Viral hepatitis and HIV co-infection in the UK collaborative HIV cohort (UK CHIC) study

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Declaration

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

Abstract

Effective treatment for HIV has led to a reduction in AIDS-related morbidity and mortality. Consequently, other co-morbidities experienced by HIV-positive people may have a significant impact on their health. Hepatitis B (HBV) and hepatitis C virus (HCV) are transmitted via the same routes as HIV, thus HIV-positive individuals are at risk of these infections.

The UK Collaborative HIV Cohort (UK CHIC) study is an observational study of HIV-positive individuals attending for care at HIV centres in the UK. This thesis takes a pragmatic approach to defining co-infection within HIV cohort studies using methods that could be implemented in other HIV cohorts where similar data are known to exist. For those individuals defined as co-infected at 11 centres, a new set of data was collected including information on liver disease progression and treatment for HBV and HCV. This novel dataset was used to examine the epidemiology of HIV and hepatitis co-infection and clinical outcomes of co-infected individuals.

From 2004 to 2011, the proportion of individuals in this cohort who had been tested for HBV and/or HCV had increased. The prevalence of HBV and HCV was 6.7% and 10.7%, respectively with ongoing incidence of both infections. The majority of HIV/HBV co-infected individuals (86%) received HBV-active treatment, usually with more than 1 HBV-active drug, as recommended in clinical guidelines. A smaller proportion (38%) had received treatment for HCV with 33% known to have failed treatment within one year. The risk of liver-related death was 9.0 times higher among HIV/HBV co-infected individuals and 5.7 times higher among HIV/HCV co-infected individuals than among HIV mono-infected individuals. Mortality rates were particularly high after the first liver decompensation event.

Understanding the current burden of HIV and hepatitis co-infection and the clinical outcomes of co-infected individuals allows effective planning of services and monitoring of the impact of interventions.

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Frequently used abbreviations

AFP	Alpha-feto protein
AIDS	Acquired immunodeficiency syndrome
AHR	Adjusted hazard ratio
ALT	Alanine amino transferase
AOR	Adjusted odds ratio
APRI	Aspartate amino transferase to platelet ratio index
ARR	Adjusted rate ratio
ART	Anti-retroviral therapy
AST	Aspartate aminotransferase
Anti-HBc	Antibody to hepatitis B core protein
Anti-HBe	Antibody to hepatitis B envelope antigen
Anti-HBs	Antibody to hepatitis B surface antigen
Anti-HCV	Antibody to hepatitis C virus
CI	Confidence interval
CODE	Cause of Death
CT	Computerised tomography scan
BHIVA	British Human Immunodeficiency Virus Association
DAA	Directly acting agents
DNA	Deoxyribose nucleic acid
HAART	Highly active anti-retroviral therapy
HBeAg	Hepatitis B envelope antigen
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HPA	Health Protection Agency
HR	Hazard ratio
IDU	Injecting drug users
IQR	Inter quartile range

IRR	Incident rate ratio
LEE	Liver enzyme elevation
LTR	Long term response
MRC	Medical Research Council
MRI	Magnetic resonance imaging
MSM	Men who have sex with men
NRTI	Nucleoside reverse transcriptase inhibitors
NNRTI	Non-nucleoside reverse transcriptase inhibitors
ONS	Office for National Statistics
OR	Odds ratio
PHE	Public Health England
PI	Protease Inhibitor
RNA	Ribose nucleic acid
RR	Rate ratio
SOPHID	Survey of Prevalent HIV Infections Diagnosed
SVR	Sustained virological response
UK CHIC	UK Collaborative HIV cohort study
US	Ultrasound scan

Chapter 1 Introduction

This thesis will focus on hepatitis B virus (HBV) and hepatitis C virus (HCV) infections among individuals who are human immunodeficiency virus (HIV) positive. In this chapter I will give an overview of the features of these three infections, which are relevant to the research presented in subsequent chapters. I will also outline the aims of this thesis.

1.1 HIV

1.1.1 A brief history of the HIV epidemic

The first reports of the disease which became known as Acquired Immunodeficiency Syndrome (AIDS) came from the USA in 1981. Five previously healthy, young, gay men had been hospitalised with *Pneumocystis carinii* pneumonia (PCP) in California (1). This was unusual since PCP is usually only observed in patients known to have severe immunosuppression. Further reports of PCP, as well as other conditions usually found only in immunocompromised patients, quickly followed (2, 3) and a case definition for AIDS was established in 1982 to allow surveillance (4). At this stage, no etiologic agent had been identified for the syndrome but evidence was building that the condition was caused by an agent which was transmitted through heterosexual sex (5), sex between men (3), through blood and blood products (6, 7) and from mother to child (8).

The viral cause of this syndrome, now known as human immunodeficiency virus (HIV), was identified in 1983 (9, 10). This significant advance allowed the development of diagnostic tests (11, 12). These could be used to diagnose those presenting with immunodeficiency, to screen therapeutically used blood and blood products, to conduct high quality surveillance and to study the natural history of the disease which, in turn, could aid the development of treatment. Since the first reports of unusual immunodeficiency in the USA, HIV has been reported in most countries in the world. There are now an estimated 35.3 million people living with HIV-infection across the globe(13) and 39 million people have died from AIDS (14). Sub-Saharan Africa has experienced the highest number of HIV infections and deaths from AIDS (15).

One of the most important changes in the epidemic occurred in 1995-1996 with the advent of highly active antiretroviral therapy (HAART) (described in detail in 1.1.4) (16). At an international level, access to effective HIV treatment is improving and the number of people

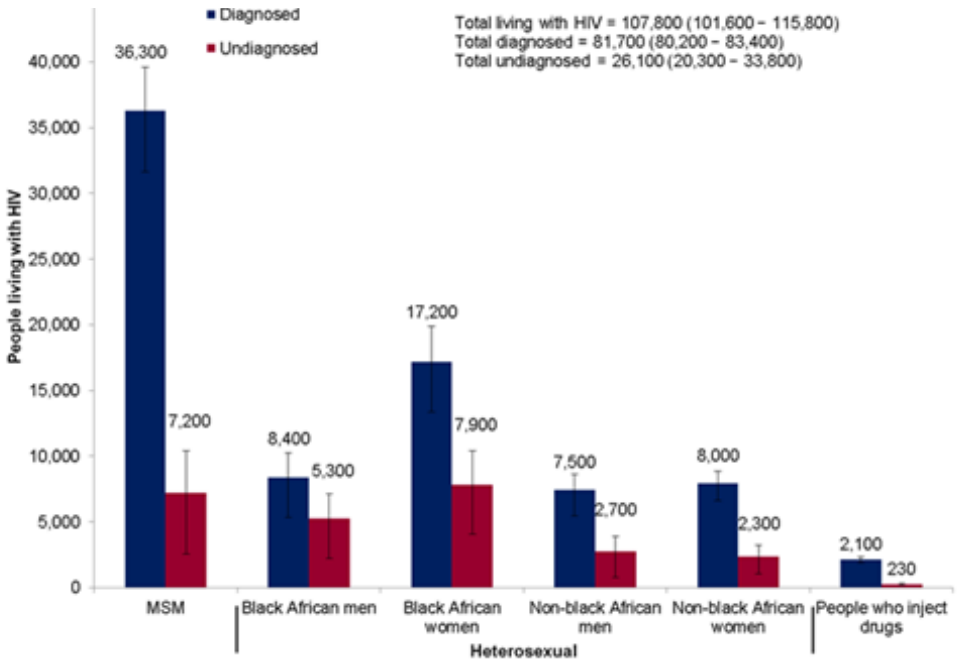
dying from AIDS has fallen with 1.6 million AIDS deaths in 2012 compared to 2.3 million in 2005 (13). People with HIV may now be expected to live a near normal life-span if they are diagnosed early and receive treatment (17, 18).

1.1.2 Epidemiology of HIV in the UK

1.1.2.1 Prevalence of HIV in the UK

In the UK, national estimates of HIV prevalence are made using a statistical model which incorporates data from HIV surveillance systems as well as survey data on risk behaviours (19). At the end of 2013, an estimated 107,800 people were living with HIV in the UK; a prevalence of 2 per 1000 population. A quarter of people living with HIV in the UK are thought to be unaware of their infection (20). Men who have sex with men (MSM) and black African heterosexuals are the population groups with the highest prevalence of HIV: 59 infections per 1000 amongst MSM; 41 per 1000 amongst black African men; and 71 per 1000 amongst black African women (21). Unlike many other countries, prevalence of HIV among injecting drug users (IDU) in the UK is low (22). The most recent estimates of the number of people living with HIV in the UK are shown in Figure 1.1. Prevalence of HIV is highest in London where, for example, one in eight MSM are living with HIV compared to 1 in 26 outside of London.

Figure 1.1 Estimated number of people living with HIV in the UK, 2013



[1]*From Public Health England. HIV in the UK, 2014 slide set*

1.1.2.2 Trends in HIV infection in the UK

The number of people living with HIV in the UK, both diagnosed and undiagnosed, has risen year-on-year since the start of the epidemic. This is partly due to ongoing transmission (23) and partly the increased survival (24) and decreased mortality (25) of people living with HIV. The increase has been seen across all sub-populations. However, there have been changes to the patterns of HIV infection over time. The number of new diagnoses of HIV infection continues to rise among MSM but among heterosexuals new diagnoses fell by 13% between 2012 and 2013. Another important change in the UK epidemic regards the country where an individual was most probably infected. Among heterosexual men and women, the number of newly diagnosed infections which were likely to have been acquired abroad has fallen over the last 10 years while the number that were probably acquired in the UK has risen (26). This marked a switch in 2010, from a situation where the majority of newly diagnosed heterosexual infections were probably acquired abroad, to a situation where the majority of heterosexual infections were probably acquired within the UK. Finally, over the last 10 years, the proportion of diagnosed HIV-positive individuals who are aged $\geq$50 has increased from 13% in 2004 to 27% in 2013. Increased survival has led to an aging cohort of HIV-positive individuals who have been diagnosed for a number of years, but there is also evidence of increasing numbers of new diagnosis among individuals aged $\geq$50 (27).

1.1.3 Natural history of HIV

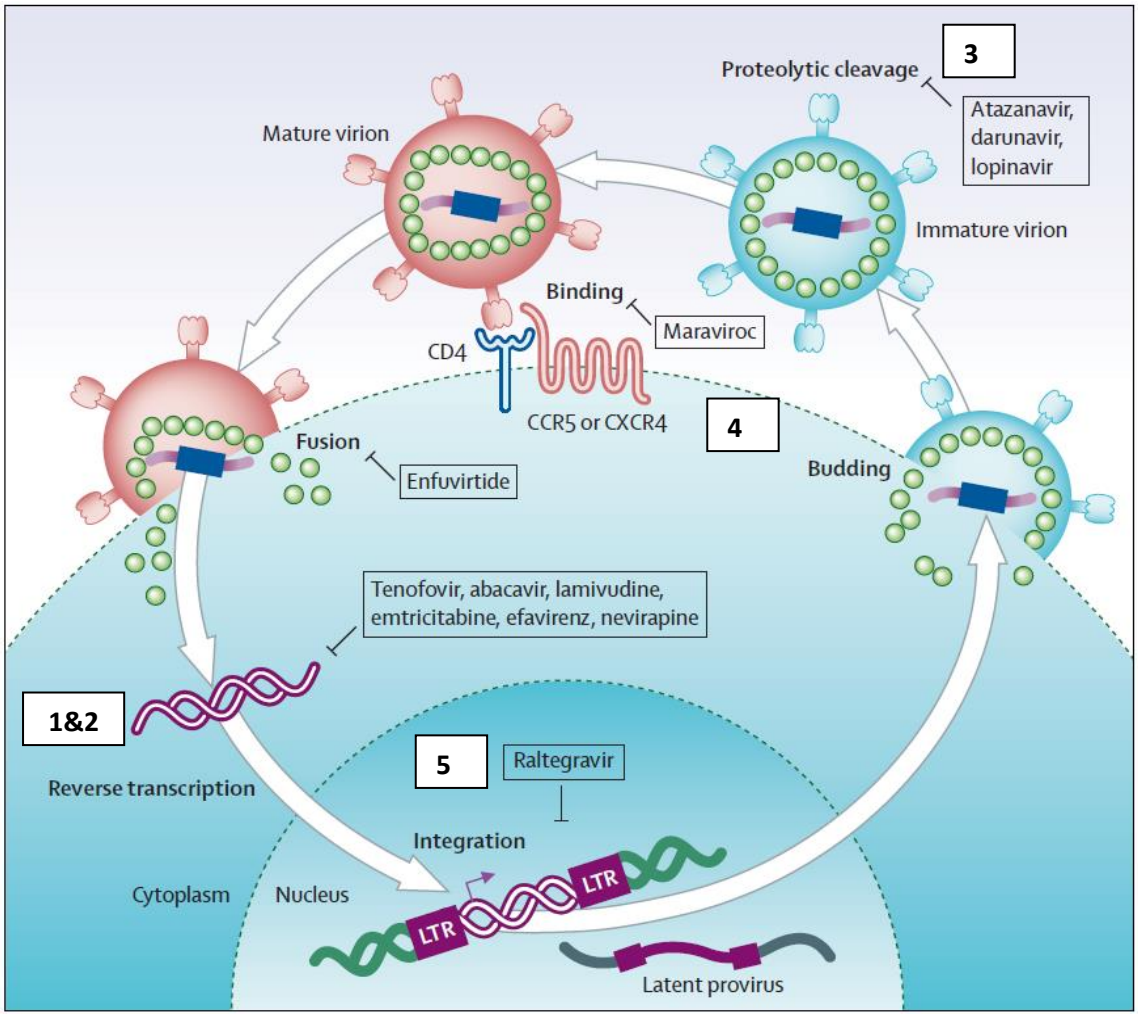
1.1.3.1 The life cycle of HIV and pathogenesis of HIV

HIV is a retrovirus. This family of viruses is distinguished from other viruses by having their genetic code stored as single-stranded ribonucleic acid (RNA) and through their mechanism of replication which involves reverse transcription of the genetic material and integration into the host cell's genome. HIV primarily infects CD4 T-cells which, ordinarily, play an important role in co-ordinating the body's immune response to pathogens. However, HIV can also infect other cells such as macrophages and dendritic cells; both of which are also involved in the body's defence against infection (28).

A representation of the life cycle of HIV is shown in Figure 1.2. The virus attaches to a host cell via the CD4 receptor and fuses with the host cell membrane using the co-receptors CCR5 or CXCR4, resulting in the release of the viral RNA into the cytoplasm of the host cell. The viral enzyme, reverse transcriptase, makes a copy of the viral RNA in the form of deoxyribonucleic acid (DNA) which enters the host cell nucleus. Using another viral enzyme, integrase, this DNA copy of the viral genome is integrated into the host cell DNA. In latent HIV this integrated viral

DNA may remain here without any further action until the cell is activated. In an activated cell the viral DNA is transcribed back into messenger-RNA, which is transported back to the cytoplasm and translated into viral polyproteins. These are packaged into immature virus particles along with copies of the viral RNA which bud off from the cell. The final stage in the replication cycle is the cleavage of the viral polyproteins into the proteins which are present in the mature viral particle. This mature virus is then available to infect further cells (28). Antiretroviral drugs used to treat HIV act at various stages of the viral life cycle (Figure 1.2) as described in section 1.1.4.

Figure 1.2 HIV life cycle and antiretroviral drug targets



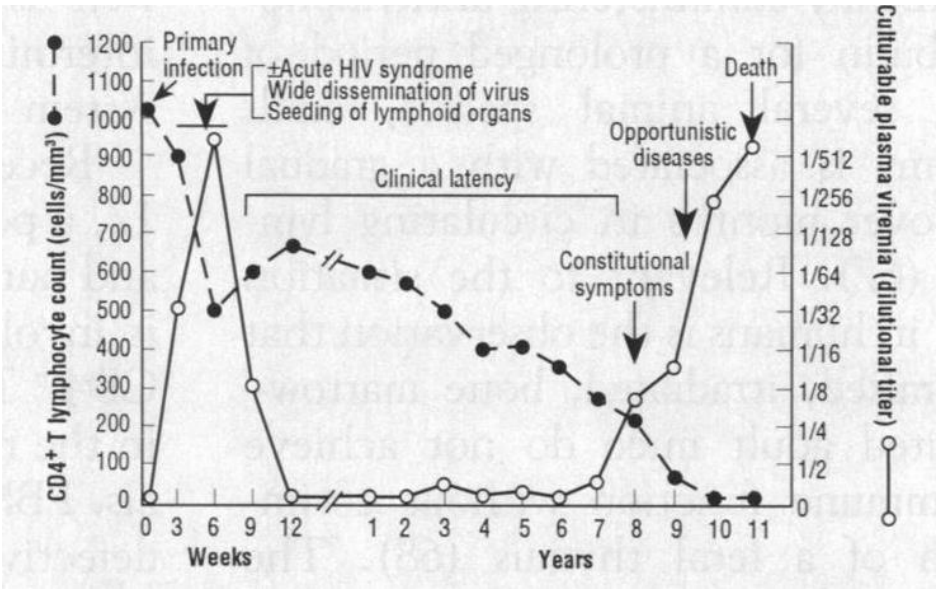
From Volberding & Deeks, 2010. Antiretroviral therapy and management of HIV infection (29)
1 Point of action of nucleoside reverse transcriptase inhibitors
2 Point of action of non-nucleoside reverse transcriptase inhibitors
3 Point of action of protease inhibitors
4 Point of action of fusion inhibitors
5 Point of action of integrase inhibitors

1.1.3.2 The course of HIV infection and markers of disease progression

It has been clear since the early stages of the epidemic that HIV infection depletes the number of CD4 cells within the immune system of an infected person. While the direct destruction of CD4 cells by HIV clearly plays a role in the pathogenesis of the infection, the exact mechanisms by which the virus destroys the CD4 cell population to such a great extent remains unclear (30).

HIV becomes detectable in the blood between 4 and 11 days after infection (31). The appearance of antibodies to HIV in the blood, known as seroconversion, occurs within weeks of the infection (32, 33). In the acute period, defined as the time between infection and seroconversion, some individuals may experience generic symptoms of viremia (34), such as fever, fatigue and rash. The acute period of infection is characterised by high levels of virus (35, 36) and a sudden fall in the number of CD4 cells in the blood (37). However, following this period, as the immune system begins to respond (38), the levels of virus fall and there is a partial recovery of the CD4 cell population. This initial period of acute infection is followed by a long asymptomatic period during which the levels of virus in the blood slowly rise (39) and the number of CD4 cells falls at a rate of 30-60 cells/mm^3 per year (40). Even in the absence of treatment the asymptomatic period may last at least 10 years (41, 42). However, when an individual's CD4 count drops to levels of 200 cells/mm^3, that individual is at high risk of opportunistic infections which the body is unable to fight effectively (43). Individuals with CD4 counts $\leq$200cells/mm^3 or opportunistic infections are considered to have AIDS (44). Typical changes in HIV viral load and CD4 count in the absence of treatment are shown in Figure 1.3.

Figure 1.3 Changes in HIV viral load and CD4 cell count after infection with HIV



From Fauci, 1993. Multifactorial nature of human immunodeficiency virus disease: implications for therapy (37)

Both CD4 cell count and HIV viral load are used in monitoring people with HIV infection. Clinical guidelines from the British HIV Association (BHIVA) recommend that an HIV-positive individual has their CD4 count monitored every 3-6 months (45). In healthy HIV-negative individuals CD4 cell count ranges from 600 to 1500 cells/mm^3 (46, 47). The change in CD4 cell count over the course of HIV infection has been shown to be a good marker of disease progression (48-51). In particular, a fall in CD4 cell count to levels of 350 cells/mm^3 or less is used as an indication for treatment in the UK (52).

HIV viral load has also been shown to predict progression of HIV disease and those with higher HIV viral loads have higher rates of AIDS and AIDS-related mortality (39, 53). Current laboratory assays can measure HIV virus to levels as low as 50 copies/ml. Below this level an individual may still have virus in their blood but it is unquantifiable using standard assays. Therefore, in analyses of clinical outcomes which include HIV viral load as a covariate, viral load is often categorised as $\leq$ 50 copies/ml or >50 copies/ml. A rise in HIV viral load while an individual is on treatment is used as indication that an individual may be experiencing treatment failure (52).

1.1.4 HIV treatment and management

The drugs used to treat HIV are divided into classes depending on the point at which they act within the virus life cycle (Figure 1.2). The first drug used to treat HIV infection was zidovudine, a drug belonging to the class known as nucleoside reverse transcriptase inhibitors (NRTI) (54). Other NRTIs were soon developed and were used in combination with zidovudine (55). These drugs all acted at the same point of the viral life cycle, by preventing the reverse transcription of the viral RNA into DNA (stage 1, Figure 1.2). When treatment is commenced there is a decrease in the level of HIV in the blood and a recovery in the number of CD4 cells.

The first protease inhibitors (PI) were licensed for use in 1995. These drugs act at the point at which the new viral particles mature and become a fully able to infect further cells (stage 3, Figure 1.2). These were the first drugs to result in long lasting suppression of viral replication when used in combination with NRTIs (16, 56). The first non-nucleoside reverse transcriptase inhibitors (NNRTI) were licensed for use in 1996 and also led to improvements in immunological and virological response when used in combination with NRTIs (57, 58). The NNRTIs act at the same point of the viral life cycle as the NRTIs (stage 2, Figure 1.2). More recently, two new classes of drugs have been developed. Fusion inhibitors act at the point when the virus enters the host cell (59) (stage 4, Figure 1.2). Integrase inhibitors prevent the integration of viral genome into the host cell DNA (60) (stage 5, Figure 1.2).

Combinations of these drugs, often referred to as HAART, are now used routinely. Cohort studies have shown that since the introduction of HAART, time from HIV infection to either AIDS or death has increased (61) and mortality rates and rates of AIDS among HIV-positive populations have fallen (62). In the HAART era, the key determinant of AIDS and/or death is the CD4. Low mortality rates are observed among individuals who start HAART with a CD4 count of $\geq$200 cells/mm^3 irrespective of the drugs included in their HAART regimen (63) and the highest mortality rates among those who start HAART at CD4 count <200 cells/mm^3 (64).

In the UK, most individuals are successfully linked into care once they are diagnosed with HIV; 90% have a CD4 count within one month of receiving a diagnosis. This means they are closely monitored and start treatment as necessary, which generally leads to good outcomes. However, challenges remain to ensure that HIV-positive individuals receive a diagnosis before their CD4 counts fall to levels where they experience symptoms of infection (20). Currently, first-line treatment recommended by BHIVA is 2 NRTIs plus one of: a PI boosted with ritonavir; an NNRTI; or an integrase inhibitor (65).

1.2 HBV

1.2.1 Global epidemiology and prevention of HBV infection

Worldwide it is estimated that 240 million people are chronically infected with HBV and every year 780,000 people die of HBV (66). The greatest prevalence of HBV is seen in sub-Saharan Africa, Asia and the Pacific region (67). HBV infection causes liver disease; half of all deaths from liver cancer and a third of all deaths from cirrhosis are attributable to HBV infection (68). HBV is carried in the blood and other body fluids of infected individuals. In areas of high prevalence HBV is usually transmitted perinatally, from mother to child, or early in childhood. In lower prevalence areas it may be transmitted via receipt of infected blood products, injecting drug use, through sex, and by close household contact with infected individuals (69).

A number of prevention strategies can be implemented to reduce transmission of HBV. As with other blood borne viruses, screening of blood and blood products has been shown to significantly reduce the risk of HBV transmission via blood transfusion (70-72). Importantly, unlike HIV and HCV, HBV infection can be effectively prevented through vaccination. In high prevalence countries, where universal HBV immunisation of new-born infants and children has been introduced, the strategy has decreased the prevalence of HBV infection (73, 74) and has been credited with a decrease in the rates of liver cancer (75, 76). A decline in HBV incidence has also been seen after introduction of universal immunisation in lower prevalence countries (77). In addition to vaccination, which aims to induce immunity to HBV infection, passive immunisation with HBV antibodies is effective in preventing an infection occurring after an exposure has occurred. This strategy is used in the context of children born to HBV-positive mothers as well as for healthcare workers who have an occupational exposure (78).

1.2.2 HBV in the UK

In the UK, clinicians and laboratories are required, by law, to notify public health authorities of newly diagnosed cases of viral hepatitis (79) and minimum datasets for reporting have been developed. These notifications allow examination of trends in new HBV infection, HBV transmission patterns and evaluation of HBV prevention strategies (80).

While laboratory reports of acute HBV have been shown to accurately describe the number of symptomatic cases, they may underestimate incidence as asymptomatic cases might not be identified (81). Therefore laboratory reports are adjusted to estimate incidence of HBV infection. In 2013, the estimated incidence of HBV in England was 0.77 per 100,000 population

(414 notifications). This figure had fallen from 1.04 per 100,000 population in 2012. At a regional level, the highest incidence was seen in London. The population group with the highest incidence was men aged 45-54. Where reported, the most common mode of transmission was sex between men and women (57% of incident cases). In addition, 16% of cases were thought to be acquired through sex between men, 4% through injecting drug use and 8% through healthcare related exposures (82). Although the proportion of cases acquired through sex between men is smaller than the proportion acquired through sex between men and women, the population of MSM is substantially smaller and therefore MSM are considered at high risk of infection.

Estimates of HBV incidence are vital for monitoring ongoing transmission. However, in order to assess the true extent of the HBV burden, and therefore the numbers of individuals at risk of HBV-related liver disease, estimates of HBV prevalence are required. There are a number of available sources of information on HBV prevalence. Women in antenatal care are all offered screening for HBV infection; the prevalence in this population, in 2013, was 0.4% (83). In addition, 22 sentinel surveillance centres report data on non-antenatal HBV testing; in 2013 prevalence in this population was 1.1% (83). This higher prevalence from sentinel surveillance compared to that in the antenatal population reflects the fact that a quarter of the tests were conducted in sexual health clinics and therefore the population tested can be considered to be of increased risk of infection. Finally, an ongoing unlinked anonymous seroprevalence survey provides estimates of HBV prevalence among IDU. In 2013, 16% of this population had evidence of ever having had HBV but only 0.6% of IDU were currently infected with HBV (84).

HBV infection is concentrated among certain ethnic groups. Among antenatal women prevalence is highest in women of black ethnicity (2.4%) and women of other or mixed ethnicity (2.2%) compared to women of Asian ethnicity (0.5%) and women of white ethnicity (0.2%). Black and other/mixed ethnic groups also had the highest prevalence in sentinel surveillance from non-antenatal sites; 6.8% among individuals of other/mixed ethnicity and 4.8% among individuals of black ethnicity, compared to 1.5% in people of Asian ethnicity and 0.6% among people of white ethnicity (83).

There is no population level HBV vaccination programme in the UK. However, high risk individuals are offered vaccination. In particular, IDU, MSM, sex workers, close contacts of known HBV cases, people who regularly receive blood products, prisoners and people who

have an occupational risk of infection are among groups who are offered HBV vaccination (85). In addition, BHIVA recommends that all newly diagnosed HIV-positive individuals are screened for HBV infection and those who have no prior evidence of exposure or immunity to HBV are vaccinated (65).

1.2.3 Natural history of HBV infection

1.2.3.1 Life cycle of HBV

HBV belongs to the Hepadnavirus family and was first identified in the 1960s (86). Viruses from this family preferentially infect liver cells (hepatocytes). Unlike HIV, the HBV genome is stored as DNA. However, like HIV, one of the key features of HBV replication is the use of the enzyme reverse transcriptase (87). The cell receptor for HBV virus is unknown. After entry into the cell, the viral DNA is transcribed into RNA in the nucleus of the cell. These RNA transcripts are translated into viral core and surface proteins in the host cell cytoplasm and reverse transcription takes place to create copies of the viral genome inside the core. The replication is completed when the core particles, including the DNA genome, bud off from the surface of the cell and acquire their envelope proteins. At this stage the mature virus is able to infect another hepatocyte (88). The HBV-DNA is also able to integrate into the host cell DNA and while this does not form part of the replication cycle it is thought to be important in the ability of HBV to cause hepatocellular carcinoma (HCC) (89). Neither the replication of HBV within hepatocytes, nor the release of the virus from these cells, directly kills the infected cells. Instead it is believed that damage to the liver is caused by the immune systems response to the infection (86).

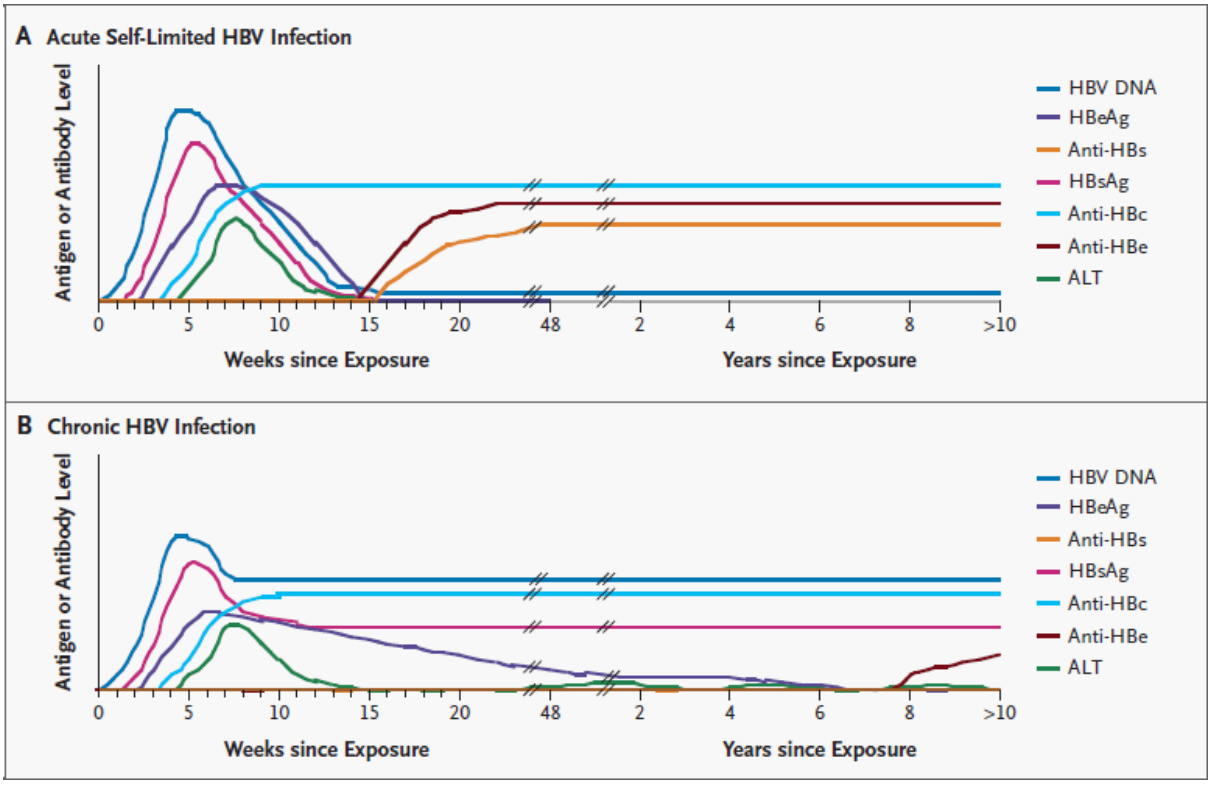
1.2.3.2 HBV disease progression and markers of infection

After HBV infection takes place the disease can take a number of courses. Among healthy individuals, who are infected as adults, around 95% will mount an immune response, clear the infection and develop lasting immunity to the virus. Only 5% will go on to develop chronic infection (90). However, individuals who are infected as children are much less likely to resolve infection and are more likely to become chronically infected (91).

The different courses of infection are characterised by the appearance and disappearance of several markers in the blood of the infected individual (Figure 1.4). In all infections, the first marker to become detectable in the blood is HBV-DNA. This is followed quickly by the appearance of hepatitis B surface antigen (HBsAg) and hepatitis B envelope antigen (HBeAg). An immune response to the infection is detectable in the blood only after a few weeks when

antibodies to hepatitis B core antigen (anti-HBc) appear. As it is the immune response to the virus which causes damage to the liver cells, it is at this stage that clinical manifestations of liver disease are first evidenced in the blood, in the form of raised liver enzymes; alanine aminotransferases (ALTs). Among those individuals who clear the infection, the levels of HBsAg, HBeAg and HBV-DNA then fall until they are all undetectable. ALT levels also fall back to normal levels and the individual is left with anti-HBc, antibodies to the surface antigen (anti-HBs) and antibodies to the envelope antigen (anti-HBe). The development of antibodies protects the individual from any further infection. Among those individuals in whom infection persists, levels of HBV-DNA and HBsAg remain high and anti-HBs does not become detectable, although anti-HBc remains present in the blood.

Figure 1.4 Patterns of serological markers in acute (A) and chronic (B) HBV infection



From Ganem, 2004. Hepatitis B Virus Infection – Natural History and Clinical Consequences (88)

Once an individual is chronically infected the course of the infection is dynamic. The stage of infection that chronically infected individuals enter is dependent on the interplay between the immune system and the virus. An important distinction in chronic disease is between those

individuals who remain HBeAg-positive and those who lose HBeAg and become positive for anti-HBe (known as seroconversion). Those who remain HBeAg-positive have high levels of replication, evidenced by high HBV-DNA titres in the blood. These individuals may have low or high ALTs depending on the response of the immune system (Table 1.1). In individuals who lose HBeAg and develop anti-HBe, HBV-DNA levels are low or undetectable and ALTs are normal (Table 1.2). This inactive state may persist throughout the lifetime, or individuals may experience a reactivation. In the case of reactivation, HBV-DNA levels will rise again and HBeAg may or may not re-appear in the blood. Among a small group of individuals, a variant with a mutation in the pre-core region is selected for during anti-HBe seroconversion. This mutation allows the virus to continue to replicate and so these individuals remain HBV-DNA positive. Infection among these individuals is distinguishable from chronic inactive infection only through the high levels of DNA present among those infected with pre-core mutants (92). A very small proportion of chronically infected individuals (0.1-2%) clear HBsAg in the natural course of infection (93). Diagnosis of HBV infection is usually made through the identification of HBsAg and chronic HBV infection is defined as the presence of two positive HBsAg tests at least 6 months apart (94). Further testing for other markers of infection is used when determining the need for treatment.

Table 1.1 Markers of chronic HBV in HBeAg-positive individuals

Disease stage	HBsAg	HBeAg	Anti-HBe	Anti-HBc	HBV-DNA	ALTs
Immune tolerant	+	+	-	+	++	Normal
Immune active	+	+	-	+	+	Increased

Table 1.2 Markers of chronic HBV in HBeAg-negative individuals

Disease stage	HBsAg	HBeAg	Anti-HBe	Anti-HBc	HBV-DNA	ALTs
Chronic inactive	+	-	+	+	-	Normal
Pre-core mutant	+	-	+	+	+	Increased

As previously mentioned, damage to the liver which results from HBV infection is due to the destruction of infected hepatocytes by the host's immune system. This occurs during the immune active stage of the infection. Around 65% of chronically infected individuals will

eventually undergo seroconversion from HBeAg positivity to anti-HBe positivity and this is associated with a decreased risk of disease progression (95, 96).

Incidence of cirrhosis in HBV-infected populations in European countries has been estimated as 3.8 per 100 person years among HBeAg-positive individuals and 9.7 per 100 person years among HBeAg-negative individuals. These equate to 5 year cumulative incidences of 17% and 38% in HBeAg-positive and HBeAg-negative individuals, respectively (97). Conversely, HBeAg is associated with increased rates of HCC in chronically infected individuals (98). Among individuals in Europe with cirrhosis, the incidence of HCC is 2.2 per 100 person years and for those without cirrhosis it is 0.3 per 100 person years, giving a 5 year cumulative incidence of 1% for non-cirrhotic individuals and 10% for cirrhotic individuals. The rate of HCC in HBV chronically infected individuals is around 100 times higher than among HBV-negative populations and, as such, HBV is considered the main cause of HCC (99). HBV-DNA has also been shown to be predictive of HCC, independent of presence of cirrhosis (100). Therefore in chronically infected individuals HBV-DNA levels are closely monitored and are used as an indication for treatment (94).

1.2.4 Treatment for HBV

European guidelines recommend that treatment is considered when an individual has HBV-DNA >2000 IU/ml, raised ALTs and liver disease which is classed as at least moderate (94). Two different types of drugs are active against HBV. Interferon and pegylated-interferon act by inducing an immune response to clear the virus. In contrast 6 NRTIs act against HBV by interfering with the reverse transcription process involved in the viral replication cycle: lamivudine; tenofovir; emtricitabine; adefovir; telbivudine; and entecavir. Three of these NRTIs are also active against HIV (lamivudine, tenofovir and emtricitabine). The interferon treatments are usually given for a finite period of time, whereas the NRTI treatments are long term therapies (101).

Cirrhosis is known to be associated with higher levels of HBV-DNA (102) and changes in HBV-DNA as a result of treatment have been shown to correlate to changes in histological activity (103). Therefore HBV-DNA levels are used to assess treatment efficacy. The aim of HBV treatment is to reduce HBV-DNA to <2000 IU/ml and to facilitate seroconversion among HBeAg-positive individuals. The ideal end point for treatment is loss of HBsAg, but this is rarely achieved (94). The different drugs available to treat HBV have different levels of efficacy with regard to each endpoint as shown in Table 1.3. Therefore the choice of treatment is

dependent on the type of disease present, any other co-existing morbidities (including HIV), potential drug interactions and the preferences of the patient.

Table 1.3 Proportion of individuals achieving various treatment outcomes after 12 months of treatment for HBV-infection

	Pegylated interferon		NRTI				
	Peg-IFN-2a	**Peg-IFN-2b**	**Lamivudine**	**Telbivudine**	**Entecavir**	**Adefovir**	**Tenofovir**
Drug dose	180µg	100µg	100mg	600mg	0.5mg	10mg	245mg
Anti-HBe seroconversion	32%	29%	16-18%	22%	21%	12-18%	21%
HBV-DNA <60-80 IU/ml	14%	7%	36-44%	60%	67%	12-21%	76%
ALT normalisation	41%	32%	41-72%	77%	68%	48%	68%
HBsAg loss	3%	7%	0-1%	0.5%	2%	0%	3%

Adapted from EASL, 2012. EASL Clinical Practice Guidelines: Management of chronic hepatitis B virus infection (94)

Choices of treatment regimens are complicated by the potential for development of resistance to the NRTIs. High levels of resistance to lamivudine have been observed, with 24% of patients showing mutations which conferred resistance to lamivudine after one year of treatment and up to 70% of patients showing mutations which conferred resistance to lamivudine after 4 years of treatment (104). Lower levels of resistance to other NRTIs have been recorded. For example, at one year of treatment with telbivudine, resistance was observed among 5% of HBeAg-positive individuals and 2.3% of HBeAg-negative individuals (105); at 2 years the proportions of patients with resistance had risen to 25.1% among HBeAg-positive individuals and 10.8% among HBeAg-negative individuals (106). Resistance to adefovir also emerges slowly with 29% HBeAg-negative of individuals (107) and 20% of HBeAg-positive individuals having developed resistance after 5 years of adefovir treatment (108). The prevalence of resistance to entecavir after 5 years of treatment remains low at 1.2% (109). Resistance to tenofovir has not been demonstrated (110). Mutations that confer resistance to lamivudine also confer a level of cross-resistance to telbivudine, adefovir and entecavir so higher rates of resistance to these drugs are observed among individuals who are known to be lamivudine

resistant (110). At present, tenofovir and entecavir are considered first-line NRTIs for treatment of chronic HBV (94).

1.3 HCV

1.3.1 Global epidemiology and risk factors for HCV infection

The World Health Organisation estimates that between 130 and 150 million people are chronically infected with HCV globally with the highest prevalence found in Central and East Asia and North Africa. It is estimated that every year 350,000-500,000 people die of liver disease related to HCV infection (111). Like both HIV and HBV, HCV prevalence estimates are complicated by a long asymptomatic period of infection which may lead to under-ascertainment of cases through surveillance. In Europe, the prevalence of HCV in the general population has been reported as ranging from 0.1% to 5.6%, depending on the country (112). However, these general population estimates should be treated with caution as high risk populations, such as those in prisons, hospitals, the military and individuals who are homeless, may be excluded leading to an underestimate of the true population prevalence (113). In general, prevalence is higher in Southern and Eastern Europe (>1.2%) than in Northern Europe ($\leq$0.1%) (114).

HCV is carried within the blood of an infected individual and is usually transmitted parenterally (115). The contribution of different routes of transmission to the overall epidemic differs by country and geographical region. Iatrogenic and nosocomial infections are those acquired as the result of a medical procedure or in hospital, for example infection as a result of a blood transfusion or from use of contaminated syringes or needles used in healthcare facilities. This is a major transmission route for HCV in the developing world (116-120). There is also evidence that this route of transmission has contributed to prevalent HCV infection in rural areas with particularly high prevalence in some European countries, for example Greece and Italy (121, 122).

In most developed countries in Europe, North America and in Australia, where blood is routinely screened and levels of hygiene in hospitals are good, nosocomial infections as less common. National surveillance data and research studies indicate that the main risk factor for new HCV infection in developed countries is now injecting drug use (116, 123, 124). For example, a study conducted in six sentinel county health departments in the USA showed that 47% of acute HCV infections between 1994 and 2006 were due to injecting drug use (124)

and between 1990 and 2000 in Australia 80% of people living with HCV infection were thought to have been infected through injecting drug use (125).

Evidence to date shows that sexual transmission of HCV is rare among heterosexuals with very low levels of incidence reported among the negative partners of HCV-infected individuals (126-128). Similarly, among HIV-negative MSM the prevalence of HCV is comparable to that among the general population and incidence is low, indicating that among this population sexual transmission is not a major route of transmission for HCV (129). However, there is now evidence that HCV is carried in the seminal fluid, irrespective of HIV status (130). In contrast to the low level of sexual transmission among HIV-negative MSM, among HIV-positive MSM there is now evidence that sexual transmission of HCV does occur with reports of outbreaks in Europe, USA and Australia and reports of increasing prevalence of HCV where sexual exposure is the predominant risk factor (131). This increase in sexual transmission of HCV among MSM will be described in the literature review (section 2.1.1).

1.3.2 HCV in the UK

In the UK, prevalence of HCV antibodies is estimated using a statistical model which brings together a variety of data sources. The size of the IDU population is estimated from drug treatment and intervention services in the community and within probation services and prisons. Prevalence of HCV among IDU is estimated from an unlinked anonymous survey of those IDU in contact with treatment services. Prevalence estimates among sexual health clinic attendees, women in antenatal care, blood donors and community surveys among the south Asian population are also included in the model (132). The most recent estimate is that there were 214,000 chronically HCV-infected individuals in the UK in 2013. In England, the figure is 160,000; an overall prevalence of 0.4% in the population. There were 11,051 new laboratory-confirmed cases of HCV in England in 2013 (133). The majority of newly identified cases were among men, 47% were among individuals aged 25-39 and more than 90% were among IDU.

Since injecting drug use remains the dominant risk factor for HCV infection, there are specific systems in place for monitoring infection in this group. Among IDU who use psychoactive drugs, in 2013, 50% had antibodies to HCV and it is estimated that 40% of IDU were chronically infected with HCV. Over the last 10 years this prevalence has remained steady (84). The same survey provides evidence of increased risk for HCV infection among individuals who inject performance enhancing drugs among whom prevalence of HCV antibodies is 3.6% (84).

The incidence of HCV among IDU is estimated in order to assess the impact of prevention strategies. Previously, the incidence had been estimated using a proxy measure of the prevalence of HCV among young injectors, since HCV is acquired at a young age in this population. However, more recently, methodology has been developed which allows incidence to be estimated using laboratory techniques performed on blood samples taken as part of an unlinked anonymous survey of IDU. This methodology has estimated incidence among HIV-negative IDU as 6-18 infections per 100 person years. A comparison of this estimate to that from previous years using the proxy method suggests that the incidence among this group has remained stable over the last 10 years (133).

1.3.3 Natural history of HCV infection

1.3.3.1 Life cycle of HCV

HCV belongs to the virus family *Flaviviridae.* The virus itself was first identified in 1989 (134), but it had been clear for some time prior to this that there was a viral cause for a post-transfusion hepatitis which was distinct from the other known viral causes of hepatitis (non-A non-B hepatitis) (115). The identification of the virus allowed the development of diagnostic tests (135, 136). However, full investigation of the life cycle of the virus was not possible until 2005 when *in vitro* models of the infection were developed (137, 138).

The primary targets of HCV are hepatocytes (115). The viral genome is stored as RNA. However, unlike both HIV and HBV, replication does not require the reverse transcriptase enzyme. The cellular receptors for the virus are thought to be low density lipoproteins and glycoaminoglycans but a number of other co-receptors are also involved in allowing the virus to enter the cell (139). Once the virus has entered the cell's cytoplasm, primary translation of the RNA genome into protein occurs, resulting in production of an HCV polyprotein. This polyprotein is cleaved by cellular and viral enzymes (proteases) to form 10 viral proteins required to complete the replication cycle. One of these proteins is the viral RNA-polymerase, NS5B, which is the major enzyme responsible for replication of the RNA genome. The virus utilises cellular machinery to complete assembly and release of mature viral particles (140). Detailed understanding of the replication cycle has aided recent development of effective treatments against HCV (see section 1.3.4).

There are 7 main HCV genotypes, named 1-7. These genotypes are divided into a number of subtypes, each assigned a letter, starting with 'a' (141). In the UK, sentinel surveillance data has indicated that the large majority of prevalent HCV infection (~90%) is genotype 1 or

genotype 3 (133). The importance of different genotypes is in predicting response to treatment.

1.3.3.2 HCV disease progression and markers of infection

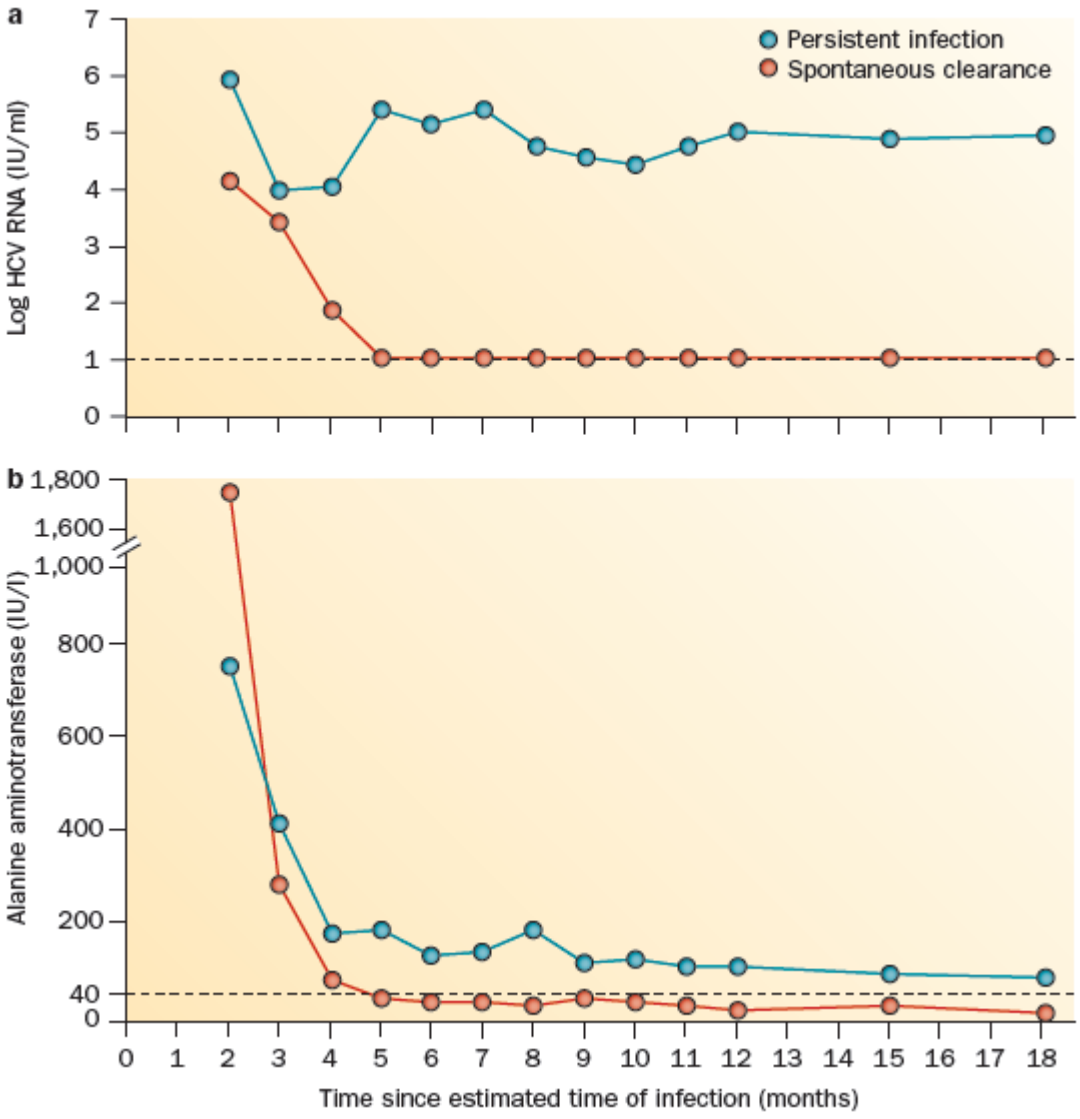
After infection with HCV, HCV-RNA quickly becomes detectable in the blood of the infected individual. The acute phase of infection can be divided into 3 distinct phases. In the first phase, early acute infection, the levels of HCV-RNA in the blood increase rapidly, doubling every 10.8 hours (142). In the second phase, which starts around 5 days after HCV-RNA first becomes detectable in the blood, the levels of HCV-RNA plateau (142). Finally, from two months post-infection the levels of HCV-RNA begin to fall and between 4-6 months after infection two different patterns of HCV-RNA emerge. Among those individuals who go on to clear infection, HCV-RNA continues to fall and the virus is cleared from the system within 6 months of the initial infection. Therefore the acute phase of HCV infection is considered to be this first 6 months of infection. Among those who develop chronic infection, HCV-RNA ceases to fall, may rise to some extent and then stabilises. These individuals remain positive for HCV-RNA (143) (Figure 1.5). Infection leads to stimulation of the immune system which includes production of antibodies against HCV (anti-HCV) within one to two months after initial infection (144, 145). These antibodies persist among patients who clear infection and among those in whom infection becomes chronic.

As HCV-RNA levels rise and plateau during the first two stages of acute infection, ALT levels also rise indicating a degree of inflammation within the liver (146). Similarly, as HCV-RNA levels fall in the later stages of acute infection, ALTs also decline (Figure 1.5). Raised ALTs during acute infection may often lead to initial diagnosis of acute infection. During the early acute phase of infection, where an individual is HCV-RNA positive but anti-HCV negative, only a minority of infected individuals will experience symptoms of hepatitis such as jaundice (144, 146).

It is estimated that around 25% of individuals will spontaneously clear infection, while the rest will remain chronically infected (147). A number of host factors are associated with whether an individual clears infection or becomes chronically infected. Female sex has been associated with spontaneous clearance (147). Importantly the extent of the immune response to the infection is key in determining clearance or persistence of infection. In particular, the action of CD8+ T-cells (148, 149) and CD4+ T-cells (150) has been shown to protect against persistent infection. One of the strongest measurable predictors of spontaneous clearance of acute HCV

infection is the host genotype with regard to IL-28B gene. This gene encodes a particular interferon involved in the immune response to infection and those individuals who have the C-C genotype are significantly more likely to clear HCV infection than individuals who have other genotypes (151, 152).

Figure 1.5 HCV-RNA and ALT level from 2 months after initial infection, split by infection outcome



From Hajarizadeh et al, 2013. Epidemiology and natural history of HCV infection (153)

Since the majority of HCV-infected individuals go on to develop chronic infection, and all individuals who are exposed to HCV develop anti-HCV, testing for anti-HCV is the first-line test used to diagnose HCV infection. However, where a negative anti-HCV test results and there is strong clinical suspicion of acute HCV infection, HCV-RNA testing is used to confirm or exclude

HCV infection. In addition, among those individuals who test positive for anti-HCV, an HCV-RNA test is conducted to assess whether the individual has active infection or has cleared the infection (154).

Among individuals who become chronically infected with HCV, damage to the liver is caused by infiltration of inflammatory cells and death of liver cells. This can lead to liver fibrosis and eventually to severe fibrosis and cirrhosis of the liver (155). The median time from HCV infection to the development of cirrhosis is estimated to be around 30 years (156). At 20 years after infection around 15% of chronically HCV-infected individuals will have developed cirrhosis; by 30 years post-infection this proportion has increased to around 35% (157). However, some individuals never develop cirrhosis (156). Male sex, high daily alcohol intake and longer duration of infection are all associated with increased levels of liver disease (156, 157). Complications of liver disease caused by HCV are observed almost exclusively among individuals who have developed cirrhosis and include HCC, ascites (fluid around the liver), oesophageal varices (upper gastrointestinal bleeding), jaundice (yellowing of the skin and eye caused by raised bilirubin levels) and encephalopathy (damage to the brain) (158, 159). These complications are known as decompensation events. Among HCV-infected individuals with cirrhosis, the estimated five year risk of HCC is 7% (an incidence of 1-3% per year) and the five year risk of any decompensation event is 18% (159). After development of complications, five year probability of survival is 50% (159).

1.3.4 Treatment for HCV

The aim of treatment for HCV is a sustained virological response (SVR) defined as a negative HCV-RNA test at least 6 months after stopping treatment. This result is considered to be a permanent cure (160) and treatment for HCV is associated with a decreased risk of all-cause and liver-related mortality (161-163) and improved liver histology (164, 165).

From 2001 until 2011 standard treatment for all HCV infection has been a combination of pegylated-interferon plus ribavirin (166). Prior to this, standard interferon (without the pegylation) was used. Clinical trials showed that the pegylated-interferon and ribavirin combination had higher efficacy in treating chronic HCV infection than the previously used interferon plus ribavirin combination (167-169). Use of pegylated-interferon and ribavirin has also been shown to be effective among 20-22% of individuals who have previously failed treatment with standard interferon and ribavirin (170, 171). Interferon and pegylated-interferon do not act directly on the virus itself but instead stimulate the infected individual's

immune system to induce antiviral activity. The method of action of ribavirin is less clear but also involves stimulation of the immune system (115). The pegylated-interferon component of the treatment is given, by injection, once a week while the ribavirin is taken orally on a daily basis (169).

The strongest predictor of SVR to pegylated-interferon and ribavirin treatment is HCV genotype. In clinical trials, 40-45% of individuals infected with genotype 1 HCV achieve SVR compared to 70-80% of individuals infected with genotype 2 or 3 HCV (167-169). SVR rates among individuals infected with genotype 4 HCV are less well defined but are thought to be between those for genotype 1 and genotypes 2 and 3 (172). Therefore genotypes 1 and 4 are considered difficult to treat while genotypes 2 and 3 are considered easier to treat. IL28-B genotype of the infected individual is also strongly associated with SVR, with the same genotype which is associated with clearing acute infection begin associated with higher rates of SVR (173, 174). Other factors which are known to be associated with treatment response include low baseline HCV viral load (175-177), younger age of the infected individual (167, 169), lower body weight (167, 177) and an absence of severe fibrosis or cirrhosis (169, 177).

Treatment of acute HCV is associated with high rates of SVR (178-181) and it is recommended that when an individual is diagnosed with acute HCV, treatment is considered in order to prevent the complications associated with chronic infection (154). In the case of acute infection pegylated-interferon may be used as monotherapy.

The duration of treatment for HCV is finite but long. The time that an individual should remain on treatment is guided by their on-treatment response but in many cases of genotype 1 infection treatment may last up to 48 weeks and in the case of genotype 2 or 3 infections may last up to 24 weeks (166). In addition, the treatment may induce side effects such as flu-like illness, altered moods, depression, neutropenia and anaemia (182). These side effects, combined with the long duration of infection mean that high proportions of infected individuals are not considered eligible for treatment (183-185) and among those who do commence treatment, high rates of early discontinuation of treatment have been observed (186-188).

Since 2001 there has been rapid development of new drugs to treat genotype 1 HCV infection. These newer treatments are known as directly acting agents (DAAs) as, in contrast to

interferon-based treatments, they act at specific points of the viral lifecycle. The first two DAAs to become available, in 2011, were boceprevir and telaprevir. These drugs both act as protease inhibitors, preventing the cleavage of the HCV polyprotein and therefore stopping the production of mature virus particles.

In clinical trials among treatment-naive patients, addition of boceprevir to a pegylated-interferon and ribavirin regimen resulted in SVR rates ranging from 42% to 75% (depending on the ethnicity of the patient and on the dose given); a significant increase compared to the control groups who received only pegylated-interferon and ribavirin (189, 190). Addition of telaprevir to a pegylated-interferon and ribavirin regimen resulted in SVR rates ranging from 60% to 79% compared to 40-46% in control groups who received only pegylated-interferon and ribavirin (191-193). Additionally, it has been shown that if patients are monitored throughout treatment and are known to have responded rapidly to treatment (undetectable HCV-RNA at both 4 and 12 weeks of treatment), duration of treatment can be reduced to 24 weeks without affecting the proportion of patients who achieve SVR (194). Impressive results are also seen for these drugs among individuals who have previously failed treatment with pegylated-interferon and ribavirin. Addition of boceprevir to a pegylated-interferon and ribavirin regimen resulted in SVR in 59-66% of individuals compared to 21% in those who received a second pegylated-interferon and ribavirin regimen without a DAA (195).

Subsequent to the licensing of boceprevir and telaprevir, in 2014, 3 new DAAs were licensed for use in Europe: sofosbuvir, simeprevir and daclatasvir. Sofosbuvir inhibits the viral RNA-polymerase, simeprevir is another protease inhibitor and daclatasvir inhibits the viral protein NS5A which is involved in a number of stages of the viral life cycle (154). A large number of trials have been conducted which have shown that addition of these agents to a pegylated-interferon regimen achieves SVR rates of up to 90% for individuals infected with all HCV genotypes, including the harder to treat genotype 1 and genotype 4 infections (196-199). Importantly, clinical trials have also shown high rates of SVR when these drugs are used without interferon (200-202). The newest European guidelines recommend a range of options including new DAAs to treat HCV based on genotype of infection, other co-morbidities present and stage of liver disease (154). Studies assessing the ability of DAAs to treat acute HCV have not yet been published.

1.4 Investigating the stages of liver disease

1.4.1 Techniques for monitoring liver disease progression

The earlier stages of HBV or HCV infection are asymptomatic. Therefore, by the time individuals are diagnosed with infection, some degree of liver damage may have already occurred. The degree of liver damage guides treatment decisions and also gives an indication of an individual's prognosis (203). Therefore once an individual is diagnosed with HBV or HCV infection, the degree of liver damage is evaluated. UK guidelines for the assessment of liver disease in HIV-positive individuals, recommend that initial investigations include a full history including questions about past or present intravenous drug use, prior vaccination for hepatitis A and B, travel history and any associated exposure risks, past and current alcohol use, family history of any kind of liver disease and any prior investigations for liver disease. Clinical examination should investigate the presence of external signs of chronic liver disease such as splenomegaly (enlargement of the spleen) and ascites (204). The full extent of liver disease then can be assessed using a number of techniques.

Liver biopsy is the gold-standard for assessing liver disease (205). The degree of liver disease seen on biopsy is commonly graded, by pathologists, using a scoring system. Various scoring systems are in use. The Histological Activity Index (HAI or Knodell score) gives patients a total score out of 18 for the level of necrosis (cell death) and inflammation, based on the sum of 4 separate scores, each of which results to a different type of inflammation or cell death . A separate score between 0 and 4 is given for the degree of fibrosis (206).

Modifications of the HAI score have resulted in the development of the Ishak score (203) which also gives a necro-inflammatory score out of 18, but provides a more detailed breakdown of the level of fibrosis, scoring the degree of fibrosis between 0 (no fibrosis) and 6 (probable or definite cirrhosis). More recently the METAVIR score has been developed which grades the degree of fibrosis on a 5 point scale from F0 (no fibrosis) to F4 (cirrhosis) (207) and the level of inflammatory activity on a 4 point scale from A0 (no activity) to A3 (severe activity) (208). Full details of the Ishak and METAVIR scoring systems are given in Appendix I. Other grading systems which are less commonly used are the Ludwig, Desmet, Brunt and Scheuer scores (209).

Although liver biopsy remains the gold-standard for assessing the extent of liver disease, its use has some disadvantages. It is invasive and may be prone to sampling error as fibrosis

occurs unevenly throughout the liver. It may not be an appropriate method of investigation in cases where the patient does not want an invasive procedure, when the procedure will be repeated a number of times to monitor the patient, or when the patient may be at risk of bleeding (for example, patients with haemophilia). Therefore a number of non-invasive methods of assessing the degree of liver damage have been developed.

Patients with, or at risk of, cirrhosis are monitored for signs of HCC and other complications of liver disease through liver imaging. Liver scans can be conducted using ultrasound (US), computerised tomography (CT) or magnetic resonance imaging (MRI) (210) . The results of these imaging techniques are usually interpreted in the context of changes in levels of various markers in the blood.

Liver function tests usually include testing for blood levels of total protein, albumin, globulins, bilirubin, ALT, aspartate aminotransferase (AST), alkaline phosphatase, gamma glutamyl transferase, alpha-feto protein (AFP) and prothrombin time (a measure of the ability of the blood to clot) as well as conducting a full blood count. In patients who are not known to be infected with HBV or HCV these tests may provide an indication of the first signs of liver disease. In those diagnosed with viral hepatitis, biochemical markers may be used to give an indication of the degree of liver disease.

A number of indices have been developed which combine levels of biochemical markers to give a score which indicates the degree of fibrosis within the liver. One example in patients with HCV is the AST to platelet ratio index (APRI) which was developed to predict the presence (APRI>1.5) or absence (APRI$\leq$0.05) of significant fibrosis and the presence (APRI>2.0) or absence (APRI$\leq$1.0) of cirrhosis (211). However, a meta-analysis of studies assessing the diagnostic accuracy of the APRI score found only moderate accuracy for prediction of significant fibrosis, severe fibrosis and cirrhosis at the previously recommended above cut-offs and a suggestion that sensitivity and specificity were further lowered in the case of HIV/HCV co-infection (212). Modified cut-offs for the exclusion or presence of fibrosis and the presence of significant fibrosis in HIV/HCV co-infection have been suggested: <0.6 indicating no significant fibrosis; and >1.8 indicating significant fibrosis (213). Variable results are seen where APRI is used to predict fibrosis and cirrhosis in patients with chronic HBV infection (214, 215) and other ratios such as the age-spleen-platelet ratio index (ASPRI) may be of more use

when assessing patients with HBV (216). Other non-invasive scoring systems which may be used are Fibrotest (217) and FIB4 which has a similar sensitivity and specify to APRI (217).

Hepatic elastography (FibroScan®) is another non-invasive method currently used to assess liver damage in individuals who are chronically infected with HBV or HCV. This measures the elasticity of the liver using the velocity at which a low frequency elastic shear wave travels through the liver. The faster the wave travels the stiffer the liver tissue and therefore the greater the degree of liver fibrosis (218). FibroScan® has been shown to discriminate well between patients with cirrhosis (METAVIR=F4) and those without cirrhosis (METAVIR<F4). The performance of FibroScan® is more variable for identifying patients with presence of significant fibrosis (METAVIR≥F2) compared to those with no or mild fibrosis (METAVIR<F2) (209) and therefore the results are usually considered in the context of the results of blood tests. (219).

1.4.2 Assessing end-stage liver disease

In individuals with HCV or HBV, severe fibrosis of the liver, without treatment, may eventually lead to cirrhosis. In patients with cirrhosis the liver architecture is, irreversibly, structurally abnormal. The damage to the liver results in the liver being unable to carry out its functions and a number of complications may result. These complications, associated with cirrhosis, are known as decompensation events. One of the most common complications of cirrhosis is portal hypertension: an increase in the pressure in the portal vein which results in blood being diverted away from the portal vein and bypassing the liver (220). Portal hypertension can lead to ascites which is defined as the build-up of fluid within the abdomen and occurs in particular around the liver. This fluid accumulation carries a risk of bacterial infection (221). Portal hypertension can also lead to oesophageal varices: extremely dilated veins in the lower portion of the oesophagus. These veins can rupture leading to variceal haemorrhage(222). In addition to these complications resulting from portal hypertension, severe damage to the liver can lead to hepatic encephalopathy. This can manifest as a wide range of neurological and psychiatric abnormalities (223).

For individuals with decompensated cirrhosis or HCC, as a result of HBV and/or HCV infection, survival is limited and liver transplantation may be the only therapeutic option. There are two methods available for predicting survival of patients with cirrhosis, a task that is required when assessing patients for liver transplant. The Child-Pugh score is based on a combination of total bilirubin, serum albumin, prothrombin time and the presence and severity of ascites and hepatic encephalopathy. The score is used to categorise the patients into one of three classes

which predict survival rates (see Table 1.4) (224). From 2002 onwards, evaluation for liver transplant has been carried out using the Model for End-Stage Liver Disease (MELD) score. This uses a combination of bilirubin, serum creatinine and prothrombin time to give a score which is closely correlated with survival rates (see Table 1.5) (225, 226).

Table 1.4 Child-Pugh score for patients with cirrhosis and corresponding probability of survival

Class	One year survival rate	Two year survival rate
A	100%	85%
B	81%	57%
C	45%	35%

Table 1.5 MELD score and 3 month mortality rates among hospitalised patients

MELD score	Three month mortality rate
<9	1.9%
10-19	6.0%
20-29	19.6%
30-39	52.6%
≥40	71.3%

1.5 Aim of this thesis and specific objectives

The reduction in the rate of AIDS events and AIDS-related mortality among HIV-positive individuals since the introduction of HAART has made the effective management of other co-morbidities an important area for research. HIV, HBV and HCV share common modes of transmission and therefore high levels of co-infection might be expected. The overall aim of this thesis is to identify a UK cohort of HIV-positive individuals who are co-infected with HBV and/or HCV and to describe the outcomes of these patients. Specifically, in the subsequent chapters, I will present:

i. **A review of the published literature on HIV and HBV and/or HCV co-infection.**
The literature review focuses on the epidemiology of HBV and HCV among HIV-positive populations and clinical outcomes for those HIV-positive individuals who are HBV and/or HCV co-infected. The literature review (Chapter 2) was conducted at the time

of commencing my research. As such, it represents the state of the scientific knowledge at that time. Some additional studies have been subsequently reported. In certain circumstances, where these newly published studies provided new insight into a particular research question, they have been added to the literature review. However, those newer studies which simply confirm findings of previous research have not been included.

ii. Methods used to identify a cohort of HIV and HBV and/or HCV co-infected individual (Chapter 3, Chapter 4, Chapter 5)

This includes a description of the methods used in, and cohort characteristics of, the UK Collaborative HIV Cohort (UK CHIC) study (Chapter 3) which was used as the basis for this thesis. I also present a description of the methods used to identify those individuals who were HBV and/or HCV co-infected within UK CHIC and the collection of a novel dataset including data on hepatitis treatment and outcomes of hepatitis infection for those individuals who are confirmed as being HBV and/or HCV co-infected (Chapter 4). Finally, I present the methods which I developed to overcome missing and inconsistent hepatitis data within HIV cohort studies (Chapter 5).

iii. Analyses of epidemiology of HIV and HBV and/or HCV co-infection (Chapter 6)

I present an analysis of patterns of testing for HBV and HCV. I assess how testing has changed over time and identify independent predictors of testing for each of HBV and HCV. Subsequently, among those individuals who have tested for HBV and/or HCV, I identify independent predictors of co-infection. I also estimate incidence of HBV and HCV co-infection within this HIV-positive cohort and identify factors associated with newly identified infection.

iv. Analyses of hepatitis treatment among HIV-positive individuals (Chapter 7 and Chapter 8)

These analyses are presented in two chapters; the first focussing on HCV (Chapter 7) and the second focussing on HBV (Chapter 8). For each infection, I assess the proportion of co-infected individuals who have received any treatment and factors associated with having received treatment. I then present an assessment of response to treatment, in the context of limited data, which includes estimating the proportion of individuals who respond to treatment and identifying predictors of different

treatment responses. I also describe the characteristics of those individuals who have not received treatment for their HBV/HCV infection and comment on the need for treatment of these individuals.

v. **Analyses of clinical outcomes of HIV and HBV and/or HCV co-infected individuals (Chapter 9)**

In this final analysis chapter I estimate the effect of HBV and or/HCV co-infection on mortality rates among this HIV-positive cohort. I identify predictors of mortality among HBV and/or HCV co-infected individuals. I also present an investigation into the prevalence of cirrhosis among the co-infected cohort, factors associated with cirrhosis and the rate of developing decompensated liver disease. Finally, among those individuals with decompensated liver I describe survival after first decompensation event.

Chapter 2 Literature review on co-infection of HIV with HBV and/or HCV

2.1 Epidemiology of HIV and HBV/HCV co-infection

HIV and hepatitis share transmission routes and risk factors. The sub-populations most affected by each of the infections and the predominant risk factor for each infection differs by geographical region. Therefore the patterns of HIV/HBV and HIV/HCV co-infection differ by country and are dependent on patterns of HIV and hepatitis mono-infection within the geographical region. Internationally, a meta-analysis of 22 studies found higher rates of HIV/HCV co-infection than HIV/HBV co-infection. However, subgroup analysis showed that while this remained the case for studies conducted in Europe it was not the case for studies conducted in Africa or Asia due to the high background prevalence of HBV in many parts of Africa and Asia (227).

Since the beginning of the HIV epidemic, researchers have studied the clinical course of HIV infection in large ongoing cohort studies. In this section I present a summary of those studies which have investigated the extent of hepatitis co-infection in HIV-positive cohorts.

2.1.1 HCV infection in HIV-positive populations

The importance of local epidemiology of co-infection is highlighted by the finding that in a large multicentre international clinical trial, country of recruitment was shown to be an important predictor of HCV infection. The prevalence of HCV co-infection among individuals recruited in Spain and Italy was more than double that among individuals recruited from northern European countries, Canada, Australia or South Africa (228).

Injecting drug use is strongly associated with HCV infection (228-231). Therefore the proportion of IDU within a cohort is an important consideration in interpreting HCV prevalence estimates. Estimates of HCV co-infection reported from HIV cohort studies are summarised in Table 2.1. In European cohorts of HIV-positive individuals prevalence of HCV varies widely from a high of 69%, in a Spanish cohort where almost two thirds of the cohort were IDU, to as low as 8.9% in the UK, where only 3.3% of the cohort were IDU.

In recent years, outbreaks of acute HCV have been recognised among HIV-positive MSM (232-234). In the UK, between 2002 and 2006, at 20 clinics in London and Brighton, incidence of

HCV among HIV-positive MSM increased by 20% per year from 6.86 per 1000 person-years in 2002 to 11.58 per 1000 person-years in 2006 (234). This estimate was based on case reports and therefore the observed increase may represent a combination of true increased incidence as well as increased identification of infections as a result of more awareness of the risk of infection among this population. In Amsterdam, a 10-fold increase in HCV incidence was seen when comparing those men under follow-up in the period 1984-1999 (incidence of 0.08 per 100 person-years) and those men followed-up in 2000-2003 (incidence of 0.87 per 100 person-years) (235). This study used stored serum samples to test for anti-HCV and therefore the incidence estimates are not affected by any increased testing for or awareness of HCV in this population. UK surveillance data has been used to estimate incidence among HIV-positive MSM at national level. This was estimated as 2.14 per 1000 person-years in 2012. This represented a significant decrease in incidence over in the past 4 years from 7.3 per 1000 person-years in 2008 (133).

In a number of outbreaks of HCV among MSM, infection through injecting drug use or other parenteral routes has been excluded (235-237). High-risk sexual behaviour, including sexual practices which may increase the risk or mucosal trauma such as fisting, use of sex toys and group sex, have been found to be associated with HCV infection (131, 232, 237).

Phylogenetic analysis of HCV infections among MSM in Amsterdam revealed 4 clusters of HCV strains which are specific to MSM and unrelated to those strains circulating among IDU. This finding supports the hypothesis that there is a network of transmission among MSM in Amsterdam. Among this group of MSM independent risk factors for HCV infection were HIV infection, prior IDU and recent fisting. However, only 17.9% of HIV/HCV co-infected men reported injecting drug use supporting the hypothesis that within this network HCV is sexually transmitted (238). A larger phylogenetic study which included MSM from England, the Netherlands Germany, France and Australia, found 11 clusters of HCV strains and concluded that there is evidence of a large international network of transmission across the European countries included (131).

There have also been case reports of HCV incidence in HIV-negative MSM however the incidence of HCV in HIV-negative MSM is thought to be much lower than among HIV-positive MSM. A recent meta-analysis of studies investigating incidence of HCV infection in HIV-positive MSM compared to HIV-negative MSM pooled data on new HCV infections from 9

studies of HIV-negative and 20 studies of HIV-positive MSM (239). The authors found that there was a 4.1 times higher risk of acquiring HCV for HIV-positive MSM compared to HIV-negative MSM. In addition, 4 studies included in the meta-analysis made direct comparisons of HCV incidence rates in HIV-positive and HIV-negative MSM. Pooling the data from these four studies resulted in a risk difference of 3.45/1000 person-years with incidence ranging from 0 to 1.7 in HIV-negative MSM and from 0 to 11.8 in HIV-positive MSM (239). It should be noted, however, that the comparison conducted in this meta-analysis did not allow for inclusion of confounding factors. In particular, differences in sexual behaviour between the HIV positive and HIV negative groups were not adjusted for. Therefore, while it is clear that there is a higher incidence of HCV among HIV-positive MSM, compared to HIV-negative MSM, it is not possible to ascertain from this analysis whether this is due to differences in sexual behaviour between the two groups. It is possible that the increased incidence among HIV-positive MSM is due to greater exposure occurring within a sexual network of HIV-positive MSM who practice particular sexual behaviour.

Table 2.1 Prevalence of HCV infection in HIV-positive cohorts

Cohort name	Reference	Country in which study was conducted	Proportion of IDU within the cohort	Prevalence of HCV infection
HIV Outpatient Study (HOPS)	Spradling *et al*, 2010 (240)	USA	13.6%	24.2% (1115/4606)
HIV Atlanta Veterans' Affairs Cohort Study (HAVACS)	Anderson *et al*, 2004(241)	USA	22.4%	31.6% (306/970)
VACH cohort (HIV aplicacio´n de control hospitalario)	Roca *et al*, 2003 (242)	Spain	63.8%	69% (3259/4709)
Australian HIV Observational database	Lincoln *et al*, 2003 (231)	Australia	8.1%	13.1% (223/1704)
Italian Cohort Naïve Anti-retrovirals (ICONA)	De Luca *et al*, 2002 (230)	Italy	38.6%	45.5% (600/1320)
Swiss HIV cohort study	Greub *et al*, 2000 (243)	Switzerland	35.6%	37.12% (1157/3111)
UK Collaborative HIV Cohort (UK CHIC)	Turner *et al*, 2010 (244)	UK	3.3%	8.9% (1807/20365)
Adult AIDS Clinical Trial Group (AACTG) cohort	Sherman *et al*, 2002 (245)	USA	18.2%	16.1%[1]

Cohort name	Reference	Country in which study was conducted	Proportion of IDU within the cohort	Prevalence of HCV infection
Johns Hopkins HIV Observational cohort	Sulkowski *et al*, 2002 (246)	USA	45.2%	44.7% (873/1955)
Adolescent/Adult Spectrum of HIV Disease Project (ASD)	Buskin *et al*, 2011 (229)	USA	18.0%	19.0% (5463/29400)
Spanish cohort of adult HIV-infected patients (CoRIS)	Serrano-Villar *et al*, 2014 (247)	Spain	11.3%	15.6% (1099/7045)
China National Free Anti-retroviral Treatment Programme	Zhang *et al*, 2014 (248)	China	22.0%	18.2% (6149/33861)
RESINA	Reuter *et al*, 2011 (249)	Germany	7.1%	10.6% (97/918)
European Collaborative Study (ECS) [2]	Landes *et al*, 2008 (250)	Pan-Europe	19.3%	12.3% (129/1050)
Immunology Case Registry (ICR). Department of Veterans Affairs	Backus *et al*, 2005 (251)	USA	Unknown [3]	37.0% (6782/18349)
EuroSIDA	Rockstroh *et al*, 2005 (252)	Pan-Europe, plus Argentina and Israel	27.7%	33.0% (1960/ 5957)

Cohort name	Reference	Country in which study was conducted	Proportion of IDU within the cohort	Prevalence of HCV infection
Danish HIV cohort	Weis *et al*, 2006 (253)	Denmark	10.2%	16.0% (443/2734)
Canadian Observational cohort collaboration (CANOC)	Raboud *et al*, 2012 (254)	Canada	Unknown	28.0% (768/2706)
Women and Infants Transmission Study (WITS)	Hershow *et al*, 2005 (255)	USA	Unknown [3]	29.0% (190/652)

[1] Weighed estimated prevalence among 1687 individuals
[2] Cohort includes pregnant women only
[3] Although the proportion of individuals who have injected drugs is not reported, a high prevalence of any drug use within the cohort is reported

2.1.2 HBV infection in HIV-positive populations

Like HCV, the prevalence of and factors associated with HBV infection have been studied in HIV-positive cohorts (Table 2.2). Prevalence is usually measured using the presence of HBsAg (a marker for current infection) and chronic infection is usually defined as having two or more positive HBsAg test results at least 6 months apart.

In the USA, the prevalence of HBV has been reported as between 4.2% (256) and 11.7% (257). The reported prevalence in European cohorts is similar, ranging from 4.5% among a cohort of pregnant woman screened in antenatal care (250) to 8.7% in the pan-European EuroSIDA cohort (258). In the UK, a previous analysis of the UK CHIC cohort estimated a prevalence of 6.9% among 25973 individuals who had ever been tested for HBsAg. However, in this earlier analysis of data from UK CHIC, conducted prior to the analyses presented in this thesis, more than a quarter of individuals had never been tested for HBsAg which may have introduced bias in the results (259).

Factors associated with HBV infection among HIV-positive individuals are HCV infection (231, 260), being male and having higher alcohol intake (229, 260). Specifically in the UK, HBV infection was associated with non-white ethnicity, having acquired HIV through sex between men or being a woman who has acquired HIV through heterosexual sex and entering the cohort in earlier years (259) .

The incidence of HBV infection has been reported in both the USA and UK. Compared to the pre-HAART era, incidence of HBV infection (after diagnosis of HIV) has decreased from 4.0 per 100 person-years to 1.1 per 100 person-years (256). However, the generalisability of this this study is limited as the cohort contains a limited number of IDU and a limited number of female patients, and prevalence may differ in these groups. HBV incidence estimates for the pre-HAART era are not available for the UK. However, from 1996 onwards HBV incidence was estimated as 1.7 per 100 person-years. Incidence was significantly associated with acquiring HIV through sex between men (259).

Table 2.2 Prevalence of HBV in HIV-positive cohorts

Cohort name	Reference	Country in which study was conducted	Definition of HBV infection	Prevalence of HBV infection
Australian HIV Observational database	Lincoln *et al*, 2003 (231)	Australia	Positive HBsAg test at any time during follow-up	6.3% (101/1605)
Italian Cohort Naïve Anti-retrovirals (ICONA)	De Luca *et al*, 2002 (230)	Italy	Positive HBsAg test at any time during follow-up	6.8% (90/1320)
UK Collaborative HIV Cohort (UK CHIC)	Price *et al*, 2012 (259)	UK	Positive HBsAg test at any time during follow-up	6.9% (1781/25973)
Muticenter AIDS cohort study (MACS)	Thio *et al*, 2002 (261)	USA	Positive HBsAg test at any time during follow-up	8.3% (231/2559)
Adolescent/Adult Spectrum of HIV Disease Project (ASD)	Kellerman *et al*, 2003 (262)	USA	Chronic HBV infection – HBsAg positivity for 6 months or more	7.6% (1506/19904)
EuroSIDA	Konopnicki *et al*, 2005 (258)	Pan-Europe, plus Argentina and Israel	Positive HBsAg test at any time during follow-up	8.7% (498/5230)
US Military HIV Natural History Study (DoD NHS)	Chun *et al*, 2010 (256)	USA	Chronic HBV infection – HBsAg positivity for 6 months or more	4.2% (117/2769)

Cohort name	Reference	Country in which study was conducted	Definition of HBV infection	Prevalence of HBV infection
Adolescent/Adult Spectrum of HIV Disease Project (ASD	Buskin *et al*, 2011 (229)	USA	Chronic HBV infection – clinical diagnosis or HBsAg and IgG anti-HBc	8.0% (2332/29490)
EuroSIDA	Soriano *et al*, 2010 (263)	Pan-Europe, plus Argentina and Israel	Positive HBsAg test at any time during follow-up	7.1% (1179/16505)
China National Free Anti-retroviral Programme	Zhang *et al*, 2014 (248)	China	Positive HBsAg test at any time during follow-up	8.7% (2958/33861)
RESINA	Reuter *et al*, 2011 (249)	Germany	Positive HBsAg test at any time during follow-up	4.5% (41/918)
European Collaborative Study (ECS) [1]	Landes *et al*, 2008 (250)	Pan -Europe	Positive HBsAg test at antenatal screening	4.9% (51/1050)
Danish HIV cohort study	Omland *et al*, 2008 (264)	Denmark	Chronic HBV infection – HBsAg positivity for 6 months or more	6.0% (178/2781)
HIV Atlanta Veterans' Affairs Cohort Study (HAVACS)	Osborn *et al*, 2007 (257)	USA	Positive HBsAg test at any time during follow-up	11.7% (157/1346)
Swiss HIV cohort study	Wandeler *et al*, 2013 (265)	Switzerland	Positive HBsAg test at any time during follow-up	6.0% (287/4773)

Cohort name	Reference	Country in which study was conducted	Definition of HBV infection	Prevalence of HBV infection
Chilean AIDS cohort	Otto-Knapp *et al*, 2013 (266)	Chile	Positive HBsAg test at any time during follow-up	8.4% (161/1907)
HIV Outpatient Study (HOPS)	Spradling *et al*, 2010 (267)	USA	Positive HBsAg or HBV-DNA test at any time during follow-up	8.4% (376/4467)

[1] Cohort includes pregnant women only

2.1.3 The importance of liver disease as a cause of death

As the HIV epidemic has evolved, with the advent of HAART, HIV-positive individuals are living longer and progression to AIDS-defining events has become less common (62, 268). Consequently, there has been a change in the leading causes of death among HIV-positive populations. In particular, the proportion of individuals who die from liver disease has increased. Mocroft *et al* examined cause of death among 1826 HIV-positive individuals who died between 1994 and 2001 in the EuroSIDA cohort. While the incidence of death had decreased from 21.6 per 100 person-years in 1995 to 2.7 per 100 person-years in 2001/2002, the proportion of individuals who died from liver-related problems has increased from 19% of deaths in 1994 to 25% of the total deaths in 2001/2002 (269). Similarly, in a large cohort of 4214 HIV-positive individuals in the USA, 1224 deaths occurred among 4241 individuals between January 1990 and December 2003. Overall there was an 80% decrease in the annual death rate over the study period. However, at the same time, liver disease had become increasingly important: whereas it was the primary cause of death in only 0.2% of individuals in the pre-HAART era, it was the primary cause of death in 3.7% of individuals in the post HAART era (1997-2003) (270).

In a smaller Spanish study, mortality and causes of death were compared in the pre-HAART era and the HAART era. As expected there was a significant decline in overall mortality and in AIDS-related mortality in the HAART era while mortality from other causes had significantly increased. In particular, death as a result of liver disease rose from 0.37 per 100 person-years follow-up in the pre-HAART era to 0.6 per 100 person-years follow-up in the HAART era. Importantly, despite the decreases in AIDS-related mortality, in the HAART era AIDS remains the predominant cause of death in this cohort, in the HAART era (271).

As the proportion of all deaths among HIV-positive individuals from liver disease has increased, the importance of HBV or HCV infection as an aetiology of liver disease has also been shown. In France, a review in 2005 of deaths among HIV-positive individuals showed that of deaths all deaths that were related to end-stage liver disease, 64% of had an aetiology of viral hepatitis (272). Among patients in the HIV Outpatients Study in the USA causes of death between 1996 and 2004 were known for 554 individuals. Among those individuals who died with at least one non-AIDS defining condition reported as the primary or secondary cause of death, the rates of death from neurological, cardiovascular and pulmonary causes had decreased but the rate of liver-related death increased (from 1.3 per 100 person-years in 1996 to 12.5 per 100 person-

years in 2004). In the final year of the study 80% of individuals who died from liver-related diseases were co-infected with HBV or HCV (273).

2.2 The impact of co-infection with HCV on HIV-infection

In this section I will discuss how co-infection with HCV affects progression of HIV with regard to CD4 cell decline, HIV viral load increases and development of AIDS.

2.2.1 The effect of HCV on progression of HIV to AIDS

There is conflicting evidence from cohort studies regarding the effect of HCV co-infection on HIV progression. Some studies show an increased progression to AIDS in patients who are co-infected with HCV compared to those are HIV mono-infected, and others showing that there is no difference in progression to AIDS between the two groups. In the pre-HAART era, 251 HCV co-infected individuals were compared to 1353 HIV mono-infected patients enrolled in the CAESAR study (in Canada, Australia, Europe and South Africa). All patients were treated with zidovudine monotherapy or zidovudine plus one of didanosine or zalcitabine at baseline. Over a 52 week period, there was no effect of HCV on CD4 count and HCV status did not impact on progression of HIV to a new AIDS event or death; 13% of HIV mono-infected patients experienced a new AIDS event or died compared to 11% of HCV co-infected patients (p=0.37). However, some aspects of this study limit the extent to which results can be generalised. For example, the study included only patients with very low initial CD4 counts (25-250 cells/mm^3) and excluded patients with very high liver enzyme elevation. Therefore the impact of HCV co-infection may have underestimated (228).

The Women and Infants Transmission Study focussed on women who were recruited in the pre-HAART era. A total of 652 HIV-positive women with known HCV status were recruited in pregnancy and followed-up for a median of 43.2 months. Of these women 29% were HCV co-infected. In multivariable mixed-effects regression analysis HCV co-infection was not associated with differences in mean HIV viral load, but it was associated with a slightly higher (1.9% higher) CD4 percentage compared to HIV-mono-infected individuals. There did not appear to be any clinical impact of this difference as no association was found between HCV status and progression to AIDS (255).

In the HAART era, a number of studies have suggested that co-infection with HCV may be associated with an increased progression of HIV. However, many of these studies did not

distinguish between progression to AIDS and mortality. Therefore the impact of HCV co-infection on HIV progression alone is difficult to elucidate. Data from the Swiss HIV Cohort Study of 3111 HIV-positive individuals (1157 co-infected with HCV) showed that there was an increased HIV progression rate among HCV co-infected persons compared to HIV mono-infected individuals (Hazard ratio (HR) 1.7, 95% CI 1.26-2.30). However, this analysis did not distinguish between AIDS events and deaths as an end point and therefore this increased risk of progression may be due to increased mortality (which might be expected in those with HCV co-infection) and not an increased risk of HIV progression. In addition, this sample contained a high proportion of IDU (4.8% of HIV mono-infected and 87.7% of HCV co-infected individuals). IDU may have a poorer adherence to HAART and increased mortality (not related to HIV). A subgroup analysis was conducted including only those individuals with well controlled HIV in order to limit the potential confounding effect of poor adherence to HAART. There was an increased progression in HCV co-infected individuals (HR 3.54, 95% CI 2.0-6.25) even in this subgroup. (243).

Likewise, an Italian study which recruited antiretroviral-naive patients who were initiating HAART compared clinical progression among 600 HCV co-infected individuals and 720 HIV mono-infected patients and found an increased risk of progression (HR 1.55, 95% confidence interval (CI) 1.0-2.41). However, this study also did not distinguish between AIDS events and death and the higher risk seen may be due to an increased death rate in the co-infected group. This cohort also included a very high proportion of IDU in the co-infected group (93.4%) which may increase the mortality rates seen (230). Finally, in the Australian HIV Observational Database, neither HBV nor HCV were associated with an increased risk of AIDS or death after the commencement of HAART, although this study also did not distinguish between rates of AIDS or rates of death (231).

In studies in which AIDS and death are considered as separate outcomes (or where only AIDS events were considered), in the HAART era, HCV co-infection has not been shown to be associated with an increased rate of HIV progression. Among 1955 HIV-positive patients in the Johns Hopkins' HIV Observational Cohort study, in the USA, there was no difference in the risk of progression to AIDS between the 44.6% who were co-infected with HCV and the mono-infected group (246). Analysis of data from the EuroSIDA cohort (comprising 5957 HIV-positive individuals with known HCV status from 6 countries across Europe and Argentina) found no difference in clinical progression when progression was defined as a new AIDS event or death.

However, when AIDS and death were considered as separate end points, the progression to a new AIDS event, was less frequent among HCV co-infected individuals than among those infected with HIV only (Incident rate ratio(IRR) 0.78, 95% CI 0.62-0.98), although this may be due to other causes of mortality acting as a competing risk in the analysis (252). One study has investigated HIV progression with regard to the development of an AIDS-related opportunistic infection. In both the pre-HAART and HAART eras there was no difference in the hazard of developing an opportunistic infection in HCV co-infected patients compared to HIV mono-infected patients (274).

2.2.2 The effect of HCV on mortality in HIV-positive individuals

In this section, I will describe studies which have investigated the impact of HCV on mortality in HIV-positive populations. Some studies report on all-cause mortality and do not include cause of death. This should not be interpreted as an increase in progression of HIV to death since the deaths may be due entirely to HCV disease or lifestyles associated with HCV infection. Therefore studies which report all-cause mortality but also differentiate between liver-related mortality, HIV-related mortality and other causes of mortality are most meaningful when assessing the impact of hepatitis co-infection on HIV progression.

A summary of studies which compared mortality in HIV mono-infected and HIV/HCV co-infected individuals is shown in Table 2.3. A meta-analysis of publications up to end of April 2008 was conducted by Chen *et al*. This showed that in the pre-HAART era, HCV co-infection did not increase mortality compared to HIV mono-infection. However, after the introduction of HAART, overall mortality was increased in co-infected patients compared to HIV mono-infected patients (with a risk ratio (RR) of 1.35, 95% CI 1.11-1.63) (275). Subgroup analysis revealed the importance of the length of follow-up when comparing mortality rates as the strength of the effect increased with longer follow-up time.

