Improving ascertainment and treatment rates of chronic viral hepatitis

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Submitted in partial fulfilment of the requirements of the

Degree of Doctor of Medicine

Statement of originality

I, Heather Ilona Lewis, confirm that the research included within this thesis is my own work or that where it has been carried out in collaboration with, or supported by others, that this is duly acknowledged below and my contribution indicated. Previously published material is also acknowledged below.

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I confirm that this thesis has not been previously submitted for the award of a degree by this or any other university.

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Date: 28th March 2015

Details of collaboration and publications and acknowledgements:

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Abstract:

Introduction and aims:

In the United Kingdom hepatitis B virus (HBV) and hepatitis C virus (HCV) disproportionately affect migrants and people who inject drugs (PWID). Ascertainment rates of HBV and HCV are 10-40% and screening is recommended in at risk groups. Treatment uptake for HCV in PWID is low at 2-18%, and the most effective way to increase uptake is not known. This research aims to evaluate methods to address the low ascertainment and treatment rates of HBV and HCV in these populations.

Methods:

A pilot observational cohort study of screening for chronic viral hepatitis in primary care. A retrospective observational cohort study into outcomes of HCV treatment in PWID. A prospective cluster randomised trial of nurse versus doctor initiated treatment for HCV in PWID and a qualitative analysis exploring the engagement with treatment for HCV of PWID.

Results:

Direct testing results in a greater uptake of screening than opportunistic testing in migrants in primary care (21% versus 1.9%, p = <0.0001). PWID have SVR rates of 55%, re-infection rates of 2.4 per 100 person years, and crack cocaine use reduces over treatment (90% to 49%, p=<0.0001). Nurse initiation of treatment does not result in a higher uptake of therapy (9.6 % versus 7.8%, p=0.53). Treatment engagement themes

included the normalisation and stigmatisation of HCV and the perception of HCV treatment as a transformative process.

Discussion:

Direct testing for HBV and HCV appears to result in a greater uptake of testing in migrants in primary care and should be investigated in a randomised controlled trial. HCV treatment in PWID is safe and effective, and illicit drug use may reduce over treatment. Further service development is unlikely to result in a greater uptake of antiviral therapy for HCV in PWID and other options should be explored to improve treatment uptake.

Contents

1 Introduction and aims

1.1 Introduction:

1.1.1 Overview:

Hepatitis C virus (HCV) and Hepatitis B virus (HBV) are hepatotropic viruses which cause chronic viral hepatitis and can lead to cirrhosis of the liver and hepatocellular carcinoma (HCC). In the United Kingdom (UK) the prevalence of chronic HCV is 0.67%, and of chronic HBV is 0.3% (DoH, 2002) (Cornberg M, 2011), but in certain groups the prevalence is much higher. Hepatitis C virus has a prevalence of 37-68% amongst people who inject drugs (PWID) and Hepatitis B virus has a prevalence of up to 9.4% in migrants from high prevalence countries, with 96% of new cases of chronic HBV occurring in this group (Sweeting MJ H. V., 2009) (HPA, 2006)(Aweis D, 2001). Chronic viral hepatitis is usually asymptomatic until the onset of end-stage liver disease, and consequently most cases in the United Kingdom probably remain unidentified, with only 10-40% of those with HCV and 18% of those with HBV having been diagnosed (Ascione A, 2007) (ELPA 2010). Chronic HCV and HBV are easily diagnosed by a blood test, and treatments are available which reduce the risk of progression to end-stage liver disease. The low ascertainment rates, long asymptomatic period, safe and low risk testing, treatment availability and serious consequences of infection with Hepatitis B and Hepatitis C have led to an interest in screening for these viruses in high risk groups.

Despite the high prevalence of Hepatitis C virus in people who inject drugs treatment rates are low, at just 2-22% of identified cases even in healthcare services that cater

specifically to their needs (Hutchinson SJ, 2005) (Grebely J, 2006) (Matthews G, 2005) (Wilkinson M, 2008) (Alavi M, 2013). Treatment of HCV in PWID accrues a benefit to the individual through viral eradication, and has the potential to markedly reduce prevalence through prevention of onward transmission (Martin NK F. G., 2014). The low rates of treatment are due to a combination of healthcare provider, patient and system barriers, and if HCV is to be eradicated these issues will need to be addressed.

This aim of this MDRes is to evaluate methods to improve the low ascertainment and treatment rates of chronic viral hepatitis B and C in the United Kingdom. The research focuses on the two groups with the highest prevalence of chronic viral hepatitis B and C in the United Kingdom, migrants from countries of high prevalence and people who inject drugs.

The introduction of thesis will review the virology, immunology, epidemiology, diagnosis, natural history and treatment of chronic viral hepatitis B and C. It will explore in detail the current literature on the ascertainment of chronic HBV and HCV in migrants in the UK and worldwide, and will examine the current evidence for the benefits, cost-effectiveness, government recommendations and most effective ways to screen for chronic viral hepatitis in migrants from endemic areas living in low prevalence countries. The introduction will also review the literature on the epidemiology of HCV in people who inject drugs, the safety, efficacy and current availability of treatment, barriers and facilitators of treatment and strategies to improve treatment rates.

Five studies were undertaken to address the aims of this MDRes and the methodology and results of each of these studies will be described in detail in the methods and

results chapters. In the discussion the findings of each of these studies will be assessed in the context of previously published literature and their strengths and limitations will be analysed.

1.1.2 Hepatitis B and Hepatitis C virus

Hepatitis B virus and hepatitis C virus are hepatotropic viruses that are the leading cause of chronic liver disease worldwide (Rehermann B, 2005). They are significant global public health concerns causing 57% of cases of cirrhosis and 78% of hepatocellular carcinoma globally (Perz JF, 2006). The virology, immunology, epidemiology, diagnosis, natural history and treatment of hepatitis B and hepatitis C are examined in this section.

1.1.2.1 Virology and immunology:

1.1.2.2 Hepatitis B Virus

1.1.2.2.1 Virology

Hepatitis B virus is a member of the hepadnaviridae virus family and consists of an outer protein envelope enclosing a nuclear capsid, inside which resides the HBV genome. The hepatitis B virus envelope consists of 3 surface antigens (Hepatitis B Surface Antigen or HBsAg). The nucleocapsid of the virus consists of hepatitis B core antigen (HBcAg) and is assembled from 240 viral capsid proteins. The HBV genome is a circular partially double stranded DNA virus, of 3200 base pairs, which is covalently linked by its 5' end to the viral polymerase (Rehermann B, 2005), (Lok & McMahon, 2001) (Gitlin, 1997) (Shephard, 2006) (Delaney, 2013) (Block TM, 2008). The structure of the Hepatitis B virus can be seen in figure one below:

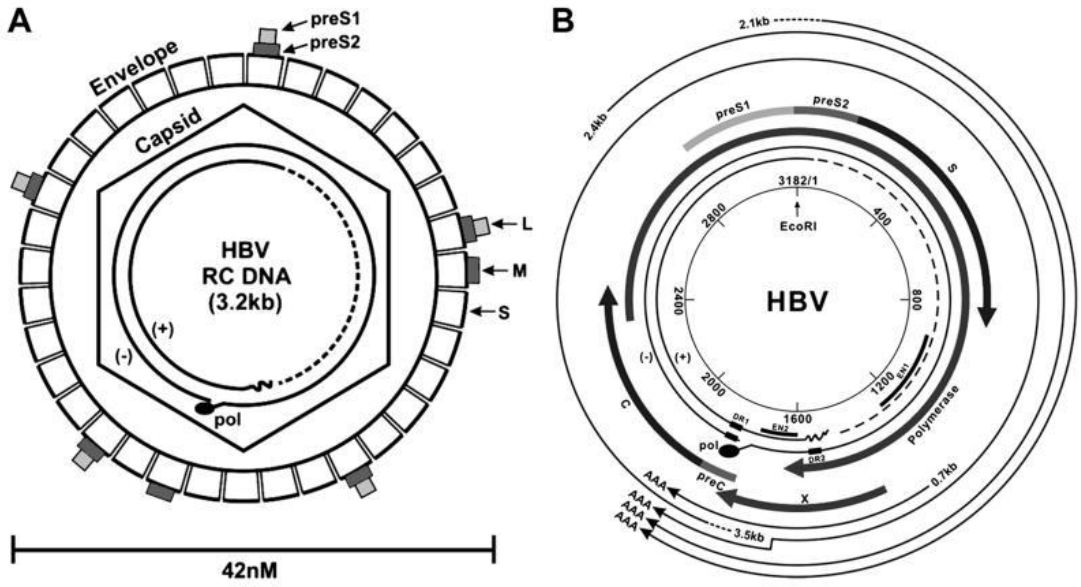


Figure 1: The HBV virion and genomic features (Reproduced from Block TM, Guo H, Guo J-T Molecular virology of hepatitis B virus for clinicians *Clin Liver Dis* 2007; 11(4): 685-706).

HBV viral replication takes place in hepatocytes, and the process of viral replication can be seen in figure two on the following page. The Hepatitis B virus attaches to the hepatocyte and undergoes endocytosis, after which the viral envelope is removed and the core particle is transported by nucleocapsids to the hepatocyte nucleus. Relaxed circular DNA is released into the nucleoplasm and is repaired into covalently closed circular (ccc) DNA and complexed with nucleosomes. The cccDNA interacts with transcription factors and is transcribed into pregenomic and subgenomic messenger RNA (mRNA). The mRNAs are transported into the cytoplasm and function as templates for viral replication and translation of proteins. The core protein subunits assemble into immature core particles, and encapsidate their own mRNA and the DNA polymerase, and maturation occurs. The mature core particle is subsequently enveloped by surface proteins and exported via multivesicular bodies from the cell as a

new HBV particle or can migrate back to the nucleus (Lok & McMahon, 2001) (Rehermann B, 2005) (Gerlich, 2013).

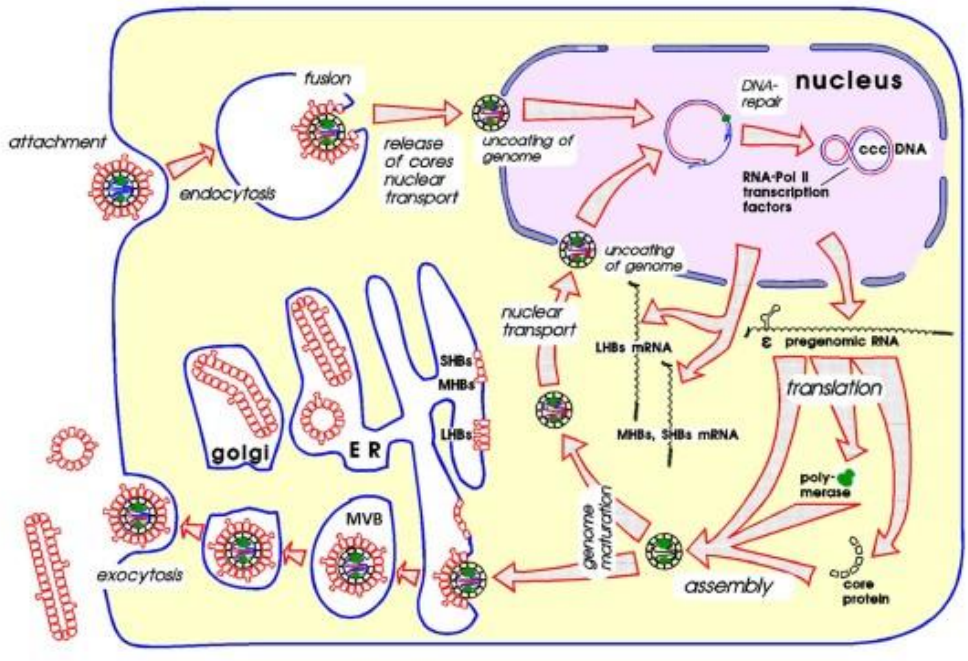


Figure 2: HBV life cycle (reproduced from Gerlich WH Medical Virology of Hepatitis B: how it began and where we are now *Virology Journal* 2013, 10:239).

1.1.2.2.2 Genotypes

The HBV genome has evolved with a high rate of nucleotide substitution, estimated at 1.4-3.2 x 10^{-5} sites per year, due to the inherent error rate present within the reverse transcriptase transcription of cccDNA to pregenomic RNA. There are 10 separate genotypes, A to J and several subgenotypes, recombinants and mutants. Genotypes have a genetic divergence of at least 8% in the surface gene or 4-8% in the total HBV genomic sequence (Lin C-H, 2013).

Genotypes A and D are predominant in Western Europe and the USA. In China, South East Asia and the Pacific region genotypes B and C are most common. In Africa genotypes A, D and E predominate.

HBV genotype affects the virology and transmission of HBV, clinical outcomes and response to treatment in HBV infection. The HBeAg replicative phase is longer for genotypes B and C and is consequently longer in Southeast and East Asia where these genotypes predominate (Norder H, 2004) (Lin C-H, 2013). Genotype B infection is associated with less active hepatic inflammation, a slower rate of progression to cirrhosis, lower rates of hepatocellular carcinoma and HBeAg seroconversion at a lower age when compared with genotype C infection (Lin C-H, 2013). Patients infected with genotype C and D HBV have a higher prevalence and a quicker rate of progression to cirrhosis and HCC, a higher rate of HBeAg positivity than those with genotype A and B infection. Patients with genotype C in particular have higher rates of HCC at an older age, higher viral loads and a lower rate of spontaneous HBeAg conversion (7.9% annually) when compared with genotype B (15.5% annually). The rate of the basal core promoter mutation A1762T/G1764A is higher in genotype C compared with genotype B, and this mutation has been associated with a higher risk of HCC. The higher rates of advanced liver disease and HCC are likely to be related to the more prolonged duration of exposure to high HBV replication rates in genotype C compared with genotype B (Lin C-H, 2013).

Genotypes A and B are associated with higher rates of HBeAg seroconversion and normalisation of ALT levels with interferon alpha therapy than C and D. The rates of HBeAg clearance according to genotype with pegylated interferon therapy are 47% in

genotype A, 44% in genotype B, 28% in genotype C and 25% in genotype D. Genotype A disease has a higher rate of HBsAg conversion than other genotypes in both HBeAg positive and negative patients treated with pegylated interferon, with rates of HBsAg clearance among HBeAg negative patients at 20% in genotype A, 6% in genotype B and D and 9% in genotype C (Marcellin P B. F., 2009) (Janssen HL, 2005) (Lin C-H, 2013) (Norder H, 2004).

In contrast with pegylated interferon therapy genotype does not predict response to nucleos(t)ide therapy with equivalent responses across all genotypes (Norder H, 2004) (Lin C-H, 2013).

1.1.2.2.3 Immunology:

In vivo infection with HBV is very efficient and in humans infections are seen after innoculations from needles with less than 100 virus particles. The risk of transmission from viraemic individuals from mucocutaneous contact or contact between damaged skin or mucosal surfaces is considerably lower, where a HBV DNA level of over 10 $x10^7$ viruses/ ml indicates a high risk of viral transmission but levels of less than 10 $x10^5$ viruses/ ml lead to a very low risk of transmission. Infectivity is also related to the stage of HBV infection with the highest infectivity occurring during the early phase of infection and in immunotolerant carriers with high a high viral load. This may be due to the presence of protective antibodies during the other stages of infection, or during the inactive carrier stage due to the low levels of HBV DNA and reduced infectivity of the virus particles (Gerlich, 2013) (Block TM, 2008).

The immune system response to infection usually requires innate and adaptive immune responses, but HBV appears to largely evade the innate immune system with the adaptive immune response playing the principal role in suppression of hepatitis B viral replication. The adaptive immune response in HBV is mediated via B and T cells. The T cell response to HBV occurs 4-7 weeks after infection with CD4 and CD8-mediated responses becoming detectable in correlation with a sharp rise in HBV DNA levels. Persistence of viral infection is associated with defective HBV-specific CD4 and CD8 T cell functions, and suppression of HBV- specific T cell response is proportional to HBV viraemia, with a stronger suppression of the T cell response in highly viraemic patients. In patients whose infection resolves HBV DNA falls rapidly after viral replication peaks, and virus destruction is caused by IFN-gamma and TNF-alpha production by activated CD8 T cells. HBV specific cytotoxic T lymphocyte and T helper response to viral antigens leads to the destruction of infected hepatocytes, with hepatocyte death leading to the recruitment of antigen non-specific cells which further enhance hepatocellular destruction (Bertoletti A, 2012) (Busca A, 2014) (Block TM, 2008).

HBV replication in itself is not usually directly toxic to hepatocytes, and hepatocellular injury occurs as a consequence of the immune response to infection. Injured hepatocytes release chemokines which recruit inflammatory cells including neutrophils, NK cells, monocytes and macrophages. These lead to hepatocellular injury through a variety of methods including release of IFN-γ and TNF-α and apoptosis of damaged hepatocytes (Busca A, 2014).

1.1.2.3 Hepatitis C Virus

1.1.2.3.1 Virology

Hepatitis C virus is an enveloped RNA virus, and is the only member of the hepacivirus genus of the flaviviridae family. The HCV particle is 50-60 nM in diameter, and consists of a lipid envelope, capsid and genome. The lipid envelope contains two glycoproteins (E1 and E2) and surrounds the nucleocapsid, which comprises the HCV genome and core protein. The HCV genome consists of a single 9.6 kilo base positive sense RNA open reading frame, which is flanked by two non-coding, untranslated regions, 5' and 3'. (Ashfaq UA, 2011) (Rehermann B, 2005) (Ploss A, 2012).

Hepatitis C virus lifecycle:

The HCV virus lifecycle consists of 3 phases; HCV entry into the cell, RNA translation and replication and viral assembly.

During HCV entry into the hepatocyte the HCV virus particle attaches to the hepatocyte by interaction of the E1/E2 envelope proteins with hepatocyte receptors, and cellular entry occurs through endocytosis (Ashfaq UA, 2011) (Delaney, 2013) (Ploss A, 2012). After entry the nucleocapsid travels through the intracellular membranes into cytoplasmic vesicles (see figure three) and is disassembled to produce the genome. It subsequently enters the hepatocyte cytoplasm and the 5' non-coding region initiates translation of the HCV genome into a single polyprotein. Cellular and viral proteases process the translated polyprotein into three structural (Core and envelope protein 1 and 2) and seven non-structural mature proteins (NS2, NS3, NS4A, NS4B, NS5A and NS5B). The translated non-structural proteins associate with

endoplasmic reticulum derived membranes and form membrane associated replication complexes. The replication complexes catalyse transcription of negative strand RNA, which subsequently acts as an intermediary for the replication of viral positive strands. The positive sense RNA strands are used to assemble new virions, translated into additional RNA templates and are used to produce further viral proteins (Ashfaq UA, 2011) (Ploss A, 2012) (Delaney, 2013).

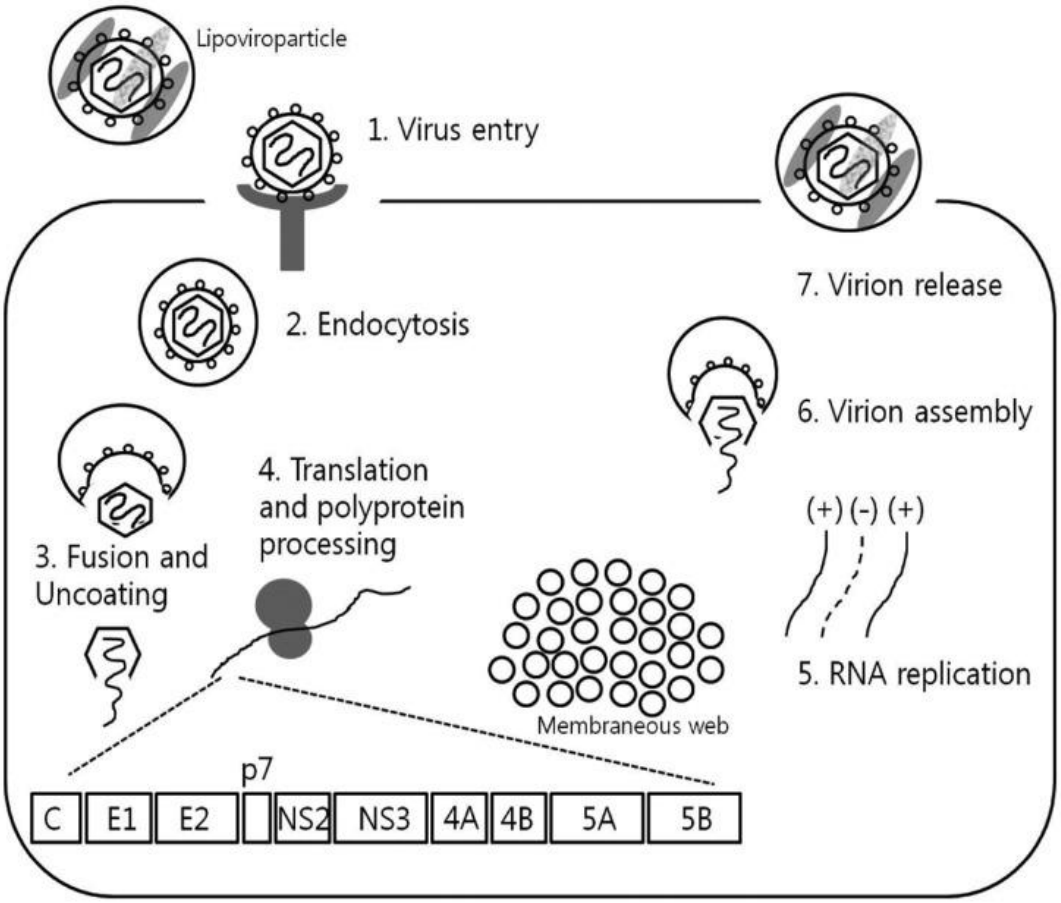


Figure 3: The Hepatitis C virus life cycle (reproduced from Kim C and Chang K-M Hepatitis C virus: virology and life cycle *Clinical and Molecular Hepatology.* 2013; 19 (1) 17-25).

HCV assembly occurs after completion of the initial RNA replication process. The newly formed virions are encapsidated, a process which is facilitated by the core and NS5A proteins and form a nucleocapsid. The nucleocapsid then buds through the

intracellular membranes into cytoplasmic vesicles, and the mature virus is secreted from the cell (Delaney, 2013)(Thomson BJ, 2005) (Rehermann B, 2005) (Flamm, 2003) (Ploss A, 2012) (Ashfaq UA, 2011).

1.1.2.3.2 Genotypes:

The hepatitis C virus has considerable genetic heterogeneity, with seven different genotypes and 67 confirmed subtypes, a further 20 provisionally assigned subtypes and 21 unassigned subtypes. There is variation of between 30 and 50% in nucleotide sequencing between different genotypes, and a 1 to 5% variation of nucleotide sequencing within each HCV infected patient. The prevalence of each genotype is dependent on geographical location. Genotype one is the most common genotype worldwide, comprising 46.4% of all diagnosed HCV, equivalent to 83.4 million cases, and is the most common genotype in Western Europe, with a third of cases occurring in East Asia. Genotype three is the next most prevalent genotype worldwide, comprising 30.1% of cases, and affecting a total of 54.3 million people. It is the most frequently seen genotype in Pakistan and India, and is seen in up to 50% of infected patients in certain European countries. Genotype four HCV is seen most commonly in the Middle East and Africa, genotype five in South Africa and genotype six is most frequently detected in South East Asia and Hong Kong. Genotypes two, four and six comprise 22.8% of HCV cases globally, and genotype five less than 1% (Thomson BJ, 2005) (Flamm, 2003) (Ashfaq UA, 2011) (Smith D, 2014) (Messina JP, 2015). HCV genotype affects response to therapy, specifically sustained viral response. The achievement of sustained viral response is defined as an undetectable HCV RNA 12 or 24 weeks after the end of treatment and is considered a cure for HCV. Patients with

genotypes two and three have a 76-80% sustained viral response (SVR) rate to pegylated interferon and ribavirin therapy (PR), whereas those with genotypes one and four have a 42 to 52% SVR rate (Manns MP M. J., 2001) (Fried MW S. M., 2002) (Hadziyannis SJ, 2004). The new generation of direct acting antiviral therapies have an increased range of efficacy against most HCV genotypes. NS5B polymerase inhibitors such as sofosbuvir and NS5A inhibitors such as daclatasvir have pan-genotypic activity (Wendt A, 2014).

1.1.2.3.3 Hepatitis C Virus immunology:

The immune system response to Hepatitis C virus involves both innate and adaptive immune responses. In common with Hepatitis B, Hepatitis C infection is hepatotropic and hepatocellular damage is caused by the immune system response to the virus, rather than by a direct hepatotoxic viral effect.

Natural killer (NK) cells, Natural Killer T (NKT) cells, dendritic cells and Kupffer cells along with the induction of interferons and inflammatory chemokines and cytokines provide the innate immune response to HCV. Natural killer cells release perforin and proteases to perform cytotoxic lysis of infected cells and produce interferon gamma (IFN-γ) and TNF-α (Ashfaq UA, 2011) (Li Kui, 2013) (Terilli R, 2013).

The adaptive immune response is mediated by cellular (CD4 T helper cells and CD8 cytotoxic T lymphocytes) and humoral immunity (neutralising antibody producing B cells (nABs)). The antibody response consists of IgG1 and develops eight to twenty weeks after infection. The T cell response to HCV develops between 5 and 12 weeks after infection and consists of activated CD4+ and CD8 T cells. CD4+ cells directly

activate macrophages and antigen specific B cells and maintain CD8 T cell response via cytokine release. Th1 cells produce cytokines which promote cell mediated immunity and inflammation. (Neuman MG, 2008) (Ashfaq UA, 2011) (Terilli R, 2013). CD8+ T cells directly eliminate infected cells by cytokine mediated non-destructive and direct cytotoxic mechanisms, and secrete IFN-γ and TNF-α which inhibit viral replication.

HCV evades the adaptive immune response through functional anergy of T cells and mutational escape. Mutational escape occurs due to the very high replicative rate of the virus (over 10^{12} virions are produced every day) and poor proof reading activity of the NS5B RNA dependent polymerase. As a result HCV replication is error prone, and the HCV virus exists as a heterogeneous population of quasispecies and accumulates mutations which aids evasion of the immune system response (Ashfaq UA, 2011) (Li Kui, 2013) (Terilli R, 2013).

1.1.2.4 Diagnosis:

1.1.2.4.1 Hepatitis B Virus

Chronic Hepatitis B virus infection is diagnosed by the presence of Hepatitis B surface antigen (HBsAg) and HBV DNA in serum. A number of different phases of infection exist, and each is diagnosed by the presence or absence of antigens, HBsAg and Hepatitis B e Antigen (HBeAg), and antibodies to the Hepatitis B surface antigen (anti-HBs), Hepatitis B core antigen (anti-HBc) and Hepatitis B e Antigen (anti-HBe) in conjunction with serum alanine transferase (ALT) levels, and HBV DNA levels. The phases of HBV infection will be explained in detail in the section on natural history of HBV below (Lok AS, 2007) (D'Souza R F. G., 2004).

1.1.2.4.2 Hepatitis C Virus

Exposure to hepatitis C virus is diagnosed by the presence of antibodies to HCV on ELISA testing. In the UK a third generation ELISA test is used. All patients who have a positive or equivocal antibody test, or those with negative antibody tests who are thought to be at high risk for infection have polymerase chain reaction (PCR) testing of the serum to detect the presence of HCV RNA. The presence of a positive ELISA antibody to HCV (HCV ab) and positive PCR for HCV RNA indicates the presence of active viraemia and chronic infection with HCV. Approximately 15-20% of those infected with HCV are believed to spontaneously clear the virus, and they will have the presence of HCV ab in serum, with no evidence of HCV RNA on serum PCR. It is possible to have a positive anti-HCV and negative PCR for a variety of other reasons including non-viraemic infection, a viraemia below the detection limit of the assay, a

non-specific ELISA result or a transient absence of viraemia. Therefore all patients with a positive ELISA but negative PCR should undergo PCR re-testing (Booth JCL, 2001).

Natural history of hepatitis B and C virus:

1.1.2.4.3 The natural history of HBV:

The natural history of HBV depends largely on the age at which the infection is acquired. Most hepatitis B virus infection in the developing world is acquired perinatally or in childhood. Of those who are infected perinatally or in the first year of life around 90% will go on to develop chronic HBV infection, 20 to 30% of those infected in childhood will develop chronic HBV, and less than 2% of those infected in adulthood will develop chronic HBV (Lok AS, 2007) (Fattovich G B. F., 2008) (McMahon, 2009). Acute infection consists of a mild and asymptomatic illness in two thirds of patients with HBV, and around a third will have signs and symptoms of hepatitis including fatigue, nausea and occasionally jaundice. In a small number of cases HBV presents with acute liver failure, which has a fatality rate of 0.2% in the US (Liang, 2009) (Gitlin, 1997).

There are four phases of chronic HBV when acquired in childhood and perinatally:

The immunotolerant phase – occurs soon after infection with chronic HBV and is characterised by HBsAg positivity, HbeAg positivity, very high levels of HBV DNA with normal ALT levels. This phase usually occurs in children who have immature immune systems and therefore there is little immune system activation and minimal hepatic damage (Villa E, 2011) (Lok AS, 2007). It should be noted that a recent study where T cells from young patients with HBV had an increased ability to produce Th1 cytokines has questioned the hypothesis that immunological tolerance characterises HBV

infection in children and young adults, but the authors cite caution in generalising their results (Kennedy PTF, 2012).

The immune active/ clearance phase – This occurs when an immune response to HBV develops and during this phase high ALT levels and lower HBV DNA levels are seen, with positive HBsAg and positive HBeAg. During this phase hepatic necrosis occurs and if this phase is prolonged it can lead to cirrhosis. This phase can result in seroconversion and clearance of HBeAg, with the development of anti-HBe leading to the inactive carrier phase (Villa E, 2011) (Lok AS, 2007).

Inactive carrier phase – During this phase the ALT normalises, there is a reduction in HBV DNA and antibodies to HBeAg develop (anti-HBe). Minimal liver damage occurs during this phase. Inactive carriers have a low risk of progression to liver cirrhosis, of the order of 0.1 per 100 years, and a low risk of HCC with an incidence of 0.02 to 0.2 per 100 person years (Villa E, 2011) (Lok AS, 2007).

Immune escape phase – Approximately 10 to 20% of people in the inactive carrier phase will develop immune escape where HBV replication is reactivated, they will have fluctuating moderate to high levels of HBV DNA and high ALT levels, but are HBeAg negative. They are considered to have HBeAg negative chronic hepatitis B and most have Hepatitis B virus variants in the pre-core or core promoter region. There is active hepatic inflammation and liver damage during this phase, and progression to cirrhosis occurs much more frequently than in inactive carriers with a risk of 2 to 9 per 100 person years, and an incidence of HCC of 0.3 to 0.6 per hundred person years in non-cirrhotic patients and 2.2 to 3.7 in cirrhotic patients (Villa E, 2011).

Once an individual has seroconverted from HBeAg positivity to anti-HBe then there is considerable movement between phases, with 20% of patients experiencing a reversion back to HBeAg positivity. This occurs most commonly in patients with genotypes C and F HBV and is usually associated with a flare of hepatitis. After seroconversion a further 70 to 80% of patients progress to the inactive HBV carrier phase, and approximately 10 to 30% of patients remain in the immune active phase with HBV DNA levels > 2000 IU/ml and raised ALT levels. After progression to the inactive phase of HBV 10% to 30% of patients will have a reactivation of HBeAg negative chronic hepatitis during their life time. The development of cirrhosis and HCC occurs in the majority of patients after HBeAg seroconversion (Lai C-L, 2007) (McMahon, 2009).

When adolescents or adults acquire HBV infection the disease course is very different. The majority (>98%) clear the virus early, but in those whom it becomes chronic there is an immediate immune clearance phase and no immune tolerance phase. They seroconvert early in the stage of their disease from HBeAg to anti-HBe and have a short disease period. Once HBeAg seroconversion occurs their disease is quiescent, and the majority have non-progressive disease (Lai CL, 2007).

Each year approximately 0.5%-0.8% of patients with chronic HBV in endemic areas will clear HBsAg, and develop anti-HBs, and 1-2% per year will do the same in areas of low endemnicity (Lok AS, 2007) (D'Souza R F. G., 2004) (Fattovich G B. F., 2008) (Villa E, 2011). This is more likely with older age and a prolonged period of the inactive carrier stage of HBV. The clearance of HBsAg has been termed the “recovery phase” of chronic HBV. HBsAg clearance reduces liver inflammation and fibrosis, and confers a

significantly better outcome than in those who do not clear HBsAg, with a reduced risk of advanced liver disease and cirrhosis providing clearance occurs at a young age and before cirrhosis has developed. Hepatocellular Carcinoma can still develop in the livers of those who have cleared the antigen and HBV DNA is still detectable in the serum and hepatocytes of approximately 20% of individuals who have cleared HBsAg so HCC screening is still required (McMahon BJ, 2009) (Villa E, 2011). Interestingly only 50% of those who have cleared HBsAg develop anti-HBs, which implies that the lack of detection of HBsAg may relate to production at below the level of quantification which cannot be detected rather than true loss which may explain the persistence of viral DNA in serum and the liver (Villa E, 2011).

Consequences of Hepatitis B virus infection:

Acute hepatitis B infection is usually asymptomatic, and so most carriers are unaware of their infection until complications occur. Severe liver disease is estimated to occur in between 15 and 40% of persons infected with chronic HBV (Lok AS, 2007). The most serious complications of hepatitis B infection are cirrhosis, and subsequent hepatic decompensation and hepatocellular carcinoma, and the likelihood of developing these complications is linked to a number of factors including viral replication (EASL, 2009). The five year incidence of cirrhosis in people diagnosed with HBeAg positive chronic HBV varies from 8% in East Asian countries to 17% in European countries, with higher rates in patients who have HBeAg negative chronic hepatitis of 13% and 38% respectively, reflecting the longer duration of active inflammation in HBeAg negative chronic HBV. The five-year cumulative rate of HCC in Europeans with HBV cirrhosis is 10%, and among East Asians is 17%, and is 1% and 3% in those with chronic hepatitis B

but without cirrhosis respectively. The five-year rate of hepatic decompensation in those with HBV cirrhosis is 15% with a mean age of decompensation of 55 to 60 years (Fattovich G B. F., 2008). Factors associated with disease progression in chronic HBV are older age (> 40 years), male gender, the presence of cirrhosis, Asian or African race and high levels of HBV replication, a family history of hepatocellular carcinoma, basal core promoter mutation, precore G1896A mutant, genotypes C and F and raised ALT levels (Fattovich G B. F., 2008) (McMahon BJ, 2009) (Lai CL, 2007) (Chen CJ, 2011). A longitudinal study indicates that the 25-year survival is significantly better in inactive carriers of HBV (95%) than in HBeAg positive carriers (40%) or those with HBeAg negative chronic hepatitis (50%) and that the worse prognosis is related to the presence of on-going viral replication. In this study liver related mortality was 15.7% (11/70 patients) and was due to HCC in 5 patients and liver failure in 6 (Fattovich G O. N., 2008). The five-year survival of patients with compensated cirrhosis is around 80%, but in decompensated cirrhosis the prognosis is much poorer with a five-year survival of 14% to 35% (EASL, 2009) (McMahon BJ, 2009).

Treatment of HBV alters the natural history of the disease with proven improvement in fibrosis scores, regression of cirrhosis, and a reduced progression to decompensation and HCC. Marcellin et al showed that treatment with five years of tenofovir produces regression of fibrosis and cirrhosis in patients with chronic Hepatitis B virus, with 176/348 (51%) showing regression of fibrosis and 71/96 (74%) showing regression of cirrhosis (Ishak score of 5 or 6 at baseline with an ≥ 1 decrease in score) (Marcellin P G. E., 2013). Progression to decompensation of cirrhosis and HCC in patients with histologically confirmed advanced fibrosis or cirrhosis is reduced with lamivudine

treatment (Liaw Y-F, 2004). The primary end point in this study was disease progression, defined as spontaneous bacterial peritonitis, HCC, hepatic decompensation, bleeding gastroesophageal varices or death related to liver disease, and was reached by 7.8% of patients receiving lamivudine and 17.7% of patients receiving placebo (p=0.001) (Liaw Y-F, 2004). A phase II trial assessing the safety of tenofovir, entecavir and emtricitabine/ tenofovir in patients with decompensated HBV cirrhosis found a reduction in Child-Turcott-Pugh score of over or equal to 2 in between 26% and 48% of patients, and a reduction in the median MELD score of two across all treatment groups (Liaw YF, 2011). Entecavir and lamivudine have both been shown to improve liver histology after at least 48 weeks of therapy, with 70% and 61% of patients treated with entecavir and lamivudine respectively showing an improvement in liver histology and 36% and 38% of patients showing an improvement in Ishak fibrosis scores (Lai CL, 2006). Long term entecavir therapy caused an improvement in the Ishak fibrosis score of over or equal to one point in 88% of patients including all 10 patients with advanced fibrosis or cirrhosis, and caused improvement in Ishak fibrosis score to less than four in the four patients with cirrhosis in a further trial (Chang TT, 2010). A 2015 review of the effect of antiviral therapy for HBV on HCC outcomes concluded that treatment with nucleos(t)ide analogues reduced, but did not eliminate the risk of HCC. This conclusion is drawn from evidence from Asian studies where antiviral therapy with nucleos(t)ide analogues resulted in a 30% risk reduction of HCC in cirrhotic patients and an approximately 80% risk reduction in non-cirrhotic patients in some studies compared with matched untreated controls (Papatheodoridis GV, 2015).

1.1.2.4.4 The natural history of Hepatitis C virus:

Acute and chronic HCV

Acute hepatitis C can present with non-specific symptoms such as right upper quadrant pain, pruritis and fatigue, but it is asymptomatic in 80% of cases (Flamm, 2003) (Ascione A, 2007). This causes problems when assessing the natural history of chronic HCV due to the inherent difficulty in ascertaining when an asymptomatic infection has been contracted. The timing of exposure to risk factors for HCV is therefore commonly used to estimate date of infection (Seeff LB, 2002). Acute hepatitis C is characterised by positive HCV antibodies and the presence of HCV RNA in serum. Approximately 14 to 46% of those with acute HCV will spontaneously clear the virus within 6 months and will not progress to chronic HCV (Seeff LB, 2002). Those in whom HCV RNA persists for over six months are considered to have chronic HCV (Seeff LB, 2002).

In common with chronic HBV the two most severe consequences of chronic HCV infection are cirrhosis of the liver and hepatocellular carcinoma (Seeff LB, 2002) (Massard J, 2006) (Ascione A, 2007). Progression of hepatitis C virus infection to cirrhosis, and HCC (which usually occurs in cirrhotic livers) is a consequence of progressive liver fibrosis due to progressive liver inflammation. Fibrosis stage is predictive of progression to cirrhosis, and the time taken for cirrhosis to occur appears to be highly variable between affected individuals. A proportion of infected individuals will be “rapid fibrosers” (progression to cirrhosis in <20 years), some will be “intermediate fibrosers” (progression in 20 to 50 years) and the remainder “slow fibrosers” (a time period of > 50 years to cirrhosis) The median progression of

untreated patients with HCV to cirrhosis is 30 years, with 31% of untreated patients taking over 50 years to progress to cirrhosis, or never progressing and 33% taking less than 20 years (Massard J, 2006) (Ascione A, 2007).

There is controversy over the natural history of HCV, with a wide range of estimates of progression to cirrhosis, decompensation and HCC. This is due to the differing methodology and patient sampling of studies, and the difficulty in charting the natural history of a disease that is commonly asymptomatic and takes many years to develop into advanced liver disease (Seeff LB, 2002). A meta-analysis estimating fibrosis progression rates in HCV cirrhosis found an estimated prevalence of cirrhosis across all studies after 20 years of infection of 16% (95% CI, 14%-19%), and after 30 years of 41% (95% CI, 36%-45%). The 20-year cirrhosis estimates ranged from 7% in retrospective-prospective studies and nonclinical setting studies to 18% in clinical studies and cross-sectional/ retrospective studies. An increased risk of progression to cirrhosis was seen in those who acquired HCV over the age of 30, in dialysis and renal transplant patients and those with genotype one infection (Thein HH, 2008). A systematic review of epidemiological studies examining progression to cirrhosis in HCV concluded that the mean progression to cirrhosis after 20 years in post transfusion cohorts is 24%, in liver clinic series is 22%, in blood donor series is 4% and in community based cohorts is 7%. The community based cohorts consisted of studies of people who inject drugs with HCV, women infected by exposure to contaminated immunoglobulin, patients who were followed up after acute HCV infection and population based assessments of chronic liver disease in high HCV prevalence regions. The wide disparity in progression to cirrhosis is attributed to selection bias in the liver clinic cohort and variability in

factors that predict progression to cirrhosis (mainly older age) in the post transfusion cohorts. In this review older age at infection, male gender, heavy alcohol consumption (>50g/day) and raised ALT were all associated with an increased risk of progression to cirrhosis. The authors conclude that the community based cohorts are likely to provide the most accurate estimates of progression to cirrhosis, and that these indicate that less than 10% of young adults who are diagnosed with HCV will develop liver cirrhosis (Freeman AJ, 2001). A retrospective cohort study supports this finding. In this study only 5.9% of healthy young adults with HCV had died of liver disease 45 years after exhibiting serological evidence of infection (Seeff LB, 2000). An analysis of liver biopsy samples from 2235 patients by Poynard et al identified a median fibrosis progression rate of 0.133 per year, equating to a median estimated duration of time from infection to cirrhosis of 30 years. Significant risk factors for increased fibrosis progression identified by this study were male sex, age of infection over 40 years and alcohol consumption of 50 g or greater per day (Poynard T B. P., 1997). In addition to the above factors progression to cirrhosis is associated with Human Immunodeficiency Virus (HIV) co-infection, a low CD4 count, co-infection with HBV, race (with black patients having a reduced fibrosis progression), the presence of haemochromatosis, co-infection with schistosomiasis, smoking, hepatic steatosis, obesity, diabetes and necrosis grade (Ascione A, 2007) (Massard J, 2006) (Missiha SB, 2008) (Massard J, 2006). There also appear to be geographical variations in the progression to cirrhosis with rates of 30 to 46% in Japan and approximately 15% in Europe and the USA (Ascione A, 2007). HCV genotype and viral load were felt not to affect disease progression (Missiha SB, 2008), but there is some data that patients with genotype 3 may have a faster rate of progression of fibrosis with an odds ratio of accelerated

fibrosis of 1.52 (95% CI 1.12-2.07, p=0.007) in patients with genotype three in single biopsy studies (Probst A, 2011).

A meta-analysis investigating the natural history of Hepatitis C virus in people who inject drugs found a 20-year cirrhosis rate of 14.8% in this group, with a progression to cirrhosis rate of 8.1 per 1000 person-years (John-Baptiste A, 2010).

Once cirrhosis has developed the progression to death or liver transplantation is 2.74% to 6.72% per year, and the risk of the development of HCC varies between 1.51% and 7.14% per year, with an overall estimated rate of decompensation of 6.37% per year (Alazawi W, 2010). A retrospective Italian study of 384 patients with compensated HCV cirrhosis reported a 91% 5 year survival and 79% 10 year survival (Fattovich G G. G., 1997).

Treatment of HCV with the attainment of a sustained viral response positively affects the natural history of HCV, and has been shown to be associated with reductions in necro-inflammatory and fibrosis scores, liver-related hospital episodes, liver-related mortality, all-cause mortality, hepatic decompensation, liver transplantation and hepatocellular carcinoma. Attainment of SVR does not entirely preclude future liver related morbidity as a proportion of patients (1-14%) will demonstrate fibrosis progression with up to 8.7% progressing to cirrhosis after SVR and patients without cirrhosis who achieve a SVR still retain a level of liver-related morbidity of two to six times greater than the general population (Marcellin P B. N., 1997) (Poynard T M. J., 2013) (Backus LI, 2011) (Poynard T M. J., 2002) (Westbrook RH, 2014) (Innes HA, 2011) (van der Meer A, 2012) (Bruno S, 2010). The benefits of attaining SVR in patients who have already progressed to compensated HCV cirrhosis are more equivocal with a

systematic review indicating that while interferon treatment significantly lowers the risk of developing HCC (2.52% ± 0.34 with treatment and 4.79% ± 0.76 without treatment, p=0.02) it does not affect progression to hepatic decompensation (mean 5.34 ± 0.79% with treatment vs 7.88 ± 1.88% without interferon treatment per year, p=0.26) or death/ liver transplantation (3.79% vs 4.62%, p=0.25). The heterogeneity of data presentation in these studies, retrospective design of many of the studies and lack of differentiation between those who responded to or failed treatment make overall conclusions from this data difficult (Alazawi W, 2010). In agreement with this a recent meta-analysis of 30 studies reported a reduction in absolute risk of HCC after attaining SVR of 4.6% and a reduction in the risk of developing HCC in patients with advanced liver disease from 17.8% (337/1893) to 4.2% (32/756) after SVR (Morgan RL, 2013).

The benefits of treatment vary depending on individual patient characteristics, with modelling showing that the greatest gain in life-years and healthy life-years are obtained by patients who are 30 years old with compensated cirrhosis (57.9% probability of gaining a benefit) and the least probability of incurring a benefit occurs in patients aged 60 years with mild fibrosis (1.6% probability of gaining life-years and 2.9% probability of gaining health life-years). While the greatest benefits are seen in 30 year old patients with established cirrhosis, this applies to relatively few patients making this finding of doubtful clinical significance (Innes H, 2014).

Public Health England reports that an estimated 10,850 individuals in England are living with HCV-related cirrhosis or HCC and this will rise to 13,950 by 2025 (Public Health England, 2014). A modelling analysis has predicted that cases of HCV related

compensated cirrhosis in the UK will rise from 3705 in 2006 to 7550 by 2015, and cases of HCC and/ or decompensated cirrhosis will rise to 2540 (Sweeting MJ D. A., 2007).

1.1.2.5 Epidemiology and risk factors:

Chronic hepatitis B and C are endemic in many regions of the world. Worldwide an estimated 2 billion people have been exposed to HBV, and 350 million people have chronic hepatitis B infection (WHO, 2000). Approximately 170 million people worldwide, amounting to 3% of the world's population are chronically infected with HCV (WHO, 2002). The distribution of chronic viral hepatitis varies considerably amongst geographic regions, and between different populations within countries.

1.1.2.5.1 Hepatitis B Virus:

1.1.2.5.1.1 Hepatitis B virus transmission:

The transmission of HBV occurs by mucous membrane or percutaneous exposure to HBV infected blood or bodily secretions. It is transmitted efficiently both by percutaneous and sexual contact, unlike HCV where most transmission is percutaneous. The main patterns of transmission differ depending on the prevalence of HBV within a country. In high prevalence countries the main route of transmission is perinatal transmission or transmission from household contacts in early childhood, which are the principal routes of transmission worldwide. In low prevalence countries the main routes of transmission are sexual or percutaneous transmission amongst people who inject drugs, men who have sex with men or sex workers (Heathcote, 2008) (WHO, 2001). In the developing world iatrogenic transmission due to unsafe injection practices including the reuse of contaminated needles without sterilisation, or transfusion of unscreened contaminated blood products account for a large number

of HBV infections. In some developing countries up to 50% of needles are reused without being sterilised (WHO, 2001).

1.1.2.5.1.2 Global epidemiology of HBV:

Hepatitis B virus is thought to have infected over one third of the world's population (WHO, 2000), and the world is split into high, medium or low endemnicity areas depending on the prevalence of chronic HBV infection in the population. Areas of high endemnicity, defined as over 8% of the population having chronic HBV, include China, where over 100 million people are estimated to be infected, most of South East Asia and the Pacific, most of Africa (except for Algeria, Egypt, Libya, Morocco and Tunisia) and some countries in Eastern Europe (Albania, Armenia, Azerbaijan, Bulgaria, Croatia and Georgia) (Heathcote, 2008) (Shephard, 2006). Around 60% of the world's population live in these areas. Intermediate levels of HBV endemnicity (HBV seroprevalence > 2%, but < 8%) are seen in South Asia, Southern Europe and the Middle East. Areas with a low HBV prevalence (<2%) include Northern and Western Europe and North America (Heathcote, 2008) (Shephard, 2006) (Merrill & Hunter, 2011). In low prevalence countries there are groups who have a higher prevalence of chronic HBV. These groups include migrants from areas of high endemnicity (Heathcote, 2008) (Rossi C, 2012) (Shephard, 2006), people who inject drugs, sex workers and men who have sex with men (MSM) (Rantala & Laar, 2008). In some European countries the prevalence of chronic HBV is 5 to 90 times greater in migrants from endemic areas, including the Netherlands where the prevalence in first generation migrants is 13 times higher than in the native population, and across Europe the average prevalence of HBV is six times higher in migrants (Rantala & Laar,

2008) (Hahne SJM, 2013) (Hahne SJM, 2011). A systematic review and meta-analysis examining the prevalence of chronic HBV in migrants and refugees from countries of high HBV endemnicity found that prevalence mirrored rates in their country of origin with an overall seroprevalence of HBSAg positivity of 7.2% in migrants, 5.1% in immigrants and 9.6% in refugees. HBSAg seroprevalence ranged from 11.3% in migrants from East Asia and The Pacific to 1.7% in migrants from Latin America and the Caribbean, with an estimated 3.5 million migrants worldwide estimated to be infected with HBV (Rossi C, 2012). In the United States (US) the prevalence of chronic HBV in Asian and Pacific Islanders at 10-15% is considerably higher than the prevalence of 0.42% in the general US population (Cohen, 2008). Amongst people who inject drugs in Europe the prevalence of anti-HBc, is estimated to be between 20-85% and the prevalence of HBSAg is 0 to 21% (Rantala & Laar, 2008). In a further high risk group, sex workers, a 6.1 to 6.7% prevalence of HBSAg is seen in the United Kingdom and Spain (Orduna A, 1992) (Ward H, 1999).

Globally 27% of cases of cirrhosis, and 53% of cases of hepatocellular carcinoma are caused by HBV infection. This led to an estimated 563,000 deaths related to HBV in 2002, 235,000 deaths due to cirrhosis and 328,000 from hepatocellular carcinoma (Perz JF, 2006).

1.1.2.5.1.3 Epidemiology of HBV in the UK:

There are no recent studies estimating the population prevalence of HBV in the UK population. The Department of Health estimates the prevalence to be 0.3%, and the UK is considered a low prevalence area by the World Health Organisation with an estimated prevalence of <1% (WHO, 2001) (DoH, 2002) (ECDC, 2010). Despite the lack

of overall population data the prevalence of HBV in 1st time blood donors in the UK, and pregnant women has been studied, with prevalence rates of 0.04% and 1% respectively. The higher rate in pregnant women may be due to the fact that migrant women, who tend to have higher rates of HBV than the general population, are better represented in pregnancy studies than in blood donor screening studies (ECDC, 2010).

In common with other low prevalence areas of the world higher rates of HBV in the UK are seen in migrant populations from highly endemic areas of the world, people who inject drugs and sex workers (Ward H, 1999). The group most affected by chronic HBV in the UK are migrants from areas of high endemnicity. Each year in the UK there are 3780 cases of acute HBV, with 269 cases of chronic HBV resulting from these, and an estimated net migration of 6571 people with chronic HBV into the UK suggesting that 96% of chronic HBV in the UK each year occurs in migrants (HPA, 2006). The European Centre for Disease Control estimated in 2010 that there are 42,920 migrants with chronic HBV living in the UK (ECDC, 2010) and more recently it has been estimated that there are 193,000 migrants with chronic HBV living in the UK (Rossi C, 2012). A Mosque based screening study showed migrants from Pakistan and Bangladesh to have a prevalence of HBsAg of 1.8% and 1.5% respectively (Uddin, 2010), and a cross sectional study in Liverpool found a HBSAg prevalence among people born in Somalia of 5.7%, with a prevalence of 9.4% among adults aged 20 to 44 years (Aweis D, 2001). In an immigration detention centre in the UK 2% of detainees were found to be HBV positive (McLaren E, 2012).

The prevalence of chronic HBV in second generation migrants to the United Kingdom has not been widely studied, but Uddin et al observed a prevalence of HBsAg of 0.2%

in second generation migrants of South Asian ethnicity screened in Mosques indicating it may not be higher than the baseline UK prevalence (Uddin G, 2009). The incidence of acute hepatitis B in adults in the Netherlands was higher in both first and second generation migrants (4.3/100000 and 3.7/100000 respectively) than in the native population (1.6/100000) (Whelan J, 2012), but over 95% of cases acute hepatitis B in adults will be cleared spontaneously and will not cause chronic hepatitis B making this less relevant when considering screening.

Acute hepatitis B in the UK is usually transmitted sexually, with a small proportion of cases occurring in people who inject drugs. The latest Public Health England update on acute HBV reports heterosexual sexual exposure as the most common reason for transmission in 57% of cases, men who have sex with men accounted for 16% of cases and PWID accounted for 4.4% of cases (PHE, 2014). In London sex workers have been reported to have 6.1% prevalence of HBSAg (Orduna A, 1992), which is considerably higher than the general population (DoH, 2002).

1.1.2.5.2 Hepatitis C virus:

1.1.2.5.2.1 HCV transmission:

Hepatitis C virus is usually transmitted parentally. Sexual transmission is possible, particularly with high-risk sexual behaviour but it is rare. Two major patterns of parenteral transmission are recognised which vary from country to country; in the developed world injection drug use (IDU) is now the principle mode of transmission and in the developing world iatrogenic transmission through contaminated medical equipment predominates (Sy T, 2006) (Alter MJ, 2007). Age specific prevalence data

has identified three distinct patterns of transmission. In the United States, the UK and Australia most infections occur in people who inject drugs who are aged between 30 and 49 years old, indicating that the risk for infection probably occurred in the last 10-30 years. In Italy, Japan, Turkey and Spain most infections occur in people of older age, indicating that the risk factors for infection were most prevalent over 40 years ago. In Egypt there is a high prevalence of HCV amongst all age groups indicating on-going risks for transmission. In the latter two transmission patterns the major risk factors are iatrogenic transmission from contaminated medical equipment, injections from inadequately sterilised needles, transfusion of blood products from unscreened donors, transfusion where viral inactivation has not occurred, and the use of unsterilized equipment for rituals, traditional medicine or tattooing or shaving (Alter MJ, 2007) (Wasley A, 2000) (WHO, 1999). In Egypt which has a HCV prevalence of 11-14% the major route of transmission was contaminated, inadequately sterilised needles that had been re-used during a schistosomiasis control campaign that took place from the 1950's to the 1980's (Strickland GT, 2006). The reason behind the high ongoing incidence in Egypt with over 150,000 new infections per year is not understood, although recent research indicates that up to 5167 HCV infections per year may be related to vertical transmission (Benova L, 2014). The epidemiology of HCV infection in Western countries has changed considerably since the early 1990s and the discovery of the HCV virus. Prior to this time iatrogenic transmission via transfused blood products was the main source of HCV transmission. The development of ELISA and then RIBA tests to the HCV antibody, enabling screening of blood donors by 2002 reduced the risk of post-transfusion HCV in the USA from 7.7% to 1 in 276,000 donations. Since this point the introduction of nucleic acid testing to identify HCV RNA

in the blood before antibodies develop has further reduced the risk of transmission and in the USA the risk of transmission is now 1 in 1,935,000 transfusions with no reported cases of transmission of HCV due to plasma products in Europe since 1984 (Thursz M, 2014) (Esteban JI, 2008).

There is conflicting evidence about the role of sexual activity in the spread of HCV from person to person. Transmission via sexual activity is possible, but it appears to be much less efficient than transmission via percutaneous contact despite the presence of HCV in semen and cervical secretions (Terrault N, 2002) (Thursz M, 2014). Modelling data from a cross sectional serological survey in Egypt estimated a risk of sexual transmission of HCV from wife to husband of 34% if the wife was HCV ab and HCV RNA positive. However no genotyping or nucleotide sequencing was performed to ensure that the couples were infected with the same virus, and while transmission between couples was assumed to be sexual there are many other routes of transmission that are possible within households, such as shared razors, toothbrushes or, in Egypt shared needles when schistosomiasis vaccination was performed (Magder LS, 2005). Two case control studies in the United States in the 1980's suggested that non-A, non-B hepatitis was independently associated with multiple sexual partners, or sex with an infected person (Alter MJ C. P., 1989) (Alter MJ G. R., 1982), but these studies also suffer from a lack of nucleotide sequencing or genotyping. In contrast an Italian study evaluated 895 heterosexual partners of HCV infected persons, for a follow up period of 8060 person-years, and found no evidence of sexual transmission although all couples denied barrier contraceptive use (Vandelli C, 2004). A number of studies have confirmed that heterosexual couples in monogamous relationships very rarely transmit

the virus, with the estimated risk of sexual transmission of HCV for an infected individual who is in a monogamous relationship being 0 to 0.6% or 1 in 190,000 sexual contacts in a large cross-sectional study of 500 HCV positive individuals and their long term partners. The risk of transmission rises to 1% per year in individuals with multiple sexual partners, and is increased in those with HIV and sexually transmitted diseases (Terrault N, 2002) (Thursz M, 2014).

A number of reports since 2000 have documented cases of acute HCV amongst HIV positive men who have sex with men (MSM). Being HIV positive appears to be a risk factor for HCV transmission among MSM, with other risk factors including the use of recreational drugs during sex, anoreceptive intercourse, multiple sexual partners and traumatic sexual practice (Thursz M, 2014).

Perinatal transmission is also possible, but this only occurs when the mother is HCV RNA-positive at the time of delivery. The risk of transmission is 4 to 7%, and it is associated with internal foetal monitoring, HIV co-infection (which increases the risk of transmission by 2 to 4 times) and prolonged labour after membrane rupture. There is no association with caesarean section, vaginal delivery or breast feeding (Alter MJ, 2007).

