group could have been excluded. They were, however, included as it is important to remember that there are women whose ART use is not in accordance with treatment guidelines. It is therefore not surprising that women in this group were more likely to experience viral rebound than women who conceived and remained on life-long ART. Previous studies have reported a high rate of women stopping ART after pregnancy, despite intending to continue ART postnatally [376].

The categorisation of ART was compared with the results of the NSHPC reported variable 'reason for ART use in pregnancy'. There were a large number of discrepancies between the two and the NSHPC variable was underreported (one-quarter of pregnancies had no reason reported). Of note, there were 183 pregnancies reported to NSHPC as using ART for PMTCT only (i.e. short-course) whilst the ART data indicated that the women started life-long ART in pregnancy. This highlights the value of using the UK CHIC data from after the pregnancy to validate ART data reported to the NSHPC.

### **Key points from this chapter**

- In women who were virally suppressed at delivery and remaining on ART after pregnancy, the risk of viral rebound in the post pregnancy year was higher in women who had started life-long ART in pregnancy than in women who had conceived on ART.
- For post-natal women who started life-long ART during pregnancy, the risk of viral rebound was higher than in non-post-natal matched controls who had recently started life-long ART. This increase in risk is seen throughout the 12 months after delivery/pseudo-delivery.
- For post-pregnant women already on life-long ART, risk of viral rebound is higher than in similar women who have been on ART for a similar duration but

who did not recently have a pregnancy. This increase in risk is seen in the first three months after pregnancy but not in the 3-12 months after pregnancy.

## Chapter 9 Concluding remarks

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The development of antiretroviral drugs for the treatment of HIV is a remarkable success story. The use of combination antiretroviral therapy (cART) is the main reason why, in the UK, the life expectancy of people living with HIV is now approaching that of the general population. The use of ART in pregnancy, alongside appropriate antenatal care and clinical management during labour and delivery, mean that the risk of mother-to-child transmission (MTCT) is now very low; in the UK, only 10 of the 4271 infants born to diagnosed women living with HIV were vertically infected with HIV in the 5 years prior to submission of this work [145]. It is therefore not surprising that, as they would have done if they were HIV-negative, many women living with HIV decide to have children, anticipating that their infant will not become infected and that they themselves will remain in good health throughout their child's upbringing.

The broadest aim of this work was to assess the impact of ART use in pregnancy on women's health during and after pregnancy. Initially, the focus was intended to be the long-term outcomes following short-course ART use in pregnancy. However, it quickly became apparent, from the results of Chapter 5, that a decreasing number of women were using short-course cART in pregnancy. This was because most women were either already on lifelong therapy when they conceived or initiated life-long therapy during pregnancy. As such, the focus of the work was redirected to examine the outcomes during and after pregnancy in women who remained on ART as well as in women who used short-course ART. Since 2009, when this work was started, there have been important changes in the clinical management of people living with HIV. The recommendation that everyone living with HIV should start ART as soon as possible after diagnosis means that women are no longer recommended short-term ART use in pregnancy and therefore some of the results presented in this thesis are no longer relevant to current practice. However, the majority of the research remains relevant since it examines ART use during or after pregnancy in women starting ART in pregnancy and/or remaining on ART following pregnancy.

The linkage between UK CHIC and the NSHPC provided a unique opportunity to identify predictors of pregnancy in a large cohort of women living with HIV in the UK and to estimate the incidence of pregnancy in this group. The results presented in Chapter 5 are essentially surveillance data. That is, rather than contributing to the

evidence base for practice, they are useful for researchers in this area and for assessing and planning HIV services. The paper reporting the results of Chapter 5 [423], published in 2013, has been cited by a number of subsequent research papers.

The number of pregnancies among women living with HIV reported to the NSHPC has plateaued in recent years [145]. Bearing this in mind, as well as changes in immigration dynamics within the UK, an update to the analyses in Chapter 5 would be useful in the near future. This would assess whether pregnancy incidence has continued to increase and whether specific groups of women are following the general trend.

In Chapter 7, I examined liver enzyme elevation in pregnancy. The results of this chapter provide further evidence that women using antiretroviral therapy in pregnancy have an increased risk of liver enzyme elevation and, for the first time, show that this risk is increased in women who are already on ART when they conceive as well as in women who initiate ART use in pregnancy. Whereas many UK based HIV clinics are moving to less regular monitoring of liver function tests in pregnancy, the results of Chapter 7, highlight the importance of maintaining regular monitoring of liver enzymes throughout pregnancy and the importance of monitoring the symptoms of toxicity, such as rash, among pregnant women on antiretroviral therapy, including women who have been on ART for some time. As with most previous studies examining hepatotoxicity in pregnancy, my analysis was fairly simplistic - limited to assessing ALT only. There are, however, other biomarkers of synthetic function, in addition to ALT, which can be used to distinguish hepatotoxicity from other pregnancy complications and could be examined in any future research. Although some of these data are collected in UK CHIC, this type of research might be better suited to a single site study with samples taken in all women at regular intervals throughout pregnancy therefore avoiding the bias introduced when using observational data, where women with a risk profile for raised liver enzymes are more likely to have liver function tests.

In Chapter 8, I examined post-pregnancy viral rebound. The results of this chapter show that women are more likely to experience viral rebound in the year after pregnancy than at other times outside pregnancy. During this post-pregnancy period, among women who remain on ART, women who started life-long ART in their pregnancy are more likely to experience viral rebound compared to women who were already on ART before their pregnancy. The interpretation of these results are limited by the fact that this was an observational study and I only used the quantitative clinical data collected by UK CHIC and the NSHPC, a limitation that I discuss further on.

Viral rebound not only has implications for the women's health but increases the risk of transmission to the baby if the woman breastfeeds, or to a partner, if the couple have unprotected sex. If we assume that the heightened risk of viral rebound is the result of reduced ART adherence, the results of Chapter 8 highlight a need for additional adherence support for post-partum women. The need for continuous high levels of ART drug adherence is well understood by the HIV community. Clinics already provide adherence advice and support, particularly when people are starting life-long ART. There are numerous on-line resources including websites, online video clips and blogs. Charities, such as Positively UK<sup>25</sup>, provide peer support and short educational/support courses. NAM<sup>26</sup>, a leading HIV information sharing charity in the UK, provides HIV and ART information in numerous languages and any website can now be translated into almost any language using online translation tools.

Not everyone will be able to or want to use these services or necessarily find them useful. For example, not all women will have access to the internet or live close to a peer support programme and not everyone will have the time or the desire to use them. There needs to be a variety of interventions for different people as there is unlikely to be a one-size-fits-all solution to improving post-partum drug adherence. Where some HIV support services are suffering from a lack of funding [513] it is crucial that support services are maintained and where possible, research and cost-effective analyses are performed to provide evidence to funders and commissioners of the value of the service. For service evaluation, services need to collect good quality data about the number and type of people attending their services. In addition, in this time of financial pressure on the National Health Service (NHS) and local authorities (who commission social services and some health services), inexpensive ways of providing adherence support need to be developed and assessed. At present there is very little research on ART adherence post pregnancy and only one study from the UK has been published which examines the use of a specific intervention to promote retention in care after pregnancy [514].

For women who have access to the internet, I would recommend that more resources are developed with specific groups of women in mind, for example, young mothers, newly diagnosed mothers and mothers who have recently arrived in the UK and where possible that online resources are translated into languages reflecting the diverse and multilingual mix of people living with HIV in the UK. Having the web page or app already translated makes it easier to find and use for non-English speakers and the

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<sup>25</sup> [www.positivelyUK.org](http://www.positivelyUK.org)

<sup>26</sup> [www.aidsmap.com](http://www.aidsmap.com)

translation will be more accurate than if the translator is performed by an online translation programme.

There are many drug adherence apps available on smartphones. A recent paper identified 461 such apps [515], but few are specifically for ART adherence and none are aimed at women living with HIV. The ownership of smartphones has increased and the use of apps for monitoring health means that developing an app for very specific scenarios can be an effective and inexpensive intervention. NHS England has already produced some apps which are free or inexpensive and which are recommended for particular patient groups. For example, the NHS developed a pelvic floor exercise app for women with urinary incontinence, Squeezy<sup>27</sup>, costing £2.99 to consumers. An app designed to help ART drug adherence could also provide HIV information and could be available in multiple languages. These could be developed by BHIVA, NHS England, an HIV charity such as NAM, who already have some HIV information apps, by one of the pharmaceutical companies which manufacture ART drugs, or by a collaboration of these groups. In time, as the databases for storing patient records become more sophisticated, such an app could link to a patient's medical records so that their clinician could be alerted to any problems with adherence and the patient could be sent updates and reminders of clinic appointments.

With just over 6000 people diagnosed with HIV each year, the number of people living with HIV will continue to increase and so the number of people receiving antiretroviral therapy (ART). This means that the overall cost to the NHS of purchasing these drugs increases yearly but NHS England is under increasing financial pressure as their drug budget does not increase at the same rate. Some antiretroviral drugs have reached the end of their patent protection. Generic drugs, i.e. drugs with the same formula but manufactured by companies which did not develop the drugs, are considerably cheaper. Because ART drugs are purchased in bulk with a negotiated discount, NHS England do not publish the purchase price of the drugs. However, it is likely that a move to using generic drugs will result in a considerable cost saving. Although HIV clinics are being urged to change patient medications to equivalent generics, the choice of drug for a particular individual will still be made based on their specific circumstances. The results of Chapter 8 highlight the post-pregnancy period as a vulnerable time. For many women this would not be an appropriate time to switch treatment, particularly to a regimen with a higher pill or dose burden. Any reduction in adherence may lead to complications and therefore the need for more clinic visits,

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<sup>27</sup> [www.squeezyapp.co.uk](http://www.squeezyapp.co.uk)

negating any cost saving achieved by switching to cheaper drugs as well as posing a risk to the woman's health.

Some regimens are more forgiving to incomplete adherence than others. Long-acting injectable antiretroviral therapy is already being trialled. This way of administering treatment would negate the need for day-to-day adherence. At the moment it requires an injection every one to two months. In this form it would not be suitable for the post-partum women. However, in the future, developments could mean that it is longer acting and administered in a range of formats such as the case with long-acting contraception, which can be administered as injections or subdermal implants.

The interpretation of the findings in Chapter 8 in particular would be greatly enhanced by the collection and analysis of qualitative data. Mixed methods research, i.e. the combined use of quantitative and qualitative research to answer the same research question, is increasingly used in health research [516]. Future research could for example include semi-structured interviews with health advisors, HIV clinicians and with pregnant and post-partum women living with HIV. Used among pregnant and post-pregnant women, interview data could provide insights into the barriers to full drug adherence, factors affecting adherence and aid the development of effective interventions to promote drug adherence which could then be tested in randomised control trials.

For obvious ethical and practical reasons it is not possible to use randomised controlled trials (RCT), the gold standard for clinical studies, to investigate the effect of pregnancy on disease progression or the impact of antenatal ART use (compared to no ART use) on the mother's health. This means that observation data are heavily relied on in this area of study. There are some benefits to using observational data. For example, large amounts of data can be collected from multiple locations. This means the data reflect clinical practice from across the UK over a long period of time. Data are already collected by the clinician for the patient's clinical notes meaning that no additional resources are needed for data collection, only for combining the data from across all sites. An important limitation of using observation data is that although it is possible to account for measured confounders, such as age and duration of ART infection, unmeasured confounders cannot be adjusted for and are unlikely to be randomly distributed across the groups examined, as is the case with RCTs. Examples of possible confounders here include socioeconomic status, educational level, home location, co-morbidities, co-medications, parental responsibilities, work status, diet, languages spoken, alcohol consumption, illicit drug use, smoking status and BMI. Many

clinics now record patient's smoking status and BMI and I would recommend that where these data are recorded, that UK CHIC start to collect them. Perhaps most importantly, no information on drug adherence was available, something which is difficult to accurately record.

The linkage of two datasets introduced its own complexities. Where variables were only available from one of the studies, they could not be used in a combined analysis. For example, parity (i.e. the number of pregnancies before and after HIV diagnosis) and the date of arrival in the UK are collected in NSHPC but not UK CHIC. For variables collected by both studies, there were sometimes discrepancies which were either impossible or time consuming to reconcile. In many cases it was difficult to assess whether discrepancies were due to inaccurate reporting or incorrect linkage even after scrutinising the two records. The most problematic and time consuming discrepancies were those relating to ART use in pregnancy as described in Chapter 4.

Whilst the combining of the two datasets resulted in some improvements to data quality for the individual studies, for example filling in gaps in missing data, it also required a huge amount of work to create harmonised variables. The combining of HIV diagnosis data from both studies exposed how inaccurate this variable is, a variable used in many of the analyses in this thesis and other UK CHIC analyses. If HIV diagnosis date was only available from one of the studies, this date would have been taken as 'true' unless there was some discrepancy with another variable for the same person. Yet, when I examined the variable, it was clear that many of the diagnosis dates reported were either estimated dates or the first visit to the clinic; even when NSHPC records were linked to UK CHIC records from the same hospital only 27% of pairs had an identical HIV diagnosis date in both records. Therefore, care must be taken when interpreting 'duration since HIV diagnosis', a variable based on HIV diagnosis date.

There were some improvements in the data quality over time - particularly for the drug resistance data - but the amount of data was not consistent at all times and for all women. For many variables it is unlikely that missing data were missing completely at random – something which must be the case if multiple imputation techniques are to be used to impute missing variables.

Clinical and demographic data on patients seen at a single clinic can be used to address some research questions. In some circumstances, this information can be used to adapt services at that centre to address local issues or needs. However, the collection of data from numerous sites increases the sample size and the heterogeneity

of patients included in the cohort. The larger number of individuals included in the cohort is particularly important to provide sufficient statistical power when studying rare outcomes or if the patient group being examined is relatively small, as was the case in Chapter 6. However, because UK CHIC is a large dataset containing many variables from numerous sites, it is a complex task for the UK CHIC data manager to collate the data and produce a finalised datasets. This results in a considerable delay of around 9 months between the end of the calendar year and the point at which any analysis of the data or data linkage can begin. This delay can be problematic in a field where clinical practice can change so rapidly.

Since the initial development of the NSHPC and UK CHIC linkage (described in Chapter 3), which created a dataset containing data to 31<sup>st</sup> December 2009, the linkage has been repeated in each subsequent year. The SAS code which I wrote contains the linkage algorithm, creates the combined variables and harmonises variables where there are discrepancies. This code can be reused each year but the linkage is by no means an automated process, since additional variables are often introduced and there is often data cleaning required as well as the need for some manual review. In the future, there may be better, faster ways of collecting this data.

In 2014, Public Health England (PHE) replaced the New HIV Diagnosis dataset and the Survey of Prevalent HIV diagnosed (SOPHID) programmes (data from SOPHID) was used to estimate the completeness of the UK CHIC - NSHPC linkage in Chapter 3) with the new HIV and AIDS reporting system (HARS)[517]. Fully rolled out at the end of 2014, HARS collects attendance based data quarterly from all HIV clinics in the UK. Not only are data collected more regularly than by UK CHIC, sites are motivated to report data in accordance with the short deadline set, since their data are required by commissioners under the scheme which allows correct reimbursement to sites according to the number and type of patients attending their service. This means that HARS has a much shorter reporting delay than UK CHIC. However, HARS is a surveillance system rather than a research database. Far fewer variables are collected compared to UK CHIC, with clinical data limited to CD4 count, viral load, AIDS/other complexities and no obstetric data are collected.

At present, there is no obvious alternative way of collecting data equivalent to that collected in UK CHIC, data which, since its inception in 2001, have contributed to numerous international collaborations, informed decision-making, led to further research and guided policy and practice in the UK and internationally. Since 2004, there are been more than 100 research papers published in clinical journals which

have arisen from the UK CHIC study and its collaborations. The UK CHIC data have been used to estimate the life expectancy of people living with HIV [518] and assess the impact of late diagnosis on life expectancy [420]. The late diagnosis findings informed the decision to expand HIV testing in the UK to additional clinical settings including primary care where the prevalence of diagnosed HIV was above 2 in 1000 and resulted in numerous auditable outcomes relating to reducing late diagnosis in the 2013 BHIVA Standards of Care Report [519]. The findings also informed the Halve It campaign<sup>28</sup>, a coalition of national experts aiming to halve the proportion of people diagnosed with a CD4 count <350 cells/mm<sup>3</sup>, and are cited in the Introduction of the 2014 BHIVA treatment guidelines [420] and the 2014 National AIDS Trust report on Commissioning HIV Testing Services in England [520]. An analysis of outcomes in the first year of life-long ART, using UK CHIC data, found a similar virological response in men and women [459] informing BHIVA's recommendation that the first line regimen be the same for women and men [86]. In the near future, UK CHIC will continue to provide important data on patient outcome, response to newer HCV drugs, the transition of people from paediatric to adult HIV services, contributing to numerous areas of research including HIV and hepatitis co-infection and HIV and ageing.

Similarly, data collected by the NSHPC have informed HIV testing policy and HIV treatment guidelines as well as contributing to numerous collaborations including with COHERE and SOPHID [521]. PHE's HIV New Diagnoses, Treatment and Care in the UK Report [9] reports the very low transmission rate using data from the NSHPC [129] as does the Halve It Position Paper which uses the success of antenatal screening as a positive case study. Two papers from NSHPC [149, 151] were key to informing recommendations on when to initiate ART in pregnancy in the 2014 BHIVA Pregnancy guidelines [169]. An analysis published in 2014, which used NSHPC data to examine viral load at delivery among women having their second pregnancy, showed that women who were not on ART at conception were less likely to achieve viral suppression by delivery than women who had conceived on ART. This paper contributed to the case for lifelong ART [490] instead of short-course cART, which at the time was still the recommendation in the UK.

Both the NSHPC and UK CHIC have well-established protocols. However, it is important that the ways in which data are collected are continuously developed, not just to improve the efficiency and speed at which data are reported but also in line with developments in data security and technology. Whilst the best attempts are currently

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<sup>28</sup> [www.halveit.org.uk](http://www.halveit.org.uk)

made to maintain the security and integrity of the data, regular reassessment of security practices are required. As new tools become available for increasing security, these must be adopted where appropriate.

Although neither dataset include any unique identifiers, such as NHS number or National Insurance number, both studies collect some demographic data which could be used to identify the record of a particularly individual, for example using their ethnicity and date of birth, for malicious intent. The chance of being able to identify an individual increases after the linkage simply because there are more data variables for each individual in the dataset. The transfer of data from one location to another and the use of data by a large number of collaborators all increase the risk of a security breach. High profile breaches by local government, health clinics, and academic institutes are unusual but there have been a number of cases in the past few years. One such incident was an email containing a list of 780 clinic patients' names and email addresses sent out incorrectly from the 56 Dean Street clinic in Soho [522]. Not only do such breaches cause distress to the patients whose data are exposed, they also cause damage to the trust of anyone using or considering using the clinic. Concerns over the security of data can be heightened for people with HIV because they may fear stigma and discrimination. It is crucial that patients can trust that their clinical and personal data will be kept accurate and confidential.

The NSHPC have for a number of years used a secure data transfer website to transfer any study data. They are now piloting the use of a similar encrypted website for sites to report their data electronically. This will hopefully improve data security, data quality and the timeliness of data reporting. It is unlikely that in the near future the NSHPC could automatically collect data from the patients centralised health record but with improvements to the way data are stored within the clinic there is potential for the reporting of the data to NSHPC by the clinics to be hugely simplified or even automated, removing or reducing the burden of data reporting for the clinic staff.

The NHS attempted to create a national patient database Care.data, potentially the biggest patient database in the world. The benefit being that any clinician could review a patient's medical history in whichever health care setting they presented, improve the care of that individual, and that the large amounts of data could be used by researchers. However, Care.data was halted in February 2012 shortly before it was put into use and was officially brought to a close in July 2016 due to concerns over confidentiality and the control of access to the data [523] after a review by Dame Fiona Caldicott, the national data guardian. Although the work will be taken forward by the

National Information Board it is unclear whether we will ever have a fully connected database and if we do, to what extent people will opt-out of having their data included.

Even if Care.data or a similar database were rolled out, it is unlikely that data held within an HIV clinic would be part of a patient's record visible to other health care providers. Under the NHS (Venereal Diseases) Regulations 1974 and the NHS Trusts and Primary Care Trusts (Sexually Transmitted Diseases) Directions 2000 [390], the data held by sexual health services have for a long time been limited in the extent to which they are shared with other health professionals. For example, data on HIV diagnosis and the use of antiretroviral therapy are not included in a hospital-wide database or sent to a patient's GP, as is standard practice with other specialist care, unless the patient consents. Also, patients who do not wish to provide their personal data can still use sexual health services. This is due to both to the sensitive nature of the information and so that people with concerns over confidentiality are not dissuaded from using the service [524]. Even if HIV clinical data were kept separately from other clinical data, the developments required to create such a national database will hopefully result in improvements to all patient data storage and result in more standardisation between clinics in the way that patient data are recorded. This will hopefully make the transfer of data for research and surveillance purposes more automated as well as improving the data security. It may also increase the public's understanding of the value of using anonymised clinical data for research and commissioning – something which can ultimately improve patient outcomes by informing service provision and clinical management.

To summarise, in this work I have developed a linkage between two existing datasets. I then used the data available to examine specific questions about hepatotoxicity, viral rebound and the outcomes in women starting life-long ART who previously used short-term ZDVm or cART in pregnancy. Here, I have discussed some of the implications of the findings of the work, most importantly, the need for close monitoring of toxicity in pregnancy and additional drug adherence support for women following pregnancy. There are many other ways in which ART use in pregnancy could impact women's health during and after pregnancy. Although the linked dataset continues to provide a valuable resource for investigating clinical outcomes in patients attending care, improving the way in which data are collected, stored and transferred would be beneficial. Additional sources of data including qualitative data are likely to provide a more insightful resource for examining further research questions in this area.

## Appendix Ia Search terms

All searches were undertaken using MeSH (Medical Subject Headings) and free-text terms.

