LONDON JOINT WORKING GROUP
ON SUBSTANCE MISUSE + HEPATITIS C

NHS
North West London

Public Health Report on Commissioning of HCV services in London for People who Inject Drugs

Foreword

Chronic hepatitis C infection in people who inject drugs represents a major health inequality in a marginalised group in society. In London the prevalence of hepatitis C is 55% in people who inject drugs compared to 1-2% in the general population, a finding reflected in the fact that people who inject drugs have three times the mortality rate of the general UK population. Despite these shocking statistics only a small minority (<3-4%) receive treatment for Hepatitis C in the UK. This report represents a call to action for commissioners of drug addiction services and specialist liver services.

This baseline assessment of services in London provides a mixed picture of commissioning arrangements and service delivery models. It is clear that a 'one-size fits all' approach is not applicable in this metropolitan setting. Although there are many areas of best practice across London and a strong foundation on which to build, there are significant gaps as well. Pathway development; communication, incorporating blood borne virus testing and care into routine roles within drug treatment services and needle exchanges, and the follow up of referrals into specialist liver services are all areas that require strengthening. While it is clear that progress in testing and treatment of hepatitis C is being made, the absence of easily shared performance data mean this cannot be evidenced nor progress monitored.

The economic assessment of this report argues for the cost-effectiveness of treating hepatitis C-related liver disease. To have a significant impact on the prevalence of hepatitis C in people who inject drugs, large scale levels of treatment would need to be reached. Given the current low baseline in London, a moderate level of treatment (around 10%) may be more attainable in the short-term and is shown in this report to be a cost-effective level of treatment delivery. Crucially, treatment alone will not solve this crisis in health equity. A multi-component prevention programme, incorporating opioid substitution therapy, needle and syringe programmes and awareness raising campaigns, should be endorsed in tandem.

Best practice evidence supports the universal delivery of hepatitis C testing and annual reviews in all drug treatment services. Blood borne virus assessment should not be a peripheral part of drug treatment services, and where possible the wider workforce should be engaged in delivering education, testing and monitoring. Models of integrated care have been developed in some London boroughs, including Lewisham and Tower Hamlets. There is strong evidence that bringing specialist hepatitis C services to where the clients are (drug treatment services or GP shared care) results in increased use. Crucially, this also allows people who are not ready to initiate treatment to have their condition monitored on an ongoing basis rather than fall out of the system. Patient-centred care is at the heart of this approach.

Under the new commissioning arrangements in England there is an opportunity to work collectively to provide effective evidence based equitable services for anyone with chronic hepatitis C infection, including some of the most vulnerable in our society. Detailed recommendations are made in this report for each commissioner audience. It is my pleasure to introduce the public health report on the commissioning of hepatitis C services in London for people who inject drugs, which I believe marks a valuable step in our work to address this important health inequality.

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Contents

Published April 2013.

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Acknowledgements: With thanks for their contributions to Dr Ike Anya, Dee Cunniffe, Claire Munro, Sinan Rabee, Thomas Harte, Dr Graham Foster, Grainne Nixon, Dr Chris Ford, Ross Harris, Alison Keating, Dima Abdulrahim and all members of the London Joint Working Group for Substance Misuse and Hepatitis C. With further thanks to all Commissioners and Providers who participated in the London baseline survey.

Executive Summary

Hepatitis C virus (HCV) among people who inject drugs (PWID) is a driver of considerable health inequality in London due to the low numbers receiving treatment. Added to which, liver disease is increasing in England, causing considerable morbidity, mortality and financial burden to the NHS. Over a third of deaths from liver disease are attributable to HCV, an entirely preventable infection.

HCV is a blood borne virus. People infected with HCV can be asymptomatic for a number of years before the liver becomes sufficiently damaged to result in symptoms, though 25% of infections resolve naturally. It can take 20-30 years to develop severe liver disease, such as decompensated cirrhosis or hepatocellular carcinoma. It has been suggested that related mortality will double between 2000 and 2020(9).

In London an estimated 52,000 people have chronic HCV(10). 69% of HCV infections are thought to have been as a result of injecting drug use. The prevalence of HCV among people who inject drugs is higher in London than elsewhere in England, 55% compared to 45%. A low proportion of people are in treatment for HCV (<3-4%). This suggests that the reduction of HCV in this population should be a priority.

Given these issues, the London Joint Working Group on Substance Misuse and HCV commissioned an independent public health report to look at how available evidence on this issue can be pragmatically applied within London. This report is comprised of three main elements:

- an evidence review of HCV epidemiology in London, HCV testing and treatment and best practice
- two baseline surveys of service delivery in drug treatment services in London
- an economic model of the impact of testing and treatment on health care costs in London.

Key Findings from the Evidence Review

Diagnosis at an early stage requires active engagement and testing. Rates of diagnosis in London are higher than elsewhere in England, at an estimated 60% compared to 20-40%, but this does not translate into higher rates of treatment and needs urgent attention. People are at greatest risk of infection from HCV in their first year of injecting but do not have regular contact with existing services at this stage.

Tests for HCV have historically involved a blood test for antibodies and a subsequent blood test to confirm chronic infection by a RNA PCR test. NICE have recently recommended reducing the number of blood samples required for these tests to one, something currently not offered by laboratories in London. Blood testing can be a problematic and off-putting step for people who inject drugs and so alternative means of testing have been recommended by NICE, including dried blood spot (DBS) testing. Pharmacies which offer a needle and syringe exchange programme have proven a useful venue to increase uptake of testing, and should be considered for roll out across London.

General practice is a valuable location for targeted testing of former PWID. Targeted testing of registered patients with risk factors for HCV has been shown to be a cost-effective approach to diagnosis in these groups(18).

A positive PCR RNA will result in a patient being referred to specialist hepatology services for assessment and either ongoing monitoring of disease progression, or treatment initiation. Hospital settings are an evidence-based blockage in the pathway for people who inject drugs. Half of all people who inject drugs receive opiate substitution therapy, and thereby come into contact with drug treatment services on a

frequent and regular basis, which is conducive to the delivery of HCV treatment. Service integration is an evidence-based approach to improving treatment outcomes.

The patient may opt out of the pathway at any point, and it is important to understand this vulnerable group in order to support them. People who inject drugs who have HCV have competing priorities of chaotic lifestyles, high social needs, financial and housing issues as well as battling the stigma surrounding infection. Treatment for HCV can be very difficult and patients need to be supported to receive it. Peer support groups and education sessions, along with other forms of support, can help to increase uptake of and compliance with treatment.

Key Findings from the London baseline surveys

The Commissioning and Provider surveys have highlighted a variation in practice among London boroughs, and even between services within the same borough. The recently published NICE guidelines(18) while met in some boroughs, are some way from being met in all boroughs.

Approximately one in three boroughs has a testing-to-treatment pathway in place. Not all drug treatment services seemed to be aware of this in boroughs where it exists, however.

DBS testing is commissioned in 63% of boroughs already, but only 37% of drug service providers stated that they offered DBS testing. DBS testing can be performed by non-clinical staff, but the best practice review highlighted that there may be reservations to this currently, and a useful first step towards implementation could be to train existing nursing staff in drug treatment services in this form of testing. 58% of drug treatment services have nursing staff as part of their establishment levels.

Two sites in London (5%) have introduced integrated services where HCV treatment is delivered through Hepatology clinics in drug treatment services. In addition, 24% reported the direct involvement of a Hepatologist in their service. There is currently variation in practice for eligibility criteria for HCV treatment across London, resulting in confusion among both patients and drug treatment service providers.

Based on our survey findings, 33% of boroughs commission needle and syringe exchange programmes from pharmacies, and 61% of services currently receive referrals from criminal justice services. These represent important areas for expansion across the region.

Key Findings from the economic model

The economic model found that drug treatment services can have a greater impact on HCV treatment uptake than general practice if blockages in the pathway are addressed. A sensitivity analysis of the testing to treatment pathway has indicated that by far the most efficient step to address is increasing treatment initiation among people attending specialist services, in order to increase numbers of people recovering from HCV. The next most important step in the pathway to tackle is attendance at specialist services among those referred.

Treatment of people with moderate disease was shown to be the most cost-effective approach. However, treatment of mild, moderate and cirrhotic disease were all found to be cost-effective, and given that all three states are asymptomatic, in practice they will all require the same approach to identification and follow up.

Economic modelling has shown that without treatment for HCV, quality of life decreases and the cost of management increases as the disease progresses. All available evidence points to it being more cost-

effective to treat patients for HCV than to manage the effects of liver disease progression, even allowing for low rates of viral clearance through treatment: 45% for genotype 1 and 80% for other genotypes(4). These findings suggest that from an economic and public health perspective, fixed annual budgets would focus on immediate and maximum spend on treatment for HCV each year in order to avert a high number of new infections and reduce 10-year prevalence.

3-4% of people with HCV are treated each year; and an aim of increasing this to 10% should be both realistic and cost-effective. This analysis is based on current prices. If new treatments are priced at a much higher level, cost-effectiveness will be called into question again. The difficulty for Commissioners is that money needs to be found now to address the double burden of the glut of patients already allowed to progress to end stage liver disease, and to proactively treating patients at an earlier stage of disease in order to avert disease progression for more people in future.

Summary of Recommendations

- All boroughs should have a strategy in place to address liver disease, in which HCV should form a significant component
- Joint commissioning arrangements should be developed between CCGs and Public Health
- All boroughs should have a HCV pathway in place, which is regularly monitored against performance
- Stretch targets should be set to encourage increased rates of treatment initiation (10% of people with HCV in treatment)
- Where possible, an integrated service of HCV treatment in drug treatment services should be commissioned
- Patient support programmes including peer support, education and awareness raising programmes should be commissioned to encourage uptake of treatment
- DBS testing should be offered in all drug treatment services and other venues, such as needle and syringe exchange programmes, including their delivery in pharmacies
- Closer links should be made with criminal justice services to increase testing in new drug initiators
- GP practices should be commissioned to offer HCV testing to former PWID
- Prison health should focus on continuity of care to improve HCV management
- Health and drug addiction professionals in all boroughs should receive training in HCV
- Laboratories should review practice so that antibody and RNA PCR tests can be performed on one sample
- There should be some standardisation of diagnostic tests and eligibility for HCV treatment in London
- There is an important role in lobbying pharmaceutical companies who are developing new treatments for HCV to set sufficiently affordable prices to optimise access to treatment in this marginalised group.

Introduction

Premature mortality from liver disease is becoming an increasingly pressing issue in England and this pattern is also seen in London. Strategies to address this must include ways of tackling hepatitis C virus (HCV), which considerably contributes to this growing problem. The majority of cases of chronic hepatitis C infection are found among people who inject drugs (PWID), (69% in London). This represents a significant health inequality which needs to be addressed through collaborative programmes.

The London Joint Working Group for Substance Misuse and Hepatitis C (LJWG) was formed in June 2009, having identified an opportunity to share best practice in the development of effective joint working care pathways for the treatment of HCV in PWID engaged in drug and alcohol services in London. In 2011 a consensus document was produced by this group to recommend priority and best practice action for London, and can be found on their website, www.ljwg.org.uk.

This independent public health report is intended to complement the work of the LJWG by reviewing services across London, and applying best evidence to the London context. The principle intended audience for this work is commissioners of health services and drug treatment services and it is hoped that the information provided will be of use in formulating future business cases for HCV services.

This report focuses on HCV testing and treatment in PWID. As shall be shown, a very low number of PWID are engaged in treatment for HCV. The reasons for low treatment coverage need to be fully understood in order to effectively improve care. Taking a pathway approach, this report assesses where and how action can be directed most effectively. HCV testing and referral to or provision of treatment is already established in many drug treatment services and general practices. This report therefore focuses on intervention in these locations.

From April 2013 new commissioning arrangements will come into force. Drug treatment services will remain under the auspices of local authority commissioning, but will move under the jurisdiction of public health departments. Clinical Commissioning Groups (CCGs) will be responsible for commissioning treatment of infectious disease and the promotion of early diagnosis as part of community health services and outpatient services. The NHS Commissioning Board (NCB) will be responsible for commissioning specialist health services and for the promotion of early detection through primary care. The NCB will also commission health and public health services within prisons. A significant proportion of PWID come into contact with prison services but its structural arrangements differ to those delivered in primary care and community drug addiction. It will therefore be touched upon under the best practice section but is not considered elsewhere in the report. Public Health England (PHE) will not have direct commissioning responsibility but will maintain oversight of the prevention and control of infectious disease.

Aim

The aim of this report is to provide commissioners of drug treatment services and commissioners of infectious disease identification and treatment services with sufficient information to commission best practice services for HCV in PWID in London.

There are four key questions that this report seeks to answer:

1. Why is HCV among PWID an issue for London?
2. What is currently being done in London to address this health inequality?

3. What more needs to be done?
4. How much will this cost and how do we ensure value for money?
5. How are we going to get there?

These questions are addressed in each of the correspondingly numbered sections of this report.

Methodology

This report applies a mixed methods approach to address the diverse questions that this report seeks to answer. These comprise a literature review, a survey of drug treatment service commissioners and providers across London and the development of an economic model for London.

The methodologies of both the economic model and the Commissioner and Provider surveys are set out in appendix A and section 2 respectively. Here is detailed the methodological approach taken to the literature review of the current situation in London and best practice in HCV services for PWID.