1.1.2.5.2.2 Hepatitis C virus global epidemiology:

The global prevalence of HCV antibodies is 2.8% equating to around over 185 million people worldwide, with 170 million people being chronically infected with HCV (Hanafiah KM, 2013) (WHO, 1999). The prevalence of HCV varies between countries and is highest in Egypt where the prevalence of HCV antibody is estimated at between

11% and 14%, with 5 to 7 million people being infected with chronic hepatitis C (Strickland GT, 2006) (Bruggmann P, 2014). In Europe the overall prevalence is estimated to be 1.03%, in Africa 5.3%, the Americas 1.7%, the Eastern Mediterranean 4.6% and in South East Asia and the Western Pacific 2.15% and 3.9% respectively (Sy T, 2006). In Europe the prevalence of HCV varies from a low level in countries such as France (0.84%), Germany (0.4% to 0.63%), and Sweden (0.5%) (Cornberg M, 2011) to higher levels in Greece where the prevalence is 1.9%, Poland (1.4% to 1.9% prevalence) and Russia (1.3% to over 3% prevalence). In Italy it rises to 5.2% amongst adults, with a divide between the North of the country (prevalence of 1.6%) and the South (prevalence of 7.3%). The total number of persons infected with HCV in 22 European countries is estimated to be between 7.3 and 8.8 million (Muhlberger N, 2009). In the United States the estimated prevalence is 1.8%, with approximately 3.9 million people affected by chronic HCV (Alter MJ K.-M. D., 1999), in Australia the prevalence is 1.3% (Sievert W, 2011) and in Puerto Rico the prevalence is 6.3% (Perez CM, 2005). In Asia most countries have an estimated prevalence of HCV of 1 to 2%, with Taiwan and Pakistan having higher prevalence rates of 4.4% and 4.95% (Sievert W, 2011) (Waheed Y, 2009). The prevalence in China is 1 to 1.9% with an estimated 13 million people having been infected with chronic HCV, more than the whole of Europe and the Americas. Within China prevalence varies from region to region, with some areas having a prevalence of over 30% among blood donors (Gao X, 2011).

Within low prevalence countries there are groups of individuals who are at much higher risk of infection, principally people who inject drugs and migrants from high endemnicity countries. In Australia approximately 80% of infections are related to

injection drug use, and 11% occur in migrants to Australia (Sievert W, 2011). In Sweden and Norway people who inject drugs account for 65% and 67% of prevalent HCV respectively. The prevalence of HCV antibodies in Europe in PWIDs is on average 47 times higher than in the general population, and a high prevalence of anti-HCV antibodies is seen worldwide in PWID with a prevalence of 60-80% in 26 countries and over 80% in 12 countries, with an estimated 10 million PWIDs worldwide having positive HCV antibodies (Hahne SJM, 2013) (Nelson P, 2011). Migration from endemic regions is an important risk factor for HCV infection with migrants from endemic countries accounting for a third of prevalent HCV infections in Switzerland, 37% in Germany and 56% in the Netherlands. In Spain anti-HCV prevalence was 9-15% in Sub-Saharan Africans and Asians, and in Europe the prevalence of HCV antibodies in migrants is on average two times higher than in the general population (Cornberg M, 2011) (Esteban JI, 2008) (Hahne SJM, 2013).

A recent systematic review of HCV in PWID in Europe reports the incidence of primary HCV infection to be between 2.7/100 person years to 66/100 person years, with a median incidence of 13/100 PY. In those with a recent or active history of injecting drugs the median incidence was higher at 26/100 PY. The most common genotype in PWID in Europe is genotype 1a (Wiessing L, 2014). The incidence of HCV in PWID appears to be reducing. In New South Wales in Australia and Canada the incidence has declined from 30.8/100 person years in 2001 to 7.9/100 per year in 2011 in Australia, and from 25/100 person years in 1996-99 to 3.1/100 person years in 2006-2012. The reduction has been attributed to increased uptake of opiod substitution therapy amongst PWID along with a reduction in the population of PWID, a reduction in syringe

borrowing amongst PWID and a move away from injection and towards smoking of crack cocaine and heroin (Bertoletti A, 2012) (White B, 2014) (Grebely J D. L.-J., 2014).

The contribution of HCV to cirrhosis and its complications worldwide is considerable. Globally 27% of cases of cirrhosis are estimated to be caused by HCV, and 25% of cases of hepatocellular carcinoma. In 2002 this equated to 235,000 deaths worldwide from HCV related cirrhosis and 328,000 deaths from HCV related HCC (Perz JF, 2006). In Europe in 2002 an estimated 86,000 deaths were attributable to HCV infection, with HCV causing 35% of cirrhosis-related deaths and 32% of HCC related deaths, and accounting for 23% of liver transplants (Muhlberger N, 2009).

1.1.2.5.2.3 HCV in Pakistan:

In Pakistan the population prevalence of antibodies to HCV is estimated to be 4.95%, and an estimated 10 million people are chronically infected with HCV (Raja NS, 2008)(Waheed Y, 2009). There is significant geographical variation between regions of the country, with a 23.8% prevalence of HCV antibodies in Karachi and 15.1% prevalence in Punjab (Janjua NZ, 2010). The cause of this geographic variability is not known, but it may be related to variability in sterilisation practices of medical equipment and screening of blood products for transfusion (Janjua NZ, 2010). The high prevalence of HCV in Pakistan is due to unsafe injections, blood transfusions, poorly sterilised medical equipment, shaving in community barber shops, and injection drug use (Janjua NZ, 2010) (Sievert W, 2011). The prevalence is highest amongst people who inject drugs, where HCV antibody prevalence is 57%, and individuals who have received multiple blood transfusions, who have a HCV antibody prevalence of 48.67% (Waheed Y, 2009) (Raja NS, 2008). In Pakistan there are an estimated 8.2 to 13.6

injections per person per year, due to a belief that injectable medication is more effective than oral medication (Waheed Y, 2009) (Sievert W, 2011). Of these 94.2% are felt to be unnecessary, and there are high rates of sharing of injection equipment ranging from 8.5% in Hyderabad to 33.6% in Sukkur, with a reported 46% of injections in Digri and Mirpur being given with previously used syringes (Waheed Y, 2009) (Sievert W, 2011). The WHO has estimated that 1.2 to 1.5 million blood transfusions occur in Pakistan per year, and only 23% of blood banks screen donated blood for HCV (Waheed Y, 2009) (Janjua NZ, 2010). A high proportion of patients with HCV give a history of facial (70%) or armpit shaving (48%) from community barbers (Waheed Y, 2009). Women and men appear to be affected by different risk factors with iatrogenic factors such as medical injections, blood transfusions and dental treatment being significantly associated with HCV infection among women and regular shaving by barbers, extramarital sexual intercourse and hospitalisation showing an association with HCV infection among men (Janjua NZ, 2010).

1.1.2.5.2.4 The epidemiology of HCV in the UK:

The prevalence of HCV in the United Kingdom population is low at 0.67%, with a slightly higher prevalence of 1% in Scotland. Estimates of the number of people living with chronic HCV in the UK vary but the latest Public Health England report estimates there to be 214,000 people living with chronic HCV in the UK (Cornberg M, 2011) (DeAngelis, 2008) (Public Health England, 2014) (Harris RJ, 2011). The incidence of HCV infection is approximately 20/100,000 each year and there were 7540 newly reported cases in 2007 (Cornberg M, 2011). In the UK, since the introduction of screening of blood products for anti-HCV in 1993 and in common with other developed countries,

the major burden of HCV infection is in people who inject drugs (PWID). Bayesian population modelling estimates that 38% of chronic HCV infections occur in people who are currently injecting drugs, 47% in people who have previously injected drugs and 15% in others (DeAngelis, 2008). The prevalence of HCV in PWID varies within the UK with an overall prevalence of 53%, and ranges from 37% in the North East to 68-70% in London and the North West (Sweeting MJ H. V., 2009) (Public Health England, 2014). Survey data in 2013 of PWID indicates 50% of PWID in England, 47% of PWID in Wales and 32% of PWID in Northern Ireland had Hepatitis C infection (Public Health England, 2014). A study from 2001 assessing the epidemiology of HCV infection in the Trent region of the UK reported an overall prevalence of HCV antibodies of 0.05%, and the top three risk factors noted among participants for HCV infection were injection drug use (64.5%), being a recipient of blood products (18.4%) and being born outside the UK (3.2%) (Mohsen, 2001). There have been two peaks in new cases of HCV in England, the first in 1990 relating to contaminated blood products, and a second peak in 2000 due to injection drug use. This led to a peak in viraemic infections in 2007 at 153000 cases, which is predicted to decline to 83700 by 2030. Liver related deaths are predicted to rise by 100% from 390 to 780 from 2013 to 2030 and cases of decompensated cirrhosis will increase by 65% from 860 to 1370 (Razavi H, 2014).

HCV prevalence in the UK is higher in migrants from endemic areas. Seroprevalence studies of blood donors indicate an increased prevalence of HCV in people of Pakistani and Polish origin (2% and 10% respectively) (Eziefula C, 2009), and in a large Mosque based screening study the prevalence of HCV in those born in Pakistan was 2.7% (Uddin, 2010). Nineteen percent of new blood donors diagnosed with HCV after blood

donation, were of South Asian origin, although less than 1% of National Blood Service donors are of South Asian origin (HPA, 2008). A recent study combining a community based survey and laboratory surveillance data reported a 2.6% (34/1288) prevalence of HCV-ab positivity among South Asians living in Glasgow, with a range of prevalence ranging from 0.6% amongst those born in the UK to 3.1% in those born in Pakistan (O'Leary MC, 2013).

In common with HBV the prevalence of HCV in second generation migrants to the UK is not well defined. In Glasgow the prevalence of HCV in South Asians born in the UK was 0.6%, and in second generation South Asian migrants screened in London, Bradford and the West Midlands the prevalence was 0.4% (O'Leary MC, 2013), which both indicate that the prevalence in second generation migrants is not higher than in the general population.

1.1.2.6 Treatment of Hepatitis B and Hepatitis C:

1.1.2.6.1 Treatment of Hepatitis B virus:

Guidelines on the treatment of HBV have been published by the European Association for the Study of the Liver (EASL, 2012), and the National Institute for Health and Care Excellence (NICE, 2013) and the following recommendations are taken from these guidelines.

The ideal end point of treatment is sustained, off-therapy HBSAg loss. If this cannot be achieved then a sustained off-therapy virological (HBV DNA below 2000 IU/ml for 12 months after the end of therapy) and biochemical (normalisation of ALT levels) response, or a sustained virological remission (undetectable HBV DNA) while on long term anti-viral therapy are desirable end points (EASL, 2012).

1.1.2.6.1.1 Treatment indications:

Treatment of chronic HBV is indicated in patients based on a combination of serum HBV DNA levels, serum ALT levels and severity of liver disease as assessed by liver biopsy or transient elastography.

NICE defines a raised ALT as over or equal to 19 IU/L in women, or greater than or equal to 30 IU/L in men. The ALT should be raised on two successive tests three months apart to qualify for treatment (NICE, 2013).

The following patients should be considered for treatment:

- Patients with HBV DNA levels over 2000 IU/ml, serum ALT levels above the upper limit of normal (ULN) and moderate to severe active necroinflammation

and/or moderate to severe fibrosis scores on liver biopsy or a raised transient elastography (TE) score of greater than 6 kPa. Treatment can be given in patients with a normal ALT if they fulfil the HBV DNA and histological criteria for treatment, and in adults aged over 30 years with a raised ALT and a HBV DNA of over 2000 IU/ml without liver biopsy or transient elastography evidence of fibrosis or necroinflammation.

- Patients with a HBV DNA over 20,000 IU/ml and an abnormal ALT level, with no need for liver biopsy or transient elastography.
- Patients with compensated cirrhosis and detectable HBV DNA
- Patients with decompensated cirrhosis and detectable HBV DNA (EASL, 2012) (NICE, 2013).

1.1.2.6.1.2 *Treatment:*

In Europe first line treatment is either with pegylated interferon for a period of 48 weeks, the nucleoside antagonist (NA) entecavir, or the nucleotide antagonist tenofovir. The benefits of treatment with pegylated interferon are a higher chance of seroconversion of HBeAg positive HBV, no development of resistance and treatment of a finite duration. Unfortunately pegylated interferon has a poor tolerability, only a moderate antiviral effect and the risk of adverse events is high. The nucleot(s)ide antagonists benefit from oral administration, good tolerability and a powerful antiviral effect, but there is a risk of resistance and treatment is of unknown duration with an unknown long term safety profile (EASL, 2012).

Pegylated interferon α-2a therapy in HBeAg positive patients leads to anti-HBe seroconversion in 32% of patients, HBsAg loss in 3% of patients, a HBV DNA < 60-80

IU/ml in 14% of patients and ALT normalisation in 41% of patients. Entecavir and tenofovir therapy in HbeAg positive patients respectively lead to anti-HBe seroconversion in 21% of patients, HBsAg loss in 2 and 3% of patients, HBV DNA levels < 60-80 IU/ml in 60% and 76% of patients, and ALT normalisation in 68% of patients. Virological remission rates of over 90% are seen with over three years of entecavir or tenofovir therapy (EASL, 2012).

In HBeAg negative chronic hepatitis B pegylated interferon α-2a leads to HBsAg loss in 4% of patients, ALT normalisation in 59% and HBV DNA < 60-80 IU/ml in 19%, whereas entecavir and tenofovir lead to ALT normalisation in 78% and 76% respectively, and HBV DNA < 60-80 IU/ml in 90 and 93% respectively. The NA's do not lead to HBSAg loss (EASL, 2012).

Recommendations on treatment differ between the EASL and NICE guidance, and guidance from both bodies will be outlined in the following paragraphs.

EASL recommends pegylated interferon α-2a treatment for 48 weeks in HBeAg positive patients who have the best chance of responding to treatment, these are patients with a low HBV DNA level (< 2 x 10^8 IU/ml), serum ALT levels of 2-5 times the ULN and high activity scores on liver biopsy, and that it can be considered in HBeAg negative patients (EASL, 2012).

NICE guidance recommends 48 weeks of pegylated interferon α-2a treatment as first line therapy in HbeAg positive and negative patients with chronic Hepatitis B and compensated liver disease (NICE, 2013). Consideration should be given to stopping pegylated interferon α-2a after 24 weeks of treatment in HbeAg positive patients if the

HBV DNA level has reduced by less than 2 $\log_{10}$ IU/ml and/or if the level of HBsAg is greater than 20,000 IU/ml and offering second line treatment (NICE, 2013). In HbeAg negative patients consideration should be given to stopping treatment at 24 weeks of therapy if the HBV DNA level has reduced by less than 2 log IU/ml and the HBsAg level has not reduced and offering second line treatment (NICE, 2013).

When considering treatment with nucleo(t)side antagonists EASL recommends that long term treatment with a nucleo(t)side antagonist is appropriate for most patients. A finite duration of NA therapy is possible for HBeAg positive patients who seroconvert to anti-HBe on therapy, but the seroconversion is not always sustainable after treatment is stopped and therefore patients should be kept under close monitoring (EASL, 2012).

NICE guidance recommends that patients with HbeAg positive hepatitis B should be treated with tenofovir disoproxil as second line therapy if they do not achieve HBeAg seroconversion or relapse with pegylated interferon α-2a, or entecavir if tenofovir disoproxil is contraindicated or not tolerated. Consideration can be given to stopping treatment 12 months after HbeAg seroconversion in patients without cirrhosis. Patients with HbeAg negative chronic hepatitis B who still have detectable HBV DNA after treatment with pegylated interferon α-2a should be offered treated with entecavir or tenofovir disoproxil. Treatment can be stopped 12 months after an undetectable HBV DNA and HBsAg seroconversion is achieved in patients without cirrhosis (NICE, 2013).

Liver transplantation is a therapeutic option in patients with decompensated HBV related cirrhosis or hepatocellular carcinoma who fulfil criteria for liver

transplantation. Current criteria for liver transplantation in the United Kingdom are a UKELD score of over 49 in the presence of chronic liver disease with no contraindications for transplantation. The criteria for liver transplant in HCC are a single lesion of equal to or less than five cm in diameter, up to five lesions all less than or equal to three cm in diameter or a single lesion over five cm or less than or equal to seven cm in diameter with no evidence of tumour progression over a 6 month period (BASL, 2012). The outcomes for patients after liver transplantation are good with 5 year survival rates of ≥ 80% (Crespo G, 2012).

1.1.2.6.1.3 Immunisation:

Immunity against hepatitis B infection is indicated by the presence of antibodies against the "a" epitope of the Hepatitis B surface envelope protein (HBsAb). Their appearance after natural infection indicates resolution of the infection, and their appearance after immunization indicates protection against the virus. Current vaccines are produced from yeast expressing recombinant genes and are purified subviral particles and give long-term immunity after a course of three injections. When given in infancy the vaccine is 94% effective in preventing chronic HBV infection. Hepatitis B surface antibodies decrease over time. When measured 5-15 years after vaccination 15-50% of children have undetectable or low levels of HBsAb, and 9-11 years post vaccination 30-60% of adults have an undetectable HBsAb level. Immunity against chronic HBV is maintained for at least 20 years and is possibly life-long despite this due to immune memory for HBsAg. The persistence of immune memory means that booster vaccinations against HBV are not required, except in immunocompromised patients who should have monitoring of hepatitis B surface antibodies and receive a

booster vaccination if their anti-Hbs levels fall below 10 mIU/mL (Block TM, 2008) (Gerlich, 2013) (Peto TJ, 2014) (Leuridan E, 2011).

1.1.2.6.2 Treatment of Hepatitis C virus:

Treatment for hepatitis C virus has developed rapidly over recent years. Prior to 2012 the only treatment for HCV was a six or 12-month course of pegylated interferon-α and ribavirin, which has suboptimal SVR rates and a range of side effects that reduce treatment tolerability. A greater understanding of hepatitis C viral replication has led to the development of treatments that directly target the proteins involved in viral replication and in 2012 two first generation protease inhibitors, telaprevir and boceprevir were licensed for use. These increased SVR rates, but further added to the burden of side effects associated with treatment. The advent of direct acting anti-virals (DAAVs) in 2014, with shorter treatment courses, greater tolerability and the potential for interferon free regimes has the potential to revolutionise treatment. NICE guidance on the use of these medications in the United Kingdom has just been published for sofosbuvir and simeprevir and EASL guidance was published in 2014. This section will review currently licensed treatments in the UK and discuss the evidence behind and use of the new direct acting anti-viral medications (NICE, 2004) (NICE, 2007) (NICE, 2012) (NICE, 2012) (EASL, 2014) (NICE, 2015) (NICE, 2015) (NICE, 2015) (NICE, 2015) (NICE, 2015).

1.1.2.6.2.1 Treatment:

All patients with chronic HCV should be considered for treatment. The aim of treatment for hepatitis C virus is to obtain a sustained viral response (SVR). SVR is

considered to be a cure as there is a very low chance of recurrence of HCV after this is achieved (1-13%). The requirement and timing of treatment differs amongst individuals based on many factors – liver fibrosis score, genotype, age, co-morbidities, patient preference, rate of fibrosis progression and extra-hepatic HCV morbidity. Current European guidelines recommend not deferring treatment for those with advanced fibrosis, but in patients with less advanced disease treatment can be deferred (EASL, 2014).

In the United Kingdom therapies that are currently recommended by NICE for the (NICE, 2015)treatment of chronic hepatitis C virus are Pegylated interferon-α (Pegylated interferon-α 2a (Reofern A, Roche) and Pegylated interferon-α 2b (Viraferon, Schering-Plough)), ribavirin (Copegus, Roche; Rebetol, Schering-Plough) and the first generation protease inhibitors telaprevir (Incivo, Janssen) and boceprevir (Victrelis, Merck Sharp and Dohme). The direct acting antivirals sofosbuvir (Sovaldi, Gilead Sciences) and simeprevir (Olysio, Janssen Therapeutics EMEA) were approved by NICE for use in the United Kingdom in March 2015 (NICE, 2015) (NICE, 2015). In November 2015 three further NICE technology appraisals were published regarding direct acting antiviral treatment with daclatasvir and sofosbuvir, ombitasvir-paritaprevir-ritonavir with or without dasabuvir and ribavirin and ledispavir-sofosbuvir for HCV (NICE, 2015) (NICE, 2015) (NICE, 2015).

1.1.2.6.2.1.1 Treatment with pegylated interferon-α and ribavirin:

The anti-viral effect of pegylated interferon-α appears to occur through altering host-cell metabolism, although the exact mechanism is not known. Ribavirin has broad

antiviral activity against a number of RNA viruses and is a nucleoside analogue (NICE, 2004).

Pegylated interferon-α and ribavirin (PR) are recommended for the treatment of genotype one to six chronic HCV in patients over the age of 18 years. Pegylated interferon-α is a subcutaneous injection administered once weekly at a dose of 180 micrograms per week. Ribavirin is administered twice daily, with a variable dose depending on patient weight. The recommended dose is 1000 milligrams (mg) per day for those who weigh less than 75 kg and 1200 mg per day in those who weigh over 75kg (NICE, 2004).

In genotypes 2 and 3, 24 weeks of treatment with PR should be given.

In genotypes 1, 4, 5 and 6 initial treatment with PR should be for 12 weeks. If the patient has at least a 2 log drop in HCV RNA at week 12 then treatment should be continued for a total of 48 weeks. If there is a less than 2 log drop in HCV RNA then treatment should be discontinued at 12 weeks. (NICE, 2007) (NICE, 2004).

A shortened course of PR can be given to adults who have a rapid virological response at week 4 (undetectable HCV RNA at week 4) identified by a sensitive test and who are considered eligible.

This combination therapy can also be given to those with chronic HCV who have previously not responded to therapy or who have responded to therapy and then relapsed (NICE, 2010).

Response rates to treatment vary dependent on the genotype of HCV and the treatment administered. Combination treatment with pegylated interferon-α and

ribavirin gives a SVR of 42-52% in patients with genotype 1 HCV and 76-82% in patients with genotype 2 and 3 HCV. Patient and disease factors also influence response to treatment such as fibrosis stage, ethnicity and sex, with reduced SVR rates in those with advanced fibrosis and cirrhosis (Fried MW, 2002) (Hadziyannis SI, 2004) (Manns MP, 2001).

1.1.2.6.2.1.2 Treatment with first generation protease inhibitors:

Telaprevir and boceprevir are linear α-ketoamide derivatives that are orally bioavailable and reversibly bind to the serine protease NS3/4A (Lewis H, 2012) (Jacobson IM M. J., 2011) (Poordad F M. J., 2011).

Twelve weeks of therapy of Telaprevir in combination with 24 or 48 weeks of pegylated interferon-α and ribavirin is recommended for treatment in previously untreated patients, or patients whose treatment has previously failed with genotype one chronic HCV (NICE, 2012).

Boceprevir in a 24, 32 or 44 week course is recommended in combination with pegylated interferon-α and ribavirin as a treatment option for patients with genotype one chronic HCV who are either treatment naïve or who have failed previous treatment (NICE, 2012).

The first generation protease inhibitors improved sustained viral response rates over those provided by pegylated interferon-α and ribavirin. In untreated G1 patients telaprevir in combination with PR gives SVR rates of 75% (Jacobson IR, 2011), and boceprevir in combination with PR gives SVR rates of 71-76% (Poordad F, 2011). In previously treated patients treated with telaprevir and PR SVR rates of 83% are seen in

previous relapsers, 59% in partial responders and 29% in null responders (Zeuzem S, 2011). When boceprevir and PR are given to previously treated patients SVR rates of 59-66% are seen (Bacon BR, 2011). The SVR rates with protease inhibitors in combination with PR are significantly higher than with PR therapy alone in genotype 1 HCV patients (Jacobson IR, 2011) (Poordad F, 2011) (Zeuzem S, 2011) (Bacon BR, 2011).

1.1.2.6.2.1.3 Treatment with currently licensed direct acting antivirals:

A number of direct acting antiviral medications for Hepatitis C have been licensed for use by the European Medicines Agency since August 2014 including sofosbuvir, simeprevir, daclatasvir (Daklinza, Bristol-Myers Squibb), sofosbuvir/ ledispavir (Harvoni, Gilead Sciences) and ombitasvir/ paritaprevir/ ritonavir (Viekirax, AbbVie).

NICE guidance on the use of sofosbuvir and simeprevir for the treatment of Hepatitis C in the United Kingdom was published at the start of March 2015 (NICE, 2015) (NICE, 2015). European Association for the Study of the Liver guidance on the use of sofosbuvir, simeprevir and daclatasvir was published in April 2014, and has been summarised in Appendix 1 (EASL, 2014).

Sofosbuvir is nucleotide analogue of the NS5B polymerase inhibitor and has pan genotypic activity (Lawitz E M. A.-T., 2013). Sofosbuvir is administered at a dose of 400mg once daily (EASL, 2014). Simeprevir is a HCV NS3/4A protease inhibitor with antiviral activity against HCV genotypes 1,2,4,5 and 6 (Manns M M. P., 2014). Simeprevir is administered at a dose of 150 mg once daily (EASL, 2014).

NICE recommends treatment with sofosbuvir in combination with pegylated interferon-α and ribavirin for the following patients:

- All adults with genotype one HCV
- Adults with treatment naïve genotype three HCV cirrhosis
- All adults with treatment experienced genotype three HCV
- Adults with genotype four, five and six HCV cirrhosis (NICE, 2015).

In the NEUTRINO trial patients with genotype one HCV had an overall SVR of 89% when treated with sofosbuvir and PR for 12 weeks (92% in patients with G1a HCV and 82% in G1b) and those with genotype one HCV cirrhosis had an SVR of 80%. Treatment naïve patients with G4 HCV had an SVR of 96%, and those with G5/6 HCV had 100% SVR, albeit with a low numbers of patients studied (Lawitz E M. A.-T., 2013). The ATOMIC study found SVR rates of 96-98% in patients with genotype 1,4 and 6 HCV treated with sofosbuvir and PR for 12 weeks (Kowdley K, 2013). In the ELECTRON study of 10 previously untreated patients with genotype two and three HCV 100% SVR was achieved with sofosbuvir and PR treatment (Gane EJ, 2013), and in the PROTON study the SVR rate was 93% in patients with genotype two and 90% in patients with genotype three HCV treated with this combination (NICE, 2015).

Treatment with sofosbuvir in combination with ribavirin is recommended for the following patients by NICE:

- Adults with treatment naïve genotype two HCV who are intolerant of or ineligible for pegylated interferon-α
- All adults with treatment experienced genotype two HCV
- Adults with treatment naïve or experienced genotype three HCV cirrhosis who are intolerant to or ineligible for interferon (NICE, 2015).

In patients with genotype two HCV treated for 12 weeks with sofosbuvir and ribavirin SVR rates of 97% in treatment naïve patients were reported in the FISSION trial (Lawitz E M. A.-T., 2013). In those with cirrhosis 78% of patients achieved SVR with 16 weeks therapy and 60% with 12 weeks therapy (Jacobson IM G. S.-T., 2013). In the VALENCE trial SVR rates in genotype two patients after 12 weeks of sofosbuvir and ribavirin therapy were 91% in treatment naïve and 88% in treatment experienced cirrhotics, and 93% overall (Zeuzem S D. G., 2013).

In the VALENCE trial patients with genotype three HCV were treated with sofosbuvir and ribavirin for 24 weeks. The SVR rate overall was 84%, and was 93% in previously untreated patients and 77% in previously treated patients. In treatment experienced non-cirrhotic patients the SVR was 87%, in treatment experienced cirrhotic patients it was 60%, and the SVR was 94% and 92% in treatment naïve non-cirrhotics and cirrhotics respectively (Zeuzem S D. G., 2013). The POSITRON and FUSION trials treated patients who were either intolerant of or ineligible for treatment with pegylated interferon-α with 12 or 16 weeks of sofosbuvir and ribavirin. In this trial patients with genotype three HCV treated for 12 or 16 weeks achieved SVR rates of 30% and 62% respectively (Jacobson IM G. S.-T., 2013). In the FISSION trial SVR rates of 56% were seen in patients with genotype three HCV treated with 12 weeks of sofosbuvir and ribavirin (Lawitz E M. A.-T., 2013).

NICE recommends that simeprevir can be used in combination with pegylated interferon-α and ribavirin to treat adults with genotype one and four chronic Hepatitis C (NICE, 2015). In the QUEST-1 and QUEST-2 trials assessing simeprevir in combination with PR in treatment naïve patients with G1 HCV SVR rates were 80% and 81%. In G1a

patients with the Q80K substitution SVR was only 58%. 60% of patients with cirrhosis and G1 HCV achieved SVR. SVR is achieved in 82% of patients with G4 HCV with this combination of therapy, 83% of treatment naïve patients, 86% of prior relapsers, 60% of prior partial responders and 40% of prior null responders (Jacobson IM D. G., 2014) (EASL, 2014) (Manns M M. P., 2014) (Moreno C, 2015).

Further NICE guidance was published in November 2015 regarding direct acting anti-viral treatment for HCV. Technology appraisal 365 recommends the use of ombitasvir-paritaprevir-ritonavir with or without dasabuvir and ribavirin for patients with genotype one and four HCV without and with compensated cirrhosis (NICE, 2015). Technology appraisal 364 recommends daclatasvir and sofosbuvir for genotype one (untreated and previously treated) and genotype four (previously treated) patients with significant fibrosis, and patients with genotype three HCV who are interferon-ineligible or intolerant with significant fibrosis. Daclatasvir and sofosbuvir with or without ribavirin is recommended for patients with genotype one and four HCV and compensated cirrhosis who are interferon-ineligible or intolerant, and with ribavirin in those with genotype three HCV and compensated cirrhosis who are interferon-ineligible or intolerant. Daclatasvir, peginterferon alfa and ribavirin is recommended for those with genotype four HCV with advanced fibrosis or compensated cirrhosis (NICE, 2015). Technology appraisal 363 recommends the use of ledispavir-sofosbuvir for eight (previously untreated) or 12 (previously treated) weeks in patients with genotype one HCV without cirrhosis and for 12 weeks in those with genotype 1 HCV and compensated cirrhosis who are untreated, or have been treated and fulfil certain criteria. In patients with genotype four HCV it is recommended in patients without

cirrhosis who have been previously treated, and those with compensated cirrhosis who have not been treated previously or who have been treated and fulfil certain criteria (NICE, 2015).

1.1.2.6.2.1.4 Side effects of treatment:

Pegylated interferon-α has a relatively poor tolerability with a side effect profile that includes influenza like symptoms, fatigue, depression and haematological abnormalities and ribavirin causes anaemia and is teratogenic (Fried MW, 2002) (Manns MP, 2001).

The main side effects of telaprevir use are rash, gastrointestinal disorders, pruritis and anaemia (Jacobson IR, 2011) In patients treated with boceprevir the principal side effects are fatigue, headache, nausea, dysgeusia and anaemia (Poordad F, 2011).

All licensed DAAVs were well tolerated in clinical studies. Side effects of sofosbuvir when administered with ribavirin in phase 3 studies were fatigue and headache in over 20% of patients, and when administered with pegylated interferon-α and ribavirin were headache, fatigue, nausea, anaemia and insomnia (EASL, 2014) (Jacobson IM G. S.-T., 2013) (Lawitz E L. J., 2013) (Lawitz E M. A.-T., 2013) (Zeuzem S D. G., 2013). Adverse reactions seen with simeprevir when given with PR were pruritis, nausea and a rash. A mild transient hyperbilirubinaemia is seen in 10% of cases due to inhibition of the OATP1B1 and MRP2 transporters (Jacobson IM D. G., 2014) (Manns M M. P., 2014) (EASL, 2014) (Moreno C, 2015).

Liver transplantation in Hepatitis C virus:

In common with Hepatitis B liver transplantation is a therapeutic option in patients with decompensated HCV related cirrhosis or hepatocellular carcinoma who fulfil criteria. The current criteria for liver transplantation in the United Kingdom for patients with HCV related decompensated cirrhosis and HCC are the same as those for hepatitis B virus (BASL, 2012). Between 1996 and 2012 in England 1280 liver transplants were performed in patients with HCV, accounting for 15% of all liver transplants (Bruggmann P, 2014). The 1 and 5 year survival rates after liver transplantation for HCV are 86% and 76% respectively which compares favourably with other indications for liver transplantation (Willems M, 2002). In patients who have detectable HCV RNA at the time of transplantation, HCV recurrence in the graft is almost universal, and fibrosis occurs at an accelerated rate in the graft (Westbrook RH, 2014).

1.1.3 Ascertainment and screening of chronic viral hepatitis:

The serious consequences and often silent nature of infection with chronic viral hepatitis have led to an interest in screening programmes in at risk groups. Screening for viral hepatitis in migrants from countries with an intermediate or high prevalence of viral hepatitis was recommended by the Advisory Group on Hepatitis in 2009 (AGH, 2009), and NICE in 2012 (NICE, 2012), but the most effective method to screen for HBV and HCV in the United Kingdom is not yet known. Screening programmes have to fulfil certain criteria, set out by the World Health Organisation in 1968, and before wide spread screening can be implemented the most effective, and cost-effective method needs to be identified. In this section the literature on screening for chronic viral hepatitis, screening in migrant groups, economic evaluation of screening for HBV and HCV and national guidance on screening for chronic viral hepatitis in migrants will be reviewed.

1.1.3.1 Requirements for a screening programme:

In 1968 the World Health Organisation published a document advising on the principles and practice of screening for disease, which set out 10 important criteria for screening programmes:

1. The condition should be an important health problem.
2. There should be a treatment for the condition.
3. Facilities for diagnosis and treatment should be available.
4. There should be a latent stage of the disease.
5. There should be a test or examination for the condition.
6. The test should be acceptable to the population.
7. The natural history of the disease should be adequately understood.
8. There should be an agreed policy on whom to treat.
9. The total cost of finding a case should be economically balanced in relation to medical expenditure as a whole.
10. Case-finding should be a continuous process, not just a "once and for all" project. (WHO, 1968).

These guidelines are still widely accepted as the “gold standard” for the identification of suitable diseases for screening programmes and if a disease does not fulfil the above criteria, then a screening programme is less likely to provide a benefit to those being screened. The discussion on Hepatitis B and C virus infection in the UK in high

risk groups in the preceding sections indicates that they do fulfil the first 8 criteria: They are important health problems, which can be treated, are diagnosable with a widely available blood test (which is a test generally considered acceptable to the population) and have a latent stage. The natural history of both is well understood and there are clearly defined guidelines as to who should be treated. The cost-effectiveness of screening will be discussed further in this section.

1.1.3.2 Screening for chronic viral hepatitis:

Chronic HBV and HCV are regarded as “silent diseases” with the majority of infected people being unaware that they have chronic viral hepatitis until they present with complications (Ascione A, 2007) (Flamm, 2003) (JT, 2009) (ELPA, 2010) (Merkinaite S, 2008). Due to this most people with chronic viral hepatitis are currently undiagnosed. In Europe only 10 to 40% of those with chronic HCV are estimated to have been diagnosed, and the European Liver Patients Association surveys suggest that up to 90% of those with HCV are unaware of their infection (ELPA 2010). Based on estimated of current prevalence there are approximately 165,000 people with HCV in the UK who are unaware of their infection status, and in Glasgow an estimated 38% (330/870) of South Asians with HCV have not been diagnosed (O'Leary MC, 2013). In Germany there are up to 450,000 undiagnosed people living with HCV (90% of those affected), and in France, Poland and Lithuania around 44%, 97% and 95% of people respectively with HCV remain undiagnosed (Merkinaite S, 2008). In the United States ascertainment is similarly poor with only 12% (2007/12155) of cases of HCV in children having been diagnosed in Florida (Delgado-Borrego A, 2012), and only 25% of adults with HCV being aware of their infection (Mitchell AE, 2010). Awareness of HBV carrier status is similarly low. Only 37% of patients who tested positive for HBsAg in an Italian dermatology clinic were previously aware of their carrier status (Brevi A, 1993) and the diagnostic rate of HBV in the USA is between 25 and 35%, in Europe is approximately 18% and in Asia is 4%, rising to 13% in Japan (Liaw Y-F, 2009) (Lin SY, 2007) (Mitchell AE, 2010).

The current epidemic of viral hepatitis B and C has been described as a “viral time bomb” due to the prolonged time period between infection and the emergence of long term complications of the disease. Modelling has predicted that the number of cases of cirrhosis, end-stage liver disease and death from chronic viral hepatitis are likely to increase over the next decade, but that treatment will reduce the morbidity and mortality associated with the infection. In the UK the number of cases of compensated HCV cirrhosis is predicted to rise to 7550 in 2015, with cases of decompensated cirrhosis and HCC predicted to rise to 2540 (Sweeting MJ D. A., 2007). Public Health England data supports this showing that hospital admissions from HCV rose from 608 in 1998 to 2390 in 2012 and HCV related deaths rose from 98 in 1996 to 428 in 2012. Registration for HCV related liver transplants has increased over the same time period from 45 to 101 (see figure four) (Public Health England, 2014) (HPA, 2012). Recent modelling predicts a 40% reduction in viraemic infections in England from 144000 in 2013 to 83700 in 2030, but an increase in HCV related HCC from 410 to 920 per year in the same period and a 100% increase in liver related mortality from 390 to 770 cases, with cases of decompensated cirrhosis increasing from 860 to 1370, a 60% increase (Razavi H, 2014). Mortality in the United States from end stage liver disease or HCC secondary to HCV is expected to peak in 2030 at 13000 cases, a 250% increase since 1998. HCV related mortality would still increase with treatment but by a reduced amount. If a 15% uptake of treatment and an 80% SVR rate were achieved mortality would increase by 214% in 2030, and with 50% coverage and 60% SVR mortality would increase by 150%. Total predicted deaths from 2005 to 2025 would be 196000 at present treatment levels (almost identical to no treatment), 182000 with 15% coverage and 160000 with 60% coverage. (Deuffic-Burban S P. T., 2007). Similar

modelling in Egypt in 2006 predicted a 350% increase in deaths from HCC in the next 20 years, and a 210% increase in deaths from HCV related liver failure (Deuffic-Burban S M. M.-J., 2006), and Markov modelling predicts 117,556 deaths from HCC and 127,821 deaths from chronic liver disease in Egypt over the next 20 years (Lehman EM, 2009). Modelling in Switzerland predicts that HCV related morbidity and mortality will rise by 70-90%, with a peak in 2015-2020. They predict that antiviral therapy would reduce mortality by 5% per year, although this was modelled on a 40% response rate to treatment. The annual costs of treatment in Switzerland were estimated to be $33 million in 2020 (Sagmeister M, 2002). This data is based on treatment with pegylated interferon-α and ribavirin and recent modelling indicates that treatment for HCV with interferon free therapy will reduce the morbidity relating to cirrhosis and HCC further, with a reduction in decompensation or HCC from 24.2% to 12.7% of treated patients with a treatment strategy based on fibrosis score, or 21.3% to 10.9% with a treat all strategy (Younossi ZM, 2014).

Given the low current ascertainment rates of chronic viral hepatitis the data above support the concept of screening of people who are at high risk of acquisition of HBV and HCV if this increases treatment rates, due to the reduction in morbidity and mortality associated with treatment.

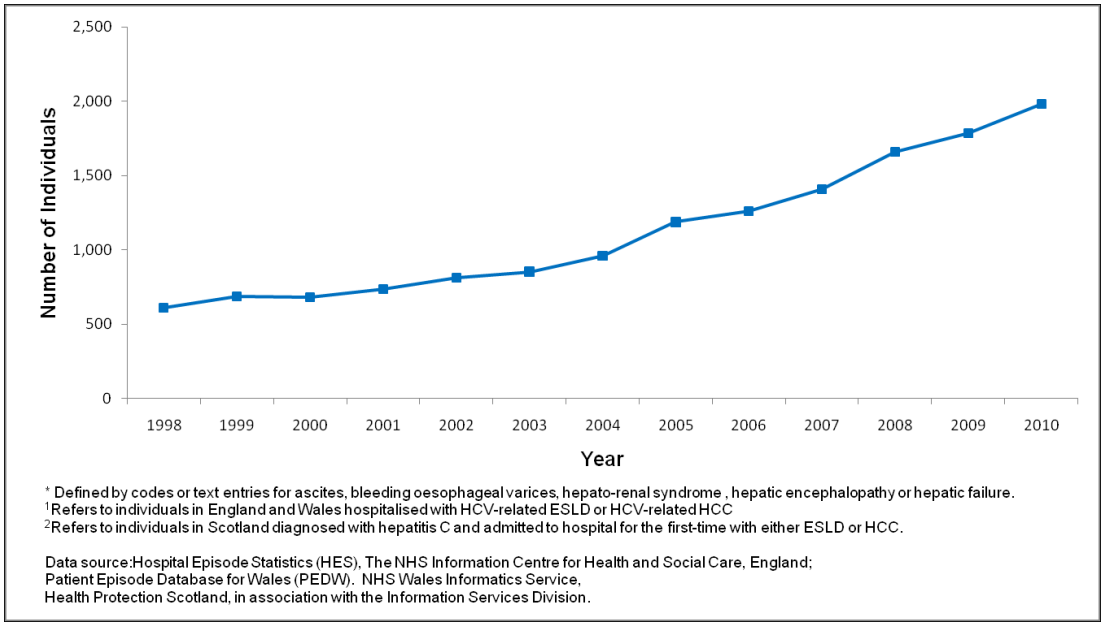


Figure 4 Annual number of individuals in England, Scotland and Wales hospitalised with HCV-related ESLD or HCV-related HCC: 1998-2010

Source: (HPA, 2012).

1.1.3.3 Screening in migrant groups:

Within the United Kingdom the group at the highest risk for chronic viral hepatitis who are not routinely screened are migrants from areas of high prevalence. Chronic viral hepatitis in migrants often presents late and appears to have a more severe disease course. Over a third (37%) of migrants with chronic HBV or HCV in an Australian study presented late due to complications of their liver disease (Guirgis M, 2012) and people from Pakistan and Bangladesh living in the UK have an estimated 7-10 times more episodes of end stage liver disease, and 16-35 times more episodes of hepatocellular carcinoma related to HCV than would be expected (AG Mann, 2008). In the United Kingdom standardised mortality ratios (SMRs) for cirrhosis of the liver and HCC are higher amongst migrant men than those born in England and Wales. The SMRs for cirrhosis of men born in India, East Africa and Bangladesh are 261, 286 and 254 respectively and for HCC are 1014 for men from the African Commonwealth (other than East Africa), 910 in those from Bangladesh and 312 in male migrants from the Caribbean. The reason for this excess mortality was not identified in this study (Haworth EA, 1999). Similarly in the US Asian Americans have the highest mortality from HBV related HCC of all ethnic groups (Wong R, 2008). In the UK rates of cirrhosis in elderly Asian patients were 78% compared with 25% in age matched Caucasian patients. The higher rates of cirrhosis in this study appeared to be related to longer duration of infection in Asian patients, who are more likely to have been infected in childhood as no other factors had a significant impact on cirrhosis outcomes (D'Souza R G. M.-L., 2005). In Sweden immigrant status has been shown to be independently associated with the development of cirrhosis in patients with HCV, although the

authors were unable to identify a cause for this (Verbaan H, 1998). These studies show that there is significant excess morbidity and mortality associated with chronic viral hepatitis in migrants, which is potentially preventable with earlier recognition of disease.

There has been an increasing trend of net migration into the European Union since the 1980s leading to Europe being a net importer of people which has led to the higher rates of chronic viral hepatitis in migrants from regions of high prevalence becoming an important public health issue (Carballo M, 2010). In 2005 there was a net migration of 1.8 million people into the EU, including 565,000 people from Asia and Africa migrating to the UK. Migrants currently make up around 8% of the population of the UK, and much of the post-World War Two migration has involved men from Pakistan, Bangladesh and India, East and Southern Africa and the Caribbean, all countries with a moderate to high prevalence of viral hepatitis. Between 2004 and 2011 the most common countries of origin of UK residents who were not born in the UK were India, Poland and Pakistan, all of which have a moderate to high prevalence of chronic viral hepatitis (ONS, 2012).

1.1.3.4 Economic evaluation of screening:

A number of economic evaluations have been performed to examine the cost effectiveness of different screening approaches in migrants. The majority of these have been performed in the US and the Netherlands, with none so far in the United Kingdom.

Economic evaluation of a one off screening programme for HBV in migrant groups, assuming a 3.4% prevalence of HBV, has been shown to be cost effective in the Netherlands if 35% of the screening target population were screened. The incremental cost effectiveness ratio (ICER) per quality adjusted life year (QALY) gained was 8966 euros, which is within the 20,000 euros per QALY that is considered cost effective for healthcare interventions in the Netherlands. The screening intervention involved Markov modelling of a one off screening intervention with treatment of eligible identified patients. Migrants from countries of intermediate and high prevalence of chronic HBV were sent a screening form in the post and invited to take it to a local testing centre to be screened, and test results were sent to the participant and their GP. The modelling estimated that treatment rates would increase from 4% of the eligible population to 15% by improving case detection and referral to primary care (Veldhuijzen, 2010).

A US study into HBV screening modelled the cost-effectiveness of a screen, treat and vaccinate approach in Asian and Pacific Islander adults in the United States who have a HBV prevalence of 10%. A screen and treat strategy had an ICER of $36,088 per QALY gained, and when vaccination was included the ICER was 39,903 per QALY. In the US interventions which cost less than $50,000 per QALY are considered cost-effective.

These outcomes assumed a 70% compliance with each intervention. They did not take into account costs such as lost work days due to HBV related illness, which if taken into consideration could make the intervention more cost effective, and these interventions were found to be cost effective even with a low prevalence of HBV of 1% (Hutton DW, 2007).

Hepatitis B screening in community clinics, outreach screening in non-clinical centres and contracting health screening companies to screen for HBV as part of general health screening in the US have been compared. The lowest cost of screening was in community clinics, and the highest cost was with contracted health screening companies, but fewer people were screened in the community clinics (106 people screened versus 765, at a cost of $40 per screen compared with $280, and a cost of $609 versus $4657 per newly identified positive case). The proportion of the target population screened in each programme was not reported (Rein DB L. S., 2011).

Markov modelling of HBV screening in the US indicates that screening in populations with a HBV prevalence of >2% was cost effective with a ICER of $29,230/QALY if screening was followed with treatment with a low cost, high resistance nucleo(t)side. Screening was cost effective in groups whose prevalence was > 0.3%, which is at the lower confidence interval for the prevalence of HBV in the US (Eckman MH, 2011).

Markov modelling of opportunistic screening in Canadian primary care centres of migrants from moderate and highly endemic regions for HBV gave an ICER of Canadian $69,209/ QALY, which was felt to be moderately cost effective with a screening uptake of 100% (Wong WL, 2011).

The four modelling analyses and one study indicate that a variety of approaches to screening are cost-effective in HBV. On a note of caution two of the modelling analyses predicted screening uptake of 70 and 100% which is likely to overestimate uptake given that a “real-life” large scale HBV screening programme had a screening uptake of only 27%, and lower screening uptake would be likely to reduce cost effectiveness (Robinson T, 2005). However a more realistic uptake of 35% in the Dutch study was predicted with screening shown to be cost-effective with this model, and in the real-life study where the proportion of the target population screened was not known screening was also cost-effective.

Most research into the cost effectiveness of screening for HCV has focused on people who inject drugs, with no studies examining screening in migrants from high prevalence countries. Modelling of screening for HCV predicts it could be cost effective in the United States in persons with a high prevalence (>10%) such as people who inject, or have previously injected drugs, with ICER’s of less than 40,000 euros/ QALY. Screening in blood recipients and general HCV screening were not modelled to be cost effective with ICER of 140,600 euros/ QALY and 140,500 euros/ QALY respectively (Sroczynski G, 2009). Markov modelling of birth cohort screening of all US residents born between 1946 and 1970, compared with risk based screening estimates an ICER of $37,700 per QALY for birth cohort screening versus risk based screening. Birth cohort screening was predicted to lead to higher overall costs ($80.4 billion) than risk based screening ($53.7 billion) but lower costs due to advanced liver disease ($31.2 billion versus $39.8 billion) and was estimated to lead to 84,000 fewer cases of decompensated cirrhosis and 78,000 fewer HCV-related deaths (McGarry LJ, 2012).

Further modelling has estimated a lower cost of screening for HCV in the United States with one time general population screening for HCV, and the cost was reduced further with targeted screening of those born between 1945 and 1965 with an ICER per QALY gained of $7900 and $4200 respectively, and modelling has estimated birth cohort screening of those born between 1945 and 1965 to be cost-effective in a US primary care setting with a screening cost of $2874 for each identified case. In the case of primary care screening treatment with pegylated interferon and ribavirin increased the ICER per QALY to $15700, and treatment with a direct acting antiviral and PR increased ICER to $35700 per QALY (Coffin PO, 2012) (Rein DB, 2012).

In the Netherlands an awareness raising and screening campaign for HCV amongst the general population, with a support programme for primary care and a screening programme targeting people who inject drugs were both found to be cost effective with ICER's of euro 11,297/ QALY and euro 7321/ QALY respectively (Helsper CW, 2012).

Most of the economic evaluations of screening are of good quality, but their main deficit is the lack of evidence underlying the assumptions that were made of screening uptake and approaches.

1.1.3.5 Government recommendations:

In 2006 the Health Protection Authority in the UK recommended that the cost effectiveness of screening for HBV in all migrants from areas of high prevalence should be considered, and that awareness of the risk of HBV should be spread to migrants from these areas and their GP's (HPA, 2006). In 2009 the Advisory Group on Hepatitis recommended that case finding for HBV and HCV should be implemented by Primary Care Trusts for individuals from minority ethnic populations who were born in countries with a high or intermediate prevalence of HBV infection (AGH, 2009) and a report was commissioned for the national screening committee. Following this in 2010 the HPA highlighted that case finding in migrant populations would be key to a reduction in the mortality and morbidity associated with chronic viral hepatitis and emphasised the need for data on the burden of infection and on the most cost effective methods for case finding (HPA, 2010).

In 2012 guidance was written by NICE, at the request of the Department of Health, exploring ways to promote and offer testing for those at increased risk of HBV and HCV. This guidance recommends testing in GP surgeries for all those at risk of HBV and HCV, including those from countries of moderate or high endemnicity of HBV (>2% HBV prevalence) (NICE, 2012), but there is no evidence that this currently occurs.

The Centres for Disease control in the US recommends screening all migrants from countries with a prevalence of > 2% of HBV for the infection with HBsAg (CDC, 2008), and in 2013 the US Preventive Services Task Force recommended screening for HCV in all at risk persons, including people who inject or have injected drugs, and one-time screening for all adults born between 1945 and 1965 (Moyer, 2013).

1.1.3.6 How should screening be performed?

While interest has increased in screening for viral hepatitis in migrants from intermediate and high-risk areas the most effective way to do this is not yet known. There have been a small number of studies that have examined the best methods for screening migrants for HBV and HCV and these will be discussed in the following section.

The largest scale screening programme in high risk migrants is New Zealand Hepatitis B screening programme which targeted Maori, Pacific and Asian populations. Overall 177,000 people were tested for HBsAg, 27% of the eligible population. A variety of methods were used including employing teams of phlebotomists who worked directly with local communities, supporting GP's and Maori and Pacific providers to recruit eligible individuals for screening, and using outreach teams at community events. Contact was made by opportunistic contact, invitation phone calls or letters. The service was promoted within communities by radio broadcasts or meetings in churches or marae. Serology was taken for HBSAg. In this evaluation women were more likely to be screened than men (28.9% of women were screened versus 25.1% of men) (Robinson T, 2005).

A community screening study in 5 areas of the UK with large South Asian populations screened 4998 people for HBV and HCV. Screening was performed by a team of health professionals and volunteers who tested eligible participants with oral screening swabs in community centres and Mosques. Public meetings were held at the sites prior to the screening sessions. The proportion of people who accepted testing is not reported in this study. The prevalence of chronic HBV and HCV in those who were born in Pakistan

was 1.8% and 2.7% respectively. In 353 second-generation migrants from Pakistan the prevalence of HBV and HCV was 0.3%. An interesting factor noted in this study was that 25% of participants who tested positive did not attend for further evaluation and follow up despite the research team's best efforts. This highlights a potential difficulty of engaging people screened in community settings in treatment in a clinical environment (Uddin, 2010).

A further UK study in London assessed a one-stop blood spot test for HIV, latent Tuberculosis (TB), HBV and HCV when new migrants attended a health check after registering with a General Practitioner for the first time. Of 1235 newly registered patients, 453 attended a new patient health check, and 47 were identified as new migrants. Of these 36 (77%) accepted screening and no cases of hepatitis B or C were found. Compliance with screening was high, but the number of eligible patients was low (Hargreaves S, 2014).

A study in the Netherlands targeted first generation migrants of Turkish origin. An awareness raising and de-stigmatising campaign was held prior to the screening and local Turkish community and religious organisations were involved. Fifteen educational meetings were held in Mosque's and community centres after which participants were offered a blood test. 430 of the 450 attendees accepted testing for viral hepatitis (96%). Participation was highest in first generation migrants, women and the elderly. Of those screened 16/544 (2.9%) were HBsAg positive and 6 were engaged in Hepatology clinic follow up. 9 patients had not yet been referred by their GP, all of whom had normal ALT levels. They found high satisfaction levels with the culturally sensitive approach taken among the Turkish population tested (Richter C, 2010). The

effect of a culturally tailored internet intervention on screening uptake has been assessed and although some favourable effects were seen, an increase in screening uptake was not seen (van der Veen YJ, 2014). In Rotterdam Chinese migrants were screened for HBV with an awareness and testing campaign. Community-based organisations were involved and outreach testing was offered in Chinese community centres, churches and schools. Out of a potential population of 8000, 1090 people were tested (13.6%) and 8.5% had chronic HBV, of whom 38% potentially needed treatment. Treatment was started in 47% of patients who required it (Veldhuijzen IK, 2012).

In Dundee a similar outreach testing approach was taken, but this was targeted at local Mosque's with the intention of screening Pakistani migrants. Here the authors spoke about HCV and HBV in 3 Mosque's and one women's centre after Friday prayers, and then set up testing clinics a couple of months later after Friday prayers. 177 out of an estimated 250 people (71%) who attended the meetings, 10.3% of the eligible population of 1723 Pakistani people in Dundee were screened. Seven patients were HCV Ab positive and one was HBsAg positive. Five of the HCV Ab patients were HCV RNA positive and all have been evaluated and started on treatment (Jafferbhoy H, 2012).

In New York a programme designed to reduce the burden of HBV in migrants offered educational outreach with advertisements in Chinese and Korean publications, outreach screening in community centres, and vaccination and treatment programmes were integrated into the programme. Nearly 9000 people were screened, and 84% were Asian Americans who were born abroad. 83% of those who were screened

overall attended follow up appointments, and 12% of newly screened participants had a positive HBsAg result, 95% of whom returned for care (Pollack H, 2011).

A further US study evaluated 3 different models of community based screening for HBV, a community clinic model integrating screening into routine primary care services, a community outreach model screening in community, non-clinical settings, mainly Asian health fairs and community centres, and a partnership contract model using for-profit health screening companies to screen for HBsAg alongside other health interventions/ screenings at Asian orientated employee wellness campaigns, large conventions and trade events. The percentage of the target population screened varied from 6.5% in the community clinic model, to 14% in the COM and 47.1% in the partnership contract model (Rein DB L. S., 2011).

The ultimate measure of success of a screening programme is whether it reduces morbidity and mortality of the disease, and this can only be fully assessed in a large randomised controlled trial (RCT) due to concerns over lead time and length time bias in observational studies (Peckham CS, 1998). Due to their slowly progressive nature any RCT assessing the impact of screening for HBV and HCV on morbidity and mortality will require a lengthy follow up period. None of the studies discussed above are randomised controlled trials, and most are observational studies assessing the feasibility and acceptability of screening, with none evaluating the effect of screening on long term morbidity and mortality. In addition none of the studies has a control arm, so it is unclear what effect the interventions have had over usual care. Overall they indicate that a variety of screening methods appear to be feasible and acceptable to migrant populations, but firm conclusions cannot be made due to the

methodological issues discussed. Screening uptake is often, and incorrectly taken as a surrogate for effectiveness of screening. In these studies a direct comparison of the screening technique with the highest uptake was made in one study, where engaging for-profit health screening companies to include HBsAg testing in general health checks was a more effective technique, with 47.1% of people accepting testing, than primary care based testing (6.5%) but at a higher cost of $4657 per newly identified positive case versus $609 (Rein DB L. S., 2011). Community Mosque based screening appears to have a high uptake and acceptability amongst participants with 71% and 94% of attendees accepting screening in two studies, but in the Dundee study this amounted to only 10% of the target population so further measures will be required to gain adequate screening coverage. Interestingly Mosque based community screening had a higher uptake than community based screening for Asian and Pacific Islanders in the US. A potential reason could be an Islamic religious focus on responsibility for one's health identified in a qualitative analysis of screening determinants by van der Veen et al (van der Veen YJJ, 2009). Most of the screening approaches have taken a culturally sensitive approach, including engaging community members in screening programme design and implementation and this approach appears to help with the acceptability of screening programmes. The potential benefit of screening is only likely to be seen if identified cases of HBV and HCV are subsequently treated, with marked variability between studies of those engaging in treatment from 47% in the Netherlands to 100% (5/5) in Dundee, albeit with a much smaller number of patients and the low rate of treatment uptake will need to be addressed by future studies.

Only one study in the US reported on the uptake of screening in primary care, where 6.5% of eligible participants attended screening and in the New Zealand Hepatitis B screening programme where a mixed community and GP approach was taken screening uptake was 27% (Robinson T, 2005) (Rein DB L. S., 2011). Primary care based screening for chronic viral hepatitis in migrants is currently recommended by NICE in the UK (NICE, 2012), but there is a dearth of published data to assess which screening approach will be most effective.

1.1.3.7 Barriers to screening

Ethnic minority populations in general and South Asians in particular have been noted to have a lower uptake of national screening programmes than other groups in the United Kingdom. An analysis of the UK colorectal cancer screening pilot found that the uptake of faecal occult blood testing (FOBt) was 62.2% among the general UK population, but was lower in a South Asian population varying between 31.9% in Muslims and 43.7% in Hindus. Psychosocial surveys and focus groups indicated that South Asians' had less knowledge and were less aware of bowel cancer than other groups and perceived their susceptibility to be lower, with the most important factor affecting FOBt uptake relating to the ease or difficulty of using the kit. Colonoscopy uptakes were also significantly lower among South Asians than non-Asians (54.9% versus 74.4%). A review of the literature on screening in ethnic minority populations identified low levels of knowledge of CRC, low levels of risk perception, poor knowledge and understanding of tests, language fluency, poor communication and the need for active doctor encouragement as factors affecting the uptake of screening (Szczepura A, 2003).

Further UK studies examining screening uptake in South Asians have looked at cervical and breast cancer screening uptake rates and found that South Asian women are significantly less likely than non-Asian women to attend for screening (67% of South Asians v 75% of non-south Asians had attended cervical screening and 53% of South Asians v 78% of non-Asians had attended breast cancer screening) (Sutton GC, 2001).