### **Pregnancy incidence and predictors of pregnancy**

Search 1: HIV terms

HIV or “human immunodeficiency virus” or HIV/AIDS or HIV[MeSH] or HIV Infections[MeSH]

Search 2:

("predictors of pregnancy") or (pattern\* AND pregnan\*) or ("pregnancy incidence")

Final search (#1 AND #2)

### **Response to treatment following short-term ART use in pregnancy:**

Search 1: HIV terms

HIV or “human immunodeficiency virus” or HIV/AIDS or HIV[MeSH] or HIV Infections[MeSH]

Search 2: Short-term use ART in pregnancy

(short-course or short-term or PMTCT) and (ART or HAART or “antiretroviral therapy” or “combination ART” or cART or “zidovudine monotherapy” or ZDVm or Anti-HIV Agents[MeSH] or Antiretroviral Therapy, Highly Active[MeSH]) and (pregnancy[MeSH] or pregnant)

Search 3: ART

(previou\* and (“treated” or “exposed”)) or Drug Resistance[MeSH] or Retreatment[MeSH] or (response and (treatment or therap\* or HAART)

Final search (#1 AND #2 AND #3)

**Hepatotoxicity:**

Search 1: HIV terms

HIV or “human immunodeficiency virus” or HIV/AIDS or HIV[MeSH] or HIV Infections[MeSH]

Search 2: Maternal/pregnancy terms

Matern\* or pregnan\* or intrapartum or intra-partum or Pregnancy[MeSH] not “in infants” not ((HIV-uninfected or uninfected or HIV-exposed or “HIV-exposed breastfed”) and (infant\* or newborn\* or children))

Search 3: ART

ART or HAART or “antiretroviral therapy” or “combination ART” or cART or Anti-HIV Agents[MeSH] or Antiretroviral Therapy, Highly Active[MeSH] or HIV Infections/Drug therapy[MeSH]

Search 4: Hepatotoxicity

Hepatotoxicity or toxicity or (liver and enzyme\*) or ALT or “alanine transaminase” or Liver[MeSH]

Final search (#1 AND #2 AND #3 AND #4)

**Postpartum viral rebound:**

Search 1: HIV terms

HIV or “human immunodeficiency virus” or HIV/AIDS or HIV[MeSH] or HIV Infections[MeSH]

Search 2: Post-pregnancy terms

“post pregnancy” or “post pregnant” or post-pregnancy or post-pregnant or postpartum or post-partum

Search 3: ART

ART or HAART or “antiretroviral therapy” or “combination ART” or cART or Anti-HIV Agents[MeSH] or Antiretroviral Therapy, Highly Active[MeSH] or HIV Infections/Drug therapy[MeSH]

Search 4: Viral rebound

“viral rebound” or “viral load” or “detectable viral load”

Final search (#1 AND #2 AND #3 AND #4)

## Appendix 1b Summary tables for published research

Table 1. Outcomes and disease progression following pregnancy in the pre-highly active antiretroviral therapy (HAART) era

Study design and setting	Inclusion group (sample size)	Outcome measures	Findings
<p>French, 1998 [186] Systematic review and meta-analysis Articles published 1983-1996</p>	<p>The impact of pregnancy on disease progression among women with HIV  (n=7 studies included in meta-analysis including Hocke,1995 [187] and Weisser, 1998 [182])</p>	<p>Death HIV disease progression Progression to AIDS Fall in CD4 count to &lt;200 cells/mm<sup>3</sup></p>	<p>Summary ORs pregnancy vs. no pregnancy:  Death: 1.8 [95% CI 0.99-3.3]  Disease progression: 1.41 [0.85-2.33]  Progression to AIDS: 1.63 [1.00-2.67]  Fall in CD4 to &lt;200: 0.73 [0.17-3.06]  HIV progression was more common in developing countries.  Summary: there does appear to be an association between pregnancy and disease progression, but the association is weak and further studies are required.</p>
<p>Alliegro, 1997 [189] Prospective study of HIV-positive women 14 HIV clinics in Italy 1981-1994</p>	<p>Women with known seroconversion date (within a 2 year period)  (n=331)</p>	<p>HIV-related diseases  AIDS  CD4 count &lt;100 cells/mm<sup>3</sup></p>	<ul style="list-style-type: none"> <li>• 11% of women were pregnant at HIV diagnosis</li> <li>• 29% of women had a pregnancy during follow-up</li> </ul> <p>Summary: Pregnant women did not experience more rapid disease progression</p>

Table 1. continued: Outcomes and disease progression following pregnancy in the pre-HAART era

Study design and setting	Inclusion group (sample size)	Outcome measures	Findings
<p>Buskin, 1998 [188] Observational study of adults attending care Seattle, US To 1997</p>	<p>Women attending care PW and non-PW were compared (n=372)</p>	<p>AIDS</p>	<ul style="list-style-type: none"> <li>• 15% of women were pregnant at HIV diagnosis</li> <li>• 29% of women had a pregnancy during follow-up</li> </ul> <p>Summary: In adjusted analysis, women pregnant at baseline were no more likely to develop AIDS than women not pregnant at baseline.</p>
<p>Bessinger, 1998 [190] Retrospective study New Orleans, US 1989-1995</p>	<p>Women aged 15-35 years old attending HIV clinical care PW (n=192) were compared to non-PW (n=164).</p>	<p>Death AIDS HIV-related disease</p>	<p>PW were more likely to be African-American, &lt;22 years old and have a higher CD4 count. Summary: Pregnancy was not significantly associated with any of the outcomes.</p>
<p>Brettell, 1995 [191] Observational study Edinburgh, UK 1985-1992</p>	<p>Women attending HIV clinical care at the city hospital. (n=145)</p>	<p>CD4 cell count CD8 cell count CD4% CD8%</p>	<p>Pregnancy had no effect on immunological markers of HIV Pregnancy after sero-conversion was associated with an increase in CD4% and decrease in CD8%</p>

Table 1. continued: Outcomes and disease progression following pregnancy in the pre-HAART era

Study design and setting	Inclusion group (sample size)	Outcome measures	Findings
Saada, 2000 [192] Prospective cohort France 1989- June 1997	Comparison of women who did not have a pregnancy during follow-up (n=124) and women who did (n=241) (no ART received).	AIDS	Pregnancy was not associated with progression to AIDS in adjusted analysis accounting for time since seroconversion.
Weisser, 1998 [182] Prospective cohort Switzerland 1986-1993	PW with 6 months post-pregnancy follow-up (n=32) were compared to controls with no pregnancy matched on age and CD4 count (n=416)	Any AIDS-defining event Specific AIDS-defining event Death Cox proportional hazards	Any AIDS event: RR 1.92 [0.80-4.64] (p-value 0.15) Recurrent bacterial pneumonia: RR 7.98 [1.73-36.8] p-value 0.01). Death: RR 1.14 [0.48-2.72] (p-value 0.8)
Hocke, 1995 [187] Prospective cohort France	Women with a pregnancy (n=57) were compared to controls, women with no pregnancy (n=114) matched on age, CD4 count, and year of HIV diagnosis	Death AIDS-defining event Fall in CD4 count <200 cells/mm <sup>2</sup>	Pregnancy vs. No-pregnancy Death: aHR 0.92 [0.40-2.12] AIDS: aHR 1.02 [0.48-2.18] CD4 <200: aHR 1.20 [0.63-2.27]

CI: confidence interval; OR: odds ratio; PW: pregnant women; RR: rate ratio; US: United States of America.

Table 2. Outcomes and disease progression after ART use in pregnancy

Study design and setting	Inclusion group (sample size)	Outcome measures	Findings
Use of zidovudine monotherapy (ZDVm) in pregnancy			
Bardeguez, 2003 [193] Placebo-controlled trial US Jan 1995 -Aug 1996	HIV-positive women (asymptomatic and with CD4>200) were randomised to receive ZDVm or a placebo drug during pregnancy (n=226)  3-6 years follow-up	Disease progression (CDC category B clinical event) Time to AIDS/death Single ZDV resistance mutation	Risk of AIDS/death was similar for both groups (RR 0.73 [90% CI 0.46-1.17] (not 95% CI) as was disease progression (RR 0.89 [90% CI 0.58-1.36])  Genotypic ZDV resistance found in 9% of zidovudine group and 11% of placebo group (not statistically significant difference – but no p-value given)
Watts, 2003 [382] Phase 3 Clinical trial US & Puerto Rico 1993-1997	Pregnant women (n=497) using short-course ZDVm or remaining on ZDVm after pregnancy	Monitored at: 12, 26, 48 & 78 weeks pp VL changes after delivery CD4 changes after delivery AIDS/death	Observed a rise in VL at 12 weeks pp in the group who remained on ZDVm/cART and short-course ART group  Women on cART had less chance of AIDS/death than women on ZDVm who had less chance than women not on any ART
Use of short-course cART in pregnancy			
Pilotto, 2011 [255] Brazil May 2005-2007	PW stopping ART after delivery with CD4 count >200 cells/mm <sup>3</sup> at start of ART – (the CD4 threshold for treatment at the time) (n=120).	WHO event 2-3 Starting ART treatment i.e. CD4<200/WHO event 4	Event 2-3 - incidence rate 13/100 PY Started therapy rate 6/100 PY  Lower CD4 count at delivery was associated with increased risk of both outcomes

Table 2. continued: Outcomes and disease progression after ART use in pregnancy

Study design and setting	Inclusion group (sample size)	Outcome measures	Findings
Comparing regimens used for short-course cART in pregnancy			
Lehman, 2009 [525] Short-course ZDVm/sdNVP compared to cART (See Table 3)			
Watts, 2009 [249] Prospective observational study Multiple US cites Jun 1994-Jun 2006	Pregnant women with CD4 >350 using ART in pregnancy (n=206) 1) short-course ZDVm (n=41) 2) remained on ZDVm (n=62) 3) short-course cART (n=18) 4) remained on cART (n=82)	Monitored during pregnancy, at delivery and for one year pp pp CD4 slope, CD4% and VL CDC class B/C events Biological markers of CVD risk	No significant differences in CD4 slope was observed after pregnancy No women developed class C event Class B events in women who stopped therapy vs. continued HR 2.09. p-value 0.14 Biomarker data too limited for statistical comparison between groups
Shapiro, 2013 [247] Randomised clinical trial of HAART used for PMTCT Botswana July 2006 - May 2008	HIV-positive ART naïve pregnant women with CD4>200 choosing to breastfeed Women were given ART until earliest of end of weaning or 6 months pp Randomised to: NRTI arm: Trizivir (ABC/ZDV/3TC) (n=285) PI arm: Kaletra (LPV/r/ZDV/3TC) (n=170)	24 month maternal outcomes: death, CD4<200. Also examined infant outcomes (i.e. HIV infection and survival)	Time to death/CD4<200 was shorter in the NRTI arm than the PI arm CD4 count increase was greater in the PI arm than the NRTI arm

Table 2. continued: Outcomes and disease progression after ART use in pregnancy

Study design and setting	Inclusion group (sample size)	Outcome measures	Findings
<p>Kesho Boro Study Group, 2012 [248]</p> <p>Randomised control trial</p> <p>Burkina-Faso, Kenya and South Africa</p> <p>Jan 2005 – Aug 2008</p>	<p>HIV-positive ART naïve pregnant women with CD4&gt;200 choosing to breastfeed.</p> <p>Women were randomised to:</p> <p>PI arm: Kaletra (LPV/r/ZDV/3TC) (n=384) until earliest of end of weaning or 6 months pp</p> <p>ZDVm/sdNVP arm: ZDVm until delivery and sdNVP at onset of labour (plus 1 pp week ZDV+3TC since Dec 2006) (n=405)</p>	<p>18 months maternal outcomes</p> <p>1a: clinical progression to WHO clinical stage 4/death</p> <p>1b: clinical/immunological progression (stage4/death/CD4&lt;200)</p> <p>2. Among women with baseline CD4&gt;350, progression to stage 3 or CD4&lt;350</p>	<p>Rates of disease progression were similar in both groups after cessation of ART but women on cART (PI) had lower progression risk whilst on ART (i.e. pp but before stopping ART)</p> <p>Low progression rates (&lt;5%) in both groups among women with baseline CD4 count ≥350</p>
<p>Souda, 2013 [469]</p> <p>Randomised control trial</p> <p>Botswana</p> <p>July 2006-May 2008</p>	<p>ART naïve PW (CD4 ≥200) were randomised to receive either</p> <p>1) NNRTI (ABC/ZDV/3TC)</p> <p>2) PI (LPV/r/ZDV/3TC)</p> <p>ART was discontinued at 6 months postpartum (total=560)</p>	<p>RNA samples were taken at 7 months pp and tested for drug resistance (total=85; NRTI arm n=42; PI arm=43)</p> <p>Stanford HIV drug resistance database</p>	<p>No major antiretroviral drug resistance mutations were detected in either arm</p> <p>Minor mutations were found but similar to those found in ART naïve groups</p>
<p>Kekehasi, 2007 [278]</p> <p>Prospective cohort</p> <p>Brazil</p> <p>Jan-Sept 2004</p>	<p>PW using cART after 24 weeks pregnancy (n=30) (63% on NFV/ZDV/3TC)</p>	<p>Genotypic resistance test at 24 weeks gestation (before ART) and at ART cessation.</p>	<p>4/17 women (24%) using NFV regimen had new resistance mutations at ART cessation.</p>

Table 2. continued: Outcomes and disease progression after ART use in pregnancy

Study design and setting	Inclusion group (sample size)	Outcome measures	Findings
Perez, 2008 [468] Prospective Argentina	PW who used short-course 3TC/ZDV/NVP in pregnancy (n=20)	Assess mutations associated with resistance to 3TC or NVP after ART discontinuation using PCR	<p>35% of pp women had <math>\leq 0.01\%</math> virus with mutation at K103N (associated with NVP resistance)</p> <p>10% of pp women had <math>\leq 0.5\%</math> virus with mutation at Y181C (associated with NVP resistance)</p> <p>65% of pp women had <math>&lt; 0.9\%</math> with mutation at M184V (associated with 3TC resistance)</p> <p>4 women restarted the same treatment and achieved viral suppression</p>
Comparing use of short-course cART to continued use of cART following pregnancy			
Melekhin, 2010 [250] Retrospective cohort Nashville, USA 1997-2008	<p>Comparison of pp women continuing cART (n=69 ) or discontinuing cART (n=54) (total=123 women)</p> <p>Categorised according to ART use up to 90 days pp</p>	<p>AIDS defining event or all-cause death;</p> <p>non-AIDS defining event or all-cause death</p>	<p>In adjusted analyses, women who discontinued cART had worse outcomes than women who continued cART but this association was NOT statistically significant</p> <p>AIDS event/death HR 0.50 [0.12-2.12]</p> <p>Non-AIDS event/death HR 0.69 [0.24-1.95]</p>

Table 2. continued: Outcomes and disease progression after ART use in pregnancy

Study design and setting	Inclusion group (sample size)	Outcome measures	Findings
Onen, 2008 [251] Observational study US 1997-2005	Women who received ZDVm or cART in pregnancy  Comparison of women who continued on ART (n=49) with those who discontinued (n=123) after delivery. Total (n=172).	Risk of opportunistic infection	Number of OI was higher in women who discontinued ART after pregnancy (4%) than in women who continued ART (9%) as was death (0% vs. 2%) but the difference in risk was not statistically significant p=0.26  No cox proportional hazards analysis
Coria, 2012 [254] Retrospective observational study Haiti 1999-2005	pp women who stopped ART after delivery (n=508 women) with CD4 count >200 at start of ART (the CD4 threshold used at the time)  Compared women on cART from delivery (n=48) with women on short-course ART, stopping at delivery (n=313)  (ZDV/3TC/NVP regimen)	Time to cART treatment initiation or death  Time to CD4 count<350  Time to subsequent pregnancy  LTFU	Women on cART from delivery: 4.0 deaths/100 PY in first 3 years after delivery  Women on short-course ART: 4.9 deaths/100 PY in first 3 years after delivery  Median CD4 count at treatment start (after pregnancy) was 106 cells/mm <sup>3</sup> - below recommended (CD4 200 cells/mm <sup>3</sup> )  In cART from delivery group, all deaths occurred <100 days after starting ART in women with CD4<350  High rates of LTFU, higher than among women remaining on therapy

Table 2. continued: Outcomes and disease progression after ART use in pregnancy

Study design and setting	Inclusion group (sample size)	Outcome measures	Findings
Giuliano, 2013 [252] Observational study Malawi Feb 2008 – Feb 2009	PW (n=311) received short-course ART (CD4 ≥350) or treatment (CD4<350) (NVP-based)	Disease progression at 24 months pp	No statistical comparison between groups  Many of the women who discontinued treatment (short-course ART group) restarted ART due to a subsequent pregnancy or indication to start life-long ART i.e. reached CD4 cut off
Minnear, 2014 [253] Prospective, non-randomised clinical trial Kenya 2003-2009	Women started cART at 34 weeks pregnancy. They either discontinued at 6 months postpartum (n=366), or, if they had CD4 count <250 or WHO stage 3/4, remained on ART (n=82).	Outcomes at 24 months postpartum: maternal TB, maternal death, infant death, vertical transmission, LTFU.  In women in the short-course ART group: risk of CD4 decline following ART cessation according to CD4 at initiation, discontinuation and viral suppression at discontinuation	Infant death/HIV infection was more common in women who discontinued ART (n=10.1%) than in women who continued on ART (n=2.4%) (unadjusted analysis)  In women who discontinued ART, the CD4 count decline was rapid.  Women who initiated ART with CD4<500 and discontinued with CD4 350-500 were at higher risk of having to start treatment within 6 months than women who initiated ART with CD4>500 or women who initiated ART at CD4<500 and discontinued with CD4 ≥500

3TC: lamivudine; ABC: abacavir; CD4: CD4<sup>+</sup> cell count (cells/mm<sup>3</sup>); CDC: US Centre for Disease Control; CI: confidence interval; CVD: cardiovascular disease; HR: hazard ratio; LPV/r: ritonavir boosted lopinavir; LTFU: lost to follow up; NFV: nelfinavir; NRTI: nucleoside reverse transcriptase inhibitor; OI: opportunistic infections; PCR: polymerase chain reaction; PI: protease inhibitor; pp: post pregnancy; RR: risk ratio; sd-NVP: single-dose nevirapine; TB: tuberculosis; US: United States of America; WHO: World Health Organization; ZDV: zidovudine; ZDVm: zidovudine monotherapy.

Table 3. Response to treatment started after use of single dose nevirapine (sdNVP) in pregnancy

Study design and setting	Inclusion group (sample size)	Outcome measures	Findings
<p>Jourdain, 2004 [274] Prospective observational study Thailand (37 sites) 2002</p>	<p>Women starting NVP-containing triple therapy who had received NVP+ZDV or ZDV for PMTCT as part of a double-blind, randomized, placebo-controlled trial comparing the use of NVP+ZDV with ZDV for PMTCT  (NVP+ZDV=221; ZDV=48; Total=269)</p>	<p>1: Virological response at 3 months and 6 months (VL&lt;50)  2: Among women with NVP exposure the association between virological failure and resistance mutations at 10 weeks pp  Drug resistance mutations at 10 days pp among women with VL&gt;400.</p>	<p>34% had VL&lt;50 at 3 months 49% had VL&lt;50 at 6 months  NVP exposure and high VL at baseline were independently associated with detectable VL after 6 months on treatment  NVP exposure was not independently associated with immunological outcome (increase in CD4 from baseline to 6 months)</p>
<p>Lockman, 2007 [280] Prospective observational study Botswana  Women recruited to clinical trial March 2001-October 2003 who started treatment before October 2004</p>	<p>Women starting NVP-containing triple therapy (symptomatic or CD4&lt;200) who had received NVP+ZDV or ZDV for PMTCT as part of a double-blind, randomized, placebo-controlled trial comparing the use of NVP+ZDV with ZDV for PMTCT  (NVP+ZDV=112; ZDV=106; Total=218)</p>	<p>1: Virological failure at 6 month (VL ≥400)  2: Virological failure at 12 and 24 months  3: Time to virological failure</p>	<p>NVP exposure was associated with virological failure if women started treatment within 12 months of NVP exposure, but not if women started treatment &gt;12 months after NVP exposure  NVP exposure and baseline CD4 count were associated with time to virological failure  NVP exposure was not independently associated with immunological outcomes</p>

Table 3. continued: Response to treatment started after use of single dose nevirapine (sdNVP) in pregnancy

Study design and setting	Inclusion group (sample size)	Outcome measures	Findings
<p>Coffie, 2008 [220] Prospective cohort study Côte d'Ivoire Aug 2003-Sept 2006 (Related study: Ekouevi, 2011 [281])</p>	<p>Women starting NNRTI-based treatment regimen (with symptoms or CD4&lt;350) Group 1: ART naïve Group 2: sdNVP or sdNVP + ZDV for PMTCT Group 3: ZDV and 3TC for PMTCT (Group 1=109; Group 2=52; Group 3=86; Total=247)</p>	<p>Outcomes at 12 months on treatment</p> <ol style="list-style-type: none"> <li>1: Immunological failure (30% fall from CD4 peak during treatment)</li> <li>2: Virological failure (VL&gt;500)</li> <li>3: Treatment failure (worsening disease/death/immunological failure/virological failure)</li> </ol> <p>Resistance test at week 4 pp (in groups 2 &amp; 3) and at virological failure</p>	<p>Overall: 11% developed immunological failure, 19% developed virological failure</p> <p>NVP resistance was not associated with virological or immunological failure at 12 months (21 months median time between NVP exposure and ART start)</p> <p>3TC resistance (at 4 weeks pp) was associated with virological failure but with immunological failure</p> <p>Virological failure was associated with poor adherence, 3TC resistance at 4 weeks pp and baseline CD4&lt;200</p>

Table 3. continued: Response to treatment started after use of single dose nevirapine (sdNVP) in pregnancy

Study design and setting	Inclusion group (sample size)	Outcome measures	Findings
<p>Ekouevi, 2011 [281] Prospective cohort study Côte d'Ivoire Aug 2003-Sept 2005 (Related study: Coffie, 2008 [220])</p>	<p>Women starting NNRTI-based treatment regimen (with symptoms or CD4&lt;350). Group 1: ART naïve Group 2: sdNVP or sdNVP and short-course ZDV for PMTCT Group 3: short-course ZDV and 3TC for PMTCT. (Group 1=109; Group 2=50; Group 3=81; Total=240)</p>	<p>Outcomes at 36 months on treatment 1: Immunological failure (50% fall from CD4 peak during treatment) 2: Treatment failure (immunological failure or death within 36 months on treatment). ART drug adherence Censored at last visit, death or treatment switch to a PI. Resistance test at week 4 pp (in groups 2&amp;3) and at virological failure.</p>	<p>Overall, 20% developed immunological failure and 26% developed treatment failure Immunological failure was not associated with NVP or 3TC exposure or the presence of a NVP or 3TC resistance mutation at week 4 pp It was associated with poor drug adherence (21 months median time between NVP exposure and ART start)</p>
<p>Kuhn, 2009 [282] Zambia May 2001-September 2004</p>	<p>Women starting cART after sdNVP exposure (n=161).</p>	<p>Association between viral suppression within 6 months (VL&lt;400) and the interval between sdNVP use and starting treatment</p>	<p>Women with &lt;6 months interval were least likely to suppress VL. Women with an interval of 6-12 months were also less likely to suppress than women with an interval of &gt;12 months.</p>

Table 3. continued: Response to treatment started after use of single dose nevirapine (sdNVP) in pregnancy

Study design and setting	Inclusion group (sample size)	Outcome measures	Findings
<p>Chi, 2007 [279] Prospective observational study Zambia (26 sites) April 2004-July 2006 (Related study: Chintu, 2010 [526])</p>	<p>Women starting NVP-containing triple therapy with and without previous exposure to NVP NVP exposed n=229 NVP-unexposed n=1530 Total n=1759</p>	<p>1: CD4 cell count change 2: Death 3: Treatment failure at 6 and 12 months</p>	<p>NVP exposure was <b>not</b> associated with CD4 response at 6 or 12 months or with mortality (within 12 months) Women with exposure to NVP &lt;6 months before starting treatment were more likely to experience treatment failure than NVP-naïve women</p>
<p>Chintu, 2010 [526] Prospective observational study Zambia April 2004-July 2006 (Related study: Chi, 2007 [279])</p>	<p>Women starting NNRTI-containing treatment with and without previous exposure to NVP in pregnancy NVP exposed n=596 NVP-unexposed n=4576</p>	<p>Mortality and treatment failure (worsening WHO clinical staging/CD4 drop below 95% pre-ART CD4/switch of regimen) after 12 months Adherence data was collected</p>	<p>Treatment failure was not significantly associated with previous NVP exposure Women with previous NVP use had better survival (p-value 0.07)</p>
<p>Lehman, 2009 [525] Randomized clinical trial Kenya</p>	<p>PW with CD4 count 200-500 cells/mm<sup>3</sup> Randomised at 34/40 weeks to 1) ZDVm and sdNVP in pregnancy or 2) cART (ZDV+NVP+3TC) for last 6 weeks of pregnancy plus 6 months breastfeeding</p>	<p>Detection of NVP resistance at 3 months after treatment cessation (using PCR)</p>	<p>Women in ZDV/NVP group were more likely to have resistance mutation at 3 months after ART cessation than women in cART group (75% vs. 18%, OR 13.5 p-value 0.007)</p>

Table 3. continued: Response to treatment started after use of single dose nevirapine (sdNVP) in pregnancy

Study design and setting	Inclusion group (sample size)	Outcome measures	Findings
Stringer, 2010 [283] Prospective observational non-inferiority study Zambia n=509 Kenya n=152 Thailand n=217 June 2006-Jan 2007	Women starting NNRTI-containing treatment with and without previous exposure to NVP in pregnancy  sdNVP exposed n=355 NVP-unexposed n=523	1: Treatment failure at 48 weeks (death, regimen switch or VL $\geq$ 400 at 24/48 weeks)	Overall, 28% of women had treatment failure at 48 weeks  Women with an interval <6 months between exposure and treatment: - NVP exposure increased the risk of treatment failure  Women with a 7-12 month interval: NVP exposure increased risk of treatment failure but not statistically significant  Women whose exposure interval was >12m - no evidence of increased risk.
Coovadia, 2009 [527] Prospective observational study Johannesburg, South Africa July 2004-May 2006	Women starting NNRTI-containing treatment with and without previous exposure to sdNVP (18-36 months earlier).  (sdNVP exposed=94; NVP-unexposed=60)	1. Time to viral suppression (VL<50) 2. Viral suppression at 24 weeks 3. Time to viral rebound (2 consecutive VL>400 following viral suppression) 4. Viral rebound at 78 weeks  Viral RNA and proviral DNA tested for K103N mutation	10% sdNVP-exposed women had K103N mutation  15% drug naïve women had K103N mutation  K103N mutation predicted inadequate virological response  A similar % of women in both groups achieved viral suppression or developed viral rebound (unadjusted analysis).

3TC: lamivudine; cART: combination antiretroviral therapy; CD4: CD4<sup>+</sup> cell count (cells/mm<sup>3</sup>); NNRTI: non-nucleoside reverse-transcriptase inhibitor; PI: protease inhibitor; PMTCT: prevention of mother-to-child transmission; pp: post-pregnancy; sdNVP: single dose nevirapine; VL: viral load (copies/ml); ZDV: zidovudine.

Table 4. Response to treatment started after use of short-course cART in pregnancy

Study design and setting	Inclusion group (sample size)	Outcome measures	Findings
Vogler, 2014 [286] Prospective clinical trial HIV treatment sites in US, Brazil & Peru Oct 2007-Dec 2009	Non-PW starting treatment on combination of EFV + TDF/FTC with ≥1 previous use of short-course ART in pregnancy No use of ART in the past 24 weeks VL ≥500 copies/ml (Brazil=22; Peru=20; US=12; Total=54)	1: Virological response (VL <400) at 24 weeks after ART start 2: Characterise drug resistance mutations among women with virological failure (defined as two consecutive VL ≥400 at ≥16 weeks after ART start) 3: Self-reported drug adherence	1: 81% women had virological response at 24 weeks. No characteristics were predictive of virological response. 3. Virological failure was associated with poor adherence. “Provides further support that virological response in HIV-1–infected women to a commonly used initial cART regimen is not compromised by prior PMTCT with cART”.

cART: combination antiretroviral therapy; EFV: efavirenz; FTC: emtricitabine; PMTCT: prevention of mother-to-child transmission; PW: pregnant women; TDF: tenofovir; US: United States of America; VL: viral load (copies/ml).