The purpose of the literature review was to inform an understanding of the London context for PWID of the epidemiology, cost-effectiveness and best practice implementation of:

- HCV testing uptake
- Knowledge, attitudes and motivations towards HCV testing and treatment
- Uptake of, and adherence to, follow up services and treatment for HCV
- Other interventions that will reduce HCV incidence and prevalence
- Organisational structures that will facilitate the above.

The PICO mnemonic was adopted to formulate a series of review questions.

Population	Current and former PWID; drug treatment services and health practitioners; from a context generalisable to London
Intervention	Any intervention or activity that aims to raise awareness of, or engagement in, testing and treatment of HCV, or the overall reduction of HCV in the target population in the last ten years
Comparison	No intervention or another type of intervention
Outcomes	Measures of testing uptake; knowledge, attitudes and motivations towards testing and treatment; measures of uptake of and adherence to follow up services and treatment; reductions in HCV incidence and prevalence Costs (regardless of how estimated) and outcomes (regardless of how specified)

A literature search performed in the PubMed database returned >500 results. The abstracts of these papers were filtered for relevance to the above PICO questions. This process formed the appraisal process of this review. 17 papers were considered to meet the criteria for review. Discussion with experts and reviews of grey literature returned an additional 27 papers for review. The evidence presented in these 44 papers is collated and discussed in this report.

Throughout this report it should be stated that where London specific data is available this is always reported. Otherwise England, UK and the European data have been sought in that order of preference to offer the most reliable information possible.

Section 1: HCV in England and London: Why is HCV among PWID an issue for London?

The contribution of HCV to the growing burden of liver disease in England

When the Chief Medical Officer published her first annual public health report on 21st November 2012, it was accompanied by a statement on the Department of Health's website drawing attention to liver diseases as a priority for England:

"An important finding to emerge from the Chief Medical Officer's first annual report is that comprehensive action is needed to address the rising rates of liver disease.

Liver disease is the only major cause of mortality and morbidity that is on the increase in England while it is decreasing among our European peers.

Between 2000 and 2009, deaths from chronic liver disease and cirrhosis in the under 65s increased by around 20% while they fell by the same amount in most EU countries. And all 3 major causes of liver disease – obesity, undiagnosed infection, and, increasingly, harmful drinking – are preventable."

There are just over 10,000 deaths due to liver disease in England each year. 2% of these deaths are directly attributable to hepatitis, 68% to cirrhosis, 29% to liver cancer and the remainder to other reasons. A 2009 study estimating the HCV-related burden of disease in Europe(1) calculated the regional HCV-attributable fraction of cirrhosis to be 35% and liver cancer to be 32%. Based on these figures, a crude calculation would put the proportion of deaths from liver disease that can be attributed to HCV at closer to 35%, or over 3500 deaths per year in England. In addition, it considered 19-23% of liver transplants to be related to HCV, which is equivalent to 110-160 liver transplants each year(2).

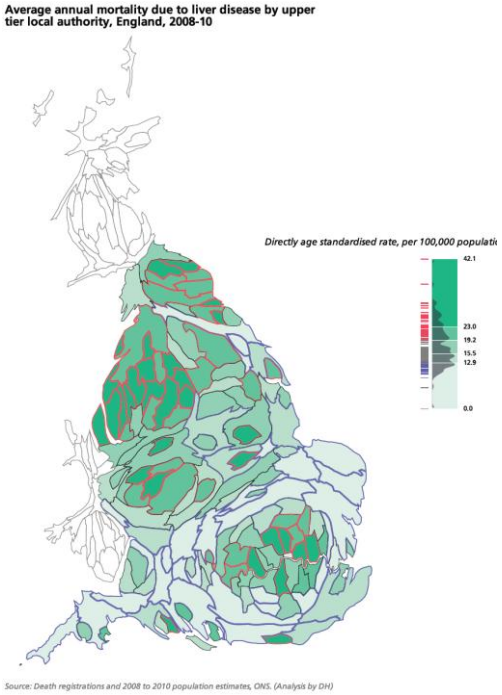


Figure 1: Average annual mortality due to liver disease by upper tier local authority, England, 2008-10 ***Reproduced with permission from the Department of Health***

High rates of mortality from liver disease cluster around deprived inner city areas, of which London is a particularly population-dense area. This is unsurprising given the four main drivers of increasing liver disease (alcohol, obesity and chronic hepatitis B and C infection), which find their risk factors in urban areas. All of these drivers are preventable, highlighting an urgent call to action.

Where a local authority age standardised liver disease mortality rate is higher than 20 per 100,000 population, this is likely to be due to local alcohol culture or undiagnosed hepatitis infection(3). This is the case in 50 local authorities, of which 11 were in London and require priority action (see table 1).

Table 1: Age standardised mortality rates from liver disease in London, 2008-10, CMO report data, compared to HPA estimates of HCV prevalence, 2007.

London Borough	Liver disease mortality rate, per 100,000 population	Prevalence of HCV, %
City of London	6.03	Combined with Hackney estimate
Barking and Dagenham	20.29	0.59
Barnet	13.01	0.58
Bexley	11.98	0.45
Brent	17.28	0.6
Bromley	12.30	0.53
Camden	27.11	1.7
Croydon	15.88	0.52
Ealing	20.00	0.62
Enfield	14.40	0.51
Greenwich	19.67	0.7
Hackney	21.45	0.79
Hammersmith and Fulham	24.71	0.92
Haringey	22.71	0.7
Harrow	14.40	0.52
Havering	11.94	0.45
Hillingdon	17.14	0.52
Hounslow	20.53	0.63
Islington	29.90	1.17
Kensington and Chelsea	18.32	0.7
Kingston upon Thames	14.98	0.36
Lambeth	25.89	0.87
Lewisham	19.34	0.73
Merton	11.27	Combined with Sutton estimate
Newham	26.12	0.52
Redbridge	15.03	0.61
Richmond upon Thames	16.20	0.5
Southwark	19.23	0.87
Sutton	10.06	0.56
Tower Hamlets	23.69	1.11
Waltham Forest	21.97	0.51
Wandsworth	17.32	0.69
Westminster	16.97	1.31

Deaths from liver disease are associated with deprivation, which is why inner city London is disproportionately affected. Mortality rates from liver disease are three times greater in the most deprived quintile than the least deprived quintile. 40% of deaths directly attributable to HCV were among the 20% most deprived population group. Men are almost twice more likely to die from liver disease than women. Mortality rates typically increase with age and this is shown to be the case with liver cancer.

However deaths from cirrhosis of the liver, and deaths that are directly attributable to HCV, follow a different pattern that peaks around the 55-59 years age group(3).

Not only does HCV significantly contribute to the growing burden of liver disease in England, it is also responsible for a high number of years of life lost.

Natural History of HCV

HCV is a blood borne virus (BBV) which can be asymptomatic for a number of years before the liver becomes sufficiently damaged for symptoms to be recognised. This means there is often a significant proportion of cases that are not diagnosed until the disease has reached a more aggressive stage. In its 'asymptomatic' stage of infection it can produce low level general symptoms, such as tiredness, which are often mistakenly attributed to drug use.

20-25% of infections are acute, and people naturally recover from infection without treatment but remain antibody positive. The remaining 75-80% are antibody and PCR positive and develop into chronic HCV, which can be categorised as mild, moderate or severe, depending on the level of liver damage. Severe HCV-related liver disease is characterised by cirrhosis of the liver and can be further categorised as compensated or decompensated. Compensated liver disease is when the liver can still perform all its functions and the individual does not experience any symptoms of jaundice, bleeding, etc. A decompensated liver is one whose function is declining, or 'end-stage' liver disease.

Disease progression is often slow, taking between 20 and 50 years to develop from mild to severe disease. About 30% of HCV infected people develop liver cirrhosis within 20 to 30 years(4). The results of a meta-analysis found the average rates of progression to different stages of disease, as presented in table 2(5).

Table 2: HCV disease progression estimates, per year

Transition	Mean probability	Of 1000 people in the initial state, how many progress to the next state
Mild to moderate	0.025	25
Moderate to cirrhosis	0.037	37
Cirrhosis to decompensated cirrhosis	0.039	39
Cirrhosis/decompensated cirrhosis to HCC	0.014	14
Decompensated cirrhosis/HCC to LT	0.030	30
Decompensated cirrhosis to death	0.130	130
HCC to death	0.430	430
LT to death	0.210	210
Post-transplant to death	0.057	57

Due to its initially asymptomatic nature, and perhaps a lack of pro-active testing, HCV is often first diagnosed at a late stage when therapeutic options are limited. Therapeutic intervention can prevent progression to severe liver disease in 54-63% (49–68%, 95% confidence intervals) of patients(1). HCV-infected individuals have a death rate three times higher than the general population, accounting for age. Excess mortality is attributed both to liver-related causes and to the consequences of chronic drug use, including suicide(6).

There are six genotypes for HCV. Genotype 1 is the most common in the UK, accounting for 40-50% of cases and requiring the most prolonged treatment. A further 40-50% of cases are among genotypes 2 and 3(4). Evidence suggests that viral load or genotype have minimal influence on disease severity or progression(7). Genotype does have an impact on treatment regimens and their duration.

There are a number of additional factors that can influence the rate of disease progression. Age is the most significant factor. HCV infection acquired in people under 40 years will progress to cirrhosis within 20 years in <5% of cases, but for people over 40 years the same rate of progression occurs in >20% of cases. The length of time that someone is infected will also increase their risk of developing cirrhosis(7).

Other factors to note are HIV co-infection and high alcohol intake. HIV co-infection can double the risk of the development of cirrhosis, depending on CD4 counts. Alcohol intake exceeding 50g alcohol/day triples the risk of progression to cirrhosis. One intervention study has indicated that weight reduction can reduce progression and there is some evidence that smoking can also play a role(7). Injecting drugs is considered the major risk factor for HCV infection, but there is no evidence that this risk factor significantly influences the risk of progression to cirrhosis(5).

Cohort studies suggest that people with decompensated cirrhosis secondary to HCV may have a worse prognosis than people with cirrhosis for other aetiologies. For example, the cumulative 5-year incidence of HCC in HCV-infected individuals is 17% in Western countries, compared with 8% in alcoholic cirrhosis(6).

The virus is most successfully transmitted via parenteral routes. Prior to the 1990s, routine screening of blood products was not established and therefore blood transfusions and other medical procedures were a major risk factor at that time. Infections dramatically increased in the 1980s due to the simultaneous associated increase in injecting drug use(8). Injecting drug use has remained the major risk factor for HCV transmission in the UK, and prevalence has increased ever since. The consequences of this wave of infections in the 80s and 90s are being felt currently as they progress to severe liver disease 20-30 years later if untreated. Models have estimated a two-fold increase in mortality from HCV-related liver disease in developed countries between 2000 and 2020(9). It is likely that a further major increased burden to health services will continue unless adequately addressed(8).

HCV in London

An estimated 52,000 people are thought to be infected with HCV in London, which accounts for around 25% of all cases in England(10). Total population prevalence ranges from 0.36% in Kingston upon Thames to 1.7% in Camden(10), as illustrated above in table 1.

HCV affects mainly men (70% men compared to 30% women), and younger people. New diagnoses peak in the 35 to 44 year age group, displaying a very different pattern to other chronic conditions(11).

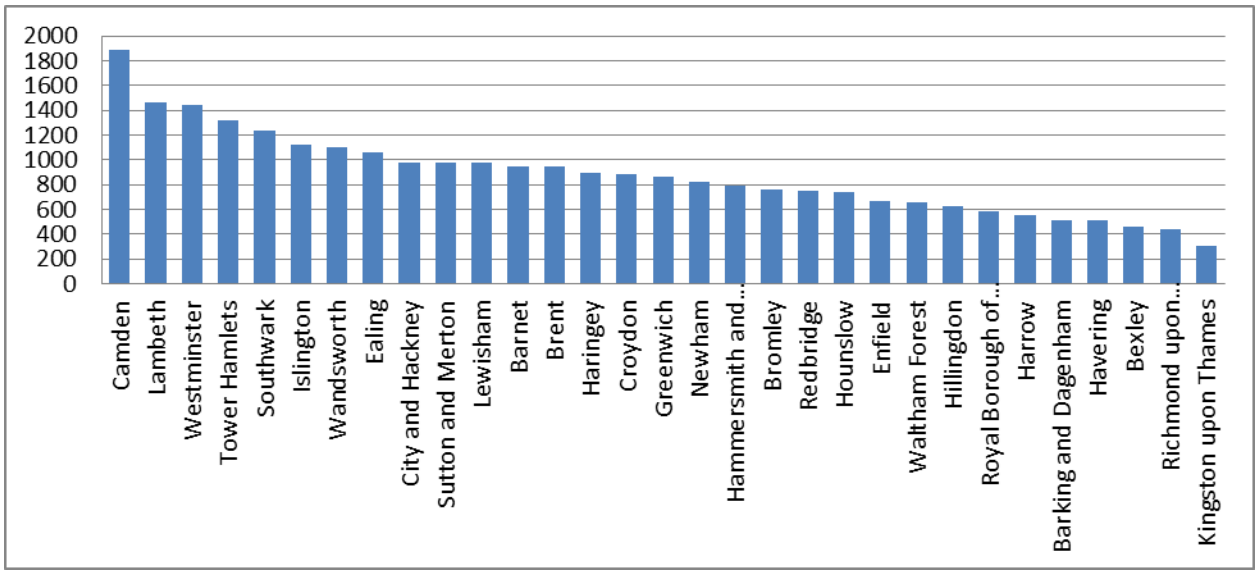
93% of cases of HCV in the UK are attributed to people who have injected drugs(3). The HPA's analysis for London considered this to be lower, at approximately 69%(11), as other factors can play a larger role here than elsewhere in the country. The second most significant risk factor for infection in London is having been born or lived in a country with a high prevalence of HCV. This accounts for 10% of cases. Individuals originating from South Asia, make up a large proportion of this group. There is an ongoing, but declining, degree of sexual transmission in HIV positive men who have sex with men (MSM). MSM transmission was a risk factor in 8% of known cases. Blood transfusion (5%), sexual, vertical infection, occupational and blood product exposure account for lower levels of HCV infection.