A qualitative study assessing new migrants to the United Kingdom's perceived barriers to screening for TB, HIV, HCV and HBV, innovative approaches to screening and

acceptability of screening found that they do not see current screening methods as being easily available to them. Barriers to screening included a perception of services as not being migrant friendly, language barriers and disease associated stigma within migrants' communities (particularly relating to HIV, with little stigma attached to viral hepatitis). Screening was acceptable to migrants, but they felt community based services and increased awareness raising of the benefits of screening were required, and suggested a generic "health check" visit incorporating screening which would reduce the stigma associated with infectious diseases screening (Seedat F, 2014).

A Dutch focus group study examining socio-cultural determinants to screening for HBV amongst Turkish migrants to the Netherlands identified a perception of low efficacy of Health Services, a perceived low control of participants over their own health and a potential damage to participants reputation due to associations of hepatitis B with sexually transmitted diseases, particularly HIV (although participants did not see HBV as a sexually transmitted disease or as particularly stigmatised) as barriers to screening. Blood testing was not seen as a barrier to screening. Motivating factors included the obligation to attend associated with an invitation for screening, a sense of religious responsibility for participants own health, and social support associated with screening (van der Veen YJJ, 2009).

An Australian study assessing barriers faced by migrants in accessing health care for viral hepatitis highlighted language (both lack of fluency in English and difficulty understanding medical terminology), fear of discrimination and stigma and lack of knowledge of treatment options as the main barriers The participants recommended

greater education and awareness as a strategy to improve access to healthcare (Guirgis M, 2012).

A number of studies in the United States have examined barriers faced by Asian and Pacific Islanders to screening for hepatitis B infection. Key barriers identified were a lack of knowledge about HBV, with less than half of respondents to one survey having heard of HBV. There was a lack of awareness about the availability of a screening test, or vaccination for HBV, the potential consequences of HBV and how it is spread, and the fact that HCC could be prevented or cured. Language barriers, cultural beliefs (such as believing that blood is a vital and non-renewable energy for the body), social stigma and concerns about healthcare costs were also determined to be obstacles to screening uptake. Health care provider recommendation was shown to have a significant impact on screening uptake (Hu K-Q, 2011) (Ma GX S. S., 2008) (Ma GX S. S., 2007). Those who had been screened felt at higher risk of HBV, and were more likely to perceive that HBV infection led to liver cancer and death than those who had not (Ma GX F. C., 2007).

In the United States healthcare provider barriers to screening are a lack of knowledge about the increased risk of HBV in Asian Americans and the correct screening test for HBV, and a lack of health insurance among Asian Americans (Hu K-Q, 2011) (Ma GX S. S., 2008). Health care provider knowledge of AASLD screening guidelines and HBV vaccination recommendations is associated with higher screening rates, while patient characteristics such as socioeconomic status had no impact emphasising the importance of physician knowledge on screening practice (Khalili M, 2011).

Common themes within these studies are the importance of language barriers, stigma and lack of knowledge of diseases and their diagnosis and treatment as barriers to screening in migrants. Health care providers appear to be able to improve screening uptake by recommending screening to at risk groups. An effective screening programme will need to address these issues if it wishes to engage its intended participants.

1.1.4 Increasing Treatment rates of HCV in people who inject drugs

People who inject drugs are the group most affected by chronic HCV in the United Kingdom, but only a small proportion are currently treated for HCV. This section will review the published evidence on the epidemiology of HCV infection in people who inject drugs, the safety and effectiveness of treatment and the reasons behind the low treatment rates of Hepatitis C virus in this group.

1.1.4.1 Epidemiology of HCV in PWID in the UK:

Injection drug use is a very efficient method of transmitting HCV, and since the identification of the HCV virus and the introduction of screening of donated blood/ serum for HCV in the early 1990's has been the principal method of transmission of HCV infection in England and Wales. An estimated 85% (120,700 of 142,000) of chronic HCV cases in the UK occur in current or former injection drug users (DeAngelis, 2008). The incidence of antibodies to HCV among injection drug users was estimated at 14 per 100 person years in a recent systematic review (Wiessing L, 2014). In 2011 there were 12,642 new diagnoses of HCV in the UK and 90% of these were as a result of injection drug use (Health Protection Agency, 2012). The incidence of HCV in PWID in some areas of the United Kingdom appears to be reducing, with a reduction in incidence in Scotland between 2008 and 2012 from 13.6/100 (95% CI 8.1-20.1) person years to 7.3/100 (95% CI 3-12.9) person years. The reduction has coincided with a high coverage of sterile needle/ syringe exchanges in combination with opiate substitution treatment (Palmateer NE, 2014).

Due to the large reservoir of untreated HCV infection amongst PWIDs and the efficiency of transmission with high-risk injection drug use practices transmission rates in this group are high. High-risk practices include the use of contaminated injecting equipment including needles, cookers, cotton filters, water and back loading (sharing drugs by injecting the contents of one syringe into another syringe). The high transmission rate is associated with injection of crack cocaine, an age of less than 27 years, injecting with users who are at least 5 years older and daily or more frequent injecting (Edlin BR, 2006) (Hagan H, 2001) (Garfein RS, 1998) (Judd A, 2005) (Hahn JA, 2002) (White B, 2014).

Rates of infection with HCV among people who inject drugs are highest during the first year after initiation of injection drug use, with up to 4 times as many new people who inject drugs being infected with HCV than more experienced users (Sutton AJ, 2006) (Sweeting MJ H. V., 2009). This may be related to higher risk behaviour in new people who inject drugs with higher rates of risky practices (such as sharing needles and filters) and higher rates of crack cocaine injection (Judd A, 2005). While the incidence of HCV in PWID overall appears to be decreasing the level of HCV transmission amongst people who have recently started injecting drugs has remained stable at 20% between 2001 and 2011 (Health Protection Agency, 2012).

Within the United Kingdom around 1% of the population, with regional variations, either currently inject, or have previously injected drugs. The estimated prevalence of opiate and/or crack use per 1000 population aged 15-64 varies from 6.44 (95% CI 5.53 to 7.47) in the East of England to 11.08 (95% CI 10.17 – 11.69) in the North West, with the prevalence in London being 9.45 (95% CI 9.08 to 9.94) (Hay G, 2010). The

prevalence of PWID's with HCV is markedly higher in London and the North West (70%) than in all other regions in the UK which have a prevalence of around 30-40% (Sweeting MJ H. V., 2009). In Scotland 57% of PWID have antibodies to HCV, whereas overall in England, Wales and Northern Ireland 47% are HCV antibody positive. These regional variations will lead to different requirements for HCV treatment services for PWID in different regions in the United Kingdom.

To prevent infection with HCV in PWID the combination approach of treatment of drug users with opiate substitution therapy (OST), reducing or eliminating drug injection, behaviour change counselling and the adoption of safe injection practices by the provision of sterile drug injection equipment and syringes has the potential to reduce infection by around 75% (Hagan H P. E., 2011). Another important prevention aspect is the diagnosis and treatment of PWID who are already infected with HCV to reduce onward transmission amongst this group ("treatment as prevention") with modelling showing a 31% reduction in prevalence of HCV over 10 years if treatment rates of 10 in 1000 PWID are achieved with a 20% prevalence of HCV (Martin NK, 2011) (Edlin, 2004). The combination of high rates of opiate substitution therapy (OST) with high-coverage needle and syringe programmes (HCNSP) and antiviral treatment has the greatest projected impact on reduction in HCV prevalence. If OST and HCNSP coverage is 40% then annual treatment of 10, 23 or 42 per 1000 PWID over 10 years would reduce HCV prevalence by half for a 20%, 40% or 60% baseline HCV prevalence respectively (Martin NK H. M., 2013).

1.1.4.2 Treatment of PWID with HCV:

When this research was planned and conducted only a small proportion of people who inject drugs with HCV had received treatment, with treatment rates in Australia of 2-3%, in Canada of 3.4% and in Scotland of less than 10% (Hutchinson SJ, 2005) (Grebely J, 2006) (Matthews G, 2005). Even in specialist services catering to their needs the number of PWID receiving antiviral therapy was low with 13% (58/441) having been treated by a London specialist nursing team based in addiction services (Wilkinson M, 2008). More recently slightly higher treatment rates have been reported, but rates are still low. In an evaluation of HCV treatment in PWID at 7 UK sites treatment rates varied from less than 5 to over 25 per 1000 PWID (Martin NK F. G., 2014). A 2014 systematic review of Hepatitis C treatment uptake amongst current and former PWID in Europe showed wide variations in treatment rates from 0% in a Spanish study to 55% in France (16/29) with a higher median treatment rate than previously of 32%. Significant deficits in the data on HCV treatment rates in PWID were noted, with data only available from 12 countries (Lazarus JV, 2014). A lower treatment rate of 1-19%, with a median of 9.5% across Europe was calculated in a further recent systematic review (Wiessing L, 2014). The marked difference in median rates of treatment is explained by the different methodological approach taken in each review, with Wiessing et al analysing observational studies set in non-clinical settings and Lazarus et al including all publications including those written in languages other than English. A meta-analysis is needed to examine the biases in the available literature and improve estimation of treatment rates for HCV in PWID across Europe.

The value of treating hepatitis C in PWID has been debated at length (Davis GL, 2001) (Edlin BR, 2006). The potential benefits of therapy include a population benefit in reduction in the rate of transmission leading to a reduction in prevalence as well as the health benefits to infected individuals that potentially accrue from viral eradication (Martin NK, 2011) (van der Meer A, 2012). Knowledge of HCV infection is associated with a reduced health-related quality of life in people who inject drugs, indicating treatment and cure may in addition offer a broader improvement in quality of life (McDonald SA H. S., 2013).

1.1.4.2.1 Barriers to accessing HCV treatment for PWID:

The low treatment rates suggest that significant barriers to HCV treatment in PWID exist and research into this question has indicated that system, health care professional and patient related barriers to treatment are present.

1.1.4.2.1.1 System barriers to treatment of HCV in PWID:

A number of system barriers and facilitators of HCV treatment in PWID have been identified from a government policy level to healthcare provider settings. Research has indicated that certain treatment settings can facilitate a higher treatment uptake such as providing opioid replacement treatment, multidisciplinary care and peer support in conjunction with HCV treatment (Mravcik V, 2013). Stigma relating to injection drug use has been shown to affect HCV treatment for people who inject drugs on a macro level, with government ambivalence to people who inject drugs impacting on funding for HCV treatment and care. Housing, geographic access to treatment, criminalisation, gender and compartmentalised health care systems are additional systemic factors

which affect PWID decision to access treatment. Systemic social factors including stigma and discrimination within the health care setting, can also be a barrier to HCV testing and treatment uptake and future healthcare access for PWID (Harris M, 2013).

1.1.4.2.1.2 Healthcare barriers to access to treatment:

Factors that have led to a reluctance amongst clinicians to treat PWID with HCV include concerns about reduced compliance with therapy related to illicit drug and alcohol use and psychiatric co-morbidities, the high morbidity and mortality related to illicit drug intake, treatment with pegylated interferon-α in a group with high rates of psychiatric co-morbidity, and the risk of re-infection with HCV in those with ongoing injection drug use. There are also concerns that injection drug use reduces cellular immunity which may negatively impact on PWIDs response to pegylated interferon (Davis GL, 2001) (Mravcik V, 2013) (Morrill JA, 2005). As a result of these concerns only 20% of respondents to a survey of Canadian physicians indicated that they would be likely to provide HCV treatment to people who inject drugs who use needle exchanges regularly (Myles A, 2011).

Sustained viral response and compliance rates in injection drug users undergoing antiviral therapy for HCV, have been examined in two meta-analyses. A meta-analysis of studies examining SVR rates in people who were actively injecting drugs found a pooled SVR rate of 56% (all genotypes), with an SVR of 37% in genotypes 1 and 4, and 67% in genotypes 2 and 3. Adherence according to the 80/80/80 rule was 82%, and treatment discontinuation was 22% (Aspinall EJ, 2013). Another recent meta-analysis gave very similar results with a completion of treatment rate of 83.4% and a pooled SVR rate of 55.5% (95% CI, 50.6%-60.3%). HCV genotype 1 and 4 infection and co-

infection with HIV were associated with a lower SVR rate, and involvement of a multi-disciplinary team in treatment positively correlated with SVR. Completion of treatment was positively correlated with treatment of addiction during HCV therapy (Dimova RB, 2013). The SVR and completion of treatment rates seen in these meta-analyses in PWID compare favourably with the original phase 3 studies of pegylated interferon-α and ribavirin where discontinuation rates were 14-22%, and pooled SVR rates were 54% and 56% (Fried MW, 2002) (Manns MP, 2001).

There is a high morbidity and mortality related to illicit drug use with mortality amongst IDU's being approximately 3-14 times higher than that in the general population. Most of the increased mortality risk is related to illicit drug use, with approximately 70% of deaths in people who inject drugs in the UK being related to fatal poisoning (Davis GL, 2001) (Griffiths C, 2008) (Nambiar D, 2015). However liver and all-cause mortality are increased in PWID with HCV at 15.8 and 5.9 respectively, with an increase in liver related deaths as the population of PWID ages (Walter SR, 2011) (Deans GD, 2013). A large linkage study in New South Wales, Australia reporting mortality trends in 82034 HCV infected people between 1992 and 2006 found the leading cause of mortality to be drug-related deaths, but these declined markedly between 1999 and 2002, with liver-related mortality becoming the main cause of death after 2002 (Walter SR, 2011). A prospective cohort study in Canada examining mortality in 2279 PWID found no increase in liver-related mortality associated with HCV infection with liver related deaths accounting for 6% of mortality, HIV-related deaths accounting for 24.7%, and overdose 23.7%. Rates of HIV in the studied population were over 15% which makes this study less relevant to the UK population

of PWID where low rates of HIV co-infection are seen. The median age of participants was relatively young at 37, with a median follow up of 60.9 months and an average estimated time since infection of 19 years which could explain the low liver related mortality reported in this study as HCV cirrhosis, the cause of liver related mortality takes 20-30 years to develop (Hayashi K, 2014).

Psychiatric co-morbidity including depression, alcohol dependence and personality disorders is more common amongst PWIDs than in the general population and treatment with pegylated interferon-α causes psychiatric side effects in at least 22% of those treated leading to concerns over its use in PWID (Dinwiddie SH, 1992) (Fried MW, 2002). In a study assessing the effect of interferon alpha in high risk patients, 16 patients with previous psychiatric disorders, 21 patients on ORT and 21 patients with previous drug addiction were compared with a control group of 23 patients with no history of psychiatric disorder. Significantly more patients in the psychiatric group received anti-depressants before or during treatment, but there was no significant difference between groups when it came to the development of interferon alpha related depression during treatment. In the whole cohort 2 patients (3%) left the study due to psychiatric side effects although 16% of patients developed new depression. Patients were seen bi-weekly for the first 8 weeks by a psychiatrist and then monthly and screened at each meeting for changes in their mental status, and it may be this intensive support that leads to these good outcomes, albeit in a small number of patients (Schaefer M, 2003). In the United Kingdom there was no significant difference in compliance between those taking anti-depressants and those not taking anti-depressants (Wilkinson M, 2008). A further study showed no difference in

antidepressant use before or during treatment between a group of patients maintained on ORT and a control group who had had no intravenous drug use or opioid for at least 5 years (Mauss S, 2004). In a study of 40 current and former injection drug users with high self-reported rates of depression (58%) prior antidepressant use did not affect successful treatment outcome (Grebely J R. J., 2007). A German study in a secondary care setting examining adherence to treatment in psychiatric risk groups including former drug addicts (n=21), those on methadone substitution programmes (n=21) and those with psychiatric disorders (n=16) comparing them with controls showed no significant difference in SVR rates between the psychiatric risk and control groups (SVR was 37% overall with interferon alfa and ribavirin treatment). 43% of those with former drug addiction stopped treatment early compared with 14% in the methadone group, 13% in the control group and 18% in the psychiatric group (p=0.04) (Schaefer M, 2003).

It should be noted that all of these studies excluded patients with recent inpatient admissions due to psychiatric illness, or uncontrolled psychosis in keeping with the licensed use of pegylated interferon. There are undoubtedly high rates of depression and high requirements for antidepressant treatment in people who inject drugs undergoing therapy with pegylated interferon-α, which cause considerable morbidity for treated patients but in these small studies this did not appear to affect treatment outcomes or completion rates providing close psychiatric support is provided. Further high quality, larger scale studies are required to confirm the safety profile of pegylated interferon-α in PWID until the wide scale adoption of treatment with interferon free regimens.

Studies evaluating re-infection in PWID after successful treatment of Hepatitis C have on the whole been small, and of relatively short follow up duration, with most studies reporting low reinfection rates. In Amsterdam a reinfection rate of 0.76/ 100 person-years was seen in a study of 42 PWID who achieved SVR with an increased rate in those reporting current injection drug use of 3.42/100 person-years, and in a prison population of 119 PWID in Spain a rate of 5.27 cases per 100 person-years over a mean follow up of 1.4 years was noted (Grady BP V. J., 2012) (Marco A, 2013). A study of 35 PWID reported rates of reinfection of 3.2 per 100 person-years overall and 5.3/ 100 person-years in those reporting ongoing injection drug use, and in Canada and the Netherlands reinfection rates of 1.8 cases per 100 person years (14/152 participants) and of 4.17/100 person-years (7/59 participants) have been recorded (Grebely J K. E., 2010) (Grebely J C. B., 2006) (van der Laar TJW, 2009). Frequent longitudinal sampling performed on 44 young PWIDs, found eight to have intermittently detectable HCV RNA with the cause being reinfection in four participants, viral intercalation in three with one unclassifiable case. The reinfection rate was 5.4 per 100 person-years, with 75% of those who were reinfected spontaneously clearing the virus. Frequent HCV sequencing and phylogenetic analysis was used to determine the cause of recurrent viraemia, and the lack of this technique explains the higher reinfection rate reported in previous studies (Page K, 2013). Higher rates of reinfection have been seen in PWID with a recent Australian study reporting a reinfection rate of 28.8 per 100 person-years (95% CI 15-55.4) in 188 PWID. They confirmed reinfection by HCV genome sequencing, and found multiple recent injecting partners and a shorter duration of injection drug use to be independent predictors of reinfection, with 50% of reinfections spontaneously clearing (Sacks-Davis R, 2013). A further Australian study of 198 PWID saw a

reinfection rate of 46.8/100 person-years (95% CI 31.1 to 70.3) with all reinfections being confirmed with HCV genome sequencing (Aitken CK, 2008). Amongst 48 PWID in a prison setting in Australia high reinfection and super infection rates of 40/100 person years have been reported. These infections were frequently transient, with a rate of viral clearance in multiple infection of 19/100 person-years which appeared to be related to HCV RNA levels, with the strain with the higher initial HCV RNA level always persisting (Pham ST, 2010). A recent review of studies of reinfection with HCV in PWID reports reinfection rates from 0.8 to 4.7 per 100 person-years of follow up, with reinfection rates of 2.5 to 28.57 per 100 person years of follow up in those with ongoing risk behaviour (Grady BP S. J., 2013). A meta-analysis of 5 studies covering 131 participants reports a pooled risk of reinfection of 2.4 per 100 person-years (95% CI, 0.9-6.1), with a risk of reinfection in those with ongoing injection drug use of 6.4 per 100 person-years (95% CI, 2.5-16.7) (Aspinall EJ, 2013). Of note 3 of the 6 studies reporting lower reinfection rates did not use sequencing to confirm reinfection, however the use of sequencing might be expected to give lower reinfection rates, with some assumed reinfections actually being caused by viraemia related to intercalation. The meta-analysis did not include the three Australian studies discussed above which report higher re-infection rates one of which was not published during the meta-analysis time frame, however the remaining two studies were good quality prospective studies using sequencing to confirm reinfection, and so it may have been the meta-analysis inclusion criteria were too narrow to include all relevant studies. In addition only one of the studies included in the meta-analysis used sequencing to confirm re-infection and therefore the results of the meta-analysis should be interpreted with caution. The available data give a broad range of estimates of reinfection risk among

PWID from a number of small studies and at present it is not possible to reach a firm conclusion, although overall reinfection risk appears to be low with the possible exception of Australia. To reach definitive conclusions further larger scale studies with longer follow up periods, short time periods between viral testing and the use of phylogenetic and genome sequencing are required.

The available evidence does not support many of the health-care provider concerns over treatment for HCV in PWID providing treatment is provided in an appropriate setting with the input of addiction and psychiatric services.

In line with the evidence national treatment guidelines on the treatment of Hepatitis C virus in PWID in the UK have changed. In 2001 the British Society of Gastroenterology guidelines for the management of hepatitis C stated that people who were actively injecting drugs should not be treated for hepatitis C infection, and only in selected cases should ex-PWIDs be treated (Booth JCL, 2001). NICE now recommends that people who inject drugs be considered for treatment for HCV on a case by case basis in line with the rest of the population (NICE, 2004) (NICE, 2010).

1.1.4.2.1.3 Patient barriers to treatment:

Barriers to treatment from a patient perspective have been examined in a number of qualitative and questionnaire studies, and will be discussed further in the next section. An Australian interview study of 100 HCV infected people who inject drugs identified the 4 most common reasons for not accepting treatment as concerns about adverse treatment effects (18/30), having other health priorities at the time (15/30), not

feeling unwell enough to have treatment (17/30) and not wanting to have a liver biopsy (13/30). Patients had a reasonable level of knowledge about HCV infection, but large gaps in knowledge about HCV treatment with 47% of the those surveyed believing that current injection drug use was an exclusion criteria for treatment and 58% stating that HCV was not curable. Nearly 80% of participants reported that they would consider treatment for HCV infection, despite the requirement for a liver biopsy prior to treatment at this time. They found that fewer than half of patients had ever discussed treatment for HCV with a health professional and 23% had unsuccessfully tried to access treatment. The most common reason for not being able to access treatment in those who had tried was early disease (n=10), followed by current injection drug use (n=5), long waiting lists (3) or physician's concerns about adherence to treatment or heavy alcohol intake (n=4) (Doab A, 2005).

A questionnaire study in Baltimore showed low levels of knowledge about HCV treatment with only 22% of participants believing that HCV could be cured. A total of 86 of 418 participants reported having had a discussion about treatment, and 30 participants had refused treatment. The main reasons for this were treatment-related perceptions or fear (42%) and a low perceived need for treatment (35%). Twenty patients chose to defer treatment most commonly due to lack of perceived need for treatment (42%) and competing priorities (26%). Only 6% of the patients surveyed had received treatment (n=36) (Mehta SH, 2008).

An Australian study where semi-structured interviews were performed with 24 people who inject drugs and had recently been diagnosed with HCV highlighted issues around poor delivery of the diagnosis of HCV affecting decisions around treatment. One patient describes how they were given the diagnosis of HCV 5 minutes before the

service closed, with no time for counselling leaving him “devastated, you know. The fact that I had a blood borne communicable disease…. And they’re like “But we can’t give you any counselling at the moment… because we’re about to close.””. This patient did not access the services for two years after that although it had previously been his primary needle exchange. The majority of patient in this study reported that they did not receive adequate information and social and psychological support after their diagnosis of HCV. Only 7 of the 24 participants reported having been referred to a Hepatologist, and three were incorrectly told they were not eligible for treatment at that time. This study shows that poor experiences at diagnosis can lead people to disengage from healthcare services. (Treloar C N. J., 2010). An analysis of homeless people’s experience of being diagnosed with HCV also identified concerns with communication of the diagnosis, with a patient who had not sought HCV testing saying “I was just stunned, I thought, you are telling me I’ve got hepatitis C and you just say it like you were saying hello to me and he just walked away” and a number of patients had not been told they were being tested for HCV indicating issues around consent and pre-test counselling. The diagnosis had a negative emotional impact on all participants with reactions including devastation, shock, disbelief, anger and disorientation. In contrast to Treloar et al the participants in this study found that the diagnosis of HCV had led them to have a strong fear of premature or imminent death. Many patients also blamed themselves or others for their infection. Some participants were reluctant to tell family or friends about their diagnosis due to the stigma attached to HCV and were concerned about how it may affect future relationships and their chance of having children, whereas others felt obliged to let others know about their diagnosis. A

number also reported negative treatment from police and health professionals, and felt stigmatised by their diagnosis (Tompkins CNE, 2005).

A cross sectional analysis at an urban community health centre identified only 27% of patients had been treated for HCV and the factors that predicted not being treated were being unmarried, female gender, current alcohol abuse and infrequent attendance at clinic appointments. In 16.1% treatment was not commenced due to patient preference but the majority of factors preventing treatment were clinician related (Morrill JA, 2005).

Perceptions of HCV and the care participants receive for HCV were explored by Swan et al. In this qualitative analysis of 36 people who inject drugs in Dublin at various stages of the diagnosis and treatment cycle certain strong themes emerged. Having HCV infection was normalised “everybody has it” and minimised “I’m not going to die of HCV” in comparison with HIV. Women in particular felt stigmatised “I know they’d (*health care professionals*)… treat ya well and be real nice, but for me anyway, I do be more embarrassed to even say it” particularly because of the route of acquisition “when you’re using drugs its self-inflicted, people aren’t going to have any sympathy for ya and they basically don’t care”. When people were feeling well they did not feel the need to engage with investigations and treatment “I was just thinking like, well I’m grand, I don’t feel sick… So why do I need to go (*to Hepatology clinic*)?”. Participant’s views on the benign nature of HCV were disrupted through information given about the health consequences of HCV, hearing their infection was “active” and through seeing others ill or dying because of HCV. This had lead some of them to access investigations and treatment. Participants reported hearing horror stories about the liver biopsy and the side effects of treatment that discouraged them from engaging

with Hepatology services. However seeing peers successfully going through treatment encouraged some to access treatment, and receiving information from health professionals and peers on investigations and treatment allayed some fears by putting risks into perspective and letting them know what to expect. Support of family and peers, and looking after others helped some through treatment, and some participants coped by using avoidant coping strategies, positive thinking and self-determination. Trust and confidence of participants in health care service providers, the health professionals concern for the participants and continuity of care positively influenced them to engage in treatment. Some patients reported past bad experiences creating distrust in health professionals. They recommended greater communication including explaining the purpose and results of investigations. HCV testing usually occurred when participants entered prison or a drug treatment programme. Convenience and distance from the hospital impacted attendance and uptake of treatment. One participant recommended a “one-stop shop” approach where all HCV services could be accessed.

Motivations for treatment included a deterioration in health, concern about the impact of a reduced length of life on their family and moving on from drug addiction. They felt that HCV was a hang-over from their drug addiction and that cessation of drug use gave them a stable space where they could focus on their health. Barriers against treatment included uncontrolled drug addiction “it just consumes every part of you”, employment which made attending hospital appointments difficult and made concern about side effects of treatment greater, and lack of access to investigations and treatment including not knowing where to access treatment and testing and not being referred for investigations and treatment (Swan D L. J., 2010).

A non-systematic review identified system-related, provider-related and patient-related factors as barriers to treatment. Patient-related factors highlighted the low perceived need for treatment, negative treatment-related perceptions, and concern about side effects of treatment and in some a lack of motivation (Mravcik V, 2013).

A questionnaire study of 132 patients attending opioid substitution clinics in Sydney, Australia found no correlation between knowledge of HCV and its treatment and willingness to have treatment or assessment for treatment. The only factor associated with willingness to have treatment was being on opiate substitution therapy. However the study may have been underpowered to detect a significant difference. There was a high level of engagement with HCV treatment assessment but poor knowledge of factors associated with progression of HCV (Treloar C H. P., 2012).

Harris et al explored the diagnosis of HCV in qualitative interviews with 40 PWID, and found that over half described a “narrative of unconcern”. They describe how reaction to a diagnosis of HCV is contextual, with some participants being devastated, and others less concerned dependant on previous experiences of hardship, illness, stigmatisation and normalisation of HCV. This then impacted on participants lived experience of HCV and wish to have treatment (Harris, 2009).

In contrast to other studies Conrad et al report patients with hepatitis C experiencing episodes of debilitating illness, described as “hep C attacks” by one participant. The participants who described these attacks all thought of Hepatitis C as a fatal disease, and all but one had symptoms of depression. A number of symptoms were also attributed to hepatitis C. Stigma around HCV infection was mentioned by a number of participants, and this was felt to be due to its association with injection drug use and community perceptions of HCV as very infectious, and of having a very poor prognosis.

This led all participants to have concerns around disclosure of their illness. They disclosed to promote trusting relationships and to protect others from inadvertent infection. Diagnosis also caused concern about telling future sexual partners about their infection and led them to abstain from relationships. A prominent theme was concern about transmitting the infection to others, which led to a great deal of anxiety and uncertainty as regards the risk of infecting others. Reassurance from health professionals that the risk of infection was low did not seem to allay the fears of infectivity. Some participants had internalised the feelings of themselves having an infectious disease to such an extent that they felt diseased and dirty. The study found that a crucial factor in how individuals viewed themselves and their infectivity as regards HCV was the sensitivity and appropriateness of HCV information provided around diagnosis by health professionals (Conrad S, 2006).

A qualitative synthesis assessing the social production of hepatitis C risk among PWID (Rhodes T T. C., 2008) identified major themes including relative viral risk, with HCV being less feared than HIV, risk ubiquity, trust and the body and hygiene. They report that HCV is accommodated within social groups and seen as inevitable and recommend that to reduce the risk around HCV in PWID interventions should emphasise the preventability of HCV, and build upon trust and hygiene narratives of PWID with HCV (Rhodes T T. C., 2008).

The social factors around HCV treatment access and uptake amongst PWID have been explored in a recent review. Issues around gender highlight that women may feel more stigmatised by having HCV and injection drug use than men, have lower knowledge levels about HCV, and be less likely to complete treatment or start treatment than

men. Women's decisions around accessing treatment may also be related to caring responsibilities, physical, emotional and sexual violence, the need to fund a regular drug supply and lack of engagement with services. In terms of competing concerns which can take precedence over treatment for HCV they identify homelessness, poverty, stigma and social isolation, lack of trust in police and healthcare providers, attempting to self-manage chronic and acute health care problems, the need to fund illicit drug use, fear of arrest and violence as factors. Therefore HCV treatment is a relative concern that needs to be factored into other competing demands. This review highlights the paucity of data available to assess the social factors determining access to treatment and uptake amongst PWID, and acknowledges there may be factors as yet unidentified due to this (Harris M, 2013).

When exploring the issue of barriers to HCV treatment from the patient's perspective prominent themes emerge relating to patient's poor experience of being diagnosed with HCV infection and lack of knowledge of HCV and its consequences and treatment. In addition people who inject drugs have often had negative experiences of health care systems and providers leading to a reluctance to engage in healthcare. Stigmatisation of Hepatitis C and its association with drug use emerge as a strong theme, which can prevent uptake of treatment. PWID in addition often live with the competing priorities of employment, education and addiction which can act as barriers to treatment (Edlin BR K. T., 2005) (Swan D L. J., 2010) (Treloar C R. T., 2009) (Groessl AK, 2008) (Treloar C H. P., 2012) (Doab A, 2005) (Grebely J G. K., 2008) (Rhodes T H. M., 2013) (Harris M, 2013) (Treloar C N. J., 2010) (Harris, 2009) (Tompkins CNE, 2005) (Mravcik V, 2013) (T Rhodes, 2008).

1.1.4.3 Strategies to improve treatment rates:

A number of successful small scale models of treatment have been developed that show the feasibility of out-reach, multidisciplinary services for treating HCV in PWIDs.

In New York a number of models of treatment are used. In one screening and treatment for HCV are delivered in community clinics where substance abuse treatment is combined with on-site medical, psychiatric and counselling care. Pegylated interferon is delivered as directly observed therapy to enhance compliance. Treated patients have high rates of psychiatric co-morbidity (67%), ongoing drug use (49%) and HIV co-infection, but SVR rates in 73 treated patients are reported as 45% and 86% of patients completed at least 12 weeks of treatment (Litwin AH, 2005) (Litwin AH, 2009). Taylor et al describe their service where HCV and HIV co-infected drug users are treated with antiviral therapy in a secondary care setting. Bi weekly clinics with a physician specialising in HIV/ HCV, and a Hepatologist were held, with co-ordinated psychiatric care, addiction treatment and counselling being provided by a community-based mental health agency. They did not exclude patients based on addiction status, but tried to stabilise patient's addiction prior to initiation of antiviral therapy. Of 146 patients referred to the clinic 92 had been seen at least once, and 17 had been treated for HCV, with 17 in an intensive pre-treatment phase. Adherence to treatment was 99%, and no patients had to stop antiviral therapy because of on-going drug use, or psychiatric complications (Taylor, 2005). A slightly different model of treatment in New York involved integrating an addiction specialist in the Hepatitis clinic, to provide continuity of care between addiction and HCV treatment. The viral

hepatitis clinic and methadone maintenance programme clinics were situated within a block of each other, and psychiatric services were available daily. Overall 61% (76/125) of referred patients attended the hepatitis clinic for evaluation, and 24 (32%) initiated treatment (Martinez AD, 2012). Peer support workers have been integrated into services in North America and Australia for PWID undergoing assessment and treatment of HCV and have shown a benefit to the individuals and organisations involved (Crawford S, 2013).

Recently the ETHOS study in Australia has reported treatment rates of 22% of HCV in PWID treated in clinics where HCV treatment was provided alongside addiction services. Treatment was significantly associated with the presence of social support and not having received opiate substitution therapy (Alavi M, 2013). Grebely et al have shown attendance at a weekly HCV support group predicts successful HCV assessment with high rates of referral for assessment (53%) and treatment (28%) amongst attendees (Grebely J K. E., 2010).

In Europe a group in Italy have reported successful treatment of PWIDs who are maintained on methadone or buprenorphine maintenance therapy, within a multidisciplinary model which provided close cooperation between drug addiction specialists and psychiatrists (Belfiori B, 2009). A further multi-disciplinary model in Italy with collaboration between clinical infectious diseases centres and drug dependency units involving addiction specialists, psychiatrists and infectious disease specialists led to good outcomes with an overall SVR of 58.5% in the 53 patients treated (Guadagnino V, 2007). In Germany integrating treatment for HCV with a drug treatment programme with support from specialist physicians, nurses and access to counselling services and a

24 hour help line led to SVR rates of 98% (48/49 treated patients) (Waizmann M, 2010).

In Nottingham, England a primary care based model where a clinical nurse specialist evaluated and treated patients in primary care based opiate substitution clinics proved feasible, safe and efficacious with 30 out of 118 patients initiating therapy with a 62% SVR rate and attendance rates of over 85% in contrast to attendance rates at the hospital clinic of less than 40% over the same time period (Jack K, 2009). In London a "Blood Borne Virus" specialist nursing team treat PWID in outreach specialist addiction service clinics where OST, other medical and psychiatric services are provided. Treatment rates are 13% at this service with a 51% SVR rate and 80% compliance with treatment (Wilkinson M, 2008). The introduction of dried blood spot testing in Scotland increased diagnosis and treatment of PWID with HCV in Scotland with 18% of those tested for HCV with dried blood spot testing having entered treatment within 18 months of their diagnosis (McAllister G, 2014).

A meta-analysis of treatment for HCV in PWID that analysed 36 studies showed that treatment for addiction and the availability of support services during HCV therapy positively correlated with improved treatment completion rates and the involvement of a multi-disciplinary team showed a strong positive correlation with SVR rates (Aspinall EJ, 2013).

These models all report successful treatment of relatively small numbers of PWID with HCV in individualised treatment services which attempt to cater to the complex social, medical and psychiatric needs of their local population of PWID. What all of these models have in common is the ready availability of substance misuse, medical and

psychiatric services in co-located, usually community based clinics. In addition two studies highlight the importance of peer-support groups in improving treatment rates.

These clinics were designed to improve treatment rates for HCV in PWID, and many have done so, but despite this treatment rates are still low and further strategies will be needed to improve uptake of treatment in PWID if HCV is to be eradicated.

1.2 Summary:

Chronic viral hepatitis B and C cause serious liver related morbidity and mortality (Fattovich G B. F., 2008) (Seeff LB, 2002) (Massard J, 2006) (Ascione A, 2007) and in the United Kingdom disproportionately affect migrants from areas of high prevalence and people who inject drugs (Sweeting MJ H. V., 2009) (HPA, 2006)(Aweis D, 2001).

Chronic viral hepatitis is usually asymptomatic and thus ascertainment rates are low, and it appears to present later and with a more severe disease course in migrants (Ascione A, 2007) (ELPA 2010) (Guirgis M, 2012) (AG Mann, 2008). Screening of migrants at higher risk of HBV and HCV is recommended in the United Kingdom (NICE, 2012), and appears to be economically viable (Veldhuijzen, 2010). However there is currently no evidence available to assess which method of screening will result in the highest uptake of testing for chronic viral hepatitis in migrants in primary care.

Up to 85% of prevalent HCV infections in the United Kingdom occur in PWID, but treatment rates in this group in the United Kingdom are low at between 8 and 18% (Matthews G, 2005) (Wilkinson M, 2008) (McAllister G, 2014). Antiviral therapy for HCV in PWID has been shown to be safe and effective in a small number of studies, but due to the low number of studies and the lack of high quality trials further research has been recommended (Aspinall EJ, 2013). Attempts have been made to increase treatment rates in PWID in the United Kingdom, principally through co-location of HCV treatment with addiction and psychiatric services, but treatment rates are still low and it is not known how these can be improved (Jack K, 2009)(Wilkinson M, 2008). Considerable barriers to antiviral therapy for HCV in PWID exist and it is recognised

that some remain unidentified and further qualitative research in this area has been recommended (Harris M, 2013). This MDRes will aim to help answer these outstanding queries by the completion of five studies; assessment of whether a Mosque based awareness raising campaign is effective at prompting at risk Mosque attendees to be tested for chronic viral hepatitis in primary care; a prospective pilot observational cohort study assessing which method of screening for chronic viral hepatitis in high risk groups in primary care results in the greatest uptake of testing; A retrospective cohort study analysing the outcomes of antiviral therapy for HCV in a large cohort of PWID; a prospective cluster randomised controlled trial exploring nurse initiation of antiviral therapy to assess if this improves treatment uptake in PWID and a qualitative analysis of semi structured interviews with PWID exploring the reasons underlying engagement with therapy.

1.3 Aim of thesis:

To explore methods to address the low ascertainment and treatment rates of chronic HBV and chronic HCV in “hard to reach” populations in England.

This will be addressed as follows:

1. To assess the effectiveness of a Mosque based awareness raising campaign in encouraging Mosque attendees who are at risk for infection with hepatitis B and C to visit their General Practitioners for testing for chronic viral hepatitis, and attend Specialist follow up if they are diagnosed with hepatitis B or C.

2. To explore which of two methods (an opportunistic or direct approach) results in the highest uptake of testing for chronic viral hepatitis in high risk migrant populations in primary care, and to identify obstacles to screening by each method in primary care.

3. To evaluate the long term health and social benefits of antiviral therapy for hepatitis C in people who inject drugs delivered by a Blood Borne virus nursing team in addiction service outreach clinics.

4. To examine if hepatitis C and health related outcomes differ between PWID who were actively injecting drugs at the start of anti-viral therapy, and those who had stopped injecting drugs prior to the start of treatment.

5. To discover if nurse initiated treatment of people who inject drugs with HCV in specialist addiction services community based clinics increases initiation and completion rates of antiviral therapy when compared with doctor initiated therapy.

6. To investigate the reasons behind low rates of antiviral therapy for hepatitis C virus amongst PWID by exploring their experiences and attitudes towards the diagnosis of hepatitis C virus, their experience of living with hepatitis C virus and of treatment of hepatitis C virus.

1.3.1 Hypotheses:

These aims are based on the following hypotheses:

1. A Mosque based awareness raising campaign will lead to “at risk” Mosque attendees being tested for chronic viral hepatitis at their General Practitioners, and attending Specialist follow up if they are diagnosed with hepatitis B or C.
2. A higher uptake of testing for hepatitis B and C in migrants from high prevalence countries in primary care will be obtained when a direct testing rather than opportunistic testing strategy is used.
3. People who inject drugs with hepatitis C virus who are treated with antiviral therapy in Specialist Addiction Services can be treated safely, will be compliant with treatment, achieve similar SVR rates to people who do not inject drugs, reduce alcohol and illicit drug use after treatment and are unlikely to be re-infected.
4. The treatment outcomes of antiviral therapy for HCV in people who are actively injecting drugs at the start of treatment will not differ from those who have ceased injecting drugs at the start of treatment.
5. Nurse initiated and led antiviral therapy for HCV in outreach clinics will result in more people who inject drugs initiating and completing HCV treatment than doctor initiated therapy.

And the following qualitative research question:

1. What are the experiences and attitudes of people who inject drugs towards the diagnosis of hepatitis C virus, the experience of living with hepatitis C virus and the treatment of hepatitis C virus?

2 Methods

Five studies were undertaken as part of this thesis and a brief overview of the methodology of each study, my contribution to the work and the ethical approval process for each will be outlined in this section. The methodology for each study will be explained in detail in each study chapter.

2.1 Mosque Awareness Study:

2.1.1 Methods summary:

An awareness raising campaign was held in Mosques in the London Borough of Newham to assess the effectiveness of Mosque based awareness campaigns in encouraging “at risk” Mosque attendees to visit their General Practitioners (GPs) to be tested for HBV and HCV. Imams preached about Hepatitis B and C and the risk factors associated with chronic viral hepatitis at Friday prayers, and leaflets were distributed by volunteers to Mosque attendees with integrated testing forms for Hepatitis B and C. Mosque attendees were asked to take the leaflets with integrated virology forms to their local GPs to be tested for HBV and HCV, if they identified themselves to be at risk after the awareness raising campaign.

2.1.2 Ethics and Research and Development

The Mosque campaign was an awareness raising campaign and therefore informed consent and ethical approval were not required.

2.1.3 My role and contribution:

I designed the awareness raising campaign in conjunction with Shabana Begum of the Hepatitis C Trust and Professor Graham Foster. I implemented the campaign, designed the leaflets and integrated virology forms, wrote and distributed the letters to local GP's informing them of the awareness raising campaign and along with other volunteers attended the Mosque's to distribute leaflets and answer questions on the day of the awareness raising campaign. In setting up the awareness raising campaign I liaised with the virology department at the Royal London Hospital to ensure the virology forms were correct and would be identified at the laboratory when received and liaised with the Hepatitis C Trust to ensure the appropriateness of the leaflets for the intended audience and as to which Mosques the campaign should be performed in. Shabana Begum was the main contact with the Mosque committees, and liaised with them to gain access for us to perform the campaign. I planned the data collection and analysis, and wrote the thesis chapters associated with this study.

2.2 Screening for chronic viral hepatitis in migrants:

2.2.1 Methods summary:

This was a prospective observational pilot study examining which of two methods (an opportunistic or direct testing approach) resulted in the highest uptake of testing for chronic viral hepatitis in high risk migrant populations in primary care.

In the opportunistic testing arm patients who were eligible for screening were offered testing for HBV and HCV by their General Practitioner when attending the practice for appointments for any other reason. This approach is current NICE recommended practice, but rarely occurs in routine clinical practice. In the direct testing (intervention) arm patients were contacted by telephone by the research fellow and invited to attend for testing for HBV and HCV. Those who agreed to be tested were invited to attend designated screening clinics at their GP surgery, where testing for HBsAg and HCV ab was performed.

2.2.2 Ethics and Research and Development

For this study the research protocol, patient letters, patient information sheets, patient results forms, GP letters and consent forms were drafted (these can be seen in appendices 5 to 9). These were submitted to Barts and the London NHS Trust Joint Research and Development Office with the Integrated Research Application System (IRAS) form and the Research Ethics Committee (REC) form. These gained Sponsorship approval from the Joint Research and Development Office on 25th August 2009 and then ethical approval was sought from East London and the City Research Ethics

Committee alpha. REC approval was gained on 4/12/2009 (REC reference number: 09/H0704/65). Research sponsorship was subsequently gained from Barts and the London R&D department on the 9th December 2009. Each practice then individually approved the project.

2.2.3 My role and contribution:

I designed the study in conjunction with my research supervisor Professor Graham Foster. I wrote the research protocol, and drafted and revised the patient information sheets, consent forms, results letters and GP letters. Professor Graham Foster wrote and submitted the REC and IRAS forms. I applied for ethical approval for the "postal testing" amendment. I wrote to all GP practices in the London Borough of Newham asking if they wished to participate and liaised with those who responded. I attended GP practices who were interested in participating in the study to explain the study and recruit the practices. For those practices who agreed to participate in the study I provided training sessions on chronic viral hepatitis in migrants from high prevalence areas, and the study. At each practice in the direct testing arm I searched the EMIS database to identify eligible patients, sent letters to all eligible patients and liaised with practice managers to organize the viral hepatitis testing clinics. Myself and Dr Katharine Burke, telephoned all eligible patients at each practice who had not opted out of the study to invite them to attend for testing, and undertook all the Viral Hepatitis screening clinics. I performed approximately 75% of the telephone calls and clinics, and Dr Burke performed approximately 25% of these. I collected and analysed the data from each practice, performed the literature search for the introduction to this thesis regarding screening for viral hepatitis in migrants from high prevalence

areas and wrote the introduction and thesis chapters pertaining to this study in their entirety.

2.3 Analysis of the outcomes of HCV therapy in PWID:

2.3.1 Methods summary:

This was a retrospective observational cohort study examining the health and social outcomes of antiviral therapy for HCV administered by Blood Borne Virus nurses in Specialist Addiction Services community outreach clinics in North East London. Data was retrospectively gathered from the EMIS records of all patients who had been treated for Hepatitis C virus by the Blood Borne Virus nursing team in Specialist Addiction Services and analysed to assess health and social outcomes.

2.3.2 Ethics and Research and Development:

Ethical approval for this study was obtained in conjunction with the Research Ethics Application for the Nurse Initiation of antiviral therapy for HCV in people who inject drugs study and a detailed description of the research development and ethical approval process is provided in the following methods section (see section 2.4.2). Ethical approval for the study was granted by the National Research Ethics Service (NRES) Committee London – City Road and Hampstead on 9th June 2011 (Reference: 11/LO/0347) The trial has been registered with the ISRCTN (Reference: CCT-NAPN-22105).

2.3.3 My role and contribution:

I designed the study, formulated the research questions, aims and hypotheses, completed the REC and IRAS forms and gained ethical approval for the study. The

source data was entered by the Blood Borne Virus Nursing Team prospectively into EMIS electronic records as patients underwent treatment. I designed the data collection spreadsheet and retrospectively interrogated the Blood Borne Virus Team EMIS records to collect the data and collated it in the study database. I received support in data collection from four medical students, Richard Igbe, Jasdip Hothi, Nader Ibrahim and Maisum Mirza but performed the majority of the data collection myself. I analysed all of the data, and received statistical support with the regression analyses from a statistician, Jessica Talbot. I performed the literature search for the introduction to this thesis and wrote the introduction and thesis chapters pertaining to this study in their entirety.

2.4 Nurse initiation of antiviral therapy for HCV in people who inject drugs:

2.4.1 Methods summary:

This was a prospective cluster randomised trial of nurse initiated versus doctor initiated antiviral therapy for Hepatitis C virus in Specialist Addiction Service outreach clinics in North East London. The trial compared current care in this service, whereby treatment for PWID with HCV is initiated by a doctor after patient review at a central clinic and then delivered by Blood Borne Virus nurses in specialist addiction service outreach community clinics with the intervention of nurse initiated treatment. Nurse initiated treatment consisted of patients who fulfilled pre-described safety criteria having antiviral therapy for HCV initiated by their nurse in their outreach clinic, without the requirement for doctor review. Aside from the initiation, treatment was the same in each study arm, and consisted of nurse led antiviral therapy delivered in community Specialist Addiction Service Clinics (the current standard care in this service).

2.4.2 Ethics and Research and Development:

The development phase of this study, the analysis of the outcomes of HCV therapy in PWID and qualitative assessment of the reasons underlying engagement in HCV treatment in PWID studies began in February 2010 and final ethical approval was received on 9th June 2011. The prolonged development phase occurred due to the complexity inherent in gaining local research office and ethical approval for the

multiple organisations involved in the research. This phase was carried out in close conjunction with the Barts and the London NHS Trust Joint Research Office.

Early in 2010 the research proposals were written and study protocols were drafted. The Blood Borne Virus nurses and charity partners were consulted on the research proposal and protocol, and when their approval was obtained drafting of the Integrated Research Application Form (IRAS) and Research Ethics Committee (REC) form began.

A total of nine different organisations were involved in the studies including three NHS organisations; Barts and the London NHS Trust, East London NHS Foundation Trust, Health E1 NHS GP practice for the Homeless; four charities, the Drugs and Alcohol Service for London (DASL), In-Volve, ISIS and Lifeline; one Local Authority/ Metropolitan Police Service organisation, the Drugs Intervention Project and Queen Mary University of London. Between April 2010 and August 2010 the management of each outreach clinic were contacted to ask for their permission for the study to be carried out on their premises. A local presentation was held for staff at each organisation to explain the study and the proposed benefits their patients. Documents were obtained from each site including public liability insurance, an honorary contract for Professor Foster to be the site physician for the duration of the research study and a Site Specific Information (SSI) form was completed for each organisation taking part in the research.

All members of the research team attended Good Clinical Practice research training.

Internal research governance review of the project was obtained in November 2010, and the IRAS and REC form were completed in early December 2010. The IRAS and REC were submitted to the Barts and The London NHS Trust Research and Development Office in December 2010, and provisional sponsorship was obtained on 24th February 2011. The IRAS and REC forms, study protocol, research proposal, patient information sheets and consent forms were submitted to the National Research Ethics Service (NRES) Committee London – City Road and Hampstead in March 2011. The NRES Committee reviewed the application on 13th April 2011. They requested that a different participant information sheets and consent forms be provided for the intervention (nurse initiated) and control (doctor initiated) arms. These were submitted on 11th May 2011 and final ethical approval for the study was obtained on 9th June 2011 (Reference: 11/LO/0347). These documents were then submitted to the Barts and the London NHS Trust and East London NHS Foundation Trust Research and Development offices, and final sponsorship was received on 8th August 2011. The study commenced on 5th September 2011.

On 12th September 2011 a substantial amendment was submitted to the REC requesting permission to prescribe a shorter treatment duration for patients with acute HCV, who have an 80% chance of achieving SVR with 12 or 24 weeks of treatment with pegylated interferon-α and ribavirin (as opposed to the usual treatment course of 24 or 48 weeks dependent on genotype). The substantial amendment was granted on 10th October 2011.

The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki, and the trial has been registered with the ISRCTN (Reference: CCT-NAPN-22105).

2.4.3 My role and contribution:

I designed the study with my research supervisor Professor Graham Foster. I wrote the research proposal, study protocol, safety protocol, data collection forms, patient information sheets and consent forms and designed the patient information poster. I liaised extensively with the Research and Development department at Barts and the London NHS Trust regarding the ethics application. I wrote and submitted the REC, IRAS and SSI forms, and attended the research ethics committee meeting to explain the study. I wrote to each organisation involved in the study to gain their approval for the research to be carried out at their site, and attended each site to provide training for staff about the study. I organised Good Clinical Practice training for the Blood Borne Virus nursing team. Treatment was delivered by the Blood Borne Virus Nursing Team. I collected the data and collated it in the database. Data collection was also performed by Dr Jan Kunkel, during the second half of the study. I performed all of the data analysis. I performed the literature search for the introduction to this thesis and wrote the introduction and thesis chapters pertaining to this study in their entirety.

2.5 Qualitative assessment of the reasons underlying engagement in HCV treatment in people who inject drugs:

2.5.1 Methods summary:

A qualitative analysis of semi-structured interviews with people who inject drugs with HCV who attend Specialist Addiction Services, who had and had not been treated for HCV, was performed to identify factors that influenced their decision to undertake antiviral therapy for HCV.

2.5.2 Ethics and Research and Development

Ethical approval for this study was obtained in conjunction with the Research Ethics Application for the nurse initiation of antiviral therapy for HCV in PWID and a detailed description of the research development and ethical approval process is provided in the previous methods section (see section 2.4.2).

2.5.3 My role and contribution:

To enable me to perform this research I underwent extensive training on qualitative research design, implementation and analysis. I attended courses at NatCen on "Qualitative Research Design" and "Depth Interviewing Skills" and at the University of Surrey on "An introduction to Qualitative Data analysis". I discussed the study with experienced qualitative researchers to gain advice on how best to perform the study. I designed the study and research questions and based on a review of previous literature on the subject wrote the theme guide. I devised the sample matrix. I

performed all 12 interviews. The interviews were typed by a professional transcription service. I analysed each interview using a grounded theory approach, coding each interview line by line, identifying themes and devising a thematic framework. I then linked the themes and analysed them in the context of previous qualitative research on this topic. I performed the literature search for the introduction to this thesis and wrote the introduction and thesis chapters pertaining to this study in their entirety.

3 Mosque Awareness Raising Campaign:

A previous study performed at Mosques in Newham, where volunteers tested Mosque attendees on site for HBV and HCV using oral fluid samples showed that testing in Mosques was popular and identified a significant number of infected people (Uddin, 2010). However a significant minority of those identified did not attend for therapy or further investigation greatly reducing the value of the intervention. We hypothesised that a screening campaign in which people attending the Mosque were alerted to viral hepatitis and then tested in their GP surgery would be more productive with greater levels of engagement.

3.1 Methods:

3.1.1 Participants:

Potential participants for the Mosque based awareness raising campaign were all attendees of participating Mosques.

3.1.2 Study design:

In Mosques in Newham an awareness raising campaign was held to encourage attendees to visit their GP to request screening for viral hepatitis. Imams were contacted by the Hepatitis C Trust (a national UK charity for hepatitis C) and asked to preach about Hepatitis B and C during Friday prayers. Information sheets were given to Imams explaining chronic viral hepatitis C and B, and the impact of these diseases in non-medical language (see appendix 2). All General Practitioners in the Borough of

Newham were also contacted by letter informing them about the awareness raising campaign, and when it was due to occur. In this letter they were asked to use the integrated virology form provided in the information leaflet to request HBV and HCV serology for patients who attended their practice rather than their usual virology request forms (see appendix 3). Volunteers attended the three Mosques where Imam's had agreed to preach and distributed leaflets written in English and Urdu explaining chronic hepatitis B and C and how they are transmitted, treated and diagnosed. The leaflets encouraged recipients to attend their local GP to request testing. To capture the number of people who requested testing for hepatitis B and C at their GP surgery via this awareness raising campaign a virology form with a unique code was integrated into the leaflets, which participants were asked to take to their General Practitioner when requesting testing. This code was designed to be read electronically on receipt of the HBV and HCV samples at the Royal London Hospital virology laboratories, resulting in a central record of all those tested for HBV and HCV due to the awareness raising campaign (see appendix four). This was felt to be an accurate way to capture the number of people who had requested testing for HBV and HCV as a result of the awareness raising campaign as all GP surgeries in the London borough of Newham send their virology specimens to the Royal London Hospital, and this capture technique had been used successfully previously. Virology staff were asked to scan for the code for three months following the awareness raising campaign.

3.1.3 Data collection:

The number of patients tested for HBV and HCV, and the results of HBsAg and HCV ab testing were recorded.

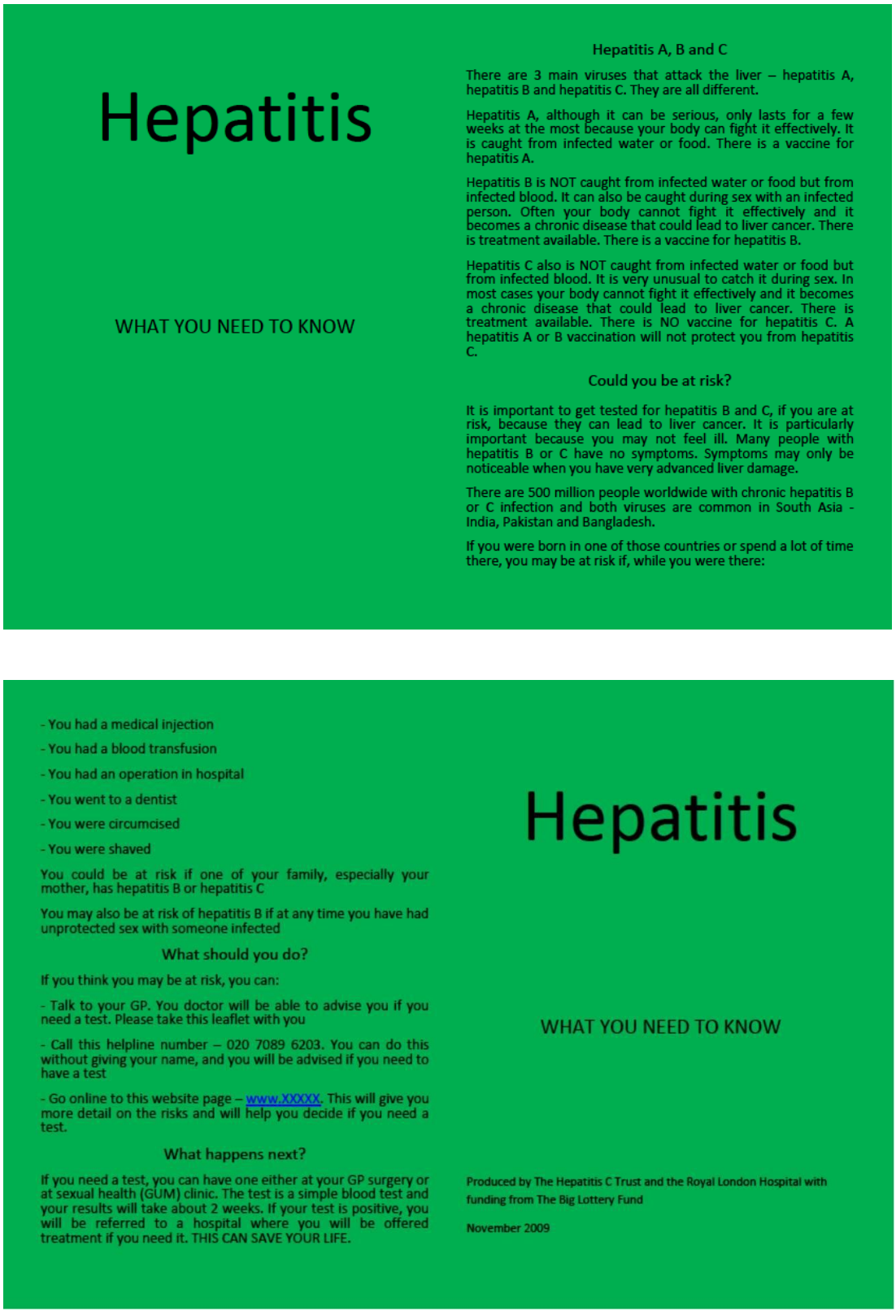
3.2 Results:

3.2.1 Site:

The Mosque awareness campaign and the prospective observational screening pilot study were undertaken in the ethnically diverse London borough of Newham. 60% of the population is non-white and 38.1% of the population was born outside of the UK. Of those born outside the UK 90% come from 47 different countries, with over half coming from the Asian sub-continent, Ghana and Nigeria. Between 2002 and 2006 the number of migrants from Eastern Europe and Lithuania in particular increased by 800% (530 to 1790) and the number of migrants from South Asia increased from 3290 to 5310, an increase of 61% (Focus on Newham: Local people and local conditions, London Borough of Newham; 2007). Five Mosques were contacted and three chose to take part, the Minhaj-ul-Quran, Al-Hira and Green Street Mosques. All three mosques are in the London Borough of Newham. Each Mosque's management committee was contacted and permission was gained from them to undertake the awareness raising project in their Mosque.