A number of studies conducted in the HAART era (and included in the above meta-analysis) showed no difference in all-cause mortality between HCV co-infected and HIV mono-infected individuals (246, 276-281). Some of these studies included high numbers of individuals who are likely to be at high risk of mortality irrespective of HCV infection, for example, individuals with AIDS (277), homeless individuals and IDU (279). Higher rates of mortality among these groups as a whole may reduce the effect of HCV infection on mortality. This was also seen among hospitalised patients in the USA, where there was no difference in mortality between HCV co-infected and HIV mono-infected patients (282). However, hospitalised HIV patients are likely

to be at very late stages of HIV disease and thus very sick. These results may not, therefore, be generalisable to a setting where patients are not hospitalised. In the Aquitaine cohort, France, which included HIV-positive patients recruited from 18 infectious disease units in the South West of France, among 576 HCV co-infected patients and 419 HIV mono-infected patients, HCV co-infection was not associated with decreased survival. However, in this cohort, and in contrast to other cohorts, HCV co-infection was more prevalent in women; women have been demonstrated to have better survival from HCV overall (283).

Among studies which showed no difference in mortality between HIV mono-infected and HCV co-infected individuals, higher rates of mortality were often observed among co-infected individuals, however the association of mortality with co-infection was lost after adjusting for demographic factors and other factors such as HAART, CD4 counts and alcohol (277, 278, 280, 281).

In agreement with the overall findings from the meta-analysis, significant increases in all-cause mortality were observed in co-infected individuals compared to HIV mono-infected individuals, even after adjustment for HAART, in a number of studies (241, 252, 253, 274, 284-287). In addition to those studies included in the meta-analysis, two more recent studies have found increased all-cause mortality rates in co-infected compared to mono-infected individuals (288, 289). These two studies were also able to adjust for additional co-morbidities.

As well as studies showing an increase in all-cause mortality in HCV co-infected persons compared to mono-infected individuals, a number of studies have shown increased liver-related mortality among HCV co-infected individuals (252, 253, 287, 290, 291). For example, in the D:A:D study (a collaborative study of 11 cohorts in Europe, the USA and Australia), where 23,441 individuals were followed for a median of 3.5 years, HCV co-infection was independently associated with liver-related death in HIV-positive individuals (291). Similarly, in the EuroSIDA cohort, despite not finding an increased progression to AIDS (see section 2.2.1), there was a significantly higher incidence of death among co-infected individuals compared to HIV mono-infected individuals. This was due to a 10 fold higher increase in liver-related deaths in the co-infected group than in the HIV mono-infected group (252)

The differences in findings highlight the importance of the particular setting in which a study has taken place, the make-up of the study, the co-variates included in the analyses and the

length of follow-up. It is important to note that very few studies include a measurement of whether patients had been or were currently being treated for HCV infection and HCV viral load is not reported in most studies. As treatment for HCV evolves (see section 2.7.2), it will be important to consider the impact of treatment on mortality and HIV progression.

Table 2.3 Studies comparing mortality rates in HIV mono-infected and HIV/HCV co-infected individuals in the era of HAART

Reference	Study setting	Number included in analysis (HIV mono-infected, HCV co-infected)	Relevant analysis	Relevant results[2]
Ananthakrishan *et al*, 2010 (282)	Nationwide Inpatient Study, USA	263062 (206758, 56304)	Multivariable logistic regression of factors associated with hospital inpatient mortality	AOR for mortality in co-infected compared to mono-infected 1.11 (95% CI, 0.97-1.29)
Anderson *et al*, 2004[1] (241)	HIV Atlanta VA Cohort study (HAVACS), USA	970 (664,306)	Multivariable Cox regression of factors associated with survival from HIV diagnosis to all-cause mortality	AHR for mortality among co-infected compared to mono-infected 2.47 (95% CI 1.26-4.82)
Backus *et al*[1](284)	HIV-infected veterans on HAART, USA	12216 (7548, 4668)	Multivariable Cox regression of survival from first HAART to all-cause mortality	AHR for mortality among co-infected compared to mono-infected 1.56 (95% CI 1.42-1.70)
Bonacini *et al*[1] (290)	University clinic cohort, USA	382 (126,256)	Unadjusted all-cause and liver-related mortality	25%(65/256) HIV/HCV co-infected individuals died compared to 33% (41/126) HIV mono-infected 13% 32/256 HIV/HCV co-infected individuals had a liver-related death compared to 6% (7/126) HIV mono-infected (p=0.05)

Reference	Study setting	Number included in analysis (HIV mono-infected, HCV co-infected)	Relevant analysis	Relevant results[2]
Braitstein *et al*[1] (285)	HIV/AIDS drug treatment programme, British Columbia, Canada	1186 (580, 6060)	Multivariable Cox regression of survival from first HAART to death from natural causes	AHR for mortality among co-infected compared to mono-infected 2.20 (95% CI 1.50-3.21)
Bruno *et al*, 2007 (292)	Single HIV centre, Italy	(140, 183)	Unadjusted mortality rates in HIV mono-infected and HCV co-infected individuals without cirrhosis	Mortality rate 8 per 1000 person-years in co-infected individuals without cirrhosis (95% CI 4-16) Mortality rate 6.5 per 1000 person-years in HIV mono-infected (95% CI 2.7-15.5)
Chen *et al*, 2009 (275)	Meta-analysis of 27 studies in HAART era comparing outcomes in HIV mono-infected and HIV/HCV co-infected individuals	20 studies	Pooled risk ratio from random effects model for all-cause mortality in HCV co-infected compared to HIV mono-infected individuals	Risk ratio for mortality among co-infected individuals compared to mono-infected individuals 1.35 (95% CI 1.11-1.63)

Reference	Study setting	Number included in analysis (HIV mono-infected, HCV co-infected)	Relevant analysis	Relevant results[2]
Crane *et al*[1](286)	University of Washington HIV cohort, USA	694 (550, 144)	Multivariable Cox regression of survival from starting HAART to all-cause mortality	AHR for mortality among co-infected compared to mono-infected individuals 1.6 (95% CI 1.0-2.6)
E-Serag *et al*[1] (293)	Hospitalised patients, USA	18018 (12761, 5320)	Multivariable Cox regression of survival from hospitalisation to all-cause mortality	AHR for mortality among co-infected compared to mono-infected individuals 0.55 (0.51-0.58)
Fischer *et al*, 2010 (288)	Veterans aging cohort study, USA	23155 (13825, 9330)	Multivariable Poisson regression of factors associated with all-cause mortality	AHR for mortality among co-infected compared to mono-infected individuals 1.23, 95% CI 1.17-1.29
Hung *et al*[1] (276)	National Taiwan University Hospital cohort, Taiwan	440 (387, 53)	Multivariable Cox regression of survival from cohort entry to all-cause mortality	AHR for mortality among co-infected compared to mono-infected individuals 0.50 95% CI 0.20-1.26
Jaggy *et al*[1] (294)	Swiss HIV cohort study, Switzerland	3963 (2318, 1645)	Excess death rate compared to the general Swiss population in HCV co-infected and to HIV mono-infected	EDR 14.0, 95% CI 11.3-17.2 among HIV mono-infected EDR 38.1 95% CI 33.2-43.7 among HCV co-infected

Reference	Study setting	Number included in analysis (HIV mono-infected, HCV co-infected)	Relevant analysis	Relevant results[2]
Klein *et al*[1](274)	Patients attending large HIV clinic in Montreal, Canada	539 (456, 83)	Multivariable Cox regression of survival from cohort entry to all-cause mortality	AHR for mortality among co-infected compared to mono-infected individuals 3.37 95% CI 1.58-7.17
Lohse *et al*, 2011 (289)	Danish HIV cohort study. 8 clinics, Denmark	1638 (1427, 211)	Multivariable Cox regression of survival from cohort entry to all-cause mortality (adjusting for additional pre-existing co-morbidities)	AHR for mortality among co-infected compared to mono-infected individuals 2.04, 95% CI 1.19-3.51
Marins *et al*[1] (277)	Nationally representative sample of AIDS patients, Brazil	833 (554, 279)	Multivariable Cox regression of survival from cohort entry to all-cause mortality	AHR for mortality among co-infected compared to mono-infected individuals 0.94, 95% CI 0.75-1.18
Mayor *et al*[1](278)	Retrovirus research centre cohort, Puerto Rico	356 (163, 193)	Multivariable Cox regression of survival from cohort entry to all-cause mortality	AHR for mortality among co-infected compared to mono-infected individuals 1.17, 95% CI 0.79- 1.72

Reference	Study setting	Number included in analysis (HIV mono-infected, HCV co-infected)	Relevant analysis	Relevant results[2]
Monga *et al*[1](287)	Veteran Affairs Medical Center, Houston, USA	429 (263, 166)	Unadjusted all-cause and liver-related mortality rates	7% HIV mono-infected individuals died compared to 11% of co-infected individuals (p=0.02) 9 liver-related deaths among co-infected and none in HIV mono-infected
Riley *et al*[1](279)	Homeless and marginally housed individuals, San Francisco, USA	330 (118, 212)	Univariable Cox regression of survival from cohort entry to all-cause mortality	CHR for mortality among co-infected compared to mono-infected individuals 0.88 (95% CI 0.51-1.50)
Rancinin *et al*, 2002 (283)	Aquitaine cohort, France	995 (419, 576)	Multivariable Cox regression of survival from cohort entry to all-cause mortality	AHR for mortality among co-infected compared to mono-infected individuals 1.20 (95% CI 0.75-1.92)

Reference	Study setting	Number included in analysis (HIV mono-infected, HCV co-infected)	Relevant analysis	Relevant results[2]
Rockstroh *et al*, 2005[1](252)	EuroSIDA cohort, including individuals from 89 centres in Europe, Israel and Argentina	5757 (3997, 1960)	Poisson regression of factors associated with all-cause and liver-related mortality	ARR for mortality among co-infected compared to mono-infected 1.80 (95% CI 1.44-2.25) ARR for liver-mortality among co-infected compared to mono-infected 12.31, 95% CI 6.77-22.41
Sulkowski *et al*[1](246)	John Hopkins HIV cohort study. A university based HIV clinic cohort, USA	1955 (1082, 873)	Multivariable Cox regression of survival from cohort entry to all-cause mortality	AHR for mortality among co-infected compared to mono-infected individuals 1.05, 95% CI 0.85-1.30
Sullivan *et al*[1](280)	Adult and adolescent spectrum of HIV disease project. Including 100 HIV inpatient and outpatient facilities, USA	10481 (8457, 2024)	Multivariable Cox regression of survival from cohort entry until all-cause mortality	AHR for mortality among co-infected compared to mono-infected individuals 1.1 (95% CI 0.9-1.2)

Reference	Study setting	Number included in analysis (HIV mono-infected, HCV co-infected)	Relevant analysis	Relevant results[2]
Tedaldi *et al*[1] (281)	HIV outpatients study. Three clinics, USA	823 (556, 267)	Multivariable Cox regression of survival from cohort entry until all-cause mortality	AHR for mortality among co-infected compared to mono-infected individuals 0.91 (95% CI 0.55-1.51)
Voirin *et al*[1] (295)	French Hospital database of HIV-positive individuals, Lyon, France	1490 (1285, 205)	Multivariable Cox regression of survival from cohort entry until all-cause mortality comparing HIV mono-infected individuals who do not inject drugs	AHR for mortality among co-infected non-IDU compared to mono-infected individuals non-IDU 0.76 (95% CI 0.28-2.08) AHR for mortality among co-infected IDU compared to mono-infected non- IDU 2.90 (95% CI 1.62-5.20)
Weber *et al*[1](291)	Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) Study, Europe, USA, Australia	23441 (18167, 5274)	Poisson regression of factors associated with liver-related mortality	ARR for 6.7 for co-infected compared to mono-infected individuals, 95% CI 4.0-11.2

Reference	Study setting	Number included in analysis (HIV mono-infected, HCV co-infected)	Relevant analysis	Relevant results[2]
Weis *et al*[1] (253)	Danish HIV cohort, nationwide cohort study, Denmark	1726 (1283, 443)	Multivariable Cox regression of survival from cohort entry to all-cause and liver-related mortality	AHR for all-cause mortality among co-infected compared to mono-infected individuals 2.4, 95% CI 1.3-2.6 AHR for liver-mortality among co-infected compared to mono-infected individuals 15, 95% CI 7.1-34.0

[1] Study included in meta-analysis from Chen *et al* (275)
[2] AOR – adjusted odds ratio; AHR – adjusted hazards ratio; 95% CI – 95% confidence interval; EDR – excess death rate; CHR – crude hazards ratio; ARR – adjusted rate ratio

2.2.3 The effect of HCV infection on the immunological and virological response to HAART

An individual's response to HAART can be described in terms of suppression of HIV replication (decreased HIV viral load) or in terms of recovery of immune restoration, measured as increases in CD4 cell count and maintenance of high levels of CD4 cells. Co-infection with HCV may affect the response to HAART. In this section I will describe the currently available knowledge on the extent to which co-infection with HCV does or does not affect an individual's response to treatment with HAART. The biological mechanisms by which HCV may affect the response to HAART are beyond the scope of this literature review.

A meta-analysis of studies published by May 2004 used median change in CD4 count after starting HAART as a measure of response to treatment. The analysis included results from 8 cohorts of HIV-positive individuals with follow up ranging from 48 months to 4 years. After at least 48 weeks of HAART the increase in CD4 cells among HCV co-infected individuals was 33.4 cells/mm^3 (95% CI -43.3-23.5 cells/mm^3) less than among HIV mono-infected individuals. This result proved to be insensitive to any one of the included studies and did not depend on year of HAART initiation (296).

A number of the studies which were included in the meta-analysis also reported on the effect of HCV co-infection on the virological response to HAART: the decrease in HIV viral load and the ability to maintain an undetectable HIV viral load. In general, these studies found that there was no difference in the virological response to HAART between HCV co-infected individuals and HIV mono-infected individuals (230, 231, 243, 274, 297). However, one study did show a trend towards smaller decreases in HIV viral load in HCV co-infected individuals compared to HIV mono-infected individuals (283). In addition to reporting on both the overall virological and immunological responses to HAART, Greub *et al* also conducted a nested study of 56 patients with well controlled viral load but differing CD4 responses. Although the numbers in this study were very small, the results indicated that there may be a link between decreased immunological response to HAART and infection with HCV genotype 3 (243).

In more recent studies, there have been a range of results with some studies showing no effect of HCV co-infection on the response to HAART and others, like the meta-analysis, showing a decreased response to HAART in HCV co-infected individuals. Among the Atlanta Veterans Affairs cohort study of 970 HIV-positive individuals, CD4 count was measured three times: within 6 months of HCV test; 6 months after initiation of HAART; and at last visit prior to study

end date (October 2001). No difference was reported in recovery of CD4 counts after starting HAART between those who were co-infected with HCV and HIV mono-infected patients at six months post initiation of HAART. The longer term model which considered difference in CD4 count from initiation of HAART to last visit also showed no difference in CD4 changes between the two groups (241).

Analysis of data from the EuroSIDA cohort also did not show any significant differences in the increase in CD4 count or the time taken to detect that increase. However, this study did find that HCV co-infected individuals were less likely to commence HAART than HIV mono-infected individuals (252). Similarly, in a previous analysis of data from the UK CHIC, there was no impact on either the virological or the immunological response to HAART in HCV co-infected compared to HIV mono-infected patients. This analysis also investigated the possibility of discordant virological and immunological responses and found no evidence for an association between HCV co-infection and discordant responses to HAART (244).

Among a cohort of individuals who were enrolled in randomised controlled trials for antiretroviral drugs in Thailand, there was no significant difference in virological response between HCV co-infected individuals and HIV mono-infected individuals. There was a decreased immunological response to HAART at weeks 4 and 8 weeks but by 48 weeks of follow-up the increases in CD4 count were comparable between HCV co-infected and HIV mono-infected individuals (298). Interestingly this study included very low proportions of individuals who were infected through injecting drug use unlike many other cohorts.

Other recent studies have found that HCV co-infection does affect the response to HAART. In a cohort of HIV-positive veterans in the USA, where there is a high prevalence of HCV, both HCV co-infected and HIV mono-infected individuals had similar virological responses to HAART. However, the immunological response to HAART was lower among HCV co-infected individuals, evidenced by lower maximum CD4 counts and lower median CD4 counts at 6 months follow up (284)

In the HAART Observational Medical Evaluation and Research study, outcomes were defined as an absolute CD4 event, defined as an increase of 75 or more cells/mm^3, and CD4 fraction event, defined as an increase of 10% of CD4 cells out of the total T cell population. HCV co-infected patients took longer to experience each of these outcomes than HIV mono-infected

patients. This cohort included a very high proportion of people with HCV infection (51%). In an adjusted Cox regression analysis, HCV co-infected patients were less likely to experience an absolute CD4 response than HIV mono-infected individuals. This study had the advantage of being able to account for adherence to HAART during the first year of HAART. This was based on the proportion of time that dispensed antiretroviral drugs would last and was classified into a binary variable of ≥95% or <95% adherence allowing the analysis to be restricted to individuals with ≥95% adherence (299).

The ICoNA study conducted an analysis of 1053 individuals with known HCV-RNA test results and compared the response in those who were HIV-positive and HCV-viremic with that among those who were HCV-negative. HCV co-infected patients were significantly less likely to achieve an increase of greater than 100 CD4 cells during follow up (maximum follow up 80 weeks). However, the CD4 recovery post-HAART initiation did not appear to be dependent on HCV viral load and did not appear to be influenced by HCV genotype (300).

There are a number of possible reasons for the contradictory results seen in published data. Firstly, most studies are unable to account for adherence to HAART. Adherence may be worse among HCV co-infected patients and therefore result in an observed decreased immune response. Secondly, many studies do not measure time on HAART and it is possible that the impact of HCV infection on response to HAART may be different at different stages of HAART treatment (i.e. decreased in earlier stages but the same over a longer period of follow-up). Similarly, the follow-up time for all the studies is different which may lead to different results. Thirdly, the prevalence of HCV within the cohorts studied and the profile of the HCV-infected cohort is different across the studies and this may affect results (for example IDU may have decreased responses to HAART and more co-infected patients may be IDU than HIV mono-infected patients). Finally, there may be other co-morbidities which affect the response to HAART and these are not recorded in studies to date. These possible reasons for conflicting results in the literature highlight the importance of forming treatment guidelines based on results of studies which are conducted in cohorts similar to the population needing treatment and also ensuring continual monitoring of individuals' responses to treatment.

2.3 The impact of co-infection with HBV on HIV infection

2.3.1 The effect of HBV on the progression of HIV to AIDS

In this section I will describe the progression of HIV infection to AIDS which may be defined either as an AIDS-defining illness or a point at which an individual has very suppressed immune function – usually defined as a CD4 count of <200 cells/mm^3.

In the pre-HAART era a small study of 347 newly HIV-positive who did not have AIDS were enrolled into a prospective cohort study. The median follow up was four years and 229 individuals showed signs of past or current HBV infection at enrolment (197 past infections and 32 current infections). A further 15 individuals became positive for HBsAg during follow up. Both progression to AIDS and progression to a CD4 count <200 cells/mm^3 from estimated date of HIV seroconversion were estimated. There were no significant differences in the time to these end points between currently HBV co-infected, HBV past-infected or HIV mono-infected individuals (301).

In the era of HAART, analysis of data from the EuroSIDA cohort showed that among 5728 individuals with known HBsAg status at enrolment there was no difference in the incidence of new AIDS-defining events between HBsAg-positive (8.7%) and HBsAg-negative individuals (ARR 0.94, 95% CI 0.74-1.19)(258) .

A large multicentre cohort study of MSM in the USA included men who initiated HAART while enrolled and who could be classified as HBV never infected, past infection, chronically infected or having isolated core antibody. Of 816 men, 350 had never been infected with HBV; 357 showed evidence of a past HBV infection; 45 were chronically infected with HBV; and 64 had isolated anti-HBc. Median follow up was 7 years and the large majority of patients (95%) received an HBV active drug as part of their HAART regimen. There was no difference in the incidence of AIDS-defining events between chronically infected and never infected individuals (302).

A retrospective study of 1792 HIV-positive individuals in Greece was conducted by testing stored serum samples for HBsAg where patients had 2 serum samples available. Patients were then classified as HBsAg-negative for both their samples, HBsAg-positive for both their samples (these individuals were considered probably chronically infected), HBsAg-negative followed by positive (classified as HBsAg convertors) or HBsAg-positive followed by negative (classified as

HBsAg revertors). Overall 13.24% of individuals experienced their first AIDS-defining event during follow-up. However, there was no significant difference in the incidence of AIDS-defining events by HBsAg status. The authors also conducted a meta-analysis of 7 studies (including their own). Three of these studies were conducted in the pre-HAART era. This also showed no effect of HBsAg status on the development of AIDS and there was no evidence of heterogeneity between the studies (p= 0.54, I^2 statistic 0%) (303).

The above studies were all conducted in geographic areas where HBV is not endemic and conclude that HBV infection does not increase progression of HIV to AIDS. By contrast, in a secondary analysis of data from two antiretroviral trials (where all patients were screened for HBsAg at entry) individuals who were co-infected with HBV had lower CD4 counts than those who were HIV mono-infected. This was a multinational study conducted in countries where HBV is endemic and infection was probably acquired in childhood. Similarly they had a higher prevalence of AIDS although this was not statistically significant, but HIV RNA levels did not differ (304). Therefore, although the majority of the literature suggests not increased progression of HIV in the context of HBV co-infection it is possible that that the impact of HBV on HIV infection is different depending on the duration of the HBV infection.

2.3.2 The effect of HBV on mortality in HIV-positive individuals

A summary of those studies which assess the effect of HBV co-infection on mortality among HIV-positive individuals is shown in Table 2.4. There are mixed results among studies with some showing a significantly increased risk of death among co-infected individuals compared to HIV mono-infected individuals and others showing no significant difference. The results of many of these studies were included in the meta-analysis conducted by Nikolopolous *et al*. In addition to reporting on progression to AIDS (see section 2.3), Nikolopoulos *et al* reported on mortality rates from a meta-analysis of 11 studies (involving 12382 individuals). The overall mortality rate in this cohort was 2.12 per 100 person-years. The incidence of death was slightly higher in the HBV chronically infected group (those with 2 positive HBsAg samples) compared to the never infected group (IRR 1.72, 95% CI 1.05-2.83). However, this difference was not maintained after adjusting for HIV viral load and CD4 count. After adjustment, no difference was seen between the mortality rates in the four HBsAg groups (never infected, chronically infected, HBV convertors and HBV revertors) (303). However, interpretation of these adjusted estimates is problematic since HBV infection may lead to difference in HIV viral load in CD4 count and these clinical factors are on the causal pathway to death.

The meta-analysis conducted by the authors included 11 studies. Four of the studies included in the meta-analysis were conducted before the HAART era. The studies did not show significant evidence of heterogeneity. The random effects model showed a significantly increased rate of mortality in HBV co-infected individuals compared to HIV mono-infected individuals (RR 1.36, 95% CI 1.12-1.64). This result appeared to be independent of any specific study (as assessed by omitting one study at a time) and the same effect was seen when conducting the analysis for studies in the pre-HAART era separately from those in the HAART era (303). The meta-analysis reported on all-cause mortality only and was not able to distinguish between liver-related deaths and other deaths. Therefore this increased mortality may not be an indication of increased progression of HIV. For example the study conducted by Thio *et al* showed that not only was all-cause mortality higher in co-infected individuals, but also that liver-related death was 8 times more likely among co-infected men compared to HIV mono-infected men.

An additional study which was not included in the above meta-analysis in the pre-HAART era is a case control study nested within a cohort of HIV-positive individuals in Italy (305). Being positive for HBsAg was significantly associated with death from liver disease compared to death from other causes. However, a high proportion of the cohort was co-infected with either HCV or HDV and so it is not possible to look at the association of HBV alone on death from liver disease compared to other causes. Other factors which were also associated with death from liver disease compared to death from other causes were alcohol abuse, higher CD4 count and older age at enrolment.

There are also a number of additional studies which were not included in the meta-analysis in the HAART era. Although in the MACS there was no difference in the incidence of AIDS-defining events between chronically infected and never-infected individuals (see section 2.3), both AIDS-related and non-AIDS-related mortality were higher among chronically HBV co-infected individuals than among HIV mono-infected individuals who had never had HBV (302). Liver-related deaths were also investigated within the D:A:D study which included 23,114 individuals followed for a median of 3.5 years. This analysis indicated that active HBV infection was associated with liver-related death. The authors also reported that liver-related disease was associated with immune-suppression as measured by decreased CD4 counts (a 2-fold lower CD4 count resulting in a 23% increased risk of liver-related death) (291).

In the US Military HIV Natural History Study, all included patients are known to have been infected with HIV for 3 years or less. Therefore the effect of duration of HIV infection was minimised in this study. Patients were classified according to their HBsAg status as negative (74%), resolved HBV infection (20%), isolated anti-HBc (3%) and chronically infected (3%). AIDS events and death were reported together in this analysis. Before adjustment for potential confounders all categories of HBV infection were associated with an increased risk of AIDS or death. After adjustment, in a multivariable model, only chronic HBV infection was associated with an increased risk of AIDS or death. Other factors associated with AIDS or death were a low CD4 count, no receipt of HAART and HCV infection. Therefore it is not possible to assess whether HBV is a surrogate marker of poor outcome or whether it has a direct harmful impact on HIV disease. In addition, the cause of death is not reported and so it is not possible to assess whether these deaths were liver-related or not (306).

Table 2.4 Studies comparing mortality rates in HIV mono-infected and HIV/HBV co-infected individuals in the era of HAART

Reference	Study setting	Number included in analysis (HIV mono-infected, HBV co-infected)	Relevant analysis	Relevant results[2]
Bonacini *et al*, 2004 [1] (290)	University clinic cohort, USA	198 (126, 72)	Unadjusted all-cause and liver-related mortality	26% (19/72) of individuals died in co-infected group compared to 33% (41/126) in the HIV mono-infected group 15% (11/720 of the co-infected individuals had liver-related death compared to 6% (7/126) of mono-infected individuals had liver-related deaths (P=0.04)
Chun *et al*, 2011 (306)	HIV sero-convertors in the US Military HIV Natural History Study, USA	2352 (2288, 64)	Multivariable Cox regression of all-cause mortality/AIDS events combined	AHR for mortality/AIDS event among co-infected compared to mono-infected 1.80 (95% CI 1.20-2.69)

Reference	Study setting	Number included in analysis (HIV mono-infected, HBV co-infected)	Relevant analysis	Relevant results[2]
Hoffman *et al*, 2009 (302)	Multicentre AIDS cohort study (MACS), USA	395 (350, 45)	Multivariable Poisson regression of factors associated with AIDS-related mortality and non-AIDS mortality	IRR for AIDS-related mortality among co-infected compared to mono-infected individuals 2.7 (95% CI 0.9-8.2) IRR for non-AIDS mortality among co-infected compared to mono-infected individuals 4.1 (1.0-16)
Konopnicki *et al*, 2005 [1] (258)	EuroSIDA cohort, including individuals from 72 centres in Europe, Israel and Argentina	5728 (5230, 498)	Poisson regression of factors associated with all-cause and liver-related mortality	IRR for all-cause mortality among co-infected compared to mono-infected individuals 1.54 (1.19-1.98) IRR for liver-related mortality among co-infected compared to mono-infected individuals 3.31 (95% CI 1.80-6.11)

Reference	Study setting	Number included in analysis (HIV mono-infected, HBV co-infected)	Relevant analysis	Relevant results[2]
Nikolopolous *et al*, 2009 [1] (303)	Retrospective cohort study, Greece	1729 (1528, 107)	Poisson regression of factors associated with all-cause mortality	Adjusted IRR for mortality among HBsAg-positive individuals compared to HBsAg-positive individuals 1.72 (95% CI 1.05-2.83)
Nikolopolous *et al*, 2009 (303)	Meta-analysis of studies comparing mortality among HBV co-infected and HIV mono-infected individuals	6 studies in the post HAART era	Pooled measure of random effects model	Pooled effect estimate of co-infection on mortality rates in post-HAART era 1.28 (95% CI 1.03-1.60)
Osborn *et al* 2007 [1] (257)	HIV Atlanta Veterans Affairs Cohort Study (HAVACS), USA	443 (286, 157)	Multivariable Cox regression of all-cause mortality	AHR for mortality among co-infected compared to mono-infected individuals 1.28 (p=0.27)
Sheng *et al*, 2004 [1] (307)	National Taiwan University Hospital cohort, Taiwan	498 (387, 111)	Multivariable Cox regression of all-cause mortality	AHR for mortality among co-infected compared to mono-infected individuals 1.71 (95% CI 1.19-2.47)

Reference	Study setting	Number included in analysis (HIV mono-infected, HBV co-infected)	Relevant analysis	Relevant results[2]
Thio *et al*, 2002 (261)	Multicentre AIDS cohort study (MACS), USA	2559 (2346, 213)	Poisson regression of liver-related mortality	ARR for mortality among HIV-positive, HBsAg-negative individuals and HIV-positive, HBsAg-positive individuals compared to HIV-negative HBsAg-negative individuals 1.7 (p<0.0001) and 14.2 (p<0.0001) respectively
Weber *et al*[1](291)	Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) Study, Europe, USA, Australia	23441 (21847, 1594)	Poisson regression of factors associated with liver-related mortality	ARR for liver-related mortality among co-infected compared to mono-infected individuals 3.7 (95% CI 2.4-5.9)
Zhou *et al*, 2007 [1] (308)	The TREAT Asia HIV Observational Database, a multicentre study at 15 sites in the Asia Pacific region	1641 (1470,171)	Multivariable Cox regression of all-cause mortality	AHR of mortality among co-infected compared to mono-infected individuals 0.80 (95% CI 0.24-2.64)

[1] Study included in meta-analysis from Nikolopolous *et al* (303)

[2] AOR – adjusted odds ratio; AHR – adjusted hazards ratio; 95% CI – 95% confidence interval; EDR – excess death rate; CHR – crude hazards ratio; ARR – adjusted rate ratio

2.3.3 The effect of HBV infection on the immunological and virological response to HAART

A number of studies have investigated whether co-infection with HBV has an impact on the virological or immunological repose to HAART and there have been some conflicting results. In general, studies which have assessed response to HAART by examining increases in CD4 count have found no difference in response to HAART between HBV co-infected and HIV mono-infected persons. This was shown in the EuroSIDA cohort (258), in the USA in the MACS cohort (302), in a nationwide Danish cohort study (264), in a South African cohort (309) and in a large Australian cohort (231). A retrospective analysis of a cohort of HIV-positive individuals investigated the response to HAART in the context of HBV co-infection only by measuring the virological response. This study also did not find any association between response to HAART and HBV co-infection (303).

In contrast to these results, there have been some studies which have shown an impaired response to HAART associated with HBV co-infection. In the Swiss cohort study patients were followed for three years after starting HAART. Throughout these three years individuals who had current or resolved HBV infection had significantly lower CD4 counts than those who were HBV uninfected. CD4 recovery was particularly impaired among those individuals who had detectable HBV-DNA one year after starting HAART (265). In a cohort of individuals in Thailand an impaired response to HAART was observed in the first four weeks of treatment where those who were HBV co-infected had significantly lower mean increases in CD4 count than those who were HIV mono-infected. However, this difference was not sustained in the longer term and by 48 weeks of treatment the mean increases in CD4 count were similar (298).

The reasons for the conflicting results described in the studies above are unclear. However, it should be noted that in HBV co-infected patients HAART regimens will almost always include an agent which is active against HBV. Few studies have included the components of HAART regimen as a covariate in the analyses performed and therefore the difference may in part be due to the impact of HAART on HBV infection as well as HIV infection. For example, where no association is observed between HBV co-infection and response to HAART this may be, in part due to successful suppression of HBV by the HAART regimen, thus limiting the impact of HBV on the response to HAART.

2.4 Co-infections with hepatitis viruses and the development of anti-retroviral induced hepatotoxicity

Hepatotoxicity, usually expressed as liver enzyme elevation (LEE), can develop in HIV-positive patients in response to treatment with antiretroviral drugs. Infection with hepatitis viruses can also lead to LEE. In this section I will describe how co-infection with hepatitis viruses affects the development of hepatotoxicity in response to HAART. This has been investigated in the literature by comparing the risk and rate of development of LEE in HIV mono-infected patients with that in hepatitis co-infected patients. Analysis of co-infection and hepatotoxicity is complicated by the fact that in many cohorts co-infection is more prevalent among IDU than in those who do not inject drugs. Since injecting drug use is also a risk factor for hepatotoxicity there is the possibility that this may affect results, particularly in smaller cohorts.

Higher rates of LEE are seen among hepatitis co-infected individuals compared to HIV mono-infected individuals. This has been shown both in cohorts with high hepatitis prevalence (310, 311) and in cohorts where hepatitis prevalence is lower (312, 313). However, these studies have not examined the effect of HBV and HCV on rates of LEE separately. For example, one of the largest studies of hepatotoxicity in hepatitis co-infected and HIV mono-infected individuals used data from patients in the ICoNA study. A total of 5272 patients were included. A high prevalence of co-infection was present but this was mostly due to HCV co-infection: 47.6% of patients were co-infected, of whom 85.6% were HCV co-infected, 7.7% were HBV co-infected and 6.8% were HBV and HCV co-infected. Co-infection with hepatitis viruses was significantly associated with increased risk of LEE (RR 5.07, $p<0.0001$). This association with co-infection was not different between those on HAART and those not on HAART, indicating that the LEE was due to hepatitis infection rather than as a result of HAART (310).

In some larger cohorts researchers have been able to examine the separate effects of HBV and HCV co-infections on the development of hepatotoxicity. For example, among a cohort of 560 HIV-positive patients, the risk of developing LEE was 2.78 times greater among co-infected individuals than among HIV mono-infected individuals (314). Specifically both chronic HBV (adjusted hazard ratio (AHR) 4.6, 95% CI 2.6-8.3) and chronic HCV (AHR 3.2, 95%CI 1.8-8.3) were associated with grade 3 or 4 LEE. In this cohort although the hazards ratios are relatively high, it is worth noting that only a small proportion of individuals in the cohort actually experienced LEE (7.7% overall) and that the clinical impact of these episodes was small – a minority were symptomatic and all resolved (315). The finding that the risk of LEE is higher

among hepatitis co-infected individuals than among HIV mono-infected individuals but the clinical impact of this is minimal has also been shown in a number of other studies (316, 317).

Some researchers have investigated factors associated with LEE in co-infected individuals. In the study previously described by Wit *et al*, neither absolute nor changes in CD4 count were associated with LEE (315). In contrast, Aceti *et al* observed that at 12 months among HCV co-infected individuals hepatotoxicity was more frequent in individuals with lower CD4 count and higher viral load and that patients with higher CD4 increases had faster decreases of ALTs than patients with lower CD4 counts (318).

It is possible that the degree of liver damage in co-infected patients may affect the development of hepatotoxicity. A significant correlation between liver fibrosis stage and incidence of hepatotoxicity has been observed with higher incidence in individuals with stage 3 or 4 fibrosis. Among only those with stage 3 or 4 fibrosis incidence of hepatotoxicity was higher in individuals who were on a NNRTI based regimen compared to those not exposed to NNRTIs. The use of NNRTIs did not affect hepatotoxicity incidence in those with stage 1 or 2 fibrosis (319). This effect was not seen in a Spanish cohort of patients treated with PIs (atazanavir or ritonavir). In this cohort almost all patients were co-infected with HCV (98%) (320).

It is clear from the literature that those individuals on HAART and co-infected with hepatitis viruses, are at increased risk of developing LEE compared to HIV mono-infected individuals. However, these events may or may not have significant clinical impact. Therefore in the context of hepatitis virus co-infection, clinicians should carefully consider the choice of drugs included in a HAART regimen with regards to their liver toxicity profiles (65) and HIV and hepatitis co-infected individuals should be frequently monitored for liver damage caused not only by their hepatitis infection but also possibly by their HIV treatment.

2.5 The impact co-infection with HIV on HCV infection

In this section I will describe the current knowledge on how HIV affects the progression of HCV. This may be with regard to levels of virus present in the blood, progression from acute to chronic infection or with regard to clinical outcomes of HCV infection including risk of development of liver fibrosis and its progression to cirrhosis, steatosis, end-stage liver disease

and HCC. I will also describe how the use of HAART may affect the progression of HCV infection in HIV co-infected individuals.

2.5.1 The effect of HIV on HCV progression

Evidence from studies conducted in the pre-HAART era suggests that co-infection with HIV is associated with higher levels of HCV-RNA. A multi-centre cohort study of haemophilia patients was initiated in 1982. In order to investigate the effect of HIV on HCV infection with regard to HCV-RNA levels data were analysed from a group of patients who were all positive for HCV before recruitment. Seventeen of these patients seroconverted to HIV during follow up and 17 remained HIV-negative. Over the total study period (up to 13 years), the mean HCV-RNA levels increased 58 fold in those who became HIV-positive, while the increase was much smaller (3-fold) in those who remained HIV-negative. There was a clear correlation between the degree of immunosuppression and the HCV-RNA level among the individuals who became HIV-positive during follow-up, with those with lower CD4 counts having higher mean HCV-RNA levels (321).

These findings have been confirmed in larger studies. HCV-RNA level was correlated with CD4 count in a study of 116 HIV co-infected individuals and 431 HCV mono-infected individuals where in the HIV-positive group CD4 counts greater than 500 cells/mm3 were associated with lower HCV-RNA levels (322). In 2 studies, HIV co-infected individuals were matched to HCV mono-infected individuals. In 80 HCV mono-infected and 80 HIV co-infected patients, followed for 52 months, HIV patients had significantly higher mean serum HCV-RNA levels than HIV-negative controls and serum high HCV-RNA level was associated with low CD4 count (323). The same pattern was seen among 38 HIV co-infected and 38 HCV mono-infected individuals with a history of injecting drug use (324).

Finally, in a more recent study of HCV-infected patients in China (25% of whom were HIV co-infected), levels of HCV core antigen (indicating chronic infection) were shown to be negatively correlated with CD4 count among the co-infected group (325).

The long asymptomatic period in HCV infection means that many new infections are undetected and therefore studying the early phases of infection is difficult. However, current evidence suggests that HIV-positive individuals are less likely to spontaneously clear acute HCV infection than HIV-negative individuals. In a small cohort of 112 HIV-positive patients with acute HCV, followed for a median of 45 months, 15% of patients cleared the infection while the others progressed to chronic infection (326). This compares to proportions of 36%-54% of

HCV mono-infected patients who have been reported as clearing HCV infection (327, 328). Among HIV-positive individuals clearance of acute infection was associated with higher CD4 counts (above 650 cells/mm3), having a rapid HCV viral decline, elevated ALT and bilirubin levels and infection with HCV genotype 1 (326). In addition, in a study of 43 HIV-positive individuals with acute HCV there was evidence for delayed development of anti-HCV with 37% of individuals remaining antibody negative at 3 months after diagnosis, 10% at 9 months and 5 % at 1 year after diagnosis (329).

The clinical impact of co-infection has also been investigated in a number of cohorts. A meta-analysis conducted predominantly in the pre-HAART era included 8 studies involving a total of 1871 HCV-positive patients (601 were HIV co-infected and 1370 were HCV mono-infected). The authors assessed the development of cirrhosis or clinically identified decompensated liver disease in HIV co-infected patients compared to HCV mono-infected patients. Two of the included studies assessed only decompensated liver disease, 4 assessed only cirrhosis and 2 assessed both outcomes. Overall, the populations studied were predominantly male. Only one study included the role of HAART in their analysis (330). Combined relative risk for development of decompensated liver disease or cirrhosis across the studies was 2.92 (95% CI 1.70-5.01) for co-infected individuals compared to HCV mono-infected individuals. When the analyses were conducted separately for decompensated liver disease and cirrhosis combined relative risks were 6.14 (95% CI 2.86-13.20) and 2.07 (95%CI 1.40-3.07), respectively. Three studies which investigated duration of HCV infection found that a higher proportion of HIV co-infected patients developed severe liver disease <15 years after HCV exposure than HCV-mono-infected patients. Five of the included studies found an increased risk of liver disease in those patients with a lower CD4 count or AIDS. Although alcohol consumption was described in 5 studies a range of measures were used and therefore this could not be included in the meta-analysis (331).

In a further meta-analysis, conducted in the era of HAART, the authors estimated the rate of fibrosis progression and identified factors associated with higher or lower rates of progression as well as comparing fibrosis progression among HIV/HCV co-infected and HV mono-infected individuals. In 17 studies, involving 3567 HIV/HCV co-infected individuals, liver fibrosis progression was shown to be constant across all stages of fibrosis but was shown to be significantly influenced by duration of HCV infection with longer duration being associated with a slower rate of fibrosis progression. The estimated weighted proportions of co-infected

individuals with cirrhosis at 20 and 30 years after HCV infection were 21% and 49%, respectively. Among 27 studies involving 7666 individuals (4970 with HCV mono-infection and 2636 with HIV co-infection) there was a significantly higher risk of cirrhosis in HIV co-infected patients compared to HCV mono-infected patients (RR 2.11, 95% CI 1.51-2.96). These effects were seen both in patients on and not on HAART. In meta-regression analysis there was no significant association between HAART, or CD4 count, and risk of cirrhosis, indicating that HAART and recovery of the immune system do not fully limit the impact of HIV in HCV progression (332).

It should be noted that selection bias may be present in a number of cohort studies included in the meta-analyses since recruitment of subjects is often dependent on referral for liver biopsy and those patients who have a liver biopsy may not be representative of all patients who are infected with HCV. They may be more adherent to antiretroviral treatment, less likely to drink alcohol and more likely to have stable HIV disease and more likely to be symptomatic for HCV disease. Factors associated with fibrosis progression in co-infected individuals have been reported as heavy alcohol intake, length of HCV infection, failure of HCV treatment and higher ALT levels (333), as reported in HCV mono-infected patients. Difficulties with comparing results arise from the fact that many different measures are used for these outcomes (particularly for measuring degree of fibrosis present) and because HCV may be asymptomatic in the acute phase, the duration of the infection is often unknown.

A number of studies, conducted after these meta-analyses, provide additional evidence of increased progression of HCV infection when individuals are co-infected with HIV. In particular, the studies examined how the degree of immunosuppression impacts on the development of cirrhosis and HCC. Among a cohort of HIV co-infected individuals in France, HCC was strongly associated with a low CD4 count at the time of cancer diagnosis. However, due to small numbers, this analysis was not conducted separately for HCC that resulted from HBV or HCV infection (334). Similarly, a case control study of individuals with HCC compared to those without, nested within the Swiss HIV Cohort Study of HIV-positive individuals, found that a higher level of immunodeficiency was associated with HCC (with an odds ratio (OR) of 1.33 per 100 CD4 cells/mm^3 lower). Again, it was not possible to distinguish between HBV and HCV infections in this analysis (335). In a cross-sectional study of HIV-positive patients in Madrid, Spain, cirrhosis was also associated with lower CD4 counts and the main cause of cirrhosis was HCV (336).

In contrast to these results a large study in the USA of patients attending one Veterans' Health Administration Hospital between 1991 and 2000 found no association between HIV co-infection and risk of developing cirrhosis in the HAART era although there was an increased risk of cirrhosis for co-infected patients in the pre-HAART era. The authors also found no association between HIV co-infection and HCC irrespective of whether patients were recruited in the HAART era or earlier (337). Although higher rates of HCC were observed in the co-infected group compared to the HCV mono-infected group, the association between co-infection and HCC disappeared after controlling for confounding factors.

Hepatic steatosis, or fatty liver, is important in HCV infection as it is associated with increased risk of fibrosis and HCC in HCV mono-infected individuals (338, 339). A meta-analysis was conducted of 12 studies, involving 1989 individuals, which aimed to investigate the prevalence of steatosis in HCV/HIV co-infected individuals and risk factors for steatosis. Four of the included studies also included data from a comparison group of HCV mono-infected patients (a total of 1540 individuals). The study showed that HIV co-infection did not increase the risk of hepatic steatosis compared to the risk in HCV mono-infected patients (pooled OR 1.67, 95% CI 0.84-2.10). In the pooled data, steatosis was not associated with HIV viral load, HCV viral load, HCV genotype, CD4 count or patient demographic characteristics. However, it was associated with body mass index, the presence of diabetes, elevated ALT levels and fibrosis (340). There was significant heterogeneity between studies included in the meta-analysis and the overall findings differ from some of the individual results of the included studies. Two of the included studies did find an association between higher HCV viral load and steatosis (341, 342) one included study found that individuals with a detectable HIV viral load had less steatosis than those with undetectable viral load (343).

In summary, evidence from cohort studies of HIV/HCV co-infected individuals combined with and comparing the results of studies which examine progression of HCV among co-infected with studies which examine progression in HCV mono-infected individuals indicates that individuals who are co-infected with HCV and HIV are at increased risk of chronic infection as well as increased risk of progression of liver disease compared to individuals infected with HCV alone.

2.5.2 The effect of HAART on liver outcomes of HCV infection

In this section I will discuss how treatment for HIV with HAART can impact on liver outcomes in co-infected individuals. This is complex since having a better immune system, as a result of

HAART, may improve liver outcomes while use of HAART may also contribute to increased liver damage in co-infected patients.

Although liver disease has been shown to be an important cause of mortality in HIV-positive patients in the era of HAART, there is some evidence that HAART is protective against progressive liver disease. For example, time from first liver decompensation event to death was increased in individuals who were treated with HAART. This analysis did not distinguish between patients who were co-infected with HBV or HCV but the total number of individuals included who had HBV infection was small (292). In addition, longer duration on HAART has been shown to be associated with less severe fibrosis (344, 345) and in a study in Los Angeles, USA, HIV/HCV co-infected individuals on HAART were shown to have similar rates of fibrosis as HCV mono-infected patients (346, 347) indicating that HAART is protective against liver disease in the context of HCV co-infection.

There may be some differences in the impact of different classes of HIV drug on liver outcomes. A number of studies have found an association between the use of specific NRTIs and the development of liver fibrosis, cirrhosis and decompensated liver disease in HIV/HCV co-infected patients. These drugs are also known to cause liver damage in HIV-mono-infected patients. In the ARNS HCO2 Ribaviric study, fibrosis was assessed over a two year period by comparing paired biopsy samples. A worsening in fibrosis was associated with use of didanosine as part of the HAART regimen (348). Similarly, in a case series of patients from the same trial, use of didanosine was associated with spontaneous hepatic decompensation (349).

In a cross-sectional study of HIV-positive patients undergoing assessment for liver disease by FibroScan® there were 389 patients who were co-infected with HCV. Among this co-infected subgroup, advanced liver fibrosis was more common in individuals who had never received HAART compared to all the others, indicating a protective effect of HAART in co-infection. However, those individuals with prolonged exposure to HAART (>6 years) had higher rates of advanced liver fibrosis than those with shorter term exposure to HAART, which may indicate some effect of HAART on fibrosis over time. In multivariate analysis, use of NRTIs (didanosine and stavudine) as a component of HIV treatment was associated with advanced liver fibrosis; this analysis was conducted for both HIV mono-infected and HIV/HCV co-infected patients combined, however, and therefore it is not possible to assess the impact of these drugs specifically in HCV co-infected patients (350).

A study of 201 co-infected patients assessed the effect of NNRTIs and PIs in fibrosis. The authors found that a shorter duration of HAART was associated with advanced fibrosis and the level of fibrosis decreased significantly with each additional year of HAART. This was shown to hold true for NNRTIs as a class and for nevirapine and efavirenz individually but not for PIs (351)

In contrast, the use of PIs as part of a HAART regimen has been shown to be associated with a reduced risk of liver disease. Among a cohort of 182 co-infected patients in France, 35% were on a PI and these patients showed significantly lower levels of liver fibrosis than patients who were not treated with a PI (352). Likewise, in a cross-sectional study of 116 HIV/HCV co-infected patients, the rate of fibrosis progression was slower among individuals who were on PIs compared to those who were not on PIs, with a trend towards higher fibrosis scores for patients who were on stavudine (353). Among 152 HIV/HCV co-infected patients treated at an infectious disease unit in Spain, use of PIs was protective against high grade fibrosis whereas use of nevirapine was associated with more advanced fibrosis (354).

The meta-analysis (described previously) of steatosis in co-infected individuals did not find any associations between antiretroviral classes and steatosis in the pooled data (340). However, one of the included studies did find an association between NRTI use and steatosis (343) while another found NNRTI use to have a protective effect (355). In a more recent study, of paired biopsies from 222 HIV/HCV co-infected individuals, a high CD4 count and HIV treatment was associated with a reduced progression of HCV to steatosis (356).

Finally, the importance of continuity of treatment has been shown in a number of studies. Permanent HAART discontinuation was associated with hepatic decompensation in a prospective study of 248 co-infected patients in a multicentre study in Spain (357) and in a multi-centre prospective study in Canada, treatment interruption was a risk factor for development of fibrosis among 541 HIV/HCV co-infected individuals (358).

While the choice of appropriate drugs to be included in the HAART regimen is clearly important, it is clear that high CD4 count achieved through HAART is highly important in preventing the development of liver disease in HIV/HCV co-infected individuals.

2.5.3 Impact of HAART on HCV viral load

A number of small studies have shown that in HIV/HCV co-infected patients after initiation of HAART, as HIV viral load decreases, there is an increase in HCV viral load (297, 359-361). Among co-infected patients in residential care homes in New York, this increase in serum HCV was maintained at 9 months. However, it is worth noting that these patients were at a very late stage of HIV infection and had a mean baseline CD4 count of <200 cells/mm^3 (360).

Conversely in a cohort of 50 co-infected patients in Australia more than half (54%) experienced a significant increase in HCV levels after initiation of HAART but for most patients this increase peaked between 1 and 3 months and then declined. Where particularly large increases in HCV viral load occurred they were associated with baseline CD4 counts of <200 cells/mm^3 (361) . Similarly, in a cohort of 60 co-infected individuals, in the USA, larger increases in HCV viral load were seen in patients with lower CD4 counts at HAART initiation; those with higher CD4 counts had initial increases in HCV levels but these returned to normal by 48 weeks (297).

2.6 The impact of co-infection with HIV on HBV infection

2.6.1 The effect of HIV on the serological profile of HBV

In this section I will describe the effect of HIV on the development of chronic HBV infection and the production of antibodies to HBV. In mono-infected patients HBV-DNA levels are correlated to the degree of cirrhosis and risk of HCC. Therefore while there may be few studies of the direct impact of HIV on progression of fibrosis, the studies which find differences in the course of HBV infection with regard to presence of antigens, antibodies and HBV-DNA are relevant to the clinical progression of infection.

Evidence for the effect of HIV on the natural history of HBV infection is available from studies conducted in the pre-HAART era. In a small study of 77 individuals acutely infected with HBV, HBsAg status was assessed at 6 months after the diagnosis of acute infection. Where HBsAg was present at 6 months these individuals were considered to be chronically infected. In this cohort, 40% were HIV co-infected and a significantly higher proportion of co-infected individuals developed chronic infection (26%) compared to HBV mono-infected individuals (4%) (362).

In a larger study, conducted in the era of HAART, a total of 2037 patients were classified as chronically infected (ever having 2 or more reactive HBsAg tests at least 6 months apart) having isolated anti-HBc, or having resolved HBV infection (positive for anti-HBc and anti-HBs). There was an increased risk of chronic infection compared to resolved or isolated anti-HBc in individuals who acquired their HBV after HIV compared to those who did not definitely acquire their HBV after HIV infection. The cohort was also stratified by CD4 count and this effect was seen in each of the strata (363). Taken together these results indicate an increased likelihood of progression to chronic infection after becoming infected in HIV-positive individuals compared to HIV-negative individuals.

The rate of loss of HBeAg and the prevalence of HBV-DNA were also investigated in the pre-HAART era. In a study of 152 MSM diagnosed with HBV before the end of 1987 and 212 HBsAg-negative controls, the HIV prevalence in the two groups was 41% and 70%, respectively. Patients were followed until April 1990. HIV/HBV co-infected individuals were more likely to be HBsAg positive and have higher HBV-DNA polymerase activity (indicating higher levels of replication) than HBV mono-infected individuals and the rate of loss of serum HBeAg was lower among HIV-positive individuals. In this study, Gilson *et al* also showed evidence of increased rates of reactivation of HBV as evidenced by the reappearance of HBeAg after its initial disappearance (364). These differences may have an impact on the clinical manifestations of HBV in HIV-positive compared to HIV-negative individuals (364).

Similarly, among 150 MSM with chronic HBV infection, HIV-positive individuals were more likely to be positive for HBeAg and HBV-DNA and this was not dependent on CD4 count. None of the individuals who were HBeAg-negative at the beginning of the study had a reactivation of HBeAg over the study period and thus the authors concluded that the higher prevalence of HBeAg and HBV-DNA among HIV co-infected individuals was not due to reactivation but due to slower clearance of HBeAg; this effect was not altered by the degree of immunosuppression (365). A study by Colin *et al* also found higher levels of HBV-DNA in co-infected patients, but like the study by Bodsworth *et al*, this was found in the context of lower ALT levels (366). In a retrospective cohort study of 141 HBeAg-positive individuals, compared to HBV mono-infected patients, HIV co-infected patients had significantly higher HBV-DNA levels and this was independently associated with lower CD4 counts (367).

Among HBV co-infected patients recruited to two trials of antiretroviral therapy, high levels of HBV-DNA were associated with low CD4 counts. The median CD4 count did not differ significantly between individuals who were HBeAg-positive and those who were HBeAg-negative. However, overall a higher proportion of individuals had low levels of HBV-DNA than had been seen in previous studies (16% of HBeAg-negative individuals and 75% of HBeAg-positive individuals had undetectable HBV-DNA). This may be due to the duration of HBV infection since most individuals in these trials were living in areas of high HBV prevalence and had probably acquired their HBV infection when they were children. The authors postulated that the long-standing chronic nature of the HBV-infection in these patients may have led to immune activation and thus an increase in CD4 cell apoptosis (304).

The finding of slower clearance of HBeAg in HIV-positive individuals has been confirmed in the HAART-era. In a retrospective multicentre study in France (the GERMIVIC group), among 477 individuals with past or present HBV infection, HIV-positive individuals were more likely to be HBeAg-positive and less likely to be anti-HBe and anti-HBc positive at baseline. Over follow-up, a significantly lower proportion of HIV co-infected individuals cleared HBeAg and seroconverted to anti-HBe compared to HBV mono-infected individuals. In this population, clearance of HBeAg was associated with histological improvement, indicating that in the presence of HIV, where HBeAg is less likely to be cleared, HBV-infected individuals may have poorer clinical outcomes than in the absence of HIV (260).

Compared to the results of studies in the pre-HAART era, there are some conflicting findings with regard to the prevalence of HBV-DNA in HIV co-infected individuals in the HAART era. A subsequent analysis of data from 451 patients seen at GERMIVIC sites showed that HIV status was not associated with HBV-DNA levels. However, the authors of this study found that a higher proportion of HIV-positive individuals were on therapy for HBV which was likely to have controlled the levels of HBV replication (368).

Occult HBV is defined as the presence of low levels of HBV-DNA measured in the serum in the absence of HBsAg after the period of acute HBV infection (369). This phenomenon has been identified among HIV/HBV co-infected individuals (370-375), however other studies of HIV-positive HBV-negative individuals have failed to identify presence of HBV-DNA (376, 377). One study in South Africa has shown higher rates of occult HBV infection in HIV-positive individuals than in HIV-negative individuals (378). The clinical implications of occult HBV infection in HIV-

positive individuals remain unclear. It has been suggested that it may play a role in reactivation of resolved HBV infection in HIV-positive individuals and in LEE (379, 380). However, this is not be confirmed by other studies (375, 381).

In general, HIV/HBV co-infected individuals are more likely to become chronically infected, have higher levels of HBV replication, reduced loss of HBeAg, reduced development of anti-HBe and higher rate of reactivation of HBV virus than HIV uninfected individuals (382). As previously stated these findings are important as changes in the serological profile of HBV infection are predictive of clinical progression of the infection.

2.6.2 The effect of HIV on clinical outcomes of HBV

Evidence to date shows that HIV negatively impacts on the clinical outcomes of HBV infection. Studies to examine the effect of HIV on the clinical outcomes of HBV compare HIV/HBV co-infected groups to HBV mono-infected groups. The effect can be studied in terms of progression of fibrosis to cirrhosis, HCC or mortality. A study in the pre-HAART era assessed HBV outcomes in a cohort of 132 non-drug-using, chronically HBV-infected MSM who had not previously been treated and were also not infected with HCV or HDV; 65 (49%) of those were HIV-positive. A significantly higher proportion of HIV-positive individuals had cirrhosis compared to HBV mono-infected individuals and HIV positivity remained associated with cirrhosis in a multivariate model after adjusting for age, alcoholism, duration of HBV infection and HBeAg positivity (366).

In the HAART era, liver fibrosis was compared in 500 HIV-positive individuals and 500 HIV-negative individuals in Uganda. The prevalence of chronic HBV was similar between the two groups and in both cases was low (5% in HIV-positive and 3% in HIV-negative individuals). The prevalence of fibrosis was significantly higher among HIV-positive individuals compared to HIV-negative individuals (17% compared to 11%, p=0.008). However, given the low prevalence of HBV in both these groups the increase in fibrosis cannot be attributed to HBV co-infection (383). A more recent study of co-infected patients identified factors which were associated with fibrosis in a co-infected population. These were shown to be HBV genotype G (the strongest independent predictor), efavirenz exposure and longer duration of HIV infection (384).

Whether HIV co-infection increases the risk of HCC in co-infected patients compared to that in HBV mono-infected patients is less clear. As previously described in section 2.5.1, Clifford *et al*

reported an increased risk of HCC in co-infected persons in the context of HIV-related immunosuppression (lower CD4 counts) but it was not possible to attribute these cases of HCC to either HBV or HCV specifically (335). In the MACS cohort in the USA, 326 individuals were HBsAg-positive and 65% of those individuals were HIV co-infected. Liver mortality was significantly higher among the co-infected individuals compared to the HBV mono-infected individuals, indicating that HIV may accelerate progression of HBV infection (261).

Linkage of data from HBV and HCV notifications, HIV notifications and death registrations in New South Wales, Australia, has also shown higher all-cause mortality among HIV/HBV co-infected individuals (378.6/10,000 person-years) compared to HBV mono-infected individuals (37.6/10,000 person-years). However, the authors of this study also noted that a high proportion (70%) of these deaths were HIV-related and therefore may not represent an impact of HIV infection on HBV (385).

2.6.3 The effect of HAART on liver outcomes in HBV

A number of drugs used to treat HIV are also effective against HBV and in particular lamivudine, tenofovir and emtricitabine are approved for use against HBV. Therefore patients who are co-infected with HBV and HIV are usually commenced on HAART with a regimen that includes one of these drugs. In this section I will focus on how treatment for HIV with HAART affects the outcomes of HBV infection as a result of immune restoration. I will not consider the effects of particular anti-HBV drugs or their combinations on HBV or the development of resistance to these drugs as this will be covered in a section 2.8. Studies have assessed the effect of HAART by considering mortality, levels of HBV-DNA, clearance of HBV antigens and development and persistence of HBV-specific antibodies (seroconversion) in patients on HAART compared to patients who were not on HAART or in patients with differing immunological responses to HAART.

In a Cox regression model considering the end point of liver-related mortality among HIV/HBV co-infected individuals, being treated with two or less than two anti-HIV drugs was significantly associated with increased liver-related mortality. The authors conclude that individuals treated with fewer than three anti-HIV drugs had commenced treatment before the widespread use of HAART. This study indicates that use of HAART is protective against liver-related mortality among HIV/HBV co-infected individuals (290).

In a small study of HIV/HBV co-infected individuals in Spain, liver fibrosis stage was measured in 72 individuals followed for a median of 35 months. Of these 17% showed an improvement in their liver disease stage over the follow-up period while they were on treatment (386). Similarly, a slightly larger study followed 148 HIV/HBV co-infected individuals starting treatment with tenofovir for 36 months. Over this time period, a significant decrease in liver disease was observed among those individuals who had F3 or F4 fibrosis at the start of treatment. This decrease occurred predominantly in the first 12 months of treatment (387). However, since these studies are small it was not possible to adjust for CD4 count and therefore it is unclear whether the observed effects are related to immune restoration or to the direct effect of the drugs on HBV infection.

Greater increases in CD4 count and undetectable HIV viral load have been associated with undetectable HBV-DNA in a small cohort of 79 co-infected patients in Madrid (388). A cohort study of 92 HIV/HBV co-infected patients at a single reference centre in France followed patients for a median of five years; in this study having an sustained virological response to HAART (defined as < 50copies/ml for at least 80% of the treatment duration) was correlated with seroconversion from HBsAg to anti-HBs and seroconversion from HBeAg to anti-HBe (389). The loss of HBV antigens and the development of HBV-specific antibodies have also been associated with better immunological response to HAART. In a larger cohort of 538 HIV-positive patients who tested positive for at least one HBV marker at baseline, individuals were followed for a median of 4.96 years. Of those patients who were anti-HBs positive at baseline, loss of anti-HBs was more likely for those with lower levels of immune restoration after the initiation of HAART. Those patients in the cohort who had isolated anti-HBc at baseline, who then developed anti-HBs also had significantly greater increases in CD4 than those who did not. Two years after the initiation of HAART an increase in CD4 count of greater than 100 cells/mm^3 was the only factor which was associated with the presence of anti-HBs in both these groups (390).

The effect of duration of HAART on HBV infection was assessed in 72 HIV/HBV co-infected individuals in the USA. Longer duration of HAART was associated with both HBsAg and HBeAg clearance. However, since this study did not include the changes in CD4 count in response to HAART, it is not possible to determine whether the clearance of these antigens is due to immune restoration as a result of HAART or due to the direct action of the HBV-active drugs

which formed a component of the HAART regimen (391). This study does, however, highlight the importance of HAART in the management of co-infected patients.

Data from the SMART trial also showed the importance of sustained HAART in co-infected patients. Participants were assigned to receive either continuous HAART or HAART with interruptions (the drug conservation arm) and plasma HBV-DNA was measured every 2 months for a year. Individuals in the drug-conservation arm were more likely to experience HBV-DNA rebound than those in the continuous-treatment arm (392).

Most studies have considered the effect of HAART on HBV irrespective of whether HBV was acquired before or after HAART. However in one study, previously described in section 2.5.1 , among those infected with HBV after HIV, use of HAART prior to HBV diagnosis was associated with a decreased risk of chronic infection; this was the case in patients both with high and low CD4 counts at the time of HBV diagnosis (363).

2.7 Treatment and management of HCV in HIV co-infected patients

Only a very small minority of HIV co-infected patients will spontaneously clear HCV infection (see section 2.5.1). Given the importance of HCV co-infection in causing liver-related morbidity and mortality in HIV co-infected individuals, ensuring successful treatment strategies is a priority.

Since 2011, there have been significant advances in the treatment of HCV with the development of a number of new drugs (154). Data analysed as part of this thesis was collected in 2012-13. Therefore the large majority of patients included in had not yet benefitted from access to these new drugs, although small numbers were involved in clinical trials of the new drugs. In this section, I will describe the effectiveness and efficacy of HCV treatments in the context of HIV, focussing mainly on the treatments available up until 2011. I will also give a brief description of the evidence for new DAAs in HIV/HCV co-infected patients, which was available at the time that the data presented in this thesis was collected. A description of further developments which have occurred over the period of my research and the relevance of this thesis in the context of those further developments is provided in the final section of this thesis (section 10.2).

2.7.1 Effective treatment for HCV in the context of HIV, until 2011

Until recently, recommended treatment for HCV infection in HCV/HIV co-infected patients has been, as for HCV mono-infected patients, a combination of pegylated-interferon and ribavirin. Earlier treatment regimens used standard interferon (without pegylation) with ribavirin (65, 166). A summary of SVR rates in trials among HIV/HCV co-infected individuals is shown in

Table 2.5. The proportion of individuals who achieved SVR ranged from 11% to 46% for individuals infected with HCV genotype 1 or 4 and from 34% to 73% in individuals infected with HCV genotype 2 or 3. Therefore genotypes 1 and 4 are considered harder to treat than genotypes 2 and 3. The results of these trials were included in a meta-analysis of 14 randomised controlled trials, involving 2269 co-infected individuals, which was conducted to assess the benefits and harm of treatment for choric HCV and compare the various regimens (393). Patients were excluded from trials if they had decompensated liver disease, significant co-morbidities (including chronic HBV infection) or if there was evidence of current drug or alcohol abuse.

In the first comparison 673 patients treated with pegylated-interferon plus ribavirin, were compared to 667 patients treated with standard interferon plus ribavirin. Those treated with pegylated-interferon plus ribavirin, were more likely to achieve SVR (RR 2.16, 95% CI 1.47-3.18 in a random effect model) than those treated with interferon plus ribavirin. In a subgroup analysis by HCV genotype, the benefit from pegylated-interferon plus ribavirin compared to interferon plus ribavirin was greater in patients infected with genotypes 1 or 4 than in patients infected with genotypes 2 or 3, but pegylated-interferon remained superior in both groups. There was no difference in mortality but a slightly increased risk of anaemia or flu-like symptoms in patients treated with pegylated-interferon plus ribavirin compared to interferon plus ribavirin (RR 1.57, 95% CI 1.16-2.14). A higher proportion of patients treated with pegylated-interferon plus ribavirin had evidence of improved liver histology compared to patients treated with interferon plus ribavirin.

In a second comparison, a total of 359 individuals treated with pegylated-interferon plus ribavirin were compared to 355 patients treated with pegylated-interferon alone in the above meta-analysis. Pegylated-interferon was also shown to be a superior treatment regimen with higher proportions of patients achieving SVR (RR 2.03, 95%CI 1.57-2.63) and this was seen for patients infected with genotype 1 and 4 as well as patients infected with genotype 2 and 3. No difference was seen between these two groups with regard to mortality or adverse events.

The results from this meta-analysis are comparable to that of a smaller meta-analysis (including only 6 trials) (394). The authors concluded that given the clear benefit of pegylated-interferon plus ribavirin treatment, further trials were not warranted.

Table 2.5 SVR to treatment with pegylated-interferon plus ribavirin in randomised controlled trials

Trial	HCV Genotype	Individuals with end of treatment response n/N (%)	Individuals with SVR n/N (%)
ACTG, 2004 (395)	1 or 4	15/51 (29)	7/51 (14)
	2 or 3	12/15 (80)	11/15 (73)
	Total	27/66 (41)	18/66 (27)
APRICOT, 2004 (396)	1 or 4	67/176 (47)	51/176 (29)
	2 or 3	61/95 (64)	59/95 (62)
	Total	136/290 (47)	116/290 (40)
Crespo, 2007 (397)	1 or 4	20/39 (51)	18/39 (46)
	2 or 3	16/21 (76)	15/21 (71)
	Total	36/60 (60)	33/60 (55)
Laguno, 2004 (398)	1 or 4	13/32 (41)	12/32 (38)
	2 or 3	13/19 (68)	10/19 (53)
	Total	27/52 (52)	23/52 (44)
RIBAVIC, 2004 (399)	1 or 4	32/125 (26)	21/125 (17)
	2 or 3	40/80 (50)	35/80 (44)
	Total	72/205 (35)	56/205 (27)
ICOS, 2005 (400)	1 or 4	6/37 (16)	4/37 (11)
	2 or 3	14/32 (44)	11/32 (34)
	Total	20/69 (29)	15/69 (22)

Treatment success rates in practice are unlikely to reach those seen in clinical trials. Therefore data from observational studies is useful in assessing the rates of SVR that can be achieved in real-world situations. Davies *el al* conducted a systematic review of treatment outcomes reported in observational cohort studies of HIV/HCV co-infected individuals. Forty studies with a primary outcome of SVR were included and a pooled estimate for the proportion of

individuals achieving SVR was calculated: 38% (95 CI, 34.7%-42.3%). When stratified by HCV genotype the pooled estimates for the proportions of individuals achieving SVR were 24.5% (95%CI 20.4-28.6%) for individuals infected with genotypes 1 or 4 and 59.8% (95% CI 47.9-71.7%) for those infected with genotypes 2 or 3 (401). Many of the cohorts included in this analysis included high proportions of IDU or those from other groups who may have poor adherence. Three studies were limited to adherent populations, but removal of these studies from the analysis did not affect the results.

Treatment for HCV in co-infected patients has a significant impact on the progression of fibrosis. Patients who have an SVR to HCV treatment are less likely to progress than those who are either not treated or who do not respond to treatment (402, 403). A study of 216 co-infected individuals in Spain showed that SVR was significantly associated with regression of both fibrosis and cirrhosis, which occurred in 71% of those individuals with SVR (404).

There is evidence from clinical trials of HCV treatment, as well as from observational studies, to show adverse interactions between HCV treatment and some of the older antiretroviral drugs. Patients treated with ribavirin and didanosine are more likely to experience mitochondrial toxicity evidenced by hyperlactatemia than patients treated with ribavirin whilst on other HIV drugs (399, 405, 406). Abacavir is known to compete with ribavirin and therefore patients who are treated with abacavir are less likely to respond to ribavirin-based HCV treatment (407, 408). In patients treated with zidovudine and ribavirin, higher rates of anaemia are observed than among patients on ribavirin with other antiretroviral drugs (409, 410). Finally, efavirenz has been associated with an increased risk of mood disorders in patients being treated for HCV (411) and atazanavir has been associated with increased risk of hyperbilirubinemia in patients being treated for HCV (320). These side-effects of efavirenz and atazanavir are also seen in HIV mono-infected individuals (412, 413).

2.7.2 HCV treatment available in the period 2011-2013

Work has recently focussed on the development of new drugs which act directly on HCV. In particular, in 2011, two PIs, boceprevir and telaprevir, were licensed for use in the USA and Europe (154, 414). Here I will describe research on the efficacy of these agents, in the context of HIV, which was available at the time of collecting the data used for analysis within this thesis.

Phase III trials in HCV mono-infected individuals showed that for patients infected with HCV genotype 1, addition of boceprevir or telaprevir to the current pegylated-interferon plus ribavirin regimen significantly increased the proportion of individuals achieving SVR; both for patients who have never previously received HCV treatment (190, 193) and for those individuals who had previously failed treatment with pegylated-interferon and ribavirin (195, 415). However, these phase III trials of boceprevir and telaprevir did not include HIV co-infected patients.

Initial data from phase II b trials of telaprevir in HIV co-infected patients were first presented at the Conference on Retroviruses and Opportunistic Infections (CROI) in 2011. Patients were randomised to receive either pegylated-interferon plus ribavirin and telaprevir, or pegylated-interferon plus ribavirin and placebo. The study was conducted in 13 patients not on ART but with high CD4 counts (> 500 cells/mm^3) and among 46 patients with on ART with undetectable viral load and CD4 greater than 300 cells/mm^3. A higher proportion of patients in the telaprevir arm achieved a rapid virological response (undetectable HCV viral load at week 4) and an early virological response (undetectable viral load at 12 weeks) than patients in the placebo arm (416). Data on SVR12 (having negative HCV-RNA 12 weeks after stopping treatment) from the same trial was presented the following year and again showed that addition of telaprevir to the standard pegylated-interferon and ribavirin regimen significantly increased the proportion of individuals who responded to treatment: 45% of patients in the control arm achieved SVR12 compared to 74% of patients in the intervention arm (417).

The final data from this study, including proportions of patients who achieve SVR at 6 months post treatment was published in 2013. A total of 62 individuals with HIV and HCV genotype 1 co-infection were randomised to one of two groups. Patients in the control group received placebo plus pegylated-interferon and ribavirin for 12 weeks followed by 36 weeks of standard pegylated-interferon and ribavirin. In the intervention arm the placebo was replaced with telaprevir. In the intervention arm 74% of individuals achieved SVR compared to 45% in the control arm. Although a slightly higher proportion of individuals in the intervention arm experienced adverse events (5%) than in the control arm (0%) the same number of individuals discontinued treatment in each arm (418).

Data from a phase II trial of pegylated-interferon and ribavirin plus boceprevir was presented in 2011 at the Infectious Disease Society of America Meeting. A total of 99 patients co-infected HIV and HCV genotype 1 were randomised to receive either pegylated-interferon plus

ribavirin and boceprevir, or pegylated-interferon plus ribavirin and placebo. At 8, 12 and 24 weeks a significantly higher proportion of patients in the boceprevir arm achieved an undetectable HCV viral load than patients in the placebo arm (419) . SVR12 data from this trial was also presented at CROI in 2012 and showed an increase from 26.5% of individuals achieving SVR12 in the control arm to 60.7% in the intervention arm (420).

Final results from this study, also published in 2013, showed a significant increase in the proportion of individuals who achieve SVR when boceprevir is included in the treatment regimen. A total of 98 individuals were randomised to receive 4 weeks of pegylated-interferon and ribavirin, followed by 44 weeks of either placebo or boceprevir. In the intervention arm 63% achieved SVR compared to 29% in the control arm. Like the telaprevir trial, a higher proportion of individuals in the intervention arm experienced adverse events (421) .

The results of a number of other studies investigating the use of boceprevir and telaprevir among HIV/HCV co-infected individuals were also presented at conferences throughout 2013, showing that results in HIV co-infected patients were comparable to those in HCV mono-infected patients (422-424). Results from studies among individuals who had previously failed treatment were also presented showed good levels of early response (425, 426). The results of these studies led to the recommendation, in 2013, by BHIVA that individuals co-infected with HIV and HCV genotype 1, who are clinically in need of treatment (defined as significant fibrosis of F4 or cirrhosis), should be treated with pegylated-interferon and ribavirin plus either boceprevir or telaprevir. However, individuals with less significant liver disease, who do not have a clinical need for immediate treatment, should consider deferring treatment until interferon free regimens are available (65).

2.8 Treatment and management of HBV in HIV co-infected patients

2.8.1 Efficacy of HBV mono-therapy and the development of drug resistance

A number of antiretroviral drugs have action against HBV and therefore use of these drugs is recommended as part of initial antiretroviral regimen for HIV/HBV co-infected individuals (204). Currently there are three licensed drugs with dual action against HIV and HBV (lamivudine, tenofovir and emtricitabine). A further four drugs, which are active only against HBV, are also licensed for use (entecavir, interferon, adefovir and telbivudine). In this section I will describe studies which show the efficacy of using single antiretroviral drugs with action

against HBV infection in co-infected individuals as well as development of resistance to these drugs.

Lamivudine was shown to inhibit HBV replication in co-infected patients in an open-label trial of 40 patients followed for one year. More than 96% of patients who had high levels of HBV replication at baseline responded to lamivudine therapy and achieved serum HBV-DNA concentrations of less than 5 pg/ml at 12 months; of those individuals who had low levels of replication at baseline, all were negative for HBsAg at 12 months (427). The effect of lamivudine on HBV suppression has also been demonstrated in the CAESAR study. This was a multi-centre study investigating the use of lamivudine to treat HIV but a sub-study was conducted investigating the effect of lamivudine on HBV replication in 122 co-infected individuals. Of these 122 patients, 25 were assigned to a placebo arm and 97 were assigned to a lamivudine containing regimen (other drugs in the regimen were not active against HBV). At 12 weeks the median log HBV-DNA decline was 2.0 in the patients on lamivudine compared to nothing in the placebo arm; at 52 weeks the median log change in HBV-DNA was 2.7 in the lamivudine arm compared to no change in the placebo arm (428).

The effect of lamivudine treatment on HBV infection has also been shown to have significant clinical impact. In the ICoNA cohort, 164 patients started HAART and 73% started with a lamivudine containing regimen. Patients on lamivudine experienced significantly lower levels of ALT over time and had a significantly reduced risk of morbidity and mortality than those patients whose HAART regimen did not include lamivudine over 2 years of follow-up. The effect of lamivudine withdrawal was also investigated in this cohort. Although withdrawal was not shown to significantly affect ALT flares, 72% of those who discontinued did have a clinically important ALT flare indicating that ALT must be closely monitored if lamivudine is discontinued (429).

A much larger study of 2041 patients from 13 cohorts of HIV/HBV co-infected patients who had initiated HAART also showed decreased mortality in patients whose regimens included lamivudine. The end-point of the study was liver-related disease as assessed by 3 clinicians who were blinded to patients' treatment. Overall, 57 liver-related deaths occurred. The risk of liver-related death was decreased for every year that patients received lamivudine therapy (RR 0.73 per year, 95% CI 0.59-0.90); this effect was not seen with any other NRTI. In addition, there was an increase in the risk of liver-related death in patients with lower CD4 counts at

HAART initiation and the decrease in liver-related death due to HAART was weaker when adjusted for most recent CD4 count and viral load, underlining the importance of maintaining immune capacity and suppressing viral load (430)

Despite the efficacy of lamivudine in treating HBV infection in co-infected individuals, a number of studies have documented the development of lamivudine resistance. Among 13 co-infected patients in the CAESAR study who were treated with lamivudine containing regimens and had high levels of HBV-DNA at 52 weeks, 5 developed resistance mutations. The authors concluded that these levels of resistance were similar to those in HBV mono-infected individuals (431). Another small study of 19 patients showed that over 2 years of follow-up 5 patients developed resistance mutations (432). In a cohort of co-infected patients in the Netherlands all patients were treated with lamivudine for at least 6 months and the percentage of patients carrying resistance mutations was 25% at 1 year and 52% at 2 years (433). In a cross-sectional study of 84 co-infected individuals in Thailand the prevalence of drug resistance was 22.6% (434).

Estimates of the proportions of patients who develop resistance are difficult to compare across studies since studies are often small and there may be other factors which influence the development of resistance in co-infected individuals and cannot be considered in such small groups of individuals. Factors which have been associated with the development of lamivudine resistance in small studies of HIV/HBV co-infected individuals are baseline CD4 count, body mass index (BMI), older age and being HBeAg-positive (433-435). In addition studies have used varying periods of follow-up which makes the development of resistance difficult to compare. One study specifically investigated the response to lamivudine monotherapy according to CD4 count. Twenty-nine patients were followed-up for 33 months. Individuals who had a baseline CD4 count of greater than $\geq$200 cells/mm^3 had significantly greater decreases in HBV-DNA than patients with baseline CD4 of <200 cells/mm^3 and a higher proportion of patients with higher CD4 counts achieved undetectable HBV-DNA levels at 6 months compared to individuals with lower CD4 counts (436).

One study compared the development of resistance in 29 HIV co-infected individuals to that in 60 HBV mono-infected individuals. Resistance mutations were more likely to be present in the co-infected group (93% versus 40%, P<0.0001) and co-infected individuals were more likely to have multiple resistance mutations after at least 3 months of treatment (437). A range of

mutations have been shown in the DNA-polymerase gene which conveys lamivudine resistance (438, 439).

Tenofovir monotherapy has also been shown to be effective treatment for HBV in HIV co-infected individuals and appears to also be effective in those patients who have previously been treated with lamivudine. Among 308 patients in France, use of tenofovir lowered fibrosis score in patients over a median of 30 months follow-up (387). More than 80% of patients treated with tenofovir in an HIV-positive cohort in Manchester, UK, achieved levels of HBV-DNA <100 copies/ml over a median of 34.2 months follow-up. Previous exposure to lamivudine did not affect the ability of tenofovir to control HBV replication in this cohort (440). In a cross-sectional study of patients who had received tenofovir in the last three months but who had also previously received lamivudine, lamivudine resistance was shown to persist but no tenofovir resistance developed (441).

2.8.2 Combination therapy for HBV infection

Combination therapy may be a more effective strategy for controlling HBV infection, both by suppressing HBV replication more effectively and also by limiting the development of resistance. In this section, I will describe studies which investigate the efficacy of combination therapy for HBV infection compared to monotherapy in controlling HBV infection and studies which compare use of combination therapy (using more than one HBV active agent at the same time) to use of sequential monotherapy (using one HBV active agent followed by another after the resistance develops).

Data from a phase 3 randomised controlled trial of tenofovir was used in a sub-study to compare control of HBV viral replication in patients who received tenofovir monotherapy and those who received lamivudine and tenofovir combination therapy. The authors observed that among antiretroviral naive patients randomised to receive lamivudine plus tenofovir there was a greater decline in HBV-DNA than was seen among patients who were randomised to receive tenofovir alone over 48 weeks of follow-up. However, this study included only small numbers of individuals (5 lamivudine alone and 6 lamivudine and tenofovir). They also observed a trend towards reduced lamivudine resistance among patients who received combination therapy compared to lamivudine alone (442).

In a study comparing 25 patients who commenced therapy with a combination of lamivudine and tenofovir with 50 patients who took lamivudine followed by tenofovir when lamivudine

treatment failed, there was no difference observed between the two groups with regard to either HBV suppression (as measured by HBV-DNA levels) or to seroconversion from HBeAg positivity to anti-HBe positivity over a 2 year period (443).

Jain *et al* compared the efficacy of 3 different treatment regimens among 45 patients: group 1 received lamivudine only for 1 year, group 2 received lamivudine and tenofovir for 1 year and group 3 received lamivudine alone for 6 months followed by lamivudine and tenofovir for 1 year. A higher proportion of patients who were treated simultaneously with lamivudine and tenofovir suppressed HBV-DNA and seroconverted from HBeAg positivity to anti-HBe than patients treated with either lamivudine monotherapy or lamivudine followed by tenofovir. However, this difference did not reach statistical significance (444).

The use of emtricitabine as part of a combination regimen has also been investigated using data from 3 studies (the Multicentre AIDS cohort study, the Melbourne Australia cohort and the Sydney Australia cohort). Of 121 co-infected patients 31, were not on HAART, 31 were on either lamivudine or emtricitabine monotherapy, 11 were on tenofovir monotherapy and 49 were on a combination of tenofovir and either or lamivudine or emtricitabine. Significantly higher proportions of patients on combination therapy achieved undetectable HBV-DNA compared to any of the monotherapy groups and monotherapy was associated with higher levels of HBV-DNA in a multivariate model (445).

In a study in Thailand, co-infected patients were randomised to receive either emtricitabine monotherapy (6 patients) or emtricitabine and tenofovir combination therapy (10 patients). There was a significantly greater decrease in HBV-DNA in those treated with combination therapy than those treated with monotherapy. At 48 weeks of follow-up a significantly higher proportion of patients on combination therapy had undetectable HBV-DNA compared to patients on monotherapy (90% versus 33%) (446).

Studies to date support the use of combination therapy, however studies are small and further research is necessary to compare different combinations of HBV active drugs since there is currently no data available which can be used to directly compare the combination of emtricitabine and tenofovir with lamivudine and tenofovir.

2.9 The outcomes of liver transplant in HIV-positive individuals

Liver transplant is the only clinical option for patients with end-stage liver disease. The outcome of liver transplant can be assessed using various measures: patient's survival post-transplant, graft survival and recurrence of the hepatitis infection. In this section, I will describe studies which report on these transplant outcomes in HIV-positive patients and studies comparing the outcomes in HIV-positive and HIV-negative patients. Research into the outcomes of liver transplant in patients co-infected with HIV and hepatitis viruses is limited as few patients undergo the procedure. Therefore much of the available data comes from case reports or case series.

A meta-analysis, published in 2011, assessed the outcomes of liver transplant in HIV-positive patients by pooling data from published cohort studies and forming a synthetic cohort of cases using published reports of individual cases. Patient survival post-transplant was similar in the pooled cohort data and the grouped case data: 84.5% & 83.3% at 12 months; 73.5% & 73.8% at 24 months; 66.2% & 68.7% at 36 months; 66.7% & 62.7% at 48 months; 63.8% & 55.9% at 60 months, respectively. Case data was used to identify factors associated with survival post transplantation. Among these 216 patients, HBV co-infection was associated with better survival compared to those individuals who were HBV-negative as was having an undetectable HIV viral load when the transplant was carried out. HCV co-infection was a negative predictor of survival in the unadjusted model but this did not remain associated in the adjusted model.

In the pooled cohort, graft survival during follow up was 82.6% at 12 months; 73.7% at 24 months; 62.0% at 36 months; 66.6% at 48 months; and 47.9% at 60 months. Graft survival appeared to be higher in the grouped case data. However, due to small sample sizes, particularly in later years of follow-up, this data is susceptible to bias. As with patient survival, analysis of the case data indicated that HBV infection was significantly associated with increased graft survival, compared to those individuals who were HBV-negative, and there was a trend toward HCV infection being associated with decreased survival. HIV viral suppression post-transplant was reported from 99 individuals in 23 case reports. High proportions of patients had undetectable viral loads at 12, 24 and 60 months post-transplant (although numbers are small particularly for the later years of follow up). These occurred in the context of patients taking immunosuppressant therapy post-transplant. Finally, the authors of this meta-analysis were able to assess the recurrence of HCV infection in co-infected patients who underwent liver transplant. Forty five case reports, including data from 184 individuals,

included data on HCV co-infection. Of these patients the large majority (94%) had HCV viremia after transplant and 51.6% were identified as having recurrence of active disease. SVR to treatment was observed in 17/49 of patients who underwent HCV treatment post-transplant (447).

The finding that HBV-positivity is associated with increased patient and graft survival is surprising. However, this is likely due to the underlying conditions present in comparison group. The HBV-negative group includes those individuals who are positive for HCV as well as those undergoing liver transplant for other reasons. The optimal survival of HBV-positive individuals compared to HBV-negative individuals who are undergoing transplant for other reasons, including HCV infection, is likely due to the effectiveness of HBV treatment. As more effective HCV treatments become more widely available this difference in survival may decrease.

A limitation of this meta-analysis is that it did not compare outcomes of liver transplants in patients with HIV infection with those without HIV infection. However, the authors compared their results to those of studies in HIV-negative individuals and concluded that one to five year survival rates were similar to those reported in HIV-negative populations in Europe but slightly lower than those reported in North America. Indeed of the cohort and case-control studies which did have HIV-negative comparison groups similar rates of patient survival, graft survival (448-454) and recurrence of HCV infection (454) post-transplant were observed in HIV-positive and HIV-negative individuals.

Another limitation of many of the cohort studies investigating outcomes of liver transplant is that the analyses are not stratified by the aetiology of liver disease (HBV or HCV). The few studies which do specifically consider HCV or HBV provide similar information to those where HCV and HBV liver disease is considered together in combination with liver disease of any other aetiology. Coffin *et al* showed that there was no difference in patient or graft survival rates in HBV mono-infected and HIV/HBV co-infected (451), while the studies from Castells *et al* and Testillano *et al* and Baccarani *et al* showed that patients and graft survival rates were also similar in HCV mono-infected and HIV/HCV co-infected individuals (449, 450, 454).

2.10 Summary of findings from the literature

In HIV-positive populations HCV and HBV infection are not only prevalent but also have significant clinical implications. Liver disease, in particular related to viral hepatitis infection, has become an important cause of morbidity among HIV-positive populations and HIV and hepatitis co-infected individuals have higher rates of mortality compared to HIV mono-infected individuals. There is some evidence to suggest that co-infected individuals may have impaired responses to HIV treatment compared to HIV mono-infected individuals. Individuals who are co-infected with HIV and hepatitis viruses are more likely to progress to chronic hepatitis infection than those who are infected with a hepatitis virus alone and HIV/HBV co-infected individuals are more likely to have active hepatitis infection than individuals with HBV mono-infection. Liver disease in co-infected individuals progresses more rapidly than in hepatitis mono-infected individuals. However, treatment for HIV, HBV and HCV is available and can limit the pathological effects of the viruses. In addition, results of liver transplants in co-infected individuals are similar to results in individuals without HIV. Therefore ensuring that the most appropriate treatment is available for co-infected individuals is vital.

Data from cohort studies is invaluable in assessing the impact of infection and the effectiveness of treatment outside of clinical trials. However, the variability in results of cohort studies investigating the outcomes of co-infected individuals highlight the importance of having locally applicable studies on which to base treatment and management decisions.

Chapter 3 Methods 1: The UK CHIC study and statistical methods

3.1 Introduction

All the data presented in this thesis have been collected as part of UK CHIC study. The standard dataset, collected annually as part of the UK CHIC study, was supplemented with additional data for those individuals in the cohort who are co-infected with HBV and/or HCV. This chapter describes the standard data collection and processing for the UK CHIC study and the key characteristics of the dataset. The collection and processing of the additional data for hepatitis co-infected individuals is described Chapter 4. A summary of statistical methods used throughout the thesis is also provided.

3.2 The UK Collaborative HIV Cohort

The UK CHIC study was initiated in 2001. The aim of the study is to collect data on a large cohort of individuals, diagnosed with HIV infection and attending for HIV care in the UK. These data can be used to assess changes over time in the frequency of AIDS-defining events, changes in virological and immunological responses to HAART and factors associated with response to HAART (455). At inception 6 centres contributed data to the study: Chelsea and Westminster Hospital, London; Kings College Hospital, London; Mortimer Market Centre, University College Hospital, London; St Mary's Hospital, London; the Royal Free Hospital, London; and Brighton and Sussex University Hospital, Brighton. These six centres provided data for 13833 HIV-positive individuals attending for HIV-related care. Additional centres have since been recruited into the study. By the end of 2012, there were 16 UK HIV centres contributing data to the study: the original six centres plus St Bartholomew's and The Royal London Hospitals, London; Western General Hospital, Edinburgh; North Middlesex University Hospital, London; Homerton University Hospital, London; Southmead Hospital, Bristol; Leicester Royal Infirmary, Leicester; James Cook University Hospital, Middlesbrough; Queen Elizabeth Hospital, Woolwich, London; St George's Hospital, London; and York teaching Hospital, York.

The analyses presented in this thesis utilise data from the UK CHIC dataset which was finalised at the end of 2012. This dataset contains information on 47,201 patients from the 16 centres: The study is conducted by a team at University College London: Teresa Hill (TH) – study manager; Sophie Jose (SJ) – statistician; Caroline Sabin (CS) – Principal investigator; Susie

Huntington (SH) – PhD student; and me (AT). The study is overseen by a steering committee consisting of clinical representatives from all contributing sites, the HIV community and epidemiologists and statisticians from the Medical Research Council's (MRC) Clinical Trials Unit and Public Health England (PHE) (Appendix II). Five separate working groups advise on specific research themes and include members of the steering group as well as experts in the specific research area. The five current research themes are: on-going monitoring of outcomes (including the development of resistance) among those infected with HIV; the impact of antiretroviral therapy received during pregnancy on the health of HIV-positive women; the impact of co-infection with HCV and/or HBV; the implications of an aging HIV population; and understanding the transmission and persistence of drug resistant HIV. The study has been approved by a Multi-centre Research Ethics Committee and by local ethics committees and is funded by the MRC (Grant numbers G000019, G0600337and G0900274).

