HIV-infected childbearing women in Europe: health, treatment and care

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Declaration

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

Abstract

This thesis aims to investigate the health of HIV-infected childbearing women living in resource-rich and resource-constrained settings in Europe, and to examine their treatment and care in the context of contemporary policies. HIV prevalence is increasing among childbearing women in Europe and particularly in the Eastern region. Highly effective interventions for the prevention of mother-to-child transmission (PMTCT) have resulted in very low transmission rates in Western Europe, but are less available in Ukraine. This thesis uses data from the European Collaborative Study, an on-going prospective cohort study of HIV-infected pregnant women and their infants (9500 mother-child pairs in Western Europe in 1986-2012, and 9600 in Ukraine in 2000-2012), to examine missed opportunities for PMTCT. Results highlight a decline in mother-to-child transmission rates in Ukraine to 4.1% (95% CI 3.4-4.9) in 2008-2010 (vs. 1.7% (95% CI 1.1-2.5) in the Western Europe sites in 2000-2009), and the importance of maternal marginalisation to continued transmissions in both settings. In Western Europe, a substantial proportion of HIV-positive pregnant women are now conceiving on antiretroviral therapy (ART); factors associated with treatment failure during pregnancy among this group are explored.

Prevalence of HIV co-infections is high in Ukraine, and this thesis uses data from a nested postnatal cohort (*n*=2066) to explore testing coverage and factors associated with hepatitis C virus and chlamydia co-infections. Detection and prevalence of cervical abnormalities (an important potential cause of morbidity in HIV-infected women) are also explored. An additional survey in Ukraine provides data on ART adherence during pregnancy and postnatally (*n*=418) and highlights gaps in information provision and support.

Against a backdrop of overall improvements in HIV care, this thesis identifies groups at heightened risk of mother-to-child transmission and/or poor maternal outcomes, and informs policy for their treatment and care.

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Acronyms and Abbreviations

3TC – Lamivudine

ABC - Abacavir

AIC – Akaike's information criterion

AIDS – Acquired immune deficiency syndrome

ALT – Alanine transaminase

AOR – Adjusted odds ratio

APR – Adjusted prevalence ratio

APRI – Aspartate transaminase to platelet ratio

ART – Antiretroviral therapy

AST – Aspartate transaminase

BIC – Bayesian information criterion

BV – Bacterial vaginosis

cART – Combined antiretroviral therapy

CASE – Case Adherence Support Evaluation (a self-report adherence measure)

CDC – United States Centers for Disease Control and Prevention

CI – Confidence interval

CIN – Cervical intraepithelial neoplasia

CS – Caesarean section

DHS – Demographic and Health Surveys

ECDC – European Centre for Disease Prevention and Control

ECS – European Collaborative Study

EFV – Efavirenz

Global Fund –the Global Fund to fight AIDS, Tuberculosis and Malaria

HAART – Highly active antiretroviral therapy

HBV – Hepatitis B virus

HCV – Hepatitis C virus

HIV – Human immunodeficiency virus

HIV-ASES – HIV Treatment Adherence Self-Efficacy Scale

HPV – Human papillomavirus

HSIL – High-grade squamous intraepithelial lesion

HSV – Herpes simplex virus

IDU(s) – Injecting drug use(rs) / injecting drug using

IDV - Indinavir

IQR – Interquartile range

IUD – Intrauterine device

LPV/r – Ritonavir-boosted lopinavir

LRT – Likelihood ratio test

LSIL – Low-grade squamous intraepithelial lesion

MSM – Men who have sex with men

MTCT – Mother-to-child transmission

NFV - Nelfinavir

NGO – Non-governmental organisation

NNRTI – Non-nucleoside Reverse Transcriptase Inhibitor

NRTI/NtRTI – Nucleoside/Nucleotide Reverse Transcriptase Inhibitor

NVP – Nevirapine

OC – Oral contraceptive

OR – Odds ratio

PCR – Polymerase chain reaction

PegIFN/RBV – Pegylated interferon and ribavirin

PHQ – Patient Health Questionnaire

PI – Protease Inhibitor

PMTCT – Prevention of mother-to-child transmission

PPAI – Perinatal Prevention of AIDS Initiative

PR – Prevalence ratio

RCT – Randomised controlled trial

REDCap – Research Electronic Data Capture

RITA – Recent infection testing algorithm

RNA – Ribonucleic acid

RR – Risk ratio

sdNVP – Single-dose nevirapine

STI – Sexually transmitted infection

TDF – Tenofovir disoproxil fumarate

TV – *Trichomonas vaginalis*

UNAIDS – Joint United Nations Programme on HIV/AIDS

UNICEF – United Nations International Children's Fund

WHO – World Health Organisation

ZDVm – Zidovudine monotherapy

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Chapter 1 Introduction

1.1 Global epidemiology of HIV

In 2010, thirty years after the first cases of acquired immune deficiency syndrome (AIDS) were reported (Gottlieb *et al.* 1981), around 30 million people had died of AIDS-related causes worldwide (WHO Global Health Observatory 2012) and an estimated 34 million (31.6-35.2 million) people were living with human immunodeficiency virus (HIV) (UNAIDS 2011b). HIV is transmitted via contact with infective bodily fluids (including genital secretions and blood). Transmission primarily occurs through sexual intercourse, sharing of injecting equipment among injecting drug users (IDUs),,iatrogenic exposure, and from mother to child (described in detail in section 1.4) (De Cock *et al.* 2012). Heterosexual transmission has been particularly important in the spread of the epidemic in sub-Saharan Africa, where an estimated 68% of HIV-positive people live (UNAIDS 2011b), while in other regions the epidemic has been focused among men who have sex with men (MSM) and IDUs (Sullivan *et al.* 2009; Wolfe *et al.* 2010). Women account for half of all people living with HIV (UNAIDS 2011b); 3.4 million (3-3.8 million) children were living with HIV in 2010 (WHO *et al.* 2011b), the majority of whom became infected via mother-to-child transmission (MTCT).

The annual number of new HIV infections has declined worldwide from a peak of 3.4 million in 1997 to 2.7 million in 2010, and the number of AIDS-related deaths has also declined from a peak of 2.2 million in 2005 to an estimated 1.8 million in 2010 (WHO *et al.* 2011b). These declines have been a result of a combination of factors, including the successful adoption of prevention measures (such as behaviour change programmes, voluntary medical male circumcision and condom promotion/distribution) and massive scale-up of access to treatment in low and middle-income settings (UNAIDS 2011b).

1.2 Epidemiology of HIV in Europe

Europe is a heterogeneous and predominantly resource-rich region, with a number of low and lower-middle-income countries in the Eastern region including Armenia, Georgia, Moldova,

Ukraine, Uzbekistan and Tajikistan[1] (The World Bank 2013). Two distinct HIV epidemics have affected the Western and Eastern regions. The epidemic in the West began around fifteen years earlier than the epidemic in the East and had affected IDU and MSM communities throughout the region by the early 1980s (Hamers *et al.* 2003; Hamers *et al.* 2004). Ukraine was the epicentre of the HIV epidemic in Eastern Europe and had just 40-80 new infections per year prior to 1995 (Hamers *et al.* 2003). In 1995, HIV began to spread explosively among IDUs in the Black Sea port cities of Odessa and Mykolaiv and by 1997 there were 25,000 cases reported nationwide (Dehne *et al.* 1999; Hamers *et al.* 2003).

Despite the more recent epidemic in Eastern Europe, it is there that the majority of Europe's burden of HIV infection is now concentrated, with an estimated 1.5 million people living with HIV compared with 840,000 in Western and Central Europe (UNAIDS 2011b). Of the 118,335 new cases of HIV diagnosed in Europe in 2010, 76% were in Eastern Europe (ECDC / WHO Regional Office for Europe 2010) and around 90% of these were accounted for by two countries, Russia and Ukraine (WHO *et al.* 2011b). The proportion of people living with HIV who are undiagnosed is estimate to be 60% in Eastern Europe vs. 30% in Western Europe (Hamers *et al.* 2008), and so the difference in HIV burden between these two regions is likely to be even greater than the number of diagnosed cases suggests. Importantly, the spread of the HIV epidemic in Eastern Europe shows little sign of stabilising, in contrast with worldwide trends (UNAIDS 2011b). Figure 1.1 summarises some key differences between the Western and Eastern European epidemics.

Information on pregnant HIV-infected women and their children is available through the European Collaborative Study (ECS), a large multi-site prospective cohort study which, along with related studies (described under 'data sources', section 2.3 page 55), forms the basis for this thesis. The ECS has enrolled women in Western Europe since 1986 and Ukraine since 2000 (European Collaborative Study 2006), and background to the HIV epidemics in these two settings is described in more detail in the section that follows. The HIV epidemic in Ukraine is the most severe in Europe (Kruglov *et al.* 2008), and a major focus of this thesis.

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[1] Europe is defined as the WHO European region throughout.

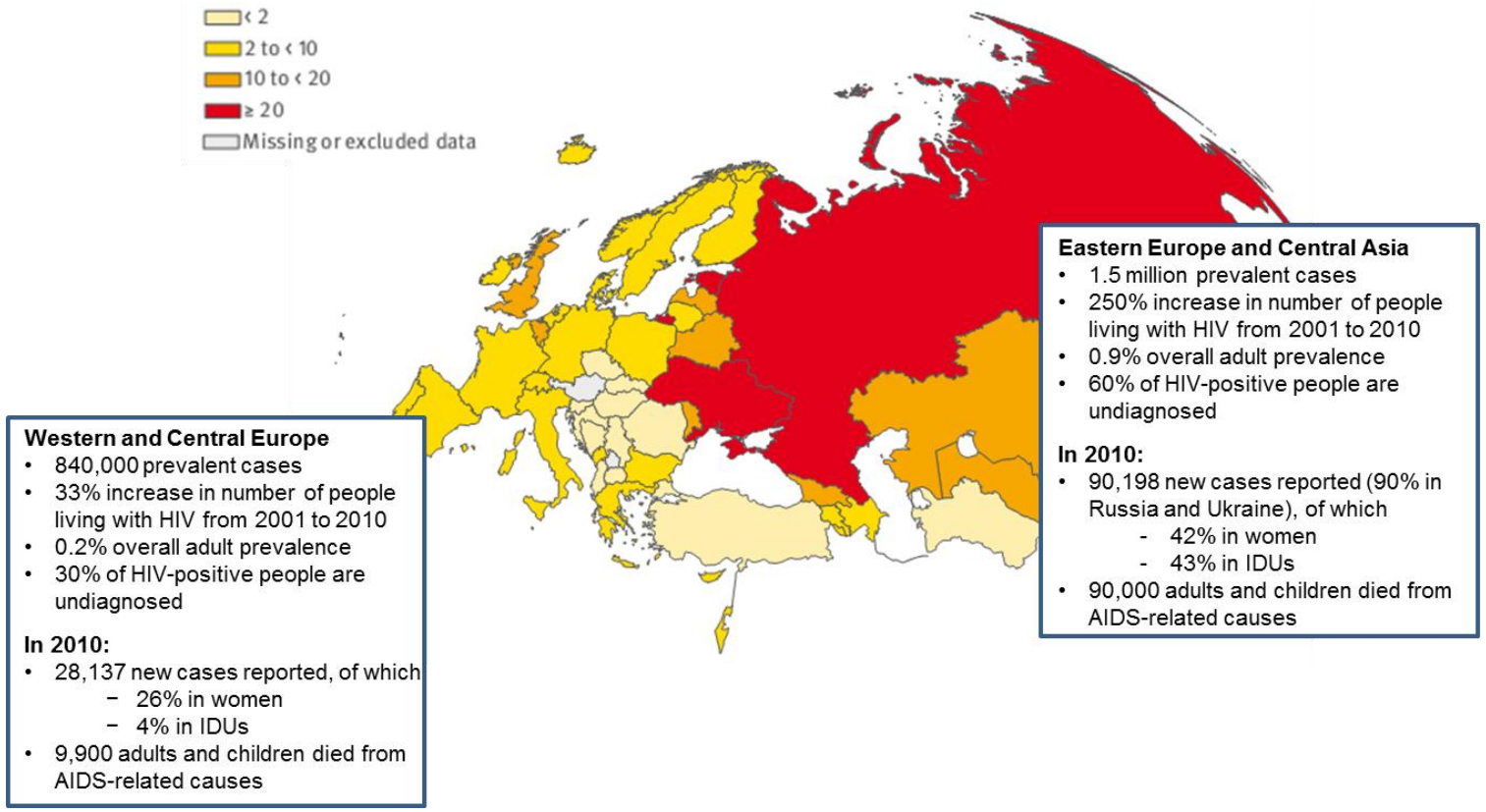


Figure 1.1: HIV infections per 100,000 population in Europe in 2010 and key estimates for the epidemics in the Eastern and Western regions

Map from: (ECDC / WHO Regional Office for Europe 2010). References: (Hamers *et al.* 2008; ECDC / WHO Regional Office for Europe 2010; UNAIDS 2011b)

All data presented here are from 2010, as the 2011 surveillance report from the European Centre for Disease Prevention and Control did not include data from Russia (ECDC / WHO Regional Office for Europe 2012).

Western Europe

Although IDUs were initially one of the groups most affected by the HIV epidemic in Western Europe, the widespread adoption of harm reduction measures (including needle and syringe exchange programmes and opiate substitution therapy) led to a fall in HIV prevalence in this group during the 1990s (Hamers *et al.* 2004; ECDC / WHO Regional Office for Europe 2010). By 2010, the proportion of newly diagnosed cases attributed to IDU in the region overall was 4% (ECDC / WHO Regional Office for Europe 2010), but with high HIV prevalence among IDUs in Spain, estimated at 39.7%(Strathdee *et al.* 2010). MSM continue to be an important risk group for new infections in Western Europe and some countries of Central Europe (Likatavicius *et al.* 2008; Bozicevic *et al.* 2010), accounting for 39% and 29% of newly diagnosed infections in 2010 in these two regions respectively (ECDC / WHO Regional Office for Europe 2010).

The proportion of new infections which are heterosexually acquired has increased over time, partly due to migration patterns from countries with generalised epidemics (Hamers *et al.* 2004). In 2010, a total of 40% of newly diagnosed infections were heterosexually acquired, of which 60% were in people originating in Western Europe (mainly in specific populations at high risk) and 40% were among people originating in countries with generalised heterosexually-driven HIV epidemics, predominantly of Eastern and Southern Africa (ECDC / WHO Regional Office for Europe 2010). As the proportion of heterosexually acquired infections has increased, so too has the proportion of new infections among women, reaching around a quarter of new cases in 2010 (ECDC / WHO Regional Office for Europe 2010).

The majority of HIV-positive women are of childbearing age (Thorne *et al.* 2003; WHO *et al.* 2011b), and surveillance of HIV infection among pregnant women provides a means of estimating the HIV prevalence in this age group on a population level (Nicoll *et al.* 2000). However, these estimates may require adjustment due to differential fertility rates by HIV status (Boisson *et al.* 1996; Nicoll *et al.* 1998). Figure 1.2 illustrates the increasing proportion of HIV-positive pregnant women in the Western Europe ECS who are of sub-Saharan African origin, and the decreasing proportion with a history of IDU. In the UK and Ireland, 79% of HIV-positive women delivering between 2000 and 2009 were from Africa (French *et al.* 2012), with an increase over time (Townsend *et al.* 2008b).

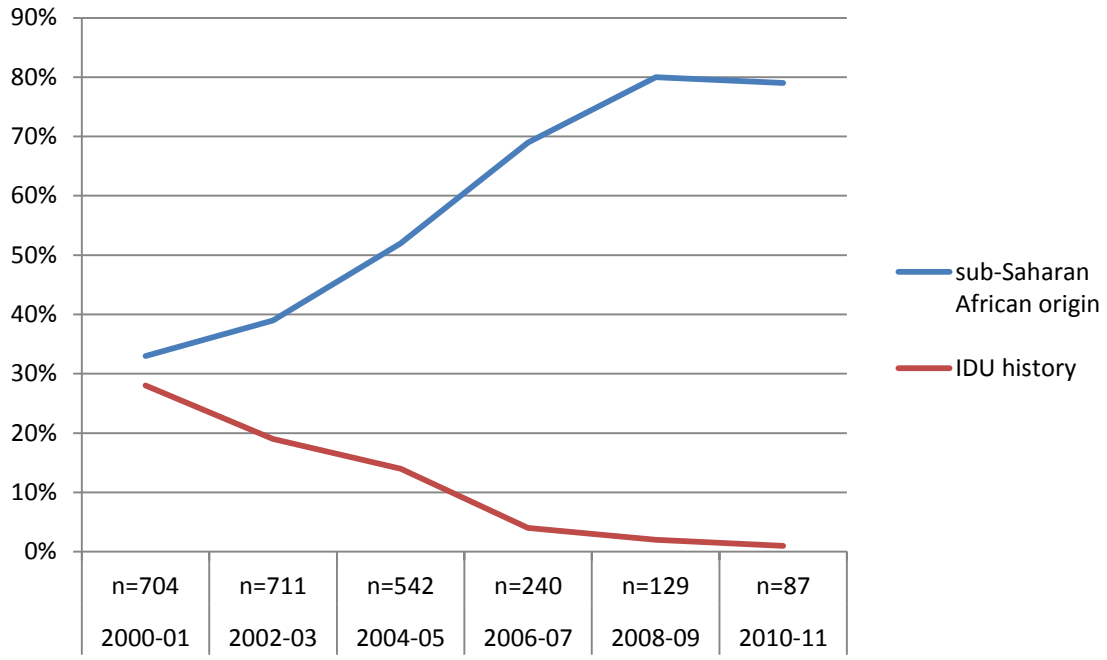


Figure 1.2: Time trends in characteristics of HIV-positive pregnant women enrolled in Western European sites of the ECS (unpublished data)

Ukraine

Ukraine is a lower-middle-income country with poor public health infrastructure (DeBell *et al.* 2005; Lekhan *et al.* 2010; The World Bank 2011). The HIV epidemic was fuelled by a huge rise in IDU following the collapse of the Soviet Union – a transition accompanied by severe economic crisis, unemployment, declining living standards, and increased local drug production as well as drug trafficking (Dehne *et al.* 1999; Atlani *et al.* 2000; Poznyak *et al.* 2002; Hurley 2010; Lekhan *et al.* 2010). Ukraine has amongst the highest prevalence of IDU in the world at 1.16% (International Harm Reduction Association 2010) and the number of IDUs is estimated at 375,000 (Wolfe *et al.* 2010). The most commonly injected drugs are homemade opiates and amphetamine-type stimulants, often used in combination (Booth *et al.* 2003; Booth *et al.* 2006; Booth *et al.* 2008; Chintalova-Dallas *et al.* 2009).

Drug dependence was criminalised and treated by abstinence under the Soviet psychiatric speciality of narcology, and harm reduction measures have been historically opposed in Ukraine (Barcal *et al.* 2005; Donoghoe *et al.* 2005; Hurley 2010). Needle and syringe exchange programmes have

expanded in recent years but coverage remains low: in 2011, 75 syringes were distributed per IDU, short of international targets of at least 200 syringes per IDU per year (WHO *et al.* 2009; Ministry of Health of Ukraine 2012). Buprenorphine became available for opioid substitution therapy in 2004 and methadone in 2008 (Schaub *et al.* 2010), but by the end of 2011 only 6632 of an estimated 250,000 people injecting opiates in Ukraine were on opioid substitution therapy (Ministry of Health of Ukraine 2012). Criminalisation of IDU remains an important barrier to uptake of harm reduction services (Spicer *et al.* 2011). Specific injecting practices which are common in Ukraine, including filling of IDUs' syringes from a dealer's syringe or common containers (Dehne *et al.* 1999; Booth *et al.* 2003), result in extremely high risk of transmission of bloodborne infections. The prevalence of HIV among IDUs is estimated at between 39% and 50% in Ukraine (Kruglov *et al.* 2008).

High-risk sexual behaviours associated with IDU have contributed to the spread of sexually transmitted infections (STIs) in Ukraine, as have other factors associated with political transition including increases in commercial sex work, income inequalities and population mobility (Rhodes *et al.* 1999; Barnett *et al.* 2000; Rhodes *et al.* 2005; Booth *et al.* 2007). In the years following the collapse of the Soviet Union there were epidemics of a number of STIs, most notably syphilis with a ten-fold increase in notification rates between 1990 and 1996 (Mavrov *et al.* 2002). Heterosexual transmission of HIV has become increasingly important over time, accounting for over half of new cases since 2008 (UNAIDS 2009; Ministry of Health of Ukraine 2010). These transmissions remain strongly linked with IDU, for example sexual partners of IDUs and other bridging populations, and have resulted in a rise in new cases among women: in 2011, women accounted for 46% of new HIV cases among people aged 25 to 49 years in Ukraine (Ministry of Health of Ukraine 2012). Ukraine has the highest adult HIV prevalence in Europe estimated at 1.6% (Kruglov *et al.* 2008); antenatal HIV prevalence was 0.47% overall in 2011 (Ministry of Health of Ukraine 2012) and >3% in some regions (Personal Communication, Natalya Nizova, Ministry of Health of Ukraine, 2012).

Public information provision about HIV and school-based sex education were completely lacking in Ukraine as late as 2005 (DeBell *et al.* 2005). Access to information about HIV prevention has now improved, with programmes targeted to specific groups including school children and high-risk groups, but quality and coverage remains low (UNAIDS 2009). Some programmes have been

described as exacerbating fear of HIV infection rather than focusing on constructive prevention messages (Spicer *et al.* 2011).

1.3 Biology, natural history and treatment of HIV

This thesis focuses on HIV-1, the predominant of the two HIV types worldwide. HIV-2 is largely confined to West Africa and is less transmissible and less pathogenic, resulting in slower disease progression than HIV-1 (Reeves *et al.* 2002). There are four groups of HIV-1 (M, N, O and P), of which the M group is by far the most common and is the cause of the worldwide AIDS pandemic (Ndung'u *et al.* 2012). The M group can be further divided into at least nine genetically distinct subtypes or clades, of which subtype A is found most commonly in Eastern Europe and subtype B in Western Europe (Thomson *et al.* 2001; Thomson *et al.* 2007).

A retrovirus, HIV targets cells of the human immune system by attaching to CD4 and chemokine receptors (CCR5 or CXCR4) on macrophages, monocytes, dendrites and T cells (LaBranche *et al.* 2001). Once it has gained entry into a cell, the single-stranded viral RNA is reverse transcribed into double-stranded DNA which is then integrated into the host genome; subsequent transcription of these viral genes produces the necessary components for new viral particles and thus viral replication (Smith *et al.* 2006). Infected cells of the human immune system are killed directly by replication of the virus and also by apoptosis. With the gradual loss of $CD4^+$ T cells (or T helper cells), the human host suffers a loss of cell-mediated immunity and increased susceptibility to opportunistic infections, eventually manifesting as AIDS. The natural history of HIV disease is characterised by a period of clinical latency between infection and the onset of AIDS of around 10 years duration (Bacchetti *et al.* 1989; Moss *et al.* 1989; Munoz *et al.* 1989). Disease stage can be assessed by measuring levels of circulating $CD4^+$ T cells (the 'CD4 count'), with progressive damage to the immune system marked by a fall in CD4 counts and a rise in HIV RNA ('viral load') (see Figure 1.3).

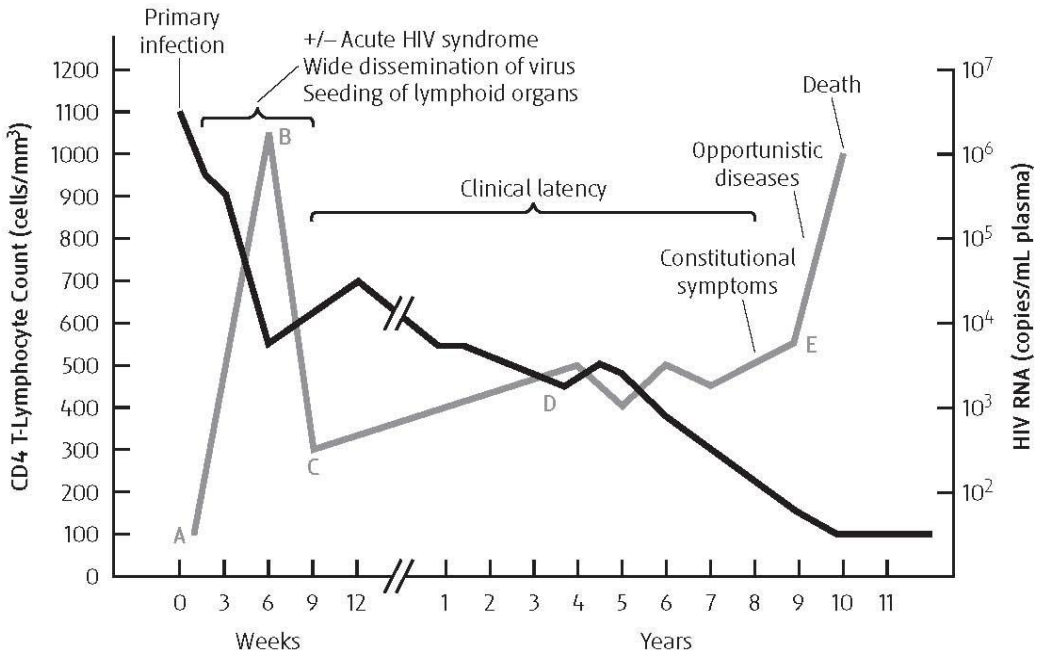


Figure 1.3: Natural history of HIV infection: CD4 count and viral load

Figure from (Martin 2009). The black line indicates CD4 T-lymphocyte count and the grey line HIV RNA load. After HIV acquisition (point A), there is a period of rapid viral replication which is curtailed by the cellular immune response (point B). The CD4 T-lymphocyte cell count recovers to a degree (point C) and a period of clinical latency ensues (point D). CD4 T-lymphocyte cell counts eventually fall to a level at which opportunistic infections manifest as symptomatic AIDS (point E), leading to death.

Antiretroviral therapy

The first antiretroviral drug that became available to treat HIV infection was zidovudine (ZDV), a nucleoside reverse transcriptase inhibitor (NRTI), found to reduce mortality over 24 weeks in patients with AIDS (Fischl *et al.* 1987). Several other NRTIs became available soon after, including didanosine, stavudine and lamivudine, but the success of treatment with these drugs was limited by the rapid development of resistance to antiretroviral drugs administered as monotherapy, and the toxicity associated with these agents (Vella *et al.* 2012).

Major breakthroughs occurred with the development of two new classes of antiretroviral agents – non-nucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs) – in the mid-1990s. Triple combination antiretroviral therapy (ART), consisting of two NRTIs plus either an NNRTI or a PI (known as highly active antiretroviral therapy (HAART) or combination ART (cART)), was shown to durably suppress viral load to very low levels and prevent disease progression (Hammer *et al.* 1997; Montaner *et al.* 1998) and was adopted as the standard of care in

resource-rich settings in 1997 (Kirk *et al.* 1998; US Centers for Disease Control and Prevention 1998). Substantial declines in AIDS-related morbidity and mortality followed (Mocroft *et al.* 1998; Palella *et al.* 1998).

Since the advent of the cART era, there has been an expansion of treatment options with fusion/entry and integrase inhibitors becoming available in 2003 and 2007 respectively (Table 1.1 summarises the five current antiretroviral drug classes). The increase in treatment options together with improved safety of agents and the introduction of fixed-dose once-daily combination preparations has improved the quality of life and clinical outcomes of HIV-positive patients (Vella *et al.* 2012). Although poorer outcomes are seen in some patient groups, low-risk patients diagnosed at an early stage of infection and with access to cART may now have a life expectancy approaching that of their HIV-negative contemporaries (Sterne *et al.* 2005; The Antiretroviral Therapy Cohort Collaboration 2008; van Sighem *et al.* 2010).

Table 1.1: The five current antiretroviral drug classes with examples

NRTIs	NNRTIs	PIs	Entry/fusion inhibitors	Integrase inhibitors
Zidovudine (ZDV)	Efavirenz (EFV)	Saquinavir (SQV)	Maraviroc (MVC)	Raltegravir (RAL)
Didanosine (ddI)	Nevirapine (NVP)	Lopinavir (LOP)	Enfuvirtide (ENF)	
Zalcitabine (ddC)	Etravirine (ETR)	Indinavir (IDV)		
Stavudine (d4T)		Nelfinavir (NFV)		
Lamivudine (3TC)		Fosamprenavir (FPV)		
Abacavir (ABC)		Atazanavir (ATZ)		
Emtricitabine (FTC)		Darunavir (DRV)		
Tenofovir (TDF)†		Ritonavir‡ (RTV)		

†Tenofovir is a nucleotide reverse transcriptase inhibitor

‡Low-dose ritonavir is used in combination with other PIs to pharmacologically 'boost' blood levels

In 2010, World Health Organisation (WHO) guidelines were updated to recommend cART initiation in asymptomatic individuals at CD4 counts of ≤350 cells/mm^3 (rather than ≤200 cells/mm^3) (WHO 2010b), reflecting evidence that clinical outcomes are better when cART is initiated at an earlier disease stage (Kitahata *et al.* 2009; Sterne *et al.* 2009). In the absence of AIDS-defining illness or other indications for treatment, UK guidelines currently recommend cART

initiation at CD4 counts of ≤350 cells/mm^3, while US guidelines recommend initiation for all HIV-positive individuals and particularly those with a CD4 count ≤500 cells/mm^3 or ≤350 cells/mm^3 (Panel on Antiretroviral Guidelines for Adults and Adolescents 2012; Williams *et al.* 2012). The effectiveness of ART in preventing onward transmissions to sexual partners has resulted in a recent focus on the use of early treatment as part of a combination prevention approach (Montaner *et al.* 2010; Cohen *et al.* 2011; WHO *et al.* 2011a; WHO 2012c).

Since 1995, the use of cART has averted an estimated 2.5 million AIDS deaths in low- and middle-income countries (WHO *et al.* 2011b). The number of people on ART recently increased substantially, by 1.4 million in the year to December 2010, to reach 6.65 million overall (WHO *et al.* 2011b). However, the estimated coverage of eligible people in low and middle-income settings with ART is still only around 47% (WHO *et al.* 2011b), leading to continued substantial AIDS-related morbidity and mortality worldwide and a focus on the need to improve the effectiveness and efficiency of the HIV/AIDS response (UNAIDS 2010; Schwartlander *et al.* 2011; WHO *et al.* 2011a; WHO 2012c). Even where services are available, optimal treatment is often hindered by the late diagnosis of infected individuals at advanced stages of disease, poor adherence to cART regimens (described in section 1.5), and marginalisation of HIV-positive and at-risk populations (Lima *et al.* 2009; Moreno *et al.* 2010; WHO *et al.* 2011b). Some of these factors contribute to the continued AIDS cases seen in Western Europe, which have declined steadily to reach 1.0 per 100,000 population in 2010 (ECDC / WHO Regional Office for Europe 2010).

Access to HIV treatment and care in Ukraine

In Ukraine, expansion of access to ART began in 2004, but scale-up has been slow and outstripped by the increasing number of HIV-positive people requiring treatment (Ministry of Health of Ukraine 2012). In 2011, 70% of individuals eligible for treatment and in HIV care were receiving cART; true coverage (i.e. including those with undiagnosed infections or not in contact with care) is estimated at 25% (Ministry of Health of Ukraine 2012). There were 20.1 AIDS cases reported per 100,000 population in 2011 (Ministry of Health of Ukraine 2012), which is probably an under-estimate due to under-reporting (ECDC / WHO Regional Office for Europe 2010).

Problems persist regarding both the level of government expenditure on HIV programmes and the efficiency with which resources are spent; ART procurement is sometimes highly inefficient, and local management of budgets has led to regional disparities in access (UNAIDS 2009). The shortfall in government funding has been partly bridged by other agencies, most notably the Global Fund to Fight AIDS, Tuberculosis and Malaria ('the Global Fund') which currently funds ART for 13% of patients on treatment in Ukraine and supports over 50 non-governmental organisations (NGOs) to deliver HIV-related services (Ministry of Health of Ukraine 2012). However, projects funded by external agencies are limited by a lack of long-term sustainability and problems with coverage, equitability of access and prioritisation of essential services (UNAIDS 2009). Illegal user fees are widespread in the healthcare system in Ukraine; although HIV-related services are usually free of charge, out-of-pocket payments are sometimes charged for diagnostic services (including client-initiated HIV tests) and for treatment of opportunistic infections (UNAIDS 2009). The highly verticalised organisation of medical services (with treatment for HIV, TB and IDU delivered at separate specialist regional or city centres) hinders a multi-sectoral response to tackle any one of these issues (Atun *et al.* 2008; Lekhan *et al.* 2010).

1.4 Mother-to-child transmission and its prevention

Fertility intentions of HIV-positive women

In the early years of the epidemic, before effective treatment and interventions for the prevention of mother-to-child transmission (PMTCT) became available, women diagnosed as HIV-positive had fewer live births due to both reduced incidence of conception and higher rates of pregnancy termination (Stephenson *et al.* 1996; De Vincenzi *et al.* 1997; van Benthem *et al.* 2000a; Blair *et al.* 2004). Since the beginning of the cART era, the incidence of live births among HIV-positive women has been increasing, and the childbearing desires of HIV-positive women have become similar to those of uninfected women (van Benthem *et al.* 2000a; Stanwood *et al.* 2007; Fiore *et al.* 2008; Huntington *et al.* 2012). Surveillance data from the UK and Ireland show that HIV-positive women are increasingly having more than one pregnancy following their HIV diagnosis (French *et al.* 2012).

Rates and modes of transmission

Rates of MTCT of HIV in the absence of intervention range from 15 to 32% in industrialised countries and 25 to 48% in resource-limited settings, where safe and acceptable alternatives to breastfeeding are not widely available (Dabis *et al.* 1993; Thorne *et al.* 2003). Plasma HIV RNA is the foremost risk factor for MTCT (Sperling *et al.* 1996; Mayaux *et al.* 1997; Mofenson *et al.* 1999). Other risk factors include cervico-vaginal viral load, vaginal delivery, preterm delivery, prolonged duration of ruptured membranes, low CD4 count and maternal co-infections (Thorne *et al.* 2003). In non-breastfeeding populations, the majority of vertical transmissions occur around delivery, when the baby is exposed to infected maternal genital secretions and blood in the birth canal (Thorne *et al.* 2003; Lehman *et al.* 2007). Other potential mechanisms of intrapartum transmission include placental microtransfusions and ascending infection following membrane rupture (Lehman *et al.* 2007). Breastfeeding has been associated with a 16% rate of transmission in the first two years of life in a randomised controlled trial (RCT), accounting for 44% of vertical infections among infants exposed to breast milk (Nduati *et al.* 2000). The risk of transmission via breastfeeding is increased when this is not the exclusive mode of feeding (Coutsoudis *et al.* 2001). MTCT can also occur in utero, possibly due to placental disruption or exposure of the foetus to HIV in the amniotic fluid (Thorne *et al.* 2005; Lehman *et al.* 2007).

Preventing HIV infection in infants

PMTCT depends on individual-level interventions for HIV-positive women and their exposed infants. On a population level however, the prevention of HIV infection in infants depends on a much broader approach which takes into account determinants of the number of HIV-exposed pregnancies – HIV prevalence among adults of childbearing age and access to family planning services – while respecting the reproductive choices of HIV-positive women and addressing stigma-related barriers to care. The WHO describes four components which make up a strategic framework for the prevention of HIV infections in infants, described in Table 1.2 (WHO 2003b).

Knowledge of HIV among women of childbearing age is essential for primary prevention of infections in this group, and therefore prevention of infant infections. Among pregnant women, knowledge of antenatal HIV screening and of the existence of effective PMTCT interventions is also crucial for the timely diagnosis of infections and opportunities for appropriate management.

Women's agency to protect themselves from HIV infection or to care for themselves and their families once infected is influenced by their experience of HIV-related stigma, itself contingent on HIV knowledge and attitudes in their community. Therefore the HIV knowledge and attitudes of women of childbearing age are of direct importance not only to their own health but to components 1, 3 and 4 of a comprehensive approach for PMTCT (Table 1.2, (WHO 2003b)).

Table 1.2: The four components of a comprehensive approach to prevent HIV infection in infants

		Some examples
1.	Primary prevention of HIV infection among women of childbearing age and their partners	Promoting use of dual contraception; counselling women testing negative in antenatal settings on strategies to remain uninfected; facilitating partner testing; prevention services tailored to high-risk groups (IDUs, sex workers).
2.	Preventing unintended pregnancies in HIV-positive women	Meeting unmet need for family planning services (including postnatally); ensuring availability of HIV counselling and testing facilities within family planning settings; supporting reproductive choices of HIV-positive women.
3.	Preventing HIV transmission from HIV-positive women to their infants	Routine offer of antenatal screening; ART for all HIV-positive pregnant women for their own health and/or PMTCT; safe delivery practices; counselling and support for infant feeding.
4.	Care and support for HIV-positive mothers, their infants and families	Continuation of ART postnatally for women with treatment indications; treatment for HIV-positive infants and care for HIV-exposed but uninfected infants; tackling of HIV-associated stigma.

(WHO 2003b)

Antenatal screening

Interventions for PMTCT depend on the timely identification of pregnant women with previously undiagnosed HIV infections. 'Opt out' provider-initiated HIV testing and counselling early in antenatal care is recommended by WHO and US guidelines (US Centers for Disease Control and Prevention 2006; WHO *et al.* 2007). In Europe, routine antenatal HIV screening for all pregnant women (i.e. regardless of perceived risk) has been widely adopted, with national policies advocating a mixture of 'opt-in' and 'opt-out' strategies (Deblonde *et al.* 2007; Mounier-Jack *et al.* 2008). An 'opt-out' approach, where an HIV test is conducted along with other antenatal tests unless specifically declined, is associated with increased coverage and detection of HIV infections among pregnant women (The UK Collaborative Group for HIV and STI Surveillance 2005) and has

become more common in Europe over time. Almost two-thirds of 21 European countries surveyed in 2012 had an 'opt-out' antenatal HIV screening policy (Aebi-Popp *et al.* 2013).

In countries with generalised epidemics, the WHO recommends that pregnant women testing negative in the first or second trimesters are re-tested between 28 and 36 weeks gestation or during labour/delivery, to identify those who may have seroconverted during pregnancy (WHO 2010c). Repeat antenatal screening is not recommended routinely in low prevalence settings such as those in Western Europe, although it remains indicated for women at on-going risk of HIV acquisition during pregnancy - for example, current IDUs and those in discordant partnerships or with sexual risk behaviours (WHO 2010c). In Ukraine, a setting with a concentrated epidemic which is increasingly affecting women (Kruglov *et al.* 2008), national guidelines recommend 'opt-out' screening at initiation of antenatal care and, if negative, repeat testing during the third trimester (Ministry of Health of Ukraine 2010).

In all settings, rapid HIV testing for women presenting in labour with an unknown status is recommended, as a maternal diagnosis even at this late stage allows for MTCT risk to be reduced with intrapartum and postpartum PMTCT interventions (WHO 2010a).

PMTCT interventions

The risk of MTCT of HIV can be lowered by reducing the infant's exposure to infective body fluids (through delivery by elective caesarean section (CS) and avoidance of breastfeeding), and by reducing the mother's level of replicating virus with ART given during pregnancy and intrapartum; in addition, ART given to the neonate after delivery provides post-exposure prophylaxis (Lehman *et al.* 2007). Breastfeeding is not considered further here, as in both Western Europe and Ukraine there are safe, acceptable and affordable alternatives to breast feeding available, and most infants born to HIV-positive women are formula fed (European Collaborative Study 2006).

The efficacy of ART for PMTCT was first shown in 1994 in the AIDS Clinical Trials Group 076 RCT, which demonstrated that a three-part ZDV regimen (administered during pregnancy for a median of 11 weeks, intrapartum and as neonatal prophylaxis) reduced MTCT by 68% (Connor *et al.* 1994). Following these results, antenatal ZDV monotherapy (ZDVm) and then antenatal cART were rapidly adopted as PMTCT interventions in Western Europe and the US (European

Collaborative Study 2001; Cooper *et al.* 2002). At the same time as scale-up of antenatal ART, delivery by elective CS became more common as a PMTCT strategy in Western Europe following observational findings that this mode of delivery reduced MTCT risk by around 50% (European Collaborative Study 1994; European Collaborative Study *et al.* 2010). By 1999, MTCT rates had fallen to <3% among non-breastfeeding women in Western Europe and the US (European Collaborative Study 2001; Cooper *et al.* 2002; Dorenbaum *et al.* 2002). An RCT and a meta-analysis were published in 1999 confirming that delivery by elective CS reduced MTCT risk, by 80% and 57% respectively, among women with no antenatal ART or only ZDVm (The European Mode of Delivery Collaboration 1999; The International Perinatal HIV Group 1999). Vertical transmission occurred in only one of 119 women who received antenatal ZDVm and were allocated to deliver by elective CS in the RCT (an MTCT rate of 0.8%) (The European Mode of Delivery Collaboration 1999).

Antenatal cART had become the standard of care for PMTCT across Western Europe by the early 2000s, and was associated with very low MTCT rates of 1% or less in observational studies (European Collaborative Study 2005; Naver *et al.* 2006; Townsend *et al.* 2008a; von Linstow *et al.* 2010; Chiappini *et al.* 2011; Jasseron *et al.* 2011). In resource-limited, high prevalence settings, the efficacy of shorter and simpler regimens for PMTCT have been the subject of investigation. An RCT in Thailand demonstrated that a shortened antenatal ZDVm regimen taken for a median of 3.6 weeks prior to delivery had an estimated efficacy in the prevention of intrapartum transmissions of 61% (Shaffer *et al.* 1999). Meanwhile, the HIVNET 012 trial in Uganda demonstrated an MTCT rate at birth of 10% and 8% respectively among infants born to women who received intrapartum ZDV or NVP (Guay *et al.* 1999). More recently in the Kesho Bora study, the transmission rate at birth among 412 women who received ZDVm and single-dose NVP (sdNVP) (all of whom had CD4 counts between 200 and 500 cells/mm^3, and 12% of whom delivered by CS) was 2.5%, not significantly higher than the 1.8% among women who received antenatal cART (de Vincenzi 2011).

An important consideration for the use of ART for PMTCT is the risk of the development of ART resistance. Although monotherapy is normally avoided outside of the context of pregnancy, zidovudine has a moderate genetic barrier to resistance (Gardner *et al.* 2009) and the short term use of ZDVm during pregnancy is not generally associated with problems; no new zidovudine-

associated resistance mutations were found among 53 women who received a median of 11 weeks of ZDVm during pregnancy in one UK study (Read *et al.* 2008). Nevirapine has a lower genetic barrier to resistance than the NRTIs and a longer half-life, which results in 'functional monotherapy' if it is given as one component of a cART regimen which is stopped abruptly (Gardner *et al.* 2009). The use of sdNVP is associated with a significant increase in the subsequent risk of virologic failure on a NVP-containing cART regimen, but this risk declines with longer intervals between sdNVP exposure and cART initiation (Lockman *et al.* 2010) and can be mitigated by the use of an NRTI 'tail', recommended for 7 days following sdNVP exposure (WHO 2010a).

In the UK, ZDVm remains an option for women with a plasma viral load <10,000 copies/ml and willing to deliver by elective CS (de Ruiter *et al.* 2012), but was received by <5% of HIV-positive pregnant women delivering in the UK in 2007-2011, with most women eligible for ZDVm instead opting for cART (Personal Communication, Pat Tookey, NSHPC, 2013). In the US, guidelines take a more conservative approach and recommend ZDVm as an option only for women with viral loads <1000 copies/ml (Panel on Treatment of HIV-infected Pregnant Women and Prevention of Perinatal Transmission 2012). For women with treatment indications and therefore the highest risk of transmission, antenatal cART continued lifelong is of crucial importance in reducing morbidity and MTCT risk (de Ruiter *et al.* 2012; Panel on Treatment of HIV-infected Pregnant Women and Prevention of Perinatal Transmission 2012).

Among women virologically suppressed on cART, who already have a very low risk of MTCT, the additional benefit of CS is uncertain (Read *et al.* 2005) and the conduct of sufficiently powered trials is challenging. This uncertainty, along with concerns around infective complications of CS among HIV-positive women (Ferrero *et al.* 2003; Fiore *et al.* 2004), has led to vaginal deliveries becoming increasingly common in Western Europe over time, but delivery practices remain heterogeneous (Read *et al.* 2005; European Collaborative Study *et al.* 2010). Most European national policies now recommend that a vaginal delivery should be an option for women with a viral load below a stated threshold at 36 weeks gestation; this threshold is <50 copies/ml for the majority of countries in Western Europe, <400 copies/ml for France and Ireland, and <1000 copies/ml for Denmark, Lithuania, Moldova, Russia and Ukraine (Aebi-Popp *et al.* 2013). Delivery by elective CS was not part of the original national PMTCT strategy in Ukraine due to concerns around complications

(Malyuta *et al.* 2006), but is currently recommended as national policy for women with a viral load >1000 copies/ml during the third trimester (Personal communication, Ruslan Malyuta, Perinatal Prevention of AIDS Initiative, 2011).

The scale-up of PMTCT interventions has been slow overall in resource-limited settings, and in 2009 only an estimated 45% of HIV-positive pregnant women worldwide were receiving any ART for PMTCT (WHO 2009b). In 2010, the WHO published recommendations to support the scale-up of effective interventions for PMTCT in low- and middle-income settings, to address continued inequities in MTCT (McIntyre *et al.* 2008; WHO 2010a). These guidelines recommend initiation of lifelong cART for all HIV-positive pregnant women with treatment indications (defined as a CD4 count ≤350 cells/mm^3 and/or WHO stage 3-4 disease), and either antenatal ZDVm plus sdNVP or antenatal cART (Options A and B respectively) for those requiring ART for PMTCT only (WHO 2010a). Use of these regimens along with infant antiretroviral prophylaxis should reduce the MTCT rate to <2% in non-breastfeeding populations, in accordance with goals for the virtual elimination of MTCT in the European region by 2015 (WHO Regional Office for Europe 2011), and in line with the very low rates of MTCT already achieved in Western Europe (Townsend *et al.* 2008a). Option B+, whereby lifelong cART is initiated in all HIV-positive pregnant women, was the subject of a recent WHO programmatic update (WHO 2012b). This strategy has potential benefits for maternal health, MTCT risk in subsequent pregnancies and the harmonisation of treatment programmes, but many questions regarding implementation are as yet unanswered, particularly concerning equitability and sustainability of access to ART, adherence and retention in care (Schouten *et al.* 2011a; WHO 2012b).

In Ukraine, the coverage of PMTCT services has been an important success of the national response to the epidemic: over eight years to 2008, 93% of HIV-infected pregnant women received ART (antenatal or intrapartum) for PMTCT (Thorne *et al.* 2009). Table 1.3 summarises the timescale of PMTCT intervention scale-up in Ukraine compared with Western Europe. From 2001 to 2007, the national Ukrainian PMTCT strategy was based on abbreviated regimens of ZDVm and sdNVP, and antenatal cART was available to only some women with treatment indications; the MTCT rate in 2006 was 7% overall (Thorne *et al.* 2009). At the end of 2007, national PMTCT policy was updated to recommend antenatal cART for all HIV-positive pregnant women (i.e. WHO

Option B) (Ministry of Health of Ukraine 2010). The scale-up of antenatal cART subsequent to the policy change and associated MTCT rates are explored in Chapter 3 of this thesis.

Lack of antenatal ART is a major reason for continued vertical transmissions in the resource-rich setting of Western Europe (Mayaux *et al.* 2003; Peters *et al.* 2003; European Collaborative Study 2005; Townsend *et al.* 2008a). Other factors include seroconversion during pregnancy or breastfeeding, use of non-suppressive antenatal ART and adverse social circumstances (for example insecure housing, poverty, poor social support) which preclude optimal antenatal care (National Study of HIV in Pregnancy and Childhood *et al.* 2007). In Ukraine, women with an IDU history continue to account for a disproportionate number of vertical transmissions due to multiple barriers to care; from 2000 to 2010, IDUs had an unadjusted MTCT rate of 11% compared with 6% for non-IDUs (Thorne *et al.* 2012).

Table 1.3: Timescale of the adoption of PMTCT interventions in Western Europe and Ukraine

<table>
<tr><td></td><td>Ukraine</td><td>Western Europe</td></tr>
<tr><td>Pre-1994</td><td colspan="2">No ART for PMTCT.</td></tr>
<tr><td></td><td>• Isolated cases of heterosexually acquired HIV reported.</td><td>• MTCT rate ~15%.</td></tr>
<tr><td>1994</td><td colspan="2">ACTG 076 trial demonstrated the efficacy of ZDV (antenatal, intrapartum and as neonatal prophylaxis) in reducing MTCT risk by 68%.
Findings from observational studies showed that delivery by CS reduced MTCT risk by around half.</td></tr>
<tr><td>1995</td><td>• HIV begins to spread explosively among IDUs in Odessa and Mykolaiv, and then nationwide</td><td>• Antenatal ZDV rapidly adopted as a PMTCT intervention.
• Elective CS accounted for an increasing proportion of deliveries between 1995 and 1999.</td></tr>
<tr><td>1997</td><td colspan="2">cART becomes the standard of care for treatment of HIV in resource-rich settings.</td></tr>
<tr><td rowspan="2">1999</td><td colspan="2">Elective CS shown to reduce MTCT risk by 50% in an RCT and a meta-analysis, among women receiving no ART or ZDVm.</td></tr>
<tr><td></td><td>• Use of antenatal cART increasing (received by 44% of women enrolled in the European Collaborative Study in 1999).
• Delivery by elective CS peaked.
• MTCT rate <3% overall.</td></tr>
<tr><td>2001</td><td>• National PMTCT programme starts, based on short course ZDVm from 36 weeks gestation and/or sdNVP.
• MTCT rate 15%.</td><td rowspan="3">• Widespread adoption of antenatal cART for use as a PMTCT intervention, and reduction in MTCT rates to <1-2%.
• Increasing proportion of HIV-positive women delivering vaginally, in reflection of uncertainties around the additional benefit of CS for MTCT risk where viral load is suppressed.
• HIV-positive women increasingly conceiving on cART.
• Shift in focus to identification of women with suboptimal PMTCT interventions, and prevention of 'residual' transmissions among women with adequate virological suppression.</td></tr>
<tr><td>2003</td><td>• PMTCT strategy updated to included longer duration of antenatal ZDVm (from 28 weeks) and neonatal ZDV, plus sdNVP if duration of maternal ART <4 weeks by delivery.</td></tr>
<tr><td>2007</td><td>• MTCT rate 7%.
• PMTCT strategy updated to include cART for all pregnant women, including those requiring PMTCT only (cART previously available to only some pregnant women with treatment indications).</td></tr>
</table>

(Connor *et al.* 1994; The European Mode of Delivery Collaboration 1999; The International Perinatal HIV Group 1999; European Collaborative Study 2001; Malyuta *et al.* 2006; Townsend *et al.* 2008a; Warszawski *et al.* 2008; Thorne *et al.* 2009; UNAIDS 2010; WHO 2010a; WHO Regional Office for Europe 2011)

Safety of ART in pregnancy and when to start

Longer duration of antenatal ART is associated with lower MTCT risk, due to both an increased probability of virological suppression by delivery and a greater duration of protection against in-utero transmissions (Cooper *et al.* 2002; European Collaborative Study 2005; Jasseron *et al.* 2008; Townsend *et al.* 2008a; Warszawski *et al.* 2008). In the UK and Ireland, the MTCT rate from 2000 to 2006 was 0.8% among women who had received at least 14 days of ART prior to delivery (vs. 1.2% overall), and each additional week was associated with a 10% decreased transmission risk (Townsend *et al.* 2008a). Mothers in the French Perinatal Cohort whose pregnancy resulted in transmission had received on average six weeks less antenatal ART than non-transmitters (Warszawski *et al.* 2008), and in the European Collaborative Study, the MTCT rate among women who began cART before pregnancy was 0.25%, vs. 1.92% among those starting cART antenatally and 11.5% among those with no ART (European Collaborative Study 2005). In the Swiss Cohort Study, 93% of women starting ART antenatally reached a viral load of <400 copies/ml around delivery, and treatment was late or suboptimal in all three pregnancies that resulted in MTCT (Keiser *et al.* 2008).

For women not on ART at conception and requiring it for PMTCT only, European guidelines on when to initiate antenatal ART are heterogeneous, with recommendations to initiate at 12-14 weeks gestation in Italy, Portugal, Greece and Poland, and at 28-32 weeks gestation in Germany and Lithuania (Aebi-Popp *et al.* 2013). Other countries fall between these two extremes; UK and Ukrainian guidelines recommend ART initiation at 14-24 weeks and 24-26 weeks respectively (de Ruiter *et al.* 2012; UNICEF 2012).

Initiation of ART during the first trimester is generally not recommended due to the theoretical heightened risk of teratogenic effects during this period. There have been particular concerns around the first-trimester use of EFV, which has been associated with teratogenicity in animal studies, accompanied by isolated case reports (De Santis *et al.* 2002; Fundaro *et al.* 2002; Panel on Treatment of HIV-infected Pregnant Women and Prevention of Perinatal Transmission 2012). However, the evidence-base for its safe use in pregnancy has been expanding over recent years, and a systematic review and meta-analysis updated in 2011 found no increased risk of birth defects among women with first-trimester exposure to EFV (Ford *et al.* 2011). The combination of ddI and

d4T is contraindicated during pregnancy due to the risk of lactic acidosis, and this is one exception to the general guidance that women conceiving on cART (including EFV) should continue with their current regimen throughout pregnancy provided that it is well-tolerated and effective (de Ruiter *et al.* 2012; Panel on Treatment of HIV-infected Pregnant Women and Prevention of Perinatal Transmission 2012). A substantial proportion of HIV-positive pregnant women in Western Europe have been on cART from before conception in recent years; national surveillance data from the UK and Ireland show that around 40% of HIV-positive women delivering in 2010 conceived on cART, up from around 20% in 2005 (National Study of HIV in Pregnancy and Childhood). In Denmark, 57% of HIV-positive women delivering in 2000-08 conceived on ART, up from 11% in 1994-1999 (von Linstow *et al.* 2010). When HIV-positive women of childbearing age need to initiate cART for their own health, consideration should be given to the possibility of a future pregnancy, and the opportunity to optimise virological control prior to conception (Huntington *et al.* 2011).

In addition to congenital abnormalities, other potential adverse effects of antenatal cART include preterm delivery and anaemia in the infant (European Collaborative Study 2003; Thorne *et al.* 2004; Thorne *et al.* 2007; Townsend *et al.* 2007). These must be balanced on an individual level with factors which will impact on the duration of ART required to achieve a fully suppressed viral load by delivery, including baseline viral load, cART regimen and treatment history, drug resistance, co-infections and ethnicity (Patel *et al.* 2007; Landes *et al.* 2008). A UK cohort study demonstrated that the probability of achieving an undetectable viral load by delivery among women with a high viral load at baseline (>10,000 or >100,000 copies/ml) was compromised where ART was initiated after 20.4 weeks gestation (Read *et al.* 2012), and although MTCT rates are very low among women who are virologically suppressed at delivery, residual transmissions have been shown to be associated with poorer virological control early in pregnancy (Tubiana *et al.* 2010).

1.5 Adherence to ART

Adherence to medication (i.e. taking prescribed doses at the prescribed intervals) is a significant challenge in chronic disease, and likely to be particularly problematic where a condition is asymptomatic and treatment is associated with significant side effects, as is often the case with HIV

infection and ART (Ammassari *et al.* 2001; WHO 2003a). When ART is taken erratically, exposure to antiretroviral agents may be insufficient to fully inhibit viral replication (Walsh *et al.* 2002). Other factors which can reduce exposure to antiretroviral agents and thus compromise its effectiveness include co-morbidities (e.g. affecting drug absorption), the physiological changes of pregnancy (e.g. the increase in plasma volume) and interactions between ART and other drugs (e.g. anti-tuberculosis agents) (Chesney *et al.* 1999; Best *et al.* 2008; Jimenez-Nacher *et al.* 2011). Virological response to treatment will also be compromised if there is transmitted resistance to the antiretroviral agents being used (Chesney *et al.* 1999).

Non-suppressive treatment is associated with HIV disease progression, mortality and development of de novo resistance to antiretroviral drugs (Ledergerber *et al.* 1999; Mocroft *et al.* 2004; Phillips *et al.* 2007), as is poor adherence to therapy (Gross *et al.* 2006; Lima *et al.* 2008b; Lima *et al.* 2009). Poor adherence is also associated with a smaller increase in CD4 count following initiation of ART, an increased risk of a discordant immunologic and virologic response to treatment and increased genital shedding of HIV RNA (Wood *et al.* 2004; Moore *et al.* 2005; Graham *et al.* 2010). During pregnancy, suboptimal ART adherence increases the risk of vertical HIV transmission, including transmission of drug resistant virus (Desai *et al.* 2003). After nine years of cART receipt an estimated 8.6% of patients will progress to extensive virologic triple class failure (Pursuing Later Treatment Options II (Plato II) project team for COHERE *et al.* 2010), highlighting the importance of optimising ART adherence and virological control as part of on-going HIV care.

Incomplete adherence to ART is extremely common, can occur from the very start of treatment and is chronic in nature (Lopez-Suarez *et al.* 1998; Haynes *et al.* 2008). Comparisons of adherence levels across studies are difficult to make due to the range of methods used to measure adherence (Paterson *et al.* 2002), but average adherence levels according to objective measures (for example dispensing records and pill counts) have been found to be around 65-75% (Bangsberg *et al.* 2000; Bangsberg *et al.* 2001; Golin *et al.* 2002; Lima *et al.* 2009). Adherence levels >95% (expressed as the percentage of prescribed doses taken) may be required for optimal virological response (Gross *et al.* 2006; Weinberg *et al.* 2009). The relationship between ART adherence and drug resistance is complex, and depends on the potency of the antiretroviral regimen, the genetic barrier to antiretroviral resistance, and the change in viral fitness caused by mutations conferring drug

resistance (Bangsberg *et al.* 2004; Gardner *et al.* 2009). Adherence to non-boosted PI-based regimens must exceed 95% to minimise the risk of resistance (Paterson *et al.* 2000), while NNRTI and boosted PI regimens are more potent and resistance is most likely to develop at adherence levels of 0-48% and 75-95% respectively (Bangsberg *et al.* 2006; Maggiolo *et al.* 2007; Gardner *et al.* 2009).

ART adherence during pregnancy and postnatally

There is some evidence that ART adherence among pregnant women may be more complete than among non-pregnant or postpartum women (Ickovics *et al.* 2002; Vaz *et al.* 2007; Bardeguez *et al.* 2008; Cohn *et al.* 2008; Mellins *et al.* 2008). Possible reasons for this include more regular contact with healthcare providers during pregnancy, enhanced support, lower chance of treatment fatigue (especially if ART is initiated for the first time during pregnancy for PMTCT), and higher levels of motivation inspired by concern for the health of the infant – cited as the greatest motivator for antenatal adherence by women in a Nigerian study (Ekama *et al.* 2012). One US study of 87 women followed during pregnancy and postnatally found that 57% reported no missed ART doses over a three-month period during pregnancy falling to 45% postnatally (p=0.03) (Cohn *et al.* 2008), while another in the US and Puerto Rico found that 61% of 309 women surveyed during the third trimester had missed no doses in the last month, compared with 44% of 220 women surveyed postpartum (p<0.01) (Mellins *et al.* 2008). A study in Brazil which used pill counts to measure adherence (i.e. by counting the number of pills remaining from a prescribed quantity) found that 43% of 72 pregnant women had taken ≥95% of their ART on two occasions, significantly more than the 18% of 79 non-pregnant women assessed (p<0.01) and the 21% of 34 women followed postnatally (p<0.01) (Vaz *et al.* 2007).

A recent meta-analysis of 51 studies estimated that 72% of HIV-positive women had adequate (>80%) adherence to ART during pregnancy (Nachega *et al.* 2012). Only two of these studies were from Western Europe, both of which were conducted in the UK and reported adherence as assessed by a clinician to be good or excellent in 75% and 84% of cases (assessment criteria not given) (Kingston *et al.* 2007; Caswell *et al.* 2011). In Eastern Europe, no published data are available on ART adherence in the perinatal period and very little data are available on ART adherence in the general population. One study from Estonia – a middle-income country with an IDU-driven HIV

epidemic similar to that in Ukraine – found that 88% of 144 participants (almost half of whom were female) reported perfect adherence to ART over the last three days (Uuskula *et al.* 2012), but there are no data specific to Ukraine. The generalizability of adherence data from the USA and Africa to Eastern Europe may be limited by differences in characteristics of HIV-positive women in these regions (for example, the proportion with an IDU history), and in the quality, organisation and financing of healthcare systems.

Barriers to adherence and interventions

Concerns around the public health implications of poor adherence to ART, given the transmissibility of resistant strains, may fuel inequalities in access to treatment for particular patient groups (Altice *et al.* 1998; Wainberg *et al.* 1998; Wolfe 2007). Barriers to ART adherence can be described as fitting into five areas: characteristics of the patient (e.g. IDU), drug regimen (e.g. complexity, side effects), patient-provider relationship (e.g. quality of communication), clinical setting (e.g. scheduling of appointments, childcare and confidentiality), and disease stage (Ickovics *et al.* 1997). Although much attention has been paid to indicators of social deprivation in relation to poor ART adherence, there is not a consistent association between the two (Chesney *et al.* 1999; Bangsberg *et al.* 2000). Among antenatal populations, the association between illicit drug use and adherence is also inconsistent (Laine *et al.* 2000; Turner *et al.* 2000; Cohn *et al.* 2008), and probably depends on the availability and uptake of supportive services for pregnant drug users (including opioid substitution therapy, shown to improve compliance with antenatal care among opiate users (Minozzi *et al.* 2008)). IDUs in Ukraine face specific barriers to adherence in the form of harassment and discrimination by the police, and the confiscation of ART (Mimiaga *et al.* 2010). Regimen complexity and pill burden have also been associated with ART adherence problems although not consistently (Chesney 2000; Turner *et al.* 2000; Fogarty *et al.* 2002; Glass *et al.* 2006; Molina *et al.* 2007). There is some evidence that patients are more likely to adhere if they have a positive relationship with their healthcare provider and feel able to trust them (Mostashari *et al.* 1998; Johnston Roberts *et al.* 1999; Golin *et al.* 2002) or, in pregnancy, if they receive HIV focused or specialist care (Laine *et al.* 2000).

Specific barriers to ART adherence exist for childbearing women, who may have little time to make a decision about disclosure to a partner before initiating ART for PMTCT, and may fear that

disclosure could result in violence or rejection (Mucheto *et al.*). Lack of disclosure during pregnancy is associated with poorer antenatal adherence and other missed opportunities for PMTCT (Jasseron *et al.* 2011; Ekama *et al.* 2012). Women are at greater risk of adverse reactions to ART than men (Ofotokun *et al.* 2003), and these may be exacerbated by the physical symptoms of pregnancy (Cohn *et al.* 2008). HIV-positive women also undertake substantial practical and emotional work during pregnancy and postnatally, including weighing up risks and benefits of interventions, redefining maternal identity and preparing strategies to avoid unintentional disclosure to family and friends when taking ART or avoiding breastfeeding (Giles *et al.* 2009). Qualitative findings have shown that women beginning ART during pregnancy for PMTCT focus more on the risk of the medication to their infant, whereas women receiving ART for their own health may focus more on its benefits (Giles *et al.* 2009). Poor adherence to neonatal prophylaxis has been associated with multiparity, low maternal social support and poor antenatal ART adherence (Turner *et al.* 2000; Demas *et al.* 2002; Mayaux *et al.* 2003; Kingston *et al.* 2007). In addition to general childcare responsibilities, the considerable anxiety around establishing the HIV status of the newborn may also contribute to poor maternal ART adherence postnatally (Vaz *et al.* 2007; Giles *et al.* 2009).

Another factor that may impact on adherence is depression, itself associated with HIV diagnosis, female gender and low socioeconomic status (Psaros *et al.* 2009). The risk of depressive symptoms is heightened during pregnancy and the postnatal period (Bennett *et al.* 2004; Oates *et al.* 2004), and may be compounded by a new HIV diagnosis; a US study found a prevalence of postnatal depression among HIV-positive women of over 30% (Kapetanovic *et al.* 2009). Swiss, Spanish, Italian and US studies among predominantly male participants have found poorer or worsening ART adherence among those with depressive symptoms (Gordillo *et al.* 1999; Safren *et al.* 2001; Ammassari *et al.* 2004; Glass *et al.* 2009; Kacanek *et al.* 2010), as has a study in Botswana which included mainly women (Do *et al.* 2010). A study among pregnant and postpartum women in the US found that those who felt happy all or most of the time were significantly more likely to report perfect ART adherence (Bardeguez *et al.* 2008). In resource-limited settings, links between mental health services and HIV care provision may be particularly lacking (Collins *et al.* 2006). One study of HIV-positive people in Russia found that 39% had probable depression and an additional 28% had possible depression (Amirkhanian *et al.* 2011).

A wide range of complex interventions have been used to improve ART adherence, employing a variety of approaches (e.g. motivational interviewing, therapy focusing on managing HIV-related stigma, educational sessions on the importance of adherence) and have generally been found to be efficacious in trial settings (Simoni *et al.* 2006b). In a modelling study, directly observed administration of antenatal cART in the third trimester (among women initiating cART by 28 weeks gestation) was associated with a relative MTCT risk of 0.39 compared with self-administered cART, and was cost-saving where average viral load at baseline was >1000 copies/ml (McCabe *et al.* 2010). However, interventions are often highly context-dependent, and the impact of an intervention is strongly influenced by the normal standard of clinical care (de Bruin *et al.* 2010). In addition, it is common for interventions to involve multiple components and be tailored to individual patients, which decreases their fidelity and complicates comparisons and the generalizability of findings (Leeman *et al.* 2010).

1.6 HIV co-infections and comorbidities

Sexually transmitted infections

STIs other than HIV are an important public health issue in Eastern Europe, where rates of bacterial STIs remain much more prevalent than in Western Europe (Landes *et al.* 2007; Uuskula *et al.* 2010; WHO Regional Office for Europe 2010). Availability and use of modern methods of contraception have been historically low in the former Soviet Union, and pregnancy terminations remain a common method of birth control (Mogilevkina *et al.* 2001; Ukrainian Center for Social Reforms *et al.* 2008; Gabhainn *et al.* 2009; Perlman *et al.* 2009; Lekhan *et al.* 2010). Although HIV-positive individuals are entitled to free supplies of condoms, provision is patchy and lack of affordability remains an important barrier to their use (Saxton *et al.* 2010). HIV-positive individuals are particularly likely to be exposed to other STIs due to shared risk behaviours, and co-infection with other STIs increases the risk of HIV acquisition and transmission due to mucosal damage (e.g. genital ulcer disease) and modulatory effects on the immune system (Ward *et al.* 2010). For example, herpes simplex virus (HSV)-2 seropositivity has been associated with a two- to four-fold increased risk of HIV acquisition, and mucosal shedding of HIV RNA is increased among HIV/HSV-2 co-infected people during subclinical HSV-2 reactivations (Corey *et al.* 2004). These biological

synergies have led to the investigation in several trials of treatment for STIs as a strategy to decrease HIV incidence, although with limited success (Hayes *et al.* 2010).

Co-infection with other STIs can have particularly negative effects on the health of HIV-positive individuals. For example, HSV-2 co-infection is associated with increased plasma HIV viral load and more rapid HIV disease progression (Duffus *et al.* 2005; Roxby *et al.* 2011), and complications of bacterial STIs (e.g. pelvic inflammatory disease) may be more severe in HIV-positive individuals (Moodley *et al.* 2002). For HIV-positive women, co-infection with another STI has implications not only for their own health and for onward transmission of both infections to a sexual partner, but also for MTCT of HIV. Genital ulcer disease has been associated with a five-fold increased risk of MTCT of HIV among HIV-positive women in Kenya with very high prevalence of HSV-2 co-infection, on adjusting for HIV RNA levels (Drake *et al.* 2007). A Thai study found over a two-fold increased risk of MTCT of HIV among women seropositive for HSV-2, independent of both cervicovaginal and plasma HIV RNA (Bollen *et al.* 2008), and a study in Zimbabwe from 1997 to 2000 of women who had not received ART during pregnancy concluded that 28% of intrapartum transmissions were potentially attributable to prevalent HSV-2 co-infection (Cowan *et al.* 2008). Maternal syphilis infection has also been associated with an increased risk of MTCT of HIV, with a two-fold and four-fold increased risk found in studies conducted in Malawi and Ukraine respectively (Mwapasa *et al.* 2006; Thorne *et al.* 2008).

Hepatitis C virus and liver fibrosis

An estimated 160 million people are chronically infected with hepatitis C virus (HCV) worldwide (a prevalence of 2.4%) (Lavanchy 2011). Among HIV-positive people, the prevalence of HCV is around ten-fold higher than the worldwide population at 20-30%, reflecting shared modes of HIV and HCV acquisition (Hernandez *et al.* 2011): HCV is predominantly transmitted via IDU or, in resource-limited settings, exposure to unsterilised medical instruments or unscreened blood transfusions (Alter 2007). Among IDUs, the prevalence of HCV antibodies (indicating acute, chronic or resolved HCV infection) varies geographically but is between 60-80% in many countries worldwide, including Ukraine and Russia (Nelson *et al.* 2011). Transmission of HCV also occurs sexually, particularly among HIV-positive MSM who are at a four to five-fold increased risk of sexual HCV acquisition than HIV-negative MSM (Tohme *et al.* 2010). The risk of heterosexual

HCV transmission in low-risk discordant monogamous partnerships is as low as 1 in 10 million sex acts, but heterosexual transmission also seems to be substantially increased in the presence of HIV co-infection (Tohme *et al.* 2010). HCV can also be transmitted from mother to child; transmission rates are around 5%, but higher among women with HIV (Ohto *et al.* 1994; Gibb *et al.* 2000; Polis *et al.* 2007).

Data on HCV prevalence in the general population in Ukraine are scarce. A report by two Ukrainian NGOs estimated that around one million people in Ukraine may be infected with HCV (i.e. 2% of the population), while seroprevalence among healthcare workers and people living with HIV is estimated at 3% and 53% respectively (Open Society Institute 2010). Ukrainian guidelines specify that donor blood should be screened for HCV RNA, but some facilities currently only screen for HCV antibodies (Personal communication, Michael Krone, Movement for Health, 2012), introducing the possibility that infectious blood may enter the supply if a donor is in the 'window period' of 8-12 weeks between infection and seroconversion (Rehermann 2009). NGOs in Ukraine have reported low levels of knowledge about HCV among clinicians, and widespread non-compliance with measures to prevent iatrogenic transmissions ((Open Society Institute 2010), Personal Communication, Michael Krone, Movement for Health, 2012).

Around 70% of people infected with HCV will develop chronic infection, with an increased risk of chronicity among HIV-positive people (Hernandez *et al.* 2011). Chronic HCV infection can cause liver fibrosis and eventually cirrhosis and hepatocellular carcinoma (de Torres *et al.* 2003); worldwide, around a quarter of cases of liver fibrosis and hepatocellular carcinoma are attributable to HCV infection (Alter 2007). In HIV-negative people chronically infected with HCV, the median time to development of liver cirrhosis in the absence of HCV treatment is around 30 years, but both HIV infection and immunosuppression are associated with more rapid disease progression (Massard *et al.* 2006). HIV infection is also itself associated with liver disease, and liver disease is a leading cause of morbidity and mortality among HIV-positive people (de Torres *et al.* 2003; Weber *et al.* 2006).

Quantification of liver fibrosis on a population level is important in order to assess the burden of liver disease caused by viral hepatitis and other factors, including alcohol use, IDU and HIV

infection. Liver biopsy is the gold standard used to quantify the degree of liver fibrosis but has recognised limitations, including that results are limited by sample variability and that taking a biopsy is an invasive procedure associated with complications (de Torres *et al.* 2003). In recent years, there has therefore been increasing interest in the development of non-invasive measures of liver fibrosis which could be used more frequently than liver biopsy and rule out the need for biopsy in some patients (Carey *et al.* 2010). Hepatic fibrosis can be measured non-invasively via hepatic elastography, direct serologic markers such as procollagen type III amino-terminal peptide, or by algorithms such as FibroIndex and Fibrometer which allow for a score indicating degree of fibrosis to be calculated from the levels of a number of biomarkers (e.g. prothrombin, gamma glutamyl, aspartate aminotransferase (AST) and alanine aminotransferase (ALT)) (Carey *et al.* 2010). Hepatic elastography and direct serologic markers of fibrosis are not routinely available in Ukraine, and so the degree of liver fibrosis among HIV/HCV co-infected women is assessed in this thesis using two algorithms: the FIB-4 index, and the aspartate transaminase (AST) to platelet ratio or 'APRI'. The FIB-4 index was developed for and validated in HIV/HCV co-infected patients (Sterling *et al.* 2006), important as HIV mono-infected individuals have elevated liver enzymes (and FIB-4 index scores) even in the absence of HCV co-infection (Blackard *et al.* 2011). The APRI score, derived and validated in individuals with chronic HCV mono-infection, may have less specificity in an HIV-positive population (Wai *et al.* 2003). These algorithms are described in more detail in Chapter 5.

HPV infection and cervical abnormalities

HIV-positive women are at increased risk of acquisition and/or persistence or reactivation of cervical infection with Human Papillomavirus (HPV) (Sun *et al.* 1997; Minkoff *et al.* 1998; Phelan *et al.* 2009), due to shared risk factors for acquisition (e.g. multiple sexual partners) and immunosuppression (Kojic *et al.* 2007; Franceschi *et al.* 2010). Cervical infection with HPV affects around 29% of women in Eastern Europe at any one time, compared with 6% in Western Europe, and age-standardised mortality rates for cervical cancer are two-fold higher (7.1 per 100,000 in Eastern vs. 3.4 per 100,000 in Western Europe (Castellsague *et al.* 2007)). Cervical abnormalities in HIV-positive women are more likely to be severe, aggressive and resistant to treatment than among HIV-negative women (Petry *et al.* 1994; Maiman 1998), and HIV-positive women are at a 5 to 8-

fold increased risk of invasive cervical cancer compared with the general population (Frisch *et al.* 2000; Clifford *et al.* 2005). Invasive cervical cancer has been included in the US Centers for Disease Control and Prevention (CDC) list of AIDS-defining illnesses since 1993, but although ART is associated with a reduced risk of many AIDS-defining cancers (e.g. Kaposi's sarcoma), its role in the prevention of HPV-related cervical lesions or promotion of their regression is unclear (Uberti-Foppa *et al.* 2003; Ahdieh-Grant *et al.* 2004; Del *et al.* 2004; Heard 2009; Minkoff *et al.* 2010).

Regular cytologic screening can reduce the incidence of invasive cervical cancer by up to 80% on a population level (Gustafsson *et al.* 1997; Peto *et al.* 2004), and is also effective for the identification of cervical cell abnormalities among HIV positive women (Kitchener *et al.* 2007). Two or three-yearly cytologic screening intervals are recommended in British and US guidelines for HIV negative women of childbearing age (Sawaya 2009; NHS Cancer Screening Programmes 2010), with more frequent (at least annual) tests for HIV positive women, given their increased risk of morbidity (Fakoya *et al.* 2008; US Centers for Disease Control and Prevention 2009). In the US Women's Interagency HIV Study, HIV positive women receiving six-monthly cytologic screening with follow-up colposcopy and treatment where necessary had an incidence of invasive cervical cancer no higher than HIV negative women (Massad *et al.* 2004). Cytologic cervical screening is not recommended during pregnancy in UK guidelines (NHS Cancer Screening Programmes 2010), because invasive cervical cancer is uncommon among pregnant women in the UK, and treatment of all other cervical abnormalities is not considered acceptable during pregnancy due to the risk of complications (Wright *et al.* 2007; NHS Cancer Screening Programmes 2010). However, the much higher incidence of invasive cervical cancer among HIV-positive women may justify antenatal screening in this group, particularly if a woman is newly diagnosed as HIV-positive and has no previous cervical screening test. Perinatal care is also an opportunity to engage with women who are unlikely to attend for screening at another time (NHS Cancer Screening Programmes 2010), although samples taken during pregnancy or less than 12 weeks after delivery (when healing of the cervix is not complete) or if infection or discharge are present are harder to interpret (Flannelly 2010).

Ukrainian policy specifies that all women of childbearing age should receive six-monthly cervical screening (Ministry of Health of Ukraine 2002) but there are no guidelines specific to HIV positive

women. Screening is available free of charge at public health clinics (including family planning clinics, women's health clinics, and some HIV/AIDS centres), and is predominantly opportunistic. There are no national figures on coverage (WHO ICO Information Centre on HPV Cervical Cancer 2010). World Health Survey data suggest that coverage with at least three-yearly screening in Ukraine, at 66%, is similar to many other European countries (Gakidou *et al.* 2008), but it is unclear whether this is the case among HIV positive women, who are more likely to be socially excluded (Kruglov *et al.* 2008).

1.7 Key points

- The majority of HIV-positive women in Europe live in the Eastern region and particularly in Ukraine and Russia, where the HIV epidemic is driven by IDU and is amongst the most rapidly accelerating worldwide. Ukraine has the most severe HIV epidemic in Europe.
- In Western Europe, migration patterns have had a large impact on the epidemiology of the HIV epidemic over the last ten years and this is especially the case among women, with the majority of pregnant HIV-positive women enrolling in Western European cohorts being from sub-Saharan Africa.
- Very effective interventions for PMTCT (most notably antenatal cART) have been in widespread use for over a decade in the West, and have resulted in MTCT rates of <1-2%.
- Meanwhile, in the resource-limited setting of Ukraine the MTCT rate has been slower to decline and was 7% in 2007. Access to antenatal cART was poor prior to 2007 but has been scaled up over the last few years with the adoption of a WHO 'Option B' policy.
- Unanswered questions regarding the health, treatment and care of HIV-positive childbearing women in Western Europe include a focus on identifying the causes of vertical transmissions which continue to occur, and optimising the health of women who are increasingly accumulating treatment experience in repeat pregnancies.
- In Ukraine, the focus is on meeting WHO goals for the virtual elimination of MTCT (a rate of <2%) by 2015, thus reducing inequalities with the West. As the epidemic continues to accelerate and the number of new infections outpaces the number of people newly started on cART, primary prevention is also a key priority for the epidemic response.
- ART adherence is crucial to the success of cART for PMTCT and to improving maternal health outcomes. Barriers to adherence which may be particularly relevant for childbearing women include poor social support and perinatal depression.
- HIV-positive women in Ukraine are particularly vulnerable to a number of co-infections and co-morbidities due to the IDU-driven nature of the HIV epidemic, the high prevalence of other STIs in this region and the lack of public health infrastructure.

Chapter 2 Aims and Methods

2.1 Rationale for this work

In an era with the necessary tools to virtually eliminate MTCT and with pressing goals for this to be achieved in Europe (WHO Regional Office for Europe 2011) and worldwide (UNAIDS 2011a), the exploration of circumstances around the suboptimal use of PMTCT interventions is a priority. This thesis focuses on a number of groups at heightened risk of MTCT and/or of poor maternal health outcomes. In chapter 3, missed opportunities for PMTCT are explored both in Ukraine, a setting where cART access is currently being scaled up, and in Western Europe, where overall transmission rates are very low (European Collaborative Study 2006; Townsend *et al.* 2008a) though some transmissions still occur (National Study of HIV in Pregnancy and Childhood *et al.* 2007; Warszawski *et al.* 2008).

With the widespread availability of ART in Western Europe and increasing number of repeat pregnancies among HIV-positive women (French *et al.* 2012), the effective management of treatment experienced women is an issue of growing importance. In the UK, an increasing proportion of HIV-positive women are conceiving with a prior history of treatment (mostly short-course ART for PMTCT) or while currently taking cART (National Study of HIV in Pregnancy and Childhood ; French *et al.* 2013). Treatment failure is associated with a heightened risk of emergence of drug resistance and HIV disease progression (Ledergerber *et al.* 1999; Mocroft *et al.* 2004; Phillips *et al.* 2007) and also has implications for MTCT, including transmission of resistant virus. In chapter 4, factors associated with treatment failure during pregnancy are explored among women conceiving on cART in Western Europe.

The expansion of the ECS to Ukraine in 2000 has made it possible to describe this country's rapidly growing epidemic among pregnant women. Little is known about the epidemiology of HIV co-infections and associated comorbidities among women in Ukraine, despite evidence that other STIs and viral hepatitis affect a significant proportion (Landes *et al.* 2007; Landes *et al.* 2008). In chapter 5, data from the Ukraine Cohort of HIV-infected Childbearing Women are used to estimate testing coverage and prevalence of co-infections, and to characterize women co-infected with chlamydia and with hepatitis C virus (including, for the latter group, extent of liver fibrosis). As cervical cancer

is an important cause of morbidity among HIV-positive women (Frisch *et al.* 2000; Clifford *et al.* 2005) but organised screening programmes are lacking in Ukraine, cervical screening coverage and factors associated with cervical abnormalities are also investigated with the aim of informing prevention programmes.

The success of expanding access to cART in Ukraine for PMTCT and maternal health outcomes depends on adherence to treatment. Lower levels of antenatal adherence have been associated with illicit drug use and alcohol and tobacco use (Kingston *et al.* 2007; Cohn *et al.* 2008; Mellins *et al.* 2008), but there are no data specific to Ukraine, where women have high levels of exposure to substance abuse and often poor access to psychosocial support. Information on levels and predictors of adherence to ART during pregnancy and postnatally are needed to strengthen treatment programmes and inform guidelines. In chapter 6, self-reported adherence behaviours of a sample of HIV-positive women during pregnancy and postpartum are described. The feasibility and utility of a short self-report adherence measure is investigated in this setting, and factors associated with poorer self-reported adherence are explored.

2.2 Aims and Objectives

Aim

To investigate the health of HIV-infected childbearing women living in resource-rich and resource-constrained settings in Europe, and to examine their treatment and care in the context of contemporary policies.

Objectives

In Western Europe and Ukraine

1. To quantify and investigate circumstances around missed opportunities for PMTCT, specifically focusing on the use of antiretroviral prophylaxis and treatment in pregnancy.

In Western Europe

2. To explore trends in the proportion of HIV-positive pregnant women who are on cART from conception and, among these women, to explore the prevalence of and risk factors for virological failure during pregnancy.

In Ukraine

3. To explore testing coverage and prevalence of HIV co-infections and associated comorbidities in a postnatal HIV-positive cohort, with a particular focus on chlamydia, hepatitis C virus, and cervical abnormalities.
4. To assess levels and predictors of adherence to maternal ART during pregnancy and in the year following delivery, and to neonatal prophylaxis.

Hypotheses and research questions for the thesis

This thesis explores circumstances around the vertical HIV transmissions which continue to occur in Western Europe and Ukraine, with the hypothesis that some maternal characteristics are associated with an increased risk of missed opportunities for PMTCT (particularly an HIV diagnosis late in pregnancy and/or lack of antenatal ART). In Ukraine, poor ART coverage of eligible individuals in the general population suggests potential challenges to the scale-up of cART for pregnant women, and this hypothesis is explored through an investigation of coverage achieved with antenatal cART since adoption of an Option B policy. Overlaps exist between groups of women at increased risk of MTCT and those at increased risk of poor maternal health; women with virological failure on treatment are an important example. This thesis explores the hypothesis that in Western Europe, where a large proportion of HIV-positive pregnant women are now conceiving on cART, some groups are at increased risk of conceiving on a non-suppressive regimen (indicating poor ART adherence or antiretroviral drug resistance), with implications for pre-conceptual and antenatal management.

In Ukraine, the high prevalence of HIV co-infections, poor public health provision and verticalised organisation of healthcare services (Atun *et al.* 2008; Lekhan *et al.* 2010) provide a basis for hypotheses that childbearing HIV-positive women have high levels of unmet need for services to diagnose, treat and prevent HIV co-infections and associated morbidity, and that some groups such as IDUs may be at particularly high risk. These hypotheses are explored using the examples of bacterial and viral co-infections (chlamydia and HCV) and cervical screening coverage and results. Modes of HCV acquisition among non-IDUs are explored in hypothesis-generating analyses.

Finally, this thesis explores hypotheses that ART adherence can be effectively measured in a childbearing population in Ukraine using a self-report measure, that some women in Ukraine experience challenges adhering to ART during pregnancy and in the first year postpartum, and that factors associated with poor ART adherence in this population may include depressive symptoms, low self-efficacy and anxiety around the use of ART, as well as socio-demographic characteristics.

The main research questions addressed by the individual studies are listed by chapter, as follows.

Chapter 3 Missed opportunities for the prevention of mother-to-child transmission

- Section 3.2: In Ukraine, what maternal characteristics are associated with late antenatal HIV diagnosis and lack of antenatal ART, and how many vertical transmissions occur among women with these missed opportunities for PMTCT? What coverage has been achieved with antenatal cART (WHO Option B) since this became policy in 2007, and what impact has this policy change had on the overall MTCT rate? What are the main barriers which remain to the virtual elimination of MTCT in Ukraine?
- Section 3.3: In Western Europe, to what extent does insufficient ART (a short duration or a complete lack of ART in pregnancy) contribute to the continuing transmissions seen in this region? What are the maternal and pregnancy characteristics associated with receiving no antenatal ART, or <14 days by delivery?

Chapter 4 Virological failure in pregnancy among women conceiving on cART

- In the Western Europe ECS, what proportion of women conceiving on cART over the last decade have had a non-suppressed viral load during pregnancy?
- What maternal and treatment factors are associated with virological failure in this population?

Chapter 5 HIV co-infections and associated morbidity in Ukraine

- What is the prevalence of genital infections in a postnatal cohort of HIV-positive women in Ukraine? With a focus on chlamydia, what is the coverage of testing within HIV care, and what are the maternal characteristics associated with a recent chlamydia diagnosis?
- What is the prevalence of HCV co-infection in this population? What are the risk factors for HCV co-infection? Among HIV/HCV co-infected women, what is the prevalence of advanced or significant liver fibrosis?
- What is the coverage of cervical screening as part of HIV care in this population? What maternal factors are associated with having a screening test? How common are cervical abnormalities, and what factors are associated with this?

Chapter 6 Adherence to ART during pregnancy and postnatally in Ukraine

- How does the CASE adherence index (a self-report ART adherence measure) perform in identifying poor adherence among childbearing women in Ukraine? Is CASE score associated with viral load? If so, which score cut-off is most useful for identifying women with a poorer virological response?
- Overall, how well do women in Ukraine adhere to ART during pregnancy and the first year postpartum? What maternal factors are associated with poor adherence to ART at these two time points (to include exploration of perinatal depression, self-efficacy and anxiety around the use of ART)? What were the most common reasons for having missed a dose of ART?

2.3 Data sources

This thesis uses data from three sources, summarised in Table 2.1. Each source is described in detail in the following sections.

Table 2.1: Data sources

	Study period	Description
European Collaborative Study (ECS)	Enrolments on-going since 1986	Observational birth cohort study of HIV-positive women and their infants enrolled at clinic sites in ten European countries (including Ukraine) (linked anonymised data).
Ukrainian Postnatal Cohort of HIV-infected Childbearing Women ("the Women's Study")	Enrolments from December 2007 to May 2012, with follow-up on-going	Observational clinic-based cohort study of postpartum HIV-positive women nested within the European Collaborative Study in Ukraine (linked anonymised data).
Adherence Study	From June 2011 to April 2012	Self-completed anonymised survey on ART adherence, nested within the European Collaborative Study in Ukraine (linked anonymised data).

The European Collaborative Study

The ECS is an observational birth cohort study of HIV-positive pregnant women and their infants, established in 1986 in Western Europe to elucidate risk factors for MTCT and the natural history of vertically-acquired HIV infection (European Collaborative Study 1988). In 2000, the ECS expanded to sites in Ukraine, allowing documentation of the emerging epidemic in Eastern Europe (European Collaborative Study 2006). The ECS includes data from 25 clinical sites in ten countries: Spain, Italy, the UK, Germany, Belgium, Sweden, the Netherlands, Denmark, Poland and Ukraine. Enrolments in Poland are grouped with those in Western Europe for the purposes of all analyses in this thesis.

As of February 2012, there were around 9500 mother-child pairs enrolled in the Western Europe ECS and around 9600 mother-child pairs enrolled in the Ukraine ECS. There have been declining enrolments in the Western ECS over recent years due to some countries setting up their own national cohorts, some sites ceasing enrolments and some seeing fewer deliveries to HIV-positive women.

Data collected

Women are enrolled and their infants prospectively followed according to a standard protocol. Any woman diagnosed with HIV before or during pregnancy, including intrapartum, is eligible for enrolment following her informed consent. Data are collected on maternal characteristics including socio-demographic factors, obstetric history, history of drug use and other HIV acquisition risk factors where known, date of first positive HIV test, clinical variables including antenatal CD4 count and viral load, and antenatal ART receipt. Information is collected on mode of delivery and on birth outcomes including gestational age at delivery, birthweight and perinatal problems. Infants are prospectively followed and details collected of any clinical signs and symptoms of disease and results of laboratory tests, including HIV RNA, HIV DNA, HIV ELISA and CD4 count tests/measures. Uninfected infants are followed up to 18-24 months of age, with continued follow-up of HIV-positive children. Maternal and perinatal data collection forms are reproduced in Appendix B, page 316.

All data collected are anonymised, with each woman assigned a unique study identifier which allows maternal data to be linked to infant follow-up data. In all sites except those in Ukraine, this unique number also allows for the identification of repeat pregnancies reported in the same woman. A survey carried out in 2005 found that the rate of non-participation in the ECS among eligible women at 11 Western Europe centres was <5% (Patel 2007). However, because of differences between Western European countries in HIV epidemiology and clinical practice (including policies for antenatal screening (Deblonde *et al.* 2007), Europe-wide findings may not be generalizable to specific countries. The Ukraine ECS began enrolment in Odessa, Mykolaiv and Simferopol in 2000, expanding to Kiev, Donetsk and Mariupol in 2006 and Krivoy Rog in 2008. In 2009, 33% of HIV-positive pregnant women nationwide were enrolled in the Ukraine ECS (1291 of 3857), making findings broadly generalizable despite some regional differences.

Data management

The main co-ordinating centre of the ECS is in London at the UCL Institute of Child Health. There is also an Eastern Europe co-ordinating centre at the Perinatal Prevention of AIDS Initiative (PPAI), a non-governmental organisation in Odessa, Ukraine. Data are entered into MS Access 2003 databases at each site or onto paper forms, and internal quality checks are conducted by key ECS collaborators at each site. The paper forms or electronic copies of the database are regularly transferred to the co-ordinating centre in London. Data consistency and logic checks are conducted prior to each analysis, and discrepancies resolved with local ECS coordinators.

Research ethics approval

The ECS has on-going research ethics approval from the Great Ormond Street Hospital for Children NHS Trust / Institute of Child Health Research Ethics Committee. Local ethics approval is also obtained at each participating site. There is no formal research ethics review process in Ukraine for studies conducted within the public healthcare system, so local institutional review board approval was granted by clinic directors on an individual clinic basis at each site participating in the Ukraine ECS.

Categories and definitions

Definition and categories common to several chapters of the thesis are described here. Definitions specific to a chapter are described in the methods section of that chapter.

History of IDU rather than current IDU was used as the exposure of interest in analyses throughout this thesis, in reflection of the fact that drug use is often a chronic and relapsing condition (Hepburn 2004) and a marker of social deprivation. In the ECS, IDU history was ascertained by any one of: self-report by the woman, clinical assessment, or neonatal abstinence syndrome in the infant. Women with no history of IDU reported in the studies are referred to as 'non-IDUs' throughout the thesis for brevity. Under-ascertainment of IDU history is explored in section 5.3.2 (page 168).

Marital status was categorised as married, cohabiting or single (including separated, divorced or widowed). Age at leaving full-time education was categorised as ≤16 years, 17-18 years and ≥19 years. For work on the Western Europe ECS, maternal region of origin was categorised as sub-Saharan Africa and other; this categorisation reflected differences in mode of HIV acquisition and immigrant status, of potential importance for access to care. Race was categorised as white, black and other.