3.2.2 Approach:

The Mosque awareness raising campaign was carried out with the UK's national Hepatitis C charity, the Hepatitis C Trust and was planned between September and November 2009. The information leaflets given to Mosque attendees were devised in conjunction with the Hepatitis C Trust, and in particular with a Hepatitis C Trust employee of Pakistani heritage to ensure they were culturally appropriate. The leaflet is shown on the following page (see figure five).



Hepatitis

WHAT YOU NEED TO KNOW

Hepatitis A, B and C

There are 3 main viruses that attack the liver – hepatitis A, hepatitis B and hepatitis C. They are all different.

Hepatitis A, although it can be serious, only lasts for a few weeks at the most because your body can fight it effectively. It is caught from infected water or food. There is a vaccine for hepatitis A.

Hepatitis B is NOT caught from infected water or food but from infected blood. It can also be caught during sex with an infected person. Often your body cannot fight it effectively and it becomes a chronic disease that could lead to liver cancer. There is treatment available. There is a vaccine for hepatitis B.

Hepatitis C also is NOT caught from infected water or food but from infected blood. It is very unusual to catch it during sex. In most cases your body cannot fight it effectively and it becomes a chronic disease that could lead to liver cancer. There is treatment available. There is NO vaccine for hepatitis C. A hepatitis A or B vaccination will not protect you from hepatitis C.

Could you be at risk?

It is important to get tested for hepatitis B and C, if you are at risk, because they can lead to liver cancer. It is particularly important because you may not feel ill. Many people with hepatitis B or C have no symptoms. Symptoms may only be noticeable when you have very advanced liver damage.

There are 500 million people worldwide with chronic hepatitis B or C infection and both viruses are common in South Asia - India, Pakistan and Bangladesh.

If you were born in one of those countries or spend a lot of time there, you may be at risk if, while you were there:

- You had a medical injection
- You had a blood transfusion
- You had an operation in hospital
- You went to a dentist
- You were circumcised
- You were shaved

You could be at risk if one of your family, especially your mother, has hepatitis B or hepatitis C

You may also be at risk of hepatitis B if at any time you have had unprotected sex with someone infected

What should you do?

If you think you may be at risk, you can:

- Talk to your GP. You doctor will be able to advise you if you need a test. Please take this leaflet with you

- Call this helpline number – 020 7089 6203. You can do this without giving your name, and you will be advised if you need to have a test

- Go online to this website page – www.XXXXX. This will give you more detail on the risks and will help you decide if you need a test.

What happens next?

If you need a test, you can have one either at your GP surgery or at sexual health (GUM) clinic. The test is a simple blood test and your results will take about 2 weeks. If your test is positive, you will be referred to a hospital where you will be offered treatment if you need it. THIS CAN SAVE YOUR LIFE.

Hepatitis

WHAT YOU NEED TO KNOW

Produced by The Hepatitis C Trust and the Royal London Hospital with funding from The Big Lottery Fund

November 2009

Figure 5 Mosque awareness campaign leaflet

The awareness raising campaign was held on the 1st of January 2010. Imams at the three Mosques preached about Hepatitis B and C to attendees and seven volunteers from the Hepatitis C Trust and Royal London Hospital were present at the Mosques to distribute leaflets and discuss Hepatitis B and C and the importance of testing with Mosque attendees.

On the day of the awareness raising campaign 5000 leaflets were distributed to the three Mosques; 1500 were distributed to Al-Hira Mosque, 1500 to Green Street Mosque and 3000 to Minhaj-ul-Quran Mosque. Leaflets that were not distributed on the day were retained by the Mosques and distributed at prayers for the following month.

No HBV and HCV testing forms received by the virology department at the Royal London Hospital were recorded as originating from the Mosque awareness raising campaign.

This study indicated that this approach to identification of infected immigrants was unlikely to be effective and this approach was therefore abandoned.

3.2.3 Discussion of methodology:

The Mosque screening campaign had a number of strengths in its design, principally related to the fact that it was led by the Hepatitis C Trust, the National UK charity for Hepatitis C where most of the staff have experience of living with Hepatitis C, the efforts taken to ensure it was culturally appropriate and that information was provided in Urdu, and the involvement of local Mosque leaders. The NICE 2012 guideline on ways to promote and offer testing to people at increased risk of HBV and HCV infection

(NICE, 2012) recommends that awareness raising campaigns should address the needs of high risk groups who do not speak English, be culturally appropriate, and be held in locations where people who are at risk are likely to attend and this campaign fulfilled these criteria. Criticisms of the campaign are that it was short lived, focused only on the three Mosques involved and an assessment was not undertaken as to whether it had raised awareness of chronic viral hepatitis within the community it was targeting.

4 Screening for chronic viral hepatitis in migrants

Chronic viral hepatitis is common in migrants and current recommendations are that all at risk migrants should be screened in primary care (NICE, 2012). However this does not commonly occur and the optimal approach to screening is not yet clear. The aim of this prospective observational pilot study was to evaluate two methods of testing for chronic viral hepatitis in primary care.

4.1 Methods

4.1.1 Participants:

Participants for the screening study were all patients coded as Pakistani/ British Pakistani who were aged over 18 years of age and registered at participating General Practitioners. Migrants from Pakistan were chosen as previous community screening has shown high prevalence rates of HBV and HCV in migrants from Pakistan living within the borough of Newham (1.8% HBV and 2.8% HCV). The primary care practices were all based in the North East London Borough of Newham.

4.1.2 Study Design:

In this study two methods of screening migrants from Pakistan for HBV and HCV were evaluated.

Initially all General Practices within the London Borough of Newham were contacted by letter asking if they would be interested in taking part in the research project (see appendix 5). Interested practices were asked to contact the research team who

subsequently visited the practice and explained the research project in more detail. If a practice chose to take part in the study they were invited to choose which arm of the study they wished to take part in.

The first, intervention method, used a direct testing approach involving a formal testing programme whereby the research fellow contacted eligible participants and invited them to attend screening clinics. Each practice was visited by the research team and a presentation was given on hepatitis B and C, their consequences and treatment, their increased prevalence in local migrant groups and a detailed explanation of the research project. In each of these practices the EMIS (Egton Medical Information Systems) database of registered patients was searched for patients coded as having Pakistani/ British Pakistani ethnicity who were over 18 years of age. All identified patients were sent an invitation letter, with a patient information sheet written in English and Urdu (see appendix six) explaining the research project and asking for permission to contact them by phone to arrange a blood test for hepatitis B and C at their GP practice. If they did not wish to be contacted they were invited to opt out by letting their GP practice know that they did not wish to be contacted. Those who did not opt out were then contacted by telephone by the research fellow, and invited to make an appointment for viral hepatitis testing. They could accept or decline the invitation at this point. If they declined they were not contacted again. A total of three phone calls were made if participants could not be contacted on the initial telephone call. If contact was not achieved with three phone calls no further contact was made. Testing was performed on site at each of the GP practices in designated

viral hepatitis screening clinics. These clinics took place weekly or more often dependent on demand, research fellow and clinic availability at each GP surgery.

The second testing method involved an opportunistic testing technique, in line with current NICE guidance (NICE, 2012) and the current recommended practice in primary care. In the participating practice a training session on viral hepatitis was held for General Practitioners and associated healthcare professionals. This covered detailed information on the risk factors, methods of transmission, diagnosis and treatment of HBV and HCV. Virology testing forms (see appendix seven) and patient information sheets in English and Urdu were distributed at the practice (see appendix eight). The EMIS database of registered patients was searched for patients coded as having Pakistani/ British Pakistani ethnicity who were over 18 years of age. The General Practitioners then offered testing for chronic viral hepatitis during routine consultations to all patients who were aged over 18 and registered as Pakistani/British Pakistani who attended their surgery over the study period for any reason. The testing was offered entirely opportunistically, in that it was only offered to patients when they attended the practice for another reason, and no patients were directly contacted by the General Practitioners to invite them to attend for testing. The numbers who accepted or declined screening were recorded in the practice EMIS database and collected by the research fellow.

All participants in the study gave full, informed, written consent. Consent forms were provided in English and Urdu for both arms of the study (see appendix nine). A copy of the consent form was given to the patient, one was kept in the site file and one was kept in the source documents.

Two months into the study, a proportion of patients who had been contacted by telephone in the direct testing arm had expressed an interest in being tested for Hepatitis B and C, but were unable to attend the dedicated testing clinics at their GP practice for a variety of reasons including poor mobility and employment. It appeared that the requirement to attend a specific clinic at the GP practice may provide a barrier to testing and that testing may be facilitated by being able to have the blood test for HBV and HCV at a local phlebotomy clinic that participants could attend at a time of their convenience. Therefore an amendment to the ethical approval was requested to allow for "postal screening" of participants in the direct testing group. This involved a letter and blood test request form being posted to potential participants who were not able to attend their GP practice but wished to be tested for chronic viral hepatitis (see appendix 10). This request form could be taken to one of five local phlebotomy centers, where a blood test for HBsAg and HCV ab would be performed. Research Ethics Committee permission for the amendment was granted on the 6th April 2010 and subsequently this option was offered to participants.

Testing for HBsAg and HCV ab was performed on serum samples for all participants at the Royal London Hospital virology laboratory.

Results letters were sent to all patients. Participants who tested positive for HBsAg or HCV ab had an appointment made with the research fellow at their General Practitioners to explain the diagnosis in more detail. They were then referred to the local tertiary referral Hepatology clinic for further assessment and treatment. Attendance records were maintained at each clinic on the EMIS database, and a proforma was completed for each patient at each study visit.

4.1.3 Data collection:

Basic demographics (age and sex) were recorded for all participants. The number contacted by letter, the number who opted out of screening after the invitation letter, the number who could be contacted by telephone (and if they could not be contacted why they could not be contacted), the number who agreed to screening at the GP practice, the number who agreed to postal screening, and the number who did not agree to screening and why they did not agree to screening were all recorded. Data was also collected on the number who were screened, the number who made an appointment for screening and did not attend and the number who tested HCV Ab and HBS Ag positive or negative. For those who tested HBsAg or HCV ab positive, serological data on their disease status was recorded, ultrasound and liver biopsy results, if they were treated and what treatment they received and their attendance at follow up appointments.

4.1.4 Cost analysis:

To ascertain the costs of screening the direct costs of the screening programme including diagnostic tests, personnel costs, stationary, translation and administrative costs were totalled. The personnel cost analysis was based on a band 4 NHS administrator performing the administrative screening tasks and a band 6 nurse performing the screening. The screening was performed principally by one medical research fellow (HL) with the assistance of another research fellow (KB) but using the salary of a screening nurse and administrator more accurately reflects the costs of a real world screening programme. The personnel costs were assessed by calculating the

mean hourly wage for each personnel member from the NHS Agenda for Change pay scales, and multiplying it by the number of hours spent on each aspect of the screening programme with the addition of 25% employer costs. The costs of the screening were recorded including the costs of stationary and translation, and where costs were not incurred during the project (for example the cost of using the GP clinic room to perform screening) they were calculated based on standard NHS costs. The cost of HBsAg and HCV ab tests were taken from Miners et al's economic evaluation of screening (Miners A, 2012).

4.1.5 Statistical analysis

Data was stored in an excel spreadsheet. Graphpad prism version 5 was used to perform statistical analysis. The Chi Squared and Fishers Exact Test were used to analyse categorical data on uptake of screening by method of screening used, sex and age.

A power calculation to estimate sample size was performed. It was estimated that to achieve an 80% power to reject the null hypothesis 75 patients would be required in each arm. To inform the power calculation it was predicted that there would be a difference in uptake between the groups of 15% (20% in the direct testing group and 5% in the opportunistic testing group). When planning the study there was very limited published data available to perform a power calculation to assess sample size, so estimations had to be made. In the New Zealand Hepatitis B screening programme 27% of the eligible population were screened with a variety of methods including supporting GP's to recruit eligible individuals for screening, similar to the direct arm in

the current study (Robinson T, 2005). As this was only one of the techniques used, and community screening techniques were used which may have been more effective a lower uptake of screening was predicted of 20%. There was no available data on uptake of opportunistic viral hepatitis screening in migrants, but as this depends on patients attending their general practitioners for another reason uptake was likely to be much lower and therefore an uptake of 5% was estimated. If the true difference between the direct and opportunistic arm means is 15%, 75 experimental subjects and 75 control subjects would need to be studied in order to reject the null hypothesis that those in the direct and opportunistic arms are equally likely to be screened with a probability of 0.8. The Type I error probability associated with this test of this null hypothesis is 0.05. Given the inherent uncertainty involved in this power calculation due to the use of estimated means, a much larger sample size was used in the study.

4.2 Results:

4.2.1 General Practices:

Five General Practices took part in the screening study, all of which were located in the London Borough of Newham.

A single GP practice, The Surgery, took part in the opportunistic testing arm.

Four GP practices, Tollgate Medical Centre, Market Street Health Group, East End Medical Centre and Esk Road Medical Centre took part in the direct testing arm.

An overview of the practices is shown in table one on the following page:

Table 1: Overview of General Practices participating in the study

	The Surgery	Tollgate Medical Centre	Market Street Health Group	East End Medical Centre	Esk Road Medical Centre
Number of General Practitioners	2	10	7	2	1
Number of practice nurses	1	5	3	1	1
Phlebotomy on site	N	Y	N	Y	N
GP training practice	N	Y	Y	N	N
Number of patients eligible for screening	1163	384	443	229	65

4.2.2 Demographics:

Demographic information was not available for participants in the opportunistic testing arm.

The baseline demographics of patients in the direct testing arm are detailed in table two below:

Table 2: Baseline demographics of eligible patients in direct testing arm

		All practices	
		N	%
Total		1133	
Sex	Male	636	56
	Female	497	44
Median age		38 (SD 13.66) (95% CI 37-38.93)	

4.2.3 Logistics of testing:

4.2.3.1 Opportunistic testing arm:

Testing began on 24th February 2010 and was completed on 1st June 2010.

In the first month of testing both General Practitioners took annual leave, which may have reduced the potential reach of testing.

The General Practitioners reported no logistical problems with this method of testing.

4.2.3.2 Direct testing arm:

Letters were sent to patients a month before testing was due to begin in each practice. The first letters were delivered in late January 2010.

A total of 1133 letters were sent to all patients who were eligible for screening in the four participating GP practices.

The first phone call was made to invite a patient for testing for HBV and HCV on 24th February 2010 and the final phone call was made on the 18th November 2010. Testing was staggered in timing amongst the four practices.

The first testing clinic was held on 2nd March 2010 at the East End Medical Centre and the last testing clinic was held on 19th November at Tollgate Medical Centre. In total testing took place over an eight and a half month period.

4.2.4 Testing uptake:

4.2.4.1 Opportunistic testing (control) arm:

There were 1163 patients who were eligible for screening registered at the primary care practice in which opportunistic testing was performed.

Figure six below details the uptake of testing in the opportunistic testing arm:

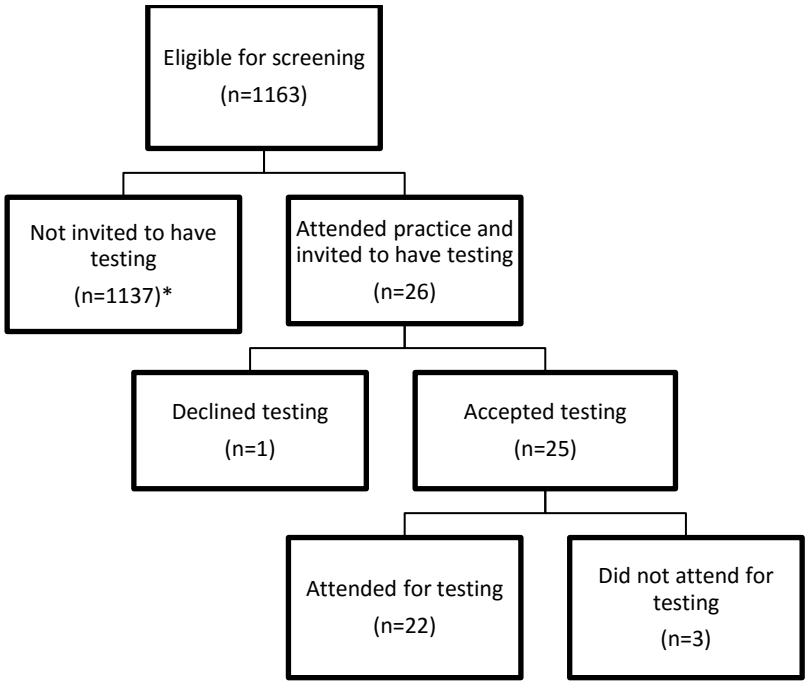


Figure 6 Testing uptake in the opportunistic testing arm

* The figure for those not invited to have testing represents all patients who were potentially eligible for testing, whether they attended the practice during the study period or not. It is not known how many eligible patients attended the practice and were not offered testing during the study period.

Twenty six patients were offered testing for HBV and HCV by their General Practitioner during routine appointments. Of these 25 patients accepted testing (96%) and 22 patients (85%) attended for testing out of a possible total of 1163 (1.9%).

4.2.4.2 Direct testing arm:

There were 1133 patients who were eligible for testing registered at the four primary care practices in which the direct testing approach was undertaken.

Figure seven below describes the uptake of testing:

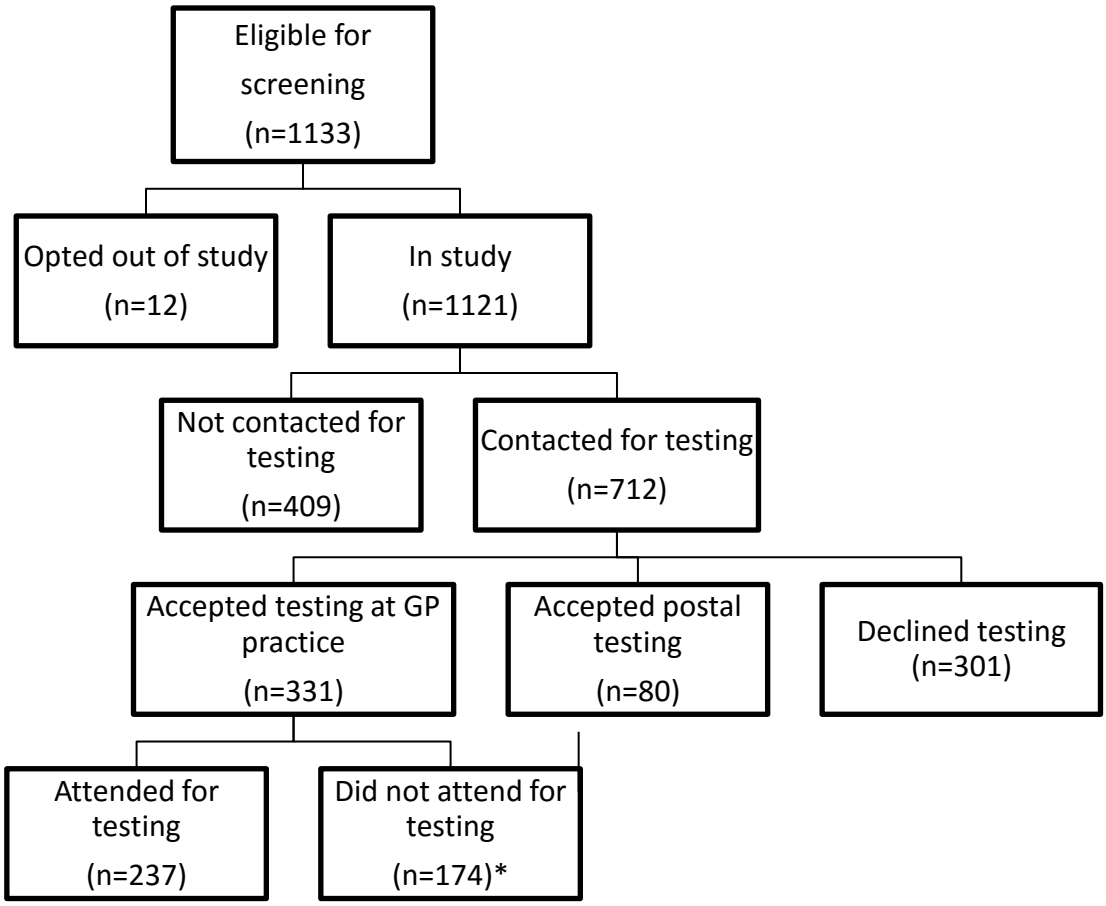


Figure 7: Testing uptake in direct testing arm

* Ninety four patients who had agreed to a test at their GP practice were not tested and no patients were tested by the postal testing method.

Testing uptake at the four participating General Practices was similar. At Esk Road Medical Centre testing uptake was 22% (14/67), at East End Medical Centre it was 19% (44/236), at Market Street Health Group it was 22% (96/446) and at Tollgate Medical Centre it was 22% (83/384) (p=ns).

4.2.4.3 Testing uptake comparison of opportunistic and direct testing arms:

In the intention to treat analysis of all patients who were eligible for testing 1.9% (22/1163) of patients in the opportunistic testing arm and 21% (237/1121) of patients in the direct testing arm attended for testing for HBV and HCV (see figure eight below). Due to the different testing approaches used statistical analysis was not undertaken to compare the two approaches.

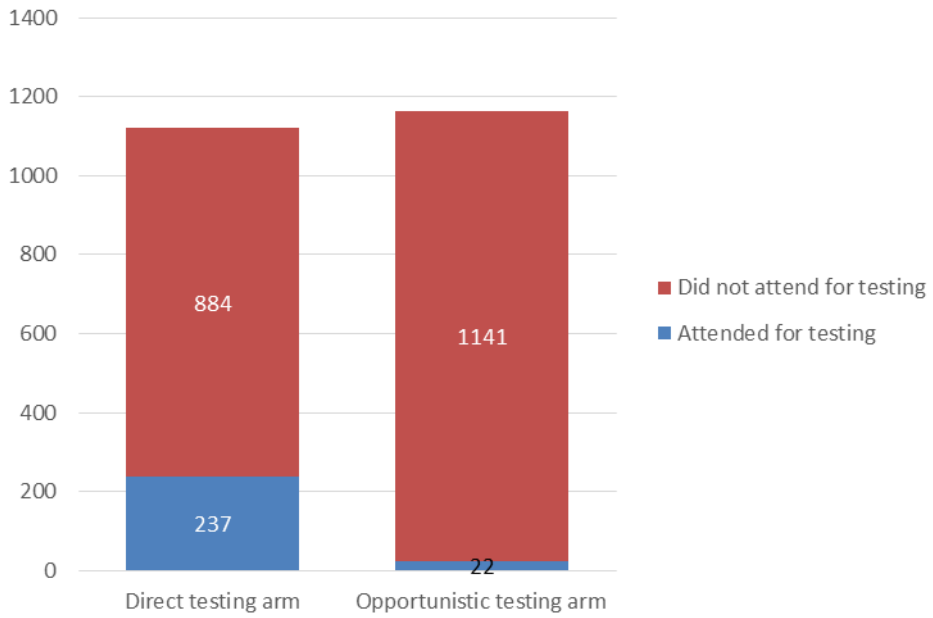


Figure 8: Comparison of attendance for testing in the opportunistic and direct testing arms

4.2.4.4 Outcomes of those who agreed to testing:

A surprising feature of this study was the relatively high proportion of patients who agreed to undergo screening but did not attend for testing. These subjects were clearly interested in testing but did not actually undergo testing. They may form a subgroup of 'easy to access patients' and were therefore analysed further. A sub-group analysis was performed of all patients who agreed to testing (n = 411 in the direct arm and

n=25 in the opportunistic testing arm) to examine whether they were more likely to attend for testing in the opportunistic or direct testing arm. The results can be seen in figure nine below and show that those who agreed to testing in the opportunistic testing arm were more likely to attend for testing than those in the direct arm with 88% (22/25) attending for testing versus 58% (237/411). As per the intention to treat analysis the results of postal testing, which was incorporated into the direct testing arm two months into the project, were included in the direct testing arm in this analysis.

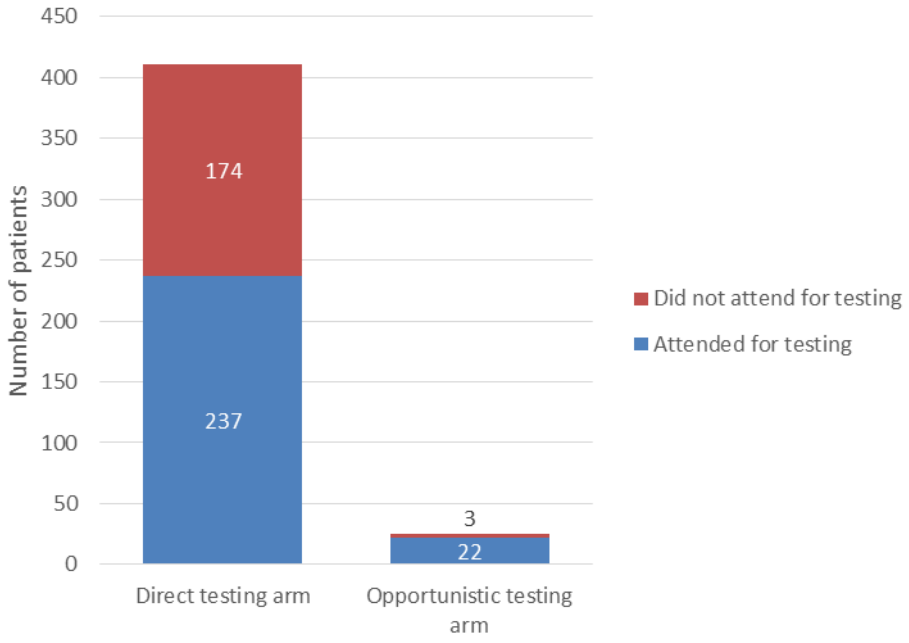


Figure 9: Subgroup analysis of attendance for testing in those who agreed to be tested

To examine the value of postal testing further a per-protocol analysis of attendance for testing in those who agreed to be tested at GP practices (in the direct and opportunistic testing arms) and those who agreed to postal testing was undertaken. Figure 10 on the following page shows the results and indicates that patients who agreed to be tested via postal contact were highly unlikely to attend for testing. In this

per-protocol analysis the removal of postal testing from the direct testing arm resulted in a minimal difference in the numbers attending for testing between the direct and opportunistic testing arms.

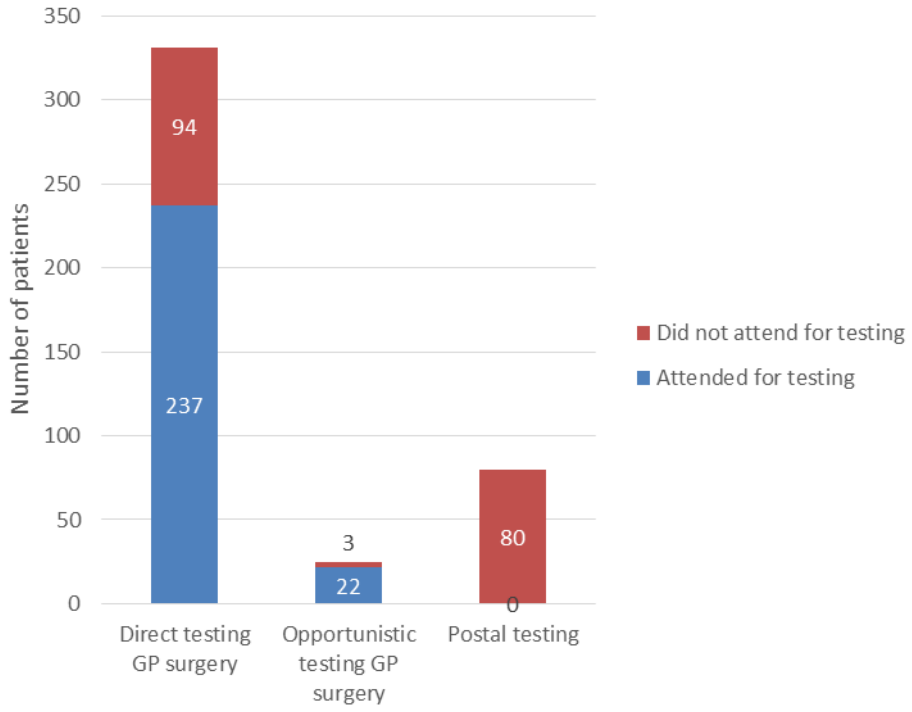


Figure 10: Per-protocol analysis of attendance for testing - postal testing analysis

4.2.5 Direct Testing arm:

Further analysis was undertaken in the direct testing arm to examine the outcomes when contact for testing was attempted, the reasons that patients declined testing for HBV and HCV and to assess whether patients age or gender affected acceptance of, and attendance for, testing.

4.2.5.1 Outcomes of attempted contact for testing:

All registered patients of each practice who had not opted out of the study were telephoned to invite them to attend their GP practice for testing. An unexpected finding was that 37% of all patients who were eligible for screening (409 patients) could not be contacted to invite them to attend for testing, and the reasons for this are summarised in figure 11 below:

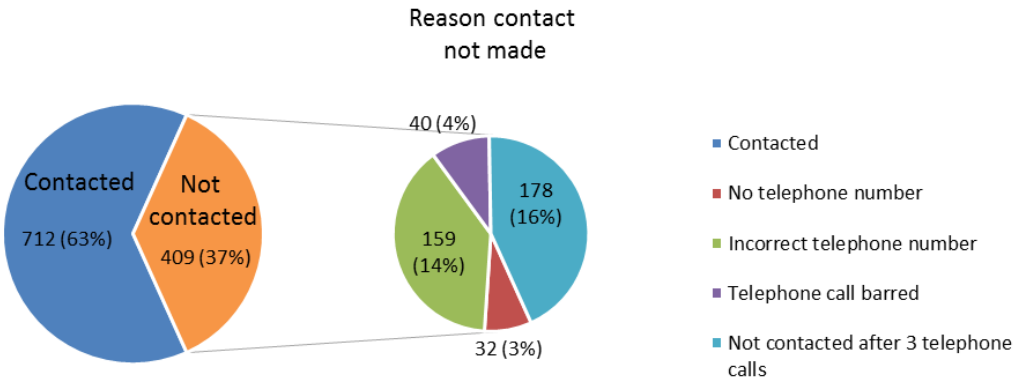


Figure 11: Outcomes of testing invitation telephone calls

4.2.5.2 Outcomes of participants who were contacted for testing:

In total 712 patients were contacted for testing and 57% of these (411/712) agreed to be tested for HBV and HCV either at their GP practice or by the postal testing method. 301 patients (43%) declined testing and the reasons for this are summarised in figure 12 below. The majority of patients who declined testing were not interested in being test for HBV and HCV (n=111, 16% of those contacted), but 90 patients (13% of those contacted) were ineligible for testing either because they were not of Pakistani/ British Pakistani ethnicity (i.e. their ethnicity had been incorrectly coded) or because they had already been tested for HBV and HCV.

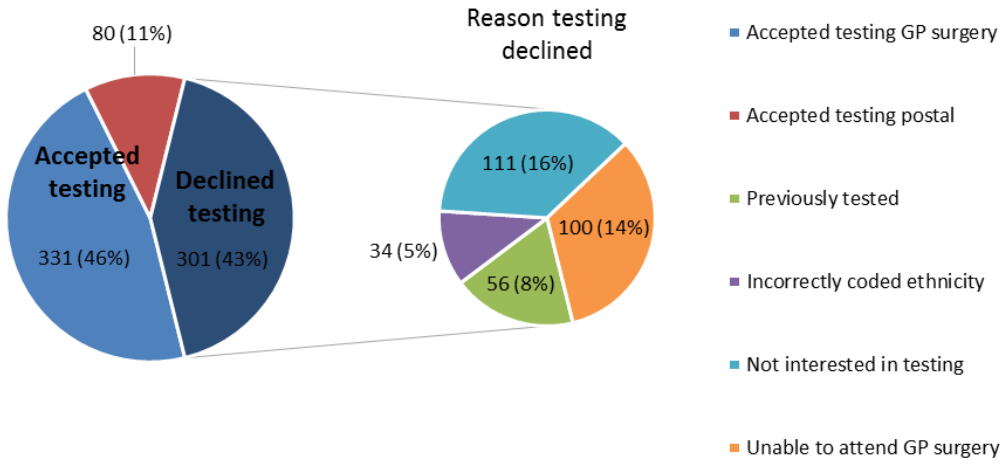


Figure 12: Outcomes of participants who were contacted for testing

4.2.5.3 Age analysis:

Date on age was available for all potential participants in the direct arm and an analysis was undertaken to assess if age impacted testing uptake.

The age range of all eligible patients is shown in figure 13 below. The majority of participants (695/1121, 62%) were under 40 years of age.

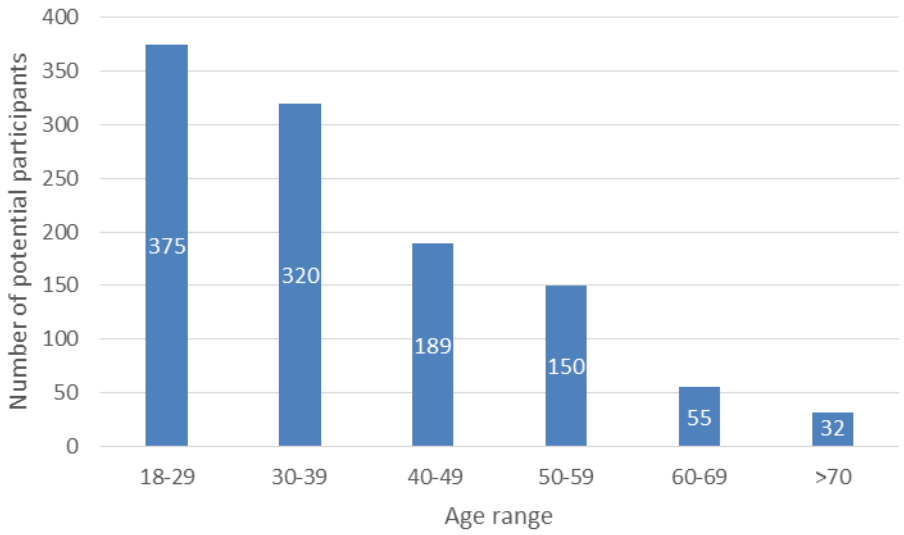


Figure 13: Age range of eligible patients

Those who could be contacted for testing were significantly older than those who could not be contacted (mean age of 39 years versus 35 years, p=0.0006).

Figure 14 on the following page shows the numbers in each age range who attended for testing.

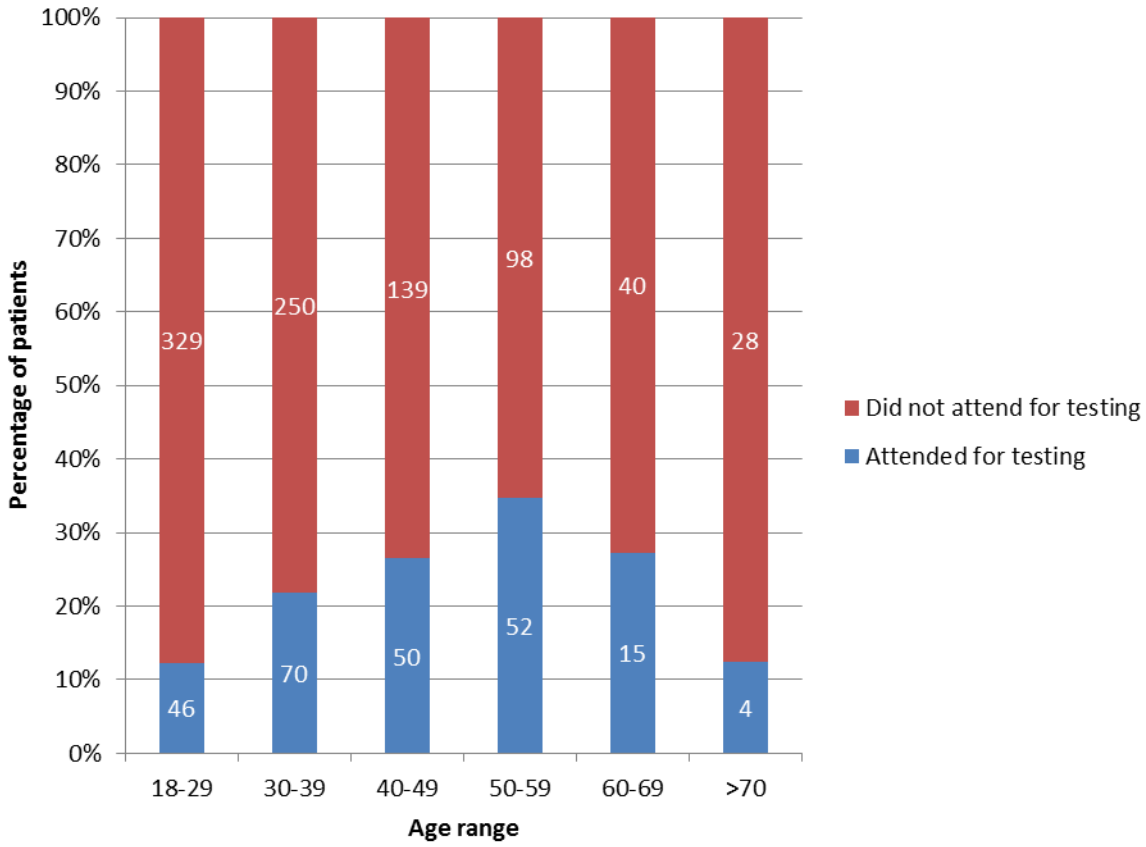


Figure 14: Attendance for testing by age

Attendance for testing was highest in the 50-59 age range with 35% of this age group attending for testing.

Patients in the age group 50-59 were significantly more likely to attend for testing than patients in the 18-29 (p= < 0.0001), 30-39 (p=0.0046) and > 70 age groups (p=0.0189). There was no significant difference in the likelihood of attending for testing amongst patients in the age groups 40-49, 50-59 and 60-69.

When comparing participants aged under and over 40, those aged over 40 were significantly more likely to attend for testing (28% vs 17%, p =<0.0001) (See figure 15 on the following page).

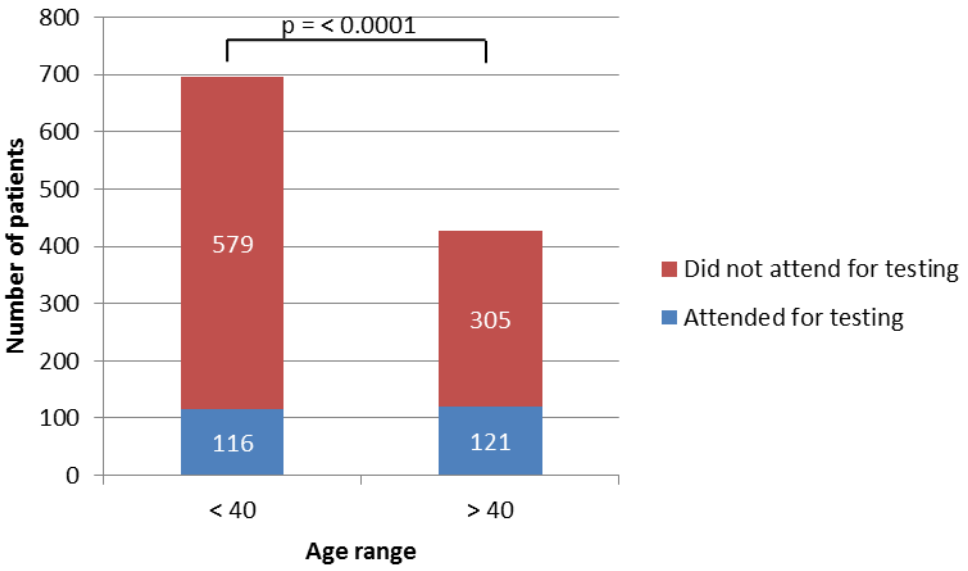


Figure 15: Attendance for testing in participants aged under or over 40 years of age

4.2.5.4 Gender analysis

Women were significantly more likely to be able to be able to be contacted for testing than men, with 69% of women (344/492) and 60% of men (377/629) being contacted (p=0.0006). Agreement to testing was also higher amongst women with 41% (202/492) of women and 32% (203/629) of men agreeing to be tested (p=0.0026).

Despite this there was no significant difference between the number of men and women who attended for testing with 23% (115/492) of women and 19% (118/ 629) of men being tested for HBV and HCV (p=ns) (see Figure 16 on the following page).

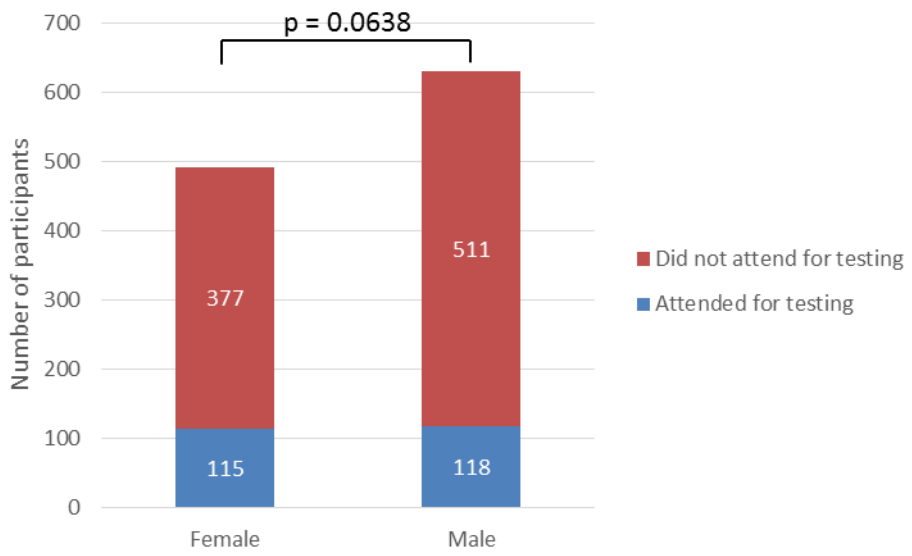


Figure 16: Attendance for testing by participant's gender

4.2.5.5 Country of birth analysis:

Data on country of birth was not available for the majority of the cohort as General Practice electronic records provide data on ethnicity rather than country of birth.

Data was available on country of birth for 115 out of 252 contacted patients at the Tollgate Medical Centre of whom 79 were born in Pakistan and 36 were born in the United Kingdom.

Attendance for testing according to country of birth is summarised in figure 17 on the following page:

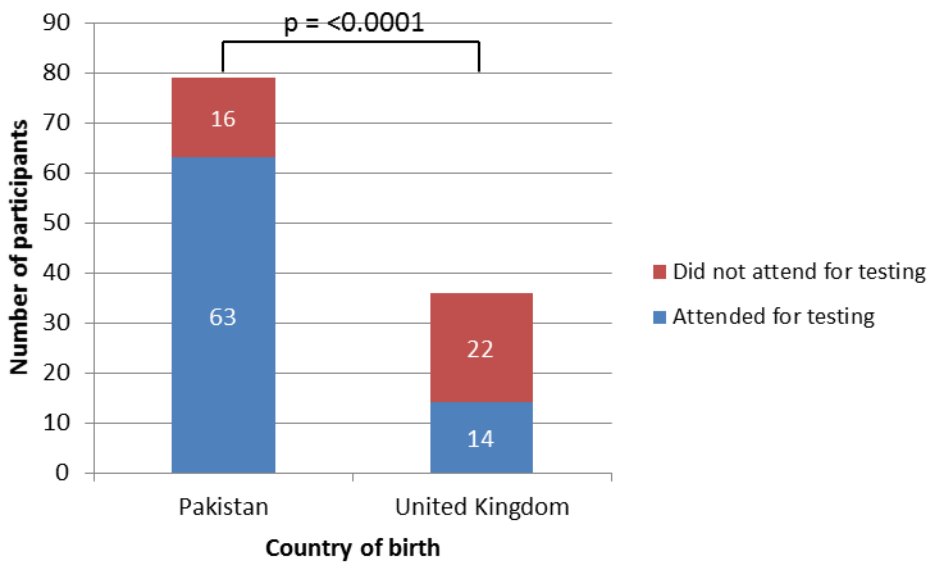


Figure 17: Attendance for testing by participants by country of birth

Of this small cohort, 80% of those born in Pakistan and 40% of those born in the UK agreed to be screened (p=<0.0001).

4.2.6 Outcomes of screened patients:

4.2.6.1 Opportunistic testing arm:

In the opportunistic testing arm 22 patients attended for testing none of whom tested positive for HBSAg or HCV antibody.

4.2.6.2 Direct testing arm:

In the direct testing arm 237 patients attended for testing, three of whom tested positive for HCV antibody (1.3%), with an additional two patients having an equivocal HCV antibody result (0.84%) and two patients testing positive for HBSAg (0.84%). None of the patients who tested positive for HCV ab or HBSAg were previously aware of their diagnosis.

The two patients who had equivocal HCV antibody tests underwent HCV RNA testing, which was negative in both cases. Both of these patients were female and were born in Pakistan. They were 54 and 25 years old.

One patient who screened positive for HCV ab was subsequently found to be HCV RNA negative indicating spontaneous clearance of the virus.

The demographic, serological and treatment outcomes of patients with a positive HCV antibody or positive HBsAg are documented in table three below:

Table 3: Demographic and disease status of patients who tested positive for HCV ab and HBsAg

Patient	Sex	Age	Country of birth	Serology	Liver biopsy	Treatment
1	M	39	Pakistan	HBsAg +ve, HBeAg -ve, HBV DNA 3.77 IU/ml, ALT 33	F 0/6 NI 1/18	Active monitoring
2	M	26	Pakistan	HBsAg +ve, HBeAg -ve, HBV DNA 2.62 IU/ml, ALT 53	F 1/6	Active monitoring
3	F	29	Pakistan	HCV Ab +ve, HCV RNA 4.38 log, Genotype 3a, ALT – 97	Not done	PR 24/52
4	F	48	Pakistan	HCV Ab +ve, HCV RNA 5.5 log, Genotype 3a, ALT – 37	F 1/6 NI 3/18	PR 24/52
5	F	31	Pakistan	HCV Ab +ve, HCV RNA –ve	Not applicable	Not required

All patients with a positive HCV ab or HBSAg test attended the local Hepatology clinic for follow up, and all those who required antiviral therapy accepted and completed treatment.

The two patients with a positive HBsAg test were both inactive carriers of HBV and did not require treatment. They have both been entered into an active monitoring programme. Both patients attended their initial follow up appointments but have not attended subsequent monitoring appointments.

4.2.7 Cost analysis:

The summary costs of the screening programme can be seen in table four below.

Table 4: Summary of screening costs

Expenditure	Cost (£)
Personnel	7330
Administration	1750
Translation	940
HBsAg and HCV ab testing	5520
Total cost	**15540**

Staff costs were calculated as follows; over the nine month period of the study a mean of one and a half days of administrative time per week or 435.375 hours in total, and a total of 122.5 nursing hours were spent. The total staff cost is calculated based on Agenda for Change hourly rates of pay for a band four administrator of £11.29 per hour, and a band six nurse of £15.77 per hour, plus a 25% employer cost.

Included in the administration costs were the costs of stationary, telephone calls, office space and General Practice clinic room rental. The cost of HCV ab and HBsAg

testing was taken to be £10 per test from a recent NICE commissioned economic evaluation of screening in migrants (Miners A, 2012).

The cost per person screened was £65.57, and the cost per positive screen was £2220. The cost per person who went on to receive treatment was £5180.
Cost effectiveness could have been assessed by calculating the incremental cost effectiveness ratio (ICER) per quality adjusted life year. The ICER in this case would reflect the ratio of the change in costs of the intervention of direct screening versus opportunistic screening (current recommended practice), to the change in effects of intervention (the identification and potential treatment of those with chronic hepatitis B and C). This was not calculated as it was felt to be outside the scope of this pilot study.

4.3 Summary:

This prospective observational pilot study indicates that a direct testing approach to screening for chronic viral hepatitis in at risk migrant populations in primary care may result in a higher uptake of testing for HBV and HCV than the currently recommended opportunistic testing approach. Participants were highly unlikely to be tested by a postal testing approach. Although only a small proportion of eligible patients were tested in the opportunistic arm (1.9%), acceptability of testing was high with 88% of those approached being tested. A number of logistical barriers to screening in primary care were identified in this study which have helped to inform the design of the larger nationwide screening study. The results of this study will be discussed in more detail in chapter eight.

4.4 Discussion of methodology:

The strength of this study is its originality as it is the only research to attempt to identify the method of screening for chronic viral hepatitis in migrants in primary care in the United Kingdom that results in the highest uptake of testing. This data therefore played a key role in planning a large scale study designed to answer this question that is being carried out by the same group and has been funded by the NIHR.

There are some significant methodological issues with the screening study that affect the generalisability and validity of the results and that should be taken into account when drawing conclusions. This was not a randomised controlled trial, and the lack of randomisation of General Practices and lack of data on baseline characteristics of patients in the opportunistic testing arm means it is not possible to discern whether the differences seen in testing uptake are due to greater efficacy of the direct testing method or a difference in the characteristics of the General Practices or populations screened. The addition of postal testing into the direct testing arm two months into the study changes the intention to treat analysis from that originally planned, and as such may have affected the power calculation, but the study was considerably over powered to detect a difference between groups so this is unlikely to have affected the results.

The prospective observational cross sectional study design was chosen for pragmatic reasons as this was a pilot study designed to inform the design of a much larger nationwide study and was undertaken with limited resources. As such it was necessary to recruit GP practices without being able to offer incentives and so each practice was given a choice as to which method of testing they wished to trial. Giving General

Practitioners the choice of which arm to be involved in, while reducing the validity of the study findings, provided some useful information to inform future research as six out of seven GP practices chose the direct testing arm, implying General Practitioners had a preference for this form of testing. The surgery which undertook opportunistic testing did not report any difficulties with this being incorporated into their routine consultations, but if this method were to be used more widely the acceptability of this method would have to be explored as the majority of GP's who were approached indicated opportunistic testing would not be feasible with their current workloads.

The lack of randomisation led to only one General Practice participating in the opportunistic arm and so the characteristics of this practice could have considerably impacted the results. Due to a database complication at the practice it was not possible to obtain demographic data from this practice, and this reduces the ability to compare the two arms. In addition testing was undertaken for less time in the opportunistic testing arm, making the results less comparable. In the three months in which testing was undertaken in the opportunistic arm a mean of seven patients per month were tested, and so it appears unlikely that considerably more patients would have been tested in this arm if screening had continued, however this is speculative and the different periods of screening represent a significant flaw in the study when comparing outcomes. The three month period of screening in the opportunistic arm of the study is very unlikely to have been a sufficient length of time for all patients who were eligible to attend the practice. In 2008 the average number of GP consultations per person-year was 5.4 (The Health and Social Care Information Centre, 2009), with the highest rates in those aged 85-89 (13.8 per person-year for males and 13.3 per

person year for females). The majority (62%) of potential participants in this study were aged less than 40, where crude consultation rates for men are around two to three consultations per year, and for women are five to six consultations per year (The Health and Social Care Information Centre, 2009), and so it is unlikely that the majority of these patients would have attended during a three month period. This report does not include data on GP attendance by ethnicity but other studies have found no difference in access to healthcare or consultation rates between Pakistani men and women and the White British population, when ill health and material disadvantage are similar, in primary care so the figures are likely to apply to the studied population (Nazroo, 2009) (Kelly B, 2016).

The Hepatitis C Trust was consulted on the design of the study to ensure it was culturally appropriate, and to gain the input of patients into the design, but local community leaders were not and the study was implemented without a wider awareness raising campaign. Other screening studies have implemented awareness raising campaigns and engaged community members in their design and found that this culturally sensitive approach led to high satisfaction levels amongst participants, although they have not shown that this increased testing uptake (Richter C, 2010) (Jafferbhoy H, 2012). These studies assessed community screening campaigns, and did not undertake screening in primary care, however a concurrent awareness raising campaign and the wider involvement of local community leaders in the design of the screening study could have improved the study design, and this should be incorporated into a larger study.

5 Analysis of the outcomes of HCV therapy in people who inject drugs

The outcomes of HCV therapy in PWID have been explored in small studies with limited follow up periods, and the effect of HCV treatment on injection drug use has not been examined. The aim of this study was to evaluate the long term health and social benefits of antiviral therapy for hepatitis C in a large cohort of people who inject drugs delivered by a Blood Borne virus nursing team in addiction service outreach clinics. A further aim was to examine if hepatitis C related outcomes, mortality and reinfection rates differed between people who were actively injecting drugs at the start of anti-viral therapy, and those who had stopped injecting drugs prior to the start of treatment.

5.1 Methods:

This retrospective observational cohort study was designed to assess whether the "East London Model" of treatment of people who inject drugs with hepatitis C delivered by Blood Borne Virus (BBV) nurses in specialist addiction unit outreach clinics provides health and social benefits to those treated.

5.1.1 Participants:

All patients who had started antiviral therapy for HCV between June 2004 and December 2010 and had received at least one injection of pegylated interferon-α in Specialist Addiction Services in North East London.

5.1.2 Study design:

This study was a retrospective observational cohort analysis of patients treated with antiviral therapy for HCV by the Blood Borne Virus nursing team in Specialist Addiction Services in North East London.

The East London model of antiviral therapy for PWID's consists of a hub and spoke model where an experienced Blood Borne Virus nursing team offer antiviral therapy for people who are currently or have previously injected drugs and are maintained on opiate replacement therapy in three central Specialist Addiction Units (SAU), and ten outreach community clinics. The outreach service was established in 2004 to provide an alternative to treatment in secondary care, as no patients attending Specialist Addiction Services had been treated for HCV using the traditional secondary care treatment model. The Specialist Addiction Units and outreach clinics are based in three North East London boroughs; Newham (4 sites), Tower Hamlets (7 sites) and Hackney (2 sites). Within each borough there is a Specialist Addiction Unit and between one and six outreach clinics which are held in a variety of settings; a GP practice for the homeless, three Community Drug Treatment team centres, two hostels for the homeless, a drug intervention project, a women's service**,** a Salvation Army hostel, and a Drug and Alcohol Service for London Centre. The BBV nursing team are all employed by East London NHS Foundation Trust and Blood Borne Virus nursing sessions are commissioned by the Drug and Alcohol Action Teams (DAT) of each of the three boroughs. Each DAT pays for a specified number of nursing sessions each week. The DAT's are funded by the National Treatment Agency. The Blood Borne Virus nurses are experienced medically trained nurses (band 6 or above), who are able to work

independently. They are specifically trained in phlebotomy techniques in patients with poor venous access and are able to obtain blood samples from central veins if required.

Each patient referred for treatment by the BBV team is registered as a patient at the local teaching hospital under a consultant Hepatologist, who has ultimate responsibility for their care even though this is delivered exclusively in the community as outreach patients. The service is restricted to patients who have active addictions (either illicit drug intake or regular methadone/buprenorphine prescriptions). Patients who do not fulfil this criteria are offered therapy in a traditional, hospital based setting.

Opiate replacement and other medical services are offered at the Specialist Addiction Units and outreach clinics, and on site psychiatric services are provided at each SAU. Patients with complex addiction or psychiatric needs are seen and treated at the Specialist Addiction Units. Screening for HCV, HBV and HIV with HBsAg, HCV ab and HIV ab 1 and 2 is offered to all attendees. HCV RNA and HBV DNA quantification is performed with the Roche Amplicor assay and all samples are processed at the Royal London Hospital virology laboratory. Patients who are found to have chronic hepatitis B or C or HIV are counselled about their diagnosis and treatment options by their Blood Borne Virus nurse in their usual clinic. If they wish to consider treatment for HCV an appointment is made at the monthly liver clinic in one of the central Specialist Addiction Units, where a consultant Hepatologist and nurse discuss treatment options with the patient. Those who decide to undergo antiviral therapy are treated in their outreach clinic of choice by their Blood Borne Virus nurse. Therapy with pegylated

interferon-α and ribavirin is offered in line with national guidelines (the study was carried out before the widespread implementation of protease inhibitors). Directly observed therapy with pegylated interferon-α is offered to some patients but most patients are taught to self-administer. Follow up on treatment occurs weekly initially and is then adapted according to individual patient needs. Monitoring for side effects of treatment is carried out by the BBV nurse at each clinic appointment, and serological samples are taken regularly to assess for cytopenias, liver injury and renal impairment. If psychiatric side effects of treatment are identified patients are urgently reviewed by a psychiatrist at one of the Specialist Addiction Units. If there are any concerns about patient's physical health they are reviewed in the Hepatology clinic by a consultant Hepatologist, or in an emergency admitted to the local Hepatology centre. HCV RNA levels are obtained at 12 weeks of treatment, at the end of treatment and 6 months after therapy finishes to assess for response to treatment. For patients who have recently commenced opiate substitution therapy antiviral therapy is deferred for 6 months to allow engagement in the substitution program but there are no other drug intake related treatment prohibitions. Active illicit drug or heavy alcohol use either with or without opiate substitution therapy does not exclude interested patients from treatment.

5.1.3 Data collection:

A retrospective notes analysis was performed of the prospectively collected electronic records (EMIS) of the Blood Borne Virus nursing team. The electronic records of all patients who had started antiviral therapy for HCV between June 2004 and December 2010 were reviewed and data on demographics, HCV status, HCV treatment, planned

duration and actual duration of treatment, compliance, end of treatment response (ETR), sustained viral response (SVR), pre- and post-treatment drug and alcohol use and psychiatric and physical health problems and mortality were recorded. The Blood Borne Virus nurses entered the source patient data onto the EMIS patient record system prospectively as patients were treated. Myself and four medical students interrogated each treated patient's electronic EMIS records, retrieved the required data and entered it into the study database. Outcomes were recorded up to and including July 2011. For patients who had left the service data from their last attendance was recorded. Death registry data was not collected.