3.2.1 Data Collection

Data collection is coordinated by the study manager (TH). Individuals are included in the study if they are HIV-positive, aged over 16 years and have attended any one of the centres in 1996 or thereafter. Although data are only collected on individuals seen for care since 1996, where individuals had attended prior to 1996 the date of their first attendance and all available historic data is also collected to give a complete clinical history at that centre. Data are requested from participating centres on an annual basis (Appendix III) and the database is held securely at the MRC Clinical Trials Unit.

At any point centres may decide to clean their own database or conduct work on a particular set of data items thus improving the quality of the data which can be extracted. Therefore, each year, the complete dataset (from 1996 onwards) is requested and re-entered into the database, overwriting the previous year's data. Data from the previous year's data collection are archived. This means that where centres have added or cleaned data retrospectively, the new data will be included in the next UK CHIC dataset. Each centre submits data in electronic format via a secure server. The data are provided in nine specified datasets: demographic information; AIDS events; antiretroviral treatment; laboratory data (CD4 and CD8 counts and viral loads); hepatitis data; adherence; drug toxicities; HLA-B57 tests; and attendance data (Table 3.1). Each dataset contains the individual's clinic number and date of birth so that the datasets can be linked.

Table 3.1 Datasets collected as part of standard UK CHIC data collection

Specified dataset	Information collected
Demographics	Soundex code Patient initial/s Sex Date of first known positive HIV antibody test Date of last negative HIV antibody test Date of first HIV attendance at centre Date when last seen by a clinician at the centre HIV exposure category Ethnicity Country of birth Whether patient is known to have died Date and cause of death (where known) Centre patient transferred from and date of transfer Centre patient transferred to and date of transfer
AIDS events	Date and description of all AIDS events
Antiretroviral treatment	Drugs Dates of starting and stopping each drug Reasons for stopping each drug (up to 3 per drug)
CD4 and CD8	Date of measurement Absolute CD4 and CD8 counts and CD4 and CD8 percentages
Viral loads	Date of measurement HIV viral load in copies per ml Whether or not HIV-RNA is detectable Specific assay used
Hepatitis	Date of each hepatitis test Hepatitis test conducted, Hepatitis test result and value if applicable [1]
Adherence	Date of clinic visit Details of pills taken and pills missed
Toxicities	Date of each toxicity test Toxicity test conducted and test result
HLA-B57	Date and result of test
Attendance data	Date of attendance Type of attendance (for example scheduled, walk-in, virtual, inpatient) Who the patient is seen by (for example doctor, nurse, dietician) Details of pills taken and pills missed

[1] Quantitative test results may be available for HBsAg, anti-HBs, HBV-DNA, HCV-RNA tests

3.2.2 Data cleaning

A range of cross-tabulations are conducted and queries are applied to the data by TH to identify inconsistencies. For example, checks are performed for missing or invalid demographic items and for illogical or conflicting dates such as an HIV-negative test occurring after an HIV-positive test or treatment occurring after death. The results of these checks are returned to the centre providing the data and are verified against clinical records. Where more accurate data are obtained, both the UK CHIC dataset and the original clinic database are updated accordingly. Locally assigned clinic identification numbers along with Soundex and patient initials are maintained in the MRC database but are removed and replaced by a unique identifier prior to data being made available for analysis. Therefore the final dataset which is used for analysis contains pseudonymised data.

3.2.3 De-duplication

Some individuals may attend more than one clinic and be reported by all the clinics which they attend. This results in multiple records for these individuals within the study dataset. These records must be combined into a single record. Initially, potential matches are identified, by the data manager, on the basis of Soundex, patient's first initial and date of birth. A computerised algorithm, which utilises other demographic variables and HIV-positive dates, is then used to categorise potential matches as definite matches, definite non-matches and indeterminate. The complete clinical data for indeterminate matches are then reviewed by two members of the study team who make a final decision about whether the records should be combined or remain separate. The reviewers assess all the available data within the records including anti-retroviral therapy (ART). Where the two reviewers come to different conclusions a third member of the team is consulted. Where the third reviewer is unable to reach a decision the records remain as two distinct records.

After this review process, where records are considered to be from the same individual, the records are merged. During the merge any missing data in one record is updated with available data from the matched record. The merged record will contain the earliest HIV-positive date, the earliest first seen dates and the latest HIV-negative and last seen dates. Inconsistent treatment information in a merged record is resolved manually.

3.2.4 Death data

Prior to 2011, the Office for National Statistics (ONS) in England and the General Register Office (GRO) for Scotland provided additional data on deaths. UK CHIC records which matched

to a record in either ONS or GRO on the basis of initial, Soundex, date of birth and sex were identified. Where this process identified matches who are recorded as having died in the UK CHIC dataset but with a missing date of death, the ONS/GRO date of death was used to update the UK CHIC dataset. Where this process identified matches who are not recorded as having died in UK CHIC, this was reported to the appropriate centre for verification before the UK CHIC dataset was updated.

From 2011 onwards, the CHIC dataset has been linked to data from the Health Protection Agency's (HPA) (now PHE) Survey of Prevalent HIV Infections Diagnosed (SOPHID) using initial, Soundex, date of birth, gender and ethnicity. All records in UK CHIC are linked to one or more record in SOPHID and a score is generated indicating the strength of the match. Where patients were recorded are having died in SOPHID but not in UK CHIC the UK CHIC dataset is updated as long as there is no conflicting information, such as later CD4 counts or clinic visits, and the matching score was high (>0.8). Where patients are recorded as having died in UK CHIC but not having died in SOPHID the record is maintained as the patient having died. Where patients are reported as having died in both datasets but there are different dates of death an algorithm is used to assign the most likely date of death. This algorithm utilises information including dates of clinic attendances and CD4 counts, matching scores and commonly used estimated dates. These processes do not include any updating of cause of death.

3.2.5 Creation of final dataset

Once de-duplication of the dataset is complete and all death data from SOPHID has been incorporated, TH exports the data into text files and passes them to the study statistician (SJ) who prepares the individual datasets to be merged to form the final dataset. This process is currently done using SAS version 9.3 (SAS Institute Inc., North Carolina, USA). Further checks are conducted in the individual specified datasets and the data amended where necessary: duplicate laboratory tests (CD4, viral load and HLA B*5701), attendance dates and AIDS events are removed; viral loads are classified as undetectable according to the lower limit of the assay; and excessively large CD4 and CD8 counts (CD4>3500 cells/mm^3, CD4 percentage>100%, CD8>10000 cells/mm^3, CD8 percentage>100) and CD4 and CD8 counts and percentages of zero are removed.

For data on antiretroviral therapy, dates that individuals stop and start drugs are checked. If a drug start date is after a drug stop date, the dates are reversed; multiple drug regimens are

split into their component parts (for example, Atripla becomes efavirenz, tenofovir and emtricitabine). Where one treatment episode for a drug lies completely within another treatment episode for the same drug or two treatment episodes of the same drug overlap, the record is amended taking the earliest start date and the latest stop date of that drug. Where there appears to be a gap of less than one month between stopping a drug and restarting it, it is assumed that this has resulted in an error in prescription datasets. Therefore this gap is closed by removing the stop and start dates in the middle of the total time period that the individual is on a drug.

Finally, the individual specified datasets are merged into one and the additional death data is also merged into this final complete dataset. Any ineligible patients (those under the age of 16 in the year of data collection) and illogical dates (for example where the first seen date is before the date of birth or where the date of birth is very early) are removed. Where a drug stop date is after a death date, it is changed to the death date since the drug stop date is likely to be the end of the prescription. Dates of any laboratory measures which occurred up to 2 days after the death date are amended to the death date as these tests are likely to have been entered into the database with the date of the test report rather than the date on which the sample was taken. Missing last seen dates are updated with the latest laboratory test date.

3.2.6 Description of UK CHIC dataset

The current UK CHIC dataset contains data on 47201 individuals, of whom 4475 individuals are known to have died, leaving 42726 who are assumed to be alive. Data from SOPHID show that in 2011, 73627 were seen for HIV-related care in the UK. Therefore it is estimated that the 2012 UK CHIC dataset contains data on approximately 58% (42726/73627) of all individuals in the UK living with diagnosed HIV infection (21). The characteristics of the current cohort are shown in Table 3.2.

Table 3.2 Characteristics of individuals on the UK CHIC 2011 dataset

	Number of individuals N=47201	**%**
Median age at entry into cohort (IQR)	34 (29, 40)	
Sex		
Male	34202	72.5
Female	12995	27.5
Unknown	4	0.01
Ethnicity		
White	24641	52.2
Black African	12796	27.1
Black other	2498	5.3
Other/ Unknown	7266	15.4
HIV exposure category		
MSM	23341	49.5
IDU	1694	3.6
Male heterosexual	6343	13.4
Female heterosexual	10847	23.0
Other/unknown	4976	10.5
Median Nadir CD4 count (cells/mm^3) (IQR)	200 (90, 328)	
HIV viral load ever undetectable	32012	67.8
Ever on HAART	33609	71.2
Centres attended for care		
Brighton	3297	7.0
St Mary's	5823	12.3
Chelsea and Westminster	11335	24.0
Mortimer Market Centre	7227	15.3
Kings	4266	9.0
Royal Free	4931	10.5
Bart's and the London	5172	11.0
Edinburgh	1153	2.4
North Middlesex	1830	3.9
Homerton	1590	3.4
Bristol	1330	2.8
Leicester	1504	3.2
Middlesbrough	526	1.1
Woolwich	1781	3.8
St George's	2587	5.5
York	304	0.6
Individuals known to have died	4475	9.5

[1] Clinics attended at any time during the study period. Individuals may have attended more than one of the centres.

As further centres have joined the study, an increased proportion of individuals included in the cohort are seen at centres outside of London and therefore the characteristics of the cohort have changed. To describe how the cohort has changed over time individuals were classified by whether or not they had been followed-up in each year from 1996 to 2010. Some patients may have gaps in their follow-up (for example where they transfer from a CHIC centre to receive their HIV care in a centre which does not participate in CHIC and then return to a CHIC centre at a later date). Therefore, to assess whether a patient is followed-up in a particular year, the first and last dates from each centre were used. Due to missing or inconsistent dates, of the total dataset, 309 individuals could not be classified as having any follow-up year. The reasons for this included, missing first or last seen dates and illogical first or last seen dates which could not be amended using any other data items. These individuals were therefore excluded from descriptions and analyses where the data are split by year.

In earlier years of follow-up the cohort has higher proportions of men: 80.4% of the cohort under follow-up in 2000 was men compared to 73.4% in 2011. MSM remain the predominant risk group in the cohort from 2000 to 2011. However, the proportion of MSM in the cohort has decreased from 63.5% in 2000 to 54.5% in 2011. The proportion of individuals under follow-up who are of black African ethnicity has also increased since 2000 with a corresponding decrease in the proportion of individuals who are of white ethnicity. Details of the characteristics of individuals under follow-up in each year are provided in Appendix IV.

Since clinical outcomes of patients are impacted by effective treatment, it is important to assess how treatment patterns may have changed over time. HAART was defined as any regimen which consisted of three or more antiretroviral drugs of any class. Patients who were HAART experienced (had ever received a treatment regimen of 3 or more drugs) were further classified according to their first HAART regimen. The proportion of patients under follow up who started HAART with a PI based regimen has decreased from 34.0% in 2000 to 26.8% in 2011 while the proportion of those who started with a NNRTI based regimen has increased from 44.0% in 2000 to 52.6% 2010 (Appendix IV). On-going improvements in treatment strategies are evidenced by the changes in immunological and virological status of patients under follow-up in each year. Over time an increasing proportion of patients under follow-up are virologically suppressed (38.4% in the year 2000 compared to 76.5% in 2011) and a decreasing proportion of patients have a CD4 count less than 200 cells/mm^3 within a given year (21.3% in the year 2000 compared to7.3% in 2011).

3.3 Standard hepatitis data in UK CHIC dataset

The standard UK CHIC data specifications sent to clinics include laboratory data on hepatitis tests which can be used to ascertain whether or not an individual is currently infected with or has previously been infected with a number of hepatitis viruses. For each test performed the centres are asked to provide the date of the test, the result of the test (positive, negative or indeterminate/equivocal) and, where a quantitative test is performed (a HBsAg or anti-HBs titre, a quantitative HBV-DNA test or a quantitative HCV-RNA test), a numeric value. The data cleaning procedures conducted during the preparation of the final dataset (described earlier, see section 3.2.5) do not include any checks on data submitted in the hepatitis dataset. Since the aims of this thesis are to examine hepatitis co-infection within the UK CHIC study, I conducted some further checks before further analysis commenced.

3.3.1 De-duplication of tests

Individuals may be tested for markers of hepatitis infection more than once. For every hepatitis test I counted the number of times an individual had been tested. This revealed a very high number of tests for some individuals. For example, 25 individuals were recorded in the dataset as having had more than 50 HBsAg tests. Manual checks of the records of some of these individuals revealed that there were duplicate tests within the dataset. Therefore I de-duplicated the hepatitis test data: where the date of test, the test code and the results of the test were all the same, additional tests were deleted leaving one record of that test in the dataset.

3.3.2 Checking for missing data

For each of the HBV tests and HCV tests I examined the dataset to identify where there were missing data items. There were no instances of a test date or result with a missing test code. Four individuals had a test code with no corresponding test date. These tests were removed from the dataset. There were higher numbers of individuals who had missing test results. Where the result was missing, but a numeric value was present, the result was updated accordingly (Table 3.3). There are a number of different assays in use for performing quantitative tests. Information on which assay was in use for each test was not available. Therefore the data was examined to identify those quantitative measurement which appeared repeatedly within the datasets and therefore may represent cut-offs for the assays in use. The thresholds for positive and negative tests were determined by examining these repeatedly reported measurements and consulting with clinical colleagues. Where a number of potential

cut-offs were identified (for example in the case of HCV-RNA and HBV-DNA) a higher threshold was chosen to ensure that all individuals who were negative were included as such. It is recognised that this may result in an overestimation of those who are HBV-DNA or HCV-RNA negative.

Table 3.3 Defining positive and negative test results from quantitative assays

Test	Value	Updated result	Number with missing result before updating with quantitative results	Number with missing result after updating with quantitative results
Anti-HBs	>10 IU/ml ≤10 IU/ml	Positive Negative	4911	3
HBsAg titre	>0 IU/ml ≤0 IU/ml	Positive Negative	7	7
HBV-DNA	>500 IU/ml ≤500 IU/ml	Positive Negative	1148	2
HCV-RNA	>615 copies/ml ≤615 copies/ml	Positive Negative	2361	0

3.3.3 Follow-up dates and hepatitis test dates

As previously described, patients were classified by whether or not they had been followed-up in a particular year. Since hepatitis tests are reported from laboratories it is possible that the date provided in fact relates to the date that the sample was received in the laboratory or the date that the result was reported. In addition, the first and last seen dates may not be accurately reported since clinics may complete these items retrospectively. Therefore, I examined how many hepatitis tests occurred after the last seen date and how long after the last seen date the subsequent hepatitis test occurred (Table 3.4). To maximise the number of patients who would be included in the analyses, I included patients as under follow-up in a particular year if they had a hepatitis test in that year and if the test was within 6 months of being last seen. After doing this 323 individuals could not be assigned to any follow-up year.

Table 3.4 Comparison of last seen dates with dates of last hepatitis tests

Dates of last hepatitis tests and last seen dates	Number of individuals
Last hepatitis test > Last seen date	2444
Last hepatitis test > Last seen date +1 day	2328
Last hepatitis test > Last seen date +3 days	2293
Last hepatitis test > Last seen date +5 days	2266
Last hepatitis test > Last seen date +30 days	2150
Last hepatitis test > Last seen date +180 days	1588
Last hepatitis test > Last seen date +365 days	886

3.3.4 Description of available hepatitis data

A full analysis of patterns of testing and epidemiology of co-infection is presented later in this thesis, after further data collection had taken place. However, at this stage, the number of HBV and HCV tests conducted and the results of those tests were examined for each calendar year and in each centre. This informed the priorities for further data collection. For those tests which are used for diagnosis of infection (HBsAg for HBV infection and anti-HCV for HCV infection), the proportion of individuals tested increases over time. However, a particular increase is seen in the early 2000s (Table 3.5and Table 3.8) There is a corresponding fall in overall positivity as a higher proportion of lower risk individuals are tested who receive negative test results (Table 3.6 and Table 3.8). Analysis by first attended centre shows that there is great variation between centres in the proportion of hepatitis tests which are recorded in the UK CHIC dataset. For example, only 20.3% of individuals had a recorded test for HBsAg at centre 114 compared to 84.4% of individuals at centre 110 (Table 3.7) and only 43.8% of individuals had a recorded test for anti-HCV at centre 109 compared to 86.5% at centre 110 (Table 3.9)

Table 3.5 Individuals tested for HBV markers 1996-2011

Year	Total number of individuals under follow-up	Tested in that year															
		HBsAg	%	Anti-HBs	%	Anti-HBc	%	HBeAg	%	Anti-HBe	%	Anti-HBc (IgM)	%	HBV-DNA	%	HBsAg titre	%
Total	46878	31440	67.1	21491	45.8	29631	63.2	1356	2.9	2434	5.2	680	1.5	2342	5.0	480	1.0
1996	10463	869	8.3	610	5.8	477	4.6	79	0.8	35	0.3	4	0.04	0	0.0	0	0.0
1997	11213	1065	9.5	640	5.7	639	5.7	94	0.8	62	0.6	2	0.02	7	0.06	0	0.0
1998	12231	1036	8.5	589	4.8	565	4.6	95	0.8	72	0.6	2	0.02	20	0.2	20	0.2
1999	13294	688	5.2	425	3.2	552	4.2	115	0.9	112	0.8	39	0.3	25	0.2	30	0.2
2000	14475	1218	8.4	658	4.5	753	5.2	171	1.2	117	0.8	26	0.2	31	0.2	23	0.2
2001	15989	2685	16.8	931	5.8	1475	9.2	255	1.6	181	1.1	15	0.1	128	0.8	37	0.2
2002	11713	2885	24.6	897	7.7	1765	15.1	265	2.3	152	1.3	14	0.1	158	1.3	41	0.4
2003	19377	3480	18.0	1020	5.3	1915	9.9	319	1.6	194	1.0	14	0.1	219	1.1	24	0.1
2004	21575	4227	19.6	1297	6.0	2466	11.4	366	1.7	256	1.2	22	0.1	228	1.1	0	0
2005	23447	5264	22.5	2335	10.0	2637	11.2	427	1.8	369	1.6	38	0.2	315	1.3	91	0.4
2006	24953	6339	25.4	2967	11.9	3745	15.0	408	1.6	378	1.5	54	0.2	334	1.3	116	0.5
2007	26270	7640	29.1	4697	17.9	6397	24.4	479	1.8	521	2.0	95	0.4	521	2.0	116	0.4
2008	27352	9976	36.4	6779	24.8	8255	30.2	493	1.8	596	2.2	110	0.4	619	2.3	153	0.6
2009	28271	10906	38.6	7117	25.2	8286	29.3	503	1.8	607	2.1	151	0.5	704	2.5	123	0.4
2010	29326	9105	31.0	6354	21.7	7071	24.1	487	1.7	600	2.0	165	0.6	662	2.3	112	0.4
2011	27670	8092	29.2	6934	25.1	7727	27.9	483	1.7	860	3.1	189	0.7	1104	4.0	127	0.5

Table 3.6 Individuals with positive HBV tests, 1996-2011

Year	Tested positive in that year															
	HBsAg	% of those tested	Anti-HBs	% of those tested	Anti-HBc	% of those tested	HBeAg	% of those tested	Anti-HBe	% of those tested	Anti-HBc (IgM)	% of those tested	HBV-DNA	% of those tested	HBsAg titre	% of those tested
Total	1828	5.8	13781	64.1	11633	39.3	879	64.8	1165	47.9	104	15.3	868	37.1	414	86.3
1996	84	9.7	330	54.1	274	57.4	51	64.6	21	60.0	3	75.0	0	0.0	0	0.0
1997	103	9.7	287	44.8	311	48.7	65	69.1	33	53.2	0	0.0	3	42.9	0	0.0
1998	110	10.6	270	45.8	285	50.4	72	75.8	38	52.8	1	50.0	9	45.0	20	100.0
1999	108	15.7	243	57.2	263	47.6	76	66.1	46	41.1	10	25.6	16	64.0	30	100.0
2000	164	13.5	381	57.9	383	50.9	111	64.9	48	41.0	5	19.2	24	77.4	23	100.0
2001	289	10.8	526	56.5	705	47.8	181	71.0	54	29.8	8	53.3	100	78.1	37	100.0
2002	326	11.3	519	57.9	842	47.7	172	64.9	63	41.4	6	42.9	126	79.7	41	100.0
2003	404	11.6	606	59.4	870	45.4	194	60.8	88	45.4	10	71.4	134	61.2	24	100.0
2004	429	10.1	814	62.8	1115	45.2	220	60.1	117	45.7	2	9.1	130	57.0	0	0.0
2005	478	9.1	1498	64.2	1097	41.6	230	53.9	180	48.8	10	26.3	145	46.0	76	83.5
2006	477	7.5	1948	65.7	1482	39.6	193	47.3	154	40.7	8	14.8	120	35.9	96	82.8
2007	526	6.9	3043	64.8	2380	37.2	196	40.9	264	50.7	7	7.4	206	39.5	96	82.8
2008	537	5.4	4005	59.1	2808	34.0	188	38.1	261	43.8	4	3.6	235	38.0	133	86.9
2009	553	5.1	4381	61.6	2734	33.0	191	38.0	267	44.0	9	6.0	240	34.1	107	87.0
2010	539	5.9	4084	64.3	2243	31.7	191	39.2	223	37.2	13	7.9	240	36.3	99	88.4
2011	503	6.2	4686	67.6	2388	30.9	181	37.5	319	37.1	22	11.6	197	17.8	115	90.6

Table 3.7 HBV tests conducted at each centre

First centre code	Total number of individuals	Ever had an HBV test															
		HBsAg	%	Anti-HBs	%	Anti-HBc	%	HBeAg	%	Anti-HBe	%	Anti-HBc (IgM)	%	HBV-DNA	%	HBsAg titre	%
Total	47201	32130	68.1	21859	46.3	30307	64.2	2022	4.3	2466	5.2	703	1.5	2396	5.1	498	1.1
101	2728	2250	82.5	2233	81.9	1136	41.6	119	4.4	199	7.3	91	3.3	252	9.2	2	0.1
102	5225	3671	70.3	3429	65.6	3402	65.1	180	3.4	753	14.4	12	0.2	251	4.8	345	6.6
103	9792	7945	81.1	2462	25.1	6389	65.2	504	5.1	545	5.6	107	1.1	501	5.1	15	0.2
104	6266	5153	82.2	4245	67.7	4429	70.7	347	5.5	319	5.1	138	2.2	352	5.6	16	0.3
105	3677	2755	74.9	1813	49.3	2913	79.2	263	7.2	303	8.2	103	2.8	164	4.5	91	2.5
106	3713	2654	71.5	2322	62.5	2823	76.0	14	0.4	17	0.5	7	0.2	199	5.4	4	0.1
107	4370	2475	56.6	1381	31.6	2455	56.2	252	5.8	28	0.6	9	0.2	25	0.6	4	0.1
108	1084	495	45.7	400	36.9	520	48.0	40	3.7	33	3.0	0	0.0	31	2.9	0	0.0
109	1598	736	46.1	137	8.6	654	40.9	76	4.8	87	5.4	59	3.7	56	3.5	3	0.2
110	1381	1165	84.4	863	62.5	1141	82.6	90	6.5	5	0.4	1	0.1	6	0.4	4	0.3
111	1221	806	66.0	25	2.0	757	62.0	4	0.3	37	3.0	26	2.1	484	39.6	0	0.0
112	1444	572	39.6	613	42.5	520	36.0	22	1.5	23	1.6	10	0.7	24	1.7	3	0.2
113	475	216	45.5	173	36.4	122	25.7	14	2.9	13	2.7	84	17.7	15	3.2	5	1.1
114	1620	329	20.3	681	42.0	427	26.4	37	2.3	33	2.0	2	0.1	24	1.5	3	0.2
115	2306	754	32.7	934	40.5	1066	46.2	59	2.6	67	2.9	54	2.3	10	0.4	2	0.1
116	301	154	51.2	148	49.2	153	50.8	1	0.3	4	1.3	0	0.0	2	0.7	1	0.3

Table 3.8 Individuals tested and positive for HCV, 1996-2011

Year	Number under follow-up	Anti-HCV tested	% of those in follow-up	HCV-RNA tested	% of those in follow-up	Anti-HCV positive	% of those tested	HCV-RNA positive	% of those tested
Total	46878	34239	73.0	6541	14.0	3039	8.9	2454	37.5
1996	10463	818	7.8	13	0.1	136	16.6	5	38.5
1997	11213	1052	9.4	94	0.8	155	14.7	41	43.6
1998	12231	960	7.8	70	0.6	120	12.5	38	54.3
1999	13294	1008	7.6	123	0.9	92	9.1	71	57.7
2000	14475	1467	10.1	133	0.9	160	10.9	91	68.4
2001	15989	2536	15.9	208	1.3	189	7.5	147	70.7
2002	11713	2999	25.6	460	3.9	258	8.6	234	50.9
2003	19377	3855	19.9	633	3.3	273	7.1	250	39.5
2004	21575	4734	21.9	619	2.9	339	7.2	268	43.3
2005	23447	6309	26.9	795	3.4	409	6.5	376	47.3
2006	24953	6912	27.7	675	2.7	439	6.4	293	43.4
2007	26270	8846	33.7	1251	4.8	513	5.8	513	41.0
2008	27352	10900	39.9	1778	6.5	640	5.9	739	41.6
2009	28271	12298	43.5	2044	7.2	656	5.3	808	39.5
2010	29326	13023	44.4	2079	7.1	578	4.4	811	39.0
2011	27670	14153	51.1	1895	6.8	558	3.9	714	37.7

Table 3.9 HCV tests conducted at each UK CHIC centre

First centre code	Total number of individuals	Anti-HCV tested	%	HCV-RNA tested	%
Total	47201	35007	74.2	6605	14.0
101	2728	2286	83.8	515	18.9
102	5225	3832	73.3	1479	28.3
103	9792	8270	84.5	1172	12.0
104	6266	5254	83.8	1175	18.8
105	3677	3005	81.7	264	7.2
106	3713	2917	78.6	633	17.0
107	4370	2622	60.0	129	3.0
108	1084	600	55.3	257	23.7
109	1598	748	46.8	57	3.6
110	1381	1195	86.5	86	6.26
111	1221	795	65.1	668	54.76
112	1444	696	48.2	56	3.9
113	475	215	45.3	19	4.0
114	1620	1090	67.3	57	3.5
115	2306	1325	57.5	32	1.4
116	301	157	52.2	6	2.0

3.4 Statistical methods

Full details of analytical methods used in this thesis are provided in the relevant chapters. However, there are some standard methods used throughout. For all analyses, the cohort included in the analysis was first described with regard to demographic and clinical characteristics. Differences between groups were assessed using chi-squared tests for categorical or binary variables and Student's t-tests for continuous variables which were Normally distributed and Wilcoxon rank sum tests for continuous variables which were non-Normally distributed. Various regression techniques were then used to identify independent predictors of outcomes after controlling for confounding – the presence of factors which are associated with both the exposure and the outcome. This section describes the regression methods used. All analyses were conducted in SAS version 9.3 (SAS Institute Inc., North Carolina, USA).

3.4.1 Logistic regression

Where the outcome of interest is a binary variable (or categorical in the case of multi-nominal logistic regression), logistic regression analysis was used to model the likelihood of a particular outcome given a number of explanatory variable (or exposures) which are assessed at one time point.

The odds ratio (OR) for an outcome is defined as the odds in the exposed group divided by the odds in the unexposed group. Using the notation shown in Table 3.10, an OR can be calculated as:

$$\textbf{Odds ratio=} \ (\frac{a}{b})/(\frac{c}{d})$$

Table 3.10 Values used to calculate an odds ratio

	Individuals with outcome	**Individuals without outcome**
Exposed group	a	b
Not exposed group	c	d

Therefore the likelihood that the outcome occurs (the odds of that outcome), given exposure to a factor of interest can be expressed as:

$$Odds\ of\ outcome = Odds\ in\ reference\ group * Odds\ ratio\ for\ exposed\ group$$

Logistic regression models are fitted on a log scale and subsequently anti-logged to give ORs with 95% CIs. Therefore the above equation is transformed to:

$$log(odds) = \log(odds\ in\ reference\ group) + \log(odds\ ratio\ for\ exposure\ group)$$

The log(odds in the reference group) and log(odds ratio for exposure) are the regression coefficients: generally referred to as β. Where more than one exposure (x_1-x_n) is included in the model the logistic regression model can be expressed as:

$$log\ (odds\ of\ outcome) = \beta_o + \beta_1 x_1 + \beta_2 x_2 + \beta_n x_n$$

The result is anti-logged to give adjusted odds ratios (AOR). Multinomial logistic regression was used where the outcome was categorical (more than 2 categories). In this case one of the outcome categories is chosen as the reference group and the log(odds) of each outcome occurring compared to this reference group are estimated with regard to the exposure variables entered into the model.

3.4.2 Poisson regression

Poisson regression was also used where the outcome of interest is binary. However, this type of analysis allows for individuals within the cohort to be followed-up for different amounts of time and therefore it was used to model the rate at which the outcome occurs. This is useful in cohort studies where individuals may enter and leave the cohort at various different time points as it allows maximal use of available data, even when individuals are followed-up for short periods of time or at different calendar time points. Within the model, exposure variables which are measured more than once may be time updated. Like logistic regression, Poisson models are also fitted on a log scale. Therefore the above equation also applies but to give the log(rate of outcome). The model assumes that the rate at which an event occurs is uniform throughout the period of follow up. There are some analyses where there is reason to believe that this is not the case. In these situations some indicator of time can be included in the model (for example, time in study) to account for changes in the rate over time. Rate ratios (RRs) and adjusted rate ratios (ARR) are produced to compare the rate of outcome in one group with that in another.

3.4.3 Survival analysis and Cox proportional Hazards Models

Survival analysis was used where the outcome of interest was binary and a clear and logical time point to begin follow-up was available (for example first positive test result or start of treatment). This type of analysis allows for the rate of the event to vary over time. Cumulative survival (the probability of not having experienced the outcome up to time, *t*) and the hazard (the instantaneous rate of the outcome at time, *t*) at any given time are predicted using the Cox proportional hazards model. For individuals whose survival is not known beyond a particular time point, follow-up is censored. The model assumes that the probability of being censored is unrelated to the probability of the event occurring.

Kapan Meier methods were used to visually display the survival function prior to any regression analysis. The times at which an event occurs are t_1, t_2, t_3, up to t_j. At all times where the outcome of interest does not occur the probability of survival is equal to 1. Therefore the probability of survival at t_1 is:

$$S(t_1)=1*S(t_1)$$

At time point 2 the probability of survival is:

$$S(t_2)= S(t_1)*s_{t2}$$

This is repeated for all time points where the outcome occurs so that the probability of survival up to and including event j is:

$$S(t_j)= S(t_{j-1})*s_{tj}= s_{t1}*s_{t2}*s_{tj}$$

The survival curve is plotted as horizontal at all time-points where an event does not occur with a step drop corresponding to the change in probability of survival each time an event occurs so that the curve represents the true population at risk which only falls when an event occurs.

The Cox proportional hazards model considers the values of each exposure variable for an individual who experiences the outcome, at the time at which the event occurs. It assumes that the hazard ratio between different exposure groups remains constant over time. This is the proportional hazards assumption. Like Poisson and logistic regression Cox models are formed on the log scale and therefore can be represented as:

$$Log\ \big(h(t)\big) = \log\big(h_0(t)\big) + \beta_1 x_1 + \beta_2 x_2 + \beta_{\mathrm{p}} x_{\mathrm{n}}$$

The hazard ratio (HR) compares the hazards between exposure groups and gives an estimate of the increased hazard given the exposure of interest. In a multivariable model adjusted hazard ratios (AHR) estimate the hazards in each exposure group after accounting for confounding factors.

3.4.4 General approach used in all regression analyses

For all regression modelling the decision as to which variables should be included in the model was based on results of univariable analysis and *a priori* decisions informed by the literature. Only those factors which were found to be associated with the outcome in univariable analysis ($p<0.05$), or those where previous research has shown a strong association between the outcome and any other exposure variables, were included in multivariable modelling. The aim of all analyses was to achieve a parsimonious model. Therefore variables were added to the model in a stepwise manner and were only retained in the model if they showed a significant result or altered the results for any other variables included. A 5% significance level was used throughout this thesis and 95% confidence intervals (95% CI) are presented where appropriate.

Chapter 4 Methods 2: Forming an HIV and hepatitis co-infection dataset

4.1 Introduction

As previously described, the standard UK CHIC dataset includes dates and results of hepatitis tests. However, the dataset does not include details of hepatitis specific treatment or the stages of liver disease in co-infected patients. Previously published analyses of hepatitis in the UK CHIC study have been limited to the presence of infection and the impact of hepatitis co-infection on HIV-related outcomes (immunological status and HIV treatment response) (244, 259). These analyses, as well as the description of available hepatitis data described in Chapter 3, section 0, have indicated that not all hepatitis tests conducted may be reported to UK CHIC. Therefore, using only these test results to define hepatitis co-infection may result in underestimation of the size of the co-infected population.

This chapter describes the process of identifying a cohort of individuals who are co-infected with HIV and HBV and/or HCV through examination of the existing UK CHIC dataset and subsequent validation with data obtained from clinics. In addition, I describe the process of expanded data collection which was conducted in order to obtain clinical hepatitis data (liver outcomes and treatment information) for these individuals.

In order to reduce the volume of data to be collected, a limited time period was chosen. Only those individuals who had been seen for care at any point since 2004 were included in this process. This time period was selected because of the changes in the proportion of individuals tested for hepatitis markers over time (0) and the publication of specific clinical guidelines for treating HIV/HCV and HIV/HBV co-infection which may have had an impact on the numbers of individuals tested within HIV clinics (456-459). However, in line with standard UK CHIC data collection, all available information was gathered for these individuals, including historical data prior to 2004.

4.2 Identification of potentially co-infected individuals

Given the concerns that not all hepatitis tests may be reported to UK CHIC we aimed to supplement the existing data within UK CHIC with clinical knowledge of hepatitis co-infection within the centres. For the purposes of identifying individuals who may be infected with HBV

or HCV, HBV co-infection was defined as ever receiving a positive result for an HBsAg test and HCV co-infection was defined as ever having a positive test for anti-HCV test or a positive result for a HCV-RNA test. These definitions were used to create a list of potentially co-infected patients at each centre from the final UK CHIC 2011 dataset (from here on referred to as the CHIC co-infected list).

The UK CHIC dataset is pseudonymised and does not contain specific patient identifiers. Individuals are assigned a unique identifier once data has been received from the centre (known as PATNUM). Clinic identifiers (IDs) are removed from the final dataset but are kept in the main UK CHIC database at the MRC. Using the MRC database, the PATNUMs of individuals in the CHIC lists of co-infected individuals were matched to clinic IDs to give a list of potentially co-infected patients who could be identified within clinic information systems. PATNUMs and clinic IDs were kept separate at all times except during the matching process at the MRC to preserve the pseudonymised nature of the dataset used in analysis.

A request was sent to each centre for a list of clinic identifiers for those individuals, seen at any point from 2004, who they believed to be co-infected with HBV or HCV. These lists formed a secondary list of potentially co-infected individuals (from here on referred to as the centre co-infected lists). The CHIC co-infected lists were cross-matched with the centre co-infected lists to create a final list of potentially co-infected individuals (Table 4.1). Of the 16 HIV centres contributing to UK CHIC in 2011, only 11 were able to provide a clinical list of co-infected individuals. Therefore all further data collection was conducted only at these 11 centres.

Table 4.1 Number of potentially co-infected patients on CHIC lists and centre lists

Centre	HBV			HCV		
	UK CHIC list[1]	Centre list[1]	Total potentially co-infected[2]	UK CHIC list [1]	Centre list[1]	Total potentially co-infected[2]
Brighton	86	80	91	480	193	504
St Mary's	176	146	184	329	462	514
Chelsea & Westminster	439	404	492	1025	991	1154
Mortimer Market Centre	239	220	290	504	431	529
Kings	163	198	223	97	236	288
Royal Free	217	189	244	157	416	440
Edinburgh	48	25	49	238	251	298
North Middlesex	75	72	116	29	79	83
Bristol	29	26	32	69	51	72
Middlesbrough	13	9	13	8	11	11
Woolwich	41	25	48	48	17	55
Total[3]	**1526**	**1394**	**1782**	**2984**	**3138**	**3948**

[1] CHIC lists and centre lists are not mutually exclusive.
[2] HBV and HCV lists are not mutually exclusive.
[3] Co-infected individuals may be seen at more than one centre.

4.3 Expanded data collection

The hepatitis subgroup of the UK CHIC steering committee agreed a list of variables for which we would collect data on all co-infected patients. Where data items could be derived from the existing data, newly collected data would be used for validation (Table 4.2). Only data which were routinely collected within the HIV clinic were collected as agreed in UK CHIC ethical agreements.

Centres were asked, for each data item, whether the data would be available in the form of an electronic download or would require a review of patient notes (either in paper format or available as part of an electronic patient record system) (Table 4.2).

Data collection was conducted from September 2012 to September 2013 in collaboration with research assistants based at the research unit of St Stephen's AIDS Trust: Ashley Moyes (AM), Laura Phillips (LP) and Elisha Seah (ES). NHS research passports and letters of access were

obtained for each Trust to allow access to patients' records. Each centre was visited by me and at least one of AM, LP and ES to gather data which was not available in the form of an electronic download. During centre visits the true status of all potentially co-infected individuals was ascertained. Data were collected on standardised Excel spread sheets as free text and were recorded exactly as it appeared in the notes. Collected data was uploaded to the File Transfer Protocol (FTP) server, a secure server run by the MRC.

Table 4.2 Data items to be collected and sources of data for those patients who are co-infected with HBV and/or HCV

Type of data item	Data collected	Sources of data
Behavioural	Sexual orientation at time of hepatitis acquisition, injected drug use, alcohol consumption	Clinical notes; HIV clinic databases; clinicians' letters
For HCV co-infected individuals	Date of last negative and first positive anti-HCV test Date first positive HCV-RNA test Date and result of most recent anti-HCV and HCV-RNA test Date and result of all HCV genotype tests	Clinical notes; HIV clinic databases; clinicians' letters; laboratory downloads
For HBV co-infected individuals	Date of first and most recent anti-HBc, HBsAg, anti-HBs, HBeAg, anti-HBe, HBV-DNA, HBV genotype	Clinical notes; HIV clinic databases; clinicians' letters; laboratory downloads
Other hepatitis serology	Date and result of first and most recent hepatitis D antibody and hepatitis A antibody	Clinical notes; HIV clinic databases; clinicians' letters; laboratory downloads
Other laboratory tests	Prothrombin time, AFP	Clinical notes; clinicians' letters; laboratory downloads
Assessments for liver disease	Dates and results of liver scans, biopsies and FibroScans®	Clinical notes; clinicians' letters; radiology downloads; pathology records; Fibroscan® machine downloads
Hepatitis treatment	Date of starting and stopping all drugs to treat HBV or HCV. Dose and frequency of drug regimen, reason for stopping drug	Clinical notes; clinicians' letters

Type of data item	Data collected	Sources of data
Complications of hepatitis infection	Date of diagnosis for all instances of: ascites; portal hypertension; hematemesis; varices; encephalopathy; hepatoma	Clinical notes; clinicians' letters; scan results
Liver transplantation	Referral date for a liver transplant (where applicable) Date of liver transplant (where applicable)	Clinical notes; clinicians' letters
Death	Date and cause of death (where applicable)	Clinical notes; HIV clinic databases

4.4 Merging data into UK CHIC

A series of standardised tables, including relevant coding was created for the newly collected data (Appendix V). For each centre the collected data were cleaned and formatted to populate these tables. Clinic IDs of all patients were matched to the 2012 UK CHIC PATNUM and the clinic IDs were deleted to anonymise the dataset. The serological data, death data and the demographic data were then merged back into the main UK CHIC dataset. Other newly collected data (hepatitis genotype, hepatitis treatment, scans, biopsies, FibroScans®, clinical events and transplant data) have been kept as separate datasets which can be merged into UK CHIC for analyses as necessary. All data management and analyses were conducted in SAS version 9.3 (SAS Institute Inc., Cary, NC, USA).

4.4.1 Demographic data

Where new data were available from the data collection which were not present in UK CHIC the UK CHIC dataset was updated. Where there were conflicts between the new demographic data and the existing UK CHIC data, the existing UK CHIC data was maintained. These conflicts were usually due to individuals being seen at more than one clinic where data cleaning processes during creation of the UK CHIC dataset had already ascertained the most likely correct data.

4.4.2 Death data

As a result of the data collection process, an additional 39 individuals were identified as having died compared to the existing UK CHIC data. The UK CHIC dataset was updated accordingly for these individuals. Where the date of death ascertained from data collection did not match the date of death in UK CHIC, the UK CHIC date was used as this has already been validated through other mechanisms. Where cause of death in existing UK CHIC data did not match the newly collected data, the most likely cause of death was determined on a case-by-case basis.

4.4.3 Hepatitis test data

The existing UK CHIC hepatitis test data for all potentially co-infected individuals were extracted, merged with the newly collected serology data and de-duplicated. Therefore the resulting dataset contained the existing UK CHIC data and any additional data from the data collection. The existing UK CHIC dataset was then compared to the new dataset and examined for conflicting information. There were a number of scenarios where the new data conflicted with the old data:

1. Same date, same test code, same result, different quantitative value
2. Same date, same test code, different result, same quantitative value
3. Same date, same test code, different result, different quantitative value

After review of the data, the following rules were used to resolve these discrepancies.

Scenario 1 (725 individuals) and scenario 2 (738 individuals): where the old value is null and the new value is not null, use the new value. Where the new value is null and the old value is not null, use the old value. Where neither the old nor the new value are null but they are different, accept the new value.

Scenario 3 (918 individuals): Accept the new data.

The updated serological data was then used to replace the original serological data for these individuals.

4.4.4 Coding Scans

Scans and biopsies were recorded in the dataset exactly as reported to the requesting clinician. A number of different types of medical imaging techniques had been used in order to visualise the liver including US, MRI and CT scans. With input from a clinical member of the hepatitis subgroup of the UK CHIC steering committee hepatitis subgroup, scan results were coded as: normal; suggestive of fatty infiltration; suggestive of cirrhosis; showing ascites; suggestive of portal hypertension; HCC; any other abnormalities. Each scan could receive multiple codes. Coding was conducted as a two stage process. At stage one, scans were coded as any of the above where the full text result explicitly mentioned the relevant conditions. However, this resulted in a number of scans that remained uncoded. Therefore at stage two of coding, complete descriptions of the imaging were used to ascertain whether any of the codes were relevant.

Scans were coded as normal where abnormalities were noted on the scan report but were not relevant to the liver (for example, enlarged spleen in the absence of any hepatic abnormality). A summary of common descriptions found in the imaging report which led to coding are shown in Table 4.3. Where scans were suggestive of portal hypertension or there was

evidence of ascites, scans were coded as suggestive of cirrhosis since these complications of liver disease would only be likely to occur in cirrhotic individuals.

Suspicious liver lesions are usually identified first on US. However, in order to make a diagnosis of HCC, further imaging such as MRI is usually conducted. Therefore where a visualised lesion on an US had triggered further imaging which then confirmed the presence of HCC the earliest scan showing the relevant lesion was coded as HCC. Finally, a further code was added to indicate benign liver lesions and a further code was added to indicate a scan which occurred subsequent to a liver transplant.

Table 4.3 Common descriptions reported in imaging results and relevant coding

Descriptions found in liver imaging report[1]	Codes applied in dataset
Coarse echotexture Fibrotic change Nodular echotexture Scarring Shrunken liver Heterogeneous echotexture	→ Suggestive of cirrhosis
Increased echotexture Increased reflectivity Areas of focal fatty sparing	→ Suggestive of fatty infiltration
Oesophageal varices Reduced hepatopetal flow Reversal of flow Portal dampening Dampened hepatic venous flow Portal vein thrombosis Prominent portal vein	→ Suggestive of portal hypertension

[1] This is not a complete list but does include the most commonly seen descriptions

4.4.5 Coding biopsies

The inclusion of data collected from multiple centres has resulted in biopsy data in a number of different formats. Some results only include a description of the biopsy material while others provide information in the form of scores of inflammatory activity and fibrosis stage. However, where scores were reported, a range of different scoring systems had been used. In

total, of 862 biopsies, 484 had one or more scores included in the report (471 Ishak activity scores, 475 Ishak fibrosis scores, 12 METAVIR activity scores and 8 METAVIR activity scores).

Therefore a set of codes were created for the types of scores used and these were included within the biopsy dataset. Where a score had been given in the pathologist's report, this result was retained. However, for those biopsies where no score was available in the pathologist's report a METAVIR score was assigned according to details given in text result of the report. In order to validate this scoring, a sample of 20 biopsies was also scored by an experienced clinician. The two scores were then compared. The activity scores matched for 13/20 of these cases and fibrosis scores matched for 15/20. Since activity score is difficult to define from text, I will not make any changes but have used the knowledge gained to make recommendations for improvement for the next round of data collection. Where fibrosis scores did not match, the reasons for this were ascertained. One was an error by one scorer which was amended (a cirrhotic individual who had been assigned a score of 1), the other four were individuals who had a description of "developing cirrhosis". The two scorers had either assigned these a 3 or a 4. Subsequent to this validation all individuals with a report including this description were assigned a METAVIR score of 4.

4.5 Summary of data collected

Data collection was completed at eleven out of sixteen UK CHIC centres. Paper notes and/or hospital record systems (for example radiology or pathology databases or electronic patient record systems) were reviewed for 95% of potentially HBV co-infected patients and 91% of potentially HCV co-infected patients at these centres. Where notes were not reviewed this was due to paper notes being physically unavailable for reviews. This was the case for patients who had not been seen in the centre for long periods of time. Clinic staff were consulted about the possibility of obtaining all notes which were not immediately available and therefore the 5% that were not reviewed were considered impossible to obtain in the necessary timeframe.

A total of 1637 individuals were confirmed as HBV-infected and 3299 individuals were confirmed as HCV-infected. A summary of new data items collected are shown Table 4.4.

Table 4.4 Total number of new data items collected

Data Item	Number of patients	Total number	Median number per patient	Inter quartile range
Scans	2339	6618	2	1, 4
Biopsies	719	870	1	1, 1
FibroScans®	1165	1592	1	1, 2
Prothrombin time[1]	2464	18563	6	3, 13
INR[1]	343	3561	11	4, 27
AFP	2452	12512	4	2, 10
HCV treatment	1098	-	-	-
HCV genotype	1818	-	-	-
Clinical events[2]	68	-	-	-
Transplants	12	-	-	-

[1] Different measures of blood clotting are reported depending on the centre. Prothrombin time is measured at Edinburgh, Bristol, Mortimer Market Centre, St Mary's, Chelsea and Westminster, Royal Free, Woolwich, North Middlesex and Middlesbrough. International Normalised Ratio (INR) is measured at Brighton, St Mary's, Kings, Woolwich and North Middlesex.

[2] Incomplete data. This includes mention of clinical event in medical notes and does not include clinical events which are reported in the results of scan

Of 3299 HCV-infected individuals 55% had a known genotype (32 individuals had more than one genotype): 1249 (69%) genotype 1; 49 (3%) genotype 2; 15 (0.8%) genotype 2/3; 284 (16%) genotype 3; 251 (14%) genotype 4; and 2 (0.1%) genotype 6. Among HCV-infected patients, 33% had records of having received hepatitis treatment.

Information on HBV treatment with tenofovir or lamivudine is available in the existing UK CHIC dataset since these drugs form part of the individual's HIV treatment as well as acting against HBV. Additional data on HBV treatment with entecavir, adefovir or interferon were collected for 30 individuals.

4.6 Inclusion criteria for analyses

As described in this chapter, expanded data collection was conducted at 11/16 CHIC centres and was limited to those patients who were seen at any point from 2004 onwards. For all further analyses presented in this thesis, unless otherwise stated, only those individuals who had been seen at any of the 11 included centres from 2004 onwards were included.

To identify the individuals to be included in the analysis, the years in which each individual was followed-up at each centre were identified using the first and last dates that an individual was reported as having been seen at each centre. Given the high number of individuals who had received a hepatitis test result after their last seen date and in order to maximise the volume of hepatitis data which could be included in the analyses, an additional 6 months at the end of follow-up were added where hepatitis tests occurred after the final last seen date.

In order to assess the potential for the introduction of bias due to exclusion of individuals who had not been seen from 2004 onwards, the characteristics of those patients who were included were compared to the characteristics of those who were not included. Differences in the groups were assessed using Chi-squared tests for categorical variables, t-tests for continuous variables with Normal distributions (age) and Wilcoxon rank sum tests for continuous variables with distributions that were not Normal (CD4 and viral load) (Table 4.5). The cohort of individuals included in analyses consisted of a higher proportion of males, a higher proportion of individuals of white ethnicity, a higher proportion of MSM, a higher proportion of individuals who had received any ART and a lower proportion of individuals who had died. These differences in the included and excluded individuals are likely due to the changes in time in the cohort overall.

Table 4.5 Comparison of individuals included in the analyses with those who are excluded

	Total N (%)	Included N (%)	Excluded N (%)	P value
Total	47201	32079	15122	-
Median age (IQR)	34 (29, 40)	34 (28, 40)	34 (29, 41)	<0.0001
Male	34202 (72.5)	24215 (75.2)	10077 (66.6)	<0.0001
Ethnicity				
White	24641 (52.2)	18443 (57.5)	6198(41.0)	<0.0001
Black African	12796 (27.1)	7945 (24.7)	4851 (32.1)	
Other black ethnicity	2498 (5.3)	1607 (5.0)	891 (5.9)	
Other	4396 (9.3)	3018 (9.4)	1378 (9.1)	
Not known	2870 (6.1)	1066 (3.3)	1804 (11.9)	
Exposure category				
MSM	23341 (49.5)	17582 (54.8)	5759 (38.1)	<0.0001
Heterosexual	17191 (36.4)	11105 (34.6)	6086 (40.3)	
IDU	1694 (3.6)	963 (3.0)	731 (4.8)	
Other	1862 (3.9)	1384 (4.3)	478 (3.2)	
Unknown	3113 (6.6)	1045 (3.3)	2068 (13.7)	
ARV experienced	34915 (74.0)	25724 (80.2)	9191 (60.8)	<0.0001
Median CD4 count at entry (IQR)	315 (145, 493)	330 (168, 510)	274 (110, 460)	<0.0001
Median log viral load at entry (IQR)	4.3 (3.0, 5.0)	4.3 (3.1, 5.0)	4.3 (2.9, 5.1)	0.51
Died	4475 (9.5)	1622 (5.1)	2853 (18.9)	<0.0001

4.7 Discussion

To my knowledge, this is the first multicentre cohort of patients who are confirmed as being HIV and HBV and/or HCV co-infected in the UK.

I experienced a number of challenges which resulted in limitations in the data collected. Since the starting point for data collection was lists of potentially co-infected patients, I was not able to make any improvements to the denominator data. It is likely that missing data still exists in the form of patients who have tested negative for HBV and HCV. However, I hope that the intense effort that has been put into the data collection and the associated discussions with clinicians and data managers at participating centres has improved overall recording of hepatitis tests in clinical databases and will therefore improve the quality of the denominator in future UK CHIC datasets.

I was only able to access data via the HIV centres and HIV clinicians. Patients may be referred to another centre for their hepatitis care. If the referral centre is also a UK CHIC site and that individual has ever received any HIV care at that site I will have collected data for that individual at both sites. However, if an individual is referred to a non-UK CHIC site or is referred to a UK CHIC site but is never seen at that site for their HIV care, I may not have been able to gather complete information. However, I believe that the volume of data missing for this reason is minimal as correspondence between centres was reviewed during the data collection process.

The data collected here will provide valuable baseline information for treatment and prevention pathways. Prospective collection of these data items in this cohort would be of benefit in evaluating any new treatment strategies which are implemented among in co-infected populations. However, given the intense nature of the data collection and the lack of systematic recoding of this data within centres, this would require further funding and dedicated research personnel.

Chapter 5 Methods 3: Characterising hepatitis co-infection using routinely collected data from HIV clinical cohorts

5.1 Introduction

Many large ongoing HIV cohort studies, including UK CHIC, collect limited data on tests conducted to assess whether an individual is co-infected with, or immune to, hepatitis viruses. In cohort studies where active follow-up of individuals occurs, known HBV or HCV status may form part of the baseline assessment of participants (230, 258, 261) and stored samples can be retested to confirm the HBV or HCV status of participants where queries remain (258, 263). However, for purely observational studies, data collection systems may not have been designed for collecting detailed information on hepatitis infection since they were initiated with the primary aim of collecting HIV clinical data (231, 256, 257, 259, 264). This means that inconsistencies may exist within the data collected. In addition, clinical practice varies with regard to the setting in which a test for hepatitis is conducted (within HIV clinics, sexual health clinics or hepatology clinics) and therefore how and where it is recorded.

Ascertaining an individual's hepatitis status at any one point in time in the dataset is often complicated by missing data and varying clinical practices with regard to testing for each of the hepatitis markers. There is no consensus among study groups as to how to deal with inconsistencies in the data and current methods are usually formed on an *ad hoc* basis as and when problems are encountered. In this chapter, I present a systematic analysis of the UK CHIC dataset which has assessed commonly occurring inconsistencies in HBV and HCV tests. Three separate problems were considered within the dataset. The first was inconsistent or changing anti-HCV test results; the second was inconsistent or changing HBsAg test results; and the third was defining the HBV infection status (infected, immune or never exposed) of an individual. After assessing the magnitude of each of these problems, methods were derived to manage these inconsistencies so that the maximum amount of data can be used in analyses where hepatitis co-infection is either the outcome of interest or an important explanatory variable.

5.2 Methods

5.2.1 Inclusion criteria

This analysis was conducted using the UK CHIC 2012 dataset prior to the addition of data collected as part of the expanded data collection. Analysis of HCV data included all individuals who had at least one anti-HCV test result recorded in the dataset. Analysis of HBsAg tests included all individuals who had at least one HBsAg test recorded in the dataset. Analysis of HBV infection status included all individuals who had at least one test result recorded in the dataset for HBsAg, anti-HBs or anti-HBc.

5.2.2 HCV antibody testing

Once an individual has been infected with HCV, anti-HCV will appear in their blood within 3 months. This antibody remains in the blood long term as a sign of past or present infection (460). Although loss of anti-HCV has been documented among HIV-positive IDU in the past (461, 462), testing for anti-HCV shows a high sensitivity even when CD4 counts are low (463). Therefore a negative result which appears after a positive result indicates an error, either in initial coding of tests at the centre or in data processing once the data has been received. The dataset was examined for the presence of these types of discrepant results. Where discrepant results were identified the complete record of the individual was reviewed. Based on subsequent results, an algorithm was used to make decisions about which result was erroneous and which was correct.

During the data collection process described in Chapter 4, those individuals who had been identified as potentially co-infected but who were not found to have any other evidence of co-infection in clinical records were noted. The final HCV status according to the algorithm was then compared to clinical data, obtained through the expanded data collection, in order to determine whether the algorithm provided a good approximation of HCV status in the absence of clinical information.

5.2.3 HBV surface antigen testing

HBsAg is a marker of current HBV infection which is often used to classify individuals as co-infected in HIV cohorts. However, individuals can clear HBsAg either after an acute infection which resolves (88) or following successful treatment (464-466). All individuals who had a positive HBsAg result were identified. In order to illustrate how changing test results could alter the results of analyses, HBV prevalence was calculated using two methods: (i) all

individuals who ever have a positive test result are considered infected; or (ii) only those individuals whose most recent HBsAg test is positive are considered positive.

Among all individuals who had a positive HBsAg test, subsequent HBsAg results were examined to identify where individuals went from positive to negative. The complete record of all individuals with changing results was reviewed. This process was conducted with input from clinicians with experience in interpreting laboratory results of hepatitis tests for HIV-positive individuals under their care. Commonly recurring situations were identified and the presence of other markers and time periods between tests were used to determine an algorithm for deciding which results should be considered as errors or anomalies in the dataset and which were true representations of clinical progression. The cumulative prevalence of HBV infection was calculated before applying the algorithm and after the algorithm as the proportion of all individuals tested for HBsAg who have ever had a positive test result recorded in the dataset.

5.2.4 HBV infection status

An individual's HBV infection status can be further characterised as active infection, naturally immune as a result of a resolved infection, immune through successful vaccination or never having been exposed (88). The status of an individual at any particular time point can be determined using the results of tests for HBsAg, anti-HBs and anti-HBc. All possible combinations of these three markers were identified and assigned the most likely infection status. This included those combinations of markers that did not provide a definitive infection status and those combinations of markers that are clinically implausible (Table 5.1). For those cases where it was not possible to assign a definitive infection status, all possible infection statuses were identified.

Using the UK CHIC dataset, at each time point where an individual was tested for any one of the three markers, the dataset was examined for results for the other markers on the same day and the individual was assigned to one of the infection categories shown in Table 5.1. In order to give an indication of the proportion of individuals who fell into each category, the data were then summarised as the number of individuals within each infection category at their first data point (the first time they were tested for any one of the three markers of interest) and at their final data point (the last time they were tested for any one of the three markers). An assessment of whether they had ever been classified into each of the possible infection categories at any time point was also carried out.

In order to reduce the number of individuals who had an unclassifiable infection status (those with an *unknown* or *not possible* status), the prior statuses of these individuals were examined. For individuals with an unknown status, potential classifiable statuses were identified and the existence of previous test results examined in order to determine whether any results could be carried forward. A detailed description of which results were carried forward is included in section 5.3.3. Briefly, where a prior status indicated the presence of an additional marker, the result of that marker was carried forward.

To assess the impact of using this method, the proportions of individuals in each category at the time of their last test were examined before any prior results were carried forward and after prior results were used to classify status. Finally, baseline factors associated with being unclassifiable at the final test were assessed using logistic regression.

Table 5.1 Summary of all possible combinations of test results and associated infection statuses[1]

HBsAg	Anti-HBs	Anti-HBc	Status
+	_	+	Infected
+	.	+	Infected
+	+	+	Clinically implausible
+	_	_	Clinically implausible
+	.	_	Clinically implausible
+	+	_	Clinically implausible
+	_	.	Infected
+	.	.	Infected
+	+	.	Clinically implausible
_	+	+	Resolved
_	_	+	Resolved
_	.	+	Resolved
_	+	_	Vaccinated
_	_	_	Never exposed
_	.	_	Unknown (never exposed or vaccinated)
_	+	.	Unknown (resolved or vaccinated)
_	_	.	Unknown (never exposed or resolved)
_	.	.	Unknown (never exposed, resolved or vaccinated)
.	+	+	Resolved
.	_	+	Unknown (infected or resolved)
.	.	+	Unknown(infected or resolved)
.	+	_	Vaccinated
.	_	_	Never Exposed
.	.	_	Unknown(never exposed or vaccinated)
.	+	.	Unknown (resolved or vaccinated)
.	_	.	Unknown (infected or never exposed)

[1] Dot denotes unknown status of the marker

5.3 Results

5.3.1 HCV antibody testing

Of 3293 individuals in the dataset with a positive for anti-HCV test, 232 (7.05%) individuals have a subsequent negative result. Further results for these individuals were examined (Figure 5.1). Where no further test results were available it was assumed that the individual was HCV-positive. Where all further test results were negative, the positive result was assumed to be an error and the individual was considered to be HCV-negative. For those individuals who had a further positive test result, similar assumptions were made regarding subsequent test results. Ten individuals had results which could not be easily assumed to be positive or negative since the pattern of their test results fluctuated between positive and negative repeatedly. The complete records of these 10 individuals were reviewed and decisions made about whether or not they would be assumed to be positive or negative.

Using this algorithm a total of 105 individuals had a positive test result at some point which was considered to be an error and 127 individuals had a negative test result at some point after their first positive test which was considered to be an error.

Among the 232 individuals who had any changing results, 222 were seen at any one of the 11 centres where clinical data was collected. For these 222 individuals, the algorithm-defined status was compared to the status ascertained through review of clinical notes. This comparison revealed that using the algorithm the correct assumption had been made in 63.1% (140/222) of cases but an incorrect assumption had been made in 36.9% (82/222) of cases. Where the incorrect assumption had been made, 10 individuals were incorrectly classified positive by the algorithm and 72 individuals were incorrectly classified as negative by the algorithm (Table 5.2).

Figure 5.1 Assumptions about anti-HCV status in individuals who have conflicting results

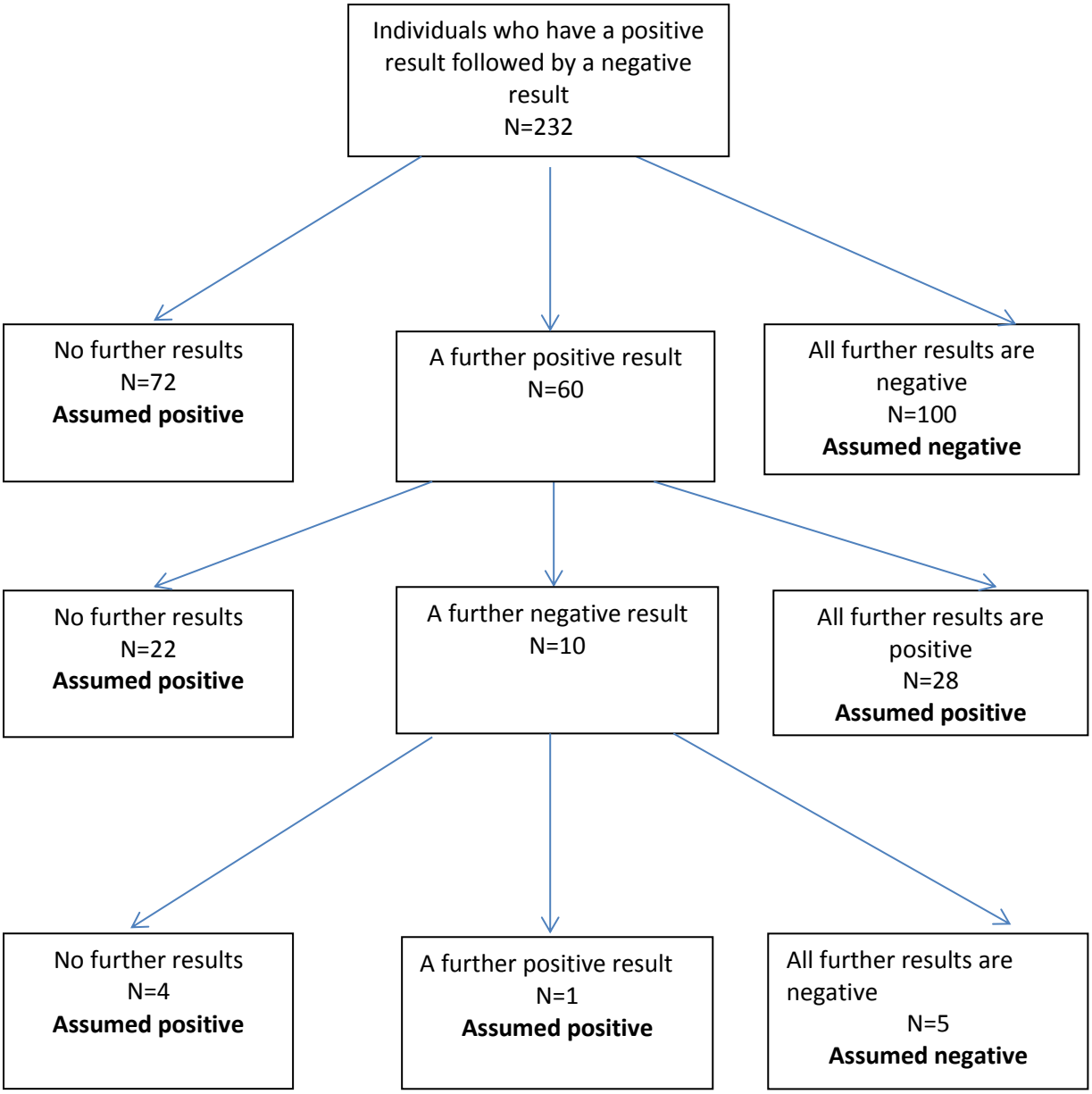


Table 5.2 Comparing HCV algorithm assigned status to information from clinics

Anti-HCV status according to algorithm	Clinical classification	Number of individuals	Performance of algorithm in defining anti-HCV status
Positive	Positive	108	Correct
Positive	Negative	10	Incorrect
Negative	Positive	72	Incorrect
Negative	Negative	32	Correct

5.3.2 HBV surface antigen testing

Of 2247 individuals in the dataset who had a positive HBsAg test result, 580 had a subsequent negative result at some point. The majority of these individuals, n=357, then had further negative results and no more positive results. These individuals were considered to have resolved the infection. However, 223 individuals had a subsequent positive result. Subsequent results for these individuals were examined to identify patterns of changing HBsAg test results recorded in the dataset.

Among those individuals who had changing results, the complete record was reviewed including tests. This included assessing time from first positive test and the presence of other infection markers such as HBeAg and HBV-DNA. Reviewing the records of these individuals resulted in the identification of eight situations which occurred repeatedly within the dataset and could be used to assess whether an individual was HBsAg positive at that time point or not. These eight situations were placed in a hierarchy depending on the certainty with which they could be used to assume an HBsAg status. These assumptions and the associated hierarchy formed an algorithm which was applied to the records of all individuals where HBsAg test results changed over time (Table 5.3). After running the algorithm the number of individuals whose results changed over time was reduced (Table 5.4).

Table 5.3 Algorithm for ascertaining a patient's HBsAg status among patients who have a positive test followed by a negative test

Test result pattern	Rational for assumed status
1. Negative HBsAg result occurs on the same day as a positive HBsAg result	Negative test result is an anomaly in the dataset and individual should be classified as HBsAg positive
2. Individual has positive HBV-DNA and/ or positive HBeAg on the same day as the negative HBsAg test result	The negative test result is likely to be an anomaly and the individual should be considered as HBsAg positive
3. First negative HBsAg result after a positive is followed by repeated negatives and no further positive	Individual has cleared the infection and should be classified as HBsAg negative from the time of their first negative result
4. The first negative HBsAg after a positive occurs less than 6 months after the first HBsAg positive result	The first positive was an acute infection which has then cleared. Individuals can be considered as HBsAg negative from the point of their negative test until another positive occurs
5. Prior to negative HBsAg result, the individual has consecutive positive HBsAg results which are at least six months apart	Individual is chronically infected and should be classified as HBsAg positive
6. Individual has evidence of anti-HBe or clearance of HBeAg at the same time as their negative test result	It is plausible that the patient may have cleared their HBsAg even if they have become chronic carriers of the virus. Therefore they should be considered as HBsAg negative from the point of their negative test until a further positive occurs indicating a reactivation
7. Prior to the first ever positive HBsAg test in the dataset the individual has had negative HBV tests at the same time as positive anti-HBc	The individual was already chronically infected and the first HBsAg positive is a reactivation. Therefore it is plausible that the negative result is real as the reactivation has subsided and the individual should be classified as negative from the point of their negative test until they have another positive test
8. The negative result is followed by at least one more negative result a month or more later	The individual may or may not be chronically infected and the stage of infection is not determinable but given repeated negative results the individual should be classified as HBsAg negative from the point of their first negative until they have a further positive result

Table 5.4 Summary of changing HBsAg results

HBsAg results pattern	Number of individuals in dataset	Number of individuals after applying algorithm
At least one positive (+)	2247	2247
At least one negative after a positive (+ -)	580	401
Revert to positive (+ - +)	223	88
Re-revert to negative (+ - + -)	92	38
Further inconsistent results (+-+-+)	58	23

Among those ever having tested for HBsAg the prevalence ranged from 6.6% (2026/30749) where cumulative prevalence was calculated, to 5.7% (1727/30744) where prevalence was calculated using the most recent HBsAg result, and 5.9% (1766/30742) where prevalence was calculated using the algorithm-defined HBsAg test results.

Predictors of HBV are investigated in depth in Chapter 6. However, in order to assess whether the different methods of classifying an individual's HBsAg status has any effect on the predictors of HBsAg positivity I constructed 3 separate multivariable logistic regression models to identify factors that were associated with HBsAg positivity. Factors considered in the multivariable models were age, HIV exposure group, ethnicity, year of entry into study, nadir CD4 count, HCV co-infection and being on HBV active antiretroviral treatment. The outcome was HBsAg positivity as defined by each of the 3 methods of classification. Independent predictors of HBsAg positivity did not vary according to the method used to classify status (Appendix VI).

5.3.3 HBV infection status

A total of 36244 individuals had been tested for at least one of HBsAg, anti-HBs or anti-HBc (32785 for HBsAg, 22238 for anti-HBs and 30648 for anti-HBc). Using results for tests conducted on the same date, individuals were classified at each time point where there was evidence of a test for one of the three markers. The number of individuals who were ever classified into each category, those classified as each status on their first hepatitis data point and those classified into each category on their final hepatitis data point are shown in Table 5.5. Using this method, high proportion of individuals have unclassifiable (either clinically

implausible or unknown due to missing data) HBV infection statuses: 24149 (66.6%) on the first data point and 20698 (57.1%) on final data point.

Table 5.5 Combinations of test results reported with the same date and used to assign HBV infection status

HBV infection status	Number of individuals classified as status (%)		
	Ever	On first data point	On final data point
Infected	2006 (5.5)	1546 (4.3)	1561 (4.3)
Resolved	9556 (26.4)	5724 (15.8)	6798 (18.8)
Vaccinated	5842 (16.1)	1980 (5.5)	3991 (11.0)
Never exposed	5369 (14.8)	2845 (7.8)	3196 (8.8)
Clinically implausible	448 (1.2)	236 (0.7)	238 (0.7)
Unknown	28094 (77.5)	23913 (66.0)	20460 (56.5)
Total	**36244**	**36244**	**36244**

In order to reduce the number of unclassifiable statuses (those either clinically implausible or unknown), prior evidence of classifiable infection statuses were used and, where possible, relevant results were carried forward. This process was carried out in a series of stages. These stages are summarised in Table 5.6 and explained in further detail below.

Stage 1: Individuals with unclassified status but with a prior infected status

Where individuals were defined as unknown at any time point but where one of the potential classifiable statuses was resolved infection, prior statuses were examined for evidence of infection. Where an individual was previously known to be infected, it was assumed that they had developed anti-HBc which would persist. Therefore at the time of the unclassifiable status they could be assumed to be anti-HBc positive.

Stage 2: Individuals with unclassified infection status but prior resolved status

Where individuals had an unclassifiable status but where one of the potential classifiable statuses was resolved, prior statuses were examined for evidence of resolved infection. Where an individual was previously known to have a resolved infection, it is assumed that this status has persisted and that they are now HBsAg negative and anti-HBc positive.

Stage 3: Individuals with a clinically implausible status

These were all individuals who had positive HBsAg test results in combination either with positive anti-HBs test results or with negative anti-HBc results. Those individuals who had negative anti-HBc negative and positive HBsAg may be at a very early stage of infection and are therefore assumed to be infected. Those individuals who are HBsAg positive and anti-HBs positive may have false positive results. In addition, the dual presence of anti-HBs and HBsAg has been reported clinically in infected individuals (467). Given the data cleaning which had already been conducted to identify errors in HBsAg results, the HBsAg results were considered more reliable and therefore these individuals were also considered to be infected. Results for these individuals were not amended within the dataset, but an additional code was created to indicate that these combinations of test results were considered infected.

Stage 4: Individuals with unclassifiable status but with prior vaccinated status

Where individuals have a prior vaccinated status it was assumed that the vaccine induced immunity persists and therefore individuals are assumed to be anti-HBs positive. In addition, those individuals who had prior evidence of a positive anti-HBs status (but unknown anti-HBc) were considered to be anti-HBs positive as long as there was no intervening evidence of clearing the anti-HBs or evidence of positive anti-HBc results.

Stage 5: Individuals with unclassifiable status but with prior never exposed status

Those individuals who had an unclassifiable status but where one of the potential classifiable statuses was never exposed were examined for any prior evidence of negative anti-HBc or anti-HBs results. Where these results were available the individual was then assumed to be never exposed to the virus and susceptible to infection.

Carrying forward prior results reduced the proportion of individuals who had an unclassifiable infection status on the final data point from 57.1% to 38.7%. The number of individuals with an unclassifiable status one final data point after each stage of assumptions is shown in Table 5.7. Age, HIV exposure group, ethnicity, HCV status, year of entry into the study and prior infection status were all strongly associated with being unclassifiable on the final data point (Table 5.8). The centre where the test took place was also significantly associated with being unclassifiable at the final data point.

Table 5.6 Summary of imputed results used to determine an individual's HBV status at any one time point

Test result combination in dataset at time point x^1			Assumed test result combination at time point x		
HBsAg	**Anti-HBs**	**Anti-HBc**	**HBsAg**	**Anti-HBs**	**Anti-HBc**
Stage 1: Individuals with prior infected status					
–	+	.	–	+	+
–	–	.	–	–	+
–	.	.	–	.	+
.	+	.	.	+	+
.	–	.	.	–	+
Stage 2: Individuals with a prior resolved status					
–	+	.	–	+	+
–	–	.	–	–	+
–	.	.	–	.	+
.	+	.	.	+	+
.	–	.	–	–	+
.	–	+	–	–	+
.	.	+	–	.	+
Stage 3: Individuals with clinically implausible combinations					
+	+	+	+	–	+
+	–	–	+	–	–
+	.	–	+	.	+
+	+	–	+	–	–
+	+	.	+	–	+

Test result combination in dataset at time point x[1]			Assumed test result combination at time point x		
HBsAg	**Anti-HBs**	**Anti-HBc**	**HBsAg**	**Anti-HBs**	**Anti-HBc**
Stage 4a: Individuals with a prior vaccinated status					
–	+	.	–	+	–
.	+	.	.	+	–
–	.	–	–	+	–
–	.	.	–	+	–
.	.	–	–	+	–
Stage 4b: Individuals with a prior unknown status which includes positive anti–HBs result and no intervening negative anti–HBs results					
–	.	–	–	+	–
.	.	–	–	+	–
Stage 4c: Individuals with a prior unknown status which includes positive anti-HBs result and no intervening positive anti-HBc test results					
–	.	.	–	+	–
Stage 5a : Individuals with a prior never exposed status or unknown status which includes negative anti-HBs result					
–	.	–	–	–	–
.	.	–	–	–	–
Stage 5b: Never exposed or unknown status which includes negative anti-HBc result					
–	–	.	–	–	–
.	–	.	–	–	–

[1] Dot denotes unknown status of the marker

Table 5.7 Individuals with unclassifiable infection status on their final data point, before and after carrying forward prior results

Stage of assumptions	Number of individuals with infection status at final data point (%)				
	Infected	**Resolved**	**Vaccinated**	**Never exposed**	**Unclassifiable (including clinically implausible statuses)**
Baseline	1561 (4.3)	6798 (18.8)	3991 (11.0)	3196 (8.8)	20698 (57.1)
Stage 1	1561 (4.3)	6950 (19.2)	3991 (11.0)	3196 (8.8)	20546 (56.7)
Stage 2	1561 (4.3)	9368 (25.9)	3991 (11.0)	3196 (8.8)	18128 (50.0)
Stage 3	1799 (5.0)	9368 (25.9)	3991 (11.0)	3196 (8.8)	17890 (49.4)
Stage 4	1799 (5.0)	9368 (25.9)	6437 (17.8)	3196 (8.8)	15444 (42.6)
Stage 5	1799 (5.0)	9368 (25.9)	6437 (17.8)	4613 (12.7)	14027 (38.7)

Table 5.8 Multivariable logistic regression of factors associated with remaining unclassifiable on final data point[1]

Predictors of remaining unclassifiable		AOR	95% CI	P value
Baseline age	Per 10 years	0.88	0.85-0.91	<0.0001
HIV exposure	MSM	1	-	-
group	Male heterosexual	1.10	1.00-2.23	0.06
	Female heterosexual	1.23	1.12-1.36	<0.0001
	Male IDU	0.95	0.77-1.17	0.61
	Female IDU	0.93	0.70-1.23	0.59
	Other	1.46	1.26-1.69	<0.0001
	Unknown	1.31	1.09-1.57	0.0004
Ethnicity	White	1	-	-
	Black African	0.64	0.59-0.71	<0.0001
	Other	0.82	0.75-0.90	<0.0001
	Unknown	0.96	0.82-1.12	0.60
Year of study	1996–1998	1	-	-
entry	1999–2001	1.18	1.06-1.31	0.0002
	2002–2004	1.08	0.98-1.18	0.13
	2005–2007	0.86	0.78-0.94	0.002
	2008–2011	0.58	0.53-0.64	<0.0001
Baseline HCV	Negative	1	-	-
infection status	Positive	0.69	0.61-0.77	<0.0001
	Untested	1.44	1.27-1.63	<0.0001
	Yes	0.88	0.82-0.94	0.0001
Nadir CD4 count	Per 100 cells/mm^3	1.01	0.99-1.03	0.22
Prior infection	Infected	0.04	0.03-0.05	<0.0001
status[2]	Resolved	0.01	0.01-0.01	<0.0001
	Vaccinated	0.02	0.02-0.03	<0.0001
	Susceptible	0.1	0.09-0.11	<0.0001
	Unknown	1.65	1.55-1.76	<0.0001

[1] Model was also adjusted for centre where the test took place

[2] Prior evidence of each infection status was compared to no prior evidence of that infection status

5.4 Discussion

5.4.1 HCV antibody testing

A minority of individuals in the dataset have discrepant anti-HCV results. Using subsequent results to classify individuals' statuses can improve accuracy of the results in the dataset. However, comparing the final status assigned with the data obtained from clinical record review indicates that using test results alone will still result in some errors. The importance of these errors in an analysis will depend on the research question being investigated, the size of the overall dataset and the impact of co-infection on the outcome being investigated. Where clinical review of notes is not feasible, this is an effective means of ascertaining the true status of individuals with discrepant results.

5.4.2 HBV surface antigen testing

More than one quarter of individuals who ever have a positive HBsAg test, subsequently have a negative test result. However, given that individuals may lose HBsAg either after clearing an acute infection (88) or following treatment (464-466), further information is required to assess whether the changing results reflect the true status of the individual or whether they represent errors in reporting of test results. Close examination of other HBV test results in the dataset provides additional context which can be used to determine the individuals' true HBsAg status where inconsistencies occur. An algorithm has been developed in order to conduct this in a systematic way. This algorithm was determined with strong input from clinicians experienced in interpreting laboratory test results for HBV. The algorithm was determined by reviewing all of the test results for those individuals who had changing results. Processing the data through the algorithm, the assumptions were checked again with a clinician who confirmed that the algorithm had resulted in the most accurate assessment of the individual's HBsAg status at each time point.

It was not possible to use clinical data to confirm the HBsAg status of the individual as was done in the case of HCV, since clearance of HBsAg is clinically possible. Therefore a further stage of data processing was conducted using the algorithm defined HBsAg status combined with anti-HBc and anti-HBs test results to define an individual's HBV infection status.

5.4.3 HBV Infection status

Using a combination of HBsAg, anti-HBs and anti-HBc tests results that were reported with the same date resulted in a high proportion of individuals with an unclassifiable HBV infection

status at their final data point. The proportion of individuals who can be definitively classified into a HBV infection category can be increased using the methods described. However, a high proportion of individuals remain unclassifiable at the time of their final HBV test. In particular, given that vaccination is recommended for all susceptible individuals (65), the proportion of individuals defined as vaccinated seems low. We were not able to ascertain vaccination status of individuals during the data collection process. Therefore we are unable to validate these methods using the clinical data. Although this system of classifying individuals is useful, it may underestimate the proportion of individuals in each category.

It is important to consider the potential for more complex statistical methods for dealing with missing data. Missing data can be classified as either *missing completely at random* (MCAR) where there is no systematic difference between the recorded and the missing data items, *missing at random* (MAR) where there are systematic differences between the observed and the missing data but these differences are measurable as other recorded factors and the missing data is not dependent on any other missing data, and *missing not at random* (MNAR) where the missing data is dependent either on unmeasured factors or on the variable itself (468).

There are three options for dealing with the remaining missing data in analyses. The first is to conduct analysis which includes only those individuals for whom the information is known. However, this may induce bias if data are not MCAR. The second option is to create a separate category for those individuals with missing data so that they can be adjusted for in the analysis. Although this allows all individuals to be included in the analysis, it remains impossible to completely remove the effects of confounding if the true category for an individual is unknown.

The third option for dealing with missing data is multiple imputation. In this method, the missing data item is imputed using other available data and linear or logistic regression methods. The data item is imputed multiple times (usually between 5 and 20) to create several copies of the separate dataset. The analysis to answer a specific research question is then conducted on each of these imputed datasets and the results pooled to give a single estimate, 95% confidence intervals and P values. However, use of multiple imputations relies on data being either MCAR or MAR (469).

The results of the multivariable model of factors associated with being unclassifiable on final data point indicate that data may be MAR. That is, although there are systematic differences in the observed and the missing data those differences could be predicted by other measured variables. It is not possible to test whether data is MNAR (469). However, the finding that the proportion of individuals with a vaccinated status is low despite universal vaccination offer for susceptible individuals indicates that the data may be MNAR. That is, the missing data is dependent on itself and those individuals who have been vaccinated are more likely to have missing data. Therefore use of multiple imputation is not considered to be appropriate for this dataset.

5.4.4 Implications of findings

To my knowledge no other observational clinical HIV cohorts have investigated methods to deal with inconsistent or missing hepatitis test results in such detail. The analysis of HBsAg tests and HBV infection status was presented at the International Workshop on HIV Observational Databases, Cavtat, Croatia (2013) (Appendix VII). A subsequent meeting was convened which included leaders from the European cohorts. There was great interest in the methods described here and the next stage in validating these methods will be to test their use in other cohorts.

All further analyses in this thesis utilise data that have been subject to the cleaning processes described in this and the previous chapter. Final definitions of co-infection are shown in Box 5.1. The final definition of HBV infection includes only those changes made in the cleaning of changing HBsAg test results. Changes made to the infection status according to other markers are not included since HBsAg was considered the most reliable marker of infection. Since it was not possible to use clinical notes to verify the HBsAg status of each individual is is possible that some errors may remain. However, the finding that predictors of HBsAg positivity are unaltered when HBsAg is defined in different ways (as shown in Appendix VI) implies that this will not impact the results of analyses which compare HBV infected and HIV uninfected individuals. The final definition of HCV infection included those changes made to changing anti-HCV test results. However, where clinical data indicated that the decision changes had resulted in an incorrect assignment of anti-HCV status, the information from clinical data was used to over-ride the results of the algorithm.

Box 5.1 Final definitions of HBV and HCV infection

> HBV infection – Any individual who, subsequent to data cleaning, has at least one positive HBsAg test result reported in the dataset, irrespective of other serological markers
>
> HCV infection – Any individual who, subsequent to data cleaning and review of clinical notes, has at least one positive anti-HCV or positive HCV-RNA test result reported in the dataset

Since this thesis is focussed on individuals who are co-infected with HBV and/or HCV it is considered that the methods described in this chapter are sufficient to allow determination of whether an individual is infected with either HBV or HCV. If further analyses using the UK CHIC dataset were to be conducted which focussed on resolution of HBV or HBV vaccination, additional efforts would be required to obtain missing data from the centres where the patients attended for care. Furthermore, determining the true HCV co-infection status of all potentially infected individuals within UK CHIC (i.e. those with any positive anti-HCV test result recorded in the dataset), should remain an important component of any future rounds of data collection. However, in cohorts where this is not possible the method presented in this chapter for cleaning anti-HCV test results represents an acceptable method for determining HCV status in the context of inconsistent results.

Chapter 6 Results 1: Patterns of hepatitis testing and infection in UK CHIC

6.1 Background

Clinical guidelines state that newly diagnosed HIV-positive individuals should be screened for HBV infection and immunity using tests for HBsAg and anti-HBc and anti-HBs. Subsequently, those individuals who are not shown to be infected with, or immune to, HBV should be screened annually. Similarly, it is recommended that newly diagnosed HIV-positive individuals are screened for HCV infection using an anti-HCV test and individuals who are negative should be screened annually thereafter (65).

Infection with HBV may be followed by resolution of the infection or persistence of the virus, resulting in chronic HBV infection. In HIV-negative populations 5-10% of individuals are expected to develop chronic infection (90). However, HIV/HBV co-infection is associated with a higher likelihood of developing chronic infection (362, 363). Individuals who resolve infection are immune to further infection. Patients with chronic infection require monitoring for the development of liver disease and may require treatment. In the UK, individuals at high risk of acquiring HBV are offered routine vaccination. However, HIV-positive individuals may have a lower rate of response to vaccine than HIV-negative individuals, depending on the dose used (470-472). The different courses of chronic HBV infection and the resulting varying serological profiles may affect both management strategies and outcomes.

Infection with HCV may be followed by clearance of the infection, either spontaneously or as a result of treatment. However, the large majority of infected individuals go on to develop chronic HCV infection (147, 326). Neither current infection nor previous clearance of HCV infection prevents re-infection at a later date. Transmission of HCV has traditionally been considered to be parenteral and therefore its prevalence is associated with injecting drug use. However, since 2003, in the UK and Europe there have been increasing numbers of diagnoses of acute HCV among HIV-positive MSM (234, 235). Ongoing sexual transmission of HCV among networks of HIV-positive MSM means that there is risk of re-infection even if an individual clears the virus (473).

Seven HCV genotypes have been identified (141). The genotype with which an individual is infected may impact decisions about treatment since some genotypes (2 and 3) are considered

easier to treat than others (1 and 4). The genotype an individual is infected with may, in part, be dependent on how they acquired their infection as different genotypes circulate more commonly among different populations.

Understanding the epidemiology of hepatitis co-infection among HIV-positive individuals allows effective planning of prevention, detection and treatment services. While a number of studies have estimated prevalence of and factors associated with co-infection among HIV-positive cohorts in developed countries (Chapter 2 Table 2.1 and Table 2.2), the differing HIV epidemics in these countries means that results are not generalisable to the UK. Previous analyses of UK CHIC, examining testing and infection rates, have shown lower than desirable levels of HBsAg and anti-HCV testing (244, 259). However, it was noted that these low reported levels of testing may be due to missing data rather than a lack of testing in clinical practice. Therefore the resulting estimates of prevalence and incidence are limited.

In the following analyses I describe patterns of testing and estimate the prevalence and incidence of HBV and/or HCV co-infection in the largest clinical cohort of HIV-positive individuals in the UK. The analyses are focused on the patients who have been seen for care at any one of the contributing centres from 2004 onwards. Prior to this period, testing for hepatitis among HIV-positive individuals was not routine practice. In addition, the process of expanded hepatitis data collection was limited to co-infected patients who had been seen since 2004 onwards. This process has improved data quality for that period and included the first collection of HCV genotype data among this cohort.

6.2 Methods

6.2.1 Patterns of hepatitis testing

6.2.1.1 Proportion of individuals tested for HBsAg and anti-HCV

The following analyses were conducted separately for HBsAg and anti-HCV. The cumulative proportion of individuals tested for each marker was calculated as a proportion of all individuals under follow-up who had ever tested. To investigate trends over time in cumulative testing, the dataset was split by year. Individuals were considered to have been followed-up in a given year if their first seen date was at any time before the end of that year and their last seen date was not before the start of that year. All individuals followed-up in a given year were included in the analysis for that year. The proportion of all individuals under follow-up in each year who had received a test by the end of that year was calculated.

Annual testing was investigated among individuals who were considered eligible for testing within a given year. The number of individuals eligible for HBsAg testing within a particular year was defined as all those individuals under follow-up in that year, who had not previously had a positive HBsAg or anti-HBs test by the start of that year (that is, they were not already known to be infected or immune). The number of individuals eligible for anti-HCV testing was defined as all those individuals under follow-up within a year, who had not had a positive anti-HCV or HCV-RNA test by the start of that year (that is, they were not already known to be infected). Of all individuals who were eligible for testing within each year, the proportion who received a test result in that year was calculated.

To describe both cumulative and annual testing in more detail, within each year data was stratified by age group at start of year, ethnicity, HIV exposure group, CD4 count at start of year and HIV viral load at start of year and the proportion tested in each subgroup per year calculated.

6.2.1.2 Factors associated with first test and repeat testing

Separate logistic regression models were constructed for each year to identify predictors of having a first test in each year and to examine whether predictors of first test had changed over time. Individuals were included in the analysis for a given year if they were under follow-up in that year and had not previously received a test. Age at start of year, ethnicity and HIV exposure group were included in each model. To maximise the number of individuals who could be included in the analysis and to ensure that those who had missing CD4 counts or

missing HIV viral load information would be included in the analysis, CD4 count and viral load were combined into one variable, HIV infection category, as shown in Table 6.1. This was also included in each model. Those individuals who had a CD4 count of ≤200 cells/mm^3 were considered to have advanced HIV infection irrespective of HIV viral load. Those individuals who had HIV viral loads of >50 copies/ml were considered to have uncontrolled HIV infection, where as those whose viral load was ≤50copies/ ml were considered to have controlled HIV infection.

Table 6.1 Categorising HIV infection

HIV viral load (copies/ml)	**CD4 count (cell/mm^3)**		
	≤200	**>200**	**Missing**
≤ 50	Advanced	Controlled	Controlled
51-10000	Advanced	Uncontrolled	Uncontrolled
>10000	Advanced	Uncontrolled	Advanced
Missing	Advanced	Uncontrolled	Unknown

Yearly datasets were then appended to give a complete dataset for the period 2004-2011. Logistic regression was used to identify independent demographic and clinical predictors of testing. Independent variables included in the analysis were age, ethnicity, exposure, year of follow-up and HIV infection category. Age and HIV infection category were time-updated at the start of each calendar year. As descriptive analysis revealed that increases in testing over time differed by demographic factors, a series of further models were constructed in order to test for the presence of interactions between year and demographic variables (age, HIV exposure group and ethnicity). This was done by including an interaction term between year and the demographic variable of interest in the model. Where significant interactions were identified the dataset was stratified by the relevant demographic factor of interest and the predicted probability of having a test for an individual within each group was calculated for each year.