Incidence is widely noted as being difficult to measure for HCV, due to a long period of asymptomatic infection prior to diagnosis, and the multifarious factors that can influence the levels of diagnosis. There is a trend of a reduction in infections in younger adults, suggestive of a decline in new infections overall(11).

It is estimated that in England, Wales and Northern Ireland there are between 2 and 10 new infections for every 100 person years of intravenous drug use(12). A number of studies have found PWID to be at greatest risk of infection in their first year of infection, compared to more experienced PWID (force for infection 0.1608 and 0.0526, respectively), (13,14,15). A 2005 London-based study put the incidence of infection in the first year of injecting drug use at 41.8 cases per 100 person years(15).

60% of the 58,000 people with HCV in London are thought to be diagnosed(11). This is higher than elsewhere in the UK, where 20-40% are estimated to be diagnosed(9). Absolute estimates of people diagnosed range from 308 to 1889 in Kingston upon Thames and Camden, respectively(10).

Figure 2: Estimated absolute numbers of diagnosed cases of HCV in each London Borough, 2011(10)



As expected, while the number of tests being performed has increased between 2007 and 2011 from 32,000 to over 37,000, the proportion of those testing positive has declined to 2.3% in 2011 from 3.5% in 2007. There were over 2000 laboratory reports of confirmed HCV in London in 2011, over twice that reported in 2010. This increase is likely to be due to improvements in reporting and is reflective of diagnosis patterns rather than incidence(11).

Antibody diagnosis does not automatically equate to treatment, as there are attrition rates for referral, attendance and treatment initiation thereafter. The most recently published data from the HPA, from 2009, suggests that over 1,478 people received treatment for HCV in London that year, a small proportion of those who would benefit(11).

People who inject drugs (PWID) in London

Home Office figures indicate that there were 13,056 current PWID in London in 2011(16). The HPA estimated prevalence model (10) used 2007 data, where current PWID were estimated as 17,909 from Home Office data, which was adjusted to 37,999 on the basis of additional data. Proportionately, this would suggest that the 2011 adjusted figure is 27,700 PWID in London. This illustrates that current

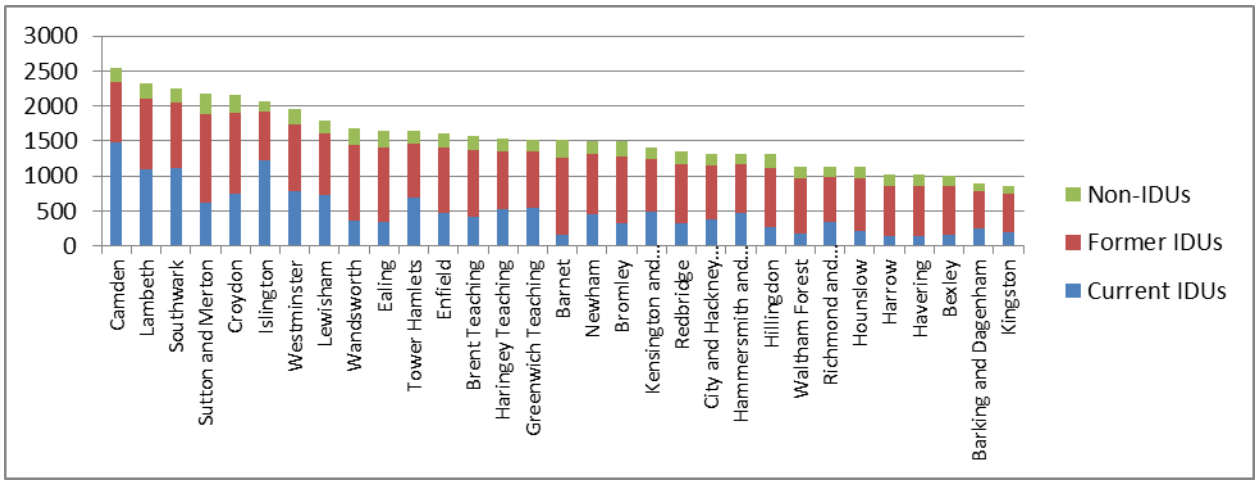
injecting drug use has dropped in more recent years, though it is unclear yet whether this is a short or long-term trend.

55% of PWID in London have HCV(10) compared to 45% in England, a figure that has remained stable for several years(11). Based on 2011 Home Office figures, and adjusting for 25% acute infections, 5386 currentPWID in London will have chronic HCV. The 2007 adjusted figures would put this figure at 15,675. The real figure is likely to sit somewhere in between. PWID inject for 11.5 years on average, putting them at ongoing risk of exposure. Based on estimates of new infections in PWID their risk of infection during their injecting career is 0.23-1.15.

Data on people who have ever injected drugs is more difficult to acquire. 2007 HPA estimates suggest there are 91,000 in London(10). This figure is less likely to have changed dramatically, as the number of PWID who have ceased since 2007 will be counterbalanced by former PWID who have been treated or died in that time. A chronic prevalence of 28% is estimated among former PWID(5) in England, and 29% in London(10). There are likely to be 26,400 former PWID in London who have chronic HCV.

Prevalence among people for whom injecting drug use is not a risk factor in London is 0.12%, accounting for the high rates in South Asian populations and MSM population. Applying the 2007 data this would estimate that 5800 people for whom injecting drug use is not a risk factor have chronic HCV in London(10).

Figure 3: Numbers of Current PWID, Former PWID and people for whom injecting drug use is not a risk factor with chronic HCV in each London borough, 2007(10)



It is estimated that a higher proportion of current PWID are diagnosed than former PWID, at 50% and 30% respectively. In London this may be higher. However, as individuals age they are increasing likely to stop injecting and so over time current PWID will become former PWID and thus the proportion of former PWID with a diagnosis will rise of its own accord without intervention(5).

Typically PWID begin their injecting career at a young age. 41% of new injectors are aged 15-19, 30% are 20-24, 16% are 25-29 and 13% are 30-54(5). This indicates the considerable impact that intervention could have on their overall quality of life and prevention of years of life lost. 50% of PWID are in receipt of opiate replacement therapy at any given time, and are in drug treatment services for an average of 9 years(5). This illustrates considerable opportunity to work with this important group.

Section 2: Baseline Survey of HCV Services for PWID in London: What is currently being done in London to address this health inequality?

In order to help shape recommendations for priority action in London, a baseline survey of current service arrangements was performed. This consisted of two surveys: one for Commissioners of drug treatment services and one for Providers of drug treatment services. A copy of these surveys can be found in Appendices B and C. Both surveys were sent to Commissioners with a request that they follow up its completion with their contracted Providers.

Commissioners' survey

24 of 33 (73%) commissioners responded to the survey, though only 14 (58%) of these respondents completed all questions. All percentages presented below will take the number of commissioners who responded to the survey as a denominator. There is no evidence to suggest that the boroughs that did not complete the survey are systematically different to those that did respond.

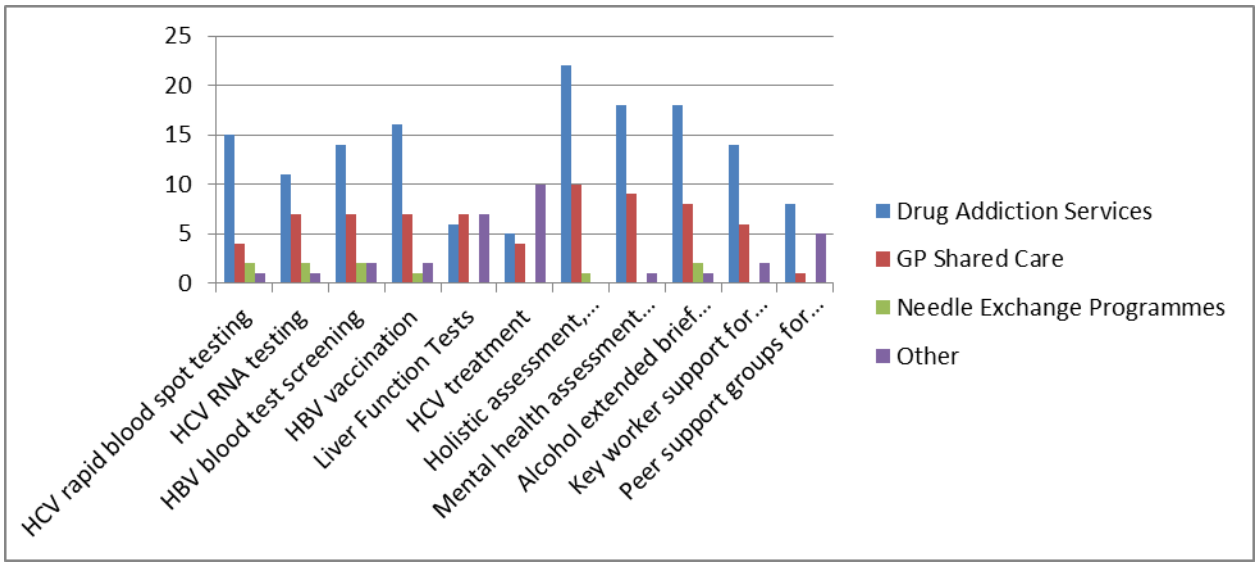
Boroughs commission a variety of drug treatment services, ranging from 1-8 different providers and averaging 3 or 4 providers per borough. Commissioning practice for GP shared care service is also variable. 13% (3/24) of boroughs do not offer GP shared care services and where it is offered practice coverage can range from one to all GP practices in the borough. One commissioner reported that HBV and HCV testing was not included under the shared care agreement. GP shared care services are typically commissioned through a Locally Enhanced Service (LES) agreement (58%, 14/24) by a different set of commissioners who sit within Commissioning Support Units. 7 (29%) commissioners indicated that their commissioned drug treatment service providers sub-commission GP shared care for the borough. 3 (13%) commissioners of drug treatment services were unable to respond to questions about GP shared care services, indicating a gap in joined up commissioning practice. From April 2013 the budget for GP shared care services will be held by Clinical Commissioning Groups and the drug treatment services budget will sit within public health in the local authority, presumably taking the sub-contracted shared care services with it. It will be for each borough to determine how it most effectively jointly commission these services.

Intelligence from the National Treatment Agency (NTA) in London suggests that needle exchange programmes are offered in all London boroughs. The survey asked which of these needle exchange programmes also offer any blood borne virus services. Needle exchange programmes are commissioned by the drug treatment commissioning team. 15 (63%) boroughs reported commissioning drug treatment services to offer, or sub-commission, needle exchange services. BBV services were included in the larger contract or, where subcontracted, detail on its inclusion was not available. 8 (33%) boroughs offer needle exchange programmes that include BBV services through pharmacies. 7 boroughs (29%) reported either not commissioning BBV services through needle exchange programmes or declined to answer this question.

7 (29%) boroughs reported having a documented patient pathway for PWID and HCV, from testing through to discharge from treatment. This differs from the findings of the HPA survey in London in 2011(11), which found that 50% of boroughs had a pathway in place.

It was clear that there is a range of practice regarding what is included in each service with drug treatment services, GP shared care, needle exchange programmes, specialist services and other services, as shown in figure 4. This is based on survey responses only and so should be interpreted with caution.

Figure 4: Number of London Boroughs reporting types of intervention delivered by each service.



This suggests that drug treatment services are further developed in providing HCV services than other services with which PWID come into contact, with the exception of HCV diagnosis and treatment where GP shared care performed slightly better. Boroughs reported more commonly referring patients to specialist hepatology services for treatment than offering HCV treatment in the community.

Dried blood spot (DBS) testing is an alternative means of testing for HCV antibodies to venous blood sampling, that has recently been recommended by NICE(18). Its appropriate application shall be discussed more fully in section 3. DBS testing was reported to be available in 63% (15/24) of drug treatment services. DBS testing is delivered in GP shared care services and needle exchanges to a much lower degree, 17% (4/24) and 8% (2/24), respectively. This survey did not capture information on venous blood sampling and so its relationship with DBS testing cannot be discussed here. In GP shared care and needle exchanges, where antibody testing is offered so are RNA PCR tests, but there are 4 fewer boroughs offering RNA PCR tests to antibody tests in drug treatment services.

HBV screening and vaccination appears to have been implemented to an equal or greater degree than HCV testing. Other services that were highlighted as offering testing and vaccination services include pharmacies and BBV specialist nurses. Best practice in holistic assessments, mental health assessment and alcohol extended brief interventions are widely implemented in drug treatment services, (92%, 75% and 75%, and 22/24, 18/24 and 18/24, respectively). However peer support groups were only reported as available through 33% (8/24) of drug treatment services, and only 21% (5/24) of boroughs indicated they offer onward referral to these groups.

58% (14/24) of boroughs who responded to the survey were able to provide an account of the mechanism employed to follow up referrals into specialist services. Of the boroughs with a mechanism in place, half (7/14) included follow up and monitoring in the remit of the BBV specialist nurse. 43% (6/14) relied on the service user's key worker to monitor outcomes of referral. One borough employed assertive outreach to increase attendance in specialist services.