Definitions:

a) Treatment was defined as receipt of at least one dose of pegylated interferon.
b) End of treatment response is defined as an undetectable HCV RNA level at the end of treatment.
c) Pre- treatment drug use was defined as the last documented illicit drug use prior to the commencement of antiviral therapy for HCV.
d) Post treatment drug use was defined as the most recently documented illicit drug use after antiviral therapy had finished.
e) Active drug use was defined as documented use of heroin or crack cocaine at, or within 3 months of, commencement of antiviral therapy for HCV.
f) No active drug use was defined as previous use of heroin or crack cocaine, with no documented use in the 3 months prior to treatment commencing.
g) Illicit drug use was quantified from entries in the medical records as daily (drug use on most days); weekly (drug use in most weeks but not most days);

occasional (some use but not every week) and none (no reported illicit drug use).

h) Alcohol use was classified as heavy (over 50 units/ week), moderate (21 to 50 units/ week), occasional (within recommended limits) or none (no current alcohol).

i) Age of infection was taken to be the age at which injection drug use began.

j) Compliance was defined as achievement of the "80/80/80" rule, which is defined as the patient achieving over 80 percent adherence (i.e. receiving over 80% of their total dose of pegylated interferon and ribavirin) for over 80 percent of the expected duration of therapy (McHutchinson JG, 2002).

When analysing the outcomes of the six patients who underwent two courses of therapy treatment and social outcomes were considered separately. When analysing treatment outcomes the first treatment episode outcome was taken and for social outcomes the most recent outcome available after the last treatment episode was taken.

This was an anonymised review of completed service and treatment outcomes and therefore individual patient consent was not required by the research ethics committee.

5.1.4 Statistical analysis:

Data was analysed to assess outcomes in the cohort as a whole and outcomes of those who were actively using illicit drugs were compared with those who were not actively using illicit drugs at the start of treatment.

Minitab 16 was used to perform regression analysis. Graphpad Prism version 5 was used to perform comparative and descriptive analyses. The Mann Whitney test was used to analyse continuous demographic variables and Fishers exact test sex was used to analyse categorical demographic variables. Predictive factors for SVR and factors associated with a reduction in illicit drug use were analysed using regression analysis. The Fishers exact test was used to compare treatment outcomes (ETR, SVR, relapse and non-response), compliance, side effects and reinfection between those were actively injecting drugs and those who had injected drugs in the past. The incidence of possible reinfection was calculated per 100 person years. The possible reinfection rate was derived by calculating the total number of years of patient follow up for subjects who had been re-tested for HCV RNA after successful completion of treatment. This was then divided by the number who tested positive for HCV RNA (indicating possible reinfection), to give the infection rate per person year and multiplied by 100 to assess the number of potential re-infections per 100 person years. The Wilcoxon signed rank test was used to analyse drug and alcohol use outcomes. Disease free survival was assessed using a Kaplan Meier curve.

5.2 Results:

5.2.1 Demographics and response to anti-viral therapy

Data from the database at the Specialist Addiction Unit (SAU) at Mile End Hospital were reviewed and patients who had undergone antiviral therapy for HCV were identified and their case notes were reviewed. A total of 152 patients were treated with pegylated interferon-α and ribavirin for chronic hepatitis C virus by the Blood

Borne Virus nursing team between September 2004 and December 2010. 915 patients were diagnosed with HCV by the Blood Borne Virus team during this period, and therefore 17% of patients commenced antiviral therapy for HCV.

77 patients were actively injecting illicit drugs at the start of treatment, and 75 had a past history of injecting illicit drugs but were not currently injecting.

The demographic and treatment outcomes of the population are shown in table five on the following page.

Table 5: Demographics and treatment outcomes of patients who underwent antiviral therapy

		Overall	%	Injecting drugs at start of treatment	%	Not injecting drugs at start of treatment	%	P value
Total		152		77		75		
Median age of infection		21 (SD 7.21) (95% CI 21.22-23.94)		20 (SD 5.881) (95% CI 19.84-23.22)		21 (SD 8.067) (95% CI 21.36-25.49)		0.35
Median age of diagnosis		38 (SD 8.10) (95% CI 36.55-39.18)		36.5 (SD 8.249) (95% CI 35.48-39.30)		38.5 (SD 8.002) (95% CI 36.5 – 40.21)		0.52
Median age of treatment		40 (SD 8.06) (95% CI 38.81-41.40)		39 (SD 8.218) (95% CI 37.64-41.37)		41 (SD 7.911) (95% CI 38.9-42.54)		0.29
Sex	**Male**	121	80	63	82	58	77	0.55 (OR 1.13) 95% CI 0.6-2.9
	Female	31	20	14	18	17	23	
HCV Genotype	**1/ 4**	69	45	31	40	38	51	0.19 (OR 0.64) (95% CI 0.34-1.22)
	2/ 3	82	54	46	60	36	48	
	Mixed (3/4)	1	1	0	0	1	1	
Compliance		106	70	52	68	54	72	0.60 (OR 0.81) (95% CI 0.4-1.61)
End of treatment response (ETR)		105	69	54	70	51	68	0.86 (OR 1.1) (95% CI 0.56-2.2)
Sustained viral response	**All**	83	55	45	58	38	51	0.42 (OR 1.34) (95% CI 0.72-2.6)
	G1/4	30	43	14	45	16	42	0.81 (OR 1.13) (95% CI 0.43-2.9)
	G2/3	52	63	31	67	21	58	0.49 (OR 1.48) (95% CI 0.6-3.66)
Non-response		39	26	19	25	20	27	0.85 (OR 0.9) (95% CI 0.43-1.87)
Relapse		18	12	9	12	9	12	0.79 (OR 0.81) (95% CI 0.28-2.3)
Lost to follow up		12	8	4	5	8	11	0.24 (OR 0.45) (95% CI 0.13-1.6)

Data was available for all patients on median age of infection, diagnosis and treatment, sex, HCV genotype and compliance. Data was available for end of treatment response in 146 patients, and overall treatment outcome in 140 patients. The data was analysed on an intent to treat basis and therefore the denominator for overall treatment outcome percentages in table five is the treated cohort of 152 patients.

There were no significant differences in demographics or treatment outcomes between those who were actively injecting heroin and those who were not. Note that all patients were attending a Specialist Addiction Unit and therefore all patients had on-going health disorders relating to drug use.

5.2.2 Follow up:

152 Patients were followed up for between 0 and 79 months after completion of HCV treatment, with a median follow up of 21 months, and an average of 27 months. 16 patients were followed up for < 6 months, 27 patients for 6-12 months, 40 patients for 1-2 years, 30 for 2-3 years, 13 for 3-4 years, 17 for 4-5 years, 4 for 5-6 years and 5 for over 6 years.

5.2.3 Mortality:

Overall survival of the cohort to the end of the follow up period was 97% (147/152). There were 5 deaths, none of which occurred on or were related to treatment. None of the deaths where the cause was known were HCV related. One death was due to suicide two years after treatment cessation, and one was due to acute renal failure and septicaemia 31 months after completion of treatment. The cause of the remaining three deaths was unknown but they occurred 48, 34 and 21 months after treatment,

and so are unlikely to be treatment related. Four of the deaths occurred in non-responders to treatment, and one death occurred in a patient who failed treatment. There were no deaths in patients who responded to treatment. Three deaths occurred in patients who were actively using illicit drugs at the start of treatment (3/77, 4%) and two deaths (2/75, 3%) occurred in patients who were not using illicit drugs at the start of treatment. There was no significant difference in mortality between people who were actively injecting drugs at the start of treatment, and those who were not (p=1).

A Kaplan Meier curve of overall survival is shown in figure 18 below:

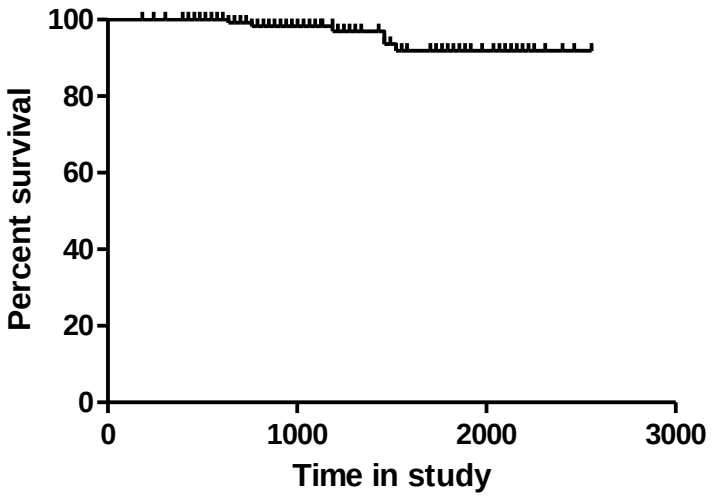


Figure 18 Kaplan Meier curve of overall survival in days

5.2.4 Patients who became HCV RNA positive after attainment of SVR:

105 patients (69%) obtained an ETR, and 83/152 (55%) achieved an SVR. In patients who achieved an SVR, 45 (54%) had undergone repeat testing for HCV RNA at the time of data analysis (July 2011). Testing was conducted an average of 31 months after treatment finished (median of 23 months). Two (2/45, 4.4%) patients became HCV

RNA positive after successful completion of treatment. This may indicate re-infection, but in the absence of repeat genotyping or phylogenetic analysis reinfection cannot be proven. Both patients were actively injecting drugs at the time of starting treatment and continued injection drug use throughout therapy. The first patient had a positive HCV RNA result 22 months after completing treatment and at the time was sharing filters. The second patient had HCV RNA detected 56 months after completion of treatment and reported ongoing injecting during and after treatment, but with clean paraphernalia.

38 of the 83 (46%) patients who attained an SVR did not have further HCV RNA samples sent. Re-testing was not performed in 18 (47%) as they were no longer attending specialist addiction services, and in 20 as they were no longer engaged in high-risk behaviour (it is the policy of the BBV team only to re-test HCV RNA in patients who are engaging in behaviour that puts them at risk of re-infection).

Thus of 83 patients who had achieved an SVR data on the presence of HCV RNA post successful treatment was available for 45 and HCV RNA was detected in two. If these HCV RNA positive results represent reinfection, the reinfection rate in the re-tested cohort is 1.75 per 100 person years. There was no significant difference ($p=0.53$) in the risk of potential re-infection between people who were and were not actively injecting drugs at the start of treatment.

5.2.5 Disease Free Survival

Disease free survival after successful treatment was 98%, with two re-infections and no deaths. A Kaplan Meier curve of disease free survival can be seen below (figure 19).

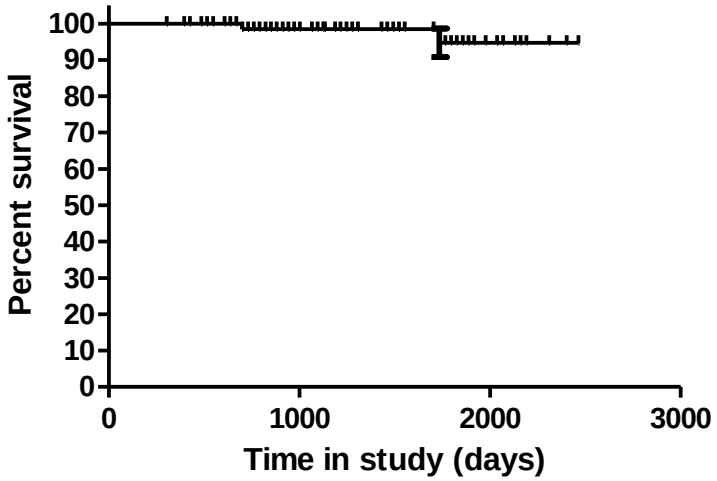


Figure 19: Kaplan Meier plot of disease free survival

5.2.6 Adverse events:

The majority of patients reported adverse events with treatment, but there was no significant difference in the prevalence of adverse events between those who were injecting drugs at the start of treatment and those who were not. The prevalence of adverse events overall and in both groups is detailed in table six on the following page

Table 6: Adverse events associated with treatment

Side effect	Overall	%	Injecting drugs at start of treatment	%	Not injecting drugs at the start of treatment	%	P value
Any	106	69	55	71	51	68	0.72
Haematological	14	9	6	8	8	11	0.59
Influenza like symptoms	29	19	13	17	16	21	0.54
Headache	24	16	14	18	10	13	0.27
Lethargy	25	16	14	18	11	15	0.66
Gastrointestinal	45	30	22	29	23	31	0.86
Dermatological	19	13	9	12	10	13	0.81
Insomnia	13	9	9	12	4	5	0.25
Pruritis	13	9	8	10	5	7	0.56
Infection	6	4	4	5	3	4	1
Psychiatric	44	29	23	30	21	28	0.86

Twenty four patients (16%) had to stop treatment due to side effects. The most common reason for discontinuation of treatment was psychiatric side effects in 7 patients (29%), followed by influenza like symptoms in 6 patients (25%) and haematological side effects in 3 patients (12.5%). One patient had a severe adverse event, a psychotic episode which required hospitalisation.

5.2.7 Analysis of factors that predict Sustained Viral Response

Nineteen factors were analysed by regression analysis to assess if they predicted sustained viral response. The analysed factors were age when treated, actual treatment course, compliance, age, age diagnosed with HCV, planned treatment course, the presence of side effects, HCV RNA at 12 weeks into treatment, presence of cirrhosis, age started injection drug use, age stopped injection drug use, year stopped injection drug use, total number of years injecting, pre-treatment heroin injection drug use, pre-treatment crack cocaine use, pre-treatment alcohol use, end of treatment response, sex and HCV genotype.

Regression analysis identified the five strongest predictors for SVR. End of treatment response was the only significant predictor. Pre-treatment heroin and crack use did not appear in the model (up to 7 decimal places) and so had very limited predictive value for SVR. The results can be seen in table seven below:

Table 7: Regression analysis of factors that predict SVR

Predictor	Coef	SE Coef	T	P	Rank of Significance
ETR	1.4187	0.3597	3.94	0.001	1
Age	-0.2075	0.1223	-1.70	0.105	2
Age when treated	0.1633	0.1032	1.58	0.129	3
Compliance	-0.4840	0.3359	-1.44	0.165	4
HCV genotype	-0.09650	0.07050	-1.37	0.186	5

This model has a high R^2, low residual error and a strong resemblance to the normal distribution as seen below in figure 20 and figure 21. It can be seen in the second figure that there are only two outliers.

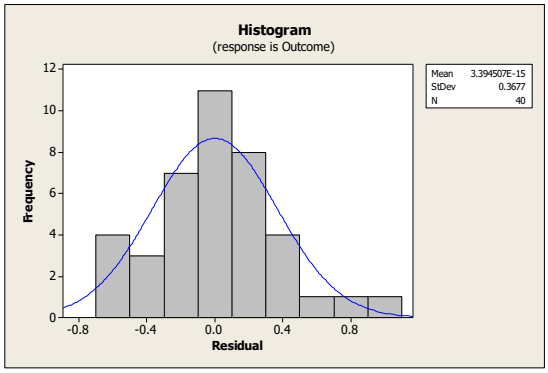


Figure 20 Histogram of response versus outcome

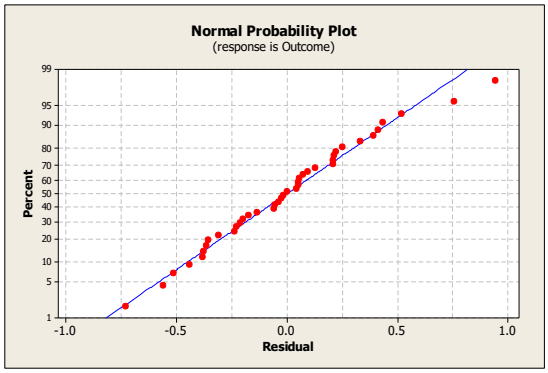


Figure 21 Normal probability plot of response versus outcome

5.2.8 Impact of anti-viral therapy on illicit drug use and alcohol consumption:

Data was recorded on heroin use (either current or previous) in 146 patients pre-treatment, and in 133 patients post-treatment. Crack cocaine use was recorded pre-treatment in 58 patients and post-treatment in 59 patients. Alcohol use was recorded pre-treatment in 74 patients and post-treatment in 72 patients.

An analysis was undertaken to assess if a participants status of being pre- or post-HCV treatment impacted on illicit drug and alcohol use. Analyses were performed on overall drug and alcohol use and quantified drug and alcohol use.

5.2.8.1 Heroin use pre- and post- antiviral therapy for HCV

The quantified difference in intravenous (IV) heroin use before and after antiviral therapy can be seen in table eight below.

Table 8: Intravenous heroin use pre- and post-treatment

	Pre–treatment (N)	%	Post-treatment (N)	%	P value
Daily IV heroin use	22	15	6	5	0.0045
Weekly IV heroin use	31	21	22	17	0.36
Occasional IV heroin use	24	17	30	23	0.22
No current IV heroin use	69	47	75	56	0.15

There was a significant reduction in daily use of heroin, but overall heroin use did not reduce post-treatment.

The number of patients who were actively injecting heroin reduced after antiviral therapy for HCV but the difference was not significant (p=0.15) (see figure 22 below).

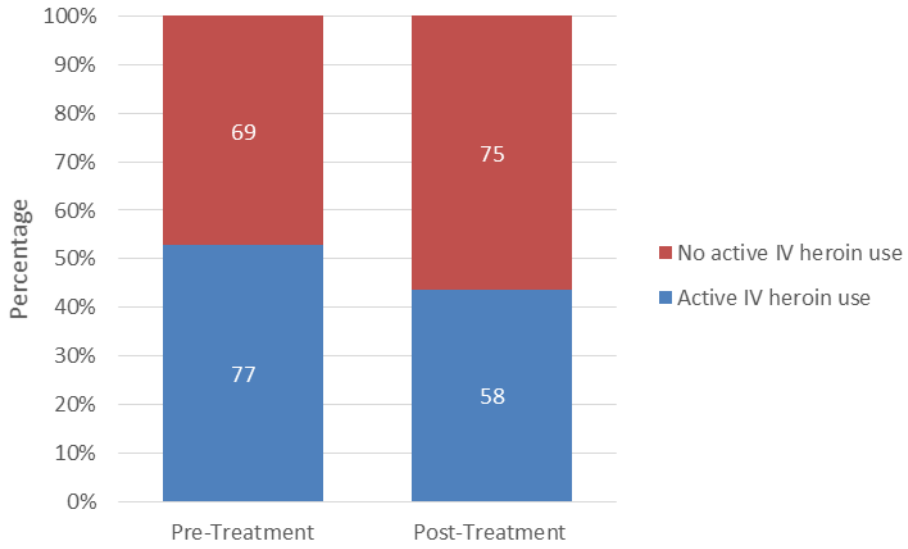


Figure 22: Intravenous heroin use pre- and post-HCV treatment

5.2.8.2 Crack cocaine use pre- and post-treatment for HCV

The overall change in crack cocaine intake of the cohort pre- and post- antiviral therapy can be seen in table nine on the following page.

Table 9: crack cocaine use pre- and post-treatment

	Pre-treatment (N)	%	Post-treatment (N)	%	P value
Daily crack cocaine use	18	31	3	5	0.0002
Weekly crack cocaine use	18	31	11	19	0.14
Occasional crack cocaine use	16	28	15	25	0.84
Ex-crack cocaine use	6	10	30	51	<0.0001

A highly significant reduction of < 0.0001 in overall crack cocaine use and daily crack cocaine use was seen post-treatment. The reduction in overall crack cocaine use can be seen in figure 23 below.

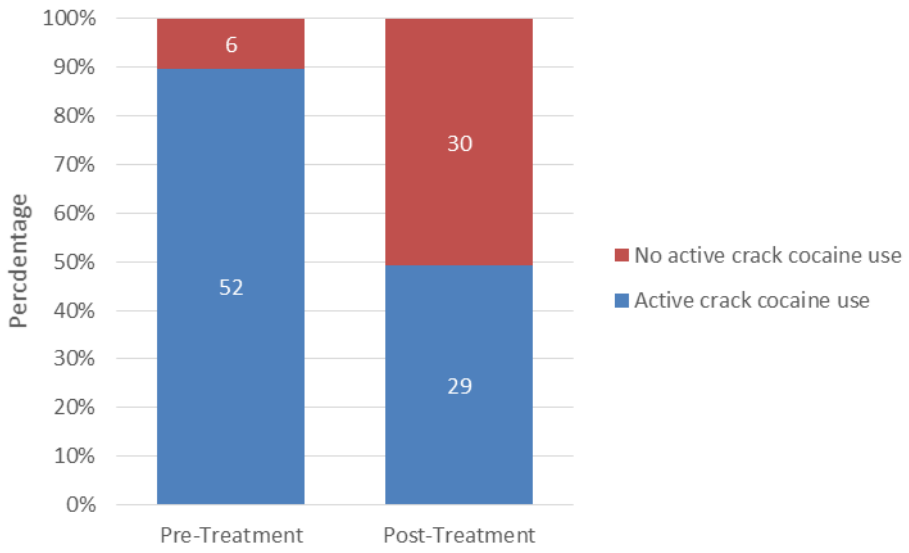


Figure 23 Overall reduction in crack cocaine use pre- and post-HCV treatment

5.2.8.3 Alcohol use pre- and post-treatment for HCV

The difference in alcohol intake of the cohort pre- and post-treatment can be seen in table 10 on the following page.

Table 10: Alcohol intake pre- and post-antiviral therapy for HCV

	Pre-treatment (N)	%	Post-treatment (N)	%	P value
Heavy alcohol intake	26	35	18	25	0.21
Moderate alcohol intake	9	12	12	17	0.49
Alcohol intake within advised limits	23	31	19	26	0.59
No alcohol intake	16	22	23	32	0.19

There was no significant difference in alcohol intake pre- and post-antiviral therapy for HCV.

5.2.9 Predictors of reduction in illicit drug and alcohol use:

Twenty factors were examined by regression analysis to see if they predicted reduction in intravenous heroin use, crack cocaine use or alcohol use post- HCV treatment. The factors were age, age when treated, actual treatment course (weeks), compliance, age diagnosed HCV, presence of side effects during treatment, post-treatment heroin injection use, post-treatment crack cocaine use, pre-treatment alcohol intake, age started injecting, age stopped injecting, years injecting, year stopped injecting, ETR, sex, HCV genotype, Pre-treatment heroin injection use, pre-treatment crack cocaine use, post-treatment alcohol use and outcome.

5.2.9.1 Predictors of reduction in heroin use:

The top 5 factors predicting a reduction in heroin use are detailed in table 11 on the following page.

Table 11: Regression analysis of factors that may contribute to a reduction in heroin use

Predictor	Coef	SE Coef	T	P	Rank of significance
Post-treatment Crack cocaine use	-0.7532	0.3091	-2.44	0.028	1
Pre-treatment Crack cocaine use	0.7214	0.3346	2.16	0.048	2
Year of birth	-0.6309	0.3756	-1.68	0.114	3
Age when treated	-0.4464	0.2806	-1.59	0.132	4
Age diagnosed with HCV	0.2035	0.1536	1.32	0.205	5

The histogram of the regression model shows a good fit to the normal distribution with a slight negative skew (see figures 24 and 25 below).

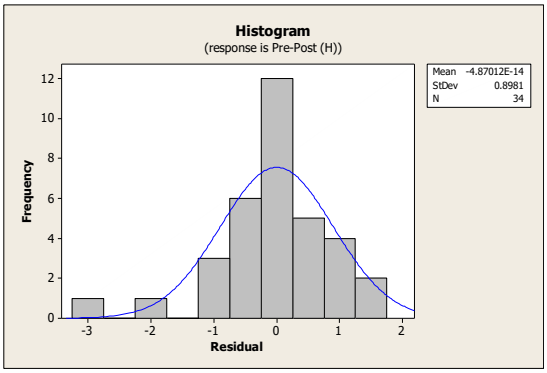


Figure 24 Histogram of model response versus treatment course

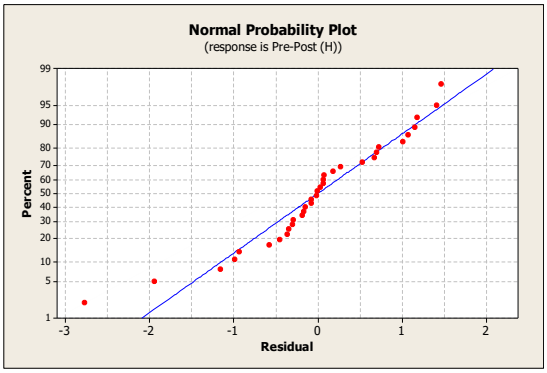


Figure 25: Normal probability plot

Regression analysis showed that pre- and post-treatment crack use were the only factors significantly associated with reduction in heroin use (p = 0.048 and 0.028 respectively).

There was a weak but positive correlation between reduction in crack cocaine use and reduction in heroin use as shown in figure 26 below.

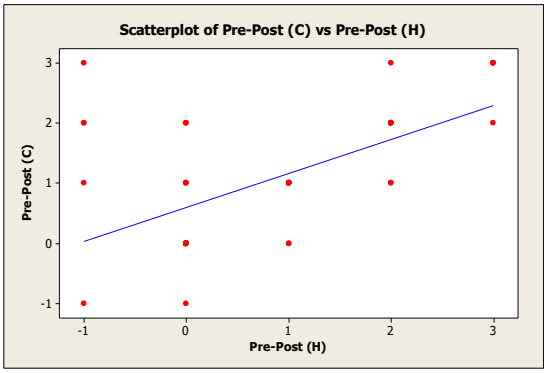


Figure 26 Reduction in crack cocaine use plotted against reduction in heroin use

5.2.9.2 Predictors of reduction in crack cocaine use:

The top five predictors of a reduction in crack cocaine use from the regression model are detailed below in table 12.

Table 12: Regression analysis five best predictors of reduction in crack cocaine use

Predictor	Coef	SE Coef	T	P	Rank of significance
Pre-treatment injection heroin use	0.5613	0.2795	2.01	0.063	1
Post-treatment injection heroin use	-0.3065	0.2058	-1.49	0.157	2
Pre-treatment alcohol use	0.3008	0.1927	1.56	0.139	3
ETR	-1.380	1.055	-1.31	0.211	4
Sex	-0.4932	0.5212	-0.95	0.359	5

There were no significant predictors of reduction in crack cocaine use.

This was a strong model with a slight negative skew, but a true likeness to normality as seen in figures 27 and 28 below.

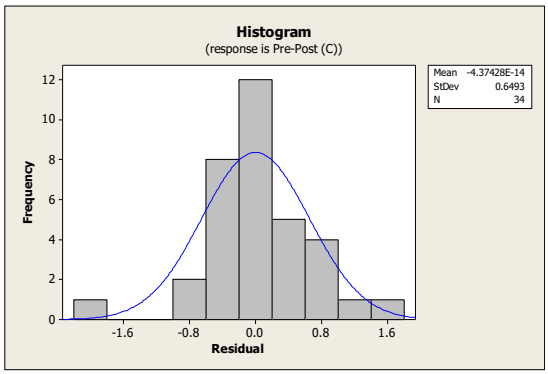


Figure 27: Histogram of response versus pre-post

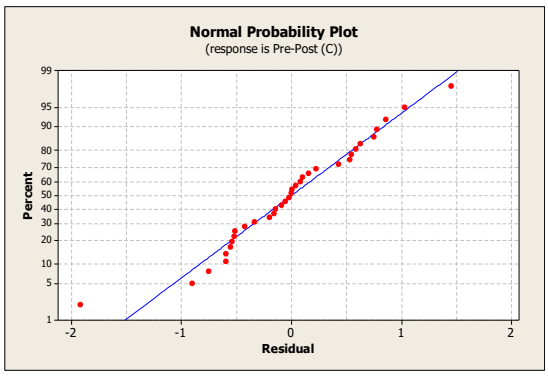


Figure 28: Normal probability plot

5.2.9.3 Predictors of reduction in alcohol intake:

The top predictive factors from the model for a reduction in alcohol use are detailed in table 13 on the following page.

None of the factors described were significantly predictive for reduction in alcohol use, with the strongest predictor on multivariate regression analysis being age of stopping injecting (p=0.177).

Table 13: Regression analysis of predictive factors for reduction in alcohol use

Predictor	Coef	SE Coef	T	P	Rank of significance
Age stopped injecting	7.519	5.309	1.42	0.177	1
HCV genotype	-0.9721	0.7073	-1.37	0.189	2
Years injecting	-7.260	5.288	-1.37	0.190	3
Age started injecting	-7.226	5.278	-1.37	0.191	4
ETR	2.282	1.932	1.18	0.256	5

This model has a larger error spread and deviates away from the normal distribution, as can be seen in figures 29 and 30 below.

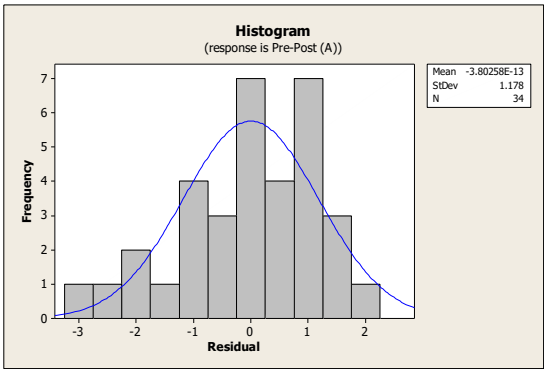


Figure 29 Histogram of response pre versus post

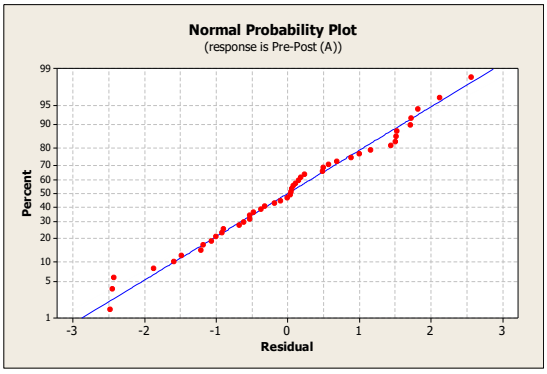


Figure 30: Histogram of normal probability plot

5.3 Summary:

This retrospective observational cohort study indicates that HCV therapy for PWID is safe and effective, and over treatment a significant reduction in overall crack cocaine use, and daily heroin use was seen. Crack cocaine use appeared to predict reduction in heroin use. Over a median follow up of 21 months there was a low rate of re-infection and low mortality. An infection free survival rate of 98% was seen in those who were successfully treated and in whom outcomes were known. The findings of this study will be discussed in detail in chapter eight.

5.4 Discussion of methodology:

The studies strength is related to the fact it was the largest study to date examining the impact and long term follow up of antiviral therapy in a cohort of patients actively using illicit drugs, and the only study to examine whether illicit drug use reduces after treatment for HCV.

There are a number of methodological issues inherent in the study design and the results must be interpreted with a great deal of caution due to these. An overview of the methodological issues is given here, and a more detailed discussion can be seen in chapter eight. The retrospective observational cohort nature of this study leads to some important limitations including recall and reporting bias, a lack of ability to control for confounding factors and the lack of a control arm (Mann, 2003). As the data source used was contemporaneous “real life” medical records there were a number of areas of missing data and a significant proportion of patients were lost to follow up, making conclusions on mortality, reinfection and drug and alcohol use outcomes unreliable. There was no control arm of patients who did not receive treatment, and so it is not possible to conclude that the reduction of drug use seen was due to treatment for Hepatitis C rather than contact with Specialist Addiction Services, and no conclusions on mortality outcomes relating to Hepatitis C treatment in PWID can be made. A matched control group of patients treated for Hepatitis C who were not illicit drug users over the same time period would have made comparisons about SVR outcomes between PWID and those who do not more valid. In addition, while some patients were followed up for over six years, the median length of follow up was 21 months, which is unlikely to be an adequate length of follow up to accurately assess mortality and reinfection. A further issue when assessing reinfection is the lack of phylogenetic analysis on samples from those who were reinfected. When considering the analysis a potential criticism is the use of statistical analysis to compare the baseline demographics of treated patients. This is not recommended in reporting of randomised controlled studies, as randomisation should ensure that any differences seen are due to chance (Knol MJ, 2011). In this study they were reported as this was a

retrospective observational cohort study, and the lack of randomisation means that any differences between groups cannot be assumed to be due to chance. It was therefore felt to be of interest to see if there were any differences in baseline characteristics between groups to aid with comparisons.

The methodological issues relating to mortality, reinfection rates and drug and alcohol outcomes are examined in greater detail in chapter eight.

6 Nurse initiation of antiviral therapy in people who inject drugs

There is a need to improve the low treatment rates of HCV in PWID, but it is not clear how this can be achieved from the currently available evidence. It was hypothesised that in the "East London model" of HCV treatment delivered in Specialist Addiction Services the requirement to see a doctor at a distant clinic before starting antiviral therapy may reduce treatment uptake. Therefore this study aimed to discover if nurse initiated treatment of HCV in PWID increased initiation and completion rates of antiviral therapy when compared with doctor initiated therapy. A matched cluster randomised design was used.

6.1 Methods:

This prospective matched cluster randomised controlled trial was designed to assess whether nurse initiation of antiviral therapy for HCV in PWID results in a higher proportion of PWID starting and complying with therapy than clinician led initiation of therapy.

6.1.1 Participants:

Participants were eligible for inclusion into the study if they were aged over 18 years old, attended a Blood Borne virus outreach clinic and had been diagnosed with chronic hepatitis C.

6.1.2 Study design:

The trial was designed as a prospective matched cluster randomised controlled trial. Nurse initiated therapy was offered in the intervention clinics while usual treatment in Specialist Addiction Services in North East London (doctor initiated therapy) was offered in the control clinics. The unit of inference was at the individual level and unit of randomisation was at the clinic level.

The three Specialist Addiction units and outreach clinics were cluster randomised into two matched groups. A matched cluster randomisation was undertaken and the clinics were matched based on location, number of patients with chronic HCV and type of clinic.

6.1.3 Study Protocol:

The doctor initiated sites acted as control arms and usual care, as detailed in section 5.1.2 was provided. At each control site all patients were made aware that they were involved in a research project by a poster (see appendix 11) and patient information sheets (see appendix 12) which were prominently displayed so that all attending the clinic were aware of the study. Patients who were found to be chronically infected with hepatitis C were provided with counselling and support and offered the opportunity to undergo antiviral therapy by their Blood Borne Virus nurse in the usual manner (see section 5.1.2). During this counselling process patients were informed about the study, provided with a written patient information sheet and informed that certain data would be collected for the purposes of the study if they decided to participate. Patients were asked to take the patient information sheet away to read.

When they returned to the clinic they were asked if they wished to participate and if they did were asked to sign a consent form (see appendix 13) agreeing to data collection. Those patients wishing to undergo antiviral therapy were provided with therapy as per standard Specialist Addiction Services protocol. Those who did not wish to undergo therapy were invited to sign a consent form agreeing to their data being collected.

The clinics in the nurse initiated arm were intervention clinics which assessed the new model of nurse initiation of therapy. At these clinics attendees who were diagnosed with chronic HCV were offered counselling and support in the usual manner by their Blood Borne Virus nurse. During this consultation patients were counselled about hepatitis C treatment and provided with written patient information sheets (see appendix 14) about the study which they were asked to take away and read. When they returned they were asked if they wished to participate in the study and if they agreed were asked to provide written informed consent (see appendix 15).

Once patients had agreed to participate in the nurse initiated arm of the study they were assessed using a defined safety protocol (see appendix 16).

The pre-determined safety criteria excluded those at higher risk of side effects including patients with clinical or biochemical evidence of cirrhosis, anaemia, thrombocytopenia or leucopenia, unhealed wounds, sepsis or unstable psychiatric disorders. Any patients who did not fulfil the safety criteria were referred to one of the Specialist Addiction Units for consideration of treatment. If participants fulfilled the safety criteria for treatment in the nurse initiated arm they were offered immediate antiviral therapy administered by Blood Borne Virus nursing staff in outreach clinics.

Treatment was administered in line with the study protocol (see figure 31 on the following page). Compliance with therapy was assessed by direct questioning, examination of dossett boxes and by review of blood tests (leucopenia, anaemia and thrombocytopenia) that suggest compliance. Therapy in the community clinics was supervised by a medically qualified research fellow for the duration of the study period.

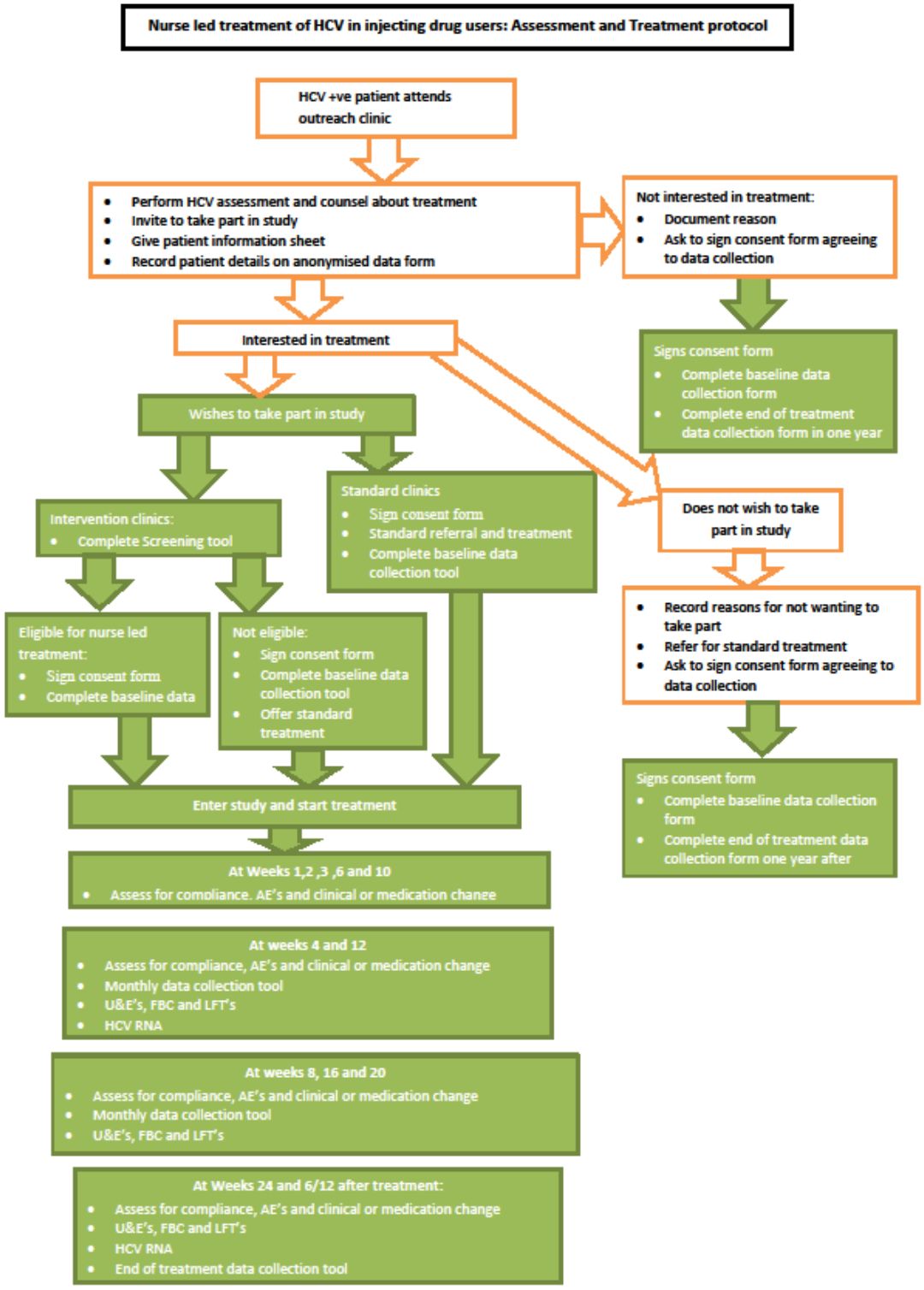


Figure 31: Study protocol

Patients who decided not to participate in either arm of the study were offered treatment in the usual way i.e. they underwent the standard Specialist Addiction Services treatment. These patients were asked to provide written consent for baseline data collection (see appendix 17).

6.1.4 Data collection:

Data collected from those who agreed to participation in the study included demographic data on age, sex, medical history, psychiatric history, drug and alcohol history, social history, accommodation status, employment status. Serological values including FBC, U&E's, LFT's, TFT's, autoantibody screen, HIV, HBsAg and HCV RNA were documented.

The following outcome data was collected; the number offered and who accepted treatment in each arm, the number refusing intervention treatment in each arm, and who wished to have treatment delivered by the alternative method, the number judged unsuitable for treatment in each arm and why and the number who initiated treatment in each arm.

In those who started treatment data on compliance with treatment, side effects of treatment, drug and alcohol use and psychiatric symptoms before, during and after treatment, planned and actual treatment course and whether they achieved an EVR, ETR or SVR were recorded.

The "80/80/80" rule was used to assess compliance, which is defined as the patient achieving over 80 percent adherence (i.e. receiving over 80% of their total dose of

pegylated interferon and ribavirin) for over 80 percent of the expected duration of therapy (McHutchinson JG, 2002).

Drug use was quantified according to the following criteria: 0 = no current usage, 1 = less than once monthly, 2 = 2-4 times per month, 3 = once a week, 4 = 2-3 times per week, 5 = once daily, 6 = more than once daily.

Depressive and psychotic symptoms were assessed using the PHQ-9 scoring system, and a five point questionnaire (see appendix 18).

6.1.5 Statistical methods:

Data was collated using Excel and analysed with Graphpad prism 5. The Mann Whitney, Chi-squared, Kruskal-Wallis, Fishers exact test and descriptive statistics were used to analyse demographic variables. The Wilcoxon signed rank test was used to assess pre- and post-treatment illicit drug and alcohol use characteristics in patients. The Fisher's exact test was used to compare categorical outcomes between the nurse initiated and doctor initiated arms, and treated versus untreated patients.

Power calculation:

It was estimated that to achieve an 80% power to reject the null hypothesis, with a significance level of 0.05 90 patients should be offered treatment in each group. As only 13% of patients currently access treatment, an increase in uptake to 30% would be a worthwhile outcome and in line with current treatment rates in people who do not inject drugs. We planned to offer therapy to 90 patients in the nurse initiated arm and 90 patients in the doctor initiated arm and anticipated that 27 and 12 patients

would access therapy respectively. This sample size was calculated to have an 80% power to detect a significant difference in treatment initiation.

6.2 Results:

6.2.1 Randomisation of clinics:

The three Specialist Addiction units and six of the outreach clinics were cluster randomised into two matched groups. Clinics were matched based on location, number of patients with chronic HCV and type of clinic (see table 14 below).

Table 14: Clinic matching

Clinic				Matched clinic			
Clinic name	**Clinic location**	**Clinic type**	**Number with HCV**	**Clinic name**	**Clinic location**	**Clinic type**	**Number with HCV**
Tower Hamlets SAU*	Tower Hamlets	Specialist Addiction Unit	95	Health E1	Tower Hamlets	GP practice for the Homeless	89
Newham Specialist Substance Misuse Team (SSMT)	Newham	Specialist Addiction Unit	76	Homerton SAU	Hackney	Specialist Addiction Unit	85
Hackney Community Drugs Team (CDT)	Hackney	Lifeline (Charity)	89	Tower Hamlets CDT	Tower Hamlets	Lifeline (Charity)	64
Drugs and Alcohol Service for London (DASL)	Newham	Charity	11	Newham Healthy Option Team (HOT)	Newham	Needle Exchange	9
Newham CDT**	Newham	In-Volve (Charity)	31				

* Health E1 was matched with a Specialist Addiction Unit, as this GP practice for the homeless serves patients with similar complex addiction needs to the Specialist Addiction Units

** The Newham CDT site was not matched as there were 9 sites in total and this site was randomly assigned independently to either arm.

One of each pair was then randomly assigned to either the intervention arm of nurse initiated therapy, or the usual care, doctor initiated therapy arm as seen in figure 32 below.

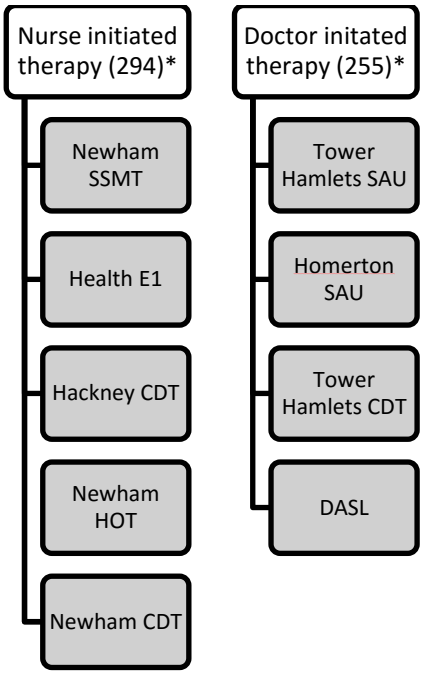


Figure 32: Initial sites in each arm

* The figure in brackets indicates the number of patients with chronic HCV in each arm

The In-Volve charity, which ran the Newham Community Drugs Team went into administration on 4th November 2011, and was no longer able to participate in the study. One further site, the Drug Improvement Project (DIP) was later recruited to the nurse initiated arm on 22nd March 2012. The delay related to the length of time it took to obtain site specific approval. At the end of the project the final sites in each arm were as follows (see Figure 33).

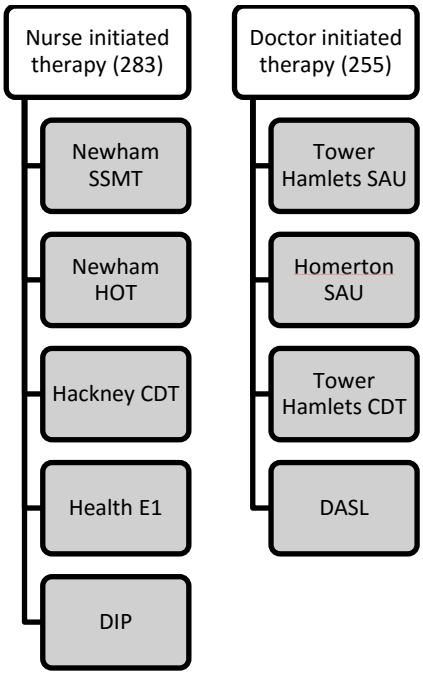


Figure 33: Final sites in each arm

6.2.2 Demographics:

The demographics of the overall study population are shown below in table 15.

Table 15: Study population demographics

		Nurse initiated therapy arm (%) (SD) (95% CI)	Doctor initiated therapy arm (%) (SD) (95% CI)
Total in study		40	65
Median age		40 (SD 8.44) (95% CI 37.2-42.6)	42 (SD 8.52) (95% CI 41.1-45.3)
Sex	**Male**	32 (80)	48 (74)
	Female	8 (20)	17 (26)
HCV Genotype	**1**	21 (53)	27 (42)
	Non-1	19 (47)	34 (52)
	NK	0	4 (6)
Median age first injected drugs		21 (SD 7.6) (95% CI 19.9–25.7)	20 (SD 8.2) (95% CI 19.4– 24.5)
Current intravenous heroin use		11 (33)	22 (34)
Current crack cocaine use		10 (30)	27 (42)
Median units of alcohol per week		8 (SD 45.83) (95% CI 12.4 – 44.9)	28 (SD 94.64) (95% CI 36.3 – 84)
Psychiatric co-morbidity		12 (36)	35 (55)
Median PHQ-9 score		11 (SD 7.42) (95% CI 6.7–12.5)	13 (SD 7.27) (95% CI 10.3–14.4)
Medical co-morbidity		13 (39)	38 (59)
No Fixed Abode		6 (18)	6 (9)
Education level > 16 years		14 (42)	12 (19)
Criminal record		29 (88)	61 (95)

There were no significant differences in baseline characteristics between the groups, except for education level (p=0.02, OR 3.2, 95% CI 1.3-8.1).

6.2.3 Patient treatment disposition:

One hundred and thirty eight patients were screened for participation in the study in total, sixty two in the nurse initiated therapy arm and seventy six in the doctor initiated therapy arm of the study.

The treatment disposition of approached patients can be seen in figure 34 below

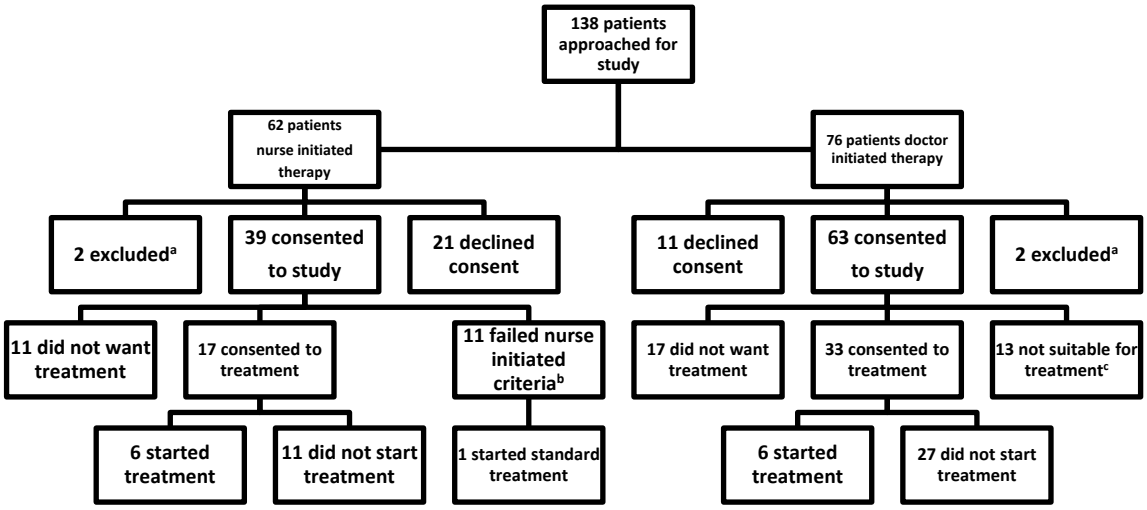


Figure 34 Patient treatment uptake

[a] Two patients in each arm were excluded as they had already been treated and were awaiting triple therapy at the time of study recruitment.

[b] Patients in the nurse initiated arm who failed the safety criteria for treatment were offered standard Specialist Addiction Services treatment and their treatment

outcomes were removed from the analysis. In the nurse initiated arm 11 of the 28 patients (39%) who wished to have nurse initiated treatment could not as they did not fulfil the safety criteria. Psychiatric co-morbidity was the most common reason and occurred in 5/11 patients (45%). Two of these patients had significant depression as measured by PHQ9 scores of 20 or over, and three of the patients had recent episodes of self-harm. Four patients did not fulfil the nurse initiated treatment criteria due to medical co-morbidities including alopecia (indicating possible underlying autoimmune disease), cirrhosis, sickle cell trait and HBV co-infection. One of these patients initiated treatment outside of the study.

[c] In the doctor initiated arm 13/46 (28%) of patients who wished to have treatment had contraindications to treatment. In 10 patients (77%) this was due to medical co-morbidities. One patient had an open leg wound, five patients had decompensated cirrhosis, one patient had HIV and TB, one patient was pregnant, one patient was being treated for TB and one patient had previously had a lung transplant and had COPD. Two patients had psychiatric co-morbidities, one of whom had recently attempted suicide.

There was no significant difference between the arms in the number of patients initiating therapy. The treatment rate, measured on an intention to treat basis was 10% (6/62) in the nurse initiated arm and 8% (6/76) in the doctor initiated arm (p=0.53, OR 1.71, 95% CI 0.51-5.71).

There was no difference between the nurse initiated and doctor initiated arms in the number of patients who could not have treatment (p=0.44, OR 1.64, 95% CI 0.61-4.43). While there were more patients who could not have treatment in the doctor initiated

arm due to medical co-morbidities than the nurse initiated arm, this did not amount to a significant difference (p=0.095, OR 0.17, 95% CI 0.02-1.10).

In the nurse initiated arm 11/39 (28%) and doctor initiated arm 17/63 (27%) chose not to have treatment (p = 1, OR = 1.06, 95% CI 0.44-2.60). There was no significant difference in the number of patients in the study who chose not to have treatment in each arm.

6.2.4 Demographics of patients by treatment uptake:

An analysis was undertaken to see if demographic characteristics differed amongst patients who consented to treatment and who subsequently did or did not start treatment in each arm. The results can be seen in table 16 on the following page.

Patients in the nurse initiated arm who started treatment were significantly more likely to have remained in education after the age of 16 (p=0.042) but there were no other differences in baseline demographics between those who started treatment and those who did not.

Table 16: Demographics of patients who consented for treatment in each arm by treatment uptake:

		Nurse initiated arm		Doctor initiated arm	
		Started Treatment (%)	**Did not start treatment (%)**	**Started treatment (%)**	**Did not start treatment (%)**
Total in study		6	11	6	27
Median age		36 (SD - 6.38) (95% CI 30.8-44.2)	41 (SD – 10.28) (95% CI 35.1-48.9)	41 (SD – 5.2) (95% CI 34.87-45.79)	41 (SD – 8.43) (95% CI 38.37-45.04)
Sex	**M/F**	5/1 (83/17)	8/3 (73/27)	5/1 (83/17)	19/8 (70/30)
HCV Genotype	**1**	2 (33)	7 (64)	4 (67)	13 (48)
	Non-1	4 (67)	4 (36)	2 (33)	14 (52)
Median age first injected drugs		20 (SD 6.24) 95% CI 14.28-27.38	19 (SD 8.25) (95% CI 15.48-29.27)	18 (SD 4.98) 95% CI 12.22-24.58	20 (SD 7.45) 95% CI 18.61-25.39
Current intravenous heroin use		1 (17)	4 (44)	2 (33)	10 (37)
Current crack cocaine use		1 (17)	1 (11)	2 (33)	8 (30)
Median units of alcohol per week		10 (SD 14.62) 95% CI 2.01-28.68	8 (SD 26.05) (95% CI 4.3-44.36)	51 (SD 61.14) 95% CI 6.9-121.3	14 (SD 88.10) 95% CI 16.67-86.37
Psychiatric co-morbidity		2 (33)	3 (33)	2 (33)	17 (63)
Median PHQ-9 score		9 (SD 4.23) 95% CI 2.89-11.77	8 (SD 7.27) 95% CI 1.55-13.7)	17 SD 10.25) 95% CI -1.81-30.81	12 (SD 6.60) 95% CI 9.98-15.84
Medical co-morbidity		0	4 (44)	3 (50)	14 (52)
No fixed abode		0	2 (22)	0	2 (7)
Education level > 16 years		5 (83)	3 (33)	1 (17)	7 (26)
Criminal record		4 (67)	7 (78)	5 (83)	26 (96)

6.2.5 Time to starting treatment:

The time from agreeing to treatment to starting treatment ranged from 14-124 days in the nurse initiated arm to 54-133 days in the SOC arm. The median number of days to starting treatment was 30 days in the nurse initiated arm and 105 days in the doctor initiated arm (p=0.026) and the mean number of days to starting treatment was 45 days in the nurse initiated arm and 99 days in the doctor initiated arm.

6.2.6 Compliance with therapy:

Compliance with therapy according to the 80/80/80 rule on an intention to treat basis was achieved by 83% (5/6) of patients in the nurse initiated arm and 83% (5/6) of patients in the doctor initiated arm (p=1, OR=1, 95% CI=0.048-20.83).

One patient in the nurse initiated arm, who was due to have 24 weeks of treatment, did not fulfil the 80/80/80 rule. This was due to the patient becoming lost to follow up after week 12 and not completing their course of treatment. They were compliant with therapy until week 12.

A further patient in the doctor initiated arm had their treatment stopped after 7 weeks due to severe thrombocytopenia and poor response to treatment. They were compliant with treatment until it was stopped due to side effects.

6.2.7 Treatment outcomes in each arm:

Six patients started treatment in each arm. 5/6 (83%) and 4/6 (67%) achieved an end of treatment response (ETR) in the nurse initiated arm and doctor initiated arm respectively (p=ns, OR 2.5, 95% CI 0.16-38.6).

Sustained virological response was achieved by 4/6 (67%) of patients in the nurse initiated, and 3/6 (50%) of patients in the doctor initiated arm (p=ns, OR = 2, 95% CI 0.19-20.63). In the doctor initiated arm one patient was a non-responder after 12 weeks of therapy and treatment was stopped in line with current guidance (EASL, 2014) and one patient was lost to follow up after treatment finished due to incarceration. In the nurse initiated arm one patient relapsed after achieving an ETR and one patient was lost to follow up during treatment.

6.2.8 Side Effects and Serious Adverse Events in each arm

Side effects of therapy are detailed below in table 17.

Table 17: Side effects of therapy

	Total		Nurse initiated arm		Doctor initiated arm		P value
	N	%	N	%	N	%	
Flu like symptoms	6	46	2	33	4	57	0.59
Lethargy/ Fatigue	5	38	0	0	5	71	0.021
Headache	4	31	2	33	2	29	1
Depression	7	54	2	33	5	71	0.28
Irritability	3	23	1	17	2	29	1
Anxiety	2	8	0	0	2	29	0.46
Reduced appetite	3	23	1	17	2	29	1
Weight loss	1	8	0	0	1	14	1
Nausea	2	15	2	33	0	0	0.19
Haematemesis	1	8	0	0	1	14	1
Bruising	1	8	1	17	0	0	0.46
Gum bleeding	1	8	0	0	1	14	1
Anaemia	0	0	0	0	0	0	NA
Thrombocytopenia	1	8	0	0	1	14	1
Neutropenia	2	15	2	33	0	0	0.19
Infection	2	15	1	17	1	14	1
Pruritis	1	8	1	17	0	0	0.46
Rash	1	8	1	17	0	0	0.46
Alopecia	1	8	1	17	0	0	0.46

Every patient undergoing treatment reported at least one side effects. The number of side effects reported per patient ranged between one and nine. Interferon related side effects were common, and the two most commonly reported adverse events were depression in 54% and flu like symptoms in 46%.

There were no serious adverse events in either arm. One patient out of thirteen (8%) had to stop treatment due to an adverse event, thrombocytopenia at week seven.