The above analyses were repeated to investigate factors associated with repeat testing. Individuals were included in the analysis for a given year if they had previously had a test before the start of that year but had not previously been shown to be infected or immune to infection. As above separate multivariable models were constructed for each year of follow-

up, followed by a model including data for all years from 2004-2011. Since individuals may be eligible for repeat testing in more than one year and may also be tested in more than one year, generalised estimating equations were used to account for the repeated tests per individual. The presence of interactions between year and demographic factors was also examined in this analysis, as described above.

6.2.2 Epidemiology of HBV

All of the following analyses were conducted using data which had been examined for inconsistencies and cleaned as previously described. Infection statuses, which had previously been defined using the results of HBsAg, anti-HBc and anti-HBs tests were also used in these analyses (Chapter 5).

6.2.2.1 Cumulative prevalence of HBV infection

All individuals who had ever been tested for HBsAg were included in this analysis. The prevalence of HBV co-infection was calculated as the proportion of all tested individuals who had received a positive HBsAg test result. A sensitivity analysis was conducted where all individuals in the cohort were included in the denominator, irrespective of whether they had been tested for HBsAg.

To examine trends over time, the annual cumulative prevalence was calculated for each year from 2004 to 2011. Annual cumulative prevalence was calculated as the proportion of all individuals under follow-up in a given year and tested by the end of that year, who had received a positive test result by the end of that year. The dataset was stratified by demographic and HIV clinical variables to investigate whether changes over time in the cumulative prevalence differed among subgroups.

Baseline characteristics of individuals who had ever received a positive HBsAg test result and those who had not were compared. Logistic regression was conducted to identify those demographic and HIV-infection factors associated with HBV-infection. Independent variables included in the analysis were age, ethnicity, exposure, HIV infection category (defined as previously described in patterns of testing section) and year. Age and HIV infection category were updated at the start of each year. Calendar year was also included in the model as a continuous variable.

6.2.2.2 Resolution of HBV infection versus chronicity

Among those individuals who had a positive HBsAg test result, subsequent infection statuses were examined to assess the proportion of individuals who resolve an infection and those who are chronically infected. Individuals were classified as being chronically infected if they had a subsequent infected status 6 months or more after their first positive HBsAg test and they were defined as having resolved infection if they had a subsequent resolved status at any point after their first positive HBsAg test. The time to resolution was calculated as the time from first positive to first resolved status. More than half of individuals who went on to resolve infection had a time to resolution of greater than 6 months. Since resolution of infection occurs within the first 6 months of infection, these times to resolution of greater than 6 months are likely due to non-availability of test results within the dataset. Given this assumption of missing information it was not possible to conduct a time-updated analysis of factors associated with resolution. Therefore logistic regression was used to identify baseline factors associated with resolution. For this analysis, baseline was defined as the date of first positive HBsAg test.

6.2.2.3 Infection status over time

HBV infection status was assessed using results of HBsAg tests, anti-HBc tests and anti-HBs tests as previously described (Chapter 5, section 5.3.3). Briefly, an HBV infection status was assigned to individuals each time they were tested for one of the three markers of interest. For individuals with an unknown status, potential clinically plausible classifiable statuses were identified. Where there was prior evidence of one of these potential infection statuses, that status was carried forward. Results were not carried forward where more than one potential status was clinically plausible. Among all individuals who had ever had a classifiable status, infection status of individuals at the end of each year was used to examine changes in infection status from 2004 to 2011. Chi-squared tests for trend were used to assess the significance of observed trends.

6.2.2.4 Incidence of HBV infection

Among individuals who had had a test for at least one of HBsAg, anti-HBc or anti-HBs from 2004 onwards, all tests up until the end of the first year of follow-up were examined in order to determine whether or not the individual was susceptible to infection. Susceptibility was defined as a negative anti-HBs result and a negative or missing HBsAg and anti-HBc result. For those individuals who had changing results for one of the markers during the first year of follow-up, only the first result for each marker was used to define susceptibility. Susceptible

individuals who had at least one further test were included in the analysis. Individuals were followed-up from the date of their first test after 2004 until they had an incident infection or until their last seen date. Follow-up was censored when an individual had a positive anti-HBs result.

HBV incident infection was defined as a new positive HBsAg or anti-HBc result. The incidence rate was calculated by dividing the number of incident infections by the total number of person-years of follow-up. Factors associated with HBV incidence were examined using univariable and multivariable Poisson regression. The following characteristics were examined: age at first test; ethnicity; HIV exposure category; current CD4 count; current HIV viral load; whether an individual was on tenofovir as part of their HIV antiretroviral regimen; and year of follow-up. CD4 count and viral load were included as time-updated variables which were updated at the start of each year of follow-up.

There were 16 individuals who had a first positive test after a positive anti-HBs test result. Data for these individuals had been censored at the time of anti-HBs as they were thought to have become immune and therefore were not considered as incident infections. There are two possible reasons for an individual to have a positive HBsAg or anti-HBc result after a positive anti-HBs result. The first is that their positive anti-HBs result is, in fact, a marker of infection rather than vaccination; the second is that the positive anti-HBs result is a marker of vaccination but the individual then loses the vaccine-induced immunity over time and becomes susceptible (474-476). Therefore two sensitivity analyses were conducted which varied the definition of incident infection. Sensitivity analysis 1 allowed individuals who had a positive HBsAg or a positive anti-HBc after a positive anti-HBs test to be considered as incident infections with the date of the positive anti-HBs used as the date of the incident infection, therefore making the assumption that the anti-HBs was actually a marker of infection. In sensitivity analysis 2, individuals who had a positive HBsAg or positive anti-HBc after a positive anti-HBs were also considered to have incident infections but the date of incident infection was taken as the date of positive HBsAg or anti-HBc therefore making the assumption that these individuals had been vaccinated but had lost their vaccine induced immunity and then become infected.

One final sensitivity analysis (sensitivity analysis 3) was conducted which varied the way that susceptible individuals were defined. In this analysis, individuals had to have had a negative

HBsAg or negative anti-HBc test as well as a negative anti-HBs test to be defined as susceptible. The incidence of HBV infection from the initial calculation was compared to the incidence calculated in the sensitivity analyses.

6.2.3 Epidemiology of HCV

All of the following analyses were conducted using data on anti-HCV tests which had been examined for inconsistencies and cleaned as previously described (Chapter 5, section 5.2.2)

6.2.3.1 Cumulative prevalence of HCV

All individuals who had ever been tested for anti-HCV or HCV-RNA were included in this analysis. The prevalence of HCV co-infection was calculated as the proportion of all individuals ever tested for anti-HCV or HCV-RNA who had received a positive result. A sensitivity analysis was conducted which included all individuals under follow-up in the denominator irrespective of whether they had ever been tested.

To examine trends over time the annual cumulative prevalence was calculated for each year from 2004 to 2011. This was calculated as the proportion of all individuals under follow-up and tested by the end of a given year, who had received a positive test result by the end of that year. Annual cumulative prevalence was calculated for the complete dataset as well as after stratification by age at start of year, ethnicity, HIV exposure group, CD4 count at start of year and viral load at start of year.

Differences in baseline characteristics of those with and without a positive HCV test result were examined. Logistic regression was performed to identify those demographic and HIV infection factors associated with HCV infection. Independent variables included in the analysis were age and HIV infection category, which were updated at the start of each year, calendar year, ethnicity and HIV exposure category.

6.2.3.2 Active HCV infection

Active HCV infection was defined as a positive HCV-RNA test result. The proportion of all individuals with any evidence of HCV infection (positive anti-HCV or HCV-RNA tests), who could be defined as having active infection at any time during follow-up was calculated. The annual prevalence of active infection was calculated for each year from 2004 to 2011 as the proportion of individuals with any evidence of infection, tested for HCV-RNA within the year of interest who had a positive HCV-RNA result in that year. In a sensitivity analysis, a more

relaxed definition of having active HCV infection within a year was used whereby individuals were considered to have active infection from the point at which they first had a positive HCV-RNA test result until there was evidence of a negative test result.

Factors associated with having active infection were examined using univariable and multivariable logistic regression. Independent variables included in the analysis were age, ethnicity, HIV exposure group, calendar year and HIV infection category. Age and HIV infection category were updated at the start of each year.

6.2.3.3 Acute HCV infection

To investigate the proportion of individuals who were diagnosed with acute HCV infection, the dataset was restricted to those individuals who had ever had a positive HCV test (either anti-HCV or HCV-RNA) after the start of 2004 and who had also been tested for HCV-RNA at any point from 2004 onwards. The date of their first positive HCV-RNA test was identified. Individuals who had a negative anti-HCV test within the 6 months preceding their first positive HCV-RNA test were defined as having acute infection. In addition, clinical data obtained from the expanded hepatitis data collection was examined. The number of individuals who had been stated as having acute infection in their clinical notes was added to those who were defined as being acutely infected according to their serology results to give a total population of individuals who were identified as having had acute HCV infection.

To investigate the proportion of individuals who spontaneously cleared acute infection, all individuals with any evidence of HCV treatment were excluded. Spontaneous clearance was defined as a subsequent negative result after being defined as acutely infected without evidence of subsequent positive HCV-RNA tests in the first 6 months after acute infection. Among those diagnosed with acute infection who cleared infection, time to clearance was estimated as the time between the first positive RNA test and the first negative after diagnosis of acute infection.

6.2.3.4 Incidence of HCV infection

Individuals were included in the analysis of HCV incidence if they had been tested for either anti-HCV or HCV-RNA at any point from 2004 onwards. All HCV tests up until the end of one year after the start of follow-up were used to define an individual's HCV status at the start of follow-up. For those individuals who had changing results in the first year of follow-up, only the first results were used to define their status. Individuals who had a negative anti-HCV test

and either negative or missing HCV-RNA test at the beginning of follow-up and who had at least one further test for either anti-HCV or HCV-RNA were included in the analysis. Incident infection was defined as any positive anti-HCV or HCV-RNA test after the start of follow-up. Individuals were followed from their first test after the start of 2004 until they had a positive anti-HCV or positive HCV-RNA test result or until they were last seen.

The incidence rate was calculated by dividing the number of incident infections by the total number of person-years of follow-up. Factors associated with HCV incidence were examined using univariable and multivariable Poisson regression. Associations between HCV incidence and the following characteristics were examined: age at first test; ethnicity; HIV exposure category; current CD4 count; current HIV viral load and year. CD4 count and viral load were included as time updated variables which were updated at the start of each year of follow-up.

6.2.3.5 HCV genotypes

Individuals with any evidence of active infection (HCV-RNA positive at any point) were included in the analysis. For each individual, the number of recorded genotypes was calculated. First reported genotype and subtype was assessed among all individuals with active infection who had at least one reported genotype. The number of individuals that had more than one different reported genotype, or more than one subtype for the same genotype, was calculated. These individuals were considered to have been re-infected.

It is possible for individuals to have the same genotype and subtype reported more than once. This may be due to reinfection with the same genotype or due to repeated laboratory assessment of the same infection. Data on dates when genotype was reported are limited (61% of all reported genotypes have no associated date). Consequently, where an individual had had more than one infection, it was not possible to assess temporality of the genotypes. Therefore, to further assess the distribution of genotypes, individuals who were defined as having been re-infected with HCV were excluded from the analysis. Reinfection was defined as either changing genotype or having a positive HCV-RNA result after 6 months or more of negative RNA tests. For all further analyses of genotype only the first reported genotype was considered.

To assess changes over time in genotype the proportion of all infections with each genotype was calculated by year of first positive HCV test both for the total population and stratified by HIV exposure category. Multinomial logistic regression was used to assess the likelihood of an

individual being infected with genotypes 2, 3, 4, or other/unknown genotypes with genotype 1 being used as the reference group.

6.3 Results

6.3.1 Patterns of hepatitis testing

6.3.1.1 Proportion of individuals tested for HBV and HCV

Among the 32079 individuals included in the analysis, the cumulative proportion of individuals who have been tested for HBsAg was 82.2% (26377/32079), 95% CI 81.8-82.6%, and the cumulative proportion of individuals who have been tested for anti-HCV was 87.6% (28111/32079), 95% CI 87.3-88.0%. The median number of HBsAg and anti-HCV tests per individuals was 2 for each test (interquartile ranges (IQRs) 1, 4 and 1, 5 respectively).

6.3.1.2 Changes in proportion tested over time

The cumulative proportion of individuals under follow-up in each year who had ever had a test for HBsAg increased significantly from 54.2% in 2004 to 87.7% in 2011 (Chi-squared test for trend p<0.0001) (Table 6.2). Among individuals eligible for annual testing, the proportion who received an HBsAg test within a given year increased from 20.5% in 2004 to 42.6% in 2009 but then declined to 29.4% over the next two years (Table 6.2). The cumulative proportion of individuals under follow-up in each year who had ever had a test for anti-HCV increased from 57.2% in 2004 to 93.4% in 2011 (Chi-squared test for trend p<0.0001) (Table 6.3). The proportion of individuals eligible for annual anti-HCV testing who received a test within a given year increased consistently year on year from 25.5% in 2004 to 55.0% in 2011 (Chi-squared test for trend p<0.0001) (Table 6.3).

Table 6.2 HBsAg testing over time

Year	Total number of individuals under follow-up	Cumulative number tested by the end of that year	% (95% CI)	Eligible for testing in that year	Number tested within that year	% (95% CI)
2004	18177	9846	54.2 (53.4-54.9)	14898	3054	20.5 (19.9-21.2)
2005	19583	11849	60.5 (59.8-61.2)	15855	4032	25.4 (24.8-26.1)
2006	20780	13720	66.0 (65.4-66.7)	16046	4585	28.6 (27.9-29.3)
2007	21817	15538	71.2 (70.6-71.8)	16216	5164	31.8 (31.1-32.6)
2008	22770	17627	77.4 (76.9-78.0)	15816	6431	40.7 (39.9-41.4)
2009	23525	19447	82.7 (82.2-23.1)	14960	6369	42.6 (41.8-43.4)
2010	24251	20521	84.6 (84.2-85.1)	14732	4944	33.6 (32.8-34.3)
2011	22460	19694	87.7 (87.2-88.1)	13635	4010	29.4 (28.7-30.2)

Table 6.3 Anti-HCV testing over time

Year	Total number of individuals under follow-up	Cumulative number tested by the end of that year	% (95% CI)	Eligible for testing in that year	Number tested within that year	% (95% CI)
2004	18177	10395	57.0 (56.3-57.7)	17285	4412	25.5 (24.9-26.2)
2005	19583	12931	66.0 (65.4-66.7)	18525	5941	32.1 (31.4-32.7)
2006	20780	14943	71.9 (71.3-72.5)	19463	6434	33.6 (32.9-34.2)
2007	21817	17059	78.2 (77.6-78.7)	20343	8196	40.3 (39.6-41.0)
2008	22770	19062	83.7 (83.2-84.4)	21101	10005	47.4 (46.7-48.1)
2009	23525	20616	87.6 (87.2-88.0)	21624	11100	51.3 (50.7-52.0)
2010	24251	21855	90.1 (89.7-90.5)	22191	11099	50.0 (49.4-50.7)
2011	22460	20982	93.4 (93.1-93.7)	20488	11259	55.0 (54.3-55.6)

When stratified by demographic and HIV-related variables, the proportion of individuals ever tested for HBsAg increased among all subgroups between 2004 and 2011 (Figure 6.1). However, the magnitude of the increase differed by subgroup. For example, when stratified by HIV exposure category, the exposure group with the highest proportion of individuals who have ever been tested for HBsAg was MSM in every year of follow-up. However, the greatest increase in proportion ever tested was seen among individuals from other or unknown HIV exposure groups and the smallest increase was seen amongst IDU. The differences in proportions of individuals who had ever tested in 2004 compared to in 2011 were: 32.5% for MSM; 28.2% for IDU; 35.9% for male heterosexuals; 35.3% for female heterosexuals; and 45.1% for individuals belonging to other HIV exposure categories (Figure 6.1c). A similar pattern was seen when the dataset was stratified by ethnicity. The group with the highest proportion of individuals tested in each year was individuals of white ethnicity. However, this group also had the smallest increase in the proportion tested over time, the greatest increase being seen among individuals of other or unknown ethnicities. The differences in proportion ever tested between 2004 and 2011 were: 31.1% for white individuals; 31.9% for black African individuals; 39.1% for individuals of black other ethnicities and 48.8% for individuals of other or unknown ethnicities (Figure 6.1b). When stratified by age, there was a greater increase among <35 year olds (a difference of 22.1% between 2004 and 2011) but the increase among 35-45 year olds and among >45 year olds was similar (13.8 and 13.3 respectively) (Figure 6.1a).

When stratified by HIV clinical factors, those individuals with missing CD4 counts and viral loads had greater increases than those with known CD4 counts and viral loads.

The proportion of eligible individuals who had an HBsAg test within a given year followed the same patterns over time for all subgroups with the exception of the groups of individuals with unknown CD4 count and unknown HIV viral load (Figure 6.2). For all but these two subgroups the proportion tested in the year increased between 2004 and 2009 and then fell between 2009 and 2012. Although the proportion of eligible individuals who tested within a given year fell between 2009 and 2011, it still remained higher than the 2004 levels in all subgroups. The increases between 2004 and 2009 were greater among some subgroups than among others. When stratified by HIV exposure group, the proportion of eligible individuals who were tested within a given year increased in every group in the period 2004 to 2009, but the increase was greatest among individuals of other/unknown exposure and the lowest increase was among IDU. The differences in proportions between 2004 and 2009 were: 26.4% for MSM; 9.0% for IDU; 17.9% for male heterosexuals; 17.2% for female heterosexuals and 33.7% for individuals of other or unknown HIV exposure group (Figure 6.2c). When stratified by ethnicity, between 2004 and 2009, white individuals had the highest proportion of eligible individuals tested for HBsAg within every year. The lowest increase in testing of eligible individuals within the year was among black African individuals (15% difference between 2004 and 2009) and the greatest increase was seen among individuals of other or unknown ethnicity (37.3% difference between 2004 and 2009) (Figure 6.2b). Smaller differences in the magnitude of increase from 2004 to 2009 were seen when data was stratified by age group: 19.4% difference among those <35 years; 2.2% difference among those aged 35-45 years; 22.3% difference among those older than 45 years) (Figure 6.2a).

The proportion of individuals ever tested for anti-HCV increased among all subgroups between 2004 and 2012 (Figure 6.3). When stratified by HIV exposure group, in 2004, the exposure group with the highest proportion of individuals who had ever been tested for anti-HCV was IDU. However, the increase in the proportion of IDU tested was less than that among MSM and thus, from 2006 onwards, the exposure category with the highest proportion of individuals who had ever tested for anti-HCV was MSM (Figure 6.3c). The differences in proportions ever tested in 2004 compared to 2011 were: 36.1% for MSM; 21.4% for IDU; 37.6% for male heterosexuals; 36.5% for female heterosexuals; and 50.4% for individuals belonging to other risk groups. When stratified by ethnicity, although white individuals remained the group with

the highest proportion ever tested in each year the increase in testing was lowest in this group and greatest among individuals of other/unknown ethnicity: 33.3% difference for white individuals; 36.2% difference for black African individuals; 36.8% difference for other black individuals and 52.7% difference for individuals of other or unknown ethnicity (Figure 6.3b). When stratified by age group the increase between 2004 and 2011 was greatest among individuals aged under 35 years (40.6% difference) while the increase among those aged 35-45 years and those over 45 years was similar (34.1% and 33.2% respectively).

The proportion of eligible individuals who had an anti-HCV test within a given year also increased in each subgroup between 2004 and 2012 (Figure 6.4). Like the patterns of cumulative testing, differences between the subgroups existed in the magnitude of the increase. For example, the differences in proportion of eligible individuals tested within a given year between 2004 and 2011 were: 34.2% for MSM; 21.9% for IDU; 21.8% for male heterosexuals; 17.5% for female heterosexuals; and 46.0% for individuals of other/unknown exposure group (Figure 6.4c). Differences in the increase in testing over time were also seen when the dataset was stratified by ethnicity (Figure 6.4b). While white individuals had the highest proportion of eligible individuals tested within each year, the greatest increase was seen among individuals of other or known ethnicity and the lowest increase was seen among individuals of black African ethnicity. Differences in the proportion of eligible individuals who tested within a given year between 2004 and 2011 were: 32.5% for white individuals; 16.9% for black African individuals; 31.5% for individuals of other black ethnicity and 42.3% for individuals of other/unknown ethnicity. Similar increases in the proportion of eligible individuals who tested within a year were seen among all age groups: differences of 35.2% for those aged <35 years; 29.1% for those aged 35-45 years; 34.0% for those aged over 45 years. When stratified by HIV clinical variables, individuals with missing CD4 or missing HIV viral loads had the greatest increases.

Figure 6.1 Change in proportion of individuals ever tested for HBsAg, by calendar year, overall and stratified by demographic and HIV clinical factors

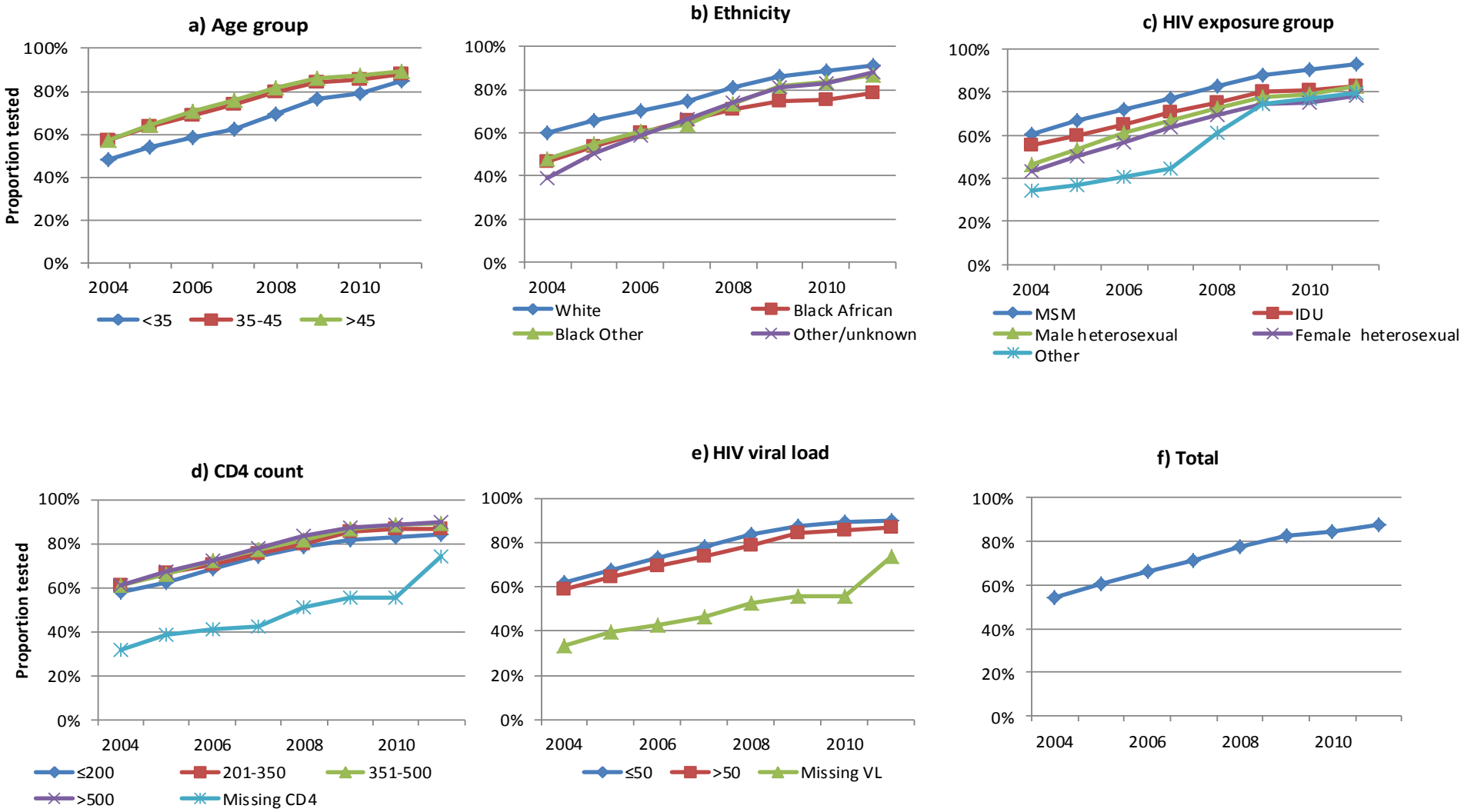


Figure 6.2 Change in proportion of eligible individuals tested for HBsAg within a year, by calendar year, overall and stratified by demographic and HIV clinical factors

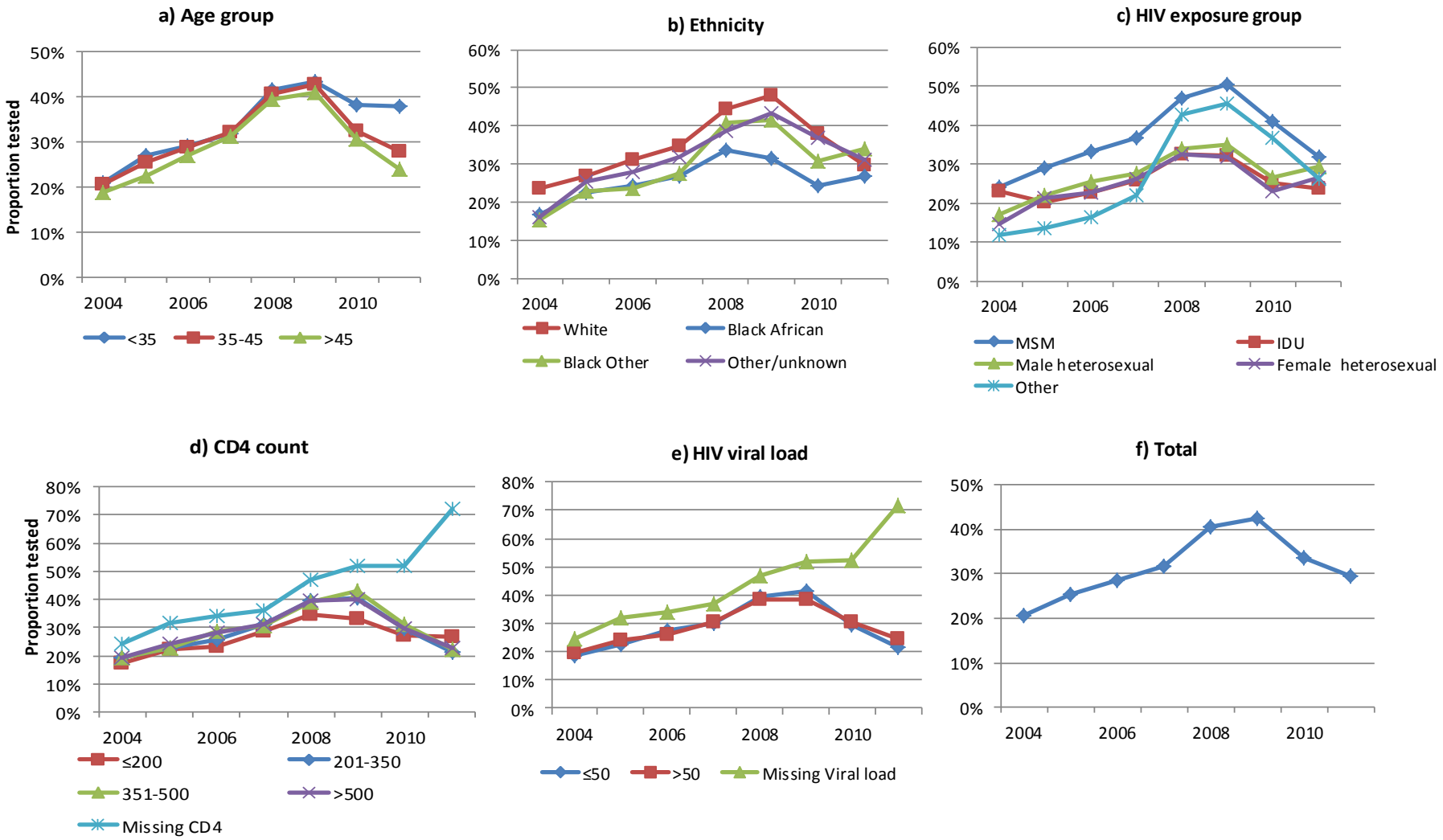


Figure 6.3 Change in proportion of individuals ever tested for anti-HCV, by calendar year, overall and stratified by demographic and HIV clinical factors

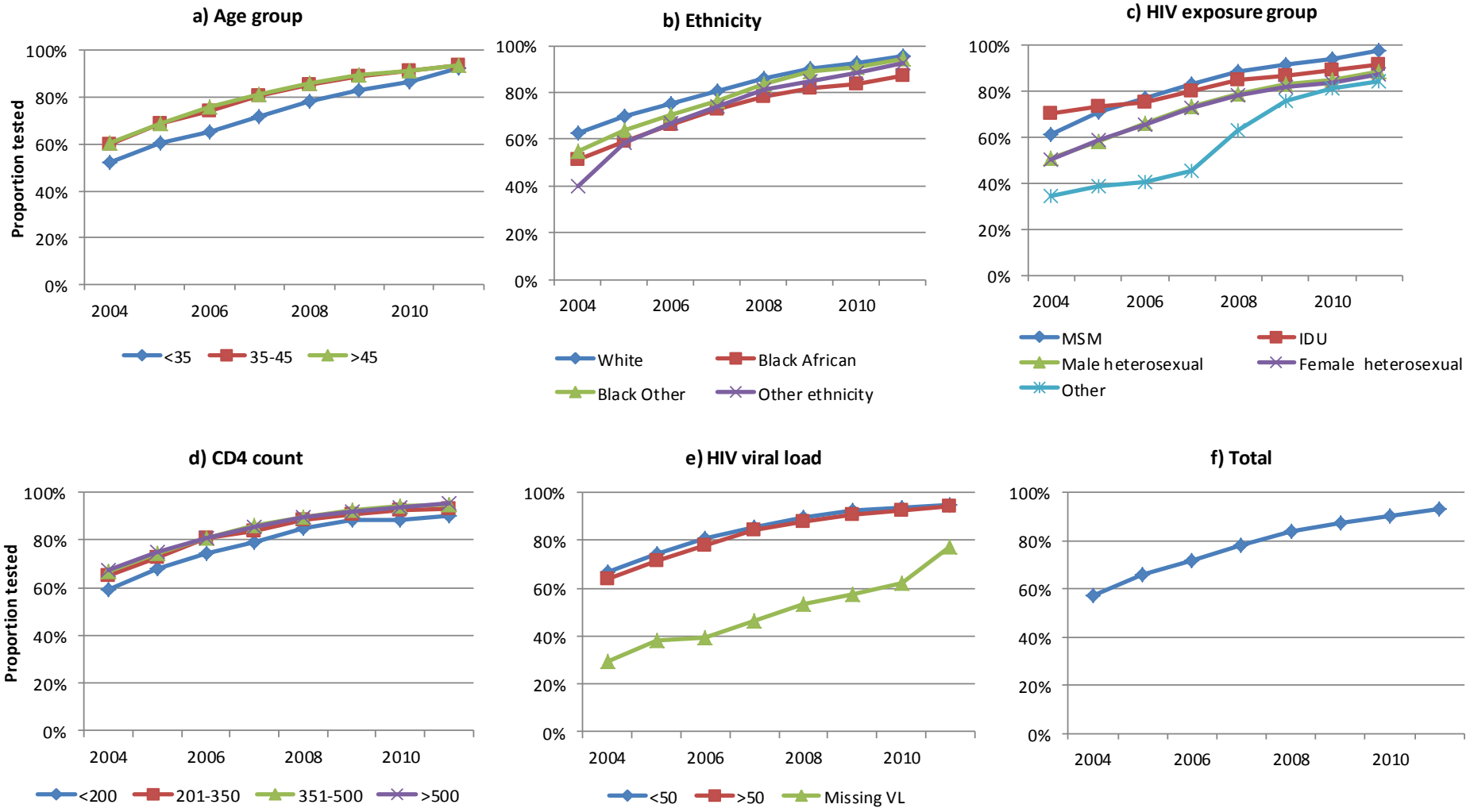
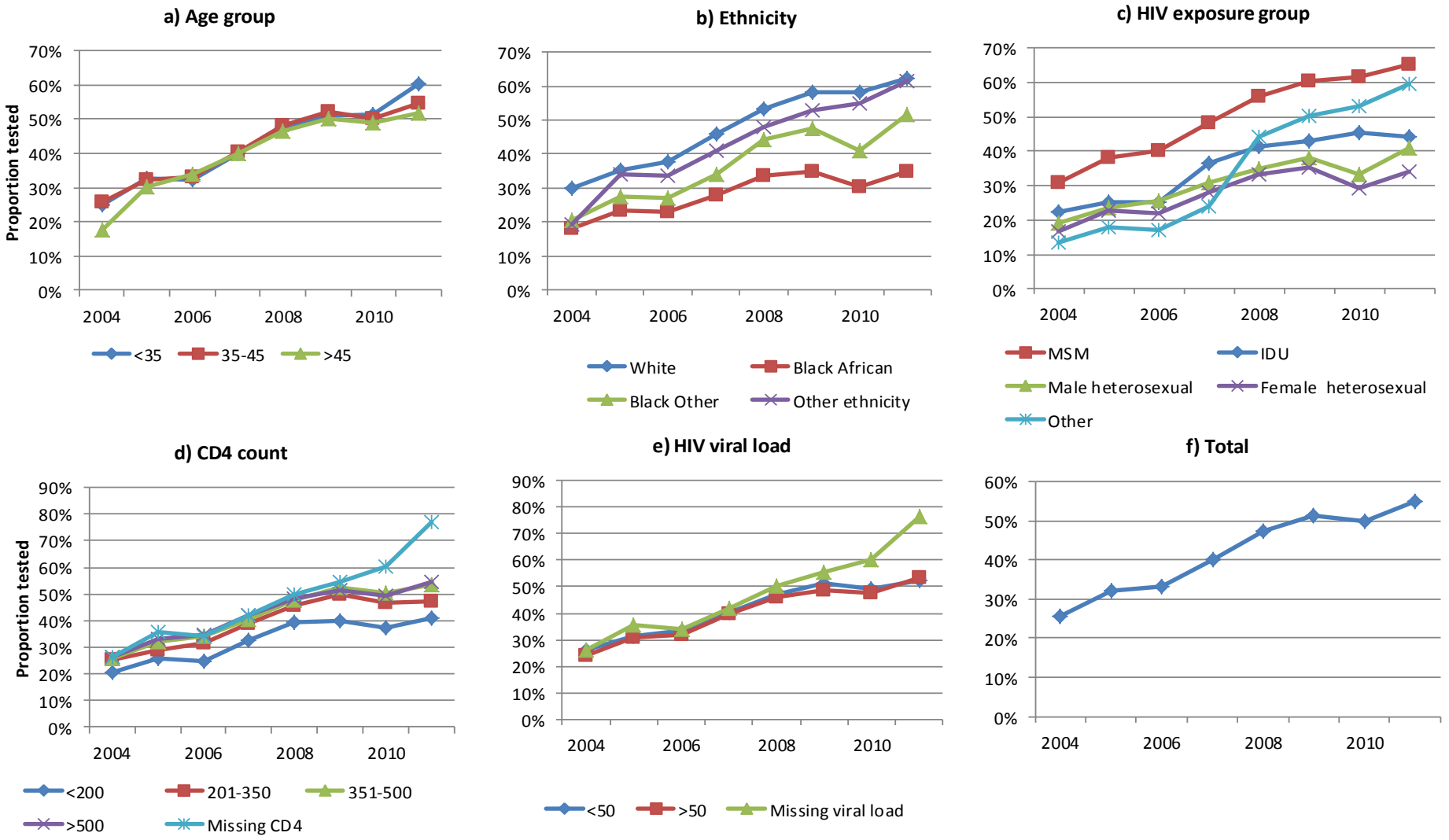


Figure 6.4 Change over time in proportion of eligible individuals tested for anti-HCV within a year overall and stratified by demographic and HIV clinical factors



6.3.1.3 Factors associated with having a first test

A separate multivariable model was conducted for each year of follow-up to examine how the factors associated with first HBsAg test by the end of that year changed over time (Table 6.4). From 2004 to 2007 there were no significant differences in the likelihood of having a first test between IDU and MSM. However, from 2008 onwards IDU were significantly less likely than MSM to have a first test. Compared to MSM, male and female heterosexuals were significantly less likely to have a first test for HBsAg each year. Comparing IDU to MSM over time, the odds ratio decreased from 1.29 (95% CI 0.97-1.72) in 2004 to 0.39 (95% CI 0.24-0.63) in 2011. Similarly, comparing individuals of black African ethnicity to individuals of white ethnicity over time the odd ratio decreased from 1.18 (95% CI 0.98-1.43) in 2004 to 0.75 (95% CI 0.61-0.93) in 2011.

Considering the complete dataset from 2004-2011, univariable and multivariable logistic regression was conducted to identify factors associated with first HBsAg test (Table 6.5). Year of follow-up was included as a covariate and age and HIV infection category were updated at the start of each year. Ethnicity and exposure were also included in the models. In univariable analysis age, ethnicity, HIV exposure group, year and HIV infection status were all associated with the likelihood of a first HBsAg test. However, in a multivariable model adjusting for all these factors, only HIV exposure group, HIV infection category and year remained associated with having a first HBsAg test. Compared to MSM, IDU were significantly less likely to test as were male and female heterosexuals and individuals of other/unknown HIV exposure groups. Calendar year was significantly associated with a first test with individuals being more likely to have a first test in later years. Compared to individuals with controlled HIV those with advanced HIV, uncontrolled or unknown HIV infection category were all more likely to have a first test.

A series of models was then run to test for interactions between time (calendar year) and demographic factors. All models were adjusted for age group, HIV exposure group, ethnicity, HIV infection category and year (Table 6.6). Model 1 included an interaction between year and age group. A significant interaction was found between all age groups and year ($p<0.0001$ for all age groups). Model 2 included an interaction between year and ethnicity. Only black ethnicity was found to have a significant interaction with year ($p<0.0001$) and therefore the other interactions were removed from this model. Model 3 included an interaction between year and HIV exposure group. A significant interaction was found between year and all HIV exposure categories ($p<0.0001$ for all interactions). The probabilities of testing per year were

calculated using parameter estimates from each of the models. Figure 6.5 shows how the probability of first test changes over time among those groups where a significant interaction was detected, compared to the probability in the reference group. The reference group are MSM of white ethnicity, aged <35 years, with controlled HIV infection (denoted by the dark blue line in all graphs).

Table 6.4 Adjusted odds ratios for likelihood of first testing for HBsAg according to characteristics at baseline, by year of follow-up

		AOR (95% CI) from multivariable models of factors associated with having a first HBsAg test							
Year		**2004**	**2005**	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**
Age (years)	<35	1	1	1	1	1	1	1	1
	35-45	0.99 (0.87-1.12)	1.03 (0.93-1.15)	0.93 (0.83-1.04)	1.18 (1.05-1.32)	0.95 (0.85-1.06)	0.94 (0.84-1.06)	0.88 (0.76-1.01)	0.77 (0.65-0.91)
	>45	1.12 (0.95-1.32)	1.02 (0.88-1.17)	1.02 (0.89-1.18)	1.22 (1.06-1.40)	0.97 (0.85-1.12)	0.95 (0.82-1.09)	0.77 (0.65-0.91	0.64 (0.53-0.77)
Ethnicity	White	1	1	1	1	1	1	1	1
	Black	1.18 (0.98-1.43)	1.39 (1.18-1.63)	1.24 (1.06-1.46)	1.16 (0.98-1.37)	0.93 (0.80-1.08)	0.71 (0.60-0.84)	0.75 (0.62-0.91)	0.75 (0.61-0.93)
	Other black ethnicity	0.64 (0.48-0.87)	0.99 (0.78-1.25)	0.96 (0.76-1.22)	0.84 (0.66-1.06)	1.13 (0.92-1.40)	1.31 (1.04-1.64)	1.01 (0.76-1.33)	1.07 (0.77-1.48)
	Other	0.64 (0.53-0.77)	1.17 (1.02-1.35)	1.06 (0.92-1.23)	1.08 (0.94-1.26)	0.93 (0.80-1.08)	0.87 (0.74-1.03)	0.92 (0.77-1.10)	0.99 (0.80-1.23)
Exposure	MSM	1	1	1	1	1	1	1	1
	IDU	1.29 (0.97-1.72)	0.82 (0.62-1.09)	0.93 (0.70-1.22)	0.87 (0.65-1.16)	0.64 (0.46-0.87)	0.68 (0.49-0.94)	0.36 (0.23-0.57)	0.39 (0.24-0.63)
	Male heterosexual	0.84 (0.69-1.03)	0.72 (0.61-0.86)	0.98 (0.83-1.16)	0.80 (0.67-0.95)	0.83 (0.70-0.98)	0.79 (0.66-0.95)	0.63 (0.51-0.77)	0.58 (0.45-0.73)

		AOR (95% CI) from multivariable models of factors associated with having a first HBsAg test							
Year		**2004**	**2005**	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**
	Female heterosexual	0.73 (0.60-0.89)	0.66 (0.56-0.77)	0.78 (0.66-0.91)	0.78 (0.66-0.91)	0.74 (0.63-0.87)	0.69 (0.59-0.82)	0.47 (0.39-0.58)	0.52 (0.42-0.66)
	Other	0.38 (0.28-0.52)	0.26 (0.20-0.35)	0.37 (0.30-0.47)	0.40 (0.32-0.49)	0.98 (0.83-1.15)	1.09 (0.92-1.30)	0.67 (0.55-0.83)	0.38 (0.30-0.48)
HIV infection category	Advanced	1.24 (0.99-1.56)	1.09 (0.90-1.32)	1.14 (0.93-1.39)	1.22 (0.99-1.50)	0.96 (0.77-1.21)	1.30 (1.03-1.65)	1.21 (0.87-1.68)	2.18 (1.58-3.01)
	Uncontrolled	1.11 (0.94-1.33)	1.10 (0.96-1.27)	1.00 (0.86-1.15)	1.08 (0.93-1.24)	1.12 (0.97-1.28)	1.24 (1.06-1.44)	1.36 (1.12-1.65)	1.36 (1.11-1.67)
	Controlled	1	1	1	1	1	1	1	1
	Unknown	3.00 (2.59-3.47)	2.44 (2.17-2.76)	2.34 (2.07-2.64)	2.44 (2.16-2.77)	2.22 (1.97-2.50)	2.44 (2.15-2.76)	4.26 (3.67-4.94)	11.4 (9.57-13.49)

Table 6.5 Univariable and multivariable logistic regression of factors associated with first HBsAg test

		Univariable analysis			Multivariable analysis		
		OR	**95% CI**	**P value**	**AOR**	**95% CI**	**P value**
Age (years)	<35	1	-	-	1	-	-
	35-45	0.79	(0.76-0.82)	<0.0001	0.97	(0.93-1.01)	0.13
	>45	0.78	(0.75-0.82)	<0.0001	0.95	(0.90-1.01)	0.08
Ethnicity	White	1	-	-	1	-	-
	Black African	0.73	(0.71-0.79)	<0.0001	0.98	(0.93-1.05)	
	Other Black ethnicity	0.88	(0.82-0.95)	0.002	0.98	(0.90-1.07)	0.62
	Other/unknown	0.93	(0.89-0.99)	0.02	0.75	(0.91-1.02)	0.72
Exposure group	MSM	1	-	-	1	-	-
	IDU	0.64	(0.57-0.71)	<0.0001	0.75	(0.67-0.84)	<0.0001
	Male heterosexual	0.74	(0.71-0.79)	<0.0001	0.79	(0.74-0.85)	<0.0001
	Female heterosexual	0.63	(0.60-0.66)	<0.0001	0.69	(0.64-0.73)	<0.0001
	Other/unknown	0.89	(0.84-0.96)	0.001	0.61	(0.56-0.65)	<0.0001
HIV infection category	Advanced	1.07	(0.99-1.16)	0.09	1.25	(1.16-1.36)	<0.0001
	Uncontrolled	1.12	(1.06-1.18)	<0.0001	1.18	(1.11-1.24)	<0.0001
	Controlled	1	-	-	1	-	-
	Unknown	2.87	(2.75-2.99)	<0.0001	2.92	(2.79-0.06)	<0.0001
Year	(per year)	1.17	(1.17-1.19)	<0.0001	1.19	(1.18-1.20)	<0.0001

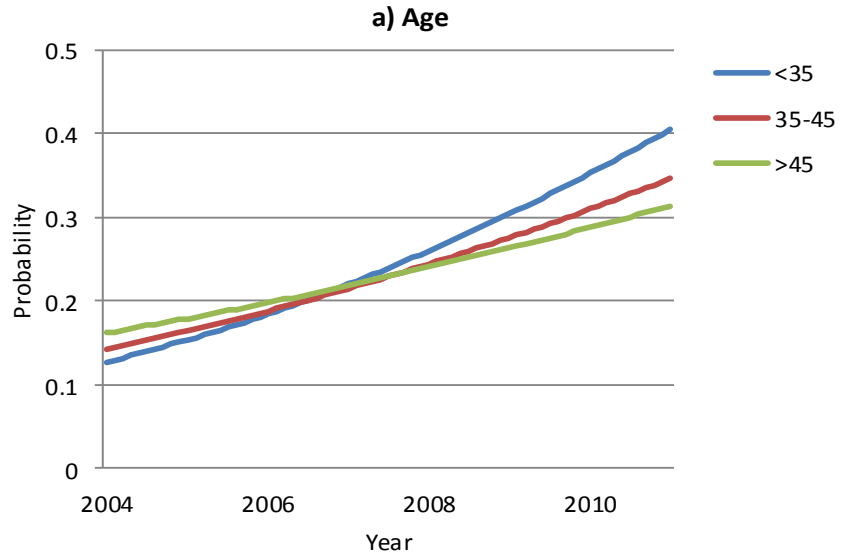
Table 6.6 Adjusted odds ratios for models predicting likelihood of first HBsAg test including interactions between year and demographic variables[1]

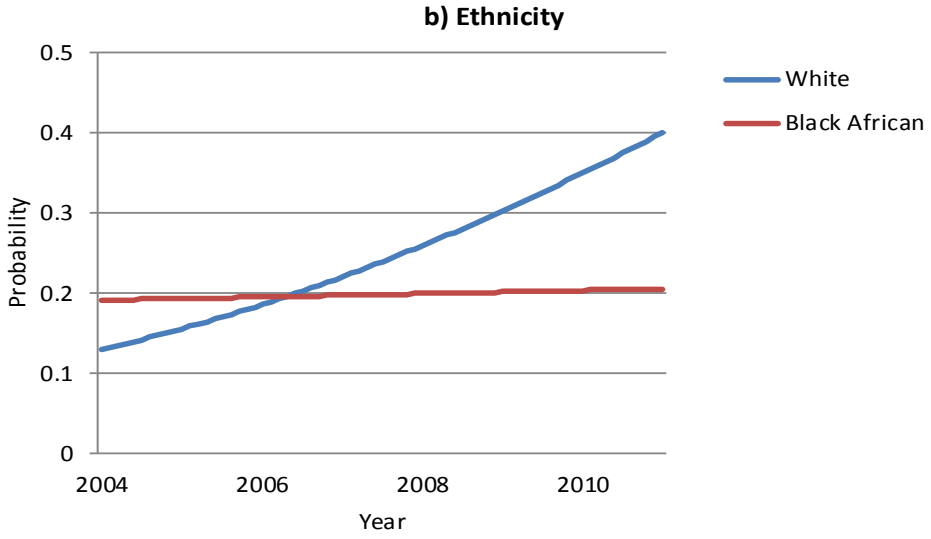
Factor	AOR	95% CI	P value
Model 1[2]			
Age <35 years	1	-	-
Age 35-45 years	1.15	1.07-1.24	0.0002
Age >45 years	1.32	1.21-1.45	<.0001
Year (per later year)	1.25	1.23-1.26	<.0001
Year*Age 35-45 years	0.94	0.93-0.96	<.0001
Year*Age >45 years	0.91	0.89-0.93	<.0001
Model 2[3]			
White	1	-	-
Black African	1.57	1.45-1.72	<.0001
Other black	0.99	0.91-1.07	0.7489
Other/unknown ethnicity	0.97	0.91-1.02	0.2259
Year (per later year)	1.24	1.23-1.25	<.0001
Year*Black African	0.87	0.85-0.89	<.0001
Model 3[4]			
MSM			
IDU	1.24	1.03-1.49	0.0242
Male heterosexual	1.11	1.00-1.23	0.0454
Female heterosexual	1.02	0.94-1.12	0.6102
Other	0.38	0.33-0.44	<.0001

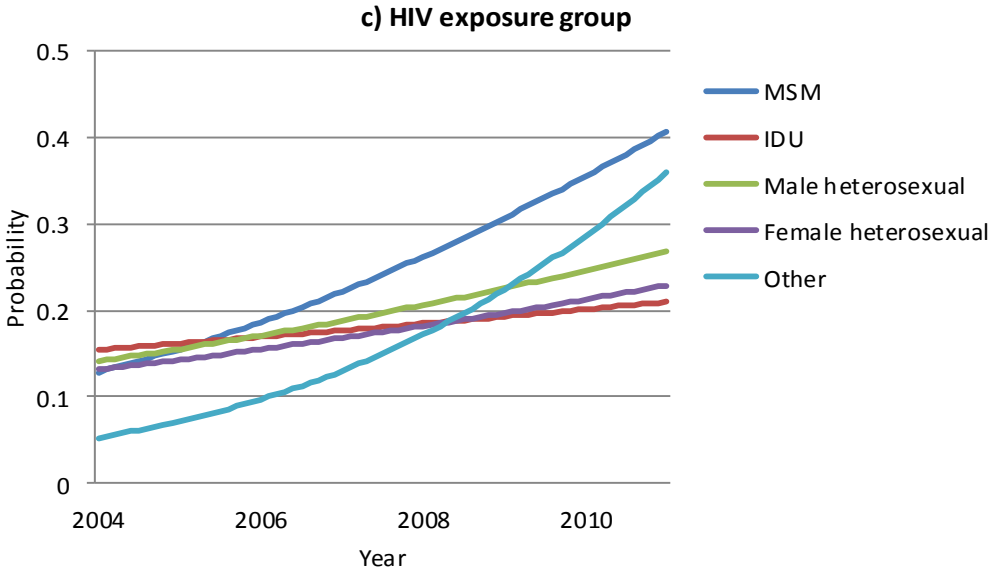
Factor	AOR	95% CI	P value
Year (per later year)	1.24	1.23-1.26	<.0001
Year*IDU	0.85	0.80-0.89	<.0001
Year*Male heterosexual	0.90	0.88-0.92	<.0001
Year*Female heterosexual	0.88	0.87-0.90	<.0001
Year*Other/unknown exposure	1.12	1.08-1.15	<.0001

[1] All models adjusted for age, ethnicity, HIV exposure group, calendar year and HIV infection category
[2]Model 1 includes an interaction between year and age group
[3]Model 2 includes an interaction between year and black African ethnicity
[4]Mode 3 includes an interaction between year and HIV exposure group

Figure 6.5 Modelled probability of having a first HBsAg test stratified by those demographic factors with significant interactions with calendar year







The same process was conducted for anti-HCV testing and separate logistic regression models were constructed for each year (Table 6.7). In 2004, there was no significant difference between MSM and IDU with regard to testing for anti-HCV. However, from 2005 onwards, IDU were significantly less likely than MSM to have a first test for HCV with the ORs decreasing year on year from 0.66 (95% CI 0.48-0.90) in 2005 to 0.27 (95% CI 0.16-0.47) in 2011. Comparing individuals of black African ethnicity to those of white ethnicity there was no significance difference from 2004 to 2008. However, from 2009 onwards, black African individuals were significantly less likely to have a first test, with the ORs decreasing from 0.99 (95 % CI 0.83-1.18) in 2004 to 0.75 (95% CI 0.60-0.93) in 2011.

Univariable and multivariable logistic regression was then conducted to identify factors associated with first anti-HCV for the complete dataset 2004-2011. Year of follow-up was included as a covariate, age and HIV infection category were updated at the start of each year and HIV exposure group and ethnicity were also included in the model. In univariable analysis age, ethnicity, HIV exposure group, HIV infection category and year were all associated with first anti-HCV test. These factors remained significant in the multivariable model (Table 6.8). Compared to individuals <35 years old, older individuals were less likely to have a first test for anti-HCV (AOR, 95% CI: 0.91 0.87-0.94 and 0.80, 0.76-0.85 for individuals aged 35-45 and those over the age of 45 respectively). Compared to white individuals, there was no significant difference between black African individuals and those with other/unknown ethnicity in the likelihood of having a first test. However, individuals of other black ethnicities were significantly more likely to have had a first test (AOR, 95% CI: 1.16, 1.06-1.26). Compared to MSM, individuals of all other exposure categories were less likely to have a first test. Compared to individuals with controlled HIV infection, those with advanced or uncontrolled and those with known HIV infection category were more likely to have a first test for HCV-Ab. Year of follow-up was significantly associated with likelihood of first test (AOR, 95% CI: 1.24, 1.23-1.25 per year).

Separate models were constructed to test for interactions between year and demographic factors (Table 6.9). All models included age group, ethnicity, HIV exposure group, HIV infection stage and year. Model 1 included an interaction between year and age category. A significant interaction was detected between year and the age group 35-45 years and between year and the age group over 45 years (P<0.0001 for both age categories). Model 2 included an interaction between ethnicity and year. A significant interaction was detected between black

African ethnicity and year, but not between year and other black ethnicity or year and other/unknown ethnicity. Therefore model 2 was rerun including only the interaction between year and black African ethnicity. Model 3 included an interaction between year and HIV exposure group. A significant interaction between year and all exposure groups ($P<0.0001$ for all HIV exposure groups) was detected. Using the parameter estimates from these models, the modelled probability of a first test among each group, per year, was calculated. Figure 6.6 shows how the probability of a first anti-HCV test changes over time in each group where a significant interaction was detected compared to the reference group. The reference group is white, MSM, aged <35 who have controlled HIV infection (denoted by the dark blue line in all graphs).

Table 6.7 Adjusted odds ratios for likelihood of first testing for anti-HCV according to characteristics at baseline, by year of follow-up

		AOR (95% CI) from multivariable models of factors associated with having a first anti-HCV test							
Year		**2004**	**2005**	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**
Age	<35	1	1	1	1	1	1	1	1
	35-45	0.94 (0.83-1.05)	0.95 (0.86-1.05)	0.93 (0.84-1.04)	1.00 (0.89-1.11)	0.86 (0.77-0.97)	0.89 (0.78-1.02)	0.86 (0.74-0.99)	0.73 (0.60-0.88)
	>45	0.89 (0.76-1.05)	0.86 (0.75-0.99)	0.98 (0.85-1.13)	0.89 (0.77-1.02)	0.76 (0.66-0.88)	0.80 (0.68-0.93)	0.72 (0.61-0.85)	0.49 (0.40-0.61)
Ethnicity	White	1	1	1	1	1	1	1	1
	Black African	0.99 (0.83-1.18)	1.28 (1.10-1.49)	1.36 (1.16-1.60)	1.20 (1.03-1.41)	1.00 (0.85-1.17)	0.78 (0.65-0.93)	0.83 (0.68-1.00)	0.75 (0.60-0.93)
	Other black ethnicity	0.80 (0.62-1.03)	1.18 (0.95-1.46)	1.31 (1.04-1.64)	1.13 (0.90-1.42)	1.31 (1.04-1.66)	1.28 (0.99-1.67)	1.10 (0.81-1.50)	1.43 (0.97-2.11)
	Other	0.64 (0.54-0.76)	1.41 (1.25-1.61)	1.22 (1.06-1.41)	1.03 (0.89-1.20)	0.94 (0.80-1.10)	0.79 (0.67-0.95)	1.00 (0.83-1.20)	0.93 (0.73-1.19)
Exposure	MSM	1	1	1	1	1	1	1	1
	IDU	0.96 (0.69-1.35)	0.66 (0.48-0.90)	0.70 (0.51-0.95)	0.71 (0.52-0.98)	0.77 (0.55-1.08)	0.45 (0.30-0.68)	0.40 (0.25-0.63)	0.27 (0.16-0.47)
	Male heterosexual	0.97 (0.81-1.17)	0.63 (0.54-0.74)	0.79 (0.67-0.93)	0.76 (0.64-0.90)	0.79 (0.66-0.94)	0.82 (0.67-1.00)	0.54 (0.44-0.67)	0.41 (0.32-0.54)

		AOR (95% CI) from multivariable models of factors associated with having a first anti-HCV test							
Year		**2004**	**2005**	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**
	Female heterosexual	0.90 (0.75-1.07)	0.66 (0.57-0.76)	0.71 (0.61-0.84)	0.70 (0.60-0.82)	0.75 (0.64-0.89)	0.73 (0.60-0.87)	0.47 (0.39-0.58)	0.34 (0.27-0.43)
	Other	0.38 (0.28-0.51)	0.31 (0.24-0.39)	0.30 (0.23-0.38)	0.32 (0.26-0.39)	0.84 (0.71-0.98)	0.90 (0.75-1.08)	0.61 (0.49-0.75)	0.29 (0.23-0.37)
HIV infection category	Advanced	1.06 (0.86-1.32)	0.98 (0.82-1.18)	0.98 (0.80-1.20)	1.19 (0.96-1.46)	1.05 (0.83-1.33)	1.70 (1.31-2.21)	0.93 (0.66-1.31)	1.28 (0.88-1.87)
	Uncontrolled	1.19 (1.01-1.40)	1.14 (1.00-1.30)	1.20 (1.05-1.39)	1.55 (1.34-1.79)	1.47 (1.26-1.72)	1.60 (1.34-1.92)	1.51 (1.22-1.87)	1.62 (1.27-2.07)
	Controlled	1	1	1	1	1	1	1	1
	Unknown	2.32 (2.02-2.65)	1.59 (1.42-1.78)	1.57 (1.39-1.78)	1.94 (1.71-2.20)	1.87 (1.64-2.13)	2.47 (2.15-2.85)	2.91 (2.49-3.40)	5.99 (4.95-7.26)

Table 6.8 Univariable and multivariable logistic regressions analysis of factors associated with first anti-HCV test

		Univariable analysis			Multivariable model		
		OR	**95% CI**	**P value**	**AOR**	**95% CI**	**P value**
Age	<35	1	-	-	1	-	-
	35-45	0.78	0.74-0.81	<0.0001	0.91	0.87-0.94	<0.0001
	>45	0.71	0.67-0.75	<0.0001	0.80	0.76-0.85	<0.0001
Ethnicity	White	1	-	-	1	-	-
	Black African	0.78	0.74-0.81	<0.0001	1.03	0.97-1.09	0.36
	Other black ethnicity	1.03	0.95-1.12	0.47	1.16	1.06-1.26	0.001
	Other/unknown	0.95	0.90-1.00	0.07	1.01	0.96-1.07	0.69
Exposure group	MSM	1	-	-	1	-	-
	IDU	0.59	0.52-0.67	<0.0001	0.63	0.55-0.72	<0.0001
	Male heterosexual	0.71	0.67-0.75	<0.0001	0.73	0.58-0.78	<0.0001
	Female heterosexual	0.67	0.65-0.70	<0.0001	0.67	0.63-0.72	<0.0001
	Other/unknown	0.74	0.70-0.79	<0.0001	0.52	0.48-0.56	<0.0001
HIV infection category	Advanced	1.00	0.92-1.08	1.00	1.15	1.05-1.25	0.001
	Uncontrolled	1.34	1.27-1.42	<0.0001	1.39	1.32-1.48	<0.0001
	Controlled	1	-	-	1	-	-
	Unknown	2.30	2.20-22.40	<0.0001	2.13	2.04-2.24	<0.0001
Year	(per year)	1.23	1.22-1.24	<0.0001	1.24	1.23-1.25	<0.0001

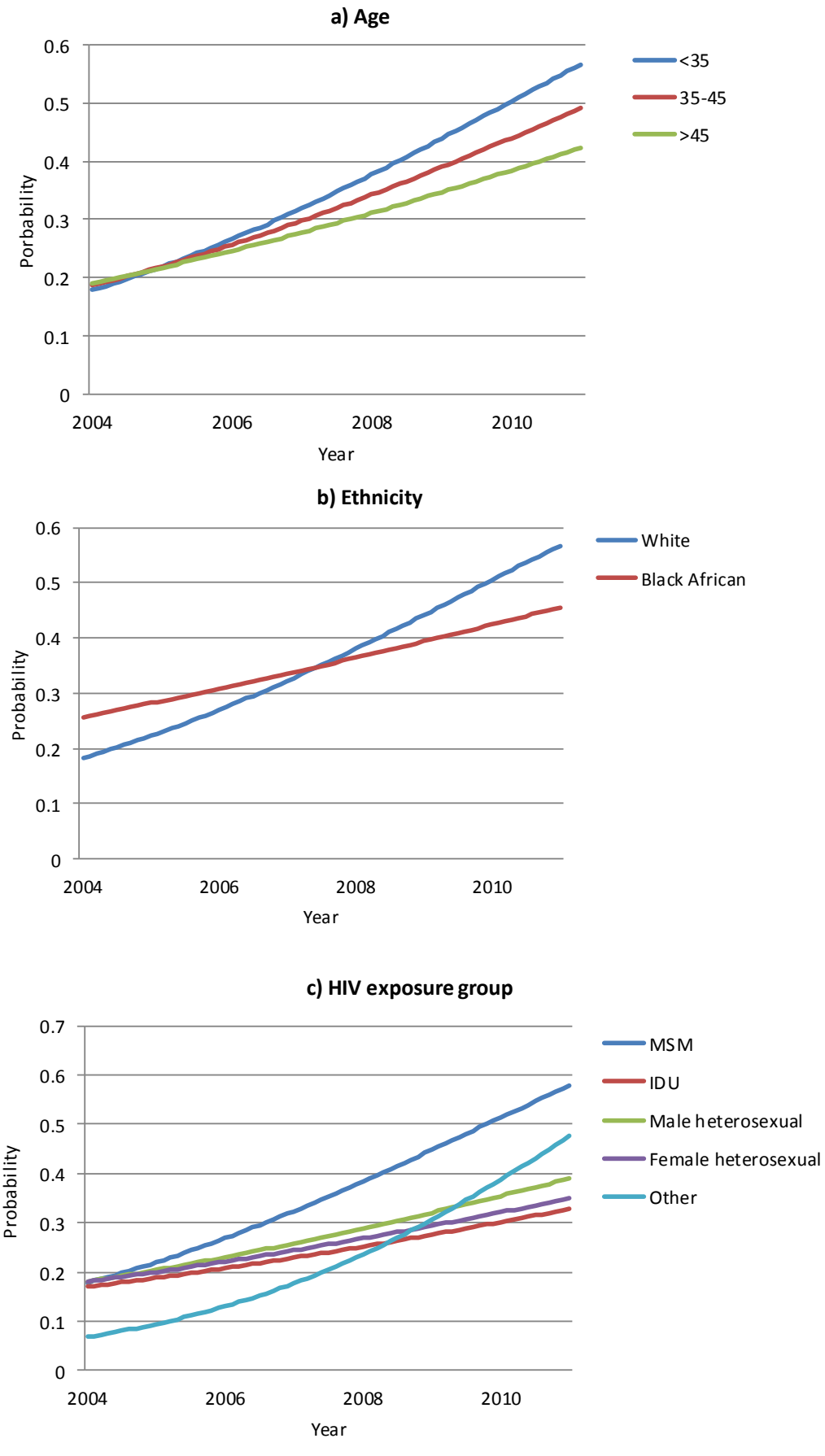
Table 6.9 Adjusted odds ratios for models predicting likelihood first anti-HCV test including interactions between year and demographic variables[1]

Factor	AOR	95% CI	P value
Model 1[2]			
Age <35 years	1	-	-
Age 35-45 years	1.05	0.98-1.13	0.1353
Age >45 years	1.09	0.99-1.19	0.0703
Year (per later year)	1.29	1.27-1.31	<.0001
Year*Age 35-45 years	0.95	0.93-0.97	<.0001
Year*Age >45 years	0.91	0.89-0.93	<.0001
Model 2[3]			
White	1	-	-
Black African	1.56	1.70-5.44	<.0001
Other black	1.17	1.28-3.58	0.0006
Other/unknown ethnicity	1.01	1.07-2.93	0.618
Year (per later year)	1.29	1.30-3.68	<.0001
Year*Black African	0.88	0.89-2.45	<.0001
Model 3[4]			
MSM	1	-	-
IDU	0.94	0.76-1.17	0.5899
Male heterosexual	1.02	0.92-1.13	0.72
Female heterosexual	1.02	0.93-1.11	0.6944
Other	0.34	0.29-0.39	<.0001
Year (per later year)	1.30	1.29-1.32	<.0001

Factor	AOR	95% CI	P value
Year*IDU	0.87	0.82-0.92	<.0001
Year*Male heterosexual	0.89	0.87-0.92	<.0001
Year*Female heterosexual	0.87	0.85-0.89	<.0001
Year*Other/unknown exposure	1.10	1.06-1.14	<.0001

[1] All models adjusted for age, ethnicity, HIV exposure group, calendar year and HIV infection category
[2] Mode 1 includes an interaction between year and age group
[3] Model 2 includes and interaction between year and black African ethnicity
[4] Mode 3 includes an interaction between year and HIV exposure categories

Figure 6.6 Modelled probability of having a first anti-HCV test stratified by those demographic factors with significant interactions with calendar year



6.3.1.4 Factors associated with repeat testing

The proportion of individuals in each year who had a repeat HBsAg test within that year increased significantly from 20.4% to 44.4% over the period 2004-2008 ($p<0.0001$) but subsequently declined significantly from 44.7% to 23.4% over the period 2009-2011 ($p<0.0001$) (Table 6.10). The proportion of individuals in each year who had a repeat anti-HCV test within that year increased significantly from 33.1% in 2004 to 54.4% in 2011 ($p<0.0001$) (Table 6.11).

Table 6.10 Proportion of individuals repeat testing for HBsAg, by year

Year	Numbers previously tested but who have never received a positive result	Number tested within year	%
2004	5382	1530	28.4%
2005	6159	1722	28.00%
2006	7229	2342	32.4%
2007	8250	3003	36.4%
2008	8540	3788	44.4%
2009	8806	3937	44.7%
2010	9522	3142	33.0%
2011	9330	2184	23.4%

Table 6.11 Proportion of individuals repeat testing for anti-HCV, by year

Year	Numbers previously tested but who have never received a positive result	Number tested within year	%
2004	7643	2531	33.1%
2005	9013	3042	33.8%
2006	11166	3930	35.2%
2007	12966	5534	42.7%
2008	14769	7325	49.6%
2009	16448	8760	53.3%
2010	17799	9036	50.8%
2011	17114	9314	54.4%

A separate multivariable model was constructed for each year. Each model included age group, ethnicity, HIV exposure category and HIV infection category. The AORs for repeat testing in a given year are shown in (Table 6.12). In most years, there was no difference in the likelihood of repeat testing between individuals aged <35 years and those aged 35-45 years. However, there was some evidence that in 2007 and 2011 individuals aged 35-45 years were significantly less likely to have a repeat test than individuals aged <35 years old. However, it appears that those aged over 45 are less likely to have a repeat HBsAg test when compared to those aged <35 in every year. Compared to MSM, IDU were significantly less likely to have a repeat test for HBsAg from 2005 to 2010. Similarly, male and female heterosexuals were less likely to have a repeat test than MSM from 2004 to 2010. With the exception of 2007 and 2009, compared to white individuals, there were no significant differences in the likelihood of individuals of black African ethnicity having a repeat test for HBsAg. In general there were few significant differences in repeat testing according to HIV infection category. However, in 2006 and 2009 individuals with advanced or uncontrolled HIV infection were significantly less likely to have a repeat HBsAg test than individuals with controlled HIV infection. In addition, in later years (2010 and 2011), individuals with missing CD4 and HIV viral load data were more likely to have a repeat test for HBsAg than those with controlled HIV infection.

In a multivariable model including the complete dataset (2004-2011), year of follow-up was included as a categorical variable as the observed changes in repeat testing over time were not linear. Table 6.13 shows the results of a model of factors associated with repeat HBsAg testing. In multivariable analysis, compared to younger individuals, those aged 34-45 years and those aged >45 years were less likely to have a repeat test, although for individuals aged 35-45 the effect size was small (AOR, 95% CI: 0.94, 0.90-0.99). Compared to white individuals, individuals of black African ethnicity were less likely to have a repeat HBsAg test (AOR, 95% CI: 0.88, 0.82-0.94). Compared to MSM, individuals of all other HIV exposure groups were less likely to have a repeat test. HIV infection category was also significantly associated with having a repeat test, with those who had advanced infection being less likely to repeat test than those with controlled HIV infection (AOR, 95% CI: 0.88, 0.82-0.94) while those with unknown HIV infection category were more likely to have a repeat HBsAg test (AOR, 95% CI: 1.12, 1.01-1.25). Taking 2004 as the reference year, there was a significant association between each year and HBsAg testing. There was no difference in the likelihood of testing in 2005 compared to 2004, but individuals under follow-up in all years until 2010 were more likely to have a repeat test than those under follow-up in 2004.

Three separate models were then constructed to test for interactions between year and demographic variables. As before, year was included as a categorical variable for each of these models. Model 1 included an interaction between age group and year; this model did not reveal any significant interactions (data not shown). Model 2 included an interaction between year and ethnicity. Significant interactions were only identified between year and black African ethnicity therefore the interaction terms between year and black other ethnicity and year and other ethnicity were removed from the model leaving only the interaction between year and black African ethnicity. Model 3 included an interaction between exposure group and year. No significant interactions were identified between male heterosexual and other exposure, and therefore these two interactions were removed from the models. In contrast, significant interactions were identified between IDU and year and female heterosexual exposure and year. Significant interactions were identified between year and black African ethnicity, year and IDU and year and female heterosexual exposure. Table 6.14 shows the significant interactions identified in these models. Where significant interactions were identified the modelled probability over time in the groups where a significant interaction was present was then plotted compared to the reference group. A stepwise graph was used since year was categorical and not continuous (Figure 6.7). The reference group was white, MSM, aged <35 with controlled HIV infection (denoted by a blue line).

This process was repeated for HCV testing and separate multivariable models were constructed to identify factors associated with repeat anti-HCV testing in each year of follow-up. Table 6.15 shows the AORs for repeat anti-HCV testing in each year. There were no significant differences in the likelihood of repeat anti-HCV testing between individuals aged <35 years and those aged 35-45 years in any year. However, in later years, those aged over 45 were less likely to have a repeat anti-HCV test than those aged <35. From 2005 onwards black African individuals were less likely to have a repeat test than white individuals and from 2004 to 2010 individuals of other black ethnicities were less likely to have a repeat anti-HCV test than white individuals. Compared to MSM, IDU were significantly less likely to have a repeat anti-HCV test in most years (2005, 2006, 2008, 2009 and 2011). Male and female heterosexuals were less likely to have a repeat anti-HCV test in every year of follow-up. Compared to individuals with controlled HIV infection those with advanced or uncontrolled HIV infection were less likely to have a repeat anti-HCV test and those whose HIV infection category was unknown due to missing CD4 and viral load measurements were more likely to have a repeat anti-HCV test from 2005 onwards.

In a multivariable model including data for all years, year of follow-up was included as a continuous variable. Table 6.16 shows the results of univariable and multivariable logistic regression of factors associated with repeat anti-HCV testing. Age group, ethnicity, HIV exposure group, HIV infection category and year were all significantly associated with having a repeat anti-HCV test in univariable analysis and these associations remained when the variables were entered into a multivariable model. Older individuals (>45 years) were less likely to have a repeat anti-HCV test than individuals aged under 35 years (AOR, 95% CI: 0.85, 0.82-0.89). Compared to white individuals, those of black African ethnicity were less likely to have a repeat anti-HCV test (AOR, 95% CI: 0.67, 0.63-0.71) as were those of other black ethnicities (AOR: 95% CI: 0.73, 0.68-0.79). Individuals of all other exposure groups were significantly less likely to have a repeat anti-HCV test than MSM, as were individuals with advanced or uncontrolled HIV infection when compared to those with controlled HIV infection. Year was significantly associated with testing, with testing being more likely in later years (AOR 1.17 per later year, 95% CI 1.16-1.18).

Three separate models were then constructed to examine potential interactions between year and demographic characteristics. Model 1 included an interaction between year and age group. There was no significant interaction between age group 35-45 and year but there was a significant interaction between year and age group >45. Therefore the interaction term for year and age 35-45 was removed from the model. Model 2 included an interaction between ethnicity and year. No significant interaction was identified between black African ethnicity and year and so this was removed from the model but significant interactions were identified between year and black other ethnicity and year and other/unknown ethnicity. Model 3 included an interaction between year and HIV exposure group. The only significant interaction identified was between year and other/unknown exposure, therefore interactions between year and all other exposure categories were removed from the model. ORs for these models are shown in Table 6.17. Where significant interactions were identified, the probability of testing in the group where an interaction was present compared to the reference group was plotted (Figure 6.8). The reference group was white MSM, aged <35 years with controlled HIV infection (denoted by the dark blue line in all graphs).

Table 6.12 Adjusted odds ratios for the likelihood of having a repeat HBsAg testing according to characteristics at baseline, by year of follow-up

		AOR (95% CI)							
Year		**2004**	**2005**	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**
Age	<35	1	1	1	1	1	1	1	1
	35-45	0.94 (0.82-1.08)	0.90 (0.79-1.03)	0.97 (0.86-1.10)	0.86 (0.76-0.96)	0.94 (0.84-1.05)	1.04 (0.93-1.16)	0.93 (0.83-1.04)	0.84 (0.74-0.96)
	>45	0.70 (0.58-0.85)	0.68 (0.57-0.81)	0.76 (0.65-0.88)	0.82 (0.71-0.93)	0.83 (0.73-0.95)	0.87 (0.77-0.99)	0.87 (0.77-0.99)	0.76 (0.66-0.87)
Ethnicity	White	1	1	1	1	1	1	1	1
	Black African	0.87 (0.68-1.11)	0.91 (0.73-1.13)	0.88 (0.72-1.06)	0.73 (0.62-0.86)	0.97 (0.84-1.13)	0.79 (0.68-0.91)	0.89 (0.77-1.03)	1.11 (0.95-1.30)
	Other black ethnicity	0.75 (0.54-1.03)	0.90 (0.67-1.19)	0.65 (0.50-0.86)	0.79 (0.63-0.99)	1.06 (0.86-1.30)	0.77 (0.63-0.94)	0.87 (0.71-1.06)	1.44 (1.17-1.76)
	Other	1.11 (0.89-1.39)	0.91 (0.74-1.12)	0.98 (0.82-1.17)	0.86 (0.74-1.01)	0.79 (0.68-0.92)	0.96 (0.83-1.12)	0.99 (0.86-1.15)	0.87 (0.74-1.04)
Exposure	MSM	1	1	1	1	1	1	1	1
	IDU	0.82 (0.60-1.11)	0.51 (0.37-0.71)	0.43 (0.32-0.58)	0.50 (0.38-0.64)	0.52 (0.41-0.66)	0.42 (0.32-0.53)	0.66 (0.51-0.85)	1.09 (0.82-1.46)
	Male heterosexual	0.57 (0.44-0.73)	0.61 (0.49-0.77)	0.52 (0.43-0.63)	0.67 (0.57-0.79)	0.50 (0.43-0.59)	0.58 (0.50-0.67)	0.66 (0.56-0.76)	1.22 (1.03-1.44)

		AOR (95% CI)							
Year		**2004**	**2005**	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**
	Female heterosexual	0.38 (0.30-0.48)	0.57 (0.46-0.70)	0.45 (0.38-0.55)	0.64 (0.55-0.75)	0.50 (0.43-0.58)	0.52 (0.45-0.59)	0.59 (0.51-0.68)	1.12 (0.95-1.31)
	Other	0.52 (0.34-0.82)	0.55 (0.36-0.83)	0.35 (0.24-0.53)	0.70 (0.52-0.94)	0.59 (0.45-0.77)	0.70 (0.57-0.84)	0.94 (0.79-1.11)	0.57 (0.46-0.70)
HIV infection category	Advanced	0.90 (0.73-1.10)	1.02 (0.83-1.24)	0.72 (0.59-0.87)	0.90 (0.76-1.06)	0.90 (0.77-1.05)	0.69 (0.58-0.82)	0.98 (0.82-1.17)	1.11 (0.90-1.38)
	Uncontrolled	1.02 (0.89-1.17)	1.02 (0.90-1.16)	0.85 (0.79-0.95)	0.99 (0.89-1.10)	0.90 (0.82-1.05)	0.83 (0.75-0.92)	1.03 (0.92-1.14)	1.03 (0.92-1.16)
	Controlled	1	1	1	1	1	1	1	1
	Unknown	0.86 (0.66-1.11)	0.84 (0.64-1.09)	0.69 (0.54-0.90)	0.95 (0.74-1.22)	1.24 (0.92-1.66)	1.32 (0.91-1.91)	2.93 (1.87-4.61)	7.03 (3.81-12.99)

Table 6.13 Univariable and multivariable logistic regression of factors associated with repeat testing for HBsAg

		Univariable analysis			Multivariable analysis		
		OR	**95% CI**	**P value**	**AOR**	**95% CI**	**P value**
Age group (years)	<35	1	-	-	1	-	-
	35-45	1.00	0.96-1.05	0.98	0.94	0.90-0.99	0.0131
	>45	0.89	0.85-0.94	<0.0001	0.82	0.78-0.87	<0.0001
Ethnicity	White	1	-	-	1	-	-
	Black African	0.63	0.61-0.66	<0.0001	0.88	0.82-0.94	0.0002
	Other black	0.78	0.71-0.85	<0.0001	0.91	0.83-1.00	0.0393
	Other/unknown	0.85	0.80-0.91	<0.0001	0.92	0.86-0.98	0.0101
	HIV exposure group						
HIV exposure group	MSM	1	-	-	1	-	-
	IDU	0.58	0.52-0.65	<0.0001	0.57	0.51-0.65	<0.0001
	Male heterosexual	0.61	0.57-0.64	<0.0001	0.64	0.60-0.69	<0.0001
	Female heterosexual	0.57	0.54-0.60	<0.0001	0.58	0.55-0.62	<0.0001
	Other/unknown	0.63	0.58-0.69	<0.0001	0.65	0.60-0.72	<0.0001
HIV infection category	Advanced	0.82	0.77-0.87	<0.0001	0.88	0.82-0.94	0.0002
	Uncontrolled	0.97	0.93-1.01	0.16	0.95	0.91-0.99	0.0236
	Controlled	1	-	-	1	-	-
	Unknown	1.28	1.16-1.42	<0.0001	1.12	1.01-1.25	

		Univariable analysis			Multivariable analysis		
		OR	**95% CI**	**P value**	**AOR**	**95% CI**	**P value**
Year	2004	1	-	-	1	-	-
	2005	0.98	0.91-1.06	0.59	0.99	0.91-1.07	0.7552
	2006	1.21	1.12-1.30	<0.0001	1.24	1.15-1.34	<0.0001
	2007	1.44	1.34-1.55	<0.0001	1.51	1.41-1.62	<0.0001
	2008	2.13	1.99-2.28	<0.0001	2.28	2.12-2.44	<0.0001
	2009	2.09	1.95-2.24	<0.0001	2.28	2.12-2.44	<0.0001
	2010	1.26	1.17-1.35	<0.0001	1.37	1.27-1.47	<0.0001
	2011	0.78	0.72-0.84	<0.0001	0.83	0.77-0.90	<0.0001

Table 6.14 Adjusted ORs for models predicting the likelihood of repeat HBsAg testing including interactions between year and demographic variables[1]

Factor	AOR	95% CI	P value
Model 2[2]			
White	1	-	-
Black African	0.67	0.56-0.80	0.56-0.80
Other black	0.91	0.83-0.99	0.83-0.99
Other/unknown ethnicity	0.92	0.86-0.98	0.86-0.98
2004	1	-	-
2005	0.94	0.86-1.02	<0.0001
2006	1.23	1.13-1.33	<0.0001
2007	1.47	1.36-1.60	<0.0001
2008	2.20	2.03-2.38	<0.0001
2009	2.29	2.11-2.48	<0.0001
2010	1.31	1.21-1.42	<0.0001
2011	0.68	0.63-0.75	<0.0001
2005*Black African	1.37	1.11-1.70	0.004
2006*Black African	1.11	0.91-1.35	0.32
2007*Black African	1.19	0.98-1.45	0.07
2008*Black African	1.26	1.05-1.52	0.01
2009*Black African	1.08	0.89-1.30	0.42
2010*Black African	1.29	1.07-1.57	0.01
2011*Black African	2.49	2.04-3.05	<0.0001

Factor	AOR	95% CI	P value
Model 3 [3]			
MSM	1	-	-
IDU	0.86	0.63-1.17	0.35
Male heterosexual	0.64	0.60-0.69	<0.0001
Female heterosexual	0.40	0.33-0.48	<0.0001
Other	0.66	00.360-0.73	<0.0001
2004	1	-	-
2005	0.95	0.87-1.03	0.21
2006	1.24	1.15-1.35	<0.0001
2007	1.46	1.35-1.58	<0.0001
2008	2.23	2.06-2.41	<0.0001
2009	2.31	2.13-2.50	<0.0001
2010	1.32	1.22-1.44	<0.0001
2011	0.68	0.62-0.74	<0.0001
2005*IDU	0.61	0.40-0.94	0.03
2006*IDU	0.52	0.35-0.80	0.003
2007*IDU	0.58	0.39-0.86	0.006
2008*IDU	0.62	0.43-0.88	0.008
2009*IDU	0.49	0.33-0.71	0.0002
2010*IDU	0.74	0.50-1.08	0.12
2011*IDU	1.09	0.71-1.67	0.67

Factor	AOR	95% CI	P value
2005*Female heterosexual	1.53	1.22-1.92	0.0002
2006*Female heterosexual	1.21	0.98-1.50	0.08
2007*Female heterosexual	1.46	1.18-1.80	0.0004
2008*Female heterosexual	1.37	1.12-1.68	0.002
2009*Female heterosexual	1.22	1.00-1.50	0.05
2010*Female heterosexual	1.40	1.13-1.72	0.0002
2011*Female heterosexual	2.91	2.35-3.62	<0.0001

[1] All models adjusted for age, ethnicity, HIV exposure group, calendar year and HIV infection category
[2] Model 2 includes an interaction between year and black African ethnicity
[3] Model 3 includes and interaction between year and IDU and year and female heterosexual HIV exposure

Figure 6.7 Modelled probability of having a repeat HBsAg test stratified by those demographic factors with significant interactions with calendar year

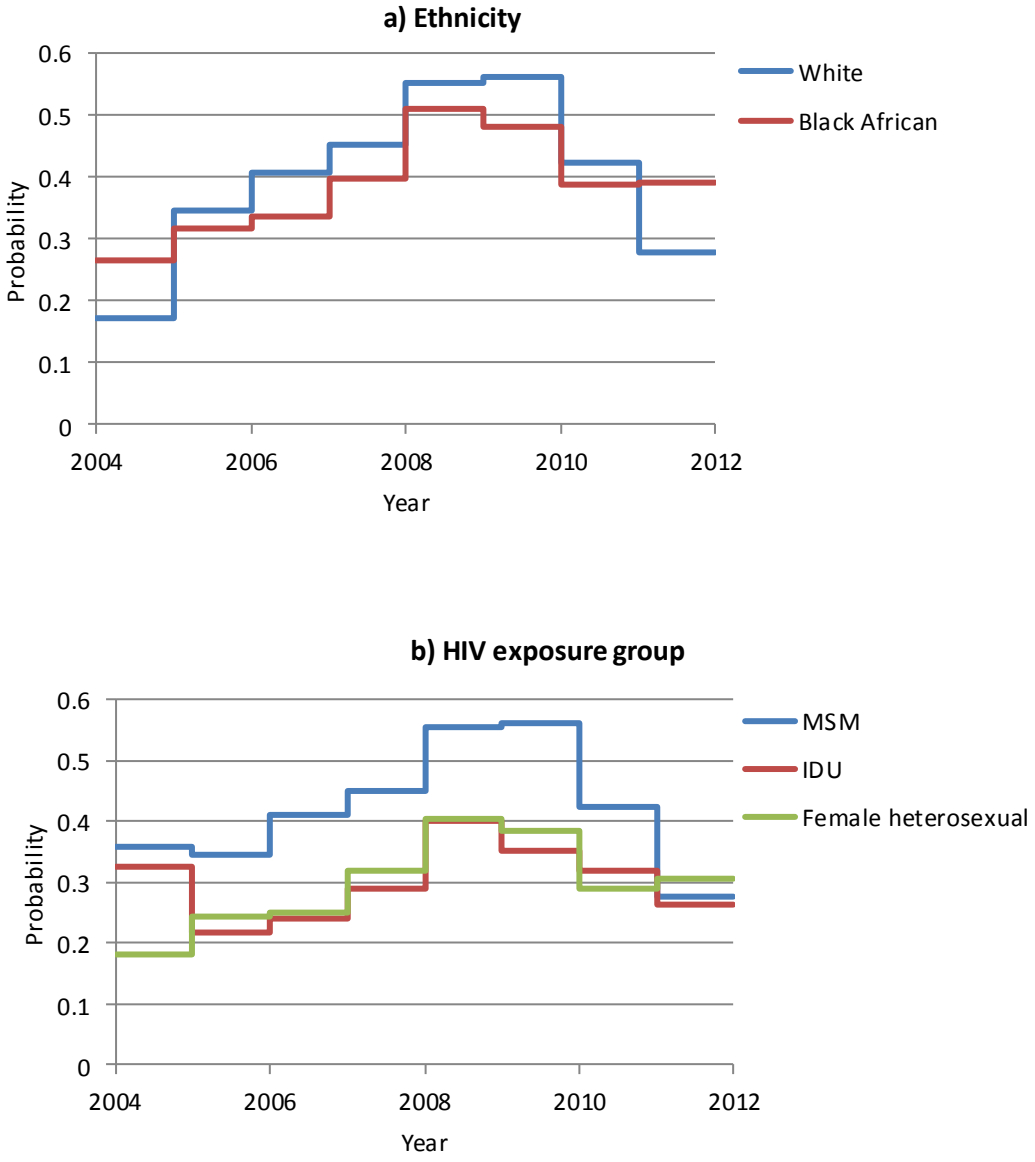


Table 6.15 Adjusted odds ratios for likelihood having repeat test testing for anti-HCV, by year of follow-up

		AOR (95% CI)							
Year		**2004**	**2005**	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**
Age	<35	1	1	1	1	1	1	1	1
	35-45	0.96 (0.85-1.09)	N/A	0.97 (0.87-1.07)	N/A	0.99 (0.91-1.08)	1.08 (1.00-1.18)	N/A	0.96 (0.88-1.04)
	>45	0.92 (0.80-1.07)	N/A	0.88 (0.78-1.00)	N/A	0.84 (0.77-0.93)	0.90 (0.82-0.99)	N/A	0.79 (0.73-0.87)
Ethnicity	White	1	1	1	1	1	1	1	1
	Black	0.91 (0.73-1.13)	0.78 (0.64-0.95)	0.60 (0.50-0.71)	0.62 (0.54-0.71)	0.77 (0.68-0.87)	0.67 (0.60-0.76)	0.67 (0.60-0.75)	0.64 (0.57-0.71)
	Other black ethnicity	0.68 (0.52-0.88)	0.67 (0.53-0.85)	0.54 (0.44-0.68)	0.65 (0.54-0.78)	0.84 (0.71-0.99)	0.78 (0.67-0.90)	0.69 (0.60-0.80)	0.90 (0.78-1.04)
	Other	0.96 (0.79-1.16)	0.87 (0.73-1.03)	0.93 (0.81-1.06)	0.94 (0.84-1.06)	0.95 (0.85-1.06)	0.99 (0.89-1.10)	1.07 (0.96-1.18)	1.10 (0.99-1.22)
Exposure	MSM	1	1	1	1	1	1	1	1
	IDU	0.68 (0.39-1.20)	0.47 (0.26-0.84)	0.41 (0.23-0.70)	0.69 (0.43-1.10)	0.52 (0.33-0.81)	0.61 (0.40-0.95)	0.75 (0.49-1.16)	0.50 (0.32-0.78)
	Male heterosexual	0.36 (0.29-0.45)	0.44 (0.36-0.53)	0.47 (0.39-0.55)	0.51 (0.45-0.59)	0.42 (0.37-0.48)	0.47 (0.42-0.53)	0.39 (0.34-0.43)	0.50 (0.45-0.56)

		AOR (95% CI)							
Year		**2004**	**2005**	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**
	Female heterosexual	0.24 (0.19-0.30)	0.33 (0.27-0.40)	0.31 (0.27-0.37)	0.43 (0.38-0.49)	0.37 (0.33-0.42)	0.43 (0.38-0.48)	0.33 (0.30-0.37)	0.37 (0.33-0.41)
	Other	0.45 (0.31-0.66)	0.51 (0.36-0.74)	0.46 (0.33-0.64)	0.54 (0.42-0.71)	0.58 (0.46-0.72)	0.73 (0.62-0.86)	0.90 (0.78-1.04)	1.05 (0.91-1.21)
HIV infection category	Advanced	0.82 (0.68-0.97)	0.80 (0.68-0.94)	0.70 (059-0.82)	0.76 (0.66-0.88)	0.83 (0.72-0.95)	0.67 (0.58-0.77)	0.76 (0.66-0.88)	0.76 (0.64-0.89)
	Uncontrolled	0.87 (0.78-0.97)	0.91 (0.82-1.00)	0.88 (0.80-0.96)	0.89 (0.82-0.96)	0.83 (0.77-0.90)	0.88 (0.81-0.95)	0.92 (0.86-1.00)	0.96 (0.89-1.04)
	Controlled	1	1	1	1	1	1	1	1
	Unknown	0.88 (0.60-1.28)	1.47 (1.05-2.05)	1.13 (0.83-1.55)	1.61 (1.17-2.22)	1.13 (0.86-1.50)	1.37 (1.00-1.86)	2.00 (1.38-2.92)	2.22 (1.29-3.83)

Table 6.16 Univariable and multivariable logistic regression of factors associated with repeat anti-HCV testing

		Univariable analysis			Multivariable analysis		
		OR	**95% CI**	**P value**	**AOR**	**95% CI**	**P value**
Age group (years)	<35	1	-	-	1	-	-
	35-45	1.09	1.04-1.13	<0.0001	0.99	0.95-1.03	0.52
	>45	1.13	1.08-1.78	<0.0001	0.85	0.82-0.89	<0.0001
Ethnicity	White	1	-	-	1	-	-
	Black African	0.33	0.32-0.34	<0.0001	0.67	0.63-0.71	<0.0001
	Other black	0.54	0.50-0.58	<0.0001	0.73	0.68-0.79	<0.0001
	Other/unknown	0.87	0.82-0.91	<0.0001	0.98	0.93-1.03	0.50
HIV exposure group	MSM	1	-	-	1	-	-
	IDU	0.54	0.44-0.67	<0.0001	0.58	0.47-0.71	<0.0001
	Male heterosexual	0.37	0.35-0.39	<0.0001	0.45	0.43-0.48	<0.0001
	Female heterosexual	0.30	0.28-0.31	<0.0001	0.37	0.35-0.38	<0.0001
	Other/unknown	0.80	0.74-0.87	<0.0001	0.76	0.70-0.83	<0.0001
HIV infection category	Advanced	0.59	0.56-0.63	<0.0001	0.76	0.72-0.81	<0.0001
	Uncontrolled	0.86	0.84-0.89	<0.0001	0.89	0.86-0.92	<0.0001
	Controlled	1	-	-	1	-	-
	Unknown	1.66	1.45-1.89	<0.0001	1.45	1.27-1.66	<0.0001
Year	(per year)	1.15	1.14-1.16	<0.0001	1.17	1.16-1.18	<0.0001

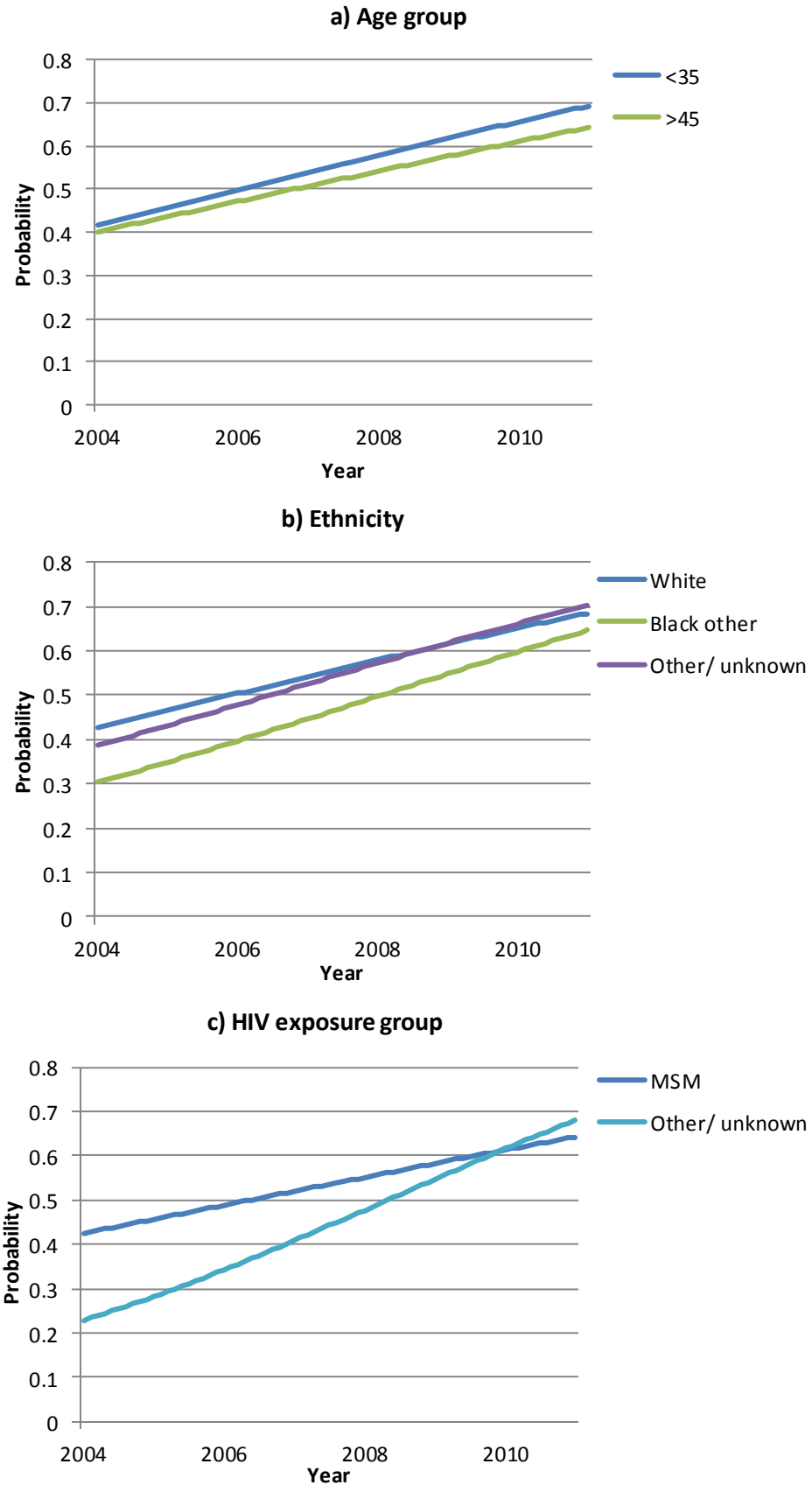
Table 6.17 Adjusted odd ratios for models predicting likelihood repeat anti-HCV test including interactions between year and demographic variables[1]

Factor	AOR	95% CI	P value
Model 1			
Age <35	1	-	-
Age 35-45 years	0.99	0.95-1.03	0.52
Age >45 years	0.95	0.88-1.02	0.14
Year	1.18	1.17-1.19	<0.0001
Year*Age >45 years	0.98	0.96-0.99	0.0003
Model 2			
White	1	-	-
Black African	0.67	0.64-0.71	<0.0001
Other black	0.58	0.50-0.67	<0.0001
Other/unknown ethnicity	0.84	0.75-0.93	0.001
Year	1.16	1.16-1.17	<0.0001
Year*Other black	1.05	1.02-1.08	0.0003
Year* Other/unknown ethnicity	1.04	1.02-1.06	0.0006
Model 3			
MSM	1	-	-
IDU	0.58	0.47-0.71	<0.0001
Male heterosexual	0.45	0.43-0.48	<0.0001
Female heterosexual	0.36	0.34-0.39	<0.0001
Other	0.40	0.32-0.50	<0.0001

Factor	AOR	95% CI	P value
Year	1.17	1.16-1.17	<0.0001
Year*Other/unknown exposure	1.14	1.09-1.18	<0.0001

[1] All models adjusted for age, ethnicity, HIV exposure group, calendar year and HIV infection category

Figure 6.8 Changing probability of having a repeat anti-HCV test over time according to varying demographic factors

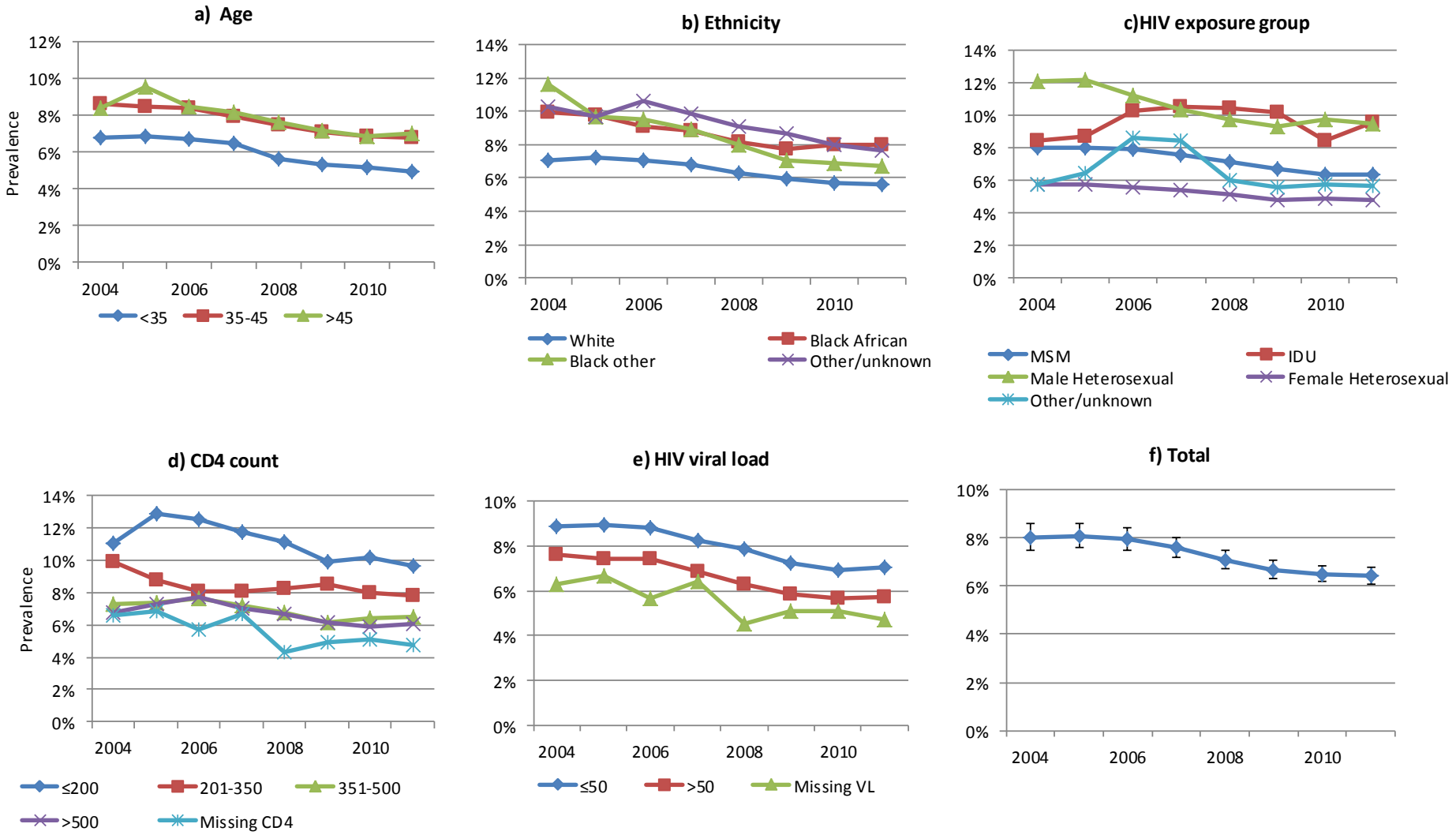


6.3.2 Epidemiology of HBV

6.3.2.1 Cumulative prevalence of HBV

Of 26377 individuals who had ever had an HBsAg test, 1778 had received at least one positive result, a prevalence of 6.7% (95% CI: 6.4-7.0%). In a sensitivity analysis, when all individuals were included in the denominator irrespective of whether they had ever been tested, the cumulative prevalence of HBsAg was 5.5% (1778/32079), 95% CI 5.3%-5.8%. Among individuals who were under follow-up in each year and had been tested for HBsAg the cumulative prevalence decreased from 8.0% in 2004 to 6.4% in 2011 (Figure 6.9). Given the differences in patterns of testing over time, the cumulative prevalence over time was also examined stratified by exposure category, ethnicity, age, CD4 count and HIV viral load. Cumulative prevalence decreased for all subgroups of age, and among all ethnicities. However, when stratified by HIV exposure category, although the prevalence of HBsAg decreased among MSM and male and female heterosexuals, it remained more stable among IDU and individuals of other or unknown HIV exposure group, with a slight rise in the period 2004 to 2006. From 2004 to 2011 there was a decrease in prevalence among all subgroups defined by CD4 count and viral load.