Table 5. Hepatotoxicity rates among pregnant HIV-positive women

Study design and setting	Inclusion group	Toxicity measure	Regimen used	Findings
Hitti, 2004 [236] Drug trial US - Aug 2003	Women starting ART in pregnancy (>late second trimester) (hepatitis co-infected women excluded)	Treatment limiting toxicity	NVP-containing	29% (5/17) experienced toxicity
			NFV-containing	5% (1/21) experienced toxicity
Marazzi, 2006 [239] Retrospective cohort Mozambique May 2002 - July 2004	PW starting ART in pregnancy	Liver enzyme elevation (LEE)	NVP-containing	12.3% (86/703) Grade 2-4 LEE 6.5% (46/703) Grade 3-4 LEE High CD4 count when starting ART was not independently associated with LEE
João, 2006 [237] Retrospective cohort Brazil Jan 1996- Dec 2003	PW starting ART in pregnancy	LEE	NVP-containing	5.1% (10/197) Grade 1-4 LEE 0.5% (1/197) Grade 3-4 LEE HCV co-infection was the only factor independently associated with hepatotoxicity. CD4 count was only protective if the cut off for 'high' CD4 category was >600 cells/mm <sup>3</sup>
Lyons, 2006 [288] Retrospective cohort 3 HIV centres Dublin Oct 2000 – Feb 2003	Women prescribed NVP-containing regimen in pregnancy	LEE	NVP-containing	8.2% (7/85) Grade 1 LEE 16.4% (14/85) Grade 2 LEE 9.4% (8/85) Grade 3-4 LEE 10% discontinued ART in preg due to LEE Pre-treatment CD4 count was associated with LEE

Table 5. continued: Hepatotoxicity rates among pregnant HIV-positive women

Study design and setting	Inclusion group	Toxicity measure	Regimen used	Findings
Jamisse, 2007 [240] Prospective cohort Mozambique Aug 2004 – Jun 2005	Women prescribed NVP-containing regimen in pregnancy	LEE	NVP-containing	7.5% (11/146) Grade 2-4 LEE 2.7% (4/146) Grade 3-4 LEE Baseline CD4 $\geq$ 250 was associated with increased risk of Grade 3-4 but not Grade 2-4.
Kondo, 2007 [241] Retrospective cohort Brazil Jan 2003 – Dec 2006	PW starting ART	LEE	NVP-containing	4.5% (6/133) Grade 1-4 LEE 1.5% (2/133) Grade 3-4 LEE
van Schalkwyk, 2008 [242] Retrospective study US Jan 1997 – Feb 2004	PW on ART (starting during and before pregnancy)	Treatment change required due to toxicity	NVP-based (54%) and non-NVP-based (46%)	7% (7/103) changed treatment due to toxicity overall 11% (6/56) NVP-based group 2.1% (1/47) non-NVP-based group
Black, 2008 [243] Retrospective study South Africa Aug 2004 – Feb 2007	Treatment naïve PW starting ART	Treatment change required due to toxicity	HAART (82% using NVP+d4T+3TC)	2.6% women (16/620) switched to a different regimen in pregnancy due to toxicity 3.5% experienced NVP associated rash

3TC: lamivudine; ALT: alanine transaminase; d4t: stavudine; LEE: liver enzyme elevation; NFV: nelfinavir; NVP: nevirapine; PW: pregnant women; ULN: upper limit of normal; US: United States of America.

Table 6. Comparing LEE in pregnant women on NVP-containing and non-NPV-containing regimens

Study design and setting	Inclusion group	Toxicity measure	Regimen used	Findings
Peters, 2012 [352] Prospective study Kenya July 2003-Nov 2006	PW starting cART at 34 weeks gestation	Severe LEE (grade 3-4)	NVP-containing NFV-containing	Overall, 3% (14/522) experienced severe LEE Women on NVP-regimen (n=254) had higher rates of severe LEE than women on NFV-regimen (4.6% vs. 1.0%, p-value 0.03) Baseline CD4 count $\geq 250$ was not associated with severe LEE in women on NVP-regimen
Ouyang, 2010 [324] Multi-centre prospective cohort US July 2002-June 2006	Women using cART in pregnancy	Any LEE (grade 1-4) Severe LEE (grade 3-4)	NVP-containing (n=218, 18%) non-NVP containing (n=1011) Cox proportional hazards regression models using time-dependent covariates (pregnancy assessed as baseline variable but includes pregnancies conceived on ART)	Any LEE: 13% PW on NVP-regimen 14% PW on non-NVP-regimen aRR: 1.00 [0.64-1.57] p-value 0.99 Severe LEE: 0.5% PW on NVP-regimen 1.4% PW on non-NVP-regimen In adjusted analysis using a NVP-regimen was not associated with LEE or severe LEE

Table 6. continued: Comparing LEE in pregnant women on NVP-containing and non-NPV-containing regimens

Study design and setting	Inclusion group	Toxicity measure	Regimen used	Findings
<p>Timmermans, 2005 [316] Retrospective study 15 HIV centres Netherlands Jan 1997-June 2003</p>	<p>PW and non-PW starting NVP-containing or NFV-containing regimens</p>	<p>ALT/AST <math>\geq 3x</math> ULN</p>	<p>NVP-containing &amp; NFV-containing</p>	<p>NVP-containing regimen: PW: 19% (11/58) experienced toxicity non-PW: 4% (4/95) experienced toxicity  NFV-containing regimens: PW: 4% (5/128) experienced toxicity non-PW: 4% (4/91) experienced toxicity  No adjusted analysis performed</p>
<p>Aaron, 2010 [358] Retrospective study 3 HIV clinics US Jan 1999-August 2005</p>	<p>PW on NVP-regimen (n=79) PW on non-NVP-regimen (n=67) Non-PW on NVP-regimen (n=61) Non-PW on non-NVP-regimen (n=392)</p>	<p>LEE (<math>\geq</math>grade 2)</p>	<p>NVP-containing (n=140) and non-NVP containing (n=459)</p>	<p>NVP-containing regimen: PW: 2.5% (2/79) experienced LEE non-PW: 6.6% (4/61) experienced LEE  NFV-containing regimens: PW: 0% (0/67) experienced LEE non-PW: 5.4% (21/392) experienced LEE  Pregnancy status (at baseline), using NVP-regimen and baseline CD4 &gt;250 were not associated with LEE in adjusted analysis.</p>

ALT: alanine transaminase; AST: aspartate transaminase; aRR: adjusted relative risk; CD4: CD4<sup>+</sup> cell count (cells/mm<sup>3</sup>); LEE: liver enzyme elevation; NFV: nelfinavir; NVP: nevirapine; PW: pregnant women; ULN: upper limit of normal; US: United States of America.

Table 7. Summary of studies comparing LEE in pregnant women and non-pregnant women

Study design and setting	Inclusion group	Toxicity measure	Regimen used	Findings
<p>Phanuphak, 2007 [320]</p> <p>Retrospective study</p> <p>Thailand</p> <p>1996 onwards</p>	<p>PW (n=244), non-PW (n=87) &amp; men (n=78)</p> <p>PW started long-term ART &gt;14 weeks gestation (CD4≤200) or started short-course cART &gt;28 weeks gestation (CD4&gt;200).</p> <p>Non-PW and men started long-term cART with CD4≤200</p>	<p>ALT LEE (grade 1/2 and grade 3/4)</p> <p>Note: ALT measurements were taken at regular intervals</p>	<p>NVP-containing regimens</p>	<p>LEE: Grade 1-2</p> <p>PW on short-course ART 19.5/100PY</p> <p>PW on therapy 12.3/100PY</p> <p>Non-PW on therapy 9.8/100PY</p> <p>Men on therapy 29.8/100PY</p> <p>LEE: Grade 3-4</p> <p>PW on short-course ART 1.6/100PY</p> <p>PW on therapy 0.0/100PY</p> <p>Non-PW on therapy 0.0/100PY</p> <p>Men on therapy 2.0/100PY</p> <p>LEE: Grade 1-4</p> <p>PW on short-course ART 21.1/100PY</p> <p>PW on therapy 12.3/100PY</p> <p>Non-PW 9.8/100PY</p> <p>Men 31.8/100PY</p> <p>Neither pregnancy status or female gender were associated with LEE in analysis adjusted for baseline characteristics</p>

Table 7. continued: Summary of studies comparing LEE in pregnant women and non-pregnant women

Study design and setting	Inclusion group	Toxicity measure	Regimen used	Findings
Ouyang, 2009 [317] 2 prospective cohorts US July 2002-June 2006	Comparison of PW and non-PW (under 45 years old) on cART  Time-dependent variables, but pregnancy was a baseline characteristic only	Any LEE (grade 1-4)  Severe LEE (grade 3-4)	19% of women were on NVP-containing regimen (18% of PW and 21% of non-PW)	14% PW experienced LEE 9.1% non-PW experienced LEE aRR 4.7 [95% CI 3.4-6.5], p<0.001  1.2% PW experienced severe LEE 0.6% non-PW experienced severe LEE (p=0.17)
Bersoff-Matcha, 2010 [359] Retrospective cohort US Jan 1995-May 2007	PW (n=42) and non-PW (n=211) starting ART in first or early second trimester	Adverse events (rash/LEE)	NVP-containing regimen	Baseline CD4 did not predict adverse events Similar rates of rash and LEE as in other non-PW cohorts  In unadjusted analysis PW were less likely to experience an adverse event (rash/LEE)
Coffie, 2010 [220] Prospective cohort Côte d'Ivoire Aug 2003-Oct 2006	PW and non-PW starting cART with CD4<350	Severe LEE (grade 3-4)	NVP-containing	Overall rate severe LEE: 2.2/100 PY (95% CI 1.1-4.0)  Pregnancy status in the first three months of ART use was not associated with risk of severe LEE (HR 1.22, p=0.82)

Table 7. continued: Summary of studies comparing LEE in pregnant women and non-pregnant women

Study design and setting	Inclusion group	Toxicity measure	Regimen used	Findings
Snijdewind, 2012 [318] Retrospective cohort Netherlands (Athena Study) Jan 1997-Feb 2008	PW and non-PW starting cART	Severe LEE (grade 3-4)	23% used NVP-containing regimen (23% PW & 24% non-PW)	3.8% PW experienced LEE 5.4% Non-PW experienced LEE Pregnancy was not independently associated with severe LEE (aOR 0.70 [0.38-1.28], p=0.25) HCV co-infection (in non-PW) and NVP use were both associated with severe LEE
Aaron, 2010 [358] (See Table 6) Timmermans, 2005 [316] (See Table 6)				

ALT: alanine transaminase; aOR: adjusted odds ratio; cART: combination antiretroviral therapy; HCV: hepatitis C virus; LEE: liver enzyme elevation; NVP: nevirapine; PW: pregnant women; aRR: adjusted relative risk; ULN: upper limit of normal; US: United States of America.

Table 8. Summary of study comparing LEE in women who conceive on ART with women who start ART in pregnancy

Study design and setting	Inclusion group	Toxicity measure	Regimen used	Findings
<p>Natarajan, 2007 [321] Retrospective study 5 HIV centres London</p>	<p>PW starting ART in pregnancy (&gt;20 weeks) compared with PW starting ART prior to pregnancy</p>	<p>ALT &gt;3 times ULN</p>	<p>NVP-containing cART regimens Either starting in pregnancy or conceiving on</p>	<p>Overall, 3% developed toxicity PW starting ART in pregnancy: 4.7% (8/170) experienced LEE PW starting ART before pregnancy: 0% (0/65) experienced LEE p-value not given but &gt;0.05 Notes a similar rate of LEE in PW as would be expected in non-PW</p>

ALT: alanine transaminase; cART: combination antiretroviral therapy; LEE: liver enzyme elevation; NVP: nevirapine; PW: pregnant women; ULN: upper limit of normal.

Table 9. Summary of studies examining post-pregnancy viral rebound in the pre-HAART era

Study design and setting	Outcome measures (sample size)	Findings
Burns, 1998 [384] Mother and infant cohort 1986-1991 New York, US	160 pregnancies (6 used ZDVm in pregnancy) VL was assessed at delivery, 2, 12 & 24 months pp	No increase in VL at 12 months pp was observed VL increase at 2 years pp – probably due to disease progression
Bardeguet, 2003 [193] Prospective observational study 1991-1994 US & France	Women randomized to receive either ZDVm (n=236) or placebo (n=238) in pregnancy VL assessed at 6, 12, 18, 24 and 36 months pp	6 months pp the median VL had increased in both groups – probably due to disease progression
Cao, 1997 [132] 1993-1996 US	204 pregnant women receiving long-term ZDVm, short-term ZDVm or no ART 5 fold elevation in VL assessed at 2 and 6 months postpartum	Increased VL and lower CD4 count at 2 and 6 months pp among women in all three groups (no statistical comparison between groups)
Watts, 2003 [382] Phase 3 clinical trial 1993-1997 US & Puerto Rico	Pregnant women (n=497) using short-course ZDVm or remaining on ZDVm after pregnancy Rise in VL from delivery to 12 weeks pp assessed	Observed a rise in VL at 12 weeks pp in group who remained on ZDVm/cART and short-course ART group
Ekpini, 2002 [197] 1996-Feb 98 Côte d'Ivoire	Short-course ZDVm=34 women Placebo = 15 women 2 & 4 weeks pp	Increase in viral load from baseline at 2-4 weeks pp in both groups

Table 9. continued: Summary of studies examining post-pregnancy viral rebound in the pre-HAART era

Study design and setting	Outcome measures (sample size)	Findings
Truong, 2010 [385] Secondary data analysis of prospectively enrolled HIV transmission study 1989-2003 US	VL at delivery and 2-8 weeks pp Group 1: n=11, no ART Group 2: n=12, short-course-ZDVm Group 3: n=37, continuous ZDVm Group 4: n=36, continuous cART	VL increased from delivery to pp 2-8 weeks in all groups

cART: combination antiretroviral therapy; pp: post-pregnancy; US: United States of America; VL: viral load; ZDVm: zidovudine monotherapy.

Table 10. Summary of studies examining post-pregnancy viral load in the HAART era

Study design and setting	Outcome measures (sample size)	Findings
Bryson, 2008 [374] Phase 1 study of NFV safety and pharmacokinetics of NFV in pregnancy 1997-2002 US	33 women on short-term cART (NFV,ZDV+3TC) 12 weeks pp Proportion with HIV-1 RNA <400 copies/ml	At delivery, 81% (25/31) had undetectable VL At 12 weeks pp, 52% (15/29) had undetectable VL
Tungsiripat, 2007 [383] Retrospective study 1999-2003 US	60 women using short-course ART in pregnancy VL at 12-24 weeks pp compared to pre-pregnancy levels	pp VL was similar to pre-pregnancy levels
Sha, 2011 [376] Prospective study 2002-2005 US	63 pregnancies – women on cART in pregnancy and remaining on cART afterwards (29 different regimens represented) VL measured at 6, 12 & 24 weeks pp ≥0.7 log <sub>10</sub> (5-fold) increase in VL or ≥500 copies/ml from 34/36 weeks gestation	29% (18/63) women remaining on ART pp experienced viral rebound at 24 weeks pp (14% (10/74) at 6 weeks pp) Drug adherence reduced after pregnancy
Melo, 2011 [381] Prospective cohort 1119 pregnancies 2002-2007 Latin America & Caribbean	Increase VL ≥1.5 log <sub>10</sub> 6-12 weeks postpartum START defined as women who did not conceive on ART and stopped before 6-12 week pp check	60% women on START experienced pp viral rebound 19% women on long-term ART experienced pp viral rebound

Table 10. continued: Summary of studies examining post-pregnancy viral load in the HAART era

Study design and setting	Outcome measures (sample size)	Findings
Cavallo, 2010 [375] Prospective cohort study 2003-2007 Brazil	112 women on short-course or continuous ART in pregnancy Viral rebound defined as a 0.5 log <sub>10</sub> increase in VL at 6 months pp compared to VL at delivery VL assessed at 6-12 weeks pp & 6 months pp	pp viral rebound was more likely to occur in women using short-course ART in pregnancy (85% 50/60) compared to women on continuous ART (15% 9/52) (p-value <0.001)
Watts, 2009 [249] Prospective observational study Multiple US cites Jun 1994-Jun 2006	Pregnant women with CD4 >350 using ART in pregnancy (n=206) 1) short-course ZDVm (n=41) 2) remained on ZDVm (n=62) 3) short-course cART (n=18) 4) remained on cART (n=82) VL and biomarkers at 2, 6 and 12 months pp	Did not compare VL at delivery with VL at 2 months pp VL between 2 months pp and 12 months pp did not significantly change
Studies examining biomarkers		
Hoffman, 2013 [387] Biomarker study US & Puerto Rico ≥2002	Biomarkers (C-reactive protein, D-dimer, interleukin-6) levels measured at delivery and 6 weeks pp Continuers; n=65 women staying on ART pp Discontinuers: n=63 women stopping ART <6 weeks pp	Biomarkers were decreased at 6 weeks pp The continuers had a steeper decrease in D-dimer than the discontinuers

3TC: lamivudine; cART: combination antiretroviral therapy; NFV: nelfinavir; US: United States of America; VL: Viral load; pp: post-pregnancy; ZDVm: zidovudine monotherapy.

## RESEARCH ARTICLE

## Open Access

# Using two on-going HIV studies to obtain clinical data from before, during and after pregnancy for HIV-positive women

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**Abstract**

**Background:** The UK Collaborative HIV Cohort (UK CHIC) is an observational study that collates data on HIV-positive adults accessing HIV clinical care at (currently) 13 large clinics in the UK but does not collect pregnancy specific data. The National Study of HIV in Pregnancy and Childhood (NSHPC) collates data on HIV-positive women receiving antenatal care from every maternity unit in the UK and Ireland. Both studies collate pseudonymised data and neither dataset contains unique patient identifiers. A methodology was developed to find and match records for women reported to both studies thereby obtaining clinical and treatment data on pregnant HIV-positive women not available from either dataset alone.

**Results:** Women in UK CHIC receiving HIV-clinical care in 1996–2009, were found in the NSHPC dataset by initially 'linking' records with identical date-of-birth, linked records were then accepted as a genuine 'match', if they had further matching fields including CD4 test date. In total, 2063 women were found in both datasets, representing 23.1% of HIV-positive women with a pregnancy in the UK (n=8932). Clinical data was available in UK CHIC following most pregnancies (92.0%, 2471/2685 pregnancies starting before 2009). There was bias towards matching women with repeat pregnancies (35.9% (741/2063) of women found in both datasets had a repeat pregnancy compared to 21.9% (1502/6869) of women in NSHPC only) and matching women HIV diagnosed before their first reported pregnancy (54.8% (1131/2063) compared to 47.7% (3278/6869), respectively).

**Conclusions:** Through the use of demographic data and clinical dates, records from two independent studies were successfully matched, providing data not available from either study alone.

**Keywords:** Data linkage, HIV, Pregnant women, Antiretroviral therapy, Cohort analysis, United Kingdom

**Background**

Antiretroviral therapy (ART) used during pregnancy in combination with appropriate management of delivery and avoidance of breastfeeding is highly effective at reducing the risk of mother-to-child-transmission (MTCT) of HIV [1,2]. As a result of this, and an increased life expectancy of those living with HIV [3,4], many HIV-positive women choose to have children [5]. Some do

not yet require ART for their own health and use combination ART, or zidovudine monotherapy, for a period during pregnancy to prevent MTCT, repeating short-term ART use in further pregnancies if they still do not need treatment for their own health [6]. Women on ART at conception are recommended to continue treatment throughout pregnancy and after [6]. The implications of exposure to short-term antenatal ART with respect to women's longer term health and future treatment responses are incompletely understood [7–10].

Adult HIV cohorts have contributed to understanding HIV disease progression and its management, but may not collect data on childbearing or pregnancy status,

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whilst MTCT cohorts initiate follow-up during pregnancy and rarely collect data on maternal disease progression and treatment post-delivery. In the UK, comprehensive national surveillance of HIV-positive pregnant women is carried out by the National Study of HIV in Pregnancy and Childhood (NSHPC), but data are limited to information available throughout pregnancy and shortly after [11,12]. The UK Collaborative HIV Cohort (UK CHIC) study collates extensive data, recorded as part of a patient's clinical record, on adults seen for HIV-related care at large HIV clinics in the UK [13]. This provides information on patients' long-term follow-up, but pregnancy-specific data are not recorded.

In order to study the long-term impact of antenatal ART use on the health of HIV-positive women, collaboration between NSHPC and UK CHIC was established and a methodology developed to find and match records for women reported to both. This paper describes the matching strategy and estimates the completeness of matching and the extent to which HIV-positive pregnant women in UK CHIC were representative of HIV-positive pregnant women in the UK.

## Methods

The NSHPC and UK CHIC datasets were compared to find and match the records of women reported to both i.e. women in UK CHIC who had been pregnant. Initial attempts using only demographic variables (date-of-birth (DOB), country-of-birth (COB), and ethnicity) led to incomplete matching and created false matches; 1575 women were matched, 156 (9.9%) matching multiple records. Therefore, deterministic decision criteria based on both demographic and clinical fields were devised.

### Data collection

The NSHPC surveillance programme collects data on HIV-positive pregnant women from all maternity units in the UK and Ireland (~240 units) under the auspices of the Royal College of Obstetricians and Gynaecologists. A designated individual from each site, typically a midwife or physician, completes standard reporting forms each quarter which are collated at the Institute of Child Health and transcribed into an electronic database. Data collected include: DOB, probable route of infection, ethnicity, COB, date of UK arrival (if born abroad), date of UK HIV-diagnosis, expected and actual dates of delivery, ART use during pregnancy including start and stop dates, pregnancy outcome and first and last CD4 count and viral load assessments during pregnancy. Soundex, a non-unique code derived from the patient's surname, has been requested since 2008 [14], and is not yet comprehensively provided (3.4%, (306/8932) records included soundex). Further details about NSHPC are available elsewhere [1,15].

The UK CHIC study is an observational cohort of HIV-positive adults (aged 16 and older) attending for clinical care at (currently) 13 large UK clinics (see acknowledgements). Each year electronic data are extracted from patients' clinical records and transferred securely to the coordinating centre where duplicate records for the same individual, seen at different sites, are merged [13]. Data collected include: DOB, soundex, probable route of infection, ethnicity, COB, date of HIV-diagnosis in the UK, date and result of all CD4 counts and viral load assessments, use of ART including start and stop dates. Further details are available elsewhere [13,16,17].

Initial matching was undertaken in 2009 [18] and repeated in 2010 using updated datasets [19]. The matching process was formalised in 2011, the results of which are presented here. The UK CHIC dataset comprised 8286 women, aged 16–49, seen since 1<sup>st</sup> January 1996 to 31<sup>st</sup> December 2009. A restricted NSHPC dataset comprised 8932 women with 11,771 pregnancies starting after 1995 and reported by the end of 2010.

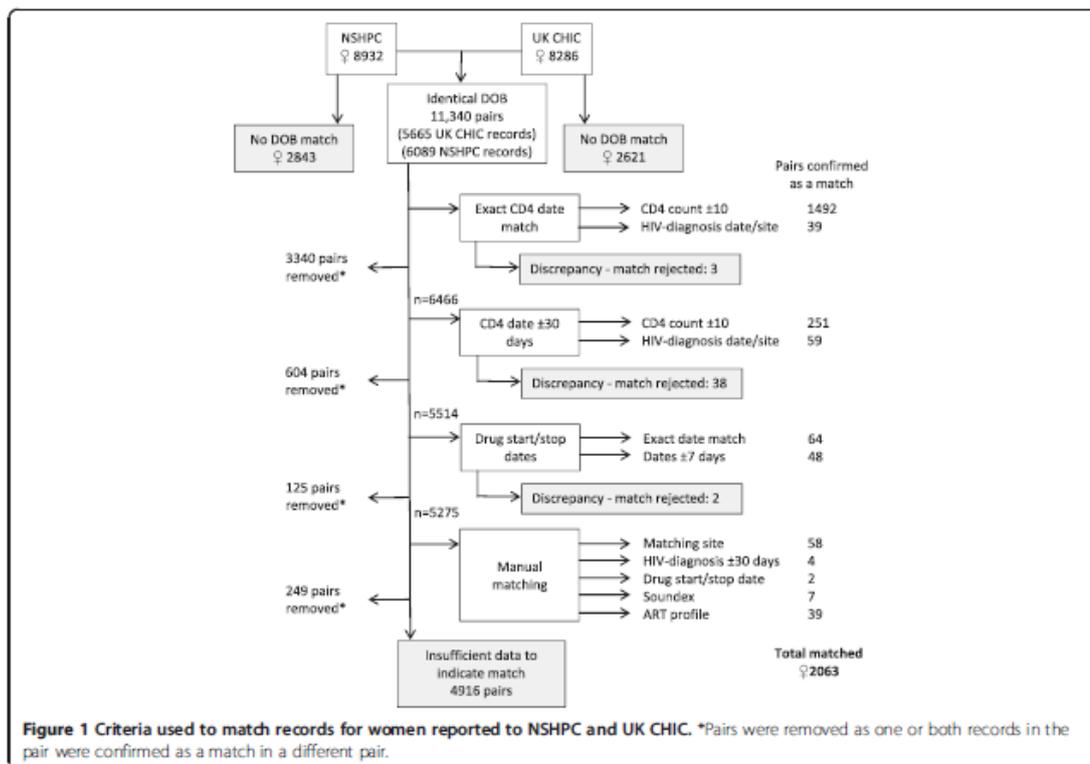
### Dataset linkage using DOB

Initially, records in NSHPC with a DOB identical to a record in UK CHIC were 'linked' and included in a temporary dataset referred to as the 'linked DOB dataset'. Some women appeared multiple times in this dataset, as they were linked to multiple records with the same DOB. A series of criteria were then used (as described below) to assess which pairs were a genuine match. If records were confirmed as a 'match' (i.e. the NSHPC record referred to the same woman as the UK CHIC record) they were merged and moved to a 'combined dataset'. All remaining occurrences of these women (i.e. as part of other linked pairs) were removed from the linked DOB dataset. The next stage of matching was then undertaken for pairs of records remaining in the linked DOB dataset (Figure 1). If at any stage a record was matched to multiple records, these were reviewed to identify the strongest match.