Lethargy was significantly more common in the doctor initiated arm, but all other side effects did not occur in significantly different numbers in either arm.

6.2.9 Drug and alcohol use pre- and post-treatment:

In the 12 treated patients an analysis was performed into whether the quantity of illicit drug and alcohol use differed significantly between the start and end of treatment. A separate analysis was undertaken to assess if there was a difference pre- and post-treatment in the number of patients who were active users of heroin or crack cocaine.

In all patients data was available on drug and alcohol use at the start of treatment.

In three patients who did not complete treatment drug and alcohol use was taken as the last recorded drug and alcohol use.

Scatter plots and graphs of pre- versus post-treatment quantified drug and alcohol use are shown on the following pages. The error bars indicate the standard error of the mean (SEM).

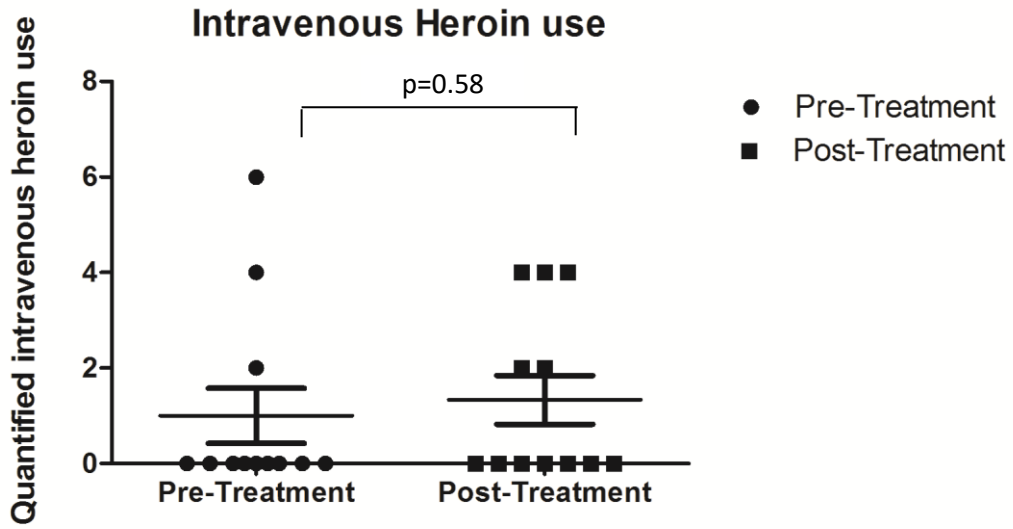


Figure 35 Quantified intravenous heroin use pre- and post-treatment

Figure 35 describes quantified intravenous heroin use pre- and post-treatment for HCV. It can be seen that there was no significant difference between intravenous heroin use before and after treatment for HCV (pre-treatment SEM 0.58, SD 2, 95% CI -0.27-2.27, post-treatment SEM=0.51, SD 1.76, 95% CI 0.21-2.46).

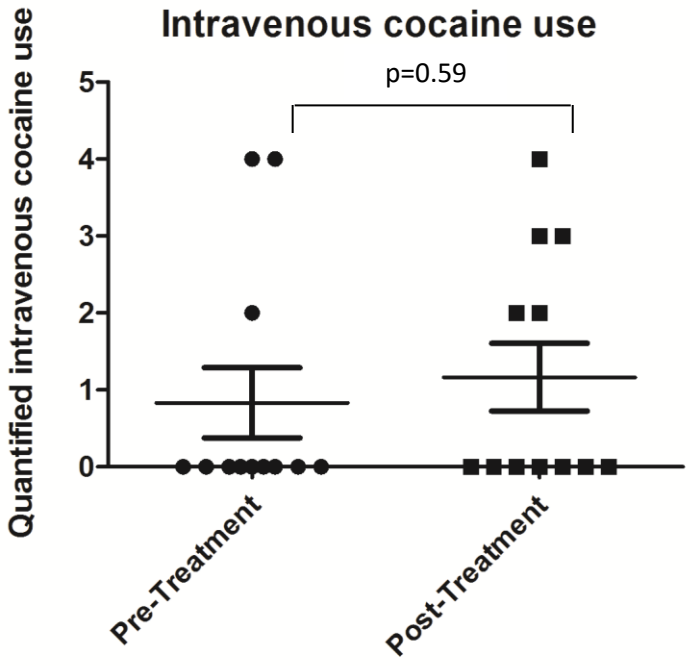


Figure 36 Pre-and post-treatment quantified crack cocaine use

Pre- and post-treatment quantified crack cocaine use is detailed in figure 36. There was no significant difference in crack cocaine use pre-and post-treatment (pre-treatment SEM=0.46, SD=1.59, 95% CI=-0.17-1.84, post-treatment SEM=0.44, SD=1.53, 95% CI=0.2-2.13).

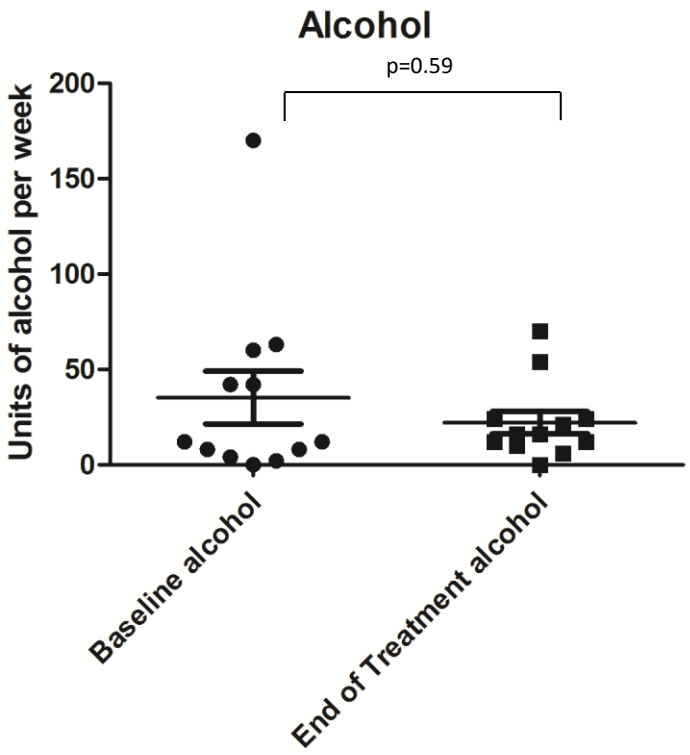


Figure 37: Units of alcohol consumed pre- and post-treatment for HCV

The units of alcohol consumed by each patient pre- and post-treatment by each patient can be seen in figure 37. There was no significant difference between quantified alcohol use pre-and post-treatment (pre-treatment SEM=13.91, SD=48.17, 95% CI=4.65-65-85, post-treatment SEM=5.83, SD=20.21, 95% CI=9.24-34.92).

A further analysis was undertaken to assess if patients were likely to cease use of heroin or crack cocaine entirely over the course of HCV treatment and the results are documented in the following two figures (see figures 38 and 39).

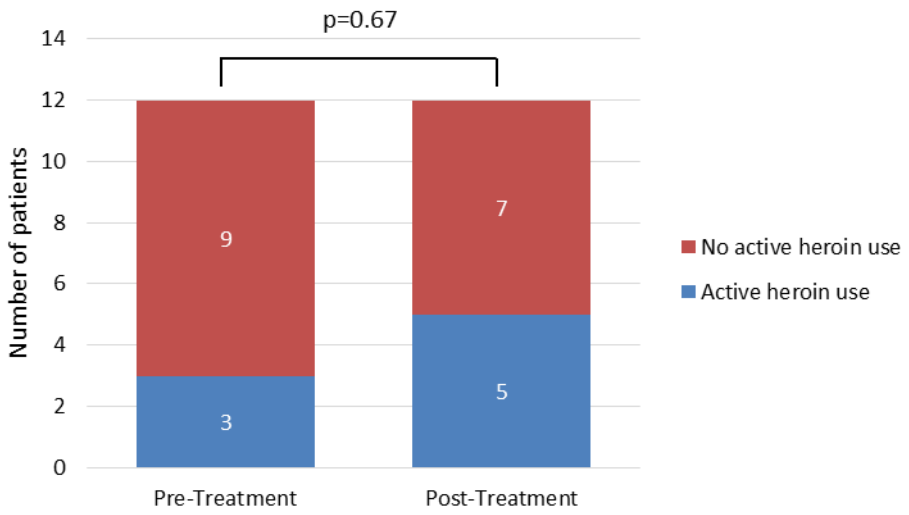


Figure 38 Number of patients actively using heroin pre- and post-treatment

Figure 38 details the numbers of patients who were actively using heroin pre- and post-treatment and shows that patients did not significantly reduce heroin use after treatment (p=0.67, OR=0.47, 95% CI=0.08-2.66).

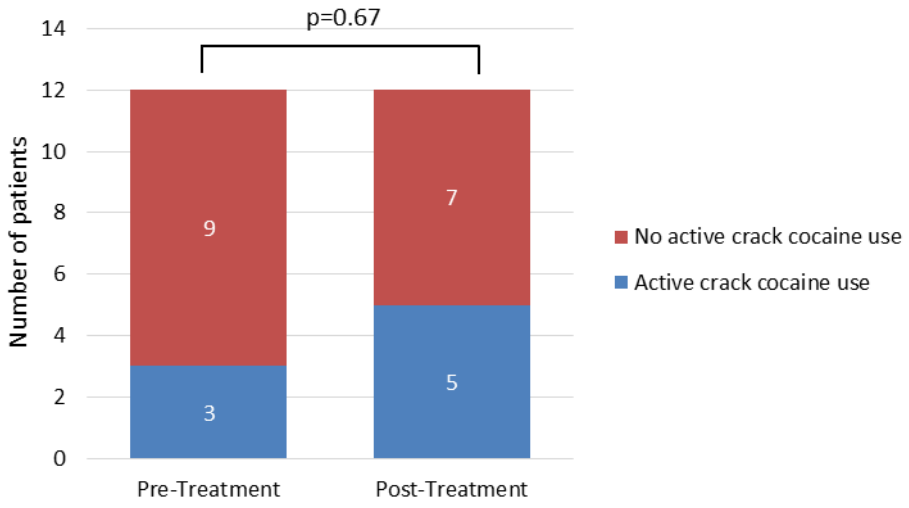


Figure 39 Total number actively using crack cocaine pre- and post-treatment

In figure 39, which shows the number of patients who had any crack cocaine use pre- and post-HCV treatment it can be seen that there is no significant reduction in crack cocaine use after treatment (p=0.67, OR=0.47, 95% CI=0.08-2.66).

6.3 Summary:

The main findings from this study are that nurse initiated therapy for HCV in PWID does not result in a higher uptake than the current doctor initiated treatment model and low rates of HCV treatment uptake were seen in both arms. Treatment was shown to be safe and effective in those who were treated, and illicit drug use did not reduce over treatment, although the study was not adequately powered to assess either of these findings. The results of this study are discussed in greater detail in chapter eight.

6.4 Discussion of methodology:

There are a number of strengths, and some limitations to the study design used. This was a prospective cluster matched randomised trial, which is a recognised and appropriate trial design to evaluate community based health initiatives (Campbell MK M. J., 2000). Cluster pair matched study designs have practical benefits, and can increase power and protect the validity of studies (Balzer LB, 2014). Benefits of using a cluster randomised design in this study included a reduced risk of experimental contamination, an effect that can occur when patients at the same clinic receive different treatment protocols, and it allowed for the intervention to be given in a closer to real life scenario without the need for individual randomisation within clinics (Campbell MK M. J., 2000). The study design was pragmatic given that the SAU services

were already delivered in a number of central and outreach clinics, that could be relatively easily matched and cluster randomised. Cluster matching was performed using geographic location and cluster size, which are valid cluster matching techniques (Campbell MK M. J., 2000). However it has been argued that cluster matching can reduce the power of a study if there are less than 10 clusters in each arm (Martin DC, 1993).

There are some limitations to this study which may have affected the outcomes. The study was designed with 90 patients in each arm to give an 80% power for detecting a difference in treatment uptake from 10 to 30% at a level of significance of 0.05. At the close of enrolment 65 and 76 patients had been offered treatment in the nurse initiated and doctor initiated arms. This led to under-powering of the study and it is possible that if further patients had been recruited a difference in treatment uptake would have been seen between the arms. There are further potential issues relating to the cluster randomised design, due to the intra-cluster correlation coefficient (ρ). This arises due to the fact that individuals within a cluster can be assumed to act more similarly than individuals in different clusters will act so the assumption of statistical independence required to use standard statistical calculations is lost (Campbell MK M. J., 2000). This can be overcome if the unit of inference and unit of randomisation are both at the cluster level, but this was not the case in this study, and so the sample size estimation should potentially have been multiplied by an estimate of the variance inflation factor to account for the potential for variance in the study outcome measure being affected by the within cluster variance (Campbell MK M. J., 2000). However this was not carried out as the impact is usually small, between 0.01 and 0.05 (Campbell

MK T. S., 2004), no estimate of the size of matching correlation was possible from previous data, and it is difficult to estimate ρ with confidence if a study has less than 40 clusters (Donner A, 2004). Due to this a conservative approach to sample size estimation was taken and a formula for a completely randomised trial design was used to estimate power size.

One clinic was not cluster matched with another clinic, as there were an uneven number of clinics in the study, and was randomly assigned to the nurse initiated arm, which is not a valid cluster randomisation technique and is a potential weakness of the study design as it has the potential to affect the power estimates. This outreach clinic was subsequently lost from the trial when the charity running it went into administration.

The results will be discussed further in chapter eight.

7 Qualitative assessment of the reasons underlying engagement in HCV treatment in people who inject drugs

The aim of this qualitative analysis was to investigate the reasons behind the low rates of antiviral therapy for hepatitis C virus amongst PWID by exploring their experiences and attitudes towards the diagnosis of hepatitis C, their experience of living with and treatment of hepatitis C virus.

7.1 Methods:

A qualitative analysis of semi structured interviews was performed with the aim of identifying factors that influenced the decision to engage with antiviral therapy for HCV amongst people who inject drugs.

7.1.1 Sample frame/ participants:

The sample frame consisted of people who inject drugs with hepatitis C who attended Specialist Addiction Services in North East London. Some participants had chosen to be treated for HCV and some had not chosen to be treated.

The sample matrix detailed in table 18 on the following page was used to identify appropriate participants. It was important to get a range of different ages of people who inject drugs, and a balance between those who were currently injecting drugs and had formerly injected drugs to identify potential differences in attitudes to treatment between these groups.

Table 18: Sample matrix

Factors		People who have agreed to HCV treatment	People who have not agreed to HCV treatment
Age	18-30	3	3
	30-40	4	4
	>40	3	3
People who currently inject drugs		5	5
People who have formerly injected drugs		5	5
Total		10	10

7.1.2 Study design:

The study was designed as a single cross sectional qualitative analysis. A six month time frame was planned to perform the interviews.

The experiences and attitudes of people who inject drugs towards the diagnosis of hepatitis C virus, the experience of living with hepatitis C virus, knowledge of hepatitis C virus and the treatment of hepatitis C virus were explored through individual semi-structured interviews. These areas were examined as previous research in this area has identified that these factors may be important elements of an individual's decision to accept or decline treatment for Hepatitis C (Swan D L. J., 2010) (Treloar C R. T., 2009) (Groessl AK, 2008) (Treloar C H. P., 2012) (Doab A, 2005) (Grebely J G. K., 2008) (Rhodes T H. M., 2013) (Harris M, 2013) (Treloar C N. J., 2010) (Harris, 2009) (Tompkins CNE, 2005) (Mravcik V, 2013).

Potential participants were approached by their Blood Borne Virus nurse and asked if they would be interested in participating in an interview. Those who expressed an interest were given a patient information sheet (see appendix 19), which they were asked to take away and read. When they returned to the clinic they were asked if they were interested in taking part in the study, and if they were an interview was booked. Participants were reimbursed £10 for their time for each interview. All participants were asked to sign a consent form agreeing to their participation in the study and data collection at the time of the interview (see appendix 20). The sample matrix indicated that useful results could be obtained by interviewing ten clients who were chronically infected with HCV and who had chosen to undergo treatment and ten who had declined treatment. If theme saturation was reached before this point then fewer interviews could be carried out. The semi structured interview was not formally structured, but was based around a theme guide, designed around the research questions (see following page). An iterative design was incorporated into the study, so if new themes emerged during the interview process the theme guide could be adapted and these could be explored in further interviews. The interviews were held in private and were planned to last for approximately one hour or until theme saturation was reached. They were recorded on a dictation device, and then transcribed by a professional transcription service.

7.1.2.1 Theme guide for In Depth Interviews

Explore the diagnosis of HCV in people who inject drugs

- How is testing for HCV in people who inject drugs approached in different settings?
- What are the motivations for testing for HCV for patients?
- What are the facilitators and barriers to diagnosis of HCV?
- What impact does the initial diagnosis of HCV have on people who inject drugs?

- Explore PWID experience of living with hepatitis C virus
  - What are the physical, psychological and emotional effects of living with HCV?
  - What impact does living with HCV have on PWID daily life? (family, partner, friends, etc.).
- Explore PWID understanding of hepatitis C virus infection
  - What is their understanding of how HCV will affect them now and in the future?
  - What are their beliefs and fears about hepatitis C virus infection?
  - What are their sources of information about HCV infection?
  - What are the facilitators and barriers to obtaining information about HCV?
  - How could their understanding of HCV be improved?
- Explore PWID's experience of healthcare services both generally and in relation to HCV
  - What access is there to healthcare services (including for HCV)?
  - How do these address their needs?

  - Are there any unmet needs?
  - What changes could be made to improve healthcare services?
  - What are the motivations for accepting or declining healthcare services?
  - What are the facilitators and barriers to taking up healthcare services?
- Explore people who inject drugs expectations of antiviral therapy for HCV
  - What is their knowledge and understanding of what is involved in treatment for HCV?
  - What do they see as the benefits or risks of treatment for HCV?
  - What are the sources of their understanding of treatment for HCV?
  - What are the facilitators or barriers to obtaining information about treatment for HCV?
- Explore the decision making process for PWID in accepting or declining treatment for HCV
  - What are the motivations for accepting or declining treatment?
  - What are the facilitators and barriers to taking up treatment?
  - How do these factors differ between those who do or don't choose treatment?
  - What would be needed to overcome the barriers for those who don't choose treatment?
  - How was treatment discussed with them, and by whom?
- Explore people who inject drugs experiences and views of antiviral therapy for HCV
  - What has been their experience of treatment for HCV?
  - How were different aspects of the treatment experienced and valued?
  - What made elements of the treatment more or less valued?

- What changes could be made to improve the HCV treatment service?
- How would they describe treatment to a friend?

7.1.3 Analysis:

Interviews were analysed to identify predominant themes using a grounded theory approach. The interviews were analysed and coded line-by-line using an inductive technique to identify all experiences related to Hepatitis C. Prominent themes were coded and a thematic framework was formed by an iterative process as the interviews were analysed, which resulted in a large data set. All interviews were subsequently re-analysed using this framework. The thematic framework was then interrogated for patterns, and concepts and to identify relationships between themes, including linking positive and negative themes where factors produced contradictory experiences and a descriptive analysis of the identified themes was undertaken. The prominent themes were then compared with previously published qualitative research into the uptake of antiviral therapy for HCV in PWID. This research deviated from grounded theory analysis towards the end as the development of new theories was not within the scope of this research so only prominent themes were used in the final analysis.

7.2 Results:

7.2.1 Data generation and analysis

Interviews were all performed in the participant's local Specialist Addiction Services clinic. The interviews lasted between 30 minutes and 60 minutes. Twelve interviews were performed before a decision was made that further interviews did not need to be performed as theme saturation had been reached.

All 12 interviews were recorded and 11 interviews were transcribed by a professional transcription service and subsequently analysed. Due to technical difficulties with the recording, the interview with patient 11 could not be retrieved and transcribed, and therefore could not be analysed.

7.2.2 Patient demographics and characteristics:

All patients were attendees of Specialist Addiction Unit and were receiving opiate substitution therapy. The interviewed patients demographic, injection drug use and Hepatitis C treatment characteristics are detailed in table 19 on the following page.

Table 1: Interview participant's characteristics

Patient	Sex	Age	Hepatitis C Treatment status	Injecting status
1	Male	53	Treated	Previous
2	Male	33	Treated	Previous
3	Male	38	On Treatment	Previous
4	Male	47	Treated	Current
5	Female	49	Not treated	Previous
6	Male	51	Treated	Current
7	Male	40	Not treated	Current
8	Male	45	Treated	Current
9	Female	60	Not treated	Current
10	Female	30	Not treated	Current
12	Male	36	Not treated	Previous

7.2.3 Themes:

A wide variety of themes emerged which were explored by an iterative process guided by the theme guide and research questions. Often contradictory and ambivalent feelings were expressed by participants and the analysis attempts to convey this. The major emergent themes have been grouped into categories by using a thematic framework and are discussed in the following section.

7.2.3.1 Knowledge of Hepatitis C and its treatment: “Most people don’t even know you can get rid of it”.

Information given at the time of diagnosis about HCV and particularly the availability of treatment strongly affected participants reaction to the diagnosis, and knowledge of the negative health effects of Hepatitis C and that treatment was available were motivators to treatment. Many participants perceived PWID to have a low knowledge that Hepatitis C can be treated, and saw this as a significant barrier to treatment. Participants gained most of their knowledge about Hepatitis C from their local nurses, but also gained it from peers, the internet and television.

A negative reaction to diagnosis was linked with a lack of knowledge by some participants as with patient 12 “And it was like, I didn’t know what hepatitis was or anything like that …… and I thought I was dying. I thought, like, oh, I’m going to die and all that”. These negative feelings could be tempered by others reassurance as patient 12 found “I thought I was dying. I thought, like, oh, I’m going to die and all that but my mate explained it all to me, because he had hepatitis”.

In contrast to those who described fear some patients described a lack of concern about HCV when given the diagnosis, and this could be related to a low perceived knowledge about Hepatitis C virus, as patient seven describes "like I remember the first time when she told me I had hepatitis C, I don’t even pay attention; for me it was just, I don’t know, maybe like flu or …!" which was not down to a perceived lack of importance but to lack of knowledge "it was not a question of *(not)* bothering; it was a question of, like, you don’t know what it is”. Patient five similarly felt “It wasn’t … it didn’t seem that important, because it didn’t seem that, erm, important, like it wasn’t

anything important really" and described that "No, no-one has said anything. To be honest, I don't really understand what it actually is".

Patients who were told that treatment was available when they were diagnosed or who were already aware of treatment appeared to feel less negatively about their diagnosis and more empowered as described by patient one "I think I felt relieved that I knew that I could have something done about it" and patient six "You know, I knew there was treatment for it….So it didn't worry me too much….it wasn't like being diagnosed with HIV in the eighties; you know, like no cure and no sign of one in the future". Patient four describes a sense of hope and excitement "But, you know, to be told that there is a chance that it can actually wipe it completely out was … wow! You know? You can't sort of give that a miss, sort of thing".

A negative impact was felt by those who were not informed about treatment at diagnosis as expressed by patient five "We were just left with that, "You've got a hep C!" and that was it. We weren't told there was a treatment. I didn't even know there was such a thing" which led to a feeling that HCV was not important "You know, it doesn't seem that important, and it makes me think it's not important, because it makes me think, well, if it was, they would have done something about it before, you know?". This experience negatively affected patient five's subsequent dealings with healthcare professionals and led to a feeling of a lack of empowerment around Hepatitis C virus as she describes "no-one talks about getting rid of it, or doing anything about it, so it's like what's the point of finding out if you've got it or not, because they can't do anything about it! That's what people were saying when I was out there".

A lack of knowledge amongst their peers that HCV could be treated was perceived as a strong barrier to seeking treatment by participants. Patient two describes how "most people don't even know you can get rid of it; most people think you've got it for life, and they think it's more serious than it is". This was a sentiment that was echoed by patient four "I know there are probably hundreds and thousands of people out there who probably don't know that there is treatment that they can actually take" and those who hadn't had treatment often described themselves as having a low level of knowledge around treatment.

Knowledge of the long term impacts of HCV and concern over these, particularly as they got older appeared to impact on some patient's decision to have treatment. Patient six emphasises that "I knew that if I didn't do it, I'd die, horribly of liver cancer or something" and patient four describes "I did read up on hepatitis, and like I say, as you get on in life, things are slowly going to get worse, as you age as such". Patient three found concerns about Hepatitis C a strong motivator to stay on treatment "Just knowing the fact that I have got hep C and what it can actually do to me if I don't kick it, don't stay on the med- … on the what's its name, on the treatment. You know, I read it on the internet and they said you can get chronic liver disease and that…… who's to say if I didn't take the medication I'd be a darn sight a lot worser in years to come, and I don't want that". Patient nine's disquiet around the effects of HCV as she got older had led her to consider treatment "Because I would like to be treated, because I'm 60 now and it's going to affect me bad soon".

When describing where they got their knowledge of Hepatitis C from the majority of patients cited their Blood Borne Virus nurse, and particularly mentioned leaflets. When

asked about the ease of getting information about Hepatitis C patient seven replied “Oh, I think so, yeah. It’s pretty simple. This country is amazing about that, you have leaflets" and patient four described “And there was always leaflets and booklets at the St C***, which were always at hand”.

Patient six described the importance of knowledge in changing people’s minds around treatment "if people have persuaded themselves that they can’t do it, when it’s obvious they can, it’s just a matter of giving them the information to see that they can do it".

When patients were asked for suggestions to increase treatment uptake a number recommended that all those attending addiction services should be offered information and testing for Hepatitis C.

As patient five suggests "if people came to places like this where you know certain people are going to be about, and you know you’re going to find people with hep C, and people are wanting to know things, and then offer to leave leaflets, or offer to have a talk or something like that". Patient four recommended "I think if you join a clinic like this, that should be something you do; you go in and you see the nurse, and you’re given these choices: Do you know if you’ve got hepatitis or not? And if you have, you know there’s treatment for it? And if you don’t know, we can check for it, and if you have, there’s possible treatment for it. I think that should be something definitely".

7.2.3.2 Normalisation of HCV: “everyone that injects has got it, or I think at least 90%, 95%".

The normalisation of Hepatitis C for participants emerged as a strong theme throughout the interviews, and this was used by some participants to help them cope with their diagnosis. Hepatitis C was seen as ubiquitously connected with drug use and as a silent disease and these two factors appeared to lead to its acceptance and normalisation.

HCV was normalised as an inevitable consequence of injection drug use. Patient nine expressed “Yeah, because a lot of people have got it and I know I’m 60, and I’ve been on drugs for 47 years, so I’m lucky not to have had it!” and patient two stated “I think everyone that injects has got it, or I think at least 90%, 95%". Patient six when discussing his diagnosis describes that "It wasn’t a bolt out of the blue, it wasn’t completely unexpected” which was related to the normalisation of HCV in his social circle of drug users, as when he told friends about his diagnosis they expressed “Erm, no shock or surprise. I think a lot of us, we all had very similar world views and very similar views on the illness as well”.

This normalisation was discussed along with a sense of acceptance as patient two says "Most people I know aren’t even thinking about treatment or nothing like that……I think hep C, they don’t really … they’ve just accepted it basically; it’s just a part of their life” and patient 12 reiterates this feeling “because I get on with my life, do you know what I mean? It’s like, well, I’ve got it, so just deal with it!”. This appears to be a coping mechanism used by participants particularly if they felt a sense of pessimism around the prospect of being able to be treated for Hepatitis C as patient 10 describes

“I could be depressed about it but at the end of the day, it’s not going to go away … well, it might but it’s not going to go away, you know? So I just have to really accept it now”. Conversely patient eight, who had been treated rejected this normalisation of Hepatitis C “it’s just something I had to get rid of, you know, had to just deal with really. It’s either that, or it’s forever going to be there, you know?” which appeared to be a motivator for treatment in this case.

The asymptomatic nature of infection with HCV and lack of impact on their daily life further normalised the illness for some, such as patient seven "But, like, maybe if I had difficulty to breath, or difficulty to walk, or difficulty … you would remember all the time of it, don’t it? It’s kind of like, yeah, a hidden illness, isn’t it?".

7.2.3.3 Experiencing HCV as an illness: "But I’d had enough of it…. because I just felt generally run down to be honest".

Those who had been treated or were considering treatment often described symptoms that they attributed to Hepatitis C which gave them an increased awareness of their illness and could motivate them towards treatment. Patient four recounts "But I’d had enough of it…. because I just felt generally run down to be honest" and patient eight reports “As I said, I just wanted to get well again, and get rid of it. Nothing more worse could happen than having it, so I was up for it really *(treatment)*”. Patients five, seven and nine had not had treatment but were considering it due to concerns that symptoms they were experiencing were related to HCV. Patient five described wanting to have treatment because "I’d be vomiting a lot, and pains in my stomach and I think that’s down to the hep C". Patient seven described the impact of their health deteriorating "And that’s when my health deteriorated, and that’s when I start finding

out that I really had … my liver was damaged because I have first stages of cirrhosis, don't I? ….. So from there…. I'm still waiting for the treatment".

Patient nine recounted "Because I'm beginning to get really ill. And you never know if it is that *(the HCV)*". However patient nine's discourse around Hepatitis C revealed an element of liminality where they existed in a state of health and illness and were unsure what effects the Hepatitis C actually had "See, I can't get down to the bottom of what effects hepatitis C has on you; what it actually does do to you, you know, how it does make you feel?".

7.2.3.4 Stigma of HCV: "A dirty junkie disease".

A strong sense of stigma around having Hepatitis C virus, with a feeling that people who have Hepatitis C are "dirty" and contagious in the minds of others emerged from the interviews. This was related to the association of HCV with injection drug use.

The stigma led participants to have strong feelings of shame as described by patient two "I felt dirty about it. I didn't want no-one to know; I was really ashamed!" due to its association with injection drug use "it's like a dirty junkie disease, that's how people I think see it". Patient four describes living with HCV as making him feel "Oh, just horrible. Dirty sort of, just … you know?". In a visceral description patient two felt "scarred" by his Hepatitis C which related to the stigma he felt and this led him to want treatment "Yeah, well, I didn't want to feel scarred. I felt scarred".

The stigma that those interviewed felt around Hepatitis C was reinforced by other people's negative reactions to their Hepatitis C, particularly relating to a perception of other people seeing them as contagious as reported by patient one "like my wife's

family, they've been really stand-offish. Since they've heard that we've had hepatitis, they've stood right back. You know, which is sad really. It's like we're contagious!". Patient six described "You know they see you cough and you say, "Why are you covering your nose?"*(they reply)* "I don't want to catch hep C!" and I'm like, "oh, bloody hell!"".

7.2.3.5 Blame: "I've only got one person to blame and that's myself".

Shame and shock or acceptance of the diagnosis of HCV was discussed commonly in association with a sense of blame around Hepatitis C, particularly in relation to its acquisition. The very strong association of Hepatitis C with injection drug use left those who perceived that their behaviour hadn't put them at risk disappointed and surprised at their diagnosis as expressed by patient 10 "I was really sort of surprised when they told me, and I was kind of really disappointed. I didn't know how to deal with it, you know, and I just couldn't understand why it had happened, to be honest, because I don't share". Patient three describes their reaction to their diagnosis: "So I got kind of upset, I cried a little bit, you know, I had my hands up, "Why have I got hep C? Why? ..... I've never injected, I don't know how I got it".

A lack of shock at the diagnosis appeared to be associated with a sense of blame around the acquisition of Hepatitis C. For instance when discussing his diagnosis patient eight describes "You know, I was sad, but at the same time I found out, I didn't really blame anyone; the more I looked at it, it was more my fault more than anyone else really. So, yeah, I more blamed myself instead of saying it was blah or blah".

Patients two and four felt similarly as expressed by patient two "I felt like I haven't got away with using drugs, basically. I felt like it's caught up with me, do you know what I mean?" and patient four who had "no sympathy with myself, because I've only got one person to blame and that's myself; you know the situations that I was putting myself in". Patient twelve also felt "Like, it's my choice to do it *(injecting)*, so I have to live with it". Where patients perceived another's actions to be to blame for their acquisition of Hepatitis C virus they described feelings of anger and shock as with patient nine "but somebody did actually tell me that he had it, and that he'd used one of mine, my syringes, without me knowing and I went absolutely mad!".

7.2.3.6 Social effects motivating treatment: "I don't want to end up like that, because I've seen what it can do".

Patients were motivated towards treatment by a variety of social factors including seeing the negative health effects of HCV in peers, seeing others being successfully treated and wanting to have treatment to motivate a partner or for their children. The support of others through treatment helped patients cope with the side effects. Conversely hearing others negative experiences of treatment, while off-putting for participants only acted as an absolute disincentive to treatment in one case. A common suggestion from patients when asked what would help increase treatment uptake was offering potential patients the chance to speak to people who had successfully completed treatment.

Patients one and three described seeing friends and others with serious liver disease as a motivator towards their own treatment "And also having a lot of friends that have passed away through liver sclerosis and stuff like that, it's a terrible way to die"

(patient one). “There was a man on the telly there with proper chronic liver disease. So I just said to myself, well, I’ll just stay on my medication, do you know what I mean? I don’t want to end up like that, because I’ve seen what it can do” (patient three).

Participants tended to report not knowing many people who had undergone treatment, but being encouraged by hearing the successful treatment experiences of peers. Patient one states "I’ve only met two people that have actually had the treatment and gone through with it. And it’s through what they’ve said that’s kept that alive in me, that they feel like they’ve got a new lease of life". Patient four recounted “So sort of listening to other people’s experiences I thought, well, that’s something, if I can … if there’s a chance of actually curing it, yeah, I’d go for it.". The opposite was also true as when participants had seen people who hadn’t completed treatment it gave them doubts, as patient two describes "It’s like you think to yourself, does it exist? Do people actually f***ing get rid of it!" although it did not stop this patient undergoing treatment. Seeing the negative effects of treatment in friends caused some, such as patient six, to delay treatment for years "And I watched various friends of mine go through the treatment and it just put me off completely". This made patient twelve decide not to undergo interferon treatment “I would love to try to get rid of it, but not with that, not with those, not with that treatment. Especially, like, because I’ve heard too much bad stuff about … I don’t know the name of it, erm, the medication?”.

Participants also described being motivated to have treatment for others, both to help others through treatment or because they felt that others gave them a motivation to live and get their Hepatitis C treated. Patient one described “What kept me going was

(1) having to be not just for myself, but thinking of my partner as well. I can see the way she's progressing, she's hyping herself up for the treatment. And not only that, if I were to stop, she would have followed suit". Patient five would consider treatment because "I've got sons and one has just had a baby, and I've had a grandchild, so I want to be alive and around a bit longer".

The support of others was perceived as important to completion of treatment by the majority of patients. As patient four describes "And if it wasn't for my partner, to be honest, I would have probably given up a long time ago" and patient one "the main one is support, you need support, you need someone around you when you're having it". Patient three when asked how he coped with treatment cited his dog as helping him through it "The dog keeps me happy, you know, he's a great thing". In agreement with this a lack of support made treatment very hard for some, with patient two describing himself as having no support and finding it "Very hard. I've had a lot of bad times this year". Conversely patient eight preferred to deal with treatment by himself and when asked if he had support through treatment replied "No, no, I just dealt with it myself. I prefer to do it that way. I just kind of gritted my teeth".

7.2.3.7 Competing priorities of addiction "when you're on drugs, you don't have much feelings, you know, for things, and it just goes over your head".

The competing priorities of addiction and Hepatitis C, with participants describing their addiction as taking precedent over everything else in their lives emerged as a strong theme. Patient two describes how "If you're living it really rough and all that, that's the last thing I think they think about is the hep C, they don't really give it … all they care

about is just today and what's going to happen and, yeah". Patient one reiterated "But when you're on drugs, you've got that 'don't care' attitude. It's like that big bubble, and you're inside that big bubble 'I'm alright, Jack!". This meant that even when patients felt their HCV was important they felt unable to engage with it due to their addiction as recounted by patient nine "It is a priority, but when you're on drugs, you don't have much feelings, you know, for things, and it just goes over your head, and you just don't think about it again".

As well as issues relating to drug use, addiction often led to a lack of income and homelessness which provided additional competing priorities to Hepatitis C treatment as described by patient two "When my life was a bit hectic, I didn't want to take the risk of starting and then f-ing it up at the end. I wanted it to be more secure, because I didn't have nowhere to live and my life was, like, I couldn't keep appointments". Patient six also describes "I was starting to fall behind with my rent, and it was basically just trying to scrape enough money together every day. I couldn't afford to spend time visiting a doctor once a week, and fiddling about with injections".

Patient six describes starting treatment some years later than his peers due to being homeless for a prolonged length of time "I knew I would have to deal with it eventually, but even then I was homeless for a long time and I didn't really want to be ill and living on the streets".

There was a perception of treatment for HCV in those who were actively injecting being a "waste of time" either because of the risk of re-infection or a nihilistic sense that those treated may not survive to see the benefits of treatment. Patient two stated "but if it's someone that drinks a lot and injecting a lot, and lives on the street, that

person, more than likely he's going to share something. And why treat him, I'd rather wait until he's ready and then treat him, instead of wasting your time, his time, do you know what I mean?". Patient one described that "A lot of people are frightened; if they're injecting, it's a waste of time – that's how they perceive it". This point was made strongly by patient six "So if you're kind of expecting to overdose or have an accident through falling over drunk in front of a bus or something, why bother making yourself suffer even more going through treatment, if you don't really expect to be there to appreciate it".

7.2.3.8 Healthcare professional and system factors: "Because if A*** never offered it to me and all that, I wouldn't have probably done it".

A strong motivator for treatment was recommendation from the Blood Borne Virus nursing team, with most patients reporting that they were not actively seeking treatment when it was offered. Patient two expressed "Because if A*** *(BBV nurse)* never offered it to me and all that, I wouldn't have probably done it" and patient four recounted"… I was going in for bloods every sort of two weeks or whatever, and then A*** said, "There's a treatment out. How do you feel about …?" Of course I snapped at it straight away". Patient eight wanted treatment, but hadn't sought it out previously: "I didn't know how to go about it, but, yeah, I wanted treatment. Then it was suggested to me and I said, yeah. Yeah, it was suggested to me if I wanted to clear it up, kind of thing, so I said, yeah. Yeah, I'd have a go at that".

Those who hadn't been treated also started to focus more on their HCV when motivated to by health care workers such as patient seven "When the nurses and

doctors around me, people were trying to help me, to treat me, they started saying that I needed to do something about it. So that's when I started dealing with it".

In conjunction with the healthcare professionals motivating them a perception of treatment being easy to access was a facilitator of treatment for a number of patients as patient two describes "It wasn't like I had to try and I had to come and ask. It was like only I got tested and then I got offered, do you know what I mean?" "then he said to me, "Look, do you want to start treatment?" and it was like straight away, bang, bang". The perception of easy access to treatment was also felt by those who hadn't started treatment "Well, I can't get it much easier, can I, than actually coming to the chemist next door and to walk in. I come here every day, so it's right on my doorstep, I'm right next to it!" (patient nine).

The positive support and accessibility of the Blood Borne Virus nurses was cited as an important factor in helping patients to complete treatment, and positive experiences associated with the addiction services meant patients felt satisfied with their care. Patient one felt "I'm lucky to have quite a good nurse. J*** even said to me if I need help or any time I get … you know, if I need to talk, she's on the end of a phone which is really helpful. She's been really good that way". Patient six perceived that "the nurse was very encouraging and I think I probably would have completed it, the treatment, without her support, but it certainly helped". Patient four felt that support generally and "Especially if it's professional support; it does make a hell of a difference. It's sort of like another safety net as such".

When discussing addiction services more generally there was a sense of being cared for as described by patient one "I know it's always been a good place to come and get

treated, SAU and, you know, they've always given you full help". Patient twelve expressed "No, they look after me really well. The key worker is brilliant, do you know what I mean? Yeah, they look after me".

Some patients felt that more encouragement from healthcare staff would have led them to start treatment as patient five recounted "Yeah, I think if the staff had said it was all right, I would have gone for it. Yeah, definitely". This patient had been told they couldn't yet have treatment due to mental health issues. Patient nine, when asked what would make them get treated replied "I'd just have to be told, you know, they'd have to just keep telling me and I'll go.". Patient nine felt a strong sense of personal responsibility relating to treatment, leading them to blame themselves for not having started treatment yet "it's only my own fault for not going out there and doing it, looking for it. I mean, if I wanted it, I could just come and get it, you know, just try!" Patient seven expressed a similar feeling "Well, they gave me all the help and all the support, now I'm the only one who has to use it".

7.2.3.9 Pegylated interferon-α treatment as a barrier: "I couldn't afford to spend time visiting a doctor once a week, and fiddling about with injections".

The perceived burdens associated with treatment with pegylated interferon-α were a barrier to treatment for many including the length of treatment course, the need for frequent appointments, the low success rates and the side effects of treatment.

When discussing treatment patient four explained it "is off-putting, it's not 100% that you're going to come out, you know, hepatitis-free at all" and patient twelve was put

off by the low success rates “I know it’s helped a lot of people, but it’s only like a 50:50 chance, something like that".

There was also a perception that the treatment involved too big a commitment. Patient six recounts “I couldn’t afford to spend time visiting a doctor once a week, and fiddling about with injections” and patient nine stated “Because they asked me to go in for the cure, but it’s every day you have to have an injection and go to the hospital for a year, and I’m never going to keep that up”. These patients were unaware that they could be taught to give themselves injections at home, or could have treatment given in addiction services.

The side effects of treatment were more often a barrier to treatment from the healthcare provider perspective, than the patient perspective as although patients perceived there to be serious side effects they usually felt that these could be dealt with. Patients five and seven were told they could not have treatment due to the psychiatric side effects of treatment with interferon as described by patient five “I think it’s because I suffer from depression and they were telling me they weren’t sure if the drugs that they were going to give me would make me worse or better, or suicidal when I was depressed”. Patient twelve was the only patient who expressed that they did not want Hepatitis C treatment due to side effects “Just like sickness, putting on weight and all of that, and if you wanted to try for a baby, you can’t try for a baby, because it can affect the baby. So that was the main reason why I never wanted to go near that treatment”.

In other patients there was less concern about side effects due to a belief that side effects could be dealt with either by healthcare professionals or by the resilience of

the patient. Patient six describes "I was so, so paranoid about getting mental health problems, you know, as part of the side effects…….but I did know that it wasn't, you know, definite that that was going to happen. I thought, you know, if it happens, I'm sure there will be some medication that might possibly work". Patient nine when discussing the potential side effects of treatment stated "They did say the side effects could be quite bad, like you'd have to come into hospital, or I would be really ill, they said, you know, after the injections or whatever….. No, that *(the side effects)* doesn't worry me a bit" as patient nine felt "if you're at home, and you're ill, you're there aren't you? I'd be able to do it at home".

7.2.3.10 Transformative process of Treatment for Hepatitis C: "I feel like I can change my life now, I can get rid of everything and say, that's my past!"

Hepatitis C treatment was seen as symbolising a move away from drug use and back to normality. This was seen in the way participants perceived treatment, their determination to carry through to the end of treatment and the sense of achievement felt by completing treatment. Patient two described a somewhat nihilistic feeling of being "scarred for life" with Hepatitis C and therefore seeing no point in ceasing injection drug use, but found that treatment for his Hepatitis C changed this perception "… I've stopped injecting now, and that's partly because I got rid of the hep C. Having hep C made me not consciously, but use more … like, you know that you've got it now and just sort of, basically, you're in it now, and you feel like, I'm scarred for life anyway, so you might as well just carry on using". Patient three saw treatment for hepatitis C as part of a broader package of moving back into the mainstream "But I

think to myself now I'm living in London, I'll get everything sorted. Now I'll get off the medication and that, you know? Get hep C treatment, and get a job".

The wish to get back to normality led to a strong determination to get through the treatment despite the side effects as patient eight describes "That's *(the side effects)* all part of it anyway, so it's not nice, but got to do it, I had to do it. To get rid of what I had. To get back to normality".

Patients reported a sense of achievement on completing the course of treatment, and a sense that completion of this arduous goal gave them the confidence that they could change other things in their life. Patient two felt a sense of pride on completing treatment; "and I feel like I've achieved, like, I'm really proud of myself for keeping a year in treatment" and patient three linked treatment with returning to a life lived within societal expectations "From my side, it's just achieving something; I'm trying to get it out of my system achieved. Just stay on the straight and narrow". Patient two describes a strong sensation of Hepatitis C representing a change in his life, away from drug use towards a more positive future "but I believe that getting rid of the hep C is a real, real booster. It boosts me. I don't feel like I'm scarred, I feel like I can change my life now, I can get rid of everything and say, that's my past!"

7.3 Summary:

The major themes identified from the semi-structured interviews were knowledge of Hepatitis C both as both a barrier and facilitator of treatment, normalisation of Hepatitis C virus infection, the experience of HCV as a felt illness, the stigmatisation of those with Hepatitis C and the social aspects of Hepatitis C virus leading to treatment.

Further major themes were the competing priorities of addiction, the importance of healthcare professional's support and easy access to treatment as facilitators of treatment, the burdens associated with pegylated interferon treatment, and the potential for Hepatitis C treatment to act as a transformative process. A number of these themes related directly to injection drug use and its ubiquitous association with HCV in participant minds. These themes are discussed in greater detail and in the context of previously published work in chapter eight.

7.4 Discussion of methodology:

The semi structured interview was chosen as the research tool as this form (as opposed to an in depth interview which covers only one or two topics in great detail) enables a wide range of topics to be explored, and a deep exploration of participants experiences and views (DiCicco-Bloom B, 2006). In addition they provide a confidential environment for discussing sensitive subjects as opposed to focus groups, which given the sensitive nature of the topics being discussed it was felt may restrict the participant's ability to discuss issues in the depth required. The design of the interview process took practical and research methodology issues into consideration. It was designed as a single cross-sectional design, whereby interviewees were interviewed once about their experience as opposed to a number of times over a prolonged period, as in a longitudinal study. A longitudinal design would be very interesting in a chronic illness like Hepatitis C in people who inject drugs, with addiction itself being an illness which relapses and resolves over time. Nonetheless when identifying and exploring issues in a number of subjects a cross-sectional design is an appropriate research methodology and the study time available of one year made a longitudinal design

impractical. The sample frame was chosen with a purposive sampling approach based on findings from previous research into people who inject drugs with Hepatitis C and the research questions, leading to the main sample frames being PWID who have, and have not had treatment for Hepatitis C as their experiences were likely to inform the answers to the research questions well. The validity of the research could have been improved by widening the sample frame to include those involved in the treatment of PWID with Hepatitis C to explore in more detail barriers and facilitators from the healthcare provider and system perspective, but time considerations meant this was not possible. This method of triangulation is recommended to look for convergence of themes between groups to help with overall interpretation of the data. This helps to ensure comprehensiveness but cannot guarantee validity as it makes assumptions that you can compensate for weaknesses in one group by strengths in another, and that a researcher can mediate between different accounts which are both controversial (Mays N, 2000). All the interviewees attended Specialist Addiction Services in North East London, making the findings potentially less reproducible or relevant to other areas. An inclusion of participants from outside these addiction services could have strengthened the design, but practical considerations meant this was not feasible. This study did not capture people when they were most affected by their addiction to discuss why they did not wish to have treatment which would have been valuable, however a number of participants were able to discuss times when they had felt unable to start treatment due to their addiction. A longitudinal study could be an answer to this difficulty, as once a participant has a rapport with the interviewer, it may be easier to engage them in the future when their life is less stable.

The introduction of interviewees to their interviewer by their nurse had a significant benefit in that trust was already established between the interviewee and nurse, so the introduction by a trusted healthcare worker helped the interviewer establish a rapport more easily (Mack N, 2005). This was particularly helpful given the stigmatising nature of the topics being discussed, where without such purposive sampling from addiction clinics is could have been difficult to find interviewees (Gubrium JF, 2001).

The interview environment of each interviewees outreach clinic was chosen to ensure participants would feel comfortable in the environment and to ensure it was accessible and convenient, and as such was a positive aspect of the study, however due to the relatively small number of people attending each outreach clinic this led to potential concerns around confidentiality for some patients including patient 10, “It’s like people know this is happening now, yeah? They know it, they see me here, they’re going to know *(she has HCV)*, isn’t it, really?”. Care was taken by the researcher and nurses not to advertise that interviews were occurring to other attendees of the addiction services to ensure confidentiality was maintained.

Given that the interview is a personal encounter, when designing and interpreting qualitative research the relationship between the participant and interviewer is vitally important to ensure the validity of the research, a concept known as reflexivity (Mays N, 2000). The interviewer should “converse with them in the original Latin meaning of conversation “to wander together”” (Kvale S, 1996), be an attentive listener and not impose their own concepts (Britten, 1995). The interviewer (HL) was a doctor, which could have inclined the interview towards a therapeutic doctor-patient relationship leading to interviewees wanting to please the interviewer, and also seeking advice and

counsel (Britten, 1995) (Gubrium JF, 2001). The interviewer tried to avoid this by focusing the encounter on the participants and being non-committal when asked questions, but this may have affected the rapport between interviewer and interviewee.

Technical difficulties meant that one interview could not be retrieved leading to the loss of this data, while this is unlikely to have affected the main identified themes, a new emergent theme could have been seen in this interview which could have led to more interviews taking place and so this could have affected the study.

Sampling was stopped when 12 interviews had been completed due to theme saturation having been reached. This is a valid technique when performing qualitative research (Britten, 1995), but as this decision was made by one researcher (HL), and one supervisor, a wider discussion of the validity of this with qualitative researchers who are experienced in the field would have ensured that there were no further themes to explore. The qualitative analysis was performed by one researcher (HL), and to improve the validity of the findings having the input of other qualitative researchers to analyse the codes, discuss the themes, and categories would have been valuable, and is considered best practice (Sofaer, 2002). While using just one interviewer ensures reproducibility across interviews, analysis is strengthened by the input of more than one researcher and this is a potential weakness of the study. The findings of this study do however triangulate well with other research in the field, so this gives some confidence about the validity of the study and the coding process.

8 Discussion

8.1 Overview

Due to low ascertainment rates, and the serious complications of chronic viral hepatitis screening for HBV and HCV in primary care is recommended for migrants from high prevalence countries living in the United Kingdom (NICE, 2012). The method of screening that will lead to the highest uptake of testing in primary care in the United Kingdom had not been examined previously, and this research attempted to address this. It found that a direct testing approach appears to be more effective at screening than the opportunistic testing approach currently recommended, but due to methodological flaws in the study firm conclusions on this cannot be made. This research also identified a number of logistical issues to screening in primary care, and the results have informed a large NIHR funded study designed to assess this question further.

The prevalence of HCV in PWID in the United Kingdom is high at up to 85% (DeAngelis, 2008), but treatment rates are low with the highest reported treatment rate in the United Kingdom being 18% (McAllister G, 2014). When this research was undertaken the outcomes of HCV treatment in PWID had only been reported in a few small, low quality studies (Taylor, 2005) (Litwin AH, 2005) (Wilkinson M, 2008), and evidence on the best way to improve treatment uptake and a comprehensive understanding of barriers to HCV treatment in PWID were lacking. This research attempted to address these deficiencies. It found that HCV treatment for PWID in Specialist Addiction Services is safe and effective, and that those who are actively injecting drugs have

similar treatment outcomes to those who have ceased injecting. This study failed to show that nurse initiated treatment improves treatment uptake, and a number of barriers to treatment of HCV in PWID were identified. The study failed to provide reliable data on reinfection and mortality rates, and drug use outcomes after HCV treatment in a significant number of patients due to methodological flaws.

This chapter will discuss the findings of each of the studies separately, reviewing them in the context of previously published research and draw conclusions from the findings. The methodological issues of each study have already been examined in detail in the results chapters, but the methodology of some studies will be discussed further in this section.

8.2 Mosque Awareness Raising Campaign

The awareness raising campaign did not appear to be effective in encouraging Mosque attendees to be tested for HBV and HCV at their GPs, as no coded virology forms were received at the Royal London Hospital virology laboratories. It is possible that some patients were tested for hepatitis B and C due to this campaign but that this was not captured either because their GP did not use the coded virology form, they were tested outside of the London borough of Newham or the campaign code was not entered on receipt of the samples at the Royal London Hospital virology laboratories. Potential reasons for the lack of success of this approach could include Mosque attendee's reluctance to attend GP surgeries to be tested for HBV and HCV due to disease related stigma (van der Veen YJJ, 2009) (Guirgis M, 2012), or the potential inconvenience in having to make an appointment with their General Practitioner for testing for a disease that they may not feel at risk for when they do not feel unwell. By

requiring participants to attend their General Practitioners for testing this awareness raising approach adds an additional step for testing to occur, when compared with on-site testing in Mosques as performed by Uddin et al (Uddin G, 2009) and this may explain the reduced uptake of testing with this approach. A systematic review of randomised controlled trials of awareness raising campaigns for Hepatitis B and C found moderate evidence that they improve participant's knowledge of the viruses, but no evidence that they improved uptake of testing (Jones L, 2013) and this campaign, although without the rigour of a randomised controlled trial, would appear to agree with these findings.

8.3 Screening for chronic viral hepatitis in migrants

The main finding of this pilot observational cohort study was that a higher proportion of patients were tested for chronic viral hepatitis in the direct testing arm than in the opportunistic testing arm. These findings are interesting as there is a lack of published data on the method of screening that will provide the greatest uptake of testing for chronic Hepatitis B and C in migrant populations in primary care in the United Kingdom. The cheapest approach to screening is clearly to ask primary care physicians to test their patients but this study suggests that this may not be sufficient and is unlikely to lead to a large increase in case identification. However the findings should be interpreted with some caution in view of the methodological issues discussed in section 4.4.

This study is unable to answer which method was the more effective screening technique as the ultimate measure of screening efficacy is whether it results in reduced morbidity and mortality from the screened for disease, and to answer this question requires a randomised controlled trial with a much longer period of follow up (Peckham CS, 1998). Due to the difficulty in showing an effect on morbidity and mortality from screening, end points which take many years to manifest, all the studies into screening for chronic viral hepatitis in at risk migrant groups have used testing uptake as a marker of efficacy, but this does not truly test screening efficacy (Robinson T, 2005) (Rein DB L. S., 2011) (Jafferbhoy H, 2012) (Veldhuijzen IK, 2012) (Richter C, 2010) (Hargreaves S, 2014).

Attendance for testing in both arms of the study was low at 1.9% and 21% of those eligible for screening respectively. No comparable studies of screening for chronic viral

hepatitis have been performed in the UK or internationally to compare these results, but some have incorporated similar elements. The large scale New Zealand Hepatitis B screening programme used a variety of techniques including supporting GPs and Maori and Pacific providers to undertake screening and using outreach teams at community events, and 27% of the eligible population accepted screening (Robinson T, 2005). A study in the United States compared three models of screening, one of which involved integrating screening into routine primary care services similar to the opportunistic testing arm in this study and showed a screening uptake in primary care of 6.5%. These studies all indicate that testing uptake rates when screening for chronic viral hepatitis in migrant groups in primary care are low, but due to significant differences in study design meaningful comparisons between these studies and the current study cannot be made.

The uptake of testing for chronic viral hepatitis in this screening study is lower than testing rates for South Asians in other screening campaigns in the UK such as breast and cervical screening where testing uptake rates of 53% and 67% are seen (Sutton GC, 2001). This may be due to infectious disease related stigma within migrant communities, although stigma is more commonly attached to HIV than Hepatitis B or C (Seedat F, 2014). A qualitative study into the reasons behind the low uptake of testing will help to answer the question as to why testing uptake was so low and to inform future studies in this area, and is recommended as an area for future research.

The proportion of patients who agreed to testing and subsequently attended for testing was higher in the opportunistic testing arm of this study (22/25, 88% versus 237/411, 58%, p=0.0026). This was despite the fact that testing was not performed on

site at the opportunistic testing arm GP practice, and so was not necessarily convenient for patients. Physician recommendation has been shown to be a strong predictor for screening uptake in colorectal cancer and viral hepatitis screening programmes (McGregor SE, 2007) (Hu K-Q, 2011) (Ma GX S. S., 2008) (Ma GX S. S., 2007) and this finding may reflect this. A London based study where screening for HIV, TB, HBV and HCV in new migrants was incorporated into new patient health checks in primary care, which has some similarities to the opportunistic testing arm of this study, showed a high acceptability of screening, with 77% (36/47) of those asked being tested (Hargreaves S, 2014). Similar to the current study the number of contacted patients was low at 47 out of 1235 newly registered patients, so while this approach is acceptable it does not appear to target a high proportion of eligible patients.

No patients were tested by the postal testing method implying that this option should not be used for screening. The postal testing method is similar to the screening method that Veldhuijzen et al used in their model to assess the cost effectiveness of screening for HBV in migrants in the Netherlands (Veldhuijzen, 2010), and could indicate their estimate of a testing uptake rate of 35% was over optimistic or may indicate differences in the populations examined. However those who were offered the postal testing option in this study were those who could not attend their GPs and were therefore already a self-selected group who were less likely to be able to be screened, and Veldhuijzen's study was set in the Netherlands health care system and so findings from this United Kingdom based study may not be applicable.

The four primary care practices that trialled the direct testing method ranged from a single handed GP practice to a large training practice with 10 General Practitioners and

multiple facilities on site. Testing uptake rates were consistent across all practices despite these differences which is an important finding when considering the wider applicability of the study findings. However it is important to note that all the practices were located within one inner London borough which reduces the relevance of the findings of this study to other areas of the United Kingdom or other countries.

Testing uptake was significantly higher in those aged over 40 (28% vs 17%, p = <0.0001), who made up a smaller proportion (38%) of the eligible testing population than those aged less than 40. Younger age has not been identified as a barrier to screening for viral hepatitis in migrants in studies that have sought to address this issue (Seedat F, 2014) (Khalili M, 2011)(Hu K-Q, 2011) (Ma GX S. S., 2008) (Ma GX S. S., 2007) (Guirgis M, 2012) (van der Veen YJJ, 2009). The majority of those who tested positive for HBsAg and HCV ab were aged under 40 (4/5), which potentially makes the lower uptake in this group more concerning, but due to the small numbers of patients who tested positive no firm conclusions can be made on this subject. Future studies will need to examine the reasons behind the lower testing uptake in the younger age group to try to address this discrepancy.