European guidelines state that infants born to HIV-infected women should receive RNA or DNA polymerase chain reaction (PCR) tests to detect transmission of the virus with diagnosis confirmed on a repeat test, and that a confirmatory antibody test is carried out at 15-18 months (PENTA Steering Committee 2009). PCR testing is widely available in resource-rich settings, and became available in Ukraine in 2006, although coverage was initially variable (Thorne *et al.* 2009). As of August 2011, 69% (2427/3535) of infants delivered from 2008 to 2010 in the Ukraine sites of the ECS had ≥1 RNA PCR test result available. In the absence of PCR testing, HIV-infected infants are diagnosed based on the persistence of HIV antibody beyond 18 months of age, since a positive antibody test prior to 18 months does not distinguish between a primary HIV infection in the newborn and passive transfer of anti-HIV antibody from the mother. For the purpose of analyses, infants with persistence of antibody beyond 18 months of age and/or a positive virological marker of infection regardless of age were categorised as infected. Infants with a negative PCR test result and/or a negative HIV antibody test were classified as uninfected, regardless of age (excluding

negative PCR test results on the day of delivery). The remaining infants and those with conflicting test results were categorised as having indeterminate HIV status.

Gestational age is reported to the nearest completed week based on ultrasound or, in absence of ultrasound, last menstrual period; preterm delivery is classified as occurring before 37 gestational weeks. The first trimester is defined as 1 to 12 completed weeks of gestation, the second trimester as 13 to 26 weeks and the third trimester as 27 weeks of gestation onwards (Royal College of Obstetricians and Gynaecologists 2010). Elective CS was defined as before rupture of membranes and onset of labour. Parity was defined as previous live and still births.

HIV disease staging in Western and Central European ECS sites was reported according to the US Centers for Disease Control and Prevention classification (severe symptomatic HIV disease corresponding to CDC stage C (US Centers for Disease Control and Prevention 1993)) and in Ukrainian sites was reported according to the World Health Organization clinical staging criteria (advanced and severe symptoms corresponding to WHO stages 3 and 4 respectively (WHO 2006)). Antenatal CD4 counts were categorised as ≤350 and >350 cells/mm^3, or as <200, 200-349 and ≥350 cells/mm^3 – categories relevant for determining treatment eligibility (WHO 2006; WHO 2010b). The quantification detection limits of viral load assays used varied over the years of the ECS and across Western and Eastern European sites. The limit below which a viral load was categorised as undetectable is defined for each analysis. Monotherapy was defined as one ARV drug, dual therapy as two ARV drugs and cART as ≥3 ARV drugs taken simultaneously. cART regimens were categorised as: PI-based, NNRTI-based, PI and NNRTI-containing, or a triple NRTI regimen.

The Ukrainian Postnatal Cohort of HIV-infected Childbearing Women

The Ukrainian Postnatal Cohort of HIV-infected Childbearing Women ("the Women's Study") was established in December 2007 as a nested sub-study of the Ukraine ECS, to investigate clinical and HIV disease progression markers and socio-demographic characteristics of women after delivery (Saxton *et al.* 2010). Postpartum women who are not already enrolled in the ECS are also eligible for Women's Study enrolment, if diagnosed as HIV-positive before or during a recent pregnancy including intrapartum. Enrolment usually takes place within 12 months of delivery. Five regional HIV/AIDS centres in Ukraine participate (situated in Odessa, Kiev, Mykolaiv, Donetsk and Krivoy Rog – see Figure 2.1). There is no specific protocol for timing of follow-up, which takes place whenever a woman returns to the HIV/AIDS centre for care.

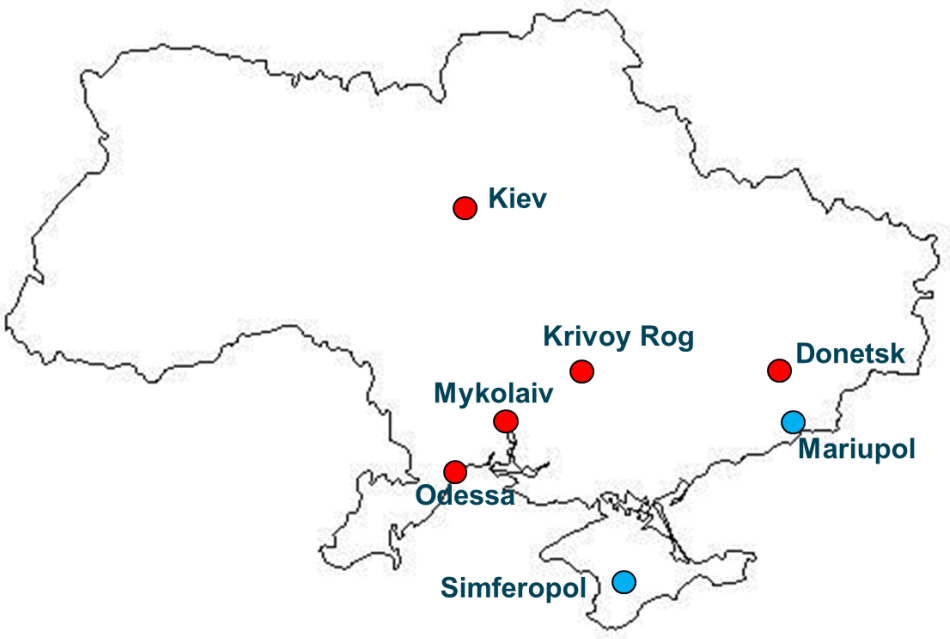


Figure 2.1: Study sites of the Ukrainian Postnatal Cohort of HIV-infected Childbearing Women

(Mariupol and Simferopol in blue are study sites for the Ukraine ECS only).

Data collected

Data collected are anonymised, with clinicians providing ECS serial numbers to enable data linkage; over 80% of women enrolled in the Women's Study are also enrolled in the ECS, allowing for investigations spanning pregnancy and the postnatal period. For women not in the ECS, background information on socio-demographic characteristics, timing of HIV diagnosis, receipt of antenatal ART in most recent pregnancy and clinical status is collected.

At enrolment into the Women's Study, baseline data are collected on two standardised questionnaires, one completed by the clinician and one by the woman. These forms are included in Appendix C, page 320. In brief, the clinician provides information on HIV disease status (CD4 count, HIV RNA viral load, current WHO stage and history of AIDS-defining illnesses) and ART received for the woman's own health (including toxicities and treatment modifications). Detailed information is collected on co-infections including viral hepatitis and STIs diagnosed during the most recent pregnancy or postnatally, and on cervical screening received as part of HIV care. Biochemical measurements collected include haemoglobin, platelet count and liver enzyme tests.

The woman's baseline form includes questions on the most recent pregnancy, the woman's living situation, the HIV status of her partner and whom she has disclosed her own status to. Questions on health behaviours cover smoking and use of alcohol and illicit drugs (including her own and her partner's injecting behaviours, sharing of injecting equipment, age at initiating illicit drug use and injecting, contact with harm reduction programmes and use of opioid substitution therapy). The woman is also asked to report use of contraception including affordability and availability, use of HIV psychosocial support services and, if continuing ART postnatally, experience of ART side effects and ART adherence (frequency of missed doses in last four weeks, whether she has had a period of >24 hours with no ART in the last four weeks).

At follow-up, the clinician provides updated information on HIV disease status and biochemical parameters, ART received (including toxicities, treatment modifications and adherence), and co-infections diagnosed and cervical screening received since last follow-up. The clinician is also asked to provide updated information on the woman's living situation, her current use of HIV psychosocial services, current use of contraception and incident pregnancies including miscarriages and terminations.

Participation rates in the Women's Study among women enrolled in the ECS vary substantially by site, from 24% in Donetsk to 87% in Kiev; these participation rates and the representativeness of the postnatal cohort are explored in section 5.2.1 (page 146).

Data management

Data collection is co-ordinated by PPAI in Odessa. Data are entered into an MS Access 2003 database with periodic electronic transfer to the UCL Institute of Child Health, every 4 to 6 weeks. Consistency and missing data checks are conducted prior to every analysis, and discrepancies resolved as far as possible with collaborators and by comparison of data from all sources - for example, woman's date of birth is collected in the ECS and on both the clinician and woman's baseline forms.

Research ethics approval

The Women's Study is nested within the Ukraine European Collaborative Study and covered by its on-going ethical approval from the Great Ormond Street Hospital for Children NHS Trust / Institute of Child Health Research Ethics Committee. Local institutional review board approval has also been granted by clinic directors at each participating site. Informed consent is obtained verbally and taken as implied by the woman's return of a completed questionnaire at enrolment.

Adherence Study

The aim of this sub-study was to investigate levels and determinants of ART adherence among HIV-positive women in Ukraine both during pregnancy and postpartum. Two surveys were conducted – one among women delivering at three maternity hospitals in Odessa, Kiev and Simferopol on their adherence behaviour during pregnancy, and one among women attending six participating HIV/AIDS centres (in Odessa, Donetsk, Kiev, Krivoy Rog, Mykolaiv or Simferopol) on adherence behaviours postpartum. The Antenatal Survey was conducted at around the time of delivery, and the Postnatal Survey at between 4 weeks and 12 months postpartum (see Figure 2.2). The surveys are reproduced in Appendix D, page 332. The Postnatal Survey included questions on adherence to neonatal prophylaxis, as well as to maternal ART. The main survey period was from July to December 2011, with extension until April 2012 at sites experiencing operational problems (including one site which was closed to patients for a period).

Survey participation was voluntary and involved completion of a paper-based questionnaire, which was designed for this study and drew on a number of previously validated tools (see ***Data Collected)***. Surveys were anonymously coded and code keys were held by clinicians for the purpose of referring women who reported adherence problems or symptoms of depression for additional support. Enrolment in either of the two on-going cohorts (the Ukraine ECS and the Women's Study) was not a pre-requisite for participation.

Data collected

Data were collected on mother's date of birth and her infant's date of birth and sex, to allow for linkage of adherence study data with information on the same participants in the ECS and Women's Study. This allowed for validation of self-reported adherence with viral load measures. As participation in the on-going cohorts was not a pre-requisite for participation in the Adherence Study, the adherence surveys also included some basic questions on socio-demographics and health behaviours (including drug use) taken from the ECS and Women's Study questionnaires. Questions specific to the adherence survey on adherence, ART-related self-efficacy and perinatal depression, are described in the pages that follow.

Adherence was measured using the self-report Case Adherence Support Evaluation (CASE) index tool, which consists of three questions (as follows). Together, the answers to these questions give a composite score of between 3 and 16, with higher scores indicating better adherence.

		Score
How often do you have difficulty taking your HIV medications on time?	All of the time	1
	Most of the time	2
	Rarely	3
	Never	4
On average, how many days per week would you say that you missed at least one dose of your HIV medications?	Every day	1
	4-6 days per week	2
	2-3 days per week	3
	Once a week	4
	Less than once a week	5
	Never	6
When was the last time you missed at least one dose of your HIV medications?	In the last week	1
	1-2 weeks ago	2
	3-4 weeks ago	3
	Between 1-3 months ago	4
	More than 3 months ago	5
	Never	6

The first evaluation of this tool was conducted between 2000-02 at 12 sites in the US among 524 patients (mostly male African Americans), and included a comparison of the CASE adherence index with the Adult AIDS Clinical Trial Group (AACTG) three-day recall adherence measure (a self-report measure of doses prescribed and missed in the previous three days) (Mannheimer *et al.* 2006). A CASE adherence index score cut-off of 10, with scores >10 indicating good adherence and scores ≤10 indicating poor adherence, was found to have the greatest sensitivity and specificity in identifying patients with 95% adherence according to the AACTG measure. Scores of >10 were significantly associated with a 1 log reduction in HIV RNA level, achievement of an HIV RNA level of <400 copies/ml and increase in CD4 count over 12 months of treatment. Self-reported adherence may more accurately reflect pill-taking behaviour if the self-report period is longer (e.g. weeks or months rather than the last 7 days or less (Lu *et al.* 2008)) – the AACTG 3-day measure may therefore lack sensitivity to identify poor adherence. A study conducted in Thailand in 2007-08 found a CASE adherence index cut-off of ≤12 to be more sensitive in identifying treatment failure than a cut-off of 10; all patients with a CASE adherence index score >12 had a viral load <400 copies/ml at 6 months (*n*=199) and <50 copies/ml at 12 months and 18 months follow-up (*n*=198

and *n*=196 respectively) (Apisarnthanarak *et al.* 2010). A more recent study, also from Thailand, found that a CASE adherence index score of ≤11 was associated with the largest probability of predicting virologic response to ART at three different thresholds (>50 copies/ml, >1000 copies/ml and >5000 copies/ml (Kerr *et al.* 2012)). In Chapter 6, CASE scores dichotomised at different values were validated against viral load in a subgroup of women with linked data available, in order to identify the best outcome measure.

Self-reported adherence levels are generally inflated compared with more objective measures of adherence (Bangsberg *et al.* 2000; Liu *et al.* 2001; Kimmerling *et al.* 2003), due to a range of factors including recall and social desirability bias, poor cognitive functioning and difficulties understanding self-report questionnaires (Kimmerling *et al.* 2003; Wagner *et al.* 2004; Johnson *et al.* 2005). One potentially valid approach to analysing self-report adherence data is to dichotomise responses according to whether any missed doses are reported (Simoni *et al.* 2006a). As a sensitivity analysis, and for comparison with the outcome of poor adherence as defined by CASE score, an outcome of 'any reported missed dose' was constructed and its relation with associated factors explored (Chapter 6). For the Antenatal Survey, 'any reported missed dose' referred to the whole of pregnancy; women in the 'ever missed a dose' group were those who provided a timing of their last missed dose (CASE question 3) and/or ≥1 reason for a missed dose on a later question (AIDS Clinical Trials Group 2010a), and/or who reported missing at least one dose a week (CASE question 2). If a woman reported missing a dose less than once a week (CASE question 2) and gave no other indication of having missed a dose, she was categorised with the 'never missed a dose' group. For adherence to maternal ART postnatally, the outcome of 'any missed dose' was constructed in the same way but limited to the four weeks preceding survey completion; most of the women completed the survey several months after delivery (Table 6.2, page 203).

Adherence to ART has been associated with knowledge of or familiarity with the prescribed regimen - for example, the ability to correctly identify pills from a selection (Parienti *et al.* 2001) and to name antiretroviral drugs currently taken (Osborn *et al.* 2010). In order to explore this, the Adherence Survey included a question on the name(s) of HIV medications currently being taken. Those reporting ≥3 drug names or, in the Antenatal Survey, one drug (if they were on ZDV), were considered to have complete knowledge of their regimen. For the 15 women who reported having

taken ZDVm, this was verified against self-reported pill burden (i.e. to check that they had not reported ZDV only from a cART regimen). Women reporting two drug names or one drug name if this was not ZDV were considered to have incomplete knowledge, while those reporting no names or only words unrecognisable as the name of an antiretroviral drug were considered to have no knowledge. Linked drug data from the ECS were used to give an indication of the accuracy of the drug names reported by the women. Lack of knowledge of regimen was investigated as a factor associated with adherence.

In addition to measures of ART adherence, the Adherence Survey also included measures of depression and ART-related self-efficacy – factors potentially relevant to adherence behaviours. Depression was measured using Patient Health Questionnaire (PHQ)-2 Screening Questions from the Primary Care Evaluation of Mental Disorders: "*During the past month, have you often been bothered by feeling down, depressed or hopeless?*" (low mood) and "*During the past month, have you often been bothered by little interest or pleasure in doing things?*" (anhedonia). A positive response to either of these two questions has an estimated sensitivity of 96% and specificity of 57% for the detection of depression in primary care settings (Whooley *et al.* 1997). The tool's specificity can be increased to 89% with the additional criteria of a "yes" response to "*Is this something with which you would like help?*"(Arroll *et al.* 2005). Patients responding positively to both of the first two questions are at high risk of depression irrespective of their response to the "help" question (Arroll *et al.* 2005). For this study, a positive depression screening test result was therefore defined as a 'yes' response to at least two of the three screening questions (summarised in Figure 6.1). Adherence Study questionnaires were anonymous to researchers but not to clinicians, to allow for referrals for mental health or adherence support where necessary.

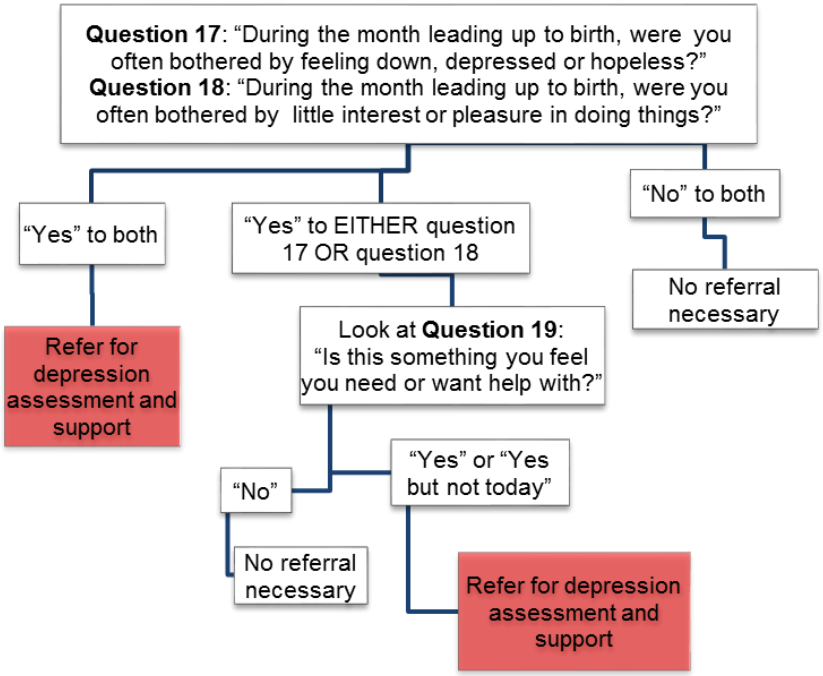


Figure 6.1: Algorithm for interpretation of PHQ-2 depression screening questions

ART-related self-efficacy was measured using questions from the HIV Treatment Adherence Self-Efficacy Scale (HIV-ASES) (AIDS Clinical Trials Group 2010b), adapted for use in the Adherence Surveys. The HIV-ASES tool asks respondents to rate their confidence in their own ability to adopt various behaviours related to HIV care. Because the Adherence Survey respondents did not generally have long ART treatment histories (particularly the Antenatal Survey respondents, most of whom would have initiated ART in pregnancy for PMTCT only), the HIV-ASES questions that were selected for inclusion in the survey focused on integration of pill-taking into daily life rather than long-term perseverance with treatment in the face of disease progression.

The original HIV-ASES tool asks respondents to rate their confidence in various areas on a scale from 0 to 10, (where 0 indicates 'cannot do' and 10 indicates 'confident I could do'). However, this layout caused confusion among respondents in the pilot Adherence Survey, and the question layout was therefore simplified to three options ('could not do' [0 points], 'fairly confident I could do' [1 point] and 'confident I could do' [2 points]). For women answering all five of the HIV-ASES integration questions, their total score was investigated as a continuous variable and also as a categorical variable dichotomised as <5 vs. ≥5 (respondents with a score of <5 having reported

that they 'could not do' at least one of the items). Two questions on the woman's confidence in her ability to ask for information and support were also included and followed the same format.

In order to give context to self-reported ART adherence problems, the Adherence Study surveys included a question on reasons for missed doses from the AIDS Clinical Trials Group adherence tool (AIDS Clinical Trials Group 2010a). In the postnatal survey, women were also asked whether their adherence had improved, deteriorated or remained unchanged following delivery (question adapted from (Mellins *et al.* 2008)). This question was important in assessing changes in adherence behaviours over the perinatal period, which could not be measured directly due to the cross-sectional nature of the antenatal and postnatal surveys. Women's attitudes towards the risks and benefits of ART for PMTCT were explored using two questions from the NIAIDS Adult AIDS Clinical Trials Group supplemental antepartum adherence questionnaire (NIAID Adult AIDS Clinical Trials Group 2001), which focused on the degree to which women felt that antiretroviral drugs were effective for PMTCT or were worried about adverse effects of ART.

Pilot study and sample size

Twenty women at both Odessa Regional Hospital and Odessa HIV/AIDS centre completed pilot surveys in May and June 2011. Feedback from participants and clinicians enabled the identification of problems with comprehensibility and layout of the questionnaires and study logistics (including referral pathways for adherence and mental health support). Both surveys were continued until 100-200 women had consented to take part and returned a completed form (200-400 forms in total). The participation rate was estimated at around 35-44% in the antenatal survey and 35% in the postnatal survey (75% among women on ART postnatally); these participation rates and the representativeness of the study population are described in detail in section 6.3, page 198.

Data management

Data collection was co-ordinated by PPAI and data entered by the data manager in Odessa into a Research Electronic Data Capture (REDCap) database (Harris *et al.* 2009), held securely on a server at the UCL Institute of Child Health. Linkage with ECS data allowed for checks to be conducted (e.g. on the eligibility of participants and the accuracy of self-reported ART regimens).

Research ethics approval

Research ethics approval was granted by the UCL Research Ethics Committee for this project (application 3061/001, May 2011). Local institutional review board approval was granted by all participating clinics and maternity hospitals in Ukraine.

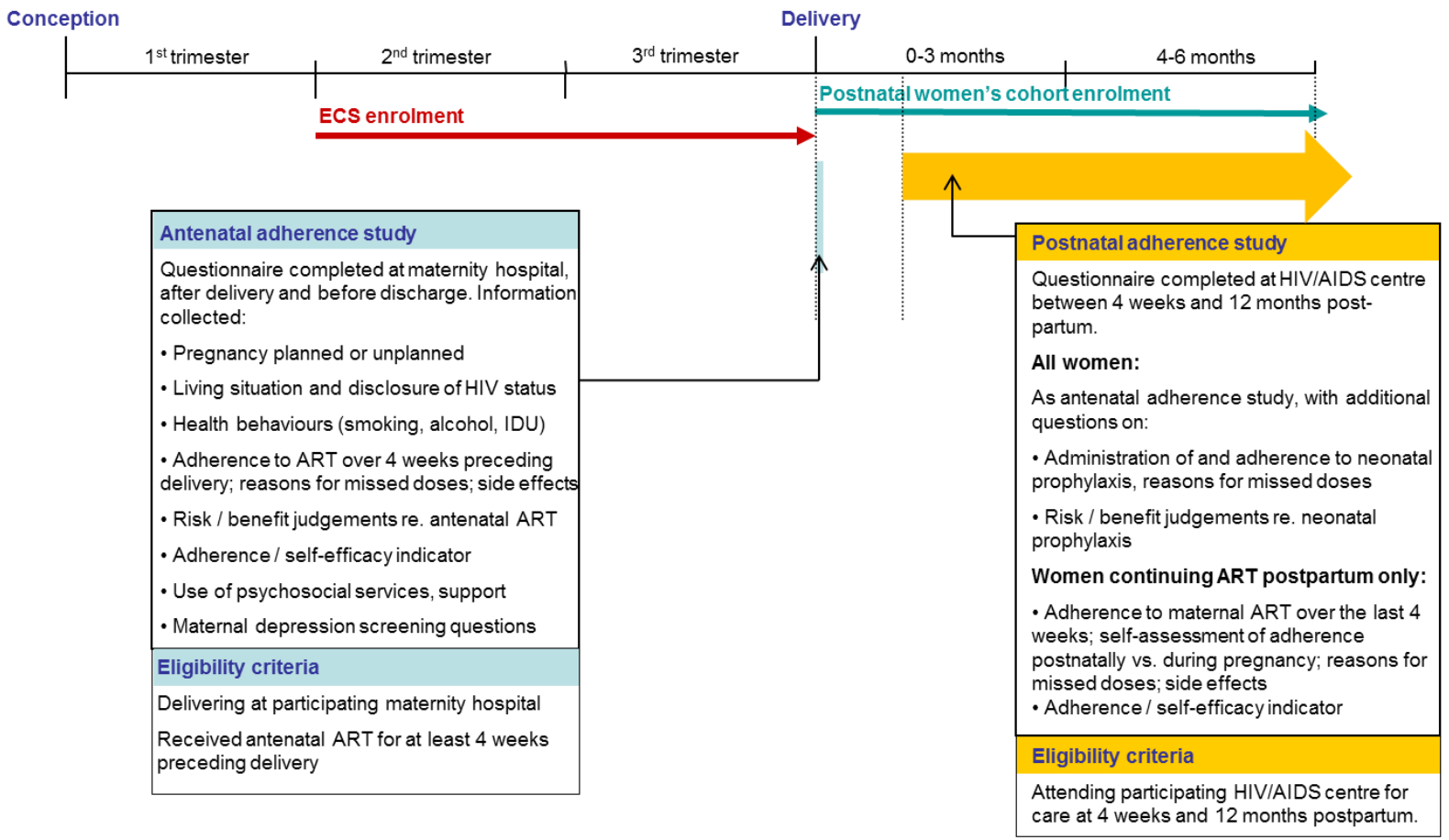


Figure 2.2: Timescale of the two Adherence Surveys, and data collected

2.4 Data analysis

Database management and data entry for all studies were conducted using MS Access 2003 (Microsoft Corp., Redmond, Washington, USA) and REDCap electronic data capture tools hosted at the UCL Institute of Child Health (Harris *et al.* 2009). All data cleaning, manipulation and analyses were carried out in Stata versions 10.0 and 11.0 for Windows (StataCorp LP, College Station, Texas, USA). For the two on-going cohort studies, extraction of data from the most up-to-date copy of the database was conducted prior to each analysis. Table 2.2 summarises the data source, time period and subjects (mother-child pairs or pregnancies) included in each analysis.

Table 2.2: Data available for each analysis

Chapter	Analysis	Dataset and centres	Time period	Subjects
3	Insufficient antenatal ART	ECS - Western and Central European sites	Jan 2000 – Jul 2009	2148 mother-child pairs
3	Use and trends of PMTCT interventions in Ukraine	ECS - Ukraine sites	Jan 2000 – Dec 2010	7346 mother-child pairs
			Jan 2008 - Dec 2010 for missed opportunities for PMTCT analyses	3535 mother-child pairs
4	Virologic failure in pregnancy among women conceiving on cART	ECS - Western and Central European sites	Jan 2000 – Dec 2011	396 mother-child pairs
5	Factors associated with chlamydia diagnosis	Ukraine postnatal women's study - Kiev, Odessa, Donetsk, Mykolaiv HIV/AIDS centres	Dec 2007 – Sep 2011	2066 women
5	HCV co-infection	Ukraine postnatal women's study - Kiev, Odessa, Donetsk, Mykolaiv HIV/AIDS centres	Dec 2007 – Sep 2011	2066 women
5	Cervical screening within HIV care	Ukraine postnatal women's study - Kiev, Odessa, Donetsk HIV/AIDS centres	Dec 2007 – Mar 2011	1120 women
6	ART Adherence	Adherence study - Kiev, Odessa and Simferopol maternity hospitals; Kiev, Odessa, Donetsk, Mykolaiv, Krivoy Rog and Simferopol HIV/AIDS centres	May 2011- April 2012	185 women in antenatal survey, 233 in postnatal survey

2.5 Statistical methods

Univariable comparisons of categorical variables were assessed using the χ^2 test or Fisher's exact test where numbers were small. Sample means of normally distributed variables were compared using the *t*-test, and sample medians of skewed continuous variables were compared using the Wilcoxon-Mann-Whitney test or the Kruskal-Wallis test (Kirkwood *et al.* 2008). Trends over time were assessed fitting logistic or linear regression models, with year of delivery specified as a continuous explanatory variable.

Univariable and multivariable logistic regression models were fitted to obtain odds ratios (OR) and adjusted ORs (AOR) and their 95% confidence intervals (CI). The contribution of each variable to a model's goodness-of-fit was assessed by comparing nested models using the Likelihood Ratio Test (LRT). Akaike's information criterion (AIC) and Bayesian information criterion (BIC) were also used to compare non-nested models (Kuha 2004).

Poisson regression models with robust variance estimators were fitted in preference to logistic regression models where the prevalence of a binary outcome was high (>10%). Odds ratios obtained from logistic regression models only approximate prevalence ratios where the prevalence of an outcome is uncommon, and so the use of logistic regression for these analyses would have resulted in odds ratios not directly interpretable as a measure of association. An outcome with high prevalence may produce under-dispersion which can be controlled by introducing a scale parameter in the models; this takes the value of 1 in ordinary Poisson regression. This extra parameter models the changes in the variance of the response variable and is estimated using a robust procedure (Barros *et al.* 2003). Univariable and multivariable Poisson regression models with robust variance estimators can be used to directly estimate prevalence ratios (PR), adjusted PRs (APR) and 95% CI when analysing cross-sectional binary data, and furthermore this approach results in more adequate controlling for confounding (which depends on measure of effect) when outcomes are common (Barros *et al.* 2003). Wald's test was used to compare the goodness-of-fit of Poisson regression models with robust variance estimators, as part of the model selection procedure.

Methods specific to each analysis are described in the corresponding chapters.

2.6 Role of researcher

As this work was conducted in the context of two on-going cohort studies, I take this opportunity to clarify my role. Data collection was the responsibility of clinicians at each participating centre and I had limited involvement with data verification and entry (in some cases this was done at the UCL Institute of Child Health and in some cases by local partners). I conducted data checks prior to each analysis and had close contact with collaborators in Ukraine to resolve data queries.

For the Adherence Study I led on the development of the protocol, questionnaires and patient information leaflets, which were translated by PPAI. I also designed the database and took responsibility for the application to the UCL Research Ethics Committee.

I performed all analyses presented in this thesis, with guidance from my supervisors Dr Claire Thorne, Dr Mario Cortina-Borja and Dr Claire Townsend. To date this work has led to three papers and one research letter accepted for publication with another paper in preparation, as well as a number of conference abstracts (Appendix F, page 345).

Chapter 3 Missed opportunities for the prevention of mother-to-child transmission

3.1 Introduction

Worldwide, the great majority of vertical transmissions occur in low- and middle-income settings, where the HIV burden is the highest and where less effective PMTCT interventions (including sdNVP) continue to be used. In Ukraine, the national PMTCT strategy was based on antenatal ZDVm and sdNVP until the end of 2007, when policy changed to recommend antenatal cART for all HIV-positive pregnant women. In the first part of this chapter, trends in socio-demographic and clinical characteristics, use of PMTCT interventions and MTCT rates in the Ukraine ECS from 2000 to 2010 are described. Factors associated with MTCT in 2008-10 are investigated as are missed opportunities for PMTCT, focusing on ART use and timing of maternal HIV diagnosis.

The second part of this chapter focuses on the resource-rich setting of Western Europe, where some vertical transmissions continue to occur despite wide availability of the full combination of measures to reduce MTCT risk (National Study of HIV in Pregnancy and Childhood *et al.* 2007). Longer durations of antenatal ART are associated with greater reductions in viral load and therefore vertical HIV transmission risk (European Collaborative Study 2005; Keiser *et al.* 2008; Townsend *et al.* 2008a; Warszawski *et al.* 2008); the role of short ART duration as a risk factor for preventable vertical transmissions is explored in the Western European sites of the ECS from 2000 to 2009.

3.2 PMTCT in Ukraine: trends and missed opportunities

3.2.1 Methods

This section uses data available by August 2011 on deliveries reported from January 2000 to December 2010 in the Ukraine ECS. Odessa, Mykolaiv and Simferopol HIV/AIDS centres contributed data from January 2000 onwards, Kiev, Donetsk and Mariupol HIV/AIDS centres from September 2006 and Krivoy Rog HIV/AIDS centre from October 2008.

Where a pregnancy resulted in twins or triplets, the second- and subsequent-born infants of the multiple birth were excluded. This approach ensured that data from a single pregnancy did not appear in duplicate in the analyses; this work focuses on use of PMTCT interventions, making pregnancies the denominator of interest. Where vertical transmission had occurred to the second- or subsequent-born infant in a multiple birth but not to the firstborn (n=2), the infected infant was retained (and firstborn excluded) to allow for the analysis of factors associated with any MTCT.

Information on whether a pregnancy was a second or subsequent delivery to a woman previously enrolled in the study was not available. The proportion of pregnancies in the ECS which were repeat pregnancies was estimated by identifying, for each set of records with matching centre and maternal date of birth, any second or subsequent pregnancy where: maternal HIV diagnosis occurred prior to conception, estimated date of conception was after previous date of delivery, and parity (previous live or stillbirth) increased by one compared with the previous pregnancy. This estimation was based on 81% (5922/7346) of pregnancies with exact maternal date of birth and all other required variables available. Mother-child pairs with maternal HIV diagnosis date after the date of delivery, and no other information to indicate that this was an error (ART receipt during pregnancy or intrapartum), were excluded (n=49).

Viral load assays with detection limits of 75 copies/ml were in use at some regional labs until 2010, when highly sensitive assays with detection limits of 40 copies/ml were adopted at all laboratories. In this work, a viral load of ≤75 copies/ml was defined as "undetectable". Dual therapy was received in a small number of pregnancies (described on page 84); these pregnancies were considered with the ZDVm group for all analyses, as were the small number of pregnancies in which a drug other than zidovudine was received as monotherapy. Women who received only

sdNVP intrapartum were classified with the 'no antenatal ART' group. Treatment indication was defined as CD4 count of ≤350 cells/mm^3 and/or WHO stage 3-4 disease (WHO 2010b). A late maternal HIV diagnosis was defined as one occurring during the third trimester or intrapartum.

Risk factor analyses were conducted for three scenarios in 2008-10: i) late HIV diagnosis among women undiagnosed at conception, ii) non-receipt of antenatal ART among women not on ART at conception and diagnosed prior to delivery; iii) initiation of ZDVm rather than cART during pregnancy. Poisson regression models with robust variance estimators were fitted to investigate factors associated with these outcomes. Each covariate was tested for its significant contribution to the model's goodness-of-fit using Wald's test (significance level of <0.10). Educational status was available for only 44% (1545/3535) of women overall and so was excluded from main analyses to avoid bias, but was investigated in sub-analyses.

In the logistic regression model fitted to investigate factors associated with MTCT from 2008 to 2010, all factors found previously to be associated with MTCT risk in this cohort were included *a priori* (Thorne *et al.* 2009) (preterm delivery, mode of delivery, receipt of antenatal and intrapartum ART, IDU history) with the exception of breast feeding, excluded as almost all women formula fed. Neonatal prophylaxis and maternal WHO stage and CD4 count were considered for inclusion at significance level of <0.10 on LRT.

In order to investigate individual-level factors associated with missed opportunities for PMTCT or MTCT in a context where relevant policy varied over time and practice varied by centre, all models in this section were adjusted *a priori* for year of delivery and centre of enrolment. For Poisson regression models, centre was included as a covariate to allow for the inclusion of a robust estimates term. Accounting for under-dispersion in highly prevalent outcomes in this way was considered more important than the retention of five additional degrees of freedom (which could have been achieved by accounting for within-centre variation with a random effects term).

The analyses on initiation of ZDVm rather than cART during pregnancy were limited to 2840 pregnancies with WHO stage and/or antenatal CD4 count available (93% (2840/3068) of those where ART was initiated antenatally), since maternal treatment indication was so important in determining cART receipt.

3.2.2 Cohort characteristics and time trends

Maternal characteristics

There were a total of 7346 deliveries reported in 2000-10. Table 3.1 (page 83) shows trends over time in maternal and delivery characteristics. A gradual increase in maternal age was seen over time, from a median of 25.4 years (IQR 22.3, 29.6) in 2000 to 27.8 years (IQR 24.2, 31.6) in 2010, with women increasingly likely to have had a previous live birth at enrolment. There was also a consistent increase in the proportion of women with known HIV infection at conception. Repeat ECS pregnancies were estimated to account for 4% (268/5922) overall (most (258/268) were 2nd pregnancies, and 10 were 3rd pregnancies), increasing from 2% to 3% of pregnancies in the period from 2003 to 2007 to 4% of pregnancies (47/1118) in 2008, 5% (60/1162) in 2009 and 11% (97/846) in 2010 (trend $p<0.01$ for 2008 to 2010). The length of time between HIV diagnosis and delivery increased significantly from a median of 18 weeks in 2000 to 29 weeks in 2010, with a concomitant increase in the proportion of women with WHO stage 3-4 disease or a CD4 count ≤350 cells/mm^3 (reaching 16% and 36% respectively in 2010, Table 3.1). Of 364 women diagnosed before pregnancy, not on cART at conception and delivering in 2010, 41% (n=150) had WHO stage 3-4 disease and/or a CD4 count ≤350 cells/mm^3 during pregnancy (i.e. treatment indications for their own health). Among those diagnosed during pregnancy in the same year, 8% (36/474) had WHO stage 3-4 disease and 32% (162/512) had WHO stage 3-4 disease and/or a CD4 count ≤350 cells/mm^3 during pregnancy.

Overall, 82% (6017/7306) of women were married or cohabiting at the time of enrolment, with no change over time (trend p=0.14). The proportion of women who had stayed in full-time education until at least the age of 17 years was 61% (576/948) in 2000-05 and 83% (1651/1990) in 2006-10 (trend $p<0.01$), although there was a dip to 70% (366/523) in 2010. IDU history was associated with lower level of education (see 'Characteristics of women with an IDU history'), and levels of education increased concomitant with a decline in the proportion of women with a personal history of IDU or IDU partner (50% prior to 2006 declining to a third in 2006-10). The proportion of women with a history of IDU varied by centre in 2008-10 (the years when all centres contributed data) from 9% (33/355) in Mariupol to 32% (180/554) in Kiev (seven centres, χ^2=177.91, $p<0.01$). Almost all women were white (99%, 7214/7312) and born in Ukraine (99.7%, 7312/7333).

Characteristics of women with an IDU history, 2008-10

Women with an IDU history were different in several important respects to non-IDUs, and are characterised here to aid interpretation of later analyses focusing on the years 2008-10. In these three years, women with an IDU history were significantly more likely to be unmarried (63% (324/513) vs. 54% (1618/2986) with no IDU history, χ^2=14.27 p<0.01), to have had at least one previous live birth (51% (254/496) vs. 46% (1367/2953) of non-IDUs, χ^2=4.12 p=0.04) and to have left full-time education at ≤16 years (33% (96/295) vs. 14% (243/1683) of non-IDUs, χ^2=61.31 p<0.01). They were also more likely to have WHO stage 3-4 disease (30% (132/446) vs. 11% (276/2529) of non-IDUs, χ^2=111.84 p<0.01) and to have been diagnosed prior to conception (60% (275/461) vs. 36% (1038/2908) of non-IDUs, χ^2=100.24 p<0.01), reflecting higher coverage of HIV testing in high-risk groups and temporal shifts in modes of HIV acquisition. Just over a quarter (26%, 882/3440) of women delivering in 2008-10 had an IDU partner; among IDUs, the proportion was 38% (182/482) vs. 24% (699/2956) of non-IDUs (χ^2=43.31 p<0.01).

Timing and trends in availability of laboratory tests

Laboratory capacity for CD4 and viral load monitoring increased over time, particularly from 2008 to 2010 (Table 3.1). In 2010, among the 75% (742/994) of women diagnosed as HIV-positive by the end of the 18th week of gestation, 78% (576/742) had at least one antenatal CD4 count available (54% (n=399) had one count at median 21 weeks gestation; 24% (n=177) had ≥2, the first and last at median 15 and 35 weeks gestation). Among the same group 66% (n=491) had at least one viral load measurement available (39% (n=291) had one measure at median 23 weeks gestation; 27% (n=200) had ≥2, the first and last at median 17 and 35 weeks gestation). Among women diagnosed after the 18th week of gestation in the same year, the proportions with at least one CD4 count or viral load measurement available were 68% (171/252) and 50% (126/252) respectively. Coverage of CD4 and viral load measurements was highest in Simferopol (94% (176/188) had a CD4 count and 93% (174/188) had a viral load measurement) and lowest in Odessa (34% (82/242) had a CD4 count and 24% (59/343) had a viral load measurement). The proportion of women diagnosed with HIV late (after the start of the third trimester) varied significantly by centre (see Table 3.3 page 95). In addition, there was geographical variability in funding available for test

reagents and lab equipment repairs, and at some labs there were periods when viral load and CD4 measurements were not available or available only to patients on ART (Igor Semenenko, Personal communication, PPAI, 2011).

Immediately following the establishment of the ECS in Ukraine in 2000, laboratory facilities for infant virological testing were not available in the country and so infant dried blood spots were sent to Amsterdam for testing (European Collaborative Study 2006). In the early years of the study, there were wide fluctuations in the proportion of infants receiving a PCR test by 6 months of age from 80% (48/60) born in 2000 to 22% (58/267) born in 2002, 65% (195/300) born in 2003 and 36% (181/500) born in 2005. In 2006, PCR testing for HIV-exposed infants was introduced nationwide in Ukraine at three inter-regional laboratories (Thorne *et al.* 2009). Coverage has been consistently above 60% since, but with no increase from 2007 to 2010 (OR 0.95 for receipt of PCR by 6 months of age by increasing year, 95% CI 0.90-1.00, p=0.06). PCR coverage is limited by laboratory capacity (in a setting with a substantial increase in the number of HIV-exposed infants born year-on-year), technical problems and uptake (Thorne *et al.* 2009).

Trends in mode of delivery

From 2007, Ukrainian policy has recommended delivery by elective CS for HIV-positive women with a viral load >1000 copies/ml at 36 weeks gestation. Mode of delivery varied significantly by centre; in 2010, 44% (82/188) of deliveries in Simferopol were by elective CS compared with 37% (17/46) in Krivoy Rog, 36% (87/242) in Odessa, 14% (12/86) in Donetsk, 14% (15/104) in Mariupol, 12% (25/215) in Mykolaiv and 8% (12/144) in Kiev (χ^2=108.97 p<0.01). The inter-centre differences were not explained by availability of viral load (elective CS deliveries accounted for 34% (615/1833) of deliveries among women with a viral load available vs. 29% (1608/5510) of those among women with no viral load, χ^2=12.43 p<0.01). In 2007-10, 44% (197/448) of women with a third trimester viral load of >1000 copies/ml delivered by elective CS compared with 25% (185/755) of women whose viral load was <1000 copies/ml. Overall, the proportion of deliveries by elective CS reached a low of 24% (250/1027) in 2010 following a gradual decline from 40% (201/500) in 2005 (trend p<0.01). This change was accounted for by the inclusion of Kiev, Donetsk, Mariuopol and Krivoy Rog HIV/AIDS centres in later years of the study, rather than by a

change in clinical practice at any one centre over time. At Odessa, Mykolaiv and Simferopol HIV/AIDS centres (the three centres enrolling women from the study's inception in 2000), there was no time trend in proportion of deliveries by elective CS (p=0.61). Deliveries by emergency CS accounted for 4% (304/7343) overall (time trend p=0.16).

Table 3.1: Time trends in maternal characteristics and availability of laboratory tests, 2000-10

	2000	**2001**	**2002**	**2003**	**2004**	**2005**	**2006**	**2007**	**2008**	**2009**	**2010**	**Time trend**
	n=60	*n*=197	*n*=267	*n*=300	*n*=458	*n*=500	*n*=694	*n*=1335	*n*=1217	*n*=1291	*n*=1027	
Maternal age, median (years)	25.4	24.9	25.2	25.2	25.9	25.9	25.6	26.0	26.4	26.6	27.8	*p*<0.01
Parous at enrolment	40% 21/53	43% 84/195	41% 104/255	42% 124/293	42% 191/458	41% 206/500	35% 242/694	38% 504/1335	41% 500/1216	46% 588/1266	57% 558/981	*p*<0.01
Diagnosed HIV+ before conception	23% 11/47	19% 34/180	19% 44/233	19% 53/286	27% 123/458	22% 110/499	25% 166/656	31% 377/1235	34% 404/1184	38% 471/1250	44% 439/994	*p*<0.01
Diagnosed HIV+ in 3rd trimester / intrapartum	38% 18/47	46% 83/180	44% 103/223	36% 104/286	33% 149/458	27% 137/499	16% 106/656	16% 203/1235	12% 143/1184	10% 128/1250	11% 111/994	*p*<0.01
Median weeks before delivery HIV diagnosed	18 weeks	15 weeks	17 weeks	19 weeks	22 weeks	22 weeks	24 weeks	26 weeks	27 weeks	28 weeks	29 weeks	*p*<0.01
IDU history	39% 21/54	35% 63/182	27% 65/238	29% 84/286	28% 127/458	20% 98/500	16% 110/694	18% 236/1334	16% 195/1215	14% 180/1273	14% 139/1017	*p*<0.01
IDU partner	45% 24/53	44% 75/172	42% 96/230	44% 124/279	36% 164/458	42% 211/500	35% 241/693	24% 326/1334	27% 321/1205	23% 288/1242	27% 273/993	*p*<0.01
No IDU history or IDU partner	47% 28/60	50% 98/197	56% 150/267	52% 156/300	52% 239/458	52% 262/500	61% 420/694	65% 871/1335	64% 784/1217	68% 884/1291	64% 654/1027	*p*<0.01
WHO stage 3-4	0/50	0/158	0/187	1/297	0	4% 22/499	6% 38/615	10% 107/1126	12% 124/1009	13% 144/1096	16% 143/885	*p*<0.01
Availability of antenatal CD4 count	0/60	1/197	1/267	2% 6/300	19% 87/458	16% 81/500	33% 228/694	42% 562/1335	50% 606/1217	70% 908/1291	73% 749/1027	*p*<0.01 (2003-10)
CD4 count ≤350 cells/mm³ (first antenatal measure)	-	0/1	0/1	1/6	25% 22/87	36% 29/81	31% 70/228	29% 163/562	33% 199/607	33% 302/908	36% 273/749	*p*<0.01 (2004-10)
Availability of antenatal viral load	0/60	1/197	0/267	0/300	0/458	0/500	0/694	3% 36/1335	34% 410/1217	60% 769/1291	60% 619/1027	*p*<0.01 (2007-10)

Trends in use of antenatal and intrapartum ART

Figure 3.1 illustrates the changing use of antenatal and intrapartum ART over time from January 2000, when less than 20% of women received any antenatal ART, to 2010, when almost 90% of women received antenatal ART and 60% received cART. Although sdNVP was superseded in the national PMTCT strategy in 2003 by ZDVm from 28 weeks gestation, sdNVP continues to be used as the main PMTCT intervention for women diagnosed as HIV-positive during labour or presenting in labour without having received antenatal care, and is used in combination with ZDVm when this is initiated later than the 28th week gestation.

Almost all women on monotherapy received ZDV (99.6%, 2964/2977), with one woman receiving TDF (enrolled in Mykolaiv in 2010) and twelve receiving ABC (enrolled across five different centres in 2008-09). Although ZDV continues to be the NRTI of choice for use as monotherapy in pregnant women (WHO 2010a), its use is associated with anaemia and Ukrainian policy specifies that if this is a concern then another NRTI or NtRTI can be substituted provided that a woman's CD4 count is >350 cells/mm^3 and viral load <10,000 copies/ml; if these conditions are not met then cART should be used (Ministry of Health of Ukraine 2007).

The majority (87%, 1585/1823) of women on cART received a protease inhibitor (PI)-based regimen, most commonly ZDV, 3TC and ritonavir-boosted lopinavir (LPV/r) which accounted for two-thirds (1178/1823) of cART regimens. Among women who received cART, use of PI-based regimens increased from 73% (79/108) in 2007 to 80% (217/270) in 2008, 94% (669/709) in 2009 and 91% (572/627) in 2010 (trend p<0.01). Of the 13% (236/1823) receiving an NNRTI-based regimen, most (200/236) received ZDV, 3TC and NVP. Dual therapy is not recommended for PMTCT, but was received by 22 women (delivering across all seven centres, 20 in 2008-10), most of whom received ZDV and 3TC. This was mainly due to drug shortages of LPV/r, and a reluctance to prescribe NVP (the only other alternative drug) because of concerns around hepatotoxic effects in pregnant women with higher CD4 counts (Lyons *et al.* 2006)(Personal communication, Igor Semenenko, PPAI, 2011).

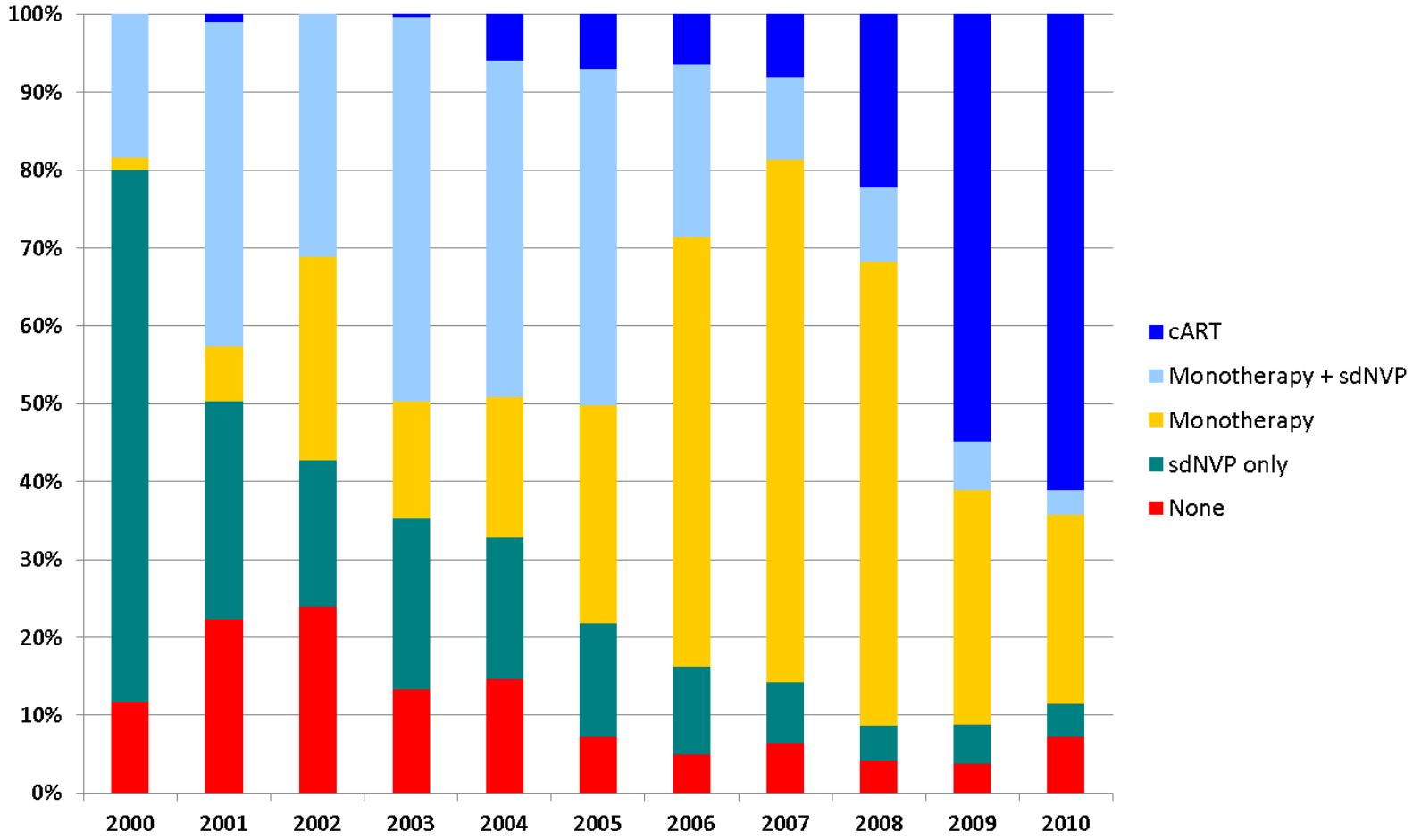


Figure 3.1: Time trends in antenatal and intrapartum ART receipt

(*n*=7355)

Timing of initiation and duration of antenatal ART

Conceptions on cART increased over time, from 2% (6/377) of women diagnosed before conception and delivering in 2007 to 12% (52/439) in 2010 (trend $p<0.01$). Prior to 2005, the majority (97%, 722/744) of women initiating ART during pregnancy did so in the third trimester. Subsequently, the proportion starting ART earlier in pregnancy has increased substantially from 12% (45/390) in 2005 to 46% (492/1078) in 2008 and 68% (577/851) in 2010 (trend $p<0.01$). The duration of ART received by delivery among those not on ART at conception increased accordingly, from a median of 5 weeks in 2004 to 10 weeks in 2006 and 14 weeks in 2010 (one-way analysis of variance (ANOVA) $p<0.01$). In 2008-10, duration of treatment received by women initiating ART during pregnancy varied by centre from a median of 10 weeks in Odessa to 13 weeks in in Krivoy Rog (one-way ANOVA $p<0.01$).

Use of single-dose nevirapine

The decrease in use of sdNVP over time reflects its replacement by more effective interventions for PMTCT, and the increased opportunity for receipt of antenatal ART where HIV diagnosis occurs earlier in pregnancy or prior to conception (Table 3.1, page 83). However, the proportion of women receiving sdNVP only (and therefore lacking antenatal care) did not decrease between 2008 and 2010, remaining at around 5% overall (trend $p=0.90$). The proportion receiving no ART was unchanged from 2005 onwards at 5% overall (range 3% to 7%, trend $p=0.51$). Around 10% of women have therefore continued to receive no ART during pregnancy in recent years. This group is the focus of a later analysis (see section 3.2.2, page 79), given their comparatively very high risk of MTCT.

Trends in use of neonatal prophylaxis

Overall, neonatal prophylaxis was given to 97% (6942/7172) of infants: 11% (760/7172) received sdNVP only, 58% (4128/7172) ZDV only, 17% (1188/7172) ZDV plus sdNVP, 1% (69/7172) other regimens (including cART) and 11% (797/7172) were missing information on type of prophylaxis received. The duration of treatment with ZDV was one week for most (86%, 4542/5298) and four weeks for 14% (728/5298) – according to Ukrainian policy, four weeks of neonatal prophylaxis are prescribed where maternal HIV diagnosis occurs after the start of the third

trimester, or where the mother has received <12 weeks of antenatal ART by delivery (Ministry of Health of Ukraine 2007). There was a shift in the type of ART used for neonatal prophylaxis, from sdNVP only in 2000-04 (59%, 751/1267) to ZDV only in 2005-10 (70%, 4115/5905). Of the 17% (1060/6064) of infants who received sdNVP in the later period, all except nine received it in conjunction with ZDV.

Achieving an undetectable viral load by delivery

Figure 3.2 shows, for the period 2008-10, the proportion of women with at least one antenatal viral load measurement and whether this was detectable or not, by ART receipt. Among women conceiving on cART, 69% (90/131) had a viral load measurement taken during pregnancy, of whom 86% (n=77) had an undetectable viral load at their last antenatal measure (median 97 days before delivery). Of women initiating cART during pregnancy, the proportion with an undetectable antenatal viral load was 43% (318/733) (measure taken a median of 74 days after initiating cART and 26 days before delivery), but substantially higher (69%, 143/207) among a sub-group who had been on cART for at least three months by the time of the measurement. Fifteen per cent (63/425) of women on ZDVm had an undetectable viral load recorded during pregnancy (measure taken a median of 57 days after treatment initiation and 29 days before delivery); only 12% (51/425) had a measurement available at least three months after ART initiation but before stopping ART at delivery, of whom 18% (9/51) had an undetectable viral load. The proportion of women with an undetectable viral load reported in pregnancy increased substantially from 17% (71/410) in 2008 to 25% (193/769) in 2009 and 35% (219/619) in 2010 (trend p<0.01), reflecting the roll-out of cART for PMTCT.

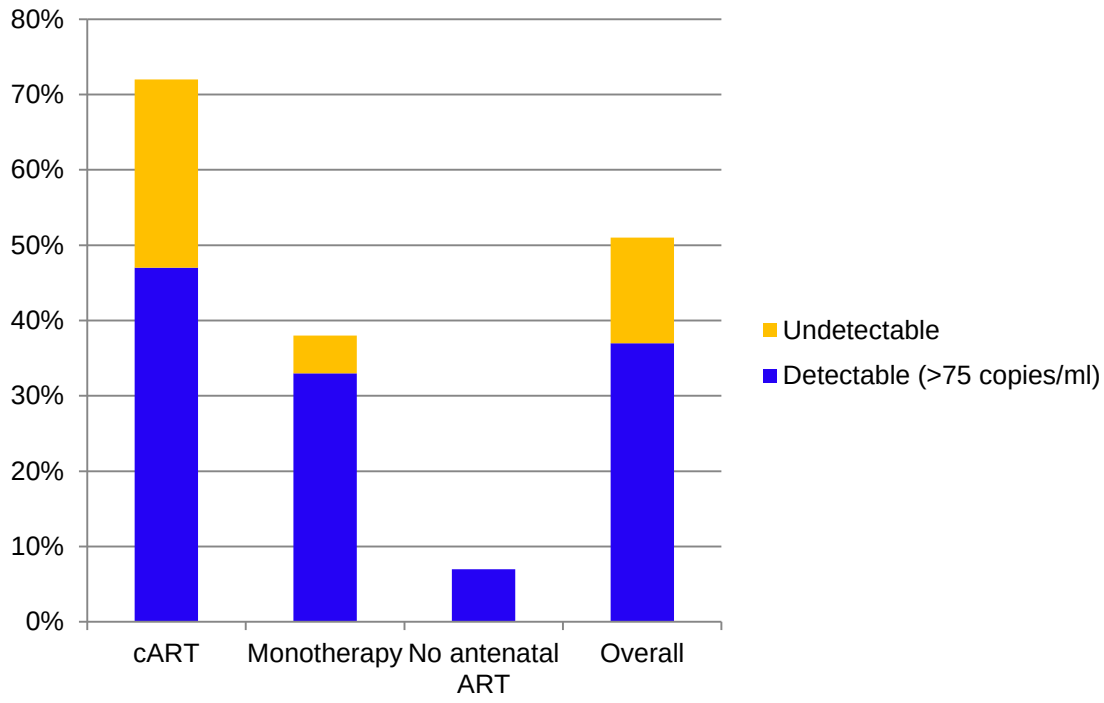


Figure 3.2: Availability of antenatal viral load measurements and proportion with detectable viral load by ART receipt (2008-10)

Where >1 measurement was available, the last before delivery was used. *n*=3515.

Trends in mother-to-child-transmission rate

Figure 3.3 shows the decline in unadjusted MTCT rates from 2000 to 2010 (trend $p<0.01$). In addition to PMTCT policy changes summarised in this Figure, other factors which will have impacted on the MTCT rate reported each year include changes over time in participating centres and differences between centres with respect to resources, policies, clinical practice and patient population (socio-demographics and clinical characteristics). The MTCT rate in 2008-10, which was 4.1% overall (95% CI 3.4-4.9), is explored in more detail in section 3.2.6 (page 106).

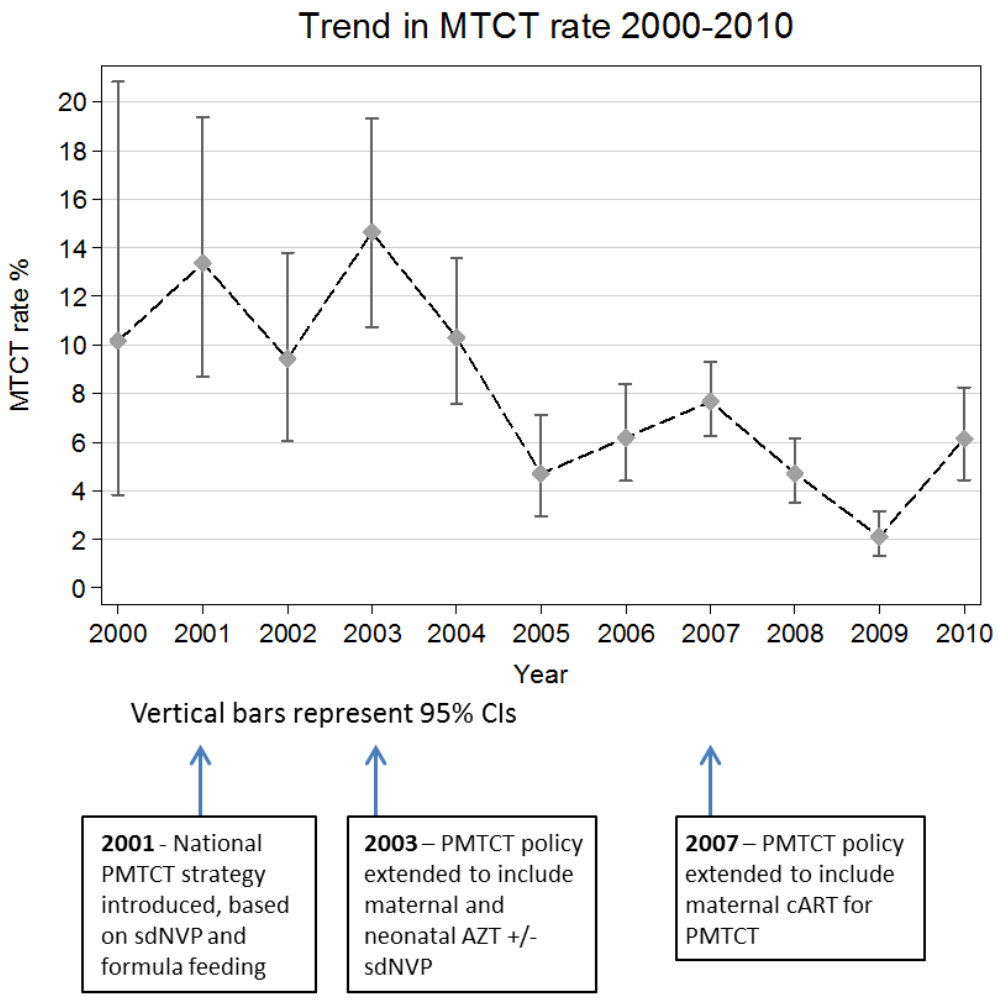


Figure 3.3: MTCT rate over time, 2000-10

3.2.3 Maternal HIV diagnosis late in pregnancy, 2008 to 2010

Overall in 2008-10, just over one in ten (382/3429) deliveries were to women diagnosed "late" (during the third trimester or intrapartum); as Ukrainian policy involves repeat testing in the third trimester for women negative at the first antenatal test, some of these women may have seroconverted during pregnancy. Figure 3.4 shows pregnancies in 2008-10 by timing of diagnosis and the number in which no antenatal ART was received.

Although the proportion of women with a late HIV diagnosis decreased significantly over time from 2000 to 2008 (Table 3.1, page 83) there was no change from 2008 to 2010 (trend p=0.46). These trends were also true for women undiagnosed at conception: 51% (308/604) were diagnosed late in 2000-03 declining to 29% (595/2072) in 2004-07 (trend p<0.01), but with no change from 2008 to 2010 (trend p=0.53). Of women undiagnosed at conception in 2008-10, significant differences in timing of diagnosis existed by centre of enrolment with 8% (14/165) of women in Krivoy Rog diagnosed late compared with 24% (44/181) in Mariupol (seven centres, χ^2=29.18 p<0.01). Overall, 22% (74/331) of women diagnosed late had WHO stage 3-4 disease and/or a CD4 count of ≤350 cells/mm^3 compared with 28% (440/1592) of women diagnosed in the first or second trimesters (χ^2=3.90 p=0.05).

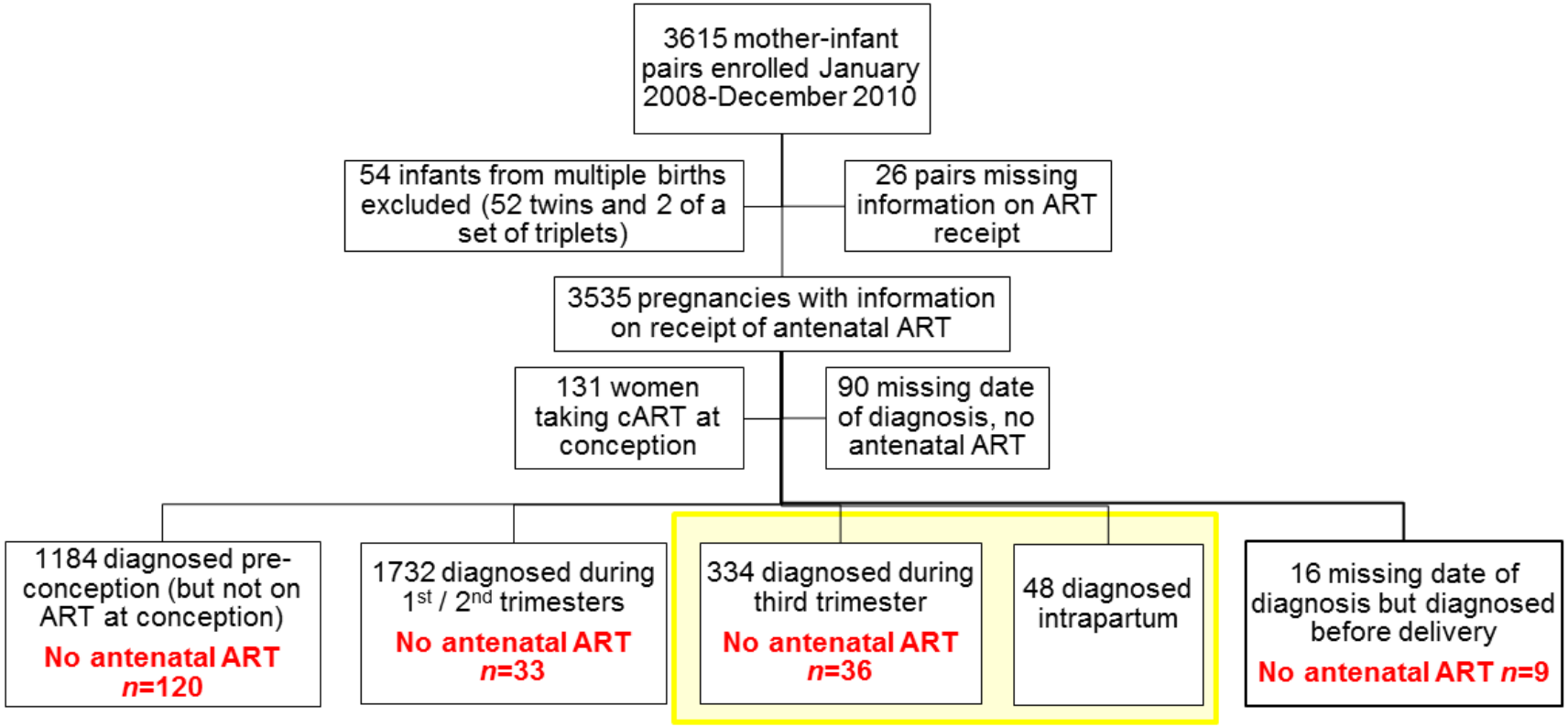


Figure 3.4: Pregnancies reported in 2008-10 by timing of diagnosis and receipt of ART

Table 3.2 shows maternal and delivery characteristics by timing of HIV diagnosis in 2008-10. Among those undiagnosed at conception, 18% (382/2114) were diagnosed late: 16% (334/2114) in the third trimester (a median of 8 weeks before delivery, IQR 6-11 weeks) and 2% (48/2114) intrapartum. Women with a late diagnosis were more likely to be single, to have had previous live birth(s) and fewer years of full-time education. The association between late diagnosis and previous live birth was stronger than that between late diagnosis and any previous pregnancy (including termination, miscarriage and stillbirth, (χ^2=3.93 p=0.05). There was no association between maternal age and late diagnosis (4 categories, χ^2=6.44 p=0.09). Of women undiagnosed at conception, 28% (56/200) of IDUs were diagnosed late compared with 17% (326/1904) non-IDUs (Table 3.2). Among non-IDUs, women delivering preterm at <37 weeks were more likely to be diagnosed intrapartum (3% (7/214) vs. 1% (27/2720) of those delivering at term, χ^2=9.12 p<0.01), probably due to less opportunity for antenatal HIV testing. This association was not observed among IDUs (χ^2=0.19 p<0.66) who were probably more likely to completely lack antenatal care.

Table 3.2: Maternal and delivery characteristics by timing of HIV diagnosis among women undiagnosed at conception, 2008-10

	Timing of HIV diagnosis		
	1st or 2nd trimester (*n*=1732)	3rd trimester or intrapartum (*n*=382)	χ^2 test for categorical variables
Maternal age – median [IQR] (*n*=2111)	26.2 [22.8, 30.2]	26.7 [22.6, 30.9]	
Marital status (*n*=2112)			
Married	816 (47%)	109 (29%)	χ^2=52.39, *p*<0.01
Cohabiting	683 (39%)	182 (48%)	
Single	231 (13%)	91 (24%)	
Previous live birth at enrolment (*n*=2080)			
0	1152 (68%)	195 (51%)	χ^2=52.18, *p*<0.01
1	428 (25%)	119 (31%)	
≥2	121 (7%)	65 (17%)	
Age at leaving full-time education (*n*=1181)			
≤16 years	111 (11%)	55 (26%)	χ^2=41.72, *p*<0.01
17-18 years	272 (28%)	73 (34%)	
≥19 years	586 (60%)	84 (40%)	
History of IDU (*n*=2104)			
No	1578 (92%)	326 (85%)	χ^2=14.41, *p*<0.01
Yes	144 (8%)	56 (15%)	
IDU partner (*n*=2068)			
No	1307 (77%)	268 (72%)	χ^2=3.45, *p*=0.06
Yes	391 (23%)	102 (28%)	
WHO stage (*n*=1788)			
1-2	1368 (93%)	278 (90%)	χ^2=2.91, *p*=0.09
3-4	110 (7%)	32 (10%)	
Mode of delivery (*n*=2113)			
Vaginal / emergency CS	1213 (70%)	300 (79%)	χ^2=11.01, *p*<0.01
Elective CS	518 (30%)	82 (21%)	
Gestation at delivery (*n*=2109)			
≥37 weeks	1603 (93%)	348 (92%)	χ^2=0.58, *p*=0.45
<37 weeks	126 (7%)	32 (8%)	
MTCT rate (95% CI) (*n*=1709)	2.6% (1.8-3.5%)	8.5% (5.6-12.2%)	χ^2=25.46, *p*<0.01

In univariable analyses, factors significantly associated with late diagnosis among women undiagnosed at conception were having an IDU history, being unmarried, having fewer years of full-time education, having had previous live birth(s) and centre of enrolment (Wald's test $p<0.01$) (Table 3.3, page 95), but not maternal age, WHO stage and IDU partner ($p>0.5$ in univariable analyses and $p>0.1$ after adjusting for centre and year). IDU history, marital status and previous live births remained associated with late diagnosis in adjusted analyses (Table 3.3). There was no heterogeneity of effect of marital status on late diagnosis by history of IDU or live births (Wald's test $p=0.78$ and $p=0.85$ respectively). Women with previous live births who were diagnosed late had either acquired HIV since their last pregnancy or had had a previous pregnancy in which their HIV infection went undetected.

Among 1148 women with educational status available, those leaving full-time education at 17-18 years or at ≤16 years (vs. ≥19 years) remained at significantly increased risk of late diagnosis in adjusted analyses (APR 1.63 95% CI 1.20-2.21 and APR 1.78 95% CI 1.26-2.51 respectively on adjusting for year, IDU history, marital status, previous live births and centre). The association between marital status and late diagnosis was reduced on adjusting for education in addition to other factors, but remained significant (from APR 1.94 95% CI 1.43-2.63 in model excluding education to APR 1.78 95% CI 1.31-2.41 in model including education for cohabiting status, and APR 2.45 95% CI 1.78-3.38 to APR 2.30 95% CI 1.68-3.16 respectively for single status). IDU, as well as being an independent risk factor for late diagnosis, was also associated with being unmarried, having previous live births and a lower level of education (see page 80).

Use of PMTCT interventions

Women diagnosed during the third trimester were significantly less likely than those diagnosed in the first or second trimesters to deliver by elective CS (24% (81/334) vs. 30% (518/1731), χ^2=4.38 p=0.04) and were more likely to lack antenatal ART (11% (36/334) vs. 2% (33/1732) diagnosed earlier in pregnancy, χ^2=68.29 p<0.01). Sixteen women received sdNVP only despite being diagnosed at least a week (median 19 days) prior to delivery. Among those receiving antenatal ART, cART was received by 45% (135/298) of women diagnosed during the third trimester compared with 44% (749/1699) of those diagnosed in the first or second trimesters (χ^2=0.15 p=0.70). Women on ZDVm were more likely to receive sdNVP in addition if they had been diagnosed in the third trimester than earlier in pregnancy (42% (66/158) vs. 11% (99/942) respectively, χ^2=103.72 p<0.01), reflecting guidelines which recommend the use of sdNVP where ZDV duration is short.

Infants born to women who had been diagnosed late were no more or less likely to lack neonatal prophylaxis than those born to women diagnosed earlier in pregnancy (3% (12/369) and 4% (61/1666) lacked neonatal prophylaxis respectively, χ^2=0.15 p=0.70). The unadjusted MTCT rate was over three-fold higher among women with a late diagnosis than among those diagnosed during the 1st / 2nd trimesters (Table 3.2).

Table 3.3: Factors associated with late maternal HIV diagnosis (3rd trimester or intrapartum) among women undiagnosed at conception, 2008-10

	Proportion (*n*) diagnosed late	Unadjusted PR (95% CI)	Adjusted PR† (95% CI) (*n*=2069)
Year of delivery (*n*=2114)			
2008	18% (143/780)	1.00	1.00
2009	16% (128/779)	0.82 (0.65-1.03) *p*=0.09	0.98 (0.79-1.23) *p*=0.87
2010	20% (111/555)	0.92 (0.73-1.15) *p*=0.44	1.02 (0.82-1.28) *p*=0.83
IDU history (*n*=2104)			
No	17% (326/1904)	1.00	1.00
Yes	28% (56/200)	1.64 (1.28-2.09) *p*<0.01	1.55 (1.22-1.96) *p*<0.01
Marital status (*n*=2112)			
Married	12% (109/925)	1.00	1.00
Cohabiting	21% (182/865)	1.79 (1.43-2.22) *p*<0.01	1.68 (1.34-2.10) *p*<0.01
Single	28% (91/322)	2.40 (1.87-3.07) *p*<0.01	2.24 (1.75-2.87) *p*<0.01
Age at leaving full-time education (*n*=1181)			
≥19 years	13% (84/670)	1.00	Omitted due to missing data
17-18 years	21% (73/345)	1.69 (1.27-2.25) *p*<0.01	
≤16 years	33% (55/166)	2.64 (1.97-3.55) *p*<0.01	
Previous live births at enrolment (*n*=2080)			
0	14% (195/1347)	1.00	1.00
1	22% (119/547)	1.50 (1.22-1.85) *p*<0.01	1.45 (1.19-1.77) *p*<0.01
≥2	35% (65/186)	2.41 (1.91-3.05) *p*<0.01	2.30 (1.82-2.91) *p*<0.01
Centre (*n*=2114)			
Odessa	17% (83/493)	1.00	1.00
Mykolaiv	21% (82/397)	1.23 (0.93-1.62) *p*=0.15	1.09 (0.83-1.43) *p*=0.52
Kiev	16% (57/362	0.94 (0.69-1.27) *p*=0.67	1.01 (0.73-1.38) *p*=0.97
Donetsk	13% (26/198)	0.78 (0.52-1.17) *p*=0.23	0.87 (0.57-1.32) *p*=0.50
Mariupol	24% (44/181)	1.44 (1.04-2.00) *p*=0.03	1.43 (1.05-1.95) *p*=0.02
Krivoy Rog	8% (14/165)	0.50 (0.29-0.86) *p*=0.01	0.51 (0.30-0.87) *p*=0.01
Simferopol	24% (76/318)	1.42 (1.08-1.87) *p*=0.01	1.26 (0.95-1.65) *p*=0.10

†Adjusted ***a priori*** for year of delivery and centre of enrolment

3.2.4 Lack of antenatal ART

Maternal and delivery characteristics by receipt of ART are given in Table 3.4. Overall, a tenth (336/3535) of women received no antenatal ART. Timing of diagnosis was available for only 71% (237/336) (compared with 99.7% (3191/3199) of women receiving antenatal ART), probably due to incomplete antenatal records among a group likely to have lacked antenatal care or been diagnosed late (Table 3.4). Of the 99 women who lacked antenatal ART and were missing timing of diagnosis, nine had an antenatal CD4 count or VL measure reported, confirming that diagnosis had occurred prior to delivery. The remaining 90 are excluded from the analyses in this section. Women diagnosed via rapid testing during labour accounted for 20% (48/246) of those without antenatal ART; these 48 women are also excluded from the subsequent analyses, in order to investigate barriers to the receipt of antenatal ART among the group with diagnosed infection. Of note, diagnosis occurred prior to conception in half of pregnancies with no antenatal ART where timing of diagnosis was available (Table 3.4).

Among 3266 women diagnosed prior to delivery and not on cART at conception, the proportion lacking antenatal ART varied significantly by centre (from 19.7% (62/332) in Mariupol to 9.4% (70/743) in Odessa, 6.5% (38/589) in Mykolaiv, 3.7% (19/509) in Simferopol, 1.6% (4/242) in Krivoy Rog, 0.8% (4/506) in Kiev and 0.3% (1/345) in Donetsk, Fisher's exact test $p<0.01$). The three centres with almost universal (>98%) antenatal ART coverage of women diagnosed prior to delivery (Krivoy Rog, Kiev and Donetsk) were omitted from the analyses of factors associated with lack of antenatal ART (Table 3.5, page 99). Maternal age was not associated with a lack of antenatal ART (PR 1.02 per increasing year, 95% CI 1.00-1.05, $p=0.10$) and neither was severity of HIV disease (WHO stage 1-2 vs. 3-4 $\chi^2=0.23$ $p=0.64$).

Table 3.4: Maternal and delivery characteristics by receipt of antenatal and intrapartum ART, 2008-10

		ART initiated during pregnancy or received at delivery		
	Conceived on cART (*n*=131)	cART initiated during pregnancy (*n*=1475)	Antenatal ZDVm‡ +/- sdNVP (*n*=1593)	No antenatal ART (*n*=336)
Maternal age – median [IQR] (*n*=3523)	30.0 years [27.2, 32.6]	27.3 years [23.7, 31.1]	26.1 years [22.9, 30.0]	27.5 years [24.0, 32.0]
Marital status (*n*=3523)				
Married	81 (62%)	698 (47%)	694 (44%)	90 (27%)
Cohabiting	43 (33%)	561 (38%)	653 (41%)	147 (45%)
Single	7 (5%)	211 (14%)	246 (15%)	92 (28%)
Previous live births at enrolment (*n*=3463)				
No	34 (27%)	781 (54%)	907 (57%)	118 (37%)
Yes	95 (74%)	654 (46%)	676 (43%)	198 (63%)
Timing of HIV diagnosis (*n*=3428)				
Before pregnancy	131 (100%)	588 (40%)	476 (30%)	120 (51%)
1st/2nd trimesters	-	749 (51%)	950 (60%)	33 (14%)
3rd trimester	-	135 (9%)	163 (10%)	36 (15%)
Delivery	-	-	-	48 (20%)
Age at leaving full-time education (*n*=1990)				
≤16 years	14 (19%)	104 (13%)	180 (20%)	41 (23%)
17-18 years	24 (32%)	253 (31%)	255 (28%)	82 (46%)
≥19 years	37 (49%)	463 (56%)	481 (53%)	56 (31%)
History of IDU (*n*=3505)				
No	86 (66%)	1251 (85%)	1431 (90%)	222 (70%)
Yes	44 (34%)	217 (15%)	158 (10%)	95 (30%)
IDU partner (*n*=3440)				
No	89 (68%)	1016 (71%)	1208 (77%)	245 (81%)
Yes	42 (32%)	415 (29%)	366 (23%)	59 (19%)
WHO stage 3-4 (2990)				
1-2	45 (39%)	1096 (82%)	1251 (95%)	187 (86%)
3-4	70 (61%)	240 (18%)	71 (5%)	30 (14%)
CD4 count† (*n*=2263)				
Median [IQR]	370 cells/mm^3 [260, 490]	360 cells/mm^3 [250, 510]	530 cells/mm^3 [410, 660]	410 cells/mm^3 [295, 530]
Proportion ≤350 cells/mm^3	49 (48%)	577 (48%)	130 (14%)	18 (45%)
Delivery / infant characteristics				
Mode of delivery (*n*=3533)				
Vaginal / emergency CS	77 (59%)	1021 (69%)	1130 (71%)	311 (93%)
Elective CS	54 (41%)	454 (31%)	461 (29%)	25 (7%)
Gestation at delivery (*n*=3520)				
≥37 weeks	113 (86%)	1336 (91%)	1482 (94%)	267 (81%)
<37 weeks	18 (14%)	137 (9%)	103 (6%)	64 (19%)
MTCT rate (95% CI) (*n*=2854)	0% (0-3.5%)	1.4% (0.8-2.2%)	3.8% (2.8-5.0%)	20.6% (15.6-26.3%)

† first in pregnancy ‡ including women who received dual therapy (*n*=20) or a non-zidovudine monotherapy regimen (*n*=13)

Factors significantly associated with lack of antenatal ART in univariable analyses were IDU history, being single or cohabiting (vs. married), leaving full-time education at ≤18 years, history of previous live birth, maternal HIV diagnosis before conception or in the third trimester (vs. 1st/2nd trimesters) and preterm delivery (<37 weeks gestation) (Table 3.5). Although women delivering in 2010 were more likely to have lacked antenatal ART compared with those delivering in 2008 (p=0.05), this was explained by an increase over time in the proportion leaving education at ≤18 years (50% (181/363) in 2008 vs. 68% (196/290) in 2009 and 79% (244/308) in 2010, χ^2=64.42 p<0.01) and an increase in the proportion who were parous at enrolment (45% (348/780) in 2008 vs. 51% (380/744) in 2009 and 58% (427/733) in 2010, χ^2=28.14 p<0.01). On adjusting for these factors and centre of enrolment, there was no association between year of delivery and the outcome (Wald's test p=0.71).

In adjusted analyses, IDU history, marital status, previous live births, timing of maternal HIV diagnosis, preterm delivery and centre of enrolment remained significantly associated with a lack of antenatal ART (Table 3.5). Preterm delivery at <37 weeks was associated with a 70% increased risk of lacking antenatal ART. Women diagnosed with HIV during the first or second trimester were the least likely to lack antenatal ART, probably because these women were a selected group in timely contact with antenatal care. Compared with these women, the 3.4-fold increased risk of not receiving antenatal ART among women diagnosed prior to conception is an indication of disengagement from on-going HIV care among a group more likely to have an IDU history. The 120 women diagnosed prior to conception who lacked antenatal ART had a MTCT rate of 22% (95% CI 13-33%, infection status available for 78 infants), highlighting substantial missed opportunities for PMTCT.

Women with at least two previous live births were significantly more likely to lack antenatal ART than those with no previous children in adjusted analyses (and were also more likely to be diagnosed late, see page 95). Among 926 women with educational status available, those leaving full-time education at 17-18 years were significantly more likely to lack antenatal ART than those educated until ≥19 years in the multivariable model (APR 2.49 95% CI 1.07-5.80 p=0.03). There

was no significant change (>10%) in the other multivariable associations after adjusting for educational status.

Table 3.5: Factors associated with lack of antenatal ART among women diagnosed with HIV before delivery and not on cART at conception, 2008-10

	Proportion (*n*) with no antenatal ART	Unadjusted Prevalence Ratio (95% CI)	Adjusted‡ PR (95% CI) (*n*=2164)
Year of delivery (*n*=2173)			
2008	7% (56/760)	1.00	1.00
2009	8% (61/719)	1.15 (0.81-1.63) *p*=0.43	1.15 (0.83-1.60) *p*=0.40
2010	10% (72/694)	1.41 (1.01-1.97) *p*=0.05	1.28 (0.93-1.78) *p*=0.13
IDU history (*n*= 2173)			
No	7% (146/1965)	1.00	1.00
Yes	21% (43/208)	2.78 (2.04-3.79) *p*<0.01	2.13 (1.59-2.87) *p*<0.01
Marital status (*n*=2171)			
Married	6% (53/898)	1.00	1.00
Cohabiting	9% (90/956)	1.60 (1.15-2.21) *p*<0.01	1.62 (1.19-2.22) *p*<0.01
Single	15% (46/317)	2.46 (1.69-3.57) *p*<0.01	1.88 (1.30-2.71) *p*<0.01
Age left full-time education (*n*=927)			
≥19 years	5% (17/327)	1.00	Omitted due to missing data
17-18 years	14% (49/348)	2.71 (1.59-4.61) *p*<0.01	
≤16 years	11% (28/252)	2.14 (1.20-3.82) *p*=0.01	
Previous live births at enrolment (*n*=2173)			
0	6% (63/1081)	1.00	1.00
1	9% (70/751)	1.60 (1.15-2.22) *p*<0.01	1.28 (0.93-1.76) *p*=0.14
≥2	16% (56/341)	2.82 (2.01-3.95) *p*<0.01	1.76 (1.26-2.46) *p*<0.01
Timing of HIV diagnosis (*n*=2173)			
1st/2nd trimester	3% (33/1104)	1.00	1.00
Before conception	14% (120/832)	4.83 (3.32-7.02) *p*<0.01	3.38 (2.28-5.01) *p*<0.01
3rd trimester	15% (36/237)	5.08 (3.24-7.98) *p*<0.01	4.15 (2.66-6.46) *p*<0.01
Preterm delivery <37 weeks (*n*=2166)			
No	8% (159/1993)	1.00	1.00
Yes	17% (30/173)	2.17 (1.52-3.11) *p*<0.01	1.70 (1.19-2.42) *p*<0.01
Centre of enrolment (*n*=2173)			
Odessa	9% (70/743)	1.00	1.00
Mykolaiv	6% (38/589)	0.68 (0.47-1.00) *p*=0.05	0.61 (0.42-0.89) *p*=0.01
Mariupol	19% (62/332)	1.98 (1.44-2.72) *p*<0.01	1.69 (1.24-2.31) *p*<0.01
Simferopol	4% (19/509)	0.40 (0.24-0.65) *p*<0.01	0.33 (0.20-0.53) *p*<0.01

‡Adjusted ***a priori*** for year of delivery and centre of enrolment

In order to examine factors associated with a lack of antenatal ART among women who were aware of their HIV diagnosis at conception, and thus should have been particularly well-placed to receive comprehensive ART for PMTCT, a model limited to this sub-group was fitted and explored separately from a model limited to women diagnosed during pregnancy (Table 3.6). The proportion of women lacking antenatal ART was 14% (120/832) in the group diagnosed prior to conception (which included women completely lacking antenatal care) and 5% (69/1341) in the group who had been diagnosed during pregnancy but before delivery. Of women diagnosed prior to conception, having an IDU history, being single (vs. married) and having ≥2 previous live births (vs. 0) were independent risk factors for lacking antenatal ART (Table 3.6). Educational status did not add significantly to the model fit (Wald's test p=0.15).

Of the group diagnosed antenatally, women who lacked antenatal ART were more likely to have an IDU history, have delivered preterm and been diagnosed in the 3rd trimester (vs. first or second trimesters) than those who received antenatal ART (Table 3.6). IDU history was associated with a three-fold independent increased risk of lacking antenatal ART in this group, but women with an IDU history were also more likely to have other risk factors including late diagnosis (see page 95) and preterm delivery (18% (90/510) of deliveries to women with an IDU history were <37 weeks gestation vs. 8% (227/2980) of those to non-IDUs, χ^2=53.05 p<0.01). Among the 547 women diagnosed antenatally and with educational status available, those leaving full-time education at 17-18 years were at increased risk of lacking antenatal ART compared with those in education until ≥19 years after adjusting for other factors in the multivariable model (APR 2.49 95% CI 1.07-5.80 p=0.03). Among the group with educational status available, the association between preterm delivery and lack of antenatal ART was larger than in the cohort as a whole (APR 3.15 95% CI 1.26-7.89) and increased to APR 3.43 (95% CI 1.46-8.04) on adjusting for education.

Table 3.6: Factors associated with lack of antenatal ART by timing of maternal HIV diagnosis, among women not on cART at conception, 2008-10

	Diagnosed before conception			Diagnosed during pregnancy (before delivery)		
	Proportion (*n*) lacking antenatal ART	Unadjusted PR (95% CI)	Adjusted PR† (95% CI) (*n*=830)	Proportion (*n*) lacking antenatal ART	Unadjusted PR (95% CI)	Adjusted PR† (95% CI) (*n*=1337)
Year of delivery						
2008	14% (39/271)	1.00	1.00	3% (17/489)	1.00	1.00
2009	14% (37/257)	1.00 (0.66-1.52) *p*=1.00	0.97 (0.65-1.46) *p*=0.92	5% (24/462)	1.49 (0.81-2.75) *p*=0.20	1.61 (0.89-2.89) *p*=0.11
2010	14% (44/304)	1.01 (0.67-1.50) *p*=0.98	1.08 (0.73-1.60) *p*=0.71	7% (28/390)	2.07 (1.15-3.72) *p*=0.02	**1.82 (1.01-3.29) *p*=0.05**
IDU history						
No	13% (88/701)	1.00	1.00	5% (58/1264)	1.00	1.00
Yes	24% (32/131)	1.95 (1.36-2.79) *p*<0.01	**1.95 (1.37-2.76) *p*<0.01**	14% (11/77)	3.11 (1.70-5.69) *p*<0.01	**2.50 (1.44-4.34) *p*<0.01**
Marital status						
Married	11% (37/352)	1.00	1.00	3% (16/546)	1.00	1.00
Cohabiting	14% (50/348)	1.37 (0.92-2.04) *p*=0.12	1.42 (0.97-2.09) *p*=0.08	7% (40/608)	2.25 (1.27-3.96) *p*<0.01	**1.91 (1.09-3.33) *p*=0.02**
Single	25% (33/130)	2.41 (1.58-3.69) *p*<0.01	**2.09 (1.37-3.17) *p*<0.01**	7% (13/187)	2.37 (1.16-4.84) *p*=0.02	1.39 (0.67-2.87) *p*=0.38
Age at leaving full-time education						
≥19 years	9% (10/106)	1.00		3% (7/221)	1.00	Omitted due to missing data
17-18 years	22% (32/147)	2.31 (1.19-4.49) *p*=0.01		8% (17/201)	2.67 (1.13-6.31) *p*=0.03	
≤16 years	15% (19/127)	1.59 (0.77-3.26) *p*=0.21		7% (9/125)	2.27 (0.87-5.96) *p*=0.10	
Previous live births at enrolment						
0	11% (27/254)	1.00	1.00	4% (36/827)	1.00	
1	13% (48/383)	1.18 (0.76-1.84) *p*=0.47	1.33 (0.87-2.03) *p*=0.19	6% (22/368)	1.37 (0.82-2.30) *p*=0.23	
≥2	23% (45/195)	2.17 (1.40-3.37) *p*<0.01	**2.20 (1.44-3.37) *p*<0.01**	8% (11/146)	1.73 (0.90-3.32) *p*=0.10	
Preterm delivery <37 weeks						
No	14% (104/747)	1.00		4% (55/1246)	1.00	1.00
Yes	20% (16/82)	1.40 (0.87-2.25) *p*=0.16		15% (14/91)	3.49 (2.02-6.02) *p*<0.01	**2.79 (1.57-4.96) *p*<0.01**
Timing of diagnosis						
1st / 2nd trimesters	-	-		3% (33/1104)	1.00	1.00
3rd trimester	-	-		15% (36/237)	5.08 (3.24-7.98) *p*<0.01	**4.66 (2.99-7.24) *p*<0.01**
Centre						
Odessa	15% (39/254)	1.00	1.00	6% (31/439)	1.00	1.00
Mykolaiv	12% (25/208)	0.78 (0.49-1.25) *p*=0.31	0.74 (0.46-1.18) *p*=0.20	3% (13/341)	0.54 (0.29-1.01) *p*=0.06	**0.52 (0.27-0.97) *p*=0.04**
Mariupol	26% (43/164)	1.71 (1.16-2.51) *p*<0.01	**1.72 (1.18-2.52) *p*<0.01**	11% (19/168)	0.78 (1.04-3.07) *p*=0.04	**1.92 (1.12-3.29) *p*=0.02**
Simferopol	6% (13/206)	0.41 (0.23-0.75) *p*<0.01	**0.43 (0.24-0.77) *p*<0.01**	2% (6/303)	0.31 (0.13-0.74) *p*<0.01	**0.23 (0.10-0.55) *p*<0.01**

Factors independently associated with outcome (*p*<0.05) in adjusted analyses are in bold. †Adjusted *a priori* for year of delivery and centre of enrolment

3.2.5 Scale-up of cART, 2008-10

Where ART was initiated during pregnancy, cART was received in 48% (1475/3068) of cases overall, increasing from 22% (240/1082) of deliveries in 2008 to 58% (660/1129) in 2009 and 67% (575/857) in 2010 (trend p=0.03). The 52% (1593/3069) of women who initiated ZDVm had a significantly higher CD4 count at the first measure in pregnancy than those who initiated cART (Table 3.4, two-sided t test p<0.01). Among women with treatment indications (WHO stage 3-4 and/or CD4 ≤350 cells/mm^3) who initiated ART during pregnancy, cART was received by 56% (137/244) delivering in 2008, 83% (276/332) delivering in 2009 and 91% (270/298) delivering in 2010 (trend p<0.01), reflecting the prioritisation of this group for limited cART supplies. Where ART appeared to be initiated for PMTCT only (i.e. among women with WHO stage and/or CD4 count available, but without WHO stage 3-4 and/or CD4 ≤350 cells/mm^3), 12% (84/709) of women received cART in 2008 increasing to 49% (360/731) in 2009 and 55% (289/526) in 2010 (trend p<0.01).