### Criteria used to find matching records

#### CD4 date

Initially CD4 date was used to assess whether linked records were a genuine match (Figure 1). Firstly, records with any exactly matching CD4 date and CD4 count within 10 cells/mm<sup>3</sup> on that date (to take account of rounding up or down to the nearest 10 cells/mm<sup>3</sup>), in their NSHPC and UK CHIC records, were considered a match and moved to the combined dataset. Next, any records with an exactly matching CD4 date but with a CD4 count (on that date) that differed by >10 cells/mm<sup>3</sup> were considered a genuine match if they had either identical HIV-diagnosis date or were seen for routine HIV care and antenatal care at the same site. Where the



difference between CD4 counts was  $>100$  cells/mm<sup>3</sup> these were manually checked. Sites providing HIV services located close to sites providing maternity care were considered as the same site.

The same criteria were then used to confirm matches among the remaining records in the linked DOB dataset which had CD4 dates that did not match exactly but which were  $<30$  days apart (Figure 1).

#### ART start and stop dates

ART drug start and stop dates were then used to identify further matches from the linked DOB dataset (records not confirmed as a match using CD4 data). Five criteria were used in the following order: where drug and start and stop dates all exactly matched; where drug matched and either the start or stop date exactly matched; where drug did not match or was missing but start and stop dates exactly matched; where either start or stop date exactly matched and records were reported from the same site; and where either start or stop date exactly matched and HIV diagnosis date matched. The process was repeated for records without exactly matching ART start and stop dates but where the respective dates were  $\leq 7$  days apart (Figure 1).

#### Manual checking

Finally, records remaining in the linked DOB dataset (records not confirmed as a match using CD4 or ART data) were manually checked to find further matches, using fields including: COB, ethnicity, HIV-diagnosis date, viral load and date, ART start and stop dates and site of care. Records were selected for manual checking if they had been reported from the same site, had HIV-diagnosis dates  $\leq 30$  days apart, any drug start or stop date match, matching soundex or an ART profile, in UK CHIC, which indicated they may have had a pregnancy. This included women with an ART start date in UK CHIC during the pregnancy (after the first trimester) and who either started zidovudine monotherapy or combination ART with CD4  $> 350$  cells/mm<sup>3</sup> or who had "pregnant" reported as a reason for starting or stopping ART (in UK CHIC).

#### Discrepancy checking

At each stage, before records were merged and moved to the combined dataset, matched records with a discrepancy in COB or ethnicity, variables collected by both studies, were manually checked. Records were also checked if there was a date of death (in UK CHIC)

before the estimated date of conception, if women were reported as drug naïve in UK CHIC after antenatal ART start dates in NSHPC or had a date of UK arrival (in NSHPC) after a CD4 count or viral load assessment in UK CHIC. Records with a discrepancy were kept as a match (and assumed to be due to typographic error) if they had sufficient data in agreement in other fields, such as viral load and HIV-diagnosis date, to indicate that they were a genuine match. Discrepancy checking resulted in 43 matched pairs being un-matched.

Where there was a discrepancy in fields collected by both studies, records were examined to identify which data should be used, as described below.

#### **HIV-diagnosis date**

The earliest HIV-diagnosis date from either study was used unless one date was either 1<sup>st</sup> January or 30<sup>th</sup> June (proxy dates used when only year of diagnosis is known/ reported) and the later date was during the same year, in which case the later date was used (n = 116). The earliest CD4 count, viral load assessment or ART start date was used if no HIV-diagnosis date was available (n = 4), or preceded the earliest HIV-diagnosis date (n = 78).

#### **Region of birth**

Region of birth (ROB) was categorized using COB, as defined by the World Health Organization [20]. Records with discrepant ROB (n = 98) were categorized as the non-European region if region was European in one dataset and non-European in the other (n = 96) (94 of which had UK as COB in one study), otherwise ROB was categorized as 'Not Known' (n = 2).

#### **Ethnicity**

Where ethnicity was somewhat discrepant, for example 'black-other' versus 'other' (n = 161), UK CHIC data was used in the final dataset (as ethnicity is reported multiple times for women seen in multiple years in UK CHIC). Where there was a strong discrepancy (n = 17), such as 'black' versus 'white', ethnicity was categorised as 'not known' (n = 8). These records had been checked during the matching process and had sufficient matching data in other fields, including COB, to indicate that they were a genuine match.

#### **Data analysis**

Matching and data analysis was carried out using SAS v 9.1 (SAS Institute Inc. Cary, NC, USA). HIV-positive women with a pregnancy (reported to NSHPC) whose record was found in UK CHIC (referred to as 'matched') were compared to HIV-positive women with a pregnancy who were not found in UK CHIC (referred to as 'non-matched'), to indicate whether women in UK CHIC with a pregnancy were representative of HIV-positive

women with a pregnancy. Logistic regression was used to compare characteristics and Mann-Whitney test was used to compare median ages.

National HIV surveillance data from the Survey of Prevalent HIV Infections Diagnosed (SOPHID) were used to estimate the proportion of women seen for HIV-related clinical care in the UK included in UK CHIC. SOPHID was also used in combination with NSHPC data to estimate the completeness of matching [21].

#### **Results**

Of the 8286 women reported to UK CHIC, 24.9% (n = 2063) had a record in the NSHPC dataset, indicating that they had ever had a pregnancy in the UK when HIV-positive. The records for these women were merged to create a 'combined dataset'. The majority of matching records were identified using exact CD4 date or CD4 date  $\pm$ 30 days (Table 1).

#### **Characteristics of women in the combined dataset**

Nearly three-quarters of women in the combined dataset were black-African, most were born in Africa and the majority were infected via heterosexual sex (Table 2). Less than half were HIV-diagnosed during their first reported pregnancy and 21 were diagnosed perinatally (12 of these women had a subsequent pregnancy). The majority of pregnancies resulted in a live birth (Table 2) and the median number of pregnancies was 1 (range 1, 6). There were 3035 pregnancies in total, the number increasing from 159 in 2000 to 280 in 2009. Most women (92.1%, n = 1899) attended HIV-clinical care and antenatal care at the same hospital.

#### **Completeness of matching**

The number of women (aged 16–49 years) in the UK CHIC dataset increased yearly; from 2036 in 1996 to 4755 in 2009, totalling 45,768 person years and representing approximately 29.5% (37,577/127,267 person years) of HIV-positive women (aged 16–49) attending HIV care in the UK in 2000–2009 [21].

In 2009, there 19,312 women (aged 16–49) seen for HIV-clinical care in the UK (according to national HIV-surveillance data) [14] and 1198 HIV-positive women with a pregnancy (1211 pregnancies) starting that year (according to the NSHPC dataset used in this study), indicating that approximately 6.2% (1198/19,312) of women seen for HIV-care in 2009 became pregnant that year. We would therefore anticipate that 279–311 women (95% confidence interval for 6.2% of 4755) in the UK CHIC dataset had a pregnancy in 2009. The combined dataset contained 275 women with a pregnancy in 2009, lower than the anticipated range.

Of the records linked using DOB which did not meet the matching criteria (4916 pairs; 3014 UK CHIC

**Table 1 Criteria used to find records for HIV-positive women reported to NSHPC and UK CHIC**

Criteria used to find records (All pairs of records have the same DOB)		Records matched (n = 2063)		
		N	%	Cumulative%
Exact CD4 date	CD4 $\pm$ 10 cells/mm <sup>3</sup>	1492	72.3	72.3
	HIV diagnosis date/site	39	1.9	74.2
CD4 date $\pm$ 30 days	CD4 $\pm$ 10 cells/mm <sup>3</sup>	251	12.2	86.4
	HIV diagnosis date/site	59	2.9	89.2
ART drug start and stop dates	Exact dates	64	3.1	92.3
	Dates $\pm$ 7 days	48	2.3	94.7
Manual	Site match	58	2.8	97.5
	Diagnosis date $\pm$ 30 days	4	0.2	97.7
	Drug start or stop dates	2	0.1	97.8
	Soundex	7	0.3	98.1
	ART profile	39	1.9	100.0

records and 3285 NSHPC records, many of which linked to multiple records with the same DOB), 137 (2.8%) pairs had ever been seen at the same site for antenatal and routine HIV care and had clinical data in UK CHIC at the time they were pregnant. Over half of these (53.3%, 73/137) had CD4 data reported to NSHPC, but only 4 were within 30 days of a CD4 date in UK CHIC and these had discrepant CD4 counts and HIV-diagnosis dates.

**Availability of pre and post-pregnancy clinical data**

Half (49.6%, n = 1024) the women in the combined dataset had data in UK CHIC prior to their first reported pregnancy; these women had clinical data in UK CHIC for a median of 2.8 (IQR 1.2-5.4) years before the pregnancy. The majority of pregnancies (starting before 2009) had CD4 or viral load data in UK CHIC following the pregnancy (92.0%, 2471/2685), for a median of 3.8 (IQR 1.8-6.4) years and the median time between delivery and next viral load or CD4 assessment was 1.8 (IQR 1.1-3.5) months. The majority of pregnancies with no postnatal data in UK CHIC, resulted in a live-birth (92.5%, 198/214) and less than half (36.0%, 77/214) had data in UK CHIC before the pregnancy. As no data on departure from the UK was available it was not possible to determine whether women with no post-delivery data had left the UK. However, women with no postnatal data did not significantly differ from women with postnatal data in the proportion with a UK date of arrival (61.0% (1523/2496) compared to 60.8% (115/189), Chi-squared test p = 0.96) or the median time between UK arrival and giving birth (4.1 (IQR 2.0-7.3) compared to 3.0 (IQR 1.0-5.8) years, Mann-Whitney test p < 0.20).

**Representativeness of pregnant women in UK CHIC**

Women found in both NSHPC and UK CHIC, referred to as 'matched' (n = 2063) differed in some ways from women in NSHPC only, referred to as 'non-matched'

(n = 6869). A smaller proportion of matched than non-matched women had a first pregnancy where the outcome had not yet been reported (i.e. outcome was reported as 'continuing to term'); 1.5% (n = 30) compared to 5.0% (n = 342) respectively, OR 0.28 [0.19-0.41], p < 0.001; the majority of pregnancies continuing to term started in 2009/10 (73%, 273/372). When first pregnancies with an 'other/missing' outcome (i.e. women who left the UK or who were lost to follow-up, 6 non-matched records and 0 matched) and pregnancies where outcome was not yet reported were excluded, the outcomes for first pregnancies were similar for matched and non-matched women (Chi-squared test p = 0.15), with 90.2% (1834/2033) compared to 88.7% (5782/6521) resulting in a live birth respectively.

Timing of HIV-diagnosis varied between matched and non-matched women; with 54.8% (n = 1131) diagnosed before their first reported pregnancy compared to 47.7% (n = 3278) respectively, OR 1.34 [1.21-1.48], p < 0.001. A somewhat higher proportion of matched than non-matched women had repeat pregnancies; 35.9% (n = 741) compared to 21.9% (n = 1502) respectively, OR 2.00 [1.80-2.23], p < 0.001.

Matched women were more likely to attend antenatal care in London than non-matched women (83.2% (n = 1717) compared to 36.8% (n = 2530) respectively, OR 8.5 [7.5-9.6], p < 0.001) and were slightly older at the start of their first pregnancy (median age: matched women 30.4 (IQR 26.5-34.3) years, non-matched women 29.6 (IQR 25.8-33.6) years, p < 0.001). Ethnicity varied somewhat - a smaller proportion of matched women were black-African compared to non-matched women (74.4% (n = 1535) compared to 78.1% (n = 5362), OR 0.82 [0.73-0.92], p < 0.001); this difference remained significant when 'ever seen for antenatal care in London' was included in the model (AOR 0.67 [0.58-0.76], p < 0.001). A higher proportion of matched women were black-

**Table 2 Characteristics of women in the combined dataset (n = 2063)**

		n	%
Ethnicity	Black-African	1535	74.4
	White	243	11.8
	Black-Caribbean	104	5.0
	Other	173	8.4
	Missing	8	0.4
Region of birth*	African	1527	74.0
	European	347	16.8
	Region of the Americas	87	4.2
	Eastern Mediterranean	53	2.6
	South-East Asia	25	1.2
	Western Pacific	16	0.8
	NK	8	0.4
Probable route of infection†	Heterosexual sex	1798	87.2
	Injecting drug use	40	1.9
	Other	135	6.5
	NK	90	4.4
Age at start of first pregnancy (years)	Median (IQR)	30.4 (26.5-34.3)	
	Range	14-49	
HIV-diagnosis in relation to first reported pregnancy	Before pregnancy	1131	54.8
	During first pregnancy	911	44.2
	At delivery	21	1.0
Pregnancy outcome (all pregnancies, n = 3035)	Live birth	2632	86.7
	Miscarriage	178	5.9
	Termination	113	3.7
	Stillbirth	33	1.1
	Ectopic pregnancy	4	0.1
	Continuing to term	75	2.5

\* WHO World Regions [31].

† Using UK CHIC categories and data.

Caribbean than non-matched women (5.0% (n = 104) compared to 3.4% (n = 230) respectively, OR 1.53 [1.21-1.94],  $p < 0.001$ ), but this difference was attenuated after adjustment for antenatal care in London (AOR 1.00 [0.78-1.29],  $p = 0.99$ ). The proportion of women who were white was similar among matched and non-matched women (11.8% (n = 243) and 13.4% (n = 919) respectively, OR 0.86 [0.74-1.01],  $p = 0.06$  and AOR 1.4 [1.18-1.65]  $p < 0.001$  after adjustment for antenatal care in London).

In the UK CHIC dataset, 84.6% (7014/8286) of women had ever attended care in London, and of those attending care in 2009, 82.1% (3906/4755) went to a London site. In the NSHPC dataset, 47.6%, (4247/8932) of women had ever had antenatal care in London. Women attending antenatal care in London differed somewhat from women attending care elsewhere, for example, they were older at the start of their first pregnancy (31.1

and 29.6 years respectively,  $p < 0.001$ ), more likely to be black-African or black-Caribbean and less likely to be white than women attending care outside London (black-African: 79.8% (3390/4247) compared to 74.9% (3507/4685), OR 1.3 [1.2-1.5],  $p < 0.001$ ; black-Caribbean: 5.7% (n = 240) compared to 2.0% (n = 94), OR 2.9 [2.3-3.7],  $p < 0.001$ ; and white: 8.1% (n = 346) compared to 17.4% (n = 816), OR 0.42 [0.37-0.48],  $p < 0.001$  respectively). The proportion of women diagnosed before their first pregnancy was similar for women seen in London and seen elsewhere, (48.5% (2061/4247) and 50.5% (2366/4685) respectively, Chi-squared test,  $p = 0.06$ ).

## Discussion

Using deterministic decision criteria based on demographic data and clinical dates collected by NSHPC and UK CHIC we were able to determine that as a minimum estimate almost one-quarter of women who received

HIV-clinical care at UK CHIC sites in 1996–2009 had a pregnancy. This method combined the use of automated matching with manual review of selected records, as has been used elsewhere [22–26] and can be repeated in future years.

As no 'gold-standard' was available to calculate the completeness of the matching, national HIV surveillance data of individuals attending HIV-related care, was used to estimate the expected number of women with a pregnancy in the UK CHIC dataset. The number of women with a pregnancy in our combined dataset was less than the anticipated range in 2009, indicating that there was a high but incomplete level of matching. This estimation assumes that all women in the NSHPC are reported to SOPHID, which previous linkage studies indicate is not the case [27], so the true level of matching may be higher than this estimate. A large number of records had identical DOB but were not matched as they did not meet the matching criteria. It is unlikely that many of these were genuine matches as we would expect some women to share birth dates given the number of women in both datasets, particularly as women who do not know their DOB sometimes use common proxy dates, for example where the date matches the month (1<sup>st</sup> January, 2<sup>nd</sup> February, etc.) [28]. Records with identical dates of birth which matched on site but no other variables (137 pairs) may have been genuine matches; however, for this dataset under-matching is preferable to creating false matches. We anticipate that with the inclusion of additional data for women with repeat pregnancies and developments in software and data collection at clinics there will be more complete matching in future years.

There are a number of limitations to the methodology, including the use of blocking to select records, in this instance DOB. This is effective at limiting the records in the matching process to those likely to be matches and is frequently used in matching large datasets [24,29,30]. However, it means that incorrect or inconsistent reporting of DOB results in a record being excluded; which may be more common among some groups than others, potentially introducing bias [28,31]. Use of demographic data for record matching, such as age, ethnicity, and COB, within any matching algorithm are likely to create some false matches. Given our study population, multiple women had the same ethnicity, COB, and age, so the additional use of clinical data was crucial for matching. However, this resulted in some selection bias, as women with more clinical data, either because they had been diagnosed prior to pregnancy or had repeat pregnancies, were more likely to be matched also indicating that the matching was somewhat incomplete. Other differences between matched and non-matched women, such as age at first pregnancy, could be

attributed to the difference in the proportion attending care in London, as much of the UK CHIC data comes from London sites. The differences in ethnicity between matched and non-matched women may also be explained by differences in ethnicity between women attending care in and outside London. However, when taking this into account, black-African women were less likely to be matched than women of other ethnicities and white women were more likely to be matched.

Data discrepancies in fields common to both studies were harmonized where possible, or else categorized as 'not known'. Discrepancies were unlikely to be a result of incorrect matching, as matched records with strong discrepancies were manually checked for additional matching variables. A woman's antenatal data, used for completing the NSHPC reporting form, and HIV clinical data extracted for inclusion in UK CHIC, are typically stored separately, even within the same hospital, in order to maintain patient confidentiality. Reasons why these databases might be discrepant include incorrect or incomplete recording of data and inconsistent or inaccurate reporting by patients, for example where language is a problem or DOB is unknown [28].

This matching approach could be replicated in other settings, specifically large datasets which contain some or all of the same individuals and which include common clinical and demographic variables but no unique identifiers, for example, investigating the transition from adolescent to adult HIV-care by matching these separate datasets. Combining two datasets can lead to problems, as experienced here, such as discrepancies in variables available in both datasets and may introduce bias in matching records containing more clinical data. Nevertheless, the combining of datasets can provide the opportunity to study data not available from either study alone. Combining NSHPC with UK CHIC allows the study of predictors of pregnancy and changes in pregnancy incidence over time among women accessing HIV-care [32] and provides the opportunity to investigate the long-term impact of antenatal ART use on the woman's health and future treatment responses.

## Conclusions

This matching process, used to identify HIV-positive women reported to NSHPC and UK CHIC, shows that with well considered use of demographic data and clinical dates, combined with careful manual review, it is possible to merge data from independent studies, providing useful data not available from either dataset alone.

## Abbreviations

ART: Antiretroviral therapy; COB: Country of birth; DOB: Date of birth; NSHPC: National Study of HIV in Pregnancy and Childhood; ROB: Region of birth; SOPHID: Survey of Prevalent HIV Infections Diagnosed; UK CHIC: the UK Collaborative HIV Cohort.

#### Competing interests

The authors declare that they have no competing interests.

#### Authors' contributions

SH developed the methodology in collaboration with LB and CT. SH carried out the statistical analysis and drafted the manuscript. CT, PT and CS advised on the analysis and interpretation. All other authors contributed to the drafting of the manuscript. All authors read and approved the final manuscript.

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UK CHIC:

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## RESEARCH ARTICLE

## Open Access

# Response to antiretroviral therapy (ART): comparing women with previous use of zidovudine monotherapy (ZDVm) in pregnancy with ART naïve women

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**Abstract**

**Background:** Short-term zidovudine monotherapy (ZDVm) remains an option for some pregnant HIV-positive women not requiring treatment for their own health but may affect treatment responses once antiretroviral therapy (ART) is subsequently started.

**Methods:** Data were obtained by linking two UK studies: the UK Collaborative HIV Cohort (UK CHIC) study and the National Study of HIV in Pregnancy and Childhood (NSHPC). Treatment responses were assessed for 2028 women initiating ART at least one year after HIV-diagnosis. Outcomes were compared using logistic regression, proportional hazards regression or linear regression.

**Results:** In adjusted analyses, ART-naïve (n = 1937) and ZDVm-experienced (n = 91) women had similar increases in CD4 count and a similar proportion achieving virological suppression; both groups had a low risk of AIDS.

**Conclusions:** In this setting, antenatal ZDVm exposure did not adversely impact on outcomes once ART was initiated for the woman's health.

**Keywords:** HIV, Pregnancy, Antiretroviral therapy, United Kingdom

**Background**

In the UK, zidovudine monotherapy (ZDVm) has been widely used for prevention of mother-to-child-transmission (PMTCT). Although combination antiretroviral therapy (ART) is now more commonly used for this purpose, ZDVm remains an option for pregnant women not on therapeutic ART with high CD4 counts (>350 cells/mm<sup>3</sup>) [1], low viral loads (<10,000 copies/ml), and who are willing to deliver by elective caesarean section [2]. The 2012 BHIVA guidelines recommend that women opting to use ZDVm for PMTCT start ZDVm before 24 weeks

of pregnancy [2]. Pregnant women not on ART with CD4 ≤ 350 cells/mm<sup>3</sup> are recommended to initiate long-term ART, as per the general UK HIV treatment guidelines [3].

Little is known about the impact of short-term ZDVm exposure on the woman's subsequent response to ART when started for her own health. In low- and middle-income settings use of single-dose nevirapine (sd-NVP) can have a negative impact on subsequent treatment responses to NVP-containing regimens, with high levels of drug resistance, particularly when ART is initiated within 6–12 months post-sd-NVP exposure [4,5]. However, whereas resistance to NVP requires a single mutation, resistance to ZDV requires multiple sequential mutations. As such, the development of resistance following short-term ZDVm for PMTCT is uncommon [6–9] and limited to women with more advanced disease [10–13] who would

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not meet clinical criteria for ZDVm PMTCT use [2]. In contrast to the UK guidelines, ZDVm for PMTCT is no longer recommended within the updated consolidated World Health Organization (WHO) guidelines on use of ART; in line with the WHO guidelines' main focus on earlier initiation of ART to decrease transmission, pregnant women not yet on therapy are recommended to start long-term combination therapy regardless of CD4 count [14]. Despite these recent changes, there are many women in low- and middle-income settings with previous antenatal exposure to ZDVm who have yet to start ART for their own health [15]. In addition, use of ZDVm in pregnancy will remain a strategy for PMTCT in some settings until combination ART becomes more accessible.

Our aim was to test whether short-term exposure to ZDVm in a previous pregnancy has an adverse effect on treatment outcomes once a woman starts ART for her own health. Record linkage between the UK and Ireland National Study of HIV in Pregnancy and Childhood (NSHPC) and the UK Collaborative HIV Cohort (UK

CHIC) study gave us the opportunity to address this issue, which has implications for women with previous ZDVm experience.

### Methods

We compared treatment outcomes among ART-naïve and ZDVm-experienced women starting therapeutic ART for their own health. Data were obtained from the UK CHIC study, an observational cohort that collates clinical data for adults receiving HIV-care at 15 large HIV clinics [16], and the NSHPC which collects antenatal data on all pregnant women diagnosed HIV-positive in the UK and Ireland [17]. Women reported to both studies were linked using demographic and clinical variables, as described elsewhere [18]. Data were not available on whether women had pregnancies prior to HIV diagnosis or infection, nor were data available on previous ART use outside the UK. Eligibility criteria were: initiating therapeutic ART at a UK CHIC site in 2000–2009 at least one year after HIV-diagnosis, either ZDVm-experienced or ART-naïve

**Table 1 Characteristics of ART-naïve and ZDVm-experienced women when starting therapeutic ART in 2000-2009**

Demographic and clinical characteristics at start of therapeutic ART		ZDVm-experienced (n = 91)	ART-naïve (n = 1937)	p-value
Age (years), median (IQR)		33 (30–37)	35 (30–40)	0.01
Time since HIV diagnosis (years), median (IQR)		5 (4–9)	4 (2–7)	<0.001
Pregnant, n (%)		27 (29.7)	147 (7.6)	<0.001
Ethnicity, n (%)	Black	67 (73.6)	1349 (69.6)	0.42
	Non-black/not known	24 (26.4)	588 (30.3)	
Risk group, n (%)	Heterosexual sex	89 (97.8)	1718 (88.7)	0.006
	Other	2 (2.2)	219 (11.3)	
Year, n (%)	2000-2002	13 (14.3)	375 (19.4)	0.40
	2003-2005	32 (35.1)	589 (30.4)	
	2006-2009	46 (50.6)	973 (50.2)	
ART regimen started, n (%)	PI based (boosted and non-boosted)	22 (24.2)	552 (28.5)	0.48
	NNRTI	57 (62.6)	1192 (61.5)	
	NRTI/other	12 (13.2)	193 (10.0)	
Baseline CD4 count (n = 75, n = 1431)	Median (IQR), (cells/mm <sup>3</sup> )	226 (162–339)	225 (150–304)	0.16
	CD4 <200 cells/mm <sup>3</sup> , n (%)	29 (38.7)	584 (40.8)	0.71
	CD4 <350 cells/mm <sup>3</sup> , n (%)	57 (76.0)	1195 (83.5)	0.09
Baseline viral load (n = 68, n = 1371)	Median (IQR), (log <sub>10</sub> copies/ml)	4.1 (3.2–4.5)	4.3 (3.4–4.9)	0.08
	≤50 copies/ml, n (%)	4 (5.9)	126 (9.2)	0.35
	≤400 copies/ml, n (%)	8 (11.8)	228 (16.6)	0.29
	≤10,000 copies/ml, n (%)	28 (41.2)	535 (39.0)	0.72
Hepatitis C co-infection, n (%)		4 (4.4)	170 (8.8)	0.14
Hepatitis B co-infection, n (%)		1 (1.1)	55 (2.8)	0.32
Previous AIDS event, n (%)		7 (7.7)	279 (14.4)	0.07

IQR, Interquartile range; PI, protease inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor.