Figure 6.9 Cumulative prevalence of HBV infection, by calendar year, stratified by demographic and HIV clinical factors and for the total cohort



The baseline characteristics of individuals who ever had a positive HBsAg test result, compared with those who never receive a positive result are shown in Table 6.18.

Table 6.18 Baseline characteristics of individuals who have ever had a positive HBsAg test compared with those whose test results remain HBsAg-negative throughout their follow-up

	HBsAg-positive N=1778	%	HBsAg-negative N=24589	%	P value
Median age at first HBsAg test (years) (IQR)	36 (31, 42)	-	36 (30, 43)	-	0.42
Ethnicity					
White	960	54.0	15181	61.7	<0.0001
Black African	472	26.5	5320	21.6	
Other black	94	5.3	1230	5.0	
Other/unknown	252	14.2	2868	11.7	
HIV exposure group					
MSM	1031	58.0	14745	60.0	<0.0001
IDU	79	4.4	661	2.7	
Male heterosexual	309	17.4	2808	11.4	
Female heterosexual	263	14.8	4811	19.6	
Other/unknown	96	5.4	1574	6.4	
Year of first HBsAg test					
<1996	155	8.7	1359	5.5	<0.0001
1996-1999	143	8.0	1310	5.3	
2000-2004	574	32.3	6519	26.5	
2005-2009	730	41.1	11765	47.9	
2010-2012	176	9.9	3646	14.8	
Median CD4 at first HBsAg test (cells/mm^3) (IQR)	340 (180, 512)	-	404 (253, 577)	-	<0.0001
Median log HIV viral load at first HBsAg test(log$_{10}$ copies/ml) (IQR)	3.6 (1.7, 4.7)	-	3.5 (1.7, 4.7)	-	0.01

In univariable and multivariable analysis, older individuals were more likely to be HBsAg-positive (AOR, 95% CI: 1.05, 1.03-1.07 per 10 years). Compared to MSM, IDU were more likely to be HBsAg-positive (AOR, 95% CI: 1.33, 1.19-1.49) as were heterosexual males (AOR, 95% CI: 1.49, 1.40-1.58). Female heterosexuals and individuals of other or unknown exposure group were less likely than MSM to be HBsAg-positive. Compared to individuals of white ethnicity those of black African, black other and other/unknown ethnicities were all more likely to be HBsAg-positive. Overall, black African ethnicity was the strongest predictor of HBsAg

positivity: AOR 2.33 (95% CI, 2.15-2.52). Individuals whose HIV infection was classified as advanced were more likely than those who had controlled HIV infection to be HBsAg-positive. However, those who had unknown or uncontrolled (but not advanced) HIV infection were less likely to be HBsAg-positive than those with controlled HIV. Conversely, those with advanced HIV were significantly more likely than those with controlled HIV to be HBsAg-positive (AOR 1.40, 95% CI: 1.31-1.51) (Table 6.19). There was a significant interaction detected between IDU and year (AOR 1.05, p<0.0001). This corresponds with the more stable trends in prevalence in this group compared to those in other exposure categories, as seen in Figure 6.9. However, adjusting for this interaction did not alter the direction or significance of any of the other effects. No other significant interactions between year and demographic factors were identified.

6.3.2.2 Resolution of infection versus chronicity

Of 1778 individuals who had a positive HBsAg result, 384 (21.6%) could not be further classified as having chronic infection or resolving infection. Of 1394 individuals who could be further classified, 1169 (83.0%) had chronic infection and 225 (16.1%) resolved their infection in the 6 months after their first positive result. In multivariable analysis, individuals of black African ethnicity were less likely to resolve infection compared to those of white ethnicity (AOR, 95% CI: 0.50, 0.28-0.91). Although male and female heterosexuals and individuals in other or unknown HIV exposure groups were less likely to resolve infection, compared to MSM in univariable analysis, these associations were not significant in the multivariable model. Being on tenofovir either at time of first positive HBsAg test, or starting tenofovir within 6 months of first positive HBsAg test, did not appear to be associated with resolving infection in univariable analysis and therefore these variables were not entered into the multivariable model (Table 6.20). While HIV infection category at time of first positive HBsAg test was associated with resolving infection in univariable analysis, the only association which remained in the multivariable model was that between resolving infection and unknown HIV infection category.

Table 6.19 Univariable and multivariable logistic regressions analysis of time-updated factors associated with HBsAg positivity

		Univariable analysis			Multivariable analysis		
		OR	**95%CI**	**P value**	**AOR**	**95%CI**	**P value**
Age	(per 10 years)	1.08	1.05-1.10	<0.0001	1.05	1.03-1.07	<0.0001
Exposure	MSM	1	-	-	1	-	-
	IDU	1.39	1.24-1.55	<0.0001	1.33	1.19-1.49	<0.0001
	Heterosexual male	1.49	1.40-1.58	<0.0001	0.85	0.79-0.92	<0.0001
	Heterosexual female	0.71	0.67-0.76	<0.0001	0.39	0.36-0.43	<0.0001
	Other	0.86	0.76-0.96	0.01	0.7	0.62-0.79	<0.0001
Ethnicity	White	1	-	-	1	-	-
	Black African	1.37	1.30-1.44	<0.0001	2.33	2.15-2.52	<0.0001
	Black other	1.3	1.18-1.43	<0.0001	1.65	1.49-1.82	<0.0001
	Other	1.45	1.35-1.55	<0.0001	1.67	1.49-1.82	<0.0001
Year	(per year)	0.96	0.95-0.97	<0.0001	0.96	0.95-0.96	<0.0001
HIV infection category	Advanced	1.55	1.45-1.67	<0.0001	1.4	1.31-1.51	<0.0001
	Uncontrolled	0.78	0.74-0.82	<0.0001	0.78	0.74-0.82	<0.0001
	Controlled	1	-	-	1	-	-
	Unknown	0.72	0.67-0.78	<0.0001	0.72	0.66-0.78	<0.0001

Table 6.20 Univariable and multivariable logistic regression of baseline factors associated with resolving HBV infection

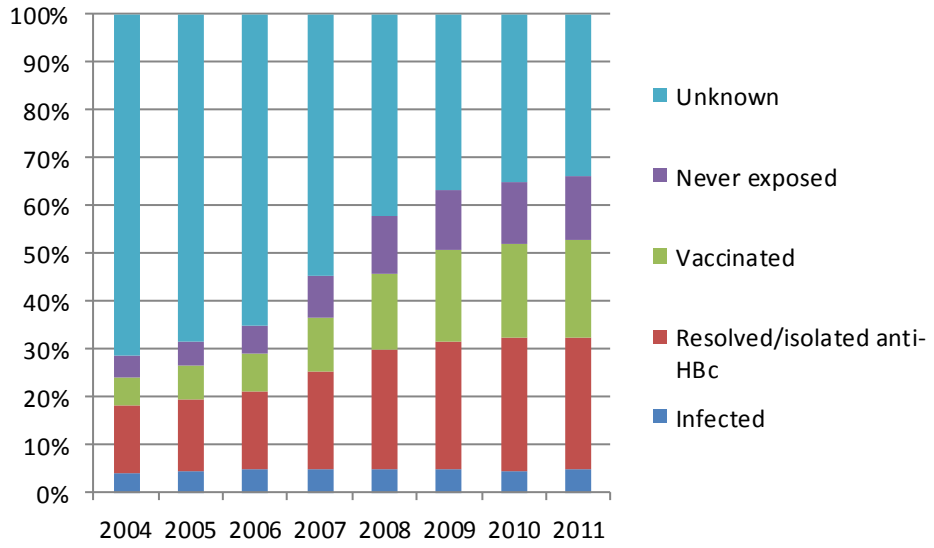
	HBV infection				Univariable analysis			Multivariable analysis		
	Resolve infection	**%**	**Chronic infection**	**%**	**OR**	**95%CI**	**P value**	**AOR**	**95%CI**	**P value**
Total	225	16.1	1169	83.9						
Median age (IQR)	37	(30, 43)	36	(31,42)	1.06	0.90-1.26	0.45			
Ethnicity										
White	144	18.0	656	82.0	1	-	-	1	-	-
Black African	33	9.9	302	90.2	0.50	0.33-0.74	0.001	0.50	0.28-0.91	0.02
Other black	12	17.1	58	82.9	0.94	0.49-1.80	0.86	1.01	0.51-1.98	0.99
Other/unknown	36	19.1	153	81.0	1.07	0.72-1.61	0.73	1.15	0.75-1.75	0.53
HIV Exposure										
MSM	162	18.2	730	81.8	1	-	-	1	-	-
IDU	9	18.0	41	82.0	0.99	0.47-2.08	0.98	1.00	0.47-2.12	0.99
Heterosexual male	27	12.0	198	88.0	0.61	0.40-0.95	0.03	0.85	0.48-1.50	0.57
Heterosexual female	20	11.7	151	88.3	0.60	0.36-0.98	0.04	0.92	0.48-1.80	0.80
Other/unknown	7	12.5	49	87.5	0.64	0.29-1.45	0.29	0.69	0.30-1.61	0.39
Year of first positive HBsAg										
<1996	24	21.1	90	79.0	1.39	0.84-2.29	0.20	1.25	0.74-2.14	0.41
1996-1999	32	24.8	97	75.2	1.71	1.09-2.71	0.02	1.64	1.02-2.64	0.04

	HBV infection				Univariable analysis			Multivariable analysis		
	Resolve infection	%	Chronic infection	%	OR	95%CI	P value	AOR	95%CI	P value
2000-2004	62	12.3	442	87.7	0.73	0.52-1.03	0.07	0.71	0.49-1.01	0.05
2005-2009	93	16.2	483	83.9	1	-	-	1	-	-
2010-2012	14	19.7	57	80.3	1.28	0.68-2.38	0.45	1.46	0.77-2.76	0.25
HIV infection category										
Advanced	54	16.1	282	83.9	1.22	0.81-1.84	0.35	1.54	1.00-2.37	0.05
Uncontrolled	77	16.5	391	93.6	1.25	0.86-1.83	0.24	1.38	0.93-2.04	0.11
Controlled	53	13.6	337	86.4	1	-	-	1	-	-
Unknown	41	18.6	159	72.3	1.64	1.05-2.57	0.03	1.84	1.16-2.94	0.01
On tenofovir at first positive HBsAg										
No	195	16.5	990	83.5	1	-	-			
Yes	30	14.4	179	85.7	0.85	0.56-1.29	0.45			
On tenofovir in 6 months after first positive HBsAg										
No	178	13.2	1169	86.8	1	-	-			
Yes	47	19.3	197	80.7	1.30	0.91-1.86	0.15			

6.3.2.3 Changes over time in HBV infection status

A total of 28338 individuals who had ever had a test for one of the three HBV markers of interest were included in the analysis of trends over time. Among these individuals the prevalence of HBV-infected status increased significantly over time from 3.9% in 2004 to 4.7% in 2008 (Chi-squared test for trend p= 0.01). Similarly, between 2004 and 2011 the proportion of individuals with an HBV resolved status increased from 14.3% to 27.4% (p<0.0001), the proportion of vaccinated individuals increased from 5.9% to 20.7% (p<0.0001) and the proportion of individuals never exposed to HBV increased from 4.6% to 13.2% (p<0.0001). Conversely, the proportion of individuals with an unknown HBV status decreased over time from 71.3% in 2004 to 34.0% in 2004 (Chi-squared test for trend p<0.0001) (Figure 6.10).

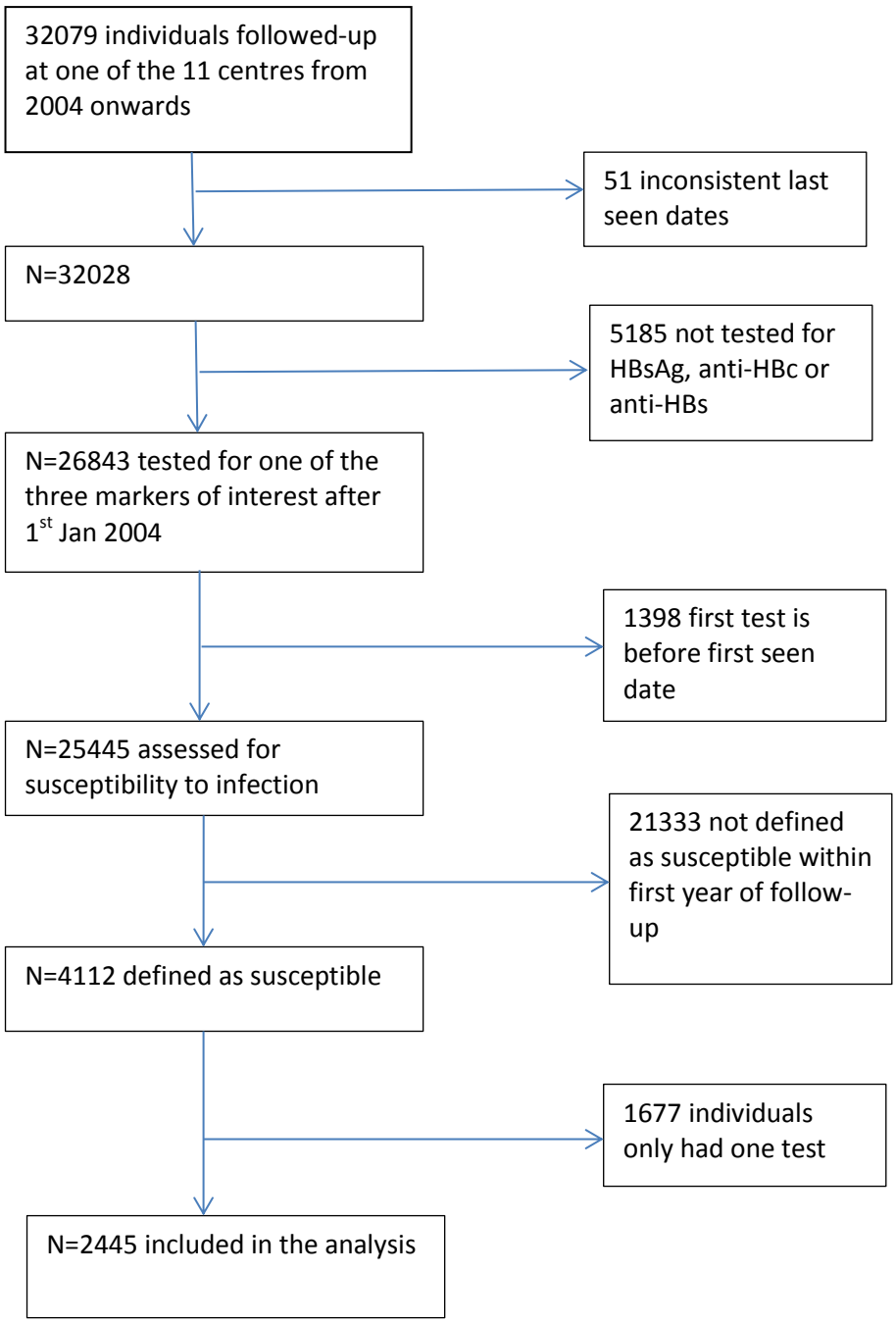
Figure 6.10 HBV infection status of individuals in the cohort, 2004-2011



6.3.2.4 Incidence of HBV infection

Details of individuals selected for inclusion in the analysis are shown in Figure 6.11. The 2445 included individuals contributed a total of 8962 person-years of follow-up. There were a total of 104 incident infections among these individuals giving an incidence rate of 1.16 infections per 100 person-years of follow-up (95% CI 0.94-1.38).

Figure 6.11 Selection of individuals included in analysis of HBV incidence



In sensitivity analysis 1, where individuals who had a positive anti-HBc or HBsAg after a positive anti-HBs were considered to have an incident infection at the point when they became anti-HBs positive, and in sensitivity analysis 2, where individuals who had a positive HBsAg or anti-HBc after a positive anti-HBs were considered to be individuals who had been vaccinated but had lost immunity the incidence rate increased to 1.35 per 100 person-years. In sensitivity analysis 3 where individuals had to have had a negative anti-HBs or HBsAg to be considered susceptible, a total of 3673 individuals were susceptible, of whom 2267 had a further test and

so were included in the analysis; 98 of these had an incident infection. Thus, the incident rate was increased to 1.18 per 100 person-years of follow-up (Table 6.21).

Table 6.21 Incidence rates of HBV infection calculated with varying methods

Method of calculation	Events/total person-years of follow-up	Incidence rate (per 100 person-years)	95% CI
Basic	104/8962	1.16	0.94-1.38
Sensitivity analysis 1	121/8964	1.35	1.11-1.59
Sensitivity analysis 2	121/8995	1.35	1.11-1.60
Sensitivity analysis 3	98/8310	1.18	0.95-1.41

Factors associated with HBV incidence are shown in Table 6.22. HIV exposure group and HIV viral load were the only variables where significant associations were observed. In multivariable analysis, individuals with higher HIV viral loads (>50 copies/ml) were more likely to have an incident infection than those with undetectable viral loads ($\leq$50 copies/ml) (ARR, 95% CI: 1.27, 1.09-1.47) and compared to MSM, female heterosexuals were less likely to have an incident HBV infection (ARR, 95% CI: 0.33, 0.16-0.65). There was no effect of age at first test, ethnicity, current CD4 count, being on a tenofovir containing HIV antiretroviral regimen, or year on the rate of incident infection.

Table 6.22 Univariable and multivariable Poisson regression of factors associated with HBV incidence

		Events / person-years	Incidence rate	Univariable analysis		Multivariable analysis	
				RR (95% CI)	P value	ARR (95% CI)	P value
Age at first test (years)	<35	36 / 2913	1.24	1	-	-	-
	35-45	35 / 3926	0.89	0.72 (0.45-1.15)	0.17	-	-
	>45	33 / 2124	1.56	1.26 (0.78-2.01)	0.34	-	-
Ethnicity	White	64 / 5784	1.11	1	-	-	-
	Black African	18 / 1740	1.03	0.93 (0.55-1.58)	0.80	-	-
	Black other	5 / 500	1.00	0.90 (0.36-2.25)	0.83	-	-
	Other/unknown	17 / 938	1.81	1.64 (0.96-2.80)	0.07	-	-
Exposure	MSM	75 / 5154	1.46	1	-	-	-
	IDU	1 / 198	0.51	0.35 (0.05-2.50)	0.29	0.35 (0.05-2.51)	0.29
	Male heterosexual	13 / 1267	1.03	0.70 (0.39-1.27)	0.24	0.7 (0.42-1.40)	0.36
	Female heterosexual	12 / 2010	0.60	0.41 (0.22-0.75)	0.004	0.33 (0.16-0.65)	0.002
	Other	3 / 334	0.90	0.62 (0.19-1.96)	0.41	0.44 (0.11-1.79)	0.25
Current CD4 (cells/mm^3)	≤200	9 / 706	1.27	1	-	-	-
	201-350	12 / 1747	0.69	0.99 (0.99-1.00)	0.21	-	-
	351-500	27 / 2279	1.18	1.00 (0.99-1.01)	0.83	-	-
	>500	50 / 3659	1.37	1.00 (0.99-1.01)	0.88	-	-
Current viral load (copies/ml)	≤50	53 / 5716	0.93	1	-	1	-
	>50	44 / 2650	1.66	1.79 (1.20-2.67)	0.004	1.27 (1.09-1.47)	0.002

		Events / person-years	Incidence rate	Univariable analysis		Multivariable analysis	
				RR (95% CI)	P value	ARR (95% CI)	P value
On tenofovir	Yes	40 / 3839	1.04	0.83 (0.56-1.24)	0.37	-	-
	No	64 / 5123	1.25	1	-	-	-
Year	2004-2005	7 / 921	0.76	1	-	-	-
	2006-2007	20 / 2413	0.83	1.09 (0.46-2.58)	0.84	-	-
	2008-2009	44 / 3143	1.40	1.84 (0.83-4.09)	0.13	-	-
	2010-2011	33 / 2485	1.33	1.75 (0.77-3.95)	0.18	-	-

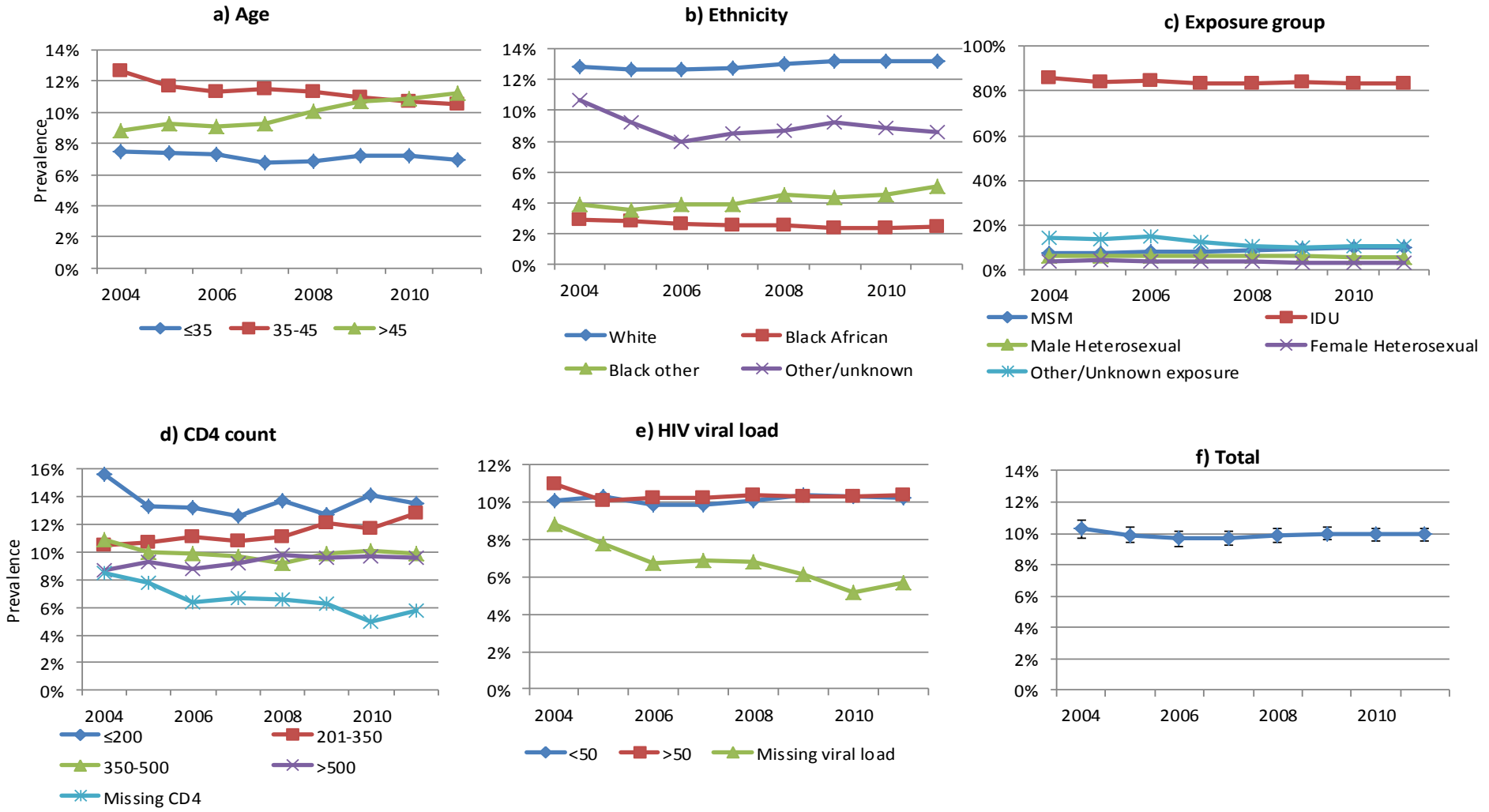
6.3.3 Epidemiology of HCV

6.3.3.1 Cumulative prevalence of HCV infection

Of the 28251 individuals who had ever been tested for anti-HCV or HCV-RNA, 2946 had ever had a positive result, a prevalence of 10.4% (95% CI 10.1-10.8%). In a sensitivity analysis where all individuals were included in the denominator, irrespective of whether or not they had ever been tested, HCV prevalence was 9.2% (95% CI 8.9-9.5%).

Cumulative prevalence of HCV among individuals under follow-up in each year remained relatively stable between 2004 (10.4%, 95% CI 9.7-10.9%) and 2011 (10.0%, 95% CI 9.6-10.4%). However, there were some differences in trends when the dataset was stratified by demographic and HIV clinical variables (Figure 6.12). When stratified by age, the cumulative prevalence appears to remain stable among those aged <35 years: 7.46% (95% CI: 6.6%-8.4%) in 2004 and 6.91% (95% CI: 6.9%-7.6%) in 2011. Among 35-45 year olds, however, the prevalence appears to have decreased over the same time period from 12.6% (95% CI: 11.7%-13.5%) in 2004 to 10.5% (9.8%-11.1%) in 2011 and among those over the age of 45 the prevalence increased from 8.8% in 2004 (95% CI: 7.6%-10.0%) in 2004 to 11.2% (95% CI: 10.5%-11.9%) in 2011. When stratified by exposure category the cumulative prevalence of HCV was highest among IDU and prevalence in this group remained stable over time: 85.7% (95% CI: 82.5%-88.8%) in 2004; and 83.3% (95% CI: 80.1%-86.5%) in 2011. In contrast, the prevalence was much lower in other exposure categories and among MSM the prevalence increases among from 7.3% (95% CI: 6.7%-7.9%) in 2004 to 9.9% (95% CI 9.4%-10.4%) in 2011.

Figure 6.12 Cumulative prevalence of HCV infection, by calendar year, stratified by demographic and HIV clinical factors and for the total cohort



The baseline characteristics of individuals who had ever had a positive test compared to those who have never received a positive test result are shown in Table 6.23.

Table 6.23 Baseline characteristics of individuals who have ever had a positive HCV test and those whose test results remain negative throughout their follow-up

	HCV-positive N=2946	%	HCV-negative N=25305	%	P value
Median age at first HCV test (years) (IQR)	36	(31, 41)	36	(30, 43)	<0.0001
Ethnicity					
White	2398	81.4	14630	57.8	<0.0001
Black African	159	5.4	6232	24.6	
Other black	69	2.3	1369	5.4	
Other/unknown	320	10.8	3074	12.1	
HIV exposure group					
MSM	1673	56.8	14860	58.7	<0.0001
IDU	695	23.6	140	0.5	
Male heterosexual	198	6.7	3191	12.6	
Female heterosexual	190	6.4	5516	21.8	
Other/unknown	190	6.4	1598	6.3	
Year of first HCV test					
<1996	205	7.0	404	1.6	<0.0001
1996-1999	392	13.3	1842	7.3	
2000-2004	978	33.2	6895	27.2	
2005-2009	1160	39.4	12304	4.9	
2010-2012	211	7.2	3660	14.5	
Median CD4 at first HCV test (cell/mm^3) (IQR)	400	(247, 580)	390	(240, 564)	0.03
Median log$_{10}$ viral load at first HCV test (copies/ml) (IQR)	3.8	(1.7-4.8)	3.7	(1.7, 4.7)	0.0004

Factors associated with ever having had a positive HCV test were investigated using a multivariable logistic regression model including calendar year and age, year and HIV infection category as time updated covariates (Table 6.24). Older individuals were more likely to have ever had a positive HCV test compared to younger individuals. Compared to white individuals, those of black African ethnicity were significantly less likely to have a positive HCV test (AOR,

95% CI: 0.22, 0.20-0.24) as were individuals of other black ethnicities (AOR, 95% CI: 0.34, 0.29-0.38) and individuals of other or unknown ethnicity (AOR, 95% CI: 0.62, 0.67-0.77). Injecting drug use was the strongest predictor of HCV positivity with an AOR of 55.16, 95% CI 50.63-60.10, compared to MSM, while male heterosexuals were also more likely than MSM to have a positive test (AOR, 95% CI: 1.27, 1.18-1.38). Calendar year was not significantly associated with HCV positivity in univariable analysis and therefore was not entered into the multivariable model. Compared to individuals defined as having controlled HIV infection there was no difference in the likelihood of those with uncontrolled HIV infection being HCV-positive. However, those with advanced HIV infection were more likely to be HCV-positive (AOR, 95% CI: 1.25, 1.26-1.35) and those with unknown HIV infection category were less likely to be HCV-positive (AOR, 95% CI: 0.65, 0.59-0.71).

Given the high prevalence of HCV among IDU (83% were HCV-positive), the model was rerun, excluding IDU in order to check that the strong association between injecting drug use and HIV infection was not masking any other associations. The associations between all other variables and HCV positivity remained unchanged. However, excluding IDU from the analysis introduced a small but statistically significant association between year and HCV positivity (AOR 1.03 per later year, 95% CI 1.02-1.04) (Table 6.25).

Table 6.24 Univariable and multivariable logistic regression of time updated factors associated with HCV positivity

		Univariable analysis			Multivariable analysis		
		OR	**95% CI**	**P value**	**OR**	**95% CI**	**P value**
Age group	<35	1	-	-	1	-	-
	35-45	1.64	1.57-1.73	<0.0001	1.45	1.37-1.53	<0.0001
	>45	1.49	1.41-1.57	<0.0001	1.17	1.10-1.24	<0.0001
Ethnicity	White	1	-	-	1	-	-
	Black African	0.17	0.16-0.19	<0.0001	0.22	0.20-0.24	<0.0001
	Black other	0.3	0.27-0.34	<0.0001	0.34	0.29-0.38	<0.0001
	Other	0.65	0.61-0.69	<0.0001	0.72	0.67-0.77	<0.0001
HIV exposure	MSM	1	-	-	1	-	-
group	IDU	53.89	49.54-58.62	<0.0001	55.16	50.63-60.10	<0.0001
	Heterosexual male	0.65	0.60-0.70	<0.0001	1.27	1.18-1.38	<0.0001
	Heterosexual female	0.37	0.35-0.40	<0.0001	0.93	0.86-1.01	0.09
	Other	1.31	1.20-1.43	<0.0001	1.93	1.76-2.11	<0.0001
Year	(per later year)	1	0.99-1.01	0.91			
HIV infection	Advanced	1.42	1.33-1.51	<0.0001	1.25	1.16-1.35	<0.0001
category	Uncontrolled	0.99	0.95-1.04	0.73	0.99	0.65-1.04	0.80
	Controlled	1	-	-	1	-	-

Table 6.25 Univariable and multivariable logistic regression of time updated factors associated with HCV positivity, excluding IDU

		Univariable analysis			Multivariable analysis		
		OR	**95% CI**	**P value**	**OR**	**95% CI**	**P value**
Age group (years)	<35	1	-	-	1	-	-
	35-45	1.57	1.48-1.65	<0.0001	1.44	1.36-1.52	<0.0001
	>45	1.42	1.34-1.51	<0.0001	1.14	1.07-1.21	<0.0001
Ethnicity	White	1	-	-	1	-	-
	Black African	0.23	0.21-0.25	<0.0001	0.22	0.20-0.24	<0.0001
	Black other	0.34	0.30-0.39	<0.0001	0.33	0.29-0.38	<0.0001
	Other	0.71	0.66-0.76	<0.0001	0.7	0.65-0.75	<0.0001
HIV exposure group	MSM	1	-	-	1	-	-
	IDU	N/A	N/A	N/A	N/A	N/A	N/A
	Heterosexual male	0.65	0.60-0.70	<0.0001	1.27	1.17-1.37	<0.0001
	Heterosexual female	0.37	0.35-0.40	<0.0001	0.92	0.85-1.00	0.06
	Other	1.31	1.20-1.43	<0.0001	1.87	1.71-2.05	<0.0001
Year	(per year)	1.03	1.02-1.04	<0.0001	1.03	1.02-1.04	<0.0001
HIV infection category	Advanced	1.07	0.99-1.16	0.11	1.28	1.18-1.39	<0.0001
	Uncontrolled	0.96	0.91-1.00	0.07	1	0.65-1.05	0.9
	Controlled	1	-	-	1	-	-

6.3.3.2 Active infection

Of the 2946 individuals who had evidence of HCV infection, 2608 (88.5%) had ever been tested for HCV-RNA and 2272 (87.1%) had ever received a positive result indicating active infection. The proportion of individuals with active infection in each year is shown in Table 6.26. The prevalence of active infection increased significantly over time between 2004 and 2011 (Chi-squared test for trend p=0.001). As a sensitivity analysis the proportion of individuals with active infection in each year was recalculated using a less strict definition of active infection. In this calculation, prior results were carried forward where no test was conducted within a given year.

Table 6.26 Proportion of anti-HCV positive individuals with active infection in each year

Year	Any evidence of HCV infection	Strict definition of active infection			Relaxed definition of active infection		
		Tested for HCV-RNA in year	Positive HCV-RNA test in year	%	Tested for HCV-RNA in year	Positive HCV-RNA test in year	%
2004	1072	372	234	62.9	372	234	62.9
2005	1285	453	292	64.5	614	402	65.5
2006	1449	436	278	63.8	785	509	64.8
2007	1659	708	467	66.0	1135	757	66.7
2008	1892	988	671	67.9	1499	1014	67.7
2009	2073	1065	730	68.5	1765	1192	67.5
2010	2182	1058	711	67.2	1919	1271	66.2
2011	2094	947	671	70.9	1860	1255	67.5

Factors associated with having active HCV infection (using the more strict definition) were investigated using logistic regression including calendar year. Age and HIV infection category were time updated at the start of each year. Generalised estimating equations were used to account for the inclusion of repeated tests for each individual. Results of this analysis are shown in Table 6.27. In univariable analysis, both age and HIV infection category were associated with having active infection. Exposure group, ethnicity and year were not found to be associated with having active HCV infection. When age and HIV infection category were entered into a multivariable model, only the association between HIV infection category and active HCV infection remained. Those individuals who had uncontrolled HIV infection were significantly more likely to have active infection than those with controlled HIV infection (AOR,

95% CI: 1.34, 1.16-1.53) as were those whose HIV infection category was unknown due to missing CD4 and viral load measurements (AOR, 95% CI: 2.27, 1.77-2.92).

Table 6.27 Univariable and multivariable logistic regressions analysis of factors associated with having active HCV infection

		Univariable analysis			Multivariable analysis		
		OR	**95% CI**	**P value**	**AOR**	**95% CI**	**P value**
Age group (years)	<35	1	-	-	1	-	-
	35-45	0.76	0.63-0.91	0.003	0.86	0.71-1.03	0. 01
	>45	0.73	0.59-0.89	0.002	0.86	0.69-1.06	0.16
Ethnicity	White	1	-	-	1	-	-
	Black African	0.94	0.62-1.42	0.78			
	Black other	0.96	0.56-1.67	0.90			
	Other	1.16	0.90-1.50	0.26			
Exposure	MSM	1	-	-	1	-	-
	Heterosexual male	1.14	0.94-1.39	0.19			
	Heterosexual female	1.30	0.90-1.88	0.16			
	Other	1.16	0.90-1.50	0.26			
Year	(per year)	0.98	0.95-1.00	0.08			
HIV infection category	Advanced	0.96	0.78-1.17	0.68	0.95	0.78-1.17	0.65
	Uncontrolled	1.36	1.19-1.56	<0.0001	1.34	1.16-1.53	<0.0001
	Controlled	1	-	-	1	-	-
	Unknown	2.34	1.84-2.99	<0.0001	2.27	1.77-2.92	<0.0001

6.3.3.3 Acute HCV infection

Of all individuals who had ever had evidence of HCV infection, 2138 received their first positive result at some time after the start of 2004. 1653 individuals had a positive RNA result from 2004 onwards and 267 had a negative anti-HCV test within the preceding 6 months and could therefore be classified as having acute infection. 408 individuals had a diagnosis of acute infection mentioned in their clinical notes. Of these 110 had also been defined as acute using their serological data. Combining all this information gave a total of 565 individuals with acute HCV infection. The characteristics of individuals defined as having acute infection are shown in Table 6.28.

Table 6.28 Characteristics of individuals defined as having acute HCV infection

	Total number with active infection	**Defined as acute**	**%**	**P value**
Total	1653	565	34%	
Median age at first positive HCV test (IQR)	39 (34, 44)	39 (34, 44)	-	0.23
Ethnicity				
White	1355	490	47%	0.0004
Black African	65	9	1%	
Other black	38	12	9%	
Other/unknown	195	54	3%	
HIV exposure group				
MSM	1140	518	47%	<0.0001
IDU	250	3	1%	
Male heterosexual	105	9	9%	
Female heterosexual	73	2	3%	
Other/unknown	121	33	27%	
Median CD4 at first positive HCV test (IQR)	457 (320, 626)	520 (380, 670)	-	<0.0001
HIV viral load at first positive HCV test				
Undetectable	840	306	37%	0.05
Detectable	813	259	32%	

Among the individuals with acute infection, 355 individuals had a single HCV-RNA test while 210 had a further HCV-RNA test, therefore the course of their infection could be examined. 145 individuals had a negative HCV-RNA result after their positive. Of these 63 had a

subsequent positive within the six months after the first positive test and therefore their negative test result was considered to be a temporary drop in viral load. Therefore 128 individuals with an acute infection were considered to have cleared the infection. Excluding those who had any evidence of HCV treatment (97 individuals), there were 31 individuals who could be classified as having acute infection which spontaneously resolved (14.8% ,31/210). Among those individuals who cleared infection without evidence of treatment the median time from first positive RNA test to first subsequent negative test was 5.2 months (IQR 2.6, 14.2 months). For 15 individuals the time from first positive HCV-RNA to evidence of cleared infection was greater than 6 months. The majority of individuals who cleared infection were white (83.3%), MSM (97%) and had undetectable HIV viral load $\leq$50 copies/ml), CD4 count was 490 cells/mm3 (IQR 340, 665).

6.3.3.4 Incidence of HCV

A total of 16386 individuals fulfilled the inclusion criteria for analysis of HCV incidence, that is they were known to be anti-HCV negative at the start of follow-up, and contributed a total of 76628 person-years to the analysis. Of these, 700 individuals had an incident infection during follow-up; an incidence of 0.91 per 100 person-years of follow-up. Overall, incidence appeared to remain stable over time: 0.82 per 100 person-years in 2004 (95% CI 0.46-1.36) and 0.88 (0.71-1.06) in 2011 as shown in Table 6.29.

Table 6.29 HCV incidence over time

Year	HCV incidence per 100 person-years (95% CI)					
	Total	MSM	IDU	Male heterosexual	Female heterosexual	Other exposure category
2004	0.82 (0.46-1.37)	1.03 (0.58-1.70)	0.00 (0.00-32.17)	0.00 (0.00-2.90)	0.00 (0.00-1.87)	0.00 (0.00-17.44)
2005	1.01 (0.74-1.28)	1.22 (0.89-1.56)	0.00 (0.00-11.36)	0.48 (0.06-1.74)	0.15 (0.00-0.85)	0.00 (0.00-4.68)
2006	0.84 (0.64-1.04)	1.02 (0.77-1.27)	6.97 (1.44-20.37)	0.42 (0.09-1.23)	0.00 (0.00-0.33)	0.00 (0.00-2.75)
2007	1.07 (0.87-1.28)	1.38 (1.11-1.64)	2.11 (0.00-11.74)	0.31 (0.06-0.91)	0.13 (0.02-0.47)	0.51 (0.00-2.83)
2008	0.96 (0.79-1.13)	1.21 (0.98-1.44)	3.21 (0.39-11.59)	0.17 (0.02-0.61)	0.10 (0.01-37)	1.74 (0.64-3.79)
2009	0.88 (0.72-1.04)	1.18 (0.96-1.40)	0.00 (0.00-5.84)	0.15 (0.02-0.54)	0.10 (0.01-0.33)	0.83 (0.27-1.93)
2010	0.83 (0.68-0.98)	1.03 (0.83-1.23)	0.00 (0.00-8.20)	0.22 (0.04-0.63)	0.09 (0.01-0.31)	1.64 (0.85-2.87)
2011	0.89 (0.71-1.06)	1.07 (0.83-1.30)	0.00 (0.00-2.90)	0.57 (0.21-1.24)	0.17 (0.03-0.49)	1.38 (0.60-2.73)

In multivariable Poisson regression, individuals over 45 years of age were significantly less likely than individuals under 35 to have an incident infection (ARR, 95% CI: 0.53, 0.42-0.68). Individuals of black African ethnicity were less likely than individuals of white ethnicity to have an incident HCV infection (ARR, 95% CI: 0.43, 0.25-0.72) as were individuals of other black ethnicities (ARR, 95% CI: 0.62, 0.39-0.98). Compared to MSM, male and female heterosexuals were less likely to have an incident HCV infection: ARR and 95% CIs 0.40, 0.25-0.65 and 0.15, 0.08-0.28, respectively. There was no difference in the likelihood of incident infection between MSM and IDU (ARR, 95% CI: 0.98, 0.37-2.62) or individuals with other or unknown HIV exposure category. Individuals with detectable HIV viral loads were more likely to have an incident infection than those with undetectable viral loads (ARR, 95% CI: 1.15, 1.08-1.22). There was no effect of year on HCV incidence (Table 6.30).

Table 6.30 Univariable and multivariable Poisson regression of factors associated with HCV incidence

		Events / person-years	Incidence rate	Univariable model		Multivariable model	
				RR (95% CI)	P value	ARR (95% CI)	P value
Age at first test (years)	<35	251/23759	1.06	1	-	1	-
	35-45	335/33566	1.00	0.98 (0.83-1.15)	0.77	0.96 (0.81-1.13)	0.62
	>45	99/17034	0.58	0.57 (0.45-0.72)	<0.0001	0.53 (0.42-0.68)	<0.0001
Ethnicity	White	586/51323	1.14	1	-	1	-
	Black African	22/13137	0.17	0.15 (0.10-0.22)	<0.0001	0.43 (0.25-0.72)	0.001
	Black other	19/3655	0.52	0.46 (0.29-0.71)	0.001	0.62 (0.39-0.98)	0.04
	Other/unknown	73/8514	0.86	0.75 (0.59-0.96)	0.02	0.82 (0.64-1.06)	0.13
Exposure	MSM	629/54619	1.15	1	-	1	-
	IDU	6/371	1.62	1.41 (0.63-3.14)	0.46	0.98 (0.37-2.62)	0.97
	Male heterosexual	21/7185	0.29	0.25 (0.16-0.39)	<0.0001	0.40 (0.25-0.65)	0.0002
	Female heterosexual	12/11764	0.10	0.09 (0.05-0.16)	<0.0001	0.15 (0.08-0.28)	<0.0001
	Other	32/2689	1.19	1.03 (0.72-1.47)	0.86	1.07 (0.72-1.58)	0.75
Current CD4 (cells/mm^3)	≤200	30/4441	0.68	1	-	-	-
	201-350	108/13792	0.78	1.00 (1.00-1.00)	0.49	-	-
	351-500	192/20301	0.95	1.00 (1.00-1.00)	0.07	-	-
	>500	340/34791	0.98	1.00 (1-00-1.01)	0.04	-	-
Current HIV viral load (copies/ml)	≤50	406/51065	0.79	1	-	1	-
	>50	263/22022	1.19	1.50 (1.29-1.75)	<0.0001	1.15 (1.08-1.22)	<0.0001

		Events / person-years	Incidence rate	Univariable model		Multivariable model	
				RR (95% CI)	P value	ARR (95% CI)	P value
Year	2004-2005	69/7170	0.96	1	-	1	-
	2006-2007	178/18329	0.97	1.01 (0.76-1.33)	0.95	1.04 (0.78-1.38)	0.81
	2008-2009	238/25905	0.92	0.95 (0.73-1.25)	0.73	1.05 (0.76-1.34)	0.73
	2010-2011	215/25224	0.85	0.89 (0.68-1.16)	0.38	1.01 (1.08-1.22)	0.95

6.3.3.5 HCV genotypes

Among 2272 individuals with any evidence of active infection, 1570 (69.1%) had at least one genotype reported and 989 had at least one subtype reported. The most commonly reported genotype in this cohort was genotype 1 with subtype "a" predominating (Table 6.31). A total of 197 individuals had more than one genotype reported. However, only 35 individuals had a subsequent genotype which was different to their first reported. Among individuals where the same genotype was reported more than once, 7 individuals had different subtypes reported.

Table 6.31 First reported HCV genotype and subtype among individuals with active HCV infection

Genotype	Subtype	Number of individuals	% of total
1	a	525	33.44%
	b	125	7.96%
	c	1	0.06%
	Unknown	423	29.94%
	Total	**1074**	**68.41%**
2	a	3	0.19%
	b	17	1.08%
	c	2	0.13%
	Unknown	21	1.34%
	Total	**43**	**2.74%**
3	a	191	12.17%
	b	1	0.06%
	Unknown	49	3.12%
	Total	**241**	**15.35%**
4	a	4	0.25%
	b	1	0.06%
	c	1	0.06%
	d	38	2.42%
	e	2	0.13%
	h	2	0.13%
	Unknown	153	9.75%
	Total	**201**	**12.80%**
6	Unknown	2	0.13%
	Total	**2**	**0.13%**
2/3	Unknown	9	0.57%
	Total	**9**	**0.57%**

Subsequent analysis excluded those individuals who were defined as having had reinfection. A total of 169 individuals were excluded (128 excluded on the basis of a serological definition, 24 excluded on the basis of changing genotypes or subtypes, and 17 excluded on the basis of serological data combined with genotype data).

Genotype 1 was the most common genotype irrespective of year of first positive test. However, from 1996 to 2010, the proportion of individuals with genotype 1 increased from 36.6% to 50.6% while the proportion of individuals with genotype 3 infections decreased from 17.1% to 9.3% and the proportion of individuals with unknown or other genotypes decreased from 39.0% to 32.6%. When stratified by risk group, the proportion of individuals infected with genotype 1 increased among MSM, male and female heterosexuals and individuals of other ethnicity while the proportion of IDU infected with genotype 1 remained stable. Similarly, while remaining stable among IDU, the proportion of individuals who were infected with an unknown or other genotype decreased among MSM, male and female heterosexuals and individuals of other/unknown exposure category (Figure 6.13).

The baseline characteristics of individuals with each genotype are shown in Table 6.32. In multinomial regression using genotype 1 as the reference category, exposure category had the strongest association with genotype. IDU and female heterosexuals were more likely than MSM to be infected with genotype 2 than genotype 1: AOR and 95% CI: 2.64, 1.14-6.14; and 4.07, 1.13-14.6, respectively. IDU and male and female heterosexuals were all more likely than MSM to be genotype 3: AORs and 95% CI 4.1, 2.7-6.1; 9.5, 4.8-18.8; and 5.2, 2.7-10.1 respectively. Male heterosexuals were also more likely than MSM to be infected with genotype 4 HCV (AOR, 95% CI: 2.71, 1.31-5.60) or have other/unknown genotypes (AOR, 95% CI: 1.84, 1.08-1.43). Year of first positive HCV test was also associated with the likelihood of being infected with different genotypes; compared to individuals with a first positive HCV test in 2006-2010, individuals whose first positive test was in the period 1996-2000 were more likely to be infected with genotype 3 than genotype 1 (AOR, 95% CI: 1.93, 1.04-3.58), as were individuals with a first positive HCV test in the period 2001-2005 (AOR, 95% CI: 1.58, 1.02-2.47). Individuals in these two groups were also more likely than individuals with a first positive test in 2006-2010 to have other or unknown genotypes than genotype 1 (Table 6.33).

Figure 6.13 Proportion of individuals infected with each HCV genotype according to year of first positive HCV test, stratified by HIV exposure category

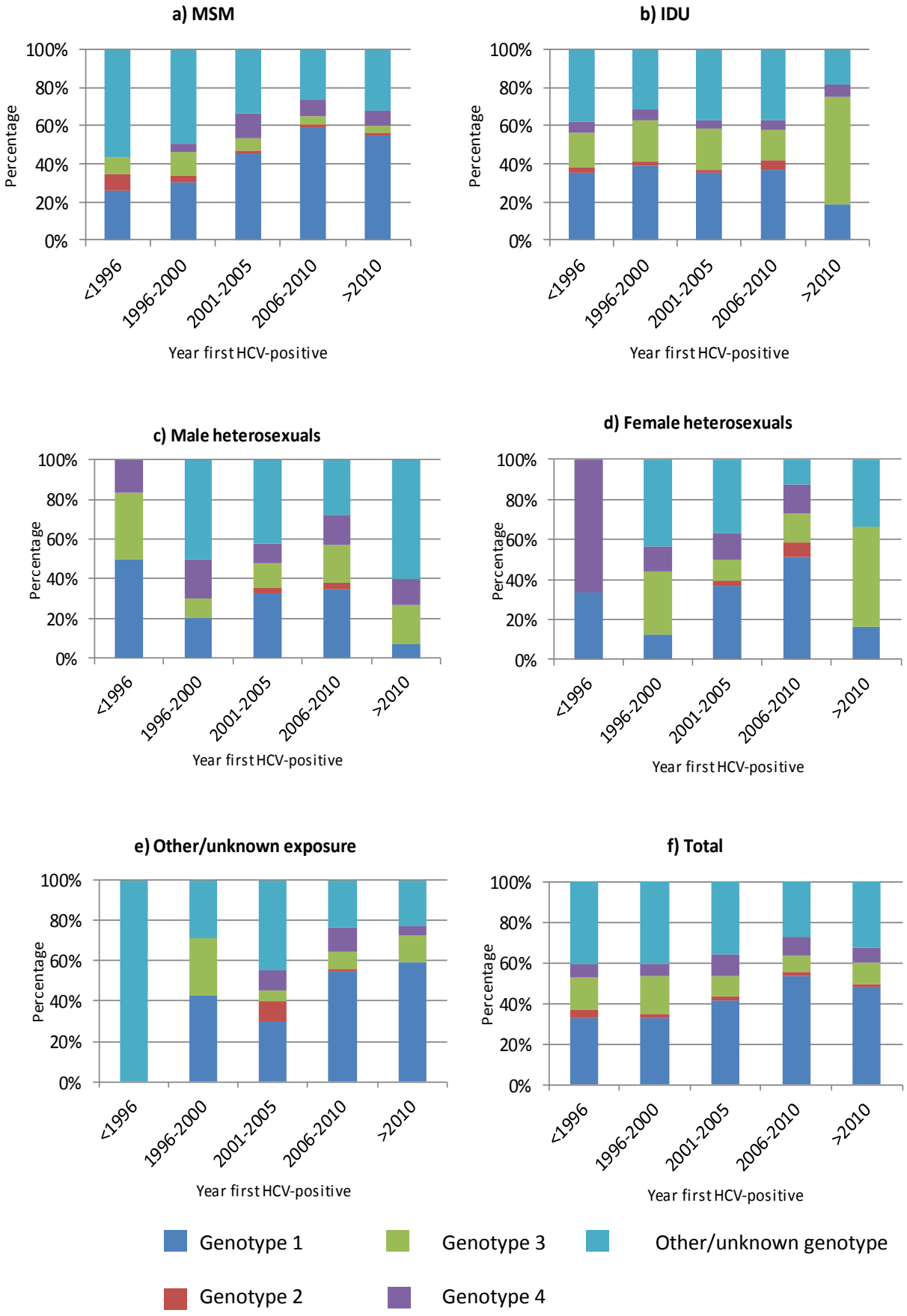


Table 6.32 Baseline characteristics of individuals infected with different HCV genotypes

	Genotype 1 n (%)	Genotype 2 n (%)	Genotype 3 n (%)	Genotype 4 n (%)	Other/ unknown genotype n (%)	P value
Median age (years) (IQR)	38 (33, 43)	38 (35, 45)	36 (31, 42)	39 (35, 44)	38 (32, 43)	0.02
Median CD4 count (cells/mm^3) (IQR)	450 (310, 610)	415 (320, 620)	390 (223, 545)	459 (302, 627)	415 (265, 598)	0.004
Log$_{10}$ HIV viral load (copies/ml) (IQR)	2.1 (1.7, 4.5)	2.2 (1.7, 3.8)	3.2 (1.7, 4.5)	1.7 (1.7, 4.5)	3.1 (1.7, 4.6)	0.01
Year of entry into UK CHIC						
1996-1999	404 (44.4)	20 (2.2)	114 (12.5)	73 (8.3)	296 (35.6)	0.0003
2000-2004	248 (46.7)	6 (1.1)	37 (7.0)	55 (10.4)	185 (34.8)	
2005-2009	281 (51.4)	12 (2.2)	51 (9.3)	45 (8.2)	158 (28.9)	
2010-2011	44 (37.9)	2 (1.7)	21 (18.1)	9 (7.8)	40 (34.5)	
Ethnicity						
White	834 (47.7)	34 (1.9)	197 (11.3)	142 (8.1)	543 (31.0)	<0.0001
Black African	21 (27.6)	2 (2.6)	1 (1.3)	16 (21.1)	36 (47.4)	
Black other	24 (54.6)	1 (2.3)	3 (6.8)	4 (9.1)	12 (27.3)	
Other/unknown	98 (42.1)	3 (1.3)	22 (9.4)	22 (9.4)	88 (37.8)	
HIV exposure category						
MSM	659 (52.3)	17 (1.4)	73 (5.8)	114 (9.1)	397 (31.5)	<0.0001
IDU	170 (36.2)	13 (2.8)	96 (20.4)	24 (5.1)	167 (35.5)	
Male heterosexual	39 (30.2)	3 (2.3)	22 (17.1)	18 (14.0)	47 (36.4)	
Female heterosexual	39 (37.5)	4 (3.9)	18 (17.3)	15 (14.4)	28 (26.9)	
Other	70 (50.0)	3 (2.1)	14 (10.0)	13 (9.3)	40 (28.6)	
Year of first positive HCV test						
<1996	35 (33.0)	4 (3.8)	17 (16.0)	6 (6.6)	43 (40.6)	<0.0001
1996-2000	70 (32.7)	5 (2.3)	39 (18.2)	13 (6.1)	87 (40.7)	
2001-2005	246 (41.5)	10 (1.7)	63 (10.6)	62 (10.5)	212 (35.8)	
2006-2010	520 (53.6)	19 (2.0)	80 (8.2)	86 (8.9)	266 (27.4)	
>2010	106 (48.4)	2 (0.9)	24 (11.0)	16 (7.3)	71 (32.4)	

Table 6.33 Multinomial logistic regression of factors associated with infection with different HCV genotype

	AOR (95% CI)				
	Genotype 1	**Genotype 2**	**Genotype 3**	**Genotype 4**	**Other/ unknown genotype**
Age (per 10 years older)	1	1.37 (0.89-2.10)	0.90 (0.72-1.12)	1.18 (0.96-1.47)	1.00 (0.86-1.14)
CD4 count (per 100 cells/mm^3 higher)	1	1.06 (0.93-1.21)	0.97 (0.91-1.04)	1.06 (0.99-1.13)	0.98 (0.94-1.03)
Year of entry into UK CHIC					
1996-1999	1	1	1	1	1
2000-2004	1	0.67 (0.24-1.85)	0.58 (0.36-0.94)	1.04 (0.68-1.60)	0.92 (0.70-1.19)
2005-2009	1	1.03 (0.39-2.72)	0.66 (0.40-1.09)	0.98 (0.60-1.61)	0.99 (0.73-1.33)
2010-2011	1	2.10 (0.38-11.6)	2.15 (0.99-4.67)	1.72 (0.69-4.28)	1.82 (1.06-3.13)
Ethnicity					
White	1	1	1	1	1
Black African	1	1.19 (0.22-6.51)	-	2.55 (1.10-5.91)	2.48 (1.31-4.69)
Black other	1	1.11 (0.14-8.81)	0.48 (0.14-1.74)	0.54 (0.12-2.37)	0.96 (0.48-1.92)
Other/unknown	1	0.79 (0.23-2.69)	0.93 (0.54-1.59)	1.41 (0.84-2.35)	1.33 (0.97-1.84)
HIV exposure category					
MSM	1	1	1	1	1
IDU	1	2.64 (1.14-6.14)	4.10 (2.74-6.14)	0.65 (0.37-1.15)	1.08 (0.81-1.43)
Male heterosexual	1	4.43 (1.11-17.60)	9.53 (4.84-18.77)	2.71 (1.31-5.60)	1.84 (1.08-1.43)
Female heterosexual	1	4.07 (1.13-14.60)	5.19 (2.66-10.14)	1.40 (0.65-3.02)	0.66 (0.37-1.17)
Other	1	1.28 (0.28-5.91)	1.51 (0.73-3.16)	0.86 (0.41-1.82)	0.77 (0.49-1.20)
Year of first positive HCV test					
<1996	1	2.43 (0.51-11.50)	1.04 (0.43-2.49)	1.81 (0.61-5.39)	2.13 (1.16-3.92)
1996-2000	1	2.14 (0.62-7.39)	1.93 (1.04-3.58)	1.46 (0.66-3.21)	2.57 (1.68-3.93)
2001-2005	1	1.05 (0.41-2.68)	1.58 (1.02-2.47)	1.63 (1.07-2.49)	2.27 (1.75-2.94)
2006-2010	1	1	1	1	1
>2010	1	0.43 (0.09-2.09)	1.26 (0.67-2.36)	0.73 (0.39-1.39)	1.13 (0.79-1.63)

6.4 Discussion

6.4.1 Summary

In this chapter I have presented the patterns of testing for HBV and HCV, and estimated prevalence and incidence of the two infections. These data show that while a high proportion of individuals in the cohort have tested for HBsAg and/or anti-HCV (82.2% and 87.6% respectively), the level of annual testing, as recommended in clinical guidelines, remains low. While the proportion of individuals ever tested for either infection has increased over time among all HIV exposure categories, it appears that the overall change is being driven by an increase in testing among MSM. I also report a decrease over time in the proportion of individuals whose HBV status cannot be classified, indicating that either testing or the reporting of these tests has increased.

The estimated prevalence of HBV and HCV among individuals who have been tested is 6.7% and 10.4% respectively and there is on-going incidence of both infections (estimated at 1.2 per 100 person-years for HBV and 0.91 per 100 person-years for HCV). IDU have the highest prevalence of both HBV and HCV. However, this is much more pronounced in HCV where the prevalence among IDU is 82.9% compared to 3.3%-10.1% in other risk groups. By contrast, the prevalence of HBV in IDU was 10.7% compared to 5.2%-9.9% in other risk groups. While the cumulative prevalence of HBV has decreased year on year from 2004 to 2011, the cumulative prevalence of HCV appears to have remained stable in the cohort over the same time period. However, this stable prevalence of HCV in the cohort overall is masking a steady increase in prevalence among MSM. I report a low level of clearance of HBsAg (16.1% with a resolved infection status after an infected status) and HCV (16.3% of acute HCV spontaneously resolving), indicating a high burden of chronic infections. A high proportion of individuals infected with HCV are shown to have active infection in each year. This pool of active infection is likely contributing to on-going incidence of the infection. Among individuals with active HCV infection genotype 1 is the most common followed by genotype 3. Genotype 3 was seen more commonly among IDU and heterosexuals than among MSM.

6.4.2 Interpretation of results

6.4.2.1 Patterns of testing

The significant interactions between time and demographic factors (in particular ethnicity and HIV exposure group) in the models of first HBsAg and first anti-HCV test reveal how patterns of testing have changed over time. In earlier years the probability of having a first HBsAg test and

that of having a first anti-HCV test was greatest among black African individuals than among white individuals. However, the probability of having a first test increased more among white individuals so that in later years white individuals had a higher probability of first test. Similarly, the probability of having a first HBsAg test and that of having a first anti-HCV test increased more among MSM over time than among any other group.

The overall increase in testing, combined with the changes in probability of testing among subgroup, may be an indication of less selective testing in more recent years. While sex between men is a known risk factor for HBV infection the majority of reported infections are the result of sex between men and women and HBV prevalence is highest among individuals of black and minority ethnic groups (83). The changes in patterns of first HBsAg test among subgroups may indicate that clinicians are moving away from targeted testing of black African individuals and are beginning to consider sex between men as an increasingly important risk factor for infection. While injecting drug use remains the greatest risk factor for HCV infection in the UK, there have been recent outbreaks of HCV infection reported among MSM. The changes in the patterns of a first anti-HCV test may represent a response to these outbreaks of HCV infection among MSM. In models of both first HBsAg and first anti-HCV test, being of unknown HIV infection category (i.e. having no data on CD4 count and no data on HIV viral load) was a strong predictor of first test. This may indicate that individuals are being screened for hepatitis infection at their first attendance (as recommended by guidelines), prior to the results of initial HIV viral load and CD4 tests.

Repeat testing for HBsAg increased over time until 2009 but then declined from 2009 onwards. This same pattern was not seen for anti-HCV testing and the reasons for it are unclear. One possibility is that individuals have been defined as eligible for repeat testing when in fact they are not. This may be the case where data on anti-HBs data is missing where individuals may have received HBV vaccination and/or are immune. For these immune individuals, testing for HBsAg would be unnecessary. Stratification by exposure group showed that the increase in repeat HBsAg testing (prior to 2009) was greater among MSM than among IDU and greater among white individuals than among black Africans. The patterns were similar to those seen for first testing. However, for repeat anti-HCV testing fewer interactions between time and demographic variables were present, indicating that repeat testing for anti-HCV had increased more consistently across subgroups.

6.4.2.2 Epidemiology of HBV

The prevalence of HBV is greatest among those subgroups known to be at highest risk of infection in the general population: IDU and black African individuals. The associations seen between HBV-positivity and HIV infection category are difficult to interpret as temporality cannot be assessed. For example, individuals with uncontrolled HIV infection were significantly more likely to be HBsAg-positive than individuals with controlled HIV infection. This could be interpreted as HBV infection leading to increased progression of HIV infection, or it could be interpreted as uncontrolled HIV infection leading to higher likelihood of acquiring HBV. However, the data within UK CHIC only provides information on the dates that an individual was tested and not the true date of infection. Therefore the causality in either direction cannot be ascertained. Conversely, having advanced HIV infection was associated with decreased likelihood of HBsAg positivity. However, it should be noted that higher HIV viral load was also associated with incident HBV infection. Previous studies have found no evidence of the impact of HBV on progression of HIV (258, 302, 303).

The decrease in prevalence over time among all subgroups, with the exception of IDU, may represent the success of vaccination for HBV, which is targeted at high risk individuals, particularly in sexual health clinics. Indeed, the proportion of individuals defined as having a vaccinated status has increased over time in this cohort. However, ongoing incidence of HBV infection indicates that there remains a need to ensure that all susceptible individuals are vaccinated for HBV. This decrease in prevalence also needs to be interpreted in the context of increases in testing. If the overall increase in testing has led to an increase in the number of lower risk individuals being tested, this will, in turn, lead to an increase in the denominator. If the numerator has not increased to the same degree and this would be observed as a decrease in prevalence. Similarly, the incidence of HBV remained steady over the period studied. However, if the denominator has increased due to higher rates of testing, but the numerator has not increased to the same extent, as a higher proportion of low risk individuals are tested, increases in incidence may be masked.

6.4.2.3 Epidemiology of HCV

While the prevalence of HCV infection is greatest among IDU, the importance of MSM as a risk group for HCV was confirmed by the increases in prevalence in this group over time as well as the ongoing incidence which is higher in MSM than in any other risk group. The incidence of HCV infection is low among IDU due to the small numbers classified as susceptible to infection. Among this group, HCV is usually acquired soon after they start injecting. In addition, among

individuals with active infection, the prevalence of acute infection was highest among MSM. This may, in part, be a reflection of the higher levels of testing among MSM in recent years. However, it is clear that, in this cohort MSM are at increased risk of HCV infection. The proportion of male heterosexuals who are positive for anti-HCV is lower than the proportion of MSM who are positive for anti-HCV and in univariable analysis, male heterosexuals were less likely to be HCV-positive than MSM. However, in multivariable analysis, this association was reversed and heterosexual males were more likely to be anti-HCV positive than MSM. In order to investigate the reasons for this, other variables were removed from the model in turn. This process identified that the reversal in the direction of association between anti-HCV positivity and heterosexual HIV exposure was due to adjusting for ethnicity. A possible explanation for this is that some males are misclassified as heterosexual where in fact they are MSM or IDU. If this misclassification occurred differentially in particular ethnic groups and those individuals who were misclassified were at increased risk of infection, this could result in the association of male heterosexual risk with anti-HCV prevalence after ethnicity is added to the model. For example, before adjusting for ethnicity, the effect of heterosexual male group on HCV prevalence is predominantly capturing the effect of black African males (who are low risk for HCV infection). However, after adjusting for ethnicity the effect of black African ethnicity on risk of HCV is removed and it is possible that the remaining association is now capturing the effect of men who are IDU but who are misclassified as heterosexual males.

The process of expanded data collection resulted in ascertainment of HCV genotype for the majority of individuals known to have active infection. In the UK CHIC cohort, there was an association between HCV genotype 3 infection and injecting drug use and heterosexual HIV exposure groups. A systematic review of HCV epidemiology across Europe, Canada and Israel found that genotype 3 HCV infection was more common in countries where IDU was the main reason for HCV infection (123). In addition several studies have found an association between IDU and HCV genotype 3 infection both in the UK (477, 478) and elsewhere in Europe (479, 480). Therefore the association of genotype 3 infection with male heterosexual exposure and IDU categories supports the theory that some IDU may have been misclassified as male heterosexuals.

6.4.3 Comparisons with published literature

The proportions of individuals tested in these analyses are higher than those previously reported for the same cohort (244, 259). There are a number of possible reasons for this. Firstly, the present analyses were limited to patients who have been followed since 2004

onwards. Patients who died or who were lost to follow-up in earlier years may have been less likely to have had a hepatitis test and therefore excluding these individuals from our analysis would lead to an increase in the estimated proportion tested. Secondly, the expanded hepatitis data collection included supplementing the existing serology data where additional information was contained within the clinical notes, therefore further tests may have been added. Finally, it is possible that individuals who attended centres not included in this analysis, which were included in the previous analyses, are less likely to have tested. A 2009-2010 BHIVA audit of 140 sites providing HIV care reported that only 71% of centres tested annually for HBsAg or anti-HBc and only 66% of centres tested annually for anti-HCV (481).

In these analyses the prevalence of HBsAg is consistent with that reported by Price et al (259). The prevalence of HCV is greater than that reported by Turner et al (244). There are a number of possible reasons for this. Firstly there may be difference in the clinic populations included in each analysis. Turner et al included all data in UK CHIC from 1996-2007, by contrast I have presented data from 11 selected centres from 2004 onwards. As previously shown (Chapter 3, section 3.2.6), the cohort of individuals included in the analyses presented in this chapter has a higher proportion of males, a higher proportion of MSM and a higher proportion of white individuals. Secondly, the difference in the prevalence of HCV presented in this chapter and that presented by Turner et al may be due to improved data quality, in particular in the reporting of HCV-RNA testing. In order to assess prevalence of HCV infection in the analyses presented in this chapter, both anti-HVC and HCV-RNA tests were used. Therefore those individuals who had been diagnosed with acute HCV infection (HCV-RNA positive and anti-HCV negative or missing) were included. This had not been possible in the previous analysis since the numbers tested for HCV-RNA were small. Finally, the higher prevalence of HCV seen in the present analysis compared to the analysis by Turner et al (244), may also be due to the impact of increased transmission of HCV among MSM which has been reported elsewhere (234, 235, 238). My estimates of prevalence are lower than those seen in many cohorts in other countries (Chapter 2 Table 2.1). This is likely due to the lower number of individuals in UK CHIC who acquired their HIV infection through injecting drug use.

The analysis presented in this chapter resulted in a lower incidence of HBV than previously reported by Price et al (259). The improvement in data as a result of the data collection process may have increased the proportion of individuals who could be classified as susceptible but who did not become infected, which may have resulted in a lower incidence.

Alternatively, it may be that there has been a decrease in incidence since the earlier years which were included in the analysis by Price et al but were excluded from my own analysis. This is the first estimate of HCV incidence in a large cohort of HIV-positive individuals in the UK. However, the finding that HCV incidence is significantly lower among heterosexuals compared to MSM is in agreement with other published work reporting incidence (235, 482-484) and outbreaks of HCV among HIV-positive MSM (232-234).

6.4.4 Strengths and weaknesses

These analyses are based on a large cohort of HIV-positive individuals attending a variety of centres across England and Scotland. The process of expanded data collection for hepatitis co-infected individuals has resulted in an increase in the volume of serological data for those individuals who have co-infection. However, I report that more than 20% of individuals are without any reported HBsAg tests and 12% do not have any tests for anti-HCV reported. It was not within the scope of the data collection process to review the testing history of all HIV-positive individuals at each centre and therefore it is possible that there are still missing data for some individuals who are not thought to be co-infected based on currently available data. This missing data may affect estimates of prevalence and incidence of HBV and HCV co-infection. However, the sensitivity analyses described in this chapter indicate that even with missing data included the estimates would not change substantially. Since these data are based on laboratory testing and individuals may be seen at more than one centre (including centres which do not contribute to UK CHIC) it is possible that individuals may have additional tests performed elsewhere and if the centre where the test was conducted is not part of UK CHIC we would be unaware of the test or the results.

As discussed previously (Chapter 5, section 5.4.3), the data on anti-HBs tests are lacking and therefore ascertainment of an individual's vaccine induced immunity is limited. This missing data may affect the number of individuals who can be defined as susceptible and are therefore included in the analysis of HBV incidence. Further work is required to improve the quality of data for those individuals who are not co-infected, in particular to gather data on anti-HBs tests so that vaccination status can be assessed.

Individual's testing patterns, in part, depend on their attendance patterns at a centre and, in part, on the practices within a centre. If an individual attends infrequently, there is less opportunity for them to be tested regularly for hepatitis infection. The UK CHIC data set does currently not include a variable which measures frequency of attendance. Therefore it was not

possible to include this in the analysis. Work in ongoing as part of another UK CHIC project, the REACH study, to develop methods for assessing frequency of attendance. Once this work is complete it would be useful to include a measure of attendance in the analyses of repeat testing since frequency of attendance impacts the number of opportunities which an individual has to test.

Independently of an individual's attendance pattern, some clinicians may choose to offer tests less or more regularly depending how "at-risk" they perceive an individual to be. These differences in testing, in combination with movement between clinics that do not contribute to UK CHIC, mean that it is not possible to ascertain the date on which an individual became infected with HBV or HCV. While it was possible to define acute HCV infection where an individual had a negative test in the preceding 6 months before their first positive, this resulted in small numbers of individuals being identified as having acute infection. In addition I have shown that a high proportion of individuals with HBV have chronic infection. However this should not be an estimate of the proportion of individuals who progress from acute to chronic infection since it is possible that these individuals were already chronically infected before the first positive result appears in the UK CHIC dataset.

Individuals in UK CHIC are assigned to only one HIV exposure category. The expanded data collection aimed to collect information on whether an individual had ever injected drugs as well as their sexual orientation at the time of hepatitis acquisition or diagnosis for those individuals who were co-infected. However, as these data were only collected for those individuals who were co-infected it is not possible to include it in analyses of prevalence or incidence. It is therefore possible that some individuals who are recorded in UK CHIC as having acquired their HIV infection through sex between men or through heterosexual sex do, in fact, have a history of injecting drug use which may or may put them at additional risk of acquiring hepatitis.

In UK CHIC an individual's ethnicity is recorded rather than their country of birth. This is due to the recognition that black African ethnicity is a risk factor for HIV infection. However, in the case of HBV infection, ethnicity may be less important than country of birth since country of birth is a major risk factor for acquiring HBV through vertical transmission and therefore is also a major risk factor for developing chronic HBV infection. Therefore in the epidemiology of HBV

infection country of birth information could lead to a more in depth understanding of the patterns of infection. However, we were unable to examine this using the UK CHIC dataset.

In the analysis of genotypes individuals were excluded where they were defined as having had a possible reinfection since it was not possible to assign the genotype to the correct infection. However, the definition used to define reinfection was broad since information on treatment was not included in this analysis. The definition of 6 months of negative results followed by a positive result may include some individuals who have 6 months of negative results while on treatment but who rebound when treatment ceases. Therefore the number of individuals here does not represent an accurate description of the proportion of individuals who are re-infected. In order to examine reinfection in detail, further analysis, including outcomes of treatment, would be necessary. However, this definition was chosen to be inclusive and therefore exclude all possible situations where a reinfection may be the case. The possible over-estimation of the number of individuals with a reinfection may reduce the number of individuals included further than is necessary and therefore, reduce the power of the analysis. However, this over estimation should not introduce any bias into the analysis as there is no reason to believe that the any genotype would be more likely to be excluded on this basis than any other.

6.4.5 Conclusions

While the prevalence of HBV and HCV is lower among this UK cohort than seen in other countries, there are still more than 3000 individuals with some evidence of hepatitis co-infection. Within clinics, in the context of high levels of HIV viral load suppression, the care of individuals with hepatitis co-infection represents a substantial proportion of the workload. The ongoing incidence, particularly of HCV among MSM, emphasises the importance of prevention. While the majority of individuals in this cohort have been tested for HBV or HCV at least once the rates of annual testing are low. Testing for HBV and HCV not only provides access to appropriate treatment for those who are diagnosed, but can also be the gateway to vaccination for those who are not immune to HBV and facilitates discussion about practices to reduce the risk of acquiring HCV.

Chapter 7 Results 2: HCV treatment strategies and outcomes

7.1 Background

In the absence of HCV treatment ~85% of individuals infected with HCV will go on to develop chronic infection (326). Compared to HCV mono-infected individuals, HIV/HCV co-infected individuals have accelerated progression of liver disease (332) and increased risk of HCC (335) and mortality (252, 291). Therefore the provision of successful treatment for HCV is important in improving clinical outcomes for co-infected individuals.

Until recently, standard treatment for HCV has been a combination of pegylated-interferon and ribavirin (204). Treatment for HCV with this combination of drugs is long (usually 48 weeks), requires weekly injections and can induce side effects which make it difficult to continue with treatment such as anaemia, neutropenia and severe depression (485, 486). Therefore, while there is substantial evidence for the efficacy of pegylated-interferon and ribavirin treatment in HIV co-infected individuals from clinical trials, the long duration of treatment and the potential for side effects and adverse events while on treatment means that, in practice, individuals may not complete courses of treatment, may have treatment breaks or may be considered ineligible for treatment due to co-existing physical or mental health conditions (186, 487-489).

The aim of HCV treatment is an SVR, defined as a negative HCV-RNA test 6 months after treatment has ceased. Among HIV/HCV co-infected individuals, achievement of an SVR is associated with a reduction in the risk of liver-related events such as death, HCC, decompensation and transplant (490) and it may reverse the fibrosis and cirrhosis caused by HCV infection (404). The overall proportion of HIV/HCV co-infected individuals who achieve SVR to pegylated-interferon with ribavirin treatment has been estimated as 37% in clinical trials (393) and 38% in cohort studies (401). However, it has not been estimated within an HIV-positive cohort in the UK.

In clinical trials of pegylated-interferon and ribavirin treatment among HIV/HCV co-infected individuals independent predictors of SVR which have been identified are HCV genotype (genotypes 1 and 4 are significantly less likely to achieve SVR than individuals infected with genotype 2 or 3), lower baseline HCV viral load male gender and younger age (<40 years old) (395-399). The effects of HCV genotype and baseline HCV viral load on the likelihood of

achieving SVR have also been observed in cohort studies (401, 491-494). In addition, some smaller cohort studies have also suggested that CD4 count and the degree of liver fibrosis at the start of treatment may predict SVR among HIV-positive individuals (177, 492, 495-498). However, these findings have not been confirmed in larger studies.

In 2011, the first anti-HCV DAAs were approved for use in the USA and Europe. Since then numerous other DAAs have entered into trials including both HCV mono-infected and HIV/HCV co-infected individuals (154). In the UK, since 2013, recommended therapy for HCV genotype 1 infection in HIV co-infected patients has been triple therapy with pegylated-interferon, ribavirin and either telaprevir or boceprevir (65). For infection with HCV genotype 2 or 3, the standard treatment regimen remained dual therapy pegylated-interferon and ribavirin for 48 weeks. In individuals without cirrhosis who have a rapid virological response, treatment could be shortened to 24 weeks. Similarly, pegylated-interferon and ribavirin remained standard of care for those with genotype 4 infection. Treatment of genotype 4 HCV infection should be for a total of 48 weeks but can be stopped at 12 weeks if HCV-RNA remains detectable as SVR is, therefore, unlikely (65).

The landscape of HCV treatment is changing fast. In 2014, three additional DAAs were licensed for use in Europe. The most recent guidelines from the European Association for the study of the liver include recommendations for treatment combinations which are interferon-free. However, access to these newer drugs is still not universal (499). Therefore, among individuals with minimal liver damage as a result of HCV infection, deferral of treatment may be considered (500). In the context of the development of new treatments, there is a need to understand current HCV treatment patterns and responses among HIV co-infected individuals in the UK. This will assist in planning within services who will deliver treatment by helping to identify those individuals who are most at need of new treatment strategies.

7.2 Methods

7.2.1 Inclusion criteria

Anti-HCV and HCV-RNA test results were cleaned as previously described (Chapter 5). All analyses presented here included only those individuals who had ever received a positive RNA test result before the end of follow-up.

7.2.2 Hepatitis treatment data cleaning

The treatment data for individuals who were known to be co-infected with HCV were examined for missing information. There were 48 individuals who had documented treatment but had no start or stop dates for this treatment. The complete treatment record for these individuals was examined and the start and stop dates were updated for one individual according to information available in the treatment notes. No information was available for the other 47 individuals preventing the dates from being updated.

There were 54 individuals who had a date of stopping treatment but for whom date of starting treatment was missing. The complete records of these individuals were examined. Where there was information in the free text treatment notes or in the reason for stopping which indicated that the individual had not received a complete course of treatment the start date was not updated and remained blank (7 individuals). Where there was information available within the treatment notes which indicated a treatment start date, the start dates were updated accordingly (4 individuals). Where there was no evidence of early termination of treatment the treatment period was assumed to be 48 weeks and therefore the treatment start date was imputed as 48 weeks prior to the treatment stop date (43 individuals).

There were 158 individuals who had a date of starting treatment available but who had missing dates for stopping treatment. The complete records of these individuals were examined. Of all individuals with missing treatment stop dates, 64 individuals started their treatment after 1st January 2012. For these individuals the treatment stop date was left blank as they may still have been completing treatment at the time of data collection. Six individuals had information in their treatment records which indicated that they had stopped but no date for stopping was available, therefore the stop date was left blank. Three individuals did not have their stop dates updated as there was further information within the treatment notes which implied that they did not complete treatment. For 92 individuals, where there was no

indication that they had stopped treatment early, the treatment stop date was imputed as 48 weeks after the start date.

The data were then examined to identify situations where there seemed to be multiple records of treatment which, in fact, formed part of the same treatment episode. Where an episode of treatment fell entirely within another episode of treatment with the same drug, that episode was removed. Where there were multiple entries for the same drug within an individual record, with different start dates but the same stop dates, the latest start date was removed. Where there were multiple entries for the same drug within an individual's record, with the same start dates but different stop dates, the earliest stop date was removed. Where there were multiple episodes of the same drug which were overlapping, these episodes were combined to form one episode of treatment including the earliest start date and the latest stop date. Examples of these situations are shown in Table 7.1.