There were significant differences by HIV/AIDS centre in the proportion of women initiating ZDVm (rather than cART) during pregnancy (seven centres, Table 3.7b on page 105, χ^2=232.70 p<0.01). Overall, almost two-thirds of women without treatment indications initiated ZDVm rather than cART, compared with 22% of those with indications for treatment (Table 3.7a, page 104). In addition to year of delivery, centre and maternal treatment indication, other factors associated with initiation of ZDVm in univariable analyses included IDU history, IDU partner, marital status, previous live births, timing of HIV diagnosis and educational status (Tables 3.7a and 3.7b). Although both IDU history and IDU partner were associated with a smaller likelihood of receiving ZDVm (i.e. greater likelihood of receiving cART) in univariable analyses, this was accounted for by more severe HIV disease in these groups (see page 80).

The probability of receiving ZDVm more than halved between 2008 and 2010, after adjusting for other factors (Table 3.7a). Having ≥2 previous live births (vs. none) and being cohabiting (vs. married) were both associated with an increased likelihood of receiving ZDVm. Women diagnosed with HIV during pregnancy were also more likely to receive ZDVm, partly because they were less likely to have indications for treatment (27% (500/1847) vs. 38% (374/987) of those diagnosed

before conception and initiating ART during pregnancy, χ^2=35.32 p<0.01). However, this association remained after adjusting for treatment indication and other factors (Table 3.7a). Among women without treatment indications, median CD4 counts were 520 cells/mm^3 and 550 cells/mm^3 for women diagnosed before conception and in first or second trimesters respectively (Wilcoxon-Mann-Whitney test p=0.28). Having an IDU partner did not contribute significantly to the multivariable model's goodness-of-fit (p=0.15) and was excluded.

In a similar multivariable model adjusting also for educational status (n=1555), women with less education were significantly more likely to receive ZDVm (APR 1.18, 95% CI 1.05-1.33, p<0.01 and APR 1.43, 95% CI 1.25-1.64, p<0.01 for those leaving full-time education at 17-18 years and ≤16 years respectively vs. those leaving education at ≥19 years). This was despite lower educational status being associated with lower CD4 counts among women without treatment indications (median CD4 count 510 cells/mm^3, 530 cells/mm^{3}and 560 cells/mm^3 for women leaving education at ≤16, 17-18 and ≥19 years respectively, Kruskal-Wallis test p=0.05). This could be because clinicians perceived these women to be more likely to experience adherence problems. Women with ≥2 previous live births were more likely to have left education <19 years (72% (170/236) vs. 52% (322/617) of women with one and 41% (445/1097) of women with no previous live births, χ^2=83.24 p<0.01), as were cohabiting women (56% (392/705) vs. 39% (361/917) of married women, χ^2=42.24 p<0.01). After adjusting for educational status, the associations between ZDVm initiation and ≥2 previous live births / cohabiting status were both reduced (APR 1.14, 95% CI 1.00-1.30, p=0.06, and APR 1.06, 95% CI 0.97-1.17, p=0.20 respectively).

Table 3.7a: Factors associated with initiation of ZDVm (rather than cART) during pregnancy, 2008-10 (continued in Table 3.7b)

	Proportion (*n*) receiving ZDVm	Unadjusted PR (95% CI)	Unadjusted PR (95% CI) – limited to 2770 women†	Adjusted PR (95% CI) (*n*=2770) ‡
Year of delivery (*n*=3068)				
2008	78% (842/1082)	2.36 (2.14-2.62) *p*<0.01	2.32 (2.09-2.57) *p*<0.01	2.32 (2.11-2.55) *p*<0.01
2009	42% (469/1129)	1.26 (1.12-1.42) *p*<0.01	1.21 (1.07-1.37) *p*<0.01	1.25 (1.12-1.39) *p*<0.01
2010	33% (282/857)	1.00	1.00	1.00
IDU history (*n*=3057)				
Yes	42% (158/375)	1.00	1.00	1.00
No	53% (1431/2682)	1.27 (1.12-1.43) *p*<0.01	1.23 (1.08-1.40) *p*<0.01	1.10 (0.99-1.23) *p*=0.09
IDU partner (*n*=3005)				
Yes	47% (366/781)	1.00		
No	54% (1208/2224)	1.16 (1.07-1.26) *p*<0.01		
Marital status (*n*=3063)				
Married	50% (694/1392)	1.00	1.00	1.00
Cohabiting	54% (653/1214)	1.08 (1.00-1.16) *p*=0.05	1.09 (1.00-1.18) *p*=0.04	1.09 (1.02-1.16) *p*=0.02
Single	54% (246/457)	1.08 (0.98-1.19) *p*=0.13	1.08 (0.97-1.21) *p*=0.16	1.01 (0.91-1.11) *p*=0.90
Maternal treatment indication (*n*=3182)				
Yes	22% (191/874)	1.00	1.00	1.00
No	63% (1233/1966)	2.87 (2.52-3.27) *p*<0.01	2.87 (2.52-3.26) *p*<0.01	2.53 (2.22-2.87) *p*<0.01
Previous live births at enrolment (*n*=3018)				
0	54% (907/1688)	1.00	1.00	1.00
1	49% (475/976)	0.91 (0.84-0.98) *p*=0.01	0.91 (0.84-0.99) *p*=0.03	1.01 (0.93-1.08) *p*=0.89
≥2	57% (201/354)	1.06 (0.96-1.17) *p*=0.29	1.07 (0.96-1.20) *p*=0.20	1.22 (1.11-1.35) *p*<0.01
Timing of HIV diagnosis (*n*=3061)				
Before conception	45% (476/1064)	1.00	1.00	1.00
1st / 2nd trimester	56% (950/1699)	1.25 (1.15-1.35) *p*<0.01	1.28 (1.18-1.40) *p*<0.01	1.11 (1.03-1.20) *p*<0.01
3rd trimester	55% (163/298)	1.22 (1.08-1.38) *p*<0.01	1.22 (1.07-1.39) *p*<0.01	1.02 (0.91-1.15) *p*=0.70

†those with complete data available on all explanatory variables included in the adjusted model ‡Adjusted ***a priori*** for year of delivery and centre

Table 3.7b: Factors associated with initiation of ZDVm (rather than cART) during pregnancy, 2008-10 (continued from Table 3.7a)

	Proportion (*n*) receiving ZDVm	Unadjusted PR (95% CI)	Unadjusted PR (95% CI) – limited to 2770 women†	Adjusted PR (95% CI) (*n*=2770) ‡
Age at leaving full-time education (*n*=1736)				
≥19 years	51% (481/944)	1.00	Omitted due to missing data	Omitted due to missing data
17-18 years	50% (255/508)	0.99 (0.89-1.10) *p*=0.78		
≤16 years	63% (180/284)	1.24 (1.12-1.39) *p*<0.01		
Centre of enrolment (*n*=3068)				
Odessa	64% (434/673)	1.00	1.00	1.00
Mykolaiv	72% (397/551)	1.12 (1.04-1.21) *p*<0.01	1.11 (1.02-1.22) *p*=0.02	1.31 (1.21-1.42) *p*<0.01
Kiev	40% (201/502)	0.62 (0.55-0.70) *p*<0.01	0.65 (0.58-0.74) *p*<0.01	0.74 (0.66-0.82) *p*<0.01
Donetsk	51% (177/344)	0.80 (0.71-0.90) *p*<0.01	0.83 (0.74-0.94) *p*<0.01	0.81 (0.73-0.89) *p*<0.01
Mariupol	39% (104/270)	0.60 (0.51-0.70) *p*<0.01	0.61 (0.52-0.72) *p*<0.01	0.69 (0.60-0.79) *p*<0.01
Krivoy Rog	39% (92/238)	0.60 (0.51-0.71) *p*<0.01	0.62 (0.52-0.74) *p*<0.01	0.89 (0.76-1.05) *p*=0.17
Simferopol	38% (188/490)	0.59 (0.52-0.67) *p*<0.01	0.61 (0.53-0.69) *p*<0.01	0.74 (0.66-0.83) *p*<0.01

†those with complete data available on all explanatory variables included in the adjusted model ‡Adjusted *a priori* for year of delivery and centre

3.2.6 Mother-to-child-transmission in 2008-10

Figure 3.5 shows unadjusted MTCT rates in 2008-10 by antenatal and intrapartum ART receipt and by timing of the woman's HIV diagnosis. Among 2854 infants with infection status reported (81%) the MTCT rate was 4.1% (95% CI 3.4-4.9); 1.3% (95%CI 0.7-2.0) among women receiving antenatal cART, 3.8% (95% CI 2.8-5.0) among those receiving ZDVm, 18.6% (95% CI 12.3-26.4) following sdNVP only and 22.9% (95% CI 15.4-32.0) among untreated women. Overall, 42% (49/116) of transmissions occurred to the 8% (*n*=238) without antenatal ART exposure. Of 1045 women without treatment indications who received ZDVm, MTCT occurred in 3.7% (95% CI 2.7-5.1).

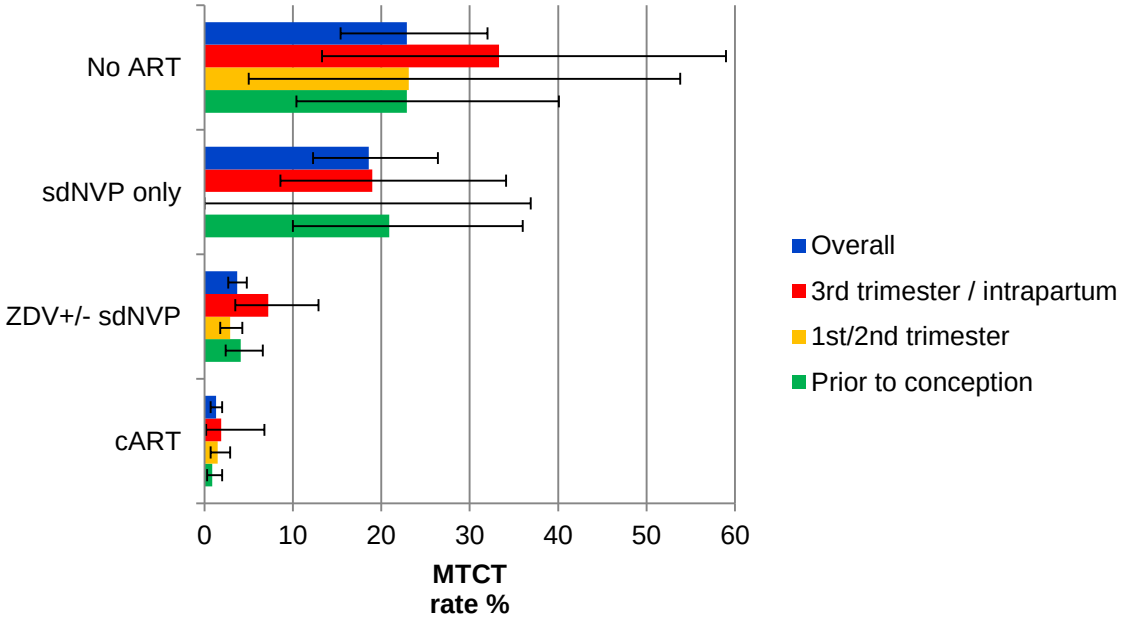


Figure 3.5: Unadjusted MTCT rates by antenatal / intrapartum ART receipt and timing of HIV diagnosis

Capped line represents 95% CI. Of those diagnosed in the first and second trimesters, no transmissions occurred among the eight women who received sdNVP only (one-sided confidence interval).

Bias and confounding in reporting of infant infection status

Despite the roll-out of cART for PMTCT from 2008 to 2010, there was no decline in MTCT rate over these years (trend *p*=0.41, see also Figure 3.3, page 89), a time period when all seven centres contributed data. At the time of the analysis, infection status was available for 65% (666/1027) of

infants born in 2010 vs. 84% (1086/1291) and 91% (1102/1217) born in 2009 and 2008, due to reporting delays and incomplete coverage with early infant PCR testing. Bias in reporting of infant's HIV status according to factors influencing vertical transmission risk was investigated among infants born in 2010. Women who had lacked antenatal ART were slightly more likely to have an infant with indeterminate status (43% (51/118) vs. 34% (310/909) of women who had received antenatal ART, χ^2=3.80 p=0.05), as were women with an IDU history (44% (61/139) vs. 34% (296/878) of non-IDUs, χ^2=5.45 p=0.02). There was no difference in reporting of infant's infection status by mother's receipt of cART vs. ZDVm (35% (204/575) and 29% (83/282) of infants had an indeterminate HIV status respectively, χ^2=3.10 p=0.08), or by preterm birth (p=0.53) or mode of delivery (p=0.67). MTCT rates were slightly higher in all maternal ART groups in 2010 compared with 2009 (cART: 2.8% (95% CI 1.4-4.9) vs. 0.3% (95% CI 0.2-1.6); ZDVm+/-sdNVP: 5.1% (95% CI 2.5-9.2) vs. 1.3% (95% CI 0.4-3.1); sdNVP only or no ART: 28.4% (95% CI 18.0-40.7) vs. 17.1% (95% CI 9.7-27.0)). When the 2010 transmission rates by maternal ART group were applied to the 361 infants born that year and with an indeterminate HIV status, the overall transmission rate increased by 0.2% to 6.4% (95% CI 5.0-8.1), indicating that the MTCT rate observed here for 2010 may be an underestimate.

The proportion of women receiving no ART increased substantially from 4% (51/1217) in 2008 to 7% (74/1027) in 2010 (trend p<0.01). This increase occurred across three centres (Odessa, Donetsk and Mariupol) and was explored in more detail in section 3.2.4 (page 96). Among those receiving cART, there was no difference in the proportion receiving less than four weeks of treatment by centre (χ^2=11.14 p=0.08) and no increase in this proportion over time from 2008 to 2010 (trend p=0.36).

To investigate the possibility of MTCT rate being biased by infant death, where improvements in neonatal and infant care over time resulted in improved case ascertainment among infants at highest risk of HIV infection, deaths occurring among infants at <6 months of age from 2003-10 were explored. There was a significant decline in infant deaths at <6 months of age over this time period (from 2.3% (7/300) in 2003 to 1.5% (20/1335) in 2007 and 0.3% (3/1027) in 2010, trend p<0.01). However, when infants who died with an indeterminate infection status were assigned to

infected and uninfected groups according to probable cause of death (Appendix E, page 343), the MTCT rate in each year changed by ≤0.2% and there remained no significant decline from 2008 to 2010.

Factors associated with MTCT

Table 3.8 (page 110) shows factors associated with MTCT in 2008-10. Antenatal cART was associated with a 70% reduction in MTCT risk compared with ZDVm +/- sdNVP, in adjusted analysis. Both sdNVP and no ART were associated with a four-fold increased risk of MTCT compared with ZDVm. Preterm delivery was associated with a two-fold increased risk of transmission overall (Table 3.8). Although there was no significant interaction between preterm delivery and ART receipt (LRT p=0.33), the overall association was driven by an increased risk of transmission to preterm infants born to women on ZDVm +/- sdNVP (APR 3.45, 95%CI 1.54-7.73, p<0.01). There was no statistically significant association between preterm delivery and MTCT among women who received antenatal cART (APR 2.32, 95% CI 0.50-10.65, p=0.28). Maternal CD4 count and WHO stage were not included in the final model (LRT p=0.20 and p=0.42 respectively). Breastfeeding, reported by only 0.5% (6/1225) of women in 2008-10, was excluded; three of the breastfed infants had an infection status available and were uninfected at the time of the test. Neonatal prophylaxis was included in the final model (LRT p=0.06) and was weakly associated with an increased likelihood of infant HIV infection (Table 3.8, p=0.08), probably due to confounding by indication; lack of neonatal prophylaxis was associated with longer duration of antenatal ART (14 weeks vs. 10.7 weeks for those who did receive neonatal prophylaxis, Wilcoxon-Mann-Whitney test p=0.07).

In the adjusted model, the vertical transmission rate was significantly lower in 2009 than in 2008, and increased in 2010 (Table 3.8). Over these years, there was an increase across several centres in the proportion of enrolments among women who had left education at ≤16 years, and this trend was particularly marked in Mykolaiv (where 5% (9/171) had left education at ≤16 years in 2008 increasing to 33% (53/159) in 2009 and 51% (96/187) in 2010, trend p<0.01 vs. p=0.06 for other centres). Given the association between fewer years of education and missed opportunities for PMTCT, this shift may have increased the overall MTCT risk at a population level through factors not captured here (e.g. poorer adherence to ART). When Mykolaiv was omitted from the

multivariable model, there was no evidence of a difference in MTCT risk during 2010 compared with 2008 (AOR 1.50 95% CI 0.82-2.72 p=0.19).

There was no association between transmission risk and mode of delivery in adjusted analyses (Table 3.8). However, elective CS deliveries were disproportionately conducted among lower risk pregnancies. For example, of women delivering at term (≥37 weeks gestation) and diagnosed before delivery, 34% (486/1449) of those receiving cART delivered by elective CS compared with 32% (396/1255) of those receiving ZDVm, 22% (46/208) who received ZDVm plus sdNVP, 11% (8/74) who received sdNVP only and 9% (8/92) who received no ART (χ^2=47.85 p=0.01). Statistical power may have been insufficient to detect any additional benefit of elective CS in the group that actually delivered in this way (i.e. the group most likely to have suppressed viral loads).

Median duration of antenatal ZDVm was shorter than for cART (12.6 weeks, IQR 9.9-14.9 and 13.9 weeks, IQR 10.1-16.6) respectively). Adjusting for ART duration (2-7, 8-11 or ≥12 weeks) in addition to other factors in Table 3.8, cART was associated with a 59% reduction in MTCT risk compared with ZDVm among 2504 women with ≥14 days of ART by delivery (AOR 0.41, 95%CI 0.21-0.79, p<0.01).

Among the subgroup of 1409 pregnancies in women receiving antenatal ART, delivering vaginally or by elective CS and with viral load available, preterm delivery was not significantly associated with MTCT risk (AOR 1.63 95%CI 0.51-5.19 p=0.41, adjusting for ART type, IDU history, mode and year of delivery, viral load, neonatal prophylaxis and centre). Each $\log_{10}$ unit increase in antenatal viral load (measured a median of 41 days before delivery) was associated with a 77% (AOR 1.77, 95% CI 1.25-2.51) increased transmission risk. After adjusting for viral load in addition to the other factors in Table 3.8, the reduction in MTCT risk associated with cART remained similar (AOR 0.36 95% CI 0.16-0.81 p=0.01).

Table 3.8: Factors associated with MTCT, 2008-10

	MTCT rate (*n*)	Unadjusted OR (95% CI)	Adjusted OR† (95% CI) (*n*=2793)
Antenatal / intrapartum			
ART			
cART	1.3% (16/1274)	0.32 (0.18-0.57) *p*<0.01	0.31 (0.17-0.58) *p*<0.01
ZDVm	3.8% (51/1342)	1	1
sdNVP only	18.6% (24/129)	5.79 (3.42-9.77) *p*<0.01	4.52 (2.45-8.29) *p*<0.01
None	22.9% (25/109)	7.53 (4.45-12.76) *p*<0.01	5.06 (2.69-9.52) *p*<0.01
Mode of delivery			
Vaginal	4.9% (94/1916)	1	1
Elective CS	2.5% (20/800)	0.50 (0.30-0.81) *p*<0.01	0.73 (0.42-1.26) *p*=0.25
Emergency CS	1.5% (2/137)	0.29 (0.07-1.18) *p*=0.08	0.26 (0.06-1.14) *p*=0.08
Gestation at delivery			
≥37 weeks	3.5% (92/2597)	1	1
<37 weeks	9.3% (23/247)	2.80 (1.74-4.50) *p*<0.01	2.23 (1.28-3.90) *p*<0.01
IDU history			
No	3.8% (92/2416)	1	1
Yes	5.3% (22/414)	1.42 (0.88-2.28) *p*=0.15	1.12 (0.64-1.97) *p*=0.70
Year of delivery			
2008	4.7% (52/1102)	1	1
2009	2.1% (23/1086)	0.44 (0.27-0.72) *p*<0.01	0.51 (0.28-0.90) *p*=0.02
2010	6.2% (41/666)	1.32 (0.87-2.02) *p*=0.19	1.76 (1.05-2.93) *p*=0.03
Neonatal prophylaxis			
No	5.6% (7/125)	1	1
Yes	4.0% (109/2701)	0.71 (0.32-1.56) *p*=0.39	2.50 (0.90-6.92) *p*=0.08
Viral load			
Per $\log_{10}$ increase		1.65 (1.24-2.20) *p*<0.01	Omitted due to lack of data – see text

†AORs are estimated including a random effect to account for unobserved variables specific to each centre of delivery

3.2.7 Key points

- In 2008-10, almost a fifth of antenatal diagnoses occurred in the third trimester or intrapartum, precluding optimal PMTCT interventions. Women with an IDU history, those who were unmarried, parous or with less education were at increased risk of a late diagnosis.
- A tenth of women delivering from 2008 to 2010 lacked antenatal ART (received no ART or sdNVP only), a fifth of whom were diagnosed intrapartum. Three centres (Krivoy Rog, Kiev and Donetsk) had >98% coverage with antenatal ART of women diagnosed before delivery. At the remaining four centres, risk factors for lacking antenatal ART were having an IDU history, being unmarried, multiparous, delivering preterm and being diagnosed as HIV-positive before conception or in the third trimester (vs. in the first or second trimesters).
- At Krivoy Rog, Kiev and Donetsk, <2% of women diagnosed prior to delivery lacked antenatal ART. At Mariupol, Odessa, Mykolaiv and Simferopol, women diagnosed during pregnancy were more likely to lack antenatal ART if diagnosed late or delivering preterm, or if they had a lower level of education. Among women diagnosed prior to conception at these four centres, 6% lacked antenatal ART (indicating disengagement from HIV care), and multiparous women were at increased risk. Unmarried women and those with an IDU history were at increased risk of lacking antenatal ART regardless of timing of HIV diagnosis.
- Of women initiating ART during pregnancy, the proportion who received cART (rather than ZDVm) increased to 67% in 2010, with priority given to those with most severe HIV disease. Women who were unmarried, multiparous and with less education were more likely to receive ZDVm (and less likely to receive cART) when initiating ART during pregnancy.
- Unmarried women, those with other children and those with less education were therefore at risk of multiple missed opportunities for PMTCT, as were IDUs.
- In 2008-10, the MTCT rate was 4.1% (95% CI 3.4-4.9) overall and 1.3% (95% CI 0.7-2.0) among those who received antenatal cART. cART was associated with a 69% reduction in MTCT risk compared with ZDVm +/- sdNVP, the standard of care for PMTCT prior to 2007 in Ukraine, demonstrating its effectiveness for PMTCT in this operational, lower-middle income setting.

3.3 PMTCT in Western and Europe: Insufficient antenatal ART

3.3.1 Methods

This analysis was limited to births from January 2000 to July 2009 at Western European sites of the ECS in nine countries (Belgium, Denmark, Germany, Italy, the Netherlands, Poland, Spain, Sweden and the UK).

The main outcome was receipt of 'insufficient antenatal ART', defined as receipt of no ART in pregnancy or short duration of ART, initiated 1-13 days before delivery. This short ART duration was chosen in order to focus on those with the most elevated risk of vertical transmission (Townsend *et al.* 2008a). Figure 3.6 summarises the availability of data on receipt and duration of antenatal ART. Pregnancies with missing information on ART receipt were excluded (n=42). Multiple births were excluded because of their association with preterm delivery, a factor potentially limiting duration of antenatal ART. Pregnancies in which ART was received but treatment duration was missing (n=246) were included in the "≥14 days of ART" group, as in the vast majority treatment was likely to have been for longer than 14 days: 84% (191/228) were diagnosed pre-conception, 33% (48/144) had undetectable viral load at delivery, and 66% (103/155) had a CD4 count >350 cells/mm^3 at last antenatal measure. Where HIV diagnosis was recorded one day either side of delivery (n=6) it was categorised as intrapartum. Where HIV diagnosis occurred more than one day post-partum (n=3) the pregnancy was excluded. Logistic regression models were fitted to explore factors associated with insufficient antenatal ART in the cohort as a whole, and in stratified analyses of women diagnosed with HIV pre- and post-conception, as different factors might be important in these two groups (Mayaux *et al.* 2003).

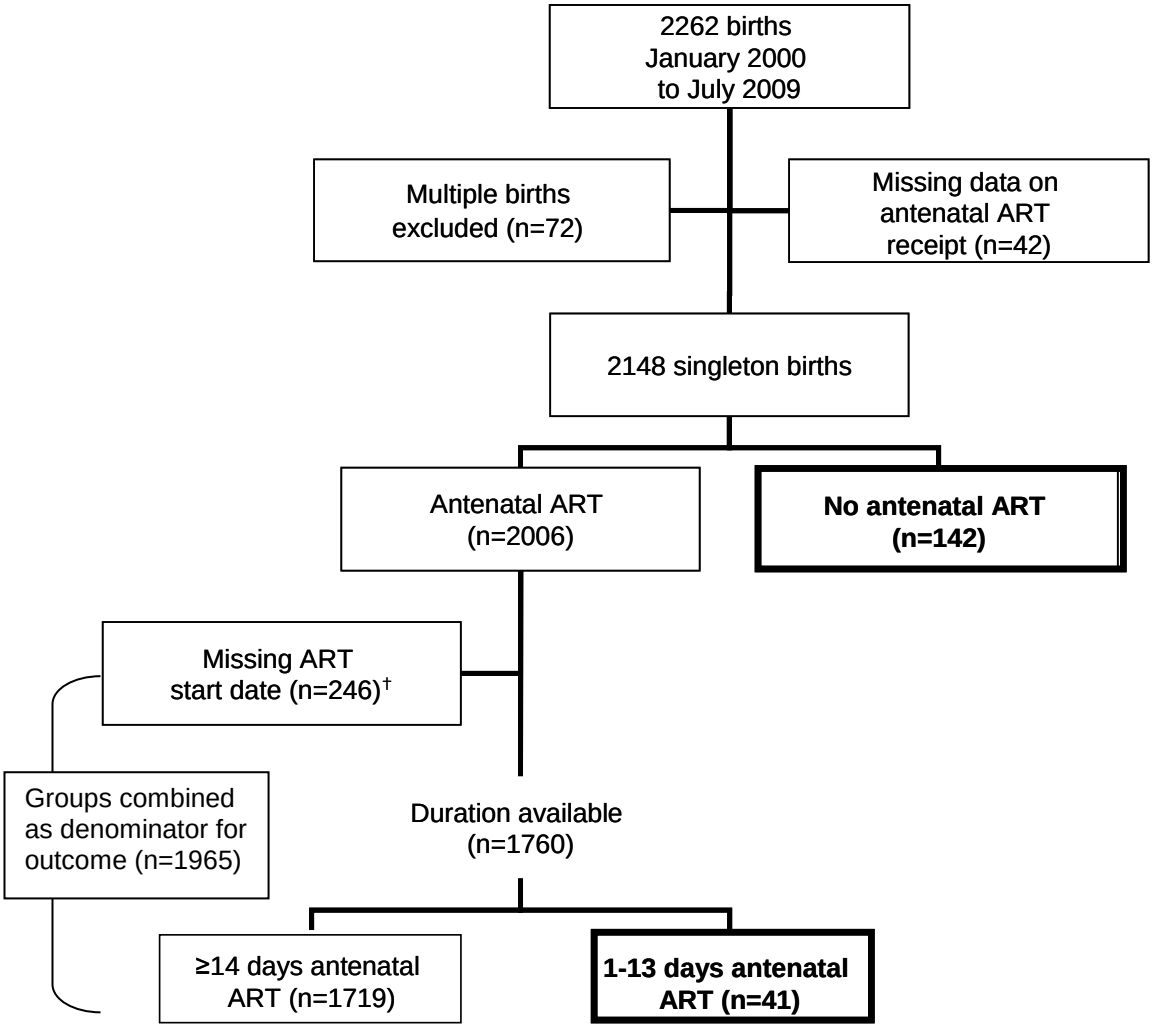


Figure 3.6: Availability of data on receipt of insufficient (none or <14 days) antenatal ART

†Women with missing ART start date are included in the ≥14 days antenatal ART group in all analyses

Timing of HIV diagnosis during pregnancy indicates access to and uptake of antenatal care in Europe, where HIV testing is offered to all pregnant women as policy in most countries (Aebi-Popp *et al.* 2013). Because HIV diagnosis occurring late in pregnancy or intrapartum is a barrier to receipt of ART, factors associated with "late" HIV diagnosis (occurring during the third trimester or intrapartum) were explored among women who were not yet diagnosed with HIV at conception.

Maternal factors were investigated (age at delivery, marital status, sub-Saharan African origin, IDU history, previous live births, severe symptomatic HIV disease) as were delivery details (year, country of delivery and gestational age). Delivery before 34 weeks gestation (precluding 14 days of antenatal ART if started at week 32, the latest suggested by British guidelines in this time period (Hawkins *et al.* 2005; de Ruiter *et al.* 2008)) was investigated as a factor associated with receiving either no ART

or 1-13 days ART before delivery. Although history of IDU was considered rather than current IDU in multivariable analyses, current IDU was described and defined as active IDU reported during pregnancy or neonatal abstinence syndrome in the infant. Mode of delivery and antenatal CD4 count were not included as explanatory variables in the logistic regression analyses, being affected by and/or a consequence of insufficient antenatal ART or HIV diagnosis late in pregnancy (including intrapartum), rather than predisposing risk factors. During model selection, each covariate's contribution to the model's goodness-of-fit was assessed with the LRT (significance level of ≤ 0.1).

Random effects models were fitted in all analyses to account for underlying, unobserved variation in the outcome by country of delivery (Rabe-Hesketh *et al.* 2002). All models were adjusted ***a priori*** for year of delivery to account for changes in clinical practice over time (European Collaborative Study *et al.* 2010).

3.3.2 Cohort characteristics

A total of 2148 deliveries between January 2000 and July 2009 were reported in 1940 women; 173 women had two pregnancies, 16 had three and one woman had four. Of the 2148 pregnancies, 142 (7%) were in women who received no ART, and a further 41 (2%) were in women who received less than two weeks of ART before delivery (Figure 3.6, page 113). Baseline maternal and pregnancy characteristics by receipt of antenatal ART are given in Table 3.9. Overall, in two fifths of mother-child pairs the mother was born in sub-Saharan Africa (ranging from 0% in Poland to 87.4% in Belgium (χ^2=618.4, p<0.01)), three-quarters were married or cohabiting and around a fifth had an IDU history (ranging from 1.3% in Belgium to 75.3% in Poland (χ^2=481.8, p<0.01)). Median age at delivery was 31.5 years (IQR 27.2, 35.4 years). In at least 27% (106/390) of the mother-child pairs where the mother had an IDU history there was evidence of current IDU. In just over a tenth of pregnancies the mother had severe symptomatic HIV disease, and median CD4 count (first recorded in pregnancy) was 410 cells/mm^3 (IQR 280, 580 cells/mm^3).

In almost three-quarters of pregnancies the woman was aware of her HIV infection before conception. Among women with unknown HIV status at conception, 79% (471/596) were diagnosed by the end of the second trimester, 17% (101/596) in the third trimester and 4% (24/596) at delivery. The proportion with late HIV diagnosis (during the third trimester or at delivery) decreased over time from 24% (94/393) of those with unknown status at conception in 2000-03, to 15% (31/203) in 2004-09 (χ2=6.04, p=0.014).

Table 3.9: Maternal and delivery characteristics by receipt of antenatal ART

	≥14 days of antenatal ART or missing duration (*n*=1965)	1-13 days of antenatal ART (*n*=41)	No antenatal ART (*n*=142)
Maternal characteristics			
Marital status (*n*=1930)			
Married or cohabiting	1334 (75%)	21 (62%)	79 (69%)
Single	447 (25%)	13 (38%)	36 (31%)
Ethnic group (*n*=2101)			
White	914 (48%)	18 (45%)	87 (63%)
Black	919 (48%)	22 (55%)	44 (32%)
Other	90 (5%)	0	7 (5%)
Sub-Saharan African origin (*n*=2089)			
No	1106 (58%)	18 (45%)	101 (73%)
Yes	804 (42%)	22 (55%)	38 (27%)
Previous live births at enrolment (*n*=2033)			
0	798 (43%)	16 (40%)	54 (41%)
1	613 (33%)	17 (43%)	40 (30%)
2 or more	450 (24%)	7 (18%)	38 (29%)
History of IDU (*n*=2091)			
No	1581 (82%)	36 (88%)	84 (64%)
Yes	337 (18%)	5 (12%)	48 (36%)
Current IDU (*n*=2091)			
No	1838 (96%)	39 (95%)	108 (82%)
Yes	80 (4%)	2 (5%)	24 (18%)
Timing of HIV diagnosis (*n*=2069)			
Pre-conception	1388 (73%)	16 (41%)	69 (52%)
1st / 2nd trimester	449 (24%)	4 (10%)	18 (14%)
3rd trimester / delivery	61 (3%)	19 (49%)	45 (34%)
HIV disease symptoms (*n*=1535)			
Asymptomatic / non-severe HIV symptoms	1229 (86%)	29 (88%)	72 (95%)
Severe symptomatic HIV disease	197 (14%)	4 (12%)	4 (5%)
CD4 count - first in pregnancy (cells/mm^3) (*n*=1722)			
<200	214 (13%)	6 (18%)	10 (14%)
200-349	414 (25%)	12 (36%)	21 (30%)
≥350	1024 (62%)	15 (45%)	38 (55%)
Delivery			
Time period (*n*=2148)			
2000-03	1224 (62%)	25 (61%)	106 (75%)
2004-09	741 (38%)	16 (39%)	36 (25%)
Mode (*n*=2044)			
Vaginal or emergency caesarean section	664 (35%)	19 (49%)	64 (48%)
Elective caesarean section	1207 (65%)	20 (51%)	70 (52%)
Gestation (weeks) (*n*=2109)			
<34	99 (5%)	8 (20%)	16 (12%)
34-36	300 (16%)	7 (17%)	23 (17%)
≥37	1531 (79%)	26 (63%)	99 (72%)

3.3.3 Maternal HIV diagnosis late in pregnancy

Although a smaller proportion of African women had been diagnosed with HIV pre-conception compared with non-African women (64% vs. 76%, χ^2=39.71, p<0.01), African women diagnosed during pregnancy were no more likely to be diagnosed late than non-African women (OR 1.32, 95% CI 0.83-2.12, p=0.24 adjusting for year and country of delivery and IDU). This indicates that access to and uptake of antenatal care was not lower among African migrants – a group at potential risk of poorer healthcare utilisation and pregnancy outcomes (Hayes *et al.* 2011). HIV diagnosis occurred pre-conception in 87% (178/205) of pregnancies in women with severe symptomatic HIV disease vs. 69% (894/1296) of those in women with no or non-severe symptoms (χ^2=24.68, p<0.01). Women with severe symptomatic HIV disease were also more likely to have been on ART at conception (56% (107/191) vs. 31% (350/1145) of women with no or non-severe symptoms χ^2=47.12, p<0.01). Among women diagnosed during pregnancy, severe symptomatic HIV disease was present in only 6% (27/1429) and was not associated with probability of a late diagnosis (Fisher's exact test p=1.00).

HIV diagnosis was more likely to have occurred pre-conception where there was a maternal history of IDU (89% (325/365) vs. 68% (1121/1657) of pregnancies with no maternal IDU history, χ^2=67.17, p<0.01). However, where HIV diagnosis occurred after conception, women with an IDU history were more likely to be diagnosed late (35% (14/40) vs. 20% (108/536) of pregnancies with no maternal IDU history, χ^2=4.92, p=0.027). Maternal IDU history was the only factor associated with late HIV diagnosis among women diagnosed during pregnancy.

3.3.4 Receipt of insufficient ART

The proportion of pregnancies where the mother received no antenatal ART decreased from 8% (106/1355) in 2000-03 to 5% (36/793) in 2004-09 (χ^2=8.73, p<0.01), but no decline was seen in the proportion with 1-13 days of antenatal ART (2% (41/2006) of those with treatment) (p=0.78). Significant differences in non-receipt of antenatal ART existed by country of delivery, from 0% (0/202) of pregnancies in the Netherlands to 21% (18/87) in Poland (nine countries, χ^2=72.31,

$p \leq 0.01$), and also in the receipt of 1-13 days of antenatal ART, from 0% (0/35) of pregnancies in Denmark to 6% (10/156) in Germany ($\chi^2=21.04$, $p<0.01$).

In the group with at least 14 days of ART, 5% (99/1930) of deliveries were at less than 34 weeks gestation compared with two and four-fold this rate among the groups who had received no ART and 1-13 days of ART respectively (Table 3.9).

In half (85/171) of pregnancies with insufficient antenatal ART the woman was aware of her HIV status before conception. These women had a median CD4 count at the last antenatal measurement of 310 cells/mm^3 (IQR 240, 440 cells/mm^3) (median 25 days before delivery) compared with 450 cells/mm^3 (IQR 320, 630 cells/mm^3) among women diagnosed pre-conception and treated for at least two weeks ($p<0.01$). In pregnancies with pre-conception HIV diagnosis, those with insufficient antenatal ART had a rate of severe maternal immunosuppression (CD4 count <200 cells/mm^3) twice as high as those with at least two weeks of treatment (20%, 10/49 versus 8%, 93/1149). Overall however, women with insufficient antenatal ART were less likely to have severe symptomatic HIV disease than those treated for longer (7%, 8/109 and 14% respectively, 197/1426, $\chi^2=3.67$, $p=0.06$).

A late maternal HIV diagnosis was received in only 3% (61/1898) of pregnancies with "adequate" treatment compared with 37% (64/171) of pregnancies with no or 1-13 days of ART ($\chi^2=323.47$, $p<0.01$). Given the overlap between late HIV diagnosis and insufficient antenatal ART (and the fact that late diagnosis to some extent precluded a sufficient ART duration) timing of maternal HIV diagnosis was not included in multivariable models.

Factors associated with receiving no antenatal ART and 1-13 days of ART before delivery are shown in Table 3.10. Preterm delivery at <34 weeks gestation was the only factor associated with short duration of ART, whereas IDU history, maternal clinical HIV stage and preterm delivery <34 gestational weeks were associated with not receiving ART in both univariable and multivariable analyses. Of pregnancies with current maternal IDU, 23% (24/106) had no antenatal ART compared with 8% (24/284) of those in ex-IDUs ($\chi^2=13.46$, $p<0.01$).

Table 3.10: Factors associated with receiving no or 1-13 days of antenatal ART – all women

	No ART (vs. any ART) (*n*=2148)			1-13 days of ART (vs. ≥14 days of ART) (*n*=2006)		
	Proportion (*n*) not receiving ART	Unadjusted Odds Ratio (95% CI)	Adjusted Odds Ratio† (95% CI)	Proportion (*n*) receiving 1-13 days ART	Unadjusted Odds Ratio (95% CI)	Adjusted Odds Ratio† (95% CI)
History of IDU						
No	4.9% (84/1701)	1.00	1.00	2.2% (36/1617)	1.00	
Yes	12.3% (48/390)	2.70 (1.86-3.92), p<0.01	2.91 (1.55-5.44) p<0.01	1.5% (5/342)	0.65 (0.25-1.67), p=0.37	
HIV Symptoms						
Asymptomatic / non-severe symptoms	5.4% (72/1330)	1.00	1.00	2.3% (29/1258)	1.00	
Severe symptomatic HIV disease	2.0% (4/205)	0.35 (0.13-0.96) p=0.042	0.23 (0.08-0.67) p<0.01	2.0% (4/201)	0.86 (0.30-2.47) p=0.78	
Preterm delivery <34 weeks gestation						
No	6.1% (122/1986)	1.00	1.00	1.8% (33/1864)	1.00	1.00
Yes	13.0% (16/123)	2.28 (1.31-3.99) p<0.01	2.93 (1.40-6.10) p<0.01	7.5% (8/107)	4.48 (2.02-9.96) p<0.01	4.37 (1.95-9.78) p<0.01
Year of delivery						
2000-03	7.8% (106/1355)	1.00	1.00	2.0% (25/1249)	1.00	1.00
2004-09	4.5% (36/793)	0.56 (0.38-0.83) p<0.01	0.69 (0.39-1.23) p=0.21	2.1% (16/757)	1.06 (0.56-2.00) p=0.86	0.98 (0.51-1.89) p=0.95

†AORs are estimated accounting for country of delivery as a random effect

Although univariable analysis suggested that maternal sub-Saharan African origin was associated with a decreased probability of non-receipt of ART (OR 0.51 for not receiving ART among African vs. non-African women, 95% CI 0.35-0.75, $p<0.01$), this association was accounted for by IDU history, a factor almost exclusive to white women (377 of 383 pregnancies with maternal IDU history were in white women). When limited to pregnancies without a maternal history of IDU, sub-Saharan African origin was not significantly associated with non-receipt of antenatal ART (OR 0.74 for African non-IDUs vs. non-African non-IDUs, 95% CI 0.47-1.14, $p=0.17$).

In the model limited to 1473 mother-child pairs with HIV diagnosis before conception, 6% ($n=85$) received insufficient ART. Being single and having an IDU history were associated with not receiving antenatal ART (Table 3.11), but these factors were not significantly associated with short duration of ART. Delivery at <34 weeks was associated with short duration of ART only (Table 3.11).

Among 596 mother-child pairs with HIV diagnosis after conception, 14% ($n=86$) received insufficient ART. History of IDU was associated with not receiving ART but not with short duration of ART (Table 3.12). Preterm delivery <34 weeks was associated with both no ART and short duration of treatment.

Table 3.11: Factors associated with receiving no or 1-13 days of antenatal ART – women diagnosed pre-conception

	No ART (vs. any ART) (*n*=1473)			1-13 days of ART (vs. ≥14 days of ART) (*n*=1404)		
	Proportion (*n*) not receiving ART	Unadjusted Odds Ratio (95% CI)	Adjusted Odds Ratio† (95% CI)	Proportion (*n*) receiving 1-13 days of ART	Unadjusted Odds Ratio (95% CI)	Adjusted Odds Ratio† (95% CI)
Marital status						
Married / cohabiting	4.0% (41/1019)	1.00	1.00	0.7% (7/978)	1.00	
Single	7.6% (24/314)	1.97 (1.17-3.32) *p*=0.01	1.88 (1.06-3.33) *p*=0.030	1.7% (5/290)	2.43 (0.77-7.73) *p*=0.131	
History of IDU						
No	3.1% (35/1121)	1.00	1.00	1.2% (13/1086)	1.00	
Yes	10.2% (33/325)	3.50 (2.14-5.74) *p*<0.01	2.00 (1.06-3.77) *p*=0.033	1.0% (3/292)	0.86 (0.24-3.03) *p*=0.810	
Preterm delivery <34 weeks gestation						
No	4.4% (60/1377)	1.00		1.0% (13/1317)	1.00	1.00
Yes	9.4% (9/96)	2.27 (1.09-4.73) *p*=0.028		3.5% (3/87)	3.58 (1.00-12.82) *p*=0.05	3.62 (1.01-12.98) *p*=0.048
Year of delivery						
2000-03	5.9% (54/911)	1.00	1.00	1.1% (9/857)	1.00	1.00
2004-09	2.7% (15/562)	0.44 (0.24-0.78) *p*<0.01	0.58 (0.31-1.09) *p*=0.088	1.3% (7/547)	1.22 (0.45-3.30) *p*=0.693	1.25 (0.46-3.40) *p*=0.656

†AORs are estimated accounting for country of delivery as a random effect

Table 3.12: Factors associated with receiving no or 1-13 days of antenatal ART – women diagnosed after conception

	No ART (vs. any ART) (*n*=596)			1-13 days of ART (vs. ≥14 days of ART) (*n*=533)		
	Proportion (*n*) not receiving ART	Unadjusted Odds Ratio (95% CI)	Adjusted Odds Ratio† (95% CI)	Proportion (*n*) receiving 1-13 days of ART	Unadjusted Odds Ratio (95% CI)	Adjusted Odds Ratio† (95% CI)
Marital status						
Married / cohabiting	9.6% (36/374)	1.00		4.1% (14/338)	1.00	
Single	6.1% (10/163)	0.61 (0.30-1.27) *p*=0.188		4.6% (7/153)	1.11 (0.44-2.81) *p*=0.826	
History of IDU						
No	8.4% (45/536)	1.00	1.00	4.5% (22/491)	1.00	
Yes	27.5% (11/40)	4.14 (1.94-8.83) *p*<0.01	2.46 (1.04-5.86) *p*=0.041	3.5% (1/29)	0.76 (0.10-5.86) *p*=0.793	
Preterm delivery <34 weeks gestation						
No	10.0% (57/571)	1.00	1.00	3.5% (18/514)	1.00	1.00
Yes	24.0% (6/25)	2.85 (1.09-7.42) *p*=0.032	5.27 (1.74-16.03) *p*<0.01	26.3% (5/19)	9.84 (3.20-30.29) *p*<0.01	11.15 (3.31-37.55) *p*<0.01
Year of delivery						
2000-03	10.9% (43/393)	1.00	1.00	4.3% (15/350)	1.00	1.00
2004-09	9.9% (20/203)	0.89 (0.51-1.56) *p*=0.682	0.77 (0.39-1.51) *p*=0.441	4.4% (8/183)	1.02 (0.42-2.45) *p*=0.963	0.85 (0.33-2.18) *p*=0.733

†AORs are estimated accounting for country of delivery as a random effect

Use of other PMTCT interventions where antenatal ART was insufficient

Delivery by elective CS was less common in pregnancies with no vs. any antenatal ART (52% (70/134) vs. 64% (1227/1910) respectively, χ^2=7.78 p<0.01), and slightly less common in pregnancies with 1-13 days vs. ≥14 days ART (51% (20/39) vs. 65% (1207/1871), χ^2=2.91 p=0.09). This was due to the association between insufficient ART and preterm birth; although HIV infection is associated with iatrogenic preterm delivery (Lopez *et al.* 2012), most (83%, 1066/1280) elective CS were conducted at ≥37 weeks of gestation. Among deliveries at ≥37 weeks, there was no association between receipt of no ART or 1-13 days ART and delivery by elective CS (χ^2=1.41 p=0.24 and χ^2=0.16 p=0.69 respectively). Among women diagnosed antenatally, there was no difference in proportion of elective CS deliveries by timing of maternal HIV diagnosis (62% (286/458) of women diagnosed in the 1st/2nd trimesters delivered by elective CS vs. 56% (53/95) of those diagnosed in the 3rd trimester, χ^2=1.47 p=0.23).

Very few infants were breastfed overall, but the rate was higher among women who received no ART than among those receiving any ART (3% (4/136) vs. 0.9% (17/1942) respectively) (Fisher's exact test p=0.04). There was no difference in rate of breastfeeding between those receiving 1-13 days or ≥14 days of therapy (0/40 and 0.9% (17/1902) respectively, Fisher's exact test p=1.00). Of the four women who received no antenatal ART and breastfed, one was diagnosed intrapartum (and may therefore have been unaware of her diagnosis at the time of breastfeeding), one was diagnosed antenatally and two were diagnosed prior to conception. Of those with follow-up information available (14/21), all had stopped breastfeeding by their first follow-up appointment at four to six weeks after the birth.

Information on neonatal prophylaxis receipt was available for 63% (1361/2148) of infants, 99.4% (1353/1361) of whom received some prophylaxis, mostly ZDVm (77%, 1040/1353). Infants born to women with insufficient antenatal ART more commonly received combination neonatal prophylaxis (i.e. ≥3 drugs) than infants born to those with ≥14 days antenatal ART (24% (27/114) vs. 3% (42/1233) respectively χ^2 =88.29, p<0.01). However, infants born to women who received no antenatal ART were also more likely to miss out on neonatal prophylaxis (6% (5/90) vs. 0.2% (3/1271) of those born to women with any ART, Fisher's exact test p<0.01). There was no

association between lack of neonatal prophylaxis and short duration of antenatal ART (p=0.79). Median duration of post-exposure ARV prophylaxis was six weeks in both the insufficient antenatal ART and ≥14 days antenatal ART groups (IQR 4-6 weeks).

Vertical transmission

The vertical transmission rate was 1.7% (95% CI 1.1-2.5%) overall and was significantly higher in pregnancies with insufficient ART: 5.8% (95% CI 2.2-12.2%) among pregnancies with no ART and 12.1% (95% CI 3.4-28.2) in those with 1-13 days of ART, compared with 1.1% (95% CI 0.6-1.9) among those with longer duration of ART (p<0.01 for both). Of the 25 HIV-infected infants, 25% (6/25) were born to the 7% of women with no antenatal ART and 16% (4/25) to the 2% of women with 1-13 days of ART.

3.3.5 Key Points

- In 2000-09, 7% of pregnancies were in women who received no antenatal ART despite diagnosis before delivery in the majority of cases. The proportion of pregnancies with no antenatal ART declined over time from 8% of deliveries in 2000-03 to 5% in 2004-09.
- In around 2% of pregnancies with antenatal ART, the duration of treatment received before delivery was less than two weeks, and this proportion stayed constant over time.
- The 9% of pregnancies with no or <14 days of antenatal ART accounted for 40% of vertical transmissions occurring in this cohort, and therefore represent important missed opportunities both for PMTCT and for optimising the health of HIV positive women.
- Late antenatal HIV diagnosis and preterm delivery are important practical barriers to receiving a sufficient duration of antenatal ART, and were associated with not receiving antenatal ART and particularly with short duration of ART in this cohort.
- Women who received no antenatal ART were more likely to be single and to have an IDU history. In over half of all pregnancies with insufficient ART the woman was diagnosed prior to conception, and a significant proportion of these women required treatment for their own health, indicating disengagement from care and possible risk of loss to follow-up postnatally.

3.4 Limitations

Data on reasons for non-receipt of ART are not routinely collected in the ECS, and so the proportion of women without ART who might have refused this and other PMTCT interventions was not known. In the Western Europe analyses, two women each had two sequential pregnancies with no antenatal ART, but it was not possible to conclude whether this was due to refusal of interventions or lack of access to or uptake of care. In Ukraine, a repeat antenatal HIV test is offered routinely in the third trimester to all women testing negative at the first test, and so a diagnosis at this time may have indicated seroconversion during pregnancy rather than a lack of timely antenatal care.

Pregnancies with insufficient ART in the Western Europe ECS were significantly more likely than those with sufficient ART to have missing data on marital status, maternal HIV disease symptoms and IDU ($p<0.02$ for each variable), probably because these pregnancies were more likely to be unmonitored or in women with a late HIV diagnosis, and therefore to have less complete antenatal care records. Similarly in the Ukraine analyses, women lacking antenatal ART were more likely to have missing data on timing of HIV diagnosis, marital status and previous live births variables ($p<0.01$ for all). The associations between these variables of interest and the outcomes may therefore have been under-estimated. IDU history was an important risk factor for multiple missed opportunities for PMTCT in this chapter. No information on biomarkers of current drug use were available in the ECS; under-ascertainment of IDU is explored in section 5.3.2, page 168.

The number of pregnancies with missing data on receipt of antenatal ART was low (Figure 3.4, page 91 and Figure 3.6, page 113) but could have led to an under-ascertainment of pregnancies with no or insufficient antenatal ART, as could the categorisation of pregnancies with missing ART duration to the "sufficient ART" group in the Western Europe analyses. The outcome measure of <14 days of ART used in section 3.3 was designed to capture women most at risk of vertical transmission but did not necessarily capture all at risk women, since there is no precise duration of ART considered sufficient to minimise MTCT risk.

Chapter 4 Virological failure in pregnancy among women conceiving on cART

4.1 Introduction

Non-suppressive treatment has implications for PMTCT and for maternal health due to its association with increased risk of emergence of drug resistance, treatment failure and disease progression (Ledergerber *et al.* 1999; Mocroft *et al.* 2004; Phillips *et al.* 2007). Previous findings from the ECS from 1998 to 2006 suggested that, of those conceiving on cART with a detectable viral load, only a minority achieve viral suppression by the final month of pregnancy (European Collaborative Study 2010). Most women conceiving on cART in this time period were taking a regimen based on unboosted NFV (European Collaborative Study 2010) which has been shown to be inferior to LPV/r in terms of virological response (Walmsley *et al.* 2002; King *et al.* 2004), and is no longer recommended for treatment (Williams *et al.* 2012).

In this chapter, trends over time in virological failure among women conceiving on cART are explored, along with associated factors. An improved understanding of the characteristics of women conceiving on a failing regimen will aid the development of interventions to optimise their pre-conceptual and antenatal management, in turn improving maternal and pregnancy outcomes.

4.2 Methods

This study uses data available by February 2012 on deliveries reported from January 2000 to December 2011 at ECS sites in nine countries in Western Europe (Belgium, Denmark, Germany, Italy, the Netherlands, Poland, Spain, Sweden and the UK). Second and subsequent born infants of multiple births were excluded, as this work focuses on maternal treatment and viral suppression, making pregnancies the denominator of interest.

Definition of group at risk of virological failure

Most patients achieve viral suppression 12-24 weeks after initiating cART (Smith *et al.* 2004; Read *et al.* 2012). Treatment guidelines recommend that patients with an unsuppressed viral load after 24 weeks should be assessed for adherence problems, drug resistance and other potential causes of treatment failure (European AIDS Clinical Society 2011; Asboe *et al.* 2012; Panel on Antiretroviral

Guidelines for Adults and Adolescents 2012). For this work, which explores virological failure in pregnancy among women conceiving on cART, the group at risk of the outcome were those who had received ≥28 days of cART by estimated date of conception and had a viral load measure available ≥24 weeks after ART initiation (within 28 days prior to conception or during pregnancy). The 22 women who had been on cART for <28 days by estimated date of conception were excluded because of the possibility that ART was actually started early in pregnancy (date of conception was approximate).

Ascertainment of cART duration

Where a woman had switched cART regimen before conception, cART duration was taken as the duration of the most recent regimen (full information on treatment history before pregnancy was not routinely collected, but was provided for some women). If a woman switched regimen during pregnancy, before the first viral load measurement and without treatment interruption, she was treated as though she had not switched (i.e. the new regimen contributed towards the total cART duration), because these switches were assumed to be due to concerns around teratogenicity rather than treatment failure. Women conceiving on ART, interrupting treatment during pregnancy and without a viral load measure ≥24 weeks after ART initiation which pre-dated the interruption were excluded. Where more than one viral load measure was available at ≥24 weeks after ART initiation, the first was used for analyses. If a viral load measure was available at ≥24 weeks after the regimen was started, but this was preceded by a viral load at <24 weeks, the later viral load was included only if there had not been a treatment switch between the two viral load measurements (i.e. possibly due to early detection of problems with treatment response). Figure 4.1 (page 130) and Figure 4.3 (page 133) summarise data available on ART receipt and on viral load measures, and show the numbers of women to whom the various exclusions applied. Women diagnosed as HIV-positive prior to conception but missing ART start dates (n=196) were excluded from the main analysis.

Definition of virological failure

The lower detection limits for viral load assays in use across the ECS sites from 2000-11 varied from 20 to 500 copies/ml. Although an optimal virological response to treatment is one in which

the viral load is below the detection limit of the assay, episodes of low level and transient detectable viraemia ("blips") in otherwise successfully treated patients can occur for a range of reasons and do not necessarily indicate an increased risk of virological failure (Havlir *et al.* 2001). Because of this, a viral load cut-off of >200 copies/ml has been suggested as a more useful criterion for distinguishing treatment failure than a cut-off of >50 copies/ml (a common detection limit of modern assays) (Aldous *et al.* 2009; Panel on Antiretroviral Guidelines for Adults and Adolescents 2012).

For the main analyses, viral suppression was defined as a viral load of ≤200 copies/ml and virological failure as a viral load of >200 copies/ml. This allowed for consistency of categorisation for the majority of assays used across the years of the study; the small number of women (n=8) with an undetectable viral load reported at a sensitivity limit of >200 copies/ml were excluded (see Figure 4.3, page 133). A sensitivity analysis was conducted using a viral load cut-off of >1000 copies/ml, to investigate factors associated with a 'high' viral load among women who conceived on cART.

Statistical analyses

Poisson regression models with robust estimates of variances were fitted to investigate factors associated with non-suppression of viral load among women conceiving on cART. Duration of current cART regimen was included *a priori* in multivariable analyses, along with year and country of delivery to account for differences in clinical practice over time and between countries. Factors which could feasibly be associated with treatment failure or adherence problems were considered for inclusion in each multivariable model if they were associated with the outcome of a non-suppressed viral load (p<0.2) on adjusting for the three *a priori* factors. During model selection, each factor was tested for its contribution to the model's goodness-of-fit using Wald's test with a significance level of <0.1.

All ECS sites included in these analyses identified sequential pregnancies reported in the same woman. Having had a previous pregnancy was considered as a possible risk factor for subsequent virological failure, due to its association with exposure to short course ART for PMTCT and socio-demographic factors. Parity was investigated separately as this variable captured reproductive

history more fully, including pregnancies which took place before a woman's HIV diagnosis and in which care was received at a non-ECS site.

Boosted PI and non-boosted PI-based regimens were considered separately when investigating the association between cART regimen type and non-suppressed viral load, because these regimens have been associated with different virological response rates in both observational studies and clinical trials (Walmsley *et al.* 2002; King *et al.* 2004; Wood *et al.* 2007). The use of boosted PIs largely replaced non-boosted PIs over the years of the ECS explored here (described on page 131).

Viral load at a second or subsequent measure among women conceiving on cART (i.e. maintenance of viral suppression, or achievement of this where first measure was not suppressed) are described. Viral load measures dated up to a week after delivery were considered with those taken at delivery, to allow for delays in obtaining test results.

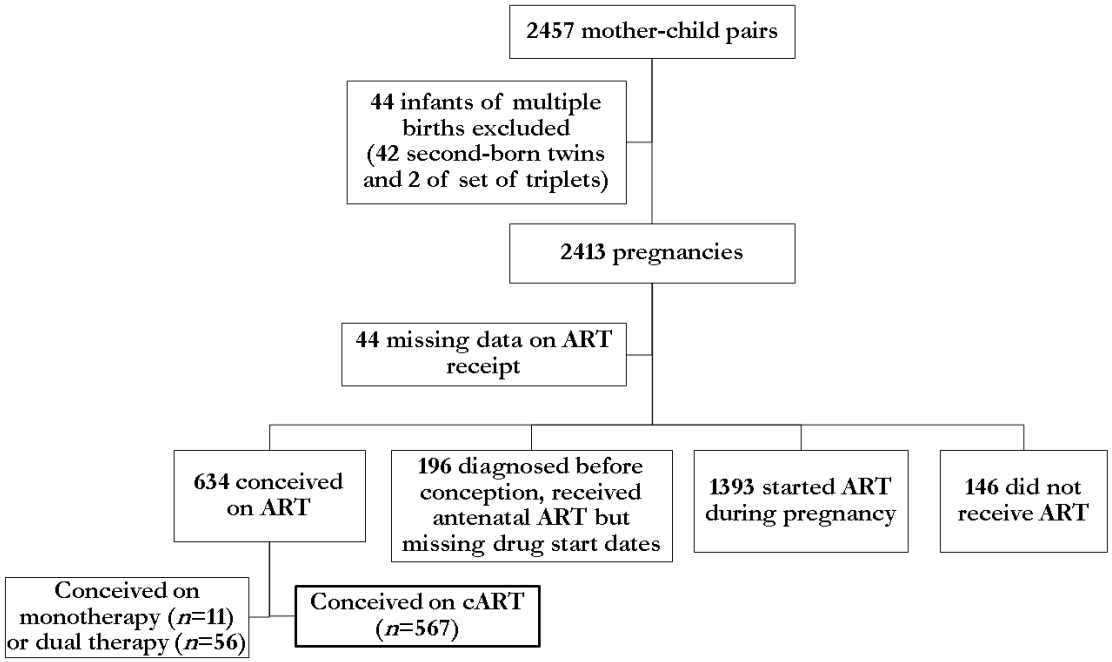


Figure 4.1: Receipt of ART and timing of initiation among women enrolled in the Western Europe sites of the ECS from 2000-11

4.3 Results

Of 2413 pregnancies from 2000-11, almost a quarter (*n*=567) were among women who conceived on cART (Figure 4.1). An additional 196 pregnancies (8% of the total) were among women diagnosed as HIV-positive before pregnancy, but missing timing of ART initiation. In total, 3% (*n*=67) of women conceived on mono or dual therapy, most (*n*=52) of whom delivered prior to 2004.

The proportion of women diagnosed as HIV-positive prior to conception was 70% (478/687) in 2000-01, increasing to 80% (68/85) in 2010-11 (trend *p*<0.01). The proportion conceiving on ART also increased over time (see Figure 4.2; for women diagnosed before pregnancy, this increase was from 35% (169/478) in 2000-01 to 54% (37/68) in 2010-11, trend *p*<0.01).

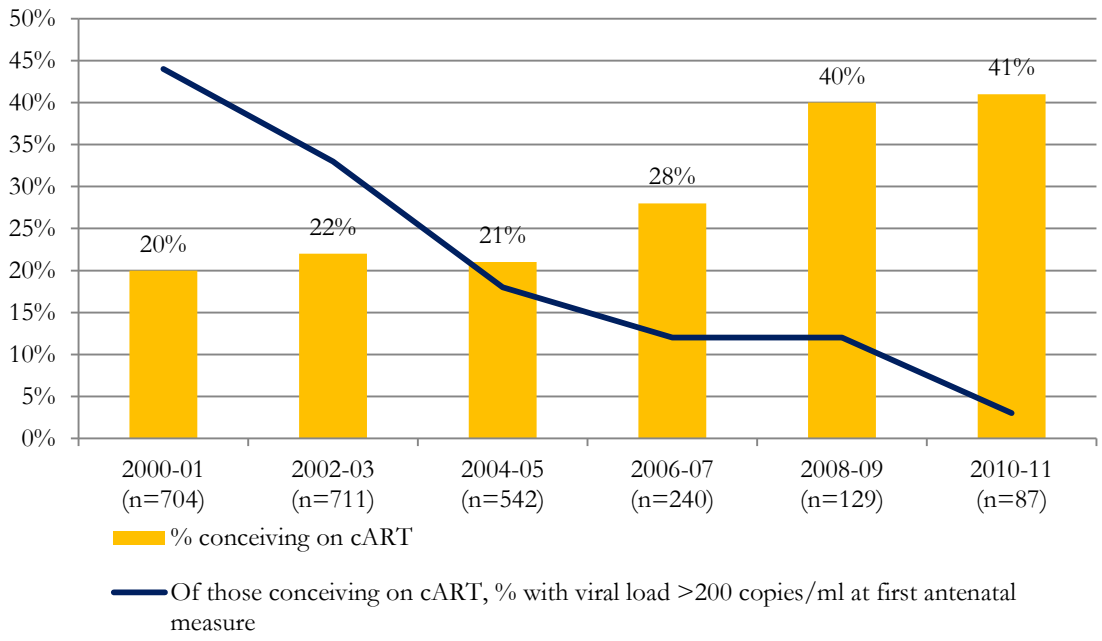


Figure 4.2: Trend in the proportion of women conceiving on cART and, among this group, the proportion with a non-suppressed viral load at first antenatal measure

The 567 women conceiving on cART had been on their current regimen for a median of 11.8 months (IQR 5.9, 26.8) by conception. The 48% (*n*=274) who conceived on a PI-based regimen were most commonly receiving NFV (40%, *n*=117), LPV/r (21%, *n*=61) or IDV (13%, *n*=38). Boosted PIs accounted for an increasing proportion of PI regimens received over these years: 17% (15/89) in 2000-01, 63% (25/40) in 2004-05 and 92% (24/26) in 2010-11 (trend *p*<0.01). Of the 40% (*n*=224) conceiving on an NNRTI-based regimen, 83% (*n*=187) received NVP and 17%

(*n*=37) EFV. One in ten (*n*=55) of the women conceiving on cART were on a triple NRTI regimen (for 39 of the 55 this consisted of ZDV, 3TC and ABC), and 2% (*n*=14) conceived on a regimen containing both a PI and an NNRTI. Almost half (47%, *n*=267) of all women conceiving on cART were on an NRTI backbone of ZDV and 3TC, with a further 16% (*n*=92) on 3TC and stavudine (all but four of whom delivered prior to 2005).

The median CD4 count at first measure in pregnancy among women conceiving on cART was 445 cells/mm^3 (IQR 318, 601) (measure available for 502 women), taken at a median of 12.8 weeks gestation. Around a third (163/502) had a CD4 count ≤350 cells/mm^3 (time trend *p*=0.82). The proportion with severe symptomatic HIV disease (i.e. CDC stage C) was 22% (108/482).

A fifth (118/567) of women conceiving on cART switched regimens during pregnancy and a total of 64 had an antenatal treatment interruption. For 33 women the interruption occurred between switching regimens. Treatment interruptions began at a median of 6.2 weeks gestation (IQR 4.9, 8.3) and lasted a median of 12.4 weeks (IQR 6.9, 17.0). Figure 4.3 shows the exclusions applied to reach the sample of 396 women included in the main analyses, all of whom initiated cART ≥28 days before conception and had a viral load measure available ≥24 weeks later, which was not pre-dated by a treatment interruption or the combination of a viral load measure and ART switch.

Of the 196 women diagnosed as HIV-positive before conception but missing drug start dates (see Figure 4.1, page 130), 112 had a viral load available at a median of 12.8 weeks gestation, of whom 57% (*n*=64) were suppressed (≤200 copies/ml). This was higher than the 24% (257/1072) suppressed at first viral load measure among women starting ART during pregnancy, and lower than the 74% (332/447) who were suppressed among those conceiving on cART before exclusion of women with treatment interruptions (see Figure 4.3). The 196 women without an ART start date were therefore likely to be heterogeneous with regards to timing of ART initiation, and were omitted from the main analyses.

Overall 81% (*n*=322) of the 396 women in the main analysis had a suppressed viral load (≤200 copies/ml) at their first eligible viral load measure, taken a median of 18.5 months (IQR 10.5, 31.0) after initiating their current regimen and at a median of 13.2 weeks of gestation (IQR 7.6, 21.3). Although all 396 women had been on cART for at least 24 weeks by the time of the viral load

measure, those in the non-suppressed group had been on cART for a slightly shorter duration - a median of 69.1 weeks, compared with 81.2 weeks for the suppressed group (Wilcoxon-Mann-Whitney test, p=0.07). The virologically suppressed group had their first viral load measure taken at a median of 13.3 weeks gestation compared with 12.9 weeks gestation for the non-suppressed group (Wilcoxon-Mann-Whitney test, p=0.74) indicating similar access to and timing of antenatal care, and there was no change in timing of first viral load measure by calendar year (trend p=0.37). The proportion of women conceiving on cART who had a non-suppressed viral load at first measure declined substantially over time (see Figure 4.2 page 131; of 396 women meeting inclusion criteria for analyses, this proportion was 34% (32/93) in 2000-01, declining to 10% (7/72) in 2004-05 and 3% (1/33) in 2010-11, time trend p<0.01). Of the 74 women with a non-suppressed viral load included in these analyses, 64 were enrolled prior to 2006.

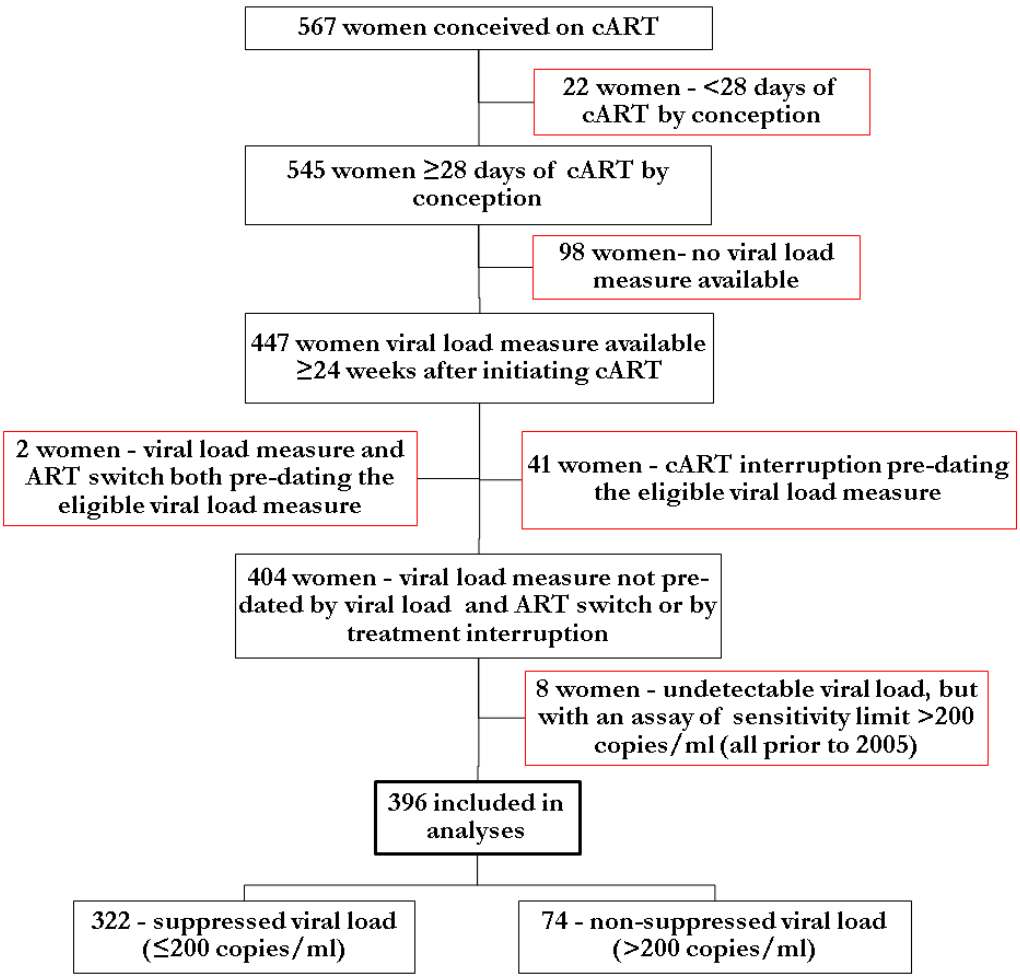


Figure 4.3: Inclusions and exclusions for the analyses of factors associated with a non-suppressed viral load in pregnancy among women conceiving on cART

Exclusions are shown in red.

Of the 322 women in the main outcome group who had a viral load ≤200 copies/ml (Figure 4.3), 92% (296/322) had a viral load below the detection limit of the assay; for 282 this was <50 copies/ml or less. The median viral load among the 74 non-suppressed women was 1370 copies/ml (IQR 480, 6000); 42 had a viral load in excess of 1000 copies/ml.

The socio-demographic and clinical characteristics of the 396 women on cART at conception according to whether they were virologically suppressed are given in Table 4.1. Women with a non-suppressed viral load had more severe HIV disease than the virologically suppressed group, and had also been diagnosed with HIV for longer, despite a shorter duration of treatment with their current cART regimen. Women with a viral load of >200 copies/ml were also more commonly IDUs, with an IDU partner and of white race than virologically suppressed women (Table 4.1). However, time trends in conception with a non-suppressed viral load coincided with important shifts over time in the characteristics of women enrolling in the study. Most notably, these years saw a decline in the proportion of women with an IDU history (from a fifth (53/271) of women delivering in 2000-05 to 2% (3/123) in 2006-11, χ^2=20.33 p<0.01), and an increase in the proportion of sub-Saharan African origin (from 45% (120/269) of women delivering in 2000-05 to 79% (98/124) in 2006-11, χ^2=40.72 p<0.01). Year of delivery therefore confounded associations between viral suppression and some factors, particularly IDU history, race and sub-Saharan African origin. There was no overall trend in maternal age (trend p=0.13), but women conceiving on cART in more recent years had been diagnosed as HIV-infected for longer (median 1.1 years by conception for 2000-01, 1.7 years for 2004-05, 2.8 years for 2010-11, trend p<0.01).

Women with non-suppressed viral load were more commonly taking a cART regimen based on a non-boosted PI, while NNRTI-based regimens were more common among the virologically suppressed group (Table 4.1). The proportion of women with a non-suppressed viral load among those conceiving on cART varied significantly by country of delivery, from 9% (2/22) in The Netherlands to 38% (12/32) in Italy (nine countries, χ^2=32.99 p<0.01). However, enrolments varied by country over time; country of delivery was not associated with virological suppression in a Poisson regression model adjusting for year of delivery (Wald's test p=0.19).

Table 4.1: Characteristics of 396 women on cART at conception by virological suppression

	Viral load ≤200 copies/ml *n*=322	Viral load >200 copies/ml *n*=74	
Maternal age, years – median (IQR)	33.5 (30.3, 36.9)	32.9 (29.0, 36.2)	p=0.24†
Marital status			
Married	150 (48%)	34 (47%)	χ^2=1.05 p=0.59
Cohabiting	73 (23%)	21 (29%)	
Single, divorced, widowed or separated	89 (29%)	18 (25%)	
Race			
White	97 (31%)	46 (63%)	χ^2=26.18 p<0.01
Black	198 (63%)	24 (33%)	
Other	18 (6%)	3 (4%)	
Born in sub-Saharan Africa			
No	123 (39%)	52 (70%)	χ^2=24.46 p<0.01
Yes	196 (61%)	22 (30%)	
Age at leaving full-time education			
≤16 years	62 (51%)	9 (43%)	χ^2=3.12 p=0.21
17-18 years	30 (25%)	9 (43%)	
≥19 years	29 (24%)	3 (14%)	
Parity			
0	108 (35%)	23 (32%)	χ^2=1.48 p=0.48
1	99 (32%)	19 (27%)	
≥2	104 (33%)	29 (41%)	
Previous pregnancy enrolled in ECS			
No	231 (72%)	51 (69%)	χ^2=1.00 p=0.61
Yes – one	71 (22%)	16 (22%)	
Yes – two or more	20 (6%)	7 (9%)	
History of IDU			
No	285 (89%)	53 (72%)	χ^2=14.99 p<0.01
Yes	35 (11%)	21 (28%)	
IDU partner			
No	265 (89%)	51 (73%)	χ^2=12.68 p<0.01
Yes	32 (11%)	19 (27%)	
Time from HIV diagnosis to conception – median (IQR)	5.2 years (2.8, 8.1)	6.9 years (3.9, 10.2)	p=0.02†
Time from initiating current cART regimen to viral load measure – median (IQR)	18.7 months (10.9, 31.6)	15.9 months (8.5, 25.4)	p=0.11†
cART regimen at conception			
PI-based (non-boosted)	66 (21%)	35 (47%)	χ^2=23.90 p<0.01
PI-based (boosted)	83 (26%)	15 (20%)	
NNRTI-based	127 (39%)	18 (24%)	
Contained both PI and NNRTI	7 (2%)	0	
Triple NRTI / NtRTI	39 (12%)	6 (8%)	
First antenatal CD4 count			
>350 cells/mm^3	227 (72%)	35 (49%)	χ^2=14.11 p<0.01
≤350 cells/mm^3	90 (28%)	37 (51%)	
HIV disease symptoms			
Asymptomatic / non-severe symptoms	234 (80%)	41 (65%)	χ^2=6.45 p=0.01
Severe symptomatic HIV disease	59 (20%)	22 (35%)	
Year of delivery			
2000-05	208 (65%)	64 (86%)	χ^2=13.41 p<0.01
2006-11	114 (35%)	10 (14%)	

†p value from Wilcoxon-Mann-Whitney test. PI: protease inhibitor, NNRTI: non-nucleoside reverse transcriptase inhibitor, NRTI / NtRTI: nucleoside/nucleotide reverse transcriptase inhibitor

Factors associated with non-suppressed viral load

Tables 4.2a and 4.2b (pages 138 and 139) give unadjusted PRs, PRs adjusted for the three *a priori* factors (year and country of delivery and cART duration) and PRs adjusted for all factors in the multivariable model. Neither marital status nor age at leaving full-time education were associated with non-suppressed viral load among women conceiving on cART (Wald's test p=0.57 and p=0.20 respectively, very small numbers for educational status) and are thus omitted from the final analysis. Because CD4 count and HIV disease staging were available only at the time of the pregnancy and not at ART initiation, these variables were also omitted from models as they were at least in part a consequence of (rather than risk factor for) treatment failure.

In univariable analyses, black women and those born in sub-Saharan Africa were at reduced risk of a non-suppressed viral load while those with an IDU history or IDU partner were at increased risk, but these associations disappeared or were much reduced on adjusting for year, country and cART duration (Table 4.2a). Other factors significantly associated with having a non-suppressed viral load in univariable analyses were being on a non-boosted PI-based (vs. NNRTI-based) cART regimen and having a longer history of diagnosed HIV infection, with each additional year conferring a 6% (95% CI 1-10%) increased risk of having a viral load >200 copies/ml. Duration of current cART regimen was not associated with viral suppression (all women included in the analyses had been on their current regimen for ≥24 weeks).

Although not associated with the outcome in univariable analyses, having ≥2 previous ECS pregnancies (vs. none) was associated with an increased risk of a non-suppressed viral load after adjusting for year, country and cART duration (Table 4.2a). Repeat ECS pregnancies became more common in the cohort as a whole between 2000-01 and 2006-07 (accounting for 10% (67/704) and 32% (77/240) of enrolments in these two time periods respectively, trend p<0.01), with no statistically significant change from 2006-11 (trend p=0.47). Among women conceiving on cART, repeat ECS pregnancies have accounted for between 31% and 38% of enrolments between 2002 and 2011 (trend p=0.39). Repeat ECS pregnancies were more common among women of sub-Saharan African origin (29% (308/1059) had ≥2 previous ECS pregnancies, 34% (358/1059) had one and 37% (393/1059) had none compared with 19% (232/1193), 33% (391/1193) and 48% (570/1193) respectively among women not born in sub-Saharan Africa, χ^2=36.84 p<0.01).

In multivariable analyses, women with two or more previous pregnancies enrolled in the ECS were three times more likely to have a non-suppressed viral load in subsequent pregnancies than women with no previous ECS enrolment. Of the 111 women included in the analyses and with ≥1 previous ECS pregnancy recorded, 98 had information available on exposure to ART in a previous pregnancy (information is not routinely collected on regimens received outside of the context of antenatal care). Of the 75 women with one previous ECS pregnancy, 73% (*n*=55) had previously received antenatal cART, 24% (*n*=18) mono/dual therapy and 3% (*n*=2) no ART. Among the 23 women with ≥2 previous ECS pregnancies, 20 had previously received antenatal cART, two mono/dual therapy and one woman had no prior exposure to antenatal ART. Only two of the 98 women had post-delivery stop dates reported for drugs received during pregnancy. However, it is possible that some of the remaining 96 women were not on ART continuously since their last delivery (which was a median of 1.8 years (IQR 0.8, 2.9) prior to their next conception), as stop dates for drugs that were stopped at some point after delivery may not have be captured, and data on treatment interruption between pregnancies are also not routinely collected.

In the fully adjusted model, women conceiving on non-boosted PI-based cART regimens remained at over a two-fold increased risk of having a non-suppressed viral load compared with those on NNRTI-based regimens. Those on boosted PI-based regimens also tended towards an increased risk, but this did not reach statistical significance (p=0.07). Women with longer duration of diagnosed HIV infection were at increased risk of having a viral load >200 copies/ml. After adjusting for this and other factors, older women were at decreased risk of having non-suppressed viral load compared with younger women (5% decrease in risk of non-suppression per year of maternal age).

Table 4.2a: Factors associated with a non-suppressed viral load, among women who conceived on cART (continued in Table 4.2b)

	Proportion with viral load >200 copies/ml at first measure	Crude PR (95% CI)	PR adjusted for year, country, cART duration	Adjusted PR (multivariable model)†, *n*=380
Race				
White	33.1% (46/139)	1.00	1	
Black	11% (24/219)	0.33 (0.21-0.52) *p*<0.01	0.59 (0.33-1.08) *p*=0.09	
Other	14.3% (3/21)	0.43 (0.15-1.27) *p*=0.13	0.90 (0.31-2.61) *p*=0.84	
Sub-Saharan African origin				
No	30.4% (52/171)	1.00	1	
Yes	10.2% (22/215)	0.34 (0.21-0.53) *p*<0.01	0.53 (0.29-0.98) *p*=0.04	
Parity at enrolment				
0	18.1% (23/127)	1.00	1	
1	16.4% (19/116)	0.90 (0.52-1.57) *p*=0.72	1.01 (0.59-1.71) *p*=0.98	
≥2	22.0% (29/132)	1.21 (0.74-1.98) *p*=0.44	1.57 (0.97-2.54) *p*=0.07	
Previous pregnancy enrolled in ECS				
No	18.3% (51/278)	1.00	1	1.00
Yes - one	18.8% (16/85)	1.03 (0.62-1.70) *p*=0.92	1.39 (0.83-2.31) *p*=0.21	1.47 (0.89-2.44) *p*=0.13
Yes - two or more	26.9% (7/26)	1.47 (0.74-2.90) *p*=0.27	2.61 (1.35-5.08) *p*<0.01	3.08 (1.49-6.36) *p*<0.01
IDU history				
No	15.9% (53/333)	1.00	1	
Yes	38.9% (21/54)	2.44 (1.61-3.70) *p*<0.01	1.20 (0.74-1.96) *p*=0.46	

†Adjusted ***a priori*** for country of delivery (not shown)

Table 4.2b: Factors associated with a non-suppressed viral load, among women who conceived on cART (continued from Table 4.2a)

	Proportion with viral load >200 copies/ml at first measure	Unadjusted PR (95% CI)	PR adjusted for year, country, cART duration	Adjusted PR (multivariable model)†, *n*=380
IDU partner				
No	16.5% (51/310)	1.00	1	
Yes	38% (19/50)	2.31 (1.50-3.57) *p*<0.01	1.10 (0.66-1.85) *p*=0.70	
Type of cART‡				
NNRTI-based	12.4% (18/145)	1.00	1	1.00
PI-based (non-boosted)	34.7% (35/101)	2.79 (1.68-4.65) *p*<0.01	2.15 (1.22-3.77) *p*<0.01	2.26 (1.28-4.00) *p*<0.01
PI-based (boosted with ritonavir)	15.3% (15/98)	1.23 (0.65-2.33) *p*=0.52	1.77 (0.94-3.35) *p*=0.08	1.90 (0.96-3.78) *p*=0.07
Triple NRTI/NtRTI	13.3% (6/45)	1.07 (0.45-2.54) *p*=0.87	1.13 (0.47-2.73) *p*=0.78	1.27 (0.52-3.12) *p*=0.60
Maternal age (per increasing year)		0.97 (0.93-1.01) *p*=0.18	0.97 (0.93-1.01) *p*=0.12	0.95 (0.91-0.99) *p*=0.02
Per year HIV diagnosed prior to conception		1.06 (1.02-1.11) *p*<0.01	1.05 (1.01-1.10) *p*=0.02	1.06 (1.01-1.10) *p*<0.01
Duration current cART regimen (per increasing year)		0.88 (0.75-1.03) *p*=0.11	1.01 (0.84-1.22) *p*=0.89	1.01 (0.83-1.23) *p*=0.92
Year of delivery (per increasing year)		0.81 (0.74-0.88) *p*<0.01	0.82 (0.74-0.92) *p*<0.01	0.80 (0.72-0.89) *p*<0.01

†Adjusted *a priori* for country of delivery (not shown) ‡7 women on both a PI and an NNRTI were excluded (all of whom were virologically suppressed)

In a sensitivity analysis of factors associated with high (>1000 copies/ml) viral load among the same group of 396 women who conceived on cART, the results were very similar (Tables 4.3a and 4.3b). In multivariable analyses, women with two or more previous ECS pregnancies were at increased risk of a high viral load, as were younger women (the risk decreasing by 7% per increasing year of maternal age), and women who had been diagnosed as HIV-positive for longer (Table 4.3b, p=0.06). Type of cART regimen was not associated with high viral load among women conceiving on cART after adjusting for year, country and cART duration (Wald's test p=0.17), and was thus excluded from the multivariable analysis. It is reassuring that women on a PI-based rather than NNRTI-based regimen were not at increased risk of a 'high' viral load, despite their increased risk of being non-suppressed. Previous ECS results have shown that women initiating PI-based regimens during pregnancy take longer to attain an undetectable viral load than those initiating NNRTI-based regimens (Patel *et al.* 2007), but the possibility of ART resistance needs to be considered and assessed for all women on non-suppressive cART (de Ruiter *et al.* 2012). The next section describes ART switches and virological outcomes among women who conceived on cART with a non-suppressed viral load at first measure.

Table 4.3a: Factors associated with a high viral load (>1000 copies/ml) at first measure in pregnancy, among women who conceived on cART (continued in Table 4.3b)

	Proportion with viral load >1000 copies/ml	Crude PR (95% CI)	PR adjusted for year, country, cART duration	Adjusted PR (multivariable model)† *n*=380
Race				
White	20.9% (29/139)	1.00	1.00	
Black	4.6% (10/219)	0.22 (0.11-0.44) *p*<0.01	0.39 (0.17-0.93) *p*=0.03	
Other	9.5% (2/21)	0.46 (0.12-1.78) *p*=0.26	0.85 (0.21-3.53) *p*=0.82	
Sub-Saharan African origin				
No	18.7% (32/171)	1.00	1.00	
Yes -SSA	4.7% (10/215)	0.25 (0.13-0.49) *p*<0.01	0.43 (0.18-1.04) *p*=0.06	
Parity at enrolment				
0	9.4%(12/127)	1.00	1.00	
1	11.2% (13/116)	1.19 (0.56-2.50) *p*=0.65	1.40 (0.68-2.91) *p*=0.36	
≥2	11.4% (15/132)	1.20 (0.59-2.47) *p*=0.62	1.69 (0.81-3.54) *p*=0.17	
Previous pregnancy enrolled in the ECS				
No	11.2% (31/278)	1.00	1.00	1.00
Yes – one	7.1% (6/85)	0.63 (0.27-1.47) *p*=0.29	0.81 (0.35-1.87) *p*=0.63	0.84 (0.37-1.92) *p*=0.69
Yes – two or more	19.2% (5/26)	1.72 (0.73-4.06) *p*=0.21	2.77 (1.13-6.80) *p*=0.03	3.20 (1.11-9.22) *p*=0.03
IDU history				
No	8.1% (27/333)	1.00	1.00	
Yes	27.8% (15/54)	3.43 (1.95-6.01) *p*<0.01	1.72 (0.81-3.67) *p*=0.16	

†Adjusted *a priori* for country of delivery (not shown)

Table 4.3b: Factors associated with a high viral load (>1000 copies/ml) at first measure in pregnancy, among women who conceived on cART (continued from Table 4.3a)

	Proportion with viral load >1000 copies/ml	Crude PR (95% CI)	PR adjusted for year, country, cART duration	Adjusted PR (multivariable model)† *n*=380
IDU partner				
No	9% (28/310)	1.00	1.00	
Yes	24% (12/50)	2.66 (1.45-4.88) *p*<0.01	1.24 (0.59-2.58) *p*=0.57	
Type of cART‡				
NNRTI-based	6.9% (10/145)	1.00	1.00	
PI non-boosted	19.8% (20/101	2.87 (1.40-5.88) *p*<0.01	1.71 (0.79-3.70) *p*=0.18	
PI boosted	10.2% (10/98)	1.48 (0.64-3.42) *p*=0.36	1.89 (0.79-4.51) *p*=0.15	
triple NRTI/NtRTI	4.4% (2/45)	0.64 (0.15-2.84) *p*=0.56	0.60 (0.14-2.67) *p*=0.50	
Maternal age (per increasing year)		0.96 (0.91-1.01) *p*=0.14	0.95 (0.89-1.01) *p*=0.13	0.93 (0.87-0.99) *p*=0.03
Per year HIV diagnosed prior to conception		1.08 (1.02-1.14) *p*<0.01	1.06 (1.00-1.13) *p*=0.05	1.06 (1.00-1.13) *p*=0.06
Duration of current cART regimen (per increasing year)		0.87 (0.72-1.05) *p*=0.16	0.96 (0.76-1.21) *p*=0.74	0.92 (0.72-1.18) *p*=0.53
Year of delivery (per increasing year)		0.81 (0.71-0.93) *p*<0.01	0.88 (0.76-1.01) *p*=0.08	0.84 (0.74-0.96) *p*=0.01

†Adjusted ***a priori*** for country of delivery (not shown) ‡7 women on both a PI and an NNRTI were excluded (all of whom were virologically suppressed)

Virological outcomes in pregnancy among women conceiving on a failing regimen

Most women who conceived on cART with a viral load ≤200 copies/ml at first measure in pregnancy had another viral load available within four weeks of delivery (90%, 291/322); 94% (273/291) remained suppressed at this time. Five of the 18 women who lost viral suppression between their first and last viral load measures had had a treatment interruption during pregnancy, compared with 1% (3/273) of those who remained suppressed (χ^2=44.96 p<0.01).

Among the 74 women who had a viral load >200 copies/ml at first measure, 65 had at least one other viral load measure available later in pregnancy. Two-thirds (41/65) of this group achieved a viral load of ≤200 copies/ml later in pregnancy at a median of 32.8 weeks gestation, and for 51% (33/65) this measure was undetectable at a sensitivity limit of <50 copies/ml. The 24 women who remained unsuppressed throughout pregnancy had a median viral load at first measure of 1861 copies/ml, compared with 1340 copies/ml for the 41 women who did go on to achieve viral suppression (Wilcoxon-Mann-Whitney test, p=0.23). Median CD4 count at first measure in pregnancy was 340 cells/mm^3 for those whose viral load remained >200 copies/ml around delivery compared with 372 cells/mm^3 for the women who went on to become virologically suppressed (Wilcoxon-Mann-Whitney test, p=0.47).

Among women with a non-suppressed viral load at first measure, subsequent treatment interruption during pregnancy was uncommon, occurring in 3/41 women who were later virologically suppressed and 1/24 women whose viral load remained >200 copies/ml (χ^2=0.26 p=0.61). ART regimen modifications were frequent however, as would be expected: 43% (32/74) of the non-suppressed group either switched regimens (n=28) or added a drug to their current regimen (n=4) during pregnancy vs. 14% (45/322) of women who conceived on cART with a viral load of <200 copies/ml (χ^2=32.91 p<0.01). Of the women who modified their regimen, 70% (21/30) became virologically suppressed compared with 57% (20/35) of the group whose regimen remained unchanged throughout pregnancy (χ^2=1.15 p=0.28). In the earlier years of the study, women conceiving on cART with a viral load of >200 copies/ml were less likely to achieve viral suppression later in pregnancy than women delivering in more recent years, although numbers in

more recent years were small: 64% (18/28) of those delivering in 2000-01 remained non-suppressed vs. 43% (9/21) in 2002-03, 33% (2/6) in 2004/05 and 20% (2/10) for 2006-11, trend $p<0.01$.