There was a poor response to data requested on the number of HCV tests performed, positive diagnoses of HCV, treatment initiation, etc. This indicates that this information is not systematically requested and monitored. Half the commissioners (12/24) were able to provide information on the number of HCV tests

performed in drug treatment services in the last year, only 8% (2/24) could provide the same information for GP shared care services, and one borough provided this information for any other service. Such low numbers will have limited generalisability to London as a whole. Where it was collected, it was obtained either from the NTA national reporting database, or from the BBV specialist nurse. Annual HCV tests in drug treatment services ranged from 17 to 800, and averaged 250 per service. 50 and 91 tests were performed in GP shared care, and 333 in another unnamed service. 5 boroughs (21%) were able to report the number of positive HCV results. These positive results ranged from 19 to 186 per borough, or achieved a 13% to 82% rate of positive diagnoses based on the number of HCV tests reported as performed in each borough.

Of the 10 boroughs who reported on how laboratory services were contracted, 30% (3/10) paid for this separately and 70% (7/10) included these costs within the overarching contract so that providers bore the responsibility for them. Laboratory tests were always commissioned from the nearest hospital trust. Anecdotal reports have suggested that there is considerable variation in the prices charged by laboratories for tests. Additional costs incurred for positive diagnoses predominantly involved secondary care costs. Follow up in GP practices also had an additional cost attached in some boroughs (13%, 3/24).

HCV services are commissioned from drug treatment services by a block contract (46%, 11/24), or as one part of a larger block contract (21%, 5/24). GP shared care services were either commissioned through a block contract or as part of larger block contract in 21% (5/24) of boroughs, by tariff in 17% of boroughs (4/24) and without a contract in 8% (2/24) boroughs. Combined with a lack of monitoring data, block contracts offer little incentive to increase testing and treatment rates for HCV.

Providers' survey

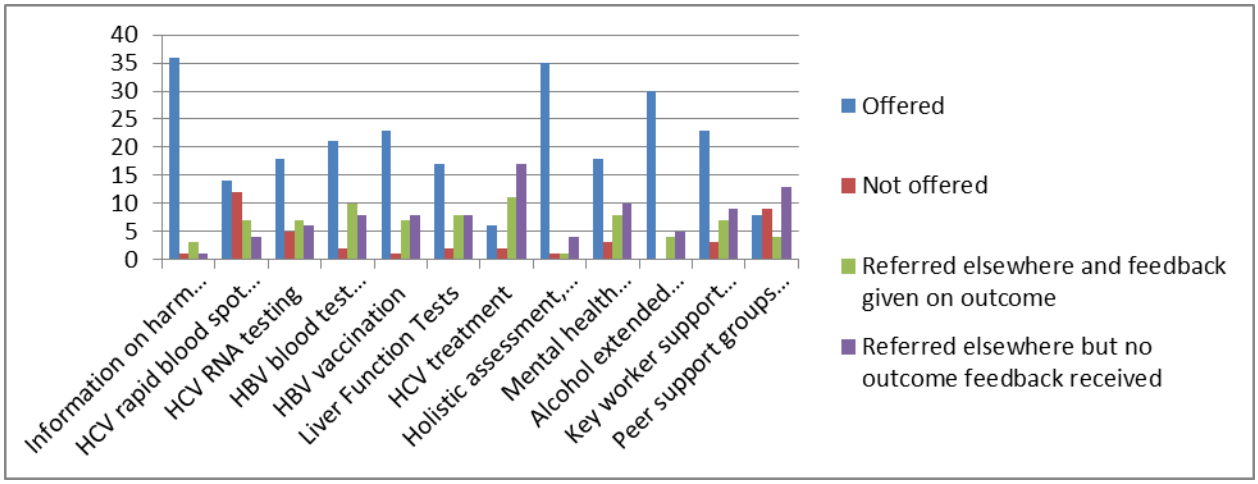
There were 38 responses to the provider survey, covering 21 of the 33 (64%) London boroughs. This compares to 87 drug treatment service providers identified by the 24 commissioners who responded to the above survey, which would equate to an approximate 115 drug treatment services across London, and a 33% (38/115) response rate. The majority of providers who responded were based in boroughs where the commissioners had also replied to the survey. There were 5 boroughs in which at least one provider responded when the commissioner did not answer the survey, and there were 8 boroughs where the commissioner responded and the provider did not. In 4 boroughs there was no response from the commissioner or provider. The number of drug treatment service providers who responded per borough ranged from 0 to 3.

32% (12/38) of providers reported having a documented patient pathway in place for PWID and HCV, from testing through to discharge from treatment, of which their service is part. These responses covered 9 boroughs, or 57% (9/21) of the boroughs where there was a provider response. These responses tended to match the responses given by commissioners, but in 2/9 (22%) of these borough responses, one but not all providers indicated that they were aware of the pathway.

The most common source of referral for HCV testing at drug treatment services was self-referral, with 68% (26/38) of services reporting this means of referral. The next most common source of referral was from criminal justice services among 61% (23/38) of services. This was followed by GP referral in 47% (18/38) of services. 39% (15/38) of services reported receiving referral from needle exchanges or extended alcohol intervention services, and 18% (7/38) of referrals came from other drug treatment services. 16% (6/38) of drug treatment services reported not receiving referrals that include HCV testing and follow up.

It was clear that there is a range of practice regarding the types of intervention that are offered by drug treatment services in London, what is referred elsewhere and whether any feedback is received in respect to these referrals, as shown in figure 5.

Figure 5: Number of drug treatment services reporting offering and/or referring types of intervention.



The interventions cited here are predominantly delivered in drug treatment services. The exception to this is HCV treatment, which is more commonly referred elsewhere. More often than not feedback is not received on the outcome of this referral. A third of all services do not offer or refer to peer support groups. The vast majority of drug treatment services offer information on harm reduction (95%, 36/38), conduct holistic assessments, including housing status and social needs (92%, 35/38), provide alcohol extended brief interventions (79%, 30/38) and offer key worker support to clients (61%, 23/38). In terms of BBV services, there is varied practice. Only 37% (14/38) of services offer DBS testing, compared to 47% (18/38) who offer PCR RNA tests. 55% (21/38) and 61% (23/38) of services offer HBV blood tests and HBV vaccinations, respectively, indicating that the clinical expertise exists to increase the level of HCV testing offered in London.

66% (25/38) of services offer HCV testing on entry to the service. 18% (7/38) of services have an ad hoc testing policy in place, whereas 11% (4/38) and 5% (2/38) have six monthly and annual testing policies in place. 24% (9/38) of services reported having outreach testing services in place, and this was largely through partnership arrangements with other drug treatment services or GP shared care in the borough. The most common reason that services gave for clients refusing treatment was that they did not consider the test relevant to them. Other common reasons given included: clients preferring to be tested at a later time, a test having been carried out recently and fear of results, in that order. 11% (4/38) of services did not record reasons for refusal.

Even where drug treatment services did not offer HCV treatment themselves, many screened clients for suitability for treatment prior to referring them elsewhere. The most common exclusion criteria cited by drug treatment services were being alcohol dependent, currently injecting drugs and displaying medical contraindication to interferon or ribavirin. 55% (21/38) of services allowed the decision to be made elsewhere as to whether the person was suitable for treatment initiation.

9/38 of services (24% of services) covering 7 boroughs (33% of boroughs) reported having the active involvement of a Hepatologist in their service. 71% (5/7) who worked closely with a Hepatologist also had a pathway in place. 58% (22/38) of services have nurse support as part of their staff establishment. 66%

(25/38) have a nominated person who is responsible for liaising with HCV treatment centres. 34% (13/38) have a nominated person to liaise with the prison services, and 50% (19/38) have a lead for liaison with primary care services.

45% (17/38) of services reported BBV being included as one component of a larger block contract. It is therefore difficult to determine how much is spent on BBV service delivery in London, nor how much emphasis on HCV is contractually applied to services. 34% (13/38) of services subcontract laboratory services to their closest hospital laboratory and the remainder did not report subcontracting any aspect of their service. 89% (34/38) of services monitor patient satisfaction, mainly though questionnaires.

The majority of services (63%, 24/38) were able to enumerate the number of PWID known to their service. The figure ranged from 0 to 1500 PWID, averaging 190 per service. Only 45% (17/38) were able to provide any supplementary data. This indicated that on average 125 people per service had HCV, or 66% (125/190) of PWID known to drug treatment services have HCV. On average, each service offered 242 (3392/14) HCV tests per year, of which 137 (2056/15) per service were performed. This equates to an average uptake rate of HCV testing of 57% (137/242).

A total of 438 HCV positive results were reported from drug treatment services, from the 11 services who were able to report this information, or 40 HCV positive results per service. 116 people were reported as having initiated treatment in these 11 services in the last 12 months, or 26% (116/438) of those with a positive HCV result. Two services reported there being very long waits for treatment currently, resulting in none of these patients being referred to secondary care actually receiving treatment in the last 12 months. 2 of these 11 (18%) services stated that HCV treatment was offered as an integrated part of the drug treatment services. Among the remaining 11 services who record this information, 143 referrals were made to secondary care over a 12 months period, and 40 of these initiated treatment (28% of all referrals made). The data reported was from a small proportion of drug treatment services so their generalisability is limited and should not be applied outside this sample.

Only 45% (17/38) of services reported any staff having received training in HCV management. 16% (14/89) of staff receiving training completed the RCGP Certificate in the Detection, Management of Hepatitis B and C in Primary Care, whereas the remaining staff completed what they considered to be an equivalent form of training.

Conclusions

The survey was designed prior to NICE guidelines being published in December 2012(18). Whilst there is not total coverage of NICE recommendations within the questions asked by the survey, we are able to comment on the level of provision of some of the recommendations across London currently.

A key recommendation is to offer and promote hepatitis B virus (HBV) and HCV testing and HBV vaccination to all PWID in drug treatment services. It further promotes the offer of an annual test to people who remain at risk of infection. The existence of a testing-to-treatment pathway is one way to standardise this process and reduce the possibility of individuals slipping through gaps in service delivery. We have seen that there are some discrepancies between commissioners' and providers' opinions as to whether there is a pathway in place, and at best only 29% of boroughs have a pathway in place. Pathway development and its communication is a gap for the majority of boroughs. 66% of drug treatment services stated that a HCV test was offered on entry to the service, 16% offered annual or six monthly HCV testing to people known to their service. 55% (21/38) of drug treatment services in London offered HBV testing and 61% (23/38) offered HBV vaccinations. Universal provision of tests, vaccines and annual

reviews should be a goal for London. A systematic and regular testing programme may help to normalise HCV for PWID; good information and patient consent will help build and maintain trust between staff and service users.

Responses to the provider survey indicate that there is already a strong link with criminal justice services in the majority of boroughs, with 61% of services receiving referrals from criminal justice services. There is opportunity to capitalise on this partnership working by embedding HCV testing and follow up in this pathway.

NICE guidance states that all drug treatment services should have access to DBS testing. Only 37% of drug treatment services reported offering this service, a surprisingly low number that was contrary to the responses of commissioners who considered this to be available in 63% of drug treatment services. This may highlight the discrepancy between staff who are technically able to be trained to deliver DBS testing and those actually willing to do it. We identified 58% of services as having nursing staff. These staff should be trained in the delivery of BBV testing, which could relieve some of the pressure on BBV nurses and, importantly, reduce the number of appointments that service users need to have for HCV testing.

NICE guidance recommends that drug treatment services should designate a hepatitis lead. 66% of services reported having a designated lead within the service, responsible for liaising with hepatology services, and 24% of services had the direct involvement of a Hepatologist in the service (though treatment was only delivered within the community in only 5% of services). It is stated in the guidelines that the lead should have sufficient knowledge and skills to promote HCV testing for the service, and discuss treatment concerns with PWID. We are unable to comment on the role of the HCV treatment link person and their involvement in providing information on HCV to service users. As a proxy, however, we can say that staff in only 45% of services have had any training on HCV, which could be improved.

With only 33% of boroughs commissioning BBV services as part of needle exchange programmes through pharmacies, there is scope to increase access to this across London boroughs and to include DBS testing here. 24% (9/38) of services reported having outreach testing services in place, and this was largely through partnership arrangements with other drug treatment services or GP shared care in the borough. One borough used their outreach service to ensure treatment compliance. This is a gold standard approach and whilst not a priority for most services at this stage is a desirable long-term goal for high quality HCV management and care. Other evidence-based means of promoting treatment compliance is through peer support groups, which are currently offered or signposted in only 54% of boroughs.

The surveys have identified some gaps in knowledge sharing. This includes regular audit and monitoring of HCV tests, diagnosis, referral and treatment outcomes, and commissioners in drug treatment services being aware of what is happening in GP shared care services. There is opportunity for these gaps to be addressed through knowledge sharing and monitoring at the Health and Wellbeing Board. Public health will be well-positioned, with the commissioning of drug treatment services moving under their remit, and their statutory responsibility to provide public health advice to CCGs.

Section 3: Best Practice: What more needs to be done?

This section explores best practice recommendations for the delivery of HCV management and care in PWID. Overwhelmingly, the evidence shows that while there are certain principles that will lead to higher quality service delivery and therefore better outcomes for patients, there is no 'one size fits all' model of care. Different boroughs in London have different models of service delivery and commissioning arrangements, which will influence what is appropriate to recommend for that area. As a group, PWID often have a number of complex and competing priorities to their long term health and so, again, a tight algorithm for testing and treating individuals will not be responsive to their situation.