Table 7.1 Examples of amendments made to hepatitis drug start and stop dates

Description of data	**Record 1**	**Record 2**	**Final record**
One episode of treatment falls entirely within another episode of treatment with the same drug	Drug start date: 01/03/2007 Drug Stop date: 31/01/2008	Drug start date: 01/05/2007 Drug Stop date: 31/07/2007	Drug start date: 01/03/2007 Drug Stop date: 31/01/2008
Multiple entries for same drug with different start date and same stop dates	Drug start date: 01/03/2007 Drug Stop date: 31/01/2008	Drug start date: 09/02/2007 Drug Stop date: 31/01/2008	Drug start date: 01/03/2007 Drug Stop date: 31/01/2008
Multiple entries for same drug with same start date and different stop dates	Drug start date: 01/03/2007 Drug Stop date: 28/11/2007	Drug start date: 01/03/2007 Drug Stop date: 31/01/2008	Drug start date: 01/03/2007 Drug Stop date: 31/01/2008
Multiple entries for same drug dates which overlap	Drug start date: 01/03/2007 Drug Stop date: 31/01/2008	Drug start date: 04/05/2007 Drug Stop date: 03/04/2008	Drug start date: 01/03/2007 Drug Stop date: 03/04/2008

Dates of starting and stopping each drug were used to define a course of treatment. Where start dates and stop dates were the same or overlapping for more than one drug this was considered as a single course of treatment. Where the date of starting a drug was after the date of stopping any other drugs, this was considered a subsequent course of treatment. Drugs used within each episode of treatment were summarised. A total of 14 different drug regimens were recorded in the dataset. Where a combination of drugs was recorded which was not clinically plausible, this combination was amended to the combination most similar which would be likely to be used in clinical practice. After making these amendments only 9 different regimens were identified (Table 7.2).

Table 7.2 Amending HCV drug combinations recorded in dataset

Treatment Regimen recorded in dataset	Amendment made	Justification
No treatment	No amendment	Individuals not treated
Pegylated-interferon alone	No amendment	May be used to treat acute infection
Interferon alone	If start date >2001 amend to pegylated-interferon	Monotherapy may be used to treat acute infection. From 2001 onwards most interferon treatment would utilise pegylated-interferon
	If start date <2001 do not amend	Prior to 2001 some non-pegylated-interferon may have been in use
Pegylated-interferon + Ribavirin	No amendment	Standard of care for all HCV until 2013 Remains standard of care for acute HCV of all genotypes and chronic HCV infection with all genotypes other than genotype 1

Treatment Regimen recorded in dataset	Amendment made	Justification
Interferon + Ribavirin	If start date >2001 amend to Pegylated-interferon + Ribavirin	From 2001 onwards most interferon treatment would utilise pegylated-interferon
	If start date <2001 do not amend	Prior to 2001 some non-pegylated-interferon may have been in use
Ribavirin alone	If start date >2001 amend to Pegylated-interferon + Ribavirin	Ribavirin alone has never been used as treatment for HCV and from 2001 onward all interferon used was pegylated
	If start date <2001 amend to Interferon + Ribavirin	Ribavirin has never been used as a sole treatment prior to 2001 interferon used was non-pegylated
Pegylated-interferon + Ribavirin + interferon	If start date >2001 amend to Pegylated-interferon + Ribavirin	From 2001 onwards most interferon treatment would utilise pegylated-interferon
	If start date <2001 amend to interferon + Ribavirin	Prior to 2001 some non-pegylated-interferon may have been in use
Pegylated-interferon + Ribavirin + Telaprevir	No amendment	Individuals in trials or on newer recommended treatments
Pegylated-interferon + Ribavirin + Boceprevir	No amendment	Individuals in trials or on newer recommended treatments

Treatment Regimen recorded in dataset	Amendment made	Justification
Pegylated-interferon + Ribavirin + unknown/other DAA	No amendment	Individuals treated with new regimens
Ribavirin + Telaprevir	Add Pegylated-interferon	Telaprevir only licensed for use in triple therapy
Ribavirin + Sofosbuvir	No amendment	Possible trial use
Ribavirin + Boceprevir	Add Pegylated-interferon + Ribavirin	Boceprevir only licensed for use in triple therapy
Telaprevir alone	Add Pegylated-interferon + Ribavirin	Telaprevir only licensed for use in triple therapy
Sofosbuvir alone	No amendment	Possible trial use

7.2.3 Factors associated with starting HCV treatment

Individuals were excluded from the analysis if the date of starting treatment was unknown, if the date of starting treatment was before the date of the first positive HCV-RNA test result, or if the date of starting treatment was before the date of entry into UK CHIC. Baseline characteristics of individuals who started treatment and those who did not were compared.

Individuals were followed-up from either their entry into UK CHIC or their first positive HCV test (anti-HCV or HCV-RNA), whichever occurred later, until their last date of follow-up or until they started treatment. Individuals' follow-up was censored if they showed evidence of clearing the infection without evidence of treatment. A further group of individuals whose date of starting follow-up and date of stopping follow-up were the same (i.e. they had a total follow-up time of 0 days) were excluded from the analysis.

Time from first positive HCV test to starting treatment was described using the Kaplan Meier method. Cox regression was used to identify demographic and HIV-related clinical factors which may be associated with starting HCV treatment. CD4 and HIV viral load were time updated in the model and other variables were fixed at the time of first positive test result. The final model was adjusted for age, HIV exposure group, year of first positive HCV test, current CD4, current viral load and whether an individual was diagnosed with acute HCV infection.

7.2.4 Characteristics of treatment episodes

For further analyses, each individual episode of treatment was included separately. Four episodes of treatment were recorded as having a duration of zero days. These episodes of treatment were excluded from further analyses. Median time on each treatment for each episode was calculated and the differences tested for significance using a Wilcoxon rank sum test.

Time spent on treatment was rounded to the nearest week. A standard course of treatment was considered to be 48 weeks. However, some recorded dates of starting and stopping treatment may have been estimated from data which was available in clinical notes. Therefore the definition of a standard course of treatment was extended to include individuals who were recorded as having received between 44 and 52 weeks of treatment. Recorded reasons for stopping treatment were investigated among episodes of treatment which were defined as having stopped prematurely (stopped at less than 44 weeks).

7.2.5 Defining serological response to HCV treatment

Analysis of response to treatment excluded those episodes of treatment which included new DAAs. The response of individuals to these newer hepatitis treatment regimens is beyond the scope of this thesis as there has not been sufficient follow-up time of individuals on these drugs as part of normal clinical practice and most individuals recorded as being on regimens including DAAs will have been participants in clinical trials. Treatment episodes were included in the analysis if they had start and stop dates available and if there was at least one HCV-RNA test result available after stopping treatment.

To examine the potential for investigating end of treatment (EOT) response using the serological data in this cohort, the time from stopping treatment to first RNA test result was examined. Since exact stop dates were may have been estimated during the data collection process the first HCV-RNA tests results in the period one month before stopping treatment, and before starting any subsequent episodes of treatment, were used (Table 7.3). Similarly, to investigate the potential for examining SVR using the serological data in this in this cohort the first test result at 6 months or more after stopping treatment was identified and the time from stopping treatment to this test was calculated (Table 7.4).

Table 7.3 First HCV-RNA test results after stopping treatment and before starting any subsequent episodes of treatment

Time to first test result after stopping treatment	Total	Number positive	%	Number negative	%
≤1 week	223	19	15.5	104	84.6
1 week- 1 month	85	12	14.1	73	85.9
1-3 months	106	37	34.9	69	65.1
3-6 months	57	23	40.4	34	59.7
>6 months	124	73	58.9	51	41.1
Total	495	164	33.1	331	66.9

Table 7.4 First HCV-RNA test results 6 months or more after stopping treatment and before starting any subsequent episodes of treatment

Time from 6 months post stopping treatment to next HCV-RNA test result	Total	Number positive	%	Number negative	%
0 days	1	0	0.0	1	100.0
1 week-1 month	20	3	15.0	17	85.0
1-3 months	161	44	27.3	117	72.7
3-6 months	46	14	30.4	32	69.6
>6 months	171	92	50.8	79	46.2
Total	399	153	38.4	246	61.7

Given that there are variable times between stopping treatment and follow-up tests in this cohort and that the dates for some episodes of treatment were estimated, EOT response and SVR could not be accurately determined using the generally adopted definitions. Therefore, an initial treatment response period was defined as the period from one month before stopping treatment to 6 months after stopping treatment. Individuals whose first test result in this time period was negative were defined as having a successful initial treatment response. Those individuals whose first result in the initial response period was positive were considered to have failed treatment in the initial treatment response period.

Where an individual with a negative result in the initial response period had a further negative test result beyond the 6 month cut off, with no intervening positive test results, it was assumed that this individual had in fact had a long term response to treatment and therefore the outcome of treatment was successful. Where an individual with a negative result in the initial response period had no further test results after the initial treatment response, it was not possible to determine the long term treatment response. Where an individual had a negative result in the initial treatment response period and their subsequent result was outside of the 6 month cut-off but was positive, it was not possible to ascertain whether this positive result was due to reinfection or treatment failure.

Among those individuals who had a successful initial treatment response, long term treatment response (LTR) was defined in a variety of ways:

Method 1: LTR was defined using the first follow-up test result at least 6 months after stopping treatment as long as this was no more than 6 months after the date of the test used to define initial treatment response.

Method2: LTR was defined as a negative follow-up test which was at least 6 months after stopping treatment but no more than 1 year after the initial treatment response.

Method 3: LTR was defined on the basis of the first follow-up test which occurred at least 6 months after stopping treatment and no time limit was included (i.e. all positive results are treated as treatment failures), irrespective of time.

Method 4: Individuals were defined as having a negative LTR if the follow-up test result was negative, irrespective of time. For those individuals where the follow-up test was positive, those who had changing genotypes were considered to have been re-infected and those who did not have changing genotypes were considered to have failed treatment.

Characteristics of individuals with successful LTR as defined using each of the methods were described.

7.2.6 Factors associated with treatment failure

In order to assess factors associated with treatment failure only those individuals who had an HCV-RNA test result in the first year after stopping treatment were included in the analysis. Individuals were followed from the date of stopping treatment for one year or until their last seen date (whichever was first). Any positive HCV-RNA test result in the follow-up period was considered as treatment failure. Follow-up was censored if there was evidence of a subsequent episode of treatment within a year of stopping treatment, even if there was no evidence of a positive result and these individuals were considered to have failed treatment.

Cox regression was used to identify individual-level, HIV-related and HCV-related factors which may be associated with treatment failure. CD4 count, HIV viral load were included as time updated covariates. A high proportion of individuals had missing HCV viral loads at baseline, and therefore when HCV viral load was included in the final model many associations were non-significant due to the small numbers. A sensitivity analysis was conducted where baseline viral load included any HCV viral load test which was conducted in the 6 months prior to starting HCV treatment or the month after starting treatment. If more than one result was

available in this time period, the result closest in time to the date of starting treatment was used.

7.2.7 Characteristics of individuals in need of treatment

To describe the characteristics of individuals who needed treatment, a cohort of individuals who had either never received treatment, or who had failed their first episode of treatment was identified. Although some individuals who have failed their first episode of treatment may have had a successful subsequent episode of treatment, this was not considered as they would have benefited from newer, more effective treatment options. The liver disease in these individuals was assessed using three methods: biopsy results, APRI score and FibroScan® results. APRI score was calculated using the formula: 100*(AST/upper limit of normal)/Platelets (211). For the purpose of this analysis the upper limit of normal for AST was taken as 30IU/L.

7.3 Results

7.3.1 HCV treatment regimens

Of 2272 individuals who ever had a positive HCV-RNA test, a total of 929 (40.9%) had evidence of receiving treatment for HCV. The majority of treated individuals (n=815) received only one course of treatment, but 100 individuals received 2 courses of treatment and 14 individuals received three courses of treatment. Treatment regimens used are shown in Table 7.5.

Table 7.5 Episode of treatment and drugs included as part of treatment regimen

Drugs included in regimen	Number of individuals on regimen (%)		
	First treatment episode	Second treatment episode	Third treatment episode
Pegylated-interferon alone	40 (4.3)	3 (2.6)	0 (0.0)
Interferon alone	3 (0.3)	0 (0.0)	0 (0.0)
Pegylated-interferon + Ribavirin	833 (89.7)	91 (79.8)	12 (85.7)
Interferon + Ribavirin	3 (0.3)	0 (0.0)	0 (0.0)
Pegylated-interferon + Ribavirin + Telaprevir	24 (2.63)	13 (11.4)	0 (0.0)
Pegylated-interferon + Ribavirin + Boceprevir	3 (0.3)	1 (0.9)	0 (0.0)
Pegylated-interferon + Ribavirin + unknown DDA	20 (2.2)	5 (4.4)	0 (0.0)
Ribavirin + Sofosbuvir	3 (0.3)	0 (0.0)	0 (0.0)
Sofosbuvir alone	0 (0.0)	1 (0.9)	2 (14.3)

7.3.2 Factors associated with starting HCV treatment

Excluding 49 individuals whose date of starting first episode of treatment was unknown, 58 individuals who started HCV treatment before their first positive test recorded in the dataset and 2 individuals whose first treatment was before entry into the cohort, 2163 individuals were included in the analysis, of whom 37.9% (820/2163) received any HCV treatment. The baseline characteristics of these individuals are shown in Table 7.6. Among the individuals who started treatment, the median time between first positive test and starting first HCV treatment was 11.2 months (IQR 3.7, 46.6 months).

In order to assess time to starting treatment, a further 22 individuals were excluded from the analysis because they had the same follow-up start date and follow-up stop date (i.e. had zero follow-up time). Therefore there were 819/2141 individuals ever treated who were included

in the analysis. The median length of follow-up among those included in the analysis was 3.0 years (IQR 0.6, 6.8 years). Median follow up was 4.3 years (IQR 1.5, 8.2) for untreated individuals and 0.9 years (IQR 0.3-3.7) for treated individuals. The probability of starting treatment over time is shown in Figure 7.1.

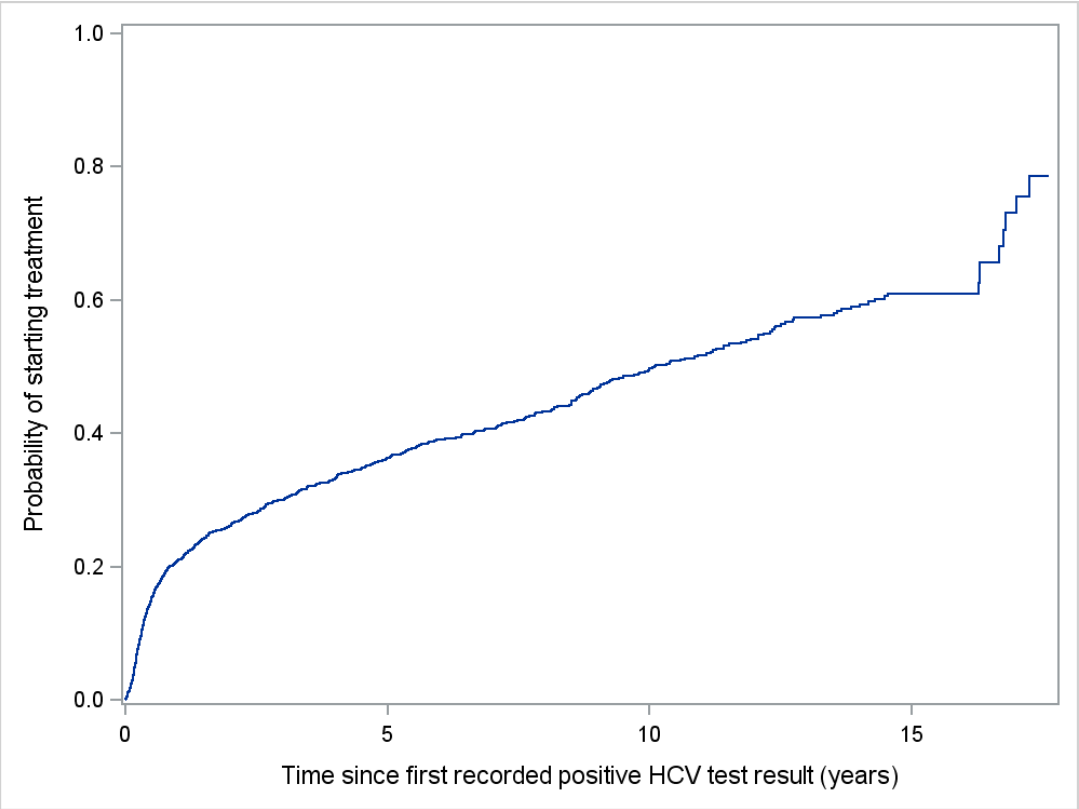
Table 7.6 Baseline characteristics of individuals who start treatment for HCV and those who do not

	Treated N=820	**%**	**Never treated N=1343**	**%**	**P value**
Median age (years) (IQR)	38	(33, 43)	37	(32, 43)	0.72
Ethnicity					
White	697	85.0	1109	82.6	0.19
Black African	21	2.6	57	4.2	
Other black	18	2.2	28	2.1	
Other/unknown	84	10.2	149	11.1	
HIV exposure group					
MSM	602	73.7	720	53.6	<0.0001
IDU	109	13.3	361	26.9	
Male heterosexual	29	3.5	102	7.6	
Female heterosexual	28	3.4	76	5.7	
Other/unknown	52	6.3	84	6.3	
Year of first positive HCV test					
<1996	36	4.4	72	5.4	0.01
1996-1999	49	6.0	117	8.7	
2000-2004	175	21.3	332	24.7	
2005-2009	395	48.2	603	44.9	
>2010	165	20.1	219	16.3	
Median CD4 (cells/mm^3) (IQR) [1]	475	(342, 640)	400	(255, 574)	<0.0001
HIV Viral load (copies/ml)					
≤50	351	42.8	448	33.4	<0.0001
>50	375	45.7	685	51.0	
Unknown	94	11.5	210	15.6	
Diagnosed in acute infection					
Yes	357	43.5	244	16.7	<0.0001
No	463	56.5	1099	81.8	
Median HCV viral load (IU/ml)(IQR)[2]	1000594	(108000, 5574112)	737059	(11405, 3375276)	0.001

[1] Baseline CD4 count is unknown for 56 treated and 133 untreated individuals

[2] Baseline HCV viral load is unknown for 336 treated and 699 untreated individuals

Figure 7.1 Kaplan Meier curve of probability of starting HCV treatment



HRs from the Cox model for factors associated with starting treatment are shown in Table 7.7. In the univariable analysis, age at start of follow-up, HIV exposure group, year of first positive HCV test, CD4 count, HIV viral load and being diagnosed with acute HCV infection were all significantly associated with starting treatment. The association between age and starting treatment was not maintained in the multivariable model. In multivariable analysis, MSM were the group most likely to start HCV treatment, IDU were significantly less likely than MSM to start HCV treatment (AHR, 95% CI: 0.60, 0.47-0.76) as were male heterosexuals (AHR, 95% CI: 0.57, 0.39-0.83) and female heterosexuals (ARH, 95% CI: 0.64, 0.43-0.95). Year of first positive HCV test remained significantly associated with likelihood of starting treatment in the multivariable model. Individuals who had their first recorded positive HCV test in earlier years were significantly less likely to start treatment than those with a first positive test in the 2005-2009 period, while individuals in the who had a first positive test from 2010 onwards were most likely to start treatment (AHR, 95% CI: 1.91, 1.57-2.32). Individuals with higher CD4 counts were more likely to start treatment (AHR, 95% CI: 1.06, 1.03-1.09 per 100 cells/mm^3 increase) and individuals with higher HIV viral loads were less likely to start treatment (AHR,

95% CI: 0.88, 0.83-0.94 per $\log_{10}$ copies/ml). Being diagnosed with acute HCV infection was the strongest predictor of starting treatment.

Table 7.7 Univariable and multivariable Cox regression analyses of factors associated with starting first HCV treatment

	Univariable			Multivariable		
	HR	**95% CI**	**P value**	**AHR**	**95% CI**	**P value**
Baseline age (per 10 years older)	1.18	1.09-1.29	<0.0001	0.93	0.85-1.02	0.10
Ethnicity						
White	1	-	-	-	-	-
Black African	0.73	0.47-1.12	0.15	-	-	-
Other black	1.05	0.66-1.67	0.84	-	-	-
Other/unknown	1.05	0.84-1.32	0.66	-	-	-
Exposure						
MSM	1	-	-	1	-	-
IDU	0.30	0.24-0.36	<0.0001	0.60	0.47-0.76	<0.0001
Male heterosexual	0.39	0.27-0.56	<0.0001	0.57	0.39-0.83	0.004
Female heterosexual	0.40	0.27-0.59	<0.0001	0.64	0.43-0.95	0.03
Other/unknown	1.02	0.77-1.35	0.91	1.25	0.93-1.67	0.14
Year of first positive HCV test						
<1996	0.10	0.06-1.15	<0.0001	0.21	0.13-0.34	<0.0001
1996-1999	0.13	0.09-0.19	<0.0001	0.24	0.16-0.35	<0.0001
2000-2004	0.40	0.33-0.49	<0.0001	0.48	0.40-0.60	<0.0001
2005-2009	1	-	-	1	-	-
≥2010	2.40	1.98-2.91	<0.0001	1.91	1.57-2.32	<0.0001
CD4 count (per 100 cells/mm^3 increase)[1]	1.13	1.11-1.16	<0.0001	1.06	1.03-1.09	0.0002

	Univariable			Multivariable		
	HR	**95% CI**	**P value**	**AHR**	**95% CI**	**P value**
HIV viral load (per log_{10} copies/ml increase)[1]	0.77	0.72-0.82	<0.0001	0.88	0.83-0.94	0.0003
Acute HCV at first positive test						
No	1	-	-	1	-	-
Yes	4.66	4.03-5.40	<0.0001	2.69	2.29-3.17	<0.0001

[1] CD4 count and HIV viral load were included in the analysis as time updated variables

7.3.3 Characteristics of treatment episodes

There were a total of 903 separate episodes of treatment. Median time on treatment was 46.6 weeks (IQR 24, 48). However this differed significantly by episode of treatment (p=0.01) (Table 7.8). Among 427 treatment episodes with a duration of less than 44 weeks, a reason for stopping was recorded for 137 episodes. These reasons for stopping are shown in Table 7.9.

Table 7.8 Time on treatment by treatment episode

Treatment Episode	Median time on treatment (IQR)
1	47.7 (24, 48)
2	26.3 (22, 48)
3	25.1 (24.1, 31.5)
Total	47.6 (24, 48)

Table 7.9 Recorded reasons for stopping HCV treatment before 44 weeks of treatment

Reason for stopping treatment early	Number of individuals N=137	%
Completed planned course	17	12.4
Virological breakthrough	9	6.6
Non-response	38	27.7
Side effects	43	31.4
Patient lost to follow-up	2	1.5
Patient choice	13	9.5
Early response	8	5.8
Other illness	5	3.7
Patient died	1	1.0
Treatment break	1	1.0

7.3.4 Defining serological response to treatment

Among all episodes of treatment (n=903), 64 were excluded as they included new DAAs as part of the regimen, 25 were excluded as there was no treatment stop date available and 319 were excluded as there were no RNA test results available after stopping treatment. Therefore a total of 495 episodes of treatment were included in the analysis of serological response to treatment. Baseline characteristics (at time of starting treatment) of included and excluded episodes of treatment are shown in Table 7.10.

Table 7.10 Baseline characteristics of those treatment episodes included in the analysis of treatment response compared to excluded episodes

	Included treatment episodes N=495	%	Excluded treatment episodes N=408	%	P value
Median age (years) (IQR)	40 (35, 45)	-	41 (36, 47)	-	0.04
Ethnicity					
White	433	87.5	338	82.8	0.21
Black African	9	1.8	14	3.4	
Other black	10	2.0	10	2.5	
Other/unknown	43	6.7	46	11.3	
HIV exposure group					
MSM	367	74.1	298	73.0	<0.0001
IDU	75	15.2	44	10.8	
Male heterosexual	22	4.4	8	2.0	
Female heterosexual	18	3.8	12	2.9	
Other/unknown	13	2.6	46	12.0	
Year of starting treatment					
1996-1999	1	0.2	3	0.7	<0.0001
2000-2004	71	14.3	10	2.5	
2005-2009	315	63.6	103	25.2	
>2010	108	21.8	292	71.6	
Median CD4 (cells/mm^3) (IQR) [1]	500 (386, 600)	-	508 (385, 660)	-	0.04
Nadir CD4 (cells/mm^3) (IQR) [2]	219 (122, 349)	-	229 (143, 320)	-	0.66
Median HIV viral load (copies/ml) (IQR) [3]	50 (50, 151)	-	40 (40, 50)	-	0.01
Diagnosed with acute HCV infection					
Yes	218	44.0	187	45.8	0.59
No	277	56.0	221	54.2	
Median HCV viral (IQR)[4]	737500 (97965, 2541476)	-	850000 (86006, 3383309)	-	0.64
Treatment episode					
First	492	99.4	323	79.2	<0.0001
Second	3	0.6	78	19.1	
Third	0	0.0	7	1.7	

	Included treatment episodes N=495	%	Excluded treatment episodes N=408	%	P value
HAART regimen					
PI based	146	29.4	128	31.4	0.51
NNRTI based	125	25.3	104	25.4	
Other	107	21.6	96	23.5	
Not on anti- HIV drugs	117	23.6	80	19.6	
HBV co-infected					
No	375	75.8	314	77.0	0.54
Yes	67	13.5	59	14.5	
Unknown	53	10.7	35	8.6	

[1] Baseline CD4 count was unknown for 22 included and 109 excluded episodes of treatment.
[2] Nadir CD4 count was unknown for 1 included and 2 excluded episodes of treatment.
[3] Baseline HIV viral load was unknown for 25 included and 109 excluded episodes of treatment.
[4] Baseline HCV viral load was unknown 295 included 225 excluded episodes of treatment.

A result within the initial treatment response period (as defined in methods section) was available for 395 individuals, of whom 300 (75.9%, 95% CI 71.7%-80.2%) were negative in this time period and 95 (24.1%, 95% CI 19.8-28.3%) were positive. The median time from treatment stop date to initial treatment response result was 4 days (IQR -1, 32). The 95 individuals who were positive in the initial treatment response period were considered to have failed treatment. Baseline characteristics (at the time of starting HCV treatment) of individuals with positive and negative results in the initial treatment response period are shown in Table 7.11. Those treatment episodes which were initially successful had lower HCV viral loads at baseline than those which failed. There were no other significant differences between these groups.

Table 7.11 Characteristics of individuals with HCV-RNA test results in the initial treatment response period

	Initial treatment success N=300	%	Initial treatment failure N=95	%	P value
Median age (years) (IQR)	40.5 (35, 45.5)	-	40 (35, 45)	-	0.13
Ethnicity					
White	266	88.7	80	84.2	0.47
Black African	5	1.7	1	1.1	
Other black	4	1.3	3	3.2	
Other/unknown	25	8.3	11	11.6	
HIV exposure group					
MSM	226	75.3	69	72.6	0.59
IDU	42	14.0	16	16.8	
Male heterosexual	13	4.3	4	4.2	
Female heterosexual	13	4.3	2	2.1	
Other/unknown	6	2.0	4	4.2	
Year of starting treatment					
1996-1999	1	0.3	0	0.0	0.87
2000-2004	40	13.3	15	15.8	
2005-2009	187	62.3	57	60.0	
>2010	72	24.0	23	24.2	
Median CD4 count (cells/mm^3) (IQR) [1]	510 (386, 679)	-	490 (385, 683)	-	0.27
Nadir CD4 (cells/mm^3) (IQR) [2]	361 (212, 537)	-	221 (74, 380)	-	0.35
Median HIV viral load (copies/ml) (IQR) [3]	50 (50, 63)	-	50 (50, 209)	-	0.46
Diagnosed in acute HCV infection					
Yes	159	53.0	60	63.2	0.08
No	141	47.0	35	36.8	
Median HCV viral load (IQR)[4]	635596 (38900, 2040539)	-	1000000 (388618, 7397260)	-	0.03
Treatment episode					
First	298	99.3	94	98.9	0.71
Second	2	0.6	1	1.1	
HAART regimen					
PI based	82	27.3	33	34.7	0.33
NNRTI based	83	27.7	21	22.1	
Other	69	23.0	17	17.9	
Not on anti- HIV drugs	66	22.0	24	25.3	

	Initial treatment success N=300	%	Initial treatment failure N=95	%	P value
HBV co-infected					
No	235	78.3	71	74.7	0.11
Yes	39	13.0	9	9.5	
Unknown	26	8.7	15	15.8	

[1] Unknown for 13 initially successful treatment episodes and 7 failed treatment episodes.
[2] Unknown for 1 initially successful treatment episode.
[3] Unknown for 12 initially successful treatment episodes and 7 failed treatment episodes.
[4] Unknown for 153 initially successful treatment episodes and 62 individuals with failed treatment episodes.

Among the 300 individuals who had a negative test result in the initial treatment response period, the median time to negative result was 3.5 days (IQR -1, 27). Among these individuals 237/300 had a further test result which was at least 6 months after the stopping treatment. LTR was examined among those who had a successful initial treatment response using each of the methods described in the methods section. The proportion of individuals with a successful LTR ranged from 78.4% to 85.7% (Table 7.12) depending on the method used to define LTR. Characteristics of individuals with successful LTR are shown in Table 7.13.

Table 7.12 LTR to HCV treatment among those with a negative result in the initial treatment response period, defined using 6 different methods

Method[1]	Total	HCV-RNA Positive	HCV-RNA Negative	% with successful treatment (95% CI)	Median time to LTR definition (IQR)
LTR method 1	37	8	29	78.4 (65.1 -91.6)	200 (190, 231)
LTR method 2	168	24	144	85.7 (80.4-91.0)	233 (199, 267)
LTR method 3	237	40	197	83.1 (78.4-87.9)	258 (210, 399)
LTR method 4	237	38	199	84.0 (79.3-88.6)	253 (209, 385)

[1] LTR method 1 utilised the first follow-up test result at least 6 months after stopping and no more than 6 months after the date of the test used to define initial treatment response; LTR method 2 utilised any negative follow-up test 6-12 months after stopping; LTR method 3 utilised the first follow-up test which occurred at least 6 months after stopping treatment; and LTR method 4 utilised used all negative results at least 6 months after stopping treatment but used additional information from genotypes to assess the positive test results see section 7.2.5 for details.

Table 7.13 Baseline characteristics of individuals with successful and LTR defined using a variety of methods

	Individuals with successful LTR response							
	LTR1 N=29	**%**	**LTR2 N=144**	**%**	**LTR3 N=197**	**%**	**LTR4 N=199**	**%**
Median age (IQR)	41 (37, 48)		41 (37, 46)		41 (37, 52)		41 (37, 45)	
Ethnicity								
White	28	77.8	130	85.5	180	82.6	183	83.9
Black African	0	0	2	66.7	2	66.7	2	66.7
Black other	0	0	1	100	2	100	2	100
Other/unknown	1	100	11	91.7	13	92.9	13	92.9
HIV exposure group								
MSM	22	78.6	112	86.8	155	84.7	158	86.3
IDU	4	66.7	21	87.5	27	81.8	27	81.8
Male heterosexual	2	100	6	100	9	90	9	90
Female heterosexual	1	100	3	50	4	50	4	50
Other	0	0	2	66.7	2	66.7	2	66.7
Year of starting treatment								
1996-1999	0	0	0	0	0	0	0	0
2000-2004	4	80	24	82.8	33	13.9	33	84.6
2005-2009	20	80	91	86.7	131	82.9	134	84.8
>2010	5	83.3	29	87.9	33	94.6	33	84.6

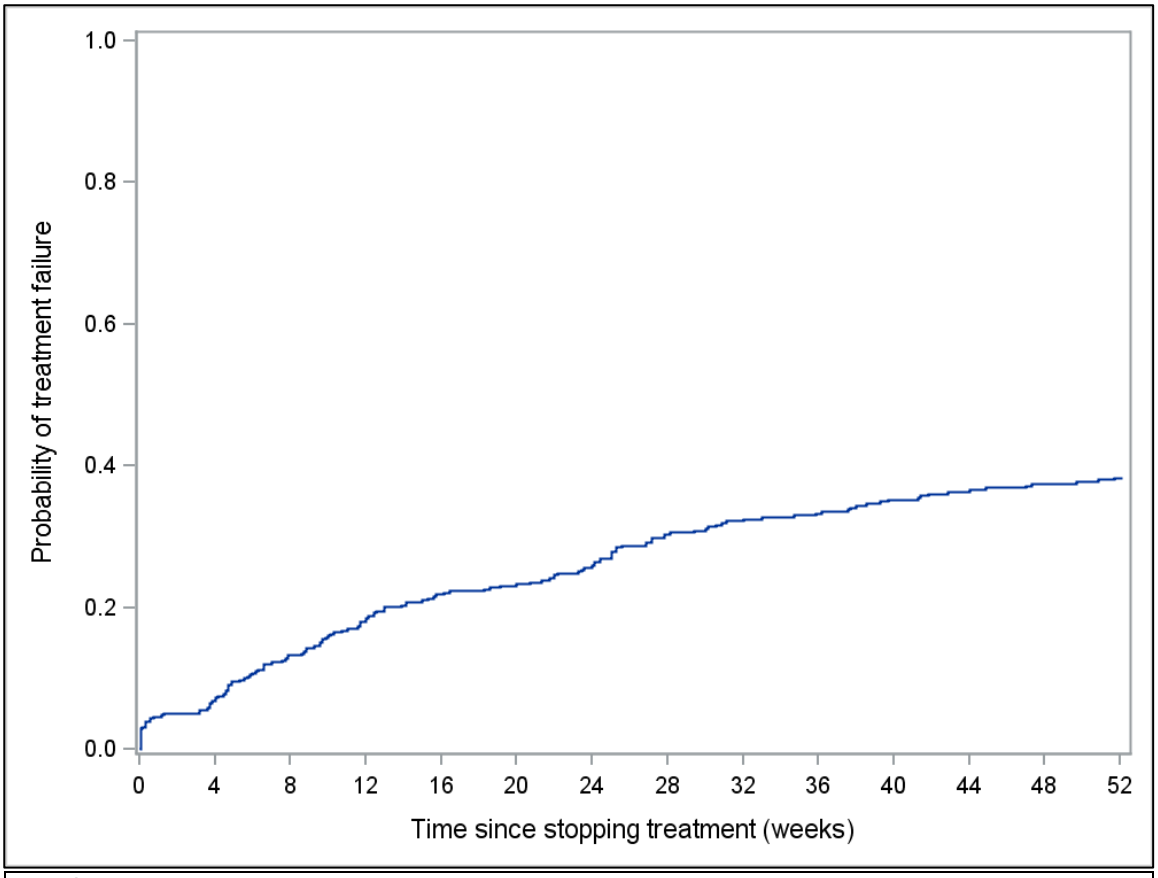
	Individuals with successful LTR response							
	LTR1 N=29	**%**	**LTR2 N=144**	**%**	**LTR3 N=197**	**%**	**LTR4 N=199**	**%**
Latest CD4 (cells/mm^3) (Median(IQR)) [1]	473	(391, 603)	500	(385, 650)	502	(384, 655)	501	(358, 658)
Nadir CD4 (cells/mm^3) (Median(IQR)) [2]	193	(98, 380)	201	(114, 340)	209	(112, 350)	204	(111, 349)
HIV viral load (copies/ml)								
≤50	24	80	103	88	140	83.8	143	85.6
>50	5	71.4	37	78.7	53	80.3	53	80.3
Unknown	0	0.0	4	100.0	4	100.0	4	100.0
Diagnosed in acute infection								
Yes	14	87.5	73	85.9	101	83.5	101	83.5
No	15	71.4	71	85.4	96	82.8	99	85.3
Median HCV viral load (IU/ml) ***(IQR)***[4]	631642	(103207, 29850000)	574642	(18206, 1797360)	520839	(13998, 1800000)	520839	(13998, 1800000)
HAART regimen								
PI based	12	80	44	88	55	84.6	55	84.6
NNRTI based	6	75	37	88.1	55	85.9	56	87.5
Other	0	0	34	87.2	43	79.6	45	83.3
No anti-HIV drugs	4	57.1	29	78.4	44	81.5	44	81.5

	Individuals with successful LTR response							
	LTR1 N=29	**%**	**LTR2 N=144**	**%**	**LTR3 N=197**	**%**	**LTR4 N=199**	**%**
HCV genotype								
1	17	73.9	73	84.8	99	80.5	100	80.7
2	1	100	6	100	8	100	9	100
3	7	100	21	91.3	32	88.9	32	88.9
4	1	100	16	88.9	25	92.6	25	92.6
Other/unknown	3	60	28	80	33	76.7	34	82.9
HBV co-infected								
No	22	75.9	119	87.5	165	85.1	167	86.1
Yes	5	100	15	83.3	19	76	20	80
Unknown	2	66.7	10	71.4	13	72.2	13	72.2

7.3.5 Factors associated with treatment failure

A total of 417 individuals had at least one HCV-RNA test in the year after stopping treatment and were included in the analysis, of whom 150 failed treatment in the year after stopping treatment. The probability of treatment failure over time after stopping treatment is shown Figure 7.2. In univariable analysis, not being diagnosed with acute HCV infection, higher baseline HCV viral load, HCV genotype 1 or 4 infection, HBV co-infection and shorter time on treatment were all associated with failing treatment in the first year (Table 7.14).

Figure 7.2 Kaplan Meier curve and corresponding life table for the probability of treatment failure in the first year after stopping treatment



Weeks from stopping treatment	4	8	12	16	20	24	28	32	36	40	44	48	52
Number at risk	375	347	324	308	302	290	261	249	245	233	227	221	215

In multivariable model 1, including all those factors associated with treatment failure in the univariable analysis, only baseline HCV viral load (AHR, 95% CI: 1.26, 1.04-1.54) and time on treatment (AHR, 95% CI: 0.64, 0.51-0.80 per additional month on treatment) remained associated with treatment failure (Table 7.15). However, a high number of individuals had

missing baseline HCV viral load measurements (234 individuals). Therefore two additional models were constructed. Model 2 was not adjusted for HCV viral load and model 3 in included HCV viral load with an expanded definition: the viral load measurement which was closest to the time of starting treatment in the 6 months before starting and the one month after stating was taken as baseline. Use of the expanded definition of baseline viral load resulted in the number of individuals with unknown baseline HCV viral load being reduced from 234 to 91.

In model 2, individuals diagnosed with acute infection were significantly less likely to fail treatment than those who were not diagnosed in the acute stage (AHR, 95% CI: 0.59, 0.41-0.84). Individuals with genotype 2 or 3 infection were significantly less likely to fail treatment than those with genotype 1 or genotype 4 infection (AHR, 95%: CI 0.34, 0.18-0.64). Longer time spent on treatment was also associated with being less likely to fail treatment (AHR, 95% CI: 0.70, 0.60-0.80 per additional month on treatment) (Table 7.15). These associations remained, with little change to the effect size, when the expanded definition HCV viral load was included (model 3). In addition, in model 3, higher baseline HCV viral load was also found to be associated with failing treatment (AHR, 95% CI: 1.26, 1.12-1.42) (Table 7.15).

Table 7.14 Characteristics of included treatment episodes and univariable Cox regression of factors associated with treatment failure in the first year after stopping treatment

	Treatment outcome		Univariable analysis[1]		
	Failure N (%)	Did not fail N (%)	HR	95% CI	P value
Total	150	267			
Median age (IQR) [2]	40 (35, 45)	41 (35, 46)	0.87	0.70-1.08	0.21
Ethnicity					
White	129 (86.0)	235 (88.0)	1	-	-
Black African	4 (2.7)	3 (1.1)	1.73	0.64-4.68	0.28
Black other	4 (2.7)	5 (1.9)	1.59	0.59-4.31	0.36
Other/unknown	13 (9.0)	24 (9.0)	1.09	0.62-1.93	0.76
HIV |Exposure group					
MSM	105 (70.0)	206 (77.2)	1	-	-
IDU	25 (16.7)	35 (13.1)	1.38	0.89-2.13	0.15
Male heterosexual	7 (4.7)	12 (4.5)	1.02	0.47-2.19	0.96
Female heterosexual	8 (5.3)	8 (3.0)	1.98	0.97-4.07	0.06
Other/unknown	5 (3.3)	6 (2.3)	1.93	0.79-4.74	0.15
Year of starting treatment					
1996-1999	1 (0.7)	0 (0.0)	2.78	0.39-19.97	0.31
2000-2004	23 (15.3)	32 (12.0)	1.34	0.85-1.13	0.21
2005-2009	86 (57.3)	173 (64.8)	1	-	-
≥2010	40 (26.7)	62 (23.2)	1.67	1.14-2.43	0.01
Median CD4 count (IQR) (cells mm^3)[3]	509 (386, 700)	503 (390,660)	0.99	0.92-1.07	0.88
Median HIV viral load (IQR) (log copies/ml)[4]	1.7 (1.7, 2.0)	1.7 (1.7, 2.6)	0.93	0.79-1.09	0.36
Acute HCV infection					
Yes	58 (38.7)	130 (48.7)	0.70	0.50-0.97	0.03
No	92 (61.3)	137 (51.3)	1	-	-
Median HCV viral load (IQR) (log_{10} IU/ml)[5]	6.0 (5.5, 6.8)	5.8 (4.5, 6.3)	1.26	1.04-1.53	0.02
Treatment episode					
First	149 (99.3)	265 (99.3)	1	-	-
Second	1 (0.7)	2 (0.7)	1.01	0.14-7.20	0.99
HAART regimen					
PI based	52 (34.7)	72 (27.0)	1	-	-
NNRTI based	32 (21.3)	75 (28.1)	0.70	0.45-1.08	0.11
Other	32 (21.3)	58 (21.7)	0.82	0.53-1.28	0.39
Not on HARRT	34 (22.7)	62 (23.2)	0.86	0.56-1.33	0.50

	Treatment outcome		Univariable analysis[1]		
	Failure N (%)	**Did not fail N (%)**	**HR**	**95% CI**	**P value**
HCV genotype					
1 or 4	104 (69.3)	174 (65.2)	1	-	-
2 or 3	11 (7.3)	52 (19.5)	0.42	0.23-0.78	0.01
Other/unknown	35 (23.3)	41 (15.4)	1.32	0.90-1.94	0.15
HBV co-infected					
No	109 (72.7)	211 (79.0)	1	-	-
Yes	19 (12.7)	35 (13.1)	1.06	0.65-1.73	0.82
Unknown	22 (14.7)	21 (7.9)	1.74	1.10-2.75	0.02
Median time on treatment (months) [6]	45 (24, 48)	48 (30, 48)	0.75	0.66-0.86	<0.0001

[1] CD4 count and HIV viral load were analysed in univariable analyses as time updated variables
[2] HR per additional 10 years of age
[3] HR per additional 100 cells/mm^3
[4] HR per additional log10 copies/ml
[5] HR per additional log IU/ml
[6] HR per additional month on treatment

Table 7.15 Multivariable Cox regression of factors associated with treatment failure in the first year after stopping treatment

	Multivariable model 1 – all factors associated with treatment failure in univariable analysis			Multivariable model 2 – excluding baseline HCV viral load			Multivariable model 3 – including baseline viral load (expanded definition)		
	AHR	**95% CI**	**P value**	**AHR**	**95% CI**	**P value**	**AHR**	**95% CI**	**P value**
Acute HCV infection									
Yes	0.62	0.36-1.07	0.09	0.59	0.41-0.84	0.003	0.61	0.41-0.92	0.01
No	1	-	-	1	-	-	1	-	-
HCV viral load (per log copies/ml)	1.26	1.04-1.54	0.02	N/A	N/A	N/A	1.26	1.12-1.42	0.0001
HCV genotype									
1 or 4	1	-	-	1	-	-	1	-	-
2 or 3	0.45	0.17-1.22	0.11	0.34	0.18-0.64	0.001	0.34	0.15-0.81	0.01
Other/unknown	1.80	0.99-3.27	0.05	1.37	0.92-2.03	0.11	1.67	1.04-2.69	0.04
HBV co-infected									
No	1	-	-	1	-	-	1	-	-
Yes	1.68	0.75-3.76	0.21	1.23	0.75-2.02	0.42	1.31	0.74-2.31	0.36
Unknown	2.36	1.01-5.53	0.05	1.60	0.99-2.60	0.06	1.65	0.85-3.30	0.16
Time on treatment (per month)	0.64	0.51-0.80	0.0001	0.70	0.60-0.80	<0.0001	0.58	0.50-0.69	<0.0001

7.3.6 Individuals in need of HCV treatment

A total of 1322 individuals who were co-infected with HCV had never received treatment for their HCV infection. 138 individuals who had started treatment were defined as having failed treatment within the one year after stopping treatment. HCV infection characteristics and stage of liver disease in these individuals are described in Table 7.16.

Table 7.16 Most recent HCV infection status and liver disease in individuals requiring HCV treatment

		Never treated	Failed treatment	Total requiring treatment (%)
HCV viral load	≤615	181	22	203 (13.9)
	615-800000	386	49	435 (29.8)
	>800000	578	66	644 (44.1)
	Unknown	177	1	178 (12.2)
HCV genotype	1 or 4	624	98	722 (49.5)
	2 or 3	153	11	164 (11.2)
	Other/unknown	545	29	574 (39.3)
APRI score	≤0.5	108	13	121 (8.3)
	0.6-1.5	183	45	228 (15.6)
	1.5-2.0	17	2	19 (1.3)
	>2.0	73	10	83 (5.6)
	Unknown	941	68	1009 (69.1)
FibroScan® result	<7 KPa	242	49	291 (20.0)
	7-9 KPa	55	9	64 (4.4)
	10-13 KPa	40	10	50 (3.4)
	≥14 KPa	36	11	47 (3.2)
	Unknown	949	59	1008 (69.0)
Biopsy result[1]	No significant fibrosis	85	14	99 (6.8)
	Fibrosis, but no	68	18	86 (5.9)
	Cirrhosis	34	4	38 (2.6)
	Unknown	1135	102	1237 (84.7)
Any evidence of cirrhosis[2]	No cirrhosis	561	90	951 (65.1)
	Cirrhosis	85	13	98 (6.7)
	Unknown	676	35	711 (48.7)

[1] No fibrosis includes those with Ishak or METAVIR score of 0-1; Fibrosis without cirrhosis includes those with Ishak score 1-5 or METAVIR score 2-3; Cirrhosis includes those with Ishak score 6 or METAVIR score 4

[2] Any cirrhosis defined as an APRI score of 2 of more a FibroScan® of 14 or more, an Ishak score of 6 or a METAVIR score of 4

7.4 Discussion

7.4.1 Summary of findings

Overall 37.9% ofHIV/HCV co-infected individuals had started treatment for HCV while under follow-up in UK CHIC although only just over of half of all episodes of treatment continued to at least 44 weeks. It was not possible to define EOT response or SVR, using the established definitions, from the serological data in this cohort. However, 33% of individuals in this cohort are known to have failed treatment within the first year of stopping treatment, with time on treatment being the strongest predictor of failure. Of those individuals who remain in need of HCV treatment a small but important group are known to have cirrhosis.

7.4.2 Interpretation of results

A high proportion of individuals started treatment within a year of their first positive test result. In addition, being diagnosed with acute HCV infection was an independent predictor for starting HCV treatment. These findings may be due to an increase in awareness of acute HCV as the result of ongoing outbreaks among MSM across Europe. Interestingly, in this cohort, individuals who had their first positive test in later years were more likely to start treatment. This would be consistent with the hypothesis that clinicians have become more aware of acute HCV in recent years. However, this finding is contrary to the suggestion in clinical guidelines that individuals may choose to defer treatment until newer, interferon-free, regimens are available (65).

MSM were the group most likely to commence HCV treatment. IDU were significantly less likely than MSM to start HCV treatment. This may reflect concerns by clinicians and the individuals themselves about lack of adherence to treatment. Indeed, it has been shown that IDU are significantly less likely to start HIV treatment, or do so at later stages of disease, compared to MSM and this is often due to concerns about adherence or irregular attendance for care (501-503). In addition, IDU may have a higher rate of co-existing mental health conditions which are a contraindication to treatment with interferon-containing regimens. Higher CD4 counts and lower HIV viral loads were also independent predictors of starting treatment which reflects clinical guidelines that an individual's HIV infection should be stable before starting HCV treatment (65, 154, 166).

Response to treatment was assessed in a number of ways: treatment success in the initial treatment response period; long term treatment response; and treatment failure within a year of stopping treatment. In this cohort, where HCV-RNA test results after treatment were

available, three quarters of individuals had an initially successful treatment. Between 78% and 86% of these individuals maintained their treatment success over the long term, giving an overall treatment success rate of 58%-67% (and, conversely, a treatment failure rate of 33%-42%). This is consistent with the calculated treatment failure rate within one year of stopping treatment (36%). In addition, factors associated with treatment failure, as identified through a Cox proportional hazards model, were consistent with known risk factors for treatment failure: not being diagnosed with acute infection, having genotype 1 or genotype 4 infection, having a high baseline HCV viral load and longer time on treatment. In observational cohort studies where only routinely recorded clinical data are available there may be insufficient HCV-RNA test results reported to allow determination of EOT response or SVR. Taken together, the agreement in treatment failure rates as defined using two methods, and the identification of known risk factors for treatment failure, indicates that in the absence of sufficient serological data to define SVR, use of relaxed definitions of initial treatment response, LTR and treatment failure within a year may be an effective alternative method to assess the outcomes of HCV treatment.

7.4.3 Comparisons with the literature

The proportion of individuals in UK CHIC who have received treatment for HCV during follow-up is greater than that reported among HIV/HCV co-infected populations in Canada (504, 505), Ireland (506) and from the EuroSIDA cohort (507) where treatment rates between 6% (in one centre in Canada) and 28% (in Ireland) of individuals have been reported. However, the estimate presented in this chapter, for the UK CHIC study, is comparable to that reported from centres across Germany and Austria (508). This may be due to the differences in the co-infected populations between the cohorts. A number of previous studies have reported that there are particularly low rates of treatment among IDU (508, 509). The co-infected population in UK CHIC contains a higher proportion of MSM and a lower proportion of IDU which may explain the higher proportions of individuals in this cohort who receive treatment compared to other cohorts. Prescribing patterns across the various settings where these cohort studies have taken place may also vary. For example treatment may be more accessible in some countries than on others.

The proportion of individuals who fail treatment within the first year after stopping and the proportion of individuals who have successful treatment (as defined as an initial successful treatment and successful long term treatment response) are higher than the SVR rates reported in trials and cohort studies (393, 401). However, since response to treatment was

estimated using a non-standard method, it is difficult to compare these results. In the analyses presented in this chapter HCV viral load at the start of treatment, HCV genotype, being diagnosed with acute infection and longer duration of treatment were all associated with being less likely to fail treatment. This is in agreement with previously published research.

HCV genotype and baseline HCV viral load are established predictors of SVR both in clinical trial settings and among cohorts of HIV/HCV co-infected individuals. For example, in a large prospective cohort study in Spain and Germany, individuals with genotype 2 or 3 infection were nearly 5 times more likely to achieve SVR than individuals with genotype 1 infection. In the same study individuals with baseline HCV viral load of <600000 IU/ml were more than twice as likely to achieve SVR than individuals with baseline HCV viral load ≥600000 IU/ml (491). Similarly, among a cohort of 1701 HIV/HCV co-infected patients in Spain, 38% achieved an SVR and SVR was more than 5 times more likely among individuals with genotype 2 or 3 infection than among individuals with genotype 1 infection. The Spanish study used a different cut-off to investigate the effect of HCV viral load. However, the effect of higher HCV viral load at baseline was also evident in this study where individuals with HCV viral load <500000 IU/ml at baseline were significantly more likely to achieve SVR than individuals with HCV viral load ≥500000 IU/ml at baseline (AOR, 95% CI 1.75, 1.34-2.23) (494).

In the present analysis, not being diagnosed with acute HCV infection was a predictor of failing treatment in the first year. This finding is in agreement with previous studies which have assessed the SVR rate among individuals who are treated in the acute phase of infection. In general SVR rates among individuals who are treated during acute infection are more than double those among individuals treated in the chronic phase of infection. For example, within a small clinic cohort in the UK 62.5% of HIV/HCV co-infected patients achieved SVR when they were treated during acute infection (510). Similarly among 141 HIV/HCV co-infected individuals treated with pegylated-interferon monotherapy, 64.8% achieved SVR (511).

I found no associations between failing HCV treatment and any HIV-related covariates investigated (CD4 count, HIV viral load or HAART regimen at time of starting HCV treatment). Previous studies have reported mixed results with regard to these factors as predictors of successful HCV treatment. Clinical trials of pegylated-interferon and ribavirin among HIV/HCV co-infected individuals have not found any associations between SVR and either CD4 count or HIV viral load (395-399). However, in these clinical trials the majority of included individuals had CD4 counts >500cells/mm^3 and therefore the trials may not have had sufficient power to

detect the impact of lower CD4 on the likelihood of SVR. One small cohort study has found that CD4 may be associated with SVR. In this study, of 32 HIV/HCV co-infected individuals those individuals who had a CD4 count ≥450 at the time of starting HCV treatment were significantly more likely to achieve SVR than those whose CD4 count was <450 cells/mm^3 and that this was related to the early decrease in HCV viral load at the start of treatment (495). A larger study of 141 HIV/HCV co-infected individuals assessing predictors of SVR found that individuals with baseline CD4 ≥300 cells/mm^3 were significantly more likely to achieve SVR than those with CD4 counts <300cells/mm^3 (512). In addition, a further small cohort study of 43 HIV/HCV co-infected individuals found that SVR was significantly lower among individuals who had previous nadir CD4 count of <350 cells/mm^3 (492). Similarly, there is evidence from cohort studies that having had a previous AIDS event may be associated with failing treatment (177, 494). The analyses presented in this chapter may confirm the hypothesis that HIV-related factors are not associated with failing treatment. However, it should be noted that the median CD4 count at starting treatment was >500 cells/mm^3, both for those individuals who fail treatment and for those who do not fail treatment. Therefore in this cohort CD4 counts may not have been low enough to detect differences in treatment outcomes for those individuals with CD4 counts <450 or <350 as has been shown in previous research.

Among those HIV/HCV co-infected individuals in UK CHIC who are in need of treatment, a small percentage were known to have cirrhosis. The proportion of untreated individuals who have significant fibrosis or cirrhosis in UK CHIC is lower than that reported elsewhere (507). The proportion of individuals who have failed treatment and have significant fibrosis or cirrhosis is also less in UK CHIC than has been reported elsewhere (513). Again, this may be due to the smaller proportion of co-infected individuals who are IDU in UK CHIC compared to other cohorts. IDU are likely to have acquired their infection very early in their injecting history and therefore many of them have been infected for long periods of time, whereas MSM have, in general, more recently acquired infection. I have previously shown that HCV incidence is higher among MSM in this cohort than among other risk groups (Chapter 6, section 6.3.3.4). Therefore liver disease has not progressed to such an extent in these individuals with more recent infections.

7.4.4 Strengths and weaknesses

Information on whether individuals are treated or not was obtained both from clinical lists compiled by the treating clinicians and nurses, and through review of notes. This has resulted in a high proportion of individuals having been recorded as having started treatment for HCV

and therefore a large cohort of treated patients whose data are available for analysis. However, the greatest limitation in the analyses presented in this chapter is missing data for post treatment HCV-RNA test results. The difference in treatment success rate reported in this chapter and SVRs reported in other cohorts may, in part, be due to the high number of individuals who do not have an HCV-RNA test result available after stopping treatment. For example, individuals without HCV-RNA test results may be poor attenders and less adherent to a treatment regimen. Therefore it is possible that these individuals may also be less likely to achieve SVR.

Early virological response (EVR) to HCV treatment is defined as a decrease in HCV viral load of $2\log_{10}$ by week 12 of treatment. EVR is strongly associated with SVR in HIV/HCV co-infected individuals (514). However, the limited number of peri and post treatment HCV-RNA test results which were available for analysis also meant that that it was not possible to assess changes in HCV-RNA levels over time and therefore EVR could not be investigated in this cohort. In addition, a small number of co-infected individuals who had been treated had one or more biopsy result or FibroScan® result available. Therefore, it was not possible to assess the effect of liver disease on response to treatment or changes in liver disease among individuals who are treated successfully compared to those who fail treatment and those who are untreated. In previous research the degree of fibrosis/cirrhosis present at the start of treatment has been shown to be associated with treatment success. In particular, those with a METAVIR fibrosis score $\geq$F2 are significantly less likely to achieve SVR than those with METAVIR <2 (177, 498). This is also seen in clinical trials (399).

There are some further limitations which are important to consider in interpreting the results of these analyses. Using the data available in UK CHIC it was not possible to assign a date of infection with HCV. Therefore, in the analysis of time to starting treatment, the first reported positive HCV test was used as a baseline. Individuals may have been infected for some time before this date and therefore time to treatment may be underestimated. However, there is no reason to believe that this underestimation would differ in subgroups and therefore this should not affect the results of the Cox model. The number of individuals who had a recorded reason for stopping treatment was low. Therefore, it was not possible to undertake any further analysis of clinical events which occur during treatment and lead to treatment cessation.

7.4.5 Conclusions

In this cohort of HIV/HCV co-infected individuals there are a high number of individuals who have never received treatment for HCV and an important group of individuals who have failed treatment. Although the rates of cirrhosis in these individuals is currently low, without treatment success liver disease in these individuals will continue to progress. Those individuals who have failed previous treatment and those who have never received treatment but who are at high risk of failing standard interferon-based treatments should be prioritised for newer DAA containing regimens. A subsequent round of hepatitis data collection for UK CHIC is planned. During this process, ensuring that post treatment HCV-RNA test results are available and recorded for all treated individuals should be a priority. Further analysis of the subsequent round of data collected for this cohort should evaluate the whether these individuals have received treatment as the number of options for treatment regimens increases.

Chapter 8 Results 3: HBV treatment strategies and response to treatment

8.1 Background

Controlling HBV replication is key to limiting the progression of HBV-related liver disease, since it has been demonstrated among HBV-mono-infected individuals that higher HBV viral load is associated with increased progression of liver disease (100, 102). HIV/HBV co-infected individuals have higher levels of HBV-DNA, slower rates of HBeAg clearance (260, 364, 382) and increased progression of HBV-related liver disease (261) than HIV mono-infected individuals. However, treatment of HBV and HIV infection has been shown to lead to regression of fibrosis among co-infected individuals (386, 387) and improvements in biochemical measures of liver function even among individuals with advanced liver disease (515).

Among HIV/HBV co-infected individuals, higher HBV-DNA levels are associated with lower CD4 count (304, 388). In addition, higher CD4 counts are associated with lower rates of HCC (334, 335, 367). Therefore the aims of HBV treatment in the context of HIV infection are to reduce the HBV viral load and facilitate seroconversion from HBeAg positivity to anti-HBe positivity while achieving high CD4 counts and suppressed HIV infection.

HIV and HBV both use reverse transcriptase as part of their replication cycle and therefore there are a number of drugs which are active against both viruses: tenofovir; emtricitabine; lamivudine; and entecavir. In addition, HBV can also be treated with adefovir, telbivudine or interferon. In the UK, current guidelines for managing HIV/HBV co-infected individuals recommend commencing treatment for all individuals with a CD4 count less than 500 cells/mm^3. Additionally, it is recommended that all individuals with CD4 counts of greater than 500 cells/mm^3 should have the option of commencing treatment with a specific recommendation to start treatment immediately where HBV-DNA levels are at least 2000 IU/ml or where the individual has significant fibrosis (a METAVIR score of ≥2, Ishak stage ≥2 or a FibroScan® result ≥9KPa) (65).

Individuals starting treatment with CD4 counts more than 500 cells/mm^3 should receive tenofovir and emtricitabine as part of their combination HIV treatment while those with CD4

counts of less than 500 cells/mm^3 should receive tenofovir and either emtricitabine or lamivudine as part of their combination HIV treatment. Use of other drugs active against HBV should be used only where a patient does not wish to or cannot use these recommended regimens (65). These recommendations are applicable to all HBV co-infected individuals irrespective of whether the individuals are chronically or newly infected.

In this chapter I will describe the strategies for treating HBV infection in the context of HIV within the UK CHIC study and assess the virological outcomes of HBV treatment among HIV/HBV co-infected individuals.

8.2 Methods

8.2.1 Inclusion criteria

Hepatitis test data was cleaned as previously described and individuals were assigned to infection categories according to results of HBsAg, anti-HBc and anti-HBs tests (Chapter 5, section 5.3.3). Only those who had ever had an infected status were included in this analysis.

While interferon can be used to treat HBV infection, it is the primary treatment option for HCV infection. Therefore, where individuals are triple-infected, and there is evidence of interferon treatment, this treatment is likely in use for HCV infection. Therefore these analyses were restricted to those individuals who were HIV/HBV co-infected without evidence of HCV infection. There were 444 individuals in the dataset who had evidence of HIV/HBV/HCV triple infection. Of these, 233 individuals had their first positive HCV test before or at the same time as their first positive HBV test. These 223 individuals were excluded from all analysis. A further 211 individuals had their first HCV-positive test after their first positive HBV test. These individuals were included in the analysis of HBV treatment but their follow-up was censored when they became HCV-positive. Differences between those individuals who were included in the analysis, those who were excluded and those who were included but whose follow-up was censored are shown in Table 8.1.

Among the HBV co-infected cohort, there were 16 individuals who had evidence of treatment for HBV infection but for whom the dates of treatment were missing. These individuals were excluded from the analyses.

Table 8.1 Characteristics of individuals included in the analysis compared to those who are excluded on the basis of HCV positivity

	Included N=1318		Excluded from start N=233		Included but censored N=211		P-value
	N	%	N	%	N	%	
Median age (years)(IQR)	37	(31, 43)	39	(34, 45)	37	(31, 41)	0.002
Ethnicity							
White	640	48.6	160	68.7	149	70.6	<0.0001
Black African	441	33.5	15	6.4	15	7.1	
Other black	79	6.0	3	1.3	11	5.2	
Other/unknown	158	12.0	55	23.6	36	17.1	
HIV exposure group							
MSM	734	55.7	114	48.9	170	80.6	<0.0001
IDU	14	1.1	55	23.6	9	4.3	
Male heterosexual	258	19.6	34	14.6	16	7.6	
Female heterosexual	236	17.9	21	9.0	5	2.4	
Other/unknown	76	5.8	9	3.9	11	5.2	
Year of first positive HIV test							
<1996	102	7.7	2	1.0	11	5.2	<0.0001
1996-1999	109	8.3	5	2.2	21	10.0	
2000-2004	473	35.9	29	12.5	48	22.8	
2005-2009	477	36.2	146	62.7	125	59.2	
≥2010	157	11.9	51	21.9	6	2.8	
Median CD4 count (cells/mm^3) (IQR)[1]	308	(150, 479)	401	(226, 605)	448	(290, 630)	<0.0001
HIV viral load (copies/ml)							
≤50	298	22.6	104	44.6	61	28.9	<0.0001
>50	756	57.4	115	49.4	109	51.7	
Unknown	264	20.0	14	6.0	41	19.4	
HIV treatment							
None	724	54.9	89	38.2	124	58.7	<0.0001
<3 drugs	59	4.5	5	2.2	3	1.4	
≥3 drugs	535	40.6	139	59.6	84	39.8	
HBV treatment							
None	832	63.1	95	40.8	138	65.4	<0.0001
1 drug	235	17.8	55	23.6	46	21.8	
>1 drug	251	19.0	83	35.6	27	12.8	

[1] CD4 count was unknown for 159 included individuals, 13 excluded individuals and 26 individuals whose follow-up was censored

8.2.2 First recorded HBV-active treatment

Baseline date was defined as the latest of the first HBsAg test or entry into the study cohort. Cohort entry was used as baseline for those individuals who had a first positive HBsAg test prior to this date as data is more reliable once an individual has entered the cohort and is under active follow-up. HBV-active treatment was defined as any regimen which included at least one of lamivudine; tenofovir; emtricitabine; adefovir; entecavir; telbivudine; or interferon (pegylated or not). HBV treatment regimens were defined as a recommended regimen type where two or more HBV-active drugs were being used; or an other regimen type where only one HBV-active drug was being used. HAART was defined as three or more HIV drugs (which may include those HIV drugs which are also active against HBV).

Individuals were defined as being on HBV treatment at the start of follow-up if there was evidence that they were currently taking any HBV-active drugs at the time of their first positive HBsAg test. Individuals who either were or were not on HBV treatment at baseline were then further characterised according to their HIV treatment: HAART; non-HAART HIV treatment (fewer than three HIV active drugs); or no HIV treatment. Similarly, those individuals who were on HBV treatment at baseline were further categorised according to the number of HBV-active drugs they were taking. The specific drugs included in the HBV treatment regimens which were in use at baseline were then described.

Multivariable logistic regression was used to assess baseline characteristics associated with being on HBV treatment at the start of follow-up. Baseline age and CD4 count were included as continuous variables. Ethnicity, HIV exposure group, HIV viral load, HBV viral load and HBeAg status were included as categorical variables. Baseline HBV-DNA value and baseline HBeAg status were unknown for 85% and 33% of individuals respectively. Therefore three separate multivariable models were constructed. Model 1 included baseline demographic and HIV-related covariates found to be associated with being on treatment in the univariable analysis. Model 2 also included baseline HBV-DNA, where known, and model 3 included baseline HBeAg where known.

Starting HBV treatment for the first time was assessed among those individuals who were not on HBV treatment at baseline. Individuals were defined as starting HBV treatment if there was evidence of them commencing any regimen including at least one agent active against HBV. These individuals were further characterised according to their HIV treatment and the number of HBV-active drugs contained in the first regimen. Those individuals who were not on HBV

treatment at baseline and who did not start HBV treatment during follow-up were characterised according to whether or not they started HIV treatment during follow-up.

Time to starting treatment was described using Kaplan Meier plots. Those individuals who did not commence treatment were followed-up until their last seen date or their date of death, where an individual had died. Predictors of starting HBV treatment were identified using a multivariable Cox proportional hazards model. CD4 count, HIV viral load, HBV viral load and HBeAg status were included in the analysis as time-updated variables. Age, ethnicity, HIV exposure group and year of first positive test were fixed at baseline.

Among those individuals whose first evidence of HBV treatment was with a regimen that included only one HBV-active agent, changes in treatment regimen were examined to identify those individuals who were still not on a recommended regimen type by the end of follow-up. The clinical characteristics of these individuals were described.

8.2.3 Virological response to treatment

Three virological outcomes of HBV treatment were assessed: loss of HBeAg; development of anti-HBe; and suppression of HBV replication. Baseline HBeAg status was assessed as the result of any HBeAg test up to two weeks after starting treatment. Individuals were included in the analysis if they were HBeAg-positive at baseline, and had at least one further HBeAg test result available after starting treatment. Loss of HBeAg was defined as any negative HBeAg test result after the start of treatment. Anti-HBe seroconversion was assessed among those individuals who had evidence of HBeAg loss after starting treatment. Seroconversion was defined as any positive anti-HBe test after loss of HBeAg. Suppression of HBV viral replication was assessed among all individuals who were known to be HBV-DNA positive at baseline. Suppression was defined as any negative HBV-DNA test result after starting treatment.

For all analyses individuals were followed from the latest of starting HBV treatment or entry into the cohort until the earliest of evidence of the outcome of interest, the last follow-up date or the date of death. Factors associated with each treatment outcome were assessed using Cox proportional hazards models (a separate model was constructed for each treatment outcome). CD4 count, HIV viral load and HBV regimen type were included in the analyses as time-updated variables. Age, ethnicity, HIV exposure group and year of first positive HBsAg test were fixed at baseline. Baseline HBeAg was also included in the analysis of factors associated with suppression of HBV viral replication. HBV treatment type (recommended or

not) was included in all models irrespective of associations in the univariable analyses in order to test whether apparent differences in treatment response according to other demographic and clinical characteristics were, in fact, due to use of different treatment strategies.

8.3 Results

8.3.1 First recorded HBV-active treatment

There were 1529 HIV/HBV co-infected individuals, included in the analysis. Of these 559 (36.6%) were taking any drugs which were active against HBV at baseline. Further details about HIV and HBV treatment at baseline are shown in Figure 8.1. The majority of individuals who were on HBV-active treatment at the start of follow-up were on a HAART regimen which included at least two HBV-active drugs. Baseline characteristics of individuals who were on treatment at the start of follow-up compared to those who were not were compared using ORs from univariable logistic regression (Table 8.2). In univariable analysis, older individuals were significantly more likely to be on HBV-active treatment at the start of follow-up. Compared to those individuals whose first positive HBV test was in 2005-9, those whose first positive HBV test was in earlier years were less likely to be on HBV-active treatment at the start of follow-up. Individuals with detectable HIV viral load and unknown HIV viral load were less likely to be in HBV-active treatment at the start of follow up than those with undetectable viral load. Individuals with higher HBV viral load ($\geq$2000 IU/ml) were more likely than those with HBV viral load <2000 IU/ml to be on treatment at the start of follow-up.

Three multivariable models were constructed to identify those factors which were independently associated with being on treatment at the start of follow-up (Table 8.3). The basic model (model 1) included those demographic and HIV-related factors identified as being significantly associated with being on treatment at the start of follow-up in the univariable analysis: age; year of first positive test; and HIV viral load. These variables remained associated with being on treatment at the start of follow-up after being entered to the multivariable model. Older individuals remained significantly more likely to be on treatment at the start of follow-up than younger individuals (AOR, 95% CI: 1.26, 1.09-1.46 per additional 10 years of age). Compared to those individuals whose first recorded evidence of HBV infection was in 2005-2009, those who were first recorded as infected before 1996 were less likely to be on treatment at the start of follow-up (AOR, 95% CI: 0.29, 0.12-0.71), as were those whose first positive HBV test was in 2000-2004 (AOR, 95% CI: 0.74, 0.56-0.98). Compared to individuals with undetectable HIV viral load, those with detectable HIV viral load (>50 copies/ml) were significantly less likely to be on HBV-active treatment at the start of follow-up (AOR, 95% CI: 0.10, 0.07-0.14).

These associations remained unchanged when either HBV-DNA status or HBeAg status were added to the model. When HBV-DNA status was included in the model (model 2), those with unknown HBV-DNA levels were less likely to be on treatment than those with lower HBV-DNA levels (AOR 0.42, 95% CI: 0.26-0.68). There was no significant difference between those with higher or lower HBV-DNA in the likelihood of being on treatment (AOR 0.58, 95% CI: 0.32-1.08). When HBeAg status was added to the basic model (model 3), there was no association shown between HBeAg status and being on treatment at the start of follow-up.

Figure 8.1 HIV and HBV treatment among co-infected individuals at baseline

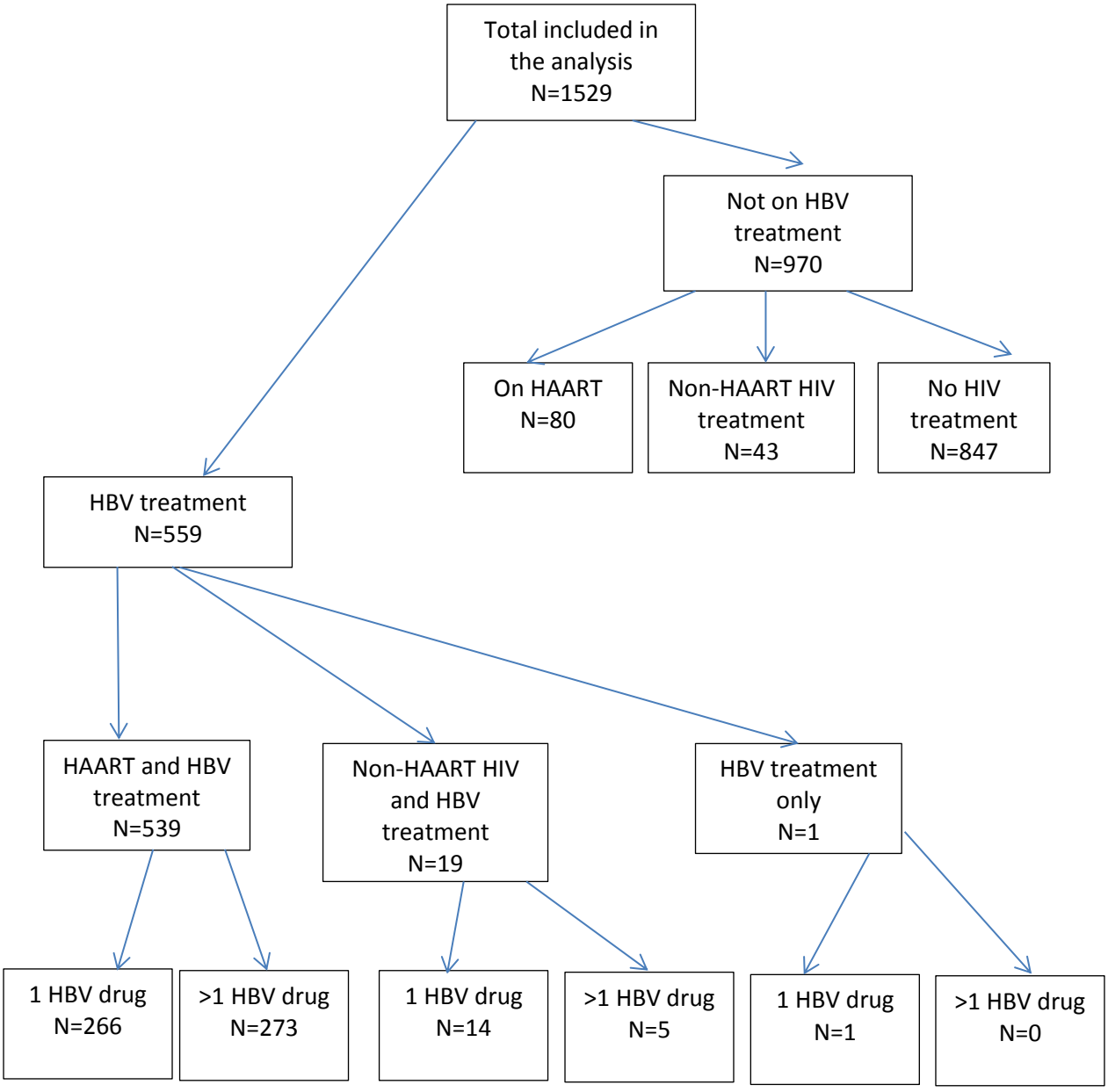


Table 8.2 Baseline characteristics and crude odds ratios from univariable logistic regression of factors associated with being on HBV-active treatment at the start of follow-up

	Not on treatment		On treatment		Univariable analysis		
	Number	**%**	**Number**	**%**	**OR**	**95% CI**	**P value**
Median age (years) (IQR)	36	(30, 41)	39	(34, 45)	1.61	1.42-1.83	<0.0001
Ethnicity							
White	509	52.5	280	50.1	1	-	-
Black African	278	28.7	178	31.8	1.16	0.92-1.48	0.21
Black other	58	6.0	32	5.7	1.00	0.64-1.58	0.99
Other/unknown	125	12.9	69	12.3	1.00	0.72-1.39	0.98
HIV exposure group							
MSM	599	61.8	305	54.6	1	-	-
IDU	12	1.2	11	2.0	1.80	0.79-4.13	0.16
Male heterosexual	157	16.2	117	20.9	1.46	1.11-1.93	0.01
Female heterosexual	146	15.1	95	17.0	1.28	0.95-1.71	0.10
Other/unknown	56	5.8	31	5.6	1.09	0.69-1.72	0.72
Year of first positive HBV test							
<1996	107	11.0	6	1.1	0.07	0.03-0.17	<0.0001
1996-1999	100	10.3	30	5.4	0.39	0.25-0.61	<0.0001
2000-2004	329	33.9	192	34.4	0.76	0.60-0.97	0.03
2005-2009	341	35.2	261	46.7	1	-	-
≥2010	93	9.6	70	12.5	0.98	0.69-1.40	0.92

	Not on treatment		On treatment		Univariable analysis		
	Number	**%**	**Number**	**%**	**OR**	**95% CI**	**P value**
Median CD4 count (cells/mm^3) (IQR)	335	(185, 504)	310	(143, 500)	0.98	0.94-1.03	0.36
HIV viral load (copies/ml)							
<50	70	7.2	289	51.7	1	-	-
>50	626	64.5	239	42.8	0.09	0.07-0.13	<0.0001
Unknown	274	28.3	31	5.6	0.03	0.02-0.04	<0.0001
HBV viral load (IU/ml)							
<2000	35	3.6	70	12.5	1	-	-
≥2000	65	6.7	56	10.0	0.43	0.25-0.74	0.002
Unknown	870	89.7	433	77.5	0.24	0.16-0.38	<0.0001
HBeAg status							
Negative	292	30.1	141	25.2	0.95	0.73-1.24	0.71
Positive	392	40.4	199	35.6	1	-	-
Unknown	286	29.5	219	39.2	1.51	1.18-1.93	0.001

Table 8.3 Adjusted odds ratios from multivariable logistic regression models of factors associated with being on HBV-active treatment at the start of follow-up

	Multivariable model 1[1]			Multivariable model 2[2]			Multivariable model 3[3]		
	AOR	**95% CI**	**P value**	**AOR**	**95% CI**	**P value**	**AOR**	**95% CI**	**P value**
Median age (years) (IQR)[4]	1.26	1.09-1.46	0.001	1.24	1.07-1.44	0.004	1.27	1.10-1.47	0.001
Year of first positive HBV test									
<1996	0.29	0.12-0.71	0.01	0.31	0.12-0.76	0.01	0.29	0.12-0.72	0.01
1996-1999	0.79	0.48-1.30	0.36	0.87	0.53-1.43	0.57	0.84	0.50-1.38	0.49
2000-2004	0.74	0.56-0.98	0.03	0.76	0.57-1.01	0.06	0.74	0.56-0.98	0.04
2005-2009	1	-	-	1	-	-	1	-	-
≥2010	0.91	0.61-1.37	0.65	0.84	0.55-1.26	0.40	0.95	0.63-1.44	0.82
HIV viral load (copies/ml)									
≤50	1	-	-	1	-	-	1	-	-
>50	0.10	0.07-0.14	<0.0001	0.10	0.08-0.14	<0.0001	0.10	0.08-0.14	<0.0001
Unknown	0.04	0.03-0.07	<0.0001	0.04	0.03-0.07	<0.0001	0.04	0.03-0.07	<0.0001
HBV viral load (IU/ml)									
<2000	-	-	-	1	-	-	-	-	-
≥2000	-	-	-	0.58	0.32-1.08	0.09	-	-	-
Unknown	-	-	-	0.42	0.26-0.68	0.001	-	-	-

	Multivariable model 1[1]			Multivariable model 2[2]			Multivariable model 3[3]		
	AOR	**95% CI**	**P value**	**AOR**	**95% CI**	**P value**	**AOR**	**95% CI**	**P value**
HBeAg status									
Negative	-	-	-	-	-	-	0.92	0.68-1.27	0.62
Positive	-	-	-	-	-	-	1	-	-
Unknown	-	-	-	-	-	-	1.19	0.88-1.60	0.26

[1] Model 1 includes those demographic and HIV-related factors associated with being on treatment in univariable analysis.
[2] Model 2 includes those demographic and HIV-related factors associated with being on treatment in univariable analysis and HBV viral load
[3] Model 3 includes those demographic and HIV-related factors associated with being on treatment in univariable analysis and HBeAg status
[4] OR per 10 additional years

Those individuals who were not on treatment at baseline were followed-up until they started treatment, were lost to follow-up or died. The majority of individuals who started treatment during follow-up commenced HAART which included at least two HIV active drugs. Of those who did not start treatment, only a small minority started any kind of HIV treatment. Details of treatment commencement among these individuals are shown in Figure 8.2. The 970 individuals contributed a total of 1985 person-years of follow-up during which 750 started treatment. Median follow-up was 0.9 years (IQR 0.2, 3.0): 0.78 (IQR 0.19, 2.71) among those who started HBV treatment during follow-up and 1.77 (IQR 0.42, 3.89) among those who did not start HBV treatment during follow-up. Time to starting treatment is shown in Figure 8.3.

In univariable analysis, starting treatment was associated with older age, black ethnicity (black African and other black ethnic groups were more likely to start treatment), heterosexual HIV exposure group (male and female), other HIV exposure group, having first positive test after 2005 and having a lower CD4 count (Table 8.4). In multivariable analysis the association with black African ethnicity was lost (AHR, 95% CI: 0.85, 0.65-1.11) while individuals of other black remained more likely than white individuals to start treatment (AHR, 95% CI: 1.45, 1.05-2.00). The association between heterosexual HIV exposure and starting treatment was lost after adjusting for other factors. In addition there was no significant difference in starting treatment between MSM and individuals of other HIV exposure groups. However, in the multivariable analysis, compared to MSM, IDU were significantly less likely to start treatment (AHR 0.45, 95% CI: 0.22-0.96). The associations seen in univariable analysis between later years of first positive and starting treatment were also observed in the multivariable model. CD4 count also remained significantly associated with starting treatment, with those individuals who had higher CD4 counts being less likely to start treatment (AHR, 95% CI: 0.61, 0.58-0.64).

Figure 8.2 HIV and HBV treatment among co-infected individuals who start treatment during follow-up

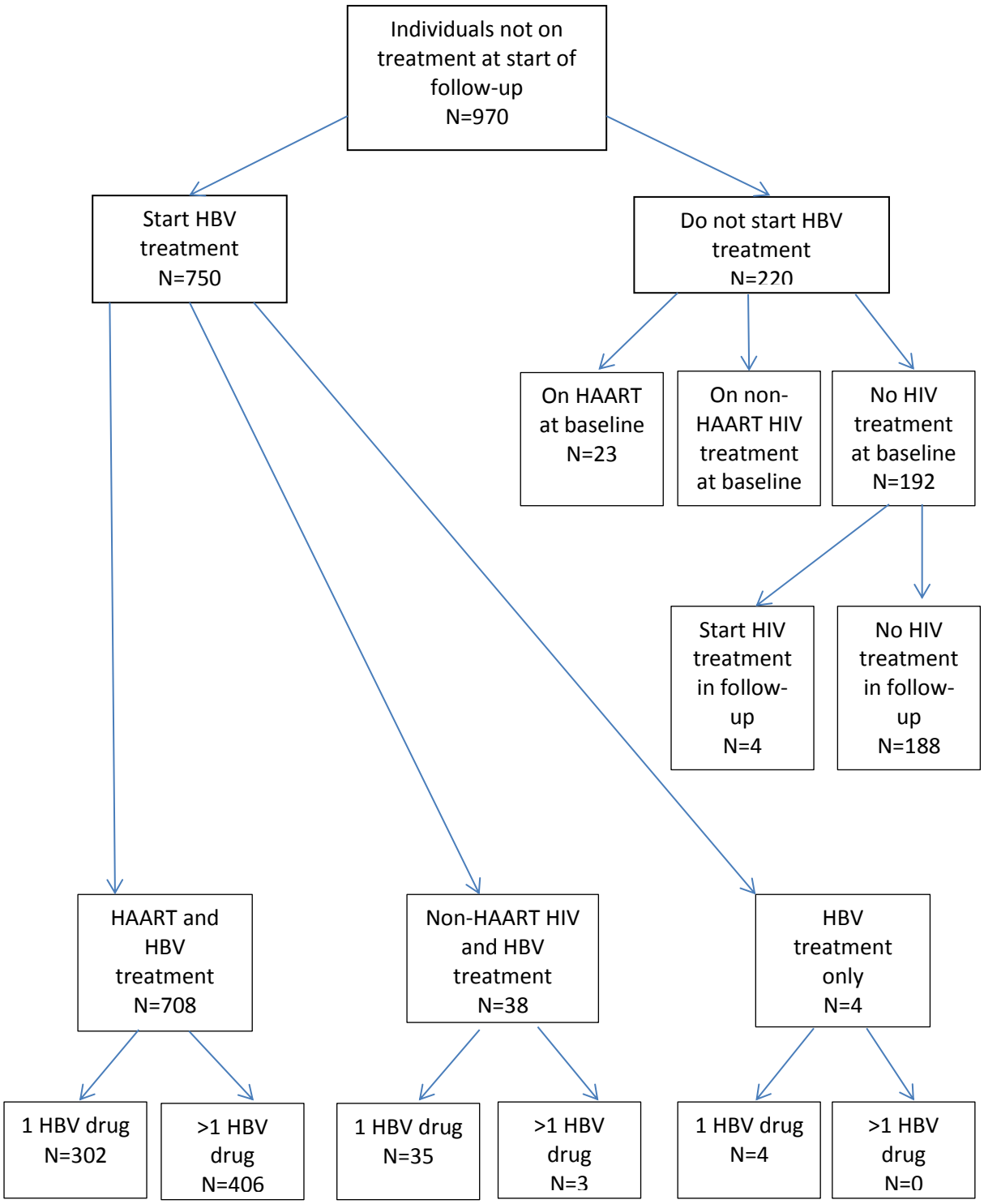


Table 8.4 Hazards ratios from univariable and multivariable Cox Proportional Hazards models of factors associated with starting treatment

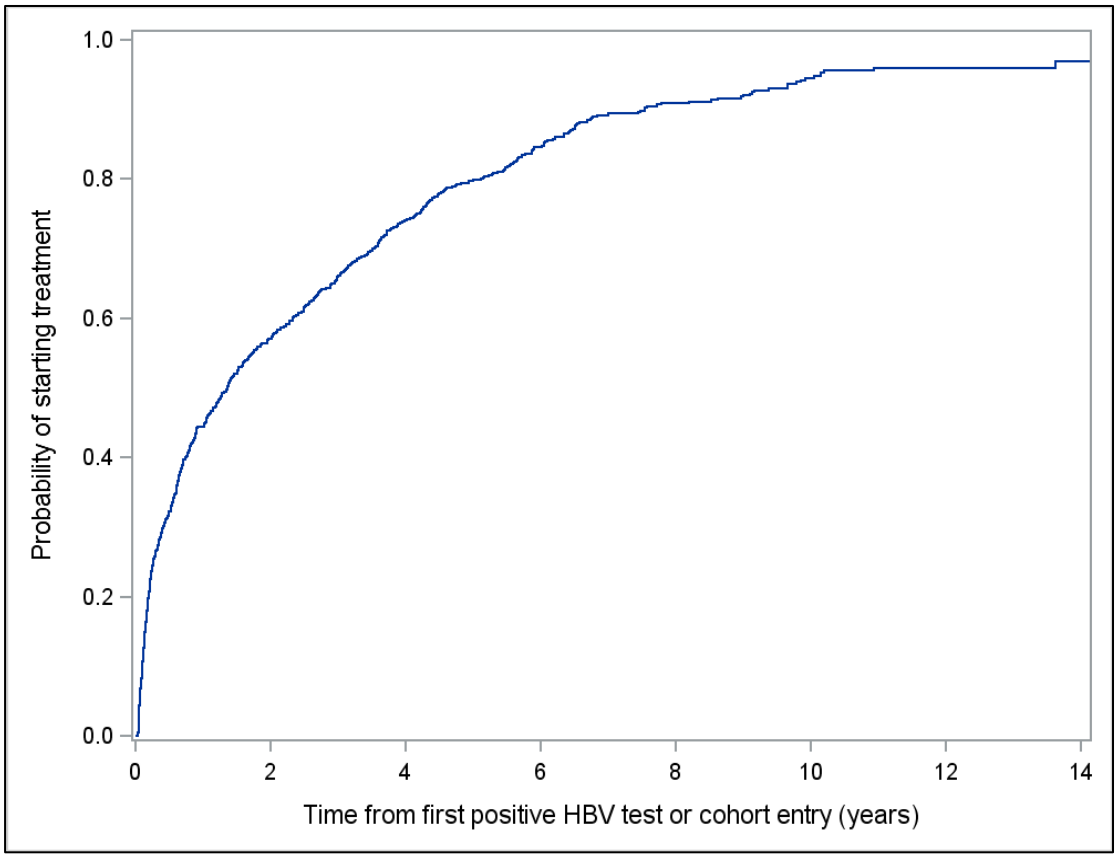
	Univariable analysis			Multivariable analysis		
	HR	**95% CI**	**P value**	**AHR**	**95% CI**	**P value**
Baseline age (per additional 10 years)	1.28	1.17-1.40	<0.0001	1.02	1.01-1.02	0.001
Ethnicity						
White	1	-	-	1	-	-
Black African	1.29	1.09-1.52	0.003	0.85	0.65-1.11	0.21
Other black	1.57	1.15-2.13	0.004	1.45	1.05-2.00	0.02
Other/unknown	0.94	0.74-1.19	0.59	0.79	0.61-1.02	0.06
HIV Exposure group						
MSM	1	-	-	1	-	-
IDU	0.71	0.34-1.50	0.37	0.45	0.22-0.96	0.04
Male heterosexual	1.57	1.29-1.92	<0.0001	0.86	0.66-1.13	0.28
Female heterosexual	1.41	1.15-1.73	0.001	1.05	0.78-1.43	0.74
Other/unknown	1.91	1.38-2.66	0.0001	1.11	0.78-1.59	0.57
Year of first HBV-positive test						
<1996	0.57	0.44-0.72	<0.0001	0.29	0.22-0.38	<0.0001
1996-1999	0.68	0.53-0.87	0.002	0.42	0.32-0.55	<0.0001
2000-2004	0.79	0.66-0.95	0.01	0.52	0.43-0.63	<0.0001
2005-2009	1	-	-	1	-	-
≥2010	1.97	1.47-2.64	<0.0001	2.39	1.48-3.22	<0.0001

	Univariable analysis			Multivariable analysis		
	HR	**95% CI**	**P value**	**AHR**	**95% CI**	**P value**
Current CD4 count (per 100 cells/mm^3)	0.67	0.64-0.69	<0.0001	0.61	0.58-0.64	<0.0001
Current HIV Viral load (copies/ml)						
≤50	1	-	-	-	-	-
>50	1.22	0.98-1.52	0.08	-	-	-
Current HBV-DNA (IU/ml)[1]						
<2000	1	-	-	-	-	-
≥2000	1.63	1.15-2.33	0.01	-	-	-
Current HBeAg status[2]						
Positive	1.09	0.92-1.28	0.32	-	-	-
Negative	1	-	-	-	-	-

[1] HBV-DNA was not included in the multivariable model as only 254 individuals had at least one measure during follow-up (158 treated individuals and 69 individuals who did not start treatment).

[2] Only 656 individuals had at least one HBeAg test during follow-up (520 treated individuals and 136 individuals who were not treated)

Figure 8.3 Kaplan Meier curve and corresponding life table showing time to starting HBV-active treatment



Time from first positive	2	4	6	8	10	12	14
Number eligible	340	170	85	42	17	8	3

Among both those who started treatment at or before the start of follow-up and those who commenced treatment after the start of follow-up, the most common initial treatment strategy was HAART which included two or more HBV-active drugs. First HBV-active treatment regimens used are shown in Table 8.5. The most commonly used first HBV-active regimen was lamivudine only followed by tenofovir plus emtricitabine.