4.4 Limitations

Data were not available on several factors which could have influenced treatment response. CD4 count and viral load at time of ART initiation (i.e. prior to conception) were not known, but previous results from the ECS on viral load trajectories during pregnancy showed that higher baseline viral loads and lower CD4 counts were associated with a longer duration of time to viral suppression (Patel *et al.* 2007; European Collaborative Study 2010), as has been shown in other studies (Smith *et al.* 2004; Katz *et al.* 2010; Read *et al.* 2012). Information was also not available on AIDS-defining conditions diagnosed prior to cART initiation, ART adherence before and during pregnancy, and history of and current ART resistance (including whether a woman was already on a salvage regimen). One or a combination of these factors may account for the reported observations - for example, younger women may have been more likely to have a non-suppressed viral load due to poorer adherence behaviours than older women, and women in the earlier years of the study may have had more severe HIV disease at ART initiation.

Exclusions from the analyses included 98 women without a viral load measure available and 41 women who interrupted treatment before a viral load measure was taken. Women in whom viral load monitoring was lacking or less frequent may have had poorer HIV care in general and may have been more likely to be on non-suppressive treatment around the time of conception, making the proportion of women conceiving on non-suppressive cART reported here an underestimate. However, these enrolments were predominantly in the earlier years of the study (73/98 of those missing a viral load measure and 38/41 of those with a treatment interruption were enrolled prior to 2006), and so these factors will have had minimal impact on estimates in the later years.
Data on age at leaving full-time education were available for only 35% (140/396) of the study population (Table 4.1, page 135), which may have precluded identification of an association between educational status and virological suppression (for example mediated through adherence behaviours).

4.4 Key points

- Although the proportion of HIV-positive pregnant women already on cART at conception has increased over time, the proportion with virological failure has declined substantially over the last 12 years. Among 396 women included in these analyses, 34% had a non-suppressed viral load in 2000-01 declining to 3% in 2010-11. Calendar year remained significantly associated with likelihood of a non-suppressed viral load in adjusted analyses.
- Among women conceiving on cART with a non-suppressed viral load, the likelihood of achieving a suppressed viral load later in pregnancy also increased over time.
- In adjusted analyses which included year and country of delivery and duration of current cART regimen, factors associated with virological failure among women conceiving on cART were younger maternal age, longer duration of diagnosed HIV infection, being on a non-boosted PI-based (vs. NNRTI-based) regimen, and having two or more previous ECS pregnancies (vs. none). These same factors, with the exception of cART type, were also associated with having high (>1000 copies/ml) viral load.
- Non-boosted PI-based regimens have been almost entirely phased out of use in this cohort, to be replaced by more potent boosted PI-based regimens. However, the proportion of enrolments among women who have already received HIV care in at least one previous pregnancy has increased over the last 12 years. The association between this and non-suppressive treatment is of potential concern.
- That younger women had poorer outcomes in terms of viral suppression after adjusting for duration of HIV diagnosis and previous pregnancy highlights the particular needs that this group may have for adherence support or support in accessing HIV services.

Chapter 5 HIV co-infections and associated morbidity in Ukraine

5.1 Introduction

Prevalence of HIV co-infections is high in Ukraine, fuelled by rapid increases in IDU and expansion of the sex industry following the collapse of the Soviet Union, and a lack of public health and harm reduction services. Data on HIV co-infections are collected in the Ukrainian Postnatal Cohort of HIV-infected Childbearing Women ("the Women's Study"). In section 5.2, women enrolled in this study are characterised in terms of their health, health behaviours and socio-demographics, and compared with women enrolled in the Ukraine ECS. Diagnosed co-infections are described in section 5.3 and two co-infections are investigated in more detail: chlamydia, which is the most prevalent bacterial STI in this population, and HCV, the most common co-infection among HIV-positive IDUs (Thorne *et al.* 2012). In the final part of this chapter (section 5.4), cervical screening coverage as part of HIV care is explored, along with prevalence of and risk factors for abnormal cervical cytology.

5.2 Description of the Women's Study

5.2.1 Enrolments and representativeness

By September 2011, 2066 women were enrolled into the Women's Study, 29% (*n*=607) of whom had follow-up information available. Most (81%, 1671/2066) had previously participated in the ECS while 19% (*n*=395) were enrolled in the Women's Study only. Enrolments by year are given in Table 5.1.

Table 5.1: Enrolments and availability of follow-up in the Women's Study by year

	Total enrolments in Women's Study	Proportion with follow-up by September 2011
December 2007 - 2008	341	38% (*n*=128)
2009	677	29% (*n*=199)
2010	655	38% (*n*=249)
2011 (January to September)	393	8% (*n*=31)

According to Ukrainian policy, clinical follow-up is indicated six-monthly for HIV-positive patients who do not yet require ART for their own health, and at least three-monthly for those on ART. The low proportion of women with follow-up available (particularly among women enrolled in the earlier years of the study) may partly be due to arrangements for follow-up of patients living far from the HIV/AIDS centre at local clinics, but also suggests substantial loss to follow-up. Systems to routinely invite patients back to the HIV/AIDS centres for follow-up are lacking, and outreach provision for patients defaulting on follow-up care is ad hoc and dependent on local resources and arrangements with social services.

Table 5.2 shows, for women enrolled in the ECS, the participation rate in the Women's Study by centre of enrolment; the highest participation rate was seen in Kiev, and the lowest in Donetsk.

Table 5.2: Participation rate in the Women's Study by HIV/AIDS centre, among women enrolled in the ECS

	Number of ECS enrolments 2008-10	Proportion also enrolled in the Women's Study
Donetsk	400	24% (*n*=97)
Kiev	568	87% (*n*=496)
Krivoy Rog	264	78% (*n*=205)
Mykolaiv	629	54% (*n*=340)
Odessa	793	29% (*n*=226)

Overall, the MTCT rate was significantly higher among women participating only in the ECS (5.2% (91/1753) vs. 2.2% (25/1119) among women also enrolled in the Women's Study, χ^2 =15.41, p<0.01). This is probably because women lacking antenatal care and PMTCT interventions were also more likely to be disengaged from HIV care postpartum, thus missing the opportunity to enrol in the Women's Study; antenatal ART was received by 96% (1311/1364) of women enrolled in the ECS and Women's Study compared with 86% (1888/2195) of those enrolled in the ECS only (χ^2 =94.40, p<0.01).

There was no difference in HIV disease severity between women enrolled in the ECS only and those also participating in the Women's Study (14% were at WHO stage 3-4 and median CD4 count at first measure in pregnancy was 440 cells/mm^3 in both groups). Women who received

cART antenatally (associated with more severe HIV disease, see Chapter 3) were no more likely to be enrolled in the Women's Study than those who received ZDVm (χ^2=0.59, p=0.44). This may indicate the importance of factors other than HIV disease severity (for example marginalisation and health care literacy) in determining attendance for postnatal HIV care, or be explained by a lower likelihood of consent for participation in the Women's Study among women with severe or advanced HIV disease.

5.2.2 Characteristics of women at enrolment

Socio-demographic characteristics

The 2066 women enrolled by September 2011 had a median age of 27.6 years (IQR 24.4, 30.9) and most were married (50%, 1022/2056) or cohabiting (34%, 697/2056), with 13% single (n=261), 3% (n=59) divorced and 1% (n=17) widowed. The latter three categories included women with non-cohabiting partners (single in terms of marital rather than relationship status). Overall, age at leaving full-time education was available for 62% (n=1284) of women. Of these, almost half (n=626) had remained in full-time education until at least the age of 19, 30% (n=381) until 17-18 years and 22% (n=277) until ≤16 years. Those in full-time education until ≥19 years were more likely to be married (66% (409/623) vs. 40% (263/653) of those with less education, χ^2=82.3, p<0.01). As in the Ukraine ECS, almost all women were white (99%, 1723/1735) and born in Ukraine (1741/1743).

At cohort enrolment (a median of 5 months (IQR 1, 11) postpartum), 98% (1985/2024) of the women were living with their infant. Overall, 90% (1828/2032) of women were living in a household with at least one other adult (57% (n=1161) with partner or husband, 12% (n=241) with family members and 21% (n=426) with both partner and family). Of the 10% (204/2032) who reported being the only adult in their household, most (75%, n=153) were single, divorced or widowed, 8% (n=16) were married and 17% (n=35) reported their marital status as "cohabiting", possibly because, of the available options, this most adequately captured the notion of a committed (albeit non-cohabiting) relationship. Of these 35 women, all reported having a sex partner, as did 40% (135/336) of women reporting their marital status as single, divorced or widowed.

Throughout the following analyses, the marital status category of 'single, divorced or widowed' includes women in non-cohabiting relationships.

At enrolment into the Women's Study, women had lived in their current accommodation for a median of 3 years (IQR 2, 5) and therefore for most since before their most recent pregnancy. Most (60%, 1221/2022) lived in their own home, 12% (248/2022) in rented accommodation and 27% (539/2022) in their parents' or grandparents' home; 1% (n=14) of women reported their housing situation as "other" which included living in a shelter, hostel, prison or being homeless. A history of ever having been in prison was self-reported by 4% (71/1942), with most recent imprisonment having occurred a median of 5 years prior to Women's Study enrolment (IQR 3, 6 years). Four women had been in prison less than a year prior to cohort enrolment.

HIV disease status

At cohort enrolment, 14% (264/1836) of women had advanced or severe HIV disease (WHO stage 3 or 4). The median CD4 count (available for 1855 women) was 452 cells/mm^3 (IQR 327, 599); 9% (172/1855) had a CD4 count ≤200 cells/mm^3 and 20% (367/1855) a CD4 count 200-350 cells/mm^3. In total, 38% (773/2052) had indications for treatment (WHO stage 3-4 and/or CD4 count ≤350 cells/mm^3 during pregnancy or postnatally).

Postnatal ART

In total, 23% (464/2046) of women were on ART at postnatal enrolment and 53% (408/770) of those with clinical or immunological indications for treatment, increasing from 34% (41/121) of those with treatment indications in 2008 to 72% (117/162) in 2011 (trend p<0.01) (3 women with treatment indications did not have information on ART available). As in pregnancy, most of the women on cART were on a PI-based regimen (75% (315/422) of those with ART information available).

Just over a third (157/453) of the women on ART postnatally reported ART side effects. This is somewhat higher than the 20% (91/464) prevalence of minor side effects and 1% (6/464) prevalence of major side effects (steatosis, hepatotoxicity, nephrotoxicity, severe skin rash, anaemia or severe diarrhoea) reported by their clinicians. The discrepancy between clinician- and patient-reported prevalence of ART side effects is likely to be due to under-reporting of minor side effects

by women to their clinicians, an under-documentation of these in the medical notes or a difference in attribution of symptoms to ART.

Use of psychosocial support services

Three-quarters (1553/2066) of women reported using at least one psychosocial support service; half (1043/2066) reported using social services, 48% (985/2066) peer counsellors, 25% (520/2066) support groups and 23% (468/2066) treatment adherence programmes. Of this last group, 48% (223/466) were not currently on ART, and so their response may have reflected past use, or included ART preparedness programmes. Use of social services was highest among women with the least education (77% (212/277) of women leaving full-time education at ≤16 years reported using social services vs. 50% (508/1007) among those leaving education at ≥17 years, χ^2 =60.02, p<0.01). However there was no association between educational status and use of support groups (χ^2 =0.00, p=1.00) or peer counselling (χ^2 =1.23, p=0.27), probably because these services are NGO-provided and available to all women, whereas eligibility for state-provided social services is limited to the most marginalised or vulnerable groups. Social services were also used more frequently by unmarried women (54% (561/1034) vs. 47% (478/1022) of married women, χ^2 =11.52, p<0.01) and those with a history of IDU (67% (290/432) vs. 46% (753/1634) without an IDU history, χ^2 =60.54, p<0.01).

Disclosure of HIV status and HIV status of partner

Overall, 60% (1231/2066) of women had disclosed their HIV status to one or both parents, 7% (149/2066) to another family member (including sibling) and 3% (52/2066) to a friend. Of the 1865 women with a current partner at enrolment, 85% (n=1577) had disclosed their HIV status to their partner. Around a third (586/1849) did not know their partner's HIV status, and these women were significantly more likely not to have disclosed their own status to their partner (31% (180/586) vs. 8% (98/1263) of those who knew their partner's HIV status (χ^2 =165.14, p<0.01)). Of those who knew their partner's status, 41% (522/1263) were in a discordant partnership and 59% (741/1263) in a concordant partnership. Overall, 7% (153/2066) of women had not disclosed their status to anyone, a third (n=52) of whom had no current partner.

Parity and pregnancy planning

For 34% (559/1635) of women, the pregnancy preceding study enrolment was their first (including terminations, miscarriages, stillbirths and live births). Overall, 44% (732/1665) of women had a history of pregnancy termination, 9% (142/1645) a history of miscarriage and 47% (777/1642) had at least one previous live birth or stillbirth (13% (210/1642) had ≥2). Parity was associated with age (74% (262/356) of women aged ≥31 years were multiparous at enrolment vs. 27% (81/305) of 16-23 year-olds, 4 age groups, χ^2 =159.35, p<0.01) and with marital status (49% (673/1369) of married/cohabiting women were multiparous at enrolment vs. 38% (100/266) of single women, χ^2 =11.95, p<0.01).

In total, 71% (1442/2036) of women reported that they had planned their most recent pregnancy. Women planning their pregnancy were more likely to be married (62% (894/1439) vs. 20% (118/592) with unplanned pregnancy χ^2 =298.70, p<0.01) and to have been in full-time education until ≥19 years (58% (528/918) vs. 26% (89/344) with unplanned pregnancy (χ^2 =100.28, p<0.01) and less likely to have an IDU history (17% (241/1442) vs. 30% (181/594) of those with unplanned pregnancies, χ^2 =48.47, p<0.01). Of those with an antenatal HIV diagnosis, women with a planned pregnancy were less likely to be diagnosed late (11% (95/843) were diagnosed during the third trimester or intrapartum vs. 29% (81/276) of those with an unplanned pregnancy, χ^2 =7.91, p<0.01). Overall, women who had been aware of their HIV diagnosis prior to conception were more likely to have an unplanned pregnancy than those diagnosed during pregnancy or at delivery (31% (395/573) vs. 25% (276/1119)), reflecting the higher proportion of IDUs in the previously diagnosed group and inadequate family planning provision for diagnosed women. There was no age difference by planning of pregnancy (p=0.4).

Contraceptive use

The 71% (1420/1996) of women who reported being sexually active at cohort enrolment were enrolled a median of six months postpartum (vs. three months for the non-sexually active group, Wilcoxon-Mann-Whitney test p<0.01). Among sexually active women, condoms were the most popular choice of contraception, used as the sole method by 54% (771/1417), in addition to withdrawal (and therefore indicating inconsistent use) by 24% (336/1417) and in conjunction with

another modern contraceptive method (injectable hormone, intrauterine device (IUD) or oral contraceptive (OC) pill) by 12% (175/1417). One in ten (135/1417) sexually active women reported no condom use; 2% (32/1417) were using another modern contraceptive method and 7% (103/1417) were using no contraception or only withdrawal. Three women had been sterilised by cohort enrolment; these women were categorised with the group using injectable hormone, IUD or OC pill.

Overall, 21% (408/1990) of women reported not being able to afford contraception, 18% (310/1758) that contraception wasn't available and accessible to them and 13% (232/1756) that both of these statements were true. There was no change over time in the proportion reporting that contraception was unaffordable (p=0.10) but the proportion reporting that contraception was not accessible declined from 25% (83/336) in 2007-08 to 7% (22/316) in 2011, p<0.01). Women with lower levels of education were significantly more likely to report that contraception was unaffordable (33% (86/257), 20% (75/368) and 11% (67/601) of those leaving full-time education at <16, 17-18 and ≥19 years of age respectively, χ^2 =60.32, p<0.01). This was also the case for women with ≥3 previous live or still births at study enrolment (41% (81/198) reported contraception to be unaffordable vs. 16% (220/1384) of those with ≤2 previous live or still births, χ^2 =70.34, p<0.01). Overall, 31% (143/464) of women in full-time education until ≥19 years reported using a non-barrier contraceptive method, compared with 5% (18/381) of those with a lower level of education (χ^2 =92.37, p<0.01).

Smoking, drug and alcohol use

Overall 21% (432/2066) of women had a history of IDU (self- and clinician-report from the Women's Study and Ukraine ECS, or mothers of infants with neonatal abstinence syndrome). At enrolment, the proportion with an IDU history varied significantly by age group from 10% (43/415) of those aged 16-23 years to 16% (67/420) of women 24-26 years, 26% (149/570) of women 27-30 years and 33% (149/447) of those ≥31 years (χ^2 =80.78, p<0.01).

Of 389 women who self-reported an IDU history on enrolment into the Women's Study, 14% (n=53) reported current use, the majority of whom (96%, 50/52) were injecting homemade opiates and 4% (n=2) heroin. Among the current injectors, 52% (25/48) reported being in contact with a

harm reduction programme and 14% (7/49) that they were participating in an opiate substitution therapy programme. Most (82%, 37/45) current injectors had an IDU partner compared with 47% (132/282) of ex-injectors and 12% (160/1328) of women without an IDU history.

Almost three-quarters (1446/2045) of women had a history of cigarette smoking: 23% (464/2045) were ex-smokers, 22% (450/2045) current light smokers (<15 cigarettes a day) and 26% (533/2045) current heavy smokers (≥15 cigarettes a day). Current smokers were significantly more likely to have a history of IDU (38% (370/983) vs. 6% (59/1053) of ex/non-smokers, χ^2 =313.75, p<0.01) as were women reporting alcohol consumption at postnatal enrolment (46% (134/291) had an IDU history vs. 17% (290/1736) of non-drinkers, χ^2 =129.72, p<0.01) (see Figure 5.1). Current smokers were also of lower socioeconomic status, indicated by their increased probability of reporting contraception to be unaffordable (26% (251/950) compared with 15% (156/1029) of ex/non-smokers, χ^2 =129.72, p<0.01). Overall, of the 14% (291/2027) who reported drinking alcohol, most (70%, 126/180) reported use on one day per week, 22% (39/180) on two days and 8% (15/180) on three days or more.

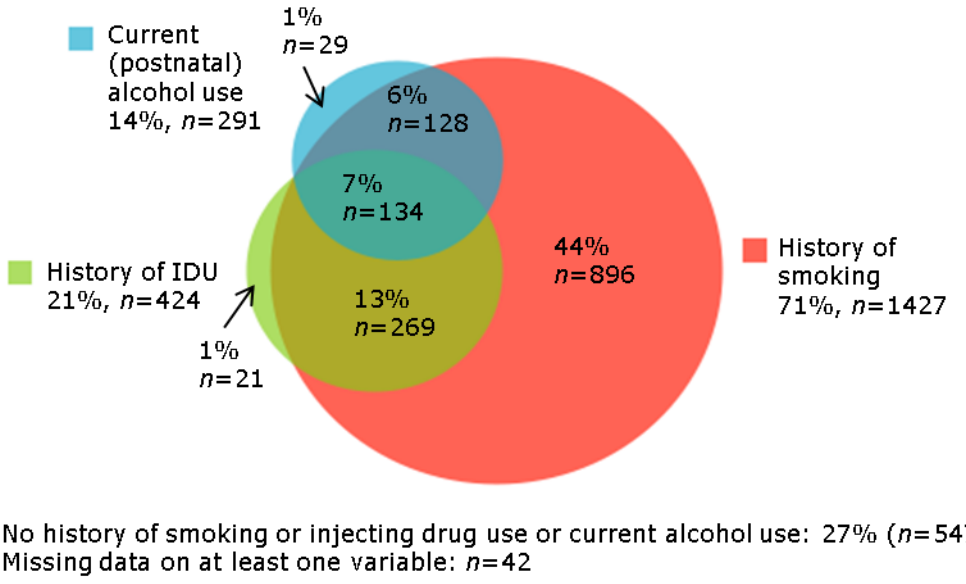


Figure 5.1: Smoking, drug and alcohol use at Women's Study cohort enrolment *(n*=2024)

HIV acquisition risk groups

Figure 5.2 shows the reported modes of HIV acquisition using data from the Women's Study and the ECS. Women with both an IDU history and an IDU partner have been assigned to the IDU history group, to reflect the category of highest HIV acquisition risk. Of the group with no reported risk factor for HIV acquisition, 14% (111/779) had no partner at Women's Study enrolment, 46% (355/779) had an HIV-negative partner and 40% (313/779) had a partner whose HIV status was unknown to them.

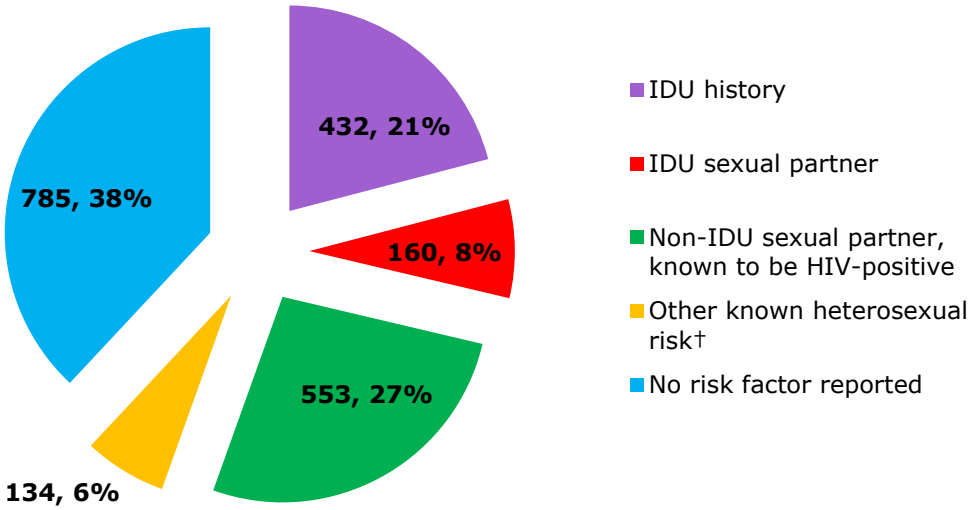


Figure 5.2: Mode of HIV acquisition among women enrolled in the Women's Study

n=2064, 2 women with occupationally-acquired HIV or exposure to blood products are omitted.
† Other known heterosexual risk includes women reporting rape, sex work or multiple sexual partners and women with sexual partners at high risk of HIV acquisition (MSM and partners who have received blood products (including haemophiliacs), are from a high prevalence country, or have a history of imprisonment).

5.2.3 Characteristics of women at follow-up

For the 607 women with follow-up available (19% (114/607) of whom had follow-up data available on ≥2 occasions), the first follow-up was a median of 5.9 months after study enrolment. Among women enrolled by the end of 2010 (eight months prior to the cut-off for analyses used here), the characteristics of women with follow-up were compared with those without follow-up. In this group, women on postnatal ART were more likely to have subsequent follow-up (42% (134/321) vs. 33% (435/1332) of those not on ART, $\chi^2 = 9.46$, $p<0.01$), reflecting policy for the closer monitoring of this group and their need to return to the HIV/AIDS centre for further ART supplies. However there was no difference in availability of follow-up by presence of severe / advanced HIV disease ($p=0.2$). Those with follow-up available were slightly older than those without (median 27.7 vs. 27.2 years, $p=0.01$) and more likely to be multiparous (55% (269/492) vs. 43% (413/969) of those with no follow-up, $\chi^2 = 19.05$, $p<0.01$). They were also significantly less likely to have an IDU history (17% (96/576) vs. 23% (255/1097) of those with no follow-up, $\chi^2 = 9.86$, $p<0.01$).

Women with follow-up had been enrolled initially a median of 37 days after delivery vs. 10.5 months for those with no follow-up (limited to those enrolled by the end of 2010, Wilcoxon-Mann-Whitney test $p<0.01$). The combination of earlier presentation at the HIV/AIDS centre postnatally and regular attendance for follow-up reflects greater engagement with care and compliance with medical advice, which may extend to other health-seeking behaviours. Among women who had been tested for ≥2 STIs during pregnancy or postnatally, only 7% (30/450) of women with follow-up had ≥2 positive tests, compared with 21% (161/753) of women with no follow-up ($\chi^2 = 45.66$, $p<0.01$), possibly reflecting more consistent condom use and better prior access to testing and treatment services.

5.3 HIV co-infections

STI definitions

Sexually transmitted infections (STIs) were defined as: *Chlamydia trachomatis* ('chlamydia'), gonorrhoea, syphilis, *Trichomonas vaginalis* (TV), HSV-2 and hepatitis B virus (HBV), which is highly sexually transmissible, but may also be transmitted via sharing of contaminated IDU equipment. Bacterial vaginosis, although positively associated with number of sexual partners and with acquisition of STIs (including HIV), is not itself considered to be sexually transmitted. Risk of heterosexual HCV transmission is thought to be low, but may be elevated among HIV-positive individuals (Tohme *et al.* 2010); this is explored further in section 5.3.2. Genital infections reported were any diagnosed during the most recent pregnancy or postnatally up to the time of cohort enrolment. Infections reported up to 28 days before estimated date of conception were included in all analyses.

Testing policies and data availability on co-infections

Data availability on each co-infection depended on local practice and testing facilities (including adequate supplies of consumables), national and local policies for testing and patients' engagement with care. Table 5.3 gives the proportion of women with a test result reported for each co-infection.

Ukrainian policy specifies that all patients should be screened for HCV at the time of HIV diagnosis, with annual screening thereafter for HCV-seronegative IDUs; screening coverage in this cohort was 74% (Table 5.3). Antenatal syphilis and HBV screening is routinely carried out for all pregnant women in Ukraine. However, tests performed as part of routine antenatal care before an HIV diagnosis is made (i.e. tests done at the same time as the HIV screening test, for women diagnosed as HIV-positive during the most recent pregnancy) may not be reported here, due to lack of data sharing between antenatal clinics and the HIV/AIDS centre. This may explain the fact that while 99% (1706/1715) of these women had an HIV test before delivery, only 75% had a syphilis test result reported here - syphilis screening coverage among women accessing antenatal care is reported to be 92% nationally (Ministry of Health of Ukraine 2012).

Testing for other STIs and genital infections (HSV-2, chlamydia, gonorrhoea, TV, BV and vulvo-vaginal candidiasis) varied by HIV/AIDS centre. Some HIV/AIDS centres aim to screen HIV-

positive pregnant women routinely for all of these infections, while other centres may provide testing only when signs or symptoms are present (for example for vulvo-vaginal candidiasis, indicated by the high prevalence of positive tests among the small proportion tested, Table 5.3). Some HIV/AIDS centres were not resourced to test and treat HIV-positive women for genital co-infections, and HIV-positive women could access these services through local women's clinics or sexual health clinics (the same channels as HIV-negative women). Of the six STIs on which data were collected, 14% (*n*=286) of women had no test results available, 24% (*n*=502) were tested for between 1 and 3 infections, 28% (*n*=588) for 4 infections, 5% (*n*=93) for 5 and 29% (*n*=597) for all six (median: 4 STI tests).

Prevalence of co-infections

Table 5.3 gives the prevalence of sexually transmitted and genital infections diagnosed during the most recent pregnancy or postnatally, and prevalence of HCV seropositivity (indicating past or chronic HCV infection). Hepatitis B surface antigen (HBsAg) positivity indicates acute or chronic HBV infection.

Table 5.3: Prevalence of co-infections

	Proportion tested (*n*=2066)	Of those tested, proportion positive
Viral		
HSV-2 seropositive	63% (*n*=1309)	60% (*n*=786)
HCV seropositive	74% (*n*=1529)	32% (*n*=492)
HBsAg positive	81% (*n*=1672)	15% (*n*=244)
Bacterial		
Chlamydia trachomatis	47% (*n*=970)	24% (*n*=229)
Syphilis	73% (*n*=1515)	2% (*n*=35)
Gonorrhea	56% (*n*=1167)	0.3% (*n*=4)
Other		
Trichomonas vaginalis (TV)	38% (*n*=784)	11% (*n*=88)
Bacterial vaginosis (BV)	61% (*n*=1260)	13% (*n*=170)
Vulvo-vaginal candidiasis	35% (*n*=717)	88% (*n*=631)

Genital infections were diagnosed as follows: chlamydia by enzyme immunoassay on endocervical swab; syphilis by specific treponema test; gonorrhea by Gram stain microscopy on vaginal swab; TV by microscopy; BV by Gram stain microscopy in 99% and by symptoms in 1%; vulvo-vaginal candida by Gram stain microscopy in 67%, culture in 12% and symptoms in 21%.

5.3.1 Chlamydia

Objectives of this section

1. To describe timing and coverage of chlamydia testing as part of HIV care among this cohort of HIV-positive childbearing women.

2. To investigate factors associated with a recent chlamydia diagnosis.

Methods

For this analysis, only enrolment data were used; women with follow-up were less likely to have a history of genital infection than those with no follow-up (see section 5.2.3), and were non-representative of the cohort as a whole. Krivoy Rog HIV/AIDS centre reported no chlamydia test results and Mykolaiv HIV/AIDS centre reported only two; these centres were excluded from the analysis of factors associated with a positive chlamydia test result.

Centre and year of enrolment were included in all models *a priori*, to account for differences in chlamydia prevalence by geographical area and over time. All variables which remained significantly associated with a positive chlamydia test result on adjusting for year and centre (Wald's test significance level <0.1) were included in the multivariable model, and then removed one-by-one if they were no longer associated with the outcome on adjusting for the other factors in the model (Wald's test significance level >0.1). Women enrolled in December 2007 (n=15) were grouped with those enrolled in 2008 for the purpose of adjusting for year of enrolment.

Characteristics by chlamydia test result

Table 5.4 gives socio-demographic and clinical characteristics of the 53% (n=1096) of women with no recent chlamydia test reported, the 36% (n=741) testing negative and the 11% (n=229) testing positive; prevalence of chlamydia among those tested was 24% (229/970). Women testing positive more often did not know their partner's HIV status than women testing negative, and were the least likely of the three groups to be using condoms as their only contraceptive method if sexually active at cohort enrolment (Table 5.4).

IDU history, current smoking and postnatal alcohol use were all more common among women with a positive chlamydia test (Table 5.4). Among those tested, 42% (96/229) of women with an IDU history or an IDU partner were positive for chlamydia (vs. 26% (190/741) of those with no IDU history or IDU partner, χ^2 =22.30, p<0.01), highlighting overlapping sexual and parenteral risk factors for transmission of infections among IDUs. Older women were slightly more likely to test positive for chlamydia (trend p=0.09), but this was mediated by the older age of IDUs; among women with no IDU history, there was no association between age and likelihood of a chlamydia diagnosis among those tested (trend p=0.65). Of the 38% of women with no reported risk factor for HIV acquisition (see Figure 5.2, page 154), 91% (711/785) were tested for at least one other STI of whom 53% (375/711) were positive; the prevalence of chlamydia among this group was 22% (84/387).

Timing of chlamydia testing

Among the 781 women who had timing of chlamydia test available, 81% (634/781) were tested during pregnancy and 19% (147/781) postnatally. The data collection form had space for one test date per infection; a positive postnatal test may therefore have indicated a lack of antenatal testing, re-infection or ineffective treatment following a prior positive test, or an incident infection. Only 16% (23/147) of postnatal tests were positive compared with 25% (161/634) of antenatal tests (χ^2 =6.30, p=0.01) (negative postnatal tests did not indicate test-of-cure for an antenatal infection, as positive test results were reported preferentially). Women with an IDU history were slightly more likely to be tested antenatally if a test was done (86% (160/186) vs. 80% (474/595) of non-IDUs, χ^2 =3.75, p=0.05), indicating that antenatal testing was to some extent targeted to higher risk women.

Table 5.4: Socio-demographics and clinical characteristics by chlamydia diagnosis

	No chlamydia test reported (*n*=1096)	Negative chlamydia test (*n*=741)	Positive chlamydia test (*n*=229)
Median age at cohort enrolment (IQR) (*n*=1852)	27.7 (24.6, 30.8)	27.3 (24.0, 30.7)	27.5 (24.6, 32.0)
Marital status (*n*=2056)			
Married	470 (43%)	435 (59%)	117 (51%)
Cohabiting	415 (38%)	198 (27%)	84 (37%)
Single / widowed / divorced	205 (19%)	105 (14%)	27 (12%)
Previous live and still births (*n*=1642)			
1	435 (49%)	332 (57%)	98 (54%)
2	310 (35%)	200 (35%)	57 (32%)
≥3	139 (16%)	46 (8%)	25 (14%)
History of pregnancy termination (*n*=1665)			
0	431 (48%)	390 (67%)	112 (62%)
1	187 (21%)	109 (19%)	29 (16%)
≥2	283 (31%)	85 (15%)	39 (22%)
Age at leaving full-time education (*n*=1284)			
<16 years	214 (27%)	43 (12%)	20 (16%)
17-18 years	297 (37%)	60 (17%)	24 (19%)
≥19 years	291 (36%)	255 (71%)	80 (65%)
Timing of HIV diagnosis in relation to most recent pregnancy (*n*=1715)			
Prior to conception	320 (34%)	210 (35%)	53 (29%)
1st and 2nd trimesters	496 (53%)	336 (56%)	116 (63%)
3rd trimester and intrapartum	114 (12%)	56 (9%)	14 (8%)
Partner's HIV status among 1849 women with a partner at enrolment			
Negative	245 (26%)	217 (32%)	60 (27%)
Positive	367 (39%)	289 (43%)	85 (39%)
Don't know	340 (36%)	171 (25%)	75 (34%)
Disclosure of HIV status to partner (*n*=1865)	828 (86%)	569 (83%)	180 (81%)
Most recent pregnancy planned (*n*=2036)	672 (63%)	600 (81%)	170 (75%)
Barrier contraceptive use among 1417 women sexually active at cohort enrolment			
Condoms as only contraceptive method	410 (60%)	296 (52%)	65 (38%)
Condoms and another method (injectable hormone, IUD, OC pill or withdrawal)	221 (32%)	207 (37%)	83 (49%)
No condom use	52 (8%)	61 (11%)	22 (13%)
Can afford family planning (self-report)	805 (77%)	599 (83%)	178 (80%)
Can access family planning (self-report)	652 (80%)	609 (84%)	187 (85%)
Using any support services	807 (74%)	554 (75%)	192 (84%)
Drug and alcohol use			
History of IDU (*n*=2066)	213 (19%)	139 (19%)	80 (35%)
History of smoking (*n*=2045)	802 (74%)	467 (63%)	177 (78%)
Current smoker (*n*=2036)	529 (49%)	319 (43%)	135 (59%)
Alcohol use postnatally (*n*=2027)	101 (9%)	127 (17%)	63 (28%)
Clinical / immune status			
WHO stage 3-4 (*n*=1836)	98 (11%)	125 (17%)	41 (18%)
Median CD4 count (IQR) (cells/mm^3) (*n*=1855)	453 (318, 608)	441 (334, 590)	456 (342, 586)
Taking ART postnatally (*n*=2042)	236 (22%)	192 (26%)	32 (14%)

Chlamydia and other STIs

Among those tested, the 24% of women who were positive for chlamydia were significantly more likely to be positive for a number of other STIs, with the exceptions of gonorrhoea (only 4 cases overall) and HBV, and to be positive for BV (Figure 5.3). Women testing positive for chlamydia were more likely to be HCV seropositive (46% (88/192) vs. 25% (152/598) of those negative for chlamydia, χ^2 =28.64, p<0.01), reflecting their more frequent history of IDU (Table 5.4), and possibly risk factors for sexual HCV acquisition (explored in section 5.3.2, page 168). Of the 229 women testing positive for chlamydia, all except one woman had ≥1 other STI test(s) available; 81% (184/228) had at least one other STI in addition to chlamydia and HIV (mostly HSV-2).

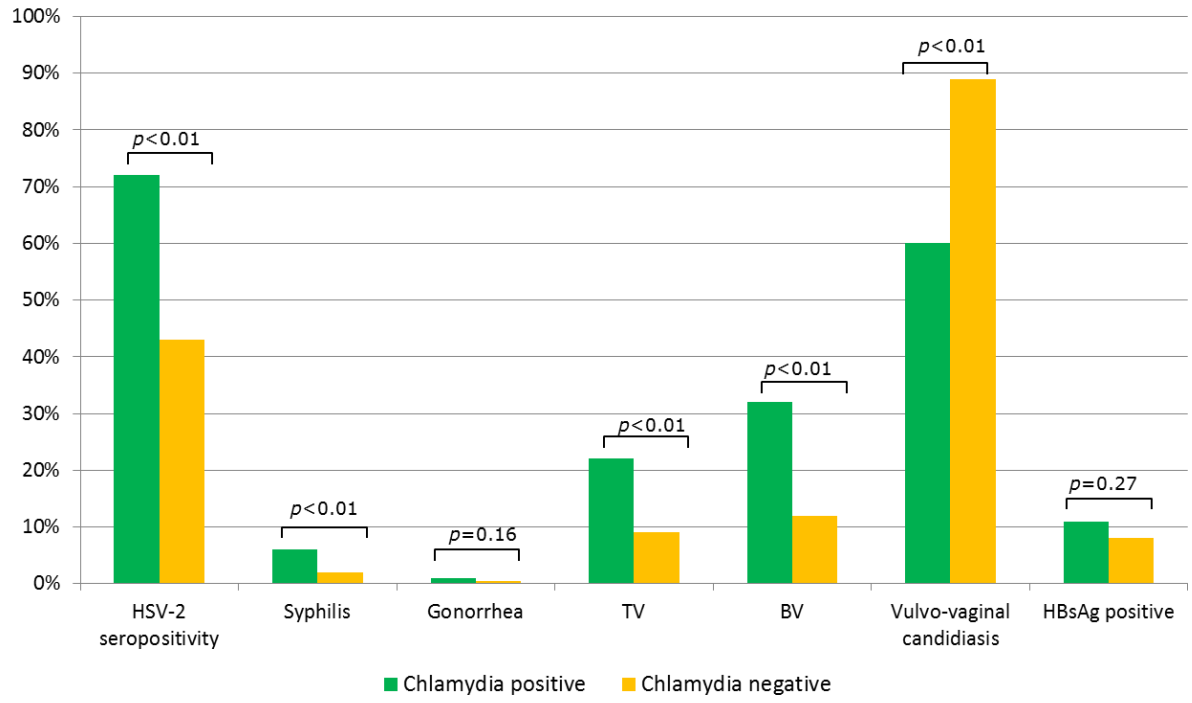


Figure 5.3: Other STIs and genital infections by recent chlamydia diagnosis
(n=970)

Women with no reported chlamydia test

The proportions of women with a chlamydia test reported by HIV/AIDS centre of enrolment were as follows: 91% (448/490) in Odessa, 63% (127/201) in Donetsk, 52% (393/759) in Kiev, 0.5% (2/409) in Mykolaiv and 0/207 in Krivoy Rog. Only 70% (247/352) of women enrolled in Mykolaiv or Krivoy Rog reported that they had access to family planning (compared with 85% (1201/1406) at Odessa, Donetsk and Kiev, χ^2 =45.07, p<0.01) and 74% (427/577) reported that

family planning was affordable (compared with 82% (1155/1413) at the other three centres, χ^2 =15.05, p<0.01). Women enrolled in Mykolaiv and Krivoy Rog were also more likely to have a history of multiple pregnancy terminations (60% (341/564) vs. 36% (391/1101) of women at the other three centres, χ^2 =94.22, p<0.01), suggesting a particular lack of access to sexual and reproductive health services among women enrolled at these two centres.

STI test results for at least one infection other than chlamydia (i.e. syphilis, gonorrhoea, TV, HSV-2 and HBV) were available for 74% (810/1096) of the women without a chlamydia test (vs. 99% (965/970) of those with a chlamydia test, median number of STI tests: 4 and 6 respectively). Most tests for other STIs were done on the same day as the chlamydia test (82% (561/684) of gonorrhoea tests, 74% (646/869) of syphilis tests, 81% (546/670) of TV tests and 87% (748/862) of HSV-2 tests). The proportion of women positive for at least one STI other than chlamydia (and HIV) was 51% (410/810) in the group with no chlamydia test and 55% (535/965) in the group tested for chlamydia (regardless of result) (χ^2 =4.11, p=0.04).

Chlamydia and other STI testing may be selectively offered in response to identification of sexual risk factors and symptoms, both of which increase the likelihood of a positive result. However, of women enrolled at Odessa, Donetsk and Kiev centres, women with no chlamydia test result were more likely to be diagnosed with HIV late (14% (53/366) vs. 9% (70/783) of those tested for chlamydia, χ^2 =8.01, p<0.01) and to have an IDU history (31% (148/482) vs. 23% (219/968) of those with a chlamydia test reported, χ^2 =11.12, p<0.01), indicating poorer access to services among those without a chlamydia test result.

Factors associated with a recent chlamydia diagnosis

The prevalence of chlamydia among those tested differed significantly by HIV/AIDS centre, from 33% (129/393) in Kiev to 21% (96/448) in Odessa and 3% (4/127) in Donetsk (χ^2 =49.09, p<0.01). There were also significant differences by year of enrolment, with the prevalence of positive test results ranging from 35% (120/345) in 2009 to 10% (15/146) in 2011 (4 year groups, χ^2 =50.32, p<0.01). Factors associated with a positive chlamydia test in univariable analyses or on adjusting for centre and year of enrolment only (Wald's test significance level <0.1) are shown in Tables 5.5a and 5.5b. Timing of HIV diagnosis, educational status, having an HIV-positive partner

and disclosure of HIV status to partner were not associated with a chlamydia diagnosis in univariable analyses, or on adjusting for year and centre (Wald's test p=0.56, p=0.20, p=0.88 and p=0.17 respectively).

The adjusted model was based on complete cases (women with no missing data on any of the variables of interest), but included the large majority (941/968) of the 67% (968/1450) of women with a chlamydia test available at the three HIV/AIDS centres. Parity, history of smoking, IDU partner, planning of most recent pregnancy, accessibility of contraception and history of pregnancy termination were associated with chlamydia diagnosis on adjusting for year and centre (Tables 5.5a and 5.5b), and were therefore initially included in the multivariable model, but subsequently removed as they did not contribute significantly to the model's final fit (Wald's test p>0.1 for all). Women who knew their partner's HIV status were more likely to have planned their most recent pregnancy (87% (561/646) vs. 69% (170/246) of those with unaware of their partner's status and 51% (33/65) with no partner at postnatal enrolment, χ^2 =71.40, p<0.01). Accessibility of contraception was associated with its affordability (retained in the model); almost all (95%, 1347/1423) women able to afford contraception reported that it was accessible to them, vs. only 30% (101/333) of women reporting that contraception was unaffordable (χ^2 =772.09, p<0.01).

Table 5.5a: Factors associated with a recent chlamydia diagnosis among those tested (continued in Table 5.5b)

	Proportion (*n*) testing positive for chlamydia	Unadjusted Prevalence Ratio (95% CI)	Prevalence Ratio (95% CI) adjusted for year and centre	Adjusted Prevalence Ratio (95% CI) *n*=941
Marital status				
Married	21% (117/551)	1.00	1.00	1.00
Cohabiting	30% (84/282)	1.40 (1.1-1.78) *p*=0.01	1.61 (1.27-2.04) *p*<0.01	1.40 (1.10-1.78) *p*<0.01
Single / widowed / divorced	21% (27/131)	0.97 (0.67-1.41) *p*=0.88	1.09 (0.77-1.55) *p*=0.63	0.89 (0.59-1.35) *p*=0.59
Parity				
1	23% (98/429)	1.00	1.00	
2	22% (57/256)	0.97 (0.73-1.30) *p*=0.86	1.00 (0.76-1.32) *p*=1.00	
≥3	35% (25/71)	1.54 (1.07-2.21) *p*=0.02	1.61 (1.14-2.27) *p*<0.01	
History of smoking				
Yes	28% (177/643)	1.00	1.00	
No	16% (51/319)	0.58 (0.44-0.77) *p*<0.01	0.70 (0.54-0.92) *p*=0.01	
History of IDU				
No	20% (149/749)	1.00	1.00	1.00
Yes	37% (80/219)	1.84 (1.46-2.30) *p*<0.01	1.70 (1.37-2.12) *p*<0.01	1.56 (1.24-1.96) *p*<0.01
IDU sex partner				
No	20% (127/620)	1.00	1.00	
Yes	31% (48/155)	1.51 (1.14-2.00) *p*<0.01	1.27 (0.97-1.67) *p*=0.08	
Most recent pregnancy planned				
Yes	22% (170/769)	1.00	1.00	
No	29% (57/194)	1.33 (1.03-1.72) *p*=0.03	1.50 (1.17-1.91) *p*<0.01	
Affordability of contraception				
Can afford	23% (178/775)	1.00	1.00	1.00
Can't afford	26% (44/171)	1.12 (0.84-1.49) *p*=0.44	1.74 (1.34-2.27) *p*<0.01	1.46 (1.11-1.92) *p*<0.01
Accessibility of contraception				
Can access	24% (187/795)	1.00	1.00	
Can't access	22% (33/147)	0.95 (0.69-1.32) *p*=0.78	1.53 (1.14-2.06) *p*<0.01	

Table 5.5b: Factors associated with a recent chlamydia diagnosis among those tested (continued from Table 5.5a).

	Proportion (*n*) testing positive for chlamydia	Unadjusted Prevalence Ratio (95% CI)	Prevalence Ratio (95% CI) adjusted for year and centre	Adjusted Prevalence Ratio (95% CI) *n*=941
Prior pregnancy termination				
None	22% (112/501)	1.00	1.00	
1	21% (29/138)	0.94 (0.65-1.35) *p*=0.74	0.85 (0.6-1.19) *p*=0.34	
≥2	32% (39/123)	1.42 (1.04-1.93) *p*=0.03	1.36 (1-1.85) *p*=0.05	
Woman's knowledge of her current partner's HIV status				
Known (positive or negative)	22% (145/650)	1.00	1.00	1.00
Unknown	30% (75/246)	1.37 (1.08-1.73) *p*=0.01	1.48 (1.17-1.87) *p*<0.01	1.39 (1.09-1.77) *p*<0.01
No current partner	12% (8/66)	0.55 (0.28-1.07) *p*=0.08	0.69 (0.36-1.32) *p*=0.26	0.80 (0.37-1.71) *p*=0.56
Centre				
Odessa	21% (96/448)	1.00	1.00	1.00
Donetsk	3% (4/127)	0.15 (0.06-0.39) *p*<0.01	0.14 (0.05-0.36) *p*<0.01	0.13 (0.05-0.34) *p*<0.01
Kiev	33% (129/393)	1.53 (1.22-1.92) *p*<0.01	1.30 (1.03-1.62) *p*=0.02	1.45 (1.15-1.84) *p*<0.01
Year of enrolment				
2007/08	15% (44/289)	1.00	1.00	1.00
2009	35% (120/344)	2.29 (1.68-3.12) *p*<0.01	2.05 (1.51-2.78) *p*<0.01	1.91 (1.41-2.57) *p*<0.01
2010	26% (50/190)	1.73 (1.20-2.48) *p*<0.01	1.69 (1.18-2.41) *p*<0.01	1.64 (1.16-2.30) *p*<0.01
2011	10% (15/145)	0.68 (0.39-1.18) *p*=0.17	0.64 (0.37-1.10) *p*=0.11	0.60 (0.35-1.03) *p*=0.06

In the multivariable model, women who were cohabiting (vs. married), had an IDU history, reported being unable to afford contraception and did not know their partner's HIV status were at increased risk of testing positive for chlamydia after adjusting for year and centre of enrolment (Table 5.5a and 5.5b). Among women who knew their partner's HIV status, there was no difference in likelihood of a chlamydia diagnosis by whether their partner was HIV-positive or HIV-negative (22% (60/277) and 23% (85/373) tested positive for chlamydia respectively, $\chi^2 = 0.12$, $p = 0.73$). There is therefore no evidence that the reduced risk of chlamydia among women who knew their partner's HIV status was driven by a greater likelihood of condom use among women in discordant partnerships. Knowledge of partner's HIV status will be partly determined by the partner's access to and uptake of HIV testing services (and therefore possibly testing and treatment for other STIs), and may also be an indicator of knowledge and skills around safer sex. Women who knew their partner's HIV status or who were married (vs. cohabiting) may also have been more likely to be in longer-term or exclusive partnerships, reducing their likelihood of STI exposure.

Although affordability of contraception was not associated with chlamydia diagnosis in univariable analysis, this was due to confounding by centre; 93% (349/377) of women enrolled in Kiev reported contraception to be affordable compared with 82% (366/446) in Odessa and only 49% (60/123) in Donetsk ($\chi^2 = 120.12$, $p < 0.01$). After adjusting for centre and other factors, those not able to afford contraception were significantly more likely to test positive for chlamydia than women who could afford contraception. Ukrainian policy specifies that HIV-positive women should have free access to condoms, but implementation varies between oblasts. These results support previous findings that women attending Kiev HIV/AIDS centre have better access than HIV-positive women elsewhere (Saxton *et al.* 2010). The association between affordability of contraception and chlamydia diagnosis may indicate direct financial barriers to use of condoms, and possibly also indirect mechanisms whereby women of lower socioeconomic status are at greater risk of STI acquisition (for example, due to lower levels of health literacy).

Recent chlamydia diagnosis and postnatal condom use

Information on contraceptive use was collected at postnatal cohort enrolment (subsequent to chlamydia diagnoses). Among sexually active women, there was no difference in "any" condom use (condom use alone or with another method, including withdrawal) by chlamydia test result (87% (148/170) of those testing positive for chlamydia reported any postnatal condom use vs. 89% (503/564) of those testing negative, $\chi^2 = 0.59$, $p = 0.44$). However, women who had tested positive for chlamydia were less likely to be using condoms exclusively (38% (65/170) vs. 52% (296/564) of women who had tested negative, $\chi^2 = 10.61$, $p < 0.01$) and more likely to be using injectable hormone, IUD or OC (25% (42/170) of those positive for chlamydia vs. 16% (93/564) of those negative, $\chi^2 = 5.88$, $p = 0.02$). Condom use may be less consistent among women using other reliable contraceptive methods.

5.3.2 Hepatitis C virus

Objectives of this section

1. To investigate prevalence of and risk factors for HCV acquisition in the Women's Study.

2. To characterise markers of liver fibrosis among HCV co-infected women.

Methods: Risk factors for HCV acquisition

History of IDU was ascertained by any one of: self-report by the woman, clinical assessment or neonatal abstinence syndrome in the infant. Two non-IDUs with occupational exposure to blood or blood transfusion reported did not have HCV serostatus available, and so were omitted from these analyses. When exploring factors associated with HCV seropositivity among non-IDUs, multivariable analyses were not presented due to problems with interpretation where some factors were markers for multiple different modes of acquisition risk. For example, previous history of pregnancy termination was more common among IDUs, but also a marker of unsafe sex and possible iatrogenic exposure to HCV.

Methods: Non-invasive markers of liver fibrosis

To characterise the likely prevalence of liver fibrosis among HIV/HCV co-infected women, two algorithms were used - the FIB-4 index and aspartate transaminase (AST) to platelet ratio ('APRI') (Wai *et al.* 2003; Sterling *et al.* 2006). These are defined below:

$$\textbf{FIB-4} = \frac{\textbf{(age [years] X AST [U/L])}}{\textbf{(PLT [10}^{9}\textbf{/L]} \times \textbf{(ALT [U/L])}^{1/2}\textbf{)}}$$

$$\textbf{APRI} = \frac{\textbf{(AST/upper limit of normal)}}{\textbf{PLT [10}^{9}\textbf{/L]} \times \textbf{100}}$$

ALT: alanine transaminase, AST: aspartate transaminase, PLT: platelet count.
Liver enzymes are measured in units per litre (U/L).

Previous work to validate the FIB-4 algorithm in a population of HIV/HCV co-infected patients, 21% of whom had advanced fibrosis, showed that a FIB-4 score of <1.45 had a negative predictive value of 90% for excluding advanced fibrosis and a sensitivity of 70%. A score of >3.25 had a positive predictive value of 65% and a specificity of 97% for detecting advanced fibrosis (Sterling *et al.* 2006). APRI cut-offs of ≤0.50 and >1.50 can be used to predict absence and presence of significant fibrosis respectively in patients with chronic HCV infection (negative predictive value of 86% for ≤0.50 and positive predictive value of 88% >1.50) (Wai *et al.* 2003).

Viral hepatitis and IDU history

Of the 2066 women enrolled by September 2011, HCV serostatus was available for 74% (*n*=1529): 76% (327/432) of IDUs and 74% (1202/1634) of non-IDUs (χ^2=0.81 *p*=0.37). Among women with an IDU history, prevalence of HCV seropositivity was 78% (256/327) vs. 20% (236/1202) among women with no IDU history (χ^2 =405.23 *p*<0.01). Overall, 48% (222/465) of the HCV seropositive women had no reported history of IDU. Figure 5.4 shows the overlap in HCV seropositivity, Hepatitis B surface antigen (HBsAg) positivity and IDU history reported in the cohort. HBV vaccination had been received by 14% (169/1224) of HBsAg negative women overall: 16% (156/977) of non-IDUs and 5% (13/247) of IDUs (χ^2 =18.90 *p*<0.01).

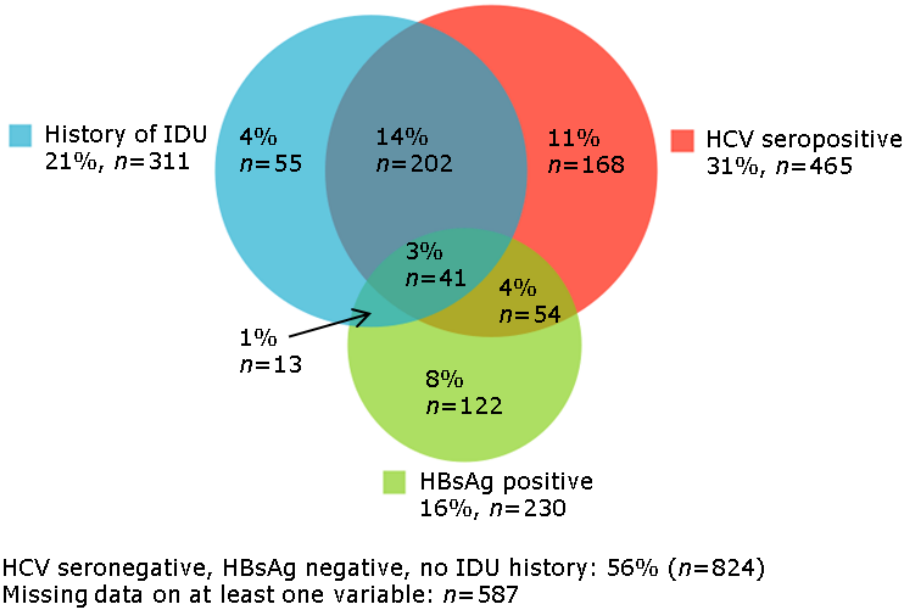


Figure 5.4: Viral hepatitis B and C and IDU history at cohort enrolment

n=1479; Prevalence of HCV seropositivity and HBsAg positivity shown here are slightly different to those in Table 5.3 (page 157), due to omission from Venn diagram of women with missing data on at least one of the three variables.

Women with no HCV serostatus available

The proportion of women with HCV serostatus reported varied by HIV/AIDS centre from 94% (385/409) in Mykolaiv to 86% (655/759) in Kiev, 78% (382/490) in Odessa, 50% (101/201) in Donetsk and 3% (6/207) in Krivoy Rog (χ^2 =752.79 *p*<0.01). HCV antibodies were detected after HIV diagnosis in 91% (366/402) of women with timing of both tests available, reflecting policy

which recommends HCV screening only for HIV-positive individuals and those with other specific risk factors for HCV acquisition. The women with unknown HCV serostatus at the centres with ≥50% coverage (Mykolaiv, Kiev, Odessa and Donetsk) were more likely to be diagnosed with HIV late (17% (40/231) had late HIV diagnosis vs. 9% (120/1272) of those with known HCV serostatus, $\chi^2 = 12.77$ $p<0.01$), and thus had less opportunity to be screened for HCV following their HIV diagnosis and by Women's Study enrolment. These women were also more likely to lack testing for all STIs (15% (39/252) vs. 0.5% (6/1196) of those with known HCV serostatus).

Timing of first positive HCV antibody test

Timing of first positive HCV antibody test was during most recent pregnancy for 67% (274/409), prior to conception for 30% (122/409) and postnatally for 3% (13/409). Among the 36 women who were diagnosed with HCV prior to or at the same time as HIV, 23 (64%) had a reported history of IDU - an indication for HCV screening independent of HIV status. None of the remaining 13 non-IDUs had an IDU partner reported – these women were enrolled over four centres, and their reason for being tested for HCV prior to their HIV diagnosis is unknown. Of women with an IDU history who tested positive for HCV antibodies, this occurred before conception in 38% (79/209) of cases (vs. 22% (43/200) among non-IDUs, $\chi^2 = 14.41$ $p<0.01$), reflecting IDUs' increased likelihood of being diagnosed as HIV-positive before their most recent pregnancy.

Risk factors for HCV acquisition

The 20% prevalence of HCV antibodies among women with no reported history of IDU may indicate under-ascertainment of IDU history, or other routes of HCV acquisition (including sexual or iatrogenic). These possibilities are explored in turn. Socio-demographic and clinical characteristics of HCV seropositive and HCV seronegative women by reported IDU history are given in Tables 5.6a and 5.6b.

Table 5.6a: Socio-demographics and clinical characteristics by IDU history and HCV serostatus (continued in Table 5.6b)

	No IDU history			History of IDU		
	HCV seronegative, (*n*=966)	HCV seropositive, (*n*=236)		HCV seronegative, (*n*=71)	HCV seropositive, (*n*=256)	
Median age at cohort enrolment, years (IQR) (*n*=1518)	26.4 (23.4, 30.1)	27.6 (25.0, 30.6)	p=0.02[2]	27.8 (24.8, 31.0)	28.7 (26.2, 32.3)	p=0.01[2]
Marital status (*n*=1520)						
Married	519 (54%)	121 (51%)	χ^2=2.63 p=0.27	32 (45%)	124 (49%)	χ^2=4.94 p=0.09
Cohabiting	318 (33%)	75 (32%)		19 (27%)	86 (34%)	
Single / divorced / widowed	124 (13%)	40 (17%)		20 (28%)	42 (17%)	
Parity (*n*=1232)						
1	408 (55%)	97 (46%)	χ^2=10.82 p<0.01	33 (52%)	100 (47%)	χ^2=0.57 p=0.75
2	256 (34%)	72 (34%)		23 (37%)	82 (39%)	
≥3	84 (11%)	41 (20%)		7 (11%)	29 (14%)	
History of pregnancy termination (*n*=1246)						
0	437 (58%)	109 (52%)	χ^2=6.88 p=0.03	36 (56%)	101 (47%)	χ^2=2.07 p=0.36
1	147 (19%)	35 (17%)		12 (19%)	44 (20%)	
≥2	171 (23%)	66 (31%)		16 (25%)	72 (33%)	
Sexual partner						
IDU partner (*n*=1261)	91 (12%)	37 (18%)	χ^2=5.48 p=0.02	22 (35%)	120 (55%)	χ^2=7.73 p<0.01
HIV-positive partner ever documented (*n*=1529)	416 (43%)	116 (49%)	χ^2=2.85 p=0.09	22 (31%)	133 (52%)	χ^2=9.80 p<0.01
Does not know current partner's HIV status (*n*=1383 with partner)	265 (30%)	51 (24%)	χ^2=2.89 p=0.09	27 (44%)	52 (22%)	χ^2=12.13 p<0.01
Disclosed own HIV status to current partner (*n*=1396 with partner)	760 (86%)	175 (83%)	χ^2=1.17 p=0.28	41 (67%)	204 (85%)	χ^2=10.68 p<0.01
Age at leaving full-time education (*n*=950)						
≤16 years	106 (19%)	42 (24%)	χ^2=2.65 p=0.27	11 (28%)	80 (47%)	χ^2=7.90 p=0.02
17-18 years	137 (24%)	40 (23%)		10 (25%)	45 (27%)	
≥19 years	325 (57%)	91 (53%)		19 (48%)	44 (26%)	
Smoking and alcohol use						
Current alcohol use (*n*=1500)	97 (10%)	18 (8%)	χ^2=1.37 p=0.24	20 (29%)	85 (34%)	χ^2=0.66 p=0.42
History of smoking (*n*=1514)	596 (62%)	150 (64%)	χ^2=0.23 p=0.63	63 (90%)	248 (97%)	χ^2=7.01 p<0.01
Current smoker (*n*=1504)	379 (40%)	97 (42%)	χ^2=0.20 p=0.65	55 (79%)	229 (90%)	χ^2=6.81 p<0.01

Table 5.6b: Socio-demographics and clinical characteristics by IDU history and HCV serostatus (continued from Table 5.6a)

	No IDU history			History of IDU		
	HCV seronegative, (*n*=966)	HCV seropositive, (*n*=236)		HCV seronegative, (*n*=71)	HCV seropositive, (*n*=256)	
Currently lives alone(*n*=1529)	66 (7%)	20 (8%)	χ^2=0.68 *p*=0.41	12 (17%)	42 (17%)	χ^2=0.03 *p*=0.87
History of being in prison (*n*=1439)	3 (0%)	2 (1%)	χ^2=1.31 *p*=0.25	12 (17%)	35 (14%)	χ^2=0.53 *p*=0.47
Postnatal condom use among 1417 women sexually active at cohort enrolment						
Condoms as only contraceptive method	392 (52%)	86 (49%)	χ^2=1.32 *p*=0.52	15 (38%)	82 (53%)	χ^2=9.97 *p*<0.01
Condoms and another method (injectable hormone, IUD, OC pill or withdrawal)	292 (39%)	77 (44%)		16 (40%)	64 (41%)	
No condom use	63 (8%)	13 (7%)		9 (23%)	10 (6%)	
Can afford contraception (*n*=1468)	804 (87%)	182 (81%)	χ^2=4.41 *p*=0.04	50 (71%)	189 (77%)	χ^2=0.76 *p*=0.38
Co-infections[1]						
Hepatitis B surface antigen positive (*n*=1479)	122 (13%)	54 (24%)	χ^2=18.35 *p*<0.01	13 (19%)	41 (17%)	χ^2=0.19 *p*=0.67
Chlamydia (*n*=790)	91 (18%)	31 (30%)	χ^2=7.37 *p*<0.01	13 (28%)	57 (42%)	χ^2=3.00 *p*=0.08
Trichomonas vaginalis (*n*=640)	41 (10%)	6 (8%)	χ^2=0.30 *p*=0.59	2 (5%)	10 (9%)	χ^2=1.01 *p*=0.32
HSV-2 antibodies (*n*=1166)	404 (56%)	141 (73%)	χ^2=19.31 *p*<0.01	21 (37%)	156 (83%)	χ^2=45.31 *p*<0.01
Vulvo-vaginal candida (*n*=607)	374 (90%)	74 (86%)	χ^2=1.10 *p*=0.29	24 (89%)	61 (78%)	χ^2=1.48 *p*=0.22
Bacterial vaginosis (*n*=1057)	72 (10%)	19 (12%)	χ^2=0.64 *p*=0.42	7 (13%)	36 (27%)	χ^2=4.22 *p*=0.04
Median years since HIV diagnosis (IQR) (*n*=1277)	1.3 (0.7, 1.9)	1.6 (0.9, 3.1)	*p*<0.01[2]	2.0 (0.9, 4.4)	1.9 (1.4, 4.6)	*p*=0.40[2]
Median years since first HCV antibody positive test (IQR) (*n*=454)	-	1.1 (0.4, 1.8)		-	1.5 (1.1, 3.4)	
Clinical / immune status						
WHO clinical stage 3-4 (*n*=1506)	90 (9%)	48 (21%)	χ^2=23.81 *p*<0.01	12 (17%)	88 (35%)	χ^2=8.41 *p*<0.01
CD4 count (cells/mm^3) (*n*=1410)						
≤200	75 (8%)	18 (8%)	χ^2=0.45 *p*=0.80	6 (10%)	34 (14%)	χ^2=1.21 *p*=0.55
201-350	162 (18%)	45 (20%)		12 (19%)	48 (20%)	
>350	651 (73%)	160 (72%)		45 (71%)	154 (65%)	
Taking ART postnatally (*n*=1512)	218 (23%)	61 (26%)	χ^2=0.91 *p*=0.34	12 (17%)	81 (32%)	χ^2=6.02 *p*=0.01

[1]Syphilis and gonorrhoea omitted due to small numbers; [2]t-test on log-transformed values

Under-ascertainment of IDU

Population level characteristics suggest that in many respects the 236 HCV-seropositive non-IDUs were more similar to HCV-seronegative non-IDUs than to women with a reported IDU history.

Smoking and postnatal alcohol use are both associated with IDU in this population (see Table 5.6a and Figure 5.1, page 153), but there was no difference in these behaviours by HCV serostatus among non-IDUs (Table 5.6a). Results from the Ukraine ECS showed that women with an IDU history were more likely to be diagnosed with HIV late in pregnancy and to miss out on antenatal ART if diagnosed (see sections 3.2.3, page 90 and 3.2.4, page 96), but neither of these outcomes were more common among HCV-seropositive than HCV-seronegative non-IDUs (16% (21/131) vs. 14% (76/559) respectively for late diagnosis (χ^2 =0.52 p=0.47), and 3% (4/158) vs. 2% (13/626) respectively for lack of antenatal ART (χ^2 =0.12 p=0.73)). Adverse birth outcomes are strongly associated with maternal IDU history among HIV-positive women in Ukraine (Thorne *et al.* 2012), and maternal HCV infection may be associated with poor perinatal outcomes independent of IDU (Connell *et al.* 2011). However, HCV-seropositive non-IDUs were not at a greater risk of preterm delivery or having a low birth weight infant than HCV-seronegative non-IDUs (Table 5.7).

Table 5.7: Birth outcomes by HCV serostatus and IDU history (among women in the ECS)

	Non-IDUs			**IDUs**			**Non-IDUs vs. IDUs**
	HCV seronegative	HCV seropositive		HCV seronegative	HCV seropositive		
Preterm delivery	6% (47/760)	10% (20/210)	χ^2=2.85 p=0.09	14% (9/63)	17% (39/224)	χ^2=0.34 p=0.56	χ^2=40.40 p<0.01
Low birth weight	9% (66/726)	7% (15/201)	χ^2=0.52 p=0.47	16% (10/63)	20% (44/217)	χ^2=0.61 p=0.44	χ^2=36.88 p<0.01

Finally, a history of imprisonment was reported by 14% (47/327) of IDUs with HCV serostatus available and only 0.4% (5/1202) of non-IDUs, with no difference by HCV serostatus (Table 5.6b).

Neonatal abstinence syndrome occurs in 60-80% of infants exposed to opiates during pregnancy (Bandstra *et al.* 2010). Of the 72 infants born with neonatal abstinence syndrome in the Ukraine ECS from 2008-10, only seven (10%) were born to women who had not reported an IDU history or had this detected by their clinician, suggesting that identification of heavy and recent opiate use

in pregnancy is fairly complete. It is more difficult to rule out a pre-conception history of opiate use, particularly among women who have only ever been infrequent injectors or experimenters. Ephedrine-based stimulants are sometimes injected alone as well as in combination with opiates in Ukraine (Booth *et al.* 2008), but their use during pregnancy is also associated with adverse birth outcomes (Minnes *et al.* 2011).

The 13 non-IDUs who were diagnosed with HCV antibodies at the same time as or prior to their HIV diagnosis (and did not have an IDU partner reported) may have an unreported history of IDU, or had another indication for HCV testing (e.g. liver dysfunction).

Among non-IDUs, those with antibodies to HCV were more likely to have been diagnosed with HIV prior to their most recent pregnancy (39% (83/214) vs. 29% (228/787) of HCV seronegative non-IDUs respectively, $\chi^2 = 7.57$ $p<0.01$) and to have WHO stage 3-4 disease (Tables 5.6a and 5.6b), both characteristics associated with an IDU history in this population (see section 3.2.2, page 80). However, among non-IDUs, a longer duration of diagnosed HIV infection and more advanced HIV disease could also be associated with an increased risk of sexual HCV acquisition (due to immunosuppression) and iatrogenic acquisition (due to longer history and more frequent episodes of hospitalisation). In addition, HBV co-infection negatively impacts on HIV disease progression (Chun *et al.* 2011) and here was associated with HCV co-infection among non-IDUs (Table 5.6b). HCV co-infection may itself also accelerate HIV disease progression, although the evidence for this is conflicting (Law *et al.* 2004; Potter *et al.* 2010).

Among non-IDUs, HCV seropositivity was also associated with having an IDU partner (Table 5.6a), which may indicate an increased likelihood of unreported IDU history (including experimenting), but also indicates sexual exposure to HCV and the possibility of household transmission.

Markers of sexual risk among HCV seropositive non-IDUs

Risk of sexual HCV transmission is thought to be low overall, but is increased in the presence of mucosal damage and HIV co-infection (Tohme *et al.* 2010). This lends plausibility to the hypothesis that HIV/HCV co-infected women who acquired HIV sexually may also have acquired HCV from a sexual partner. No data were collected in the Women's Study on specific risky sexual practices (e.g. anal sex), and only seven women reported sex work as a risk factor for HIV acquisition (five non-IDUs, one of whom was HCV seropositive). However, other STI diagnoses indicate risky sexual behaviours, and STIs may also increase the risk of sexual HCV acquisition in their own right – for example, by causing genital ulcer disease.

Prevalence of other STIs by HCV serostatus was therefore explored among non-IDUs. Analyses were stratified by centre as there were significant centre differences in the prevalence of HCV among non-IDUs (see Table 5.8, $\chi^2 = 40.36$ $p<0.01$; Note: Krivoy Rog was excluded due to very low screening coverage). The three infections that were more common overall among HCV seropositive than seronegative non-IDUs (HBsAg, chlamydia and HSV-2 – see Table 5.6b, page 172) also had varying prevalence by HIV/AIDS centre (Table 5.8). This likely reflects local differences in important aspects of the risk environment, for example access to STI prevention and treatment services and prevalence of sex work and IDU in the general population. Although only 10% (128/1261) of non-IDUs were aware of and reported IDU in their partner (Table 5.6a, page 171), the proportion exposed to HCV sexually will be much larger; around half of all HIV-positive people in Ukraine are estimated to be HCV seropositive and this figure is probably higher among men, who account for the majority of IDUs (Pinkham *et al.* 2008; Open Society Institute 2010). Table 5.8 summarises national and regional data available from Ukraine on prevalence of HCV among IDUs and HIV-positive people - important in understanding sexual HCV acquisition risk among HIV-positive non-IDUs.

Table 5.8: Indicators of sexual risk environment among non-IDUs.

	Kiev	Odessa	Mykolaiv	Donetsk
Regional HIV prevalence among IDUs – sentinel surveillance data (Ministry of Health of Ukraine 2012)	18.1%	31.6%	43.8%	28.5%
HCV seroprevalence among IDUs: National estimate	62% (Open Society Institute 2010) (no regional sentinel data)			
HCV seroprevalence among female IDUs in Women's Study:				
Proportion tested	85% (204/239)	78% (75/96)	86% (38/44)	31% (10/32)
Of tested, proportion positive	89% (182/204)	56% (42/75)	79% (30/38)	20% (2/10)
Proportion of non-IDUs with IDU partner	14% (60/428)	10% (26/263)	16% (51/321)	7% (9/138)
Estimated national HCV seroprevalence among people living with HIV (Open Society Institute 2010)	No regional data – estimated at 53% nationally			
Prevalence of HCV-seropositivity among non-IDUs	25% (112/452)	10% (30/307)	24% (83/347)	7% (6/91)
Proportion reporting contraception to be affordable among non-IDUs	96% (486/504)	84% (329/392)	76% (252/331)	51% (82/162)
Proportion reporting contraception to be accessible among non-IDUs	98% (486/497)	85% (334/391)	91% (117/129)	60% (97/162)
Proportion using condoms (any) among non-IDUs sexually active at postnatal cohort enrolment	95% (392/411)	82% (272/332)	93% (240/259)	92% (84/91)
Coverage and results of recent STI tests among non-IDUs				
HSV-2:				
Proportion tested	62% (322/520)	93% (366/394)	86% (315/365)	18% (31/169)
Of tested, proportion positive	81% (260/322)	21% (77/366)	80% (251/315)	10% (3/31)
Chlamydia:				
Proportion tested	53% (278/520)	93% (367/394)	1% (2/365)	62% (104/169)
Of tested, proportion positive	27% (74/278)	20% (72/367)	0% (0/2)	3% (3/104)
HBsAg:				
Proportion tested	88% (459/520)	96% (377/394)	92% (337/365)	89% (151/169)
Of tested, proportion positive	2% (7/459)	15% (56/377)	36% (122/337)	1% (2/151)

Shaded cells indicate national or regional data

No consistent associations were found between recent STI diagnosis and HCV seropositivity among non-IDUs across centres (Table 5.9), although power was limited by the small number of women tested for each combination of infections at some of the centres. When data from Odessa and Kiev centres were pooled, recent chlamydia diagnosis was associated with a 42% increased risk of HCV seropositivity among non-IDUs overall (APR 1.42 95% CI 0.99, 2.04 p=0.06, adjusted for centre), suggesting a possible association between recent risky sexual behaviour and HCV antibodies. Of note, a recent chlamydia diagnosis was also associated with an IDU history (see Table 5.5a page 164), and so this association could also be explained by under-ascertainment of IDU.

Table 5.9: Association between recent STI diagnoses and HCV seropositivity among non-IDUs, by centre†

	Kiev		**Odessa**		**Mykolaiv**	
	Proportion (*n*) seropositive for HCV among those tested	Unadjusted Prevalence Ratio (95% CI)	Proportion (*n*) seropositive for HCV among those tested	Unadjusted Prevalence Ratio (95% CI)	Proportion (*n*) seropositive for HCV among those tested	Crude Prevalence Ratio (95% CI)
HSV-2 antibody test						
Negative	23% (14/61)	1.00	9% (20/234)	1.00	22% (14/63)	1.00
Positive	30% (70/237)	1.29 (0.78, 2.12) p=0.32	14% (8/59)	1.59 (0.73, 3.43) p=0.24	25% (63/248)	1.14 (0.69, 1.90) p=0.61
Chlamydia test						
Negative	25% (48/193)	1.00	9% (23/244)	1.00	0% (0/2)	Omitted due to lack of data
Positive	37% (25/68)	**1.48 (0.99, 2.20) p=0.05**	12% (6/51)	1.25 (0.53, 2.91) p=0.61	0% (0/0)	
HBsAg						
Negative	24% (104/436)	1.00	10% (26/256)	1.00	15% (33/215)	1.00
Positive	14% (1/7)	0.60 (0.10, 3.71) p=0.58	8% (4/49)	0.80 (0.29, 2.20) p=0.67	42% (49/118)	**2.71 (1.85, 3.96) p<0.01**

†Donetsk is excluded from the table, as only six non-IDUs were HCV-seropositive at this centre.

Possible markers of iatrogenic risk among HCV-seropositive non-IDUs

No data are available in the ECS or Women's Study on receipt of tattoos, dental work or acupuncture, and data on receipt of blood transfusions are also not routinely collected (unless reported as the mode of HIV acquisition). However, parity and history of pregnancy termination give some indication of prior exposure to medical procedures and/or a healthcare environment. Table 5.10 shows the associations between these factors and HCV seropositivity among non-IDUs, adjusting for centre, to account as much as possible for regional variation in HCV seroprevalence and thus risk of acquisition in a medical setting.

Table 5.10: Association between possible markers of iatrogenic risk and HCV seropositivity among non-IDUs

	Proportion (*n*) seropositive for HCV among those tested	**Unadjusted PR (95% CI)**	**PR adjusted for centre (95% CI)**
History of pregnancy termination (*n*=965)			
0	20% (109/546)	1.00	1.00
1	19% (35/182)	0.96 (0.68, 1.36) *p*=0.83	1.01 (0.72, 1.43) *p*=0.94
≥2	28% (66/237)	1.39 (1.07, 1.82) *p*=0.01	1.42 (1.07, 1.87) *p*=0.02
Parity (*n*=958)			
1	19% (97/505)	1.00	1.00
2	22% (72/328)	1.14 (0.87, 1.50) *p*=0.34	1.14 (0.87, 1.49) *p*=0.34
≥3	33% (41/125)	1.71 (1.25, 2.32) *p*<0.01	1.67 (1.23, 2.26) *p*<0.01

In this cohort of childbearing women, non-IDUs with ≥2 previous pregnancy terminations or ≥3 previous births were significantly more likely to be HCV seropositive than those with no history of termination or only one birth respectively. However, both of these characteristics were also more common among women with a reported IDU history (31% (110/359) of IDUs had a history of multiple pregnancy terminations vs. 23% (297/1306) of non-IDUs, χ^2 =9.87 *p*<0.01, and 52% (182/348) of IDUs had ≥3 previous births vs. 46% (595/1294) of non-IDUs, χ^2 =4.39 *p*=0.04). Risky sexual behaviour is associated with IDU (Booth *et al.* 2007) and may also be independently associated with multiparity and a history of multiple pregnancy terminations. In the absence of more direct measures of iatrogenic risk, inferences cannot be made regarding the acquisition of HCV in medical settings in this population.

Other methods of drug administration

Non-injection drug use, particularly of crack, has been implicated in HCV transmission elsewhere (Neaigus *et al.* 2007; Nurutdinova *et al.* 2011). However, cocaine costs around €130 per gram in Ukraine, making it unaffordable for the vast majority of drug users (use is reported at <3% drug users overall (Viyevskyy *et al.* 2010)). In the Women's Study, only one woman reported using cocaine. No data are available on other drugs and methods of administration in this study (e.g. smoked opium and snorted dried poppy juice, previously reported by 8% and 4% of drug users in central Ukraine respectively (Dumchev *et al.* 2009)). It is possible that non-injection drug use contributes to HCV acquisition risk among non-IDUs.

Markers of liver fibrosis among HCV co-infected women

Only 1% (5/441) of the HCV seropositive women had received HCV treatment by enrolment, with an additional three women (of 33 with information available) receiving treatment at follow-up (median duration of follow-up of HCV seropositive women was 11 months). Pegylated interferon and ribavirin (PegIFN/RBV), the standard of care for HCV treatment during these years, is not publicly funded in Ukraine. Its cost ($16,667 for a 48 week course in 2009 (Open Society Institute 2010)) is prohibitive to the vast majority of HCV-infected individuals.

Median FIB-4 scores were 0.62 (IQR 0.43, 0.95) for HCV seronegative women and 0.92 (IQR 0.62, 1.38) for HCV seropositive women (*t*-test $p<0.01$). Median APRI scores were also significantly higher in the presence of HCV co-infection (0.50 (IQR 0.33, 0.82) compared with 0.29 (IQR 0.19, 0.45) among HCV seronegative women, *t*-test $p<0.01$). Among co-infected women, both scores were higher among women with an IDU history (Table 5.11), indicating greater likelihood of liver fibrosis.

Table 5.11: FIB-4 and APRI scores among HCV seropositive women by IDU history

	HCV seronegative	**HCV seropositive**		
		No IDU history (*n*=236)	**IDU history (*n*=256)**	***t*-test for difference by IDU history among HCV seropositive**
Median FIB-4 score (IQR) (*n*=430)	0.62 (0.43, 0.95)	0.78 (0.57, 1.08)	1.11 (0.72, 1.56)	$p<0.01$
Median APRI score (IQR) (*n*=433)	0.29 (0.19, 0.45)	0.42 (0.27, 0.60)	0.60 (0.38, 0.99)	$p<0.01$

Compared with non-IDUs, IDUs were more likely to be using alcohol postnatally and also to be on ART (27% (116/432) of IDUs were on ART postnatally vs. 22% (348/1614) of non-IDUs, $\chi^2=5.44$ $p=0.02$) - both factors increasing the risk of liver dysfunction. IDUs may also have been infected with HCV for longer, both because of earlier exposure and older age at cohort enrolment, and thus have more advanced HCV disease. Among 41 women with information available, median age at initiating IDU was 17 years. Median time to HCV infection following IDU initiation is estimated to be 3-4 years in cohorts in Canada, the US and Australia (Hagan *et al.* 2004; Maher *et al.* 2006; Roy *et al.* 2009), but may be shorter in Ukraine where coverage of harm reduction services is low and high-risk injection practices are commonplace. IDUs were a median of 29 years of age at cohort enrolment, and so many may have been infected with HCV for 10 or more years. Only ten women were taking ≥1 antituberculosis drugs associated with liver toxicity at cohort enrolment (isoniazid (*n*=9), pyrazinamide (*n*=1) and unspecified tuberculosis treatment (*n*=2)), five of whom were HCV seropositive.

Overall, 79% (338/430) of HCV seropositive women had a FIB-4 score <1.45 indicating no advanced fibrosis and 1% (3/430) had a FIB-4 score >3.25 associated with advanced fibrosis. Using the APRI score (which is possibly less specific than FIB-4 due to validation in mono-HCV infected patients only), 51% (220/433) had a score of ≤0.5 which indicates the absence of significant fibrosis and 8% (34/433) had a score of >1.50, predicting significant fibrosis. In total, 843 HCV seronegative women and 430 HCV seropositive women had data allowing for calculation of both APRI and FIB-4 scores. Table 5.12 shows the distribution of these women's scores.

Table 5.12: FIB-4 and APRI scores among 843 HCV seronegative women (blue) and 430 HCV seropositive women (red).

		APRI score		
		≤0.5 (no significant fibrosis)	0.5-1.50 (indeterminate)	>1.50 (significant fibrosis)
FIB-4 score	<1.45 (no advanced fibrosis)	**663**	**115**	**0**
		212	**120**	**6**
	1.45-3.25 (indeterminate)	**2**	**51**	**4**
		1	**64**	**24**
	>3.25 (advanced fibrosis)	**0**	**3**	**5**
		0	**0**	**3**

5.4 Cervical screening and factors associated with an abnormal finding

Objectives of this section

1. To explore coverage of cervical screening as part of HIV care.

2. To investigate factors associated with an abnormal finding on cervical screening.

Methods

This analysis is limited to 1120 women enrolled at Odessa, Kiev and Donetsk HIV/AIDS centres by March 2011 (Krivoy Rog and Mykolaiv HIV/AIDS centres did not report any cervical screening results and are excluded from these analyses). Information on cervical screening tests received as part of HIV care was collected at enrolment and at follow-up.

Study centre and year of enrolment (December 2007-08, 2009, 2010-11) were included *a priori* in the multivariable analysis of factors associated with having a test reported, to account for differences in local policy and changing clinical practice over time. Variables which remained significantly associated with the outcome after these adjustments (Wald's test $p<0.1$) were included in the multivariable model. In analysis of factors associated with an abnormal finding on cervical screening, all variables known to be associated with invasive cervical cancer and available in the dataset were included *a priori* (use of oral hormonal contraception, smoking, parity, HSV-2 antibodies, chlamydia infection and CD4 count) (Muñoz *et al.* 2006). Other variables were considered for inclusion in the multivariable model only if significant in univariable analyses.

Results of cervical cytology were reported according to the 2001 Bethesda System as negative for intraepithelial lesion or malignancy ('normal'), low-grade squamous intraepithelial lesion (LSIL) (corresponding to HPV / mild dysplasia / cervical intraepithelial neoplasia (CIN) 1) and high-grade squamous intraepithelial lesion (HSIL) (corresponding to moderate and severe dysplasia, carcinoma in situ; CIN 2 and CIN 3) (Solomon *et al.* 2002). A finding of LSIL or HSIL was defined as an abnormal result.

Previous pregnancy (including stillbirths, live births, miscarriages and terminations) was examined as a measure of previous access to gynaecological or obstetric care.

Cervical screening test receipt

Just under one third of women (337/1120) had a cervical screening test reported at enrolment. Cohort characteristics and prevalence of co-infections by cervical screening test receipt are shown in Tables 5.13 and 5.14 respectively. The 1120 women included in this analysis were enrolled into the Women's Study at a median 10 months postpartum (83% (924/1120) at ≥12 weeks postpartum, beyond the period in which cervical screening may be postponed to allow for regression of hormonal changes and healing of the cervix (NHS Cancer Screening Programmes 2006). Women diagnosed as HIV-positive fewer than six months before enrolment - six months being the screening interval specified for all women of childbearing age by Ukrainian policy - accounted for 7% (69/970).

Timing of screening tests reported at enrolment

Over half of those with date of cervical screening test reported (180/310) had received their most recent test postnatally (median 28 weeks after delivery, 17% (30/180) <12 weeks after delivery), 24% (74/310) during pregnancy and 18% (56/310) pre-conception. Most (69%, 232/334) had been tested over six months and 34% (115/334) over one year previously (median 40 weeks prior to enrolment). There were differences in timing of cervical screening tests by centre: almost half (44/90) of tests reported in Odessa and 13/15 of those at Donetsk were conducted during pregnancy vs. only 17/205 at Kiev, where the majority of tests reported were performed postnatally. Overall, women diagnosed with HIV prior to conception were more likely than those diagnosed antenatally or intrapartum to have a screening test reported at enrolment (44% (136/306) versus 26% (176/665), $\chi^2 = 31.06$ $p<0.01$). Of the 783 women with no test at baseline, 22% (n=176) had follow-up data available, of whom 39% (68/176) had been screened at follow-up.

Table 5.13: Cohort characteristics by cervical screening test report

	Test reported at enrolment (*n*=337)	No test at enrolment (*n*=783)
Median age at enrolment (IQR)	28.0 (25.2, 31.3)	27.0 (23.7, 30.2)
Marital status (*n*=1113)		
Married	225 (67%)	412 (53%)
Cohabiting	73 (22%)	235 (30%)
Single† / widowed / divorced	38 (11%)	130 (17%)
Previous pregnancies‡ (*n*=903)		
1	95 (32%)	287 (47%)
2	87 (29%)	147 (24%)
3 or more	116 (39%)	171 (28%)
Age at leaving full-time education (*n*=653)		
≤16 years	32 (14%)	71 (16%)
17-18 years	44 (20%)	84 (19%)
≥19 years	146 (66%)	276 (64%)
History of injecting drug use (*n*=1120)		
No	247 (73%)	616 (79%)
Yes	90 (27%)	167 (21%)
Alcohol use postnatally (*n*=1104)		
No	268 (81%)	603 (78%)
Yes	63 (19%)	170 (22%)
History of smoking (*n*=1114)		
No	98 (29%)	238 (31%)
Yes	236 (71%)	542 (69%)
Current smoking (*n*=1111)		
No	153 (46%)	389 (50%)
Yes	181 (54%)	388 (50%)
Disclosure of HIV status to anyone (*n*=1120)		
No	15 (4%)	42 (5%)
Yes	322 (96%)	741 (95%)
Disclosure of HIV status to family / friends (*n*=1120)		
No	107 (32%)	293 (37%)
Yes	230 (68%)	490 (63%)
Disclosure of HIV status to partner (*n*=1120)		
No	67 (20%)	189 (24%)
Yes	270 (80%)	594 (76%)
WHO stage (*n*=1109)		
1-2	255 (76%)	657 (85%)
3-4	82 (24%)	115 (15%)
CD4 count (*n*=959)		
≤ 200 cells/mm^3	22 (7%)	63 (10%)
201-350 cells/mm^3	56 (18%)	114 (18%)
> 350 cells/mm^3	234 (75%)	470 (73%)
Median	468 cells/mm^3	456 cells/mm^3
Taking ART postnatally (*n*=1114)		
No	262 (78%)	643 (82%)
Yes	72 (22%)	137 (18%)
Any OC‡ use reported postnatally (*n*=1120)		
No	291 (86%)	715 (91%)
Yes	46 (14%)	68 (9%)
Can afford family planning (self-report) (*n*=1089)		
No	40 (12%)	179 (24%)
Yes	292 (88%)	578 (76%)

†Includes non-cohabiting partnerships; ‡Previous pregnancies include still births, live births, miscarriages and terminations. OC, oral hormonal contraceptive.

Table 5.14: Co-infections by cervical screening test report at enrolment

	Test reported at enrolment (*n*=337)	No test at enrolment (*n*=783)
Chlamydia (*n*=851)	71 (25%)	144 (25%)
Syphilis (*n*=907)	13 (4%)	17 (3%)
Trichomonas vaginalis (n=645)	19 (6%)	52 (15%)
HSV-2 antibodies (*n*=806)	156 (55%)	255 (49%)
Vulvo-vaginal candida (*n*=739)	134 (43%)	232 (54%)
Bacterial vaginosis (*n*=731)	67 (22%)	59 (14%)
Hepatitis C seropositive (*n*=872)	120 (41%)	179 (31%)
Hepatitis B surface antigen positive (*n*=1002)	23 (7%)	61 (9%)

Factors associated with having a cervical screening test result reported

There was no significant change over time in the proportion of women with a screening test reported as part of HIV care at study enrolment (30% overall, p=0.87) but significant differences by centre from 11% (19/173) in Donetsk to 26% (111/419) in Odessa and 39% (207/528) in Kiev (χ^2 =53.46, p<0.01). In univariable analyses, age, marital status, number of previous pregnancies, IDU history, WHO clinical stage, timing of HIV diagnosis, affordability of contraception and centre were significantly associated with having a screening test at the HIV/AIDS centre (Tables 5.15a and 5.15b). HCV seropositivity and IDU history were both associated with report of a screening test in univariable analysis (χ^2 =9.69, p<0.01 and χ^2 =3.85, p=0.05 respectively), but not after adjusting for year and centre (p=0.44 and p=0.48 respectively) and were therefore excluded from the multivariable model. Other factors that were not associated with having a test reported were smoking (current or history), current alcohol use, disclosure of HIV status to a partner, postnatal ART receipt and CD4 count.

BV was more common among women with a cervical screening test result reported than among those without (22% (67/311) vs. 14% (59/420) respectively, χ^2 =7.04, p<0.01). The opposite was true for TV (6% (19/297) prevalence among those with a cervical screening test vs. 15% (52/348) among those without, χ^2 =11.94, p<0.01) and vulvo-vaginal candida (43% (134/309) prevalence among those with a cervical screening test vs. 54% (232/430) among those without, χ^2 =8.06, p<0.01). There was no difference in probability of having a screening test reported HSV-2 antibody status (χ^2 =2.47, p=0.12). All of these infections are associated with genital symptoms which may prompt a pelvic examination and opportunistic cervical screening test. Conversely, if an incidental

finding of genital infection is made during pelvic examination for cervical screening and discharge or bleeding is present, the screening test may be postponed until the infection is treated. Due to these problems with interpretation, diagnosis of genital infection was not examined as an explanatory variable in analyses investigating factors associated with having a cervical screening test result reported.

Of note, women who had not been tested for BV, TV, candida or HSV-2 antibodies were less likely to have a cervical screening test result reported than women who were tested and negative for these infections ($p<0.01$ for all three infections), indicating that common factors underlie access to and uptake of both tests for genital infections and cervical screening.

In the multivariable model (Tables 5.15a and 5.15b), there were significant differences in reporting of cervical screening tests by centre (Wald's test $p<0.01$), and women were twice as likely to have a test reported if diagnosed prior to their most recent pregnancy than during the 3rd trimester or intrapartum. Women with one previous pregnancy (vs. ≥2) were less likely to have a test reported ($p=0.05$).

In order to investigate factors associated with being screened among women with the longest exposure to HIV care, a sub-analysis was conducted limited to the 306 women diagnosed with HIV before their most recent pregnancy. In this group, 44% (136/306) of whom had a cervical screening test result reported at enrolment, age, marital status, affordability of contraception, HIV disclosure, WHO stage and centre were significantly associated with reporting of a test result in univariable analyses (Table 5.16). In multivariable analyses adjusting for year, centre and affordability of contraception, women leaving full-time education at ≤16 (vs. ≥19) years of age and who were cohabiting (vs. married) were less likely to have a test reported, although the latter was not statistically significant ($p=0.06$). The four-category age variable did not significantly contribute to fit of the model when adjusting for year and centre (Wald's test $p=0.14$), however women ≥27 years were significantly more likely to have a test reported than those <27 years when a binary variable was used (APR 1.57, 95% CI 1.11-2.20 adjusting for marital status, education, affordability of contraception, year and centre, $p=0.01$).