It was not possible to collect data on country of birth for the entire eligible screening population as GP practices in the United Kingdom collect demographic data on ethnicity rather than country of birth. A small sub-group analysis on testing uptake according to country of birth indicated testing uptake was higher amongst first generation migrants than second generation migrants. This is potentially of interest as previous research indicates the prevalence of HBV and HCV is higher in first generation migrants (Uddin, 2010) and these results accord with the findings of a study targeting

Turkish migrants in the Netherlands where a higher screening uptake was seen in first generation migrants (Richter C, 2010). However this was an unrepresentative sample which had a much higher agreement to testing than the cohort as a whole (81%) and included only patients who could be contacted for testing from one primary care centre. As such the results should be interpreted with great caution and no firm conclusions can be made from them. All the patients who had a positive screening test, and the two with equivocal HCV ab tests were born in Pakistan and this concurs with Uddin et al's finding of a higher rate of chronic viral hepatitis in first generation migrants (Uddin, 2010).

In this study a lower prevalence of chronic viral hepatitis was seen in migrants from Pakistan living in the United Kingdom than previously reported (Jafferbhoy H, 2012)(Uddin, 2010). It is not clear why this was the case, but these studies screened in community environments, rather than primary care, and so may have targeted a different population. The lower positivity rate seen will affect the cost effectiveness of any screening intervention.

All patients who had a positive screening test engaged in follow up and treatment was completed by all patients in whom it was required. Previous screening studies for chronic viral hepatitis in the United Kingdom have shown mixed results when engaging patients in follow up. In one community based study 25% of those with a positive screening test did not attend follow up (Uddin, 2010) and in another all those who screened positive were evaluated and commenced treatment if required (Jafferbhoy H, 2012). Patients who have been tested for viral hepatitis in primary care may be more

likely to attend follow up than those tested in the community as they have already engaged with a formal healthcare environment.

A surprising finding was that over a third of the eligible population in the direct testing arm could not be contacted to invite them to attend for testing by telephone, and in 192 patients (17% of those eligible for screening) this was due to incorrect telephone contact details being held at their GP surgery. This has not been reported previously as a barrier to screening, but was a significant barrier to testing in this study. This has the potential to significantly reduce the reach of testing, and before a wider screening programme is implemented efforts should be taken to address this, perhaps by General Practitioners contacting all registered patients by letter asking them to update their contact details with the practice.

In summary this pilot study indicates that a direct testing approach to screening for chronic viral hepatitis in primary care may result in a higher uptake of screening than an opportunistic testing approach, and appears to be more acceptable to General Practitioners but the methodological flaws and observational study design means firm conclusions are not possible. It is the only prospective study of its kind to have been carried out in the United Kingdom to examine this question and as such the results are interesting and have informed future research. A number of logistical difficulties with screening for chronic viral hepatitis in primary care have been identified and recommendations from this study will inform the design of a nationwide study.

The major recommendations from this study are that a randomised controlled trial should be performed comparing direct and opportunistic testing for chronic viral hepatitis in primary care. This trial should be undertaken over a wider geographical

area and should incorporate an awareness raising campaign. A qualitative analysis of the barriers and facilitators to testing for chronic viral hepatitis amongst high risk migrant groups within the United Kingdom, and a formal cost effectiveness analysis of screening should be performed as part of this trial. Furthermore this trial should attempt to address the logistical issues encountered in this study, including ensuring access to all the required data, attempting to improve the accuracy of GP contact details and should explore whether GP records can be updated to include country of birth.

8.4 Analysis of the outcomes of HCV therapy in people who inject drugs

This retrospective observational cohort study is the largest study to date examining the impact and long term follow up of antiviral therapy in a cohort of patients actively using illicit drugs. Treatment was shown to be safe and effective and over a median follow up of 21 months there was a significant reduction in crack cocaine use, and only two patients became HCV RNA positive after obtaining an SVR. An infection free survival rate of 98% was seen in those who were successfully treated and were still in contact with the treatment service. These findings, while they should be viewed with some caution due to the retrospective cohort design of the study, appear to confirm previous, smaller scale studies showing that effective treatment for PWID with HCV is possible within an appropriate clinical setting and expand these data to demonstrate beneficial effects on behaviour.

Outcomes of 152 treated patients were examined in this study, with the previous largest cohort study examining the outcomes of HCV therapy in 73 PWID in New York (Litwin AH, 2009). A larger retrospective cohort analysis has been published since this work was undertaken examining SVR rates in the East of Scotland after treatment for HCV in 169 people who inject drugs with 87 being active drug users, and 82 having previously injected drugs (Jafferbhoy H M. M., 2012). In contrast with the work in the current study they do not report on mortality, infection free survival, change in characteristics of drug use or whether participants tested positive for HCV after attainment of SVR, and therefore the current study addresses wider research questions. A further important study undertaken since this study was devised is the

ETHOS study, a prospective observational cohort study evaluating treatment of HCV in addiction clinics which has been discussed in detail in the introduction to this thesis (Alavi M, 2013). Of 387 enrolled participants specialist assessment was undertaken in 191, and 84 commenced treatment for HCV. Although it examines a smaller number of treated patients this study is particularly important as it is the largest prospective study examining HCV treatment outcomes in PWID.

Sustained viral response rates were 55% overall, 43% in those with genotype 1 and 4 and 63% in those with genotype 2 and 3 HCV. The SVR rate in this study is very similar to those reported in two meta-analyses of antiviral therapy for HCV in PWID, where pooled SVR rates of 55% and 55.5% were seen (Aspinall EJ, 2013) (Dimova RB, 2013) and the registration studies of pegylated interferon-α and ribavirin report which reported pooled SVR rates of 54% and 56% (Manns MP, 2001) (Fried MW, 2002). This indicates PWID have very similar virological outcomes to the general population when being treated for HCV, but as the groups were not directly compared firm conclusions cannot be made. Treatment was discontinued in 16% of patients in this study due to adverse events, which compares favourably with the treatment discontinuation rates of 14% and 22% in the registration studies (Manns MP, 2001) (Fried MW, 2002). Compliance with the 80/80/80 rule was 70%, which is lower than the pooled adherence of 82% seen in a recent meta-analysis of studies into PWID (Aspinall EJ, 2013). These findings are not unique, but provide further evidence in a larger cohort of patients than has previously been examined that PWID can be treated for HCV safely and effectively. Virological outcomes were similar when comparing those who were actively using illicit drugs at the start of treatment and those who were not. This

question has been examined only twice before, with conflicting results. Jafferbhoy et al found ex-PWID had a significantly better SVR than active PWID (54.8% versus 47.1%) and Sasadeusz et al found that SVR rates were similar (63% in active injectors and 53% in non-injectors) (Jafferbhoy H M. M., 2012) (Sasadeusz JJ, 2011). When considering all these findings it is important to note that only 17% of the infected population underwent therapy and this is likely to be a self-selected, compliant group of patients.

The disease free survival rate of 98% observed in this cohort indicates there is a low risk of reinfection and death in the years immediately post treatment for HCV. Due to the retrospective nature of the study data was missing for follow up of both mortality and reinfection and this should be borne in mind when considering the results. However this finding challenges the assumption that high morbidity and mortality levels and the potential for reinfection mitigate the benefits of treatment in PWID. The outcomes seen in those who did not clear their virus appeared less favourable, with all five deaths occurring in this cohort a 7% mortality over the six year period studied. However it is unclear what contribution, if any, active HCV infection made to mortality and it is therefore difficult to determine whether viral eradication reduces short term mortality. Overall mortality in the group studied was low at 3.2% over the six year period, for a group recognised to have high mortality rates, and compares favourably to long term follow up of mortality in this population (Degenhardt L, 2010). The limitations of the retrospective cohort design mean the mortality data is potentially unreliable, as a number of patients were lost to follow up and death registry data was not collected. Reporting of mortality of ex-patients to the SAU service is however

reasonably comprehensive as four of the five patients who died were not attending specialist addiction services at the time of their death.

Only 2/45 patients tested positive for HCV RNA after achieving SVR, which if this finding represents reinfection, gives a low reinfection rate of 1.75 per 100 person years, and is an interesting finding particularly in this chaotic population where over 50% of patients were actively injecting drugs when treatment was commenced. Where HCV RNA testing was undertaken in this study post SVR the aim was to assess for re-infection, but as phylogenetic analysis was not performed on the two patients who tested positive for HCV RNA, it is possible the positive results could have represented a late relapse of the original infection rather than reinfection.

At the time this study was undertaken there was very limited data on reinfection rates in PWID with only two published small scale studies (Dalgard, 2005) (Backmund M, 2001). Since this point further data has been published and the findings from this study if they represent reinfection are in keeping with a recent meta-analysis reporting a pooled risk of reinfection of 2.4 per 100 person years (Aspinall EJ, 2013). The figures seen in this study must be interpreted in light of the retrospective cohort study design. The rate of HCV RNA positivity post SVR reported may be an underestimate of the true prevalence as 46% of patients who attained an SVR were not retested for HCV RNA. Those patients who were not re-tested were either deemed to be at low risk of re-infection through self-reported cessation of high risk behaviour, or were lost to follow up. A reliance on self-reporting to assess risk of re-infection can be criticised, however objective assessment of risk taking behaviour around illicit drug use is difficult and a review of studies assessing the self-reporting of drug use, risk taking and criminal

behaviour amongst PWID showed respectable reliability and validity of self-reporting indicating that this is a reasonable method to assess risk (Darke, 1998). Despite this to enable accurate reporting the whole cohort would need to have been retested. It may also be that those lost to follow up were, by this very fact, more chaotic and thus more likely to engage in high risk behaviour and become re-infected. A further caveat to this finding is the relatively short length of median follow up of 21 months. Nevertheless in those who were re-tested the rate of HCV RNA positivity was low. It is unclear why the rate was low but this may relate to a reduction in risk taking injection behaviour such as sharing of paraphernalia due to education by addiction services or low level immunity to re-infection.

This study is the first to report a significant reduction in crack cocaine use and a reduction in the quantity of injection heroin use during treatment for HCV. Reduction in illicit drug use has benefits to both the individual and society by reducing the multiple harms associated with drug use but it can be difficult to achieve even when patients are maintained on opiate replacement therapy. A recent systematic review of opiate replacement therapy showed that over a third of PWID continue to use illicit drugs even while maintained on opiate replacement treatment (Amato L, 2005). Any additional interventions that may have an impact on illicit drug use are likely to be beneficial. The cause of the reduction in illicit drug use seen in our study is not clear but may include increase in contact with support services due to the weekly requirement for pegylated interferon-α injections (a ‘re-mothering’ effect). Alternatively due to the strong association of injection drug use and HCV, patients may perceive HCV treatment as part of a return to normality and a rejection of their drug

using past as suggested by qualitative research into HCV in PWID (Swan D L. J., 2010) (Rhodes T H. M., 2013) (Groessl AK, 2008). The retrospective cohort design of this study must lead again to caution in interpreting this data, and due to this no firm conclusions regarding drug use can be made. The retrospective cohort design led to a considerable amount of missing data relating to drug and alcohol use, and meant that standardised drug and alcohol use questionnaires were not used to assess drug and alcohol consumption which reduces the validity of the data as a whole and the reliability of estimates of the quantities of illicit drugs and alcohol used. It is probable that this data suffered from a reporting bias, as data was only included on drug use where it was explicitly documented that a patient was or was not using a drug and it is more likely a positive finding of drug use will be documented than a negative finding. As an example, where crack cocaine use was documented prior to the start of treatment the patient was actively using crack cocaine in 90% of cases, which is unlikely to reflect the true prevalence of crack cocaine use, and may be the reason there appeared to be such a marked reduction in crack cocaine use. The reduction in quantity of injection heroin use is interesting and would be consistent with a reduced use due to harm reduction messages delivered by Specialist Addiction Services, but suffers from the same difficulty of reliability of the conclusions. However heroin use was documented much more widely (in 133 patients pre- and post-treatment) and so may suffer from less of a reporting bias.

As part of this analysis predictive factors for drug use reduction were assessed and only compliance with antiviral therapy is predictive of a reduction in overall illicit drug

use. This may reflect general compliance with treatment, including opiate replacement therapy.

Only end of treatment response was predictive of SVR on multivariate analysis indicating that in this relatively young group of patients age and age of infection do not reduce viral response. Interestingly pre-treatment heroin and crack use do not predict likelihood of SVR, indicating that illicit drug use does not affect treatment outcomes, and the SVR rates seen in this cohort support this finding.

Systematic reviews and meta-analyses of studies into PWID treated for Hepatitis C have highlighted the lack of high quality data in this area. In the systematic review carried out by Lazarus et al into HCV treatment uptake of PWID they included only one randomised controlled trial, three cross-sectional studies, 11 retrospective cohort studies and 10 prospective cohort studies (Lazarus JV, 2014), and Aspinall et al included six studies in their meta-analysis of SVR, all of which were cohort studies, three being prospective, two retrospective and one providing too little data to be able to discern (Aspinall EJ, 2013). This study was performed before many of the studies that have been reported in Aspinall's meta-analysis to try to fill the deficit in outcome data on the treatment for HCV in PWID, hence its retrospective design.

It can be concluded from this study that in this cohort of PWID treatment with antiviral therapy for HCV using a community based nurse led model is effective and safe. Re-infection within the first few years after treatment and overall survival rates appeared to be low, but the unreliability related to missing outcomes and whether HCV RNA positivity reflects reinfection mean these findings have to be interpreted with caution. Illicit drug use may reduce during treatment for HCV, but again caution needs to be

taken in concluding this due to the potential for reporting bias and missing data. However this finding, when viewed with the qualitative analysis indicating PWID perceive HCV treatment to have a transformative potential means there may be an important harm reduction benefit in addition to the recognised health benefits and reduced viral transmission seen after successful treatment and further prospective studies are required to examine this issue in more detail.

8.5 Nurse initiation of antiviral therapy for HCV in people who inject drugs

This study aimed to ascertain whether nurse-led initiation of antiviral therapy for chronic hepatitis C increases treatment rates in PWID when compared with doctor led initiation of therapy. The main finding is that this is not the case, with no difference in treatment rates between the nurse initiated and doctor initiated arm. A possible explanation for this is that, as evidenced by the findings of the qualitative study, patients find the "East London model" for delivering HCV treatment convenient and easy to access already.

Few patients initiated treatment in either arm and the finding is consistent with a recent systemic review which showed median HCV treatment uptake rates of 9.5% in PWID across Europe (Wiessing L, 2014). The reasons behind this are explored in the qualitative analysis, with a number of barriers to treatment being identified (Harris M, 2013) (Rhodes T H. M., 2013). This study suggests treatment rates will not be increased by nurse initiation of treatment. Although service improvement with community health services collaborating with addiction services has enabled more PWIDs to access therapy (Wilkinson M, 2008) the results from this study substantiate that further service improvement may only have a limited effect. Pegylated interferon-α treatment is a considerable barrier to treatment in PWID (Swan D L. J., 2010) (Doab A, 2005) (Grebely J G. K., 2008) and the advent of new and interferon free regimens for HCV is likely to make a bigger difference in treatment rates than changes in service design by eliminating the treatment burden and adverse events of interferon-based treatment.

A considerable proportion of patients, 39% in the nurse initiated and 28% in the doctor initiated arm (p=0.44, OR 1.64, 95% CI 0.61-4.43) were considered unsuitable for treatment due to medical or psychiatric co-morbidities. While the criteria for treatment were different in each arm due to the stringent safety criteria in the nurse initiated arm, there was no difference in the proportion of patients who were felt to be unsuitable for treatment due to medical comorbidities between arms (46% in the nurse initiated arm versus 77% in the doctor initiated arm, p=0.095, OR 0.17, 95% CI 0.02-1.10). Psychiatric comorbidity was the primary reason that patients in the nurse initiated arm failed the safety protocol, but all these patients were assessed to be suitable for treatment with appropriate psychiatric support when considered for treatment in the usual way. This suggests that facilitated access to a psychiatrist, possibly by nurse referral, could increase the number of patients who commence treatment within a nurse initiated model of care.

Treatment in PWID is known to be safe and effective (Aspinall EJ, 2013) and this study confirms this. While all patients experienced some adverse events, no serious adverse events occurred and only one patient (8%) had to stop treatment due to side effects of treatment. This figure is in line with the registration studies of pegylated interferon-α and ribavirin treatment (Fried MW S. M., 2002) (Manns MP M. J., 2001). In addition there were not more compliance issues in this study than in other populations with 83% of patients fulfilling the 80/80/80 rule. (McHutchinson JG, 2002).

Treatment outcomes in the form of SVR rates did not differ between the nurse initiated and doctor initiated arms. This was to be expected and furthermore the study was not powered to detect a difference in treatment outcomes.

Patients in the nurse initiated arm started treatment significantly earlier confirming that the need to attend the consultant led clinic delays the start of treatment. While this can be seen as an advantage of nurse initiation of treatment, it did not affect uptake of treatment. The delay of an average 54 days can at least partly be explained by the fact that the clinic is only held on a monthly basis. From a public health point of view an earlier start of treatment is desirable as this can reduce the likelihood of transmission to others, but whether the delay of 54 days will have made a difference to transmission rates cannot be known.

Drug and alcohol use did not reduce over the course of HCV treatment. The retrospective cohort study had indicated that illicit crack cocaine use, and the frequency of heroin use may reduce over the course of antiviral therapy but this study was not able to confirm this finding. The current data can be regarded as more accurate than that from the previous study as it was collected prospectively with standardised questionnaires rather than retrospectively from case notes. However the qualitative data indicate that some PWID associate HCV treatment with a move away from drug use, and so the absence of a reduction in drug use may reflect the fact that the study was not adequately powered to detect a difference in these outcomes. This question should be examined in a trial that is adequately powered to detect a difference in drug use outcomes.

An important finding, when considering the lack of randomised controlled trials into the treatment and outcomes of PWID with HCV is that a third of treated patients in this cluster randomised controlled trial were actively using illicit drugs when enrolled. Although the numbers are small this shows that people who are actively using illicit

drugs can be recruited to and retained in randomised controlled trials. In this study 17% of treated patients (2/12) were lost to follow up during the study period, one due to incarceration after treatment was completed and one during treatment. Attrition of patients is always a concern in prospective studies (Mann, 2003) and the rate of patients lost to follow up compares favourably with the mean attrition rate in randomised controlled trials of 13% (Crutzen R V. W., 2013) and in health behaviour studies of 18% (Crutzen R V. W., 2015). This should encourage others to consider the inclusion of PWID in a larger number of clinical trials as a clear anomaly exists when the group most affected by HCV are the least likely to be included in trials of HCV therapy.

In conclusion, nurse initiated treatment of selected PWID with HCV is safe and effective, but does not increase the numbers commencing or completing treatment. This is consistent with the findings of the qualitative study which indicated that patients at using Specialist Addiction Services in East London find that Hepatitis C virus treatment is easy to access. Early adoption of interferon free regimens in PWID may be required to significantly increase treatment rates and reduce onward transmission in and by this population, as Zeremski et al remark the full impact or direct acting antivirals will only be seen if innovative approaches are pursued to engage all HCV infected individuals into treatment (Zeremski M, 2013).

8.6 Qualitative assessment of reasons underlying engagement in HCV treatment in people who inject drugs

The qualitative aspect of this research project was incorporated as it was felt to be important to understand people who inject drug's social construction and understanding of Hepatitis C and its treatment, in order to understand why such low treatment uptake rates exist. It is hoped that the insights from this study will help inform changes in services to better meet the needs of PWID with HCV.

A number of strong themes emerged from the qualitative analysis relating to the research questions and showed that many factors which are dependent on circumstances and exist in a state of flux over time affect each individual's decision to have treatment for Hepatitis C and these will be discussed in more detail in this section.

Knowledge of Hepatitis C, particularly the negative health effects, and Hepatitis C treatment options were discussed by participants as motivating them to have treatment and feeling more empowered to deal with their Hepatitis C. The importance of being given information about HCV and its treatment at diagnosis was particularly emphasised and could ameliorate to some extent the shock and fear surrounding the diagnosis. Participants reported that lack of knowledge of Hepatitis C and its treatment led to a sense of nihilism or a lack of concern surrounding Hepatitis C. A lack of knowledge of Hepatitis C and its treatment amongst PWID and healthcare professional's imparting inaccurate or minimal information to patients at diagnosis, with subsequent frustration, confusion or lack of concern are well recognised (Harris,

2009) (Jordan AE, 2013) (Lally MA, 2008) (Tompkins CNE, 2005) (Rhodes T H. M., 2013). The sense of personal empowerment that knowledge appeared to provide has not been previously noted, and indicates that better information at diagnosis could help patients feel more in control of their illness. Previous studies have shown that PWID get most of their knowledge of HCV from peers and found accessing knowledge difficult (Jordan AE, 2013) and where this study differs is that most participants gained their knowledge from their nurses and generally felt that knowledge was easy to obtain.

The normalisation of HCV amongst PWID was related to its ubiquitous association with injection drug use and the asymptomatic nature of the disease. Participants also normalised the illness as a coping mechanism, particularly when they felt it could not be treated. Poor information at diagnosis reinforced a normalisation and lack of concern towards the diagnosis of Hepatitis C in some participants which has been recognised previously (Harris, 2009). In Harris et al's study the normalisation of Hepatitis C is described as manifesting in "narratives of unconcern" which were particularly affected by a participants injecting status and HCV being seen as a marker of belonging within a community (Harris, 2009). In the current study some patients normalised their Hepatitis C within this context of a "narrative of unconcern" particularly when they were still actively injecting drugs, but others were concerned about their diagnosis, despite their acceptance of Hepatitis C as part of "normal life" and their normalisation developed as a coping mechanism for a chronic disease that they perceived as untreatable. This is recognised as a commonly used coping strategy

used in other chronic illnesses such as Alzheimers disease (MacRae, 2008) but has not been reported in the qualitative literature in relation to Hepatitis C virus.

The asymptomatic nature of Hepatitis C can be a factor in its normalisation, and in this study it was seen that when feeling well participants had a low perceived need for treatment, but that this changed when they developed symptoms that were attributed to Hepatitis C. This supports the concept of body dys-appearance, discussed by Harris et al in relation to Hepatitis C, where an individual becomes more aware of their body through illness, pain or body dysfunction, which consequently disrupts their narrative of normalisation of Hepatitis C virus (Harris, 2009). The finding of a low perceived need for treatment related to lack of symptoms is consistent with previous findings in surveys and qualitative research on this subject (Harris, 2009) (Swan D L. J., 2010) (Rhodes T H. M., 2013) (Mehta SH, 2008) (Doab A, 2005) (Mravcik V, 2013).

The stigmatisation of Hepatitis C virus was an almost universal theme in these interviews due to the association of Hepatitis C and injection drug use, others lack of knowledge relating to HCV and its perception as a contagious disease. The stigma associated with HCV and its connection with injection drug use is a strong thread of many studies in Hepatitis C infection in PWID (Conrad S, 2006) (Swan D L. J., 2010) (Lally MA, 2008) and a 2009 qualitative synthesis concluded that the social stigma of Hepatitis C virus is often indistinguishable from the stigma associated with injection drug use (Treloar C R. T., 2009). Stigmatisation from others due to their lack of knowledge around Hepatitis C, particularly of its transmission has been noted previously (Tompkins CNE, 2005). In previous studies stigmatisation was seen most frequently in healthcare settings (Treloar C R. J., 2013) but this was not a feature in this

study. Stigmatisation in healthcare settings has been reported to be due to a lack of understanding and stigmatisation of drug use and leads patients to feel they have not been treated with compassion or respect (Lally MA, 2008) (Swan D L. J., 2010) (Sgorbini M, 2009) (Jordan AE, 2013) (Tompkins CNE, 2005). Treloar et al note that the building of trust between PWID who have HCV and their healthcare workers can reduce the felt effects of stigma (Treloar C R. J., 2013) and the strong relationships developed by healthcare workers with participants in this study may be the reason for the low perceived stigmatisation from healthcare professionals.

Many participants referred to Hepatitis C as being their "fault" and associate it with a sense of blame, particularly around previous injection drug use. The perception of self-blame in PWID has been postulated to reflect a neo-liberal attitude of personal responsibility for health (Harris, 2009) and to be important in constructing a case for deservedness for treatment (Rhodes T H. M., 2013). An emphasis on individual responsibility predominated in harm reduction campaigns targeting Hepatitis C which may have inadvertently informed participants own sense of judgement around their feeling of responsibility for acquiring Hepatitis C (Harris, 2009) (Treloar C R. T., 2009).

The impact of others on participants decisions to have treatment for Hepatitis C virus were reported in a number of ways; seeing peers become unwell as a consequence of Hepatitis C or seeing them complete treatment acted as motivators to start treatment, and for a number of patients care for others provided an incentive to start or stay on treatment. Seeing peers complete treatment successfully even when they had struggled with difficult side effects has been noted previously to encourage people to seek treatment (Swan D L. J., 2010) and the support of peers, partners and families

(including dogs) is known to help those undergoing treatment cope with side effects (Swan D L. J., 2010) (Sgorbini M, 2009). The findings of this study support the previous findings and indicate that peer support groups or networks should be set up as an important way to support those considering and undertaking HCV treatment.

The competing demands of active drug use were a prominent theme in this study, with a narrative of the all-consuming nature of active injection drug use leaving a lack of space to consider treatment for Hepatitis C. Participants perceived treatment for those actively injecting drugs as a "waste of time" both due to a belief they may be reinfected, and a nihilistic element relating to their perception of high short term mortality associated with injection drug use. In their belief that those who were actively injecting should not be treated the participants in this study supported Rhodes' hypothesis of "treatment negotiation" around HCV treatment in PWIDs, whereby they feel they have to fulfil certain social criteria, including the cessation of injection drug use to qualify for treatment (Rhodes T H. M., 2013).

This study noted the importance of the motivation and support felt by patients from healthcare professionals, along with ease of access to services in aiding them to engage with treatment. A general sense of well-being related to services was reported, and particularly a sense of feeling cared for. The Specialist Addiction Unit treatment services are relatively successful in treating PWID with HCV as shown by the findings of the retrospective study where 17% of patients had accessed treatment, and the support felt by patients may have been a factor in this. Convenience is particularly important given that most patients reported not actively seeking treatment, but accepting it when it was offered. Information and support from health professionals,

particularly a feeling that they had concern for their welfare and convenience of services have been shown to help engage people in treatment (Swan D L. J., 2010). However staff motivation being cited as a principal factor in PWID deciding to have treatment has not been reported previously. In fact the opposite has been seen whereby most patients have felt discouraged from pursuing treatment by their healthcare provider and have reported not being referred for treatment and investigations (Jordan AE, 2013) (Swan D L. J., 2010). This shows the impact that supportive, non-judgemental healthcare workers and a convenient environment can have in uptake of treatment for Hepatitis C virus. These findings may be related to the co-location of Hepatitis C treatment with local outreach addiction services where staff are knowledgeable about addiction, and services are conveniently located. Although the model of co-location of Hepatitis C treatment and addiction services has been shown to be effective (Swan D L. J., 2010) (Alavi M, 2013) (Belfiori B, 2009) (Waizmann M, 2010) (Jack K, 2009) (Aspinall EJ, 2013) there have been cautions raised that co-locating Hepatitis C treatment with opiate substitution services further entrenches stigma against people who inject drugs with HCV, an already marginalised group (Rance J, 2012).

The burdens associated with interferon treatment emerged as a barrier from the patient and healthcare provider perspective to treatment. Healthcare providers did not offer treatment to two patients due to concerns over psychiatric side effects, and patients were concerned about the perceived need for multiple appointments and low success rates of treatment with interferon. Interestingly fear of side effects was not a significant barrier in this study, in contrast with other studies (Jordan AE, 2013) which

appeared to be due to patient's belief in their own resilience and their trust that side effects could be treated by healthcare providers. Overall concerns about the barriers associated with interferon therapy were a prominent theme, and while education can address some of these (for instance the belief that daily injections, or weekly hospital appointments are needed) early access for PWID to interferon free treatments would effectively ameliorate the majority of these barriers.

The perception of the transformative nature of treatment for Hepatitis C was striking in this study. Hepatitis C virus was seen as symbolising a life dominated by drugs, and therefore treatment of it was constructed to symbolise a reconfiguration of that life back towards normal. Very similar experiences have been described by Rhodes et al, where Hepatitis C treatment is described by the authors as a potential "technology of hope", with patients in their study describing treatment as something they did "to get my life together" and "to live like a normal person" (Rhodes T H. M., 2013). Other studies describe the reformative perception of HCV treatment and its link with recovery from addiction, with Hepatitis C virus being described as representing the last straw hanging over them from drug use (Swan D L. J., 2010) (Groessl AK, 2008).

This study has identified a number of barriers and facilitators to Hepatitis C treatment in PWID. Overall the findings provide a valuable reinforcement of conclusions from previous qualitative research on the subject of PWID with HCV. These findings are important given that a number of the identified themes have only been previously noted in one or two studies, so this research enhances the validity of previous findings. New themes were identified around normalisation as a coping mechanism for Hepatitis C virus, knowledge of Hepatitis C virus providing empowerment, the lack of

stigma participants perceived from healthcare staff in Specialist addiction services and their perception of easy access to services. These new themes will help to inform future service design.

The findings indicate that patients are quite satisfied with the model of treatment given at Specialist Addiction Services and that changing the model of service is unlikely to improve treatment uptake. This is in keeping with the findings of the nurse initiated treatment study. A number of areas where access to treatment could be facilitated have been identified, these include ensuring adequate information about Hepatitis C is imparted at diagnosis, and that those with Hepatitis C are aware of the long term consequences as this is a motivator for treatment. Emphasising to healthcare staff the importance of their motivation in helping patients to decide to have treatment could potentially lead them to encourage more patients, and lead to a greater access of treatment. The importance of seeing peers completing successful treatment, indicates a peer support group could be very helpful in motivating patients towards and keeping them in treatment. Given the predominance of uncontrolled addiction in participant's lives then treatment for addiction, and help with housing and income will be important to help PWID deal with these competing priorities to enable them to access treatment for Hepatitis C virus. Interferon treatment is a significant barrier to treatment indicating the importance of early access to interferon free treatment for PWID. The narrative of Hepatitis C as transformative could also be developed with patients in addiction services to help motivate them towards treatment, possibly as part of a peer support group where people who have been treated can share their narratives of transformation.

Future research should focus on widening the sample frame to include healthcare professionals who treat Hepatitis C virus, both in Specialist Addiction Services and within the hospital environment, and to PWID from other addiction services and those who are not accessing addiction services.

9 Appendices

Appendix 1: EASL recommendations on treatment of Hepatitis C 2014

Current treatment recommendations from the European Association of the Liver with the currently licensed DAAVs are summarised below by genotype.

Treatment for patients with Genotype one and four HCV:

1. Sofosbuvir, pegylated IFN-α and weight based ribavirin for 12 weeks. In the NEUTRINO trial patients with G1a HCV had an overall SVR of 89% (92% in patients with G1a HCV and 82% in G1b) Patients with cirrhosis and genotype 1 HCV had an SVR of 80%. Treatment naïve patients with G4 HCV had an SVR of 96%. (EASL, 2014) (Lawitz E M. A.-T., 2013).
2. Simeprevir, pegylated IFN-α and ribavirin, for 12 weeks, followed by an additional 12 weeks of PR in treatment naïve and prior relapse patients, or an additional 36 weeks in prior partial or none responders. If HCV RNA is > 25 IU/ml at week 4, 12 or 24 treatment should be stopped. This is not recommended for patients with subtype 1a infection who have a detectable Q80K substitution in the NS3 protease sequence. In the QUEST-1 and QUEST-2 trials in treatment naïve patients with G1 HCV SVR rates were 80% and 81%. In G1a patients with the Q80K substitution SVR was only 58%. 60% of patients with cirrhosis and G1 HCV achieved SVR. SVR is achieved in 82% of patients with G4 HCV with this combination of therapy, 83% of treatment naïve

patients, 86% of prior relapsers, 60% of prior partial responders and 40% of prior null responders. (Jacobson IM D. G., 2014) (EASL, 2014) (Manns M M. P., 2014) (Moreno C, 2015).

3. Daclatasvir, pegylated IFN-α and ribavirin for 12 weeks. The triple combination should then be continued for an additional 12 weeks in patients whose HCV RNA is over 25 IU/ml at week 4 and is not undetectable at week 10. PR alone should be continued in patients whose HCV RNA is < 25 at week 4 and undetectable at week 10. Genotype 1 treatment naïve patients who received this treatment achieved SVR in 59.6% of cases, those with genotype 4 achieved an SVR in 100% (12/12) of cases. (Hezode C, 2014) (EASL, 2014).
4. Patients who are interferon intolerant or ineligible can receive sofosbuvir in combination with ribavirin for 24 weeks (EASL, 2014) SVR rates in G1 patients were 84% in treatment naïve patients, but much lower at 10% (1/10) in treatment experienced patients (Gane EJ, 2013), and in the QUANTUM trial SVR rates were 47% in treatment naïve patients. Preliminary data in genotype 4 patients indicates SVR rates of 79% in treatment naïve patients and 59% in treatment experienced patients (EASL, 2014).
5. A further option for interferon intolerant or ineligible patients is sofosbuvir in combination with simeprevir for 12 weeks. In genotype 1 patients preliminary phase 2 data shows an SVR rate of 93% (13/14) in prior non-responders with F0-F2 METAVIR scores treated with this combination. There is no data in genotype 4 patients with this combination, however both have high antiviral efficacy in treating this genotype. (EASL, 2014).

6. The third option for patients who are intolerant to or ineligible for interferon treatment is sofosbuvir in combination with daclatasvir for 12 weeks in treatment naïve patients or 24 weeks in treatment experienced patients. SVR rates with this combination were 98% (40/41) in treatment naïve patients. With 24 weeks of treatment 95% (19/21) of treatment experienced patients achieved SVR (Suklowski MS, 2014) (EASL, 2014).

Treatment of Genotype 2 HCV:

1. Ribavirin and sofosbuvir for 12 weeks, which should be prolonged to 16 to 20 weeks in patients with cirrhosis. SVR rates of 95 to 97% in treatment naïve patients are reported (Lawitz E M. A.-T., 2013). In those with cirrhosis 78% of patients achieved SVR with 16 weeks therapy and 60% with 12 weeks therapy (Jacobson IM G. S.-T., 2013). In a further trial SVR rates with 12 weeks of therapy were 91% in treatment naïve and 88% in treatment experienced cirrhotics (Zeuzem S D. G., 2013) (EASL, 2014).
2. Patients with cirrhosis and/ or who have already received treatment can be treated with pegylated IFN-α and ribavirin and sofosbuvir for 12 weeks. An SVR rate of 96% (22/23) was seen with this treatment combination in treatment experienced patients, 14 of whom had cirrhosis (EASL, 2014).

Treatment of Genotype 3 infection:

1. Pegylated IFN-α, ribavirin and sofosbuvir for 12 weeks. 90% (9/10, with 1 lost to follow up) of patients achieved an SVR with this combination therapy (Lawitz E L. J., 2013).

2. Ribavirin and sofosbuvir for 24 weeks. This treatment should not be used in treatment experienced patients with cirrhosis as it is not as effective as other treatments. The SVR rate with this combination for 24 weeks in treatment naïve patients was 60% in treatment experienced cirrhotics, and 94% and 92% in treatment naïve non-cirrhotics and cirrhotics respectively and 87% in treatment experienced non-cirrhotics (Zeuzem S D. G., 2013).
3. Sofosbuvir and daclatasvir in combination for 12 weeks in treatment naïve patients, or 24 weeks in treatment experienced patients. A phase 2b trial with this combination showed an SVR rate of 89% (Suklowski MS, 2014) (EASL, 2014).

Treatment for Genotype 5 and 6 HCV infection:

1. Pegylated IFN-α, ribavirin and sofosbuvir for 12 weeks. In the NEUTRINO trial into treatment naïve patients, the 1 patient with G5 HCV and all patients with G6 HCV achieved an SVR (Lawitz E M. A.-T., 2013).
2. In patients who are interferon intolerant or ineligible, treatment with ribavirin and sofosbuvir for 24 weeks can be given, however no data is available for SVR outcomes with this treatment regime in G5/6 patients (EASL, 2014).

Appendix 2: Imam fact sheets

Hepatitis

Hepatitis is a major problem in our community because it is very common in South Asia.

You can have hepatitis without knowing it because you may not feel ill. Some people get jaundiced meaning that their eyes go yellow but many people have no symptoms at all.

The only way to know if you are infected is by having a test.

This is important because hepatitis can cause liver cancer if it is not diagnosed and treated.

There are 3 main viruses that attack the liver – hepatitis A, hepatitis B and hepatitis C. They are all different.

Hepatitis A, although it can be serious, only lasts for a few weeks at the most because your body can fight it effectively. It is caught from infected water or food.

Hepatitis B is NOT caught from infected water or food but from infected blood. It can also be caught during sex with an infected person. Often your body cannot fight it effectively and it becomes a chronic disease.

Hepatitis C also is NOT caught from infected water or food but from infected blood. It is very unusual to catch it during sex. In most cases your body cannot fight it effectively and it becomes a chronic disease.

It is hepatitis B and hepatitis C that can cause liver cancer and these are the ones you should think about.

If you were born in India, Pakistan or Bangladesh or spend a lot of time there, you may be at risk if, while you were there:

- You had a medical injection from a family doctor, especially in rural areas, unless both the syringe and needle were brand new

- You had a blood transfusion, especially if the blood might not have been properly screened.

- You had an operation in hospital and you are not certain that they had the best techniques for sterilising equipment

- You went to a dentist, especially in the street

- You were circumcised by a barber

- You were shaved by a barber unless it was with a disposable razor

You may also be at risk of hepatitis B if at any time you have had unprotected sex with someone infected

If someone in your family has hepatitis B or hepatitis C you should certainly get tested. You might have accidentally come into contact with their blood or you might both have got it in the same way, for example from a family doctor who used the same syringe for injections.

But hepatitis is NOT caught from normal social contact like shaking hands, hugging or kissing. It is NOT caught from using the same toilet.

If you think you could possibly have hepatitis B or hepatitis C, pick up a leaflet on the way out and think about having a test. If you find out soon enough, you can get treatment from your local hospital. The treatment for hepatitis C can cure it completely and stop it causing liver cancer. The treatment for hepatitis B, although it will not cure it, can make it extremely unlikely that you will get liver cancer.

Appendix 3: GP letters

Professor Graham Foster

Institute of Cell and Molecular Science

Adult & Paediatric Gastroenterology

Barts and The London

Queen Mary's School of Medicine & Dentistry

Turner Street, London E1 2AD

Telephone: 020 7882 7242

Facsimile: 020 7882 724

Dear GP,

Re Viral Hepatitis in Ethnic Minorities

We are writing to you to inform you of a campaign that we are currently undertaking to raise awareness of hepatitis B and C, among local high risk communities.

Chronic viral hepatitis (hepatitis B and C) is a significant global health problem, with over 500 million people infected worldwide. Certain countries in the world have very high prevalence rates of chronic viral hepatitis, and immigrants from these countries who live in the UK are often infected. Our previous research has shown that among people who were born in Pakistan, living in the Newham borough there is a 5% prevalence of chronic viral hepatitis i.e. 1 in 20 people born in Pakistan have viral hepatitis. As you know, untreated hepatitis B and C can lead to liver cirrhosis and hepatocellular carcinoma. We are concerned that a significant proportion of people with chronic viral hepatitis in the Newham Borough are unaware that they are infected.

We are trying to raise awareness of these treatable diseases among high risk populations, to encourage them to be tested and treated. Over the next two months we will be asking three local Imams and community leaders to speak about viral hepatitis to large community gatherings. They will discuss the nature of chronic viral hepatitis, the consequences of untreated disease and the benefits of treatment. Leaflets will be handed out encouraging people to visit their local GP for testing. These leaflets have a specific virology request form attached, with viral hepatitis B and C screening requested. On the back of this form is information for General Practitioners, explaining the campaign.

If a patient approaches you with this leaflet and virology form, we would be very grateful if you could fill in the patient's details, and arrange for a blood sample to be taken. The forms already have the necessary tests requested. Should a patient test positive for viral hepatitis we will

arrange for them to be reviewed and treated at the Royal London Hospital. If you would prefer that the patient is referred elsewhere please do state this on the referral form.

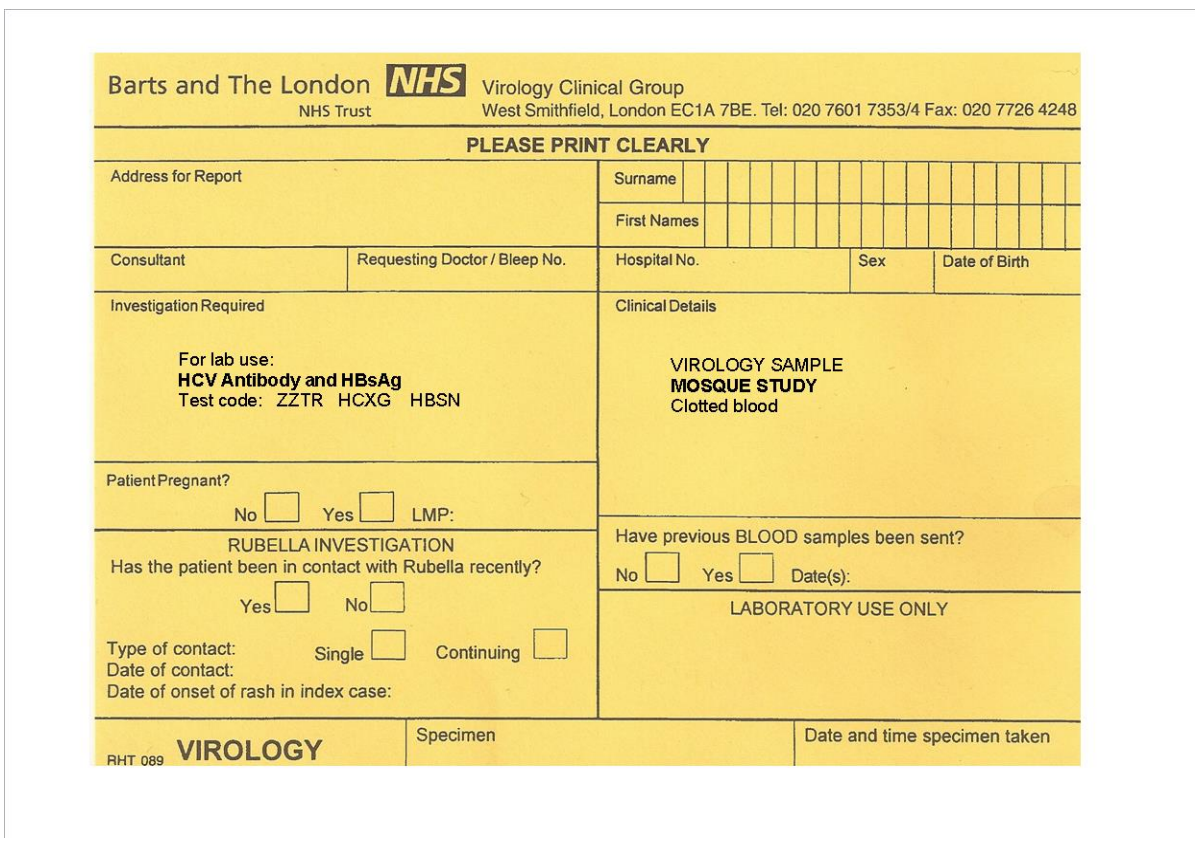
Should you require any further details about the awareness campaign, or chronic viral hepatitis please contact my research fellow Dr Heather Lewis on 07967551567 or heatherilewis@hotmail.com or the Hepatitis C Trust on ..... e-mail .....

Many thanks in anticipation of your support.

Yours sincerely

Professor Graham Foster

Appendix 4: Mosque awareness raising virology testing forms



Barts and The London NHS NHS Trust

Virology Clinical Group
West Smithfield, London EC1A 7BE. Tel: 020 7601 7353/4 Fax: 020 7726 4248

PLEASE PRINT CLEARLY

Address for Report

Surname

First Names

Consultant | Requesting Doctor / Bleep No. | Hospital No. | Sex | Date of Birth

Investigation Required

For lab use:
HCV Antibody and HBsAg
Test code: ZZTR HCXG HBSN

Clinical Details

VIROLOGY SAMPLE
MOSQUE STUDY
Clotted blood

Patient Pregnant?
No ☐ Yes ☐ LMP:

RUBELLA INVESTIGATION
Has the patient been in contact with Rubella recently?
Yes ☐ No ☐

Type of contact: Single ☐ Continuing ☐
Date of contact:
Date of onset of rash in index case:

Have previous BLOOD samples been sent?
No ☐ Yes ☐ Date(s):

LABORATORY USE ONLY

RHT 089 **VIROLOGY** | Specimen | Date and time specimen taken

Information for General Practitioners:

Chronic viral hepatitis caused by hepatitis B and C infection is a growing global health problem, with over 500 million people infected.

Hepatitis B and C are silent conditions until cirrhosis or hepatocellular carcinoma develop. This occurs twenty to thirty years after infection.

Chronic viral hepatitis is very common in some countries, including Pakistan, Bangladesh and all of Africa.

In people from Pakistan living in Newham we know that the prevalence of chronic viral hepatitis is 5%

In the developed world hepatitis B is often transmitted sexually and hepatitis C is often transmitted by injecting drug use. Transmission in developing countries is different and these viruses may be transmitted within families, by dental work, by vaccinations and by other non obvious routes. **Hence being born in the developing world is a major risk factor for viral hepatitis.** All those at high risk should be tested for hepatitis B or C, even if they have no symptoms and normal liver function tests.

With current treatments we can cure the majority of people with chronic viral hepatitis C, and prevent progression to hepatocellular carcinoma and cirrhosis in the majority of those with hepatitis B.

We are currently trying to raise awareness among at risk communities about chronic viral hepatitis B and C, and encourage them to attend for testing.

This person has identified themselves as being at risk. Please complete the opposite side of this form, and ask them to have their bloods taken to ensure they are tested for hepatitis B and C.

Appendix 5: Invitation letter to General Practitioners

Barts and The London
School of Medicine and Dentistry

Centre for Gastroenterology
Institute of Cell & Molecular Science
London E1 2AT
4 Newark Street
London E1 2AT

Tel: +44 (0)20 7882 7242
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Fax: +44 (0)20 7882 2187
Email: g.r.foster@qmul.ac.uk

Professor Graham Foster
Professor of Hepatology

25 August 2009

Dear Dr ,

Re: Case finding for viral hepatitis in people from Pakistan

Thank you very much for agreeing to participate in our research project investigating the most effective way to undertake case finding in primary care, of viral hepatitis in high risk communities in East London.

We are currently planning a pilot feasibility study which will precede a larger population study, and would be very grateful if you would agree to consider participating in this pilot study.

In brief the study will involve examining different approaches to case finding for viral hepatitis in two primary care centres in Newham. This will take place over a four to six month period. In one practice we will adopt a "clinician led" case finding approach. This will involve a research fellow spending time in the practice and contacting all patients who are at risk and inviting them to attend for testing. We will adopt an "opt out" policy, where all patients from Pakistan will receive letters in English and Urdu asking for permission to contact them for an appointment for testing. If they do not wish to be approached they will be invited to contact the surgery to "opt out". If they do not do this they will be telephoned and invited to attend for viral hepatitis testing. Testing will be performed by the research fellow in the surgery.

In the other practice we will adopt an opportunistic approach in which the general practitioners will receive formal training in viral hepatitis testing, and they will then be asked to offer a test to all patients from Pakistan who attend the surgery.

We will aim to test around 500 patients in total, with at least 250 patients in each practice.

***Case finding for viral hepatitis in people from Pakistan*/2.....**

We believe that this is an important study with the potential to improve the health of the local population both by identifying undiagnosed cases of viral hepatitis, and determining the best way to approach population screening. If you are still willing to consider helping in the study I would be grateful if you could contact either me (details above) or my research fellow heatherilewis@hotmail.com and we will then arrange a convenient time to come and visit the practice and discuss the study and its feasibility in more detail.

I look forward to hearing from you.

Once again many thanks for considering taking part in this research.

With best wishes,

Yours sincerely,

Graham Foster PhD FRCP
Professor of Hepatology

Appendix 6: Patient information sheets for direct testing arm

1: Patient information sheet (English)

Professor Graham R Foster

Institute of Cell and Molecular Science

Barts and The London
Queen Mary's School of Medicine and Dentistry

Adult & Paediatric Gastroenterology
Barts and The London
Queen Mary's School of Medicine
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Turner Street, London E1 2AD

Telephone: 020 7882 7242
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Case finding for viral hepatitis in High Risk Communities in East London. Pilot project to examine the feasibility of case finding in GP surgeries in Newham

Patient Information Sheet

Invitation to participate in a research project

We invite you to take part in a research study which we think may be important. The information which follows tells you all about it. It is important that you understand what is in this leaflet. It says what will happen if you take part and what the risks might be. Try to make sure you know what will happen to you if you decide to take part. It is entirely your choice whether or not you take part. Please ask any questions you want to about the research and we will try our best to answer them.

1. Nature and purpose of the study

From previous research we know that people who were born in Pakistan are often infected with viruses that can cause liver disease, but many people will be unaware of their infection, as the viruses often remain silent until they have caused serious liver disease. We would like to identify people who have these viruses at an early stage, so we can offer them treatment to try to prevent more serious liver disease. Treatment is successful in most cases.

We can identify viral hepatitis easily with a blood test, and offer treatment. The earlier we are able to offer treatment, the more likely we are to be able to treat the virus and prevent liver damage. This is why it is very important to pick up viral hepatitis early, in people who do not yet know they are infected

We do not yet know the best way to identify within the Pakistani population, who is infected with chronic hepatitis and who is not, and this study is designed to answer this question.

Chronic Viral hepatitis – what is it and what does it do ?

Chronic viral hepatitis is commonly caused by two viruses – hepatitis B and hepatitis C. These viruses can cause damage to the liver, but most people who have these viruses can be treated for them. Both of these viruses travel in blood and can be passed on by contact with another person's blood. Both viruses can be passed on by unsterile medical equipment and they can be passed on by mothers to their children. Chronic viral hepatitis may be a mild illness that does not cause any problems but sometimes chronic viral hepatitis causes liver disease that may need treatment. We have drugs that we can use to treat viral hepatitis and will treat most infected patients. Unfortunately chronic viral hepatitis usually causes a silent disease and people who are infected often don't realise that they are infected until serious liver damage has occurred.

2 Study Design

This study is designed to find out the best way of identifying patients from Pakistan in primary care, who are infected with chronic hepatitis.

3 Study Medications

Case finding for viral hepatitis in High Risk Communities in East London. Pilot project to examine the feasibility of case finding in GP surgeries in Newham

None – no new drugs will be given if you take part in this study.

4 Study Procedures

We will be assessing two different methods of finding out which patients from Pakistan are infected with chronic hepatitis. In your GP practice, all patients who are registered with the GP, who originate, or whose families originate, from Pakistan will be invited to take part. You will be contacted by letter, and asked if you wish to attend an appointment for testing for viral hepatitis. If you do not wish to be approached you will need to contact your GP surgery to inform them you do not wish to be contacted. If you do not do this, you will be contacted by a doctor taking part in the research. They will invite you to attend your GP's surgery for testing for viral hepatitis. We call this an "opt out" testing strategy, as you will be assumed to have agreed to testing unless you specifically indicate you do not wish to take part. We are using this method as we wish to pick up the maximum number of people we can with viral hepatitis, so that we can offer advice and treatment to as many people as possible. When you are contacted the doctor will talk to you about viral hepatitis. You will then be asked to donate a small amount of blood (10 mls – two teaspoonsful) which will be sent to a central laboratory for testing. After testing the sample will be kept for 2 years (to allow confirmatory tests to be performed) and then destroyed. You will be invited to re-attend two weeks later when you will be told the results. We may also use a small amount of this blood to test immediately for hepatitis C. If we do this you will be told of the result of this test after about half an hour. Your GP will be informed of the results. If you don't have viral hepatitis no further action is needed. We will test only for viral hepatitis – we will not test you for any other diseases and we will not test you for other conditions that can damage the liver.
We are aware that being invited for a test for viral hepatitis may cause concern, and we would like to explore this further. If you agree to be tested for viral hepatitis, we may ask if you would be willing to answer some further questions about your feelings around being invited to have the test. These questions will take approximately half an hour, and you are under no obligation to answer the questions if you do not wish to. Your answers will be stored anonymously on a computer database, and will only be used for the purposes of the study.

If you do have viral hepatitis you will be asked to attend the Royal London Hospital where one of the doctors will talk to you about further tests that are needed. You may need treatment to protect your liver and the doctor who sees you in the clinic will explain this. You will be treated just like every other patient with viral hepatitis. However if you are taking part in this study we will ask some extra questions about how you contracted the disease. Details about your case, how you caught the virus, how long you have been infected for, other illnesses that you have and the severity of your liver disease will be stored on a computer in an anonymous form. If further special tests on your liver are needed, such as a liver biopsy, the details of this investigation will be stored on a database. A sample of your virus will be sent to the Public Health Laboratory where the type of virus that you are infected with will be determined. We will also look at the amount of sugar in your blood (this is a standard test that is done in all patients with hepatitis C) and the amount of insulin that your body produces (this is an extra test that will involve us taking an extra 5mls (one teaspoon full) of blood).

If you do not wish to answer additional questions you will be able to decline to answer and if you do not wish samples of your virus to be sent to the central laboratory in Colindale you will be able to tell us not to send the samples to Colindale. You will also be able to decline to donate an extra sample of blood for insulin testing. This will not affect your treatment or subsequent medical care.

5 Risks and Discomforts

The study involves 15 minutes of your time to learn about viral hepatitis and you will be asked to allow us to take a blood sample. This is an uncomfortable procedure. You will have to wait for the results of the test and this can cause anxiety.

6 Benefits

We hope that the results of this study will tell us how best to identify people from high risk communities, who are infected with viral hepatitis.

Patients who participate in the study will learn whether or not they have viral hepatitis and if they do have viral hepatitis then they will be able to get treatment which may be helpful.

7 Confidentiality of Records

Your participation in this study will be kept confidential and your name will not be made known to anyone other than study personnel. All information which is collected about you during the course of the research will be kept strictly confidential. If you consent to take part in the research the people conducting the study will abide by the Data Protection Act 1998, and the rights you have under this Act.

8 Further information

You are encouraged to ask questions at any time in the study. If you have a problem or concerns about the study or your rights as a subject, please call Prof Foster at 020 7882 7242.

9 What if there is a problem?

We believe that this study is safe and do not expect you to suffer any harm because of your participation. If you are harmed by taking part in this research project, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds for a legal action but you may have to pay for it. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service complaints mechanisms should be available to you and you can obtain advice on this, or any other aspect of the study from :-

Patient Advice and Liaison Service (PALS)Telephone: 020 7943 1335, Minicom: 020 7943 1350E-mail: pals@bartsandthelondon.nhs.uk

10 Basis of Participation

You don't have to join this study. Participation in this protocol is completely voluntary. You are free to decide not to be in this trial or to drop out at any time. If you decide not to be in the study, or drop out, this will not put at risk your ordinary medical care.