(combination ART-experienced women were excluded), and aged  $\leq 49$  years at HIV-diagnosis. Women were categorised as ZDVm-experienced if, according to NSHPC or UK CHIC data, they had ever used short-term ZDVm during pregnancy.

Baseline CD4 count and viral load were taken as the latest measurement within the three months before ART initiation. Characteristics of women starting treatment were compared using the Chi-square, Fisher's exact or Wilcoxon two-sample test. ART outcomes were compared using logistic regression, proportional hazards regression or linear regression.

The UK CHIC Study has multicentre ethics committee approval (MREC/00/7/47). Ethics approval for NSHPC was renewed following review by the London Multi-Centre Research Ethics Committee in 2004 (MREC/04/2/009).

**Results**

Overall, 1937 ART-naïve and 91 ZDVm-experienced women started therapeutic ART in 2000–2009. ZDVm-experienced women had used ZDVm in either one (n = 84) or two pregnancies (n = 7). No infants acquired HIV. ZDVm was used for a median of 12 weeks (IQR 8–16) and was typically started at 28 weeks gestation (range 17–39, IQR 24–31). The median duration between delivery (of the latest pregnancy) and starting therapy was 43 months (IQR 30–63); six women started within 12 months of delivery, none within 6 months.

In both groups some women were known to have had one or more previous pregnancies during which no ART was used (2.6% (51/1937) ART-naïve women and 11.0% (10/91) ZDV-experienced women). These pregnancies either ended early, due to termination or miscarriage, or resulted in a live birth where HIV was not diagnosed until delivery.

The baseline demographic and clinical characteristics of ZDVm-experienced and ART-naïve women at the time of starting therapeutic ART are summarised in Table 1. The median follow-up time was the same for both groups (4 [IQR 2–6] years, p = 0.77). Median time since HIV-diagnosis was 5 [4–9] years for ZDVm-experienced and 4 [2–7] years for ART-naïve women (p < 0.001). ZDVm-experienced women were younger than ART-naïve women (33 [30–37] and 35 [30–40] years, respectively, p = 0.01), more likely to have been infected heterosexually (97.8% vs. 88.7%, p = 0.006) and more likely to start therapy during pregnancy (29.7% vs. 7.6%, p = 0.001). A similar proportion of women were of black ethnicity (black-African, black-Caribbean or black-other) (ZDVm-experienced: 73.6%; ART-naïve: 69.6%, p = 0.42). Overall, 28.3% (n = 574) used a PI-based regimen (ritonavir-boosted or non-boosted), 61.6% (n = 1249) an NNRTI-based regimen and 10.1% (n = 205) an NRTI or other regimen. The regimens used were similar regardless of prior ZDVm experience (p = 0.48). ZDVm-experienced women were more likely to have at least one viral load measurement recorded in the first year of treatment (ZDVm-experienced: 95.6%;

**Table 2 Treatment outcomes for ART-naïve and ZDVm-experienced women starting therapeutic ART in 2000-2009**

Variable	ZDVm-experienced N = 91		ART-naïve N = 1937		Unadjusted/ Adjusted*	95% CI	p-value
Death/AIDS event within 1 year, n (%)	1	(1.1)	92	(4.8)	0.45	0.16-1.19	0.11
					0.59	0.22-1.60	0.30
CD4 cell count change at 6 months, median cells/mm <sup>3</sup> (IQR) <sup>a</sup>	106	(41-171)	106	(34-197)	-0.66	-495-24.6	0.51
					-0.68	-446-29.2	0.68
CD4 cell count change at 12 months, median cells/mm <sup>3</sup> (IQR) <sup>b</sup>	153	(61-233)	160	(70-256)	-1.2	-71.3-18.1	0.24
					-0.83	-63.3-25.7	0.41
Virological suppression at 6 months, n (%) <sup>c</sup>	53	(74.7)	1115	(74.4)	1.01	0.59-1.75	0.96
					1.00	0.56-1.73	0.97
Virological suppression at 12 months, n (%) <sup>d</sup>	52	(78.8)	1108	(77.8)	1.06	0.58-1.94	0.85
					1.06	0.57-1.96	0.86
Achieved virological suppression within 1 year, n (%) <sup>e</sup>	75	(86.2)	1408	(84.7)	1.30	1.03-1.64	0.03
					1.28	1.01-1.62	0.04
Virological rebound among those achieving virological suppression within 6 months, n (%) <sup>f</sup>	16	(22.9)	197	(16.6)	1.54	0.93-2.57	0.10
					1.51	0.90-2.53	0.12

<sup>a</sup>ZDVm: n = 59 and ART-naïve: n = 1272; <sup>b</sup>ZDVm: n = 58 and ART-naïve: n = 1192; <sup>c</sup>ZDVm: n = 71 and ART-naïve: n = 1499; <sup>d</sup>ZDVm: n = 66 and ART-naïve: n = 1424; <sup>e</sup>ZDVm: n = 70 and ART-naïve: n = 1189; <sup>f</sup>ZDVm: n = 70 and ART-naïve: n = 1189.

Estimates are odds ratios (viral suppression at 6 and 12 months), hazard ratios (death/AIDS event, virological suppression within 1 year, virological rebound) or difference in medians (CD4 cell count change at 6 and 12 months).

\*Variables adjusted for are: age at start of ART, exposure group, ethnicity, time since HIV-diagnosis, year of starting ART, previous AIDS event, baseline viral load category, baseline CD4 count category and hepatitis B/C co-infection.

ART-naïve: 85.9%, adjusted Odds Ratio 3.24 [95% confidence interval 1.08-9.75],  $p = 0.04$ ), however the median number of measurements recorded was the same (ZDVm-experienced: median 4 [IQR 3-5]; ART-naïve: median 4 [2-5],  $p = 0.83$ ).

ZDVm-experienced and ART-naïve women started therapeutic ART at similar baseline CD4 counts (ZDVm-experienced: 226 [162-339] cells/mm<sup>3</sup>; ART-naïve: 225 [150-302] cells/mm<sup>3</sup>,  $p = 0.16$ ) and viral load (ZDVm-experienced: 4.1 [3.2-4.5] log<sub>10</sub> copies/ml; ART-naïve: 4.3 [3.4-4.9] log<sub>10</sub> copies/ml,  $p = 0.08$ ). Few women in either group were known to have hepatitis B (ZDVm-experienced: 1.1%; ART-naïve: 2.8%,  $p = 0.32$ ) or hepatitis C co-infection (ZDVm-experienced: 4.4%; ART-naïve: 8.8%,  $p = 0.14$ ). Few women had previously had an AIDS event (ZDVm-experienced: 7.7%; ART-naïve: 14.4%,  $p = 0.07$ ).

ZDVm-experienced and ART-naïve women had similar treatment outcomes (risk of an AIDS event or death, CD4 cell count change) in the first year of therapy (Table 2). Where viral load data were available, most women had undetectable viral load at 12 months (77.9%, 1160/1490). ZDVm-experienced women were more likely to achieve virological suppression ( $\leq 50$  copies/ml) within the first year of treatment (Table 2) and achieved virological suppression more quickly than ART-naïve women (median 2.5 [IQR 1.3-3.4] months versus 3.0 [1.7-4.8] months, respectively, hazard ratio (HR): 1.30 [95% CI 1.03-1.64],  $p = 0.03$ , aHR: 1.28 [1.01-1.62],  $p = 0.04$ ).

## Discussion

This UK study indicates that where ZDVm is used in pregnancy to prevent MTCT among women with high CD4 count and viral load  $< 10,000$  copies/ml it does not have a deleterious effect on treatment outcomes when ART is subsequently started. This adds support to the limited number of studies which indicate that short-term use of ZDVm for PMTCT is not detrimental to women's long-term health [7,9,19,20] and provides some reassurance with respect to the large number of women in lower-resourced settings with prior antenatal ZDVm exposure who have not yet initiated treatment. However, as a substantial proportion of these women may have had higher viral load in pregnancy [21,22], their outcomes may be different. The increased likelihood of achieving viral suppression among ZDV-experienced women may be due to better treatment adherence or frequency of viral load monitoring. ZDVm-experienced women were more likely to have a viral load measure reported in the first year of treatment indicating that they had better contact with clinical care. If having a previous pregnancy, and short-term use of ART in that pregnancy, results in better engagement in clinical care when a woman subsequently starts therapy for her own health, this could mask any deleterious effect of the previous ART exposure. No data

were available on previous pregnancies before HIV diagnosis or ART use outside the UK, something that may impact treatment outcomes. Therefore, further investigation is required to assess the long-term impact of short-term antenatal ART used for PMTCT.

## Conclusions

In this setting, antenatal ZDVm exposure did not adversely impact on outcomes once ART was initiated for the woman's health. This was a small study with limited statistical power and further research is required to support these findings.

## Competing interests

The authors declare that they have no competing interests.

## Authors' contributions

SH carried out the statistical analysis and drafted the manuscript. TH undertook data acquisition. All authors contributed to the interpretation of data and drafting of the manuscript. All authors read and approved the final manuscript.

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## The risk of viral rebound in the year after delivery in women remaining on antiretroviral therapy

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**Objective:** The objective of this study is to assess the risk of viral rebound in postpartum women on suppressive combination antiretroviral therapy (cART).

**Methods:** Using data from the UK Collaborative HIV Cohort (UK CHIC) study and the UK and Ireland National Study of HIV in Pregnancy and Childhood (NSHPC), women with HIV-RNA 50 copies/ml or less at delivery in 2006–2011, who started life-long cART during pregnancy ( $n = 321$ ) or conceived on cART ( $n = 618$ ), were matched by age, duration on cART and time period, with at least one control (non-postpartum). The cumulative probability of viral rebound (HIV-RNA >200 copies/ml) was assessed by Kaplan–Meier analysis; adjusted hazard ratios (aHRs) for the 0–3 and 3–12 months postdelivery (cases)/pseudo-delivery (controls) were calculated in Cox proportional hazards models.

**Results:** In postpartum women who conceived on cART, 5.9% [95% confidence interval (95% CI) 4.0–7.7] experienced viral rebound by 3 months, and 2.2% (1.4–3.0%) of their controls. The risk of viral rebound was higher in postpartum women than in controls during the first 3 months [aHR 2.63 (1.58–4.39)] but not during the 3–12 months postdelivery/pseudo-delivery. In postpartum women who started cART during pregnancy, 27% (22–32%) experienced viral rebound by 3 months, and 3.0% (1.6–4.4%) of their controls. The risk of viral rebound was higher in postpartum women than in controls during both postdelivery/pseudo-delivery periods [ $<3$  months: aHR 6.63 (3.58–12.29); 3–12 months: aHR 4.05 (2.03–8.09)].

**Conclusion:** In women on suppressive cART, the risk of viral rebound is increased following delivery, especially in the first 3 months, which may be related to reduced adherence, indicating the need for additional adherence support for postpartum women.

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**Keywords:** adherence, HAART, HIV, postpartum women, pregnant women, viral load

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## Introduction

Historically, women living with HIV not yet eligible for life-long combination antiretroviral therapy (cART) used short-course cART or zidovudine monotherapy in pregnancy to prevent mother-to-child transmission, before initiating life-long treatment when their CD4<sup>+</sup> cell count reached a specified level. However, with expanding CD4<sup>+</sup> criteria for treatment initiation, the number of women already on life-long cART at conception or who are eligible to start when diagnosed during pregnancy has increased [1–3]. Since 2013, the WHO has recommended that in low and middle-income countries, all pregnant women not yet on treatment start life-long cART [4]. However, in the UK, the use of short-course cART in pregnancy remains an option for women with a CD4<sup>+</sup> cell count above 350 cells/ $\mu$ l. Pregnant women with a CD4<sup>+</sup> cell count of 350–500 cells/ $\mu$ l have the option of continuing cART use if there are no contraindications such as poor adherence, as are women with a CD4<sup>+</sup> cell count more than 500 cells/ $\mu$ l with a discordant partner [5]. Thus, an increasing proportion of women now remain on cART after pregnancy.

Viral rebound generally occurs rapidly following cessation of short-course cART after delivery [6–9]. However, viral rebound has also been observed in postpartum women remaining on cART, even when viral suppression was achieved in pregnancy [9–11]. Using pooled data from two observational studies, we assess, among women on suppressive cART, the risk of viral rebound in women with a pregnancy in the previous year and in matched controls who had not been pregnant, with the postpartum group stratified by timing of cART initiation (before or during pregnancy).

## Materials and methods

### Data collection

The UK Collaborative HIV Cohort (UK CHIC) study is an ongoing observational study of adults attending HIV clinical care, which annually collates pseudonymised data from (currently 19) UK-based HIV clinics. Data include all viral load measurements, CD4<sup>+</sup> cell counts, hepatitis B virus (HBV)/hepatitis C virus (HCV) coinfection status, ART drug regimen and demographic information. The UK and Ireland's National Study of HIV in Pregnancy and Childhood (NSHPC) is a comprehensive, observational, active surveillance study of HIV-positive women accessing antenatal care, with data reported by all maternity units in the UK and Ireland [12], including ethnicity, age and expected delivery date, details of ART use, CD4<sup>+</sup> cell counts and viral loads in pregnancy. Both studies had ethics approval and informed consent was not required.

Record linkage between these two pseudonymised datasets is based on an algorithm that utilizes basic demographic and clinical data. Since 2010, linkage was undertaken yearly using the most recent datasets [13].

A woman was categorized as having attended for clinical care if any viral load or CD4<sup>+</sup> cell count data were reported to UK CHIC during the period of interest. ART use at conception, delivery and within 6 months of delivery was assessed using data from both studies.

Women with a pregnancy resulting in a live birth in 2006–2011, an HIV-RNA 50 copies/ml or less at latest viral load 3 months or less before delivery and who remained on cART (use of at least three ART drugs) for at least 6 months after delivery and with at least one viral load measurement in the year after delivery were included in this analysis, including only a woman's earliest pregnancy meeting the criteria.

Two controls were sought from the UK CHIC dataset for each postpartum woman. Controls were HIV-positive women accessing HIV-related care who had not recently been pregnant. For women who had conceived on cART, controls were matched on age (by year), calendar year and number of years since starting life-long ART. For women who started life-long cART in pregnancy, controls were matched on the basis of age (grouped as 16–19; 20–24; 25–29; 30–34; 35–39; 40–44; 45–49 years), calendar year (grouped as 2006–2007; 2008–2009; 2010–2011), months since starting treatment (grouped as 0 to <3; 3 to <6; 6 to <9 months) and CD4<sup>+</sup> cell count when starting treatment (grouped as  $\leq$ 200; 201–350; 351–500; >500 cells/ $\mu$ l).

To select suitable controls, reference dates were created by splitting the period 2006–2011 into equal-sized intervals and establishing each woman's clinical characteristics (of interest) on each date. The period was split into 3-month intervals, to find controls for women conceiving on cART, and 1-month intervals, for women starting cART in pregnancy. For controls, the reference date was used as the pseudo-delivery date. Eligibility criteria for controls were: not currently pregnant, not pregnant within the previous year, latest viral load 50 copies/ml or less, at least one viral load measurement in the following year and on cART for at least the following 6 months. If multiple potential controls were identified, two were selected at random. For postpartum women conceiving on cART, women could act as controls on multiple occasions for non-overlapping time periods.

The primary outcome was viral rebound (defined as a single measure of HIV-RNA >200 copies/ml) within 12 months of delivery (postpartum women) or pseudo-delivery (controls). In sensitivity analysis, viral rebound was defined as a single measure of HIV-RNA more than 1000 copies/ml.

### Analysis

Characteristics of postpartum women and controls were compared using the chi-square test for categorical variables and Kruskal–Wallis test for continuous (non-normally distributed) variables. Kaplan–Meier analysis was used to assess the cumulative probability of viral rebound and Cox proportional hazards models to calculate crude and adjusted hazard ratios (aHRs). As the Kaplan–Meier analyses suggested that hazards were likely to diverge after 3 months, separate models are presented for the periods less than 3 and 3–12 months postdelivery/pseudo-delivery, with the latter model including only women who had not experienced viral rebound or censoring during the less than 3-month period. In unadjusted analyses, the baseline characteristics assessed were postpartum status (postpartum/control), CD4<sup>+</sup> cell count category, type and duration of ART regimen, parity (the number of live births since HIV diagnosis), HBV/HCV coinfection, ethnicity and exposure group. Follow-up was censored at 12 months postdelivery/pseudo-delivery, if a woman died, interrupted ART or became pregnant again, whichever occurred first. In sensitivity analysis, follow-up was also censored if the ART regimen was altered in any way.

### Results

#### Postpartum women conceiving on combination antiretroviral therapy and controls

There were 623 postpartum women who conceived on cART, with two controls identified for 607, only one for 11 and none for five women, giving a total of 1225 controls.

The postpartum women and controls were similar with regard to age, year and duration on cART (the matching characteristics) (Table 1). They were also similar with regard to time since HIV-diagnosis (median 5.9 years), type of regimen used [overall, 55% used a nonnucleoside reverse transcriptase inhibitor (NNRTI)-based regimen], the percentage with HBV/HCV coinfection (7% overall) and ethnic group (73% black-African overall). The two groups differed with regard to HIV exposure category, parity, latest CD4<sup>+</sup> cell count and use of efavirenz (EFV).

In the month following delivery/pseudo-delivery, 10% (64/618) of postpartum women had a viral load measurement and 26% (320/1225) of controls ( $P < 0.001$ ). After 3 months, 70% (435/618) of postpartum women and 70% (862/1225) of controls had had at least one viral load measurement ( $P = 0.99$ ). The median number of viral load measurements overall was 3 [interquartile range (IQR) 2–4] for both groups ( $P = 0.11$ ).

#### Viral rebound in postpartum women conceiving on combination antiretroviral therapy and controls

A larger percentage of postpartum than control women experienced viral rebound [postpartum: 10.7% (66/618); controls: 7.4% (91/1225)]. The cumulative probability of viral rebound at 1, 3 and 6 months postdelivery/pseudo-delivery was 1.1% [95% confidence interval (95% CI) 0.3–2.0], 5.9% (95% CI 4.0–7.7) and 8.6% (95% CI 6.3–10.8), respectively, in postpartum women, and 0.9 (95% CI 0.0–1.4), 2.2% (95% CI 1.4–3.0) and 4.5% (95% CI 3.3–5.6) in controls (Fig. 1a).

In adjusted analysis, the risk of viral rebound in the 0–3 months postdelivery/pseudo-delivery was associated with postpartum status, calendar year and CD4<sup>+</sup> cell count (Table 2). Postpartum women were more likely to experience viral rebound than controls (aHR 2.63), although the risk of viral rebound itself decreased in later calendar years (aHR 0.81 per later year). A CD4<sup>+</sup> cell count of 200 cells/ $\mu$ l or less at delivery/pseudo-delivery was also significantly associated with viral rebound (aHR 2.89).

The risk of viral rebound in the 3–12 months postdelivery/pseudo-delivery was associated with years since HIV diagnosis, type of drug regimen and number of drugs. In this subgroup, who had maintained viral suppression for at least 3 months, there was no statistically significant association between viral rebound and postpartum status. Women who were diagnosed with HIV more than 10 years ago were more likely to experience viral rebound than women diagnosed 2–10 years ago (aHR 1.83). Women on a drug regimen containing at least four drugs were more likely to experience viral rebound than women on a triple regimen (aHR 2.41) as were women on a protease inhibitor-based regimen compared with women on a NNRTI-based regimen (aHR 1.89). The use of EFV was not associated with viral rebound and was not included in the model.

#### Postpartum women starting combination antiretroviral therapy in pregnancy and controls

There were 363 postpartum women who started cART during pregnancy, with two controls identified for 247, one for 74 and none for 42 women, giving a total of 568 controls.

Postpartum women and controls were similar with regard to age, year, duration on cART and CD4<sup>+</sup> cell count when starting cART (the matching characteristics) (Table 1). They were also similar with regard to the type of drug regimen used but differed with regard to ethnicity, exposure category, parity, HBV/HCV coinfection, duration since HIV diagnosis and latest CD4<sup>+</sup> cell count. On average, postpartum women had been diagnosed more recently, had a higher median CD4<sup>+</sup> cell count (391 vs. 350 cells/ $\mu$ l), were less likely to use EFV

Table 1. Baseline characteristics of postpartum women and controls.

Baseline characteristic <sup>c</sup>	On ART at conception <sup>a</sup>				Started ART during the pregnancy <sup>b</sup>			
	Postpartum n = 618		Controls n = 1225		Postpartum n = 321		Controls n = 568	
	n	(%)	n	(%)	n	(%)	n	(%)
Year <sup>d</sup>								
2006–2007	206	(33.4)	407	(33.3)	114	(35.5)	207	(36.4)
2008–2009	207	(33.6)	413	(33.7)	99	(30.8)	176	(31.0)
2010–2011	205	(33.2)	405	(33.1)	108	(33.6)	185	(32.6)
Age <sup>d</sup>								
Median [IQR] years	34	[31–37]	34	[31–37]	34	[28–35]	32	[28–35]
Ethnicity								
Black African	479	(77.5)	882	(72.0)	251	(78.2)	375	(66.0)
White	61	(9.9)	163	(13.3)	25	(7.8)	78	(13.7)
Black Caribbean	14	(2.3)	36	(2.9)	14	(4.4)	30	(5.3)
Other/NK	64	(10.4)	139	(11.8)	31	(9.7)	85	(15.0)
Exposure category								
Heterosexual sex	604	(97.7)	1140	(93.1)	309	(96.3)	520	(91.6)
Injecting drug use	6	(1.0)	31	(2.5)	0	–	10	(1.8)
Other/NK	8	(1.3)	54	(4.4)	12	(3.7)	38	(6.7)
Parity <sup>e</sup>								
0	353	(57.1)	855	(69.8)	280	(87.2)	470	(82.8)
1	196	(31.7)	252	(20.6)	37	(11.5)	68	(12.0)
≥2	69	(11.2)	118	(9.6)	4	(1.3)	30	(5.3)
HBV/HCV coinfection								
Latest CD4 <sup>+</sup> cell count (cells/μl)								
≤200	37	(6.0)	93	(7.6)	8	(2.5)	46	(8.1)
201–350	39	(6.3)	58	(4.7)	51	(15.9)	113	(19.9)
351–500	153	(24.8)	201	(16.4)	93	(29.0)	172	(30.3)
>500	191	(31.0)	315	(25.7)	81	(25.2)	159	(28.0)
Median time since HIV diagnosis [IQR] (years)	234	[37.9]	651	[53.1]	96	[29.9]	124	[21.8]
Duration of current period of ART use <sup>d</sup>								
0–2 months	5.9	[3.7–8.3]	5.9	[3.6–8.7]	0.6	[0.5–3.8]	2.8	[0.7–6.5]
3–5 months	–	–	–	–	65	(20.3)	106	(18.7)
6–8 months	–	–	–	–	233	(72.8)	416	(73.2)
8–12 months	39	(6.3)	78	(6.4)	–	–	–	–
1–4 years	394	(63.8)	785	(64.1)	–	–	–	–
≥5 years	185	(29.9)	362	(29.6)	–	–	–	–
Type of ART regimen								
PI	221	(35.8)	404	(33.0)	84	(26.2)	160	(28.2)
NRTI	7	(1.1)	22	(1.8)	3	(0.9)	3	(0.5)
NNRTI	332	(53.7)	676	(55.2)	221	(68.9)	388	(68.3)
Other	58	(9.4)	123	(10.0)	13	(4.1)	17	(3.0)
EFV-containing regimen	88	(14.2)	407	(33.2)	11	(3.4)	293	(51.6)
Number of drugs in regimen								
2	12	(1.9)	43	(3.5)	–	–	–	–
3	552	(89.3)	1064	(86.9)	308	(96.0)	557	(98.1)
≥4	54	(8.7)	118	(9.6)	13	(4.1)	11	(1.9)

ART, antiretroviral therapy; EFV, efavirenz; IQR, interquartile range; NK, not known; NNRTI, nonnucleoside/nucleotide reverse transcriptase inhibitor; PI, protease inhibitor.