Table 5.15a: Factors associated with having a cervical screening test reported at study enrolment (continued in Table 5.15b)

	Proportion (*n*) with test	Unadjusted PR(95% CI)	PR (95% CI) adjusted for year and centre	PR (95% CI) adjusted for year and centre *n*=870†	Adjusted PR‡ – (95% CI) *n*=870
Age at enrolment					
16-23 years	21% (55/265)	1.00	1.00	1.00	1.00
24-26 years	31% (78/255)	1.47 (1.09,1.99) *p*=0.01	1.37 (1.02,1.84) *p*=0.04	1.18 (0.86,1.62) *p*=0.32	1.07 (0.78,1.47) *p*=0.68
27-30 years	33% (111/339)	1.58 (1.19,2.09) *p*<0.01	1.40 (1.06,1.85) *p*=0.02	1.33 (0.99,1.79) *p*=0.06	1.13 (0.84,1.51) *p*=0.42
≥31 years	36% (92/257)	1.72 (1.29,2.30) *p*<0.01	1.64 (1.23,2.17) *p*<0.01	1.49 (1.10,2.10) *p*<0.01	1.24 (0.90,1.69) *p*=0.18
Marital status					
Married	35% (225/637)	1.00	1.00	1.00	1.00
Cohabiting	24% (73/308)	0.67 (0.54,0.84) *p*<0.01	0.74 (0.59,0.93) *p*=0.01	0.77 (0.60,0.98) *p*=0.04	0.81 (0.63,1.04) *p*=0.10
Single / widowed/ divorced	23% (38/168)	0.64 (0.47,0.86) *p*<0.01	0.70 (0.52,0.94) *p*=0.02	0.73 (0.54,0.99) *p*=0.04	0.84 (0.61,1.16) *p*=0.29
Previous pregnancies at enrolment					
≥2	39% (203/521)	1.00	1.00	1.00	1.00
1	25% (95/382)	0.64 (0.52,0.78) *p*<0.01	0.65 (0.53,0.80) *p*<0.01	0.66 (0.54,0.81) *p*<0.01	0.80 (0.65,1.00) *p*=0.05
History of IDU					
No	29% (247/863)	1.00	1.00		
Yes	35% (90/257)	1.22 (1.00,1.49) *p*=0.05	1.07 (0.88,1.31) *p*=0.48		
WHO clinical stage					
1-2	28% (255/912)	1.00	1.00	1.00	1.00
3-4	42% (82/197)	1.49 (1.22,1.81) *p*<0.01	1.36 (1.11,1.65) *p*<0.01	1.30 (1.06,1.59) *p*=0.01	1.07 (0.87,1.32) *p*=0.51

†Limited to 870 women included in the multivariable model ‡Adjusted for all factors in final model: age, marital status, previous pregnancies, WHO stage, timing of HIV diagnosis, affordability of contraception, year and centre of enrolment

Table 5.15b: Factors associated with having a cervical screening test reported at study enrolment (continued from Table 5.15a)

	Proportion (*n*) with test	Unadjusted PR(95% CI)	PR (95% CI) adjusted for year and centre	PR (95% CI) adjusted for year and centre *n*=870†	Adjusted PR‡ – (95% CI) *n*=870
Timing of HIV diagnosis					
Prior to conception	44% (136/306)	1.00	1.00	1.00	1.00
1st / 2nd trimesters	28% (155/545)	0.64 (0.53,0.77) *p*<0.01	0.59 (0.49,0.70) *p*<0.01	0.57 (0.47,0.68) *p*<0.01	0.62 (0.51,0.75) *p*<0.01
3rd trimester / intrapartum	18% (21/120)	0.39 (0.26,0.59) *p*<0.01	0.36 (0.24,0.53) *p*<0.01	0.37 (0.25,0.55) *p*<0.01	0.42 (0.28,0.63) *p*<0.01
Affordability of contraception					
Can afford	34% (292/870)	1.00	1.00	1.00	1.00
Can't afford	18% (40/219)	0.54 (0.40,0.73) *p*<0.01	0.71 (0.52,0.95) *p*=0.02	0.77 (0.56,1.06) *p*=0.12	0.76 (0.54,1.07) *p*=0.12
Year of enrolment					
2007/08	30% (101/339)	1.00	1.00	1.00	1.00
2009	31% (135/435)	1.04 (0.84,1.29) *p*=0.71	0.90 (0.73,1.12) *p*=0.36	0.94 (0.74,1.18) *p*=0.59	0.96 (0.76,1.20) *p*=0.71
2010/11	29% (101/344)	0.99 (0.78,1.24) *p*=0.90	0.93 (0.74,1.17) *p*=0.54	1.04 (0.81,1.32) *p*=0.78	0.97 (0.76,1.23) *p*=0.80
Centre of enrolment					
Odessa	26% (111/419)	1.00	1.00	1.00	1.00
Kiev	39% (207/528)	1.48 (1.22,1.79) *p*<0.01	1.51 (1.24,1.84) *p*<0.01	1.28 (1.03,1.59) *p*=0.03	1.32 (0.07,1.63) *p*<0.01
Donetsk	11% (19/173)	0.41 (0.26,0.65) *p*<0.01	0.42 (0.27,0.67) *p*<0.01	0.43 (0.26,0.72) *p*<0.01	0.49 (0.29,0.82) *p*<0.01

†Limited to 870 women included in the multivariable model ‡Adjusted for all factors in final model: age, marital status, previous pregnancies, WHO stage, timing of HIV diagnosis, affordability of contraception, year and centre of enrolment

Table 5.16: Factors associated with cervical screening test reported at study enrolment, among women diagnosed with HIV prior to most recent pregnancy

	Proportion (*n*) with test	Unadjusted PR(95% CI)	PR (95% CI) adjusted for year and centre	PR (95% CI) adjusted for year and centre, *n*=207†	Adjusted PR‡(95% CI) *n*=207
Age at enrolment					
16-23 years	27% (12/44)	1.00	1.00		
24-26 years	39% (24/62)	1.42 (0.80,2.53) *p*=0.23	1.32 (0.76,2.29) *p*=0.33		
27-30 years	51% (56/110)	1.87 (1.11,3.13) *p*=0.02	1.66 (1.00,2.75) *p*=0.05		
≥31 years	49% (44/89)	1.81 (1.07,3.07) *p*=0.03	1.66 (1.00,2.76) *p*=0.05		
Marital status					
Married	55% (99/180)	1.00	1.00	1.00	1.00
Cohabiting	30% (24/80)	0.55 (0.38,0.78) *p*<0.01	0.63 (0.44,0.90) *p*=0.01	0.51 (0.29,0.90) *p*=0.02	0.58 (0.32,1.03) *p*=0.06
Single / widowed / divorced	27% (12/44)	0.50 (0.30,0.82) *p*<0.01	0.58 (0.36,0.94) *p*=0.03	0.63 (0.36,1.09) *p*=0.10	0.74 (0.42,1.31) *p*=0.30
Age at leaving full-time education					
≥19 years	50% (60/121)	1.00	1.00	1.00	1.00
17-18 years	46% (21/46)	0.92 (0.64,1.32) *p*=0.66	0.73 (0.52,1.04) *p*=0.08	0.76 (0.54,1.08) *p*=0.13	0.79 (0.56,1.13) *p*=0.20
≤16 years	36% (17/47)	0.73 (0.48,1.11) *p*=0.14	0.55 (0.36,0.83) *p*<0.01	0.56 (0.37,0.84) *p*=0.01	0.66 (0.44,1.01) *p*=0.05
Affordability of contraception					
Can afford	51% (114/223)	1.00	1.00	1.00	1.00
Can't afford	25% (19/75)	0.50 (0.33,0.75) *p*<0.01	0.68 (0.45,1.02) *p*=0.06	0.57 (0.33,0.98) *p*=0.04	0.79 (0.44,1.43) *p*=0.44
HIV status disclosure to family or friends					
Yes	51% (95/188)	1.00	1.00		
No	35% (41/118)	0.69 (0.52,0.91) *p*=0.01	0.89 (0.68,1.17) *p*=0.41		
WHO stage					
1-2	41% (82/202)	1.00	1.00		
3-4	53% (54/101)	1.32 (1.03,1.69) *p*=0.03	1.19 (0.94,1.51) *p*=0.15		
Year of enrolment					
2007/08	38% (36/95)	1.00	1.00	1.00	1.00
2009	45% (44/98)	1.18 (0.84,1.66) *p*=0.33	1.13 (0.79,1.60) *p*=0.51	0.95 (0.63,1.45) *p*=0.82	0.85 (0.58,1.24) *p*=0.39
2010/11	50% (56/112)	1.32 (0.96,1.81) *p*=0.09	1.26 (0.90,1.75) *p*=0.18	1.06 (0.69,1.63) *p*=0.78	0.91 (0.61,1.36) *p*=0.66
Centre of enrolment					
Odessa	48% (49/102)	1.00	1.00	1.00	1.00
Kiev	56% (78/139)	1.17 (0.91,1.50) *p*=0.22	1.10 (0.84,1.44) *p*=0.48	1.24 (0.79,1.94) *p*=0.35	1.11 (0.73,1.69) *p*=0.63
Donetsk	14% (9/65)	0.29 (0.15,0.55) *p*<0.01	0.28 (0.15,0.55) *p*<0.01	0.38 (0.18,0.82) *p*=0.01	0.38 (0.18,0.80) *p*=0.01

†Limited to 207 women included in the multivariable model ‡Adjusted for: marital status, age at leaving full-time education, affordability of contraception, year and centre of enrolment

Cervical abnormalities

At enrolment, among the 30% with a screening test result reported, prevalence of cervical abnormalities at the most recent test was 21% (68/325) overall (17% (*n*=54) LSIL and 4% (*n*=14) HSIL). Results were not available for 4% (12/337) of those tested, presumably because the sample was inadequate. In total, 38% (123/325) of women with a screening test result reported at enrolment had the test conducted on the same day as a positive sample was taken or diagnosis made for at least one of: chlamydia, gonorrhoea, syphilis, HSV-2, candida, TV or BV. Among the 68 women who only had a test reported at follow-up, prevalence of cervical abnormalities was 31% (21/68).

In crude analyses, women with BV infection were more likely to have a diagnosis of LSIL or HSIL, as were those who were HSV-2 seropositive and those with two or more previous pregnancies (Table 5.17). No other factors were significantly associated with abnormal findings. In the multivariable model, HSV-2 seropositivity was associated with an 83% increased risk of an abnormal finding and BV diagnosed antenatally or postnatally with over a three-fold increased risk (Table 5.17). Because the 30% of women with a cervical screening test result were more likely to have tested positive for BV, the prevalence of cervical abnormalities reported here may be an over-estimate.

Table 5.17: Factors associated with an abnormal finding (LSIL or HSIL) on cervical screening

	Proportion (*n*) with abnormal result	Unadjusted PR (95% CI)	Unadjusted PR (95% CI) *n*=213†	Adjusted PR‡ (95% CI) *n*=213
Age at enrolment				
16-23 years	23% (15/65)	1.00	1.00	1.00
24-26 years	23% (18/77)	1.02 (0.53-1.96) *p*=0.95	1.60 (0.55-4.68) *p*=0.39	1.52 (0.57-4.04) *p*=0.41
27-30 years	24% (21/89)	1.04 (0.57-1.91) *p*=0.90	1.97 (0.72-5.40) *p*=0.19	1.72 (0.69-4.31) *p*=0.24
≥31 years	20% (14/69)	0.93 (0.49-1.78) *p*=0.83	1.81 (0.65-5.05) *p*=0.26	1.42 (0.56-3.60) *p*=0.46
Previous pregnancies at enrolment				
≥2	26% (51/195)	1.00	1.00	1.00
1	15% (14/92)	0.58 (0.34-1.00) *p*=0.05	0.44 (0.21-0.93) *p*=0.03	0.56 (0.26-1.22) *p*=0.15
CD4 count				
>350 cells/mm^3	22% (50/228)	1.00	1.00	1.00
201-350 cells/mm^3	21% (11/53)	0.95 (0.53-1.69) *p*=0.85	1.21 (0.65-2.27) *p*=0.55	1.36 (0.74-2.49) *p*=0.33
≤200 cells/mm^3	25% (5/20)	1.14 (0.51-2.53) *p*=0.75	1.57 (0.65-3.77) *p*=0.31	2.07 (0.93-4.57) *p*=0.07
Currently smoking				
No	25% (38/151)	1.00	1.00	1.00
Yes	19% (33/171)	0.77 (0.51-1.16) *p*=0.21	0.99 (0.59-1.67) *p*=0.98	0.78 (0.49-1.26) *p*=0.31
Oral contraceptive use postnatally (any)				
No	22% (61/279)	1.00	1.00	1.00
Yes	24% (11/46)	1.09 (0.62-1.92) *p*=0.76	0.94 (0.46-1.93) *p*=0.86	0.95 (0.48-1.88) *p*=0.88
HSV-2 antibodies				
No	18% (22/125)	1.00	1.00	1.00
Yes	27% (40/150)	1.52 (0.95-2.41) *p*=0.08	1.73 (1.00-3.00) *p*=0.05	1.83 (1.07-3.11) *p*=0.03
Chlamydia				
No	20% (41/205)	1.00	1.00	1.00
Yes	25% (17/68)	1.25 (0.76-2.05) *p*=0.38	1.32 (0.75-2.32) *p*=0.33	0.79 (0.46-1.36) *p*=0.40
Bacterial vaginosis				
No	17% (40/236)	1.00	1.00	1.00
Yes	39% (25/64)	2.30 (1.52-3.50) *p*<0.01	3.36 (2.07-5.45) *p*=<0.01	3.49 (2.11-5.76) *p*=<0.01
Trichomonas vaginalis				
No	19% (52/269)	1.00	1.00	
Yes	44% (8/18)	2.30 (1.30-4.07) *p*<0.01	1.80 (0.76-4.24) *p*=0.18	

†Limited to 213 women included in the multivariable model ‡Adjusted ***a priori*** for age, previous pregnancies, CD4 count, current smoking, oral contraceptive use, HSV-2 and chlamydia, and additionally for BV

5.5 Limitations

Data availability on testing for HIV co-infections in this observational study will have been affected by factors including local policy and resources (indicated by the almost complete lack of cervical screening and chlamydia test results among women enrolled at Krivoy Rog and Mykolaiv HIV/AIDS centres), assessment of women's infection risk and their attendance for HIV care, and possibly also the provision of sexual and reproductive healthcare by other local providers. Testing coverage was only 80% for HCV, 67% for chlamydia and 30% for cervical screening among centres included in analyses. Bias in availability of test results may have led to under- or over-estimation of infection prevalence; IDUs were more likely to test positive for chlamydia but less likely to have received a test, while women with BV were more likely to have a finding of cervical abnormality when screened and more likely to have a screening result reported. Bias may also have influenced the associations found between cervical abnormalities and BV or HSV-2, if women at increased risk of HPV infection and other infections (e.g. those with high-risk sexual behaviours) were selectively tested. Results may not be generalizable to women who were not tested, who enrolled at centres excluded from the various analyses, and to HIV-positive women not in contact with HIV services.

HCV analyses focusing on possible non-IDU modes of HCV acquisition were exploratory and hypothesis-generating in nature, and were limited by a lack of direct measures of sexual and iatrogenic risk. Proxies of these risks were problematic due to possible confounding by under-ascertainment of IDU. These results are discussed in more detail in section 7.4.3, page 264. Some of the HCV seropositive women included in the work on non-invasive markers of liver fibrosis will have spontaneously resolved their infection, but could not be identified because qualitative HCV RNA tests are not routinely carried out in Ukraine.

Data are not routinely shared between HIV/AIDS centres and other primary healthcare providers or referral hospitals, and so there was no information available on testing or investigations received elsewhere (including on colposcopy and histology, for women with cervical abnormalities). Rates of false positives or negatives on cytologic screening may have been elevated by the fact that a quarter of samples were taken during pregnancy, 10% at <12 weeks postpartum and 38% on the same day as a positive sample for a genital infection (Flannelly 2010).

5.6 Key points

- Prevalence of genital infections was high among women tested in this cohort: 88% for vulvo-vaginal candidiasis, 60% for HSV-2 antibodies, 24% for chlamydia, 15% for HBsAg, 13% for BV, 11% for TV, 2% for syphilis and 0.3% for gonorrhoea. Coverage with HBV vaccination of HBsAg negative women was very low.
- Of those with chlamydia, 81% had at least one other STI in addition to HIV (mostly HSV-2). In adjusted analyses, factors associated with a positive chlamydia test were: history of IDU, being in a cohabiting partnership (vs. married), not knowing their partner's HIV status and reporting contraception to be unaffordable.
- The HIV/HCV co-infection rate was 32% overall; 78% among IDUs and 20% among non-IDUs. The prevalence of HCV antibodies among non-IDUs may be partially explained by an under-ascertainment of IDU history in this cohort, but also by acquisition of HCV via sex, iatrogenic contact, or through non-injecting drug use.
- Coverage with cervical screening as part of HIV care was low: 30% of women had been screened by cohort enrolment. Women with a longer duration of diagnosed HIV infection were more likely to have been screened as part of HIV care. Those leaving full-time education at ≤16 years had poorer coverage with screening than those educated beyond the age of 18.
- The prevalence of cervical abnormalities (low or high grade squamous intraepithelial lesions) among those screened was 21%. HSV-2 antibodies and a recent BV diagnosis were both associated with an increased risk of an abnormal finding in adjusted analyses.
- There was significant variation in the availability of test results for HIV co-infections and cervical screening by HIV/AIDS centre, highlighting the inconsistency of provision as part of HIV care in Ukraine.
- There is substantial unmet need for sexual and reproductive healthcare among women in this cohort, all of whom were in contact with HIV services following delivery.

Chapter 6 Adherence to ART during pregnancy and postnatally in Ukraine

6.1 Introduction

In this chapter, ART adherence during pregnancy and postnatally among women in Ukraine is explored using the results of an anonymous self-report survey conducted at maternity hospitals and HIV/AIDS centres. Data were matched to the ECS and postnatal Women's Study to provide additional clinical information. The survey included questions on a number of factors potentially influencing adherence behaviour including perinatal depression, self-efficacy, and self-perception of the risks and benefits of ART. Responses to these questions as well as characteristics of the study population are described in section 6.3, followed by levels of self-reported adherence to maternal ART during pregnancy and postnatally and to neonatal prophylaxis (sections 6.4 and 6.5). In section 6.6, the self-report adherence measure is validated against antenatal viral load among a small sub-group of women with both measures available. Factors associated with poor adherence, according to this measure and to the outcome of 'any reported missed dose', are explored in section 6.7. Survey results on aspects of local policy and practice relevant to the results in this chapter (e.g. adherence and psychosocial support available at the HIV/AIDS centres) are given in Chapter 2 (page 76).

6.2 Methods

The design of the Antenatal and Postnatal Adherence Surveys is described in Chapter 2 and copies of the questionnaires are provided in Appendix D, page 332. Specific details of the CASE adherence index tool used are given starting on page 64, followed by details of the other tools used (e.g. to measure perinatal depression and self-efficacy). The CASE score cut-off used to define 'poor' adherence was informed by the results of validation analyses exploring the associations between CASE scores and viral load measures (section 6.6, page 215). This definition was compared with the outcome of 'any missed dose', the most sensitive measure of poor adherence available using a self-report tool.

Data analysis

Availability of viral load measures to validate CASE adherence index scores was limited and particularly measures taken at least 12 weeks after initiating ART when viral suppression might be achieved. It was therefore not possible to calculate the sensitivity and specificity of different CASE score cut-offs in identifying non-suppressed patients. Instead, the frequency distribution of viral load suggested fitting zero-inflated negative binomial models (Ridout *et al.* 2001), which account for an excess of zeros and over-dispersion. These models were used to investigate the strength of association between shifted, censored HIV RNA load values (whereby a value of 0 corresponded to an undetectable measure) and CASE scores dichotomised at different values. These models were limited to women who had been on ART for at least 4 weeks by the time of the viral load measure. The use of the zero-inflated negative binomial model is described further in section 6.6. ART duration and type of cART (PI-based or not) were included in the models *a priori* but were subsequently removed if not associated with the outcome. The BIC was used to identify the model maximising goodness-of-fit (section 6.6). The BIC was preferred to the AIC for this work as it yields models more conservative against over-fitting (Kuha 2004) and the number of data points was small.

For analyses of factors associated with poor adherence during pregnancy and postnatally, univariable comparisons were made using Fisher's exact test. Poisson regression models with robust estimates of variances (Barros *et al.* 2003) were fitted to obtain PRs adjusted for hospital of

enrolment, as there was some evidence of between-hospital variation in adherence. For factors associated with poor adherence postnatally, the small number of enrolments at some centres and scarcity of the outcome precluded between-centre comparisons and PRs are presented unadjusted for centre. Multivariable analyses were not conducted, because many of the factors associated with poor adherence were correlated and statistical power was insufficient to adjust for confounding. The aim of this work was to broadly characterise women most likely to experience adherence problems, in order to identify groups of women likely to benefit most from targeted adherence support, rather than to establish the relative importance of independent factors.

6.3 Description of Adherence Survey participants

Enrolment and study matching

In total, 198 forms were returned in the Antenatal Survey and 185 included in analyses (exclusions shown in Figure 6.2). Over half (97/185) of those included in the analyses were returned by women already enrolled in the ECS by September 2012. Of the 274 forms returned in the Postnatal Survey, 41 were excluded from analyses, most (*n*=29) because eligibility criteria were not met (see Figure 6.3). Of the 233 postnatal surveys included in analyses, 49% (*n*=114) were returned by women enrolled in the ECS only and 41% (*n*=96) by women also enrolled in the postnatal Women's Study. Thirteen women took part in both the Antenatal and Postnatal Adherence Surveys.

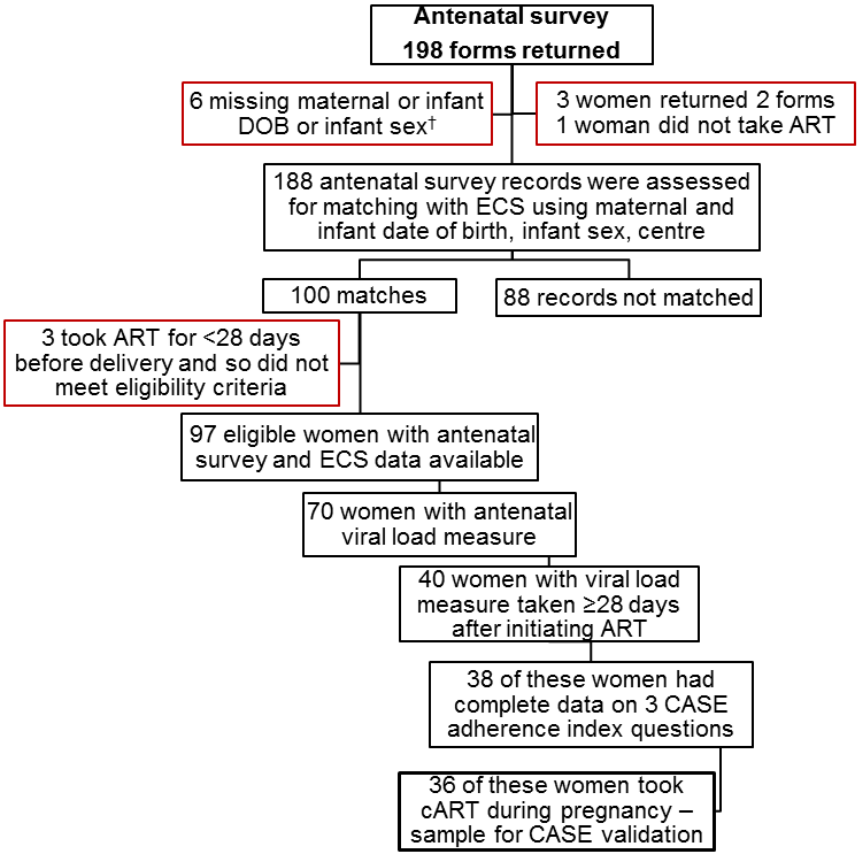


Figure 6.2: Availability of matched Antenatal Survey and ECS data, and identification of surveys with matched viral load measures for validation of CASE adherence index scores

Exclusions shown in red. †These six responses were excluded from all analyses, as it was not possible to verify that they were from unique responders.

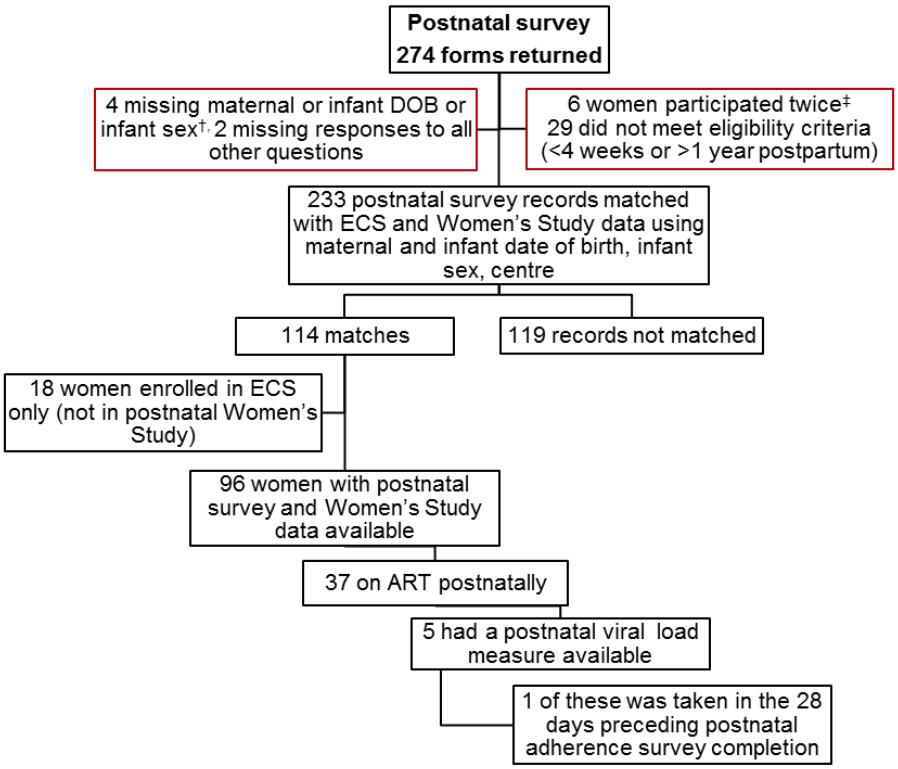


Figure 6.3: Availability of matched Postnatal Survey and Women's Study data

Exclusions shown in red. †These four responses were excluded from all analyses, as it was not possible to verify that they were from unique responders. ‡Among the six woman who participated twice, the first completed survey (i.e. closest to delivery) was retained for analyses.

Survey participation

The 185 Antenatal Surveys included in analyses were returned by women delivering at Kiev (*n*=74), Odessa (*n*=83) and Simferopol (*n*=28) maternity hospitals. The 233 postnatal surveys were completed by women receiving HIV care in the year following delivery at six HIV/AIDS centres: Kiev (*n*=13), Odessa (*n*=75), Mykolaiv (*n*=38), Donetsk (*n*=38), Krivoy Rog (*n*=55) and Simferopol (*n*=14).

Participation rates were estimated over the main six-month survey period (i.e. excluding the pilot period and extension period for sites with operational problems). Over this period, the 106 respondents in the Antenatal Survey represented an estimated participation rate of 35-44% (240-300 HIV-positive women deliver across the three participating hospitals over a six month period). The participation rate among eligible women (i.e. those who received antenatal ART for at least the last four weeks of their pregnancy) could be estimated to be in the region of 39-49%, based on the assumption that 10% of women did not receive ≥4 weeks of antenatal ART (see Chapter 3).

For the Postnatal Survey, the participation rate at the five HIV/AIDS centres enrolling into the Women's Study (and therefore with denominator data available) was estimated at 35% (137/396) overall and 75% (63/84) among those on postnatal ART. This estimate considered only women attending the HIV/AIDS centre for the first time postnatally and not those returning for follow-up – the true participation rate may therefore have been lower.

Representativeness of Adherence Survey participants

Table 6.1 shows characteristics of the 97 Antenatal Adherence Survey respondents and 114 Postnatal Adherence Survey respondents with linked ECS data available, compared with 1596 women participating only in the ECS and enrolled at the same centres in 2010-2012.

Postnatal Survey participants currently on ART were in substantially worse clinical and immunological health than the other study groups, and were more likely to have been diagnosed as HIV-positive before the most recent pregnancy and to have conceived on cART. They were also more likely to have an IDU history (associated with more advanced HIV disease, page 80).

Among the Antenatal Adherence Survey group, prevalence of an IDU history or IDU partner, severity of HIV disease and timing of HIV diagnosis were all similar to the group enrolled in the ECS only. However, women in the Antenatal Adherence Survey group were more likely to have received cART (vs. ZDVm) and less likely to be single than women enrolled only in the ECS (Table 6.1). Duration of ART by delivery was similar: 13.7 weeks (IQR 11.3, 17) for the Antenatal Adherence Survey group (n=93) and 14.6 weeks (IQR 11.3, 17.1) for women enrolled only in the ECS (n=1426) (Wilcoxon-Mann-Whitney test p=0.97). For the Postnatal Adherence Survey group, median duration of ART by date of survey participation was 43.7 weeks for women who continued on ART (IQR 26.0, 54.9, n=41).

Educational status of women in all three adherence survey groups was higher than among women enrolled only in the ECS. This reflects the association between educational status and receipt of ART reported in Chapter 3. It is also possible that those with less education were less likely to consent to take part. This under-representation of women with the lowest levels of education in the Adherence Survey samples has implications for the generalizability of results.

Table 6.1: Representativeness of Adherence Survey respondents in terms of ECS enrolments

		Adherence Surveys, linked ECS data available		
	ECS enrolment only (*n*=1596)	Antenatal (*n*=97)	Postnatal, on ART (*n*=44)	Postnatal, not on ART (*n*=70)
Marital status				
Married	634 (40%)	49 (51%)	24 (55%)	27 (39%)
Cohabiting	738 (47%)	43 (44%)	13 (30%)	34 (49%)
Single	214 (13%)	5 (5%)	7 (16%)	9 (13%)
Age at leaving full-time education				
≤16 years	204 (26%)	1 (6%)	2 (9%)	3 (8%)
17 years or above	595 (74%)	15 (94%)	20 (91%)	33 (92%)
History of IDU				
No	1398 (88%)	87 (90%)	35 (80%)	69 (99%)
Yes	191 (12%)	10 (10%)	9 (20%)	1 (1%)
IDU partner				
No	1055 (68%)	67 (71%)	35 (85%)	56 (82%)
Yes	491 (32%)	27 (29%)	6 (15%)	12 (18%)
History of pregnancy termination				
0	540 (41%)	40 (45%)	14 (39%)	18 (34%)
1	338 (26%)	27 (31%)	8 (22%)	18 (34%)
2 or more	435 (33%)	21 (24%)	14 (39%)	17 (32%)
Parity at ECS enrolment				
0	514 (38%)	29 (32%)	12 (34%)	19 (38%)
1	543 (40%)	44 (48%)	16 (46%)	28 (56%)
2 or more	296 (22%)	18 (20%)	7 (20%)	3 (6%)
Timing of HIV diagnosis				
Before pregnancy	693 (44%)	44 (46%)	23 (52%)	23 (33%)
1st/2nd trimesters	736 (46%)	48 (50%)	21 (48%)	42 (60%)
3rd trimester/intrapartum	159 (10%)	4 (4%)	0	5 (7%)
Antenatal CD4 count (first in pregnancy)				
≤350 cells/mm^3	484 (39%)	19 (28%)	26 (76%)	14 (22%)
>350 cells/mm^3	773 (61%)	48 (72%)	8 (24%)	50 (78%)
Antenatal viral load available				
No	437 (27%)	26 (27%)	8 (18%)	11 (16%)
Yes	1159 (73%)	71 (73%)	36 (82%)	59 (84%)
WHO stage				
1-2	1160 (81%)	67 (78%)	25 (61%)	67 (99%)
3-4	269 (19%)	19 (22%)	16 (39%)	1 (1%)
Timing of ART initiation				
Before conception	95 (7%)	7 (8%)	7 (17%)	0
1st/2nd trimester	929 (65%)	61 (66%)	23 (56%)	45 (64%)
3rd trimester	402 (28%)	25 (27%)	11 (27%)	25 (36%)
Antenatal ART regimen				
mono/dual	314 (22%)	11 (12%)	3 (7%)	12 (17%)
cART	1139 (78%)	83 (88%)	39 (93%)	58 (83%)
Gestation at delivery				
≥37 weeks	1402 (88%)	88 (91%)	35 (80%)	67 (96%)
<37 weeks	187 (12%)	9 (9%)	9 (20%)	3 (4%)
Year of delivery				
2010	571 (36%)	0	12 (12%)	8 (6%)
2011	774 (48%)	118 (64%)	86 (84%)	113 (86%)
2012	251 (16%)	67 (36%)	4 (4%)	10 (8%)

Characteristics of Adherence Survey participants

Table 6.2 summarises characteristics of all Adherence Survey participants (i.e. including women without linked ECS data available). Postnatal respondents took part a median of 5.7 months after delivery, and women on postnatal ART were slightly older than the other two groups. Only five women in the Antenatal Survey and six in the Postnatal Survey were adolescents (<20 years of age). Over 90% of women in each survey group had disclosed their HIV status to their partner, a family member or a friend at the time of survey participation. Most women were living with their husband or partner. Of those who were single, over half (18/33) in the Antenatal Survey and 41% (19/46) in the Postnatal Survey were living with their parents or other family members.

Reporting of current illicit drug use was very low; two women reported current marijuana use in the Antenatal Survey and an additional two reported current use of another illicit substance (with the same numbers in the Postnatal Survey, although different women). With the exception of smoking, alcohol and marijuana use, a history of drug use was more common among Antenatal Survey participants and postnatal participants on ART than among women participating in the Postnatal Survey and not currently on ART (Table 6.2). Support groups, peer counselling and adherence programmes were much more commonly used by the Postnatal Survey group than by the Antenatal Survey group (Table 6.2), which may be explained by better engagement with services among women who return for postnatal follow-up, greater opportunity where a woman has been diagnosed as HIV-positive for longer, and specific targeting of NGO-provided support to new mothers.

Table 6.2: Characteristics of Adherence Survey participants

	Antenatal Survey (*n*=185)	Postnatal Survey, on ART (*n*=102)	Postnatal Survey, not on ART (*n*=131)
Median age at participation (IQR)	27.5 years (25.0, 30.9)	29.5 years (25.9, 33.5)	27.3 years (24.2, 30.8)
Median time since delivery (IQR)	1 day (1, 2)	5.3 months (2.4, 7.8)	6.0 months (2.0, 7.7)
Marital status			
Married	100 (54%)	55 (54%)	47 (36%)
Cohabiting	51 (28%)	23 (23%)	61 (47%)
Single	34 (18%)	24 (24%)	23 (18%)
Pregnancy unplanned	50 (28%)	26 (27%)	44 (38%)
Living with:			
Husband/partner	132 (72%)	80 (79%)	102 (79%)
Extended family (including parents)	60 (33%)	23 (23%)	42 (33%)
Living as only adult in household	12 (7%)	13 (13%)	16 (12%)
Disclosure of HIV status			
To husband/partner	135 (74%)	80 (79%)	103 (82%)
Family or friend(s)	108 (59%)	55 (54%)	78 (62%)
No one at all	16 (9%)	7 (7%)	5 (4%)
Do you have someone you can rely on to help you care for your baby?			
Yes	164 (91%)	89 (88%)	112 (88%)
No	17 (9%)	12 (12%)	15 (12%)
Smoking, alcohol and drug use			
Current smoker	49 (27%)	28 (28%)	48 (37%)
Current alcohol use	168 (9%)	8 (8%)	10 (8%)
Ever used marijuana	25 (14%)	15 (15%)	14 (11%)
Ever used illicit drugs other than marijuana	24 (13%)	17 (17%)	6 (5%)
Severity of ART side effects			
Not bothered by side effects or only slightly	132 (75%)	76 (76%)	N/A
Somewhat/ terribly bothered by side effects	44 (25%)	24 (24%)	N/A
Use of support services			
Currently using support group	10 (5%)	21 (21%)	14 (11%)
Currently using peer counselling	10 (5%)	27 (26%)	60 (46%)
Currently using social services	40 (22%)	28 (27%)	55 (42%)
Currently using adherence programme	4 (2%)	39 (38%)	4 (3%) †

†These four women may have been engaged in a programme focusing on ART preparedness.

Perinatal depression

About a quarter of respondents in each of the three survey groups had a positive screening test result for depression. Low mood was reported more frequently than anhedonia; the proportions of women reporting each and both of these symptoms are shown in Table 6.3.

Table 6.3: Self-reported symptoms of depression and depression screening test results

	Antenatal Survey (*n*=180)	Postnatal Survey – women on ART (*n*=101)	Postnatal Survey – women not currently on ART (*n*=127)
Low mood	61 (34%)	31 (31%)	38 (30%)
Anhedonia	28 (16%)	19 (19%)	27 (21%)
Both low mood and anhedonia	21 (12%)	18 (18%)	19 (15%)
Positive depression screening test	**49 (27%)**	**27 (27%)**	**30 (24%)**

ART-related self-efficacy

Responses to the five HIV-ASES questions on integration of HIV treatment into daily life are shown in Figure 6.4 (Antenatal Survey) and Figure 6.5 (Postnatal Survey – respondents currently on ART only). Responses to all five questions were given by 76% (141185) of Antenatal Survey participants and 65% (66/102) of Postnatal Survey participants on ART. When scores were applied to each answer to give a maximum of 10 points (see 68), the median score in both Antenatal and Postnatal surveys was 5 (Wilcoxon-Mann-Whitney test p=0.47, women with scores in both surveys were omitted from the antenatal group because this was the larger sample).

The area in which most women lacked confidence was the ability to keep taking ART even if side effects began to interfere, with 15% of antenatal and 20% of postnatal respondents reporting that they could not do this (a quarter of respondents in both surveys reported being somewhat or terribly bothered by side effects, see Table 6.2). In the Antenatal Survey, a greater proportion of women reported not being able to keep taking ART if their routine was disrupted and not being able to keep medical appointments if they interfered with daily activities compared with the Postnatal Survey (Figures 6.4 and 6.5), but these differences were not statistically significant (χ^2=3.55 p=0.06 and χ^2=2.41 p=0.12 respectively). As the postnatal survey only included women attending for care (and not those lost to follow-up postnatally), their confidence to attend appointments is likely to be higher than for the population overall. The Antenatal Survey group were more confident that they could keep taking medication when not feeling well (43% (74/172)

said that they could do this, 47% (80/172) were fairly sure and 10% (18/172) said that they could not, compared with 24% (20/85), 62% (53/85) and 14% (12/85) respectively in the Postnatal Survey, χ^2=9.32, p<0.01). Linked ECS data indicated that women on ART in the Postnatal Survey had more advanced HIV disease (and thus more experience of HIV-related ill health).

In the four weeks before birth, how confident did you feel that you could…?

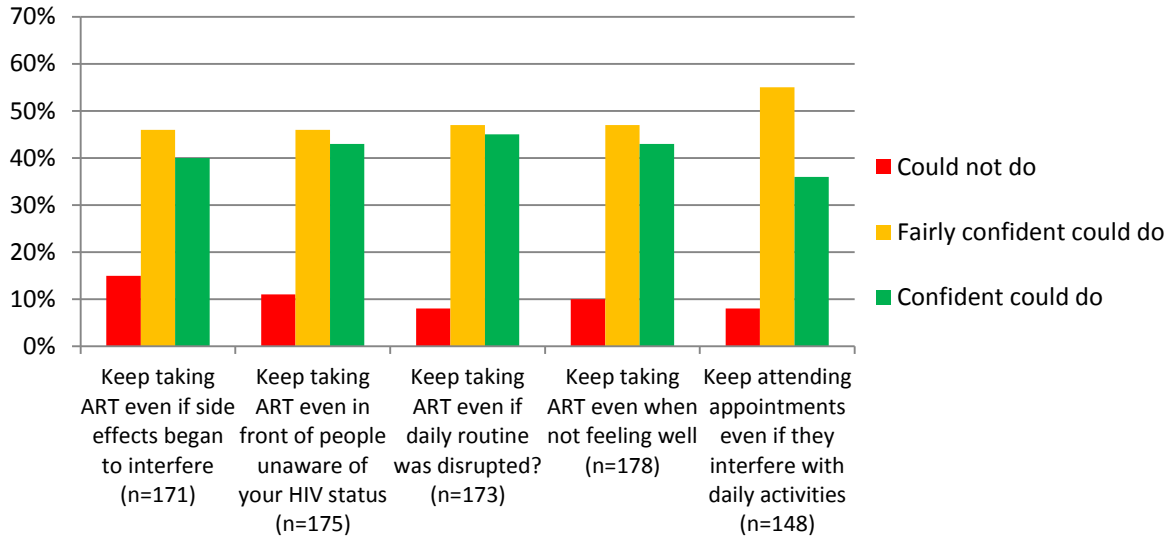


Figure 6.4: Measures of self-efficacy related to ART adherence, Antenatal Survey

In the last four weeks (postnatally), how confident have you been that you could…?

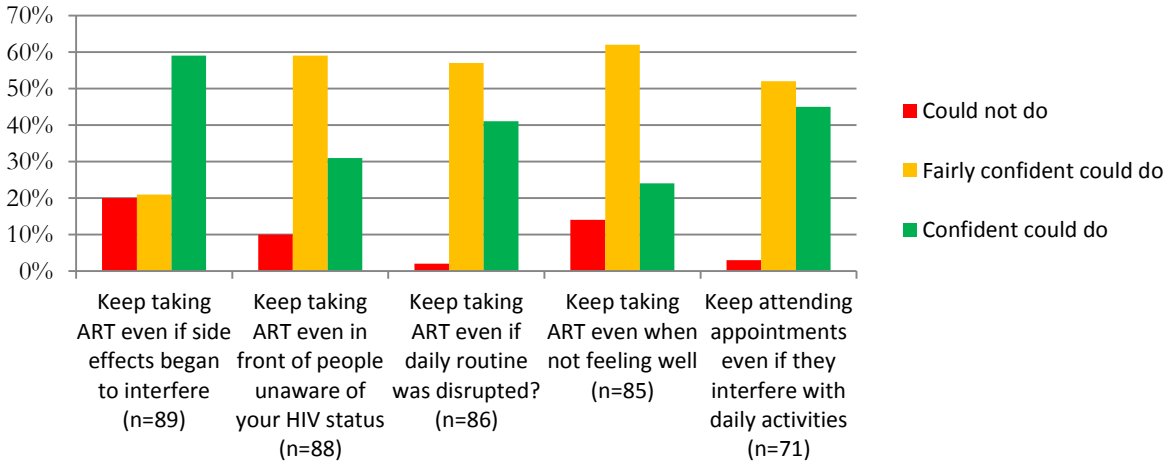


Figure 6.5: Measures of self-efficacy related to ART adherence, Postnatal Survey

Overall almost 95% (238/253) of women were confident or fairly confident that they could ask their clinician for more information and support if they needed to, with slightly fewer reporting being confident that they could ask someone for support with taking their medication (Table 6.4, comparisons between Antenatal and Postnatal Surveys, $\chi^2 = 3.64$ $p=0.16$ and $\chi^2 = 1.49$ $p=0.48$ respectively).

Table 6.4: Measures of self-efficacy related to seeking support

	Antenatal Survey	**Postnatal Survey – women currently on ART**
In the last four weeks, how confident did you feel that you could ask your clinician for more information if you needed to, and tell them about your concerns or worries?		
Confident I could do	37% (61/167)	48% (41/86)
Fairly confident I could do	56% (94/167)	49% (42/86)
Could not do	7% (12/167)	3% (3/86)
In the last four weeks, how confident did you feel that you could ask someone for support with taking your medication if you needed it?		
Confident I could do	33% (54/165)	30% (26/86)
Fairly confident I could do	47% (78/165)	43% (37/86)
Could not do	20% (33/165)	27% (23/86)

In the Postnatal Survey, women not able to ask someone for support with taking their medication were significantly more likely to have a positive screening test for depression (48% (11/23) vs. 22% (15/68) of those confident/fairly confident that they could ask for support, $\chi^2 = 5.59$ $p=0.02$), but there was no association between these factors in the Antenatal Survey ($\chi^2 = 0.14$ $p=0.71$). Those screening positive for depression more commonly reported being unable to do at least one of the five items related to integration of HIV treatment into daily life (in the Antenatal Survey: 32% (12/37) vs. 16% (16/101) of those not depressed, $\chi^2 = 4.61$ $p=0.03$; in the Postnatal Survey: 26% (5/19) vs. 13% (6/47) of those not depressed, Fisher's exact test $p=0.17$). The high prevalence of depression among even women with high levels of self-efficacy (who were confident that they could ask for help) may reflect the poor provision of mental health care in Ukraine, discussed in section 7.4.2.

Self-perception of ART risk and benefit

The large majority of Antenatal Survey respondents were either completely or fairly sure that taking antenatal ART was effective for PMTCT (44% (80/180) and 51% (91/180) respectively), with only nine women (5%) reporting that they were not at all sure of this. Because this was a sample selected on the basis that they had taken ART for at least the last four weeks of pregnancy, the true proportion of women with doubts about the effectiveness of ART for PMTCT may be higher than observed here. However, most women were a little worried (39%, 70/181) or worried (44%, 79/181) that antenatal ART might harm their baby; only 18% (32/181) reported that they weren't worried about this. Women who were completely sure about the effectiveness of ART for PMTCT had lower levels of anxiety than those who were only fairly sure (Figure 6.6, $\chi^2 = 6.65$ $p = 0.04$).

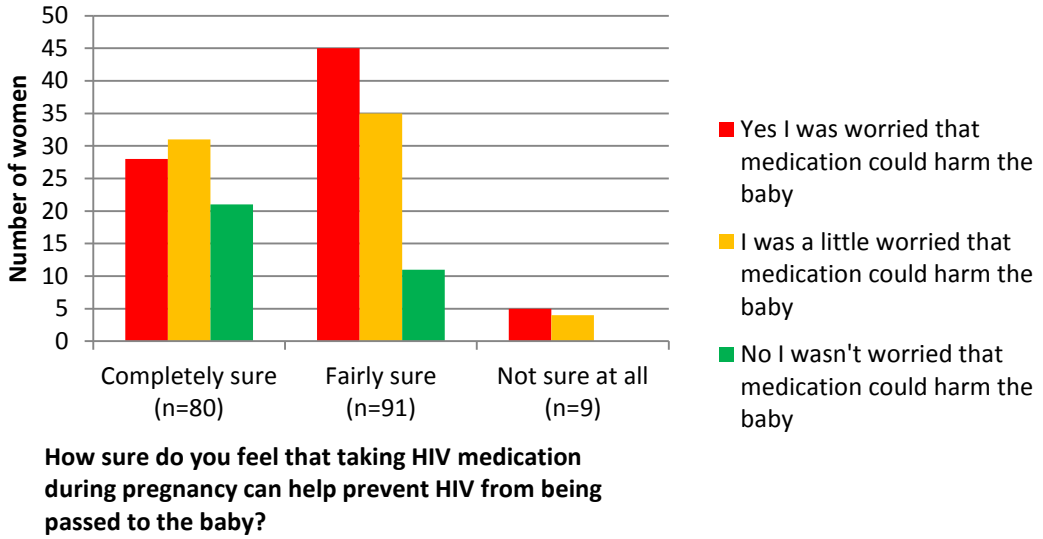


Figure 6.6: Levels of worry that antenatal ART might harm the baby, by level of confidence that HIV medication is effective for PMTCT

(n=180)

In the Postnatal Survey, 72% (156/218) of women agreed that neonatal prophylaxis could help to prevent HIV from being passed to their baby, 27% (58/218) didn't know/weren't sure and four (2%) disagreed. Although the proportion of women worried about neonatal prophylaxis causing harm was the same as for antenatal ART (44%, 95/218), fewer women were a little worried (23%, 50/218) and more women not worried at all (33% (73/218) for neonatal prophylaxis vs. 18% (32/181) for antenatal ART). As with antenatal ART, there was a significant association between confidence in the effectiveness of neonatal prophylaxis and a lower level of anxiety about the

possibility of it causing harm (Figure 6.7, $\chi^2 = 7.46$ $p=0.02$ for women agreeing that neonatal prophylaxis was effective vs. those not sure).

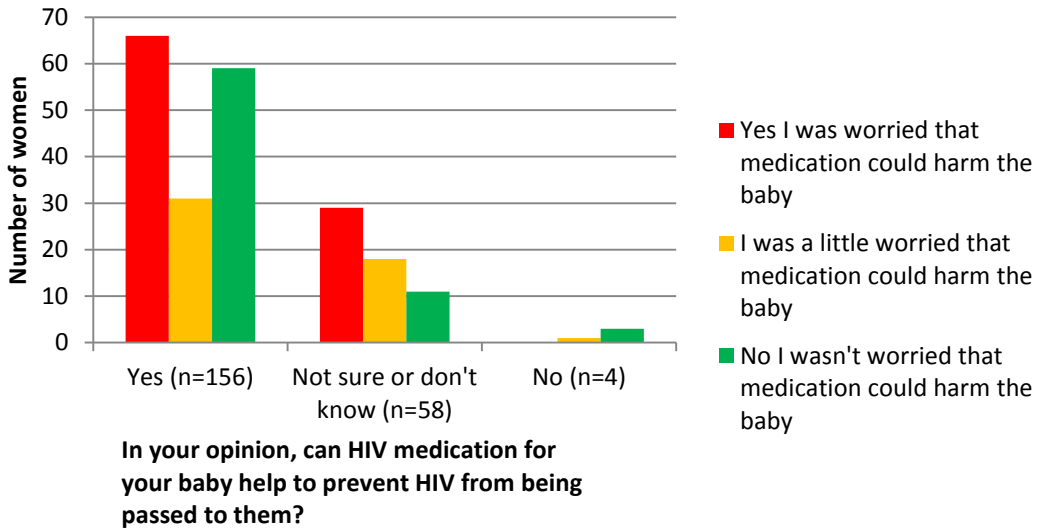


Figure 6.7: Levels of worry that neonatal prophylaxis might harm the baby, by opinion on whether neonatal prophylaxis is an effective intervention for PMTCT

(n=218)

6.4 Adherence to ART during pregnancy and postnatally

Pill burden and knowledge of ART regimen

In both Antenatal and Postnatal Surveys, over half of women were able to report the names of the HIV medications that they had been taking (Table 6.5, see page 66 for definition of '*complete knowledge'*). Matched ECS drug data were available for 47% (51/109) of Antenatal Survey participants categorised as having *'complete'* knowledge of their regimen: for 86% (*n*=44) of these, there were no differences between the regimen reported by the woman and that reported by the clinician. Two women gave three drug names but omitted a fourth reported by their clinician, three women reported ABC or ZDV when the other of the two drugs was reported by their clinician, and two women reported regimens with two or more differences – one of whom completed the survey five days after delivery, introducing the possibility of postnatal regimen alterations.

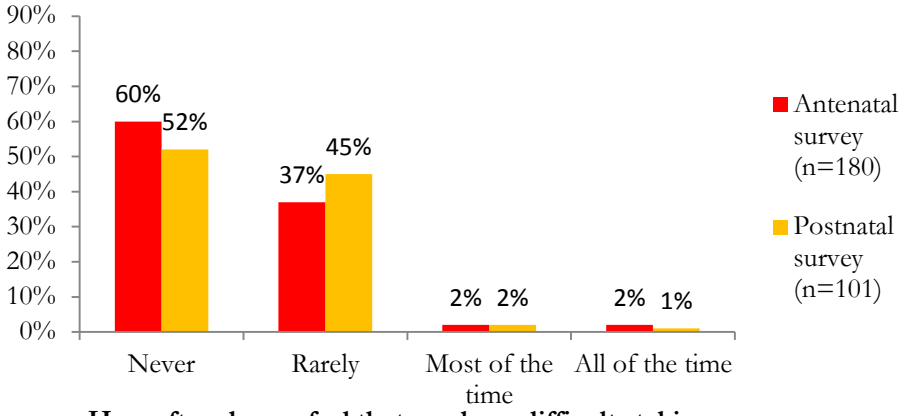
Table 6.5: Knowledge of the names of antiretroviral drugs currently being taken

	Antenatal Survey (*n*=185)	Postnatal Survey (*n*=102)
Complete knowledge	109 (59%)	59 (58%)
Partial knowledge (i.e. one or two drugs reported of cART regimen)	52 (28%)	25 (25%)
No knowledge	24 (13%)	18 (18%)

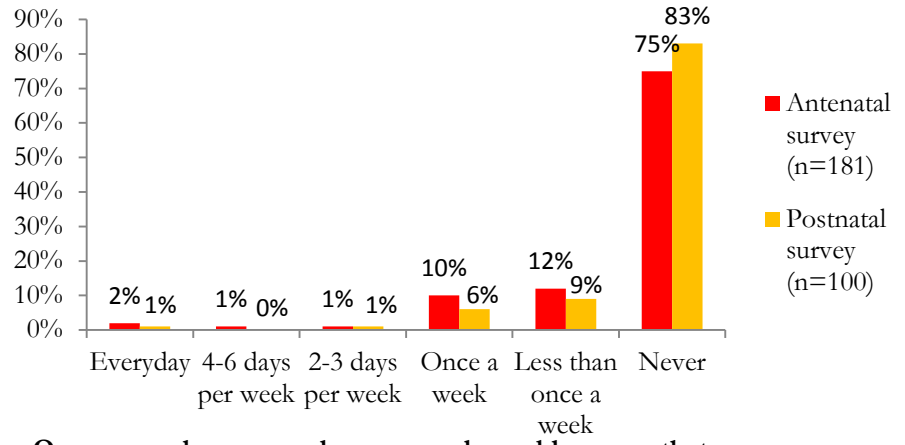
Of the antenatal group with complete knowledge, 14% (15/109) had been taking ZDVm and 86% (94/109) cART, 91% (86/94) of whom were on a LPV/r based regimen. Among the 59 women completing the Postnatal Survey and with complete knowledge of their regimen, most (80%, 47/59) were taking a LPV/r based cART regimen and 15% (9/59) a NVP-based cART regimen. The daily pill burden ranged from 2 to 12 pills for 142 antenatal respondents and 2 to 8 for 72 postnatal respondents. The median number of pills taken per day was six (taken by 72% (102/142) in the Antenatal Survey and 56% (40/72) in the Postnatal Survey).

CASE adherence index

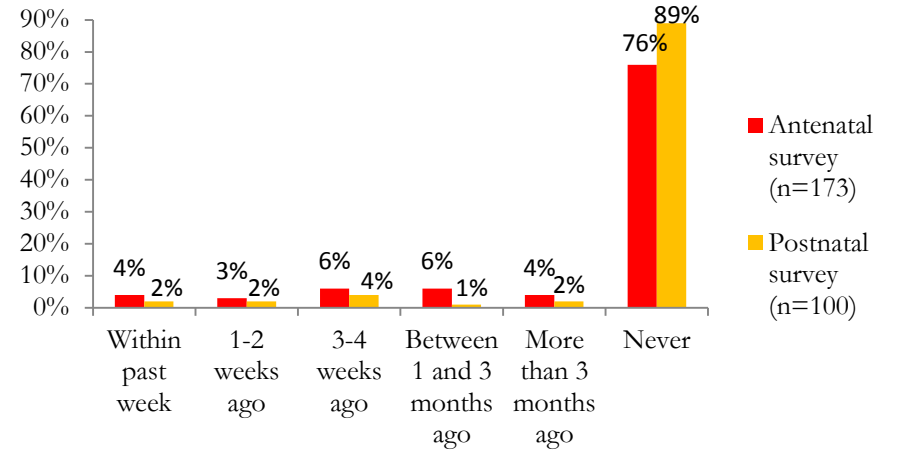
Responses given to the three CASE adherence index questions in Antenatal and Postnatal Surveys are summarised in three graphs, Figure 6.8.



How often do you feel that you have difficulty taking your HIV medications on time?



On average, how many days per week would you say that you missed at least one dose of your HIV medications?



When was the last time you missed at least one dose of your HIV medications?

Figure 6.8: Summary of responses to three CASE adherence index questions

Of 185 Antenatal Survey respondents and 102 Postnatal Survey respondents currently on ART, 94% (173/185) and 97% (99/102) respectively answered all three CASE adherence index questions, allowing for calculation of a CASE index score. Median CASE scores in both groups were 15 (of a possible 16), with slightly wider variance in scores among Antenatal Survey respondents (IQR 13, 16 and range 6, 16) than among Postnatal Survey respondents (IQR 14, 16 and range 7, 16). Figure 6.9 shows the distribution of CASE scores in each survey (the seven women with CASE scores in both surveys were included only in the postnatal group, making the total number of respondents for the Antenatal Survey 166). There was no statistically significant difference in overall scores between the two groups (Wilcoxon-Mann-Whitney test, p=0.25).

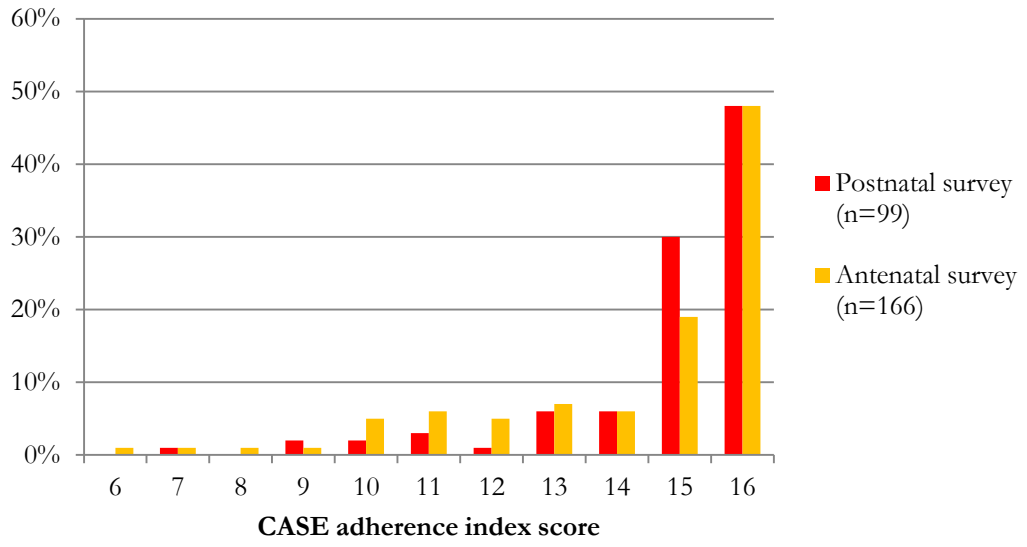


Figure 6.9: Distribution of CASE adherence index scores in the two surveys

Reasons for missed doses

Table 6.6 shows the number and proportion of Antenatal and Postnatal Survey respondents selecting each of a range of reasons for missing a dose of ART. The most common reasons reported for missing doses during pregnancy were being away from home (8%), simply forgetting (5%) and feeling sick/ill (5%). In the Postnatal Survey, the most common reasons for missing a dose in the preceding four weeks were simply forgetting (15%), sleeping through the dose (9%) and being away from home (8%).

Table 6.6: Reasons for missed doses of ART in the Antenatal and Postnatal Surveys

Reason for missed dose	Antenatal Survey (*n*=185)	Postnatal Survey – currently on ART (*n*=102)
I was away from home	**14 (8%)**	**8 (8%)**
I was busy with other things	6 (3%)	7 (7%)
I simply forgot	**10 (5%)**	**15 (15%)**
I had too many pills to take	3 (2%)	3 (3%)
I wanted to avoid side effects	1 (1%)	3 (3%)
I did not want others to notice me taking medication	2 (1%)	2 (2%)
I had a change in my daily routine	2 (1%)	1 (1%)
I felt that the drug was toxic / harmful	2 (1%)	4 (4%)
I fell asleep / slept through the dose	8 (4%)	**9 (9%)**
I felt sick or ill	**10 (5%)**	5 (5%)
I felt depressed or overwhelmed	1 (1%)	2 (2%)
I ran out of pills	6 (3%)	3 (3%)
I couldn't find my pills	2 (1%)	2 (2%)
I felt good	1 (1%)	0

Most common three reasons in bold.

In all, 25% (26/201) of postnatal respondents gave at least one reason for having missed a dose of ART, of whom 19 had answered *'Never'* to the question *'When was the last time you missed at least one dose of your HIV medications?'* This discrepancy was also found in responses to the questions on adherence to ART during pregnancy (12 Antenatal Survey respondents reported never missing a dose but went on to give ≥1 reason for having done so), and in responses to questions on adherence to neonatal prophylaxis (see section 6.4). When responses to the question on timing of last missed dose were taken together with reasons for missing a dose, a total of 35% (61/176) of antenatal respondents indicated directly or indirectly that they had missed a dose during pregnancy and 31% (31/100) of postnatal respondents indicated that they had missed a dose in the last four weeks.

Respondents' self-assessment of their adherence postnatally compared with during pregnancy

Postnatal respondents were asked to compare their current ART adherence with that during their most recent pregnancy. In total, 13% (12/93) reported missing fewer doses when pregnant than postnatally, 2% (2/93) that they missed more doses when pregnant than postnatally, 6% (6/93) that their adherence was similar antenatally and postnatally, and 78% (73/93) that they had not missed any doses in either time period. Of the 12 women who reported that their adherence had been

better during pregnancy than postnatally, cited reasons were: concern about MTCT (*n*=11), more frequent clinic appointments during pregnancy (*n*=3), having more time to take care of oneself during pregnancy (*n*=2), being more concerned about one's own health (*n*=1) and being less tired of taking pills (*n*=1) (>1 answer possible).

6.5 Adherence to neonatal prophylaxis

Almost all women in the Postnatal Survey reported that their infant had been prescribed neonatal prophylaxis (228/230), most (91%, 204/223) for one week (5% (11/223) for four weeks and 4% (8/223) could not recall. Women were asked to identify all of the individuals who had been involved in administering neonatal prophylaxis to their baby (multiple answers possible). Overall, 81% (183/225) reported that medical staff had administered at least one dose. Although 59% (133/225) indicated administration by medical staff only, 72% (96/133) of these women went on to answer questions about their administration of neonatal prophylaxis and 12 gave reasons for missed doses, suggesting administration of some doses at home, or confusion over the survey questions. Overall, 40% (91/225) of women reported giving their baby neonatal prophylaxis themselves (for over half (50/91) the drug administration was shared with medical staff), 6% (13/225) reported that the baby's father had given some HIV medication to their baby, 3% (6/225) that another family member had given dose(s) and 1% (2/225) that a friend had been involved with administering the medication.

Self-reported adherence to neonatal prophylaxis was high, probably partly reflecting the involvement of medical staff in giving a substantial proportion of doses. Of the 186 women who responded to the question *'How often did you have difficulty giving your baby their medicine on time?',* 81% (151/186) reported that this was never the case, 17% (31/186) that this was rare, 1% (2/186) that they experienced difficulty most of the time and 1% (2/186) that they had difficulty all of the time. These proportions were 74% (67/90), 24% (22/90), 0% (0/90) and 1% (1/90) for the 90 women who reported giving neonatal prophylaxis to their baby themselves and answered this adherence question. When asked how many days per week on average their baby missed at least one dose of medication, only two women reported that this had ever happened. However, a further 14 women went on to give reasons for missed doses, and it is possible that this question format was

more permissive for reporting of adherence problems. When responses to the two questions (average frequency of missed doses and reasons for missed doses) were taken together, 9% (16/187) of women reported that ≥1 dose of neonatal prophylaxis had been missed overall (3% (3/88) of those who reported having given doses themselves). Of note, women may not have been aware of any doses that their infant missed while in hospital and under the care of medical personnel.

Reasons reported for doses of neonatal prophylaxis being missed were: concerns that the drug was toxic or harmful (*n*=6), wanting to avoid side effects (*n*=6), that the baby was asleep (*n*=4), that supplies of medicine ran out (*n*=3), not wanting to ask other people caring for the baby to administer the medicine (*n*=2), that there was no one to help (*n*=1), being away from home (*n*=1) or simply forgetting (*n*=1) (>1 answer possible).

6.6 Validation of CASE adherence index scores

Table 6.7 shows the number and proportion of women reporting 'poor' adherence in the Antenatal and Postnatal Surveys according to various CASE score cut-offs.

Table 6.7: Proportion of women reporting poor adherence antenatally and postnatally, according to different CASE score cut-offs

	Antenatal Survey (*n*=173) *n* (%, 95% CI)	Postnatal Survey (*n*=99) *n* (%, 95% CI)
CASE score ≤10	15 (9%, 5-14%)	5 (5%, 2-11%)
CASE score ≤11	25 (14%, 10-21%)	8 (8%, 4-15%)
CASE score ≤12	33 (19%, 14-26%)	9 (9%, 4-17%)
CASE score ≤13	45 (26%, 20-33%)	15 (15%, 9-24%)

Validation of CASE scores against viral load measures was not possible for Postnatal Survey participants, due to the small number that had enrolled in the Women's Study by time of the analysis and the lack of postpartum virological monitoring in this group (see Figure 6.3, page 199). For the Antenatal Survey participants, a subgroup of 36 women had an antenatal viral load measure reported in the ECS at least 28 days after initiating ART (see Figure 6.2, page 198); the subsequent validation was performed in this subgroup. There was no difference in CASE scores between the 36 women included in the validation analyses and the remaining 137 women with an antenatal CASE score available but no suitable viral load (Wilcoxon-Mann-Whitney test p=0.96); in the validation subgroup, the proportions with a CASE score of ≤10, ≤11, ≤12 and ≤13 were 5% (2/36), 16% (6/36), 25% (9/36) and 28% (10/36) respectively.

Fitting statistical models to the data was severely limited by the small number of viral load measures available in the validation dataset and the fact that 23 of the 36 were undetectable (<40 copies/ml) (20/30 of those with a CASE score of >11 and 3/6 of those with a CASE score of ≤11, viral load measures given in Table 6.8). The viral load values used for this work were the last available in pregnancy, taken a median of 31 days prior to delivery (IQR 18, 49 days). For women with a low CASE score and an undetectable viral load, it is possible that their adherence deteriorated after the viral load measure was taken (for 4/6 of women with a CASE score ≤12 and an undetectable viral load, the measure was taken more than two weeks prior to delivery).

Table 6.8: Viral load measures of 36 women in validation subset, by CASE score

	CASE score†				
	≤10	≤11	≤12	≤13	≥14
Number of women with undetectable viral loads (<40 copies/ml)	1	3	6	6	17
Viral load where measure detectable (copies/ml)	1608	967 1507 1608	967 1507 1608	114 967 1507 1608	42 50 52 56 102 194 264 285 298
Total number of women	2	6	9	10	26

† Categories from CASE score ≤10 to ≤13 are cumulative (i.e. the 1608 copies/ml measure which appears in all four categories is from the same woman).

One hypothesis that accounts for this distribution of viral load measures is that the measurements come from two latent populations whose identity is not observed. The first population is composed of women who have been on a successful regimen for a sufficient duration by the time of the viral load measure and have no other factors compromising virological response – a population who contribute 'excess' undetectable viral load measures. Meanwhile the second population consists of women with shorter durations of cART and/or other factors that might affect virologic control, whose viral load may or may not be undetectable. A zero-inflated negative binomial model is a latent-class model with two parts - an extra-zero part, which models the probability of being in the first population (an 'excess' undetectable viral load) via a logit link function, and a negative binomial part which models the mean level of viral load in a logarithmic scale via a negative binomial distribution. The use of the logit and logarithmic links respectively transform the dependent variables to allow estimation of predicted values within a given range (i.e. 0 and 1 in the case of the probability of being in the extra zero component, and positive values in the case of viral load). The equations that follow describe the two parts of the zero-inflated negative binomial model in terms of two linear predictors.

Equation 1: Extra-zero component $$log\left(\frac{\pi_0}{1-\pi_0}\right) = X_i\beta$$

Equation 2: Negative binomial component $$log(\mu) = Z_i\gamma$$

Where π_0 is the probability of any woman being an 'excess' undetectable viral load, μ is the mean viral load, X_i and Z_i are vectors of covariates predicting viral load (e.g. cART duration, CASE score), β and γ are vectors of the regression coefficients (Ridout *et al.* 2001).

Different covariates can be considered in each of the two components of the model. Initially, both components were adjusted *a priori* for ART duration and whether cART was PI-based or not. For comparison, four models were fitted with CASE score dichotomised at 10, 11, 12 and 13 (these four covariates are referred to as CASE 10, CASE 11, CASE 12 and CASE 13). These dichotomised CASE scores were included in both the zero-inflated and the negative binomial components. Type of cART regimen (i.e. whether PI-based or not) was not significantly associated with either being an 'excess' undetectable viral load or with level of viral load in any of the four models. Its removal resulted in improved model fit as indicated by BIC (Table 6.9, compare step 1 and step 2). CASE score was not associated with being an 'excess' undetectable viral load (i.e. in the zero-inflated part of the model, p=1.00 for CASE 10, p=0.46 for CASE 11, p=0.82 for CASE 12 and p=0.59 for CASE 13 after excluding cART type). Its removal from this component resulted in improved fit of all models except the CASE 10 model, which was not preferred over the others at any stage (Table 6.9, compare step 2 and step 3). Finally, ART duration was significantly associated with the outcome of being an 'excess' undetectable viral load, but not with mean level of viral load. Its removal from the negative binomial component was associated with a further improvement in model fit (Table 6.9, compare step 3 and step 4). The models with the best fit were those which included the CASE 11 and CASE 12 covariates, with little difference between them (Table 6.9, shaded cells).

The BIC value for a negative binomial regression model without zero-inflation component and including CASE 11 and ART duration was 225.84 (vs. 219.55 for zero-inflated negative binomial model, Table 6.9), demonstrating the substantial improvement in goodness-of-fit with a zero-inflated negative binomial approach.

Table 6.9: BIC values for zero-inflated negative binomial regression models with different combinations of covariates

	Step 1	Step 2	Step 3	Step 4
CASE 10 covariate	238.31	232.59	225.40	228.35
CASE 11 covariate	229.66	223.63	220.61	**219.55**
CASE 12 covariate	230.14	224.18	220.65	219.57
CASE 13 covariate	234.07	228.04	224.76	222.21
Covariates included in logit (extra zero) component	ART duration Type of cART CASE covariate	ART duration CASE covariate	ART duration	ART duration
Covariates included in the negative binomial component	ART duration Type of cART CASE covariate	ART duration CASE covariate	ART duration CASE covariate	CASE covariate

The shaded cells indicate the models with the best fit. ART duration was a categorical variable (≥12 weeks vs. 4-11 weeks). Type of cART was PI-based vs. not PI-based.

Table 6.10: Coefficients and 95% confidence intervals from two zero-inflated negative binomial regression models of CASE score regressed against viral load.

	Logit coefficients(zero inflation) (95% CI)	Predicted probability of belonging to the population of 'excess' undetectable viral loads	Negative binomial exponentiated coefficients (95% CI)	BIC
Model 1				**219.55**
CASE score ≤11 vs. >11			12.72 (3.12-51.91) $p<0.01$	
ART duration				
4-11 weeks	1.00	0.40		
≥12 weeks	2.05 (0.47-3.63) $p=0.01$	0.84		
Model 2				**219.57**
CASE score ≤12 vs. >12			12.70 (3.12-51.66) $p<0.01$	
ART duration				
4-11 weeks	1.00	0.40		
≥12 weeks	2.05 (0.47-3.64) $p=0.01$	0.84		

Table 6.10 shows coefficients from the two best-fitting zero-inflated negative binomial regression models. These models indicate that, of women who were not in the 'excess' zero population, those with a lower CASE score (≤11 or ≤12) had a viral load around 12-fold greater than those with a higher CASE score (>11 or >12). Women who had been on cART for 4-11 weeks by the viral load measurement had a probability of 0.40 of being an 'excess' undetectable viral load (antilog of intercept -0.3935) compared with a probability of 0.84 for those on cART for ≥12 weeks. The lack of an association between ART duration and viral load in the negative binomial part of the model is probably due to the limitations of the data. These results must be interpreted with caution given the small number of data points, but nevertheless indicate support for the CASE score tool and for cut-offs of 11 and 12 to identify poor adherence of potential clinical relevance.

In order to explore factors associated with poor adherence, a CASE score cut-off of 11 was chosen over a cut-off of 12. This outcome was supported by the BIC value and was more specific than a cut-off of 12, thus providing a comparison for the outcome of 'any reported missed dose' (the outcome providing the most sensitive measure of poor adherence). Overall, 14% of 175 Antenatal Survey respondents had a CASE score of ≤11 as did 8% of 99 Postnatal Survey respondents currently on ART. The proportions who reported (directly or indirectly) having ever missed a dose during pregnancy or in the last four weeks postnatally were 35% (61/176) and 31% (31/100) respectively. Factors associated with these two outcomes are explored in the next section.

6.7 Factors associated with poor adherence

ART adherence during pregnancy

Characteristics of Antenatal Survey respondents by whether they had a CASE adherence index score of ≤11 (n=173) and by whether they reported ever missing a dose during pregnancy (n=176) are shown in Table 6.11. There was no difference in proportion of women with a CASE score ≤11 by hospital at which they delivered (Fisher's exact test p=0.64), but there was a difference between hospitals in the proportion reporting ever having missed a dose (43% (30/69) in Kiev, 34% (28/82) in Odessa and 12% (3/25) in Simferopol, Fisher's exact test p=0.01).

Women living with their extended family more commonly had a CASE score of ≤11 (Table 6.11), and this was particularly true for women who had not disclosed their HIV status to a family member (40% (8/20) of whom had poor adherence, compared with 14% (5/37) of those living with their family who had disclosed their status to a family member, Fisher's exact test p=0.03). A third (18/57) of women living with their extended family also lived with a partner. Overall, women living with their family were younger (median age 26.6 years vs. 28.6 years for women living only with a partner or alone, Wilcoxon-Mann-Whitney test p=0.02) and more likely to have had an unplanned pregnancy (36% (21/58) vs. 23% (27/120) of those living only with a partner or alone, χ^2=3.73 p=0.05).

It was surprising that poor adherence (CASE score of ≤11) was slightly more common among women who had disclosed their HIV status to a friend than among those who had not. Women disclosing to a friend were more likely to have a history of drug use excluding marijuana (41% (7/17) vs. 10% (16/160) of those not disclosing to a friend, Fisher's exact test p<0.01), and were also more likely to have disclosed to another HIV-positive person (53% (9/17) vs. 10% (16/166) of those not disclosing to a friend, Fisher's exact test p<0.01). Drug use and disclosure to an HIV-positive person were not themselves associated with a CASE score of ≤11 (Table 6.11, Fisher's exact test p=0.40 for disclosure to an HIV-positive person), but these characteristics together may indicate social marginalisation among women disclosing to a friend. It is also possible that women failing to cope with treatment were more likely to have disclosed to a friend or peer in order to ask for support. Finally, women disclosing to a friend may have been better adapted to their HIV status

and more likely to report adherence problems accurately, resulting in less inflated self-report measures.

Being a current smoker was associated with ever having missed a dose during pregnancy, but not with a CASE score of ≤11 (Table 6.11). Low CASE scores were more common among women with a positive depression screening test, reaching statistical significance with the 'ever having missed a dose' outcome (Table 6.11). Women who received ZDVm during pregnancy rather than cART were also more likely to report poor adherence, and this was statistically significant for the 'any missed dose' outcome. As shown in Chapter 3 (Table 3.7 page 104), ZDVm was more commonly initiated during pregnancy among women with ≥2 previous live births and those with less education. Poor adherence tended towards being more common among multiparous women (35% (6/17) of multiparous women reported ever missing a dose vs. 27% (12/44) women with one previous live/stillbirth and 21% (6/29) of women no previous births, Fisher's exact test p=0.54), but too few data were available to assess the association between education level and adherence.

Of the 18 women categorised as having no knowledge of the names of the drugs that they were taking, two (11%) had a CASE score of ≤11 compared with 15% (23/155) of those who had partial or complete knowledge of their regimen (Fisher's exact test p=0.50). Among 93 women with matched ECS data available, there was also no difference in either adherence outcome measure by whether the woman had been diagnosed as HIV-positive prior to or during her most recent pregnancy (Fisher's exact test p=0.38 for CASE score ≤11 and p=0.53 for reporting any missed dose). Although women with longer duration of antenatal ART had more opportunity to miss a dose during pregnancy, there was also no difference in reporting of a missed dose by timing of ART initiation (3/7 (43%) of women starting ART pre-conception reported ever missing a dose vs. 15/60 (25%) of those starting in the 1st/2nd trimesters and 9/24 (38%) of those starting in the 3rd trimester, Fisher's exact test p=0.39; Fisher's exact test p=1.00 for outcome of CASE score ≤11).

There was no significant difference in adherence by severity of HIV disease; 13% (8/64) and 11% (2/17) of women with WHO stage 1-2 and 3-4 disease respectively had a CASE score of ≤11 (Fisher's exact test p=0.59), and 20% (12/60) and 29% (7/24) respectively reported ever missing a dose (Fisher's exact test p=0.26). Women who reported being somewhat or terribly bothered by

side effects were not more likely to have a CASE score of ≤11 (16% (7/43) vs. 14% (18/126) of those not bothered or only slightly bothered by side effects, Fisher's exact test p=0.46; Fisher's exact test p=0.38 for outcome of any missed doses). There was also no association between confidence in ability to ask someone for support with taking the medication and either adherence measure (Fisher's exact test p=0.84 for CASE score ≤11 and p=1.00 for any missed dose).

Median self-efficacy score on the five HIV-ASES questions related to integration of ART-taking into daily life was 7 (IQR 2, 8) for women with a CASE score of ≤11 and 5 (IQR 5, 10) for those with a CASE score >11 (Wilcoxon-Mann-Whitney test p=0.13). Those with a total score of <5 over the five questions (i.e. who reported that they '*could not do'* at least one of the items) were more likely to report ever having missed a dose (Table 6.11).

Table 6.11: Factors associated with poor ART adherence during pregnancy

	CASE score ≤11 points (25/173)	**Fisher's exact test**	**Ever missed a dose** (61/176)	**Fisher's exact test**
Age				
<25 years	26% (11/42)	*p*=0.13	52% (23/44)	*p*=0.03
25-27 years	10% (5/48)		23% (11/48)	
28-30 years	12% (5/41)		29% (12/41)	
≥31 years	10% (4/42)		35% (15/43)	
Marital status				
Married	14% (13/93)	*p*=0.96	34% (32/95)	*p*=0.83
Cohabiting	15% (7/48)		33% (16/48)	
Single	16% (5/32)		39% (13/33)	
Pregnancy planned				
Yes	11% (13/120)	*p*=0.02	30% (36/122)	*p*=0.01
No	25% (12/48)		49% (24/49)	
Lives with extended family				
No	10% (12/115)	*p*=0.03	29% (34/117)	*p*=0.02
Yes	23% (13/57)		46% (26/57)	
Lives with partner				
No	18% (9/49)	*p*=0.25	45% (22/49)	*p*=0.05
Yes	13% (16/123)		30% (38/125)	
Disclosed status to partner				
No	19% (9/47)	*p*=0.21	42% (20/48)	*p*=0.16
Yes	13% (16/125)		32% (41/127)	
Disclosed status to family				
No	18% (13/74)	*p*=0.22	39% (30/77)	*p*=0.20
Yes	12% (12/98)		32% (31/98)	
Disclosed status to friend				
No	13% (20/156)	*p*=0.06	33% (53/159)	*p*=0.15
Yes	31% (5/16)		50% (8/16)	
Current smoker				
No	14% (18/127)	*p*=0.58	30% (39/129)	*p*=0.04
Yes	14% (6/44)		47% (21/45)	
History of marijuana use				
No	13% (20/149)	*p*=0.37	33% (50/152)	*p*=0.18
Yes	18% (4/22)		45% (10/22)	
History of other drug use				
No	2% (2/127)	*p*=0.65	35% (52/149)	*p*=0.55
Yes	14% (3/21)		33% (7/21)	
Is antenatal ART effective for PMTCT?				
Yes, completely / fairly sure	12% (20/162)	*p*=0.10	33% (54/165)	*p*=0.15
Not sure	33% (3/9)		56% (5/9)	
Self-efficacy score				
≥5 (higher self-efficacy)	12% (13/107)	*p*=0.15	28% (30/108)	*p*=0.02
<5 (lower self-efficacy)	22% (6/27)		50% (14/28)	
Positive depression screen				
No	13% (16/124)	*p*=0.20	31% (39/125)	*p*=0.05
Yes	20% (9/46)		46% (22/48)	
Can you ask doctor for support?				
Certain / fairly certain can do	14% (21/155)	*p*=0.06	33% (52/156)	*p*=0.19
Cannot do	36% (4/11)		50% (6/12)	
ART received				
ZDVm	29% (4/14)	*p*=0.13	64% (9/14)	*p*=0.02
cART	13% (19/141)		31% (44/143	

Table 6.12 shows PRs adjusted *a priori* for hospital of delivery, for the eight factors with a *p* value of <0.20 (Fisher's exact test) in univariable comparisons with CASE score of ≤11. The women with a CASE score of ≤11 were younger, more likely to have an unplanned pregnancy and to be living with their family, more likely to have disclosed their HIV status to a friend, and more likely to lack confidence in their ability to ask their doctor for more information or to share with them concerns and worries.

Table 6.12: Factors associated with poor adherence (CASE score ≤11) during pregnancy

	PR adjusted for hospital of delivery (95% CI)	
Age		
<25 years	1	
25-27 years	0.38 (0.14-0.98)	*p*=0.05
28-30 years	0.44 (0.17-1.16)	*p*=0.10
≥31 years	0.34 (0.12-1.00)	*p*=0.05
Pregnancy planned		
Yes	1	
No	2.35 (1.16-4.73)	*p*=0.02
Living with extended family		
No	1	
Yes	2.12 (1.01-4.47)	*p*=0.05
Disclosed HIV status to friend		
No	1	
Yes	2.34 (1.01-5.40)	*p*=0.05
Opinion on whether ART is effective for PMTCT		
Yes completely/fairly sure	1	
Not sure	2.52 (0.89-7.13)	*p*=0.08
Able to ask doctor for support?		
Confident / fairly confident could do	1	
Could not do	2.65 (1.06-6.66)	*p*=0.04
Regimen received during pregnancy		
cART	1	
ZDVm	2.17 (0.82-5.72)	*p*=0.12
Self-efficacy score HIV-ASES – integration of HIV treatment into daily living		
Score of ≥5 (higher self-efficacy)	1	
Score of <5 (lower self-efficacy)	1.76 (0.75-4.15)	*p*=0.20
Positive depression screening test		
No	1	
Yes	1.52 (0.72-3.20)	*p*=0.27
Hospital		
Kiev	1	
Odessa	0.90 (0.42-1.92)	*p*=0.79
Simferopol	0.49 (0.12-2.05)	*p*=0.33

Factors associated with the other outcome of ever having missed a dose during pregnancy after adjusting for hospital of delivery included being a current smoker, having received ZDVm (rather than cART) during pregnancy and having a lower level of self-efficacy (Table 6.13). Women not living with a partner and not disclosing their HIV status to a partner were also more likely to report ever having missed a dose (p=0.07 and p=0.09 respectively). Women with low self-efficacy were more likely to report having missed a dose, regardless of their depression screening test result (Mantel-Haenszel test of homogeneity of ORs p=0.67).

Table 6.13: Factors associated with reporting ever having missed a dose during pregnancy

	PR adjusted for hospital of delivery (95% CI)	
Age		
<25 years	1	
25-27 years	0.41 (0.23-0.73)	$p<0.01$
28-30 years	0.52 (0.30-0.91)	$p=0.02$
≥31 years	0.62 (0.38-1.00)	$p=0.05$
Pregnancy planned		
Yes	1	
No	1.71 (1.16-2.51)	$p<0.01$
Living with extended family		
No	1	
Yes	1.48 (0.99-2.21)	$p=0.06$
Living with partner		
No	1	
Yes	0.69 (0.46-1.03)	$p=0.07$
Disclosed HIV status to friend		
No	1	
Yes	1.37 (0.82-2.28)	$p=0.23$
Disclosed HIV status to partner		
No	1	
Yes	0.69 (0.45-1.05)	$p=0.09$
Current smoker		
No	1	
Yes	1.67 (1.12-2.51)	$p=0.01$
History of marijuana use		
No	1	
Yes	1.25 (0.76-2.06)	$p=0.38$
Able to ask doctor for support?		
Confident / fairly confident could do	1	
Could not do	1.45 (0.75-2.80)	$p=0.27$
Is antenatal ART effective for PMTCT?		
Yes, completely / fairly sure	1	
No	1.45 (0.78-2.69)	$p=0.24$
Regimen received during pregnancy		
cART	1	
ZDVm	2.46 (1.51-4.00)	$p<0.01$
Self-efficacy score		
≥5 (higher self-efficacy)	1	
<5 (lower self-efficacy)	1.67 (1.06-2.64)	$p=0.03$
Positive depression screening test		
No	1	
Yes	1.37 (0.92-2.04)	$p=0.12$
Hospital		
Kiev	1	
Odessa	0.79 (0.52-1.18)	$p=0.24$
Simferopol	0.28 (0.09-0.83)	$p=0.02$

ART adherence postnatally

Table 6.14 shows characteristics of the Postnatal Survey respondents currently on ART by whether they had a CASE adherence index score of ≤11 (n=99), and by reporting of any missed dose in the last four weeks (n=100). The available sample size was limited by the fact that only around a quarter of women attending the HIV/AIDS centres postnatally continue on ART, and a substantial proportion return infrequently (if at all) for follow-up (see Chapter 5). Numbers enrolled at each of the six HIV/AIDS centres were insufficient to make between-centre comparisons, and none of the respondents in Kiev, Mykolaiv and Simferopol had a CASE score of ≤11 (out of 7, 10 and 4 respondents respectively). The proportions with a CASE score of ≤11 at the remaining three centres were 4/43 in Odessa, 2/15 in Donetsk and 2/20 in Krivoy Rog. The proportions reporting any missed dose in the last four weeks were 3/7 in Kiev, 11/44 in Odessa, 0/10 in Mykolaiv, 7/15 in Donetsk, 9/20 in Krivoy Rog and 1/4 in Simferopol.

Although self-efficacy score was the only factor in Table 6.14 associated with a CASE score of ≤11 to a significance level of p<0.10, this was probably due to the small sample size and lack of statistical power for other comparisons. In particular, differences in proportions indicated that cohabiting women may have been more likely to have a CASE score of ≤11 than married women, and also that current smokers and drinkers may have been less adherent. The more sensitive outcome measure of ever missing a dose in the last four weeks was associated with being a current smoker, having a history of illicit drug use (excluding marijuana) and with not having used a treatment adherence programme. Unmarried and particularly single women were slightly more likely to report having ever missed a dose than married women (p=0.08 for comparison of three groups), and women not living with a partner were also slightly more likely to report a missed dose (p=0.06). Of the subgroup with matched data available, 36% (9/25) of women with WHO stage 1-2 disease reported having missed a dose in the last four weeks vs. 13% (2/16) of those with WHO stage 3-4 disease (Fisher's exact test p=0.10). Of 35 women with data available from the Women's Study on self-reported affordability of contraception, those reporting a missed ART dose were slightly more likely to report that contraception was unaffordable (4/10 vs. 3/25 of those without any missed dose of ART, Fisher's exact test p=0.08).

Only 3/86 women on ART postnatally reported being unable to ask their doctor for information and to share concerns and worries; none of these three women had 'poor' adherence by either outcome measure. Of the 23 women who reported not being able to ask someone for support with taking their medication, 6 (26%) reported having missed a dose in the last four weeks (vs. 35% (22/62) of those fairly confident / certain that they could ask for support, Fisher's exact test p=0.29), and there was also no association between confidence in ability to ask for support and having a CASE score of ≤11 (Fisher's exact test p=0.50). The degree to which a woman reported being bothered by side effects was also not associated with the likelihood of either adherence outcome (Fisher's exact p=0.63 for CASE score of ≤11 and p=0.31 for missed dose in the last four weeks). Of the 16 women not giving any of the names of the drugs in their regimen, 7 (44%) reported missing a dose in the last four weeks (vs. 24 (29%) of those reporting ≥1 drug name, Fisher's exact test p=0.18) and 3 (19%) had a CASE score of ≤11 (vs. 5 (6%) of those reporting ≥1 drug name, Fisher's exact test p=0.12).

Tables 6.15 and 6.16 give unadjusted PRs for factors with a p value of ≤0.20 (Fisher's exact test) in univariable comparisons with the two adherence outcomes (CASE score of ≤11 and any missed dose reported over the last four weeks).

The statistically significant association between a lower level of self-efficacy and a CASE score of ≤11 must be interpreted with caution, in view of the very small numbers and wide confidence interval (Table 6.15), but supports findings from the Antenatal Survey. The measure of self-efficacy used here, which focused on various aspects of HIV treatment, was not associated with current smoking or drinking (Fisher's exact p=0.55 and 0.68 respectively), or with report of any missed dose over the last four weeks (Table 6.14).

Women living with a partner were slightly less likely to report a missed dose, indicating the potentially important role that a partner may play in supporting adherence behaviours during the postpartum period. All types of substance use were associated with an increased likelihood of a missed dose (reaching statistical significance for smoking and history of drug use other than marijuana). Use of social services was associated with a non-significant increased likelihood of reporting a missed dose (p=0.19) - these services are targeted at the most socially vulnerable women

(see Chapter 5, page 150). Participation in a treatment adherence programme was associated with a reduced likelihood of reporting a missed dose postnatally (Table 6.14).