In November 2011, the LJWG published its consensus document(20). The recommendations published therein should be viewed as an aspirational standard for HCV testing and treatment based on expert opinion. This chapter reviews available literature to suggest practical steps that providers and commissioners can take to improve the management of HCV in PWID across London.

Prevention

While treating existing cases of HCV is one way of reducing the spread of infection, there are other strategies for the prevention of HCV. Incidence is an important measure of the effect of policy changes on underlying transmission rates. A reduction of up to 80% in incident infection is thought to be required to control the HCV epidemic(6).

Communicable disease control programmes often pursue new or recent cases of infection in order to identify and control source(s) of infection through contact tracing. NICE does not recommend contact tracing for HCV due to the low transmission rates to both sexual and household contacts. One case series suggested that whilst PWID were comfortable referring injecting partners, a low proportion of these referrals resulted in the injecting partner being tested for HCV(18). Rather, it was deemed good practice to have a discussion with the infected individual about any close contacts who may have been exposed to infection.

Multiple studies have demonstrated the value of multi-component prevention programmes for HCV. A 2010 systematic review provided tentative evidence that opiate substitution treatment (OST) programmes have limited effectiveness in reducing HCV transmission, and insufficient evidence to suggest that needle and syringe exchange programmes (NSPs) and drug consumption rooms (DCRs) have any impact on HCV transmission. However, there was tentative evidence to suggest that pharmacy access, in addition to primary NSP, is effective in reducing injecting risk behaviour(38). A subsequent 2011 study pooled UK data to investigate the impact of OST and high coverage NSP (where PWID have more needles and syringes than needed) on HCV transmission. After adjustment for confounding factors, (gender, homelessness and crack use,) exposure to high NSP coverage and OST approximately halved the risk of HCV infection and the study concluded that OST and NST in combination could reduce HCV incidence by up to 80%(39). A 2012 mathematical modelling study extended such findings further. Taking the UK average baseline of 40% chronic HCV prevalence among PWID, OST and 100%NSP was scaled up from 0% to 20% coverage and was found to reduce HCV prevalence by 13% after 10 years(40). This body of evidence indicates that multi-component prevention interventions are required to lower HCV incidence and prevalence.

A qualitative review of PWID's attitudes and perspectives to HCV, found there was some confusion about the various forms of hepatitis, how it is transmitted and what symptoms are involved. This confusion is compounded by the perception that expert and scientific opinion on HCV is shifting and uncertain. HCV is often viewed in relation to HIV, and its seriousness is thereby trivialised. These beliefs appear to play a role in how PWID perceive their risk of acquiring HCV. They may perceive themselves as never being completely safe from or in control of HCV transmission. They may take steps to minimise risk of transmission through safe injecting practices, though it was not clear whether this extended to injecting paraphernalia. Many PWID found it difficult to consistently employ harm reduction strategies due to trusting injecting relations, uncontrolled drug use, restricted access to needles at certain times, prison settings, homelessness, policing and gender(37).

Awareness raising campaigns both for the general population and for people at increased risk of infection are considered fundamental to successfully promoting and offering HCV testing. Reported approaches include leaflet and poster distribution, education programmes, media campaigns, social marketing and incentives for people participating in screening programmes(23). Guidance promotes the inclusion of groups at increased risk of infection in the design of materials and delivering of awareness-raising activities, and for these activities to take place in venues and at events that are popular with these groups(18). One study found that a peer outreach worker offering testing and education to PWID had a positive impact on knowledge and understanding of HCV transmission(37).

To summarise, the evidence suggests that commissioners should focus on a multi-component approach to HCV prevention. This includes making contact count with people who have chronic HCV bys discussing safe injecting practices and close contacts at risk of infection. OST and NSP programmes in the community should be provided. These interventions could be supported by an awareness campaign to dispel myths and improve understanding of HCV.

Care Pathways

NICE guidance recommends that Commissioners ensure that a local pathway is in place for HCV testing and treatment from drug treatment services. Where possible this should include provision of treatment services in the community(18). A sample HCV testing and treatment pathway is provided in appendix E for local adaptation.

The traditional testing and treatment pathway from drug treatment services would involve an initial discussion about testing, information-giving session and access to or signposting to harm reduction programmes. If the individual accepts testing, a blood sample would be taken by a clinically trained member of staff. Typically this would be on a BBV nurse who runs a clinic in the drug treatment service, or they would be directed to their GP if this service is not offered. This first sample would be sent to the laboratory of the nearest secondary care trust for antibody testing. Results are fed back to the individual by the same service that performed the blood test. A follow up RNA PCR test is required to confirm chronic HCV but this would normally be performed in secondary care services. As part of the feedback of a positive antibody result, a discussion of referral to secondary care or specialist services would take place and, if accepted, a referral made.

Individuals are then expected to attend an appointment in secondary care for this RNA PCR test. If this is positive an assessment would be made of the state of their liver and a discussion of treatment options. Generally treatment initiation decisions are based on individual choice, whether clinicians consider lifestyle and drug and alcohol intake to be sufficiently stable to comply with treatment, and whether

there are any physical or mental health issues that would contraindicate the recommended medications. During treatment individuals will be required to attend weekly appointments for injections and other follow up.

The most complete dataset of attrition rates along the HCV pathway was produced by the Trent study group, taking a two-year cohort from 2000-2002(34). This showed that of people with a positive RNA PCR test, 49% were referred for further treatment, 27% attended an appointment, 17% had a liver biopsy, 10% were treated and 5% had a SVR and were therefore considered cured.

Additional support services, such as key worker monitoring and counselling, or peer support groups can assist with treatment compliance. Some areas have introduced more integrated services where treatment is delivered in the community through drug treatment services and so referral into secondary care is not required. This is an important consideration and will be discussed later in this section.

Types of HCV testing

Venous blood sampling is the preferred means of testing for HCV as it offers the most accurate and low cost results. However, a venous blood sample can only be taken by clinically trained professionals. Opportunities to offer HCV testing to people at risk of HCV are probably missed when a system relies on appointments or availability of staff trained in venepuncture. In theory offering DBS testing or oral fluid testing should increase uptake by enabling professionals not trained in phlebotomy to offer the test in a range of settings.

In Haringey funding for DBS testing came from the Drug and Alcohol Team (DAT) pooled treatment budget, which is ring-fenced money allocated to DAT. A staff member reported that their experience was that although substance misuse workers were trained to offer DBS testing, they remained reluctant to offer the test to clients and were unwilling to give test results. Consequently in most Haringey services DBS is offered by clinical staff only; apart from one site where they do not have access to nursing staff (this service is for clients who use crack and powder cocaine). In this service the team leader is very committed to the idea of opportunistic BBV testing and DBS is widely used by non-clinical staff.

This also appears to have been the experience of the Nottinghamshire DBS Pathfinder Project (45) in which there was a lack of ‘buy in’ amongst drug service manager and drug workers; these issues had not been anticipated prior to the project starting. Once the initial project failed to flourish, renewed promotion of the project with refresh training rectified this in some services but not all and was thought to possibly reflect the commitment of some services managers to the project. Some drug workers emerged as ‘champions’ of the intervention. The Pathfinder Project evaluation recommended that DBS should complement and not replace venous blood sampling and be used by drug workers on clients who are unwilling or unable to be tested using a venous blood sample.

In England, testing is mainly provided through the provision of BBV nurse outreach services in a range of community settings, including community drug treatment services. Other clinical staff could be trained to perform this test in order that only more complex referrals were referred to the more finite resource of a BBV nurse in drug treatment service settings. Increasing the number of staff who can perform this test has had the knock on effect of increasing the number of venues in which testing can be performed. There is encouraging evidence form pilot sites in community pharmacies to show the feasibility of providing dried spot testing to PWID(18).

Concerns over DBS testing include related issue of reduced sensitivity of DBS tests and the availability of laboratory testing. A detailed, unpublished, analysis of the relative costs and accuracy of HCV tests was conducted by the North East North Central London Health Protection Unit (NENCL HPU) (24) is provided as appendix D (this includes further discussion of diagnostic tests, for which there is no accredited approach currently, for those interested). It illustrates that DBS testing is less sensitive than venous blood sampling, and the latter should therefore always be employed in preference where possible. HCV antibody testing of oral fluid is a further option. These tests are considered to be less accurate than serology samples, but have the added advantage of being easily conducted by non-clinical staff in outreach services. However, a blood sample would be required to confirm a positive antibody result (18). As such, HPA records charter a phased sample collection from oral fluid to DBS testing between 2009 and 2011 (12).

Due to the high cost of PCR testing, it is only performed once a positive antibody test has first been returned. One London laboratory reported in conversation that separate samples are required for the ELISA and PCR RNA tests to avoid cross contamination, and that laboratories in London are not configured to be able to easily receive two samples and store one in case needed for a subsequent test. Therefore blood samples for each test are typically taken on two separate occasions, which fits in with traditional patient pathways where PCR RNA tests are conducted in specialist hepatology services. Laboratories in Manchester have developed a technique to perform an ELISA and PCR RNA test on the same blood spot sample. This requires a highly meticulous procedure to avoid cross-contamination, and a full evaluation of the accuracy of the results has not been completed. A review of services across England indicated that over half of all testing procedures have been modified so that a second sample is no longer required(23). A review of practice in London may be beneficial.

Location of HCV Testing

The proportion of tests returning a positive result varies considerably according to setting. Drug treatment services account for around 2% of all tests done overall, but 27% of tests return a positive result. This compares with GP services that account for 27% of all tests, only 3.6% of which test positive(11). Given the relative current levels of testing and positive results, the providers survey (section 5) has chosen to focus on drug treatment services with a view to increasing testing in that setting.

The same study also disaggregated these figures for source of original referral. 21.8% of all anti-HCV tests were sent by secondary care, 23.8% from drug and alcohol services, and 21.8% and 14.8% from general practice and prisons respectively. The outcome of these tests is reported in table 3. The further down the table, the smaller the numbers involved and therefore the wider the confidence intervals will be(34).

Table 3: Proportion (%) of patients arriving in each stage of the pathway, based on setting of referral

	General Practice	Drug and Alcohol Services	Prisons	Secondary Care
HCV positive patients referred to specialist care	66.1%	42.6%	18.4%	54.5%
Patients who were referred who attend	78.1%	47.4%	100%	74.4%

Key motivators for testing, as identified by PWID, were convenient and opportunistic testing and a good relationship with health professionals built on trust and rapport. Support and encouragement from health

professionals also facilitated engagement with the testing process in the first place. Education around testing, alternatives to venepuncture and follow up and treatment options also helped to allay anxiety(37). NICE guidance recommends that peer mentors and health champions are trained from drug treatment services to promote and support HCV testing(18). This directly alleviates fear of isolation and social exclusion.

Given that building rapport between staff and clients, and providing clear and accurate information about HCV are key to encouraging testing among PWID, the low level of awareness among staff is of concern. Educational interventions for practitioners were shown to have positive short-term impacts on knowledge of HCV, as shown over three studies. A UK study showed poor attendance at training sessions among healthcare professionals and no clear evidence of an improvement in HCV management resulting from training(42). A review of services across England showed that efforts to improve knowledge and awareness among primary care professionals, primarily GPs, do not appear to have been extensively implemented(23).

Drug treatment services

PWID who are in contact with drug treatment services should form a key target group for HCV testing and treatment referral in any borough strategy for a number of reasons. Since this group is often still injecting, they continue to pose a risk to others through unsafe injecting practices. A qualitative study found that PWID who proactively requested testing for HCV tended to be more controlled in their drug use, (a frequently reported requirement for treatment initiation,) and be more integrated within mainstream society(37). Incidentally, this was also shown to play a protective role in the risk of re-infection following successful treatment. They are also already in regular contact with a service which would facilitate follow up.

A 2-year retrospective observational study of HCV treatment in an Opiate Substitution Therapy (OST) Programme in New York showed that an assertive testing and treatment programme for PWID was feasible in this setting. HCV testing was easily achieved as part of the OST programme, (99% uptake of HCV antibody testing). The embedded service resulted in 25% of PWID with HCV initiating HCV treatment, though they still remained prone to many of the common reasons for drop-out, such as contraindications and personal preference(43). An evidence review in Italy found that opiate maintenance therapy for opiate-using PWID reduced re-infection and transmission of the disease. PWID who remained poorly integrated socially remained at increased risk of re-infection(44).

The opportunities that drug treatment services present are discussed further under ‘Integrated services’.

General Practice

NICE guidance recommends that GPs and practice nurses offer HCV testing to adults and children at increased risk of infection, including migrants from medium and high-prevalence countries, and current and former PWID. Where there is continued risk of infection, people who test negative for HCV should be re-tested on an annual basis. New registration consultations should include questions on whether the individual has ever injected drugs. GPs and practice nurses should also take responsibility for ensuring that patients with positive test results are referred to specialist services(18).

The literature indicated that the most common intervention available for the identification of HCV in former PWID was through testing in GP practices. Two UK studies have found that targeted case finding in primary care, by reviewing patient records for any patient with a history of injecting drug use, increased the number of patients offered and accepting a test. There was a mixed impact on patients starting

treatment as a result of this test and referral and it was felt that further support may be required for these patients to address adverse socioeconomic and family circumstances in order to improve attendance at appointments and follow-up services(42). In some models, such as Lewisham, a service hub is provided for a cluster of GP practices as their model of shared care. The GPs prescribe the appropriate treatments, but psychosocial support and other means of follow up are provided through the service hub.