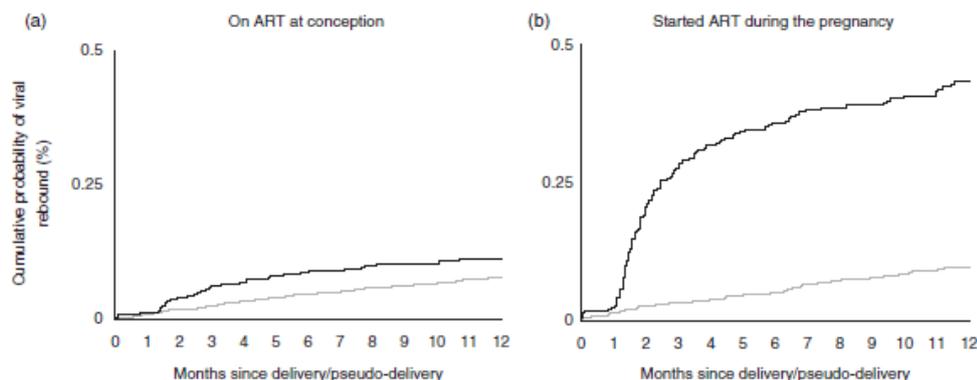
<sup>a</sup>Or 9 months prior to pseudo-delivery for controls.

<sup>b</sup>Or in the 8 months prior to pseudo-delivery for controls.

<sup>c</sup>At delivery (postpartum women) or pseudo-delivery (controls).

<sup>d</sup>Characteristics used to identify suitable controls for postpartum women. In addition, postpartum women who started ART during pregnancy were also matched to controls using CD4<sup>+</sup> cell count at ART start.

<sup>e</sup>Previous live births reported to NSHPC. This does not include live births prior to HIV infection.



**Fig. 1.** Kaplan–Meier plot showing cumulative probability of viral rebound among women on antiretroviral therapy: postpartum women (black line) and controls (grey line).

**Table 2.** Adjusted hazard ratios for viral rebound in postpartum women conceiving on antiretroviral therapy and controls stratified by time since delivery.

Baseline characteristic at delivery/pseudo-delivery		<3 months since delivery/pseudo-delivery		3–12 months since delivery/pseudo-delivery	
		aHR (95% CI)	P	aHR (95% CI)	P
Group	Control	Reference	<0.001	Reference	0.76
	Postpartum	2.63 (1.58–4.39)		0.93 (0.59–1.47)	
Calendar year (per additional year)		0.81 (0.70–0.95)	0.01	0.96 (0.84–1.09)	0.50
Age (per 10 additional years)		0.93 (0.55–1.55)	0.77	0.84 (0.55–1.28)	0.42
Ethnicity	Black African	Reference	0.41	Reference	0.59
	White	1.79 (0.87–3.71)		0.75 (0.36–1.57)	
	Black Caribbean	1.52 (0.36–6.35)		0.45 (0.06–3.28)	
	Other/NK	1.34 (0.62–2.91)		0.69 (0.33–1.45)	
Exposure category	Heterosexual sex	Reference	0.63	Reference	0.87
	Injecting drug use	0.41 (0.05–3.72)		0.73 (0.14–3.84)	
	Other/NK	0.56 (0.08–4.17)		1.21 (0.45–3.25)	
Previous live birth		1.31 (0.79–2.20)	0.10	1.37 (0.89–2.11)	0.16
HBV/HCV coinfectd		1.43 (0.58–3.55)	0.44	1.25 (0.59–2.65)	0.57
Latest CD4 <sup>+</sup> cell count (cells/μl)	≤200	2.89 (1.14–7.31)	0.10	2.05 (0.96–4.34)	0.05
	201–350	1.74 (0.88–3.46)		1.12 (0.65–1.95)	
	351–500	1.79 (0.96–3.36)		0.64 (0.36–1.13)	
	>500	Reference		Reference	
Duration of ART use	8–12 months	1.34 (0.56–3.25)	0.19	0.98 (0.41–2.34)	0.77
	1–4 years	Reference		Reference	
	≥5 years	0.57 (0.29–1.13)		0.83 (0.50–1.37)	
Time since HIV diagnosis	8–23 months	0.66 (0.25–1.74)	0.69	1.66 (0.82–3.37)	0.04
	2–9 years	Reference		Reference	
	≥10 years	1.04 (0.49–2.21)		1.83 (1.08–3.09)	
Type of ART regimen	PI	1.13 (0.66–1.93)	0.96	1.89 (1.19–3.00)	0.06
	NRTI	–		0.92 (0.12–6.87)	
	NNRTI	Reference		Reference	
	Other	0.95 (0.38–2.34)		1.39 (0.66–2.95)	
Number of drugs in the regimen	2	2.36 (0.51–11.0)	0.17	2.17 (0.73–6.50)	0.01
	3	Reference		Reference	
	≥4	1.86 (0.91–3.81)		2.41 (1.36–4.25)	

Baseline refers to the delivery date (postpartum women) or pseudo-delivery date (controls). aHR, adjusted hazard ratio; ART, antiretroviral therapy; CI, confidence interval; NK, not known; NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside/nucleotide reverse transcriptase inhibitor; PI, protease inhibitor.

and were less likely to have had a previous live birth (since HIV diagnosis) (Table 1).

More than half [53% (171/321)] of postpartum women were diagnosed with HIV during the recent pregnancy, of whom 65% (111/171) had a CD4<sup>+</sup> cell count less than 350 cells/ $\mu$ l when starting cART, with 47% (81/171) having a CD4<sup>+</sup> cell count less than 200 cells/ $\mu$ l. In women already diagnosed when they became pregnant, 59% (89/150) had a CD4<sup>+</sup> cell count less than 350 cells/ $\mu$ l when starting cART, with 32% (48/150) having a CD4<sup>+</sup> cell count less than 200 cells/ $\mu$ l; of these, almost two-thirds [65% (98/150)] attended care at a UKCHIC site in the year prior to the pregnancy, of whom 53% (52/98) started cART with a CD4<sup>+</sup> cell count less than 350 cells/ $\mu$ l.

In the month following delivery/pseudo-delivery, 14% (44/321) of postpartum and 27% (152/568) of controls ( $P < 0.001$ ) had a viral load measurement. At 3 months postdelivery/pseudo-delivery, 80% (256/321) of postpartum women and 79% (450/568) of controls had had at least one viral load measurement ( $P = 0.85$ ). The median number of viral load measurements in the year following delivery/pseudo-delivery was 3 (IQR 2–4) for the postpartum women and 3 (3–4) for the controls ( $P < 0.001$ ).

#### Viral rebound in postpartum women starting combination antiretroviral therapy in pregnancy and controls

A larger percentage of postpartum women experienced viral rebound than controls [postpartum: 37.1% (119/321); controls: 9.2% (52/568)]. The cumulative probability of viral rebound at 1, 3 and 6 months postdelivery/pseudo-delivery was 1.9% (95% CI 0.4–3.5), 27% (95% CI 22–32) and 35% (95% CI 30–41), respectively, in postpartum women, and 1.1% (95% CI 0–1.9), 3.0% (95% CI 1.6–4.4) and 4.8% (95% CI 3.0–6.6), respectively, in controls (Fig. 1b).

In adjusted analysis, the risk of viral rebound in the first 3 months postdelivery/pseudo-delivery was associated with postpartum status (aHR 6.63 for postpartum women) and CD4<sup>+</sup> cell count (aHR 0.18; CD4<sup>+</sup> cell count <200 vs. >500 cells/ $\mu$ l) (Table 3).

The risk of viral rebound in the 3–12 months postdelivery/pseudo-delivery was associated with postpartum status (aHR 4.05 for postpartum women), calendar year (aHR 0.83 per later year), age (aHR 0.51 per 10 additional years) and ethnicity (aHR 2.94 for women of black-Caribbean ethnicity) (Table 3).

The findings were not affected when, in sensitivity analysis, follow-up was censored at any regimen change.

In sensitivity analysis, when viral rebound was defined as HIV-RNA more than 1000 copies/ml, similar

associations were observed, although some lost statistical significance. The association between age and viral rebound became statistically significant for women who had started cART in pregnancy and controls [0–3 months postdelivery/pseudo-delivery: aHR 0.46 (0.24–0.88) per 10 additional years]. Postpartum status remained associated with viral rebound when 143 women (46 postpartum and 97 controls) with previous cART experience were excluded.

## Discussion

We show that HIV-positive women on cART with a live-born infant in the preceding year and an undetectable viral load at delivery had a higher risk of viral rebound than matched control women who had not recently been pregnant. Among women already on cART at conception, the risk of viral rebound was 2.6-fold higher in the first 3 months after delivery than among matched controls, but similar in the 3–12 months after delivery. In contrast, among women who started cART during pregnancy, viral rebound risk was 6.6-fold higher than matched controls during the first 3 months and 4.1-fold higher 3–12 months after delivery. A number of studies have observed a high prevalence of viral rebound in postpartum women remaining on cART [7,10,14], but this study is the first to compare the risk of viral rebound in postpartum women with rates seen in a demographically matched group of non-postpartum women.

Overall, 9% of women who conceived on cART experienced viral rebound within 6 months of delivery, less than in a Brazilian study in which 15% (nine out of 52) of postpartum women, who conceived on and remained on cART after pregnancy, developed viral rebound (0.5 log<sub>10</sub> increase) at 6 months postpartum [14]. This difference may be because women in the Brazilian study had more advanced disease and not all had achieved viral suppression during pregnancy. Two further studies [7,10] reported that 19 and 18% (respectively) of postpartum women who remained on cART experienced viral rebound (defined as  $\geq 0.7$  log<sub>10</sub> increase at 24 weeks postpartum and  $\geq 0.5$  log<sub>10</sub> increase at 6–12 weeks postpartum, respectively). However, neither of these studies stratified by timing of cART initiation (before or during the pregnancy), which limits comparison with our study.

Physiological changes during pregnancy and at delivery may result in a temporary viral load peak and may have contributed to the increased incidence in the first 3 months after delivery. However, this temporary peak is most likely to occur shortly after delivery [8], a time during which few women in our study had a viral load measurement. Also, this would not explain the ongoing increased risk of viral rebound after 3 months among

**Table 3. Adjusted hazard ratios for viral rebound in postpartum women starting antiretroviral therapy during pregnancy and controls stratified by time since delivery.**

Baseline characteristic at delivery/pseudo-delivery		<3 months since delivery/pseudo-delivery		3–12 months since delivery/pseudo-delivery	
		aHR (95% CI)	<i>P</i>	aHR (95% CI)	<i>P</i>
Group	Control	Reference	<0.001	Reference	<0.001
	Postpartum	6.63 (3.58–12.3)		4.05 (2.03–8.09)	
Calendar year (per additional year)		1.02 (0.90–1.16)	0.72	0.83 (0.69–0.99)	0.04
Age (per 10 additional years)		0.71 (0.48–1.05)	0.08	0.51 (0.29–0.90)	0.02
Ethnicity	Black African	Reference	0.81	Reference	0.19
	White	0.68 (0.29–1.61)		1.29 (0.52–3.22)	
	Black Caribbean	1.16 (0.50–2.73)		2.94 (1.11–7.76)	
	Other/NK	0.97 (0.49–1.91)		1.19 (0.52–2.73)	
Exposure category	Heterosexual sex	Reference	0.41	Reference	0.66
	Injecting drug use	4.65 (0.49–44.1)		2.37 (0.25–22.6)	
	Other/NK	1.00 (0.35–2.87)		1.38 (0.47–4.10)	
Previous live birth		1.44 (0.78–2.65)	0.24	1.78 (0.48–6.56)	0.39
HBV/HCV coinfectd		0.71 (0.21–2.39)	0.58	1.05 (0.30–3.65)	0.94
Latest CD4 <sup>+</sup> cell count (cells/ $\mu$ l)	≤200	0.18 (0.07–0.48)	<0.001	0.73 (0.32–1.66)	0.35
	201–350	0.39 (0.22–0.70)		0.70 (0.33–1.47)	
	351–500	0.81 (0.49–1.32)		0.44 (0.18–1.08)	
	>500	Reference		Reference	
Duration of ART use	0–2 months	0.82 (0.49–1.38)	0.76	0.91 (0.44–1.87)	0.35
	3–5 months	Reference		Reference	
	6–8 months	–		0.74 (0.26–2.14)	
Time since HIV diagnosis	8–23 months	0.83 (0.51–1.35)	0.73	1.11 (0.55–2.22)	0.62
	2–9 years	Reference		Reference	
	≥10 years	1.08 (0.37–3.11)		0.41 (0.05–3.24)	
Type of ART regimen	PI	0.83 (0.51–1.36)	0.90	1.34 (0.69–2.60)	0.86
	NRTI	–		–	
	NNRTI	Reference		Reference	
	Other	0.89 (0.32–2.52)		–	
Use of EFV-containing regimen		0.20 (0.07–0.60)	0.004	0.88 (0.38–2.06)	0.77
Number of drugs in the regimen	3	Reference	0.86	Reference	0.86
	≥4	1.11 (0.34–3.65)		0.88 (0.20–3.84)	

Baseline refers to the delivery date (postpartum women) or pseudo-delivery date (controls). aHR, adjusted hazard ratio; ART, antiretroviral therapy; CI, confidence interval; EFV, efavirenz; HBV, hepatitis B virus; HCV, hepatitis C virus; NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside/nucleotide reverse transcriptase inhibitor; PI, protease inhibitor.

women who started cART in pregnancy or the much higher incidence in women who started cART in pregnancy than women conceiving on cART. The more likely explanation for the increase in viral rebound incidence following pregnancy is reduced adherence to cART. Studies have observed a fall in adherence following pregnancy [10,15,16], when the risk of vertical transmission has passed (if breastfeeding is avoided) and the demands of looking after the baby are high. Treatment interruptions and changes to medication are also more likely in this period [10]. When, in sensitivity analysis, follow-up was censored if the regimen was changed, the association between post-pregnancy status and viral rebound remained.

Older age was associated with a decreased risk of viral rebound in women who started ART in pregnancy and their controls. This is likely to be a result of better drug adherence in older women [17–19].

Engagement with HIV care may have also been reduced following pregnancy; in our observational study, data were collected as part of HIV clinical care. We used the

average number of viral load measurements recorded as a proxy for clinic attendance. For all groups, the median number of viral loads was three in the postdelivery/pseudo-delivery year. However, for women who recently started cART, there was evidence that postpartum women attended care less often than controls ( $P < 0.001$  for the distribution of viral load measurements). Previous studies have noted low attendance rates in clinical care in the 3 months following childbirth [20] and delay in seeking HIV care [21] or inability to complete postpartum follow-up [22] among women with children in the household.

We cannot rule out resistance as the reason for viral rebound; however, in sensitivity analysis excluding women with known previous exposure to ART, postpartum status remained significantly associated with an increased risk of viral rebound.

In women who started cART in pregnancy and their controls, the risk of viral rebound in the first 3 months after delivery/pseudo-delivery was lower in women with a low CD4<sup>+</sup> cell count than in women with a high CD4<sup>+</sup>

cell count. Despite only including women who, according to the data, remained on cART for at least 6 months, some discontinuations may not have been recorded in the clinical notes. A woman's CD4<sup>+</sup> cell count at cART initiation could indirectly affect adherence; for example, women with a high CD4<sup>+</sup> cell count may not perceive the need for perfect adherence as much as women starting cART with a low CD4<sup>+</sup> cell count. In some settings wherein WHO Option B+ has been implemented, high rates of lost-to-follow-up have been observed among pregnant women starting life-long cART with a high CD4<sup>+</sup> cell count [23,24]. We do not know whether a similar incidence of postpartum viral rebound would occur if all pregnant women not yet on ART started long-term treatment in pregnancy, as is increasingly the case in low and middle-income settings [4]. Remaining on treatment after pregnancy may be beneficial for the woman's health and to minimize HIV transmission risk in subsequent pregnancies [25,26]. The PROMISE study is currently assessing the benefits, in a resource-limited settings, of women with higher CD4<sup>+</sup> cell counts remaining on cART after delivery (Trial reference: NCT01061151).

For women who started cART in pregnancy and their controls, a quadruple regimen was associated with an increased risk of viral rebound in the 3–12 months postdelivery/pseudo-delivery. As the standard first-line treatment in the UK during the study period was a triple regimen (wherein ritonavir use as a pharmacological booster is not counted as a component of the regimen) [27], use of a quadruple regimen suggests that they were on a subsequent regimen due to developing resistance or problems with a previous regimen/s. Adherence could be more of an issue for women on a quadruple regimen, as adherence is negatively associated with pill burden [28].

In both groups, fewer postpartum women were on an EFV-containing regimen than the controls. Until recently, EFV has been avoided in pregnancy and in women planning a pregnancy due to the possible risk to foetal development [29], although a recent meta-analysis found no increase in birth defects with EFV use [30]. In women who started ART in pregnancy and their controls, use of EFV was associated with a lower risk of viral rebound in the first 3 months postdelivery/pseudo-delivery. No such association was found in women who had conceived on ART.

Although several relevant variables were included in our adjusted model, we may not have accounted for all potential confounders. To avoid detecting viral blips, viral rebound is often defined on the basis of two consecutive HIV-RNA more than 200/400/1000 copies/ml; we were unable to take this approach due to the limited number of viral load measurements reported in this group.

Increased viral load following pregnancy could have a detrimental impact on women's health and future treatment options and increases the risk of transmission to an HIV-negative partner, or to the infant, if the mother chooses to breastfeed. Therefore, our findings indicate a need for additional support for ART adherence and to remain engaged in regular HIV clinical care, which could include support from clinicians, specialist nurses and peer support (via charities) from women living with HIV who have experience of taking ART after pregnancy. The findings of this study suggest that adherence support is particularly needed by women starting life-long treatment during pregnancy, especially younger women. It is encouraging that the risk of viral rebound was lower in later years of the study, indicating that adherence may have improved over time and that regimens have become more forgiving to lapses in adherence. The UK CHIC study does not collect data on pill burden or use of fixed-dose regimens (FDRs), so these could not be assessed as potential factors associated with viral rebound. However, other studies have found that use of a single-pill regimen can improve adherence [31]. For pregnant women starting long-term cART, a once-a-day FDR may promote good adherence. Regimens more forgiving to poor adherence could also be considered as the initial regimen. Further studies are required to identify the most effective strategies for improving postpartum ART adherence.

In conclusion, in women on suppressive cART, the risk of viral rebound is higher in postpartum women than in similar women who have not recently had a pregnancy. This may be a result of reduced adherence to ART, highlighting the need for additional adherence support for pregnant and postpartum women remaining on cART.

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S.H. carried out the statistical analysis and drafted the manuscript. T.H. undertook data acquisition. All coauthors contributed to the interpretation and drafting of the manuscript.

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### Conflicts of interest

All authors report no potential conflicts.

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Appendix IIIa NSHPC pregnancy notification form

<b>NSHPC confidential pregnancy notification</b>																											
MREC approval ref: MREC/04/2/009	Form date: 07/08	www.nshpc.ucl.ac.uk																									
<b>CONFIDENTIAL</b>		Office use only: <input style="width: 100px; height: 20px;" type="text"/> <input style="width: 100px; height: 20px;" type="text"/> <input style="width: 100px; height: 20px;" type="text"/>																									
Woman's date of birth ___/___/___ Hospital number (or other ref): ..... Soundex ..... Postcode (leave off last letter) <input type="checkbox"/> Previous livebirths ..... stillbirths ..... miscs/terms ..... Ethnic origin <input type="checkbox"/> White <input type="checkbox"/> Black African <input type="checkbox"/> Black Caribbean <input type="checkbox"/> Black Other <input type="checkbox"/> Asian, Indian Subcontinent <input type="checkbox"/> Asian, other / Oriental <input type="checkbox"/> Other or mixed, specify ..... Country of birth ..... If not UK/Ireland, date arrived ___/___/___																											
<b>PROBABLE SOURCE OF MATERNAL INFECTION</b> Maternal infection probably acquired: <input type="checkbox"/> In UK/Ireland <input type="checkbox"/> Abroad, specify ..... <input type="checkbox"/> NK where Likely exposure: <input type="checkbox"/> Heterosexual - specify partner's likely risk factor, if known ..... <input type="checkbox"/> Injecting drug use <input type="checkbox"/> Vertical transmission <input type="checkbox"/> Other, specify .....																											
<b>TIMING OF DIAGNOSIS</b> Date of first positive test: ___/___/___ If type 2 only, please tick here <input type="checkbox"/> Diagnosed when: <input type="checkbox"/> During this pregnancy <input type="checkbox"/> Before this pregnancy Diagnosed where: <input type="checkbox"/> Antenatal <input type="checkbox"/> GUM clinic <input type="checkbox"/> Other ..... Any evidence of seroconversion in this pregnancy? <input type="checkbox"/> No <input type="checkbox"/> Yes, specify details overleaf <input type="checkbox"/> Not known																											
<b>PREGNANCY</b> Booking date: ___/___/___ EDD ___/___/___ (and/or LMP ___/___/___) <input type="checkbox"/> Continuing to term - if continuing, planned mode of delivery: <input type="checkbox"/> Vaginal <input type="checkbox"/> CS <input type="checkbox"/> Not yet decided <input type="checkbox"/> Miscarriage } Date of misc/TOP: ___/___/___ at ..... weeks gestation <input type="checkbox"/> Termination } Any congenital abnormality? <input type="checkbox"/> No <input type="checkbox"/> Yes, please specify .....																											
<b>DRUG TREATMENT DURING THIS PREGNANCY</b> Was this woman on antiretroviral drugs when she became pregnant? <input type="checkbox"/> Yes <input type="checkbox"/> No Did she receive antiretroviral drugs in pregnancy? <input type="checkbox"/> Not yet <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Declined Please provide details of antiretrovirals: <table style="width: 100%; border-collapse: collapse; margin-top: 5px;"> <thead> <tr> <th style="width: 40%;"></th> <th style="width: 15%; text-align: center;">Before preg? (please circle)</th> <th style="width: 20%; text-align: center;">Date started (or gest week) (if in pregnancy)</th> <th style="width: 25%; text-align: center;">Date stopped (or gest week)</th> </tr> </thead> <tbody> <tr> <td>Drug 1 .....</td> <td style="text-align: center;">Yes / No</td> <td style="text-align: center;">___/___/___</td> <td style="text-align: center;">___/___/___</td> </tr> <tr> <td>Drug 2 .....</td> <td style="text-align: center;">Yes / No</td> <td style="text-align: center;">___/___/___</td> <td style="text-align: center;">___/___/___</td> </tr> <tr> <td>Drug 3 .....</td> <td style="text-align: center;">Yes / No</td> <td style="text-align: center;">___/___/___</td> <td style="text-align: center;">___/___/___</td> </tr> <tr> <td>Drug 4 .....</td> <td style="text-align: center;">Yes / No</td> <td style="text-align: center;">___/___/___</td> <td style="text-align: center;">___/___/___</td> </tr> <tr> <td>Drug 5 .....</td> <td style="text-align: center;">Yes / No</td> <td style="text-align: center;">___/___/___</td> <td style="text-align: center;">___/___/___</td> </tr> </tbody> </table>					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	___/___/___	___/___/___	Drug 5 .....	Yes / No	___/___/___	___/___/___
	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	___/___/___	___/___/___																								
Drug 5 .....	Yes / No	___/___/___	___/___/___																								
<b>MATERNAL CLINICAL STATUS DURING THIS PREGNANCY</b> <input type="checkbox"/> CDC Stage C disease, details: <input type="checkbox"/> Asymptomatic <input type="checkbox"/> Symptomatic - not Stage C disease, details ..... Concurrent infection(s)? <input type="checkbox"/> None <input type="checkbox"/> HBV <input type="checkbox"/> HCV <input type="checkbox"/> Syphilis <input type="checkbox"/> Other, specify .....																											
<b>MATERNAL TEST RESULTS</b> <i>first test results available this pregnancy</i> 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 7829 8686 if you have any queries or email nshpc@ich.ucl.ac.uk																											



## Appendix IV UK CHIC Coding Frame (November 2008)

### General points:

- **Data to be provided on all patients seen at your HIV centre**
- All data can be provided as access tables, excel spreadsheets or text files with the variables comma or tab delimited
- All dates should be provided in dd/mm/yyyy format, including leading zeros
- All files should include the clinic ID and date of birth for each patient so that the files can be easily merged
- **Important:** Please submit data files by FTP method. When you are ready to send data please contact or email [t.hill@pcps.ucl.ac.uk](mailto:t.hill@pcps.ucl.ac.uk) for FTP details
- **Important:** If possible encrypt data using Axcrypt which is free open source software available from [www.axantum.com/AxCrypt](http://www.axantum.com/AxCrypt). Please password protect data files or folder with a strong password or phrase (not 'ukchic', or the clinic name)
- **Variables in bold in the data tables (Files 1 – 11) have codes listed in the data specifications. Data must be coded using UK CHIC codes otherwise it will not be accepted. If you need help in coding any data please contact us**