Table 6.14: Factors associated with poor postnatal ART adherence

	CASE score ≤11 points (8/99)	**Fisher's exact test**	**Ever missed a dose** (31/100)	**Fisher's exact test**
Age				
<25 years	9% (2/22)	*p*=0.95	23% (5/22)	*p*=0.37
25-27 years	7% (1/15)		19% (3/16)	
28-30 years	5% (1/21)		29% (6/21)	
≥31 years	10% (4/40)		40% (16/40)	
Marital status				
Married	6% (3/54)	*p*=0.13	22% (12/55)	*p*=0.08
Cohabiting	19% (4/21)		38% (8/21)	
Single	4% (1/24)		46% (11/24)	
Pregnancy planned				
Yes	7% (5/70)	*p*=0.35	30% (21/71)	*p*=0.24
No	12% (3/25)		40% (10/25)	
Lives with partner				
No	10% (2/21)	*p*=0.55	48% (10/21)	*p*=0.06
Yes	8% (6/77)		27% (21/78)	
Lives with extended family				
No	8% (6/75)	*p*=0.60	30% (23/76)	*p*=0.43
Yes	9% (2/23)		35% (8/23)	
Lives alone				
No	7% (6/86)	*p*=0.25	30% (26/87)	*p*=0.30
Yes	17% (2/12)		42% (5/12)	
Disclosed status to partner				
No	10% (2/20)	*p*=0.52	45% (9/20)	*p*=0.12
Yes	8% (6/78)		28% (22/79)	
Disclosed status to friend				
No	8% (7/89)	*p*=0.55	30% (27/90)	*p*=0.30
Yes	9% (1/9)		44% (4/9)	
Current smoker				
No	6% (4/71)	*p*=0.13	25% (18/72)	*p*=0.02
Yes	15% (4/26)		50% (13/26)	
Current drinker				
No	7% (6/91)	*p*=0.13	29% (27/92)	*p*=0.17
Yes	25% (2/8)		50% (4/4)	
History of marijuana use				
No	7% (6/84)	*p*=0.35	28% (24/85)	*p*=0.13
Yes	13% (2/15)		47% (7/15)	
History of other drug use				
No	8% (6/78)	*p*=0.44	28% (22/79)	*p*=0.05
Yes	12% (2/17)		53% (9/17)	
Using treatment adherence programme				
No	7% (4/60)	*p*=0.39	38% (23/61)	*p*=0.05
Yes	10% (4/39)		21% (8/39)	
Using social services				
No	7% (5/71)	*p*=0.40	28% (20/72)	*p*=0.19
Yes	11% (3/28)		39% (11/28)	
Self-efficacy score				
≥5 (higher self-efficacy)	5% (3/55)	*p*=0.05	36% (20/55)	*p*=0.21
<5 (lower self-efficacy)	27% (3/11)		55% (6/11)	
Positive depression screen				
No	7% (5/71)	*p*=0.39	28% (20/72)	*p*=0.26
Yes	11% (3/27)		37% (10/27)	

Table 6.15: Factors associated with having a CASE score ≤11 in the year following delivery

	Crude PR (95% CI)	
Marital status		
Married	1	
Cohabiting	3.43 (0.83-14.14)	*p*=0.09
Single	0.75 (0.08-6.92)	*p*=0.80
Current smoker		
No	1	
Yes	2.73 (0.73-10.20)	*p*=0.14
Current drinker		
No	1	
Yes	3.79 (0.90-15.92)	*p*=0.07
Reported ≥1 drug name in regimen		
Yes	1	
No	3.11 (0.82-11.82)	*p*=0.10
Self-efficacy score		
≥5 (higher self-efficacy)	1	
<5 (lower self-efficacy)	5.0 (1.14-21.85)	*p*=0.03

Table 6.16: Factors associated with reporting any missed dose over the last four weeks postnatally

	Crude PR (95% CI)	
Marital status		
Married	1	
Cohabiting	1.75 (0.83-3.67)	*p*=0.14
Single	2.10 (1.08-4.09)	*p*=0.03
Live with partner		
No	1	
Yes	0.57 (0.32-1.01)	*p*=0.06
Disclosed HIV status to partner		
No	1	
Yes	0.62 (0.34-1.13)	*p*=0.12
Current smoker		
No	1	
Yes	2.00 (1.15-3.49)	*p*=0.02
Current drinker		
No	1	
Yes	1.70 (0.79-3.66)	*p*=0.17
History of marijuana use		
No	1	
Yes	1.65 (0.87-3.14)	*p*=0.13
History of other drug use		
No	1	
Yes	1.90 (1.07-3.38)	*p*=0.03
Using treatment adherence programme		
No	1	
Yes	0.54 (0.27-1.10)	*p*=0.09
Using social services		
No	1	
Yes	1.41 (0.78-2.56)	*p*=0.25
Reported ≥1 drug name in regimen		
Yes	1	
No	1.53 (0.80-2.94)	*p*=0.20
WHO Stage (ECS subgroup)		
1-2	1	
3-4	0.35 (0.08-1.43)	*p*=0.14

6.8 Limitations

As self-reported adherence measures are generally inflated, actual levels of adherence are likely to be lower than reported here. The recall period for neonatal prophylaxis was particularly long (around six months) and this could have resulted in further inflation of measures, although responses indicated that a substantial proportion of doses were administered by medical staff before hospital discharge. The involvement of physicians in reviewing completed questionnaires to identify and refer women with possible adherence problems or depression may have resulted in further inflation of self-reported adherence measures due to social desirability bias. Respondents in the Antenatal Survey who had received dual therapy for PMTCT may have been miscategorised as having only partial knowledge of their ART regimen, but this was likely to apply to one or two women at most (dual therapy was received by 20 women enrolled in ECS from 2008-10, see Chapter 3, page 84).

Limited viral load data were available to validate CASE adherence index scores; a quarter of women in the Antenatal Survey with ECS data available did not have a viral load measure taken during pregnancy, and a further 31% had a viral load measure taken before ART was initiated, or less than four weeks later. The date of birth of some women in the Ukraine ECS is reported only to the year, which precluded matching with Adherence Survey data and possibly further limited the validation sample; among deliveries in 2011, this proportion was 5% (56/1120).

Despite the bias inherent in self-report measures and the limitations affecting the validation analyses, the association found between CASE score and level of viral load points to the utility of a short self-report adherence measure in this setting. Validation will need to be reproduced with a larger sample, as virological monitoring is further scaled up in Ukraine, and compared with other short self-report measures of adherence.

Power to detect differences in adherence by maternal characteristics and centre of enrolment was limited by the study sample size. There were important differences between Antenatal and Postnatal Survey groups (particularly with respect to HIV disease stage) which could not be adjusted for in analyses due to the limited size of the sample with linked ECS data available, and this precluded meaningful comparisons of adherence in the two time periods. Adherence Study

participants had higher levels of education than ECS participants overall, and women receiving antenatal cART at the time of this study and engaged with HIV care postnatally were non-representative (explored further in section 3.2.5, page 102 and section 5.2.1, page 146 respectively). The high levels of adherence reported in this study may therefore not be generalizable to the wider HIV-positive population as cART coverage increases, and as individuals accumulate longer durations on ART.

Limitations affecting the self-efficacy measure included the simplification of the measure from its previously validated form (see page 68) and the fact that no measure of a woman's need for support was included in the questionnaire. Previous experiences of needing support and of trying to access it (including from healthcare professionals) may have positively or negatively affected a woman's confidence in her ability to seek support in the future.

6.9 Key points

- Use of the CASE index self-report adherence measure was feasible in this population of childbearing women. CASE scores of ≤11 or ≤12 were associated with higher viral load measures in a validation subset of 36 women.
- Overall, 14% of 175 Antenatal Survey respondents reported poor ART adherence during pregnancy (CASE score of ≤11) and a third reported having missed a dose of ART during pregnancy.
- Women reporting poor adherence in the Antenatal Survey were younger, more likely to have an unplanned pregnancy and to be living with their family (rather than with a partner), more likely to lack confidence in their ability to ask their doctor for support, and more likely to have disclosed their HIV status to a friend. In addition to these factors, a positive depression screening test, lower level of self-efficacy and being a current smoker were associated with reporting a missed dose of ART during pregnancy.
- Of the smaller postnatal sample of women currently on ART (*n*=99), 8% reported poor adherence during the last month (CASE score of ≤11) and a third of respondents reported missing a dose of ART during the last four weeks.
- Factors associated with reporting a missed dose over the preceding four weeks postnatally were being unmarried, not living with a partner, not disclosing HIV status to a partner, being a current smoker, having a history of drug use and not using a treatment adherence programme. Lower levels of self-efficacy were associated with having a CASE score of ≤11.
- Two of the three most common reported reasons for missing a dose in both the Antenatal and Postnatal Surveys were simply forgetting and being away from home. Lack of support from a partner was associated with poorer ART adherence in both time periods.
- Around 1 in 4 women screened positive for depression in both Antenatal and Postnatal Surveys.
- Levels of anxiety about the safety of ART for the infant were high: 83% of women were anxious about the safety of ART for the infant in utero, and two-thirds were worried about the safety of neonatal prophylaxis.

Chapter 7: Discussion

7.1: Introduction

This thesis highlights the diversity of the HIV epidemics affecting childbearing women in Europe, the convergence of PMTCT policy and practice in Ukraine with the Western region, and continued missed opportunities for PMTCT in both settings. Despite changes over recent years, there remain important differences in the characteristics of HIV-positive women living in Ukraine and Western Europe, most notably the much greater prevalence of IDU in Ukraine (14% of women enrolling in the ECS in 2010, compared with 1% at Western Europe sites) and associated HIV co-infection and co-morbidity. Although the proportion of new HIV infections attributable to IDU has declined in Ukraine since 2006, this is against a backdrop of an accelerating HIV epidemic, and the decline in the absolute number of new infections among IDUs is therefore less marked (Ministry of Health of Ukraine 2012). The increase in sexual transmission of HIV from IDUs and other high-risk groups to bridging populations and beyond is evidenced by the fact that almost two-thirds of women delivering in the Ukraine ECS in 2010 had no reported IDU history or IDU partner, up from 45% in 2000. Antenatal HIV screening, coverage of which is >99% (Ministry of Health of Ukraine 2012), has provided important evidence of the increasing heterosexual transmission of HIV in the general population in Ukraine.

In Western Europe, the predominantly African women enrolling into the ECS in 2010 were slightly older than those enrolled in Ukraine (median maternal age was 30 years and 27 years respectively). Surveillance data from the UK and Ireland have shown an increasing proportion of repeat pregnancies among HIV-positive women, particularly among those from Middle and Western Africa (French *et al.* 2012). Around a third of pregnancies in Western ECS sites since 2006 were repeat pregnancies to women previously enrolled in the study. In the Ukraine ECS, this proportion was smaller – estimated at 11% in 2010 – probably due to the shorter history of the HIV epidemic in Ukraine, poorer access to ART and HIV-related services, and the low birth rate in the general population (1.5 births per woman (Lekhan *et al.* 2010)). Linked to the prevalence of repeat pregnancies is the increasing proportion of women diagnosed as HIV-positive prior to conception, which reached 80% of enrolments in the Western sites of the ECS in 2010-11 (up from 70% in

2000-01), and 44% of enrolments in the Ukraine ECS in 2010 (up from 20% in 2000-01). These trends indicate opportunities for optimising the pre-conceptual care of diagnosed HIV-positive women, explored in the next section.

7.2: Pre-conceptual care of HIV-positive women

The comprehensive care of HIV-positive women requires appropriate management of their HIV disease (monitoring of clinical and immunological status and prompt initiation of cART when indicated), but also reproductive care and access to family planning. Achieving and maintaining an undetectable viral load is the aim of treatment for all individuals on cART; for women who may become pregnant this is particularly important, as MTCT risk is lowest when viral load is undetectable throughout pregnancy (Tubiana *et al.* 2010). For maternal health it may also be important to maximise immune status prior to pregnancy (Le Moing *et al.* 2008).

Many pregnancies among HIV-positive women are unplanned – for example, 31% of pregnancies among previously diagnosed women in the Women's Study were unplanned, and this is an underestimate of unplanned conceptions since it excludes pregnancy terminations. Italian surveillance data from 2001-06 showed that almost two-thirds of HIV-positive pregnant women had not planned their pregnancy (Floridia *et al.* 2007), while in a European survey in 2003-04 this proportion was 50%, with 31% of pregnancies both unplanned and undesired (Fiore *et al.* 2008). Of note, ART initiation was associated with an increased incidence of pregnancy in an African cohort study, possibly due to an association between improving health and changes in sexual behaviour or fertility desires (Carter *et al.* 2010). Data from the general population show that the risk of adverse neonatal or maternal outcomes is higher when a pregnancy is unintended (Tsui *et al.* 2010). For HIV-positive women, unintended or mistimed pregnancies will be associated with missed opportunities to optimise virological control and ART regimen. In a UK study, 31% of 375 women conceiving on ART since 1995 were taking an antiretroviral drug not recommended for use during pregnancy (Huntington *et al.* 2011), highlighting the need to consider the possibility of a future conception when managing HIV-positive women of reproductive age. Maternal IDU, an independent risk factor for lack of antenatal care in Western Europe and Ukraine (Chapter 3), is a potential challenge to the delivery of pre-conceptual care. Women with an IDU history accounted

for 21% of women diagnosed before conception and 9% diagnosed antenatally in the Ukraine ECS in 2008-10; in Western European sites these proportions were 22% and 7% respectively in 2000-09. IDUs were more likely to have an unplanned pregnancy than non-IDUs in the Women's Study, and this was reflected in a higher rate of unplanned pregnancies among women diagnosed preconception than among those diagnosed during pregnancy.

7.2.2 Conception on cART and virological failure in pregnancy

Investigation of the growing subgroup of women who conceive on cART provides a better understanding of how well the HIV disease of these women is being managed before pregnancy, the implications for virological control during pregnancy for women who conceive on a non-suppressive regimen, and potential strategies to improve outcomes. In Chapter 4, conception on cART at the Western Europe sites of the ECS is investigated, showing a substantial increase over the last twelve years; the proportion of women conceiving on cART exceeded 40% in 2010-11 and was 54% among those diagnosed prior to conception. Among those conceiving on cART with ≥24 weeks of treatment, the proportion with a non-suppressed viral load was 34% in 2000-01 declining to 3% in 2010-11. This is consistent with improvements over time in virological outcomes reported among treated individuals elsewhere (Mocroft *et al.* 2000; Bannister *et al.* 2006; Lampe *et al.* 2006; Vo *et al.* 2008; Raboud *et al.* 2010).

Non-boosted PI-based cART has been shown to be associated with poorer virological response than NNRTI and boosted PI-based regimens previously in the Western Europe ECS (Patel *et al.* 2007) and elsewhere (Walmsley *et al.* 2002; King *et al.* 2004; Bannister *et al.* 2006; Willig *et al.* 2008) and this is supported by findings reported in this thesis (Table 4.2b, page 139). However, the secular improvements in virological outcomes (Chapter 4) were independent of the increasing potency of first-line regimens (APR 0.80 (95% CI 0.72-0.89) per year after adjusting for cART type and other factors), as has been found in other studies (Bannister *et al.* 2006; Lampe *et al.* 2006). This may be due to general improvements in HIV care and accumulation of clinical expertise, as well as reduced toxicity, improved tolerability, and decreased pill burden and dosing frequency of newer regimens (Heath *et al.* 2002; Willig *et al.* 2008; Atkinson *et al.* 2009). These advances have helped to reduce the substantial impact of ART on health-related quality of life, including the frequency and

severity of ART side effects such as diarrhoea and lipodystrophy, thus improving ART adherence (Gakhar *et al.* 2013). Given expanding treatment options, it is also possible that women conceiving on cART in later years had already switched away from regimens that they were not tolerating well or were responding to sub-optimally. In the Swiss Cohort Study, patients were more likely to switch regimen in 2000-05 than in 1995-98, but switches in later years were less likely to be due to virological failure and more likely to be due to intolerance (Vo *et al.* 2008).

Among women conceiving on cART, those who had been diagnosed with HIV for longer were more likely to have a non-suppressed antenatal viral load (APR 1.06 (95% CI 1.01-1.10) per year HIV diagnosed prior to conception). Possible reasons include poor adherence due to treatment fatigue, and the development of ART resistance (Glass *et al.* 2006). Women enrolling in more recent years tended to have been diagnosed with HIV for longer (a median of 2.8 years for deliveries in 2010-11, compared with 1.1 years for deliveries in 2000-01), highlighting the increasing importance of the management of women with treatment experience. After adjusting for time since diagnosis, older women were more likely to achieve virological suppression than younger women. Younger age has been shown to be associated with an increased risk of poor ART adherence and/or poor virological outcomes in the UK and North America (Porter *et al.* 2008; Sabin *et al.* 2008; Sherr *et al.* 2010; Ryscavage *et al.* 2011; Hadland *et al.* 2012), and now also in Ukraine (Chapter 6). Older age was associated with better virological outcomes among women receiving HIV care in a second or subsequent pregnancy in the UK (odds of a detectable viral load at delivery were 0.76 (95% CI 0.63-0.92) for 25-34 years vs. <25 years (French *et al.* 2013)). Although IDU has been associated with poorer ART adherence (discussed in section 7.4.2, page 258), the two-fold increased risk of a non-suppressed viral load among IDUs (vs. non-IDUs) conceiving on cART was accounted for by their increased probability of enrolment in earlier years. Of note, IDUs may have been under-represented overall, because barriers to treatment might have made them less likely to meet the eligibility criteria for these analyses.

Women who conceived on cART and had at least two previous pregnancies in the ECS were at a three-fold increased risk of treatment failure compared with those who had no previous ECS pregnancies (Chapter 4). Most women with a previous ECS pregnancy had a history of antenatal cART receipt, and this may or may not have been continued between pregnancies (full treatment

histories are not routinely collected in the ECS). In the general HIV-positive population, poorer treatment outcomes have been reported when cART was stopped at higher CD4 counts and reinitiated at CD4 counts of <250 cells/mm^3 than when it was taken continuously (El-Sadr *et al.* 2008; Lundgren *et al.* 2008), but pregnant women are a more immunocompetent group. Studies investigating the effect of exposure to short-course PI-based cART in pregnancy have found no accumulation of resistance mutations (Gingelmaier *et al.* 2010), nor increased risk of virological failure when cART is received subsequently for PMTCT (Briand *et al.* 2011; French *et al.* 2013). However, an analysis of UK and Ireland surveillance data showed an increased risk of detectable viral load at delivery among women previously receiving short-course NNRTI-based cART for PMTCT (French *et al.* 2013). Other factors including child-care responsibilities may have had a negative impact on health-seeking behaviour or adherence among multiparous women; of note, such women were at increased risk of multiple missed opportunities for PMTCT in the Ukraine ECS (Chapter 3, discussed in section 7.3.2). More research is needed to understand treatment response among multiparous women, both with and without a history of HIV care in previous pregnancies.

Virological outcomes among women conceiving on a non-suppressive regimen

Pregnancy is a time when virological control may improve due to enhanced monitoring and support as well as improvements in ART adherence (Nachega *et al.* 2012). Among women conceiving on cART and with a non-suppressed viral load at first antenatal measure, 63% had a suppressed viral load (≤200 copies/ml) recorded before delivery and it is reassuring that this proportion increased over time (Chapter 4). In a previous ECS analysis which included 127 women conceiving on non-suppressive cART and enrolled from 1998 to 2006, 103 had a viral load available within four weeks of delivery, of whom 39 (38%) had a suppressed viral load at this time (European Collaborative Study 2010). Possible reasons for this difference are that a 'suppressed' viral load measure was defined as below the assay detection limit (<50 copies/ml) in the earlier analysis, and that the earlier study analysis was of data before widespread use of boosted PIs. The earlier study also included women with a treatment interruption pre-dating their first (non-suppressed) viral load during pregnancy, who may have had poorer virological control overall – treatment interruptions during pregnancy have become less common over time and are no longer recommended due to their

association with increased MTCT risk (Galli *et al.* 2009; de Ruiter *et al.* 2012; Panel on Treatment of HIV-infected Pregnant Women and Prevention of Perinatal Transmission 2012).

7.2.3 Management of HIV-positive women in Ukraine

A substantial proportion of women in the Ukraine ECS had been diagnosed before conception in recent years (31% in 2007, increasing to 44% in 2010). However, within this group the proportion conceiving on cART was much lower than in Western Europe (2% in 2007 and 12% in 2010, Chapter 3). Among those diagnosed but not on cART prior to conception and enrolling in 2010, over 40% had indications for treatment for their own health during pregnancy, demonstrating substantial unmet need for treatment prior to conception. This figure partly reflects poor cART coverage in the general population in Ukraine; although cART scale-up started in 2004, 52% of individuals with advanced HIV infection were not receiving it in 2009 (Ministry of Health of Ukraine 2010). Disengagement from HIV care was also a contributory factor, evidenced by the fact that one in ten women who were diagnosed with HIV but not on cART prior to conception in 2008-10 did not receive antenatal ART (the corresponding proportion in the Western Europe ECS sites in 2000-09 was 5%). Untreated women with indications for cART are not only at increased risk of morbidity and mortality, but also of MTCT (European Collaborative Study 2005).

Of 207 women initiating cART during pregnancy in 2008-10 and with a viral load measure available at least three months later, 69% had an undetectable viral load. As the laboratory capacity for virological monitoring in Ukraine expands, there will be opportunities to explore virological response rates to ART both within and outside the context of pregnancy, including among women who have previously received PMTCT interventions.

7.3. Progress towards the virtual elimination of MTCT

The virtual elimination of MTCT (a rate of <2%) is a target for the WHO European region by 2015 (WHO Regional Office for Europe 2011) and has already been achieved for some countries in Western Europe (European Collaborative Study 2005; Townsend *et al.* 2008a; Jasseron *et al.* 2011). From 2000 to 2009, 25 HIV-infected infants were reported in the Western Europe ECS – an overall MTCT rate of 1.7%, and 1.1% among women receiving at least 14 days of antenatal ART.

The huge successes of PMTCT programmes in Western Europe are increasingly being replicated in Ukraine, where scale-up of the most effective interventions has been hindered over the last decade by the challenges of resource-limitation and a rapidly accelerating epidemic driven by IDU. As the interventions used for PMTCT have become more similar in Ukraine to those used in Western Europe, so too have the circumstances surrounding missed opportunities for PMTCT. In both regions, missed opportunities are concentrated among marginalised groups with poorer access to and uptake of antenatal and HIV care, and with clustering of characteristics indicating potential marginalisation including IDU history, lack of a partner and, in Ukraine, multiparity and lower level of education.

7.3.1 Scale-up of cART for PMTCT in Ukraine

In Chapter 3, the substantial improvements in access to antenatal cART in Ukraine since the adoption of an 'Option B' policy are described; overall, 22% of women who initiated ART in pregnancy and delivered in 2008 received cART, increasing to 67% in 2010. The MTCT rate declined from 7% in 2007 (Thorne *et al.* 2009) to 4.1% in 2008-10, and 1.3% among the 45% of women who received antenatal cART in this later time period. This is compared with a 3.1% overall MTCT rate reported in St. Petersburg in 2007, a year when coverage with dual or triple antenatal ART was around 50% (Kissin *et al.* 2011). By 2010, 91% of women in the Ukraine ECS with treatment indications received cART in pregnancy (up from 56% in 2008), indicating their prioritisation for limited cART supplies as per WHO guidelines (WHO 2010a). CD4 count measurements are crucial for identification of women with treatment indications during pregnancy (Carter *et al.* 2010; Liu *et al.* 2011), with important implications for the decision to stop or continue ART after delivery. Although substantial advances have been made in the availability of CD4 count and viral load monitoring in Ukraine (Table 3.1, page 83) there is still unmet need for immunological monitoring, evidenced by the 27% of women delivering in 2010 who lacked an antenatal CD4 count; this also suggests that true coverage of women with treatment indications may have been lower than 91%.

In adjusted analyses, there was evidence that women with lower educational status were more likely to initiate ZDVm (rather than cART), despite the fact that lower educational status was associated

with poorer immunological health among women without treatment indications (Chapter 3). The barriers to care experienced by this group as well as by multiparous and unmarried women are explored in the next section ('late HIV diagnosis and/or lack of antenatal ART'). Women diagnosed as HIV-positive before conception but not on ART were more likely to start antenatal cART than those diagnosed in the first or second trimesters, possibly as they had more opportunity to undergo preparatory counselling. Among women who did receive antenatal cART, the potential for treatment interruptions around the time of delivery due to a lack of drug supplies at maternity hospitals (Personal Communication, Igor Semenenko, PPAI, 2012) has concerning implications for their virological control and risk of MTCT.

Resource limitation is a major barrier to universal access to cART in Ukraine. The cost of one year's treatment with LPV/r, ZDV and 3TC (the combination received by over 90% of women receiving cART in the Ukraine ECS from 2008-10) was estimated to be ~$500 in a lower-middle income European setting in 2011, according to the WHO (WHO 2012a). Most ($410) of this cost was attributed to LPV/r. This regimen is much more expensive than EFV-based alternatives, recommended by WHO as first-line treatment for adults outside of the context of pregnancy (WHO 2010b) and, as of June 2012, also supported as a first-line option during pregnancy (WHO 2012d). The 2012 guidance cites the accumulating evidence of the safety of EFV during pregnancy (Ford *et al.* 2011), its superior tolerability and efficacy compared with NVP, and the pressing need to simplify and harmonise regimens ('Treatment 2.0') in order to reduce cost and maximise the public health benefit of treatment programmes (WHO *et al.* 2011a; WHO 2012d). A once-daily fixed dose combination of TDF, 3TC and EFV has the advantage over the currently used LPV/r-based regimens of reduced pill burden and lower cost – $172 per year in 2011 (WHO 2012a). It also meets recommendations for the treatment of HIV-positive individuals co-infected with HBV with a regimen which has dual HBV activity (Brook *et al.* 2010) - important in avoiding the development of HBV resistance to 3TC (Pillay *et al.* 2000; Matthews *et al.* 2006). Of women enrolled in the postnatal Women's Study, 15% were co-infected with HBV (Chapter 5).

First-line cART regimens used outside of pregnancy in Ukraine are currently NVP-based (WHO 2005), Personal Communication, Ruslan Malyuta, PPAI, 2012), which precludes harmonisation with antenatal regimens due to the risk of NVP-related hepatotoxicity during pregnancy (Lyons *et*

al. 2006). It is unclear what impact the new WHO recommendations for the use of EFV-based regimens will have on national policy.

7.3.2 Lack of antenatal ART and late HIV diagnosis

Maternal ART during pregnancy is the most effective intervention for PMTCT (WHO 2010a), and most cases of MTCT occur when this has not been received (Mayaux *et al.* 2003; European Collaborative Study 2005; Townsend *et al.* 2008a). Overall, the proportion of women without antenatal or intrapartum ART in the Ukraine ECS in 2008-10 was 5% (vs. 7% in 2007 (Thorne *et al.* 2009)), and an additional 5% received sdNVP only. In the Western Europe ECS, 8% of women delivering in 2000-03 received no antenatal ART declining to 5% in 2004-09. These groups of women without antenatal ART accounted for 42% and 25% of vertical transmissions in Ukraine and Western Europe in these time periods respectively. To explore the relative importance of overall ART coverage and roll-out of cART for achieving a MTCT rate of <2% in Ukraine, two hypothetical scenarios were explored. By applying MTCT rates stratified by ART receipt, the overall predicted MTCT rate would have been 2.9% (95% CI 2.3-3.6) if all women on ZDVm had received cART, compared with 2.2% (95% CI 1.8-2.8) if cART coverage remained unchanged but the 336 women without antenatal ART had received ZDVm. These results confirm the importance of expanded ART coverage for the virtual elimination of MTCT in Ukraine as well as the prevention of residual transmissions in Western Europe. The performance of health systems, both in terms of identifying pregnant women with undiagnosed HIV infection and preventing subsequent loss to follow-up, are key (Mahy *et al.* 2010; Barker *et al.* 2011); postnatal follow-up is also crucial for successful implementation of an Option B+ approach (discussed further in section 7.4.1).

Lack of maternal HIV diagnosis is a major barrier to the elimination of MTCT worldwide (Barker *et al.* 2011). The studies in this thesis include only women with known HIV diagnosis by the time of delivery, and this thesis explores the frequency and impact of diagnosis late in pregnancy (i.e. after the end of the second trimester). Diagnosis at this time precludes initiation of antenatal ART at or soon after 14 weeks gestation (WHO 2010a), and compromises the chances that an undetectable viral load will be achieved by delivery (Read *et al.* 2012). Overall, late diagnoses accounted for 15% of enrolments in Western Europe ECS sites in 2004-09 and 11% of enrolments in the Ukraine ECS

in 2008-10. In Ukraine, the MTCT rate among women diagnosed late (in the third trimester or intrapartum) in 2008-10 was 8.5% (95% CI 5.6-12.2%), compared with 2.6% (95% CI 1.8-3.5%) among those diagnosed during the first or second trimester. The proportion of women diagnosed late in Western Europe and Ukraine ECS sites has been declining over time, related to the increasing proportion of women diagnosed prior to conception (Jasseron *et al.* 2008; Townsend *et al.* 2008b; Thorne *et al.* 2009; von Linstow *et al.* 2010) and the spread of the epidemic to less marginalised groups who are more likely to engage promptly with antenatal care. Among women undiagnosed at conception, the proportion of late diagnoses has also declined over time in both settings, although in Ukraine this stayed constant at around 18% in 2008-10. In the Ukraine ECS in 2008-10, a fifth of women completely lacking antenatal ART had been diagnosed late but 51% had been diagnosed prior to conception, highlighting the importance of retaining diagnosed women in care. Similarly in the Western Europe ECS in 2000-09, over a third of women with no or <14 days of antenatal ART had been diagnosed late, but around half were diagnosed before pregnancy.

Barriers to diagnosis and antenatal ART for IDUs

Women with an IDU history were more likely to be diagnosed late in Ukraine and Western Europe, and were also more likely than non-IDUs to lack antenatal ART if diagnosed before conception, suggesting that barriers to care exist for diagnosed as well as undiagnosed women. Other studies and earlier analyses in the ECS have also shown maternal IDU to be associated with a lack of antenatal care among HIV-positive women (European Collaborative Study 2001; Peters *et al.* 2003; Whitmore *et al.* 2010; Kissin *et al.* 2011), reflecting the often poorer access to HIV services among IDUs compared with non-IDUs in the general population (Lucas *et al.* 2001; Moore *et al.* 2004; Rodriguez-Arenas *et al.* 2006; Weber *et al.* 2009; Spicer *et al.* 2011). Even where HIV and harm reduction services are tailored to IDUs, they frequently do not take into account the needs of women, who constitute around 20% of people who use drugs in Eastern Europe and 40% in Western Europe (Harm Reduction International 2012). Female IDUs are at high risk of HIV acquisition and HIV-related stigma (El-Bassel *et al.* 2010), and pregnant IDUs may be particularly stigmatised, especially in countries where IDU is criminalised, leading to active avoidance of healthcare services (Pinkham *et al.* 2008; Open Society Institute 2009). Previous findings from the Ukraine ECS have shown women with an IDU history to be at increased risk of MTCT, over and

above that associated with their lack of PMTCT interventions and increased risk of preterm delivery (Thorne *et al.* 2012), and that IDUs without antenatal care are at particularly high risk of abandoning their infant at birth (Bailey *et al.* 2010).

Opiate substitution therapy is strongly recommended by WHO guidelines for opioid-dependent pregnant women (WHO 2009a), but lack of access is a particular issue for childbearing women in Ukraine (Nieburg *et al.* 2012). This is underscored by the fact that only 14% of current injectors enrolled in the postnatal Women's Study were participating in an opiate substitution programme. Methadone and buprenorphine are currently only available at narcology treatment centres, which are extremely stigmatising to attend, often a site of police harassment, and rarely accommodate the childcare needs of IDU mothers (Mimiaga *et al.* 2010; Spicer *et al.* 2011; Nieburg *et al.* 2012). Daily attendance at these centres presents substantial logistical challenges, particularly for pregnant women and mothers who have complex health and social needs.

Other aspects of a comprehensive package of care required for the prevention, treatment and care of HIV among IDUs include access to needle and syringe programmes, prevention and treatment of STIs, condom provision, and prevention, diagnosis and treatment of viral hepatitis and TB (WHO *et al.* 2012). Female childbearing IDUs require services which are sensitive to gender, and address healthcare needs in the context of exposure to intimate partner violence, sex work and social adversity. Multidisciplinary, case management approaches which integrate healthcare with social and legal services may improve engagement with care, as may psychosocial interventions and on-site childcare and parenting support (Pinkham *et al.* 2012).

Ecological theory postulates that structural factors are key determinants of individual behaviours, and that by altering the environmental conditions in which people live it is possible to influence health behaviours (Stokols 1992). The structural barriers that IDUs face to healthcare include not only a lack of access to harm reduction and integrated services as outlined above, but also the social structural barriers of stigma and discrimination. Stigma can be understood in Parker and Aggleton's conceptual framework as a cultural construct to establish and maintain social order, power differentials and social inequalities (Parker *et al.* 2003). Police harassment of IDUs in Ukraine is common: of 200 IDUs who participated in a recent study in Odessa, 35% had been held without arrest or charge, 13% had had new syringes taken by the police, 11% had been arrested for carrying

syringes, 17% reported not buying syringes due to fear of the police, and 24% had been beaten or tortured (Booth *et al.* 2013). IDUs who reported negative experiences with the police, and especially those who had experience of rushing injections due to fear of the police, were more likely to be HIV-positive (ibid). Stigma and discrimination are also widespread within healthcare services in Ukraine. A quarter of HIV-positive individuals in a recent national survey reported having their access to health or social care restricted in the last year as a result of their HIV status, and this proportion was 30% among high-risk groups (including IDUs) (Demchenko *et al.* 2011). Involuntary HIV testing exacerbates stigmatisation of testing and diagnosis (WHO *et al.* 2007) but is commonplace in Ukraine, with 22% of 1500 HIV-positive people surveyed in 2010 reporting that they had been tested without their knowledge or forcibly, and a third lacking pre- or post-test counselling (Demchenko *et al.* 2011). Such experiences are likely to undermine trust for healthcare professionals among IDUs and other high-risk groups with deleterious impact on engagement with care, possibly leading to active avoidance of healthcare services (Treloar *et al.* 2013). Rights-based approaches to delivering HIV-related services are needed to tackle structural determinants of individual-level risk, and are crucial for improving engagement of IDUs with healthcare services (Jurgens *et al.* 2010).

Other groups with barriers to HIV care in Ukraine

Other factors associated with suboptimal HIV care in Ukraine were being unmarried (cohabiting or single), having less education and multiparity (Chapter 3). These risk factors were clustered and also associated with IDU. Their independent associations with late HIV diagnosis and with lack of ART indicate multiple barriers among the most socially disadvantaged groups. Of note, cohabiting status is much more common among women enrolled in the Ukraine ECS than among women in the general population in Ukraine (40% of ECS enrolments in 2008-10, compared with 5% in the Ukraine DHS 2007 (Ukrainian Center for Social Reforms *et al.* 2008)), and may be a marker of social deprivation in this setting. Being unmarried, having less education and multiparity were also associated with receipt of ZDVm rather than cART among women initiating ART during pregnancy, possibly because clinicians were less likely to initiate cART among women attending infrequently for care as reported in other studies (Giordano *et al.* 2003; McNaghten *et al.* 2003) or because these groups were perceived to be less likely to adhere to cART. Results from the Ukraine

Adherence Study confirmed that women not living with a partner were more likely to report poor ART adherence during pregnancy (Table 6.11, page 223). In the Western Europe ECS, single women were more likely to lack ART than married or cohabiting women among the group diagnosed pre-conception. Health literacy (the ability to understand and act on health information) has been associated with self-perceived social support (Gordillo *et al.* 1999). Lack of a partner has been associated with late antenatal HIV diagnosis (Whitmore *et al.* 2010) and, in non-pregnant populations, with treatment delay (Samet *et al.* 1998; Torian *et al.* 2008).

Low level of education was associated with financial hardship (proxy: inability to afford contraception) in the Ukraine Women's Study (Chapter 5, page 152), consistent with national data on socioeconomic status and education, with 39% of women in the highest wealth quintile having some university education and 6% in the lowest quintile (Ukrainian Center for Social Reforms *et al.* 2008). Poor socioeconomic status and lower education levels are important factors associated with lack of healthcare utilisation in the general population in Ukraine (Balabanova *et al.* 2004). Although HIV care is one of the few areas where out-of-pocket payments are not normally applied (UNAIDS 2009), the fact that these are otherwise widespread may dissuade women in poor financial circumstances from seeking care, as may the other attendant costs (e.g. transport and childcare). Less educated patients and those with lower socioeconomic status have also been found to be less likely to initiate cART in the resource-rich settings of Switzerland and the US (Junghans *et al.* 1999; Wood *et al.* 2002).

Multiparous women had lower socioeconomic status than other women in the postnatal Women's Study, and this reflects demographic patterns in Ukraine's population overall (the total fertility rate is 1.0 in the highest wealth quintile and 1.7 in the lowest (Ukrainian Center for Social Reforms *et al.* 2008)). The relationship between economic deprivation and higher parity is likely to be complex, and mediated via other socioeconomic factors including employment. Many HIV-positive women will have experienced negative attitudes of health-care professionals concerning their reproductive potential; in a national survey in Ukraine, 28% of 677 HIV-positive women reported that they had been advised by healthcare professionals not to have children, 17% reported being worried that they would be forced to terminate a pregnancy if they tested positive and 5% had been coerced to

do so (Demchenko *et al.* 2011). Women who have already encountered stigma related to their child-bearing may have been less likely to seek care in a subsequent pregnancy.

Findings on the individual-level characteristics of women with missed opportunities for PMTCT can be used to inform the design of specific interventions for these highest-risk groups, but also underscore the broader socioeconomic determinants of health in this population. The Health Impact Pyramid illustrates the different levels at which public health interventions might act, with socioeconomic and contextual factors at the base (requiring the greatest political commitment, but also offering the largest impacts on public health outcomes), and targeted clinical and counselling interventions at the top (interventions which are easier to implement, but require greater individual effort and offer smaller public health gains) (Frieden 2010). Interventions to alter factors at the bottom of the pyramid, although more challenging, would have the potential to improve outcomes not only among the highest-risk groups identified in this thesis but also for the entire HIV-positive childbearing population in Ukraine by shifting the whole population to lower risk, as conceptualised in a structural model of health behaviour by Cohen et al. (Cohen *et al.* 2000). For example, interventions which tackled socioeconomic inequalities in health could facilitate earlier antenatal HIV diagnosis, longer durations of ART and better virological control among women on ART, by reducing barriers to optimal PMTCT interventions for all women. Such a shift could have wider ranging benefits for HIV outcomes (e.g. by reducing postnatal disengagement from services), and for outcomes in other disease areas (Frieden 2010).

Lack of HIV knowledge

A lack of knowledge about HIV and about the availability of effective PMTCT interventions may contribute to delays in accessing care, and to a complete lack of antenatal ART for some groups; for example, sixteen women delivering in the Ukraine ECS in 2008-10 received only sdNVP despite being diagnosed as HIV-positive at least a week prior to delivery. Results from the Ukraine DHS 2007 showed that in the general antenatal population, only 50% of women knew that risk of MTCT of HIV could be reduced by the woman "taking special drugs during pregnancy" (Ukrainian Center for Social Reforms *et al.* 2008), highlighting the importance of post-test counselling in antenatal care. Models of health behaviour which focus on motivational factors, such as the Theory of

Planned Behaviour, postulate intention as a proximal determinant of action, suggesting that education to improve perceptions of HIV care and its benefits could increase an individual's intention to attend and result in better actual engagement with care (Armitage *et al.* 2000). However, although these models take some account of environmental constraints on an individual's behaviour, they are likely to under-estimate the substantial impact of social determinants on missed opportunities for PMTCT (indicated by the findings discussed in the previous section). Multi-stage models which conceptualise actions as resulting from separate motivational and volitional phases (Armitage *et al.* 2000) may provide a more adequate explanation of uptake of PMTCT services, as may a biopsychosocial perspective which more explicitly incorporates predictors such as social stressors and support (Suls *et al.* 2004; Hampanda 2013). The multiple associations between social marginalisation and missed opportunities for PMTCT described in this thesis suggest that comprehensive education, while necessary, will not be sufficient to ensure adequate uptake of PMTCT services among diagnosed women.

Preterm delivery

In Western Europe sites of the ECS in 2000-09, delivery at <34 weeks gestation was associated with an almost three-fold increased risk of no antenatal ART and over four-fold increased risk of receiving only 1-13 days antenatal ART (section 3.3). In the Ukraine ECS in 2008-10, preterm delivery at <37 weeks was also associated with a lack of antenatal ART among women diagnosed during pregnancy (section 3.2). Missed opportunities for PMTCT among women who deliver preterm should be mitigated by the earlier initiation of antenatal ART (from 12 weeks and by 24 weeks) now recommended by most national guidelines within Europe (Aebi-Popp *et al.* 2013), which reflects the changing risk-benefit around ART use in pregnancy. HIV-positive women with a history of or other risk factors for preterm delivery such as IDU or smoking are likely to particularly benefit from initiation of antenatal ART earlier than the 24-26 weeks gestation currently recommended in Ukrainian guidelines (UNICEF 2012). Preterm delivery is not only a barrier to receipt of sufficient antenatal ART but also an independent risk factor for MTCT (European Collaborative Study 1999; Kuhn *et al.* 1999), and further increases MTCT risk by precluding elective CS delivery (McDonald *et al.* 2006), highlighting the importance of achieving virological suppression early in pregnancy (National Study of HIV in Pregnancy and Childhood *et al.* 2007).

Other circumstances leading to late diagnosis and/or lack of antenatal ART

Two other scenarios which may lead to a late antenatal HIV diagnosis and/or lack of antenatal ART are refusal of PMTCT interventions and acquisition of maternal HIV infection during the course of pregnancy. UK studies have found both positive and negative associations between refusal of antenatal screening and infection risk, also linking refusal to religious affiliation, parity and previous testing for HIV (Boxall *et al.* 2004; Conaty *et al.* 2005). Data on refusal of HIV testing or PMTCT interventions are not collected as part of the ECS protocol, but refusals have been reported on an ad hoc basis. In the French Perinatal Cohort, the proportion of women without antenatal ART who had declined treatment was about a third (Mayaux *et al.* 2003). In Ukraine, over 80% of respondents to the Antenatal Adherence Survey reported being worried about the safety ART in pregnancy (Chapter 6), highlighting the substantial burden of anxiety even among a group accepting antenatal ART as an intervention. Lower levels of worry were reported among women who were more confident about the effectiveness of ART for PMTCT. The strengthening of counselling about PMTCT for HIV-positive women in Ukraine is therefore a priority.

In Ukraine, diagnosis during the third trimester may be due to seroconversion during pregnancy, since repeat testing during the third trimester is routinely conducted among women testing negative earlier in pregnancy. Dates of negative antenatal HIV tests are not currently collected in the ECS, and it was therefore not possible to distinguish women seroconverting during pregnancy from those who were diagnosed late having not had a previous antenatal test. There is some (although inconsistent) evidence from African studies of an increased risk of acquiring HIV sexually during pregnancy, possibly due to hormonal changes or to heightened risk behaviours of women or their partners (Gray *et al.* 2005; Morrison *et al.* 2007; Mugo *et al.* 2011). Some groups at increased risk of being diagnosed late in the ECS (e.g. IDUs) may have poor access to antenatal care but also high HIV incidence rates. A study using a recent infection testing algorithm (RITA) among 1313 HIV-positive people in Odessa found that a quarter had recent HIV infection at the time of their HIV diagnosis, and that recent infection was particularly likely among young adults <25 years (Smith *et al.* 2012). Antenatal seroconversions have important implications for MTCT, not only because the infection may remain undiagnosed and untreated, but also as acute HIV infection is associated with

high plasma viral load (Pilcher *et al.* 2007) (see also Figure 1.3, page 25) and thus heightened MTCT risk, particularly if other STIs are present.

The contribution of incident HIV infections during pregnancy and breastfeeding to MTCT rates in Europe is difficult to quantify, particularly in Western Europe where repeat antenatal testing is not carried out unless a women is known to be at risk of HIV acquisition during pregnancy. In resource-rich settings, a substantial proportion of perinatal transmissions are now likely to be to undiagnosed women, including those with acute HIV infection who had not yet seroconverted at the time of their antenatal test (Patterson *et al.* 2007). In the UK and Ireland, an audit of the circumstances surrounding the perinatal infection of 87 HIV-positive infants born between 2002 and 2005 found that 54 were born to undiagnosed women, with maternal seroconversion occurring during pregnancy in at least 20% of these cases (National Study of HIV in Pregnancy and Childhood *et al.* 2007). Among these 54 infants, 17% died within the first two years of life (compared with 6% of the 33 infants born to diagnosed women), highlighting the importance of timely maternal diagnosis to infant health.

Over the last few years in Ukraine, between 200 and 400 women annually have tested positive at their second antenatal HIV test having tested negative at their first (approximately 3 months earlier), which translates to an annual estimated 0.2% incidence rate (UNICEF 2012). Because the second antenatal test is conducted around 10-12 weeks before the end of pregnancy, and >95% of women in the general population in Ukraine breastfeed for a median duration of 10 months (Ukrainian Center for Social Reforms *et al.* 2008), the number of seroconversions occurring among women who remain undiagnosed and at risk of transmitting the infection to their infant is likely to be significant. Partner testing of pregnant women is an important strategy to reduce maternal seroconversions, since the identification of HIV-negative women in discordant partnerships provides motivation for the use of condoms during pregnancy when contraception is not required (Saxton *et al.* 2010), and an opportunity for the use of treatment as prevention (Cohen *et al.* 2011). On a population level, people who are aware of their own HIV-positive status are less likely to transmit the infection sexually due to modified risk behaviours and reduced infectiousness associated with treatment (Marks *et al.* 2006). HIV testing for all partners of pregnant women can be cost saving, even in a setting with low HIV prevalence where only one or two vertical

transmissions are averted per 100,000 seronegative early pregnancies (Postma *et al.* 2000). Women with on-going risk of HIV acquisition such as IDUs or sexual partners of IDUs could benefit from rapid testing at delivery (currently only conducted in the absence of antenatal screening) and HIV testing postnatally, to allow for intrapartum and postpartum PMTCT interventions (Nielsen-Saines *et al.* 2012) in the event of seroconversions.

7.3.3 Antenatal adherence to ART in Ukraine

Results from the Antenatal Adherence Survey in Ukraine are presented in Chapter 6 (results from the Postnatal Survey are discussed later, page 258). There are no previously published data on ART adherence among childbearing women in Eastern Europe and very little information on adherence in the non-pregnant population, none of which is specific to Ukraine. Poor adherence as defined by a CASE index measure score of ≤11 was associated with poorer virological outcomes in this thesis, as found previously (Kerr *et al.* 2012). Overall, 14% of respondents in the Antenatal Adherence Survey had a CASE score of ≤11, and 35% of respondents reported missing at least one dose during pregnancy. Comparisons with other studies of adherence among pregnant women are difficult to make due to the range of adherence assessment methods and outcome measures used. The 72% of women estimated to have adequate (>80%) adherence to ART during pregnancy in a recent meta-analysis (Nachega *et al.* 2012) is similar to the 65% of women here who reported not having missed a dose during pregnancy. Two African trials which defined poor adherence as any self-reported missed dose or day without medication during pregnancy (and possibly therefore provide a better comparison with the Ukraine data) found perfect adherence levels to be 86% (two arms: ZDVm or placebo) (Shapiro *et al.* 2006) and 73% (Kesho Bora, two arms: cART or ZDVm plus sdNVP) (de Vincenzi 2011). The care received in the context of these African trials was more intensive than standard antenatal care in Ukraine (e.g. follow-up every two weeks in the Kesho Bora study (de Vincenzi 2011)), and duration of ART was also shorter (a median of 5 weeks in the ZDVm/placebo study (Shapiro *et al.* 2006)). These and other context-specific factors, as well as the potential differences between trial populations and Ukraine Adherence Survey participants, may account for the difference in adherence levels reported.

The CASE questions were generally well-completed in the Ukraine Survey. However, some women who reported never having missed a dose went on to give reasons for missed doses, which suggests that the CASE questions may have lacked permissiveness, or that confusion may have arisen over the wording of one or other of the questions. This issue was not apparent during the pilot (n=20 for each of the two surveys). Future work could investigate the reasons for these discrepancies, and the sensitivity and specificity of the CASE questions alone and in combination with the 'reasons for missed dose' question in predicting virological suppression.

Because a criterion for participation in the Ukraine Survey was receipt of at least four weeks of antenatal ART, some groups were under-represented – notably women with lower levels of education and those without a partner. Too few data were available to assess the association between educational status and antenatal adherence, but poor adherence was more commonly reported among women living with their extended family (two-thirds of whom did not live with a partner) compared with the remainder who mostly lived with a partner. Lack of financial support from a partner and lower levels of education have been associated with poor ART adherence among women in South Africa (El-Khatib *et al.* 2011). The multiple barriers to antenatal HIV care experienced by women without a partner and with less education in the Ukraine ECS (Chapter 3) have implications for adherence (e.g. access to and uptake of adherence support). The prevalence of poor adherence reported in this thesis may therefore be an under-estimate of that seen on a population level, particularly as cART is rolled out to more marginalised groups over time.

Women living with their extended family, and thus probably requiring practical and financial support, were more often young (<25 years) and with an unplanned pregnancy. The association between youth and increased risk of poor ART adherence, also discussed earlier (page 237), has been documented in pregnant and postpartum women in the US (Laine *et al.* 2000; Turner *et al.* 2000) and may be partly due to more chaotic lifestyles in this group; elsewhere, youth has been associated with reduced retention in HIV care (Bygrave *et al.* 2012; Fleishman *et al.* 2012). Two of the most common reasons for missing a dose here were being away from home and simply forgetting. The poorer levels of adherence reported by women with unplanned pregnancies is particularly concerning as this group are at increased risk of STI co-infections (see Table 5.5a page

164 for association with chlamydia), some of which further increase MTCT risk (Drake *et al.* 2007; Thorne *et al.* 2008).

Current smokers were more likely to report poor ART adherence both during pregnancy and postnatally. Smoking was more common among women unable to afford contraception in the postnatal Women's Study (see Chapter 5, page 153), and thus a marker of economic deprivation. Alcohol and tobacco use have been associated with poorer levels of self-reported adherence during pregnancy among HIV-positive women in the US (Mellins *et al.* 2008), where smoking is also associated with lower socioeconomic status among women in the general population (Friestad *et al.* 2003).

Perinatal depression

An important finding of the Adherence Study was the substantial burden of depressive morbidity among participants, with a quarter in both Antenatal and Postnatal Surveys screening positive for depression (Chapter 6). Screening for depression is not currently part of routine perinatal or HIV care in Ukraine, and the depression screening tool used in the Adherence Surveys has not yet been validated in Russian. However, this tool has been successfully used elsewhere as part of routine perinatal care (Olson *et al.* 2006; National Collaborating Centre for Mental Health 2007) and had a high level of acceptance among Adherence Survey respondents. Because depression is associated with lack of self-care (Angelino *et al.* 2001), the overall prevalence of perinatal depression may be higher than the ~25% found in the Adherence Surveys among women accessing services.

Depressive symptoms during pregnancy were associated with an increased probability of reporting a missed dose of ART (Chapter 6); negative affect has also been associated with poorer ART adherence among pregnant women in the US (Bardeguez *et al.* 2008). Other studies using various definitions of depressive symptoms have reported very high rates of perinatal and postpartum depression of 44% to 74% among HIV-positive women in Thailand, the US and Zimbabwe (Chibanda *et al.* 2010; Ross *et al.* 2011; Rubin *et al.* 2011). In Ukraine, it is estimated that 6.6% of women in the general population have a major depressive disorder in any one-month period, with increased risk among those unmarried or of lower educational or socioeconomic status (Bromet *et al.* 2005) – characteristics disproportionately found among marginalised HIV-positive populations.

Of concern to outcomes beyond pregnancy, depression has also been associated with HIV disease progression in a number of studies (Ickovics *et al.* 2001; Antelman 2007; Willig *et al.* 2008).

Access to mental health services in Ukraine is poor. In the 2002 World Mental Health Survey, only 17.4% of women who had ever had a mood disorder had sought help from a medical professional (28% among those acknowledging suicidal thoughts), and where professional help had been sought this was mostly from general medical physicians with very little expertise in diagnosing and treating mental health problems (Bromet *et al.* 2005). Barriers to psychiatric care may be particularly severe for HIV-positive women and include the lack of integration of psychiatric with HIV care, a poorly developed outpatient infrastructure for mental health services, out-of-pocket payments for psychiatric medication, and severe stigma associated with seeking treatment for mental health problems (Bromet *et al.* 2005; Lekhan *et al.* 2010). Women screening positive for depression in the Adherence Surveys were referred for additional support as per the study protocol, but some women were known to have refused. Services which may help to maintain or improve psychological wellbeing among HIV-positive women, such as support groups and peer counselling, are provided by NGOs on an often ad-hoc basis and are predominantly accessed by women after delivery (see Table 6.2, page 203). However, depression is a recurrent condition, and symptoms pre-conception are associated with antenatal depression, which is a major risk factor for postnatal depression (Leigh *et al.* 2008; Rubin *et al.* 2011). The high prevalence of depression during pregnancy among women who may be lost to follow-up after delivery provides evidence of the need for on-going mental health support for HIV-positive women.

Lower level of self-efficacy was related to greater prevalence of depressive symptoms as well as to poorer ART adherence in the Antenatal Survey, and is a potential area for intervention. Cognitive-behavioural interventions to increase self-efficacy have been associated with reduced depressive symptoms, increases in CD4 count and decreases in viral load among HIV-positive women in the US (Ironson *et al.* 2005; Jones *et al.* 2010). In South Africa, a 'mothers2mothers' peer support programme had a beneficial impact on a range of psychosocial outcomes in HIV-positive women during pregnancy and postnatally, including improved feelings of agency and reduced hopelessness (Baek *et al.* 2007). Similar peer programmes may also be of relevance to HIV-positive women in Ukraine, given resistance to and poor availability of professional mental health support; peer

programmes to reduce HIV risk behaviours have been piloted among MSM and commercial sex workers with some success (Ministry of Health of Ukraine 2012).

Adherence to neonatal prophylaxis

The very high levels of adherence to neonatal prophylaxis reported in this study are partly due to the short duration of neonatal prophylaxis (one week) and relatively long postnatal hospital stays for HIV-positive women in Ukraine (around 3-5 days, Personal Communication, Igor Semenenko, PPAI, 2011). Around half of all neonatal doses were therefore given in hospital, where medical personnel could administer them or assist the mother or other family members in doing so. Two-thirds of women expressed worries about neonatal prophylaxis harming their baby and this anxiety was more common among women who were unsure about its effectiveness, suggesting unmet needs for counselling and information provision. Poor antenatal ART adherence has been associated with poor adherence to neonatal prophylaxis in the US (Demas *et al.* 2002) and lack of attendance for neonatal follow-up (Kingston *et al.* 2007), but these associations could not be assessed in this study due to its cross-sectional nature. Adherence problems during pregnancy may persist after delivery; postnatal adherence is discussed in the next section.

7.4. Keeping HIV-positive mothers alive in Ukraine

PMTCT programmes are an important entry point to HIV care for HIV-positive mothers (UNAIDS 2011a). Women diagnosed through antenatal screening tend to be healthier than the newly HIV-diagnosed population as a whole, which includes individuals diagnosed as a result of symptomatic presentation. In the Ukraine ECS, among women diagnosed during pregnancy and delivering in 2010, 8% had WHO stage 3-4 disease and 32% had WHO stage 3-4 disease and/or a CD4 count ≤350 cells/mm^3, while in Ukraine as a whole the proportion of people newly diagnosed as HIV-positive with advanced disease or AIDS was 40% (coverage with CD4 count testing not stated) (Ministry of Health of Ukraine 2012).

To preserve the health of HIV-positive childbearing women, access to cART for those with treatment indications and CD4 count monitoring for those ineligible for treatment are crucial, but both are compromised by resource limitations in Ukraine. HIV care and treatment for mothers is also important for preventing poor outcomes in HIV-exposed infants (Newell *et al.* 2004; Kuhn *et al.* 2005; Marinda *et al.* 2007), including those associated with orphanhood. However, the PMTCT programme in Ukraine does not make specific provision for the needs of HIV-positive women following pregnancy and delivery, and there are currently no population-level indicators to assess postpartum care and outcomes of these women (UNICEF 2012).

7.4.1 Continuation of cART postpartum

Within the current Option B policy in Ukraine, women who do not require treatment for their own health stop ART at delivery, while ART-eligible pregnant women are recommended to continue cART lifelong (WHO 2010a). Universal coverage of individuals eligible for cART is a target for the WHO European Region by 2015 (WHO Regional Office for Europe 2011). Only 53% of women requiring treatment for their own health were on ART postnatally at Women's Study enrolment in 2008-11 but this doubled from 34% in 2008 to 72% in 2011 (Chapter 5), reflecting scale-up of cART more widely for ART-eligible individuals in Ukraine (Ministry of Health of Ukraine 2012). These figures will be an overestimate of the true level of coverage of ART-eligible women due to unidentified indications for treatment among women without a CD4 count measure during pregnancy (27% of women delivering in 2010). Among the 15% of women who were co-infected

with HBV, ART discontinuation after delivery is of concern regardless of treatment indication for HIV disease, because these women are at risk of HBV viral rebound, hepatic flares, and more rapid deterioration of immune function if an antiretroviral drug with anti-HBV activity such as 3TC is stopped (Nuesch *et al.* 2008; Bellini *et al.* 2009; Dore *et al.* 2010).

The importance of postpartum CD4 count monitoring for women stopping ART at delivery is highlighted by fact that 25% and 46% of women in the Kesho Bora and MTCT-Plus Initiative studies respectively progressed to a CD4 count of <350 cells/mm^3 in the two years following delivery (from 350-500 cells/mm^3 and 400-499 cells/mm^3 during pregnancy respectively) (Ekouevi *et al.* 2012; The Kesho Bora Study Group 2012). Benefits of earlier ART initiation at CD4 counts of 350-500 cells/mm^3 in preventing HIV-related clinical events and sexual transmissions have recently been demonstrated in the HPTN 052 trial (Cohen *et al.* 2011), and have implications for risk-benefit decisions around continuation of ART after delivery. An Option B+ strategy (in which lifelong cART is initiated in all HIV-positive pregnant women) is not yet under consideration for the PMTCT programme in Ukraine (UNICEF 2012), but would reduce reliance on CD4 monitoring for determining postpartum treatment eligibility and have potential benefits for maternal health (WHO 2012b). Option B+ could also reduce onward sexual transmissions, of particular relevance given that at least a quarter of women in the Women's Study were in discordant partnerships and use of barrier contraception in this group is poor (Saxton *et al.* 2010). However, there are major obstacles to its implementation, most obviously resource limitation and problems retaining diagnosed women in care (evidenced by missed opportunities for PMTCT in this group). Roll-out of cART to all eligible individuals (as currently defined) and then more widely would involve the monitoring and treatment of vastly increasing numbers of patients and require health-system strengthening. The willingness of young women with no symptoms of HIV disease to initiate and adhere to lifelong ART, particularly in a setting with a low fertility rate and high levels of HIV-related stigma, also needs to be investigated. Results from Chapter 4 showed an increased risk of virological failure among women who already had at least two children; this may partly reflect challenges adhering to ART while caring for a family, and requires further investigation in the context of Option B+. Of note, about a quarter of participants in the Adherence Surveys here

reported being somewhat or terribly bothered by ART side effects; although these women were not more likely to report poor ART adherence, very few had accumulated long periods on ART.

7.4.2 Postnatal ART adherence

High levels of adherence are important for the success of current and future treatment programmes, particularly given the lack of second-line treatment options currently available in Ukraine (Judice *et al.* 2011). Levels of adherence reported were similar in the Antenatal and Postnatal Surveys (Chapter 6), but these surveys were cross-sectional and women with adherence problems may have been less likely to continue ART after delivery. When postpartum participants were asked to compare their own current adherence with that during pregnancy, a minority (12/93) reported that it had declined but only two reported an improvement. It is therefore not possible to rule out declining adherence levels postpartum, as have been reported elsewhere (Ickovics *et al.* 2002; Vaz *et al.* 2007; Bardeguez *et al.* 2008; Cohn *et al.* 2008; Mellins *et al.* 2008), when the demands of caring for a new baby may compromise health-seeking behaviours (Stein *et al.* 2000). A longitudinal study design is required to directly assess changes in adherence following delivery.

More advanced HIV disease or health-related symptoms have been associated with poorer ART adherence among pregnant and postpartum women (Bardeguez *et al.* 2008; Mellins *et al.* 2008), including in a predominantly IDU, non-pregnant population in Eastern Europe (Uuskula *et al.* 2012). In contrast, there was no association here between WHO stage and adherence during pregnancy, while postnatally women with WHO stage 3-4 disease seemed to adhere better than those with less severe disease (13% and 36% respectively reported missing at least one dose in the last four weeks, p=0.10).

Other characteristics associated with poor adherence postnatally were similar to those relevant during pregnancy, including being unmarried, a current smoker and having low treatment-related self-efficacy. Depression was not associated with poorer adherence among women surveyed here at a median 6 months postpartum, but elsewhere has been associated with declining adherence over time (Byakika-Tusiime *et al.* 2009). Interestingly, history of drug use was associated with poor ART adherence postnatally but not during pregnancy. Women with an IDU history had barriers to antenatal care but were not under-represented in the postnatal Women's Study (21% prevalence

since 2007, vs. 14-18% per year in the ECS), probably due to care-seeking prompted by their more advanced HIV disease stage and symptoms. IDUs accessing care in pregnancy for PMTCT may be less marginalised than those coming into contact with HIV care only when symptomatic. There was no evidence that current drug use was more common postnatally (as might be the case if resumption of drug use after delivery led to a deterioration in adherence), but reporting of current drug use may be subject to particularly strong social desirability bias among new mothers. In other studies, a history of or current drug use has been associated with poorer adherence among HIV-positive childbearing women (Laine *et al.* 2000; Cohn *et al.* 2008) and in the general population, where IDUs have been found to be at higher risk of virological failure and development of resistance than non-IDUs (Lampe *et al.* 2006; Lima *et al.* 2008a; Mann *et al.* 2012). There is some evidence that harm reduction programmes for IDUs support ART adherence (Weber *et al.* 2009; Uhlmann *et al.* 2010).

Only 38% of women accessed treatment adherence programmes postnatally, but these women were more likely to report complete adherence in the last four weeks. More work is needed to disentangle the impact of the programmes from the characteristics of the women who accessed them, and to describe the programmes in operation at different HIV/AIDS centres. Women with caring responsibilities for children had lower ART adherence in two US studies (Demas *et al.* 2002; Merenstein *et al.* 2008), and the multiple barriers to care during pregnancy for multiparous HIV-positive women indicate that this is as an important area for future investigation. Executive skills are important for the management of ART (Waldrop-Valverde *et al.* 2010), but a number of factors which are associated with an increased risk of cognitive impairment such as HCV co-infection, substance use and depression (Schouten *et al.* 2011b) are very common among HIV-positive people in Ukraine. Work is needed to ensure that cognitive impairment does not negatively impact on adherence and treatment outcomes in this setting.

The Information-Motivation-Behavioral Skills Model provides a framework within which to understand barriers to adherence and design interventions. This model describes determinants of adherence as falling into three categories: information (about the regimen, side effects, drug interactions, importance of adherence), motivation (in terms of personal attitudes and beliefs about the outcomes of adherence, and social perceptions of others' support and motivation to comply

with others' wishes), and behaviour skills (e.g. for acquiring and administering medication, incorporating the regimen into daily life, acquiring adherence support) (Fisher *et al.* 2008). The effects of information and motivation levels on adherence are mediated via behavioural skills and other factors (e.g. structural barriers, substance use and psychological illness), with the implication that interventions targeting information and motivation will not be effective if behavioural skills are inadequate, or other barriers are insurmountable. As an example, poor adherence among women with an IDU history may be associated with deficiencies in all three areas, as well as specific IDU-related structural barriers, all of which will need to be addressed for an intervention to be effective.

7.4.3 HIV co-infections and associated comorbidities

Prevalence of a number of HIV co-infections (sexually transmitted and blood-borne) were very high among women with test results available in the Women's Study: 60% of women were positive for HSV-2 antibodies, 32% for HCV antibodies, 15% for HBsAg, 24% for chlamydia, 11% for *T. vaginalis*, 2% for syphilis and 0.3% for gonorrhoea (Chapter 5). Against a backdrop of STI epidemics in Ukraine following independence (see Introduction, page 23), women in the Ukraine ECS were previously found to be at a ten-fold increased risk of being diagnosed with chlamydia, syphilis or *T. vaginalis* during pregnancy compared with women at Western Europe ECS sites (data from 1999 to 2005) (Landes *et al.* 2007). The results in this thesis highlight the continued high prevalence of HIV co-infections in Ukraine, in contrast to the much lower prevalence seen recently among HIV-positive pregnant women in the UK and Ireland (1.9% for HCV antibodies, 5.8% for HBV and 0.5% for chlamydia, Personal Communication, Pat Tookey, NSHPC, 2011) and among asymptomatic HIV-positive heterosexuals in the Netherlands (STI prevalence of 1.6%, (Heiligenberg *et al.* 2012)). This partly reflects the IDU-driven nature of the HIV epidemic in Ukraine and associated high-risk sexual behaviours (Booth *et al.* 2007) as well as low condom use (Saxton *et al.* 2010). At an earlier stage in the epidemic in Western Europe, among a cohort of HIV-positive women with an IDU prevalence of 29%, 15% had an acute STI (chlamydia, gonorrhoea or syphilis) (van Benthem *et al.* 2000b). Given the synergy between other STIs and the acquisition and transmission of HIV (Cohen 2006), these results are of substantial concern to the on-going heterosexual spread of the HIV epidemic in Ukraine. The prevalence of HIV co-infections on a

population level may be even higher than reported here, as the Women's Study is a clinic-based cohort of women engaged with care.

There was considerable local variation in coverage of testing for HIV co-infections and cervical screening as part of HIV care among sites participating in the Women's Study: coverage of testing for HCV antibodies ranged by HIV/AIDS centre from 6% to 94%, and coverage of testing for chlamydia ranged from 0% to 91%. Structural-level barriers to testing were particularly notable at Mykolaiv and Krivoy Rog HIV/AIDS centres, where testing for chlamydia was almost completely unavailable, and where other findings (low self-reported accessibility of family planning and high prevalence of pregnancy termination) indicated particularly poor access to reproductive health services.

Importantly, routine data sharing does not take place between HIV/AIDS centres and other services which may diagnose and treat HIV co-infections (e.g. contraceptive and sexual health services), and so it is possible that women lacking testing or cervical screening as part of HIV care were accessing these services elsewhere. However, user fees are often charged for diagnostic services in non-HIV specific settings (UNAIDS 2009), and a number of factors indicate that utilisation of testing in other settings (with the exception of testing for syphilis and HBsAg as part of routine antenatal care) is likely to be low. These include the very high prevalence of chlamydia and the fact that only 15% of sexually active women were using modern non-barrier contraceptive methods, which are only available through contraceptive clinics. HIV-related stigma may dissuade women from seeking sexual and reproductive healthcare from other providers (Demchenko *et al.* 2011). Where services are accessed elsewhere, women may conceal their HIV status – of particular detriment to the management of cervical abnormalities, as HIV-positive women may benefit from a lower threshold for referral to colposcopy and more intensive surveillance than the standard of care for HIV-negative women (Fakoya *et al.* 2008; US Centers for Disease Control and Prevention 2009). The European Action Plan for HIV/AIDS 2012-15 lays out a target that more than 60% of sexual and reproductive health services should have links with or offer HIV-related services in the majority of Member States by 2015 (WHO Regional Office for Europe 2011), reflecting the importance of service integration for improving the quality of care of vulnerable populations.

At centres where testing or screening were offered, the main individual-level barrier to uptake was lack of HIV care, indicated by the association between late antenatal HIV diagnosis and lack of a chlamydia test or cervical screening test. However, as the Women's Study is a clinic-based cohort of women in HIV care postnatally, opportunities for testing are also likely to have been missed. In particular there were some indications that marginalised women were more likely to miss out on opportunities for testing: for example, IDUs were more likely than non-IDUs to lack a chlamydia test result, despite their 50% increased risk of a positive result where tested. Among women diagnosed as HIV-positive prior to their most recent pregnancy, those with less education were less likely to have ever had a cervical screening test as part of HIV care, reflecting inequalities seen in the general population in Ukraine (where three-yearly cervical screening coverage is 87% and 68% in the top and bottom wealth quintiles respectively (Gakidou *et al.* 2008)).

Overall, 30% of women had ever received a cervical screening test as part of HIV care at cohort enrolment at the three HIV/AIDS centres offering this, and a third of these tests had been done more than a year previously. A quarter of those screened had a finding of LSIL or HSIL, which is comparable to the 23% prevalence found among 285 HIV-positive women in a study in Brooklyn in 1990-93 (Maiman *et al.* 1998), and 27% prevalence of abnormalities among 1134 HIV-positive women at the European sites of a multi-centre cohort study (Kitchener *et al.* 2007). Higher rates of abnormalities (30% and 48%) have been reported among HIV-positive women in Africa (Mbizvo *et al.* 2005; Kitchener *et al.* 2007), and a lower rate of 15% in the U.S. Women's Interagency HIV Study, possibly because all women in this study participated in six-monthly screening (Massad *et al.* 2004). Of note, the prevalence of LSIL and HSIL reported in the Women's Study may not be generalizable to the cohort as a whole, as the women who were screened had a higher prevalence of BV than the rest of the cohort, which was an independent risk factor for cervical abnormalities in adjusted analyses.

In adjusted analyses, BV and HSV-2 seropositivity were associated with a three-fold and 80% increased risk of a finding of LSIL or HSIL respectively. Selective screening of women at high risk for HPV and HSV-2 infection or BV (e.g. women with multiple sexual partners) could account for these associations, but further exploration was precluded by a lack of data on HPV infection or sexual risk behaviours in the Women's Study. HSV-2 and BV may increase the risk of cervical

cancer by acting as cofactors to HPV or through local inflammatory processes (Castle *et al.* 2003), and a large pooled analysis has found an association between HSV-2 seropositivity and cervical cancer independent of HPV infection and sexual risk behaviours (Smith *et al.* 2002). Although evidence of an association between BV and HPV acquisition / persistence or cervical abnormalities is less well established (Guijon *et al.* 1992; Platz-Christensen *et al.* 1994; Peters *et al.* 1995; Moscicki *et al.* 2001; Boyle *et al.* 2003; Verteramo *et al.* 2009), a recent meta-analysis of twelve studies demonstrated a significantly increased risk of cervical HPV infection among women with BV (combined OR 1.43, 95% CI 1.11-1.84) (Gillet *et al.* 2011). Among HIV-positive women, two studies have showed an association between BV and cervical HPV infection, independent of sexual risk factors (Watts *et al.* 2005; King *et al.* 2011). BV is associated with other adverse outcomes relevant to HIV-positive childbearing women, including preterm delivery and STI acquisition (Leitich *et al.* 2003; Allsworth *et al.* 2011), and thus screening and treatment should be a priority.

As cervical screening is conducted on a predominantly opportunistic basis for the general population in Ukraine (Introduction, page 47), an organised screening programme for HIV-positive women (whereby they receive written invitations for screening at the HIV/AIDS centre) could lessen disparities in screening coverage of these high-risk women. As the majority of women stop ART at delivery and therefore do not need to return to the HIV/AIDS centre for ART supplies, a regular invitation for cervical screening could also facilitate retention of this group in postpartum HIV care. Around 70% of cervical cancer cases in Eastern Europe are attributed to vaccine-preventable HPV types 16 and 18 (Clifford *et al.* 2006), but HPV vaccination programmes have not yet been introduced in Ukraine (WHO ICO Information Centre on HPV Cervical Cancer 2010). A recent meta-analysis found a doubling of HIV acquisition risk among women infected with HPV (Houlihan *et al.* 2012), suggesting that HPV vaccination programmes could potentially reduce the incidence of sexually acquired HIV, although many questions remain unanswered regarding the potential impact of this approach (Schim van der Loeff *et al.* 2012). Issues regarding the acceptability of vaccinations in Ukraine (Bazylevych 2011) may impact on the coverage of a future HPV vaccination programme. Acceptability issues and out-of-pocket payments in some settings have likely contributed to the very low coverage with HBV vaccination of HBsAg negative individuals in the Women's Study (16% among non-IDUs and 5% among IDUs).

There was no change over time in the proportion of women reporting that contraception was unaffordable (Chapter 5, page 152), but the decline in the proportion reporting that it was inaccessible is encouraging, and in line with recommendations for availability of free condoms as part of HIV care (UNAIDS 2009). Only 15% of sexually active women were using modern non-barrier contraceptive methods and these women had higher education levels than other women, reflecting the fact that modern contraceptive use is more common among higher socioeconomic groups in Ukraine (Ukrainian Center for Social Reforms *et al.* 2008; Janevic *et al.* 2012). The finding that modern non-barrier contraceptive use was more common among women testing positive for chlamydia (25% vs. 16% of those testing negative, p=0.02) highlights the importance of messages around dual protection. In Russia, consistent condom use was independently associated with the belief that condoms provide reliable protection against unwanted pregnancy, but not with the belief that they provide protection against STIs (Bobrova *et al.* 2005), suggesting that use may be low where STI prevention is required without contraception. Provision of comprehensive family planning within HIV care (the second component of a comprehensive PMTCT approach, Table 1.2 page 30) can improve uptake of contraception (Kosgei *et al.* 2011), and may facilitate discussion of prevention of other STIs and superinfection with other HIV strains.

At 78%, the HCV seroprevalence among women with an IDU history in this cohort is slightly higher than the 61-73% reported previously among IDUs in Ukraine (Nelson *et al.* 2011), as would be expected in an HIV-positive cohort. HCV is more transmissible than HIV among IDUs (van Beek *et al.* 1998; Patrick *et al.* 2001), and so IDUs infected with HIV are likely to have had particularly high levels of exposure to HCV, for example because of a long injecting history or needle-sharing. Female IDUs also tend to be at higher risk of acquisition of blood-borne infections, as they are often injected by their male partners and 'second on the needle' (El-Bassel *et al.* 2010).

Apart from sentinel surveillance surveys among IDUs, very little is known about HCV seroprevalence and transmission in Ukraine. Interestingly, the 20% prevalence of HCV antibodies among non-IDUs in the Women's Study is similar to the 24% HCV seroprevalence reported among HIV-positive non-IDU women in St Petersburg in 2008 (Kissin *et al.* 2011). These figures raise questions about the potential under-ascertainment of IDU history, but also invite discussion regarding alternative modes of HCV transmission among the HIV-positive population in this

region. As biomarkers of current drug use (e.g. urine or hair) were not available, two indirect markers of IDU were examined in Chapter 5 – adverse birth outcomes and lack of antenatal care. Among non-IDUs, these outcomes were not associated with HCV seropositivity, as might have been expected if current IDU had been under-ascertained. Kissin *et al* similarly found that indicators of perinatal transmission among HCV seropositive non-IDUs were more similar to HCV seronegative non-IDUs than to IDUs. Although there was no evidence of under-ascertainment of current IDU, past IDU is more difficult to rule out, particularly if this was in the form of brief experimentation.

Of 236 HCV seropositive non-IDUs, 13 were diagnosed with HCV at the same time as or prior to HIV, suggesting that they may have been identified as being at high risk of blood-borne infections before being diagnosed as HIV-positive, and may have accessed outreach testing services for IDUs (none of these 13 women reported an IDU partner). HCV seropositive non-IDUs were also more likely to have a number of characteristics associated with IDU than their HCV seronegative counterparts, including a recent chlamydia diagnosis (at two centres) and a history of pregnancy termination, and also tended to have been diagnosed with HIV infection for longer. Importantly, these characteristics could also indicate sexual or iatrogenic HCV acquisition risk. One survey of HCV seroprevalence in New York among migrants from the former Soviet Union reported HCV seroprevalence to be 31% among 29 migrants from Ukraine, 29% among 31 migrants from Uzbekistan and 11% among 18 migrants from Russia, whilst overall prevalence of drug use history was only 2%, and concluded that inadequately sterilised medical equipment and blood transfusions were the most likely sources of most of these infections (Batash *et al.* 2008). An HCV seroprevalence of 8% has also been found among the antenatal population in Kiev, where HCV testing is now conducted routinely for all pregnant women (Personal Communication, Bila Zerkva, Kiev Antenatal Clinic, 2012).

In order to better understand modes of HCV acquisition among HIV-positive women in Ukraine, longitudinal data are needed on HCV serostatus and on possible sources of infection, including IDU, sexual and iatrogenic risk factors, non-injection drug use and exposure to infected household contacts. HCV antibody avidity assays allow for identification of recent HCV infection (Gaudy-Graffin *et al.* 2010), which may be helpful in establishing HCV incidence as well as the relative

timing of HCV and HIV acquisition. The results presented in Chapter 5 suggest that HCV seroprevalence may not be an appropriate proxy for HIV injecting risk behaviour in Ukraine, unlike in the European Union (Wiessing *et al.* 2006). In centres other than Kiev, where HCV testing is currently only repeated annually for HIV-positive individuals with known risk behaviours (e.g. IDUs), it may be appropriate to extend screening to include those with high-risk sexual partners, or to all HIV-positive individuals; almost half of the HCV seropositive women in this study had no reported history of IDU.

HCV RNA PCR testing is not routinely carried out in Ukraine due to its relative expense, and so it was not possible to distinguish individuals with active infection from those who had spontaneously cleared it. Spontaneous clearance rates are lower among HIV-positive than HIV-negative individuals (Thomas *et al.* 2000); in a large European cohort of HIV-positive individuals, the spontaneous clearance rate was 23% (Soriano *et al.* 2008). It was also not possible to exclude HCV exposure among HCV seronegative individuals, as some individuals may have lost antibodies following spontaneous clearance (Heintges *et al.* 1997). Severely immunosuppressed individuals may also not mount a detectable HCV antibody response, although only 8% of HCV seronegative individuals in the Women's Study had a CD4 count ≤200 cells/mm^3 (Table 5.6b, page 172). These scenarios might explain the fact that 22% of IDUs were HCV seronegative – a group at high risk of infection or re-infection, and an important focus for prevention activities.

Among this young population of HIV/HCV co-infected women who were almost entirely untreated for HCV and at an early stage of HIV disease, non-invasive markers of liver fibrosis indicated that the proportion with advanced/significant liver fibrosis was low: 1% according to FIB-4 scores and 8% according to the possibly less specific APRI scores. However, differences in FIB-4 and APRI scores were already detectable by HCV serostatus and by IDU status, with HCV-seropositive IDUs tending to have higher scores than HCV-seropositive non-IDUs. The field of HCV treatment is undergoing rapid expansion with the development of numerous directly acting antivirals which have the potential to make regimens less toxic, more potent and of shorter duration than the standard of care of PegIFN/RBV (Soriano *et al.* 2011) (anti-HCV therapy is not currently publicly funded in Ukraine). Telaprevir and boceprevir, two protease inhibitors licensed for the treatment of HCV genotype 1 infection in Europe and North America in 2011, improve the

rate of sustained virological response when used in combination with PegIFN/RBV in HIV-negative and HIV-positive individuals (Cooper *et al.* 2012). However, uptake of these new therapies is limited by cost and, among HIV/HCV co-infected individuals, by high prevalence of contraindications and drug interactions with ART (Klein *et al.* 2012). Most antivirals in development for HCV are active mainly or only against HCV genotype 1 (Soriano *et al.* 2011), a "hard to treat" genotype (Kalinina *et al.* 2001). The HCV genotypes circulating in Ukraine are unknown, but the 3a subtype predominates among IDUs in Western Europe and the US (Hnatyszyn 2005), and was also the most common subtype among both IDUs and non-IDUs in a study in St. Petersburg (Kalinina *et al.* 2001). A better understanding of the modes of HCV transmission in Ukraine and improved coverage of harm reduction measures are of utmost importance, not only for primary prevention but also for preventing the re-infection of treated individuals should treatment become available.

7.5 Strengths and weaknesses

This thesis uses data from a variety of sources: an established multi-centre prospective cohort study of HIV-infected women and their infants, a nested postnatal cohort in Ukraine, and a survey on adherence. Limitations specific to each analysis are discussed in the corresponding chapters; this section describes the general strengths and weaknesses of the studies.

As pregnancy/delivery-based observational cohorts, major strengths of the ECS and Women's Study lie in their ability to capture information on 'real world' implementation of policies affecting the health and MTCT risk of HIV-positive women in Europe. Data collected in these studies allow for coverage with testing and interventions to be investigated, as well as the divergence of clinical practice from policy and variation in practice in areas where policy is poorly defined. These cohorts also capture information on women who are more often asymptomatic and in better health than clinic-based cohorts of predominantly ART-eligible individuals. The ECS enrols highly marginalised women, some of whom engage with healthcare services only when in labour and are unlikely to be included in other clinic-based cohorts (as indicated by their under-representation in the Women's Study). Information about these high-risk groups is important for the development of strategies to eliminate MTCT in Ukraine and to prevent residual transmissions in Western Europe, as well as for

the design of outreach services. Of note, even among women receiving a rapid test in labour, marginalised groups may be less likely to receive a diagnosis before delivery (as shown among IDUs in Russia (Kissin *et al.* 2008)) and thus be ineligible for ECS enrolment. Women terminating their pregnancies are not included in the ECS, and groups who are least likely to complete their pregnancy will therefore have been under-represented.

The clinical centres which participate in the ECS are regional referral centres for HIV-positive pregnant women. Although participation rates among eligible women at these centres are very high (>95% at Western Europe sites (Patel 2007)), their characteristics may differ from women receiving care at non-participating centres, as may the treatment and care they receive. This is particularly the case in Ukraine where there is substantial regional variation in access to cART and to CD4 count and viral load monitoring (Chapter 3), and where ECS and Women's Study sites are situated in some of the worst affected regions of the country, where staff may be more experienced in the management of HIV in pregnancy but may also be operating within greater resource constraints. Analyses using data from the Western Europe ECS were adjusted for by country (to reflect national policy differences) rather than by centre, because of the large number of participating centres and sometimes small number of women enrolled at each. Unmeasured confounding between centres could therefore not be accounted for. In Ukraine ECS analyses, adjustment by centre was possible, but differences between the centres (and between countries in Western Europe) may limit the generalizability of results to specific sites. Changes over time in the characteristics of women participating at a particular site (and in centres participating in the study) will have had some impact on overall trends, an example being the impact of the changing demographics of women enrolling in Mykolaiv on overall MTCT rates reported in the Ukraine ECS in 2008 to 2010 (section 3.2.6). However, the good nationwide coverage of the Ukraine ECS, which enrolled around a third of HIV-positive women delivering in the country in 2009, makes findings broadly generalizable.

Of women enrolled in the ECS at each site, participation rates in the Women's Study varied from 24% in Donetsk to 87% in Kiev, probably because some centres more systematically invited or supported women to enrol rather than because of large variation in refusal rates. Participation rates were highest at the best resourced centres (e.g. Kiev), possibly reflecting the fact that staff had more time to counsel women about the study and complete the study forms. Participation rates in the

Adherence Study, estimated to be between 39% and 49% of eligible women for the antenatal survey and 35% of women attending HIV care after delivery in the postnatal survey (75% among women on ART) also varied by centre (section 6.3). In both the Women's Study and the Adherence Study, women with the poorest access to and uptake of care were under-represented, because eligibility was limited to women who had received ART for at least the last four weeks of pregnancy (for the antenatal adherence survey) or those attending HIV care postnatally (for the Women's Study and postnatal adherence survey); representativeness of the study samples is explored in section 5.2 and section 6.3. Taken together, these data have important implications for interpretation of the results. Specifically, prevalence of outcomes positively associated with health behaviours and access to care (e.g. receipt of a cervical screening test) are likely to have been over-estimated and those linked to poor access to or uptake of care (e.g. a recent chlamydia diagnosis) under-estimated when compared with these outcomes among HIV-positive childbearing women in Ukraine overall. The substantial unmet need for care and support among women participating in the Women's Study and Adherence Study – groups of women who were comparatively well-served – underscores the inadequacies of service provision on a population basis.

The Adherence Study had a number of specific limitations related to its cross-sectional design. A cross-sectional design was chosen because a longitudinal design would have required an unfeasibly large number of participants in the antenatal survey to allow for a sufficient number to be followed up postnatally (a time when many women stop ART and/or are lost to follow-up), and a longer study duration. The cross-sectional design allowed for adherence levels at the two time points to be broadly described, but precluded a more detailed analysis of changes in ART adherence and perinatal depression following delivery. Future studies could consider active follow-up of women postnatally to facilitate longitudinal data collection, but the acceptability of this approach would need to be investigated given that researchers would require access to identifying information including name and address/phone number. The paper-based format of the Adherence Study surveys may have dissuaded less literate women from taking part. Audio computer-assisted self-interview techniques, which may result in more accurate self-report of sensitive information than face-to-face interviews (Gorbach *et al.* 2013), could be considered for use in future surveys to increase accessibility and reduce bias.

Missing data limited the interpretation of some findings in this thesis. In Ukraine, availability of data on some variables, particularly CD4 count, viral load and diagnosis of co-infections, depended on local budgets and other factors with substantial variation between centres. Individual-level engagement with HIV services also played an important role in determining availability of test results (Chapter 5) and data on other variables; for example, women without antenatal ART were more likely to be missing information on marital status and timing of HIV diagnosis (Chapter 3). As data were systematically missing for some groups, imputation of missing data was not considered appropriate and a complete case approach was taken throughout. The possible effects of the resulting selection bias include under- or over-estimation of size of association between explanatory and outcome variables (respective examples are between IDU and insufficient ART, Chapter 3 and between BV and cervical abnormalities, Chapter 5) and under- and over-estimation of the prevalence of an outcome (respective examples are the MTCT rate in 2010, Chapter 3, and possible over-estimation of cervical abnormality prevalence, Chapter 5).

Maternal characteristics associated with poor access to or uptake of services were explored throughout this thesis, and although some markers of marginalisation were available (such as IDU), the lack of direct measures of socioeconomic status limited characterisation of marginalised groups. Information on sexual risk behaviours was not available in the Women's Study, precluding more detailed exploration of factors associated with a recent chlamydia diagnosis, HCV seropositivity among non-IDUs, and of the relationship between BV or HSV-2 and cervical abnormalities. Self-reported IDU history was likely to have been subject to social desirability bias and in the absence of objective measures of drug use, IDU may have been under-ascertained (explored in section 5.3.2). The lack of data sharing between HIV/AIDS centres and other healthcare providers in Ukraine limited conclusions in some areas. Access to other sources of sexual and reproductive health care, although suspected to be low, could not be verified. These barriers to data collection reflect barriers to the delivery of integrated clinical care, as described in Chapter 1, and to decision-making by HIV physicians, and thus highlight important weaknesses of the health system in caring for HIV-positive childbearing women.

The Adherence Study was designed to collect detailed data on a range of psychosocial factors possibly important in understanding the adherence behaviours of HIV-positive women in Ukraine.

These factors had not been previously measured in this population and the measures used in the Adherence Study, although previously validated in English and some other languages, had not previously been validated in Russian. Linkage of Adherence Study data with data from the ECS allowed for some validation of CASE adherence index scores against viral load; despite the sparseness of viral load data available, the results of the validation analyses lent weight to the use of the CASE self-report adherence measure. Depression screening test results using the PHQ-2 screening tool could not be validated, both due to lack of access to mental health services at some centres and lack of data sharing with these services if they did exist. As characterisation of depression is influenced by culture and language (Oates *et al.* 2004), it is possible that the PHQ-2 tool performed differently in this Ukrainian population than in previous validation analyses in the UK (Arroll *et al.* 2005). Measurement of HIV-related self-efficacy in the Adherence Study was limited by the use of an abbreviated version of the HIV-ASES tool, after pilot study results indicated that use of the full tool was not feasible. It was therefore not possible to compare the results on self-efficacy with those from other studies; however, the responses to these questions and their associations with depression and ART adherence highlight some potentially useful areas for intervention.

7.6 Conclusions and future work

This thesis explores a number of issues pertinent to the contemporary management of HIV-positive childbearing women in Europe and particularly to the substantial and growing proportion living in the resource-limited setting of Ukraine. Missed opportunities for PMTCT persist and are concentrated in the East, where the MTCT rate was 4.1% in Ukraine in 2008-10 compared with 1.7% in Western European sites of the ECS in 2000-09. Findings in Chapter 3 indicate social marginalisation to be a key factor impeding access to antenatal ART in both settings, and suggest that strategies to engage marginalised groups are essential for achieving an overall MTCT rate of <2% in Ukraine, as elsewhere (Mahy *et al.* 2010; Barker *et al.* 2011; Ciaranello *et al.* 2012). Findings in this thesis focus on individual-level characteristics of women lacking care, important for the design of interventions for specific high-risk groups (see section 7.7, Recommendations). However, further work exploring the context of these women's behaviour is also needed because interventions which address social and structural determinants of health, while more challenging to implement, are likely to have larger and wider-ranging benefits, not only for HIV-positive women but for all childbearing women in Ukraine (Frieden 2010). Of note, IDUs and other marginalised groups constitute a declining proportion of HIV-positive childbearing women, and so overall declines in MTCT rates may not reflect improvements in their access to care. MTCT rates specific to these groups need to be monitored to evaluate the success of outreach strategies, not only in terms of reducing transmissions but also in improving other treatment and care outcomes.

An increasing proportion of HIV-positive women are having multiple pregnancies following their HIV diagnosis and this thesis highlights some important challenges regarding the management of multiparous HIV-positive women. The increased risk of virological failure among women conceiving on cART with prior exposure to HIV care in ≥2 pregnancies, or with longer duration of diagnosed HIV infection, has potential implications for the risk-benefit of an Option B+ strategy. More work is needed to understand the mechanisms underlying these findings and to clarify the support that treatment-experienced women may require prior to and during pregnancy to achieve optimal outcomes. In Ukraine, HIV-positive women with two or more children had pervasive barriers to antenatal and HIV care. Qualitative work with this group, who were also more likely to have indicators of social deprivation, could inform the design of services sensitive to their needs.

The virological response to treatment of women with prior exposure to pregnancy-related HIV care in Ukraine requires specific exploration, because sdNVP has been used more widely and more recently here than in Western Europe (Chapter 3), and without the recommended NRTI 'tail' to prevent the development of NNRTI resistance (Lockman *et al.* 2010; WHO 2010a). NNRTI resistance will be of particular relevance to women starting cART outside of the context of pregnancy, where first-line regimens are currently NVP-based. Further work is needed to explore the equitability and sustainability of cART provision in Ukraine, particularly with regard to possible future policy changes around the use of Option B+ and harmonisation of treatment programmes.

Findings from the postnatal Women's Study in Ukraine (Chapter 5) provide evidence that barriers to antenatal care persisted postpartum and that, even among women engaged with HIV services, there was a substantial unmet need for sexual and reproductive healthcare. These results highlight a lack of preventative healthcare for HIV co-infections and integrated diagnostic and treatment services, placing HIV-positive women at risk of preventable co-morbidity. The lack of functional linkages between HIV/AIDS centres and other primary care providers poses barriers to both healthcare and research. Future work to link data from multiple primary care sources could help advance understanding in areas related to the detection and management of HIV co-infections (for example, the sensitivity and specificity of cytologic screening). Many questions remain regarding the transmission and impact of HIV/HCV co-infection in this population and further work is needed to ascertain non-IDU modes of HCV acquisition, circulating genotypes and impact on liver function.

The Ukraine Adherence Study (Chapter 6) is the first study to investigate ART adherence among HIV-positive childbearing women in Ukraine. The utility of the self-report CASE adherence index used in this study is an important finding and further validation against virological outcomes in this population is required, as is comparison with other short self-report measures. Future work is needed to assess adherence among groups who were under-represented in the Ukraine Adherence Study, such as women with low levels of education, as well as among individuals with longer treatment durations. Further investigations into depressive symptoms and anxiety about the safety of ART reported in the Adherence Study were beyond the scope of this thesis but are important

areas of enquiry. Interventions which could improve adherence as well as outcomes in other areas such as mental health and drug use (e.g. those raising self-efficacy) require evaluation.

7.7 Recommendations

The practical implications of results from this thesis for the treatment and care of HIV-positive childbearing women in Europe are summarised below.

Western Europe

Results from Chapter 3 highlight the need for supportive outreach for IDUs and other women at risk of disengaging from on-going HIV care, in order to optimise their own health (with prompt initiation of ART when this is indicated) and to avoid missed opportunities for PMTCT in future pregnancies. Provision of low-barrier antenatal services, and support for marginalised groups to access these, could reduce the number of HIV diagnoses late in pregnancy. The shift in national and international guidelines to recommend earlier initiation of antenatal ART for PMTCT from 14 weeks gestation will be particularly beneficial for women with risk factors for preterm delivery; implementation of these policies should be monitored. Women diagnosed as HIV-positive may benefit from education about the benefits of accessing HIV care as soon as they become pregnant (and ideally before conception, if the pregnancy is planned) so that MTCT risk can be minimised. For those already on ART at conception, results highlight the need for careful monitoring of women with long durations of treatment, including those who have received ART in previous pregnancies. Adherence support tailored to the needs of young and multiparous women is particularly important, as these groups are at potentially increased risk of virological failure.

Ukraine

Findings show that pregnant women with characteristics indicating potential marginalisation or social or economic disadvantage are at risk of multiple missed opportunities for PMTCT. Healthcare services are needed which prioritise the needs of these pregnant women (including IDUs and women without a partner). These services would ideally be locally accessible, have an outreach component, provide practical and emotional support, and integrate antenatal and HIV care with sexual health and other services (e.g. harm reduction), as these women are likely to experience challenges accessing a wide range of services. Results highlight the importance of expansion of opioid substitution therapy programmes, including programmes which cater for the

needs of female IDUs in general and for those who are pregnant or have childcare responsibilities in particular. For all HIV-positive women, stronger links between HIV care and other healthcare services are needed, particularly links with services which diagnose and treat HIV co-infections and associated morbidity. Improvements in preventative healthcare (e.g. HBV vaccination and cervical screening) should be a priority.