The NICE economic analysis(5) considered an intervention combining GP education with GP remuneration for the testing of former PWID in the age range 30-54, which was found to be cost-effective at an estimated £13,900 per QALY gained at a baseline of 30% diagnosis. The average cost per test of this intervention was £193.13, taking into account GP education sessions, informing eligible patients and providing a £100-per-test reimbursement. The introduction of this intervention resulted in a 3.4-fold (1.57, 7.37) increase in rates of testing, and doubled the number of positive test results. Higher rates of testing were associated with increased diagnosis and were more cost-effective. To promote cost-effectiveness LES contracts could offer stepped levels of remuneration, such as £80 for each test up to 30% of former PWID, £100 for up to 50% of former PWID, and so on.

The provision of patient information in GP waiting rooms has been associated with an increase in patient requests for testing, but this did not translate to an increase in overall numbers being tested(42). Targeted and systematic testing is therefore the more effective approach to increased diagnosis.

Targeting recent initiators of injectable drugs

Recent initiators of injectable drugs are at increased risk of infection. However, PWID do not typically come into contact with drug treatment services until a later stage in their injecting career. It may be necessary therefore to think creatively about capitalising on opportunities when this group may come into contact with services. GP services receive all types of patient and should be alert to the signs and symptoms of HCV infection.

The Drug Interventions Programme identifies drug users when they first come into contact with the criminal justice system and follows them through their individual journey to release and management in the community. Drug testing on arrest is part of this programme and is implemented intensively within London (22/33 London boroughs to date, with all participating from March 2013) with legal sanctions for those unwilling to address their drug misuse and drug-related offending. Any offenders found positive are referred into a drug intervention or harm reduction programme. This may prove a key opportunity for identifying individuals in their first year of injecting drugs and offering them testing and treatment for HCV. Criminal Justice Liaison and Divergence nurses are based within this service and could be commissioned to offer testing.

Prisons

This report does not consider prison health in great detail due to the complex arrangements that are unique to this setting. Access to care is influenced by security arrangements and this will have a significant impact on the cost of treatment. Imprisonment is viewed by health practitioners as both a barrier to and facilitator of HCV management. Institutional barriers include long waiting times, lack of information provision, provision of detoxification and withdrawal, and prison transfers. Personal issues focused on stigma, lack of motivation and concerns about confidentiality. However, the structured environment of a prison may support appointment attendance and treatment compliance, and the availability of peer support during treatment was considered beneficial(42).

The introduction of DBS in prisons was not considered cost effective, and did not result in a statistically significant increase in rates of testing. The incremental cost effectiveness ratio (ICER) was estimated at £59,400 per QALY gained, where it was assumed that there was no continuity of care when an individual entered or left prison. The average cost per test was £66.27, including training and coordination costs. Insufficient data currently exists on levels of continuity of care, treatment initiation and completion rates, and SVR rates in prisons. However, models indicate that the ICER was extremely sensitive to continuity of care, which needs to be in place for at least 40% of prisoners for DBS in prisons to be a cost effective intervention(5).

Reported testing in prisons is poor, with less that 4% of new receptions having a record of having been tested. A 2009 audit in HMP Leeds found that 24% of those diagnosed were treated(5). Prisoners are frequently transferred between prisons or released before HCV test results have been received or acted on. Medical records do not always follow the prisoner. The Nottingham Trent study found that prisons have a high prevalence of HCV, a low referral rate into specialist care but a 100% attendance rate of those referred. It has been suggested that one option to address these problems would be to delay prison transfer until the results of HCV tests had been received and a management plan agreed with the prisoner(34).

Within the prison setting it can be seen that HCV testing and treatment interventions will only be cost-effective once the issue of continuity of care has been addressed. This is a wider issue, affecting a number of different health care issues, and should therefore form priority action in these institutions.

Referral to specialist services

The literature found that referrals to and attendance at specialist hepatology services were dependent on whether there was trust in the service. The perspectives of both the referring service, and the service user were important.

The view among many drug service providers was that hospital consultants consider their clients unsuitable for treatment. Our survey suggested that 45% of drug treatment services provided these restrictions themselves.

Some service users reported judgemental experiences with hospital doctors who based their treatment decision on the notion of stability, and whether they perceived the PWID as able to adhere to the treatment regimen. Stability is a notion that is hard to gauge in an individual, however standardisation of eligibility criteria for treatment, particularly in light of the new treatments due to be available in the next few years, would assist in discussions with patients and help build a supportive and trusting relationship. Several service users reported being given conflicting information from different providers about whether or not they could access treatment, and few reported being able to discuss or question the criteria presented to them. This led to distrust of providers among the service users, with several reporting that they thought these decisions were based on financial pressures rather than concern for their welfare(35).

Treatment uptake and compliance

A key motivator to seek treatment is when people with HCV start experiencing symptoms. However, earlier identification and treatment is associated with better sustained virological response (SVR) and lower health care costs. Increasing PWID's knowledge about HCV, at all stages along the pathway, encouraged PWID to consider their treatment options. Support from family members, partners and peers also proved motivational for engagement with treatment. In the absence of this support, and preferably in addition to it, perceiving health professionals to be supportive, concerned and caring also motivated

individuals to engage in treatment(37). One study has found that attending a mandatory HCV education session prior to attending a hepatology clinic was associated with short-term impacts on knowledge of HCV among patients. This was maintained in the medium-term and increased the patient's interest in treatment. It was further shown to increase attendance at specialist hepatology services(42).

An appointments-based system and long waiting times in an unfamiliar environment, such as secondary care, are considered to reduce attendance. Reasons given for this were the anxiety this generates, and the physical discomfort of not having access to drugs during this time. Referring drug treatment services can counter these concerns by supporting the PWID to prepare for their hospital visit and to manage their expectations. Strategies that involved a nurse accompanying the patient for their first appointment proved too resource intensive to be sustainable. Appointment reminders and larger timeslots for drop-ins were additional solutions suggested by PWID(35).

Major depression, bipolar disorders and anxiety disorders are considered high among PWID and may be even higher among those who are HCV-infected. Treatment of HCV is associated with neuropsychiatric adverse effects, which must be addressed with the patient. However, past episodes of psychiatric disorders are not absolute contraindications for treatment, and can be proactively managed to optimise treatment compliance. Strong links with mental health services, whether on-site or in the community, are an essential component of comprehensive health programmes for PWID and are particularly important during treatment for HCV(44). Our survey suggests that mental health assessment is included in 47% of drug treatment services in London.

Attendance at a weekly support group has been shown to increase treatment initiation and compliance. Self-referral to specialist services is also associated with increased attendance and compliance as compared to those who are referred by their GP or key worker(42).

Service Integration

Integrated services are defined as where HCV treatment is offered, along with other BBV treatment, within drug treatment services. BBV nurses attending services to provide testing for HCV are not considered to qualify as an integrated service if not delivered alongside treatment services as well. Examples of this model of service provision in London include Tower Hamlets and Lewisham.

Antiviral therapy has not been consistently and systematically offered to the PWID population(6). The hospital-based setting is an evidenced barrier to HCV treatment among PWID(35). Multi-disciplinary or shared care approaches, delivered within community settings such as mental health programmes, drug treatment services and opiate substitution clinics, and targeting PWID are associated with higher uptake of both testing and treatment, to a degree that is comparable with the general population(25, 28, 42). These services were also seen as useful in providing information about HCV treatment to encourage engagement with HCV services(37).

A cohort study in Tayside described a service transformation from a traditional primary to secondary care referral pathway to a rapid nurse-led service delivering antiviral therapy that was located in both the hospital and the community setting, including drug treatment services and prisons. The model utilizes existing staff working in a smarter way and minimising additional costs (apart from the travel costs associated with outreach work). The care pathway was patient-focussed, such that patients receiving drug addiction treatment had HCV treatment built into their care plan, removing the need to access other services and building on the relationship with the key worker. This transformation resulted in a significantly increased number of patients receiving HCV treatment, of which many were in the early

stages of drug addiction treatment. This increased demand meant that a 0.5wte. nurse needed to be employed in order to deal with the increased workload(29).

A qualitative review of two undisclosed sites in London described community-based partnership as having been developed in response to high DNA rates among PWID in hospital settings. An appointment-based clinic alongside a drop-in service, both co-located with drug treatment services, proved popular among service users. Providing service users with the phone number of the clinic nurse also meant that they could cancel appointment and reschedule if needed. Generally appointments were overbooked in the knowledge that attendance rates would be low. The following structural elements were reported as important to their success. An integrated service is ideally provided by nurses with a wide range of experience above Agenda for Change band 7. In addition to nursing experience, experience of working with PWID was very important to ensure understanding of the issues they face, not only medical issues. Conversely it is also important for drug and alcohol workers to have a basic understanding of HCV to support promotion of testing, to accurately answer any queries from service users and to monitor people in receipt of HCV treatment(35).

Integrated models of care would have difficulty complying with a 'one size fits all' recommendation. Configurations needed to be sufficiently flexible to suit the environment in which they operate, or at least be prepared to undergo a cultural shift in readiness for a new model of care. When introducing BBV services, staff need to be prepared to adapt to the needs of an unorthodox group of patients, by, for example, taking blood from unusual sites on the body due to small veins found in long-term PWID. It should be acknowledged that bringing hepatology clinics out of secondary care is not a practical arrangement for all localities, and alternative recommendations for these areas have been provided above.

Commissioning arrangements

The key to ensuring the adoption of best practice HCV care for PWID is twofold: by commissioning each element from the right pots of money, and by securing commitment from commissioners and providers from all parts of the service to its success. Drug treatment services have a number of competing partnership priorities, such as with the police and criminal justice sector, family services, as well as health services. Its ring-fenced funding comes to an end in April 2013, after which there may be increasing political pressure to fund programmes in each of these partnership areas, of which BBV testing and treatment is one small area of many. It is not always possible to fund all services to the degree commissioners would like, which can lead to some politically contentious decision-making. Each area will need to consider how best to jointly commission services that include BBV testing and HCV treatment of PWID. Some areas have already been proactively pooling budgets in order to meet shared aims.

There is an argument to be made that the budgets that would otherwise bear the burden of the health care costs associated with end-stage liver disease should be the ones who fund increased testing and treatment in order to prevent advanced liver disease. From April 2013 these budgets will be the responsibility of CCGs, with accountability to the NHS Commissioning Board.

The NHS Outcomes Framework 2013/14 forms the mandate for the NHS Commissioning Board to uphold health outcomes. These outcomes fall into five domains, three of which are pertinent to the commissioning of HCV services for PWID. Domain 1: Preventing people from dying prematurely is of particular importance in light of the CMO's annual report highlighting the growing rate of premature deaths from liver cancer. Our economic model suggests that the average person who starts injecting

drugs at age 21 will be dead at the age of 66, 9 years younger than the 75 year cut-off point for premature mortality. Domain 3: Helping people recover from episodes of ill-health or following injury has a particular focus on psychological therapies. Mental health is a common comorbidity and is integral to drug treatment services, and must be fully integrated into HCV treatment to avoid unpleasant side effects. HCV treatment often forms part of the recovery process from chaotic drug taking, and the behaviour change process must take psychological impact into account here. Domain 4: Ensuring people have a positive experience of care has two cornerstones of patient satisfaction and integrated care. We saw that 89% of services include ascertaining patient satisfaction as part of their service. The best practice review highlights integrated care as a pivotal way of ensuring that people do not slip through the gaps in the patient pathway. This illustrates how commissioning of HCV testing and treatment for PWID is fundamental for NHS Commissioners to achieve their mandated responsibilities.

NICE guidance stipulates the inclusion of HCV in the Health and Wellbeing Board's Joint Strategic Needs Assessment (JSNA), as a responsibility for Directors of Public Health and Clinical Commissioning Groups to uphold. In areas where there is a higher than average number of people at increased risk of HCV, Commissioners should encourage the development of Locally Enhanced Services with general practices(18).

NICE recommends a minimum dataset for commissioners, and public health colleagues, to collect and audit:

- The number of people tested for HCV
- The number of people diagnosed with HCV
- The number of people with chronic infection who are referred to a treatment service, attend a treatment service and receive treatment in accordance with treatment guidelines
- The number of people with HCV who obtain a SVR on antiviral therapy
- Ensure there is a mechanism in place for following up patients who defer treatment.

The majority of commissioners and providers were unable to provide this information when requested through the baseline survey, reported in section 2. We would therefore recommend that monitoring of these indicators is improved and included in the JSNA of each borough. This will ensure that Health and Wellbeing Boards maintain a focus on this issue and collaborative commissioning arrangements.

At the time of writing a consultation is underway for the regional Specialist Commissioning Groups to take on some of the responsibility for commissioning specialist HCV services. The Groups' role is to oversee the commissioning of complex cases or hard to reach groups within a region. The current suggestion is that liver services would be rationalised to 30 liver centres across England, each serving a population of 1-2 million people, and supported by facilitated MDTs, as is the case for certain rare cancers. The Specialist Commissioning Groups would additionally take responsibility for commissioning the treatment of difficult cases of cirrhosis, genotype 1 and HCV with HIV co-infection. This would naturally have to incorporate some consideration of equity of access through outreach services. This consultation will be completed by April 2013.

Section 4: Testing and treatment costs: How much will this cost and how do we ensure value for money?