Table 8.5 HBV-active drug combinations used in first recorded HBV-active regimen

HBV drug combination	Individuals on HBV treatment at baseline		Individuals starting HBV treatment after baseline		Total	
	Number	%	Number	%	Number	%
Regimens of 1 HBV-active drug						
Lamivudine	245	43.8	276	36.8	521	39.8
Tenofovir	32	5.7	49	6.5	81	6.2
Adefovir	1	0.2	6	0.8	7	0.5
Emtricitabine	3	0.5	4	0.5	7	0.5
Interferon	0	0.0	1	0.1	1	0.1
Unknown drug	0	0.0	3	0.4	3	0.2
Regimens including >1 HBV-active drug						
Tenofovir + emtricitabine	178	31.8	315	42.0	493	37.7
Lamivudine + tenofovir	94	16.8	94	12.5	188	14.4
Tenofovir + emtricitabine + interferon	1	0.2	0	0.0	1	0.1
Lamivudine + tenofovir + emtricitabine	5	0.9	2	0.3	7	0.5

Among all those individuals who have any HBV treatment (N=1309), 679 start treatment on a recommended regimen (one which includes at least three HIV-active drugs and 2 HBV-active drugs). Of the 630 individuals whose first HBV treatment is not a recommended regimen, 445 (70.6%) subsequently switch to a recommended regimen (median time to switching to recommended regimen was 3.1 years, IQR 0.9-5.7 years). Clinical characteristics of the 185 individuals who did not receive a recommended regimen during follow-up are shown in Table 8.6. The majority of these individuals had high CD4 counts (>60% had a CD4 count >350 cells/mm^3) and detectable HIV viral load (>50 copies/ml). HBV-DNA was unknown for 70% of these individuals but where known the majority had HBV-DNA <2000 IU/ml. Almost half of these individuals were known to be HBeAg-negative. There was a very small group of individuals (N=6) who had evidence of cirrhosis. For all these individuals cirrhosis had been identified by liver biopsy.

Table 8.6 Clinical Characteristics of individuals on non-standard HBV-active regimens at the end of follow-up

		Number of individuals	%
Median age (years) (IQR)		45	(38, 51)
CD4 count (cells/mm^3)	≤200	29	15.7
	201-350	37	20.0
	351-500	37	20.0
	>500	80	43.2
	Unknown	2	1.1
HIV viral load (copies/ml)	≤50	131	70.8
	>50	51	27.6
	Unknown	3	1.6
HBV viral load (IU/ml)	<2000	45	24.3
	≥2000	10	5.4
	Unknown	130	70.3
HBeAg status	Negative	91	49.2
	Positive	47	25.4
	Unknown	47	25.4
APRI Score	0-0.5	10	5.4
	0.6-1.5	10	5.4
	1.5-2.0	0	0.0
	>2.0	1	0.5
	Unknown	164	88.6
FibroScan® Result (KPa)	<7	5	2.7
	7-9	1	0.5
	10-13	0	0.0
	≥14	0	0.0
	Unknown	179	96.8
Biopsy result	No significant fibrosis	1	0.5
	Fibrosis, but no cirrhosis	7	3.8
	Cirrhosis	6	3.52
	Unknown	171	92.4
Any evidence of cirrhosis	No cirrhosis	32	17.3
	Cirrhosis	6	3.2
	Unknown	147	79.5

8.3.2 Virological response to treatment

Of all treated individuals, 769 had a baseline HBeAg status, 319 were HBeAg-negative and 450 were HBeAg-positive. Of the 450 who were positive at baseline 372 had at least one further HBeAg test result after starting treatment and so were included in the analysis. Of the 372 HBeAg-positive individuals with a further test result available, 147 (39.5%) had a negative test at some point during follow-up. Median time follow-up time was 4.1 years (IQR 1.5, 10.9 years): 1.6 years (IQR 0.7, 4.3 years) for individuals who lost HBeAg; and 5.9 years (IQR 3.0, 9.4 years) for those who did not lose HBeAg. Of the 147 individuals who lost HBeAg, an anti-HBe test result was available for 137 individuals. Of these, 79/137 (57.7%) could be defined as having seroconverted to anti-HBe positive after starting treatment.

Baseline HBV-DNA status was known for 404 individuals: 296 (73.3%) were positive and 108 (26.7%) were negative. Of those who were positive at baseline, 252 had at least one further test result after starting treatment so response to treatment could be assessed. Among these individuals 206 (81.7%) had a response to treatment defined as a negative test result after starting treatment. Median follow-up among those who did not suppress HBV was 1.8 years (IQR 0.8, 3.8) and median time to suppression was 0.9 years (IQR 0.4, 1.7 years).

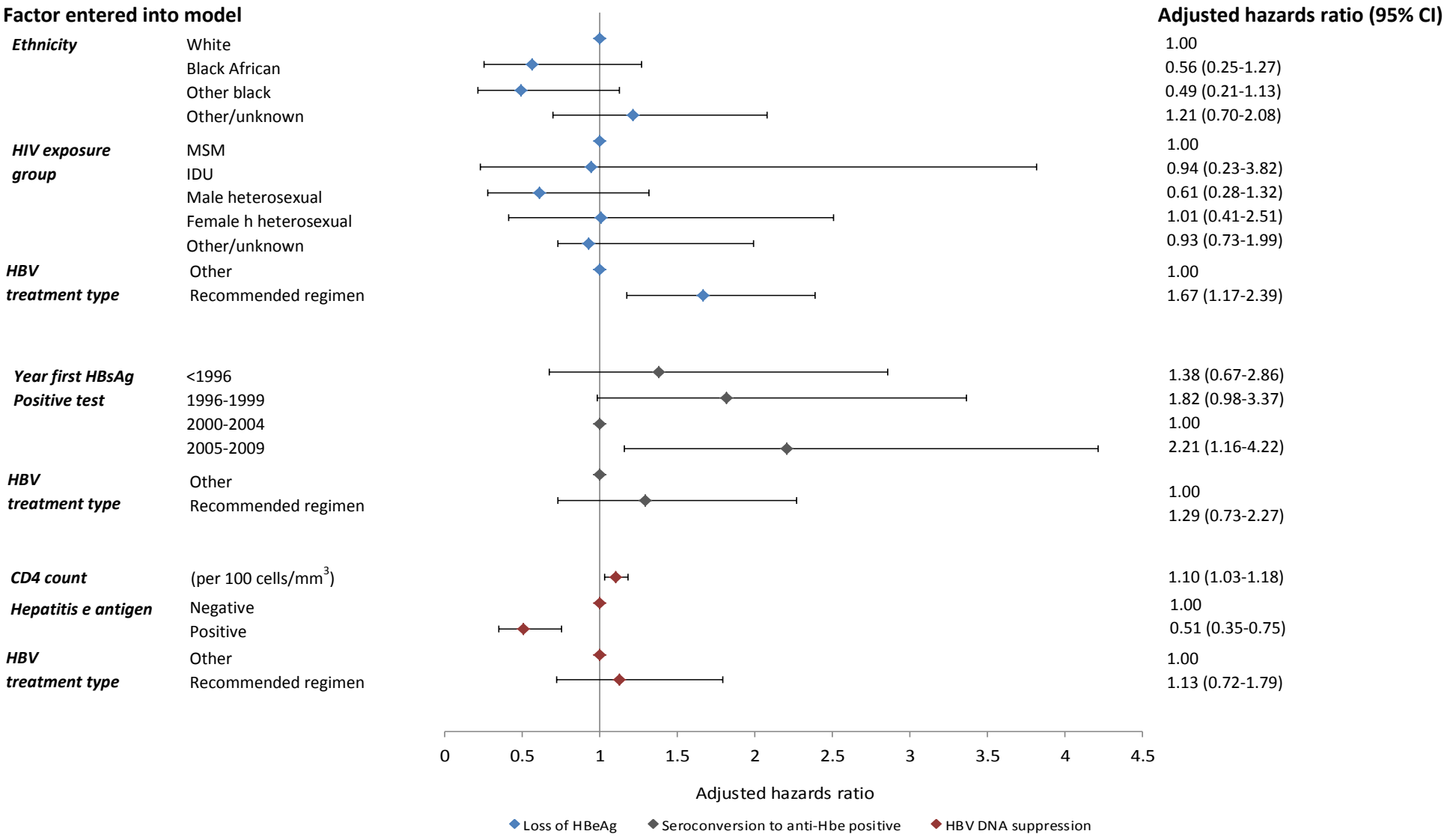
Independent predictors of each of the three treatment outcomes were investigated using separate Cox proportional hazards models. Results of the univariable analyses are shown in Table 8.7. Results of the multivariable analyses are shown in Figure 8.4. Being on a recommended HBV treatment regimen was significantly associated with loss of HBeAg after commencing treatment (AHR 1.67, 95% CI: 1.17-2.39) compared to being on other treatment regimens. Compared to those who commenced HBV treatment in the years 2000-2004, those who commenced treatment in later years (2005-2009) were significantly more likely to have evidence of anti-HBe seroconversion (AHR 2.21, 95% CI: 1.16-4.22). Higher CD4 count was significantly associated with HBV-DNA suppression, although the effect size was small (AHR 1.10, 95% CI: 1.03-1.18 per 100 cells/mm^3 increase). Compared to those who were HBeAg-negative at baseline, those who were HBeAg-positive were less likely to supress HBV-DNA (AHR 0.51, 95% CI: 0.35-0.75).

Table 8.7 Hazard ratios from univariable Cox proportional hazards models of predictors of HBV treatment response

	HBeAg loss			Anti-HBe seroconversion			HBV-DNA suppression		
	HR	**95% CI**	**P value**	**HR**	**95% CI**	**P value**	**HR**	**95% CI**	**P value**
Age (per 10 years)	1.16	0.95-1.42	0.16	0.90	0.67-1.20	0.47	1.08	0.91-1.29	0.36
Ethnicity									
White	1	-	-	1	-	-	1	-	-
Black African	0.45	0.27-0.76	0.003	1.08	0.53-2.18	0.83	0.82	0.60-1.13	0.23
Other black	0.47	0.21-1.08	0.08	0.53	0.07-3.80	0.52	0.64	0.33-1.28	0.21
Other/unknown	1.21	0.72-2.02	0.047	1.21	0.62-2.37	0.58	0.78	0.51-1.21	0.27
HIV Exposure group									
MSM	1	-	-	1	-	-	1	-	-
IDU	1.11	0.27-4.50	0.88	0.93	0.13-6.71	0.94	1.14	0.36-3.59	0.82
Male heterosexual	0.43	0.24-0.78	0.01	1.25	0.57-2.75	0.57	0.77	0.53-1.13	0.18
Female heterosexual	0.65	0.34-1.24	0.19	0.27	1.61-0.69	0.27	0.82	0.55-1.22	0.32
Other/unknown	0.85	0.41-1.74	0.65	1.00	0.36-2.75	0.99	0.70	0.39-1.27	0.24
Year of first HBV-positive test									
<1996	1.45	0.84-2.50	0.18	1.27	0.63-2.58	0.51	1.28	0.52-0.35	0.60
1996-1999	1.15	0.73-1.83	0.55	1.65	0.93-2.94	0.09	1.84	0.66-4.95	0.25
2000-2004	1	-		1	-		1	-	-
2005-2009	1.17	0.76-1.79	0.47	2.41	1.30-4.47	0.01	0.98	0.74-1.32	0.92
≥2010	1.78	0.71-4.51	0.22	5.75	1.31-25.30	0.02	1.02	0.58-1.80	0.94

	HBeAg loss			Anti-HBe seroconversion			HBV-DNA suppression		
	HR	**95% CI**	**P value**	**HR**	**95% CI**	**P value**	**HR**	**95% CI**	**P value**
Current CD4 count (per 100 cells/mm^3)	1.04	0.98-1.10	0.16	0.94	0.85-1.03	0.19	1.07	1.02-1.13	0.01
Current HIV viral load (copies/ml)									
≤50	1	-	-	1	-	-	1	-	-
>50	0.80	0.54-1.18	0.26	1.34	0.79-2.28	0.27	0.89	0.64-1.24	0.49
Timing of starting HBV treatment									
Before first positive	1	-	-	0.66	0.41-1.07	0.09	0.83	0.62-1.11	0.20
After first positive	0.73	0.53-1.02	0.06	1	-	-	1	-	-
HBV treatment type									
Recommended regimen	1.65	1.15-2.35	0.01	1.31	0.81-2.11	0.27	1.42	0.97-2.07	0.07
Other regimen	1	-	-	1	-	-	1	-	-
HBeAg status									
Negative	N/A	N/A	N/A	N/A	N/A	N/A	1	-	-
Positive	N/A	N/A	N/A	N/A	N/A	N/A	0.55	0.38-0.79	0.001

Figure 8.4 Adjusted hazard ratios from multivariable Cox proportional hazards models of factors associated with each of the three virological responses to HBV treatment (HBeAg loss, anti-HBe seroconversion and HBV-DNA suppression)



8.4 Discussion

8.4.1 Summary of findings

In this cohort of HIV/HBV co-infected individuals, the large majority commenced treatment for HIV and HBV either before or during follow-up. In addition, the most common treatment regimens included at least 3 anti-HIV and 2 anti-HBV drugs. Tenofovir and emtricitabine was the most commonly used combination of anti-HBV drugs followed by tenofovir and lamivudine. These results indicate that guidelines for treatment of HIV/HBV co-infection are largely well adhered to among this group of patients.

Among those where response to treatment could be assessed, being on a recommended treatment regimen (compared to being on a regimen containing only one anti-HBV drug), having a higher CD4 count, starting treatment in later years and being HBeAg-negative at baseline were all predictors of favourable treatment responses. However, more than 60% of individuals remained HBeAg-positive and almost 20% of individuals did not suppress HBV-DNA throughout follow-up despite receiving treatment.

8.4.2 Interpretation of results

Although the majority of individuals in this cohort did start treatment for HBV during follow-up it is important to understand who those individuals who have not been treated are. There were several predictors of not starting treatment. Firstly, in this cohort, not starting treatment for HBV infection was independently associated with higher CD4 count. Since the guidelines for treatment recommend commencing treatment when CD4 count falls below 500 cells/mm^3, it is likely that the association between higher CD4 counts and not starting treatment is due to individuals who have yet to reach the threshold for commencing treatment. Secondly, individuals who had a very long standing HBV infection (a first positive result prior to 1996) were less likely to be on treatment at the start of follow-up and less likely to commence treatment during follow-up. One explanation for this is that this group of individuals may include those who have cleared their HBV infection previously. Finally, IDU were less likely to start HBV treatment compared to MSM. This finding is consistent with other analyses which have shown that IDU are less likely to start HIV treatment than individuals who acquired their HIV through sex or other transmission modes (516, 517) and are more likely to be lost to follow-up at all stages of care (518).

Similarly, although most individuals either commenced treatment with 2 or more HBV drugs or switched to a regimen of 2 or more HBV drugs it is important to understand the possible reasons why a small group of individuals start treatment with a regimen containing only one HBV-active drug. A high proportion of these individuals was known to be HBeAg-negative and had low levels of HBV-DNA and high CD4 counts. These results indicate that these individuals have yet to reach any of the thresholds for treatment commencement.

An important finding of the analyses presented in this chapter is that those individuals who started treatment on a recommended regimen (at least two HBV drugs) were more likely to lose HBeAg than those who started on any other regimen. Since HBeAg loss is associated with favourable liver outcomes (260) and low levels of HBV-DNA (519), this finding reinforces the importance of using at least two HBV-active drugs within an HIV/HBV treatment regimen. Although this analysis did not specifically investigate the impact of HAART on HBV infection, the finding that higher CD4 counts were associated with suppression of HBV replication also highlights the importance of successful HIV treatment as a key component of HBV management in the co-infected population.

Individuals whose first positive HBsAg tests were in later years were more likely to develop anti-HBe. It is possible that this is due to use of lamivudine monotherapy for HBV infection among those who were first positive for HBV in earlier years. This association remained even after adjusting for HBV treatment regimen type. However, given the limited number of individuals in earlier years who would have been treated using more than one HBV-active drug, it may not be possible to explain all of the calendar year effect by adjusting for treatment type and it is possible that the effect of calendar year is still due, in part, to the use of less effective single drug treatment regimens in the earlier years.

8.4.3 Comparisons with literature

In UK CHIC, 37% of co-infected individuals were already on HBV-active treatment at the time of their first positive HBsAg test and of those who were not 77% subsequently started treatment, giving a total of 86% of co-infected patients in UK CHIC who receive any treatment for HBV infection. This is comparable with findings from a cohort of 427 HIV/HBV co-infected individuals seen for care at Italian hospitals; 88% of whom had received treatment for HBV at some point during their infection (520). A recent study of the management of HBV in mono-infected individuals found that only one third of individuals were on treatment and that only 18% were on a recommended regimen (521). Therefore the finding that the majority of co-

infected individuals in this cohort do commence treatment and either do so with, or switch to, a recommended regimen is encouraging.

Previous studies investigating HBeAg loss among cohorts of HIV/HBV co-infected individuals have shown variation from 18% to 46% in the proportions of individuals who lose HBeAg after starting treatment (386, 388, 391, 444, 446, 522). All of these studies included very small numbers of individuals (<100 HBeAg-positive individuals in each study). However, the estimates of the number of individuals who lose HBeAg are comparable with the figure of 39.5% reported in this chapter. In the analyses presented in this chapter, of those individuals who lose HBeAg, 57.7% were known to seroconvert to anti-HBe positive. This estimate is comparable with that from Kosi *et al* (523) who observed seroconversion among 25/57 HBeAg-positive individuals who were followed-up for 5 years. Other studies have shown lower proportions of individuals who seroconvert to anti-HBe positive. Jain *et al* reported that only 16% of patients showed evidence of seroconversion (444) and Lacombe *et al* reported that 17% of individuals seroconverted (524). Again, both of these studies include small numbers of HBeAg-positive individuals (N=32 in Jain *et al* and N=24 in Lacombe *et al*). In addition, shorter durations of follow-up were observed in these studies; all individuals were followed for 1 year in the study by Jain *et al* and median follow-up in the study by Lacombe *et al* was 1.4 years. By contrast, in the present study median follow-up among HBeAg-positive individuals was 4.1 years. This shorter follow-up in previous studies may, in part, explain the differences in the proportion of individuals who have evidence of anti-HBe seroconversion seen in previous studies and that reported in this chapter.

Among HIV/HBV co-infected individuals in UK CHIC, being on a recommended HBV treatment regimen ($\geq$2 HBV-active drugs) was significantly associated with losing HBeAg. The association between treatment regimen and likelihood of losing HBeAg was investigated in three of the previously mentioned studies (386, 388, 444). None of these studies found significant associations between treatment type and HBeAg loss, but this is likely to be due to the small number of individuals included in the studies. However, Jain *et al* did report that a higher proportion of individuals who received tenofovir and lamivudine in combination lost HBeAg compared to those who received lamivudine alone.

The finding in this chapter that the large majority of treated individuals suppress HBV replication (measured by loss of HBV-DNA) is in agreement with other studies (386, 440, 446,

522, 523) as is the association of baseline HBeAg status with suppression of HBV replication (388, 522, 525). A number of previous studies have found an association between HBV treatment regimen and HBV viral suppression. For example Jain *et al* showed that 80% of individuals who received tenofovir and lamivudine in combination suppressed HBV replication compared to only 60% of individuals who received lamivudine alone. However, small numbers mean that this difference was not statistically significant (444). In addition, significantly greater decreases in HBV-DNA have been observed among individuals who receive a combination of tenofovir and emtricitabine compared to those who receive emtricitabine alone (446). A recently published study, of 115 HIV/HBV co-infected individuals receiving lamivudine or emtricitabine monotherapy or tenofovir plus lamivudine or emtricitabine, followed individuals for a total of 144 weeks of treatment. While there were not significant differences in viral suppression at 24 weeks, by the end of follow-up a significantly higher proportion of those receiving dual therapy had suppressed HBV replication than those receiving monotherapy (526). In agreement with these studies, in the present analysis a higher proportion of individuals on a recommended regimen suppressed HBV replication than those on other regimens. However, after adjusting for CD4 count and baseline HBeAg status the association was not significant.

In this cohort higher CD4 count was significantly associated with HBV viral suppression when entered into the model as a time updated covariate. This finding is in agreement with the study published by Nunez *et al,* which showed that greater CD4 gains in response to treatment are significantly associated with having undetectable HBV-DNA after a median of 52 weeks of follow-up (388). Therefore, the finding in the present analysis that HBV treatment type is not significantly associated with HBV suppression may be due to a lack of power, with too small a sample to detect any difference in HBV suppression between the two treatment groups. However, it is also possible that CD4 count is acting as a confounder since it is associated both with treatment type and with HBV suppression and therefore adjusting for CD4 removes associations between treatment type and HBV suppression.

8.4.4 Strengths and weaknesses

Compared to previous analyses of HBV treatment among cohorts of co-infected individuals, this analysis included a large sample of individuals who have attended for care at multiple centres. Therefore, I have been able to assess the association of a large number of factors and response to treatment. However, the analyses are limited by a lack of availability of some data. The HBV-DNA status was unknown for a high proportion of individuals. It is unclear

whether this is due to non-reporting of these test results to UK CHIC or whether co-infected individuals are not being monitored for HBV-DNA levels in clinical practice. A previous study conducted in a clinical cohort in the USA indicated that monitoring HBV-DNA levels in co-infected individuals was suboptimal among a co-infected group of patients (527). Similarly, a higher proportion of individuals did have HBeAg and anti-HBe test results available but there were still a significant proportion of individuals who were not included in the analysis of treatment response as test results were not available. Therefore, when future data collection is undertaken, the availability of information on HBV-DNA, HBeAg and anti-HBe test results should be investigated.

There are several additional factors which may influence the response to treatment, which were not included in the analyses presented in this chapter. Individuals may enter the UK CHIC cohort at any point either prior or subsequent to acquiring HBV infection. Therefore we were unable to assess the effect of the duration of HBV infection on the response to treatment. We are also unable to assess the effect of HBV genotype on response to treatment. Currently, clinical guidelines do not recommend routinely assessing HBV genotype and therefore there is no routinely collected data available (65). However, previous studies have not found any association between HBV treatment response and infection with different genotypes (528). In addition we were not able to assess the impact of resistance to anti-HBV drugs in this cohort. However, given the high levels of viral suppression demonstrated this is unlikely to have been an important factor in this cohort. It is known that use of lamivudine monotherapy can lead to the development of resistance. However, in this cohort, while some individuals did commence treatment on lamivudine monotherapy, most later switched to a regimen of two or more drugs. Other studies have shown that prior exposure to lamivudine monotherapy does not affect the response to subsequent use of tenofovir containing regimens (440, 441).

There are several known side effects from long term use of tenofovir. In particular, it is associated with renal damage and this has been observed in co-infected individuals (529, 530). This may lead to discontinuation of tenofovir as treatment which may have implications for the ongoing suppression of the infection. Investigating changes in treatment due to renal toxicity was beyond the scope of this analysis. However, further analyses in this cohort should investigate this.

8.4.5 Conclusions

The analyses presented in this chapter have shown high levels of treatment for HBV infection with appropriate treatment regimens and a high proportion of individuals supressing their infection in this large cohort of co-infected individuals. Although this is encouraging, treatment for HBV does not clear the virus and therefore it is important that co-infected individuals are continually monitored for the development of liver disease.

Chapter 9 Results 4: Mortality and clinical progression of liver disease among HIV and hepatitis co-infected individuals

9.1 Background

Among HIV-positive populations, since the introduction of HAART, an increasing proportion of deaths have been due to liver disease and HBV and/or HCV co-infection (269, 270, 272, 273, 531). HIV-positive individuals co-infected with HBV and/or HCV have higher rates of progression to chronic hepatitis infection (326, 363, 382) and faster progression to fibrosis, cirrhosis, HCC and end-stage liver disease (261, 331, 332, 366) than individuals with hepatitis infection alone.

Meta-analyses investigating the impact of HBV and/or HCV co-infection on mortality among HIV-positive individuals have shown that co-infection is significantly associated with increased mortality (275, 303). However there is variation in results when the included studies are examined independently. These differences may be due to variations in underlying mortality rates in the cohorts studied as well as differences in treatment and management strategies for both HIV and hepatitis. Therefore, previous findings may not be generalizable to a UK setting.

A number of studies which have found no significant difference in mortality rates between HIV/HCV co-infected and HIV mono-infected individuals have observed higher numbers of deaths among co-infected individuals, but the association between co-infection and mortality is lost after adjusting for HIV infection related parameters (such as use of HAART and CD4 cell count) (277, 278, 280, 281). Similarly, for studies that found no significant association between HIV/HBV co-infection and mortality, higher rates of mortality were often observed which were found to be non-significant only after entry into a multivariable model (257, 302). The large majority of previous studies examining mortality among co-infected individuals have reported on all-cause mortality and therefore it is not possible to examine whether the apparent increase in mortality is due to liver disease among co-infected individuals or due to other causes.

The aims of this chapter are to compare mortality rates in co-infected individuals and HIV mono-infected individuals and to identify factors which may be associated with mortality among co-infected individuals in a UK context. In addition, this chapter aims to identify factors

associated with progression of liver disease to cirrhosis; development of complications of liver disease; and survival among individuals with complicated liver disease.

9.2 Methods

9.2.1 Inclusion criteria

Only those individuals who had been tested for HBsAg and for HCV-Ab/HCV-RNA were included in the analysis. HBV and HCV data were cleaned as previously described (Chapter 5). For all analyses presented, individuals were defined as being HBV-infected from the date of their first positive HBsAg test and being HCV-infected from the date of their first positive anti-HCV or HCV-RNA test.

9.2.2 Defining causes of death

In UK CHIC cause of death is received from the centres as part of the standard annual data submission. Additional information on cause of death was collected as part of the expanded hepatitis data collection and any additional information was merged into the main UK CHIC dataset as previously described (Chapter 4, section 4.4.2). In addition to the information on cause of death that was available to me at the time of the expanded data collection, there has been a subsequent standard UK CHIC data submission since the completion of the hepatitis data collection. This may include further causes of death. Finally, as part of an on-going project examining causes of death, UK CHIC data has been linked to death data from several additional sources. In creating the UK CHIC standard dataset, data are obtained from ONS and PHE and the date of death updated where necessary (Chapter 3, section 3.2.4). However, ONS and PHE datasets also include information on causes of death which, until now, had not been added into the UK CHIC dataset. In addition, UK CHIC centres submit Cause of Death (CODE) forms for those individuals at their centres who have died. CODE forms are standardised case report forms used by a number of HIV cohort studies in Europe which provide detailed information on cause of death where known (532). In order to maximise the number of individuals for whom there was a known cause of death in the subsequent analyses, relevant information from all these sources of data were combined.

For this analysis, recorded causes of death were coded as liver-related or not liver-related and as AIDS-related or not AIDS-related. In order to ensure that all information on causes of death was utilised, cause of death information was divided into three datasets: UK CHIC data (including data collected from the expanded hepatitis data collection); updated UK CHIC data from the latest data submission; and external data from PHE, ONS and CODE forms. Deaths in

each of these three datasets were coded separately. Coding was done without knowledge of an individual's hepatitis status although there may have been reference to co-infection within the information recorded on cause of death.

Deaths were coded as liver-related where there was clear evidence that disease in the liver had contributed to death. This included, for example, decompensated liver disease, HCC, liver failure and cancers with liver metastases. Where a non-liver-related cause of death was recorded but there was additional mention of viral hepatitis, this was not coded as a liver-related death. Deaths were coded as AIDS-related either where AIDS was stated as a cause of death or where the cause of death included any condition included on the Centers for Disease Control (CDC) list of AIDS-defining conditions (44). The three coded datasets were then combined and compared to make a final decision about whether a death should be coded as liver-related or not and as AIDS-related or not.

There were a total of 1622 deaths among individuals included in the analyses. When coding from the three datasets was compared, there were conflicting liver-related death codes for 29 individuals and conflicting AIDS-related death codes for 81 individuals. For these individuals all stated causes of death were reviewed in order to make a final decision about whether or not the death was liver-related, AIDS-related or neither. Where coding from two of the datasets were in agreement and only one dataset was conflicting, the coding from the agreeing datasets was used this was used. Where coding was available in one or more datasets but missing from another dataset, the available coding was used as the final code. Where no decision could be made the death was left uncoded (2/29 conflicting liver-related deaths and 8/81 conflicting AIDS-related deaths). A cause of death, from any data source, which could be coded as liver-related or not liver-related, was available for 1319 individuals. A cause of death which could be coded as AIDS-related or not AIDS-related was available for 1312 individuals (Table 9.1)

Table 9.1 Data sources used to code deaths as liver-related or AIDS-related

Data source	Individuals with a cause of death which could be defined as liver-related or non-liver-related[1]	Individuals with a cause of death which could be defined as AIDS-related or non-AIDS-related[1]
UK CHIC plus expanded hepatitis data collection	302	302
Updated UK CHIC standard data	412	412
External data (PHE, ONS or CODE)	1240	1229
Total	**1319**	**1312**

[1] Individuals may have a cause of death recorded in more than one data source.

9.2.3 Defining cirrhosis status

In a number of the analyses presented throughout this chapter, data were included on whether a hepatitis co-infected individual had cirrhosis or not. Confirmed cirrhosis status was defined using either APRI score, biopsy result or FibroScan® result. APRI scores of greater than 2, FibroScan® results of greater than 14, biopsies with Ishak scores of 5 or 6 and biopsies with METAVIR scores of 4 were considered to be evidence of cirrhosis.

There was further evidence of cirrhosis in the results of liver imaging. However, liver imaging has a much lower sensitivity for diagnosis of cirrhosis (533, 534). In the analysis of complications of liver disease, which utilised scan data in determining an outcome, those individuals who had a scan which had been coded as suggestive of cirrhosis were also considered to have been diagnosed with cirrhosis. The number of individuals with confirmed cirrhosis, as diagnosed though APRI score, biopsy and FibroScan® and the number of individuals with scans suggestive of cirrhosis are shown in Table 9.2.

Table 9.2 Diagnosis of cirrhosis by APRI score, Biopsy, FibroScan® and other imaging methods

Liver disease assessment	Total with measurement	Number with any evidence of cirrhosis	%
APRI score	972	354	36.4
Biopsy	583	135	23.1
FibroScan®	1043	104	10.0
Total confirmed	**1872**	**522**	**27.9**
Scans suggestive of cirrhosis	1190	217	5.5
Total (confirmed + suggestive)	**2729**	**611**	**22.4**

9.2.4 Comparing mortality rates among HIV mono-infected and HIV/hepatitis co-infected individuals

Individuals were followed from the latest of their first HBV or HCV test, entry into UK CHIC, or 1st January 2004. A last date of follow-up was determined as the maximum of CD4 counts, viral loads, hepatitis dates and recorded last seen dates. Individuals who had not died were included in the analysis until their last follow-up date. For those who had a recorded death, follow-up was continued until their date of death. Seven individuals were known to have died but there was no death date available. For these individuals the date of death was imputed as the last date of follow-up. Baseline characteristics of individuals who had died compared to those who had not died were described and compared.

For all individuals with a date of death, 180 days was added to the last date of follow-up, if the date of death occurred within that 180 days the individual was included in the analysis as having died. If the date of death occurred after that 180 days, the individual was included in the analysis but was censored at their last date of follow-up and were not considered to have died while under follow-up since most individuals will be seen in clinic at least once every 6 months. This methodology was used in order to minimise bias that may be introduced from the inclusion of deaths that are reported through ONS after follow-up within the cohort has ceased. There were 15 individuals in this dataset who had a date of death that was more than 6 months after their last date of follow-up and whose follow-up was therefore censored prior to death. A comparison between these individuals and those individuals who died during follow-up is shown in Table 9.3.

Table 9.3 Baseline characteristics of those individuals whose deaths occurred during follow-up compared to those whose deaths occurred after follow-up

	Deaths occurring ≥6 months after last date of follow-up N=15	**%**	**Deaths occurring <6 months after their last date of follow-up N=1065**	**%**	**P value**
Median age (years) (IQR)	38 (34,43)	-	41 (36, 49)	-	0.19
Ethnicity					
White	13	86.67	735	69.01	0.19
Black African	0	0.00	185	17.37	
Other/unknown	2	13.33	145	13.62	
HIV exposure group					
MSM	2	13.33	587	55.12	<0.0001
IDU	12	80.00	120	11.27	
Male heterosexual	0	0.00	152	14.27	
Female heterosexual	1	6.67	141	13.24	
Other unknown	0	0.00	65	6.10	
Median CD4 count (cells/mm^3) (IQR)	386 (190, 515)	-	290 (133, 497)	-	0.28
HIV viral load (copies/ml)					
≤50	5	33.33	402	37.75	0.58
>50	10	66.67	608	57.09	
Unknown	0	0.00	55	5.16	
HAART regimen					
NNRTI based	1	6.67	221	20.75	0.35
PI based	4	26.67	149	13.99	
Other regimen	4	26.67	237	22.25	
Not on ART	6	40.00	458	43.00	
Year of entry into cohort					
1996-1999	11	73.33	552	51.83	0.005
2000-2004	2	13.33	253	23.76	
2005-2009	0	0.00	236	22.16	
≥2010	2	13.33	24	2.25	
Hepatitis infection status					
HIV mono-infected	4	26.67	816	76.62	<0.0001
HIV/HBV co-infected	1	6.67	87	8.17	
HIV/HCV co-infected	10	66.67	145	13.62	
HIV/HBV/HCV triple-infected	0	0.00	17	1.60	

Individuals were categorised at baseline as HIV mono-infected, HIV/HBV co-infected, HIV/HCV co-infected or HIV/HBV/HCV triple-infected. Individuals moved in one direction from HIV mono-infected to a co-infection or triple-infection category if there was evidence of a positive test result during follow-up. The total number of person-years of follow up was calculated for each co-infection category using the date at which an individual entered that co-infected category and their last date of follow-up within that category. Mortality rates were calculated as the total number of deaths divided by the total person-years of follow-up.

In order to investigate whether the different mortality rates in each co-infection group were confounded by other variables, Poisson regression was used to identify predictors of all-cause mortality, liver-related mortality and AIDS-related mortality. Fixed covariates were ethnicity and HIV exposure group. Age, CD4 count, HIV viral load, HAART and calendar year were updated every three months. Hepatitis co-infection status was updated where a change occurred (as described above).

Final models of all-cause mortality, liver-related mortality and AIDS-related mortality were arrived at using the same systematic approach in order to allow comparison of the results. Initially all covariates were included in the multivariable model. However, variables included in the final models were selected using a backwards selection process to identify those factors that confounded the effect of co-infection on mortality and to achieve a parsimonious model. This process resulted in ethnicity being removed from the final model as, although it showed weak association with mortality in the univariable model, its removal from the model did not affect the estimates for co-infection.

HIV-positive IDU have higher mortality rates than HIV-positive individuals who acquired their HIV infection through other routes (24, 61, 535). To test the effect of this on the model, all individuals who had acquired their HIV through injecting drug use were excluded and the results compared to the model which included IDU.

All-cause, liver-related and AIDS-related mortality rates were particularly high in the most recent year of follow-up (2012). This is likely to be due to a bias in the dataset resulting from the data collection process which was conducted from 2012-2013. Where individuals who were co-infected had died in 2012, this may have been recorded during the data collection as the information was available in the clinical records of that individual. However, there are far

fewer years of follow-up in 2012 in the dataset as a whole (including HIV mono-infected individuals) than in other years, due to a delay in reporting standard data to UK CHIC. Therefore the mortality rate in 2012 may be overestimated. For this reason, in a final model data from 2012 were excluded.

9.2.5 Predictors of mortality among co-infected individuals

To further investigate mortality among co-infected individuals, including parameters that are specific to hepatitis co-infection, separate datasets of the HBV-positive (n=1689) and HCV-positive (n=2657) individuals were created. Individuals who were triple-infected were included in both datasets and the presence of triple-infection was adjusted for in all analyses.

For each co-infection dataset, individuals were followed from the latest of their first evidence of infection with the hepatitis virus of interest, or 1st January 2004 until their date of death (for those who died) or their last date of follow-up.

Independent predictors of mortality among the two co-infected groups were identified using univariable and multivariable Cox regression. Baseline age, ethnicity and exposure category were treated as fixed covariates in all models. CD4 count, HIV viral load and HIV/HBV/HCV triple-infection were treated as time-updated covariates. CD4 count was included as a continuous variable while HIV viral load was included as a categorical variable.

In the HIV/HBV co-infected group, HAART use and HBV treatment were initially investigated separately as predictors of mortality in univariable analysis. However, the large majority of individuals on hepatitis treatment are on treatment as part of their HAART regimen (for example with lamivudine or tenofovir (Chapter 8). Therefore in the final model HBV treatment was included as a time dependent covariate, but use of HAART was excluded. All other factors that were associated with mortality in univariable analysis were included in the multivariable model. Only 1187/1679 individuals had any HBeAg test results available and 654/1679 had any measure of cirrhosis (a biopsy, FibroScan® or APRI score) available. Therefore these variables were added to the final model separately.

In the HIV/HCV co-infected group, use of HAART was included as a time updated covariate. HCV treatment was defined as successful, failed or of unknown outcome using the initial treatment response and long-term treatment response as described in Chapter 7. HCV treatment outcome was then included as a time dependent categorical variable. Whether an

individual had been diagnosed with acute HCV and HCV genotype were included as fixed co-variates. All factors associated with mortality in univariable analysis were included in the multivariable model.

Of all HIV/HCV co-infected individuals included in the analysis, 1415/2651 individuals had any measure of cirrhosis and 2382/2651 individuals had HCV-RNA test results available. Separate models also included HCV-RNA as a time updated covariate and cirrhosis status as a time updated covariate as large numbers of individuals did not have RNA test results or measures of cirrhosis available. Given the very high prevalence of HCV among IDU, a sensitivity analysis was conducted where IDU were removed from the model.

9.2.6 Predictors of cirrhosis among hepatitis co-infected individuals

Cirrhosis may remain asymptomatic for long periods of time, therefore confirmation of cirrhosis by laboratory tests, biopsy or FibroScan® may occur long after damage to the liver has occurred and, as such, the date at which an individual is confirmed as having cirrhosis may not represent the point at which liver damage has occurred. Therefore, cirrhosis was treated as a binary variable: ever having had cirrhosis or never having had cirrhosis. Logistic regression of baseline characteristics was carried out to investigate factors associated with this outcome measure.

For HIV/HBV co-infected individuals, baseline characteristics included in the analysis were age, ethnicity, HIV exposure group, CD4 count, HIV viral load, HBV treatment, HAART, HBeAg status and HCV infection. A second model excluded HBeAg status as a large number of individuals had unknown HBeAg status at baseline. For HIV/HCV co-infected individuals, baseline characteristics included in the analysis were age, ethnicity, HIV exposure group, CD4 count, HIV viral load, HAART, HCV-RNA status, HBV infection, HCV genotype and whether or not an individual was diagnosed with acute HCV infection. HCV treatment was not included in the analysis since evidence of advanced fibrosis or compensated cirrhosis may be an indication for starting HCV treatment (204).

9.2.7 Complications of liver disease

Complicated liver disease was defined as: decompensated cirrhosis (that is, cirrhosis with any of ascites, portal hypertension, gastroesophageal varices or hematemesis (vomiting of blood), HCC or liver transplant (536)); HCC without evidence of cirrhosis; or evidence of having undergone a liver transplant but without a diagnosis of cirrhosis. For the purpose of these

analyses, in addition to those who had a confirmed diagnosis of cirrhosis through APRI score, biopsy or FibroScan®, those individuals who had other imaging that was coded as suggestive of cirrhosis were also considered to be cirrhotic. Evidence of complicated liver disease was available from three data sources collected as part of the expanded hepatitis data collection: scans; biopsies; record in clinical notes (Table 9.4).

Table 9.4 Data sources for information on complications of liver disease

Evidence of complicated liver disease	Possible data source		
	Scan results	Biopsies	Clinical notes
Ascites	✓	✗	✓
Portal hypertension	✓	✗	✓
Hematemesis	✗	✗	✓
Gastroesophageal varices	✓	✗	✓
Hepatocellular carcinoma	✓	✓	✓
Transplant	✓	✗	✓

Baseline characteristics of individuals who experienced any complications of liver disease and those who did not were compared. Individuals were followed from the date of a first positive hepatitis test or 1st January 2004, whichever was the latest, until their first recorded complication of liver disease or their last follow-up date for those who did not experience complications. Rates of developing complications were calculated among individuals who experienced their first complication after the start of follow-up as the total number of individuals who experienced a complication out of the total person-years of follow-up. Predictors of first complications of liver disease were assessed using Cox regression models.

In models of predictors of first complications among HIV/HBV and HIV/HCV co-infected groups, baseline age, ethnicity and HIV exposure group were treated as fixed covariates. CD4 count, HIV viral load and triple-infection were treated as time updated covariates. Among HIV/HBV co-infected individuals, HAART, HBV treatment and HBeAg status were also treated as time updated covariates. Among HIV/HCV co-infected individuals, HCV-RNA status was treated as a time updated co-variate while HCV genotype and whether an individual was diagnosed with acute infection or not were treated as fixed covariates.

Finally, among those individuals who experienced a complication of liver disease, survival after first complication was described using Kaplan Meier curves and overall mortality rates. Individuals who had undergone a liver transplant were excluded from this analysis as it was assumed that liver transplant would increase their survival.

9.3 Results

9.3.1 Comparing mortality rates among HIV mono-infected and HIV/hepatitis co-infected individuals

Of the 26377 individuals who had ever been tested for HBsAg and the 28251 individuals who had ever been tested for HCV-Ab and/or HCV-RNA, 25753 individuals had been tested for both infections. Twenty-three individuals had a date of death which was before or on the same date as the start of follow-up and were therefore excluded from the analysis. 244 individuals had a last follow-up date which was the same as their date of starting follow-up and were therefore removed from the analysis. Therefore a total of 25486 individuals were included. Overall 4.2% (1065/25486) of individuals died during follow-up. Baseline characteristics of individuals who died during follow-up and those who did not are shown in Table 9.5.

The 25486 individuals contributed a total of 121814 person-years of follow-up. Median follow up time was 4.6 years (IQR 2.0, 7.2 years) per person. A total of 1065 individuals died, giving an overall all-cause mortality rate of 8.7 per 1000 person-years (95% CI 8.2-9.3). A total of 95 individuals died of liver-related causes (a mortality rate of 0.8 per 1000 person-years, 95% CI 0.6-1.0) and 198 individuals died of AIDS (a mortality rate of 1.6 per 1000 person-years, 95% CI 1.4-1.9). Allowing individuals to move between co-infection categories in one direction where new evidence of infection was available, all-cause mortality was higher among co-infected individuals than among HIV mono-infected individuals; 7.4 per 1000 person-years in HIV mono-infected individuals compared to 13.8 per 1000 person-years and 16.9 per 1000 person-years in HBV and HCV co-infected individuals, respectively. Similarly liver-related mortality was also higher among hepatitis co-infected individuals than in HIV mono-infected individuals; 0.3 per 1000 person-years in HIV mono-infected compared to 3.5 per 1000 person-years and 3.3 per 1000 person-years in HIV/HBV and HIV/HCV co-infected individuals, respectively. AIDS-related mortality appeared to be higher among HIV/HBV co-infected individuals (2.2 per 1000 person-years) and among HIV/HBV/HCV triple-infected individuals (3.6 per 1000 person-years) compared to HIV mono-infected individuals (1.6 per 1000 person-years) but there was little difference in AIDS-related mortality rates between HIV-mono-infected and HIV/HCV co-infected individuals (1.3 per 1000 person-years) (Table 9.6).

Table 9.5 Baseline characteristics of individuals who died and those who did not die during follow-up

	Remained alive N=24421	%	Died N=1065	%	P- value
Median Age (years) (IQR)	37	(31, 43)	41	(36, 49)	<0.0001
Ethnicity					
White	15050	61.6	735	69.0	<0.0001
Black African	5263	21.6	185	17.4	
Other/unknown	4108	16.8	145	13.6	
HIV exposure group					
MSM	14903	61.0	587	55.1	<0.0001
IDU	583	2.4	120	11.3	
Male heterosexual	2803	11.5	152	14.3	
Female heterosexual	4652	19.1	141	13.2	
Other/unknown	1480	6.1	65	6.1	
Median CD4 count (cells/mm^3) (IQR)[1]	413	(273, 582)	497.5	(290, 698)	<0.0001
HIV viral load (copies/ml)					
≤50	9162	37.5	402	37.8	0.001
>50	13243	54.2	608	57.1	
Unknown	2016	8.3	55	5.2	
HAART regimen					
NNRTI based	5079	20.8	221	50.8	<0.0001
PI based	2603	10.7	149	14.0	
Other regimen	3094	12.7	237	22.3	
Not on ART	13645	55.9	458	43.0	
Year of entry into UK CHIC					
1996-1999	7952	32.6	552	51.8	<0.0001
2000-2004	6478	26.5	253	23.8	
2005-2009	7697	31.5	236	22.2	
≥2010	2294	9.4	24	2.3	
Hepatitis infection status at start of follow-up					
HIV mono-infected	21923	89.8	816	76.6	<0.0001
HIV/HBV co-infected	1129	4.6	87	8.2	
HIV/HCV co-infected	1259	5.2	145	13.6	
HIV/HBV/HCV triple-infected	110	0.5	17	1.6	

[1]Baseline CD4 count was unknown for 1730 individuals who did not die and 37 individuals who died

Table 9.6 All-cause, liver-related and AIDS-related mortality by hepatitis co-infection category

HIV/ hepatitis infection	Person-years follow-up	All-cause mortality		Liver-related mortality		AIDS-related mortality	
		Number of deaths	Mortality rate[1] (95% CI)	Number of deaths	Mortality rate[1] (95% CI)	Number of deaths	Mortality rate[1] (95% CI)
HIV N=22739	103057	761	7.4 (6.9-7.9)	27	0.3 (0.2-0.4)	164	1.6 (1.4-1.9)
HIV/HBV N=1427	6933	96	13.8 (11.2-16.9)	24	3.5 (2.2-5.2)	15	2.2 (1.2-3.6)
HIV/HCV N=2325	10180	172	16.9 (14.5-19.6)	34	3.3 (2.3-4.7)	13	1.3 (0.7-2.2)
HIV/HBV/ HCV N=435	1644	36	21.9 (15.3-30.3)	10	6.1 (2.9-11.2)	6	3.6 (1.3-7.9)
Total N=25486	121814	1065	8.7 (8.2-9.3)	95	0.8 (0.6-1.0)	198	1.6 (1.4-1.9)

[1] Mortality rates per 1000 person-years of follow-up

In order to assess whether the observed differences in mortality rates between co-infection groups were due to co-infection or confounding factors, Poisson regression models were used to adjust for potential confounders and to obtain crude and adjusted rate ratios.

9.3.1.1 Association of HIV/hepatitis co-infection with all-cause mortality

The results of analyses to test the association between hepatitis co-infection and all-cause mortality after adjusting for confounding factors are shown in Table 9.7. In multivariable model 1, compared to HIV mono-infection, hepatitis co-infection was strongly associated with all-cause mortality with ARRs of 1.43 (95% CI 1.15-1.79) for HIV/HBV co-infection, 1.28 (95% CI 1.04-1.57) for HIV/HCV co-infection and 1.80 (95% CI 1.27-2.54) for HIV/HBV/HCV triple-infection.

Some other associations were also observed in model 1. Older individuals were more likely to die (ARR 1.66, 95% CI: 1.56-1.77, per 10 years). Compared to MSM, IDU has significantly higher rates of mortality (ARR, 95% CI: 2.51, 1.96-3.21) as did those individuals whose HIV exposure group was other/unknown (ARR, 95% CI: 1.88, 1.42-2.47). Individuals with higher CD4 counts were less likely to die (ARR, 95% CI: 0.72, 0.69-0.75 per additional 100 cells/mm^3). Compared to individuals with undetectable HIV viral loads, those with HIV viral loads 50-10000

copies/ml and those with HIV viral loads >10000 copies/ml were significantly more likely to die (ARRs, 95% CIs: 1.46, 1.26-1.76 and 2.52, 2.19-2.89, respectively). Compared to those individuals who were not on HIV treatment, all-cause mortality was significantly higher among those individuals who were on HIV treatment (ARR, 95% CI: 1.42, 1019-1.71). Taking 2009 as the reference group, it appeared that individuals under follow-up in 2004 had significantly lower mortality rates (ARR, 95% CI: 0.74, 0.58-0.96) and those under follow-up in 2011 had significantly higher mortality rates (ARR, 95% CI: 1.40, 1.10-1.78). Those under follow-up in 2012 also had significantly higher rates of all-cause mortality. However as this is likely due to ascertainment bias (as discussed in 9.2.4), 2012 data was excluded in model 3.

In model 2, where IDU were excluded from the analysis, HIV/HBV co-infection remained significantly associated with all-cause mortality. However, the association of increased mortality with HCV co-infection and with HIV/HBV/HCV triple-infection was lost in this model. This may indicate the effect of HIV/HCV and HIV/HBV/HCV co-infection on all-cause mortality is higher among IDU than among individuals who did not acquire their HIV through IDU. All other associations with all-cause mortality remained unchanged when IDU were excluded from the analysis.

In model 3, IDU were included but follow-up in 2012 was excluded from the analysis. HIV/HBV, HIV/HCV and HBV/HCV co-infection all remained associated with increased mortality compared to HIV mono-infection in this model, however the associations were slightly stronger than they had been in model 1: ARRs, 95% CIs: 1.60, 1.28-2.00 for HIV/HBV co-infection; 1.43, 1.16-1.76 for HIV/HCV co-infection; and 2.29, 1.62-3.24 for HIV/HBV/HCV triple-infection. All other associations with mortality remained, in the same direction and with similar ARR, as described for model 1.

9.3.1.2 Association of HIV/hepatitis co-infection with liver-related mortality

The results of the analyses testing the association between hepatitis co-infection and liver-related mortality are shown in Table 9.8. In model 1, hepatitis co-infection was strongly associated with liver-related mortality compared to HIV mono-infection (ARRs, 95% CIs: 8.97, 5.07-15.88 for HIV/HBV co-infection; 5.70, 3.13-10.37 for HIV/HCV co-infection; and 12.35, 5.70-26.77 for HIV/HBV/HCV triple-infection). In addition to co-infection there were a number of other factors which were significantly associated with liver-related mortality. Older individuals were more likely to have a liver-related death than younger individuals (ARR, 95% CI: 1.56 1.23-1.93, per 10 years). IDU had significantly higher liver-related mortality compared

to MSM (ARR, 95% CI: 2.76, 1.54-4.91). Liver-related mortality was significantly lower among individuals with higher CD4 counts (ARR, 95% CI: 0.63, 0.56-0.72). Compared to those with undetectable HIV viral load, liver-related mortality was significantly higher among those with HIV viral loads >10000 copies/ml (ARR, 95% CI: 3.64, 2.06-6.45) and compared to those not on HIV treatment, mortality rate was significantly higher among those who were on HIV treatment (ARR, 95% CI: 3.10, 1.61-5.97).

In model 2, where IDU were excluded from the analysis, the association between liver-related mortality and hepatitis co-infection remained compared to HIV mono-infection. ARRs comparing HBV co-infection and HCV co-infection to HIV mono-infection were similar to those obtained from model 1 (8.83 and 5.14, respectively). However, while there was still a strong association between liver-related mortality and HIV/HBV/HCV triple-infection compared to HIV mono-infection, the effect size was smaller when IDU were excluded than it had been in model 1. Other associations remained as described in model 1.

In model 3, where follow-up from 2012 was excluded from the analysis, the association between liver-related mortality and hepatitis co-infection remained. The effect of hepatitis co-infection on liver-related mortality was increased compared to in model 1: ARR, 95% CIs 10.43, 5.78-18.80 for HIV/HBV co-infection; 6.19, 3.31-11.60 for HIV/HCV co-infection; and 15.19, 6.94-33.23 for HIV/HBV/HCV triple-infection. All other associations with liver-related mortality remained similar to those seen in model 1 with regard to size and direction of effect.

In each of the three models, individuals on HAART were at least 4 times more likely to have a liver-related death than individuals who were not on HAART. Being on HAART was significantly associated with liver-related death in univariable analysis and the effect size increased after adjusting for HIV viral load. No other variables had a substantial impact on the effect of HAART on the rate of liver-related death. This effect size was large and unexpected and was highly significant in each of the models. Given that the effect size appeared to be dependent on HIV viral load some further investigations into the HIV viral load, HAART and liver-related death associations were undertaken.

Firstly, the analysis was repeated stratified by hepatitis co-infection status. Among HIV mono-infected individuals, HAART was not found to be associated with liver-related death in univariable analysis (RR, 95% CI: 2.19, 0.76-6.34), but became associated with liver-related

death after adjusting for HIV viral load (ARR, 95% CI: 8.06, 2.43-26.81), and remained associated with liver-related death when other co-variates were included in the model (ARR, 95% CI: 5.21, 1.51-18.02). Among the HIV/HBV co-infected group, HAART was not associated with liver-related death in univariable analysis, after adjusting for HIV viral load, or in the complete multivariable model. Finally, among HIV/HCV co-infected individuals, being on HAART was associated with liver-related death in univariable analysis (RR, 95% CI: 5.06, 1.21-21.11) and the effect size was increased after adjusting for HIV viral load (ARR, 95% CI: 18.95, 4.18-85.84). This association between being on HAART and liver-related death, remained after adjusting for all other covariates (ARR, 95% CI: 6.96, 1.53-31.75).

Subsequently, the dataset was stratified by HAART status in order to examine the effect of HIV viral load on liver-related death. Among individuals who were on HAART, in univariable analysis, compared to those with undetectable HIV viral load, those with HIV viral loads of 50-10000 copies/ml had significantly higher rates of liver-related mortality (RR, 95% CI 2.38, 1.32-4.32). The effect size was greater among those with very high HIV viral loads (>10000 copies/ml) (RR, 95% CI 9.05, 5.33-15.34). After adjusting for other covariates, in multivariable analysis, the association between liver-related mortality and mid-level HIV viral load was attenuated (ARR, 95% CI 1.57, 0.86-2.89), while the association between liver-related mortality and very high HIV viral load remained (ARR, 95% CI 3.42, 1.88-6.24). Among individuals who were not on HAART there were no events among individuals with undetectable HIV viral loads.

Individuals on HAART with high viral loads are likely to be very different to those with high viral loads who are not on HAART. For example, those who are off HAART with high viral loads may be more newly infected, have good immune function and not yet be in need of HAART. However, those who are on HAART and have high viral loads are likely to be failing treatment and therefore may have more advanced disease. Given, these likely differences, and the results described above which show a close association between HAART, HIV viral load, and liver-related mortality, HAART and HIV viral load were combined into one covariate with the following categories: On HAART with undetectable HIV viral load; on HAART with viral load 50-10000 copies/ml; on HAART with high viral load (>10000 copies/ml); not on HAART with HIV viral load $\leq$10000 copies/ml; and not on HAART with high HIV viral load (>10000 copies/ml).

In univariable analysis, there was no significant difference in liver-related mortality between those who were off HAART with high viral loads and those who were off HAART with

undetectable viral loads. There was also no significant difference between those who were off HAART with high viral loads and those who were on HAART with undetectable viral loads. However, those who were on HAART and had HIV viral loads of 50-10000 copies/ml or >10000 copies/ml had higher rates of liver-related mortality than those who were not on HAART with high HIV viral loads.

In multivariable analysis, compared to those individuals who were off HAART with high HIV viral loads, there were no significant differences in liver-related mortality for individuals who were not on HAART with high viral loads and those who were not on HAART with mid/low HIV viral loads. However, individuals who were on HAART and had high HIV viral loads had significantly higher rates of liver-related mortality than those who were not on HAART with high HIV viral loads (ARR, 95% CI: 3.91, 1.75-8.78). These associations are shown in Table 9.10. Including HIV viral load and HAART as a combined co-variate did not alter any of the other association with liver-related mortality, in particular, the associations between liver-related mortality and hepatitis co-infection remained as shown in Table 9.8

9.3.1.3 Association of hepatitis co-infection with AIDS-related mortality

In contrast to all-cause and liver-related mortality, HIV/HBV co-infection and HIV/HBV/HCV triple-infection were not associated with AIDS-related mortality after adjusting for confounding (Table 9.9). However, HIV/HCV co-infection was associated with a decreased risk of AIDS-related mortality (ARR, 95% CI: 0.34, 95% CI 0.17-0.70 in model 1). The results of these analyses are shown in Table 9.9. Like the all-cause and liver-related mortality, AIDS-related mortality was significantly higher among older individuals (ARR, 95% CI: 1.27, 1.09-1.49). Compared to MSM, AIDS-related mortality was significantly higher among IDU (ARR, 95% CI: 3.16, 1.64-6.12) and individuals from other/unknown HIV exposure groups (ARR, 95% CI: 2.02, 1.11-3.69). AIDS-related mortality was also significantly higher among individuals with lower CD4 counts (ARR, 95% CI: 0.42, 0.37-0.47 per additional 100 cells/mm^3) and compared to individuals with undetectable HIV viral loads, mortality was significantly higher among individuals with HIV viral loads of 50-10000 copies/ml (ARR, 95% CI: 1.67, 1.10-2.53) and among individuals with HIV viral loads >10000 copies/ml (ARR, 95% CI: 2.30, 1.51-3.50).

When IDU were excluded from the analysis (model 2), the association between reduced AIDS-related mortality and HIV/HCV co-infection was weakened (ARR, 95% CI: 0.38, 0.16-0.95). Other associations remained similar in size and direction to those described in model 1.

Excluding data from 2012 from the model did not alter the associations with regard to effect size or direction (model 3).

Table 9.7 Poisson regression of factors associated with all-cause mortality

	Univariable analysis			Multivariable model 1			Multivariable model 2 – excluding IDU			Multivariable model 3 – excluding 2012		
	RR	**95% CI**	**P value**	**ARR**	**95% CI**	**P value**	**ARR**	**95% CI**	**P value**	**ARR**	**95% CI**	**P value**
Age (per 10 years)	1.57	1.67-5.30	<0.0001	1.66	1.56-1.77	<0.0001	1.70	1.60-1.81	<0.0001	1.68	1.58-1.79	<0.0001
Ethnicity												
White	1	-	-	-	-	-	-	-	-	-	-	-
Black African	0.82	0.70-0.97	0.02	-	-	-	-	-	-	-	-	-
Other/unknown	0.86	0.72-1.03	0.11	-	-	-	-	-	-	-	-	-
HIV Exposure group												
MSM	1	-	-	1	-	-	1	-	-	1	-	-
IDU	4.45	3.66-5.41	<0.0001	2.51	1.96-3.21	<0.0001	-	-	-	2.47	1.92-3.17	<0.0001
Male heterosexual	1.56	1.30-1.86	<0.0001	1.04	0.87-1.25	0.66	1.03	0.86-1.25	0.71	1.05	0.87-1.27	0.58
Female heterosexual	0.87	0.72-1.04	0.13	0.92	0.76-1.12	0.42	0.92	0.76-1.12	0.42	0.91	0.75-1.11	0.37
Other/unknown	1.99	1.53-2.57	<0.0001	1.88	1.42-2.47	<0.0001	1.89	1.43-2.48	<0.0001	1.91	1.45-2.52	<0.0001
CD4 count (per 100 cells/mm^3)	0.68	0.65-0.70	<0.0001	0.72	0.69-0.75	<0.0001	0.71	0.69-0.74	<0.0001	0.71	0.69-0.74	<0.0001

	Univariable analysis			Multivariable model 1			Multivariable model 2 – excluding IDU			Multivariable model 3 – excluding 2012		
	RR	**95% CI**	**P value**	**ARR**	**95% CI**	**P value**	**ARR**	**95% CI**	**P value**	**ARR**	**95% CI**	**P value**
HIV viral load (copies/ml)												
≤50	1	-	-	1	-	-	1	-	-	1	-	-
51-10000	1.49	1.26-1.76	<0.0001	1.75	1.46-2.08	<0.0001	1.77	1.47-2.14	<0.0001	1.71	1.42-2.04	<0.0001
>10000	2.52	2.19-2.89	<0.0001	2.91	2.40-3.52	<0.0001	2.96	2.41-3.64	<0.0001	2.86	2.35-3.48	<0.0001
Calendar year												
2004	0.95	0.75-1.22	0.72	0.74	0.58-0.96	0.02	0.76	0.58-1.00	0.05	0.75	0.58-0.96	0.02
2005	0.98	0.76-1.26	0.86	0.78	0.60-1.01	0.07	0.81	0.61-1.08	1.15	0.78	0.60-1.01	0.07
2006	0.92	0.72-1.17	0.50	0.79	0.61-1.02	0.07	0.78	0.59-1.02	0.07	0.79	0.62-1.02	0.07
2007	1.23	0.99-1.54	0.06	1.06	0.84-1.32	0.64	1.12	0.88-1.43	0.36	1.06	0.84-1.32	0.63
2008	0.96	0.76-1.21	0.74	0.87	0.69-1.20	0.25	0.87	0.68-1.12	0.29	0.87	0.69-1.10	0.25
2009	1	-	-	1	-	-	1	-	-	1	-	-
2010	0.96	0.77-1.21	0.73	0.97	0.77-1.21	0.78	1.03	0.81-1.32	0.78	0.97	0.77-1.22	0.77
2011	1.38	1.09-1.77	0.01	1.40	1.10-1.78	0.01	1.51	1.17-1.95	0.001	1.39	1.09-1.77	0.01
2012	19.23	13.79-28.83	<0.0001	14.29	10.11-20.19	<0.0001	18.75	13.01-27.02	<0.0001	-	-	-
On HIV treatment												
Yes	0.97	0.85-1.12	0.71	1.42	1.19-1.71	0.0001	1.46	1.20-1.77	0.0002	1.45	1.21-1.74	<0.0001
No	1	-	-	1	-	-	1	-	-	1	-	-

	Univariable analysis			Multivariable model 1			Multivariable model 2 – excluding IDU			Multivariable model 3 – excluding 2012		
	RR	**95% CI**	**P value**	**ARR**	**95% CI**	**P value**	**ARR**	**95% CI**	**P value**	**ARR**	**95% CI**	**P value**
Hepatitis infection status												
HIV mono-infected	1	-	-	1	-	-	1	-	-	1	-	-
HIV/HBV co-infected	1.88	1.52-2.31	<0.0001	1.43	1.15-1.79	0.001	1.37	1.09-1.72	0.01	1.60	1.28-2.00	<0.0001
HIV/HCV co-infected	2.89	1.94-2.70	<0.0001	1.28	1.04-1.57	0.02	1.24	0.98-1.56	0.07	1.43	1.16-1.76	0.001
HIV/HBV/HCV triple-infected	2.97	2.12-4.14	<0.0001	1.80	1.27-2.54	0.001	1.39	0.88-2.21	0.16	2.29	1.62-3.24	<0.0001

Table 9.8 Poisson regression of factors associated with liver-related mortality

	Univariable analysis			Multivariable model 1			Multivariable model 2 – excluding IDU			Multivariable model 3 – excluding 2012		
	RR	**95% CI**	**P value**	**ARR**	**95% CI**	**P value**	**ARR**	**95% CI**	**P value**	**ARR**	**95% CI**	**P value**
Age (per 10 years)	1.51	1.24-1.83	<0.0001	1.56	1.23-1.98	0.0002	1.54	1.19-2.00	0.01	1.54	1.21-1.98	0.001
Ethnicity												
White	1	-	-	-	-	-	-	-	-	-	-	-
Black African	0.42	0.22-0.81	0.01	-	-	-	-	-	-	-	-	-
Other/unknown	0.39	0.18-0.85	0.02	-	-	-	-	-	-	-	-	-
HIV Exposure group												
MSM	1	-	-	1	-	-	1	-	-	1	-	-
IDU	11.32	7.04-18.18	<0.0001	2.76	1.54-4.91	0.001	-	-	-	2.94	1.63-5.33	0.0004
Male heterosexual	0.84	0.38-1.86	0.67	0.48	0.22-1.08	0.08	0.50	0.22-1.12	0.09	0.51	0.23-1.14	0.10
Female heterosexual	0.50	0.23-1.11	0.10	0.62	0.28-1.38	0.24	0.60	0.27-1.35	0.22	0.57	0.24-1.35	0.20
Other/unknown	1.79	0.72-4.50	0.21	1.41	0.50-3.94	0.52	1.42	0.51-3.99	0.51	1.13	0.35-3.67	0.84
CD4 count (per 100 cells/mm^3)	0.56	0.50-0.63	<0.0001	0.63	0.56-0.72	<0.0001	0.68	0.59-0.79	<0.0001	0.63	0.55-0.73	<0.0001

	Univariable analysis			Multivariable model 1			Multivariable model 2 – excluding IDU			Multivariable model 3 – excluding 2012		
	RR	**95% CI**	**P value**	**ARR**	**95% CI**	**P value**	**ARR**	**95% CI**	**P value**	**ARR**	**95% CI**	**P value**
HIV viral load (copies/ml)												
≤50	1	-	-	1	-	-	1	-	-	1	-	-
51-10000	1.23	0.69-2.18	0.49	1.53	0.85-2.78	0.16	2.27	1.67-4.39	0.02	1.48	0.80-2.74	0.21
>10000	2.36	1.49-3.75	0.0003	3.64	2.06-6.45	<0.0001	5.53	2.79-10.95	<0.0001	3.36	1.87-6.04	<0.0001
Calendar year												
2004	0.43	0.17-1.08	0.07	0.32	0.12-0.82	0.02	0.36	0.10-1.38	0.13	3.00	1.15-7.80	0.02
2005	1.21	0.60-2.43	0.60	0.96	0.48-1.94	0.91	1.51	0.59-3.86	0.39	2.21	0.82-5.99	0.12
2006	0.81	0.38-1.72	0.59	0.71	0.33-1.51	0.37	1.11	0.41-2.97	0.84	1.45	0.50-4.19	0.49
2007	0.66	0.31-1.43	0.29	0.47	0.20-1.07	0.07	1.06	0.40-2.85	0.89	1.73	0.62-4.77	0.29
2008	0.60	0.28-1.29	0.19	0.56	0.26-1.20	0.13	0.88	0.32-2.44	0.81	3.12	1.23-7.91	0.02
2009	1	-	-	1	-	-	1	-	-	1	-	-
2010	0.83	0.42-1.64	0.59	0.82	0.41-1.62	0.56	1.61	0.67-3.88	0.29	2.55	0.98-6.64	0.06
2011	0.48	0.18-1.30	0.15	0.43	0.16-1.17	0.10	0.80	0.24-2.66	0.72	1.35	0.41-4.47	0.62
2012	21.06	8.53-54.18	<0.0001	6.62	2.59-16.93	<0.0001	16.34	5.53-48.35	<0.0001	-	-	-
On HIV treatment												
Yes	3.10	1.61-5.97	0.001	4.49	2.16-9.34	<0.0001	5.56	2.31-13.38	0.0001	4.63	2.15-9.98	<0.0001
No	1	-	-	1	-	-	1	-	-	1	-	-

	Univariable analysis			Multivariable model 1			Multivariable model 2 – excluding IDU			Multivariable model 3 – excluding 2012		
	RR	**95% CI**	**P value**	**ARR**	**95% CI**	**P value**	**ARR**	**95% CI**	**P value**	**ARR**	**95% CI**	**P value**
Hepatitis infection status												
HIV mono-infected	1	-	-	1	-	-	1	-	-	1	-	-
HIV/HBV co-infected	13.21	7.62-22.90	<0.0001	8.97	5.07-15.88	<0.0001	8.83	4.95-15.73	<0.0001	10.43	5.78-18.80	<0.0001
HIV/HCV co-infected	12.75	7.69-21.13	<0.0001	5.70	3.13-10.37	<0.0001	5.14	2.65-9.95	<0.0001	6.19	3.31-11.60	<0.0001
HIV/HBV/HCV triple-infected	23.22	11.24-47.98	<0.0001	12.35	5.70-26.77	<0.0001	7.98	2.74-23.21	0.0001	15.19	6.94-33.23	<0.0001

Table 9.9 Poisson regression of factors associated with AIDS-related mortality

	Univariable analysis			Multivariable model 1			Multivariable model 2 – excluding IDU			Multivariable model 3 – excluding 2012		
	RR	**95% CI**	**P value**	**ARR**	**95% CI**	**P value**	**ARR**	**95% CI**	**P value**	**ARR**	**95% CI**	**P value**
Age (per 10 years)	1.31	0.98-1.31	0.09	1.27	1.09-1.49	0.02	1.27	1.09-1.50	0.002	1.32	1.13-1.54	0.001
Ethnicity												
White	1	-	-	-	-	-	-	-	-	-	-	-
Black African	1.73	1.26-2.37	0.001	-	-	-	-	-	-	-	-	-
Other/unknown	1.19	0.80-1.79	0.39	-	-	-	-	-	-	-	-	-
HIV Exposure group												
MSM	1	-	-	1	-	-	1	-	-	1	-	-
IDU	4.35	2.58-7.32	<0.0001	3.16	1.64-6.12	0.001	-	-	-	3.13	1.61-6.08	0.001
Male heterosexual	2.69	1.84-3.95	<0.0001	1.13	0.75-1.70	0.60	1.12	0.75-1.69	0.58	1.16	0.77-1.75	0.47
Female heterosexual	1.82	1.26-2.63	0.001	1.30	0.88-1.91	0.19	1.29	0.88-1.91	0.19	1.25	0.84-1.87	0.27
Other/unknown	3.17	1.83-5.48	<0.0001	2.02	1.11-3.69	0.02	2.00	1.09-3.67	0.04	2.13	1.16-3.91	0.01
CD4 count (per 100 cells/mm^3)	0.38	0.34-0.42	<0.0001	0.42	0.37-0.47	<0.0001	0.42	0.37-0.47	<0.0001	0.42	0.37-0.47	<0.0001

	Univariable analysis			Multivariable model 1			Multivariable model 2 – excluding IDU			Multivariable model 3 – excluding 2012		
	RR	**95% CI**	**P value**	**ARR**	**95% CI**	**P value**	**ARR**	**95% CI**	**P value**	**ARR**	**95% CI**	**P value**
HIV viral load (copies/ml)												
≤50	1	-	-	1	-	-	1	-	-	1	-	-
51-10000	2.29	1.54-4.00	<0.0001	1.67	1.10-2.53	0.02	1.73	1.13-2.68	0.01	1.81	1.19-2.74	0.01
>10000	5.09	3.69-7.02	<0.0001	2.30	1.51-3.50	0.0001	2.48	1.60-3.84	<0.0001	2.48	1.62-3.80	<0.0001
Calendar year												
2004	1.01	0.60-1.70	0.98	0.58	0.33-1.00	0.05	0.57	0.32-1.01	0.05	0.58	0.33-1.01	0.05
2005	0.78	0.42-1.42	0.41	0.47	0.25-0.89	0.02	0.44	0.22-0.86	0.02	0.47	0.25-0.89	0.02
2006	0.91	0.54-1.58	0.75	0.69	0.40-1.20	0.19	0.61	0.34-1.10	0.10	0.69	0.40-1.20	0.19
2007	1.44	0.90-2.31	0.12	1.03	0.63-1.67	0.91	1.03	0.61-1.70	0.93	1.03	0.63-1.68	0.90
2008	0.91	0.54-1.52	0.71	0.73	0.43-1.24	0.24	0.76	0.44-1.30	0.31	0.73	0.43-1.24	0.25
2009	1	-	-	1	-	-	1	-	-	1	-	-
2010	0.47	0.25-0.86	0.01	0.53	0.29-0.98	0.04	0.53	0.28-1.01	0.05	0.53	0.28-0.98	0.04
2011	0.87	0.48-1.58	0.65	1.03	0.56-1.88	0.92	1.04	0.56-1.94	0.89	1.02	0.56-1.86	0.95
2012	12.10	5.06-28.94	<0.0001	15.76	6.39-38.85	<0.0001	20.35	8.19-50.61	<0.0001	-	-	-
On HIV treatment												
Yes	0.73	0.54-0.98	0.04	1.23	0.87-1.79	0.29	1.41	0.94-2.10	0.09	1.32	0.90-1.93	0.16
No	1	-	-	1	-	-	1	-	-	1	-	-

	Univariable analysis			Multivariable model 1			Multivariable model 2 – excluding IDU			Multivariable model 3 – excluding 2012		
	RR	**95% CI**	**P value**	**ARR**	**95% CI**	**P value**	**ARR**	**95% CI**	**P value**	**ARR**	**95% CI**	**P value**
Hepatitis infection status												
HIV mono-infected	1	-	-	1	-	-	1	-	-	1	-	-
HIV/HBV co-infected	1.36	0.80-2.31	0.25	0.92	0.53-1.58	0.76	0.85	0.48-1.49	0.57	1.08	0.63-1.84	0.78
HIV/HCV co-infected	0.80	0.46-1.41	0.44	0.34	0.17-0.70	0.003	0.38	0.16-0.95	0.04	0.40	0.20-0.81	0.01
HIV/HBV/HCV triple-infected	2.29	1.01-5.18	0.05	1.26	0.52-3.02	0.61	0.77	0.19-3.13	0.70	1.54	0.64-3.69	0.33

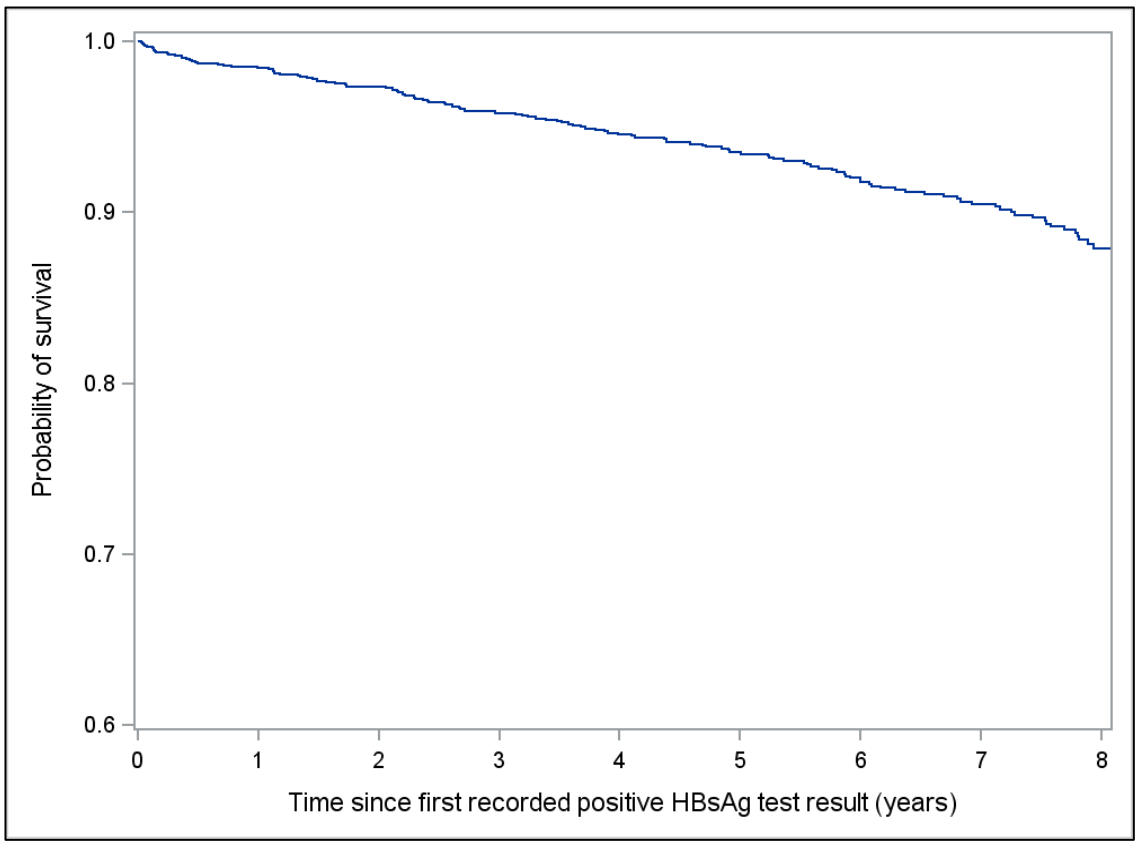
Table 9.10 Rate ratios from Poisson regression showing associations between liver-related mortality and composite HAART and HIV viral load covariate

HAART/HIV viral load category	Univariable analysis			Multivariable analysis		
	RR	95% CI	P value	ARR	95% CI	P value
Off HAART & HIV viral load ≥50 copies/ml	1	-	-	1	-	-
Off HAART & HIV viral load <50 copies/ml	0.13	0.02-1.02	0.05	0.19	0.02-1.51	0.12
On HAART & HIV viral load <50 copies/ml	1.13	0.56-2.31	0.73	1.13	0.54-2.36	0.74
On HAART & HIV viral load 50-10000 copies/ml	2.70	1.17-6.25	0.02	1.78	0.77-4.15	0.19
On HAART & HIV viral load >10000 copies/ml	10.25	4.64-22.67	<0.0001	3.91	1.75-8.78	0.001

9.3.2 Predictors of mortality among HIV/HBV co-infected individuals

A total of 1679 HIV/HBV co-infected individuals were included in the analysis, of whom 132 died. Median follow-up time for the group, from first recorded positive HBsAg test, was 5.7 years (IQR 2.6, 7.8): 5.9 years (IQR 2.8, 7.9) for individuals who did not die; and 3.3 years (IQR 1.4, 5.8) for those who died. Probability of survival over time is shown in Figure 9.1. At 2 years, 3% of HIV/HBV co-infected individuals had died, at 4 years, 5% of HIV/HBV co-infected individuals had died and by 6 years, 8% of HIV/HBV co-infected individuals had died.

Figure 9.1 Kaplan Meier estimations of probability of survival from first evidence of HIV/HBV co-infection



Years	1	2	3	4	5	6	7	8
Number at risk	1494	1366	1213	1078	946	791	618	325

Results of the univariable and three multivariable Cox regression models are shown in Table 9.11. Model 1 includes all HIV/HBV co-infected individuals, model 2 includes only those individuals who have known HBeAg status during follow up and model 3 includes only those who have known liver disease status (cirrhotic or not cirrhotic) during follow-up.

In model 1, individuals who were older at baseline were more likely to die (AHR, 95% CI: 1.73, 1.41-2.11 per additional 10 years of age). Compared to MSM, IDU were 3.56 times more likely to die (95% CI 1.98-5.69) and individuals of other or unknown exposure category were 2.29 times more likely to die than MSM (95% CI 1.09-4.79). Individuals with higher CD4 counts were less likely to die (AHR, 95% CI: 0.84, 0.77-0.92 per 100 cells/mm^3) as were individuals with undetectable HIV viral load. Being on HBV treatment was protective in univariable analysis and in the in multivariable analysis (AHR, 95% CI: 0.56, 0.35-0.89).

In model 2, including those individuals who had HBeAg results available, individuals who were HBeAg-positive were significantly more likely to die than those who were HBeAg-negative (AHR, 95% CI: 1.79, 1.16-2.76). All other associations remained the same. In model 3, including those individuals who had measures of cirrhosis available, individuals who had confirmed cirrhosis were almost 5 times more likely to die than those who were not cirrhotic (AHR, 95% CI: 4.77, 2.39-9.51). In this model there was no significant association between HBV treatment and survival. The association seen between higher CD4 counts and survival was also lost after adjusting for cirrhosis status. Baseline age, IDU and high HIV viral loads remained associated with increased likelihood of dying, even after adjusting for cirrhosis.

Table 9.11 Cox regression models of factors associated with mortality among HIV/HBV co-infected individuals

	Univariable analysis			Multivariable model 1			Multivariable Model 2 – including HBeAg status			Multivariable model 3 – including cirrhosis		
	HR	**95% CI**	**P value**	**AHR**	**95% CI**	**P value**	**AHR**	**95% CI**	**P value**	**AHR**	**95% CI**	**P value**
Baseline age (per 10 years)	1.67	1.38-2.02	<0.0001	1.73	1.41-2.11	<0.0001	1.72	1.38-2.14	<0.0001	1.86	1.28-2.71	0.001
Ethnicity												
White	1	-	-	-	-	-	-	-	-	-	-	-
Black African	0.66	0.42-1.04	0.07	-	-	-	-	-	-	-	-	-
Other/unknown	0.66	0.40-1.10	0.10	-	-	-	-	-	-	-	-	-
HIV exposure group												
MSM	1	-	-	1	-	-	1	-	-	1	-	-
IDU	4.71	2.87-7.71	<0.0001	3.56	1.98-5.69	<0.0001	2.90	1.53-5.48	0.001	2.48	0.96-6.41	0.06
Male heterosexual	0.95	0.56-1.61	0.85	0.64	0.35-1.17	0.15	0.60	0.30-1.21	0.15	0.18	0.02-1.39	0.10
Female heterosexual	0.61	0.31-1.22	0.16	0.53	0.24-1.17	0.11	0.64	0.27-1.54	0.32	0.36	0.05-2.67	0.31
Other/unknown	2.38	1.19-4.76	0.01	2.29	1.09-4.79	0.03	2.58	1.21-5.49	0.01	2.13	0.62-7.30	0.23
CD4 count (per 100 cells/mm^3)	0.62	0.56-0.67	<0.0001	0.84	0.77-0.92	<0.0001	0.87	0.79-0.97	0.01	0.99	0.86-1.13	0.82

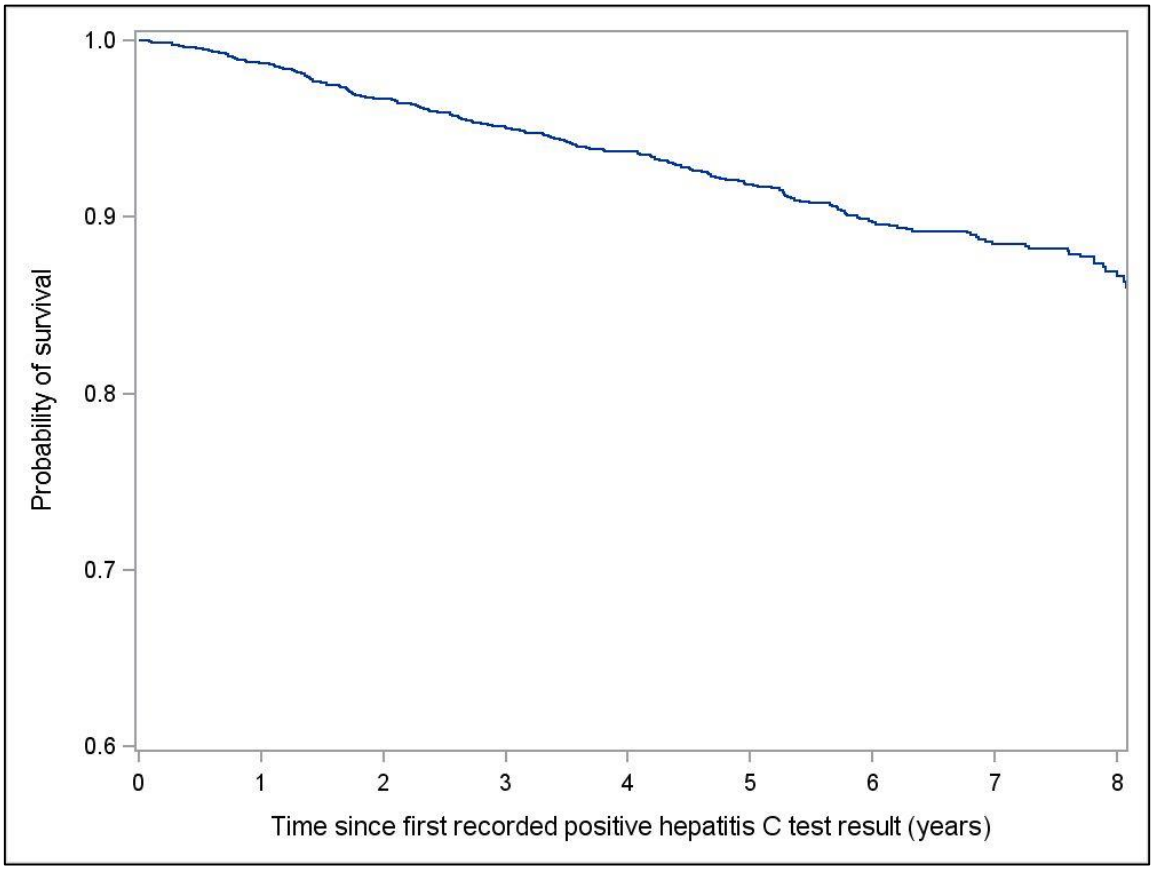
	Univariable analysis			Multivariable model 1			Multivariable Model 2 – including HBeAg status			Multivariable model 3 – including cirrhosis		
	HR	**95% CI**	**P value**	**AHR**	**95% CI**	**P value**	**AHR**	**95% CI**	**P value**	**AHR**	**95% CI**	**P value**
HIV viral load (copies/ml)												
≤50	1	-	-	1	-	-	1	-	-	1	-	-
50-10000	3.63	2.38-5.53	<0.0001	2.99	1.85-4.82	<0.0001	2.87	1.64-5.01	0.0002	3.04	1.36-6.78	0.01
>10000	6.85	4.45-10.53	<0.0001	5.27	3.11-8.93	<0.0001	5.64	3.09-10.29	<0.0001	7.16	2.57-19.96	0.0002
On HAART												
Yes	0.03	0.02-0.04	<0.0001	-	-	-	-	-	-	-	-	-
No	1	-	-	-	-	-	-	-	-	-	-	-
On HBV treatment												
Yes	0.28	0.19-0.41	<0.0001	0.56	0.35-0.89	0.02	0.49	0.29-0.84	0.01	0.69	0.27-1.79	0.45
No	1	-	-	1	-	-	1	-	-	1	-	-
HCV co-infected												
Yes	1.20	0.82-1.76	0.36	-	-	-	-	-	-	-	-	-
No	1	-	-	-	-	-	-	-	-	-	-	-
HBeAg												
Negative	1	-	-	-	-	-	1	-	-	-	-	-
Positive	2.15	1.47-3.15	0.0001	-	-	-	1.79	1.16-2.76	0.01	-	-	-

	Univariable analysis			Multivariable model 1			Multivariable Model 2 – including HBeAg status			Multivariable model 3 – including cirrhosis		
	HR	**95% CI**	**P value**	**AHR**	**95% CI**	**P value**	**AHR**	**95% CI**	**P value**	**AHR**	**95% CI**	**P value**
Liver Disease												
Cirrhotic	5.59	2.96-10.57	<0.0001	-	-	-	-	-	-	4.77	2.39-9.51	<0.0001
Not cirrhotic	1	-	-	-	-	-	-	-	-			

9.3.3 Predictors of mortality among HIV/HCV co-infected individuals

A total of 2651 HIV/HCV co-infected individuals were included in the analysis, of whom 208 died during follow-up. Median follow-up time was 4.3 years (IQR 2.0, 7.1 years): 4.5 years (IQR 2.1, 7.3) for individuals who did not die; and 2.8 years (IQR 1.4, 4.9) for individuals who died. The probability of survival over time is shown in Figure 9.2. At 2 years after first HCV-positive test 3% of individuals had died, at 4 years 6% of individuals had died and by 8 years 13% of HIV/HCV co-infected individuals had died.

Figure 9.2 Kaplan Meier estimations of probability of survival from first evidence of HCV co-infection



Years	1	2	3	4	5	6	7	8
Number at risk	2310	2000	1713	1410	1154	957	712	315

Results of the univariable and three multivariable Cox regression models are shown in Table 9.12. Model 1 includes all individuals, model 2 includes only those individuals with an HCV-RNA test result during follow-up and model 3 includes only those individuals with a measure of liver disease (cirrhotic or not) during follow-up.

In univariable analysis, individuals who were older at baseline were more likely to die. However in model 1, after adjusting for other variables age was no longer associated with mortality among HIV/HCV co-infected individuals (AHR, 95% CI: 1.19, 0.98-1.44). After adjusting for all other factors there was no significant difference in survival of individuals from different HIV exposure categories. Individuals with higher CD4 counts were less likely to die (AHR, 95% CI: 0.78, 0.73-0.83 per additional 100 cells/mm^3) as were those on HAART compared to those who were not (AHR, 95% CI: 0.07, 0.04-0.08). Compared to individuals who had not received treatment for HCV infection, those who had successful treatment were less likely to die (AHR, 95% CI: 0.11, 0.02-0.78). There was no significant difference in survival among individuals infected with different HCV genotypes. While acute HCV appeared to be protective in univariable analysis, this association was lost after adjusting for other factors, in particular after adjusting for HCV treatment (AHR, 95% CI: 0.71, 0.40-1.25).

When only those individuals with HCV-RNA test results were included (model 2), those who were known to be HCV-RNA positive were significantly more likely to die than those who were HCV-RNA negative (AHR, 95% CI: 1.52, 1.09-2.12). All other associations remained unchanged. In model 3, including only those individuals who had a measurement of liver disease, cirrhotic individuals were 2.5 times more likely to die than those individuals who were not cirrhotic (95% CI 1.52-4.10). After adjusting for cirrhosis, the association between HCV treatment and survival was lost. All other associations remained the same.