The scale-up of antenatal cART since the adoption of an Option B policy has been encouraging, but further expansion is required along with strategies to improve equity of access. Programmes for postnatal follow-up of HIV-positive women should be expanded and evaluated and should include improved cART coverage of women with treatment indications and supportive outreach for women at high risk of loss to follow-up (e.g. those with poor uptake of antenatal services). Regular assessment of ART adherence and depressive symptoms during pregnancy and postnatally using validated tools could help to identify women in need of additional support; improved access to high quality mental health care is urgently required. Improvements in information provision and peer support for pregnant women could help to alleviate their high levels of anxiety about the safety of ART for PMTCT, and could also improve health behaviours such as prompt attendance for postnatal follow-up.

References

Aebi-Popp, K., Mulcahy, F., Rudin, C., Hoesli, I. and Thorne, C. (2013). "A survey of national guidelines for the prevention of mother-to-child transmission of HIV across Europe." European Journal of Public Health **In press**.

Ahdieh-Grant, L., Li, R., Levine, A. M., Massad, L. S., Strickler, H. D., Minkoff, H., Moxley, M., Palefsky, J., Sacks, H., Burk, R. D. and Gange, S. J. (2004). "Highly active antiretroviral therapy and cervical squamous intraepithelial lesions in human immunodeficiency virus-positive women." J.Natl.Cancer Inst. **96**(14): 1070-1076.

AIDS Clinical Trials Group (2010a). Center for AIDS Prevention Studies (CAPS) Instruments: ACTG Adherence Baseline Questionnaire. Accessed September 2012. http://caps.ucsf.edu/uploads/tools/surveys/pdf/2098.4186.pdf.

AIDS Clinical Trials Group (2010b). Center for AIDS Prevention Studies (CAPS) Instruments: The HIV Treatment Adherence Self-Efficacy Scale. Accessed September 2012. http://caps.ucsf.edu/uploads/tools/surveys/pdf/HIV-ASES.pdf.

Aldous, J. L. and Haubrich, R. H. (2009). "Defining treatment failure in resource-rich settings." Current opinion in HIV and AIDS **4**(6): 459-466.

Allsworth, J. E. and Peipert, J. F. (2011). "Severity of bacterial vaginosis and the risk of sexually transmitted infection." Am.J.Obstet.Gynecol. **205**(2): 113.e111-113.e116.

Alter, M. J. (2007). "Epidemiology of hepatitis C virus infection." World J Gastroenterol **13**(17): 2436-2441.

Altice, F. L. and Friedland, G. H. (1998). "The Era of Adherence to HIV Therapy." Ann Intern Med **129**(6): 503-505.

Amirkhanian, Y. A., Kelly, J. A., Kuznetsova, A. V., DiFranceisco, W. J., Vladimir, B. M. and Dmitry, G. P. (2011). "People with HIV in HAART-Era Russia: Transmission Risk Behavior Prevalence, Antiretroviral Medication-Taking, and Psychosocial Distress." AIDS Behav **15**(4): 767.

Ammassari, A., Antinori, A., Aloisi, M. S., Trotta, M. P., Murri, R., Bartoli, L., D'Arminio Monforte, A., Wu, A. W. and Starace, F. (2004). "Depressive Symptoms, Neurocognitive Impairment, and Adherence to Highly Active Antiretroviral Therapy Among HIV-Infected Persons." Psychosomatics **45**(5): 394-402.

Ammassari, A., Murri, R., Pezzotti, P., Trotta, M. P., Ravasio, L., De Longis, P., Lo Caputo, S., Narciso, P., Pauluzzi, S., Carosi, G., Nappa, S., Piano, P., Izzo, C. M., Lichtner, M., Rezza, G., Monforte, A., Ippolito, G., d'Arminio Moroni, M., Wu, A. W., Antinori, A. and Ad, I. S. G. (2001). "Self-reported symptoms and medication side effects influence adherence to highly active antiretroviral therapy in persons with HIV infection." J Acquir Immune Defic Syndr **28**(5): 445-449.

Angelino, A. F. and Treisman, G. J. (2001). "Management of psychiatric disorders in patients infected with human immunodeficiency virus." Clin Infect Dis **33**(6): 847-856.

Antelman, G. (2007). "Depressive symptoms increase risk of HIV disease progression and mortality among women in Tanzania." J Acquir Immune Defic Syndr. **44**(4): 470-477.

Apisarnthanarak, A. and Mundy, L. M. (2010). "Application of a 3-Item Adherence Metric to Monitor Antiretroviral Medication Adherence in a Resource-Limited Setting." J Acquir Immune Defic Syndr. **55**(4): 528.

Armitage, C. and Connor, M. (2000). "Social cognition models and health behaviour: A structured review." Psychology and Health **15**(2): 173-189.

Arroll, B., Goodyear-Smith, F., Kerse, N., Fishman, T. and Gunn, J. (2005). "Effect of the addition of a "help" question to two screening questions on specificity for diagnosis of depression in general practice: diagnostic validity study." BMJ **331**(884).

Asboe, D., Aitken, C., Boffito, M., Booth, C., Cane, P., Fakoya, A., Geretti, A. M., Kelleher, P., Mackie, N., Muir, D., Murphy, G., Orkin, C., Post, F., Rooney, G., Sabin, C., Sherr, L., Smit, E., Tong, W., Ustianowski, A., Valappil, M., Walsh, J., Williams, M. and Yirrell, D. (2012). "British HIV Association guidelines for the routine investigation and monitoring of adult HIV-1-infected individuals 2011." HIV medicine **13**(1): 1-44.

Atkinson, M. J. and Petrozzino, J. J. (2009). "An evidence-based review of treatment-related determinants of patients' nonadherence to HIV medications." AIDS Patient Care STDS **23**(11): 903-914.

Atlani, L., Carael, M., Brunet, J., Frasca, T. and Chaika, N. (2000). "Social change and HIV in the former USSR: the making of a new epidemic." Social Science & Medicine **50**: 1547-1556.

Atun, R. and Olynik, I. (2008). "Resistance to implementing policy change: the case of Ukraine." Bulletin of the World Health Organization **86**(2): 147-154.

Bacchetti, P. and Moss, A. R. (1989). "Incubation period of AIDS in San Francisco." Nature **338**(6212): 251-253.

Baek, C., Mathambo, V., Mkhize, S., Friedman, I., Apicella, L. and Rutenberg, N. (2007). Key findings from an evaluation of the mothers2mothers program in KwaZulu-Natal, South Africa. Horizons Final Report. Washington, DC, Population Council.

Bailey, H., Semenenko, I., Pilipenko, T., Thorne, C., Malyuta, R. and Ukraine European Collaborative Study Group (2010). "Factors associated with abandonment of infants born to HIV positive women: results from a Ukrainian birth cohort." AIDS care.

Balabanova, D., McKee, M., Pomerleau, J., Rose, R. and Haerpfer, C. (2004). "Health service utilization in the former soviet union: evidence from eight countries." Health Serv Res **39**(6 Pt 2): 1927-1950.

Bandstra, E. S., Morrow, C. E., Mansoor, E. and Accornero, V. H. (2010). "Prenatal drug exposure: infant and toddler outcomes." Journal of addictive diseases **29**(2): 245-258.

Bangsberg, D. R., Acosta, E. P., Gupta, R., Guzman, D., Riley, E. D., Harrigan, P. R., Parkin, N. and Deeks, S. G. (2006). "Adherence-resistance relationships for protease and nonnucleoside reverse transcriptase inhibitors explained by virological fitness." AIDS **20**: 223-231.

Bangsberg, D. R., Hecht, F. M., Charlebois, E. D., Zolopa, A., Holodniy, M., Sheiner, L., Bamberger, J. D., Chesney, M. A. and Moss, A. (2000). "Adherence to protease inhibitors, HIV-1 viral load, and development of drug resistance in an indigent population." AIDS **14**: 357-366.

Bangsberg, D. R., Moss, A. and Deeks, S. G. (2004). "Paradoxes of adherence and drug resistance to HIV antiretorviral therapy." Journal of Antimicrobial Therapy **53**: 696-699.

Bangsberg, D. R., Perry, S., Charlebois, E. D., Clark, R. A., Roberston, M., Zolopa, A. and Moss, A. (2001). "Non-adherence to highly active antiretroviral therapy predicts progression to AIDS." AIDS **15**(9): 1181-1183.

Bannister, W. P., Kirk, O., Gatell, J. M., Knysz, B., Viard, J. P., Mens, H., Monforte, A. D., Phillips, A. N., Mocroft, A. and Lundgren, J. D. (2006). "Regional changes over time in initial virologic response rates to combination antiretroviral therapy across Europe." J Acquir Immune Defic Syndr **42**(2): 229-237.

Barcal, K., Schumacher, J., Dumchev, K. and Moroz, L. (2005). "A situational picture of HIV/AIDS and injection drug use in Vinnitsya, Ukraine." Harm Reduction Journal **2**(16).

Bardeguez, A. D., Lindsey, J. C., Shannon, M., Tuomala, R. E., Cohn, S. E., Smith, E., Stek, A., Buschur, S., Cotter, A., Bettica, L. and Read, J. S. (2008). "Adherence to antiretrovirals among US women during and after pregnancy." J.Acquir.Immune.Defic.Syndr. **48**(4): 408-417.

Barker, P. M., Mphatswe, W. and Rollins, N. (2011). "Antiretroviral drugs in the cupboard are not enough: the impact of health systems' performance on mother-to-child transmission of HIV." Journal of acquired immune deficiency syndromes **56**(2): e45-48.

Barnett, T., Whiteside, A., Khodakevich, L., Kruglov, Y. and Steshenko, V. (2000). "The HIV/AIDS epidemic in Ukraine: its potential social and economic impact." Social Science & Medicine **51**(9): 1387-1403.

Barros, A. J. and Hirakata, V. N. (2003). "Alternatives for logistic regression in cross-sectional studies: an empirical comparison of models that directly estimate the prevalence ratio." BMC.Med.Res.Methodol. **3**: 21.

Batash, S., Khaykis, I., Raicht, R. F. and Bini, E. J. (2008). "High prevalence of hepatitis C virus infection among immigrants from the former Soviet Union in the New York City metropolitan area: results of a community-based screening program." Am J Gastroenterol **103**(4): 922-927.

Bazylevych, M. (2011). "Vaccination campaigns in postsocialist Ukraine: health care providers navigating uncertainty." Med Anthropol Q **25**(4): 436-456.

Bellini, C., Keiser, O., Chave, J. P., Evison, J., Fehr, J., Kaiser, L., Weber, R., Vernazza, P., Bernasconi, E., Telenti, A. and Cavassini, M. (2009). "Liver enzyme elevation after lamivudine withdrawal in HIV-hepatitis B virus co-infected patients: the Swiss HIV Cohort Study." HIV Med **10**(1): 12-18.

Bennett, H. A., Einarson, A., Taddio, A., Koren, G. and Einarson, T. R. (2004). "Prevalence of depression during pregnancy: systematic review." Obstet Gynecol **103**(4): 698-709.

Best, B. M. and Capparelli, E. V. (2008). "Implications of gender and pregnancy for antiretroviral drug dosing." Curr Opin HIV AIDS **3**(3): 277-282.

Blackard, J. T., Welge, J. A., Taylor, L. E., Mayer, K. H., Klein, R. S., Celentano, D. D., Jamieson, D. J., Gardner, L. and Sherman, K. E. (2011). "HIV mono-infection is associated with FIB-4 - A noninvasive index of liver fibrosis - in women." Clin.Infect.Dis. **52**(5): 674-680.

Blair, J. M., Hanson, D. L., Jones, J. L. and Dworkin, M. S. (2004). "Trends in pregnancy rates among women with human immunodeficiency virus." Obstetrics and gynecology **103**(4): 663-668.

Bobrova, N., Sergeev, O., Grechukhina, T. and Kapiga, S. (2005). "Social-cognitive predictors of consistent condom use among young people in Moscow." Perspect Sex Reprod Health **37**(4): 174-178.

Boisson, E., Nicoll, A., Zaba, B. and Rodrigues, L. C. (1996). "Interpreting HIV seroprevalence data from pregnant women." J Acquir Immune Defic Syndr Hum Retrovirol **13**(5): 434-439.

Bollen, L. J., Whitehead, S. J., Mock, P. A., Leelawiwat, W., Asavapiriyanont, S., Chalermchockchareonkit, A., Vanprapar, N., Chotpitayasunondh, T., McNicholl, J. M., Tappero, J. W., Shaffer, N. and Chuachoowong, R. (2008). "Maternal herpes simplex virus type 2 coinfection increases the risk of perinatal HIV transmission: possibility to further decrease transmission?" AIDS **22**(10): 1169-1176.

Booth, R. E., Dvoryak, S., Sung-Joon, M., Brewster, J. T., Wendt, W. W., Corsi, K. F., Semerik, O. Y. and Strathdee, S. A. (2013). "Law Enforcement Practices Associated with HIV Infection Among Injection Drug Users in Odessa, Ukraine." AIDS Behav.

Booth, R. E., Kennedy, J., Brewster, T. and Semerik, O. (2003). "Drug injectors and dealers in Odessa, Ukraine." J Psychoactive Drugs **35**(4): 419-426.

Booth, R. E., Kwiatkowski, C. F., Brewster, J. T., Sinitsyna, L. and Dvoryak, S. (2006). "Predictors of HIV sero-status among drug injectors at three Ukraine sites." AIDS **20**(17): 2217-2223.

Booth, R. E., Lehman, W. E., Brewster, J. T., Sinitsyna, L. and Dvoryak, S. (2007). "Gender differences in sex risk behaviors among Ukraine injection drug users." J Acquir Immune Defic Syndr **46**(1): 112-117.

Booth, R. E., Lehman, W. E., Kwiatkowski, C. F., Brewster, J. T., Sinitsyna, L. and Dvoryak, S. (2008). "Stimulant injectors in Ukraine: the next wave of the epidemic?" AIDS and behavior **12**(4): 652-661.

Boxall, E. H. and Smith, N. (2004). "Antenatal screening for HIV; are those who refuse testing at higher risk than those who accept testing?" Journal of Public Health **26**(3): 285.

Boyle, D. C., Barton, S. E., Uthayakumar, S., Hay, P. E., Pollock, J. W., Steer, P. J. and Smith, J. R. (2003). "Is bacterial vaginosis associated with cervical intraepithelial neoplasia?" Int.J.Gynecol.Cancer **13**(2): 159-163.

Bozicevic, I. and Begovac, J. (2010). "The emerging HIV epidemic among men who have sex with men in southeastern Europe." Expert review of anti-infective therapy **8**(12): 1351-1358.

Briand, N., Mandelbrot, L., Blanche, S., Tubiana, R., Faye, A., Dollfus, C., Le Chenadec, J., Benhammou, V., Rouzioux, C. and Warszawski, J. (2011). "Previous antiretroviral therapy for prevention of mother-to-child transmission of HIV does not hamper the initial response to PI-based multitherapy during subsequent pregnancy." J Acquir Immune Defic Syndr **57**(2): 126-135.

Bromet, E. J. and et al. (2005). "Epidemiology of psychiatric and alcohol disorders in Ukraine: findings from the Ukraine World Mental Health survey." Soc Psychiatry Psychiatr Epidemiol. **40**(9): 681-690.

Brook, G., Main, J., Nelson, M., Bhagani, S., Wilkins, E., Leen, C., Fisher, M., Gilleece, Y., Gilson, R., Freedman, A., Kulasegaram, R., Agarwal, K., Sabin, C., Deacon-Adams, C. and BHIVA Viral Hepatitis Working Group (2010). "British HIV Association guidelines for the management of coinfection with HIV-1 and hepatitis B or C virus 2010." HIV Medicine **11**: 1-30.

Byakika-Tusiime, J., Crane, J., Oyugi, J. H., Ragland, K., Kawuma, A., Musoke, P. and Bangsberg, D. R. (2009). "Longitudinal antiretroviral adherence in HIV+ Ugandan parents and their children initiating HAART in the MTCT-Plus family treatment model: role of depression in declining adherence over time." AIDS Behav **13 Suppl 1**: 82-91.

Bygrave, H., Mtangirwa, J., Ncube, K., Ford, N., Kranzer, K. and Munyaradzi, D. (2012). "Antiretroviral Therapy Outcomes among Adolescents and Youth in Rural Zimbabwe." PLoS One **7**(12): e52856.

Carey, E. and Carey, W. D. (2010). "Noninvasive tests for liver disease, fibrosis, and cirrhosis: Is liver biopsy obsolete?" Cleveland Clinic journal of medicine **77**(8): 519-527.

Carter, R. J., Dugan, K., El-Sadr, W. M., Myer, L., Otieno, J., Pungpapong, N., Toro, P. L. and Abrams, E. J. (2010). "CD4+ cell count testing more effective than HIV disease clinical staging in identifying pregnant and postpartum women eligible for antiretroviral therapy in resource-limited settings." Journal of acquired immune deficiency syndromes **55**(3): 404-410.

Castellsague, X., Sanjos, S. d., Aguado, T., Louie, K., Bruni, L., Mu¤oz, J., Diaz, M., Irwin, K., Gacic, M., Beauvais, O., Albero, G., Ferrer, E., Byrne, S. and Bosch, F. (2007). HPV and Cervical Cancer in the World. 2007 Report. Barcelona, Spain, WHO/ICO Information Centre on HPV and Cervical Cancer (HPV Information Centre).

Castle, P. E. and Giuliano, A. R. (2003). "Chapter 4: Genital tract infections, cervical inflammation, and antioxidant nutrients--assessing their roles as human papillomavirus cofactors." J.Natl.Cancer Inst.Monogr(31): 29-34.

Caswell, R. J., Phillips, D., Chaponda, M., Khoo, S. H., Taylor, G. P., Ghanem, M., Poulton, M., Welch, J., Gibbons, S., Jackson, V. and Lambert, J. S. (2011). "Utility of therapeutic drug monitoring in the management of HIV-infected pregnant women in receipt of lopinavir." Int J STD AIDS **22**(1): 11-14.

Chesney, M. A. (2000). "Factors Affecting Adherence to Antiretroviral Therapy." Clinical Infectious Diseases **30**(Suppl 2): S171-S176.

Chesney, M. A., Ickovics, J., Hecht, F. M., Sikipa, G. and Rabkin, J. (1999). "Adherence: a necessity for successful HIV combination therapy." AIDS **13**(Suppl A): S271-S278.

Chiappini, E., Galli, L., Lisi, C., Gabiano, C., Giaquinto, C., Giacomet, V., Buffolano, W., Esposito, S., Badolato, R., Berbardi, S., Cellini, M., Dodi, I., Faldella, G., Osimani, P., Genovese, O., Nicastro, E., Viscoli, C., Salvini, F., Tovo, P. A. and Maurizio de, M. (2011). "Risk of perinatal HIV infection in infants born in Italy to immigrant mothers." Clinical infectious diseases : an official publication of the Infectious Diseases Society of America **53**(3): 310-313.

Chibanda, D., Mangezi, W., Tshimanga, M., Woelk, G., Rusakaniko, S., Stranix-Chibanda, L., Midzi, S. and Shetty, A. K. (2010). "Postnatal depression by HIV status among women in Zimbabwe." J Womens Health (Larchmt) **19**(11): 2071-2077.

Chintalova-Dallas, R., Case, P., Kitsenko, N. and Lazzarini, Z. (2009). "Boltushka: a homemade amphetamine-type stimulant and HIV risk in Odessa, Ukraine." Int J Drug Policy **20**(4): 347-351.

Chun, H. M., Roediger, M. P., Hullsiek, K. H., Thio, C. L., Agan, B. K., Bradley, W. P., Peel, S. A., Jagodzinski, L. L., Weintrob, A. C., Ganesan, A., Wortmann, G., Crum-Cianflone, N. F., Maguire, J. D. and Landrum, M. L. (2011). "Hepatitis B Virus Coinfection Negatively Impacts HIV Outcomes in HIV Seroconverters." J.Infect.Dis. **205**(2): 185-193.

Ciaranello, A. L., Perez, F., Keatinge, J., Park, J. E., Engelsmann, B., Maruva, M., Walensky, R. P., Dabis, F., Chu, J., Rusibamayila, A., Mushavi, A. and Freedberg, K. A. (2012). "What will it take to eliminate pediatric HIV? Reaching WHO target rates of mother-to-child HIV transmission in Zimbabwe: a model-based analysis." PLoS medicine **9**(1): e1001156.

Clifford, G., Franceschi, S., Diaz, M., Munoz, N. and Villa, L. L. (2006). "Chapter 3: HPV type-distribution in women with and without cervical neoplastic diseases." Vaccine **24 Suppl 3**: S3/26-S23/34.

Clifford, G. M., Polesel, J., Rickenbach, M., Dal, M. L., Keiser, O., Kofler, A., Rapiti, E., Levi, F., Jundt, G., Fisch, T., Bordoni, A., De, W. D. and Franceschi, S. (2005). "Cancer risk in the Swiss HIV Cohort Study: associations with immunodeficiency, smoking, and highly active antiretroviral therapy." J.Natl.Cancer Inst. **97**(6): 425-432.

Cohen, D. A., Scribner, R. A. and Farley, T. A. (2000). "A structural model of health behavior: a pragmatic approach to explain and influence health behaviors at the population level." Prev Med **30**(2): 146-154.

Cohen, M. S. (2006). "Amplified transmission of HIV-1: missing link in the HIV pandemic." Trans Am Clin Climatol Assoc **117**: 213-224; discussion 225.

Cohen, M. S., Chen, Y. Q., McCauley, M., Gamble, T., Hosseinipour, M. C., Kumarasamy, N., Hakim, J. G., Kumwenda, J., Grinsztejn, B., Pilotto, J. H., Godbole, S. V., Mehendale, S., Chariyalertsak, S., Santos, B. R., Mayer, K. H., Hoffman, I. F., Eshleman, S. H., Piwowar-Manning, E., Wang, L., Makhema, J., Mills, L. A., de Bruyn, G., Sanne, I., Eron, J., Gallant, J., Havlir, D., Swindells, S., Ribaudo, H., Elharrar, V., Burns, D., Taha, T. E., Nielsen-Saines, K., Celentano, D., Essex, M. and Fleming, T. R. (2011). "Prevention of HIV-1 infection with early antiretroviral therapy." The New England journal of medicine **365**(6): 493-505.

Cohn, S. E., Umbleja, T., Mrus, J., Bardeguez, A. D., Andersen, J. W. and Chesney, M. A. (2008). "Prior illicit drug use and missed prenatal vitamins predict nonadherence to antiretroviral therapy in pregnancy: adherence analysis A5084." AIDS Patient Care and STDs **22**(1): 29-40.

Collins, P. Y., Holman, A. R., Freeman, M. C. and Patel, V. (2006). "What is the relevance of mental health to HIV/AIDS care and treatment programs in developing countries? A systematic review." AIDS **20**(12): 1571-1582.

Conaty, S. J. and et al. (2005). "Women who decline antenatal screening for HIV infection in the era of universal testing: results of an audit of uptake in three London hospitals." Journal of Public Health **27**(1): 114-117.

Connell, L. E., Salihu, H. M., Salemi, J. L., August, E. M., Weldeselasse, H. and Mbah, A. K. (2011). "Maternal hepatitis B and hepatitis C carrier status and perinatal outcomes." Liver international : official journal of the International Association for the Study of the Liver **31**(8): 1163-1170.

Connor, E. M. and et al. (1994). "Reduction of Maternal-Infant Transmission of Human Immunodeficiency Virus Type 1 with Zidovudine Treatment. Pediatric AIDS Clinical Trials Group Protocol 076 Study Group." New England Journal of Medicine **331**(18): 1173-1180.

Cooper, C., Lester, R., Thorlund, K., Druyts, E., El Khoury, A. C., Yaya, S. and Mills, E. J. (2012). "Direct-acting antiviral therapies for hepatitis C genotype 1 infection: a multiple treatment comparison meta-analysis." QJM.

Cooper, E. R., Charurat, M., Mofenson, L., Hanson, I. C., Pitt, J., Diaz, C., Hayani, K., Handelsman, E., Smeriglio, V., Hoff, R., Blattner, W., Women and Infants' Transmission Study, G. (2002). "Combination antiretroviral strategies for the treatment of pregnant HIV-1-infected women and prevention of perinatal HIV-1 transmission." Journal of Acquired Immune Deficiency Syndromes **29**(5): 484-494.

Corey, L., Wald, A., Celum, C. L. and Quinn, T. C. (2004). "The effects of herpes simplex virus-2 on HIV-1 acquisition and transmission: a review of two overlapping epidemics." J Acquir Immune Defic Syndr **35**(5): 435-445.

Coutsoudis, A., Pillay, K., Kuhn, L., Spooner, E., Tsai, W. Y. and Coovadia, H. M. (2001). "Method of feeding and transmission of HIV-1 from mothers to children by 15 months of age: prospective cohort study from Durban, South Africa." AIDS **15**(3): 379-387.

Cowan, F. M. and et al. (2008). "Maternal Herpes simplex virus type 2 infection, syphilis and risk of intra-partum transmission of HIV-1: results of a case control study." AIDS **22**: 193-201.

Dabis, F. and et al. (1993). "Estimating the rate of mother-to-child transmission of HIV. Report of a workshop on methodological issues Ghent (Belgium), 17-20 February 1992. The Working Group on Mother-to-Child Transmission of HIV." AIDS **7**(8): 1139-1148.

de Bruin, M., Viechtbauer, W., Schaalma, H. P., Kok, G., Abraham, C. and Hospers, H. J. (2010). "Standard care impact on effects of highly active antiretroviral therapy adherence interventions: A meta-analysis of randomized controlled trials." Arch Intern Med **170**(3): 240-250.

De Cock, K. M., Jaffe, H. W. and Curran, J. W. (2012). "The evolving epidemiology of HIV/AIDS." AIDS **26**(10): 1205-1213.

de Ruiter, A., Mercey, D., Anderson, J., Chakraborty, R., Clayden, P., Foster, G., Gilling-Smith, C., Hawkins, D., Low-Beer, N., Lyall, H., O'Shea, S., Penn, Z., Short, J., Smith, R., Sonecha, S., Tookey, P., Wood, C. and Taylor, G. (2008). "British HIV Association and Children's HIV Association guidelines for the management of HIV infection in pregnant women 2008." HIV Medicine **9**: 452-502.

de Ruiter, A., Taylor, G., Clayden, P., Dhar, J., Gandhi, K., Gilleece, Y., Harding, K., Hay, P., Kennedy, J., Low-Beer, N., Lyall, H., Palfreeman, A., Tookey, P., Welch, S. and Wilkins, E. (2012). "British HIV Association guidelines for the management of HIV infection in pregnant women 2012." HIV Medicine **13**(Suppl. 2): 87-157.

De Santis, M., Carducci, B., De Santis, L., Cavaliere, A. F. and Straface, G. (2002). "Periconceptual exposure to efavirenz and neural tube defects." Arch Intern Med **162**: 355.

de Torres, M. and Poynard, T. (2003). "Risk factors for liver fibrosis progression in patients with chronic hepatitis C." Annals of hepatology **2**(1): 5-11.

de Vincenzi, I. (2011). "Triple antiretroviral compared with zidovudine and single-dose nevirapine prophylaxis during pregnancy and breastfeeding for prevention of mother-to-child transmission of HIV-1 (Kesho Bora study): a randomised controlled trial." The Lancet infectious diseases **11**(3): 171-180.

De Vincenzi, I., Jadand, C., Couturier, E., Brunet, J. B., Gallais, H., Gastaut, J. A., Goujard, C., Deveau, C. and Meyer, L. (1997). "Pregnancy and contraception in a French cohort of HIV-infected women. SEROCO Study Group." AIDS **11**(3): 333-338.

DeBell, D. and Carter, R. (2005). "Impact of transition on public health in Ukraine: case study of the HIV/AIDS epidemic." BMJ **331**(7510): 216-219.

Deblonde, J., Claeys, P. and Temmerman, M. (2007). "Antenatal HIV screening in Europe: a review of policies." European Journal of Public Health **17**(5): 414-418.

Dehne, K. L., Khodakevich, L., Hamers, F. F. and Schwartlander, B. (1999). "The HIV/AIDS epidemic in eastern Europe: recent patterns and trends and their implications for policy-making." AIDS **13**(7): 741-749.

Del, M. A., Bertorelle, R., Franzetti, M., Cattelan, A., Torrisi, A., Giordani, M. T., Sposetti, R., Bonoldi, E., Sasset, L., Bonaldi, L., Minucci, D. and Chieco-Bianchi, L. (2004). "Antiretroviral therapy and the clinical evolution of human papillomavirus-associated genital lesions in HIV-positive women." Clin.Infect.Dis. **38**(5): 737-742.

Demas, P. A., Webber, M. P., Schoenbaum, E. E., Weedon, J., McWayne, J., Enriquez, E., Bamji, M., Lambert, G. and Thea, D. M. (2002). "Maternal adherence to the zidovudine regimen for HIV-exposed infants to prevent HIV infection: a preliminary study." Pediatrics **110**(3).

Demchenko, I. L., Sosidko, T. I., Kostyuchok, M. M., Belonosova, N. A., Salabai, N. V., Hvozdetska, O. M., Bryzhovata, O. S. and Poliantsev, P. I. (2011). The People Living with HIV Stigma Index: Analytical Report Based on Research Findings. Kyiv, All-Ukrainian Network of PLWH.

Desai, N. and Mathur, M. (2003). "Selective transmission of multidrug resistant HIV to a newborn related to poor maternal adherence." Sexually Transmitted Infections **79**: 419-421.

Do, N. T., Phiri, K., Bussmann, H., Gaolathe, T., Marlink, R. G. and Wester, C. W. (2010). "Psychosocial Factors Affecting Medication Adherence Among HIV-1 Infected Adults Receiving Combination Antiretroviral Therapy (cART) in Botswana." AIDS Research and Human Retroviruses **26**(6): 685-691.

Donoghoe, M., Lazarus, J. and Matic, S. (2005). "HIV/AIDS in the transitional countires of eastern Europe and central Asia." Clinical Medicine **5**(5): 487-490.

Dore, G. J., Soriano, V., Rockstroh, J., Kupfer, B., Tedaldi, E., Peters, L., Neuhaus, J., Puoti, M., Klein, M. B., Mocroft, A., Clotet, B. and Lundgren, J. D. (2010). "Frequent hepatitis B virus rebound among HIV-hepatitis B virus-coinfected patients following antiretroviral therapy interruption." AIDS **24**(6): 857-865.

Dorenbaum, A. and et al. (2002). "Two-dose intrapartum/newborn nevirapine and standard antiretroviral therapy to reduce perinatal HIV transmission: A randomised trial." JAMA **288**(2).

Drake, A. L., John-Stewart, G. C., Wald, A., Mbori-Ngacha, D. A., Bosire, R., Wamalwa, D. C., Lohman-Payne, B. L., Ashley-Morrow, R., Corey, L. and Farquhar, C. (2007). "Herpes simplex virus type 2 and risk of intrapartum human immunodeficiency virus transmission." Obstet Gynecol **109**(2 Pt 1): 403-409.

Duffus, W. A., Mermin, J., Bunnell, R., Byers, R. H., Odongo, G., Ekwaru, P. and Downing, R. (2005). "Chronic herpes simplex virus type-2 infection and HIV viral load." Int J STD AIDS **16**(11): 733-735.

Dumchev, K. V., Soldyshev, R., Qian, H. Z., Zezyulin, O. O., Chandler, S. D., Slobodyanyuk, P., Moroz, L. and Schumacher, J. E. (2009). "HIV and hepatitis C virus infections among hanka injection drug users in central Ukraine: a cross-sectional survey." Harm reduction journal **6**: 23.

ECDC / WHO Regional Office for Europe (2010). HIV/AIDS surveillance in Europe 2010. Stockholm, Sweden.

ECDC / WHO Regional Office for Europe (2012). HIV/AIDS surveillance in Europe 2011. Stockholm, Sweden.

Ekama, S. O., Herbertson, E. C., Addeh, E. J., Gab-Okafor, C. V., Onwujekwe, D. I., Tayo, F. and Ezechi, O. C. (2012). "Pattern and Determinants of Antiretroviral Drug Adherence among Nigerian Pregnant Women." J Pregnancy **2012**: 851810.

Ekouevi, D., Abrams, E. J., Schlesinger, M., Myer, L., Phanuphak, N. and Carter, R. J. (2012). "Maternal CD4+ cell count decline after interruption of antiretroviral prophylaxis for the prevention of mother-to-child transmission of HIV." PLoS One **7**(8): e43750.

El-Bassel, N., Terlikbaeva, A. and Pinkham, S. (2010). "HIV and women who use drugs: double neglect, double risk." Lancet **376**(9738): 312-314.

El-Khatib, Z., Ekstrom, A. M., Coovadia, A., Abrams, E. J., Petzold, M., Katzenstein, D., Morris, L. and Kuhn, L. (2011). "Adherence and virologic suppression during the first 24 weeks on antiretroviral therapy among women in Johannesburg, South Africa - a prospective cohort study." BMC Public Health **11**: 88.

El-Sadr, W. M., Grund, B., Neuhaus, J., Babiker, A., Cohen, C. J., Darbyshire, J., Emery, S., Lundgren, J. D., Phillips, A. and Neaton, J. D. (2008). "Risk for opportunistic disease and death after reinitiating continuous antiretroviral therapy in patients with HIV previously receiving episodic therapy: a randomized trial." Ann Intern Med **149**(5): 289-299.

European AIDS Clinical Society (2011). European AIDS Clinical Society Guidelines, version 6 October 2011. Paris, France.

European Collaborative Study (1988). "Mother-to-child transmission of HIV infection." Lancet **332**: 1039-1043.

European Collaborative Study (1994). "Caesarean section and risk of vertical transmission of HIV-1 infection. The European Collaborative Study." Lancet **343**(8911): 1464-1467.

European Collaborative Study (1999). "Maternal viral load and vertical transmission of HIV-1: an important factor but not the only one." AIDS **13**: 1377-1385.

European Collaborative Study (2001). "HIV-infected pregnant women and vertical transmission in Europe since 1986." AIDS **15**: 761-770.

European Collaborative Study (2003). "Exposure to antiretroviral therapy in utero or early life: the health of uninfected children born to HIV-infected women." Journal of Acquired Immune Deficiency Syndromes **32**(4): 380-387.

European Collaborative Study (2005). "Mother-to-child transmission of HIV infection in the era of highly active antiretroviral therapy." Clinical Infectious Diseases **40**: 458-465.

European Collaborative Study (2006). "The mother-to-child HIV transmission epidemic in Europe: evolving in the East and established in the West." AIDS **20**: 1419-1427.

European Collaborative Study (2010). "Factors associated with HIV RNA levels in pregnant women on non-suppressive HAART at conception." Antiviral Therapy **15**(1): 41-49.

European Collaborative Study, Boer, K., England, K., Godfried, M. H. and Thorne, C. (2010). "Mode of delivery in HIV-infected pregnant women and prevention of mother-to-child transmission: changing practices in Western Europe." HIV Medicine **11**(6): 368-378.

Fakoya, A., Lamba, H., Mackie, N., Nandwani, R., Brown, A., Bernard, E., Gilling-Smith, C., Lacey, C., Sherr, L., Claydon, P., Wallage, S. and Gazzard, B. (2008). "British HIV Association, BASHH and FSRH guidelines for the management of the sexual and reproductive health of people living with HIV infection 2008." HIV.Med. **9**(9): 681-720.

Ferrero, S. and Bentivoglio, G. (2003). "Post-operative complications after caesarean section in HIV-infected women." Archives of gynecology and obstetrics **268**(4): 268-273.

Fiore, S. and et al. (2008). "Reproductive experience of HIV-infected women living in Europe." Human Reproduction **23**(9): 2140-2144.

Fiore, S., Newell, M. L. and Thorne, C. (2004). "Higher rates of post-partum complications in HIV-infected than in uninfected women irrespective of mode of delivery." AIDS **18**(6): 933-938.

Fischl, M. A., Richman, D. D., Grieco, M. H., Gottlieb, M. S., Volberding, P. A., Laskin, O. L., Leedom, J. M., Groopman, J. E., Mildvan, D., Schooley, R. T. and et al. (1987). "The efficacy of azidothymidine (AZT) in the treatment of patients with AIDS and AIDS-related complex. A double-blind, placebo-controlled trial." The New England journal of medicine **317**(4): 185-191.

Fisher, J. D., Amico, K. R., Fisher, W. A. and Harman, J. J. (2008). "The information-motivation-behavioral skills model of antiretroviral adherence and its applications." Curr HIV/AIDS Rep **5**(4): 193-203.

Flannelly, G. (2010). "The management of women with abnormal cervical cytology in pregnancy." Best.Pract.Res.Clin.Obstet.Gynaecol. **24**(1): 51-60.

Fleishman, J. A., Yehia, B. R., Moore, R. D., Korthuis, P. T. and Gebo, K. A. (2012). "Establishment, retention, and loss to follow-up in outpatient HIV care." J Acquir Immune Defic Syndr **60**(3): 249-259.

Floridia, M., Tamburrini, E., Bucceri, A., Tibaldi, C., Anzidei, G., Guaraldi, G., Meloni, A., Guerra, B., Ferrazzi, E., Molinari, A., Pinnetti, C., Salerio, B. and Ravizza, M. (2007). "Pregnancy outcomes and antiretroviral treatment in a national cohort of pregnant women with HIV: overall rates and differences according to nationality." BJOG **114**(7): 896-900.

Fogarty, L., Roter, D., Larson, S., Burke, J., Gillespie, J. and Levy, R. (2002). "Patient adherence to HIV medication regimens: a review of published and abstract reports." Patient Education and Counseling **46**: 93-108.

Ford, N., Calmy, A. and Mofenson, L. (2011). "Safety of efavirenz in the first trimester of pregnancy: an updated systematic review and meta-analysis." AIDS **25**(18): 2301-2304.

Franceschi, S. and Ronco, G. (2010). "The prevention of cervical cancer in HIV-infected women." AIDS **24**(16): 2579-2580.

French, C. E., Cortina-Borja, M., Thorne, C. and Tookey, P. A. (2012). "Incidence, patterns, and predictors of repeat pregnancies among HIV-infected women in the United Kingdom and Ireland, 1990-2009." Journal of acquired immune deficiency syndromes **59**(3): 287-293.

French, C. E., Tookey, P., Cortina-Borja, M., Ruiter, A. d., Townsend, C. L. and Thorne, C. (2013). "Influence of short-course antenatal antiretroviral therapy on viral load and mother-to-child transmission in subsequent pregnancies among HIV-infected women." Antiviral Therapy **18**(2): 183-192.

Frieden, T. R. (2010). "A framework for public health action: the health impact pyramid." Am J Public Health **100**(4): 590-595.

Friestad, C., Pirkis, J., Biehl, M. and Irwin, C. E., Jr. (2003). "Socioeconomic patterning of smoking, sedentary lifestyle, and overweight status among adolescents in Norway and the United States." J Adolesc Health **33**(4): 275-278.

Frisch, M., Biggar, R. J. and Goedert, J. J. (2000). "Human papillomavirus-associated cancers in patients with human immunodeficiency virus infection and acquired immunodeficiency syndrome." J.Natl.Cancer Inst. **92**(18): 1500-1510.

Fundaro, C., Genovese, O., Rendeli, C., Tamburrini, E. and Salvaggio, E. (2002). "Myelomeningocele in a child with intrauterine exposure to efavirenz." AIDS **16**(2): 299-300.

Gabhainn, S. N., Baban, A., Boyce, W., Godeau, E. and Grp, H. S. H. F. (2009). "How well protected are sexually active 15-year olds? Cross-national patterns in condom and contraceptive pill use 2002-2006." Int J Public Health **54**: 209-215.

Gakhar, H., Kamali, A. and Holodniy, M. (2013). "Health-related quality of life assessment after antiretroviral therapy: a review of the literature." Drugs **73**(7): 651-672.

Gakidou, E., Nordhagen, S. and Obermeyer, Z. (2008). "Coverage of cervical cancer screening in 57 countries: low average levels and large inequalities." PLoS.Med. **5**(6): e132.

Galli, L., Puliti, D., Chiappini, E., Gabiano, C., Ferraris, G., Mignone, F., Vigano, A., Giaquinto, C., Genovese, O., Anzidei, G., Badolato, R., Buffolano, W., Maccabruni, A., Salvini, F., Cellini, M., Ruggeri, M., Manzionna, M., Bernardi, S., Tovo, P. and de Martino, M. (2009). "Is the interruption of antiretroviral treatment during pregnancy an additional major risk factor for mother-to-child transmission of HIV type 1?" Clin Infect Dis **48**(9): 1310-1317.

Gardner, E. M., Burman, W. J., Steiner, J. F., Anderson, P. L. and Bangsberg, D. R. (2009). "Antiretroviral medication adherence and the development of class-specific antiretroviral resistance." AIDS **23**(9): 1035-1046.

Gaudy-Graffin, C., Lesage, G., Kousignian, I., Laperche, S., Girault, A., Dubois, F., Goudeau, A. and Barin, F. (2010). "Use of an anti-hepatitis C virus (HCV) IgG avidity assay to identify recent HCV infection." J Clin Microbiol **48**(9): 3281-3287.

Gibb, D. M., Goodall, R. L., Dunn, D. T., Healy, M., Neave, P., Cafferkey, M. and Butler, K. (2000). "Mother-to-child transmission of hepatitis C virus: evidence for preventable peripartum transmission." Lancet **356**(9233): 904-907.

Giles, M. L., Hellard, M. E., Lewin, S. R. and O'Brien, M. L. (2009). "The "work" of women when considering and using interventions to reduce mother-to-child transmission (MTCT) of HIV." AIDS care **21**(10): 1230-1237.

Gillet, E., Meys, J. F., Verstraelen, H., Bosire, C., De, S. P., Temmerman, M. and Broeck, D. V. (2011). "Bacterial vaginosis is associated with uterine cervical human papillomavirus infection: a meta-analysis." BMC.Infect.Dis. **11**: 10.

Gingelmaier, A., Eberle, J., Kost, B. P., Bogner, J. R., Hofmann, J., Weissenbacher, T., Kastner, R., Friese, K. and Weizsaecker, K. (2010). "Protease inhibitor-based antiretroviral prophylaxis during pregnancy and the development of drug resistance." Clin Infect Dis **50**(6): 890-894.

Giordano, T. P., White, A. C., Jr., Sajja, P., Graviss, E. A., Arduino, R. C., Adu-Oppong, A., Lahart, C. J. and Visnegarwala, F. (2003). "Factors associated with the use of highly active antiretroviral therapy in patients newly entering care in an urban clinic." Journal of acquired immune deficiency syndromes **32**(4): 399-405.

Glass, T. R., Battegay, M., Cavassini, M., De Geest, S., Furrer, H., Vernazza, P. L., Hirschel, B., Bernasconi, E., Rickenbach, M., Gunthard, H. F., Bucher, H. C. and the Swiss, H. I. V. C. S. (2009). "Longitudinal Analysis of Patterns and Predictors of Changes in Self-Reported Adherence to Antiretroviral Therapy: Swiss HIV Cohort Study." J Acquir Immune Defic Syndr. **54**(2): 197-203.

Glass, T. R., De Geest, S., Weber, R., Vernazza, P. L., Rickenbach, M., Furrer, H., Bernasconi, E., Cavassini, M., Hirschel, B., Battegay, M., Bucher, H. C. and Swiss HIV Cohort Study (2006). "Correlates of Self-Reported Nonadherence to Antiretroviral Therapy in HIV-Infected Patients. The Swiss HIV Cohort Study." J Acquir Immune Defic Syndr. **41**(3): 385-392.

Golin, C. E., Liu, H., Hays, R. D., Miller, L. G., Beck, C. K., Ickovics, J., Kaplan, A. H. and Wenger, N. S. (2002). "A Prospective Study of Predictors of Adherence to Combination Antiretroviral Medication." J Gen Intern Med **17**: 756-765.

Gorbach, P. M., Mensch, B. S., Husnik, M., Coly, A., Masse, B., Makanani, B., Nkhoma, C., Chinula, L., Tembo, T., Mierzwa, S., Reynolds, K., Hurst, S., Coletti, A. and Forsyth, A. (2013). "Effect of computer-assisted interviewing on self-reported sexual behavior data in a microbicide clinical trial." AIDS Behav **17**(2): 790-800.

Gordillo, V., del Amo, J., Soriano, V. and Gonzalez-Lahoz, J. (1999). "Sociodemographic and psychological variables influencing adherence to antiretroviral therapy." AIDS **13**: 1763-1769.

Gottlieb, M., Schanker, H., Fan, P., Saxon, A. and Weisman, J. (1981). "Pneumocystis pneumonia--Los Angeles." MMWR. Morbidity and mortality weekly report **30**(21): 250-252.

Graham, S. M., Masese, L., Gitau, R., Jalalian-Lechnak, Z., Richardson, B. A., Peshu, N., Mandaliya, K., Kiarie, J. N., Jaoko, W., Ndinya-Achola, J., Overbaugh, J. and McClelland, R. S. (2010). "Antiretroviral Adherence and Development of Drug Resistance Are the Strongest Predictors of Genital HIV-1 Shedding among Women Initiating Treatment." The Journal of Infectious Diseases **202**(10): 1538-1542.

Gray, R. H., Li, X., Kigozi, G., Serwadda, D., Brahmbhatt, H., Wabwire-Mangen, F., Nalugoda, F., Kiddugavu, M., Sewankambo, N., Quinn, T. C., Reynolds, S. J. and Wawer, M. J. (2005). "Increased risk of incident HIV during pregnancy in Rakai, Uganda: a prospective study." Lancet **366**(9492): 1182-1188.

Gross, R., Yip, B., Lo Re, V., 3rd, Wood, E., Alexander, C. S., Harrigan, P. R., Bangsberg, D. R., Montaner, J. S. G. and Hogg, R. S. (2006). "A Simple Dynamic Measure of Antiretroviral Therapy Adherence Predicts Failure to Maintain HIV-1 Suppression." Journal of Infectious Diseases **194**: 1108-1114.

Guay, L. A., Musoke, P., Fleming, T., Bagenda, D., Allen, M., Nakabiito, C., Sherman, J., Bakaki, P., Ducar, C., Deseyve, M., Emel, L., Mirochnick, M., Fowler, M. G., Mofenson, L., Miotti, P., Dransfield, K., Bray, D., Mmiro, F. and Jackson, J. B. (1999). "Intrapartum and neonatal single-dose nevirapine compared with zidovudine for prevention of mother-to-child transmission of HIV-1 in Kampala, Uganda: HIVNET 012 randomised trial." Lancet **354**(9181): 795-802.

Guijon, F., Paraskevas, M., Rand, F., Heywood, E., Brunham, R. and McNicol, P. (1992). "Vaginal microbial flora as a cofactor in the pathogenesis of uterine cervical intraepithelial neoplasia." Int.J.Gynaecol.Obstet. **37**(3): 185-191.

Gustafsson, L., Ponten, J., Zack, M. and Adami, H. O. (1997). "International incidence rates of invasive cervical cancer after introduction of cytological screening." Cancer Causes Control **8**(5): 755-763.

Hadland, S. E., Milloy, M. J., Kerr, T., Zhang, R., Guillemi, S., Hogg, R. S., Montaner, J. S. and Wood, E. (2012). "Young age predicts poor antiretroviral adherence and viral load suppression among injection drug users." AIDS Patient Care STDS **26**(5): 274-280.

Hagan, H., Thiede, H. and Des Jarlais, D. C. (2004). "Hepatitis C virus infection among injection drug users: survival analysis of time to seroconversion." Epidemiology **15**(5): 543-549.

Hamers, F. and Downs, A. (2003). "HIV in central and eastern Europe." The Lancet **361**: 1035-1044.

Hamers, F. F. and Downs, A. M. (2004). "The changing face of the HIV epidemic in western Europe: what are the implications for public health policies?" Lancet **364**(9428): 83-94.

Hamers, F. F. and Phillips, A. N. (2008). "Diagnosed and undiagnosed HIV-infected populations in Europe." HIV Med **9 Suppl 2**: 6-12.

Hammer, S. M., Squires, K. E., Hughes, M. D., Grimes, J. M., Demeter, L. M., Currier, J. S., Eron, J. J., Jr., Feinberg, J. E., Balfour, H. H., Jr., Deyton, L. R., Chodakewitz, J. A. and Fischl, M. A. (1997). "A controlled trial of two nucleoside analogues plus indinavir in persons with human immunodeficiency virus infection and CD4 cell counts of 200 per cubic millimeter or less. AIDS Clinical Trials Group 320 Study Team." The New England journal of medicine **337**(11): 725-733.

Hampanda, K. (2013). "Vertical Transmission of HIV in Sub-Saharan Africa: Applying Theoretical Frameworks to Understand Social Barriers to PMTCT." ISRN Infectious Diseases **2013**(Article ID 420361).

Harm Reduction International (2012). The global state of harm reduction 2012 - towards an integrated response. London.

Harris, P. A., Taylor, R., Thielke, R., Payne, J., Gonzalez, N. and Conde, J. G. (2009). "Research electronic data capture (REDCap)-A metadata-driven methodology and workflow process for providing translational research informatics support." Journal of Biomedical Informatics **42**(2): 377-381.

Havlir, D. V., Bassett, R., Levitan, D., Gilbert, P., Tebas, P., Collier, A. C., Hirsch, M. S., Ignacio, C., Condra, J., Gunthard, H. F., Richman, D. D. and Wong, J. K. (2001). "Prevalence and predictive value of intermittent viremia with combination hiv therapy." JAMA : the journal of the American Medical Association **286**(2): 171-179.

Hawkins, D., Blott, M., Clayden, P., de Ruiter, A., Foster, G., Gilling-Smith, C., Gosrani, B., Lyall, H., Mercey, D., Newell, M. L., O'Shea, S., Smith, R., Sunderland, J., Wood, C. and Taylor, G. (2005). "Guidelines for the management of HIV infection in pregnant women and the prevention of mother-to-child transmission of HIV." HIV Med **6 Suppl 2**: 107-148.

Hayes, I., Enohumah, K. and McCaul, C. (2011). "Care of the migrant obstetric population." Int J Obstet Anesth **20**(4): 321-329.

Hayes, R., Watson-Jones, D., Celum, C., van de Wijgert, J. and Wasserheit, J. (2010). "Treatment of sexually transmitted infections for HIV prevention: end of the road or new beginning?" AIDS **24 Suppl 4**: S15-26.

Haynes, R. B., Ackloo, E., Sahota, N., McDonald, H. P. and Yao, X. (2008). "Interventions for enhancing medication adherence." Cochrane Database of Systematic Reviews(4).

Heard, I. (2009). "Prevention of cervical cancer in women with HIV." Curr.Opin.HIV.AIDS **4**(1): 68-73.

Heath, K. V., Singer, J., O'Shaughnessy, M. V., Montaner, J. S. and Hogg, R. S. (2002). "Intentional nonadherence due to adverse symptoms associated with antiretroviral therapy." J Acquir Immune Defic Syndr **31**(2): 211-217.

Heiligenberg, M., van der Loeff, M. F., de Vries, H. J., Speksnijder, A. G., Geerlings, S. E., Coutinho, R., Prins, M. and Prins, J. M. (2012). "Low prevalence of asymptomatic sexually transmitted infections in HIV-infected heterosexuals visiting an HIV clinic in the Netherlands." AIDS **26**(5): 646-649.

Heintges, T. and Wands, J. R. (1997). "Hepatitis C virus: epidemiology and transmission." Hepatology **26**(3): 521-526.

Hepburn, M. (2004). "Substance abuse in pregnancy." Current Obstetrics & Gynaecology **14**(6): 419-425.

Hernandez, M. D. and Sherman, K. E. (2011). "HIV/hepatitis C coinfection natural history and disease progression." Curr Opin HIV AIDS **6**(6): 478-482.

Hnatyszyn, H. J. (2005). "Chronic hepatitis C and genotyping: the clinical significance of determining HCV genotypes." Antivir Ther **10**(1): 1-11.

Houlihan, C. F., Larke, N. L., Watson-Jones, D., Smith-McCune, K. K., Shiboski, S., Gravitt, P. E., Smith, J. S., Kuhn, L., Wang, C. and Hayes, R. (2012). "Human papillomavirus infection and increased risk of HIV acquisition. A systematic review and meta-analysis." AIDS **26**(17): 2211-2222.

Huntington, S. E., Bansi, L. K., Thorne, C., Anderson, J., Newell, M. L., Taylor, G. P., Pillay, D., Hill, T., Tookey, P. A. and Sabin, C. A. (2011). "Treatment switches during pregnancy among HIV-positive women on antiretroviral therapy at conception." AIDS **25**(13): 1647-1655.

Huntington, S. E., Thorne, C., Bansi, L. K., Anderson, J., Newell, M. L., Taylor, G. P., Pillay, D., Hill, T., Tookey, P. A. and Sabin, C. A. (2012). "Predictors of pregnancy and changes in pregnancy incidence among HIV-positive women accessing HIV clinical care at 13 large UK clinics." AIDS.

Hurley, R. (2010). "The worst HIV epidemic in Europe." BMJ **341**: 124-126.

Ickovics, J. R., Hamburger, M. E., Vlahov, D., Schoenbaum, E. E., Schuman, P., Boland, R. J., Moore, J. and for the, H. I. V. E. R. S. G. (2001). "Mortality, CD4 Cell Count Decline and Depressive Symptoms Among HIV-Seropositive Women." JAMA **285**(11): 1466-1474.

Ickovics, J. R. and Meisler, A. W. (1997). "Adherence in AIDS Clinical Trials: A Framework for Clinical Research and Clinical Care." J Clin Epidemiol **50**(4): 385-391.

Ickovics, J. R., Wilson, T. E., Royce, R. A., Minkoff, H. L., Fernandez, M. I., Fox-Tierney, R. and Koenig, L. J. (2002). "Prenatal and postpartum zidovudine adherence among pregnant women with HIV: results of a MEMS substudy from the Perinatal Guidelines Evaluation Project." Journal of acquired immune deficiency syndromes **30**(3): 311-315.

International Harm Reduction Association (2010). Global State of Harm Reduction 2010 - Key issues for broadening the response, Available at http://www.ihra.net/contents/245 (Accessed January 2013). London, UK.

Ironson, G., Weiss, S., Lydston, D., Ishii, M., Jones, D., Asthana, D., Tobin, J., Lechner, S., Laperriere, A., Schneiderman, N. and Antoni, M. (2005). "The impact of improved self-efficacy on HIV viral load and distress in culturally diverse women living with AIDS: the SMART/EST Women's Project." AIDS Care **17**(2): 222-236.

Janevic, T., Sarah, P. W., Leyla, I. and Elizabeth, B. H. (2012). "Individual and community level socioeconomic inequalities in contraceptive use in 10 Newly Independent States: a multilevel cross-sectional analysis." Int J Equity Health **11**: 69.

Jasseron, C., Mandelbrot, L., Dollfus, C., Trocme, N., Tubiana, R., Teglas, J. P., Faye, A., Rouzioux, C., Blanche, S. and Warszawski, J. (2011). "Non-Disclosure of a Pregnant Woman's HIV Status to Her Partner is Associated with Non-Optimal Prevention of Mother-to-Child Transmission." AIDS and behavior.

Jasseron, C., Mandelbrot, L., Tubiana, R., Teglas, J. P., Faye, A., Dollfus, C., Le Chenadec, J., Rouzioux, C., Blanche, S., Warszawski, J. and Cohort, A. F. P. (2008). "Prevention of mother-to-child HIV transmission: similar access for sub-Sahara African immigrants and for French women?" AIDS **22**: 1503-1511.

Jimenez-Nacher, I., Alvarez, E., Morello, J., Rodriguez-Novoa, S., de Andres, S. and Soriano, V. (2011). "Approaches for understanding and predicting drug interactions in human immunodeficiency virus-infected patients." Expert Opin Drug Metab Toxicol **7**(4): 457-477.

Johnson, T. and Fendrich, M. (2005). "Modeling Sources of Self-report Bias in a Survey of Drug Use Epidemiology." Ann Epidemiol **15**: 381-389.

Johnston Roberts, K. and Volberding, P. (1999). "Adherence communication: a qualitative analysis of physician-patient dialogue." AIDS **13**: 1771-1778.

Jones, D. L., Ishii Owens, M., Lydston, D., Tobin, J. N., Brondolo, E. and Weiss, S. M. (2010). "Self-efficacy and distress in women with AIDS: the SMART/EST women's project." AIDS Care **22**(12): 1499-1508.

Judice, N., Zaglada, O. and Mbuya-Brown, R. (2011). HIV Policy Assessment: Ukraine. Washington, DC, Futures Group, Health Policy Project.

Junghans, C., Low, N., Chan, P., Witschi, A., Vernazza, P. and Egger, M. (1999). "Uniform risk of clinical progression despite differences in utilization of highly active antiretroviral therapy: Swiss HIV Cohort Study." AIDS **13**(18): 2547-2554.

Jurgens, R., Csete, J., Amon, J. J., Baral, S. and Beyrer, C. (2010). "People who use drugs, HIV, and human rights." Lancet **376**(9739): 475-485.

Kacanek, D., Jacobson, D. L., Spiegelman, D., Wanke, C., Isaac, R. and Wilson, I. B. (2010). "Incident Depression Symptoms Are Associated With Poorer HAART Adherence: A Longitudinal Analysis from the Nutrition for Healthy Living Study." J Acquir Immune Defic Syndr. **53**(2): 266-272.

Kalinina, O., Norder, H., Vetrov, T., Zhdanov, K., Barzunova, M., Plotnikova, V., Mukomolov, S. and Magnius, L. O. (2001). "Shift in predominating subtype of HCV from 1b to 3a in St. Petersburg mediated by increase in injecting drug use." J Med Virol **65**(3): 517-524.

Kapetanovic, S., Christensen, S., Karim, R., Lin, F., Mack, W. J., Operskalski, E., Frederick, T., Spencer, L., Stek, A., Kramer, F. and Kovacs, A. (2009). "Correlates of Perinatal Depression in HIV-Infected Women." AIDS Patient Care and STDs **23**(2): 101-108.

Katz, I. T., Shapiro, R., Li, D., Govindarajulu, U., Thompson, B., Watts, D. H., Hughes, M. D. and Tuomala, R. (2010). "Risk factors for detectable HIV-1 RNA at delivery among women receiving highly active antiretroviral therapy in the women and infants transmission study." Journal of acquired immune deficiency syndromes **54**(1): 27-34.

Keiser, O., Gayet-Ageron, A., Rudin, C., Brinkhof, M. W., Gremlich, E., Wunder, D., Drack, G., Hirschel, B., de Tejada, B. M., Swiss HIV Cohort Study and Swiss Mother and Child HIV Cohort Study (2008). "Antiretroviral treatment during pregnancy." AIDS **22**(17): 2323-2330.

Kerr, S. J., Avihingsanon, A., Putcharoen, O., Chetchotisakd, P., Layton, M., Ubolyam, S., Ruxrungtham, K., Cooper, D. A., Phanuphak, P. and Duncombe, C. (2012). "Assessing adherence in Thai patients taking combination antiretroviral therapy." International journal of STD & AIDS **23**(3): 160-165.

Kimmerling, M., Wagner, G. and Ghosh-Dastidar, B. (2003). "Factors associated with accurate self-reported adherence to HIV antiretrovirals." International Journal of STD & AIDS **14**: 281-284.

King, C. C., Jamieson, D. J., Wiener, J., Cu-Uvin, S., Klein, R. S., Rompalo, A. M., Shah, K. V. and Sobel, J. D. (2011). "Bacterial vaginosis and the natural history of human papillomavirus." Infect.Dis.Obstet.Gynecol. **2011**: 319460.

King, M. S., Bernstein, B. M., Walmsley, S. L., Sherer, R., Feinberg, J., Sanne, I., Cernohous, P., Montaner, J. S., Brun, S. C. and Sun, E. (2004). "Baseline HIV-1 RNA level and CD4 cell count predict time to loss of virologic response to nelfinavir, but not lopinavir/ritonavir, in antiretroviral therapy-naive patients." The Journal of infectious diseases **190**(2): 280-284.

Kingston, M. A. and et al. (2007). "Adherence to antiretroviral therapy in pregnancy." International Journal of STD & AIDS **18**(11): 787-789.

Kirk, O., Mocroft, A., Katzenstein, T. L., Lazzarin, A., Antunes, F., Francioli, P., Brettle, R. P., Parkin, J. M., Gonzales-Lahoz, J. and Lundgren, J. D. (1998). "Changes in use of antiretroviral therapy in regions of Europe over time. EuroSIDA Study Group." AIDS **12**(15): 2031-2039.

Kirkwood, B. and Sterne, J. (2008). Essential Medical StatisticsOxford, Blackwell Publishing.

Kissin, D. M., Akatova, N., Rakhmanova, A. G., Vinogradova, E. N., Voronin, E. E., Jamieson, D. J., Glynn, M. K., Yakovlev, A., Robinson, J., Miller, W. C. and Hillis, S. (2008). "Rapid HIV testing and prevention of perinatal HIV transmission in high-risk maternity hospitals in St. Petersburg, Russia." Am J Obstet Gynecol **198**(2): 183 e181-187.

Kissin, D. M., Mandel, M. G., Akatova, N., Belyakov, N. A., Rakhmanova, A. G., Voronin, E. E., Volkova, G. V., Yakovlev, A. A., Jamieson, D. J., Vitek, C., Robinson, J., Miller, W. C. and Hillis, S. (2011). "Five-year trends in epidemiology and prevention of mother-to-child HIV transmission, St. Petersburg, Russia: results from perinatal HIV surveillance." BMC infectious diseases **11**: 292.

Kitahata, M. M., Gange, S. J., Abraham, A. G., Merriman, B., Saag, M. S., Justice, A. C., Hogg, R. S., Deeks, S. G., Eron, J. J., Brooks, J. T., Rourke, S. B., Gill, M. J., Bosch, R. J., Martin, J. N., Klein, M. B., Jacobson, L. P., Rodriguez, B., Sterling, T. R., Kirk, G. D., Napravnik, S., Rachlis, A. R., Calzavara, L. M., Horberg, M. A., Silverberg, M. J., Gebo, K. A., Goedert, J. J., Benson, C. A., Collier, A. C., Van Rompaey, S. E., Crane, H. M., McKaig, R. G., Lau, B., Freeman, A. M. and Moore, R. D. (2009). "Effect of early versus deferred antiretroviral therapy for HIV on survival." The New England journal of medicine **360**(18): 1815-1826.

Kitchener, H., Nelson, L., Adams, J., Mesher, D., Sasieni, P., Cubie, H., Moore, C., Heard, I., Agarossi, A., Casolati, E., Denny, L., Bradbeer, C., Lyons, F., Beattie, G. and Niemiec, T. (2007). "Colposcopy is not necessary to assess the risk to the cervix in HIV-positive women: an international cohort study of cervical pathology in HIV-1 positive women." Int.J.Cancer **121**(11): 2484-2491.

Klein, M. B., Rollet, K. C., Hull, M., Cooper, C., Walmsley, S., Conway, B. and Pick, N. (2012). "Who needs direct acting antivirals for HCV? Challenges faced in advancing HCV therapy for HIV-HCV co-infected persons." Antivir Ther.

Kojic, E. M. and Cu-Uvin, S. (2007). "Update: human papillomavirus infection remains highly prevalent and persistent among HIV-infected individuals." Curr.Opin.Oncol. **19**(5): 464-469.

Kosgei, R. J., Lubano, K. M., Shen, C., Wools-Kaloustian, K. K., Musick, B. S., Siika, A. M., Mabeya, H., Carter, E. J., Mwangi, A. and Kiarie, J. (2011). "Impact of integrated family planning and HIV care services on contraceptive use and pregnancy outcomes: a retrospective cohort study." J Acquir Immune Defic Syndr **58**(5): e121-126.

Kruglov, Y. V., Kobyshcha, Y. V., Salyuk, T., Varetska, O., Shakarishvili, A. and Saldanha, V. P. (2008). "The most severe HIV epidemic in Europe: Ukraine's national HIV prevalence estimates for 2007." Sexually Transmitted Infections **84**: 37-41.

Kuha, J. (2004). "AIC and BIC - Comparisons of assumptions and performance." Sociological Methods & Research **33**(2): 188-229.

Kuhn, L., Kasonde, P., Sinkala, M., Kankasa, C., Semrau, K., Scott, N., Tsai, W. Y., Vermund, S. H., Aldrovandi, G. M. and Thea, D. M. (2005). "Does severity of HIV disease in HIV-infected mothers affect mortality and morbidity among their uninfected infants?" Clinical infectious diseases : an official publication of the Infectious Diseases Society of America **41**(11): 1654-1661.

Kuhn, L., Steketee, R. W., Weedon, J., Abrams, E. J., Lambert, G., Bamji, M., Schoenbaum, E., Farley, J., Nesheim, S. R., Palumbo, P., Simonds, R. J. and Thea, D. M. (1999). "Distinct risk factors for intrauterine and intrapartum human immunodeficiency virus transmission and consequences for disease progression in infected children. Perinatal AIDS Collaborative Transmission Study." Journal of Infectious Diseases **179**(1): 52-58.

LaBranche, C. C., Galasso, G., Moore, J. P., Bolognesi, D. P., Hirsch, M. S. and Hammer, S. M. (2001). "HIV fusion and its inhibition." Antiviral research **50**(2): 95-115.

Laine, C., Newschaffer, C. J., Zhang, D., Cosler, L., Hauck, W. W. and Turner, B. J. (2000). "Adherence to antiretroviral therapy by pregnant women infected with human immunodeficiency virus: a pharmacy claims-based analysis." Obstet Gynecol. **95**(2): 167-173.

Lampe, F. C., Gatell, J. M., Staszewski, S., Johnson, M. A., Pradier, C., Gill, M. J., de Lazzari, E., Dauer, B., Youle, M., Fontas, E., Krentz, H. B. and Phillips, A. N. (2006). "Changes over time in risk of initial virological failure of combination antiretroviral therapy: a multicohort analysis, 1996 to 2002." Arch Intern Med **166**(5): 521-528.

Landes, M. and et al. (2007). "Prevalence of sexually transmitted infections in HIV-1 infected pregnant women in Europe." Eur J Epidemiol **22**: 925-936.

Landes, M., Newell, M. L., Barlow, P., Fiore, S., Malyuta, R., Martinelli, P., Posokhova, S., Savasi, V., Semenenko, I., Stelmah, A., Tibaldi, C. and Thorne, C. (2008). "Hepatitis B or hepatitis C coinfection in HIV-infected pregnant women in Europe." HIV Med. **9**(7): 526-534.

Lavanchy, D. (2011). "Evolving epidemiology of hepatitis C virus." Clin Microbiol Infect **17**(2): 107-115.

Law, W. P., Duncombe, C. J., Mahanontharit, A., Boyd, M. A., Ruxrungtham, K., Lange, J. M., Phanuphak, P., Cooper, D. A. and Dore, G. J. (2004). "Impact of viral hepatitis co-infection on response to antiretroviral therapy and HIV disease progression in the HIV-NAT cohort." AIDS **18**(8): 1169-1177.

Le Moing, V., Taieb, A., Longuet, P., Lewden, C., Delcey, V., Drobacheff, M. C., Chene, G. and Leport, C. (2008). "Pregnancy may be followed by an inflexion of the immune reconstitution in HIV-infected women who receive antiretroviral drugs before conception." HIV Med **9**(10): 897-900.

Ledergerber, B. and et al. (1999). "Clinical progression and virological failure on highly active antiretroviral therapy in HIV-1 patients: a prospective cohort study." The Lancet **353**: 863-868.

Leeman, J., Chang, Y. K., Lee, E. J., Voils, C. I., Crandell, J. and Sandelowski, M. (2010). "Implementation of antiretroviral therapy adherence interventions: a realist synthesis of evidence." J Adv Nurs **66**(9): 1915-1930.

Lehman, D. A. and Farquhar, C. (2007). "Biological mechanisms of vertical human immunodeficiency virus (HIV-1) transmission." Reviews in Medical Virology **17**: 381-403.

Leigh, B. and Milgrom, J. (2008). "Risk factors for anteantal depression, postnatal depression and parenting stress." BMC Psychiatry **8**(24).

Leitich, H., Bodner-Adler, B., Brunbauer, M., Kaider, A., Egarter, C. and Husslein, P. (2003). "Bacterial vaginosis as a risk factor for preterm delivery: a meta-analysis." Am.J.Obstet.Gynecol. **189**(1): 139-147.

Lekhan, V., Rudiy, V. and Richardson, E. (2010). Ukraine: Health system review. Health Systems in Transition. **12:** 1-183.

Likatavicius, G., Klavs, I., Devaux, I., Alix, J. and Nardone, A. (2008). "An increase in newly diagnosed HIV cases reported among men who have sex with men in Europe, 2000-6: implications for a European public health strategy." Sexually transmitted infections **84**(6): 499-505.

Lima, V. D., Gill, V. S., Yip, B., Hogg, R. S., Montaner, J. S. and Harrigan, P. R. (2008a). "Increased resilience to the development of drug resistance with modern boosted protease inhibitor-based highly active antiretroviral therapy." J Infect Dis **198**(1): 51-58.

Lima, V. D., Harrigan, R., Bangsberg, D. R., Hogg, R. S., Gross, R., Yip, B. and Montaner, J. S. G. (2009). "The Combined Effect of Modern Highly Active Antiretroviral Therapy Regimens and Adherence on Mortality Over Time." J Acquir Immune Defic Syndr. **50**(5): 529-536.

Lima, V. D., Harrigan, R., Murray, M., Moore, D. M., Wood, E., Hogg, R. S. and Montaner, J. S. G. (2008b). "Differential impact of adherence on long-term treatment response among naive HIV-infected individuals." AIDS(22): 2371-2380.

Liu, H., Golin, C. E., Miller, L. G., Hays, R. D., Beck, C. K., Sanandaji, S., Christian, J. M. T., Duran, D., Kaplan, A. H. and Wenger, N. S. (2001). "A Comparison Study of Multiple Measures of Adherence to HIV Protease Inhibitors." Ann Intern Med **134**: 968-977.

Liu, K. C., Mulindwa, J., Giganti, M. J., Putta, N. B., Chintu, N., Chi, B. H., Stringer, J. S. and Stringer, E. M. (2011). "Predictors of CD4 eligibility for antiretroviral therapy initiation among HIV-infected pregnant women in Lusaka, Zambia." Journal of acquired immune deficiency syndromes **57**(5): e101-105.

Lockman, S., Hughes, M. D., McIntyre, J., Zheng, Y., Chipato, T., Conradie, F., Sawe, F., Asmelash, A., Hosseinipour, M. C., Mohapi, L., Stringer, E., Mngqibisa, R., Siika, A., Atwine, D., Hakim, J., Shaffer, D., Kanyama, C., Wools-Kaloustian, K., Salata, R. A., Hogg, E., Alston-Smith, B., Walawander, A., Purcelle-Smith, E., Eshleman, S., Rooney, J., Rahim, S., Mellors, J. W., Schooley, R. T., Currier, J. S. and Team, O. A. S. (2010). "Antiretroviral therapies in women after single-dose nevirapine exposure." New England Journal of Medicine **363**(16): 1499-1509.

Lopez-Suarez, A., Fernandez-Gutierrez del Alamo, C., Perez-Guzman, E. and Giron-Gonzalez, J. A. (1998). "Adherence to the antiretroviral treatment in asymptomatic HIV-infected patients." AIDS **12**(6): 685-686.

Lopez, M., Figueras, F., Hernandez, S., Lonca, M., Garcia, R., Palacio, M. and Coll, O. (2012). "Association of HIV infection with spontaneous and iatrogenic preterm delivery: effect of HAART." AIDS **26**(1): 37-43.

Lu, M., Safren, S. A., Skolnik, P. R., Rogers, W. H., Coady, W., Hardy, H. and Wilson, I. R. (2008). "Optimal Recall Period and Response Task for Self-Reported HIV Medication Adherence." AIDS Behav **12**: 86-94.

Lucas, G. M., Cheever, L. W., Chaisson, R. E. and Moore, R. D. (2001). "Detrimental effects of continued illicit drug use on the treatment of HIV-1 infection." J Acquir Immune Defic Syndr **27**(3): 251-259.

Lundgren, J. D., Babiker, A., El-Sadr, W., Emery, S., Grund, B., Neaton, J. D., Neuhaus, J. and Phillips, A. N. (2008). "Inferior clinical outcome of the CD4+ cell count-guided antiretroviral treatment interruption strategy in the SMART study: role of CD4+ Cell counts and HIV RNA levels during follow-up." J Infect Dis **197**(8): 1145-1155.

Lyons, F., Hopkins, S., Kelleher, B., McGeary, A., Sheehan, G., Geoghegan, J., Bergin, C., Mulcahy, F. M. and McCormick, P. A. (2006). "Maternal hepatotoxicity with nevirapine as part of combination antiretroviral therapy in pregnancy." HIV.Med. **7**(4): 255-260.

Maggiolo, F., Airoldi, M., Kleinloog, H. D., Callegaro, A., Ravasio, V., Arici, C., Bombana, E. and Suter, F. (2007). "Effect of Adherence to HAART on Virologic Outcome and on the Selection of Resistance-Conferring Mutations in NNRTI- or PI-Treated Patients." HIV Clin Trials **8**(5): 282-292.

Maher, L., Jalaludin, B., Chant, K. G., Jayasuriya, R., Sladden, T., Kaldor, J. M. and Sargent, P. L. (2006). "Incidence and risk factors for hepatitis C seroconversion in injecting drug users in Australia." Addiction **101**(10): 1499-1508.

Mahy, M., Stover, J., Kiragu, K., Hayashi, C., Akwara, P., Luo, C., Stanecki, K., Ekpini, R. and Shaffer, N. (2010). "What will it take to achieve virtual elimination of mother-to-child transmission of HIV? An assessment of current progress and future needs." Sex Transm.Infect. **86 Suppl 2**: ii48-ii55.

Maiman, M. (1998). "Management of cervical neoplasia in human immunodeficiency virus-infected women." J.Natl.Cancer Inst.Monogr **23**: 43-49.

Maiman, M., Fruchter, R. G., Sedlis, A., Feldman, J., Chen, P., Burk, R. D. and Minkoff, H. (1998). "Prevalence, risk factors, and accuracy of cytologic screening for cervical intraepithelial neoplasia in women with the human immunodeficiency virus." Gynecol.Oncol. **68**(3): 233-239.

Malyuta, R., Newell, M. L., Ostergren, M., Thorne, C. and Zhilka, N. (2006). "Prevention of mother-to-child transmission of HIV infection: Ukraine experience to date." European Journal of Public Health **16**(2): 123-127.

Mann, B., Milloy, M. J., Kerr, T., Zhang, R., Montaner, J. and Wood, E. (2012). "Improved adherence to modern antiretroviral therapy among HIV-infected injecting drug users." HIV Med **13**(10): 596-601.

Mannheimer, S. B., Mukherjee, R., Hirschhorn, L. R., Dougherty, J., Celano, S. A., Ciccarone, D., Graham, K. K., Mantell, J. E., Mundy, L. M., Eldred, L., Botsko, M. and Finkelstein, R. (2006). "The CASE adherence index: A novel method for measuring adherence to antiretroviral therapy." AIDS care **18**(7): 853-861.

Marinda, E., Humphrey, J. H., Iliff, P. J., Mutasa, K., Nathoo, K. J., Piwoz, E. G., Moulton, L. H., Salama, P. and Ward, B. J. (2007). "Child mortality according to maternal and infant HIV status in Zimbabwe." The Pediatric infectious disease journal **26**(6): 519-526.

Marks, G., Crepaz, N. and Janssen, R. S. (2006). "Estimating sexual transmission of HIV from persons aware and unaware that they are infected with the virus in the USA." AIDS **20**(10): 1447-1450.

Martin, D. (2009). Immunology of HIV Infection and the Host Response, available at http://ftguonline.org/ftgu-232/index.php/ftgu/article/view/1970/3936, accessed November 2012. .From the Ground Up: Buildling Comprehensive HIV/AIDS Care Programs in Resource-Limited Settings.Marlink, R., Teitelman, ST Washington, DC, Elizabeth Glaser Pediatric AIDS Foundation.

Massad, L. S., Seaberg, E. C., Watts, D. H., Hessol, N. A., Melnick, S., Bitterman, P., Anastos, K., Silver, S., Levine, A. M. and Minkoff, H. (2004). "Low incidence of invasive cervical cancer among HIV-infected US women in a prevention program." AIDS **18**(1): 109-113.

Massard, J., Ratziu, V., Thabut, D., Moussalli, J., Lebray, P., Benhamou, Y. and Poynard, T. (2006). "Natural history and predictors of disease severity in chronic hepatitis C." J Hepatol **44**(1 Suppl): S19-24.

Matthews, G. V., Bartholomeusz, A., Locarnini, S., Ayres, A., Sasaduesz, J., Seaberg, E., Cooper, D. A., Lewin, S., Dore, G. J. and Thio, C. L. (2006). "Characteristics of drug resistant HBV in an international collaborative study of HIV-HBV-infected individuals on extended lamivudine therapy." AIDS **20**(6): 863-870.

Mavrov, G. and Bondarenko, G. (2002). "The evolution of sexually transmitted infections in the Ukraine." Sexually Transmitted Infections **78**: 219-221.

Mayaux, M. J. and et al. (1997). "Maternal virus load during pregnancy and mother-to-child transmission of human immunodeficiency virus type 1: The French perinatal cohort studies." The Journal of Infectious Diseases **175**(1): 172-175.

Mayaux, M. J., Teglas, J. P., Blanche, S. and French Pediatric, H. I. V. I. S. G. (2003). "Characteristics of HIV-infected women who do not receive preventive antiretroviral therapy in the French Perinatal Cohort." Journal of Acquired Immune Deficiency Syndromes **34**(3): 338-343.

Mbizvo, E. M., Msuya, S. E., Stray-Pedersen, B., Chirenje, M. Z. and Hussain, A. (2005). "Cervical dyskaryosis among women with and without HIV: prevalence and risk factors." Int.J.STD AIDS **16**(12): 789-793.

McCabe, C. J., Goldie, S. J. and Fisman, D. N. (2010). "The Cost-Effectiveness of Directly Observed Highly-Active Antiretroviral Therapy in the Third Trimester in HIV-Infected Pregnant Women." PLOS ONE **5**(4).

McDonald, C., Curtis, H., De Ruiter, A., Johnson, M. A., Welch, J. and BHIVA (2006). "National review of maternity care for women with HIV infection." HIV Medicine **7**: 275-280.

McIntyre, J. and Lallemant, M. (2008). "The prevention of mother-to-child transmission of HIV: are we translating scientific success into programmatic failure?" Current opinion in HIV and AIDS **3**(2): 139-145.

McNaghten, A. D., Hanson, D. L., Dworkin, M. S. and Jones, J. L. (2003). "Differences in prescription of antiretroviral therapy in a large cohort of HIV-infected patients." Journal of acquired immune deficiency syndromes **32**(5): 499-505.

Mellins, C. A., Chu, C., Malee, K., Allison, S., Smith, R., Harris, L., Higgins, A., Zorrilla, C., Landesman, S., Serchuck, L. and Larussa, P. (2008). "Adherence to antiretroviral treatment among pregnant and postpartum HIV-infected women." AIDS care **20**(8): 958-968.

Merenstein, D. J., Schneider, M. F., Cox, C., Schwartz, R., Weber, K., Robison, E., Gandhi, M., Richardson, J. and Plankey, M. W. (2008). "Association between living with children and adherence to highly active antiretroviral therapy in the Women's Interagency HIV Study." Pediatrics **121**(4): e787-793.

Mimiaga, M. J., Safren, S. A., Dvoryak, S., Reisner, S. L., Needle, R. and Woody, G. (2010). ""We fear the police, and the police fear us": structural and individual barriers and facilitators to HIV medication adherence among injection drug users in Kiev, Ukraine." AIDS care **22**(11): 1305-1313.

Ministry of Health of Ukraine (2002). On Improvement of Ambulatory Obstetric and Gynecological Help in Ukraine. **Order 503**.

Ministry of Health of Ukraine (2007). On approval of the clinical protocol for obstetric care - prevention of HIV transmission from mother to child. **Order 716**.

Ministry of Health of Ukraine (2010). Ukraine: National Report on Monitoring Progress Towards the UNGASS Declaration of Commitment on HIV/AIDS, January 2008-December 2009. Kiev, Ministry of Health of Ukraine.

Ministry of Health of Ukraine (2012). Ukraine Harmonized AIDS Response Progress Report. Reporting period: January 2010 - December 2011. Kiev, Ukraine.

Minkoff, H., Feldman, J., Dehovitz, J., Landesman, S. and Burk, R. (1998). "A longitudinal study of human papillomavirus carriage in human immunodeficiency virus-infected and human immunodeficiency virus-uninfected women." Am.J.Obstet.Gynecol. **178**(5): 982-986.

Minkoff, H., Zhong, Y., Burk, R. D., Palefsky, J. M., Xue, X., Watts, D. H., Levine, A. M., Wright, R. L., Colie, C., D'Souza, G., Massad, L. S. and Strickler, H. D. (2010). "Influence of adherent and effective antiretroviral therapy use on human papillomavirus infection and squamous intraepithelial lesions in human immunodeficiency virus-positive women." J.Infect.Dis. **201**(5): 681-690.

Minnes, S., Lang, A. and Singer, L. (2011). "Prenatal tobacco, marijuana, stimulant, and opiate exposure: outcomes and practice implications." Addiction science & clinical practice **6**(1): 57-70.

Minozzi, S., Amato, L., Vecchi, S. and Davoli, M. (2008). "Maintenance agonist treatments for opiate dependent pregnant women." Cochrane Database of Systematic Reviews **16**(2).

Mocroft, A., Ledergerber, B., Viard, J. P., Staszewski, S., Murphy, M., Chiesi, A., Horban, A., Hansen, A. B., Phillips, A. N. and Lundgren, J. D. (2004). "Time to virological failure of 3 classes of antiretrovirals after initiation of highly active antiretroviral therapy: results from the EuroSIDA study group." The Journal of infectious diseases **190**(11): 1947-1956.

Mocroft, A., Miller, V., Chiesi, A., Blaxhult, A., Katlama, C., Clotet, B., Barton, S. and Lundgren, J. D. (2000). "Virological failure among patients on HAART from across Europe: results from the EuroSIDA study." Antivir Ther **5**(2): 107-112.

Mocroft, A., Vella, S., Benfield, T. L., Chiesi, A., Miller, V., Gargalianos, P., d'Arminio Monforte, A., Yust, I., Bruun, J. N., Phillips, A. N. and Lundgren, J. D. (1998). "Changing patterns of mortality across Europe in patients infected with HIV-1. EuroSIDA Study Group." Lancet **352**(9142): 1725-1730.

Mofenson, L. M. and et al. (1999). "Risk factors for perinatal transmission of human immunodeficiency virus type 1 in women treated with zidovudine." New England Journal of Medicine **341**(6): 385-393.

Mogilevkina, I., Tyden, T. and Odlind, V. (2001). "Ukrainian medical students' experiences, attitudes, and knowledge about reproductive health." J Am Coll Health **49**(6): 269-272.

Molina, J. M., Podsadecki, T. J., Johnson, M. A., Wilkin, A., Domingo, P., Myers, R., Hairrell, J. M., Rode, R. A., King, M. S. and Hanna, G. J. (2007). "A Lopinavir/Ritonavir-Based Once-Daily Regimen Results in Better Compliance and Is Non-inferior to a Twice-Daily Regimen Through 96 Weeks." AIDS Research and Human Retroviruses **23**(12): 1505-1514.

Montaner, J. S., Lima, V. D., Barrios, R., Yip, B., Wood, E., Kerr, T., Shannon, K., Harrigan, P. R., Hogg, R. S., Daly, P. and Kendall, P. (2010). "Association of highly active antiretroviral therapy coverage, population viral load, and yearly new HIV diagnoses in British Columbia, Canada: a population-based study." Lancet **376**(9740): 532-539.

Montaner, J. S., Reiss, P., Cooper, D., Vella, S., Harris, M., Conway, B., Wainberg, M. A., Smith, D., Robinson, P., Hall, D., Myers, M. and Lange, J. M. (1998). "A randomized, double-blind trial comparing combinations of nevirapine, didanosine, and zidovudine for HIV-infected patients: the INCAS Trial. Italy, The Netherlands, Canada and Australia Study." JAMA : the journal of the American Medical Association **279**(12): 930-937.

Moodley, P., Wilkinson, D., Connolly, C., Moodley, J. and Sturm, A. W. (2002). "Trichomonas vaginalis is associated with pelvic inflammatory disease in women infected with human immunodeficiency virus." Clin Infect Dis **34**(4): 519-522.

Moore, D. M., Hogg, R. S., Yip, B., Wood, E., Tyndall, M., Braitstein, P. and Montaner, J. S. G. (2005). "Discordant Immunologic and Virologic Responses to Highly Active Antiretroviral Therapy Are Associated With Increased Mortality and Poor Adherence to Therapy." J Acquir Immune Defic Syndr Hum Retrovirol **40**(3): 288-293.

Moore, R. D., Keruly, J. C. and Chaisson, R. E. (2004). "Differences in HIV disease progression by injecting drug use in HIV-infected persons in care." J Acquir Immune Defic Syndr **35**(1): 46-51.

Moreno, S., Mocroft, A. and Monforte, A. (2010). "Medical and societal consequences of late presentation." Antiviral therapy **15 Suppl 1**: 9-15.

Morrison, C. S., Wang, J., Van Der Pol, B., Padian, N., Salata, R. A. and Richardson, B. A. (2007). "Pregnancy and the risk of HIV-1 acquisition among women in Uganda and Zimbabwe." AIDS **21**(8): 1027-1034.

Moscicki, A. B., Hills, N., Shiboski, S., Powell, K., Jay, N., Hanson, E., Miller, S., Clayton, L., Farhat, S., Broering, J., Darragh, T. and Palefsky, J. (2001). "Risks for incident human papillomavirus infection and low-grade squamous intraepithelial lesion development in young females." JAMA **285**(23): 2995-3002.

Moss, A. R. and Bacchetti, P. (1989). "Natural history of HIV infection." AIDS **3**(2): 55-61.

Mostashari, F., Riley, E., Selwyn, P. A. and Frederick, L. A. (1998). "Acceptance and Adherence With Antiretroviral Therapy Among HIV-Infectd Women in a Correctional Facility." J Acquir Immune Defic Syndr Hum Retrovirol **18**: 341-348.

Mounier-Jack, S., Nielsen, S. and Coker, R. J. (2008). "HIV testing strategies across European countries." HIV Medicine **9**(Suppl. 2): 13-19.

Mucheto, P., Chadambuka, A., Shambira, G., Tshimanga, M., Gombe, N. and Nyamayaro, W. (2011). "Determinants of nondisclosure of HIV status among women attending the prevention of mother to child transmission programme, Makonde district, Zimbabwe, 2009." Pan Afr Med J **8**: 51.

Mugo, N. R., Heffron, R., Donnell, D., Wald, A., Were, E. O., Rees, H., Celum, C., Kiarie, J. N., Cohen, C. R., Kayintekore, K. and Baeten, J. M. (2011). "Increased risk of HIV-1 transmission in pregnancy: a prospective study among African HIV-1-serodiscordant couples." AIDS **25**(15): 1887-1895.

Munoz, A., Wang, M. C., Bass, S., Taylor, J. M., Kingsley, L. A., Chmiel, J. S. and Polk, B. F. (1989). "Acquired immunodeficiency syndrome (AIDS)-free time after human immunodeficiency virus type 1 (HIV-1) seroconversion in homosexual men. Multicenter AIDS Cohort Study Group." American journal of epidemiology **130**(3): 530-539.

Muñoz, N., Castellsagu,, X., de Gonzalez, A. B. and Gissmann, L. (2006). "Chapter 1: HPV in the etiology of human cancer." Vaccine **24 Suppl 3**: S3/1-S310.

Mwapasa, V., Rogerson, S. J., Kwiek, J. J., Wilson, P. E., Milner, D., Molyneux, M. E., Kamwendo, D. D., Tadesse, E., Chaluluka, E. and Meshnick, S. R. (2006). "Maternal syphilis infection is associated with increased risk of mother-to-child transmission of HIV in Malawi." AIDS **20**(14): 1869-1877.

Nachega, J. B., Uthman, O. A., Anderson, J., Peltzer, K., Wampold, S., Cotton, M. F., Mills, E. J., Ho, Y. S., Stringer, J. S., McIntyre, J. A. and Mofenson, L. M. (2012). "Adherence to antiretroviral therapy during and after pregnancy in low-income, middle-income, and high-income countries: a systematic review and meta-analysis." AIDS **26**(16): 2039-2052.

National Collaborating Centre for Mental Health (2007). NICE clinical guideline 45: Antenatal and postnatal mental health, Clinical management and service guidance. London, National Institute for Health and Clinical Excellence.

National Study of HIV in Pregnancy and Childhood, NHS Audit Information Analysis Unit and Children's HIV Association (2007). Perinatal transmission of HIV in England 2002-2005, Audit Information and Analysis Unit for London, Kent, Surrey and Sussex, Essex, Beds & Herts.

National Study of HIV in Pregnancy and Childhood, A. "Quarterly slide set, reporting up to June 2012, available at http://www.ucl.ac.uk/nshpc/slides." Accessed 2012.

Naver, L., Lindgren, S., Belfrage, E., Gyllensten, K., Lidman, K., Gisslen, M., Ehrnst, A., Arneborn, M. and Bohlin, A. B. (2006). "Children born to HIV-1-infected women in Sweden in 1982-2003: trends in epidemiology and vertical transmission." Journal of acquired immune deficiency syndromes **42**(4): 484-489.

Nduati, R. and et al. (2000). "Effect of Breastfeeding and Formula Feeding on Transmision of HIV-1: A Randomised Clinical Trial." JAMA **283**(9): 1167-1174.

Ndung'u, T. and Weiss, R. A. (2012). "On HIV diversity." AIDS **26**(10): 1255-1260.

Neaigus, A., Gyarmathy, V. A., Zhao, M., Miller, M., Friedman, S. R. and Des Jarlais, D. C. (2007). "Sexual and other noninjection risks for HBV and HCV seroconversions among noninjecting heroin users." The Journal of infectious diseases **195**(7): 1052-1061.

Nelson, P. K., Mathers, B. M., Cowie, B., Hagan, H., Des, J. D., Horyniak, D. and Degenhardt, L. (2011). "Global epidemiology of hepatitis B and hepatitis C in people who inject drugs: results of systematic reviews." Lancet **378**(9791): 571-583.

Newell, M. L., Coovadia, H., Cortina-Borja, M., Rollins, N., Gaillard, P. and Dabis, F. (2004). "Mortality of infected and uninfected infants born to HIV-infected mothers in Africa: a pooled analysis." Lancet **364**(9441): 1236-1243.

NHS Cancer Screening Programmes (2006). Taking Samples for Cervical Screening - a Resource Pack for Trainers. NHS Cancer Screening Programmes Clinical Primary Care Quality Assurance Coordinating Group. Sheffield, NHS Cancer Screening Programmes.

NHS Cancer Screening Programmes (2010). Colposcopy and Programme Management - Guidelines for the NHS Cervical Screening Programme, 2nd Edition. Luesley, D. and Leeson, S. Sheffield, UK, NHS Cancer Screening Programmes. **20**.

NIAID Adult AIDS Clinical Trials Group (2001). Supplemental Antepartum Adherence Questionnaire. Accessed September 2012. Available at https://www.fstrf.org/apps/cfmx/apps/common/QOLAdherenceForms/index.cfm?project=ACTG.

Nicoll, A., Gill, O. N., Peckham, C. S., Ades, A. E., Parry, J., Mortimer, P., Goldberg, D., Noone, A., Bennett, D. and Catchpole, M. (2000). "The public health applications of unlinked anonymous seroprevalence monitoring for HIV in the United Kingdom." Int J Epidemiol **29**(1): 1-10.