The costing data reported here, unless otherwise stated, is from the most recent NICE commissioned economic analysis, published in February 2012(5). Costs are accurate as of 2011 for the UK, but there has been no area uplift in price for London.

A London-specific economic model has been produced as part of this review, and is detailed in Appendix A. It is not included in the main body of the report as this would add disproportionate and unfounded weight to this analysis compared to the body of health economic literature on HCV among PWID. It will be discussed and referenced alongside other literature in this section.

HCV testing

The average costs of a positive HCV test (both for acute and chronic infection) is £188.88, including consultant and nurse time. A negative HCV test will cost, on average, £115.21. The breakdown of costs incurred by these tests is summarised in table 4. This is based on a consultant cost per hour of £127, and staff-nurse cost of £87 per hour, assuming band 5 GP nurse. These costs can therefore be assumed to reduce if less than 30 minutes are allocated to the pre-test discussion and test, which is probably. Additional test costs and time involved in the prison setting, increases the cost per test by £144.21(5). Follow-up RNA PCR tests are generally included in the secondary care cost bundle, which is delivered under a separate budget.

Table 4: Cost per HCV test(5)

HCV tests	Mean value (in 2011, £)	Average time spent, minutes
Assessment	1.78	1
Pre-test discussion and test	53.50	30
Post-test results	44.58	25
ELISA test	15.35	-
PCR RNA test (if antibody positive)	73.67	-

DBS testing has been introduced in a number of different settings, as it enables nurses and keyworkers to test for antibodies in the absence of a venepuncture. A cost-effectiveness assessment recently commissioned by NICE(5) found that the introduction of DBS testing in drug treatment services resulted in a 3.61-fold (2.26, 5.77) increase in testing. The average cost per test of the intervention was £95.57, including training and coordination costs. (This can be supplemented with data from another study which found that the cost of the DBS antibody test kit and nurse time was £19.84, based on 2008/09 prices, 22). It was found to be cost-effective at £14,600 per QALY gained, even with low estimated treatment and referral rates for current PWID (5.5% and 35% respectively). This had the effect of a yearly treatment initiation rate of <1%, which could certainly be improved upon. Increasing these rates had the double effect of improving cost-effectiveness and reducing overall HCV prevalence in current PWID.

One of the major contributors to health utility of this intervention is the number of new infections averted by a reduced prevalence. The HCV chronic prevalence reduction was 1% at 10 years and 2% at 20 years. If continuity of treatment/referral is assured, these relative prevalence reductions reach 3% and

5% at 10 and 20 years respectively, highlighting the benefit of addressing pathway blockages. If no prevention benefit was modelled, the incremental cost-effectiveness ratio (ICER) doubled to £29,900, just scraping the upper reaches of the NICE acceptability limits.

The first element of this report's economic model, appendix A, took this assessment of blockages in the pathway further by evaluating which transitions in the pathway are most sensitive to change. This analysis is intended to identify which aspects of the pathway could be most efficiently be targeted for improvement in order to increase numbers of people receiving treatment for HCV. It found that the cost of testing all current PWID for HCV on an annual basis, as per NICE recommendations, is less than £800,000 in London. The cost of testing all former PWID in London is less than £500,000 and would be a one-off cost for this cohort. For both groups, increasing the numbers who attend specialist hepatology services who then go on to initiate treatment would be the most efficient way of increasing overall treatment coverage. This is largely due to the current low conversion rates (<1%). As shall be discussed, there are a number of considerations that result in this low initiation rate that are beyond the gift of commissioners to influence. The next most efficient point in the pathway to target is increasing the rate of referral into specialist hepatology services. Section 3 discusses ways to achieve this at length.

Drug treatment

Referral rates to secondary care services from different testing services currently average at 35%, (25% from drug treatment services and 45% from GP services). Testing is increasing in different community settings, and therefore if the current level of referral is not addressed here, the overall rate of referral is likely to reduce. Of the 35% who attend secondary care, 1-10% initiate treatment in the first two years and, thereafter an additional 1% of those outstanding will begin treatment each year(5).

Treatment typically comprises a combined therapy of Peginterferon and Ribivirin. Broadly speaking, duration of treatment is 24 or 48 weeks, depending on a number of factors such as HCV genotype, viral load and speed of virological response. Genotypes 1 and 4 would typically receive a 48 week treatment, whereas genotypes 2 and 3 would expect 24 weeks of treatment. All patients with HIV coinfection would receive 48 weeks treatment, regardless of genotype(4). It has recently been established that there are some 'super responders' who have no detectable virus in the peripheral blood after 4 weeks of combination therapy, and can therefore reduce their treatment length by half with the same degree of efficacy(6). A SVR to treatment is considered an indication of permanent resolution of treatment, though relapse occurs in 5% of cases after 5 years(4). Approximately 75% to 85% of people with moderate or severe infection with HCV genotype 2 or 3 have a SVR within 6 months. For genotype 1 SVR is 40% to 50%. For other genotypes SVR is 50% to 75%. The same regimens are indicated for re-treatment when SVR was not achieved(4). However, the available evidence suggests that negligible levels of non-responders are re-treated(22). A treatment regimen that produced higher rates of SVR than those currently available would have the potential to have the greatest impact on HCV prevalence(25).

HCV treatment causes a number of common side effects in 5% of patients, and severe side effects in 2%. These include malaise, fever, myalgia, headaches, hair loss, red cell haemolysis leading to anaemia on occasion, depression, anxiety and thyroid disorders. All side effects cease once treatment comes to an end, with the exception of thyroid disorders. These side effects need to be fully explored and discussed with patients prior to treatment initiation(26).

The current treatment regimens recommended by NICE for treatment of chronic HCV, and the available licensed drugs are summarised in table 5.

Table 5: Summary of licensed available drugs in the UK for the treatment of HCV(30)

HCV genotype	Type of drug	Make of drug (Manu-facturer)	Taken in conjunctions with other drugs	Dose	Cost (exc. VAT)
ALL mild - severe	Ribavirin	Copegus (Roche)	With interferon alfa or peginterferon alfa	800mg /day (genotypes 2 and 3)	£8.81 /day
				1000mg / day genotypes 1, 4, 5, 6 with body weight <75kg	£11.01 / day
				1200mg / day genotypes 1, 4, 5, 6 with body weight >75kg	£13.21 / day
ALL mild - severe	Ribavirin	Rebetol (MSD)	With interferon alfa or peginterferon alfa	800mg / day body weight <65 kg	£7.65 / day
				1000mg / day body weight 65-81 kg	£9.56 / day
				1200mg / day body weight 81-105 kg	£11.48 / day
				1400mg / day body weight >105 kg	£13.39 / day
ALL mild - severe	Peginterferon Alfa	Pegasys (Roche)	Monotherapy or with Ribavirin	1.5 mg / kg bodyweight weekly. Average dose 180mcg / week.	£124.40 / week (syringe)
ALL mild - severe	Peginterferon Alfa	ViraferonPeg (MSD)	Monotherapy or with Ribavirin	1.5 mg / kg bodyweight weekly. Average dose 180mcg / week.	£239.26 / week (pen)
Genotype 1	Boceprevir	Victrelis (MSD)	With Ribavirin and Peginterferon alfa	2400mg / day	£100 / day
Genotype 1	Telaprevir	Incivo (Janssen)	With Ribavirin and Peginterferon alfa	2250mg / day	£267 / day

This illustrates that a 24 week treatment for all genotypes at an average Ribavirin daily dose of 1000mg can range from £4,591.68 to £7,591.92, depending on whether the lowest cost medications are chosen. This costing is based on the assumption that the most cost-efficient size of blister pack is always purchased. This highlights the importance of ensuring that policies are in place for minimising costs of treatment. However, cost is not the only factor in the clinical decision making process and there can be important and valid reasons for prescribing more costly regimens, such as contra-indications and side-effects, which would need to be borne in mind for policies of this nature.

The 48 week course of lowest cost course of treatment for genotype 1 is £42,783.36 with protease inhibitors, or £9,183.36 without. NICE reviews found protease inhibitors to have a positive influence on SVR rates when taken in conjunction with standard treatment. NICE considered the most plausible ICERs for telaprevir(31) to be £18,000 and £10,000 per QALY gained and for boceprevir(32) to be £11,601 and £2,909 per QALY gained for previously untreated and previously treated patients respectively. This assessment is based on manufacturer's data. An independent study(47) found higher ICERs than this analysis: $50,000 per QALY among treatment naïve patients with advanced fibrosis, and $100,000 per QALY in treatment naïve patients with mild fibrosis, which was no longer considered to be cost-effective.

Phase 3 trials are currently underway for a new formula of drugs, which are thought to offer high SVR rates and for which course duration is 12 weeks. As the drugs are still at the trial stage, further research is required to make a full assessment of efficacy, safety and costs, which are some way from being determined. It is estimated that it is at least 18 months until these new drugs would be launched, subject to the findings of current trials, and a further 12-24 months for NICE review. NICE could avoid a delay of this length if the new drugs were proven to be more effective and were priced as equal to, or cheaper than, current regimens.

Given the potential benefits that these new drugs would offer there is some debate, anecdotally, as to whether to delay treatment for some people with chronic HCV until the new drugs become available. Whilst this is always a clinical decision, it should be borne in mind that it is not certain that these drugs will meet all the requirements to enter the market, nor that they will meet cost-effectiveness requirements for NICE approval. This process could take up to three years from now to be completed, in which time the untreated population remains at risk of infecting others. At an incidence of 2-10 new infections per 100 person years, if 100 current PWID had their treatment delayed there would be approximately an additional 3-19 people infected over this three year time frame that could have been averted, taking prevailing SVR from treatment into account.

These costs only relate to HCV drug treatment and there are, of course, other costs associated with treating people with HCV. A summary of health care costs for the HCV disease stages are presented in table 6, which synthesises considerations of health care costs, antiviral treatment delivery and monitoring costs as well drug costs(5).

Missing from this costing data is the costs of monitoring and care following treatment. Equally important is the cost of monitoring and care following diagnosis and prior to treatment. Due to the possible barriers to PWID receiving treatment soon after diagnosis discussed above, the importance of early and ongoing assessment of RNA positive individuals should ideally be built into a health economic assessment of HCV testing and care pathways.

Table 6: Average annual costs of each stage of HCV disease progression(5)

HCV state	Mean cost (in 2011, £)
Mild diagnosed	169
Moderate diagnosed	880
Cirrhosis diagnosed	1,397
Decompensated cirrhosis	11,199
Hepatocellular carcinoma	9,980
Liver transplant	33,561
Cost of care in year of liver transplant	11,614
Post transplant	1,701
Mild SVR	318
Moderate SVR	880
Cirrhosis SVR	1,397
Undiagnosed states	0

The costs of treating the later stages of disease rise dramatically. Treatment of the condition is the priority for end stage liver disease, rather than treating the underlying HCV infection. HCV treatment is prioritised in the earlier states of the infection. The opportunity cost of not treating cases of HCV sooner should be factored into any consideration of the cost-effectiveness of HCV services.

Strategic approaches to targeted treatment

From a public health and economic perspective a fixed annual budget would focus on an immediate programme of maximum spend on treatment each year(22). Whilst this would result in high health care costs it would avert a high number of infections which would lead to reductions in ten year prevalence. At the baseline prevalence of 55% in PWID in London, the programme is not cost-saving overall but it does minimise cost per QALY and is well within the NICE defined limits of cost-effectiveness. The greater the annual budget, the bigger the impact on each of these indicators and for infections averted the impact is exponential.

In regions with high baseline prevalence, such as London's 55%, high rates of treatment are shown to be necessary to have any substantial impact on HCV prevalence(9,27). For example, where 5 PWID per 1000 were treated annually there was a 6% relative prevalence reduction after 10 years, compared to a 57% relative prevalence reduction when 40 PWID per 1000 were in HCV treatment(25).

A study in France demonstrated that at least half of all the HCV-infected population would require anti-viral therapy to address the future rise in mortality from HCV-related deaths and to reduce the incidence of decompensated cirrhosis by 25% over the next 20 years(9). These findings suggest that vast treatment costs are incurred to only reduce incidence by 25%. Other strategies beyond treatment of PWID with HCV are required to reduce incidence therefore.

Accepting the limitations of a policy based on treatment alone, attention turns to the cost-effectiveness of targeting different groups within the population for treatment. Whilst antiviral therapy for current PWID with HCV has been deemed cost-effective by NICE, few are treated in practice, (in the region of <3-4%,) in part due to clinicians' concerns over treatment compliance and re-infection(25). However evidence does not support this concern, with current PWID displaying similar levels of compliance to people who have never or no longer inject drugs(27) and, importantly, similar SVRs are achieved between these populations(29). One cohort study found that 66.0% of current PWID adhered to the acceptable

level of 80% of the antiviral therapy course, compared to 60.5% in the control group(28). There is little data available on re-infection rates, but small scale studies suggest low rates of re-infection in the first year(25). In fact where equal SVRs are achieved across populations following treatment, more HCV-free life years are achieved in the active PWID population than in other groups despite the persistent risk of re-infection(25).

There is some debate whether treatment of mild or more severe chronic infection is the most cost-effective approach. Age, genotype, stage of disease progression and treatment completion have all been found to influence treatment outcomes(6,28,29). Current PWID are typically a younger cohort than former PWID and therefore experience a greater SVR, which is thought to counter-balance any reduction in SVR resulting from lower adherence rates(29).