Table 9.12 Cox regression models of factors associated with mortality among HIV/HCV co-infected individuals

	Univariable analysis			Multivariable model 1			Multivariable model 2 – including HCV-RNA test results			Multivariable model 3 – including cirrhosis		
	HR	**95% CI**	**P value**	**AHR**	**95% CI**	**P value**	**AHR**	**95% CI**	**P value**	**AHR**	**95% CI**	**P value**
Baseline age (per 10 years)	1.31	1.10-1.57	0.002	1.19	0.98-1.44	0.08	1.23	0.99-1.53	0.06	1.13	0.80-1.58	0.50
Ethnicity												
White	1	-	-	-	-	-	-	-	-	-	-	-
Black African	0.68	0.32-1.44	0.31	-	-	-	-	-	-	-	-	-
Other/unknown	0.85	0.54-1.33	0.47	-	-	-	-	-	-	-	-	-
HIV exposure group												
MSM	1	-	-	1	-	-	1	-	-	1	-	-
IDU	3.12	2.33-4.18	<0.0001	1.20	0.86-1.66	0.28	1.19	0.82-1.73	0.35	0.99	0.60-1.66	0.98
Male heterosexual	1.34	0.71-2.52	0.36	0.84	0.44-1.60	0.59	1.06	0.55-2.07	0.86	1.81	0.69-4.72	0.23
Female heterosexual	0.97	0.47-2.01	0.94	0.72	0.34-1.50	0.38	0.52	0.19-1.44	0.21	0.58	0.17-1.95	0.38
Other/unknown	1.14	0.50-2.63	0.75	0.82	0.35-1.90	0.64	0.68	0.24-1.88	0.46	0.42	0.06-3.08	0.39
CD4 count (per 100 cells/mm^3)	0.67	0.62-0.71	<0.0001	0.78	0.73-0.83	<0.0001	0.78	0.72-0.84	<0.0001	0.79	0.70-0.88	<0.0001

	Univariable analysis			Multivariable model 1			Multivariable model 2 – including HCV-RNA test results			Multivariable model 3 – including cirrhosis		
	HR	**95% CI**	**P value**	**AHR**	**95% CI**	**P value**	**AHR**	**95% CI**	**P value**	**AHR**	**95% CI**	**P value**
HIV viral load (copies/ml)												
≤50	1	-	-	1	-	-	1	-	-	1	-	-
50-10000	2.70	1.89-3.76	<0.0001	0.95	0.66-1.38	0.79	0.83	0.53-1.29	0.41	1.31	0.71-2.43	0.39
>10000	4.60	3.29-6.44	<0.0001	0.80	0.55-1.17	0.25	0.86	0.56-1.33	0.50	0.98	0.49-1.95	0.95
On HAART												
Yes	0.05	0.04-0.08	<0.0001	0.07	0.05-0.10	<0.0001	0.08	0.05-0.11	<0.0001	0.09	0.05-0.16	<0.0001
No	1	-	-	1	-	-	1	-	-	1	-	-
HCV treatment												
Untreated	1	-	-	1	-	-	1	-	-	1	-	-
Successful	0.04	0.01-0.31	0.002	0.11	0.02-0.78	0.03	0.15	0.02-1.07	0.06	0.24	0.03-1.76	0.16
Failed	0.21	0.07-0.65	0.01	0.39	0.12-1.24	0.11	0.41	0.13-1.32	0.14	0.32	0.04-2.36	0.26
Unknown outcome	0.31	0.17-0.59	0.0003	0.55	0.29-1.07	0.07	0.64	0.33-1.25	0.19	0.69	0.24-1.99	0.49
HCV genotype												
1 or 4	1	-	-	1	-	-	1	-	-	1	-	-
2 or 3	1.06	0.62-1.82	0.83	0.66	0.37-1.15	0.14	0.66	0.36-1.17	0.16	0.73	0.31-1.72	0.48
Unknown	2.12	1.56-2.87	<0.0001	1.31	0.95-1.80	0.11	1.30	0.90-1.87	0.16	1.48	0.90-2.42	0.12

	Univariable analysis			Multivariable model 1			Multivariable model 2 – including HCV-RNA test results			Multivariable model 3 – including cirrhosis		
	HR	**95% CI**	**P value**	**AHR**	**95% CI**	**P value**	**AHR**	**95% CI**	**P value**	**AHR**	**95% CI**	**P value**
Acute HCV												
Yes	0.29	0.17-0.48	<0.0001	0.71	0.40-1.25	0.23	0.85	0.47-1.53	0.59	0.64	0.24-1.74	0.64
No	1	-	-	1	-	-	1	-	-	1	-	-
HCV-RNA												
Negative	1	-	-	-	-	-	1	-	-	-	-	-
Positive	1.80	1.32-2.45	0.0002	-	-	-	1.52	1.09-2.12	0.01	-	-	-
Liver disease												
Cirrhotic	4.83	3.10-7.54	<0.0001	-	-	-	-	-	-	2.50	1.52-4.10	0.0003
Not Cirrhotic	1	-	-	-	-	-	-	-	-	1	-	-

9.3.4 Predictors of cirrhosis among hepatitis co-infected individuals

Among 658 HIV/HBV co-infected individuals and 1418 HIV/HCV co-infected individuals who had any measurement of cirrhosis, 178 (27.1%) and 411 (29.0%) respectively had a confirmed diagnosis of cirrhosis through APRI score, biopsy or FibroScan®. Baseline characteristics of individuals who ever had a diagnosis of cirrhosis compared to those who did not and the results of a logistic regression of baseline characteristics associated with ever having a diagnosis of cirrhosis are shown in Table 9.13 and Table 9.14.

Among HIV/HBV co-infected individuals, there was no association between age at first HBsAg test, ethnicity or HIV exposure group and the development of cirrhosis. Those individuals with higher baseline CD4 counts were significantly less likely to have a confirmed diagnosis of cirrhosis in univariable analysis and this association was maintained after adjusting for HBeAg and HCV infection (AOR, 95% CI: 0.89, 0.82-0.96 per 100 cells/mm^3). Individuals who were HIV/HBV/HCV triple-infected were 52% more likely to develop cirrhosis than those who did not have HCV infection. Compared to individuals who were HBeAg-negative, those with unknown HBeAg status were more likely to have a diagnosis of cirrhosis (AOR, 95% CI: 2.48, 1.43-4.31), but there was no significant difference in the likelihood of having cirrhosis between HBeAg-negative and HBeAg-positive individuals (AOR, 95% CI: 1.65, 0.91-3.01).

Among HIV/HCV co-infected individuals, there was no association with developing cirrhosis and baseline age or ethnicity. However, compared to MSM, IDU and male heterosexuals were significantly more likely to have cirrhosis: AOR 1.78 (95% CI 1.29-2.45); and 2.18 (95% CI 1.30-3.65) respectively. Individuals who were not on HAART at baseline were significantly more likely to have cirrhosis than those who were on HAART at baseline (AOR 1.36, 95% CI: 1.07-1.75), as were those with unknown HCV genotype (AOR, 95% CI: 1.67, 1.29-2.16) and those who were diagnosed with acute HCV infection (AOR, 95% CI: 2.35, 1.75-3.15).

Table 9.13 Characteristics of individuals at first positive HBsAg test and logistic regression of factors associated with ever having a confirmed diagnosis of cirrhosis among HIV/HBV co-infected individuals

	No cirrhosis		Cirrhosis		Univariable analysis			Multivariable analysis		
	N	%	N	%	OR	95% CI	P value	AOR	95% CI	P value
Median age (years) (IQR) [1]	39	(34,45)	38	(32, 43)	1.18	0.97-1.44	0.09	-	-	-
Ethnicity										
White	278	57.9	117	65.7	1	-	-	-	-	-
Black African	107	22.3	30	16.9	0.67	0.42-1.05	0.08	-	-	-
Other/unknown	95	19.8	31	17.4	0.78	0.49-1.23	0.28	-	-	-
HIV exposure group										
MSM	303	63.1	117	65.7	1	-	-	-	-	-
IDU	23	4.8	9	5.1	1.01	0.46-2.25	0.97	-	-	-
Male heterosexual	70	14.6	31	17.4	1.15	0.71-1.84	0.57	-	-	-
Female heterosexual	60	12.5	14	7.9	0.6	0.33-1.12	0.11	-	-	-
Other/unknown	24	5.0	7	3.9	0.76	0.33-1.80	0.53	-	-	-
Median CD4 count (cells/mm^3) (IQR) [2,3]	385	(210, 556)	313	(209, 480)	0.92	0.86-1.00	0.04	0.89	0.82-0.96	0.003
HIV viral load (copies/ml)										
<50	148	30.8	58	32.6	1	-	-	-	-	-
>50	238	49.6	94	52.8	1.01	0.69-1.48	0.97	-	-	-
Unknown	94	19.6	26	14.6	0.71	0.42-1.20	0.2	-	-	-

	No cirrhosis		Cirrhosis		Univariable analysis			Multivariable analysis		
	N	%	N	%	OR	95% CI	P value	AOR	95% CI	P value
On HAART										
Yes	321	66.9	123	69.1	1	-	-	-	-	-
No	159	33.1	55	30.9	0.91	0.63-1.31	0.59	-	-	-
HBV treatment										
Yes	140	29.2	43	24.2	1	-	-	-	-	-
No	340	70.8	135	75.8	1.29	0.87-1.92	0.2	-	-	-
HBeAg status										
Negative	126	26.3	25	14.0	1	-	-	1	-	-
Positive	149	31.0	47	26.4	1.59	0.93-2.73	0.1	1.65	0.91-3.01	0.1
Unknown	205	42.7	106	59.6	2.61	1.60-4.25	0.0001	2.48	1.43-4.31	0.001
Ever HCV-infected										
No	343	71.5	111	62.4	1	-	-	1	-	-
Yes	137	28.5	67	37.6	1.51	1.05-2.17	0.03	1.52	1.02-2.26	0.04

[1] Odds ratios per 10 years

[2] Baseline CD4 count was unknown for 73 individuals with no cirrhosis and 10 individuals with cirrhosis.

[3] Odds ratios per 100 cells/mm^3

Table 9.14 Characteristics of individuals at first positive HCV test and odds ratios from logistic regression of factors associated with ever having a confirmed diagnosis of cirrhosis among HIV/HCV co-infected individuals

	No cirrhosis		Cirrhosis		Univariable analysis			Multivariable analysis		
	N	%	N	%	OR	95% CI	P value	AOR	95% CI	P value
Median age (years) (IQR) [1]	38	(32, 44)	39	(33,43)	1.11	0.97-1.28	0.14	-	-	-
Ethnicity										
White	837	83.1	350	85.2	1	-	-	-	-	-
Black African	42	4.2	13	3.2	0.74	0.39-1.40	0.35	-	-	-
Other/unknown	128	12.7	48	11.7	0.89	0.63-1.28	0.54	-	-	-
HIV exposure group										
MSM	649	64.4	242	58.9	1	-	-	1	-	-
IDU	194	19.3	103	25.1	1.42	1.08-1.89	0.01	1.78	1.29-2.45	0.0004
Male heterosexual	45	4.5	28	6.8	1.67	1.02-2.74	0.04	2.18	1.30-3.65	0.003
Female heterosexual	54	5.4	22	5.4	1.09	0.65-1.83	0.74	1.45	0.85-2.49	0.18
Other/unknown	65	6.5	16	3.9	0.66	0.38-1.16	0.15	0.72	0.41-1.29	0.27
Median CD4 count (cells/mm^3) (IQR) [2,3]	430	(300, 601)	423	(260, 611)	1	0.95-1.04	0.81	-	-	-
HIV viral load (copies/ml)										
<50	400	39.7	133	32.4	1	-	-	-	-	-
>50	486	48.3	194	47.2	1.2	0.93-1.55	0.16	-	-	-
Unknown	121	12.0	84	20.4	2.09	1.49-2.94	<0.0001	-	-	-

	No cirrhosis		Cirrhosis		Univariable analysis			Multivariable analysis		
	N	%	N	%	OR	95% CI	P value	AOR	95% CI	P value
HAART										
Yes	671	66.6	243	59.1	1	-	-	1	-	-
No	336	33.4	168	40.9	1.38	1.09-1.75	0.01	1.36	1.07-1.75	0.01
HCV-RNA status										
Negative	196	19.5	70	17.0	1	-	-	-	-	-
Positive	536	53.2	211	51.3	1.1	0.80-1.51	0.55	-	-	-
Unknown	275	27.3	130	31.6	1.32	0.94-1.87	0.11	-	-	-
HCV genotype										
1 or 4	596	59.2	200	48.7	1	-	-	1	-	-
2 or 3	107	10.6	50	12.2	1.39	0.96-2.02	0.08	1.4	0.95-2.07	0.09
Unknown	304	30.2	161	39.2	1.58	1.23-2.03	0.0003	1.67	1.29-2.16	0.0001
Diagnosed with acute HCV infection										
No	765	76.0	274	66.7	1	-	-	1	-	-
Yes	242	24.0	137	33.3	1.58	1.23-3.03	0.0003	2.35	1.75-3.15	<0.0001
Ever HBV-positive										
No	870	86.4	344	83.7	1	-	-	-	-	-
Yes	137	13.6	67	16.3	1.24	0.90-1.70	0.19	-	-	-

[1] Odds ratios per 10 years

[2] Baseline CD4 count was unknown for 81 individuals with no cirrhosis and 29 individuals with cirrhosis.

[3] Odds ratios per 100 cells/mm^3

9.3.5 Complications of liver disease

Among 1689 HIV/HBV co-infected individuals, 71 individuals (4.2%) had evidence of complications of liver disease. Among 2657 HIV/HCV co-infected individuals, 89 individuals (3.3%)had evidence of complications of liver disease. The large majority of these complications occurred among cirrhotic individuals. In both HIV/HBV and HIV/HCV co-infected groups the most commonly reported complication was gastroesophageal varices (Table 9.15). Baseline characteristics of HIV/HBV co-infected and HIV/HCV co-infected individuals with any evidence of complicated liver disease are shown in Table 9.16 and Table 9.17.

Table 9.15 Reported complications of liver disease

Reported complication	HIV/HBV co-infected individuals (% of total)	HIV/HCV co-infected individuals (% of total)
Individuals with evidence of cirrhosis	**62 (87.3)**	**86 (62.9)**
Ascites	25 (35.2)	43 (48.3)
Portal hypertension	42 (59.2)	62 (69.7)
Hematemesis	3 (4.2)	3 (3.4)
Gastroesophageal varices	46 (64.8)	64 (71.9)
Hepatic encephalopathy	3 (4.2)	3 (3.4)
Hepatocellular carcinoma	15 (21.1)	9 (10.1)
Transplant	1 (1.4)	4 (4.5)
Individuals without evidence of cirrhosis		
Hepatocellular carcinoma	7 (9.9)	3 (3.4)
Transplant	2 (2.8)	0 (0.0)
Total	**71 (100.0)**	**89 (100.0)**

Table 9.16 Baseline characteristics of HIV/HBV co-infected individuals who do and do not have evidence of complicated liver disease

	No complications		Reported complications		P-value
	N	%	N	%	
Total	1618		71		
Median age (years) (IQR)	39	(33, 44)	44	(39, 47)	<0.0001
Ethnicity					
White	883	54.6	48	67.6	0.07
Black African	418	25.8	11	15.5	
Other/unknown	317	19.6	12	16.9	
HIV exposure group					
MSM	962	59.5	41	57.7	0.04
IDU	68	4.2	8	11.3	
Male heterosexual	277	17.1	11	15.5	
Female heterosexual	229	14.2	6	8.5	
Other/unknown	82	5.1	5	7.0	
Median CD4 count (cells/mm^3) (IQR) [1]	370	(230, 556)	280	(160, 415)	0.01
HIV viral load **(copies/ml)**					
≤50	670	41.4	29	40.8	0.36
>50	800	49.4	32	45.1	
Unknown	148	9.1	10	14.1	
On HAART					
Yes	1191	73.6	57	80.3	0.21
No	427	26.4	14	19.7	
HBV treatment					
Yes	637	39.4	28	39.4	0.99
No	981	60.6	43	60.6	
HBeAg status					
Negative	526	32.5	25	35.2	0.27
Positive	535	33.1	28	39.4	
Unknown	557	34.4	18	25.4	
Ever HCV-positive					
No	1192	73.7	46	64.8	0.10
Yes	426	26.3	25	35.2	

[1] Baseline CD4 was unknown for 135 individuals with no evidence of complicated liver disease and 9 individuals with complicated liver disease

Table 9.17 Baseline characteristics of HIV/HCV co-infected individuals who do and do not have evidence of complicated liver disease

	No complications		Reported complications		P-value
	N	%	N	%	
Total	2568		89		
Median age (years) (IQR)	39	(24, 44)	43	(39, 48)	<0.0001
Ethnicity					
White	2095	81.5	77	86.5	0.49
Black African	128	5.0	3	3.4	
Other/unknown	245	9.5	9	10.1	
HIV exposure group					
MSM	1560	60.7	33	37.1	<0.0001
IDU	540	21.0	39	43.8	
Male heterosexual	164	6.4	7	7.9	
Female heterosexual	151	5.9	6	6.7	
Other/unknown	153	6.0	4	4.5	
Median CD4 count (cells/mm^3) (IQR)[1]	440	(300, 605)	350	(210, 495)	<0.0001
HIV viral load (copies/ml)					
≤50	1161	45.2	51	57.3	0.07
>50	1265	49.3	33	37.1	
Unknown	142	5.5	5	5.6	
On HAART					
Yes	1804	70.2	78	87.6	0.0004
No	764	29.8	11	12.4	
HCV-RNA status					
Negative	605	23.6	12	13.5	0.02
Positive	1311	51.1	58	65.2	
Unknown	652	25.4	19	21.3	
HCV genotype					
1 or 4	1133	44.1	33	37.1	0.23
2 or 3	254	9.9	13	14.6	
Unknown	1181	46.0	43	48.3	
Diagnosed with acute HCV infection					
No	1915	74.6	81	91.0	0.0004
Yes	653	25.4	8	9.0	
Ever HBV-positive					
No	2142	83.4	64	71.9	0.005
Yes	426	16.6	25	28.1	

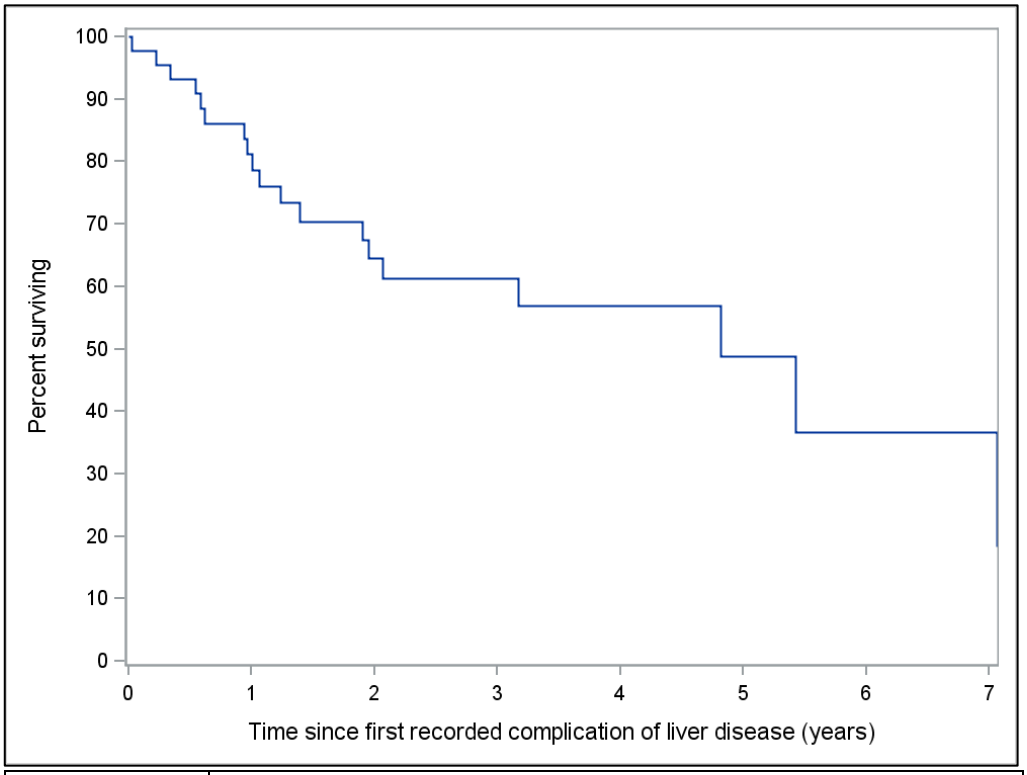
[1] Baseline CD4 was unknown for 126 individuals with no evidence of complicated liver disease and 4 individuals with complicated liver disease

To investigate predictors of developing complicated liver disease, individuals were excluded from the analyses if their final follow-up date or first evidence of complication was on or before the date that they were first entered into the co-infected group. Among those individuals, with evidence of liver disease complication prior to evidence of co-infection, it was assumed that liver disease in these had aetiology other than viral hepatitis infection. A total of 1665 HIV/HBV co-infected individuals contributed a total of 8485 person-years of follow-up and 56 individuals experienced complications giving an overall rate of complications of liver disease of 0.66 per 100 person-years follow-up. Among 2633 HIV/HCV co-infected individuals (contributing 11679 person-years of follow-up), 71 individuals experienced a complication, giving an overall complication rate of 0.61 per 100 years of follow-up

Among HIV/HBV co-infected individuals, older age, black African ethnicity, having acquired HIV through IDU exposure category, lower CD4 count and higher HIV viral load were associated with greater probability of complications in univariable analysis. However, in multivariable analysis, the association between developing complications of liver disease and baseline age was lost as was the association between developing complications and HIV viral load (Table 9.18). Other associations remained. IDU were more likely than MSM to develop complications of liver disease (AHR, 95% CI: 3.06, 1.30-7.20). There was no significant difference in the rate of developing complications among any other risk group, compared to MSM. Individuals with higher CD4 counts were less likely to experience complications of liver disease (AHR, 95% CI: 0.78, 0.68-0.90).

There were 44 HIV/HBV co-infected individuals who had further follow-up after their first complication of liver disease and who had no evidence of having received a liver transplant. Median follow for these individuals after first reported complication was 2.0 years (IQR 1.0, 4.1). Of these 44 individuals, 19 were known to have died, giving a mortality rate of 17.4 per 100 person-years. Survival after first liver disease complication is shown in Figure 9.3.

Figure 9.3 Kaplan Meier graph of survival after first recorded complication of liver disease among HIV/HBV co-infected individuals



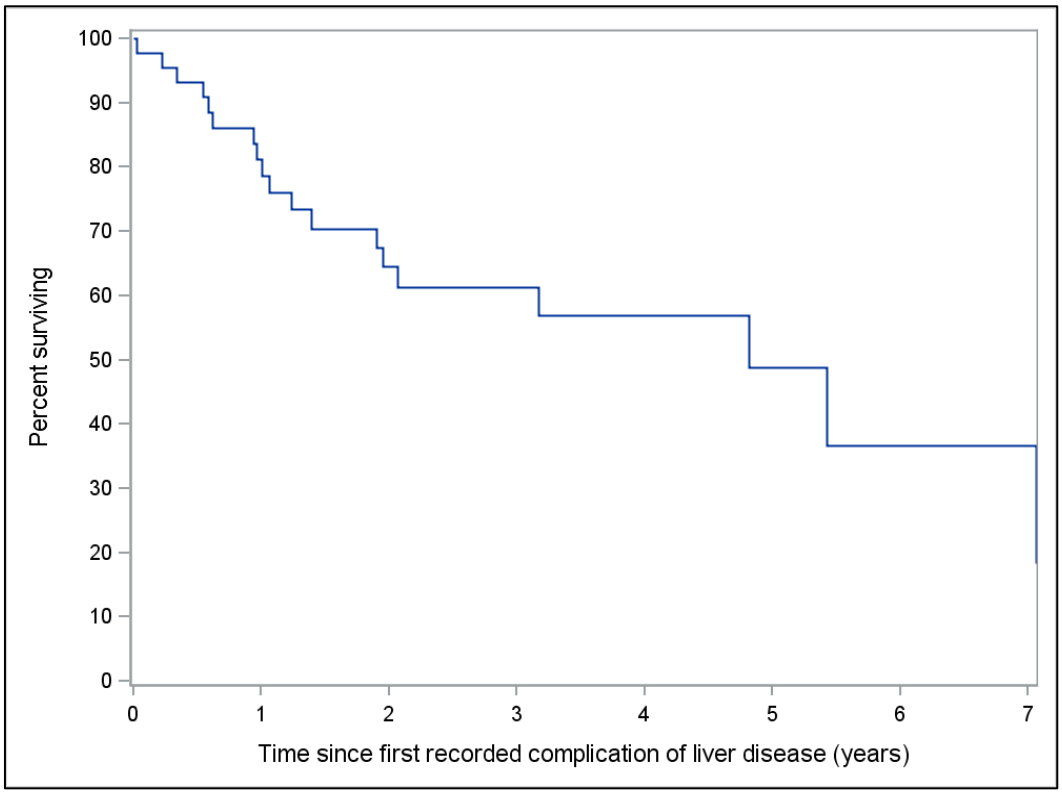
Years	1	2	3	4	5	6	7
Number at risk	32	20	15	12	4	2	1

Among HCV co-infected individuals, older age, HIV exposure group, a higher CD4 count, higher HIV viral load, being HCV-RNA positive, HCV genotype, not being diagnosed with acute infection and HBV triple-infection were all associated with increased rates of developing complications in univariable analysis (Table 9.19). In multivariable analysis, older individuals had significantly higher rates of first complication than younger individuals (ARR, 95% CI: 1.81, 1.91-2.53). Individuals with higher CD4 counts were less likely to develop complications than those with lower CD4 counts (ARR, 95% CI: 0.71, 0.61-0.82 per 100 cells/mm^3). However, the association between complications and HIV viral load was not maintained in the multivariable model. Compared to individuals who were HCV-RNA negative, those who were HCV-RNA positive were significantly more likely to develop complications (AHR, 95% CI: 2.12, 1.22-3.69). There was no significant difference in the development of complications when comparing those who were infected with genotype 1/4 and those infected with genotype 2/3. However, being infected with an unknown HCV genotype was associated with a higher likelihood of developing complications. Those individuals who were triple infected with HBV were more

likely to develop complications than those who were not HBV-infected (ARR, 95% CI: 2.13, 1.15-3.97).

There were 54 HIV/HCV co-infected individuals who had further follow-up after their first complication of liver disease and who had no evidence of undergoing a liver transplant. Median follow-up time for these individuals was 1.9 years (IQR 0.5, 3.6). Of these individuals, 25 were known to have died; a mortality rate of 20.6 per 100 person-years. Survival after first liver disease complication is shown in Figure 9.4.

Figure 9.4 Kaplan Meier graph of survival after first reported complication of liver disease among HIV/HCV co-infected individuals



Years	1	2	3	4	5	6	7
Number at risk	35	27	20	9	4	1	0

Table 9.18 Cox regression of time-updated and fixed covariates associated with first recorded complication of liver disease among HIV/HBV co-infected individuals

	Univariable analysis			Multivariable analysis		
	HR	**95% CI**	**P value**	**AHR**	**95% CI**	**P value**
Baseline age (per 10 years)	1.45	1.07-1.95	0.02	1.36	0.98-1.90	0.07
Ethnicity						
White	1	-	-	1	-	-
Black African	0.40	0.18-0.90	0.03	0.29	0.08-1.00	0.05
Other/unknown	0.67	0.31-1.43	0.27	0.54	0.21-1.37	0.19
HIV exposure group						
MSM	1	-	-	1	-	-
IDU	4.00	1.76-9.08	0.001	3.06	1.30-7.20	0.01
Male heterosexual	0.96	0.44-2.09	0.91	1.33	0.45-3.98	0.61
Female heterosexual	0.61	0.22-1.73	0.36	1.75	0.46-6.66	0.41
Other/unknown	1.93	0.59-6.33	0.28	1.95	0.45-8.43	0.37
CD4 count (cells/mm^3) (per 100 cells)	0.76	0.67-0.86	<0.0001	0.78	0.68-0.90	0.001
HIV viral load (copies/ml)						
≤50	1	-	-	1	-	-
51-10000	1.13	0.48-2.70	0.78	0.99	0.40-2.47	0.99
>10000	2.62	1.16-5.94	0.02	1.24	0.51-2.01	0.63

	Univariable analysis			Multivariable analysis		
	HR	**95% CI**	**P value**	**AHR**	**95% CI**	**P value**
On HAART						
Yes	1	-	-	-	-	-
No	0.59	0.30-1.16	0.13	-	-	-
On HBV treatment						
Yes	1	-	-	-	-	-
No	2.25	0.69-7.36	0.18	-	-	-
HBeAg status						
Negative	1	-	-	-	-	-
Positive	1.81	0.98-3.33	0.06	-	-	-
HCV-infected						
No	1	-	-	-	-	-
Yes	1.62	0.92-2.86	0.10	-	-	-

Table 9.19 Cox regression of time updated and fixed covariates associated with first recorded complication of liver disease among HIV/HCV co-infected individuals

	Univariable analysis			Multivariable analysis		
	HR	**95% CI**	**P value**	**AHR**	**95% CI**	**P value**
Age (per 10 years)	1.72	1.28-2.31	0.0003	1.81	1.29-2.53	0.001
Ethnicity						
White	1	-	-	-	-	-
Black African	0.30	0.04-2.16	0.23	-	-	-
Other/unknown	0.61	0.26-1.43	0.26	-	-	-
HIV exposure group						
MSM	1	-	-	1	-	-
IDU	2.40	1.42-4.07	0.001	1.23	0.64-2.37	0.53
Male heterosexual	2.22	0.91-5.37	0.08	0.90	0.30-2.71	0.86
Female heterosexual	1.77	0.68-4.61	0.24	1.33	0.44-3.99	0.61
Other/unknown	1.22	0.29-5.13	0.79	1.23	0.29-5.29	0.78
CD4 count (cells/mm^3) (per 100 cells)	0.70	0.62-0.79	<0.0001	0.71	0.61-0.82	<0.0001
HIV viral load (copies/ml)						
≤50	1	-	-	1	-	-
51-10000	0.68	0.27-1.72	0.42	0.53	0.20-1.27	0.19
>10000	2.17	1.09-4.29	0.03	1.23	0.54-2.80	0.63

	Univariable analysis			Multivariable analysis		
	HR	**95% CI**	**P value**	**AHR**	**95% CI**	**P value**
On HAART						
Yes	1	-	-	-	-	-
No	0.95	0.51-1.74	0.85	-	-	-
HCV-RNA status						
Negative	1	-	-	1	-	-
Positive	1.84	1.11-3.09	0.02	2.12	1.22-3.69	0.01
HCV genotype						
1 or 4	1	-	-	1	-	-
2 or 3	2.20	1.07-4.51	0.03	1.52	0.67-3.46	0.32
Unknown	1.85	1.08-3.19	0.03	2.03	1.11-3.73	0.02
Diagnosed with acute HCV infection						
No	1	-	-	1	-	-
Yes	0.45	0.21-0.99	0.05	0.99	0.42-2.36	0.98
HBV-positive						
No	1	-	-	1	-	-
Yes	1.92	1.12-3.29	0.02	2.13	1.15-3.97	0.02

9.4 Discussion

9.4.1 Summary of results

In this chapter I have compared mortality rates among HIV mono-infected individuals to those among hepatitis co-infected individuals and identified independent predictors of liver disease progression and mortality among co-infected individuals.

In the UK CHIC study, among patients under follow-up in an era of effective treatment for HIV infection, co-infection with HBV or HCV was significantly associated with increased all-cause mortality even after adjusting for other known predictors of mortality. Compared to HIV mono-infected individuals, HIV/HBV co-infected individuals were 1.4 times more likely to die, HIV/HCV co-infected individuals were 1.3 times more likely to die and triple-infected individuals were 1.8 times more likely to die after adjusting for confounding variables. The association between liver-related mortality and co-infection was even more striking: HIV/HBV co-infected individuals were 9.0 times more likely to die, HIV/HCV co-infected individuals were 5.7 times more likely and HIV/HBV/HCV triple-infected individuals were 12.4 times more likely to die of liver disease than HIV mono-infected individuals. In contrast, co-infection was not associated with AIDS-related deaths in this cohort.

A diagnosis of cirrhosis was a strong predictor of mortality among both HIV/HBV and HIV/HCV co-infected individuals. Among HIV/HBV co-infected individuals, cirrhosis was significantly more likely to be diagnosed among those with lower baseline CD4 cell counts than those with higher baseline CD4 cell counts, and among those who were HIV/HBV/HCV triple-infected compared to HIV/HBV co-infected individuals. Among HIV/HCV co-infected individuals, cirrhosis was significantly more likely to be diagnosed among IDU, male heterosexuals, those not on HAART at baseline, those with unknown genotype and those who were diagnosed in the acute phase of infection.

Although reported complications of liver disease in the co-infected groups were rare (reported for 4.2% of HIV/HBV co-infected and 3.3% of HIV/HCV co-infected individuals), mortality among the individuals who had experienced complications of liver disease was high with only 60% of co-infected individuals surviving up to 2 years after their first reported complication of liver disease.

9.4.2 Interpretation of results

The very high adjusted rate ratios for liver-related mortality in co-infected individuals compared to HIV mono-infected individuals, combined with the lack of association between co-infection and AIDS-related mortality indicate that the increase in all-cause mortality among co-infected individuals compared to mono-infected individuals is a result of liver disease rather than increased progression of HIV disease among co-infected individuals.

In assessing the association of hepatitis co-infection with all-cause, liver-related and AIDS-related mortality, some other associations were also observed. A number of these associations were as expected. For example, IDU and older age were significantly associated with increased all-cause, liver-related and AIDS-related mortality. Lower CD4 count and higher HIV viral load were also associated with each of the three types of mortality investigated. Low CD4 count and high HIV viral load are markers of HIV disease progression and therefore the association with all-cause mortality is expected since individuals with advanced HIV disease are more likely to die. Both are known to be associated with mortality (537).

The observed association between all-cause mortality and being on HAART, and the even stronger association between liver-related mortality and being on HAART is less intuitive. While a previous study has shown that HAART is associated with adverse liver events (291), the size of the effect in the present analysis was not expected. On further investigation this association was found to be closely related to HIV viral load and after repeating the analysis using a composite measure of HAART and HIV viral load, comparing to those individuals who were not on HAART and had detectable HIV viral loads, only those individuals who were on HAART but also had very high HIV viral loads were found to have significantly higher rates of liver-related mortality. Being on HAART and having a high HIV viral load is likely to be a sign of treatment failure and therefore these individuals could be expected to be very unwell compared to individuals in the other HAART/viral load categories. This additional analysis indicates that the observed association of HAART and liver-related mortality may not be as a result of HAART. Instead the observed association is due to a group of individuals who are on HAART and are very unwell (as indicated by their high HIV viral loads) prior to dying.

Another reason for being on HAART and having high HIV viral load may be poor adherence to treatment. HIV and HBV are treated with common agents and therefore those individuals who are poorly adherent to HIV treatment could also be considered to be poorly adherent to their HBV treatment. Therefore the finding that HBV/HIV co-infected individuals have a higher rate

of mortality than HIV mono-infected individuals may be driven by a group of individuals who are not adherent to treatment and therefore have uncontrolled HIV and HBV infections.

In addition, the association between mortality and year of follow-up was unexpected. Being under follow-up in 2004 was associated with significantly lower all-cause mortality when taking 2009 as a reference year, while 2011 had significantly higher all-cause mortality. Similarly, being under follow-up in 2004 was associated with significantly lower liver-related mortality when compared to 2009, and being followed-up in 2005 was associated with significantly lower AIDS-related mortality. Given the efforts that have been made to improve the quality of death data within UK CHIC, these findings may be due to under-reporting of deaths in 2004. In particular, linkage to PHE data was first conducted in 2011 using a dataset that contained data up to the end of 2010. Therefore it is likely that from 2010 onwards a higher proportion of individuals who had died would have information recorded in UK CHIC.

The results of the Cox models used to identify predictors of mortality and the logistic model used to identify predictors of cirrhosis further illustrate the important role of liver disease in mortality among HIV/HBV co-infected individuals. The addition of cirrhosis to the model of mortality, among HIV/HBV co-infected individuals removed the previously seen association between mortality and lower CD4 counts. In addition, HIV/HBV co-infected individuals with lower baseline CD4 counts were more likely to ever have a diagnosis of cirrhosis in logistic regression and were more likely to develop complications of liver disease than individuals with higher CD4 counts. Therefore it appears that although CD4 count and liver disease are associated, once an individual has established liver disease, CD4 count no longer predicts mortality. It is not possible from these data to assess whether CD4 count impacts development of cirrhosis or cirrhosis impacts CD4 count.

Among HIV/HCV co-infected individuals, the addition of cirrhosis to the model of predictors of mortality did not remove the previously seen associations between mortality and lower CD4 count or mortality and not being on HAART, indicating that even if an individual has developed cirrhosis, HIV treatment and immune system function are important determinants of survival of HIV/HCV co-infected individuals. In the logistic model of predictors of cirrhosis among HIV/HCV co-infected individuals, not being on HAART at baseline was associated with an increased likelihood of ever being diagnosed with cirrhosis, again indicating that HAART is an important protective factor for HIV/HCV co-infected individuals. The addition of cirrhosis to

the model of mortality among HIV/HCV co-infected individuals did remove the association between successful HCV treatment and mortality indicating that the observed reduced mortality among individuals successfully treated for HCV may be a result of lower rates of cirrhosis among these individuals. HCV treatment was not included in the logistic regression model of predictors of cirrhosis (see section 9.2.6), however, so this cannot be confirmed. The finding that having an unknown HCV genotype is associated with ever having a confirmed diagnosis of cirrhosis may be explained by the fact that individuals would likely have a genotype test before undergoing HCV treatment. Therefore those with unknown genotype are likely to include a higher proportion of individuals who have not been treated.

The very high mortality rates observed following first report of complications of liver disease, in both HIV/HBV and HIV/HCV co-infected individuals, confirms the importance of liver disease in mortality of co-infected individuals.

9.4.3 Comparisons with the literature

The association of HIV/HBV co-infection with increased all-cause mortality and the even larger effect of HBV infection on the risk of liver-related mortality has been seen in other cohorts (257, 258, 261, 290, 291, 303). The degree to which HBV co-infection increases the risk of all-cause mortality is also in line with other studies. The analyses presented in this chapter indicate that HIV/HBV co-infected individuals are 1.4 times more likely to die than HIV mono-infected individuals. In the largest previously published study comparing mortality among HIV/HBV co-infected and HIV mono-infected individuals, in the EuroSida cohort, individuals who were HIV/HBV co-infected were 1.54 times more likely to die than HIV mono-infected individuals (258). The magnitude of increased risk of liver-related mortality among HIV/HBV co-infected individuals compared to HIV mono-infected individuals in this UK cohort is higher than previously reported. For example, in EuroSida the risk of liver-related mortality among HIV/HBV co-infected individuals was 3.3 times more likely than among HIV mono-infected individuals (258). Similarly, in another Pan-European study (D:A:D) the risk of liver-related mortality was 3.7 times higher among HIV/HBV co-infected compared to HIV mono-infected individuals. In the present analysis the risk of liver-related mortality was 8.9 times higher among HIV/HBV co-infected compared to HIV mono-infected individuals. This difference in effect size may be due to different levels of liver-related mortality in the mono-infected individuals in each cohort. As UK CHIC has lower proportions of IDU than other cohorts, the rate of liver deaths in the mono-infected group is likely to be lower within UK CHIC, and therefore the additional risk of liver-related mortality among the co-infected group will be

greater. Finally, the finding that HIV/HBV co-infection is strongly associated with liver-related mortality but not with AIDS-related mortality is in line with research which has shown that, in the era of HAART, HBV co-infection is not associated with an increased progression of HIV to AIDS (258, 302, 303).

The association between increased mortality and HIV/HCV co-infection has also been shown in other cohorts (252, 253, 274, 284-286, 288, 289, 291, 295, 538). In the present analysis, the risk of all-cause mortality was 1.28 times higher among HIV/HCV co-infected individuals compared to HIV mono-infected individuals. This is similar to the effect size seen in a meta-analysis of 20 studies comparing mortality in HIV/HCV co-infected to that in HIV mono-infected individuals. In the meta-analysis HIV/HCV co-infected individuals had a risk of mortality which was 1.35 times higher than HIV mono-infected individuals (275). Other cohort studies which have shown an increased risk of all-cause mortality among co-infected individuals have also shown effect sizes of between 1.2 and 2.5 (Chapter 2, Table 2.3). The analyses presented in this chapter indicate that HIV/HCV co-infection leads to a greater increase in risk of liver-related death than the increase seen for all-cause mortality: the risk of liver-related mortality was 5.7 times higher among HIV/HCV co-infected than among HIV mono-infected individuals. This magnitude of increased risk for liver-related mortality among HIV/HCV co-infected compared to HIV mono-infected individuals was smaller than that seen in other cohorts (as described for HBV co-infection). For example, in the EuroSida cohort the risk of liver-related mortality was 11.7 times higher among HIV/HCV co-infected individuals than among HIV mono-infected individuals (252). Similarly, among a cohort of Danish patients the risk of liver-related mortality was 15 times higher among HIV/HCV co-infected individuals than among HIV mono-infected individuals (253). As described for HBV, this difference is likely due to higher liver-related mortality in the mono-infected group, possibly as a result of the higher proportion of IDU in other cohorts compared to in UK CHIC. As with HIV/HBV co-infection, HIV/HCV co-infection was not associated with AIDS-related mortality. This supports the hypothesis that HIV/HCV co-infection does not alter progression of HIV to AIDS in the era of HAART (246, 252).

Importantly, in addition to the association between liver-related mortality and HIV hepatitis co-infection, the analyses presented in this chapter show a strong association between liver-related mortality and CD4 count. Those individuals who had good immune function (higher CD4 counts) were less likely to have liver-related mortality. In this cohort a 100 cell/mm^3 increase in CD4 count was associated with a 37% reduction in risk of mortality. This finding is

in agreement with the study by Weber et al, which also showed a strong association of immune function with liver-related death: for every 2-fold increase in CD4 cell count, the risk of liver-related death decreased by 23% (291). The same study found an increased risk of liver-related mortality with cumulative exposure to HAART after adjusting for most recent CD4 count. The authors postulated that the modest increase in liver-related deaths may be due to an increased risk of hepatotoxicity and that the protective effect of increased CD4 count, to some extent counteracts this increased risk. The analyses presented in this chapter indicate that although HAART is associated with increased liver-related death, this association occurs only among those individuals who have high HIV viral loads and could be considered to be failing HIV treatment.

Among HIV/HBV co-infected individuals in this cohort, lower CD4 count and higher HIV viral load were associated with mortality. However, after adjusting for liver disease in the analysis, HIV-related parameters were no longer associated with increased mortality among co-infected individuals. A slightly different result was seen among HIV/HCV co-infected individuals where lower CD4 count and not being on HAART were associated with an increased risk of mortality even after adjusting for liver disease. Although previous studies have shown that higher CD4 counts and HAART use are associated with decreased mortality among co-infected individuals, these studies have not adjusted for liver disease. For example, Bonacini et al, found that among co-infected individuals, initial CD4 count was associated with liver-related mortality, though in their analysis co-infection was considered together and was not split by specific hepatitis virus and no markers of the stage of liver disease were included in the analysis (290). The analysis presented in this chapter, however, also found a strong association between lower CD4 cell count and cirrhosis. Other researchers have also reported the association between low CD4 counts and cirrhosis (386, 387) which support our findings. The finding that not being on HAART is significantly associated with cirrhosis is supported by previous research comparing the progression of liver disease in the pre-HAART and post-HAART eras (332).

A previous study investigating complications of liver disease in HIV-positive individuals has shown that one third of all cirrhotic patients have decompensated liver disease. However, this study does not break this prevalence down by aetiology of cirrhosis (336). Among a small Spanish cohort of patients receiving treatment for HBV the rate of liver decompensation was 2.9 per 100 person-years. Among HCV co-infected patients the proportion of individuals who have liver decompensation events has been reported as 5.8% - 10% among all co-infected

(287, 539) and 23% among cirrhotic individuals (540). It is difficult to compare these results with those from the UK CHIC co-infected groups given the varying follow-up times. However, it is clear from these studies as well as the results presented in this chapter that mortality following liver disease complications is high (541).

9.4.4 Strengths and weaknesses

The analyses presented in this chapter provide the first estimations of mortality among hepatitis co-infected HIV-positive individuals in the UK. The links made between the UK CHIC dataset and data from ONS and PHE have resulted in very reliable data on the number of individuals who have died. However, accurately establishing cause of death is difficult and obtaining reliable causes of death is an ongoing project in UK CHIC. Therefore it is possible that the number of AIDS-related and liver-related deaths are underestimated as cause of death data remains incomplete.

Given the potential for under ascertainment of cause of death and the methods used to code the deaths within the dataset, it was not possible to examine mortality rates for non-AIDS, non-liver related causes of death as part of this analysis. This additional analysis would be useful since it is possible that co-infected individuals may have higher mortality rates due to reasons which are not related direction to their hepatitis infection. For example, IDU might be more likely to die than individuals of other exposure categories for reasons such as of suicide or drug overdose. However, as it is not possible to assess the non-AIDS non-liver-related causes of death in this dataset, it is not possible to examine the impact of other causes of death on mortality rates in each co-infection group.

Conversely, it is also possible that the number of liver-related deaths is overestimated in co-infected individuals since a known hepatitis diagnosis may influence how a death is reported. In this analysis, the impact of this was minimised by not coding a death as liver-related purely on the basis of a mention of viral hepatitis infection and by coding the deaths without knowledge of the individual's hepatitis status. However, some bias in reporting deaths as liver-related among co-infected individuals may exist.

Measurements of cirrhosis were only available for 39% of HIV/HBV co-infected individuals and 53% of HIV/HCV co-infected individuals. It is likely that individuals are only investigated for cirrhosis where there is clinical suspicion of liver damage. Therefore the prevalence of cirrhosis may be over-estimated. In addition, the bias towards investigating liver damage

among individuals with clinical signs of liver damage means that it is not possible to accurately estimate the point at which an individual becomes cirrhotic. Therefore, using these data it was not possible to investigate rates of progression to cirrhosis and predictors of cirrhosis could only be investigated using "ever cirrhotic" as an outcome. Investigating progression to cirrhosis would require active follow-up of individuals known to be non-cirrhotic with regular measurements of liver damage.

Individuals who develop complications of liver disease may become very seriously unwell and require hospital treatment. This may or may not occur within the same facility where they receive their HIV care. Data on complications of liver disease were gathered from the centres where individuals receive their HIV care. Therefore, where individuals received care for liver disease away from their HIV clinic, it may not be possible to gather these data. Even where care for liver disease is received at the same facility as HIV care, different communication systems between departments may mean that some information on liver disease complications was not obtained. Therefore the number of individuals who have recorded complications may be an underestimate of the true number of co-infected individuals who experience complicated liver disease. However, this underestimate does not affect the findings of high mortality results among individuals with reported complications.

Finally, using the data from UK CHIC it is not possible to determine the date of infection with HBV or HCV since individuals may have been infected for some time before their first positive result in the dataset. Therefore it is not possible to examine the effect of timing of hepatitis infection compared to HIV infection on the clinical outcomes.

9.4.5 Conclusions

These analyses represent the first in-depth description of mortality among HIV and hepatitis co-infected individuals in a UK setting. The results of the analyses presented in this chapter have shown that compared to HIV mono-infected individuals, hepatitis co-infected individuals have increased mortality and that development of liver damage in the form of cirrhosis and the complications caused by cirrhosis are important factors in this increased mortality. The association between CD4 cell count and liver disease demonstrates the impact of HIV on the progression of damage as a result of viral hepatitis infection. The strong association between cirrhosis and mortality illustrates the importance of preventing liver damage as a result of hepatitis infection. Therefore, in an era where HIV-positive individuals can expect successful suppression of HIV infection, identifying hepatitis co-infected individuals early in their hepatitis

infection and ensuring their successful treatment in order to prevent the development of cirrhosis is vital in improving outcomes for co-infected individuals.

Chapter 10 Concluding remarks

10.1 Summary of main findings

Since the introduction of HAART, the rate of AIDS-related morbidity and mortality has fallen and with prompt access to treatment, HIV-positive individuals can be expected to live a near normal life-span. Treatment and management of non-AIDS morbidity such has viral hepatitis has, therefore, become an increasingly important component of HIV care.

I began my research by conducting a literature review, presented in chapter 2, through which I assessed the current knowledge on the burden of HBV/HCV co-infection among HIV-positive populations and clinical outcomes for co-infected individuals. Both HBV and HCV have been shown to be prevalent in HIV-positive populations, with 4.5-8.7% of individuals being HBV-infected in European cohorts. A wider range in prevalence of HCV has been reported: 8.9-69%; the prevalence is higher where IDU make up a higher proportion of the HIV-positive population. The published research shows that HBV and/or HCV co-infection has an important impact on the clinical outcomes of HIV-positive individuals. Firstly, HIV-positive individuals are more likely to develop chronic hepatitis infection (rather than clearing infection) than HIV-negative individuals. Secondly, those who are co-infected with HIV and HBV and/or HCV have higher rates of liver disease progression than individuals who are infected with HBV or HCV alone. In addition, while hepatitis co-infection does not appear to affect the progression of HIV to AIDS, there is some evidence to suggest that compared to HIV mono-infected individuals, hepatitis co-infected individuals may have decreased responses to HAART. Higher mortality rates are observed among HIV-positive individuals co-infected with HBV and/or HCV than among individuals who are infected with HIV alone and liver disease appears particularly important in as a cause of death. In the context of these detrimental effects of HBV/HCV co-infection on HIV-positive individuals, understanding who is at the greatest risk of co-infection, the effectiveness of treatment outside of clinical trials and the determinants of disease progression is particularly important.

Given the findings of the literature review, the aim of this thesis was to investigate clinical outcomes for HIV/HBV and HIV/HCV co-infected individuals in the UK. The UK CHIC study is the largest clinical cohort of HIV-positive individuals in the UK. However, prior to commencing my research, the study collected limited information on hepatitis co-infection. Dates and results of hepatitis laboratory test results were available, but lower than expected proportions

of individuals were recorded as ever having had a test for HBV or HCV (as reported in chapter 3). In addition, no information was available regarding liver disease among individuals who were HBV and/or HCV co-infected or treatment for HBV or HCV infections. Therefore, as described in chapter 4, I undertook a process of data collection during which I identified a subset of individuals from 11 UK CHIC centres who were confirmed as being HBV and/or HCV co-infected. For this group, I then collected additional data on liver disease and treatment for hepatitis infection. The information was gathered from a range of sources including electronic patient records, hard copy clinical notes and downloads from specific databases such as laboratory records, FibroScan® machines and radiology records. The resulting dataset was then standardised, pseudonymised, cleaned and merged with the UK CHIC dataset. This process resulted in a cohort of 1637 individuals who were confirmed as HBV co-infected and 3299 individuals who were confirmed as HCV-co-infected.

In order to assess the value of routinely recorded laboratory test results in defining an individual as HBV or HCV co-infected, I conducted a detailed examination of the available results within UK CHIC. This work is presented in chapter 5. Specifically, for HBV I focussed on the results of tests for HBsAg, anti-HBs and anti-HBc and for HCV I focussed on anti-HCV tests. With clinical input I developed algorithms for making decisions about erroneous results and defining an individual's true HBV or HCV infection status. An important finding from this chapter was that for a high proportion of individuals it was not possible to assign a definitive HBV-infection status. Therefore whilst I have been able to confidently define a cohort of HBV co-infected individuals as a result of the data collection, the proportion of individuals who are immune to HBV-infection (either through vaccination or previous cleared infection) and the proportion who have never been exposed to HBV remain uncertain.

In the context of this newly collected data, in chapter 6 I investigated the proportion of individuals who had been tested for HBV and/or HCV co-infection and the prevalence and incidence of these infections within UK CHIC. A key finding from this chapter is that from 2004 to 2011, the proportion of individuals who have ever had a test for HBsAg or anti-HCV has significantly increased. In addition the proportion of individuals not known to be infected who test within each calendar year has also increased. Testing has increased differentially among subgroups. For example, the probability of having a first HBsAg test has increased more among white individuals than among black African individuals and the probability of having a first anti-HCV test has increased more among MSM than among IDU. The prevalence of HBV-

infection in this cohort was 6.7% and the incidence of newly identified infection was estimated as 1.2 per 1000 person years. Prevalence of HCV was 10.7% in this cohort with incidence estimated as 0.91 per 1000 person years. Prevalence of HBV appears to have decreased from 2004 to 2011 while that of HCV has remained stable. However, changes in prevalence and incidence may be impacted by increasing testing. Another key finding from this chapter is that although prevalence of HCV has remained stable for the cohort as a whole the prevalence among MSM has increased.

In chapter 7 I present an analysis investigating receipt of treatment for HCV-infection and responses to treatment. More than a third of HCV-infected individuals in UK CHIC had received treatment with those individuals who were diagnosed with acute infection being more likely to receive treatment than those not diagnosed in the acute stage. MSM were more likely than IDU and heterosexuals to receive treatment. A particularly important, but disappointing, finding reported in this chapter was that with the data available in UK CHIC it was not possible to define SVR to HCV treatment. Therefore in order to identify predictors of treatment failure I investigated time to treatment failure among all individuals who had an HCV-RNA test available within a year of stopping treatment. I reported that 33% of these individuals had evidence of failing treatment. Those factors shown to be associated with treatment failure in other studies were also identified as independent predictors of treatment failure in this cohort particularly higher baseline HCV viral load, shorter time on treatment, not being treated in acute infection and being infected with genotype 1 or 4 HCV. Of particular importance is the finding that there is a large group of HCV co-infected individuals who are in need of HCV treatment, either because they have never received treatment or because they have failed treatment. These individuals are at risk of developing liver disease and a small proportion already have evidence of cirrhosis.

In chapter 8 I report on the strategies in use within UK CHIC to treat HBV-infection and I assess response to treatment with regard to suppression of viral replication (evidenced by loss of detectable HBV-DNA), loss of HBeAg and seroconversion to anti-HBe positivity. In this cohort, the majority of HBV co-infected individuals received treatment. In addition, the most commonly used treatment was with two NRTIs. Whilst the majority of individuals suppressed HBV replication, less than half lost HBeAg and of those even fewer (57.7%) were known to develop anti-HBe. These individuals remain at risk of developing cirrhosis. The analysis of treatment response identified some important independent predictors of treatment response:

being on 2 or more drugs was significantly associated with loss of HBeAg; and higher CD4 count and being HBeAg negative was associated with suppression of HBV replication.

Finally, in chapter 9 I examined the impact of HBV and/or HCV co-infection on clinical outcomes of HIV-positive individuals. Like a number of other studies I reported a strong association between hepatitis co-infection and increased all-cause mortality. HBV and/or HCV co-infection had an even greater effect on the rate of liver-related mortality in this cohort. Among HBV co-infected individuals the analyses showed the importance of treatment as those who received HBV active treatment were significantly less likely to die than those who did not. In addition, those with higher CD4 counts were less likely to die than those with lower CD4 counts. I reported similar findings among HCV co-infected individuals; individuals with higher CD4 counts were less likely to die than those with lower CD4 counts as were individuals on HAART compared to those not on HAART. Importantly, those individuals who had evidence of successful or failed HCV-treatment were less likely to die than those who were untreated.

In addition, among the co-infected groups evidence of cirrhosis was a strong predictor of mortality when added to the model. Therefore predictors of cirrhosis were also assessed. Among HBV co-infected individuals CD4 count was a predictor of cirrhosis. Among HCV co-infected individuals, cirrhosis was associated with injecting drug use. Another important finding is that not being on HAART was associated with cirrhosis among HCV co-infected individuals.

The consequences of developing cirrhosis can be serious. I only identified small proportions of HBV and/or HCV co-infected individuals who had experienced complications of liver disease. However, the survival curves for individuals who experience complications of liver disease and mortality rates following first recorded complication indicate the importance of preventing liver disease from progressing.

10.2 Relevance of findings and limitations

As shown in the literature review HIV and HBV/HCV co-infection has previously been studied within a number of different cohorts. However, the range of results indicates the importance of having locally applicable data on which to base clinical guidelines. This work has resulted in the creation of the largest research cohort of HIV and HBV and/or HCV co-infected individuals

in the UK. The results will be particularly important in guiding decisions about treatment and management of co-infected individuals in the UK.

Although estimates of the prevalence of HBV and HCV in this cohort had been published previously, these newer estimates are important for two reasons. Firstly, the work which I have undertaken to confirm the status of individuals means that the data can be considered to be more complete than that used in previously published estimates. Secondly, these estimates provide a more up-to-date picture of co-infection at a time where there are a number of new treatments for HCV becoming available. The estimates of incidence and prevalence of co-infection as well as the estimates of treatment uptake and response can be used to predict future requirements for treatment and to estimate the potential impact of any new interventions Indeed, the results of the HCV analyses are currently being used to inform a model predicting the impact of new DAAs on the HCV epidemic among MSM in the UK (542).

The ongoing incidence of both HBV and HCV highlights the need for ongoing prevention of these infections. An effective vaccine is available to protect against HBV-infection. A limitation of the work presented here is that a high proportion of individuals have an unknown HBV-infection status. Therefore it was not possible for me to assess the proportion of individuals in this cohort who have received HBV vaccination. No vaccine against HCV exists. However, I have shown that MSM are significantly more likely than heterosexuals to have incident HCV-infection. Prevention efforts should therefore be particularly targeted to this group. A further limitation of this work is that there were limited test results available which allowed me to assess whether infected individuals have cleared HBV or HCV infection. I estimated the proportion of individuals with resolved HBV infection as well as the proportion of individuals known to have acute HCV infection who spontaneously cleared infection. However, these calculations included only a subset of the infected groups who had the necessary data available.

The development of DAAs for treatment of HCV in the last 3 years has changed the outlook for HCV-infected individuals. Since conducting the expanded data collection in 2012-13, three new DAAs have been licensed for use against HCV (sofosbuvir, simeprevir and daclatasvir). As described in section 1.3.4, these newer drugs result in SVR in up to 90% of HCV mono-infected individuals in clinical trials. However, phase III trials of these drugs excluded HIV-positive individuals. Subsequent studies have been conducted among HIV-positive populations. These

studies have mainly been small in size but have included both interferon containing regimens and interferon free regimens. A recent systematic review of clinical trials to date compared the results in studies including HCV mono-infected with studies including HIV-positive individuals and concluded that where assessed the proportion of HIV co-infected individuals who achieve SVR with these new drugs is comparable to the SVR rates seen among HCV mono-infected individuals (543). Although European treatment guidelines now recommend use of DAAs for HIV co-infected individuals, access to these treatments is still limited since treatments are costly (499). The results presented in chapter 7 which show that a high proportion of HIV-positive individuals have never been treated or have failed treatment, outline the urgent need for access to newer, more effective HCV treatments for HIV-positive individuals in particular.

A major limitation of the work presented in chapter 7 is that I was unable to define SVR due to the limited number HCV-RNA test results within the dataset. As newer treatment regimens become more easily accessible and are used outside of clinical trials it will be very important to monitor their effectiveness. The UK CHIC dataset, including the additional data collected for HCV co-infected individuals presents an excellent opportunity for this monitoring. However, in order to compare findings in this cohort with others, it will be vital to calculate SVR rates. Therefore a key aim of further rounds of data collection will be to ensure that treatment response is recorded in the dataset.

Although the effectiveness of NRTIs to treat HIV/HBV co-infected individuals has been previously reported, studies have been small. Therefore the findings in chapter 8, which assess predictors of viral suppression and HBeAg clearance, are of great relevance in ensuring effective treatment for this co-infected group. In particular, these data provide additional evidence that use of two HBV active drugs is preferable over use of monotherapy.

I believe that the results presented in chapter 9 are especially important since they quantify the effect of HBV and/or HCV co-infection with regard to mortality among HIV-positive populations and therefore add additional weight to the importance of ensuring that the most effective treatment options are used. The very high rates of mortality after the first liver decompensation event raise the question of how to manage end-stage liver disease in HIV-positive individuals with HBV and/or HCV co-infection. Research has shown that survival after liver transplant is comparable among HIV-positive and HIV-negative individuals and therefore

HIV should not be considered a contraindication for liver transplant (Chapter 2, section 2.9). As part of the expanded data collection, I aimed to collect information on whether an individual had been referred for or received a liver transplant. However, the number of individuals reported as having been referred for liver transplant in this cohort was very low. As an extension to this research, work is ongoing to obtain information from transplant centres on all liver transplants carried out among HIV-positive individuals. This information will be linked back into UK CHIC so that it is possible to assess whether HIV-positive individuals are being appropriately referred for liver transplant and how transplant affects survival. A final limitation of the work on mortality is the number of individuals for whom a cause of death is not reported in UK CHIC. Further work to obtain additional causes of death is ongoing and this work is part of one of the major research themes conducted in the UK CHIC study.

10.3 Future work

Data collected for this thesis included individuals seen from 2004-2012. The additional data does not form part of the standard UK CHIC data submission. Since the data collected came from a range of sources and was not recorded in a standardised manner within HIV clinics the process of gathering the data was very time consuming. Prospective data collection will be necessary in order to assess the frequency of the use of new drugs, responses to new drugs and the development of resistance to HBV/HCV treatments. In addition, the impact of new drugs on the burden of disease, the potential for HCV re-infection and any effects which new drugs may have on response to HAART could be monitored.

It is clear from the limitations described above that the main priority for future data collection should be ensuring that all treated individuals have full serological data recorded during and after their treatment. The experience of the first round of data collection has shown that a number of the variables which we aimed to collect were not easily accessible or were not available in a form which could easily be used in analyses. For example, alcohol consumption was recorded at different points in an individual's diagnosis and a person's use of alcohol may change over time. Therefore it was not possible to record this is a meaningful manner which could be easily included as a covariate in analyses. The lessons learned throughout the initial round of data collection which I conducted will be used to inform the refinement of the dataset collected in subsequent rounds of data collection. If the hepatitis data collection is to continue prospectively, given the importance of country of birth in the epidemiology of hepatitis infection, consideration should be given to including country of birth as an additional

data item. This would allow more meaningful comparisons between this research data and national surveillance data. In addition to monitoring the impact of treatment, there are a number of other areas of research questions which can be addressed using information from the expanded dataset. In particular, questions around the rate of progression of liver disease, the development of HCC and monitoring of HIV and HBV/HCV co-infected individuals. Some of these topics are already being addressed.

10.4 Final comments

For individuals living with HIV in the UK, access to HAART means a normal length life expectancy which can be spent in good health. However, this means that HIV-positive individuals are at risk of suffering the ill-effects of other co-morbidities such as HBV and HCV. These two infections, both serious in their own right, have increased rates of progression among HIV-positive individuals and I have shown that HIV-positive individuals in the UK, who are co-infected with HBV and HCV, are at increased risk of mortality as a result of their hepatitis infection. Despite the limitations in the data, I have shown that HBV treatment in the form of two active agents successfully supresses the virus whereas currently used treatments for HCV are less effective. I have shown that IDU are less likely to have received treatment than other groups and that a high proportion of individuals failed treatment. Some of these individuals already have evidence of cirrhosis. Therefore it is hoped that the results presented in this thesis can be used to help prioritise those most at need of new treatments as they become available, thus preventing serious complications of liver disease.

Appendix I Commonly used scoring systems in use for assessing the stages of liver disease

Table I.1 Ishak scoring for assessing the degree of liver damage

Description	Score
Necro-inflammatory scores	
A. Periportal or periseptal interface hepatitis (piecemeal necrosis)	
Absent	0
Mild	1
Mild/moderate	2
Moderate	3
Severe	4
B. Confluent necrosis	
Absent	0
Focal	1
Zone 3 necrosis in some areas	2
Zone 3 necrosis in most areas	3
Zone 3 necrosis and occasional portal-central bridging	4
Zone 3 necrosis and multiple portal-central bridging	5
Panacinar or multi acinar necrosis	6
C. Focal lytic necrosis, apoptosis and focal inflammation	
Absent	0
One focus or less per 10X objective	1
Two to four foci per 10X objective	2
Five to ten foci per 10X objective	3
More than ten foci per 10X objective	4
D. Portal inflammation	
None	0
Mild, some or all portal areas	1
Moderate, some or all portal areas	2
Moderate/marked, all portal areas	3
Marked, all portal areas	4
Architectural change, fibrosis and cirrhosis	
No fibrosis	0
Fibrous expansion of some portal areas with or without short fibrous septa	1
Fibrous expansion of most portal areas with or without short fibrous septa	2
Fibrous expansion of most portal areas with occasional portal to portal bridging	3
Fibrous expansion of portal areas with marked portal to portal and portal to central bridging	4
Marked bridging with occasional nodules (incomplete cirrhosis)	5
Cirrhosis probable or definite	6

Table I.2 METAVIR scoring for assessing the degree of liver damage among individuals with chronic viral hepatitis

Fibrosis Score	Description
F0	No fibrosis
F1	Portal fibrosis without septa
F2	Portal fibrosis with few septa
F3	Numerous septa without cirrhosis
F4	Cirrhosis
Activity score	**Description**
A0	No activity
A1	Mild activity
A2	Moderate activity
A3	Severe activity

Appendix II UK CHIC study organisation

II.1 UK CHIC coordinating group

Caroline Sabin (Principle Investigator), Andrew Phillips, Teresa Hill (study coordinator), Sophie Jose (research statistician), Susie Huntington (PhD student), Alicia Thornton (PhD student); UCL Research Department of Infection and Population Health.

David Dunn, Adam Glaby; Medical Research Council Clinical Trials Unit (MRC CTU at UCL)

II.2 UK CHIC Steering Committee

Jonathan Ainsworth, Sris Allan, Jane Anderson, Abdel Babiker, David Chadwick, Valerie Delpech, David Dunn, Martin Fisher, Brian Gazzard, Richard Gilson, Mark Gompels, Phillip Hay, Teresa Hill, Margaret Johnson, Sophie Jose, Stephen Kegg, Clifford Leen, Fabiola Martin, Mark Nelson, Chloe Orkin, Adrian Palfreeman, Andrew Phillips, Deenan Pillay, Frank Post, Jillian Pritchard, Caroline Sabin (PI), Roy Trevelion, Achim Schwenk, Anjum Tariq, John Walsh.

II.3 Hepatitis subgroup of the UK CHIC steering committee

Sanjay Bhagani, Andrew Burroughs, David Chadwick, David Dunn, Martin Fisher, Richard Gilson, Janice Main, Mark Nelson, Alison Rodger, Chris Taylor

II.4 UK CHIC centres

Brighton and Sussex University Hospitals NHS Trust, Brighton

Chelsea & Westminster Healthcare NHS Trust, London

Kings College Hospital NHS Foundation Trust, London

Mortimer Market Centre, Royal Free and University College Medical School, London

Royal Free NHS Trust and Royal Free University College Medical School, London

St. Mary's Hospital, Imperial College Healthcare NHS Trust, London

Bart’s and The London NHS Trust, London

North Middlesex University Hospital NHS Trust, London

Homerton University Hospital NHS Trust, London

The Lothian University Hospitals NHS Trust, Edinburgh

North Bristol NHS Trust, Bristol

University Hospitals of Leicester NHS Trust

South Tees Hospitals NHS Foundation Trust, Middlesbrough

South London Healthcare NHS Trust

St. George's Healthcare NHS Trust, London

York Teaching Hospitals NHS Foundation Trust

Coventry & Warwickshire NHS Trust

The Royal Wolverhampton NHS Trust

Ashford & St. Peter’s Hospitals NHS Foundation Trust

II.5 UK CHIC centres contributing to expanded hepatitis data collection and key contacts within centres

Brighton (M Fisher, E Youssef, Elton John Centre Staff)

St Mary’s (N Mackie, G Cooke, J Main, S Reeves, Wharfside clinic staff)

Chelsea and Westminster (M Nelson, C Fletcher, A Moyes, L Phillips, E Seah)

Mortimer Market (R Gilson, P Muniina, N Brima)

Kings (F Post, L Campbell, K Childs, C Taylor)

Royal Free (A Rodger, S Bhagani, C Chaloner, K Singh)

Edinburgh (C Leen, S Morris, A Wilson)

North Middlesex (A Schwenk, A Waters, S Miller)

Bristol (M Gompels, S Allen, H Wilson)

Middlesbrough (D Chadwick, J Gibson)

Woolwich (S Kegg, T Leitao)

Appendix III Timelines for the preparation of an annual UK CHIC dataset

Data collection and processing stage	Time for completion	Deadline
Data specification and request • Distribution of data specifications including new variables, as agreed by the steering committee and request for data sent to centres: data for all patients ever seen, not just those seen since 01/01/1996. • Data submitted via FTP server.	6 weeks	Request data beginning of November to be sent by end of December
General checks on integrity of data from sites (not checking of individual records) • Identify obvious errors by cross tabulating all variables and check new data against previous data submission for each centre and resolve and problems with the local data manager • Manipulate centre-specific data so that conforms with data specification	3.5 months	Mid-April
Import of data into UK CHIC database • Prepare all data for one centre as tab delimited text file and import into MRC database	4 weeks	Mid-May
Data cleaning of individual records • Run within-centre data queries and consistency checks and resolve errors with local data managers and clinicians • Edit to the CHIC database and ask centres to update local databases as necessary • Send centres a summary of data cleaning for example, how many inconsistencies identified and resolved	3 months	Mid-August
De-duplication • Run de-duplication process and manually resolve ambiguous matches • Merge data from matched records	6 weeks	End of September

Data collection and processing stage	Time for completion	Deadline
Preparation of final dataset • Export merged data tables to text files • Resolve outstanding data quirks using SAS program (study statistician)	1 month	End of October

Appendix IV Changes over time in the characteristics of individuals under follow-up in UK CHIC

Year of follow-up	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011
Total number of individuals in follow-up	14475	15989	17713	19377	21575	23447	24953	26270	27352	28271	29326	27670
Median age at entry (IQR)	33 (29, 38)	33 (28, 38)	33 (28, 39)	33 (28, 39)	33 (28, 39)	33 (28, 39)	33 (28, 39)	33 (28, 39)	34 (28, 40)	34 (28, 40)	34 (28, 40)	34 (28, 40)
Male (%)	11640 (80.4)	12587 (78.7)	13700 (77.3)	14730 (76.0)	16169 (74.9)	17374 (74.1)	18382 (73.7)	19366 (73.7)	20176 (73.8)	20925 (74.0)	21638 (73.8)	20421 (73.8)
Ethnicity												
White (%)	9511 (65.7)	10130 (63.4)	10853 (61.3)	11550 (59.6)	12519 (58.0)	13428 (57.2)	10780 (43.2)	11411 (43.4)	15473 (56.6)	16050 (56.8)	16541 (56.4)	15532 (56.1)
Black African (%)	2533 (17.5)	3161 (19.8)	3900 (22.0)	4672 (24.1)	5518 (25.6)	6119 (26.1)	6623 (26.5)	7009 (26.7)	7402 (27.1)	7566 (26.8)	7868 (26.8)	7423 (26.8)
Black other (%)	612 (4.2)	722 (4.5)	868 (4.9)	953 (4.9)	1101 (5.1)	1209 (5.2)	1305 (5.2)	1409 (5.4)	1511 (5.5)	1576 (5.6)	1644 (5.6)	1596 (5.8)
Other/unknown (%)	1819 (12.6)	1976 (12.4)	2092 (11.8)	2202 (11.4)	2437 (11.3)	2691 (11.5)	2852 (11.4)	2993 (11.4)	2966 (10.8)	3079 (10.9)	3273 (11.2)	3119 (11.3)
HIV exposure group												
MSM (%)	9187 (63.5)	9872 (61.7)	10603 (59.9)	11315 (58.4)	12321 (57.1)	13181 (56.2)	13841 (55.5)	14484 (55.1)	14962 (54.7)	15477 (54.8)	16058 (54.8)	15082 (54.5)
IDU (%)	715 (4.9)	712 (4.5)	709 (4.0)	703 (3.6)	721 (3.3)	738 (3.2)	769 (3.1)	767 (2.9)	765 (2.8)	753 (2.7)	741 (2.5)	670 (2.4)

Year of follow-up	**2000**	**2001**	**2002**	**2003**	**2004**	**2005**	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**
Male heterosexual (%)	1412 (9.8)	1673 (10.5)	2017 (11.4)	2309 (11.9)	2703 (12.5)	3007 (12.8)	3237 (13.0)	3440 (13.1)	3617 (13.2)	3713 (13.1)	3798 (13.0)	3523 (12.7)
Female heterosexual (%)	2363 (16.3)	2891 (18.1)	3499 (19.8)	4153 (21.4)	4870 (22.6)	5467 (23.3)	5919 (23.7)	6202 (23.6)	6518 (23.8)	6657 (23.6)	6896 (23.5)	6445 (23.3)
Other/unknown (%)	798 (5.5)	841 (5.3)	885 (5.0)	897 (4.6)	960 (4.5)	1054 (4.5)	1187 (4.8)	1377 (5.2)	1490 (5.5)	1671 (5.9)	1833 (6.3)	1950 (7.1)
***CD4 <200 cells/mm^3* (%)**												
Within year (%)	3087 (21.3)	3161 (19.8)	3490 (19.7)	3716 (19.2)	3734 (17.3)	3828 (16.3)	3577 (14.3)	3231 (12.3)	3058 (11.2)	2670 (9.4)	2487 (8.5)	2007 (7.3)
By the end of the year (%)	6085 (42.0)	6889 (43.1)	7987 (45.1)	9016 (46.5)	10179 (47.2)	11272 (48.1)	12154 (48.7)	12878 (49.0)	13531 (49.5)	13897 (49.2)	14201 (48.4)	13287 (48.0)
Undetectable viral load (≤ 50 copies/ml)												
Within year (%)	5551 (38.4)	6764 (42.3)	7969 (45.0)	9494 (49.0)	11725 (54.4)	13129 (56.0)	14684 (58.9)	15939 (60.7)	18220 (66.6)	20290 (71.8)	21678 (73.9)	21165 (76.5)
By the end of year (%)	12224 (84.5)	13666 (85.5)	15234 (86.0)	16805 (86.7)	18756 (86.9)	20376 (86.9)	21715 (87.0)	22852 (87.0)	23930 (87.5)	24679 (87.3)	25246 (86.1)	23231 (84.0)
***HAART experienced* (%)**	8277 (57.2)	9506 (59.5)	10897 (61.5)	12392 (64.0)	14157 (65.6)	15897 (67.8)	17434 (69.9)	13124 (72.8)	21034 (76.9)	22621 (80.0)	24169 (82.4)	23400 (84.6)
Initial HAART regimen												

Year of follow-up	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011
PI based (% of HAART experienced)	4914 (34.0)	5155 (32.2)	5448 (30.8)	5696 (29.4)	6186 (28.7)	6699 (28.6)	7152 (28.7)	7486 (28.5)	7793 (28.5)	8049 (28.5)	8252 (28.1)	7414 (26.8)
NNRTI based (% of HAART experienced)	6372 (44.0)	7401 (46.3)	8502 (48.0)	9692 (50.0)	11050 (51.2)	12150 (51.8)	13006 (52.1)	13778 (52.5)	14495 (52.0)	14928 (52.8)	15343 (52.3)	14543 (52.6)
Other regimen (% of HAART experienced)	3189 (22.0)	3433 (21.5)	3763 (21.2)	3989 (20.6)	4339 (20.1)	4598 (19.6)	4795 (19.2)	5006 (19.1)	5064 (18.5)	5294 (18.7)	5731 (19.5)	5713 (20.7)

Appendix V Tables produced from expanded data collection for merging into UK CHIC

Table V.1 Hepatitis co-infection lists

Includes all potentially HBV and/or HCV co-infected individuals identified either through the UK CHIC 2011 dataset or though centre specific lists of co-infected individuals.

Field name	Data Type	Description	Relevant Coding
CLINIC_ID	Text	ID number used within HIV clinics to identify individual	N/A
CENTRE	Numeric (3 digits)	Centre where data was collected. Using same codes as MRC database	N/A
CHIC_HBV	Numeric (1 or 0)	Whether the individual is identified as HBV-positive in UK CHIC	1 = Patient identified as HBV - positive in CHIC list 0= Patient not identified as HBV-positive in CHIC list
CENTRE_HBV	Numeric (1 or 0)	Whether the individual is identified as HBV-positive by the centre	1 = Patient identified as HBV-positive in centre list 0 = Patient no identified as HBV-positive in centre list

CHIC_HCV	Numeric (1 or 0)	Whether the individual is identified as HCV-positive in UK CHIC	1 = Patient identified as HCV-positive in CHIC list 0 = Patient not identified as HCV-positive in CHIC list
CENTRE_HCV	Numeric (1 or 0)	Whether the individual is identified as HCV-positive by the centre	1 = Patient identified as HCV-positive in centre list 0 = Patient not identified as HCV-positive in centre list

Table V.2 Not Co-infected according to clinical data

Field name	Data Type	Description	Relevant coding
CLINIC_ID	Text	ID number used within HIV clinics to identify individual	N/A
CENTRE	Numeric (3 digits)	Centre where data was collected. Using same codes as MRC database.	N/A
NOT_HBV_COINF	Numeric	After reviewing patient notes and electronic records at the centre it was ascertained that this individual was not HBV co-infected	1 = Not HBV co-infected
NOT_HCV_COINF	Numeric	After reviewing patient notes and electronic records at the centre it was ascertained that this individual was not HCV co-infected	1 = Not HCV co-infected

Table V.3 Demographics

Field Name	Data Type	Description	Relevant coding
CLINIC_ID	Text	ID number used within HIV clinics to identify individual	N/A
CENTRE	Numeric (3 digits)	Centre where data was collected. Using same codes as MRC database.	N/A
N_SEX	Number	Gender of individual	1 = Male 2 = Female
N_SEXORI	Number	Sexual orientation at time of hepatitis diagnosis. This may or may not also be the individual's HIV risk factor	1 = homosexual 2 = heterosexual 3 = bisexual 99 = unknown
N_ETHNICITY	Number	Ethnic group to which individual belongs	1 = White 2 = Black Caribbean 3 = Black African 4 = Black other/ unspecified 5 = Indian/ Pakistani/ Bangladeshi 6 = Other Asian/ Oriental 7 = Other/ mixed 98 = Other 99 = Not known
DRUGS	Text	Has the individual ever injected drugs?	0 = No 1 = Yes

Field Name	Data Type	Description	Relevant coding
DRUGS_ YEAR	Numeric	If the individual has injected drugs the year in which they first did so	N/A
AL_DX_TXT	Text	In words	N/A
AL_DX_VAL	Numeric	Number of stated units	N/A
AL_DX_UNIT	Text	The unit in which alcohol consumption at hepatitis diagnosis was measured	
AL_CURR_TXT	Text	As recorded in the clinical notes	N/A
AL_CURR_VAL	Numeric	Current amount of alcohol consumption	N/A
AL_CURR_UNITS	Text	The unit in which current alcohol consumption was measured	N/A

Table V.4 Hepatitis serology

Field Name	Data Type	Description	Relevant coding
CLINIC_ID	Text	ID number used within HIV clinics to identify individual	N/A
CENTRE	Numeric (3 digits)	Centre where data was collected. Using same codes as MRC database.	N/A
N_HEPTEST	Numeric	The specific hepatitis test which was	1= Hep A antibody (total)

Field Name	Data Type	Description	Relevant coding
	(1-14)	conducted	2= Hepatitis B surface antigen 3= Hepatitis B surface antibody 4= Hepatitis B core antibody (total) 5= Hepatitis B e antigen 6= Hepatitis B e antibody 7= Hepatitis C antibody 8= Hepatitis C RNA 9 = Hepatitis B core antibody (IgM) 10 = Hepatitis A antibody (IgM) 11 = Hepatitis B DNA 12 = Hepatitis D antibody (total) 13 = Hepatitis B surface antigen titre 14 = Hepatitis D antibody (IgM) 98 = Other 99= Unknown
N_HEPDATE	Date	Date on which hepatitis test was conducted	N/A
N_HEPRESULT	Numeric	Result of hepatitis test	0=negative 1= positive 2=indeterminate/weakly reactive/equivocal

Field Name	Data Type	Description	Relevant coding
N_HVAL	Numeric	The value of quantitative tests for HBV-DNA and HCV-RNA	N/A
N_HVAL_UNIT	Text	The unit used for measuring quantitative DNA and RNA tests.	N/A

Table V.5 Hepatitis C virus genotype

Field Name	Data Type	Description	Relevant coding
CLINIC_ID	Text	ID number used within HIV clinics to identify individual	N/A
CENTRE	Numeric (3 digits)	Centre where data was collected. Using same codes as MRC database.	N/A
D_GENO	Date/Time	Date genotype reported.	N/A
HCV_GENO	Text	Genotype	N/A
HCV_SUBGENO	Text	Subtype	N/A

Table V.6 Acute HCV

Field Name	Data Type	Description	Relevant coding
CLINIC_ID	Text	ID number used within HIV clinics to identify individual	N/A

Field Name	Data Type	Description	Relevant coding
CENTRE	Numeric (3 digits)	Centre where data was collected. Using same codes as MRC database.	N/A
ACUTE_HCV	Numeric	Mention in clinical notes that an individual was diagnosed with acute HCV infection	1 = diagnosed with acute infection

Table V.7 Alpha-feto protein tests

Field Name	Data Type	Description	Relevant coding
CLINIC_ID	Text	ID number used within HIV clinics to identify individual	N/A
CENTRE	Numeric (3 digits)	Centre where data was collected. Using same codes as MRC database.	N/A
AFP_DATE	Date	Date of AFP test	N/A
AFP_RESULT	Numeric	Result of test (quantitative)	N/A
AFP_UNIT	Text	Units of measurement	N/A

Table V.8 Prothrombin time tests

Field Name	Data Type	Description	Relevant coding
Clinic_ID	Text	ID number used within HIV clinics to identify individual	N/A

Field Name	Data Type	Description	Relevant coding
Centre	Numeric (3 digits)	Centre where data was collected. Using same codes as MRC database.	N/A
PT_DATE	Date	Date of prothrombin time test	N/A
PT_RESULT	Numeric	Result of test in seconds	N/A

Table V.9 International Normalised Ratio (INR) tests

Field Name	Data Type	Description	Relevant coding
CLINIC_ID	Text	ID number used within HIV clinics to identify individual	N/A
CENTRE	Numeric (3 digits)	Centre where data was collected. Using same codes as MRC database.	N/A
INR_DATE	Date	Date of INR test	N/A
INR_RESULT	Numeric	Result of INR test	N/A

Table V.10 Results of liver imaging

Field Name	Data Type	Description	Relevant coding
CLINIC_ID	Text	ID number used within HIV clinics to identify individual	N/A

Field Name	Data Type	Description	Relevant coding
CENTRE	Numeric (3 digits)	Centre where data was collected. Using same codes as MRC database.	N/A
SCAN	Numeric	The technique used to assess the liver	1 = US scan 2 = CT scan 3 = MRI scan 4 = ultrasound elastography
SCAN_DATE	Date	Date of scan	N/A
SCAN_RESULT	Text	Result of scan	N/A

Table V.11 Liver biopsies

Field Name	Data Type	Description	Relevant coding
CLINIC_ID	Text	ID number used within HIV clinics to identify individual	N/A
CENTRE	Numeric (3 digits)	Centre where data was collected. Using same codes as MRC database.	N/A
BIOPSY_DATE	Date	Date if biopsy	N/A
BIOPSY_RESULT	Text	Result of biopsy	N/A

Table V.12 FibroScans®

Field Name	Data Type	Description	Relevant coding
CLINIC_ID	Text	ID number used within HIV clinics to identify individual	N/A

Field Name	Data Type	Description	Relevant coding
CENTRE	Numeric (3 digits)	Centre where data was collected. Using same codes as MRC database	N/A
FIBROSCAN_DATE	Date	Date of FibroScan®	N/A
FIBROSCAN_RESULT	Numeric	Result of FibroScan® (KPa)	N/A
FIBROSCAN_IQR	Numeric	IQR of FibroScan® result	N/A
FIBROSCAN_SR	Numeric	Success rate for FibroScan® (%)	N/A

Table V.13 Hepatitis specific treatment

Field Name	Data Type	Description	Relevant coding
CLINIC_ID	Text	ID number used within HIV clinics to identify individual	N/A
CENTRE	Numeric (3 digits)	Centre where data was collected. Using same codes as MRC database	N/A
HEPDRUG	Numeric	The specific drug used to treat hepatitis infection	1 = Pegylated-interferon 2 = Ribavirin 3 = Adefovir 4 = Entecavir 5 = IFN 6 = Telaprevir 7 = Sofosbuvir 8 = Boceprevir 10 = Any other directly acting agent
HEPDRUG_DOSE	Text	Dose of drug given	N/A

Field Name	Data Type	Description	Relevant coding
HEPDRUG_FREQ	Text	Weekly, daily, twice daily	N/A
HEPDRUG_START	Date	Date of starting drug	N/A
HEPDRUG_STOP	Date	Date of Stopping drug	N/A
HEPDRUG_STOP_REASON	Numeric	Coded reason for stopping See codes ion data cleaning notes	1 = Completed course of treatment 2 = Lack of efficacy (relapse) 3 = Lack of efficacy(non-response) 4 = Side effects 5 = Unable to adhere to regimen 6 = Patient lost to follow-up 7 = Patient choice 8 = Drug interaction 9 = Early response 10 = Other illness 11 = Patient died 12 = Treatment break
REASON_STOP_SIDEEFFECT	Text	Where the reason for stopping was a side effect, the specific side effect which was stated	N/A
HEP_RX_NOTES	Text	Any additional information on treatment, time of treatment or treatment response	N/A

Table V.14 Complications of liver disease

Field Name	Data Type	Description	Relevant coding
CLINIC_ID	Text	ID number used within HIV clinics to identify individual	N/A
CENTRE	Numeric (3 digits)	Centre where data was collected. Using same codes as MRC database.	N/A
COMPLICATION	Numeric	Complications of liver disease which were mentioned in clinical notes	1 = Ascites 2 = Portal Hypertension 3 = Hematemesis 4 = Endoscopy with varices 5 = Encephalopathy 6 = Hepatoma
COMPLICATION_DATE	Date	Date when complication was diagnosed	N/A

Table V.15 Liver transplants

Field Name	Data Type	Description	Relevant coding
CLINIC_ID	Text	ID number used within HIV clinics to identify individual	N/A

Field Name	Data Type	Description	Relevant coding
CENTRE	Numeric (3 digits)	Centre where data was collected. Using same codes as MRC database.	N/A
TRANSPLANT_REFER	Numeric	Evidence in the clinical notes that the patient has been referred for a liver transplant assessment	1 = Patient has been referred for a liver transplant
TRANSPLANT_REFER_DATE	Date	Date patient was referred for liver transplant	N/A
TRANSPLANT	Numeric	Evidence in the clinical notes that the patient has received a liver transplant	1 = patient has received a liver transplant
TRANSPLANT_DATE	Date	Date liver transplant occurred	N/A

Table V.16 Deaths

Field Name	Data Type	Description	Relevant coding
CLINIC_ID	Text	ID number used within HIV clinics to identify individual	N/A
CENTRE	Numeric (3 digits)	Centre where data was collected. Using same codes as MRC database.	N/A
DIED	Numeric	Evidence in the clinical notes that patient has died	1 = patient is known to have died

Field Name	Data Type	Description	Relevant coding
DEATH_DATE	Date	Date patient died	N/A
DEATH_CAUSE	Text	Cause of death as reported in clinical notes	N/A

Appendix VI Independent predictors of HBsAg using three methods of defining HBsAg status

	AOR and 95 % CI from multivariable model[1]					
	Ever positive		Most recent test is positive		Positive according to algorithm	
	OR (95% CI)	P value	OR (95%CI)	P value	OR (95% CI)	P value
Age (per 10 years)	1.01 (0.96-1.07)	0.73	1.01 (0.95-1.07)	0.75	1.00 (0.95-1.06)	0.89
HIV exposure group						
MSM	1	-	1	-	1	-
IDU	0.64 (0.50-0.81)	0.0002	0.79 (0.62-1.02)	0.08	0.78 (0.61-1.00)	0.05
Male heterosexual	1.06 (0.90-1.25)	0.48	1.13 (0.95-1.34)	0.18	1.09 (0.92-1.30)	0.33
Female heterosexual	0.49 (0.41-0.58)	<0.0001	0.52 (0.43-0.62)	<0.0001	0.50 (0.42-0.60)	<0.0001
Other/ unknown	0.90 (0.73-1.11)	0.34	0.99 (0.80-1.23)	0.95	0.95 (0.77-1.18)	0.64
Ethnicity						
White	1	-	1	-	1	-
Black African	2.24 (1.93-2.67)	<0.0001	2.45 (2.07-2.90)	<0.0001	2.52 (2.13-2.99)	<0.0001
Other black	1.56 (1.26-1.94)	<0.0001	1.55 (1.23-1.96)	0.0002	1.57 (1.24-1.98)	0.0001
Other/ Unknown	1.53 (1.33-1.76)	<0.0001	1.53 (1.31-1.78)	<0.0001	1.58 (1.36-1.84)	<0.0001
Year of entry into cohort						
1996-1998	1	-	1	-	1	-
1999-2001	0.82 (0.70-0.95)	0.01	0.84 (0.71-0.99)	0.04	0.82 (0.69-0.96)	0.01

	AOR and 95 % CI from multivariable model[1]					
	Ever positive		**Most recent test is positive**		**Positive according to algorithm**	
	OR (95% CI)	**P value**	**OR (95%CI)**	**P value**	**OR (95% CI)**	**P value**
2002-2004	0.72 (0.62-0.82)	<0.0001	0.80 (0.69-0.93)	0.004	0.79 (0.68-0.92)	0.002
2005-2007	0.71 (0.61-0.81)	<0.0001	0.73 (0.62-0.85)	<0.0001	0.73 (0.62-0.95)	<0.0001
2008-2011	0.63 (0.54-0.73)	<0.0001	0.84 (0.72-0.99)	0.03	0.84 (0.72-0.98)	0.03
Nadir CD4 (per 100cells/mm^3)	0.89 (0.87-0.93)	<0.0001	0.90 (0.87-0.94)	<0.0001	0.90 (0.87-0.94)	<0.0001
HCV co-infection						
Not infected	1	-	1	-	1	-
Infected	3.44 (3.03-3.90)	<0.0001	3.02 (2.62-3.47)	<0.0001	3.19 (2.78-3.66)	<0.0001
Not tested	1.71 (1.38-2.11)	<0.0001	2.09 (1.69-2.57)	<0.0001	2.04 (1.65-2.52)	<0.0001
On HBV active ARVs	1.25 (1.12-1.41)	0.0001	1.25 (1.11-1.42)	0.0004	1.25 (1.11-1.42)	0.0004

Appendix VII Conference presentations arising from this work

1. Thornton A, Gilson R and Sabin C on behalf of the UK Collaborative HIV cohort study. A Method for ascertaining hepatitis B infection status in HIV cohorts in the presence of missing and/or inconsistent data: An example from the UK CHIC study. Poster presentation. International Workshop on HIV Observational Databases (IWHOD), 2013. Cavtat, Croatia.

2. Thornton A, Bhagani S, Burroughs A, Chadwick D, Dunn D, Fisher M, Gilson R, Jose S, Main J, Nelson M, Rodger A, Taylor C and Sabin C. Viral hepatitis testing patterns among HIV-positive individuals in the UK Collaborative HIV cohort (UK CHIC) study. Poster presentation. Third Joint conference of the British HIV Association (BHIVA) with the British Association for Sexual Health and HIV (BASHH), 2014, Liverpool, UK.

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