**File 1 – PATIENTCENTRE table**

Field Name	Description	Type
ClinicNo	HIV Clinic's unique patient identifier	text (12)
DOB	Date of birth	dd/mm/yyyy
Soundex	Soundex code	text (4)
Initial	Patient initial/s	text (2)
SexID	Patient sex code	integer
HIVPos	Date of first known positive HIV antibody test	dd/mm/yyyy
HIVNeg	Date of last negative HIV antibody test	dd/mm/yyyy
Firstseen	Date of first HIV attendance at centre	dd/mm/yyyy
Lastseen	Date when last seen by a clinician at the centre	dd/mm/yyyy
ExposureID	HIV exposure category	integer
EthnicityID	Ethnicity code	integer
CountryID	Country of birth code	text (30)
DiedID	Is patient known to have died code	integer
DDeath	Date of death	dd/mm/yyyy
Cause	Cause of death (where known)	text (60+)
TransferFr	Transfer from centre	text (50)
TransferFrDate	Transfer from centre date	dd/mm/yyyy
TransferTo	Transfer to centre	text(50)
TransferToDate	Transfer to centre date	dd/mm/yyyy

**File 2 – AIDSEVENT table**

Field Name	Description	Type
ClinicNo	HIV Clinic's unique patient identifier	text (12)
DOB	Date of birth	dd/mm/yyyy
DAIDS	Date of AIDS event	dd/mm/yyyy
AIDSID	AIDS event code	integer

**File 3 – ANTIRETRO table**

Field Name	Description	Type
ClinicNo	HIV Clinic's unique patient identifier	text (12)
DOB	Date of birth	dd/mm/yyyy
DStart	Date started taking drug	dd/mm/yyyy
DStop	Date stopped taking drug	dd/mm/yyyy
DrugID	Drug code	integer (15)
ReasonStopID1	Reason for stopping drug	integer
ReasonStopID2	Reason for stopping drug (if multiple codes)	integer
ReasonstopID3	Reason for stopping drug (if multiple codes)	integer

**File 4 – CD4 table**

Field Name	Description	Type
ClinicNo	HIV Clinic's unique patient identifier	text (12)
DOB	Date of birth	dd/mm/yyyy
Dlab	Date of lab measurement	dd/mm/yyyy
CD4A	Absolute CD4 count in cells/mm <sup>3</sup>	integer
CD4P	CD4 percentage	number (1dp)
CD8A	Absolute CD8 count in cells/mm <sup>3</sup>	integer
CD8P	CD8 percentage	number (1dp)

**File 5 – RNA/Viral Load table**

Field Name	Description	Type
ClinicNo	HIV Clinic's unique patient identifier	text (12)
DOB	Date of birth	dd/mm/yyyy
Dlab	Date of lab measurement	dd/mm/yyyy
RNA	HIV Viral Load level in copies/ml	long integer
UndetID	Status of HIV RNA measurement code	integer
AssayID	HIV RNA assay code	integer

**File 6 – Hepatitis table**

Field Name	Description	Type
ClinicNo	HIV Clinic's unique patient identifier	text (12)
DOB	Date of birth	dd/mm/yyyy
DHeptest	Date of hepatitis test	dd/mm/yyyy
HepTestID	Hep test code	integer
HepResultID	test result (-/+/indet)	integer
Hepvalue	test result value, if appropriate	long integer
UndetID	please ignore this	
Hepassay	please ignore this	

**File 7 – ADHERENCE table**

Field Name	Description	Type
ClinicNo	HIV Clinic's unique patient identifier	text (12)
DOB	Date of birth	dd/mm/yyyy
DAdherence	Date of clinic visit	dd/mm/yyyy
AdherPeriodID	Adherence period codes	integer
AdherPerOther	Adherence period other	text (50)
DosesMiss	No / % of doses missed	integer
ReasonMissID	Reason for missing treatment code	integer

**File 8 – PCPPROP table**

Field Name	Description	Type
ClinicNo	HIV Clinic's unique patient identifier	text (12)
DOB	Date of birth	dd/mm/yyyy
PCPpDrugID	PCP Drug code	integer
PCPpStart	Date of starting PCP prophylaxis	dd/mm/yyyy
PCPpStop	Date of stopping PCP prophylaxis	dd/mm/yyyy

**File 9 – Toxicity table**

Field Name	Description	Type
ClinicNo	HIV Clinic's unique patient identifier	text (12)
DOB	Date of birth	dd/mm/yyyy
DToxtest	Date of toxicity test	dd/mm/yyyy
ToxTestID	Tox test code	integer
ToxResult	Test result value	integer
ToxUnitID	Test results units	text (10)

**File 10 – HLA-B57 table**

Field Name	Description	Type
ClinicNo	HIV Clinic's unique patient identifier	text (12)
DOB	Date of birth	dd/mm/yyyy
DHLAB57	Date of HLA-B57 test	dd/mm/yyyy
HLAB57ResultID	test result (-/+/indet)	integer

## File 11 – Attendance table

Field Name	Description	Type
ClinicNo	HIV Clinic's unique patient identifier	text (12)
DOB	Date of birth	dd/mm/yyyy
DAttend	Date of attendance	dd/mm/yyyy
AttSeenBy	Who patient is seen by eg. Dr, nurse, dietician, psychologist, other etc	integer
AttType	Attendance: scheduled, walk-in, virtual, in-patient, other	integer
Ddischarge	Date of discharge if in-patient	dd/mm/yyyy

## Reference Tables

	Table Name
Variable1	Variable2
<b>AdherPeriodID</b>	<b>AdherPeriod</b>
1	No in last 3 days
2	No in last 14 days
3	No in last 30 days
4	% in last 30 days
98	Other
99	Not known
<b>AIDSID</b>	<b>AIDS</b>
1	Bacterial infections (multiple or recurrent) at age < 13 years
2	Candidiasis, oesophageal
3	Candidiasis, trachea/bronchi/lungs
4	Candidiasis, site unknown
5	Cervical cancer, invasive
6	Coccidioidomycosis, extrapulmonary
7	Cryptococcosis, extrapulmonary
8	Cryptosporidiosis, duration > 1 month
9	Cytomegalovirus retinitis
10	Cytomegalovirus disease, other
11	Cytomegalovirus, site unknown
12	Herpes simplex disease, duration > 1 month
13	Histoplasmosis, extrapulmonary and/or disseminated
14	HIV Encephalopathy
15	Isosporiasis, duration > 1 month
16	Kasposi's sarcoma

17	Lymphoid interstitial pneumonia or pulmonary lymphoid hyperplasia at age <13 years
18	Lymphoma, Burkitt's, immunoblastic or equivalent
19	Lymphoma, primary in brain
20	Mycobacterium avium, extrapulmonary (MAI/MAC)
21	Mycobacterium tuberculosis, pulmonary
22	Mycobacterium tuberculosis, extrapulmonary
23	Mycobacterium, other (disseminated)
24	Pneumocystis carinii pneumonia (P. jiroveci)
25	Pneumonia, recurrent in a 12-month period
26	Progressive multifocal leukoencephalopathy
27	Salmonella Septicaemia, recurrent
28	Toxoplasmosis, cerebral
29	HIV wasting syndrome
31	Lymphoma Site Unknown
51	Mycobacterium tuberculosis, Site Unknown
98	AIDS disease, not specified
99	Not Known
<b>AssayID</b>	<b>Assay</b>
1	Roche v1.0 (<400)
2	Roche non-B (<400)
3	Roche v1.5 (<400)
4	Roche v1.5 US (<50)
5	Roche – version unknown
6	Cobas v1.5 (<400)
7	Cobas v1.5 US (<50)
9	Cobas – version unknown
10	NASBA (<400)
11	NASBA US
12	NASBA – version unknown
13	Chiron b-DNA v1.0
14	Chiron b-DNA v2.0 (<500)
15	Chiron b-DNA v3.0 US (<50) (also known as Bayer?)
16	Chiron – version unknown
17	Nuclisens (<400)
18	Nuclisens US (<50?)
19	Nuclisens – version unknown
21	Cobas<10 copy assay
98	Other

99	Not known
<b>AttSeenBy</b>	<b>Attendance</b>
1	Clinician
2	Nurse
3	Health advisor
4	Pharmacy/Pharmacist
5	Dietician
6	Psychologist / Counsellor
98	Other
99	Not known
<b>AttType</b>	<b>Type of attendance</b>
1	Scheduled or booked
2	Walk-In
3	Virtual – telephone or email contact
4	In-patient
98	Other
99	Not known
<b>DiedID</b>	<b>Died</b>
0	No
1	Yes
99	Not known
<b>DrugID</b>	<b>Drug</b>
1	Zidovudine (AZT)
2	Zalcitabine (ddC)
3	Didanosine (ddI)
4	Stavudine (d4T)
5	Lamivudine (3TC)
6	Abacavir
7	Combivir (AZT+3TC)
8	Lodenosine
9	Trizivir (AZT + 3TC + abacavir)
10	Tenofovir (TDF)
11	Emtricitabine (FTC)
12	Kivexa (3TC + Abacavir)
13	Truvada (Tenofovir/TDF + emtricitabine /FTC)
19	Other NRTI
20	Nevirapine
21	Efavirenz

22	Loviride
23	Delavirdine
24	Etravirine / TMC125
39	Other NNRTI
40	Saquinavir hard gel (invirase)
41	Indinavir
42	Ritonavir – any dose
43	Nelfinavir
44	Saquinavir soft gel (fortovase)
45	Amprenavir
46	Lopinavir (ABT 378) (kaletra)
47	Saquinavir (form unknown)
48	Atazanavir
49	Other PI
50	Hydroxyurea / hydroxycarbamide
51	IL-2
60	Acyclovir
61	Fos amprenavir
62	Tipranavir
63	Darunavir / TMC114
70	Enfuvirtide / T20
80	Adefovir
90	Blinded treatment in clinical trial
95	Maraviroc
96	Vicriviroc
98	Other drug
99	Not known
110	Raltegravir / MK-0518
120	Atripla (Efavirenz/Tenofovir/Emtricitabine)
<b>EthnicityID</b>	<b>Ethnicity</b>
1	White
2	Black-Caribbean
3	Black-African
4	Black – unspecified/black-other
5	Indian/Pakistani/Bangladeshi
6	Other Asian/Oriental
7	Other/mixed
98	Other

99	Not known
<b>ExposureID</b>	<b>Exposure</b>
1	Homosexual/bisexual (including homo / bi sex who also injected drugs)
2	Injecting drug use
3	Heterosexual
4	Blood/blood products recipient
5	Mother-to-child transmission
98	Other
99	Not Known
<b>HepResultID</b>	<b>HepResult</b>
0	Negative
1	Positive
2	Indeterminate /weakly reactive/equivocal
<b>HepTestID</b>	<b>HepTest</b>
1	Hep A antibody (total)
2	Hep B surface antigen (HbsAg)
3	Hep B surface antibody (anti-HBs)
4	Hep B core antibody (anti-HBc)
5	Hep B e antigen
6	Hep B e antibody
7	Hep C antibody
8	Hep C virus PCR/bDNA
9	Hep B core antibody (IgM)
10	Hep A antibody (IgM)
11	Hep B DNA (Type unknown)
12	Hep D antibody (total)
13	Hep B surface antigen (titre)
14	Hep D antibody (IgM)
98	Other
99	Not known
<b>HLAB57ResultID</b>	<b>HLAB57Result</b>
0	Negative
1	Positive
2	Indeterminate /weakly reactive/equivocal
<b>PCPpDrugID</b>	<b>PCPpDrug</b>
1	Co-trimoxazole/septrin
2	Dapsone

3	Pentamidine
4	Atovaquone
5	Azithromycin
6	Clarithromycin
7	Clindamycin
8	Fansidar (=pyrimethamine + sulphadoxine)
9	Primaquine
10	Pyrimethamine
11	Sulphadiazine
12	Sulphadimidine
13	Sulfametopyrazine
14	Trimetrexate
15	Trimethoprim
16	Sulfadoxine
17	Maloprim (pyrimethamine + dapsone)
18	Eflornithine
98	Other
99	Not known
<b>ReasonMissID</b>	<b>ReasonMiss</b>
1	Forgot
2	Ran out of medicaiton
3	Wanted a short break
4	Side effects
5	Away from home/supply
6	In company
7	Treatment holiday
98	Other
99	Not known
<b>ReasonStopID</b>	<b>ReasonStop</b>
10	Failure-cause unknown
11	Virological
12	Immunological
13	Clinical
14	VL / CD4
20	Toxicity-type unknown
30	Skin
31	Hypersensisity – Abacavir
32	Rash

40	GI
41	Nausea/Vomiting
42	Diarrhoea
43	Pancreatitis
44	Abnormal LFT
50	Neuro
51	CNS Disturbance
52	Peripheral Neuropathy
53	Headache
60	Metabolic
61	Lipids
62	Glucose Intolerance
63	Hyperlactataemia
64	Osteopaenia
70	Lipodystrophy
80	Myelotoxicity
81	Anaemia
82	Neutropenia
83	Thrombocytopenia
91	Myotoxicity
92	Nephrolithiasis/Renal Dysfunction
100	Patient Choice
110	Clinician decision
120	Interaction
130	Simplification
140	Poor Adherence
150	Joined clinical trial
160	Study/Trial End
170	New drug available
180	Known treatment interruption
190	Protocol amendment
200	Pregnancy
201	At start/during pregnancy
202	End of short-course ART
210	Intercurrent illness, not HIV/ drug related
220	VL sufficiently low
230	CD4 sufficiently high
240	Regimen change

250	Transfer of care
260	Drug Experience / Resistance
998	Other
999	Not Known
<b>SexID</b>	<b>Sex</b>
1	Male
2	Female
99	Not known
<b>ToxTestID</b>	<b>ToxTest</b>
1	ALT
2	Albumin
3	Alkaline phosphatase
4	Amylase
5	AST
6	Bilirubin
7	Cholesterol total (non fasting or unknown)
8	CPK (creatine phosphokinase)
9	Creatinine
10	Glucose
11	GGT(g-glutamyl transferase)
12	Haemoglobin
13	HDL
14	Lactate
15	LDL
16	Triglycerides
17	Urea
18	Lactate dehydrogenase
19	Cholesterol (fasting)
98	Other
99	Not known
<b>ToxUnitID</b>	<b>ToxUnit</b>
1	IU/L
2	g/L
3	U/L
4	μmol/L
5	μmol/L(plasma)
6	mmol/L
7	mmol/L(urine)

8	g/dL
9	mg/L
98	Other
99	Not known
<b>UndetID</b>	<b>Undet</b>
-1	< Below lower limit of detectability
0	Any value that is detectable but below the upper limit of quantification
1	> Above upper limit of quantification

## Appendix V Summary of matching

Figure 1. Matching records for women reported to NSHPC and UK CHIC to create a combined 2011 dataset

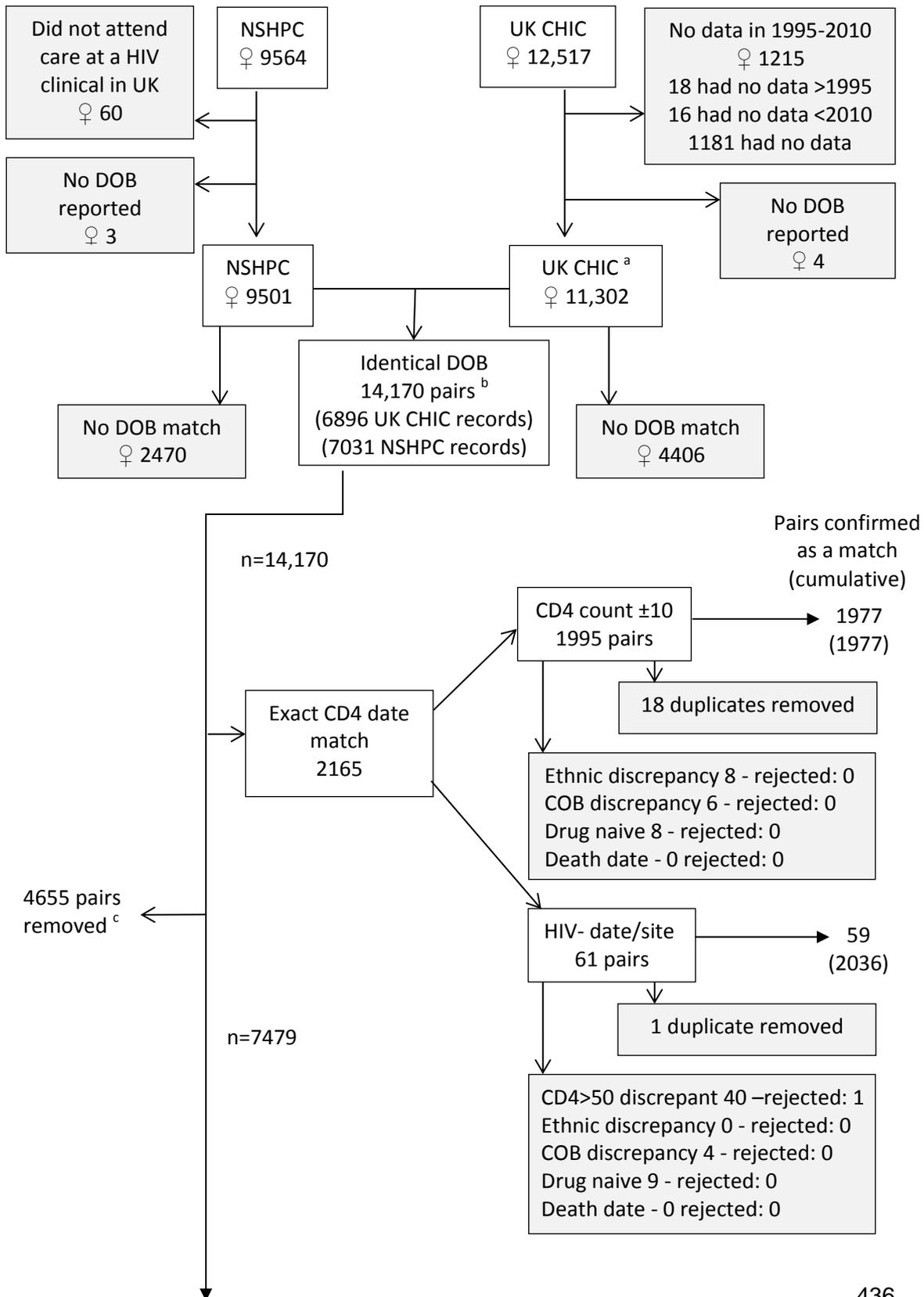


Figure 1  
cont.

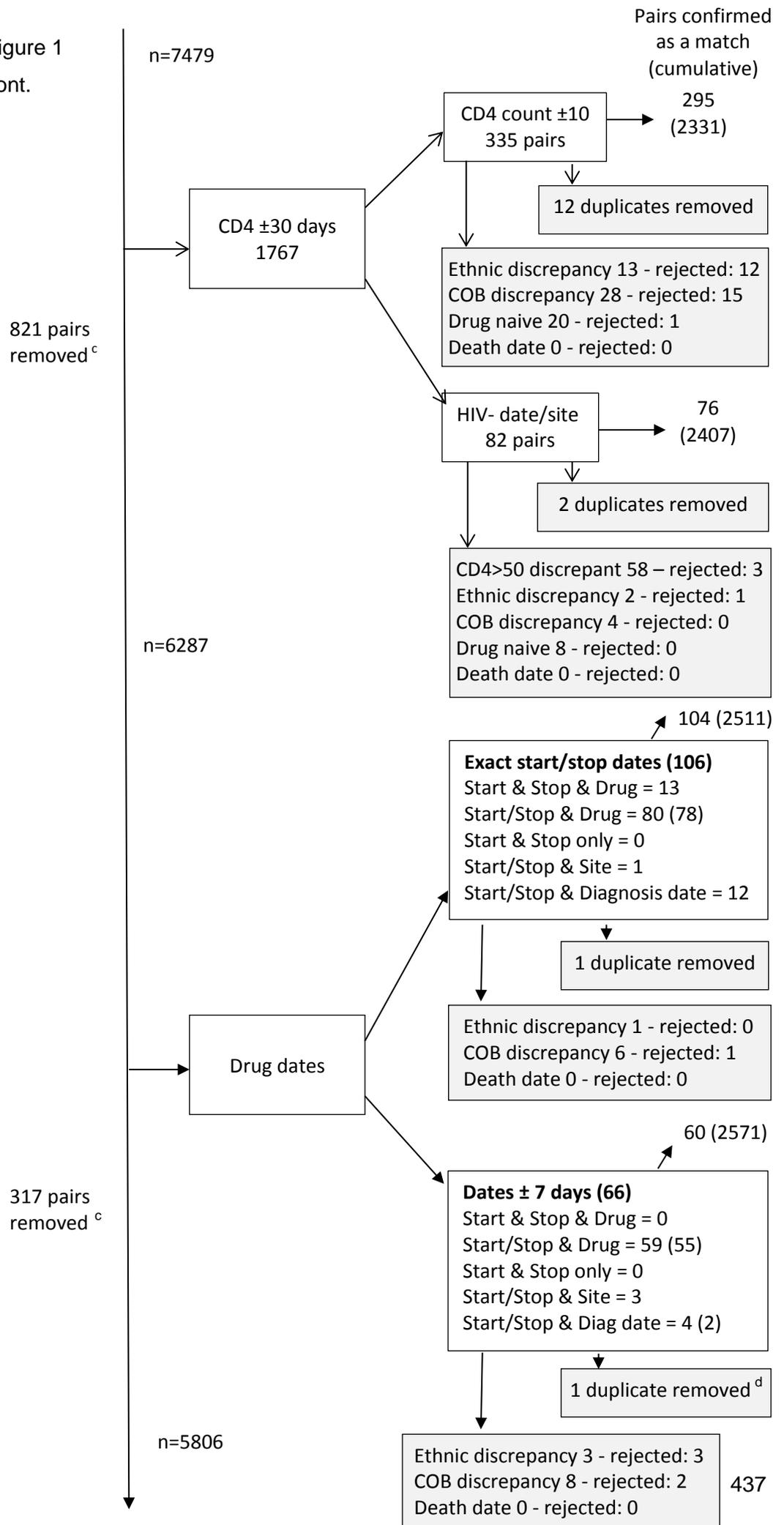


Figure 1 cont.

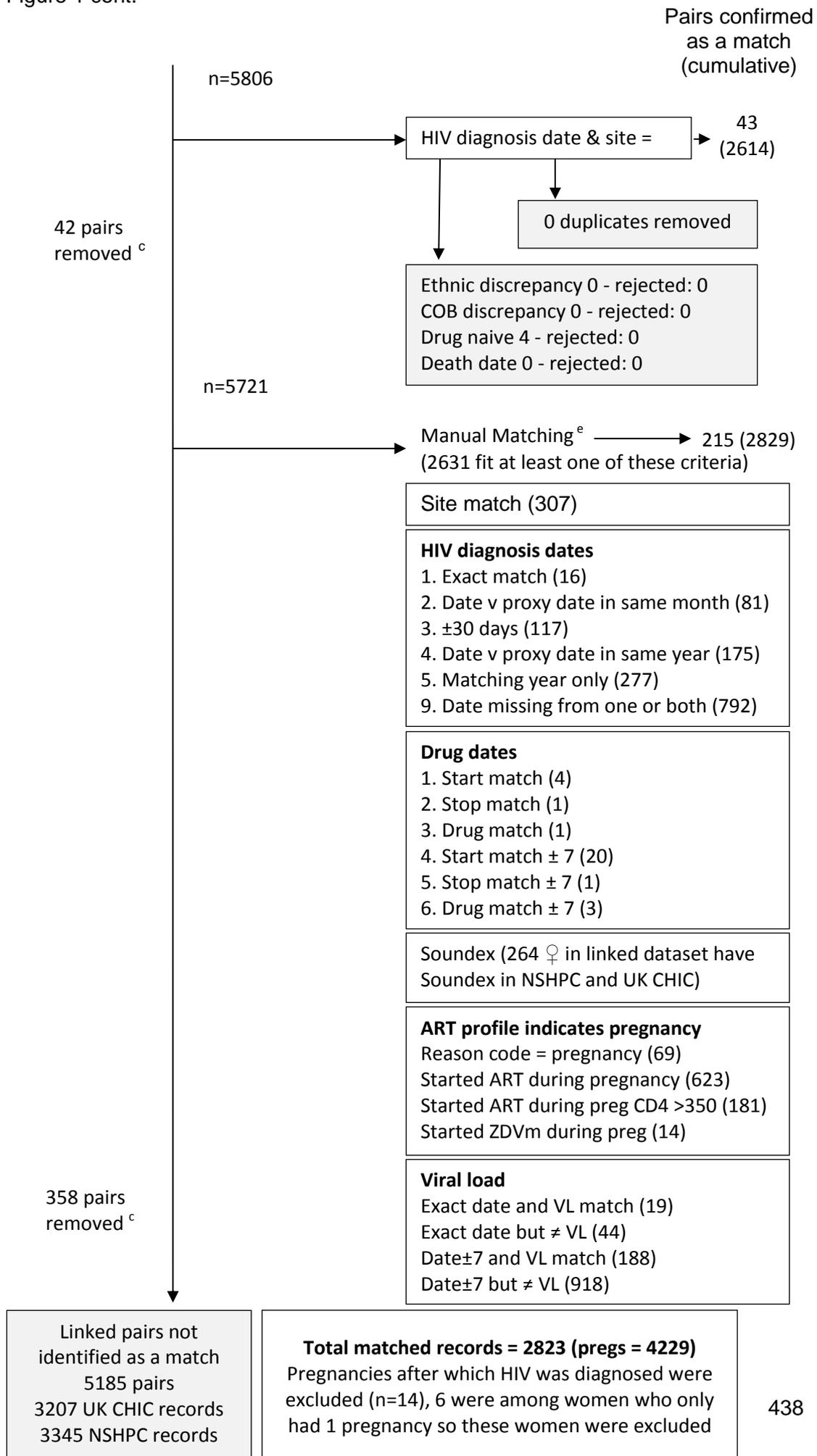


Figure 1 footnotes:

- <sup>a</sup> Women older than childbearing age were not excluded at this stage.
- <sup>b</sup> The maximum number of pairs with the same DOB was 88 where DOB was 1<sup>st</sup> January and 48 where DOB was not 1<sup>st</sup> January.
- <sup>c</sup> Pairs were removed as one or both records in the pair were confirmed as a match in a different pair.
- <sup>d</sup> These linked to multiple UK CHIC records which on examination were two records for the same woman.
- <sup>e</sup> The manual matching categories are not exclusive; they are categories which allow the reviewer to select records which can be manually assessed using multiple fields including site, HIV-diagnosis date, ethnicity, viral load dates and viral loads, COB, date of UK arrival and so on.