Nicoll, A., Stephenson, J., Griffioen, A., Cliffe, S., Rogers, P. and Boisson, E. (1998). "The relationship of HIV prevalence in pregnant women to that in women of reproductive age: a validated method for adjustment." AIDS **12**(14): 1861-1867.

Nieburg, P. and Carty, L. (2012). Injection Drug Use in Ukraine - The Challenges of Providing HIV Prevention and Care. Washington, DC, Centre for Strategic and International Studies.

Nielsen-Saines, K., Watts, D. H., Veloso, V. G., Bryson, Y. J., Joao, E. C., Pilotto, J. H., Gray, G., Theron, G., Santos, B., Fonseca, R., Kreitchmann, R., Pinto, J., Mussi-Pinhata, M. M., Ceriotto, M., Machado, D., Bethel, J., Morgado, M. G., Dickover, R., Camarca, M., Mirochnick, M., Siberry, G., Grinsztejn, B., Moreira, R. I., Bastos, F. I., Xu, J., Moye, J. and Mofenson, L. M. (2012). "Three postpartum antiretroviral regimens to prevent intrapartum HIV infection." N Engl J Med **366**(25): 2368-2379.

Nuesch, R., Ananworanich, J., Srasuebkul, P., Chetchotisakd, P., Prasithsirikul, W., Klinbuayam, W., Mahanontharit, A., Jupimai, T., Ruxrungtham, K. and Hirschel, B. (2008). "Interruptions of tenofovir/emtricitabine-based antiretroviral therapy in patients with HIV/hepatitis B virus co-infection." AIDS **22**(1): 152-154.

Nurutdinova, D., Abdallah, A. B., Bradford, S., O'Leary, C. C. and Cottler, L. B. (2011). "Risk factors associated with Hepatitis C among female substance users enrolled in community-based HIV prevention studies." BMC research notes **4**: 126.

Oates, M. R., Cox, J. L., Neema, S., Asten, P., Glangeaud-Freudenthal, N., Figueiredo, B., Gorman, L. L., Hacking, S., Hirst, E., Kammerer, M. H., Klier, C. M., Seneviratne, G., Smith, M., Sutter-Dallay, A. L., Valoriani, V., Wickberg, B., Yoshida, K. and Group, T.-P. (2004). "Postnatal depression across countries and cultures: a qualitative study." Br J Psychiatry Suppl **46**: s10-16.

Ofotokun, I. and Pomeroy, C. (2003). "Sex differences in adverse reactions to antiretroviral drugs." Top HIV Med **11**(2): 55-59.

Ohto, H., Terazawa, S., Sasaki, N., Hino, K., Ishiwata, C., Kako, M., Ujiie, N., Endo, C., Matsui, A. and et al. (1994). "Transmission of hepatitis C virus from mothers to infants. The Vertical Transmission of Hepatitis C Virus Collaborative Study Group." N Engl J Med **330**(11): 744-750.

Olson, A. L., Dietrich, A. J., Prazar, G. and Hurley, J. (2006). "Brief Maternal Depression Screening at Well-Child Visits." Pediatrics **118**: 207-216.

Open Society Institute (2009). Women, Harm Reduction and HIV: Key findings from Azerbaijan, Georgia, Kyrgyzstan, Russia and Ukraine.

Open Society Institute (2010). Ignorance is No Longer an Option: Why and How to Respond to the Hepatitis C Epidemic in Ukraine, available at http://www.harm-reduction.org/files/pdf/4-country/43en_Ukraine.pdf (accessed January 2013).

Osborn, C. Y., Davis, T. C., Bailey, S. C. and Wolf, M. S. (2010). "Health Literacy in the Context of HIV Treatment: Introducing the Brief Estimate of Health Knowledge and Action (BEHKA) - HIV Version." AIDS Behav **14**: 181-188.

Palella, F. J., Jr., Delaney, K. M., Moorman, A. C., Loveless, M. O., Fuhrer, J., Satten, G. A., Aschman, D. J. and Holmberg, S. D. (1998). "Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV Outpatient Study Investigators." The New England Journal of Medicine **338**(13): 853-860.

Panel on Antiretroviral Guidelines for Adults and Adolescents (2012). Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents.

Panel on Treatment of HIV-infected Pregnant Women and Prevention of Perinatal Transmission (2012). Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States. Available at: http://www.aidsinfo.nih.gov/contentfiles/lvguidelines/perinatalGL.pdf, Accessed November 2012.

Parienti, J., Verdon, R., Bazin, C., Bouvet, E. and Massari, V. (2001). "The Pills Identification Test: A Tool to Assess Adherence to Antiretroviral Therapy." JAMA **285**(4): 412-412.

Parker, R. and Aggleton, P. (2003). "HIV and AIDS-related stigma and discrimination: a conceptual framework and implications for action." Soc Sci Med **57**(1): 13-24.

Patel, D. (2007). Statistical modelling of virological and immunological patterns in HIV-1 infected pregnant women in Europe. PhD, University College London.

Patel, D., Cortina-Borja, M., Thorne, C. and Newell, M. L. (2007). "Time to undetectable viral load after highly active antiretroviral therapy initiation among HIV-infected pregnant women." Clinical infectious diseases : an official publication of the Infectious Diseases Society of America **44**(12): 1647-1656.

Paterson, D. L., Potoski, B. and Capitano, B. (2002). "Measurement of Adherence to Antiretroviral Medications." J Acquir Immune Defic Syndr. **31**(Supplement): S103-S106.

Paterson, D. L., Swindells, S., Mohr, J., Brester, M., Vergis, E. N., Squier, C., Wagener, M. M. and Singh, N. (2000). "Adherence to Protease Inhibitor Therapy and Outcomes in Patients with HIV Infection." Ann Intern Med **133**: 21-30.

Patrick, D. M., Tyndall, M. W., Cornelisse, P. G., Li, K., Sherlock, C. H., Rekart, M. L., Strathdee, S. A., Currie, S. L., Schechter, M. T. and O'Shaughnessy, M. V. (2001). "Incidence of hepatitis C virus infection among injection drug users during an outbreak of HIV infection." CMAJ **165**(7): 889-895.

Patterson, K. B., Leone, P. A., Fiscus, S. A., Kuruc, J., McCoy, S. I., Wolf, L., Foust, E., Williams, D., Eron, J. J. and Pilcher, C. D. (2007). "Frequent detection of acute HIV infection in pregnant women." AIDS **21**(17): 2303-2308.

PENTA Steering Committee (2009). "PENTA 2009 guidelines for the use of antiretroviral therapy in paediatric HIV-1 infection." HIV Medicine **10**: 591-613.

Perlman, F. and McKee, M. (2009). "Trends in Family Planning in Russia, 1994-2003." Perspectives on Sexual and Reproductive Health **41**(1): 40-50.

Peters, N., Van Leeuwen, A. M., Pieters, W. J., Hollema, H., Quint, W. G. and Burger, M. P. (1995). "Bacterial vaginosis is not important in the etiology of cervical neoplasia: a survey on women with dyskaryotic smears." Sex Transm.Dis. **22**(5): 296-302.

Peters, V., Liu, K. L., Dominguez, K., Frederick, T., Melville, S., Hsu, H. W., Ortiz, I., Rakusan, T., Gill, B. and Thomas, P. (2003). "Missed opportunities for perinatal HIV prevention among HIV-exposed infants born 1996-2000, Pediatric Spectrum of HIV Disease Cohort." Pediatrics **111**(5 part 2): 1186-1191.

Peto, J., Gilham, C., Fletcher, O. and Matthews, F. E. (2004). "The cervical cancer epidemic that screening has prevented in the UK." Lancet **364**(9430): 249-256.

Petry, K. U., Scheffel, D., Bode, U., Gabrysiak, T., Kochel, H., Kupsch, E., Glaubitz, M., Niesert, S., Kuhnle, H. and Schedel, I. (1994). "Cellular immunodeficiency enhances the progression of human papillomavirus-associated cervical lesions." Int.J.Cancer **57**(6): 836-840.

Phelan, D. F., Gange, S. J., Ahdieh-Grant, L., Mehta, S. H., Kirk, G. D., Shah, K. and Gravitt, P. (2009). "Determinants of Newly Detected Human Papillomavirus Infection in HIV-Infected and HIV-Uninfected Injection Drug Using Women." Sex Transm.Dis. **36**(3): 149-156.

Phillips, A. N., Leen, C., Wilson, A., Anderson, J., Dunn, D., Schwenk, A., Orkin, C., Hill, T., Fisher, M., Walsh, J., Pillay, D., Bansi, L., Gazzard, B., Easterbrook, P., Gilson, R., Johnson, M. and Sabin, C. A. (2007). "Risk of extensive virological failure to the three original antiretroviral drug classes over long-term follow-up from the start of therapy in patients with HIV infection: an observational cohort study." Lancet **370**(9603): 1923-1928.

Pilcher, C. D., Joaki, G., Hoffman, I. F., Martinson, F. E., Mapanje, C., Stewart, P. W., Powers, K. A., Galvin, S., Chilongozi, D., Gama, S., Price, M. A., Fiscus, S. A. and Cohen, M. S. (2007). "Amplified transmission of HIV-1: comparison of HIV-1 concentrations in semen and blood during acute and chronic infection." AIDS **21**(13): 1723-1730.

Pillay, D., Cane, P. A., Ratcliffe, D., Atkins, M. and Cooper, D. (2000). "Evolution of lamivudine-resistant hepatitis B virus and HIV-1 in co-infected individuals: an analysis of the CAESAR study. CAESAR co-ordinating committee." AIDS **14**(9): 1111-1116.

Pinkham, S. and Malinowska-Sempruch, K. (2008). "Women, harm reduction and HIV." Reproductive health matters **16**(31): 168-181.

Pinkham, S., Stoicescu, C. and Myers, B. (2012). "Developing effective health interventions for women who inject drugs: key areas and recommendations for program development and policy." Adv Prev Med **2012**: 269123.

Platz-Christensen, J. J., Sundstrom, E. and Larsson, P. G. (1994). "Bacterial vaginosis and cervical intraepithelial neoplasia." Acta Obstet.Gynecol.Scand. **73**(7): 586-588.

Polis, C. B., Shah, S. N., Johnson, K. E. and Gupta, A. (2007). "Impact of maternal HIV coinfection on the vertical transmission of hepatitis C virus: a meta-analysis." Clin.Infect.Dis. **44**(8): 1123-1131.

Porter, K., Walker, S., Hill, T., Anderson, J., Leen, C., Johnson, M., Gazzard, B., Walsh, J., Fisher, M., Orkin, C., Schwenk, A., Gilson, R., Easterbrook, P., Delpech, V. and Sabin, C. A. (2008). "Changes in outcome of persons initiating highly active antiretroviral therapy at a CD4 count less than 50 Cells/mm3." J Acquir Immune Defic Syndr **47**(2): 202-205.

Postma, M. J., Beck, E. J., Hankins, C. A., Mandalia, S., Jager, J. C., de Jong-van den Berg, L. T., Walters, M. D. and Sherr, L. (2000). "Cost effectiveness of expanded antenatal HIV testing in London." AIDS **14**(15): 2383-2389.

Potter, M., Odueyungbo, A., Yang, H., Saeed, S. and Klein, M. B. (2010). "Impact of hepatitis C viral replication on CD4+ T-lymphocyte progression in HIV-HCV coinfection before and after antiretroviral therapy." AIDS **24**(12): 1857-1865.

Poznyak, V., Pelipas, V., Vievski, A. and Miroshnichenko, L. (2002). "Illicit Drug Use and Its Health Consequences in Belarus, Russian Federation and Ukraine: Impact of Transition." Addiction Research in Central and Eastern Europe **8**: 184-189.

Psaros, C., Geller, P. A. and Aaron, E. (2009). "The importance of identifying and treating depression in HIV infected pregnant women: a review." Journal of Psychosomatic Obstetrics and Gynecology **30**(4): 275-281.

Pursuing Later Treatment Options II (Plato II) project team for COHERE, Lodwick, R., Costagliola, D., Reiss, P., Torti, C., Teira, R., Dorrucci, M., Ledergerber, B., Mocroft, A., Podzamczer, D., Cozzi-Lepri, A., Obel, N., Masquelier, B., Staszewski, S., Garcia, F., De Wit, S., Castagna, A., Antinori, A., Judd, A., Ghosn, J., Touloumi, G., Mussini, C., Duval, X., Ramos, J., Meyer, L., Warsawski, J., Thorne, C., Masip, J., Perez-Hoyos, S., Pillay, D., van Sighem, A., Lo Caputo, S., Gunthard, H., Paredes, R., De Luca, A., Paraskevis, D., Fabre-Colin, C., Kjaer, J., Chene, G., Lundgren, J. D. and Phillips, A. N. (2010). "Triple-class virologic failure in HIV-infected patients undergoing antiretroviral therapy for up to 10 years." Arch Intern Med **170**(5): 410-419.

Rabe-Hesketh, S., Skrondal, A. and Pickles, A. (2002). "Reliable estimation of generalised linear mixed models using adaptive quadrature." The Stata Journal **2**(1): 1-21.

Raboud, J., Blitz, S., Walmsley, S., Thompson, C., Rourke, S. B. and Loutfy, M. R. (2010). "Effect of gender and calendar year on time to and duration of virologic suppression among antiretroviral-naive HIV-infected individuals initiating combination antiretroviral therapy." HIV Clin Trials **11**(6): 340-350.

Read, J. S. and Newell, M. K. (2005). "Efficacy and safety of cesarean delivery for prevention of mother-to-child transmission of HIV-1." Cochrane database of systematic reviews(4): CD005479.

Read, P., Costelloe, S., Mullen, J., O'Shea, S., Lyons, F., Hay, P., Welch, J., Larbalestier, N., Taylor, G. and de Ruiter, A. (2008). "New mutations associated with resistance not detected following zidovudine monotherapy in pregnancy when used in accordance with British HIV Association guidelines." HIV Med **9**(7): 448-451.

Read, P. J., Mandalia, S., Khan, P., Harrisson, U., Naftalin, C., Gilleece, Y., Anderson, J., Hawkins, D. A., Taylor, G. P. and de Ruiter, A. (2012). "When should HAART be initiated in pregnancy to achieve an undetectable HIV viral load by delivery?" AIDS **26**(9): 1095-1103.

Reeves, J. D. and Doms, R. W. (2002). "Human immunodeficiency virus type 2." The Journal of general virology **83**(Pt 6): 1253-1265.

Rehermann, B. (2009). "Hepatitis C virus versus innate and adaptive immune responses: a tale of coevolution and coexistence." The Journal of clinical investigation **119**(7): 1745-1754.

Rhodes, T., Ball, A., Stimson, G. V., Kobyshcha, Y., Fitch, C., Pokrovsky, V., Bezruchenko-Novachuk, M., Burrows, D., Renton, A. and Andrushchak, L. (1999). "HIV infection associated with drug injecting in the newly independent states, eastern Europe: the social and economic context of epidemics." Addiction **94**(9): 1323-1336.

Rhodes, T. and Simic, M. (2005). "Transition and the HIV risk environment." BMJ **331**(7510): 220-223.

Ridout, M., Hinde, J. and Demetrio, C. G. (2001). "A score test for testing a zero-inflated Poisson regression model against zero-inflated negative binomial alternatives." Biometrics **57**(1): 219-223.

Rodriguez-Arenas, M. A., Jarrin, I., del Amo, J., Iribarren, J. A., Moreno, S., Viciana, P., Pena, A., Sirvent, J. L., Vidal, F., Lacruz, J., Gutierrez, F., Oteo, J. A., Asencio, R., Castilla, J. and Hoyos, S. P. (2006). "Delay in the initiation of HAART, poorer virological response, and higher mortality among HIV-infected injecting drug users in Spain." AIDS Res Hum Retroviruses **22**(8): 715-723.

Ross, R., Sawatphanit, W., Mizuno, M. and Takeo, K. (2011). "Depressive symptoms among HIV-positive postpartum women in Thailand." Arch Psychiatr Nurs **25**(1): 36-42.

Roxby, A. C., Drake, A. L., John-Stewart, G., Brown, E. R., Matemo, D., Otieno, P. A. and Farquhar, C. (2011). "Herpes simplex virus type 2, genital ulcers and HIV-1 disease progression in postpartum women." PLoS One **6**(5): e19947.

Roy, E., Boudreau, J. F. and Boivin, J. F. (2009). "Hepatitis C virus incidence among young street-involved IDUs in relation to injection experience." Drug Alcohol Depend. **102**(1-3): 158-161.

Royal College of Obstetricians and Gynaecologists (2010). Medical Terms Explained http://www.rcog.org.uk/womens-health/patient-information/medical-terms-explained (Accessed January 2013).

Rubin, L. H., Cook, J. A., Grey, D. D., Weber, K., Wells, C., Golub, E. T., Wright, R. L., Schwartz, R. M., Goparaju, L., Cohan, D., Wilson, M. L. and Maki, P. M. (2011). "Perinatal depressive symptoms in HIV-infected versus HIV-uninfected women: a prospective study from preconception to postpartum." J Womens Health (Larchmt) **20**(9): 1287-1295.

Ryscavage, P., Anderson, E. J., Sutton, S. H., Reddy, S. and Taiwo, B. (2011). "Clinical outcomes of adolescents and young adults in adult HIV care." J Acquir Immune Defic Syndr **58**(2): 193-197.

Sabin, C. A., Smith, C. J., d'Arminio Monforte, A., Battegay, M., Gabiano, C., Galli, L., Geelen, S., Gibb, D., Guiguet, M., Judd, A., Leport, C., Dabis, F., Pantazis, N., Porter, K., Raffi, F., Thorne, C., Torti, C., Walker, S., Warszawski, J., Wintergerst, U., Chene, G. and Lundgren, J. (2008). "Response to combination antiretroviral therapy: variation by age." AIDS **22**(12): 1463-1473.

Safren, S. A., Otto, M. W., Worth, J. L., Salomon, E., Johnson, W., Mayer, K. and Boswell, S. (2001). "Two strategies to increase adherence to HIV antiretroviral medication: Life-Steps and medication monitoring." Behaviour Research and Therapy **39**: 1151-1162.

Samet, J. H., Freedberg, K. A., Stein, M. D., Lewis, R., Savetsky, J., Sullivan, L., Levenson, S. M. and Hingson, R. (1998). "Trillion virion delay; Time from testing positive for HIV to presentation for primary care." Archives of Internal Medicine **158**: 734-740.

Sawaya, G. F. (2009). "Cervical-cancer screening--new guidelines and the balance between benefits and harms." N.Engl.J.Med. **361**(26): 2503-2505.

Saxton, J., Malyuta, R., Semenenko, I., Pilipenko, T., Tereshenko, R., Kulakovskaya, E., Adejnova, I., Kvasha, L. and Thorne, C. (2010). "Previous reproductive history and post-natal family planning among HIV-infected women in Ukraine." Human Reproduction **25**(9): 2366-2373.

Schaub, M., Chtenguelov, V., Subata, E., Weiler, G. and Uchtenhagen, A. (2010). "Feasibility of buprenorphine and methadone maintenance programmes among users of home made opioids in Ukraine." Int J Drug Policy **21**(3): 229-233.

Schim van der Loeff, M. F. and Giuliano, A. R. (2012). "Human papillomavirus vaccination: component of an integrated HIV prevention program?" AIDS **26**(17): 2251-2252.

Schouten, E. J., Jahn, A., Midiani, D., Makombe, S. D., Mnthambala, A., Chirwa, Z., Harries, A. D., van Oosterhout, J. J., Meguid, T., Ben-Smith, A., Zachariah, R., Lynen, L., Zolfo, M., Van Damme, W., Gilks, C. F., Atun, R., Shawa, M. and Chimbwandira, F. (2011a). "Prevention of mother-to-child transmission of HIV and the health-related Millennium Development Goals: time for a public health approach." Lancet **378**(9787): 282-284.

Schouten, J., Cinque, P., Gisslen, M., Reiss, P. and Portegies, P. (2011b). "HIV-1 infection and cognitive impairment in the cART era: a review." Aids **25**(5): 561-575.

Schwartlander, B., Stover, J., Hallett, T., Atun, R., Avila, C., Gouws, E., Bartos, M., Ghys, P. D., Opuni, M., Barr, D., Alsallaq, R., Bollinger, L., de Freitas, M., Garnett, G., Holmes, C., Legins, K., Pillay, Y., Stanciole, A. E., McClure, C., Hirnschall, G., Laga, M. and Padian, N. (2011). "Towards an improved investment approach for an effective response to HIV/AIDS." Lancet **377**(9782): 2031-2041.

Shaffer, N., Chuachoowong, R., Mock, P. A., Bhadrakom, C., Siriwasin, W., Young, N. L., Chotpitayasunondh, T., Chearskul, S., Roongpisuthipong, A., Chinayon, P., Karon, J., Mastro, T. D. and Simonds, R. J. (1999). "Short-course zidovudine for perinatal HIV-1 transmission in Bangkok, Thailand: a randomised controlled trial. Bangkok Collaborative Perinatal HIV Transmission Study Group." Lancet **353**(9155): 773-780.

Shapiro, R. L., Thior, I., Gilbert, P. B., Lockman, S., Wester, C., Smeaton, L. M., Stevens, L., Heymann, S. J., Ndung'u, T., Gaseitsiwe, S., Novitsky, V., Makhema, J., Lagakos, S. and Essex, M. (2006). "Maternal single-dose nevirapine versus placebo as part of an antiretroviral strategy to prevent mother-to-child HIV transmission in Botswana." AIDS **20**(9): 1281-1288.

Sherr, L., Lampe, F. C., Clucas, C., Johnson, M., Fisher, M., Leake Date, H., Anderson, J., Edwards, S., Smith, C. J., Hill, T. and Harding, R. (2010). "Self-reported non-adherence to ART and virological outcome in a multiclinic UK study." AIDS Care **22**(8): 939-945.

Simoni, J. M., Kurth, A. E., Pearson, C. R., Pantalone, D. W., Merrill, J. O. and Frick, P. A. (2006a). "Self-Report Measures of Antiretroviral Therapy Adherence: A Review with Recommendations for HIV Research and Clinical Management." AIDS Behav **10**: 227-245.

Simoni, J. M., Pearson, C. R., Pantalone, D. W., Marks, G. and Crepaz, N. (2006b). "Efficacy of interventions in improving highly active antiretroviral therapy adherence and HIV-1 RNA viral load. A meta-analytic review of randomized controlled trials." J Acquir Immune Defic Syndr **43 Suppl 1**: S23-35.

Smith, C. J., Staszewski, S., Sabin, C. A., Nelson, M., Dauer, B., Gute, P., Johnson, M. A., Phillips, A. N. and Gazzard, B. (2004). "Use of viral load measured after 4 weeks of highly active antiretroviral therapy to predict virologic outcome at 24 weeks for HIV-1-positive individuals." Journal of acquired immune deficiency syndromes **37**(1): 1155-1159.

Smith, J. A. and Daniel, R. (2006). "Following the path of the virus: the exploitation of host DNA repair mechanisms by retroviruses." ACS chemical biology **1**(4): 217-226.

Smith, J. S., Herrero, R., Bosetti, C., Munoz, N., Bosch, F. X., Eluf-Neto, J., Castellsague, X., Meijer, C. J., Van den Brule, A. J., Franceschi, S. and Ashley, R. (2002). "Herpes simplex virus-2 as a human papillomavirus cofactor in the etiology of invasive cervical cancer." Journal of the National Cancer Institute **94**(21): 1604-1613.

Smith, R., Semenenko, I., Tolpina, M., Tereshenko, R., Kotlik, L., Zasyptka, L., Murphy, G., McKinney, E., Malyuta, R., Porter, K. and On behalf of the CASCADE Collaboration in EuroCoord (2012). High percentage of recent HIV infection leading to onward transmission in Odessa, Ukraine associated with young adults. XIX International AIDS Conference. Washington DC, USA.

Solomon, D., Davey, D., Kurman, R., Moriarty, A., O'Connor, D., Prey, M., Raab, S., Sherman, M., Wilbur, D., Wright, T., Jr. and Young, N. (2002). "The 2001 Bethesda System: terminology for reporting results of cervical cytology." JAMA **287**(16): 2114-2119.

Soriano, V., Mocroft, A., Rockstroh, J., Ledergerber, B., Knysz, B., Chaplinskas, S., Peters, L., Karlsson, A., Katlama, C., Toro, C., Kupfer, B., Vogel, M. and Lundgren, J. (2008). "Spontaneous viral clearance, viral load, and genotype distribution of hepatitis C virus (HCV) in HIV-infected patients with anti-HCV antibodies in Europe." The Journal of infectious diseases **198**(9): 1337-1344.

Soriano, V., Vispo, E., Poveda, E., Labarga, P., Martin-Carbonero, L., Fernandez-Montero, J. V. and Barreiro, P. (2011). "Directly acting antivirals against hepatitis C virus." J Antimicrob Chemother **66**(8): 1673-1686.

Sperling, R. S. and et al. (1996). "Maternal viral load, zidovudine treatment, and the risk of transmission of human immunodeficiency virus type 1 from mother to infant." New England Journal of Medicine **335**(22): 1621-1629.

Spicer, N., Bogdan, D., Brugha, R., Harmer, A., Murzalieva, G. and Semigina, T. (2011). "'It's risky to walk in the city with syringes': understanding access to HIV/AIDS services for injecting drug users in the former Soviet Union countries of Ukraine and Kyrgyzstan." Globalization and health **7**: 22.

Stanwood, N. L. and et al. (2007). "Contraception and fertility plans in a cohort of HIV-positive women in care." Contraception **75**(4): 294-298.

Stein, M. D., Crystal, S., Cunningham, W. E., Ananthanarayanan, A., Andersen, R. M., Turner, B. J., Zierler, S., Morton, S., Katz, M. H., Bozzette, S. A., Shapiro, M. F. and Schuster, M. A. (2000). "Delays in seeking HIV care due to competing caregiver responsibilities." Am J Public Health **90**(7): 1138-1140.

Stephenson, J. M. and Griffioen, A. (1996). "The effect of HIV diagnosis on reproductive experience. Study Group for the Medical Research Council Collaborative Study of Women with HIV." AIDS **10**(14): 1683-1687.

Sterling, R. K., Lissen, E., Clumeck, N., Sola, R., Correa, M. C., Montaner, J., Sulkowski, S., Torriani, F. J., Dieterich, D. T., Thomas, D. L., Messinger, D. and Nelson, M. (2006). "Development of a simple noninvasive index to predict significant fibrosis in patients with HIV/HCV coinfection." Hepatology **43**(6): 1317-1325.

Sterne, J. A., Hernan, M. A., Ledergerber, B., Tilling, K., Weber, R., Sendi, P., Rickenbach, M., Robins, J. M. and Egger, M. (2005). "Long-term effectiveness of potent antiretroviral therapy in preventing AIDS and death: a prospective cohort study." Lancet **366**(9483): 378-384.

Sterne, J. A., May, M., Costagliola, D., de Wolf, F., Phillips, A. N., Harris, R., Funk, M. J., Geskus, R. B., Gill, J., Dabis, F., Miro, J. M., Justice, A. C., Ledergerber, B., Fatkenheuer, G., Hogg, R. S., Monforte, A. D., Saag, M., Smith, C., Staszewski, S., Egger, M. and Cole, S. R. (2009). "Timing of initiation of antiretroviral therapy in AIDS-free HIV-1-infected patients: a collaborative analysis of 18 HIV cohort studies." Lancet **373**(9672): 1352-1363.

Stokols, D. (1992). "Establishing and maintaining healthy environments. Toward a social ecology of health promotion." Am Psychol **47**(1): 6-22.

Strathdee, S. A. and Stockman, J. K. (2010). "Epidemiology of HIV among injecting and non-injecting drug users: current trends and implications for interventions." Curr HIV/AIDS Rep **7**(2): 99-106.

Sullivan, P. S., Hamouda, O., Delpech, V., Geduld, J. E., Prejean, J., Semaille, C., Kaldor, J., Folch, C., Op de Coul, E., Marcus, U., Hughes, G., Archibald, C. P., Cazein, F., McDonald, A., Casabona, J., van Sighem, A. and Fenton, K. A. (2009). "Reemergence of the HIV epidemic among men who have sex with men in North America, Western Europe, and Australia, 1996-2005." Annals of epidemiology **19**(6): 423-431.

Suls, J. and Rothman, A. (2004). "Evolution of the biopsychosocial model: prospects and challenges for health psychology." Health Psychol **23**(2): 119-125.

Sun, X. W., Kuhn, L., Ellerbrock, T. V., Chiasson, M. A., Bush, T. J. and Wright, T. C., Jr. (1997). "Human papillomavirus infection in women infected with the human immunodeficiency virus." N.Engl.J.Med. **337**(19): 1343-1349.

The Antiretroviral Therapy Cohort Collaboration (2008). "Life expectancy of individuals on combination antiretroviral therapy in high-income countries: a collaborative analysis of 14 cohort studies." Lancet **372**(9635): 293-299.

The European Mode of Delivery Collaboration (1999). "Elective caesarean-section versus vaginal delivery in prevention of vertical HIV-1 transmission: a randomised clinical trial." The Lancet **353**(9158): 1035-1039.

The International Perinatal HIV Group (1999). "The Mode of Delivery and Risk of Vertical Transmission of Human Immunodeficiency Virus Type 1: A Meta-Analysis of 15 Prospective Cohort Studies." New England Journal of Medicine **340**(13): 977-987.

The Kesho Bora Study Group (2012). "Maternal HIV-1 disease progression 18-24 months postdelivery according to antiretroviral prophylaxis regimen (triple-antiretroviral prophylaxis during pregnancy and breastfeeding vs zidovudine/single-dose nevirapine prophylaxis): The Kesho Bora randomized controlled trial." Clin Infect Dis **55**(3): 449-460.

The UK Collaborative Group for HIV and STI Surveillance (2005). Mapping the Issues. HIV and other Sexually Transmitted Infections in the United Kingdom: 2005. London, Health Protection Agency Centre for Infections.

The World Bank (2011). The World Bank - Ukraine Data http://data.worldbank.org/country/ukraine, Accessed November 2012.

The World Bank (2013). The World Bank - Country and Lending Groups, http://data.worldbank.org/about/country-classifications/country-and-lending-groups#Lower_middle_income, Accessed January 2013.

Thomas, D. L., Astemborski, J., Rai, R. M., Anania, F. A., Schaeffer, M., Galai, N., Nolt, K., Nelson, K. E., Strathdee, S. A., Johnson, L., Laeyendecker, O., Boitnott, J., Wilson, L. E. and Vlahov, D. (2000). "The natural history of hepatitis C virus infection: host, viral, and environmental factors." JAMA **284**(4): 450-456.

Thomson, M. M., de Parga, E. V., Vinogradova, A., Sierra, M., Yakovlev, A., Rakhmanova, A., Delgado, E., Casado, G., Munoz, M., Carmona, R., Vega, Y., Perez-Alvarez, L., Contreras, G., Medrano, L., Osmanov, S. and Najera, R. (2007). "New insights into the origin of the HIV type 1 subtype A epidemic in former Soviet Union's countries derived from sequence analyses of preepidemically transmitted viruses." AIDS research and human retroviruses **23**(12): 1599-1604.

Thomson, M. M. and Najera, R. (2001). "Travel and the introduction of human immunodeficiency virus type 1 non-B subtype genetic forms into Western countries." Clinical infectious diseases : an official publication of the Infectious Diseases Society of America **32**(12): 1732-1737.

Thorne, C. and et al. (2008). "Correspondence: Mother-to-Child transmission risk is increased among HIV-infected pregnant women in Ukraine with serological test results positive for syphilis." Clinical Infectious Diseases **47**: 1114.

Thorne, C. and Newell, M. L. (2003). "Mother-to-child transmission of HIV infection and its prevention." Current HIV Research **1**: 447-462.

Thorne, C. and Newell, M. L. (2005). "Treatment options for the prevention of mother-to-child transmission of HIV." Current Opinion in Investigational Drugs **6**(8): 804-811.

Thorne, C. and Newell, M. L. (2007). "Safety of agents used to prevent mother-to-child transmission of HIV: Is there any cause for concern?" Drug Safety **30**(3): 203-213.

Thorne, C., Patel, D. and Newell, M. L. (2004). "Increased risk of adverse pregnancy outcomes in HIV-infected women treated with highly active antiretroviral therapy in Europe." AIDS **18**(17): 2337-2339.

Thorne, C., Semenenko, I. and Malyuta, R. (2012). "Prevention of mother-to-child transmission of human immunodeficiency virus among pregnant women using injecting drugs in Ukraine, 2000-10." Addiction **107**(1): 118-128.

Thorne, C., Semenenko, I., Pilipenko, T., Malyuta, R. and Ukraine European Collaborative Study Group (2009). "Progress in prevention of mother-to-child transmission of HIV infection in Ukraine: results from a birth cohort study." BMC Infectious Diseases **9**(40).

Tohme, R. A. and Holmberg, S. D. (2010). "Is sexual contact a major mode of hepatitis C virus transmission?" Hepatology **52**(4): 1497-1505.

Torian, L. V., Wiewel, E. W., Liu, K. L., Sackoff, J. E. and Frieden, T. R. (2008). "Risk factors for delayed initiation of medical care after diagnosis of Human Immunodeficiency Virus." Archives of Internal Medicine **168**(11): 1181-1187.

Townsend, C. L., Cortina-Borja, M., Peckham, C. S., de Ruiter, A., Lyall, H. and Tookey, P. A. (2008a). "Low rates of mother-to-child transmission of HIV following effective pregnancy interventions in the United Kingdom and Ireland, 2000-2006." AIDS **22**(8): 973-981.

Townsend, C. L., Cortina-Borja, M., Peckham, C. S. and Tookey, P. A. (2007). "Antiretroviral therapy and premature delivery in diagnosed HIV-infected women in the United Kingdom and Ireland." AIDS **21**: 1019-1026.

Townsend, C. L., Cortina-Borja, M., Peckham, C. S. and Tookey, P. A. (2008b). "Trends in management and outcome of pregnancies in HIV-infected women in the UK and Ireland, 1990-2006." BJOG **115**(9): 1078-1086.

Treloar, C., Rance, J. and Backmund, M. (2013). "Understanding barriers to hepatitis C virus care and stigmatization from a social perspective." Clin Infect Dis **57 Suppl 2**: S51-55.

Tsui, A. O., McDonald-Mosley, R. and Burke, A. E. (2010). "Family planning and the burden of unintended pregnancies." Epidemiol Rev **32**(1): 152-174.

Tubiana, R., Le Chenadec, J., Rouzioux, C., Mandelbrot, L., Hamrene, K., Dollfus, C., Faye, A., Delaugerre, C., Blanche, S. and Warszawski, J. (2010). "Factors associated with mother-to-child transmission of HIV-1 despite a maternal viral load <500 copies/ml at delivery: a case-control study nested in the French perinatal cohort (EPF-ANRS CO1)." Clinical infectious diseases : an official publication of the Infectious Diseases Society of America **50**(4): 585-596.

Turner, B. J., Newschaffer, C. J., Zhang, D., Cosler, L. and Hauck, W. W. (2000). "Antiretroviral Use and Pharmacy-Based Measurement of Adherence in Postpartum HIV-Infected Women." Medical Care **38**(9): 911-925.

Uberti-Foppa, C., Ferrari, D., Lodini, S., Reina, S., Ameglio, F., Grasso, M. A., Gallotta, G., Ferrari, A., Taccagni, G., Lazzarin, A. and Lillo, F. B. (2003). "Long-term effect of highly active antiretroviral therapy on cervical lesions in HIV-positive women." AIDS **17**(14): 2136-2138.

Uhlmann, S., Milloy, M. J., Kerr, T., Zhang, R., Guillemi, S., Marsh, D., Hogg, R. S., Montaner, J. S. and Wood, E. (2010). "Methadone maintenance therapy promotes initiation of antiretroviral therapy among injection drug users." Addiction **105**(5): 907-913.

Ukrainian Center for Social Reforms, State Statistical Committee, Ministry of Health and Macro International Inc (2008). Ukraine Demographic and Health Survey 2007, UCSR and Macro International.

UNAIDS (2009). Comprehensive External Evaluation of the National AIDS Response in Ukraine: Consolidated Report. Kyiv, Ukraine.

UNAIDS (2010). UNAIDS 2011-2015 strategy: Getting to Zero, available at http://www.unaids.org/en/media/unaids/contentassets/documents/unaidspublication/2010/jc2034_unaids_strategy_en.pdf (accessed January 2013).

UNAIDS (2011a). Countdown to zero: Global plan towards the elimination of new HIV infections among children by 2015 and keeping their mothers alive 2011-2015, available at http://www.unaids.org/en/media/unaids/contentassets/documents/unaidspublication/2011/20110609_JC2137_Global-Plan-elimination-HIv-Children_en.pdf (accessed January 2013).

UNAIDS (2011b). UNAIDS World AIDS Day Report. How to get to zero: Faster. Smarter. Better., available at http://www.unaids.org/en/media/unaids/contentassets/documents/unaidspublication/2011/jc2216_worldaidsday_report_2011_en.pdf (accessed September 2012).

UNICEF (2012). 2012 Ukraine PMTCT Assessment Summary Report - Draft. Geneva, Switzerland.

US Centers for Disease Control and Prevention (1993). 1993 Revised Classification System for HIV Infection and Expanded Surveillance Case Definition for AIDS Among Adolescents and Adults.

US Centers for Disease Control and Prevention (1998). "Report of the NIH Panel to Define Principles of Therapy of HIV Infection and Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents." MMWR **47**(RR-5): 1-82.

US Centers for Disease Control and Prevention (2006). "Revised Recommendations for HIV Testing of Adults, Adolescents, and Pregnant Women in Health-Care Settings." MMWR **55**(RR-14).

US Centers for Disease Control and Prevention (2009). "Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents - Recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America." **MMWR 58, No. RR-4**.

Uuskula, A., Laisaar, K. T., Raag, M., Smidt, J., Semjonova, S., Kogan, J., Amico, K. R., Sharma, A. and Dehovitz, J. (2012). "Antiretroviral therapy (ART) adherence and correlates to nonadherence among people on ART in Estonia." AIDS Care **24**(12): 1470-1479.

Uuskula, A., Puur, A., Toompere, K. and DeHovitz, J. (2010). "Trends in the epidemiology of bacterial sexually transmitted infections in eastern Europe 1995-2005." Sexually Transmitted Infections **86**: 6-14.

van Beek, I., Dwyer, R., Dore, G. J., Luo, K. and Kaldor, J. M. (1998). "Infection with HIV and hepatitis C virus among injecting drug users in a prevention setting: retrospective cohort study." BMJ **317**(7156): 433-437.

van Benthem, B. H., de Vincenzi, I., Delmas, M. C., Larsen, C., van den Hoek, A. and Prins, M. (2000a). "Pregnancies before and after HIV diagnosis in a european cohort of HIV-infected women. European Study on the Natural History of HIV Infection in Women." AIDS **14**(14): 2171-2178.

van Benthem, B. H., Prins, M., Larsen, C., Delmas, M. C., Brunet, J. B. and van den Hoek, A. (2000b). "Sexually transmitted infections in European HIV-infected women: incidence in relation to time from infection. European Study on the Natural History of HIV Infection in Women." AIDS **14**(5): 595-603.

van Sighem, A. I., Gras, L. A., Reiss, P., Brinkman, K. and de Wolf, F. (2010). "Life expectancy of recently diagnosed asymptomatic HIV-infected patients approaches that of uninfected individuals." AIDS **24**(10): 1527-1535.

Vaz, M. J., Barros, S. M., Palacios, R., Senise, J. F., Lunardi, L., Amed, A. M. and Castelo, A. (2007). "HIV-infected pregnant women have greater adherence with antiretroviral drugs than non-pregnant women." International Journal of STD & AIDS **18**: 28-32.

Vella, S., Schwartlander, B., Sow, S. P., Eholie, S. P. and Murphy, R. L. (2012). "The history of antiretroviral therapy and of its implementation in resource-limited areas of the world." AIDS **26**(10): 1231-1241.

Verteramo, R., Pierangeli, A., Mancini, E., Calzolari, E., Bucci, M., Osborn, J., Nicosia, R., Chiarini, F., Antonelli, G. and Degener, A. M. (2009). "Human Papillomaviruses and genital co-infections in gynaecological outpatients." BMC.Infect.Dis. **9**: 16.

Viyevskyy, A. M., Zhdanova, M. P., Sidyak, S. V., Beznogykh, V. S., Hryshchenko, A. I., Kryvenok, K. I., Lepekha, K. O., Matveeva-Kukurudz, K. O., Taran, S. P. and Turchenko, L. V. (2010). National Report on Drug Situation (2009 data) for the European Monitoring Centre for Drugs and Drug Addiction. Ukraine. Trends and In-depth Information on Selected Issues. Kiev, Ukrainian Medical and Monitoring Centre for Alcohol and Drugs of the Ministry of Health of Ukraine.

Vo, T. T., Ledergerber, B., Keiser, O., Hirschel, B., Furrer, H., Battegay, M., Cavassini, M., Bernasconi, E., Vernazza, P. and Weber, R. (2008). "Durability and outcome of initial antiretroviral treatments received during 2000--2005 by patients in the Swiss HIV Cohort Study." J Infect Dis **197**(12): 1685-1694.

von Linstow, M. L., Rosenfeldt, V., Lebech, A. M., Storgaard, M., Hornstrup, T., Katzenstein, T. L., Pedersen, G., Herlin, T., Valerius, N. H. and Weis, N. (2010). "Prevention of mother-to-child transmission of HIV in Denmark, 1994-2008." HIV Medicine: 1-9.

Wagner, G. and Miller, L. G. (2004). "Is the Influence of Social Desirability on Patients' Self-reported Adherence Overrated?" J Acquir Immune Defic Syndr. **35**(2): 203-204.

Wai, C. T., Greenson, J. K., Fontana, R. J., Kalbfleisch, J. D., Marrero, J. A., Conjeevaram, H. S. and Lok, A. S. (2003). "A simple noninvasive index can predict both significant fibrosis and cirrhosis in patients with chronic hepatitis C." Hepatology **38**(2): 518-526.

Wainberg, M. A. and Friedland, G. (1998). "Public Health Implications of Antiretroviral Therapy and HIV Drug Resistance." JAMA **279**(24): 1977-1983.

Waldrop-Valverde, D., Jones, D. L., Gould, F., Kumar, M. and Ownby, R. L. (2010). "Neurocognition, health-related reading literacy, and numeracy in medication management for HIV infection." AIDS Patient Care STDS **24**(8): 477-484.

Walmsley, S., Bernstein, B., King, M., Arribas, J., Beall, G., Ruane, P., Johnson, M., Johnson, D., Lalonde, R., Japour, A., Brun, S. and Sun, E. (2002). "Lopinavir-ritonavir versus nelfinavir for the initial treatment of HIV infection." The New England journal of medicine **346**(26): 2039-2046.

Walsh, J. C., Pozniak, A. L., Nelson, M. R., Mandalia, S. and Gazzard, B. G. (2002). "Virologic Rebound on HAART in the Context of Low Treatment Adherence Is Associated With a Low Prevalence of Antiretroviral Drug Resistance." J Acquir Immune Defic Syndr. **30**: 278-287.

Ward, H. and Ronn, M. (2010). "Contribution of sexually transmitted infections to the sexual transmission of HIV." Curr Opin HIV AIDS **5**(4): 305-310.

Warszawski, J., Tubiana, R., Le Chenadec, J., Blanche, S., Teglas, J. P., Dollfus, C., Faye, A., Burgard, M., Rouzioux, C., Mandelbrot, L. and Cohort, A. F. P. (2008). "Mother-to-child HIV transmission despite antiretroviral therapy in the ANRS French Perinatal Cohort." AIDS **22**(2): 289-299.

Watts, D. H., Fazzari, M., Minkoff, H., Hillier, S. L., Sha, B., Glesby, M., Levine, A. M., Burk, R., Palefsky, J. M., Moxley, M., Ahdieh-Grant, L. and Strickler, H. D. (2005). "Effects of bacterial vaginosis and other genital infections on the natural history of human papillomavirus infection in HIV-1-infected and high-risk HIV-1-uninfected women." J.Infect.Dis. **191**(7): 1129-1139.

Weber, R., Huber, M., Rickenbach, M., Furrer, H., Elzi, L., Hirschel, B., Cavassini, M., Bernasconi, E., Schmid, P. and Ledergerber, B. (2009). "Uptake of and virological response to antiretroviral therapy among HIV-infected former and current injecting drug users and persons in an opiate substitution treatment programme: the Swiss HIV Cohort Study." HIV Med **10**(7): 407-416.

Weber, R., Sabin, C. A., Friis-Moller, N., Reiss, P., El-Sadr, W. M., Kirk, O., Dabis, F., Law, M. G., Pradier, C., De Wit, S., Akerlund, B., Calvo, G., Monforte, A., Rickenbach, M., Ledergerber, B., Phillips, A. N. and Lundgren, J. D. (2006). "Liver-related deaths in persons infected with the human immunodeficiency virus: the D:A:D study." Archives of internal medicine **166**(15): 1632-1641.

Weinberg, A., Harwood, J. E. F., McFarland, E. J., Pappas, J., Davies, J., Kinzie, K., Barr, E., Paul, S., Salbenblatt, C., Soda, E., Vazquez, A., Peloquin, C. A. and Levin, M. J. (2009). "Kinetics and Determining Factors of the Virologic Response to Antiretrovirals during Pregnancy." Infectious Diseases in Obstetrics and Gynecology **2009**(621780).

Whitmore, S. K., Patel-Larson, A., Espinoza, L., Ruffo, N. M. and Rao, S. (2010). "Missed opportunities to prevent perinatal human immunodeficiency virus transmission in 15 jurisdictions in the United States during 2005-2008." Women Health **50**(5): 414-425.

WHO (2003a). Adherence to long-term therapies: Evidence for action. Geneva, Switzerland, World Health Organisation.

WHO (2003b). Strategic approaches to the prevention of HIV infection in infants: report of a WHO meeting, Morges, Switzerland, 20-22 March 2002.

WHO (2005). Summary country profile for HIV/AIDS scale-up, available at http://www.who.int/hiv/HIVCP_UKR.pdf, Accessed November 2012.

WHO (2006). WHO case definitions of HIV for surveillance and revised clinical staging and immunological classification of HIV-related disease in adults and children. Geneva, Switzerland, World Health Organisation.

WHO (2009a). Guidelines for the Psychosocially Assisted Pharmacological Treatment of Opioid Dependence. Geneva, Switzerland.

WHO (2009b). Towards universal access: scaling up priority HIV/AIDS interventions in the health sector. Progress report September 2009. Available http://www.who.int/hiv/pub/tuapr_2009_en.pdf, accessed November 2012. Geneva, Switzerland.

WHO (2010a). Antiretroviral drugs for treating pregnant women and preventing HIV infection in their infants: Recommendations for a public health approach. 2010 version. Geneva, Switzerland, World Health Organisation.

WHO (2010b). Antiretroviral therapy for HIV infection in adults and adolescents: recommendations for a public health approach. 2010 revision. Geneva.

WHO (2010c). Delivering HIV test results and messages for re-testing and counselling in adults, http://whqlibdoc.who.int/publications/2010/9789241599115_eng.pdf Accessed November 2012. Geneva, Switzerland.

WHO. (2012a). "Global Price Reporting Mechanism for HIV, tuberculosis and malaria." Retrieved 30 August, 2012, from http://apps.who.int/hiv/amds/price/hdd/Default2.aspx.

WHO (2012b). Programmatic update: Use of antiretroviral drugs for treating pregnant women and preventing HIV infection in infants.

WHO (2012c). The strategic use of antiretrovirals to help end the HIV epidemic. Geneva, Switzerland.

WHO (2012d). Technical update on treatment optimization - use of efavirenz during pregnancy: a public health perspective. Geneva, Switzerland.

WHO and UNAIDS (2007). Guidance on provider-initiated HIV testing and counselling in health facilities, http://whqlibdoc.who.int/publications/2007/9789241595568_eng.pdf Accessed November 2012. Geneva, Switzerland.

WHO and UNAIDS (2011a). The treatment 2.0 framework for action: catalysing the next phase of treatment, care and support. Geneva, Switzerland.

WHO, UNAIDS and UNICEF (2011b). Global HIV/AIDS response. Epidemic update and health sector progress towards Universal Access. Progress report 2011.

WHO, UNODC and UNAIDS (2009). Technical guide for countries to set targets for universal access to HIV prevention, treatment and care. Geneva, Switzerland.

WHO, UNODC and UNAIDS (2012). Technical guide for countries to set targets for universal access to HIV prevention, treatment and care for injecting drug users, 2012 revision. Geneva, Switzerland, WHO.

WHO Global Health Observatory. (2012). "HIV/AIDS global situation and trends, http://www.who.int/gho/hiv/en/index.html, Accessed November 2012." 2012.

WHO ICO Information Centre on HPV Cervical Cancer (2010). Human Papillomavirus and Related Cancers in Ukraine. Summary Report 2010. Barcelona, Spain, WHO/ICO Information Centre on HPV and Cervical Cancer (HPV Information Centre). **3rd Edition**.

WHO Regional Office for Europe (2010). Centralised Information Service for Infectious Disease, http://data.euro.who.int/cisid, Accessed October 2011.

WHO Regional Office for Europe (2011). European Action Plan for HIV/AIDS 2012-2015. Copenhagen, Denmark.

Whooley, M. A., Avins, A. L., Miranda, J. and Browner, W. S. (1997). "Case-Finding Instruments for Depression: Two Questions Are as Good as Many." JGIM **12**: 439-445.

Wiessing, L. and Nardone, A. (2006). "Ongoing HIV and viral hepatitis infections in IDUs across the EU, 2001-2005." Euro Surveill **11**(11): E061123 061122.

Williams, I., Churchill, D., Anderson, J., Boffito, M., Bower, M., Cairns, G., Cwynarski, K., Edwards, S., Fidler, S., Fisher, M., Freedman, A., Geretti, A. M., Gilleece, Y., Horne, R., Johnson, M., Khoo, S., Leen, C., Marshall, N., Nelson, M., Orkin, C., Paton, N., Phillips, A., Post, F., Pozniak, A., Sabin, C., Trevelion, R., Ustianowski, A., Walsh, J., Waters, L., Wilkins, E., Winston, A. and Youle, M. (2012). "British HIV Association guidelines for the treatment of HIV-1-positive adults with antiretroviral therapy 2012." HIV medicine **13 Suppl 2**: 1-85.

Willig, J. H., Abroms, S., Westfall, A. O., Routman, J., Adusumilli, S., Varshney, M., Allison, J., Chatham, A., Raper, J. L., Kaslow, R. A., Saag, M. S. and Mugavero, M. J. (2008). "Increased regimen durability in the era of once-daily fixed-dose combination antiretroviral therapy." AIDS **22**(15): 1951-1960.

Wolfe, D. (2007). "Paradoxes in antiretroviral treatment for injecting drug users: Access, adherence and structural barriers in Asia and the former Soviet Union." International Journal of Drug Policy **18**: 246-254.

Wolfe, D., Carrieri, M. P. and Shepard, D. (2010). "Treatment and care for injecting drug users with HIV infection: a review of barriers and ways forward." Lancet **376**(9738): 355-366.

Wood, E., Hogg, R. S., Yip, B., Harrigan, P. R., O'Shaughnessy, M. V. and Montaner, J. S. G. (2004). "The Impact of Adherence on CD4 Cell Count Responses Among HIV-Infected Patients." J Acquir Immune Defic Syndr Hum Retrovirol **35**(3): 261-268.

Wood, E., Hogg, R. S., Yip, B., Moore, D., Harrigan, P. R. and Montaner, J. S. (2007). "Superior virological response to boosted protease inhibitor-based highly active antiretroviral therapy in an observational treatment programme." HIV medicine **8**(2): 80-85.

Wood, E., Montaner, J. S., Chan, K., Tyndall, M. W., Schechter, M. T., Bangsberg, D., O'Shaughnessy, M. V. and Hogg, R. S. (2002). "Socioeconomic status, access to triple therapy, and survival from HIV-disease since 1996." AIDS **16**(15): 2065-2072.

Wright, T. C., Jr., Massad, L. S., Dunton, C. J., Spitzer, M., Wilkinson, E. J. and Solomon, D. (2007). "2006 consensus guidelines for the management of women with cervical intraepithelial neoplasia or adenocarcinoma in situ." Am.J.Obstet.Gynecol. **197**(4): 340-345.

Appendices

Appendix A: ECS and Women's Study Collaborators

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Appendix B: ECS data collection forms

ECS3
INTENSIVE PROSPECTIVE STUDY OF CHILDREN BORN TO HIV POSITIVE MOTHERS

MATERNAL INFORMATION AT DELIVERY

Centre
Mothers Study Number
Child Study Number

Mother's date of birth (day, month, year)
Country of birth .....

Marital Status

Single (1), Married (2), Divorced, Separated, Widowed (3), Cohabiting (4)

Ethnic Group

Asian (1), White (2), Black (3), Oriental (4), Other (5)
Age when leaving full-time education, years .....

Obstetric History

Number of previous livebirths .....
Number of previous stillbirths .....
Number of previous miscarriages .....
Number of previous terminations .....

Mothers Risk Group

History of intravenous Drug Abuse (Y/N)
Trimester of last use: pre-conception (0), 1st (1), 2nd (2), 3rd (3), unknown (9)
Needle sharing? never (1) past (2) present (3) unknown (9)
Sexual partner of Bisexual (Y/N)
Sexual partner of Haemophiliac (Y/N)
Sexual partner of Intravenous Drug Abuser (Y/N)
Sexual partner of Other high risk group (Y/N)
(Specify) .....
Other .....

Mothers HIV History

Date of first HIV+ test (day, month, year)

Current clinical status

Current HIV staging (CDC) .....
Specify symptoms .....
Date of onset .....

Details of treatment during pregnancy

Has the woman received any antiretroviral therapy at any time during this pregnancy? Y/N
Please give details of both ART and other prophylaxis (eg. TMP-SMX)

Drug	Date started	Date stopped	Currently taken? (yes/no)

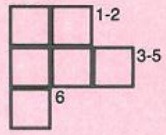
ECS 3
PROSPECTIVE STUDY OF CHILDREN BORN TO HIV POSITIVE MOTHERS

Page 2

MATERNAL INFORMATION

Laboratory investigations during pregnancy and at delivery:

Centre Number
Mothers Study Number
Child Study Number



Virology

	Date:	Date:	Date:
HIV-DNA PCR	Pos / Neg	Pos / Neg	Pos / Neg

HIV-RNA PCR	copies/ml	copies/ml	copies/ml
Sample type	Plasma / Serum	Plasma / Serum	Plasma / Serum
Assay used			

Other laboratory investigations

	Date:	Date:	Date:
Total lymphocytes			
CD4 (10^9/litre)			
CD8 (10^9/litre)			
IgG (gm/litre)			
IgA (gm/litre)			
IgM (gm/litre)			
p24 Ag			
HIV Elisa			

ECS3
INTENSIVE PROSPECTIVE STUDY OF CHILDREN BORN TO HIV POSITIVE MOTHERS

PERINATAL INFORMATION

Centre
Mothers Study Number
Child Study Number
Child's date of birth (day, month, year)
Sex (M, F)
Gestational age (weeks)
Birthweight (gm)
OFC (cm

Hospital where delivery took place .....
Obstetrician (initals) .....
Antiretroviral therapy during labour/delivery Y/N
If yes, which drug? .....Orally / IV?
Delivery
Caesarean Section: Elective (1), Emergency (2)
If Caesarean Section, reason .....
Vaginal: Spontaneous (3), vacuum (4), forceps (5)
Presentation: breech (Y/N)
Duration of labour 1st stage (if known).....
Duration of labour 2nd stage (if known) .....
Time from rupture of membranes to delivery (if known).....
Scalp Electrodes (Y/N)
Episiotomy or vulvovaginal tear (Y/N)
Perinatal Problems (Y/N). Specify Details:
Hepatomegaly .....
Splenomegaly .....
Drug Withdrawal Symptoms .....
Thrombocytopenic Purpura .....
Infection: suspected (1) confirmed (2) .....
Transfusion ..... *
Congenital Abnormalities ..... *
Other .....
Disposition
with parents (1) fostered (2) adopted (3)
remained in hospital (4) other (5) ..... *
if remained in hospital, say why: .....
Feeding: breast (1) bottle (2) breast and bottle (3)
was breast feeding tried and abandoned? Y/N
Died? Y/N
Date of death: (day/month/year)
Postmortem results, if available ..... *
.....

Take sample required; Please record laboratory results on yellow form

9 2

Appendix C: Women's Study data collection forms

Centre: _____ Study no:_____

Baseline Questionnaire

This questionnaire is for completion by the woman's doctor within 3-6 months of delivery. If the woman hasn't been enrolled in the European Collaborative Study (ECS) during pregnancy, then please complete the ECS "Maternal information at delivery" form as well.

Centre: Odessa AIDS Centre ☐ Simferopol AIDS Centre ☐

Kiev AIDS Centre ☐ Donetsk AIDS Centre ☐

Date form completed (DD/MM/YY): _____ - _____ - _____

Clinician completing questionnaire:_____

Study Number: _____

Study number will be the ECS mother's study number for those women already enrolled in the ECS. For women not enrolled in the ECS please provide a new number, starting with 9001,then 9002, 9003 etc. (to distinguish these women from those in the ECS)

Woman's birth date (DD/MM/YY): _____ - _____ - _____

Current clinical status

Weight (kg): ___ ___ • ___ ___ Height (cm): ___ ___ ___

Wrist circumference (cm):

Systolic and diastolic blood pressure (mm/Hg): ___ ___ ___ / ___ ___ ___

Body temperature:

Laboratory values	Date of measurement	Value
Haemoglobin (gm/dl)	_____ - _____ - _____	___ ___ • ___
Platelet count (10^9/litre)	_____ - _____ - _____	___ ___ _____
Neutrophil count (10^9/litre)	_____ - _____ - _____	___ ___ • ___
Total lymphocytes (10^9/litre)	_____ - _____ - _____	___• ___ _____
CD4 count (cells/mm^3)	_____ - _____ - _____	___ ___ _____
CD8 count (10^9/litre)	_____ - _____ - _____	___• ___ _____
HIV RNA viral load	_____ - _____ - _____	_____

HIV RNA assay used: _____

Below level of detection? Yes ☐ No ☐

Ukrainian Cohort Study of HIV-infected childbearing women
Clinician baseline questionnaire **Centre: _____ Study no:_____**

Current WHO Clinical Stage I ☐ II ☐ III ☐ IV ☐

Which of the following symptoms has the woman had? Please tick all that apply, provide the diagnostic method (presumptive or definitive) and the date of onset.

Condition	**Tick if yes**	**Diagnostic method: "P" if presumptive "D" if definitive**	**Date of onset DD-MM-YY**
Persistent generalized lymphadenopathy			
Moderate and unexplained weight loss (<10% of body weight)			
Recurrent respiratory tract infections			
Herpes zoster			
Recurrent oral ulcerations			
Papular pruritic eruptions			
Angular cheilitis			
Seborrhoeic dermatitis			
Fungal finger nail infections			
Unexplained chronic diarrhoea for >1 month			
Unexplained persistent fever, intermittent or constant for > 1 month			
Severe weight loss (>10% body weight)			
Oral candidiasis			
Oral hairy leukoplakia			
Pulmonary TB diagnosed in last 2 years			
Acute necrotizing ulcerative stomatitis, gingivitis or periodontitis			
Severe presumed bacterial infections e.g. pneumonia, empyema, meningitis, bacteraemia, bone or joint infection			
Unexplained anaemia (< 80 g/l) and/or neutropenia (<500/µl) and/or thrombocytopenia (<50 000/ µl) for >1 month			
HIV wasting syndrome			
Pneumocystis pneumonia			
Recurrent severe or radiological bacterial pneumonia			
Chronic herpes simplex infection (orolabial, genital or anorectal of > 1 month's duration)			
Oesophageal candidiasis			
Extrapulmonary Tuberculosis			
Kaposi's sarcoma			
Central nervous system toxoplasmosis			
HIV encephalopathy			

Extrapulmonary cryptococcosis including meningitis			
Disseminated non-tuberculous mycobacteria infection			
Progressive multifocal leukoencephalopathy			
Candida of trachea, bronchi or lungs			
Cryptosporidiosis			
Visceral herpes simplex infection			
Cytomegalovirus infection (retinitis or of an organ other than liver, spleen or lymph nodes)			
Any disseminated mycosis e.g. histoplasmosis, coccidiomycosis, penicilliosis			
Recurrent non-typhoidal salmonella septicaemia			
Lymphoma (cerebral or B cell non-Hodgkin)			
Invasive cervical carcinoma			
Visceral leishmaniasis			

Coinfections

HCV antibody positive? Yes ☐ No ☐ Unknown ☐

If yes: Date of first positive HCV antibody test: _____ - _____ - _____

HCV RNA _____ Unit: _____ Date: _____ - _____ - _____

ALT(UI/L) _____ Date: _____ - _____ - _____

HCV genotype _____

Has she ever received any HCV treatment? Yes ☐ No ☐

If yes, please provide details of the type and dates of treatment:

_____

_____

HBV surface antigen positive? Yes ☐ No ☐ Unknown ☐

If yes: Date of first positive test: ____ - _____ - _____

Has she ever received any HBV treatment? Yes ☐ No ☐

If yes, please provide details of the type(s) and dates of treatment:

_____

_____

Has the woman ever received an HBV vaccination? Yes ☐ No ☐ Unknown ☐

Ukrainian Cohort Study of HIV-infected childbearing women
Clinician baseline questionnaire

Centre: _____ Study no:_____

Sexually transmitted and vaginal infections?

Were any of the following infections diagnosed during her most recent pregnancy or postnatally?

	Not done	No	Yes	Test date	Test details (please specify)	
Syphilis	☐	☐	☐	____ - ____ - ____	Non-treponemal test	☐
					Specific treponema test	☐
Chlamydia	☐	☐	☐	____ - ____ - ____	Urine sample	☐
					Endocervical swab	☐
HSV	☐	☐	☐	____ - ____ - ____	Clinical diagnosis	☐
					HSV antibodies	☐
N.gonorrhea	☐	☐	☐	____ - ____ - ____	Urine sample	☐
					Endocervical swab	☐
					Vaginal swab	☐
T.vaginalis	☐	☐	☐	____ - ____ - ____	Clinical diagnosis	☐
					Microscopic examination	☐
					Culture	☐
					Other test	☐
Bacterial vaginosis	☐	☐	☐	____ - ____ - ____	Clinical diagnosis	☐
					Gram stain microscopy	☐
Vulvo-vaginal	☐	☐	☐	____ - ____ - ____	Clinical diagnosis	☐
candidiasis					Gram stain microscopy	☐
					Culture	☐
					Other _____	☐

Most recent smear test Date of specimen: _____ - _____ - _____

Result	Normal		☐		
	Low grade SIL (squamous intraepithelial lesion) (CIN I)		☐		
	High grade SIL (CIN II-III, CIS)		☐		
	Biopsy carried out?	No	☐	Yes	☐
	Was squamous cell carcinoma diagnosed?	No	☐	Yes	☐

Ukrainian Cohort Study of HIV-infected childbearing women
Clinician baseline questionnaire **Centre: _____ Study no:_____**

HIV treatment and prophylaxis

Did the woman receive any antiretroviral prophylaxis for PMTCT other than sdNVP (ie zidovudine)?

No ☐ Yes ☐ If yes, when did she stop taking this prophylaxis? _____ - _____ - _____

Excluding antiretroviral prophylaxis for PMTCT, has the woman ever received any antiretroviral treatment?

If yes, please give details:

Drug name	Date started	Date stopped	Currently Taken? (√)
_____	____ - ____ - ____	____ - ____ - ____	☐
_____	____ - ____ - ____	____ - ____ - ____	☐
_____	____ - ____ - ____	____ - ____ - ____	☐
_____	____ - ____ - ____	____ - ____ - ____	☐
_____	____ - ____ - ____	____ - ____ - ____	☐

Has she had any **minor** side effects of this treatment (eg diarrhea, nausea, vomiting, headache, dizziness, mild skin rash, insomnia etc)? Yes ☐ No ☐

Has she had any of the following **major** side effects? (please √ if any apply)

- Hepatic steatosis ☐
- Pancreatitis ☐
- Lactic acidosis ☐
- Stevens-Johnson syndrome ☐
- Hepatotoxicy ☐
- Nephrolithiasis ☐
- Nephrotoxicity ☐
- Severe skin rash ☐

Other (please specify) _____

Is the patient experiencing loss of fat from her arms, legs, buttocks or face? Yes ☐ No ☐

Is she experiencing fat accumulation around her abdomen, on her back or in her breasts? Yes ☐ No ☐

Ukrainian Cohort Study of HIV-infected childbearing women
Clinician baseline questionnaire

Centre: _____ Study no:_____

If any of the following test results are available, please provide them below:

Test	**Value**	**Units (eg IU/l, mg/dl)**	**Date of test** DD-MM-YY
ALT			
AST			
Fasting serum total cholesterol			
Fasting serum LDL cholesterol			
Fasting serum HDL cholesterol			
Fasting serum triglycerides			
Fasting plasma glucose			
Other _____			

Is the woman currently receiving any prophylaxis?

Cotrimoxazole Yes ☐ No ☐ Date started: _____ - _____ - _____

INH prophylaxis Yes ☐ No ☐ Date started: _____ - _____ - _____

Is she receiving any other prescribed drugs (e.g. for treatment for TB)? If so, please specify:

_____ Date started: _____ - _____ - _____

_____ Date started: _____ - _____ - _____

Thank you for completing this questionnaire
Please return to the completed questionnaire to .....

Centre: _____ **Study no:**_____

Woman's Baseline Questionnaire

This questionnaire is for completion within 3-6 months of delivery

Centre:	Odessa AIDS Centre	☐	Simferopol AIDS Centre	☐
	Kiev AIDS Centre	☐	Donetsk AIDS Centre	☐

Study Number: _____

Study number will be the ECS mother's study number for those women already enrolled in the ECS. For women not enrolled in the ECS please provide a new number, starting with 9001,then 9002, 9003 etc. (to distinguish these women from those in the ECS)

Today's date: (DD/MM/YY): _____ - _____ - _____ **Your birth date** (DD/MM/YY): _____ - _____ - _____

Information on your most recent pregnancy

Did you receive antenatal care during your most recent pregnancy? Yes ☐ No ☐

Was the pregnancy planned? Yes ☐ No ☐

Do you live with your baby currently? Yes ☐ No ☐

How often did you use condoms during this pregnancy?

- Never used a condom ☐
- Used a condom some of the time ☐
- Used a condom most of the time ☐
- Used a condom all of the time ☐

Living situation

What is your current marital status?

Married ☐ Cohabiting ☐ Divorced ☐ Single ☐ Widowed ☐

Is your husband / partner / boyfriend also HIV infected?

Yes ☐ No ☐ Don't know ☐ I don't have a husband/partner/boyfriend ☐

Who do you currently live with (excluding your children)? (please tick all that apply)

- Husband / partner / boyfriend ☐
- Extended family (eg your parents, aunt, grandparents) ☐
- On my own ☐
- Other _____

How many of your own children do you live with at the moment? _____

Where are you living now?

- In a rented house or apartment ☐
- In a house or apartment that you or your partner/family own ☐
- In a shelter ☐
- Homeless or living on the street ☐
- In some other situation (please specify) _____

How long have you lived there? _____ years _____ months

Have you ever been to prison? Yes ☐ No ☐

If yes, when was the last time you were in prison? (please give year) _____

Which of the following people have you told that you are HIV-infected? (please tick all that apply)

- Husband / current partner / current boyfriend ☐
- Your mother and/or father ☐
- Other close family member (eg sister, brother, aunt) ☐
- Friend(s) ☐

Current behaviours

Alcohol, smoking and drug use

Have you ever smoked cigarettes? Yes ☐ No ☐

Do you currently smoke? Yes ☐ No ☐

If yes, approximately how many cigarettes per day? _____

Does you currently drink alcohol? Yes ☐ No ☐

If yes, approximately how many units per week? _____
(One unit = a small glass of wine, a small measure of spirits or a small bottle of beer)

How many days in a week do you drink alcohol? _____

Have you ever used any non-prescribed (illicit) drugs (eg heroin, shirka, cocaine, hashish/cannabis etc)?

- Yes – currently using ☐ **please complete the section at the end of the questionnaire**
- Yes – in the past ☐ **please complete the section at the end of the questionnaire**
- No ☐

Contraception

Did you receive any contraception counselling after you had your most recent baby? (for example, did anyone talk to you about the possible options available) No ☐ Yes ☐

If yes: who provided this counselling?
- Doctor ☐
- Nurse ☐
- Peer counsellor ☐
- Other (please specify) _____

Where did you receive contraceptive counselling? Maternity ☐ AIDS Center ☐ Women's clinic ☐

Can you afford to buy contraceptives? No ☐ Yes ☐

Are contraceptives available and accessible to you? No ☐ Yes ☐

Are you currently sexually active? No ☐ Yes ☐

What contraception are you using currently?
- Oral contraceptive pill ☐
- Condoms ☐
- Intra-uterine device ☐
- Injectable contraceptive ☐
- Sterilized ☐
- None ☐
- Other _____

HIV treatment

Are you currently receiving antiretroviral therapy? No ☐ Yes ☐

If yes, have you had any side effects of this treatment (eg diarrhea, nausea, vomiting, headache, dizziness, mild skin rash, insomnia etc)? Yes ☐ No ☐

If you have been receiving antiretrovirals for at least the past four weeks please complete these next two questions on **adherence**:

How often have you missed a dose in the last four weeks? (tick one only)

Daily	☐	More than once a week	☐
Once every two weeks	☐	Once a month	☐

Never ☐

Have you had a period lasting more than 24 hours where you didn't take any of your antiretroviral drugs during the last four weeks? Yes ☐ No ☐

HIV psycho-social services

Do you currently using any of the following services? (please tick all that apply)

Support group ☐

Peer counselors ☐

Social services ☐

Treatment adherence programme ☐

Other _____

Please complete the following section if you have used illicit drugs in the past or are using them currently:

Please answer the question below about your past and current drug use. Tick the boxes if you are currently or have ever used any of the drugs in the list.

	Currently use	Used in the past	If past use, please specify the year that you last used it (eg 2001)
Heroin	☐	☐	_____
Home made opiates	☐	☐	_____
Cocaine	☐	☐	_____
Hashish/cannabis	☐	☐	_____
Other (specify) _____		_____	_____

Have you ever injected drugs? Yes ☐ No ☐

Does your current boyfriend / husband / partner inject drugs? Yes ☐ No ☐ Not applicable ☐

Do you use injecting drugs at the moment ? Yes ☐ No ☐

If yes:

How many times in the past four weeks have you used a syringe or needle after another person without cleaning it? _____

With how many different people have you shared a syringe or needle in the past four weeks? _____

How old were you when you first: used any illicit drug _____ years

injected drugs _____ years Not applicable ☐

Are you in contact with any harm reduction programme or organisation? (eg needle exchange, support group etc)

Yes ☐ No ☐

Are you participating in substitution treatment program (methadone, buprenorfin)?

Yes ☐ No ☐

Thank you for completing this questionnaire
Please return to the completed questionnaire to your doctor.

Appendix D: Adherence Study data collection forms

For clinician to complete

Maternity hospital name_____ **Study number**_____

Today's Date: ___/___/2011 **Your date of birth:** ____/____/_____

Date that your baby was born: ___/____/___ **Is your baby…** a boy? ☐ a girl? ☐

1. Are you..

Single ☐ Married ☐ Divorced, separated or widowed ☐ Cohabiting ☐

2. Was this pregnancy planned?

Yes ☐ No ☐

3. Who do you currently live with (excluding your children)? (Tick all that apply)

Husband / partner / boyfriend ☐

Extended family (e.g. your parents, aunt, grandparents) ☐

On my own ☐

4. Which of the following people have you told that you are HIV-infected? (Tick all that apply)

Husband / current partner / boyfriend ☐

Mother and/or father ☐

Other close family member (e.g. sister, brother, aunt) ☐

Friend(s) ☐

Other HIV positive people ☐

I haven't told anyone ☐

5. Do you currently smoke?

Yes ☐ No ☐

If yes, how many cigarettes do you smoke a day? _____

6. Did you use alcohol during your pregnancy?

Yes ☐ No ☐

If yes, in average how many days during a week you have used alcohol? _____

7. Have you ever used marijuana (hashish)?

Yes – currently using ☐

Yes – in the past ☐

No ☐

8. Have you ever used any non-prescribed (illicit) drugs apart from marijuana? (e.g. heroin, shirka, cocaine, stimulants such as vint, jeff, mul'ka, hypnotics or benzodiazepines etc.)

Yes – currently using ☐

Yes – in the past ☐

No ☐

If yes:

➔ Are you currently in contact with any harm reduction programme or organisation?

Yes ☐ No ☐

➔ Are you participating in a substitution treatment programme (methadone, buprenorphine)?

Yes ☐ No ☐

9. How sure do you feel that taking HIV medications during pregnancy can help prevent HIV from being passed on to the baby?

Completely sure ☐ Fairly sure ☐ Not sure at all ☐

10. Were you worried that taking HIV medication during pregnancy might harm your baby?

Yes I was worried ☐ A little ☐ No I wasn't worried ☐

Many people find it difficult to take HIV medication exactly as prescribed. We would like to find out how you took your medication during pregnancy and about any problems that you had, so that we can find ways of helping people to take their medicines in the future.

11. Do you know the name(s) of the HIV medication you have been taking? If so, please write below

_____

How many pills do you take a day? _____ pills

12. During your pregnancy, how often did you have difficulty taking your HIV medications on time? (no more than two hours before or after the time your doctor told you to take it)

Never ☐ Most of the time ☐

Rarely ☐ All of the time ☐

13. On average, how many days per week when taking ARVs during pregnancy would you say that you missed at least one dose of your HIV medications?

Everyday ☐ Once a week ☐

4-6 days/week ☐ Less than once a week ☐

2-3 days/week ☐ Never ☐

14. When was the last time before the birth of your baby that you missed at least one dose of your HIV medications?

In the week before birth	☐	Between 1 and 3 months before birth	☐
1-2 weeks before birth	☐	More than 3 months before birth	☐
3-4 weeks before birth	☐	Never	☐

15. How bothered were you by side effects to your medication (e.g. nausea, vomiting, diarrhoea, headache) during pregnancy?

Not at all bothered	☐	Somewhat bothered	☐
Slightly bothered	☐	Terribly bothered	☐

16. Do you currently use any of the following services?

Support group	☐	Social services	☐
Peer counsellors	☐	Treatment adherence programme	☐
Other_____	☐		

17. Below is a list of common reasons why people miss doses of their HIV medications. If you missed any doses of medication during your pregnancy, please read the list and tick any reasons that were true for you. If you didn't miss any doses, move on to question 18.

	I missed a dose of HIV medication because…	Tick all that apply
1	I was away from home	
2	I was busy with other things	
3	I simply forgot	
4	I had too many pills to take	
5	I wanted to avoid side effects	
6	I did not want others to notice me taking medication	
7	I had a change in my daily routine	
8	I felt that the drug was toxic / harmful (to me or my baby)	
9	I fell asleep / slept through dose	
10	I felt sick or ill (including "morning sickness")	
11	I felt depressed or overwhelmed	
12	I ran out of pills	
13	I couldn't find my pills	
14	I felt good	

18. During the last month of your pregnancy, were you often bothered by feeling down, depressed or hopeless?

Yes ☐ No ☐

19. During the last month of your pregnancy, were you often bothered by little interest or pleasure in doing things?

Yes ☐ No ☐

20. If you answered "Yes" to question 18 OR question 19, is this something you feel you need or want help with?

Yes ☐ Yes, but not today ☐ No ☐

21. Do you have someone you feel you can rely on to help you care for your baby?

Yes ☐ No ☐

22. In the <u>4 weeks before birth</u>, how confident did you feel that you could..

a. Keep taking your medication even if side effects began to interfere with daily activities?

Confident I could do ☐ Fairly confident I could do ☐ Could not do ☐

b. Keep taking your medication even if you needed to take it in front of people who didn't know you were HIV-infected?

Confident I could do ☐ Fairly confident I could do ☐ Could not do ☐

c. Keep taking your medication when your daily routine was disrupted (e.g. at weekends, staying away from home)?

Confident I could do ☐ Fairly confident I could do ☐ Could not do ☐

d. Keep taking your medication when you weren't feeling well?

Confident I could do ☐ Fairly confident I could do ☐ Could not do ☐

e. Keep attending your appointments at the AIDS centre even if they interfere with your daily activities?

Confident I could do ☐ Fairly confident I could do ☐ Could not do ☐

f. Ask your clinician for more information if you needed to, and tell them about your concerns or worries?

Confident I could do ☐ Fairly confident I could do ☐ Could not do ☐

g. Ask someone for support with taking your medication, if you needed it?

Confident I could do ☐ Fairly confident I could do ☐ Could not do ☐

Thank you very much for taking part in this study.

Please return this questionnaire to your obstetrician or clinician.

For clinician's use only Was a referral made? Yes ☐ No ☐

If yes, please make a note of the reason for the referral and the service the woman was referred to:

For Clinician to complete

AIDS Centre name_____ ECS / study number_____

Today's Date: ___/___/2011 Your date of birth: ____/____/_____

Date that your youngest baby was born: ___/____/20__

Is your baby..a boy? ☐ a girl? ☐

1. Are you..

Single ☐ Married ☐ Divorced, separated or widowed ☐ Cohabiting ☐

2. Did you plan your most recent pregnancy?

Yes ☐ No ☐

3. Who do you currently live with (excluding your children)? (Tick all that apply)

Husband / partner / boyfriend ☐

Extended family (e.g. your parents, aunt, grandparents) ☐

On my own ☐

4. Which of the following people have you told that you are HIV-infected? (Tick all that apply)

Husband / current partner / boyfriend ☐

Mother and/or father ☐

Other close family member (e.g. sister, brother, aunt) ☐

Friend(s) ☐

Other HIV positive people ☐

I haven't told anyone ☐

5. Do you currently smoke?

Yes ☐ No ☐

If yes, how many cigarettes do you smoke a day? _____

6. Do you currently drink alcohol?

Yes ☐ No ☐

If yes, how many days a week on average do you drink alcohol? _____

7. Have you ever used marijuana (hashish)?

Yes – currently using ☐

Yes – in the past ☐

No ☐

8. Have you ever used any non-prescribed (illicit) drugs apart from marijuana? (e.g. heroin, shirka, cocaine, hashish/cannabis, stimulants such as vint, jeff, mul'ka etc.)

Yes – currently using ☐

Yes – in the past ☐

No ☐

If yes:

➔ Are you currently in contact with any harm reduction programme or organisation?

Yes ☐ No ☐

➔ Are you participating in a substitution treatment programme (methadone, buprenorphine)?

Yes ☐ No ☐

Babies born to women with HIV are usually prescribed some HIV medicine in the first week(s) of life. We are interested in your thoughts about this.

9. In your opinion, can HIV medication for your baby help to prevent HIV from being passed to them?

Yes ☐ Not sure / don't know ☐ No ☐

10. Have you been worried (either now or in the past) that giving HIV medication to your baby might harm them?

Yes ☐ A little worried ☐ No ☐

11. Was your baby prescribed HIV medicine after birth?

Yes ☐→ for how long? 1 week ☐ 4 weeks ☐ Not sure ☐ **continue to question 12**

No ☐ **go to question 16**

12. Who gave the HIV medicine to your baby? (tick all that apply)

Me ☐

The baby's father ☐

Family member(s) (including baby's grandparents) ☐

Friend(s) ☐

Other carer(s) (e.g. babysitter, child minder) ☐

Medical staff ☐

Nobody – we didn't give any medicine to the baby ☐

When caring for a newborn baby, it can be difficult to give them all of the doses of HIV medicine. We would like to find out about any problems that you had with this, so that we can find ways of helping new mothers in the future.

13. How often did you have difficulty giving your baby their medicine on time?
(By 'on time' we mean no more than two hours before or two hours after the time your doctor told you to give it.)

Never ☐ Most of the time ☐

Rarely ☐ All of the time ☐

14. On average, how many days per week would you say that your baby missed at least one dose of their HIV medication?

Every day ☐ Less than once a week ☐

More than once a week ☐ Never ☐

15. Below is a list of common reasons why people may find it difficult to give their baby the HIV medicines prescribed by the doctor. If your baby missed any doses of medication, please read the list and tick any reasons that apply. If your baby didn't miss any doses, please go to question 16.

	My baby missed a dose of medication because..	Tick all that apply
1	I was away from home	
2	I was busy with other things	
3	I simply forgot	
4	I was worried that my baby would have side effects	
5	I didn't want others to notice my baby being given medication	
6	I didn't want to ask other people caring for my baby to give him/her the medicine	
7	I didn't have anyone to help	
8	I had a change in daily routine	
9	I felt like the drug was toxic / harmful to my baby	
10	The baby fell asleep / slept through dose	
11	The baby seemed unwell	
12	I felt depressed or overwhelmed	
13	I ran out of medicine to give the baby	
14	I couldn't find the medicine to give the baby	
15	The baby seemed healthy	

16. During the past month, have you often been bothered by feeling down, depressed or hopeless?

Yes ☐ No ☐

17. During the past month, have you often been bothered by little interest or pleasure in doing things?

Yes ☐ No ☐

18. If you answered "Yes" to question 16 OR question 17, is this something you feel you need or want help with?

Yes ☐ Yes, but not today ☐ No ☐

19. Do you currently use any of the following services?

Support group	☐	Social services	☐
Peer counsellors	☐	Treatment adherence programme	☐
Other_____	☐		

20. Do you have someone you feel you can rely on to help you care for your baby?

Yes ☐ No ☐

21. Are you currently taking HIV medication?

Yes ☐ **Continue to question 22.**

No ☐ **Stop here. Thank you very much for taking part in this study**

The following questions are for women who are **currently** taking HIV medication

22. Do you know the names of your HIV medications? If so, please write below

_____

How many pills do you take a day? _____ pills

23. How often do you feel that you have difficulty taking your HIV medications on time? (By 'on time' we mean no more than two hours before or two hours after the time your doctor told you to take it.)

Never	☐	Most of the time	☐
Rarely	☐	All of the time	☐

24. On average, how many days per week would you say that you missed at least one dose of your HIV medications?

Every day	☐	Once a week	☐
4-6 days/week	☐	Less than once a week	☐
2-3 days/week	☐	Never	☐

25. When was the last time you missed at least one dose of your HIV medications?

Within the past week	☐	Between 1 and 3 months ago	☐
1-2 weeks ago	☐	More than 3 months ago	☐
3-4 weeks ago	☐	Never	☐

26. How bothered have you been by side effects (nausea, vomiting, diarrhea, headache etc.) to your HIV medication over the past 4 weeks?

Not at all bothered ☐ Somewhat bothered ☐

Slightly bothered ☐ Terribly bothered ☐

27. Thinking about taking your medicines when you were pregnant and taking them now (since the baby was born), which of the following do you agree with?

I missed fewer doses when I was pregnant than I do now ☐ **Go to Q 28**

I miss fewer doses now than I used to when I was pregnant ☐ **Go to Q 29**

I miss about the same number of doses now as when I was pregnant ☐ **Go to Q 29**

I haven't missed any doses at all ☐ **Go to Q 29**

28. Why do you think you took your medicine better when you were pregnant than you do now? (tick all that apply)

I was worried about the risk of passing on HIV to my baby ☐

I was more concerned about my own health ☐

I was going to the doctor more ☐

I had more encouragement / support from friends and family ☐

I had more time to take care of myself ☐

I was less tired of taking pills ☐

I felt more positive about the benefits of treatment ☐

Other_____☐

29. Below is a list of common reasons why people miss doses of their HIV medication. If you have missed any doses over the last 4 weeks, please read the list and tick any reasons that were true for you. If you didn't miss any doses, please continue to question 30.

		Tick all that apply
1	I was away from home	
2	I was busy with other things	
3	I simply forgot	
4	I had too many pills to take	
5	I wanted to avoid side effects	
6	I did not want others to notice me taking medication	
7	I had a change in daily routine	
8	I felt like the drug was toxic / harmful	
9	I fell asleep / slept through dose	
10	I felt sick or ill	
11	I felt depressed or overwhelmed	
12	I ran out of pills	
13	I couldn't find my pills	
14	I felt good	

30. In the <u>past 4 weeks</u>, how confident have you been that you could..

a. Keep taking your medication even if side effects began to interfere with daily activities?

Confident I could do ☐ Fairly confident I could do ☐ Could not do ☐

b. Keep taking your medication even if you needed to take it in front of people who didn't know you were HIV-infected?

Confident I could do ☐ Fairly confident I could do ☐ Could not do ☐

c. Keep taking your medication when your daily routine was disrupted (e.g. at weekends, staying away from home)?

Confident I could do ☐ Fairly confident I could do ☐ Could not do ☐

d. Keep taking your medication when you weren't feeling well?

Confident I could do ☐ Fairly confident I could do ☐ Could not do ☐

e. Keep attending your appointments at the AIDS centre even if they interfere with your daily activities?

Confident I could do ☐ Fairly confident I could do ☐ Could not do ☐

f. Ask your clinician for more information if you needed to, and tell them about your concerns or worries?

Confident I could do ☐ Fairly confident I could do ☐ Could not do ☐

g. Ask someone for support with taking your medication, if you needed it?

Confident I could do ☐ Fairly confident I could do ☐ Could not do ☐

Thank you very much for taking part in this study.

Please return this questionnaire to your obstetrician or clinician.

For clinician's use only Was a referral made? Yes ☐ No ☐

If yes, please make a note of the reason for the referral and the service the woman was referred to:

Appendix E: Infant deaths and ascertainment of HIV infection status in Ukraine

Infant deaths at <6 months of age in Ukraine ECS by year and HIV status

	2003	2004	2005	2006	2007	2008	2009	2010
Number of deaths at <6 months of age	7	5	3	8	20	11	11	3
HIV status at death								
Infected	2	0	3	0	3	3	1	1
Uninfected	0	2	0	1	2	2	2	0
Indeterminate	5	3	0	7	15	6	8	2
Of indeterminate infants								
Probable HIV-related death	1	1	0	1	8	2	2	0
Probable non HIV-related	3	1	0	2	3	3	3	0
Death indeterminate with relation to HIV infection	1	1	0	4	4	1	3	2
MTCT rate, omitting all indeterminate infants (as in Figure) (95% CI)	**14.6%** (10.7-19.3)	**10.3%** (7.6-13.6)	**4.7%** (2.9-7.1)	**6.2%** (4.4-8.4)	**7.7%** (6.2-9.3)	**4.7%** (3.5-6.1)	**2.1%** (1.3-3.1)	**6.2%** (4.5-8.3)
MTCT with probable HIV-related and non-HIV related deaths assigned as infected and uninfected respectively (95% CI)	**14.8%** (10.9-19.5)	**10.5%** (7.7-13.8)	**4.7%** (2.9-7.1)	**6.3%** (4.5-8.5)	**8.3%** (6.8-9.9)	**4.9%** (3.7-6.3)	**2.3%** (1.5-3.4)	**6.2%** (4.5-8.3)

Where infants died with an indeterminate HIV status, their deaths were categorised as probable HIV-related, probable non HIV-related and indeterminate with relation to HIV infection according to guidelines: *Estimating the rate of mother-to-child transmission of HIV. Report of a workshop on methodological issues Ghent (Belgium), 17-20 February 1992.* Probable HIV-related deaths were those in infants with AIDS or dying from severe infection (pneumonia or septicaemia) beyond 4 weeks of age; probable non-HIV-related deaths were those in infants with no AIDS and dying from non-infectious cause (accident, sudden infant death syndrome, severe asphyxia, respiratory distress syndrome, congenital heart malformation, prematurity, intracranial haemorrhage), deaths indeterminate with relation to HIV status were those in infants dying from severe infection (pneumonia or septicaemia) within the first four 4 weeks of life, and those with no cause of death reported.

Appendix F: Abstracts and publications arising from this research

List of conference abstracts

Bailey H, Townsend CL, Semenenko I, Malyuta R, Cortina-Borja M, Thorne C for the Ukraine European Collaborative Study. Adherence to antiretroviral therapy during pregnancy and the first year postpartum among women in Ukraine. 7th IAS Conference on HIV Pathogenesis, Treatment and Prevention, Kuala Lumpur, Malaysia, 30 June-3 July 2013

Bailey H, Townsend C, Cortina-Borja M and Thorne C for the European Collaborative Study. Trends and factors associated with virological failure among women conceiving on cART in Western Europe. 20th Conference on Retroviruses and Opportunistic Infections, Atlanta, Mar 3-6 2013.

Bailey H, Malyuta R, Semenenko I, Townsend C L, Cortina-Borja M and Thorne C for the European Collaborative Study in Ukraine. Receipt of cART among childbearing women in Ukraine: implications for vertical and horizontal transmission. 4th International Workshop on HIV Paediatrics, Washington DC, July 20-21 2012.

Bailey H, Semenenko I, Malyuta R, Cortina-Borja M, Townsend C, Thorne C. Evaluation of an HIV educational intervention in an antenatal clinic in Odessa, Ukraine. 4th International Workshop on HIV Paediatrics, Washington DC, July 20-21 2012.

Bailey H, Malyuta R, Semenenko I, Townsend C L, Cortina-Borja M and Thorne C for the Ukrainian Cohort Study of HIV-infected Childbearing Women. Factors associated with HCV prevalence among HIV-positive women with no history of injecting drug use in a Ukrainian cohort of childbearing women. 16th International Workshop on HIV Observational Databases, Athens, Mar 29-31 2012.

Bailey H, Malyuta R, Semenenko I, Townsend C and Thorne C for the Ukrainian Cohort Study of HIV-infected Childbearing Women. Cervical smear abnormalities among HIV-infected postnatal women in Ukraine. 6th IAS Conference on HIV Pathogenesis, Treatment and Prevention, Rome, July 17-20 2011.

Bailey H, Semenenko I, Malyuta R, Townsend C and Thorne C for the Ukrainian Cohort Study of HIV-infected Childbearing Women. Chlamydia prevalence and risk factors among HIV-infected childbearing women in Ukraine. 3rd International Workshop on HIV Paediatrics, Rome, July 15-16 2011.

Bailey H, Malyuta R, Semenenko I, Townsend C and Thorne C for the Ukrainian Cohort Study of HIV-infected Childbearing Women. Cervical smear abnormalities among HIV-infected postnatal women in Ukraine. 15th International Workshop on HIV Observational Databases, Prague, Mar 24-26 2011.

Bailey H, Townsend C and Thorne C for the European Collaborative Study. Insufficient antiretroviral therapy in pregnancy: missed opportunities for PMTCT in Europe. XVIII International AIDS Conference, Vienna, July 18-23 2010.

Bailey H, Semenenko I, Malyuta R and Thorne C for the European Collaborative Study in Ukraine. Increasing antenatal HAART use for PMTCT in Ukraine. 2nd International Workshop on HIV Paediatrics, Vienna, July 16-17 2010.

List of publications

Bailey H, Townsend CL, Cortina-Borja M, Thorne C for the European Collaborative Study in EuroCoord. Improvements in virological control among women conceiving on cART in Western Europe. AIDS 2013 (in press).

Bailey H, Townsend C L, Semenenko I, Malyuta R, Cortina-Borja M and Thorne C for the Ukraine European Collaborative Study Group in EuroCoord. Impact of expanded access to combination antiretroviral therapy in pregnancy: results from a cohort study in Ukraine. Bull World Health Organ. 2013;91(7):491-500. PMID:23825876.

Bailey H, Thorne C, Semenenko I, Malyuta R, Tereschenko R, Adeyanova I, Kulakovskaya E, Ostrovskaya L, Kvasha L, Cortina-Borja M, Townsend C L. Cervical Screening within HIV Care: Findings from an HIV-Positive Cohort in Ukraine. PLoS ONE 2012 7(4): e34706. PMID:22545087.

European Collaborative Study in EuroCoord prepared by Bailey H, Townsend C L, Cortina-Borja M and Thorne C. Insufficient antiretroviral therapy in pregnancy: missed opportunities for the prevention of mother-to-child transmission of HIV in Europe. Antiviral Therapy 2011;16(6):895-903. PMID:21900722.