Thank you for reading this document

2. Direct testing arm patient information sheet (Urdu)

Adult & Paediatric Gastroenterology
Barts and The London
Queen Mary's School of Medicine &
Dentistry
Turner Street, London E1 2AD

ٹیلی فون : 020 7882 7242
فیکس : 020 7882 7241
ای میل : g.r.foster@qmul.ac.uk

ایسٹ لندن میں زیادہ خطرے والی برادریوں میں وائرل جگر کی سوزش کیلئے مرض کے حالات تلاش کرنا ۔ نیو ہیم میں جی پی سرجریوں میں مرض کو تلاش کرنے کے امکانات کا معائنہ کرنے کیلئے رہنما پراجیکٹ (Case finding for viral hepatitis in High Risk Communities in East London. Pilot project to examine the feasibility of case finding in GP surgeries in Newham)

مریض کیلئے معلوماتی پرچہ (Patient Information Sheet)

تحقیقی پراجیکٹ میں حصہ لینے کی دعوت (Invitation to take part in a research project)

ہم آپ کو ایک تحقیقی مطالعہ میں حصہ لینے کی دعوت دیتے ہیں جو ہم سمجھتے ہیں کہ اہم ہوسکتا ہے ۔ درج ذیل معلومات میں آپ کو اس کے بارے میں سب کچھ بتایا گیا ہے ۔ اس لیف لیٹ میں جو کچھ ہے یہ ضروری ہے کہ آپ اسے سمجھیں ۔ اس میں بتایا گیا ہے کہ اگر آپ حصہ لیتے ہیں تو کیا ہوگا اور کون سے خطرات ہو سکتے ہیں ۔ اس بات کو یقینی بنانے کی کوشش کریں کہ اگر آپ حصہ لینے کا فیصلہ کرتے ہیں تو آپ کو معلوم ہو کہ آپ کو کیا ہوگا ۔ یہ سراسر آپ کا فیصلہ ہے کہ آپ اس میں حصہ لیتے ہیں یا نہیں ۔ اگر آپ تحقیق کے بارے میں کوئی سوالات پوچھنا چاہتے ہیں تو براہ کرم ضرور پوچھیں اور ہم ان کا جواب دینے کی پوری کوشش کریں گے ۔

1. مطالعہ کی نوعیت اور مقصد

سابقہ تحقیق سے ہم جانتے ہیں کہ وہ لوگ جو پاکستان میں پیدا ہوئے تھے انہیں اکثر ایسی وائرس لگی ہوئی ہوتی ہیں جن سے جگر کی بیماری لگ سکتی ہے، لیکن بہت سے لوگ اپنی انفیکشن سے آگاہ نہیں ہوں گے ، کیونکہ وائرس اکثر خاموش رہتی ہیں جب تک کہ یہ جگر کی شدید بیماری کا باعث نہیں بن جاتیں ۔ ہم ان لوگوں کی شناخت کرنا چاہیں گے جنہیں یہ وائرس ہیں جو ابتدائی مرحلے پر ہیں ، تاکہ ہم انہیں علاج کی پیشکش کرسکیں تاکہ جگر کی مزید شدید بیماری سے بچا جاسکے ۔ بیشتر معاملوں میں علاج کامیاب ہوتا ہے ۔

ہم ایک بلڈ ٹیسٹ کے ساتھ آسانی سے وائرل ہیپاٹائٹس کی شناخت کرسکتے ہیں ، اور علاج کی پیشکش کرسکتے ہیں ۔ ہم جتنی جلدی علاج کی پیشکش کریں گے ، اس بات کا امکان اور زیادہ بڑھ جاتا ہے کہ ہم وائرس کا علاج کرسکیں اور جگر کو نقصان پہنچنے سے بچا سکیں ۔ اس لئے یہ بہت ضروری ہے کہ وائرل ہیپاٹائٹس کا جلدی پتہ چلایا جائے ، ایسے لوگوں میں جنہیں ابھی یہ معلوم نہیں ہے کہ انہیں انفیکشن لگ چکی ہے ۔

ہم ابھی یہ نہیں جانتے کہ پاکستانی برادری کے اندر اس کی شناخت کرنے کا کون سا بہترین طریقہ ہے ، جنہیں دیرینہ ہیپاٹائٹس ہو چکی ہے اور جنہیں نہیں ہوئی ہے ، اور یہ مطالعہ اس سوال کا جواب دینے کیلئے تیار کیا گیا ہے ۔

دیرینہ وائرل جگر کی سوزش (chronic viral hepatitis) ۔ یہ کیا ہے اور یہ کیا کرتی ہے؟

دیرینہ وائرل ہیپاٹائٹس عام طور پر دو وائرس کی وجہ سے ہوتی ہے ۔ دل کی سوزش بی (ہیپاٹائٹس بی (hepatitis B)) اور دل کی سوزش سی (ہیپاٹائٹس سی (hepatitis C)) ۔ ان وائرس سے جگر کو نقصان پہنچ سکتا ہے ، لیکن بیشتر لوگ جنہیں یہ وائرس ہیں ان کا اس کیلئے علاج کیا جاسکتا ہے ۔ یہ دونوں وائرس خون میں سفر کرتی ہیں اور کسی اور فرد کے خون کو چھونے سے آگے منتقل ہوسکتی ہیں ۔ دونوں وائرس غیر جراثیم کش طبی ساز و سامان سے آگے منتقل اور ماؤں سے ان کے بچوں میں آگے منتقل ہوسکتی ہیں ۔ ہوسکتا ہے کہ دیرینہ وائرل ہیپاٹائٹس ایک معتدل بیماری ہو جس سے کوئی مسائل نہ ہوں لیکن بعض اوقات دیرینہ وائرل ہیپاٹائٹس سے جگر کی بیماری ہو جاتی ہے ہوسکتا ہے جس کا علاج کرنا درکار ہو ۔ ہمارے پاس ایسی ادویات موجود ہیں جنہیں ہم وائرل ہیپاٹائٹس کا علاج کرنے کیلئے استعمال کرسکتے ہیں اور یہ بیشتر معتدی مریضوں کا علاج کریں گی ۔ بدقسمتی سے دیرینہ وائرل ہیپاٹائٹس عام طور پر ایک خاموش بیماری کا سبب بنتی ہے اور وہ لوگ جنہیں انفیکشن ہو چکی ہے انہیں اکثر اس بات کا احساس نہیں ہوتا کہ انہیں چھوت کی بیماری (انفیکشن) لگ چکی ہے جب تک کہ جگر کو شدید نقصان نہیں پہنچ چکا ہوتا ۔

2. مطالعہ کا ڈیزائن

یہ مطالعہ ڈیزائن کیا گیا ہے تاکہ پرائمری کیئر میں پاکستان سے ایسے مریضوں کا بہترین طریقے سے پتہ چلا کر شناخت کی جاسکے ، جنہیں دیرینہ ہیپاٹائٹس کی انفیکشن ہو چکی ہے ۔

3. Direct testing arm patient invitation letter (English)

Professor GR Foster
Institute of Cell and Molecular Science
Queen Mary's School of Medicine
4 Newark Street, London E1 2AD

Telephone: 020 7882 7242
Facsimile: 020 7882 7241
Email: heatherilewis@hotmail.com

6th October 2010

Version 1 – 7th July 2009

Dear sir/madam,

Identifying people from Pakistan with viral hepatitis. Invitation to take part in a research project.

I am writing to you from your local GP surgery on behalf of a research team to ask if you would take part in a research project.

We know that some people who were born in Pakistan are infected with viruses that can cause liver problems. These viruses cause a disease called chronic viral hepatitis. Chronic viral hepatitis may be a mild illness that does not cause any problems but sometimes chronic viral hepatitis causes liver disease that may need treatment. We have drugs that we can use to treat viral hepatitis and these work for most infected patients. Unfortunately these are often "silent" diseases, and people are often unaware that they are infected.

We would like to identify people within the Pakistani community in Newham, who are infected with viral hepatitis, so that we can offer them treatment. At the moment we do not know the best way to identify the people who have chronic viral hepatitis. We would like your help in finding out the best way to identify people with chronic viral hepatitis.

We would like to offer you the opportunity to have a blood test for hepatitis. This will involve a 15 minute visit to your general practitioner, where one of our team will discuss viral hepatitis with you and take a small amount of blood (10mls – about two teaspoons) from your arm. They will send this blood test to a central laboratory, and we will invite you back to your GP's surgery two weeks later, where you will be given the results. If the results are negative nothing more will happen. If they are positive you will be asked along to the Royal London Hospital, where further tests may need to be undertaken and you may be offered treatment for your disease. This will all be explained to you fully at the time.

One of our team will be contacting you by telephone to invite you to participate. If you would not like to take part in this study, please contact your GP surgery and we will not contact you.

If you do not contact your GP surgery, we will assume that you are happy to be contacted and we will phone you to invite you along for a blood test.

I have included a patient information sheet along with this letter to explain what we are doing in more detail, and which will hopefully answer any questions you may have.

Please do contact us if you have any further queries on the above number or e-mail address.

Yours sincerely

Dr Heather Lewis

4. Direct testing arm patient invitation letter (Urdu)

پروفیسر جی آر فاسٹر (Professor GR Foster)
Institute of Cell and Molecular Science
Queen Mary's School of Medicine
4 Newark Street, London E1 2AD

ٹیلی فون: 020 7882 7242
فیکس: 020 7882 7241
ای میل: heatherilewis@hotmail.com

11 دسمبر 2009

محترم جناب / محترمہ

پاکستان سے وائرل جگر کی سوزش (ہیپاٹائٹس) والے لوگوں کی شناخت کرنا۔ تحقیقی پراجیکٹ میں حصہ لینے کی دعوت (Identifying people from Pakistan with viral hepatitis. Invitation to take part in a research project)

میں آپ کو آپ کے مقامی جی پی (GP) کی سرجری سے ایک تحقیق کرنے والی ٹیم کی جانب سے لکھ رہا/رہی ہوں تاکہ آپ سے پوچھ سکوں کہ اگر آپ ایک تحقیقی پراجیکٹ میں حصہ لینا پسند کریں گے۔

ہم جانتے ہیں کہ کچھ لوگ جو پاکستان میں پیدا ہوئے تھے انہیں ایسی معتدی وائرس ہیں جن سے جگر کے مسائل ہو سکتے ہیں۔ ان وائرس سے ایک بیماری ہو سکتی ہے جو دیرپا وائرل جگر کی سوزش (ہیپاٹائٹس) (chronic viral hepatitis) کہلاتی ہے۔ ہو سکتا ہے کہ دیرپا وائرل ہیپاٹائٹس ایک معتدل بیماری ہو جس سے کوئی مسائل نہ ہوں لیکن بعض اوقات دیرپا وائرل ہیپاٹائٹس سے جگر کی بیماری ہو جاتی ہے ہو سکتا ہے جس کا علاج کرنا درکار ہو۔ ہمارے پاس ایسی ادویات موجود ہیں جنہیں ہم وائرل ہیپاٹائٹس کا علاج کرنے کیلئے استعمال کر سکتے ہیں اور یہ بیشتر معتدی مریضوں کیلئے کام کرتی ہیں۔ بدقسمتی سے یہ اکثر "خاموش (silent)" بیماریاں ہیں، اور لوگوں کو اکثر معلوم نہیں ہوتا ہے کہ انہیں انفیکشن لگ چکی ہے۔

ہم نیوہیم (Newham) میں پاکستانی برادری کے اندر ایسے لوگوں کی شناخت کرنا چاہیں گے، جنہیں وائرل ہیپاٹائٹس کی چھوت کی بیماری لگ چکی ہے، تاکہ ہم انہیں علاج کی پیشکش کر سکیں۔ اس وقت ہم یہ نہیں جانتے کہ ایسے لوگوں کی کس بہترین طریقے سے شناخت کی جا سکتی ہے جنہیں دیرپا وائرل ہیپاٹائٹس ہے۔ ہم دیرپا وائرل ہیپاٹائٹس والے لوگوں کی شناخت کرنے کیلئے بہترین طریقے سے انہیں تلاش کرنے میں آپ کی مدد حاصل کرنا چاہیں گے۔

ہم آپ کو موقع فراہم کرنا چاہیں گے تاکہ آپ جگر کی سوزش (ہیپاٹائٹس) کیلئے خون کا ٹیسٹ کروا سکیں۔ اس کیلئے آپ کو 15 منٹوں کیلئے اپنے جنرل پریکٹیشنر کو وزٹ کرنا ہوگا، جہاں پر ہماری ٹیم میں سے کوئی فرد آپ کے ساتھ وائرل ہیپاٹائٹس پر بات چیت کرے گا/گی اور آپ کے بازو سے تھوڑا سا خون لے گا/گی (10 ایم ایل ایس۔ تقریباً چائے کے دو چمچوں کے برابر)۔ وہ اس خون کے ٹیسٹ کو ایک سنٹرل لیبارٹری کو بھیجیں گے، اور ہم آپ کو دو ہفتوں کے بعد اپنے جی پی کی سرجری (GP's surgery) میں واپس آنے کی دعوت دیں گے، جہاں پر آپ کو نتائج سے آگاہ کیا جائے گا۔ اگر نتائج منفی ہوئے تو پھر آگے کچھ نہیں ہوگا۔ اگر یہ مثبت ہوئے تو آپ سے کہا جائے گا کہ آپ رائل لندن ہسپتال (Royal London Hospital) آئیں، جہاں پر ہو سکتا ہے کہ آپ کے مزید ٹیسٹ کئے جائیں اور ہو سکتا کہ آپ کو آپ کی بیماری کیلئے علاج کی پیشکش کی جائے۔ اس سب کی آپ کو اس وقت پوری وضاحت کی جائے گی۔

ہماری ٹیم میں سے کوئی فرد آپ کو اس میں حصہ لینے کی دعوت دینے کیلئے بذریعہ ٹیلی فون آپ سے رابطہ کرے گا۔ اگر آپ اس مطالعہ میں حصہ نہ لینا چاہیں، تو براہ کرم اپنے جی پی کی سرجری سے ..... پر رابطہ کریں اور ہم آپ سے رابطہ نہیں کریں گے۔

اگر آپ اپنے جی پی (GP) کی سرجری سے رابطہ نہیں کرتے، تو ہم فرض کر لیں گے کہ آپ خوش ہیں کہ آپ سے رابطہ کیا جائے اور ہم آپ کو فون کریں گے تاکہ ایک بلڈ ٹیسٹ کیلئے آنے کی دعوت دی جا سکے۔

27845/09 - Urdu

Appendix 7: Virology testing form

Newham University Hospital NHS Trust
Virology enquiries (Royal London Hospital): 020 3 246 0364

VIROLOGY REQUEST FORM

GP details Practice: Address:		**NHS number**		**DOB**
		SURNAME:		**SEX :**
CLINICAL DETAILS: VIROLOGY SAMPLE **GP OPPORTUNISTIC SCREENING** Clotted blood For lab use: **HCV Antibody and HBsAg** Test code: ZZTR HCXG HBSN NHS ☐		**FIRST NAME:**		
		ADDRESS:		
		SPECIMEN DETAILS DATE: / / TIME:		HIGH RISK?

Newham University Hospital NHS Trust
Virology enquiries (Royal London Hospital): 020 3 246 0364

VIROLOGY REQUEST FORM

GP details Practice: Address:		**NHS number**		**DOB**
		SURNAME:		**SEX :**
CLINICAL DETAILS: VIROLOGY SAMPLE **GP OPPORTUNISTIC SCREENING** Clotted blood For lab use: **HCV Antibody and HBsAg** Test code: ZZTR HCXG HBSN NHS ☐		**FIRST NAME:**		
		ADDRESS:		
		SPECIMEN DETAILS DATE: / / TIME:		HIGH RISK?

Appendix 8: Patient information sheets – opportunistic testing arm

1. Patient information sheet (English)

Professor Graham R Foster

Institute of Cell and Molecular Science

Barts and The London
Queen Mary's School of Medicine and Dentistry

Adult & Paediatric Gastroenterology
Barts and The London
Queen Mary's School of Medicine
& Dentistry
Turner Street, London E1 2AD

Telephone: 020 7882 7242
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Email: g.r.foster@qmul.ac.uk

Case finding for viral hepatitis in High Risk Communities in East London. Pilot project to examine the feasibility of case finding in GP surgeries in Newham

Patient Information Sheet for those considering screening in a GPs surgery

Invitation to participate in a research project

We invite you to take part in a research study which we think may be important. The information which follows tells you all about it. It is important that you understand what is in this leaflet. It says what will happen if you take part and what the risks might be. Try to make sure you know what will happen to you if you decide to take part. It is entirely your choice whether or not you take part. Please ask any questions you want to about the research and we will try our best to answer them.

1. Nature and purpose of the study

From previous research we know that people who were born in Pakistan are often infected with viruses that can cause liver disease, but many people will be unaware of their infection, as the viruses often remain silent until they have caused serious liver disease. We would like to identify people who have these viruses, at an early stage, so we can offer them treatment to try to prevent more serious liver disease. Treatment is successful in most cases.

We can identify viral hepatitis easily with a blood test, and offer treatment. The earlier we are able to offer treatment, the more likely we are to be able to treat the virus and prevent liver damage. This is why it is very important to pick up viral hepatitis early, in people who do not yet know they are infected.

We do not yet know the best way to identify within the Pakistani population, who is infected with chronic viral hepatitis and who is not, and this study is designed to answer this question.

Chronic Viral hepatitis – what is it and what does it do?

Chronic viral hepatitis is commonly caused by two viruses – hepatitis B and hepatitis C. These viruses can cause damage to the liver, but most people who have these viruses can be treated for them. Both of these viruses travel in blood and can be passed on by contact with another person's blood. Both viruses can be passed on by unsterile medical equipment and they can be passed on by mothers to their children. Chronic viral hepatitis may be a mild illness that does not cause any problems but sometimes chronic viral hepatitis causes liver disease that may need treatment. We have drugs that we can use to treat viral hepatitis and these will treat most infected patients. Unfortunately chronic viral hepatitis usually causes a silent disease and people who are infected often don't realise that they are infected until serious liver damage has occurred.

2 Study Design

This study is designed to find out the best way of identifying patients from Pakistan in primary care, who are infected with chronic hepatitis.

3 Study Medications

None – no new drugs will be given if you take part in this study.

4 Study Procedures

There will be two different methods of finding which patients from Pakistan are infected with chronic hepatitis. In your GP practice, all patients attending their GP for any reason, who originate, or whose families originate, from Pakistan will be invited to take part. If you would like to participate one of the doctors will talk to you about viral hepatitis. You will then be asked to donate a small amount of blood (10 mls – two teaspoonsful) which will be sent to a central laboratory for testing. After testing the sample will be kept for 2 years (to allow confirmatory tests to be performed) and then destroyed. You will be invited to re-attend two weeks later when you will be told the results. We may also use a small amount of this blood to test immediately for hepatitis C. You will be told of the result of this test after about half an hour. Your GP will be informed of the results. If you don't have viral hepatitis no further action is needed. We will test only for viral hepatitis – we will not test you for any other diseases and we will not test you for other conditions that can damage the liver.

We are aware that being invited for a test for viral hepatitis may cause concern, and we would like to explore this further. If you agree to be tested for viral hepatitis, we may ask if you would be willing to answer some further questions about your feelings around being invited to have the test. These questions will take approximately half an hour, and you are under no obligation to answer the questions if you do not wish to. Your answers will be stored anonymously on a computer database, and will only be used for the purposes of the study.

If you do have viral hepatitis you will be asked to attend the Royal London Hospital where one of the doctors will talk to you about further tests that are needed. You may need treatment to protect your liver and the doctor who sees you in the clinic will explain this. You will be treated just like every other patient with viral hepatitis. However if you are taking part in this study we will ask some extra questions about how you contracted the disease. Details about your case, how you caught the virus, how long you have been infected for, other illnesses that you have and the severity of your liver disease will be stored on a computer in an anonymous form. If further special tests on your liver are needed, such as a liver biopsy, the details of this investigation will be stored on a database. A sample of your virus will be sent to the Public Health Laboratory where the type of virus that you are infected with will be determined. We will also look at the amount of sugar in your blood (this is a standard test that is done in all patients with hepatitis C) and the amount of insulin that your body produces (this is an extra test that will involve us taking an extra 5mls (one teaspoon full) of blood).

If you do not wish to answer additional questions you will be able to decline to answer and if you do not wish samples of your virus to be sent to the central laboratory in Colindale you will be able to tell us not to send the samples to Colindale. You will also be able to decline to donate an extra sample of blood for insulin testing. This will not affect your treatment or subsequent medical care.

5 Risks and Discomforts

The study involves 15 minutes of your time to learn about viral hepatitis and you will be asked to allow us to take a blood sample. This is an uncomfortable procedure. You will have to wait for the results of the test and this can cause anxiety.

6 Benefits

We hope that the results of this study will tell us how best to identify people from high risk communities, who are infected with viral hepatitis.

Patients who participate in the study will learn whether or not they have viral hepatitis and if they do have viral hepatitis then they will be able to get treatment which may be helpful.

7 Confidentiality of Records

Your participation in this study will be kept confidential and your name will not be made known to anyone other than study personnel. All information which is collected about you during the course of the research will be kept strictly confidential. If you consent to take part in the research the people conducting the study will abide by the Data Protection Act 1998, and the rights you have under this Act.

8 Further information

You are encouraged to ask questions at any time in the study. If you have a problem or concerns about the study or your rights as a subject, please call Prof Foster at 020 7882 7242.

9 What if there is a problem?

We believe that this study is safe and do not expect you to suffer any harm because of your participation. If you are harmed by taking part in this research project, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds for a legal action but you may have to pay for it. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service complaints mechanisms should be available to you and you can obtain advice on this, or any other aspect of the study from :-

Patient Advice and Liaison Service (PALS) Telephone: 020 7943 1335, Minicom: 020 7943 1350E-mail: pals@bartsandthelondon.nhs.uk

10 Basis of Participation

You don't have to join this study. Participation in this protocol is completely voluntary. You are free to decide not to be in this trial or to drop out at any time. If you decide not to be in the study, or drop out, this will not put at risk your ordinary medical care.

Thank you for reading this document

2. Patient information sheet opportunistic arm (Urdu)

Adult & Paediatric Gastroenterology
Barts and The London
Queen Mary's School of Medicine &
Dentistry
Turner Street, London E1 2AD

ٹیلی فون : 020 7882 7242
فیکس : 020 7882 7241
ای میل : g.r.foster@qmul.ac.uk

ایسٹ لندن میں زیادہ خطرے والی برادریوں میں وائرل جگر کی سوزش (ہیپاٹائٹس) کیلئے مرض کے حالات تلاش کرنا۔ نیوہیم میں جی پی سرجریوں میں مرض کو تلاش کرنے کے امکانات کا معائنہ کرنے کیلئے رہنما پراجیکٹ (Case finding for viral hepatitis in High Risk Communities in East London. Pilot project to examine the feasibility of case finding in GP surgeries in Newham)

وہ لوگ جو جی پی کی سرجری میں سکریننگ پر غور کررہے ہیں ان کیلئے مریض کا معلوماتی پرچہ (Patient Information Sheet for those considering screening in a GPs surgery)

تحقیقی پراجیکٹ میں حصہ لینے کی دعوت (Invitation to take part in a research project)

ہم آپ کو ایک تحقیقی مطالعہ میں حصہ لینے کی دعوت دیتے ہیں جو ہم سمجھتے ہیں کہ اہم ہوسکتا ہے۔ درج ذیل معلومات میں آپ کو اس کے بارے میں سب کچھ بتایا گیا ہے۔ اس لیف لیٹ میں جو کچھ ہے یہ ضروری ہے کہ آپ اسے سمجھیں۔ اس میں بتایا گیا ہے کہ اگر آپ حصہ لیتے ہیں تو کیا ہوگا اور کون سے خطرات ہو سکتے ہیں۔ اس بات کو یقینی بنانے کی کوشش کریں کہ اگر آپ حصہ لینے کا فیصلہ کرتے ہیں تو آپ کو معلوم ہو کہ آپ کو کیا ہوگا۔ یہ سراسر آپ کا فیصلہ ہے کہ آپ اس میں حصہ لیتے ہیں یا نہیں۔ اگر آپ تحقیق کے بارے میں کوئی سوالات پوچھنا چاہتے ہیں تو براہ کرم ضرور پوچھیں اور ہم ان کا جواب دینے کی پوری کوشش کریں گے۔

1. مطالعہ کی نوعیت اور مقصد

سائنسی تحقیق سے ہم جانتے ہیں کہ وہ لوگ جو پاکستان میں پیدا ہوئے تھے انہیں اکثر ایسی وائرس لگی ہوئی ہوتی ہیں جن سے جگر کی بیماری لگ سکتی ہے، لیکن بہت سے لوگ اپنی انفکشن سے آگاہ نہیں ہوں گے، کیونکہ وائرس اکثر خاموش رہتی ہیں جب تک کہ یہ جگر کی شدید بیماری کا باعث نہیں بن جاتیں۔ ہم ان لوگوں کی شناخت کرنا چاہیں گے جنہیں یہ وائرس ہیں جو ابتدائی مرحلے پر ہیں، تاکہ ہم انہیں علاج کی پیشکش کرسکیں تاکہ جگر کی مزید شدید بیماری سے بچا جاسکے۔ زیادہ تر معاملوں میں علاج کامیاب ہوتا ہے۔

ہم ایک بلڈ ٹیسٹ کے ساتھ آسانی سے وائرل ہیپاٹائٹس کی شناخت کرسکتے ہیں، اور علاج کی پیشکش کرسکتے ہیں۔ ہم جتنی جلدی علاج کی پیشکش کریں گے، اس بات کا امکان اور زیادہ بڑھ جاتا ہے کہ ہم وائرس کا علاج کرسکیں اور جگر کو نقصان پہنچنے سے بچا سکیں۔ اس لئے یہ بہت ضروری ہے کہ وائرل ہیپاٹائٹس کا جلدی پتہ چلایا جائے، ایسے لوگوں میں جنہیں ابھی یہ معلوم نہیں ہے کہ انہیں انفکشن لگ چکی ہے۔

ہم ابھی یہ نہیں جانتے کہ پاکستانی برادری کے اندر اس کی شناخت کرنے کا کون سا بہترین طریقہ ہے، جنہیں دیرینہ وائرل ہیپاٹائٹس ہو چکی ہے اور جنہیں نہیں ہوئی ہے، اور یہ مطالعہ اس سوال کا جواب دینے کیلئے تیار کیا گیا ہے۔

دیرینہ وائرل جگر کی سوزش (chronic viral hepatitis) ۔ یہ کیا ہے اور یہ کیا کرتی ہے؟

دیرینہ وائرل ہیپاٹائٹس عام طور پر دو وائرس کی وجہ سے ہوتی ہے ۔ دل کی سوزش بی (ہیپاٹائٹس بی (hepatitis B)) اور دل کی سوزش سی (ہیپاٹائٹس سی (hepatitis C))۔ ان وائرس سے جگر کو نقصان پہنچ سکتا ہے، لیکن جن لوگوں کو یہ وائرس ہیں ان میں سے بیشتر کا ان کیلئے علاج کیا جا سکتا ہے۔ یہ دونوں وائرس خون میں سفر کرتی ہیں اور کسی اور فرد کے خون کو چھونے سے آگے منتقل ہوسکتی ہیں۔ دونوں وائرس غیر جراثیم کش طبی ساز و سامان سے آگے منتقل اور ماؤں سے ان کے بچوں میں آگے منتقل ہوسکتی ہیں۔ ہوسکتا ہے کہ دیرینہ وائرل ہیپاٹائٹس ایک معتدل بیماری ہو جس سے کوئی مسائل نہ ہوں لیکن بعض اوقات دیرینہ وائرل ہیپاٹائٹس سے جگر کی بیماری ہو جاتی ہے ہوسکتا ہے جس کا علاج کرنا درکار ہو۔ ہمارے پاس ایسی ادویات موجود ہیں جنہیں ہم وائرل ہیپاٹائٹس کا علاج کرنے کیلئے استعمال کرسکتے ہیں اور یہ بیشتر معتدی مریضوں کا علاج کریں گی۔ بدقسمتی سے دیرینہ وائرل ہیپاٹائٹس عام طور پر ایک خاموش بیماری کا سبب بنتی ہے اور وہ لوگ جنہیں انفکشن ہو چکی ہے انہیں اکثر اس بات کا احساس نہیں ہوتا کہ انہیں چھوت کی بیماری (انفکشن) لگ چکی ہے جب تک کہ جگر کو شدید نقصان نہیں پہنچ چکا ہوتا۔

2. مطالعہ کا ڈیزائن

یہ مطالعہ ڈیزائن کیا گیا ہے تاکہ پرائمری کیئر میں پاکستان سے ایسے مریضوں کا بہترین طریقے سے پتہ چلا کر شناخت کی جاسکے، جنہیں دیرینہ ہیپاٹائٹس کی انفکشن ہو چکی ہے۔

Appendix 9: Consent forms

1. Consent form (English)

Queen Mary University of London

Barts and The London NHS Trust

Consent form 1 – 11th December 2009

Case finding for viral hepatitis in High Risk Communities in East London. Pilot project to examine the feasibility of case finding in GP surgeries in Newham

Patient information sheet

Centre Number: Study Number: Patient Identification Number for this trial:

Please initial box to indicate agreement

1.	I confirm that I have read and understand the information sheet dated 11th December 2009 (version 1) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	
2.	I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.	
3.	I understand that my medical notes and data collected during the study, may be looked at by responsible individuals from regulatory authorities or from the Barts and the London/ Queen Mary University of London, where it is relevant to my taking part in this research. I understand that this may involve individuals reviewing my medical records. For the purpose of this study I give permission for these individuals to have access to my medical records.	
4.	I agree to my GP being informed of my participation in the study.	
5.	I agree to take part in the above study.	

Name of Patient	Date	Signature
Name of Person taking consent (if different from Investigator)	Date	Signature
Investigator	Date	Signature

1 copy for Patient, and original to investigator

Page 1 of 1

2. Consent form (Urdu)

رضامندی فارم11 - 1 دسمبر 2009 (Consent form 1-11th December 2009)

ایسٹ لندن میں زیادہ خطرے والی بر اوریوں میں وائرل جگر کی سوزش (ہیپاٹائٹس) کیلئے مرض کے حالات تلاش کرنا۔
(Case finding for viral hepatitis in High Risk Communities in East London. Pilot project to examine the feasibility of case finding in GP surgeries in Newham)

مریض کیلئے معلوماتی پرچہ (Patient information sheet)

سیفٹر نمبر : مطالعہ نمبر : اس ٹرائل کیلئے مریض کا شناختی نمبر :

براہ کرم رضامندی کی نشاندہی کرنے کیلئے خانے میں مختصر دستخط کریں

.1	میں تصدیق کرتا/ کرتی ہوں کہ میں نے درج بالا مطالعہ کیلئے معلوماتی پرچے تاریخ 11 دسمبر 2009 (طرز 1) کو پڑھ اور سمجھ لیا ہے۔ مجھے موقع ملا ہے کہ میں معلومات پر غور کر سکوں، سوالات پوچھ سکوں اور ان سوالوں کے تسلی بخش جواب ملے ہیں۔	
.2	میں سمجھتا/ سمجھتی ہوں کہ میرا حصہ لینا رضاکارانہ ہے اور میں کسی بھی وقت اس سے علیحدہ ہو سکتا ہوں، کوئی وجہ بتانے کے بغیر، میری طبی دیکھ بھال کے بغیر یا میرے قانونی حقوق کے متاثر ہونے کے بغیر۔	
.3	میں سمجھتا/ سمجھتی ہوں کہ مطالعہ کے دوران میرے بارے میں جو طبی نوٹس اور ڈیٹا اکٹھا کیا جائے گا، ہو سکتا ہے کہ اسے باضابطہ اتھارٹیوں، یا بارٹس (Barts) اور لندن/ کوین میری یونیورسٹی آف لندن (London/Queen Mary University of London) سے ذمہ دار افراد اسے دیکھیں، میرے اس تحقیق میں حصہ لینے کیلئے۔ میں سمجھتا/ سمجھتی ہوں کہ ہو سکتا ہے کہ اس میں افراد کی جانب سے میرے طبی ریکارڈز کا جائزہ لینا درکار ہو۔ اس مطالعہ کے مقصد کیلئے میں ان افراد کو اجازت دیتا/دیتی ہوں کہ وہ میرے طبی ریکارڈز تک رسائی حاصل کریں۔	
.4	میں اتفاق کرتا/ کرتی ہوں کہ میرے اس مطالعہ میں حصہ لینے کے بارے میں میرے جی پی کو آگاہ کیا جائے۔	
.5	میں درج بالا مطالعہ میں حصہ لینے سے اتفاق کرتا/ کرتی ہوں۔	

مریض کا نام (Name of Patient)	تاریخ	دستخط
رضامندی لینے والے فرد کا نام (Name of Person taking consent) (اگر تحقیق کرنے والے/ والی سے مختلف ہے)	تاریخ	دستخط
تحقیق کرنے والے/ والی (Investigator)	تاریخ	دستخط

1 کاپی برائے مریض، اور اصل تحقیق کرنے والے/ والی کیلئے

27845/09 - Urdu

Appendix 10: Postal testing form

Queen Mary University of London

Barts and The London NHS

Professor GR Foster
Institute of Cell and Molecular Science
Queen Mary's School of Medicine
4 Newark Street, London E1 2AD
Telephone: 020 7882 7242

Dear Sir or Madam,

Please find enclosed a blood test request form for chronic viral hepatitis B and C screening as discussed on the phone recently.

We are screening people who were born in Pakistan, or those whose families come from Pakistan, as we know that people from these groups have a higher risk of chronic viral hepatitis as compared to other people. Viral hepatitis can have no signs or symptoms and is often not identified until serious liver damage has occurred. Most people who have chronic viral hepatitis can now be treated and cured of the virus, which will prevent long term liver damage occurring.

Blood forms for the test can be taken to the following centres at the stated time:

Newham University Hospital, Plaistow, Monday to Friday, between 9am – 5pm

Shrewsbury Road Health Centre, Plashet Grove, Forest Gate, E7 8QP, Monday to Friday, between 7am – 3.30pm

Appleby Health Centre, Canning town, E16 1LQ, Monday to Friday between 7am – 3.15pm

The Centre, Manor Park, Church road, Monday to Friday between 8 – 3.30pm

Vicarage Lane Health Centre, Stratford, Monday to Friday between 7am – 3pm

This test forms part of a study looking at the best way to identify people who might have viral hepatitis in high risk communities. Enclosed is a form giving your permission to take part in this study, and a stamped addressed envelope for you to return the form to us. This form is very important as it gives your permission to participate, and allows us to identify who has had the test. Please return this form when you have been for your blood test, and we will be in touch with your results around 2 weeks later. If you do not send the form back then we will not be able to include you in the study, and we will not be able to send you your results.

As hepatitis is a treatable disease, identifying cases enables us to offer treatment early, reducing the risk of long term liver damage.

Thank you very much for agreeing to be sent this request form through the post; we hope you will have your test, and we will be in touch with your results as soon as these are available.

If you have any questions please contact either your GP practice, or Professor Foster on 0207 882 7242,

Yours sincerely

Dr Heather Lewis

Appendix 11: Poster outreach clinics

Version 1
Date: 10.2.2011

Have you been diagnosed with Hepatitis C?

If you have we would like to invite you to take part in a research study.

Why is the research study being performed?

Hepatitis C is a virus that affects the liver and can cause serious liver damage. It is passed on when the blood of someone who has the virus comes into contact with another person's blood, for instance through a blood transfusion or sharing needles when injecting drugs.
Most people who have Hepatitis C can be cured with a course of treatment.
Hepatitis C is very common in people who have injected drugs, but very few of these people currently receive treatment.
We would like to explore the reasons behind this and see if offering treatment in a different way can improve the number of people starting and completing treatment, and being cured of Hepatitis C.

What does this mean for me?

If you are diagnosed with hepatitis C in this clinic, your nurse may invite you to take part in the research study. They will explain the treatment for hepatitis C and the research study in detail and give you some information about the study. If you wish to take part in the study then you will be asked to sign a consent form.
You are under no obligation to take part in the study, and it will not affect your medical care or your Hepatitis C treatment in any way should you choose not to take part.

Who can I contact for more information?

If you have any questions about the study please speak to you blood borne virus nurse at this clinic, or contact Heather Lewis, the research doctor on 07967551567

Appendix 12: Patient information sheet doctor initiated arm

East London NHS
NHS Foundation Trust

Institute of Cell and Molecular Science
Adult & Paediatric Gastroenterology
Barts and The London
Queen Mary's School of Medicine & Dentistry
Turner Street, London E1 2AD

Telephone: 020 7882 7242
Facsimile: 020 7882 7241

Version 2 – 10th May 2011

Addressing low treatment rates of chronic hepatitis C virus in injecting drug users

Participant Information Sheet - Non-intervention clinics

We would like to invite you to take part in a research study.

The information that follows tells you all about the study. Please take time to read the information carefully. It is important that you understand what is in this leaflet. The leaflet says what will happen if you take part and what the risks might be. It is entirely your choice whether or not you take part. Ask us if there is anything that is not clear, or if you would like any more information about the research.

1. What is the purpose of the study?

We know that infection with chronic hepatitis C virus is common in people who inject drugs, or have done so in the past. There are effective treatments for hepatitis C, and it is possible to cure up to 4 out of every 5 people with the virus. Unfortunately, only a small number of people who have injected drugs who have hepatitis C receive treatment. We are not sure why this is the case and we would like to explore the reasons for this in more detail. We are also concerned that current hepatitis C treatment services are not as accessible as they could be, and that this may be contributing towards the low treatment rates. We want to extend our current service to enable nurses to initiate treatment of hepatitis C in the community. We think that this will be more convenient for patients and will increase the proportion of people with chronic hepatitis C who receive treatment and are cured of this virus.

2 Hepatitis C virus– what is it and what does it do?

Hepatitis C is a virus that can cause damage to the liver. The virus travels in the blood and can be passed on by contact with another person's blood. It is commonly passed from one person to another via needles used when injecting drugs, contaminated medical equipment, or blood transfusions. Hepatitis C may initially be a mild illness that does not cause any problems but it usually becomes chronic and can cause serious liver disease. There are effective drugs to treat hepatitis C and these will cure most infected patients but if left untreated the virus can lead to cancer of the liver and cirrhosis (permanent damage of the liver).

3 Why have I been invited to take part in the study?

You have been invited to take part in the study because you have been diagnosed with hepatitis C virus, and we would like to offer you treatment for hepatitis C.

4 Do I have to take part?

You are under no obligation to take part. It is up to you to decide. We will explain the study and go through this information sheet with you. You will then have time to think about the study and decide if you wish to take part. If you wish to take part we will ask you to sign a

consent form. You will be free to withdraw from the study at any time without giving any reason. This will not affect the care you receive.

2 What will happen if I take part?

Currently if you are found to have hepatitis C virus at any of the 12 addiction services outreach clinics you will be referred to a monthly clinic at the Specialist Addiction Unit at either Mile End or Homerton Hospital for consideration of treatment. You will see a doctor who will assess you and decide on whether antiviral medication is appropriate. If the decision is made to start treatment you will return to your community clinic and the treatment will be given by your nurse. Treatment consists of daily tablets and weekly injections for 6-12 months depending on the type of hepatitis C you have and how well you respond to the treatment.

The clinic that you are attending will continue to offer this standard service i.e. your treatment will not change. We need to continue to provide standard care in some clinics so we can compare our current way of delivering treatment to our new way of delivering treatment to assess which of these is best.

Although we will not change your treatment we would like to collect some information about your background and your treatment. This will include questions on your age, sex, ethnicity, offender status, housing status, employment status, and if you have ever been an injecting drug user and, if so the duration and quantity of drug use. We would also like to obtain information on your medical and psychiatric history, and on your treatment for hepatitis C from your medical notes.

We would also like to understand the reasons why people choose, or do not choose to have treatment for hepatitis C in more detail and you may be invited to take part in an interview where you will be asked questions about your experience of hepatitis C and its treatment. This will take about an hour of your time. We will reimburse you with £10 for your time if you choose to take part in the interview.

3 What are the possible risks and disadvantages of taking part?

The treatment for hepatitis C virus has potential side effects of depression, anxiety, and can worsen other underlying mental health problems. It can also cause suppression of the white and red cells and platelets in the blood and cause an increased risk of infection. Participation in this study should not increase these risks but you should be aware of them before starting your treatment.

If you choose to take part in the interview you may find some of the questions we ask about your experience of hepatitis C and treatment for hepatitis C difficult to answer. You may also find you do not wish to answer some of the questions. The interview will be conducted in private, by a doctor who should be able to resolve any questions or concerns, and you do not have to answer any questions you do not wish to.

4 What are the possible benefits of taking part?

You should receive closer monitoring throughout your treatment for hepatitis C virus. There may, however, be no benefits to you of participating in the study.

5 Will my taking part in the study be kept confidential?

Yes, the fact that you are taking part in this study and all information we collect about you will be kept completely confidential. The only exception to this will be if you tell us that you are feeling suicidal or disclose details of a serious crime. If this is the case then this information will have to be reported to the appropriate agencies. If you consent to take part

in the research the people conducting the study will abide by the Data Protection Act 1998, and the rights you have under this Act. If at any time you wish to withdraw from the study all the information you have given will be destroyed.

2 Where can I get more information about the study?

You are encouraged to ask questions at any time in the study. Please speak to your blood borne virus nurse if you have any questions about the study. If you have a problem or concerns about the study or your rights as a subject, please call Professor Graham Foster on 020 7882 7242.

3 What if there is a problem?

We believe that this study is safe and do not expect you to suffer any harm because of your participation. If you are harmed by taking part in this research project, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds for a legal action but you may have to pay for it. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service complaints mechanisms should be available to you and you can obtain advice on this, or any other aspect of the study from :-

Patient Advice and Liaison Service (PALS) Telephone: 020 7943 1335, Minicom: 020 7943 1350E-mail: pals@bartsandthelondon.nhs.uk

Thank you for reading this document

Appendix 13: Consent form doctor initiated arm

East London NHS
NHS Foundation Trust

Consent form 1 – 10th May 2011 – Version 2

Addressing low treatment rates of Chronic Hepatitis C virus in injecting drug users – Non-Intervention Group

Patient Identification Number for this trial:

Please initial box to indicate agreement

1	I agree to participate in the standard treatment group. I understand that this means my treatment will not change but that my data will be collected.	
2	I confirm that I have read and understand the information sheet for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	
3	I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.	
4.	For the purpose of this study I give permission for the researchers to have access to my medical records.	
5	I agree that any data collected about me as part of the study may be used, anonymously, in the presentation of the research.	
6	I understand that my participation in this study and all information collected about me in this study will be kept fully confidential. I understand that the only exception to this is if I disclose details of feeling suicidal or a serious crime, where the appropriate authorities will be informed.	
7.	I agree to take part in the above study.	

Name of Patient	Date	Signature
Name of Person taking consent (if different from Investigator)	Date	Signature
Investigator	Date	Signature

1 copy for Patient, and original to investigator

Appendix 14: Patient information sheet nurse initiated arm

East London NHS
NHS Foundation Trust

Institute of Cell and Molecular Science

Adult & Paediatric Gastroenterology
Barts and The London
Queen Mary's School of Medicine
& Dentistry
Turner Street, London E1 2AD

Telephone: 020 7882 7242
Facsimile: 020 7882 7241
Email: g.r.foster@qmul.ac.uk

Version 2 – 10th May 2011

Addressing low treatment rates of chronic hepatitis C virus in injecting drug users

Participant Information Sheet – Nurse led treatment group

We would like to invite you to take part in a research study.

The information that follows tells you all about the study. Please take time to read the information carefully. It is important that you understand what is in this leaflet. The leaflet says what will happen if you take part and what the risks might be. It is entirely your choice whether or not you take part. Ask us if there is anything that is not clear, or if you would like any more information about the research.

1. What is the purpose of the study?

We know that infection with chronic hepatitis C virus is common in people who inject drugs, or have done so in the past. There are effective treatments for hepatitis C, and it is possible to cure up to 4 out of every 5 people with the virus. Unfortunately, only a small number of people who have injected drugs who have hepatitis C receive treatment. We are not sure why this is the case and we would like to explore the reasons for this in more detail. We are also concerned that hepatitis C treatment services are not as accessible as they could be, and that this may be contributing towards the low treatment rates. We want to extend our current service to enable nurses to initiate treatment of hepatitis C in the community. We think that this will be more convenient for patients and will increase the proportion of people with chronic hepatitis C who receive treatment and are cured of this virus.

2 Hepatitis C virus– what is it and what does it do?

Hepatitis C is a virus that can cause damage to the liver. The virus travels in the blood and can be passed on by contact with another person's blood. It is commonly passed from one person to another via needles used when injecting drugs, contaminated medical equipment, or blood transfusions. Hepatitis C may initially be a mild illness that does not cause any problems but it usually becomes chronic and can cause serious liver disease. There are effective drugs to treat hepatitis C and these will cure most infected patients but if left untreated the virus can lead to cancer of the liver and cirrhosis (permanent damage of the liver).

3 Why have I been invited to take part in the study?

You have been invited to take part in the study because you have been diagnosed with hepatitis C virus, and we would like to offer you treatment for hepatitis C.

4 Do I have to take part?

You are under no obligation to take part. It is up to you to decide. We will explain the study and go through this information sheet with you. You will then have time to think about the study and decide if you wish to take part. If you wish to take part we will ask you to sign a consent form. You will be free to withdraw from the study at any time without giving any reason. This will not affect the care you receive.

2 What will happen if I take part?

Currently if you are found to have hepatitis C virus at any of the 12 addiction services outreach clinics you will be referred to a monthly clinic at the Specialist Addiction Unit at either Mile End or Homerton Hospital for consideration of treatment. You will see a doctor who will assess you and decide on whether antiviral medication is appropriate. If the decision is made to start treatment you will return to your community clinic and the treatment will be given by your nurse.

In this study half of the community clinics will continue to provide this service.

In your clinic when you are diagnosed with hepatitis C, and if you fulfil the safety criteria, your nurse will offer you immediate treatment for hepatitis C and if you agree to treatment this will be started by your nurse in your local clinic the following week. There will be no requirement to attend the Specialist Addiction Unit and be seen by a doctor before treatment is started.

The treatment and monitoring you receive will be exactly the same, whether the decision to start your treatment is made by a nurse or by a doctor.

If you want to be treated with a different approach to that taken by your clinic then you will be able to opt out of the study and your treatment will be delivered using the current standard of care.

As part of this study we would like to collect some information about your background and your treatment. This will include questions on your age, sex, ethnicity, offender status, housing status, employment status, and if you have ever been an injecting drug user and, if so the duration and quantity of drug use. We would also like to obtain information on your medical and psychiatric history, and on your treatment for hepatitis C from your medical notes.

We would also like to understand the reasons why people choose, or do not choose to have treatment for hepatitis C in more detail and you may be invited to take part in an interview where you will be asked questions about your experience of hepatitis C and its treatment. This will take about an hour of your time. We will reimburse you with £10 for your time if you choose to take part in the interview.

3 What are the possible risks and disadvantages of taking part?

The treatment for hepatitis C virus has potential side effects of depression, anxiety, and can worsen other underlying mental health problems. It can also cause suppression of the white and red cells and platelets in the blood and cause an increased risk of infection. Participation in this study should not increase these risks but you should be aware of them before starting your treatment.

If you choose to take part in the interview you may find some of the questions we ask about your experience of hepatitis C and treatment for hepatitis C difficult to answer. You may also find you do not wish to answer some of the questions. The interview will be conducted in private, by a doctor who should be able to resolve any questions or concerns, and you do not have to answer any questions you do not wish to.

2 What are the possible benefits of taking part?

If you choose to participate in this study you will have a decision on treatment for your hepatitis C virus made at an earlier stage, by your own nurse, and at a more convenient location than currently occurs. We think that this will make it more likely that you will start and complete treatment and be cured of hepatitis C. There may, however, be no benefits to you of participating in the study.

3 Will my taking part in the study be kept confidential?

Yes, the fact that you are taking part in this study and all information we collect about you will be kept completely confidential. The only exception to this will be if you tell us that you are feeling suicidal or disclose details of a serious crime. If this is the case then this information will have to be reported to the appropriate agencies. If you consent to take part in the research the people conducting the study will abide by the Data Protection Act 1998, and the rights you have under this Act. If at any time you wish to withdraw from the study all the information you have given will be destroyed.

4 Where can I get more information about the study?

You are encouraged to ask questions at any time in the study. Please speak to your blood borne virus nurse if you have any questions about the study. If you have a problem or concerns about the study or your rights as a subject, please call Professor Graham Foster on 020 7882 7242.

5 What if there is a problem?

We believe that this study is safe and do not expect you to suffer any harm because of your participation. If you are harmed by taking part in this research project, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds for a legal action but you may have to pay for it. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service complaints mechanisms should be available to you and you can obtain advice on this, or any other aspect of the study from :-

Patient Advice and Liaison Service (PALS) Telephone: 020 7943 1335, Minicom: 020 7943 1350E-mail: pals@bartsandthelondon.nhs.uk

Thank you for reading this document

Appendix 15: Consent form nurse initiated arm

East London NHS
NHS Foundation Trust

Consent form 1 – 10th May 2011 – Version 2

Addressing low treatment rates of Chronic Hepatitis C virus in injecting drug users – Intervention Group

Patient Identification Number for this trial:

Please initial box to indicate agreement

1	I agree to participate in the nurse led treatment group.	
2	I confirm that I have read and understand the information sheet for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	
3	I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.	
4.	For the purpose of this study I give permission for the researchers to have access to my medical records.	
5	I agree that any data collected about me as part of the study may be used, anonymously, in the presentation of the research.	
6	I understand that my participation in this study and all information collected about me in this study will be kept fully confidential. I understand that the only exception to this is if I disclose details of feeling suicidal or a serious crime, where the appropriate authorities will be informed.	
7.	I agree to take part in the above study.	

Name of Patient	Date	Signature
Name of Person taking consent (if different from Investigator)	Date	Signature
Investigator	Date	Signature

1 copy for Patient, and original to investigator

Appendix 16: Assessment protocol

Version 2 – 12th September 2011

Nurse initiated treatment of injecting drug users – Assessment protocol

HCV screening:

- Viral screening undertaken in outreach clinic
- HCV RNA positive

Assessment by Blood Borne Virus nurse:

Mental health status

PHQ-9 questionnaire to assess depression – see attachment

If they have a score of over 9 (i.e. moderate depression or above) or answer yes to any of the following questions they are not suitable for the trial

	Yes	No
Do you hear voices that other people cannot hear?		
Do you feel that people are trying to harm you?		
Do you have special powers that other people do not have?		
Do you take any antipsychotic medication?		

Have you ever been admitted to hospital for psychiatric inpatient care?		
Have you ever intentionally harmed yourself or others or attempted to commit suicide?		

Physical health status

If any of the following conditions are present they are not eligible for the trial

Medical condition	**Yes**	**No**
Chronic obstructive pulmonary disease		
Bronchiectasis		
Ischaemic heart disease – angina, heart attack, stroke		
Heart failure		
Renal failure		
Liver cirrhosis		
Decompensated liver disease (ascites, varices, hepatic encephalopathy)		
Any current infections (i.e. dental abscess, cellulitis, pneumonia, urinary infection)		

Current psoriasis/ dermatological condition		
Sickle cell trait/ disease		
Thalassaemia trait/ Thalassaemia A/B		

Investigations:

- Length of injecting history
- Blood tests:
- LFT, U&E's, FBC, Coagulation, HCV RNA, TFT's, autoantibodies, haemoglobin electrophoresis, HBsAg, HIV, alpha feto protein, HCV genotype
- ECG
- Pregnancy test in females of child bearing age
- USS (IF INJECTING HISTORY >10 YEARS).

Pre-Treatment counselling and study information:

- Benefits and side effects of treatment fully explained to patient
- Study explained to patient and Patient Information Sheet given
- Women of child bearing age (or men whose female partners are of child bearing age) should be informed of the requirement for two forms of contraception during treatment and for 6 months after treatment finishes due to the potential teratogenicity of ribavirin. They cannot be considered for treatment if they are/ plan to become pregnant.

Assessment of inclusion and exclusion criteria:

- Discuss in SAU team meeting if suitable for treatment when results available and assessment of inclusion/ exclusion criteria has been made

Inclusion criteria for treatment in nurse initiated arm		
Inclusion Criteria	**Date**	**Document result**
HCV Ab positive		
HCV RNA positive		
AST<1.3x ALT		
ALT <250		
AST < 250		
Bilirubin < 30		
Albumin > 30		
Platelets > 150		
Haemoglobin > 12		
WCC > 3		
INR < 1.2		

Creatinine <100		
Urea < 6		
USS (if done) - no cirrhosis, ascites, or lesions suspicious of hepatocellular carcinoma		
No ascites/ jaundice on examination		
Negative pregnancy test (females of child bearing age)		
No contraindications to treatment with pegylated interferon/ ribavirin (see appendix 1)		

Exclusion criteria for treatment in nurse initiated arm		
Exclusion criteria	**Present: Document details below**	**Not present: Sign and date when checked**
Severe depression, self-harm or psychosis IN THE LAST 2 YEARS		

Admission to hospital for any psychiatric condition		
Current self-harm or suicidal ideation		
Current treatment with anti-psychotics		
Ongoing sepsis		
Cirrhosis		
Renal failure		
Known varices		
Hepatocellular carcinoma		
Hepatic encephalopathy		

- Those who do not fulfil inclusion criteria, or who have any exclusion criteria, or who wish to be reviewed in the consultant led clinic should be referred to the consultant led outreach clinic at the Specialist Addiction Unit via the usual pathway
- Those who fulfil the inclusion criteria and wish to have treatment will be started on treatment immediately by the BBV nurse in the outreach clinic.

- Those who do not wish to have treatment will not be commenced on treatment and general healthcare and addiction services will continue to be given as is standard practice.

Appendix 1:

Contraindications to treatment with ribavirin
Renal failure
Severe cardiac disease
Severe respiratory disease
Pregnancy or planned pregnancy of patient or female partner while on treatment or within 6 months of finishing treatment
Haemoglobinopathies
Autoimmune disease
Severe psychiatric disease

Contraindications to treatment with pegylated interferon:
Ongoing sepsis

Psychosis or severe depression
Hepatic decompensation
Autoimmune disease
Severe cardiac disease/ history of arrhythmias

Appendix 2:

Side effects of pegylated interferon:
Nausea
Anorexia
Diarrhoea
Hair loss
Flu like symptoms
Depression/ anxiety/ psychosis
Myelosuppression
Arrhythmias
Thyroid abnormalities
Psoriaform rash
Nephrotoxicity

Hepatotoxicity Confusion, coma, seizures

Side effects of ribavirin Myelosuppression Haemolytic anaemia Cough Rash

Appendix 17: Consent form data collection only

East London NHS
NHS Foundation Trust

Consent form 1 – 10th May 2011 – Version 2

Addressing low treatment rates of Chronic Hepatitis C virus in injecting drug users

Agreement to data collection

Patient Identification Number for this trial:

Please initial box to indicate agreement

1	I agree for my data to be collected as part of the above study even though I am not participating in the study	
2	I confirm that I have read and understand the information sheet for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	
3	I understand that my agreement to allow my data to be used is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected	
4	For the purpose of data collection I give permission for the researchers to have access to my medical records.	
5	I agree that any data collected about me as part of the study may be used, anonymously, in the presentation of the research.	
6	I understand that my agreement to my data being used and all information collected about me in this study will be kept fully confidential. I understand that the only exception to this is if I disclose details of feeling suicidal or a serious crime, where the appropriate authorities will be informed.	
7	I agree to my data being used in the above study.	

Name of Patient	Date	Signature
Name of Person taking consent (if different from Investigator)	Date	Signature
Investigator	Date	Signature

1 copy for Patient, and original to investigator

Appendix 18: PHQ-9 Depression scoring scale and psychosis questionnaire

PHQ-9 Depression scoring scale:

Mental Health Assessment:

Over the *last 2 weeks*, how often have you been bothered by any of the following problems?

	Not at all	**Several Days**	**More than half the days**	**Nearly every day**
Score	0	1	2	3
Little interest or pleasure in doing things				
Feeling down, depressed or hopeless				
Trouble falling/staying asleep or sleeping too much				
Feeling tired or having little energy				
Poor appetite or overeating				
Feeling bad about yourself – or that you are a failure or have let yourself or your family down				
Trouble concentrating on things such as reading the newspaper or watching television could have noticed. Or the opposite – being so fidgety or restless that you have been moving around a lot more than usual				
Thoughts that you would be better off dead or of hurting yourself in some way				
Total for each column				
Total score				

How difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?

Not difficult at all Somewhat difficult Very difficult Extremely difficult

Psychotic symptoms were assessed using the following questions:

	Yes	No
Do you hear voices that other people cannot hear?		
Do you feel that people are trying to harm you?		
Do you have special powers that other people do not have?		
Do you take any antipsychotic medication?		
Have you ever been admitted to hospital for psychiatric inpatient care?		
Have you ever intentionally harmed yourself or others or attempted to commit suicide?		

Appendix 19: Patient information sheet – semi structured interview

Institute of Cell and Molecular Science

East London NHS
NHS Foundation Trust

Adult & Paediatric Gastroenterology
Barts and The London
Queen Mary's School of Medicine
& Dentistry
Turner Street, London E1 2AD

Telephone: 020 7882 7242
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Version 2 – 10th May 2011

Addressing low treatment rates of chronic hepatitis C virus in injecting drug users

Participant Information Sheet – In depth Interview

We would like to invite you to take part in a research study.

The information that follows tells you all about the study. Please take time to read the information carefully. It is important that you understand what is in this leaflet. The leaflet says what will happen if you take part and what the risks might be. It is entirely your choice whether or not you take part. Ask us if there is anything that is not clear, or if you would like any more information about the research.

1. What is the purpose of the study?

We know that infection with chronic hepatitis C virus is common in people who inject drugs, or have done so in the past. There are effective treatments for hepatitis C, and it is possible to cure up to 4 out of every 5 people with the virus. Unfortunately, only a small number of people who have injected drugs who have hepatitis C receive treatment. We are not sure why this is the case and we would like to explore the reasons for this in more detail.

2 Why have I been invited to take part in the study?

You have been invited to take part in the study because you have been diagnosed with hepatitis C virus, and have been offered treatment for hepatitis C virus by the blood borne virus team.

3 Do I have to take part?

You are under no obligation to take part. It is up to you to decide. We will explain the study and go through this information sheet with you. You will then have time to think about the study and decide if you wish to take part. If you wish to take part we will ask you to sign a consent form. You will be free to withdraw from the study at any time without giving any reason. This will not affect the care you receive.

4 What will happen if I take part?

We would like to understand the reasons why people choose, or do not choose to have treatment for hepatitis C in more detail and we would like to invite you to take part in an interview where you will be asked questions about your experience of hepatitis C and it's treatment. This will take about an hour of your time and the interview will be tape recorded.

We will reimburse you with £10 for your time if you choose to take part in the interview.

As part of this study we would like to collect some information about your background and your treatment. This will include questions on your age, sex, ethnicity, offender status,

housing status, employment status, and if you have ever been an injecting drug user and, if so the duration and quantity of drug use. We would also like to obtain information on your medical and psychiatric history, and on your treatment for hepatitis C from your medical notes.

2 What are the possible risks and disadvantages of taking part?

If you choose to take part in the interview you may find some of the questions we ask about your experience of hepatitis C and treatment for hepatitis C difficult to answer. You may also find you do not wish to answer some of the questions. The interview will be conducted in private, by a doctor who should be able to resolve any questions or concerns, and you do not have to answer any questions you do not wish to.

3 What are the possible benefits of taking part?

You will have the opportunity to discuss your experience of living with hepatitis C virus, and to have your questions answered by a doctor.

4 Will my taking part in the study be kept confidential?

Yes, the fact that you are taking part in this study and all information we collect about you will be kept completely confidential. The only exception to this will be if you tell us that you are feeling suicidal or disclose details of a serious crime. If this is the case then this information will have to be reported to the appropriate agencies. If you consent to take part in the research the people conducting the study will abide by the Data Protection Act 1998, and the rights you have under this Act. If at any time you wish to withdraw from the study all the information you have given will be destroyed.

5 Where can I get more information about the study?

You are encouraged to ask questions at any time in the study. Please speak to your blood borne virus nurse if you have any questions about the study. If you have a problem or concerns about the study or your rights as a subject, please call Professor Graham Foster on 020 7882 7242.

6 What if there is a problem?

We believe that this study is safe and do not expect you to suffer any harm because of your participation. If you are harmed by taking part in this research project, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds for a legal action but you may have to pay for it. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service complaints mechanisms should be available to you and you can obtain advice on this, or any other aspect of the study from :-

Patient Advice and Liaison Service (PALS) Telephone: 020 7943 1335, Minicom: 020 7943 1350E-mail: pals@bartsandthelondon.nhs.uk

Thank you for reading this document

Appendix 20: Consent form semi structured interview

East London NHS
NHS Foundation Trust

Consent form 1 – 10th May 2011 – Version 2

Addressing low treatment rates of Chronic Hepatitis C virus in injecting drug users –
Agreement to take part in an in-depth Interview

Patient Identification Number for this trial:

Please initial box to indicate agreement

1	I agree to participate in the in depth interview.	
2	I confirm that I have read and understand the information sheet for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	
3	I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.	
4.	For the purpose of this study I give permission for the researchers to have access to my medical records.	
5	I agree that any data collected about me as part of the study may be used, anonymously, in the presentation of the research.	
6	I understand that my participation in this study and all information collected about me in this study will be kept fully confidential. I understand that the only exception to this is if I disclose details of feeling suicidal or a serious crime, where the appropriate authorities will be informed.	
7.	I agree to take part in the above study.	

Name of Patient	Date	Signature
Name of Person taking consent (if different from Investigator)	Date	Signature
Investigator	Date	Signature

1 copy for Patient, and original to investigator

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