Note that the discrepancy checks are hierarchical; if a woman had discrepant ethnicity and country of birth (COB), she would be excluded based on discrepant ethnicity and would therefore not be included in the COB discrepancies.

After the creation of the final matched dataset it is cleaned and new variables are created.

1. Creating variables using combined data
  - HIV-diagnosis date
  - Ethnicity
  - Exposure
2. Data cleaning
  - Removing all pregnancies where HIV-diagnosed occurred after delivery (n=6)
3. Deriving new variables (for each pregnancy)
  - Timing of diagnosis before/during pregnancy
  - ART use during pregnancy
  - ART use prior to pregnancy
  - ART experience at conception
  - ART status at conception
4. All women in UK CHIC – includes antenatal data from NSHPC for those with a pregnancy
  - Date of starting ART for women's own health
  - Boolean variable indicating if they have started ART by the end of follow-up

## Appendix VI NSHPC and UK CHIC criteria used to assess ART use

Table 1. Criteria used to assess ART use at conception

Dataset	Criteria			n
NSHPC	Yes	if	PRETRT = Yes	531
		or	PRETRT = No/NK P_DRUG_CON=Yes	1
		or	PRETRT=No/NK P_DRUGSTART<EDC P_DRUGSTOP≥EDC/null	498
	No	if	PRETRT=No	1571
	NK	if	PRETRT=NK	19
UK CHIC	Yes	if	DSTART < EDC DSTOP ≥ EDC /null	996
		NK	if	EARLIEST_DATE ≥ EDC HIV diagnosis date < EDC
		or	EARLIEST_DATE = null HIV diagnosis date < EDC	0
		or	SEEN_12MB4 = No Date HIV diagnosis < EDC <sup>1</sup>	113
	No		DSTART=Null/> EDC	1388

DSTART: ART drug start date; DSTOP: ART drug stop date; EDC: Estimated date of conception; PRETRT: ART use at conception (Yes/No/NK); P\_DRUG\_CON: on specific ART drug at conception (Yes/No); SEEN\_12MB4: Attended care at a UK CHIC site during the 12 months before conception (Yes/No).

<sup>1</sup>Although these women were HIV diagnosed, there were no data in UK CHIC during the year prior to the pregnancy, it was not clear from the UK CHIC data whether or not they started ART during that period.

Table 2. Criteria used to assess ART status at 6 months before conception

Dataset	Criteria	n
NSHPC	Yes if P_DRUGSTART <EDC-6 months P_DRUGSTOP >EDC-6 months/null	387
	No if HIV diagnosis date > EDC-6 months	862
	NK	1371
UK CHIC	Yes if DSTART <EDC-6 months DSTOP >EDC-6 months/null	903
	NK if EARLIEST_DATE > EDC-6months/null	1061
	or EARLIEST_date = null	1
	or SEEN_12MB4 = No	170
	No	485

DSTART: ART drug start date (UK CHIC); DSTOP: ART drug stop date (UK CHIC); EDC-6 months: 6 months before the estimated date of conception; P\_DRUGSTART: ART drug start date (NSHPC); P\_DRUGSTOP: ART drug stop date (NSHPC). SEEN\_12MB4: attended care at a UK CHIC site during the 12 months before conception (Yes/No).

Table 3. UK CHIC criteria used to assess ART status at 6 and 12 months after delivery

Criteria			Months after delivery	
			6 months n	12 months n
Yes	if	DSTART <6/12m post-delivery DSTOP ≥6/12m post-delivery	660	588
	or	DSTART <6/12m post-delivery DSTOP = null SEEN_12MB4 = Yes	588	587
NK	if	EARLIEST_DATE >6/12m post-delivery	56	46
	or	6/12m post-delivery year ≥ 2010	324	469
	or	EARLIEST_DATE >6/12m post-delivery DSTART1 = null TRT = Yes or PRETRT = Yes	58	53
	or	DSTART <6/12m post-delivery DSTOP = null SEEN_12MB4 = yes	124	110
No			810	767

DSTART: ART drug start date; DSTOP: ART drug stop date; 6/12m post-delivery: the date 6/12 months after delivery; PRETRT: ART use at conception (Yes/No/NK); SEEN\_12MB4: attended care at a UK CHIC site during the 12 months before conception (Yes/No); TRT: ART use during pregnancy (Yes/No).

Table 4. Criteria used to assess ART status during pregnancy

Dataset	Criteria	n	
NSHPC	Yes	if P_DRUGSTART < EDC P_DRUGSTOP > EDC/null	2421
		or TRT=Yes	4
		or TRT=null/NK NSHPC indicates ART use at conception	28
	No <sup>1</sup>	if TRT=No	86
	NK	if TRT=NK	81
UK CHIC	Yes	if DSTART<DELIVERY DSTOP=null/>DELIVERY	2248
	NK	if EARLIEST_DATE≥DELIVERY	79
		or SEEN_6MB4=No	49
		or SEEN_PREG=No	
		or CHIC_on_ART_at_conc=No SEEN_PREG=No	29
	No		215

CHIC\_on\_ART\_at\_conc: ART status at conception according to the UK CHIC data; P\_DRUGSTART: ART drug start date; P\_DRUGSTOP: ART drug stop date; TRT: ART use during pregnancy (Yes/No); SEEN\_6MB4: attended care at a UK CHIC site in the 6 months prior to pregnancy (Yes/No); SEEN\_PREG: attended HIV care at a UK CHIC site during the pregnancy (Yes/No).

<sup>1</sup>The outcomes for these pregnancies were: miscarriage (n=39); termination (n=16); and live birth (n=31).

Table 5. Criteria used for categorising ART use for each pregnancy (n=2620)

ART use						n
6 months before conception	At conception	During pregnancy	6 months after delivery	12 months after delivery	Category of ART use	
-	Yes	Yes	Yes	Yes	Long-term use	623
-	Yes	Yes	NK	Yes		0
-	Yes	Yes	Yes	NK		81
Yes	NK	Yes	Yes	Yes		1
Yes	Yes	Yes <sup>a</sup>	NK	NK		183
-	No/NK	No	-	-	No ART use	103
No	No	Yes	No	No	Short-course ART	543
NK	No	Yes	No	No		5
No	NK	Yes	No	No		2
No	No	Yes	No	NK		9
No	No	Yes	NK	No		3
Yes*/No/NK	No/NK	Yes <sup>b</sup>	Yes*/No	Yes*/No		22
Yes*/No/NK	No/NK	Yes <sup>b</sup>	Yes*/NK	Yes*/NK		196
Yes*/No/NK	No/NK	Yes <sup>c</sup>	No	Yes		27
Yes*/No/NK	No/NK	Yes <sup>b</sup>	Yes	No		16
No/NK	No	Yes	Yes**	Yes**	Start long-term use	382
No	No	Yes	NK	Yes**		3
No	No	Yes	Yes**	NK		20
No/NK	No/NK	Yes <sup>d</sup>	NK	NK/No		37
No/NK	No/NK	Yes <sup>d</sup>	NK/No	NK/Yes		6
No/NK	No/NK	Yes <sup>d</sup>	Yes (preg)	Yes (preg)		33
No/NK	No/NK	Yes <sup>d</sup>	Yes	No		12
Yes/NK	Yes	Yes	No	No		46
Yes/NK	Yes	Yes	No	NK		4
Yes/NK	Yes	Yes	NK	No	Long-term use (but interrupts after pregnancy)	1
Yes/NK	Yes	Yes	No	Yes		12
Yes/NK	Yes	Yes	Yes	No		14
Yes/NK	Yes/NK	Yes <sup>a</sup>	No/NK	No/NK	Long-term use <sup>f</sup>	15
No	Yes	Yes <sup>e</sup>	No/NK	No/NK		17
Yes*	No	Yes <sup>a</sup>	-	-		18
No	Yes	Yes <sup>a</sup>	-	-	8	
-	-	NK	-	-	Not known	67
-	-	Yes	NK	NK		83
All other combinations						28

Footnotes for Table 5

Categories are hierarchical

<sup>a</sup> Where start date for long-term ART use is before the pregnancy

<sup>b</sup> Where start date for long-term ART use is after the pregnancy or start\_treatment=0 (i.e. they have not started long-term ART yet)

<sup>c</sup> Where start date for long-term ART use is within 12 months after the pregnancy

<sup>d</sup> Where start date for long-term ART use is during the pregnancy

<sup>e</sup> Where start date for long-term ART use is within 6 months before the pregnancy

<sup>f</sup> but interrupts before pregnancy – or there is no record of that ART use in UK CHIC

\* Woman does not have a pregnancy at this time

\*\* Woman does not have a pregnancy at this time or start date for ART during pregnancy

## Appendix VII UK CHIC study collaborators

### **Steering Committee**

Jonathan Ainsworth, Sris Allan, Jane Anderson, Abdel Babiker, David Chadwick, Duncan Churchill, Valerie Delpech, David Dunn, Brian Gazzard, Richard Gilson, Mark Gompels, Phillip Hay, Teresa Hill, Margaret Johnson, Sophie Jose, Stephen Kegg, Clifford Leen, Dushyant Mital, Mark Nelson, Chloe Orkin, Adrian Palfreeman, Andrew Phillips, Deenan Pillay, Frank Post, Jillian Pritchard, Caroline Sabin, Achim Schwenk, Anjum Tariq, Roy Trevelion, Andy Ustianowski, John Walsh.

### **Central Co-ordination**

University College London (Teresa Hill, Susie Huntington, Sophie Jose, Andrew Phillips, Caroline Sabin, Alicia Thornton); Medical Research Council Clinical Trials Unit at UCL (MRC CTU at UCL), London (David Dunn, Adam Glabay).

### **Current collaborating sites**

Barts Health NHS Trust, London (Chloe Orkin, Janet Lynch, James Hand, Carl de Souza); Brighton and Sussex University Hospitals NHS Trust (Duncan Churchill, Nicky Perry, Stuart Tilbury, Elaney Youssef, Duncan Churchill); Chelsea and Westminster Hospital NHS Foundation Trust, London (Brian Gazzard, Mark Nelson, Rhiannon Everett, David Asboe, Sundhiya Mandalia); Homerton University Hospital NHS Trust, London (Jane Anderson, Sajid Munshi); King's College Hospital NHS Foundation Trust, London (Frank Post, Ade Adefisan, Chris Taylor, Zachary Gleisner, Fowzia Ibrahim, Lucy Campbell); Medical Research Council Clinical Trials Unit (MRC CTU), London (Abdel Babiker, David Dunn, Adam Glabay); Middlesbrough, South Tees Hospitals NHS Foundation Trust, (David Chadwick, Kirsty Baillie); Mortimer Market Centre, University College London (Richard Gilson, Nataliya Brima, Ian Williams); North Middlesex University Hospital NHS Trust, London (Jonathan Ainsworth, Achim Schwenk, Sheila Miller, Chris Wood); Royal Free NHS Foundation Trust/University College London (Margaret Johnson, Mike Youle, Fiona Lampe, Colette Smith, Rob Tsintas, Clinton Chaloner, Samantha Hutchinson, Caroline Sabin, Andrew Phillips, Teresa Hill, Sophie Jose, Alicia Thornton, Susie Huntington); Imperial College Healthcare NHS Trust, London (John Walsh, Nicky Mackie, Alan Winston, Jonathan Weber, Farhan Ramzan, Mark Carder); The Lothian University Hospitals NHS Trust, Edinburgh (Clifford Leen, Alan Wilson, Sheila Morris); North Bristol NHS Trust (Mark Gompels, Sue Allan); Leicester, University Hospitals of Leicester NHS Trust (Adrian

Palfreeman, Khurram Memon, Adam Lewszuk); Woolwich, Lewisham and Greenwich NHS Trust (Stephen Kegg, Akin Faleye, Dr Mitchell, Dr Hunter), St. George's Healthcare NHS Trust (Phillip Hay, Mandip Dhillon, Christian Kemble); York Teaching Hospital NHS Foundation Trust (Fabiola Martin, Sarah Russell-Sharpe, Janet Gravely); Coventry, University Hospitals Coventry and Warwickshire NHS Trust (Sris Allan, Andrew Harte, Stephen Clay); Wolverhampton, The Royal Wolverhampton Hospitals NHS Trust (Anjum Tariq, Hazel Spencer, Ron Jones); Chertsey, Ashford and St.Peter's Hospitals NHS Foundation Trust (Jillian Pritchard, Shirley Cumming, Claire Atkinson); Milton Keynes Hospital NHS Foundation Trust (Dushyant Mital, Veronica Edgell, Julie Allen); The Pennine Acute Hospitals NHS Trust (Andy Ustianowski, Cynthia Murphy, Ilise Gunder); Public Health England, London (Valerie Delpech); i-Base, London (Roy Trelvelion).

### **Funding**

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## Appendix VIII The NSHPC collaborators

### **Steering Committee**

M Cortina-Borja, A Brown, A de Ruiter, S Donaghy, S Farthing, K Harding, A Judd, L Logan, H Lyall, A Namiba, F Ncube, C Peckham (chair), L Primrose, C Thorne, P Tookey (PI), S Webb.

### **Funding**

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We gratefully acknowledge the contribution of the midwives, obstetricians, genitourinary physicians, paediatricians, clinical nurse specialists and all other colleagues who report to the NSHPC through the British Paediatric Surveillance Unit of the Royal College of Paediatrics and Child Health, and the obstetric reporting scheme run under the auspices of the Royal College of Obstetricians and Gynaecologists.

Appendix IX Major drug resistance mutations in women who were ART-naïve or ART-experienced prior to starting life-long ART

Major NRTI resistance mutations															
	Non-TAMS							TAMS						Additional	
	M184V	M184I	K65R	K70E	K70R	L74V	Y115F	M41L	D67N	L210W	T215F	T215Y	K219E	V108I	P225H
Before starting treatment															
Naïve	4	1	2	1	2	-	-	3	2	3	2	1	1	6	-
Experienced a	-	-	-	-	-	1	-	-	-	-	-	-	-	-	-
Experienced b	-	-	-	-	1	-	-	1	1	-	1	-	-	1	-
On treatment - failed to achieve viral suppression within 6 months															
Naïve	3	2	-	-	-	-	-	-	-	-	-	-	-	-	-
Experienced	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-
On treatment – viral rebound following viral suppression															
Naïve	2	1	-	-	-	-	-	-	-	-	-	-	-	-	-
Experienced	1	-	-	-	-	1	-	-	-	-	-	-	-	-	-

In women who start life-long ART with some prior use of ART experience, 'Experienced a' refers to a resistance test when ART naïve (prior to any reported ART use), 'Experienced b' refers to a resistance test in the 12 months prior to starting life-long ART. Non-TAMS: Non-Thymidine analog mutations; TAMS: Thymidine analog mutations; Additional refers to Additional Accessory mutations. 'Major mutations' refers to mutations which are generally selected for first under drug pressure and which reduce drug susceptibility.

Major NNRTI resistance mutations															
	L100I	K101E	K103N	K103S	V106A	V106M	E138A	E138G	E138K	E138Q	Y181C	Y188H	Y188L	G190A	H221Y
Before starting treatment															
Naïve	2	2	12	1	-	2	32	1	-	1	1	-	1	1	-
Experienced a	-	-	-	-	-	-	1	-	-	-	-	-	-	-	-
Experienced b	-	-	-	-	1	-	2	-	-	-	-	-	-	-	1
On treatment - failed to achieve viral suppression within 6 months															
Naïve	-	1	1	-	-	-	2	-	-	-	1	-	-	2	2
Experienced	-	-	-	-	-	-	-	-	-	-	1	-	-	-	1
On treatment – viral rebound following viral suppression															
Naïve	-	-	-	-	-	1	1	-	-	-	-	-	-	-	-
Experienced	-	-	1	-	-	-	-	-	-	-	2	-	-	1	-

Major Protease resistance mutations											
	D30N	V32I	M46L	M46I	Q58E	L76V	V82A	V82S	I84V	N88S	L90M
Before starting treatment											
Naïve	-	-	2	-	5	-	1	-	-	1	1
Experienced a	-	-	-	-	1	-	-	-	-	-	-
Experienced b	-	-	-	-	-	-	-	-	-	-	-
On treatment - failed to achieve viral suppression within 6 months											
Naïve	-	-	-	-	1	-	-	-	-	-	-
Experienced	-	-	-	-	-	-	-	-	-	-	-
On treatment - viral rebound following viral suppression											
Naïve	-	-	1	-	-	-	-	-	-	-	-
Experienced	-	-	-	-	-	-	-	-	-	-	-

# Appendix X Mutations associated with resistance to ART drugs

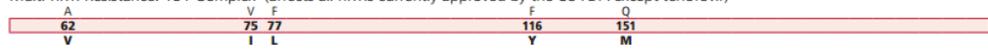
## MUTATIONS IN THE REVERSE TRANSCRIPTASE GENE ASSOCIATED WITH RESISTANCE TO REVERSE TRANSCRIPTASE INHIBITORS

### Nucleoside and Nucleotide Analogue Reverse Transcriptase Inhibitors (nRTIs)<sup>a</sup>

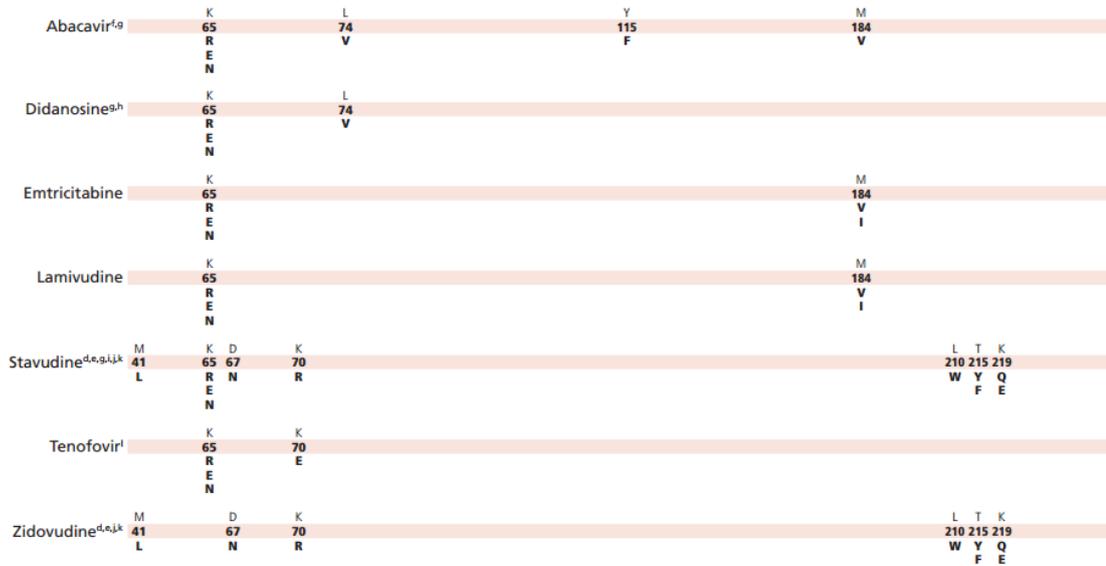
Multi-nRTI Resistance: 69 Insertion Complex<sup>b</sup> (affects all nRTIs currently approved by the US FDA)



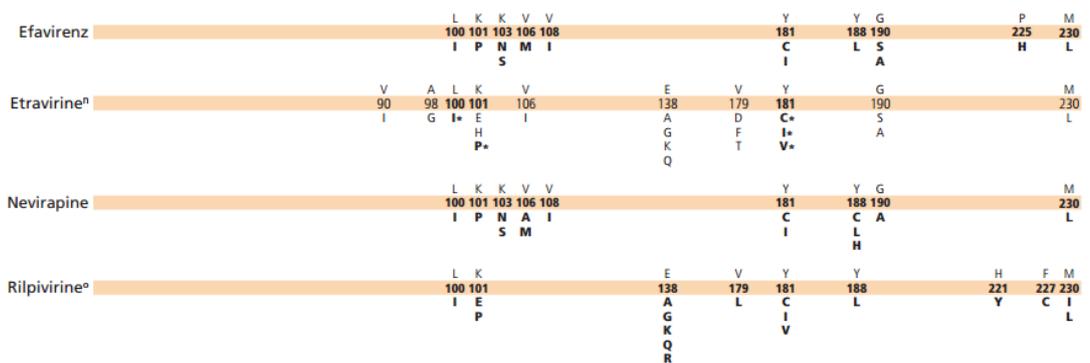
Multi-nRTI Resistance: 151 Complex<sup>c</sup> (affects all nRTIs currently approved by the US FDA except tenofovir)



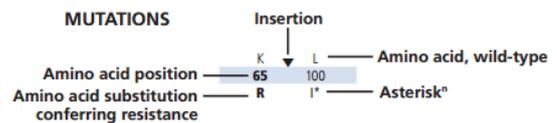
Multi-nRTI Resistance: Thymidine Analogue-Associated Mutations<sup>d,e</sup> (TAMs; affect all nRTIs currently approved by the US FDA)



### Nonnucleoside Analogue Reverse Transcriptase Inhibitors (NNRTIs)<sup>a,m</sup>



Amino acid abbreviations: A, alanine; C, cysteine; D, aspartate; E, glutamate; F, phenylalanine; G, glycine; H, histidine; I, isoleucine; K, lysine; L, leucine; M, methionine; N, asparagine; P, proline; Q, glutamine; R, arginine; S, serine; T, threonine; V, valine; W, tryptophan; Y, tyrosine.



Source: Wensing *et al.* [102]

**MUTATIONS IN THE PROTEASE GENE ASSOCIATED WITH RESISTANCE TO PROTEASE INHIBITORS<sup>P-97</sup>**

Atazanavir +/- ritonavir <sup>t</sup>	L 10	G 16	K 20	L 24	V 32	L 33	E 34	M 36	M 46	G 48	I 50	F 53	I 54	D 60	I 62	I 64	A 71	G 73	V 82	I 84	I 85	N 88	L 90	I 93
	I	E	R	I	I	I	Q	I	I	V	L	L	L	E	V	L	V	C	A	V	V	S	M	L
	F	M	I		F			L			Y	V	M			M	I	S	T				M	
	V	I			V			V								V	T	T	F				M	
	C	T			V			V			A					L	A		I				M	
Darunavir/ ritonavir <sup>t</sup>	V 11				V 32	L 33			I 47		I 50	I 54						T 74	L 76		I 84		L 89	
	I				I	F			V	V	M	L						P	V		V		V	
Fosamprenavir/ ritonavir <sup>t</sup>	L 10				V 32				M 46	I 47	I 50	I 54						G 73	L 76	V 82	I 84		L 90	
	F				I				I	V	V	L						S	V	A	V		M	
	I								L			V	M							F				
	R																			A				
	V																			S				
Indinavir/ ritonavir <sup>u</sup>	L 10	K 20	L 24		V 32			M 36	M 46		I 54							A 71	G 73	L 76	V 77	V 82	I 84	L 90
	I	M	I		I			I	I		V							V	S	V	I	A	V	M
	R	R			I			I	L									T	A			F		
	V																					T		
Lopinavir/ ritonavir <sup>u</sup>	L 10	K 20	L 24		V 32	L 33		M 46	I 47	I 50	F 53	I 54		L 63				A 71	G 73	L 76	V 77	V 82	I 84	L 90
	F	M	I		I	F		I	V	V	V	L		P				V	S	V		A	V	M
	I							L	A			L						T				F		
	R	R																				A		
	V																					T		
																						S		
Nelfinavir <sup>uw</sup>	L 10				D 30			M 36	M 46									A 71		V 77	V 82	I 84	N 88	L 90
	F				N			I	I									V		I	A	V	D	M
	I							I	L									T			F		S	
																					T			
																					S			
Saquinavir/ ritonavir <sup>u</sup>	L 10		L 24						G 48		I 54			I 62				A 71	G 73	V 77	V 82	I 84	L 90	
	I		I						V		V			V				V	S	I	A	V	M	
	R										L							T			F			
	V																				T			
																					S			
Tipranavir/ ritonavir <sup>t</sup>	L 10				L 33			M 36	K 43	M 46	I 47	I 54	Q 58					H 69	T 74		V 82	N 83	I 84	L 89
	I				F			I	T	L	V	A	E					K	P		L	D	V	I
	R							L				M						R			T			M
	V							V				V												V

Source: Wensing *et al.* [102]

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