Mild HCV responds much better to treatment than more advanced disease (SVRs of up to 95% have been achieved following a 12 week course of interferon), something that the recent NICE guidance was at pains to emphasise(6,18). Additionally, early identification of infection enables patient education and contact tracing, which has the potential to address the source of infection. The economic model conducting as part of this study found treatment of mild, moderate and cirrhotic disease to be cost-effective, which is supported by the body of evidence. Given the optimistic SVR rates applied for cirrhotic patients in this model, we would downgrade the evidence for this stage of disease however and favour a focus on treatment of mild and moderate disease.

Other studies have concluded that it would be of most value to focus treatment on people who are at greatest risk of developing liver failure or cancer (namely people with moderate disease or compensated cirrhosis rather than mild disease) (9). This is echoed by the current NICE guidelines which allow optional treatment of mild disease(4). However, this needs to balanced against the knowledge that lower SVR is achieved following treatment of people with more advanced. In effect treatment is least effective in those at greatest immediate risk.

All of these states are however largely asymptomatic and would therefore require proactive testing for diagnosis. The discussion is therefore moot as once diagnosed, people would not be denied the offer of treatment regardless of their stage of progression. It may be that some patients at early stages of disease decide to delay until a time when they are more ready to receive treatment and therefore have a higher chance of adherence. These patients would require ongoing monitoring to avoid disease progressing too far before treatment is initiated.

A cost effectiveness analysis is based on a calculation of quality adjusted life years (QALYs), the measure that informs all NICE guidelines. Two economic analyses of HCV testing and treatment programmes calculated the QALYs for different patient groups. The health state of former PWID or people for whom it is not a risk factor with mild chronic disease was placed at 0.77-0.78 QALYs per year, gradually reducing by age group to 0.56 QALYs in the 75+ age group. Healthy active PWID begin at a lower baseline of 0.85 QALYs per year, which drops to 0.66 QALYs with HCV. If a QALY is valued at £20,000 as per the lower limit of a NICE assessment of a cost-effective intervention, the monetary value of treating a chronically infected PWID would be £3,800 per year. However, being on HCV antiviral therapy reduces quality of life by 0.10 QALY per year for the duration of treatment, which is an important barrier to treatment initiation. This reduction needs to be balanced against the alternative to treatment of disease progression. The health utility of patients with decompensated cirrhosis, hepatocellular carcinoma and liver transplant are each consider to be 0.45 QALYs per year(5,22).

A comparison of lifetime costs to the health services of HCV patients receiving treatment and not receiving treatment found that in most cases the short term costs of the intervention were more than offset by the reductions in morbidity costs from preventing disease progression(33). This could not be said for patients with genotype 1 HCV either in its mild form or with cirrhosis. However, once the impact on QALYs is considered, treatment only ceased to be cost-effective for patients over 50 years with genotype 1 HCV and cirrhosis, where protease inhibitors were not included in the analysis(33).

Our analysis (appendix A) supports this finding of life time costs where the role of discounting and return on investment being realised decades in the future, is not taken into consideration. A very optimistic finding of this analysis was that a treatment rate of 10% would result in £200million lifetime savings to the health services. There are a number of limitations that would call this figure into dispute discussed in the appendix. However, the broader objective of 10% treatment rates could be set for London to achieve cost-effective investment.

In practice, treatment strategy is not determined purely on public health grounds to avoid onward transmission. Information needs to be provided to patients about treatment options in order for them to make an informed decision about when they would like to receive treatment. The focus for management is typically on reduction of the burden of disease rather than reduction of prevalence. Many stakeholders, including the HPA and the HCV Trust, advocate diagnosis and assessment. This enables HCV-infected individuals to be monitored until they can be appropriately treated, and current PWID will be offered harm reduction interventions as an alternative means of reducing onward transmission if treatment is delayed. The perception among service users is typically that referral means treatment, which may explain some of the low referral and attendance rates. However, there are many benefits to be gained from alternative options, such as assessment and monitoring accompanied by harm reduction interventions.

Section 5: Recommendations: How are we going to get there?

Health and Well-being Boards

- Health and Well-being Boards, particularly those operating in boroughs with a high mortality rate from liver disease as shown in table 1, are urged to develop a strategy to address the rising levels of liver disease. HCV should be a significant component of this strategy, with at least a third of resource directed towards addressing HCV management. This strategy should, in particular, address the following public health outcomes: 4.3 Mortality from causes considered preventable; 4.6i Under 75 mortality rate from liver disease.

- Health and Well-being Boards should facilitate a discussion between CCGs and DPHs to establish joint commissioning arrangements for HCV testing and treatment in current and former IDUs.

- It is debatable whether the focus for treatment should be on mild, moderate or cirrhotic cases of HCV. Treatment for HCV in all of these stages has been shown to be cost-effective and so should be promoted. People with HCV do not experience symptoms in any of these stages and therefore in practice, the same strategy of diagnosis and offer of treatment should be applied to all stages of HCV.

- Health and Well-being Boards should ensure they review the recently published guidelines on HBV and HCV testing in high risk groups and address any gaps in their local area.

Directors of Public Health

- Each borough should have a testing to treatment pathway for HCV established that all services in the borough offering any aspect of the pathway are aware of and signed up to. An example pathway is available that can be adapted to the local context in appendix E. Public Health should request monitoring information from services to track how they are performing against this pathway, as per the NICE recommended dataset defined on page 40 of this report.

- Public health should commission universal provision of HBV and HCV tests, vaccines and annual reviews in drug treatment services.

- Public health needs to capitalise on the high diagnosis rate already established in London by promoting the conversion of testing into treatment. Monitoring of data for the patient pathway should involve setting stretch targets for treatment initiation in those who attend treatment appointments, as this part of the pathway has been shown to have the biggest and most cost-effective impact on numbers recovering from HCV.

- Where integrated services are not immediately possible, public health commissioners of drug treatment services should focus efforts on providing support for attendance at treatment services. The most resource efficient approach is by providing information about the process, preparing service users for what to expect in hospital and how to cope with appointments. Harm reduction approaches should also be a significant component of these education packages. Peer support groups are strongly recommended to encourage uptake of testing and treatment, and

compliance with treatment. Good practice is demonstrated in half of all drug treatment services offering or sign-posting PWID to peer support groups, and King's College Hospital has experimented with patient support packages.

- As per recently published NICE guidelines, DPHs should ensure DBS testing is offered in all drug treatment services and in other venues that PWID frequently access, such as needle and syringe exchange programmes. Training in DBS testing should be considered for all staff with a nursing or equivalent background in these venues. All venues that offer testing should be part of a robust testing to treatment pathway to ensure follow up occurs.

- Boroughs should consider developing an intervention directed towards PWID in their first year of injecting, as evidence suggests this is when they are at greatest risk of infection. There already appears to be referral links between the criminal justice system and drug treatment services in the majority of boroughs. Where this is not in place it should be developed. Other boroughs should consider capitalising on the drug testing programme for people in police custody by embedding harm reduction messages and HCV testing in the management pathway for those who test positive for drug use.

- Public health should consider commissioning pharmacies to deliver BBV services as part of needle exchange programmes. Five London boroughs have been involved with pilots of this intervention, with some success.

- Local strategies and commissioning should incorporate a multi-component prevention programme, including opiate substitution programmes, needle and syringe exchange and awareness campaigns. It is recommended that the materials for such campaigns should be co-produced with service users and that venues and events that they frequently attend should be targeted by these campaigns.

- Training in HCV for local health professionals and drug addiction workers should be promoted across drug treatment services, GP shared care and needle and syringe exchange programmes.

Clinical Commissioning Groups

- 50% of PWID are on OST at any given time, necessitating frequent and regular appointments within drug treatment services. This presents an opportunity to offer treatment for HCV, as well as testing, within drug treatment services as part of an integrated service. Integration involves providing hepatology clinics within drug treatment services, removing the need to attend hospital. Examples of good practice are available in Inner North East London and through King's College Hospital, and should be adopted elsewhere in a way that suits the local service environment.

- It is recommended that all CCGs develop a LES with GP practices in the borough to deliver targeted testing of former PWID, people born or spending time in high prevalence countries, and men who have sex with men. The LES should include identifying and inviting people for testing, training for GP staff, and a recommended level of remuneration of £100 per test completed. A stepped tariff to increase the level of remuneration once a high proportion of the eligible

population had been tested would incentivise testing of the harder to reach, and mean that the intervention is more cost effective due to this higher coverage. The cost effectiveness of this intervention is dependent on there being a robust pathway and supportive interventions in place to encourage access to treatment among those diagnosed.

- CCGs should encourage laboratories in London to review their practice in testing for antibodies and RNA PCR in order that only one blood sample needs to be taken from the individual, in line with the average practice for England. It is intended that this will reduce the number of people falling out the system when a second test is required.

Public Health England

- Public Health England should encourage boroughs to achieve a 10% target of treatment of people with HCV, in order to achieve a conservative estimate of £200million savings for the NHS in London.

- Public Health should facilitate a process with specialist hepatology services in London to standardise diagnostic tests and eligibility criteria for access to treatment. This information needs to be clearly communicated to all organisations making referrals in to specialist services in order to overcome confusion and improve rates of referral. This is particularly important in the current climate where some patients are advised to delay treatment until new regimens are available. This could take three years. Where clinical guidelines are not available, a London consensus could be established on these issues. This will reduce confusion and build trust with patients and drug treatment services.

NHS Commissioning Board

- The NHS Commissioning Board should hold CCGs to account for their contributions to tackling HCV. CCGs should play a role in the commissioning of testing as well as treatment, as they are likely to benefit most from the future budget savings.

- Depending on the outcome of the current consultation on Specialist Commissioning Groups, the NHS Commissioning Board should oversee a cohesive and equitable approach to all HCV, including active outreach services.

- The NHS Commissioning Board, in its role of commissioning prison health care, should focus on continuity of care, as the most cost-effective way to promote HCV testing and treatment in this setting. Continuity of care will benefit a number of other health programmes also.

Third sector organisations and other interested bodies

- A treatment regimen with higher SVR would have a significant impact on the prevalence of HCV, and there is understandable anticipation about treatment regimens under trial that promise this improved SVR. If these new drugs meet expectation, there will still be delays in their reaching the market if the price is too high as they would not have automatic approval by NICE. There is a role for lobbying pharmaceutical companies to set prices at a sufficiently low level (similar to current levels) that more effective treatments will be available on the NHS and as soon as possible.

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Appendix A: Health economic impact for London

This section aims to model the health impacts and financial costs of HCV found in the literature review and apply them to London. This modelling work aimed to answer the following questions:

1. How can we most efficiently affect the testing and treatment pathway to increase the number of HCV-infected patients in treatment?
2. What are the likely prevalence, health care costs and health utility of people in London in each stage of disease from HCV in London over the next 10, 20 and 50 years?
3. What are the relative costs of treatment and non-treatment for HCV in the London cohort?

It is intended that the results will provide valuable information on the future costs to NHS budgets depending on the level of treatment available.

Methodology

Three models were developed to address each of the above questions, each employing a Markov approach. TreeAge software was used to build the decision tree and apply the parameters to each model.

1. **How can we most efficiently affect the testing and treatment pathway to increase the number of HCV-infected patients in treatment?**

To assess how the testing-to-treatment pathway could be efficiently addressed in order to increase access to treatment, a Markov chain was built to model the probability of an individual passing to the next step in the pathway. Two key locations for testing in the community were compared: drug treatment services and GP practices, as distinct from GP shared care which delivers drug treatment services. A baseline pathway was first completed with the parameters detailed in table 1a, which are based on the best available evidence of current probabilities of progress through the pathway. These parameters varied according to the setting for testing, and each of these settings predominantly relates to a different group. Testing in GP surgeries was assumed to predominantly target former and non-PWID (even though current PWID can receive testing in this setting) and therefore the estimated London prevalence of 91,000 former PWID was employed to model the number of people expected to complete treatment under the current scenario. Drug treatment services are assumed to cater for current PWID and therefore this pathway applied a cohort of 27,700 PWID. These estimates are based on HPA data(10).

Table 1a: Transition parameters employed in the baseline testing-to-treatment pathway for HCV in GP and Drug treatment service settings.

	GP	Drug treatment services
Testing to positive result(11)	0.036	0.27
Positive result to referral to specialist services(34)	0.661	0.426
Referral to attendance at specialist services(34)	0.781	0.474
Attendance at specialist services to positive RNA result	0.75	0.75
Positive RNA result to initiate treatment(5)	0.055	0.055
Initiate treatment to >80% compliance and completion of treatment(28)	0.66	0.66

A one-factor-at-a-time (OFAT) sensitivity analysis was performed, where the impact of changing the level of each parameter is assessed in turn while all other factors are kept constant. The probabilities of positive results were kept constant as it was considered that these could not easily be affected by service changes. All probabilities (from 0-1 with an increment of 1%) of progress to the next step in the pathway were modelled in order to make a marginal analysis of impact on numbers completing testing in London. The number of tests performed in general practice and in drug treatment services were referenced against the costs provided in table 2a. Here it is assumed that the first test involves assessment, pre-test discussion and test, and the ELISA test. To increase the likelihood of a patient accepting a referral, a consultation following test results needs to take place. To access assessment for treatment a PCR RNA will need to have been completed. The costs are attached to each step of the pathway accordingly. These are the costs incurred in primary care, for which local authority or CCG commissioners will take responsibility. Increased costs to secondary care services are not considered in this analysis, but are considered more fully in the other two models.

Table 2a: Average annual costs of each stage of HCV disease progression(5)

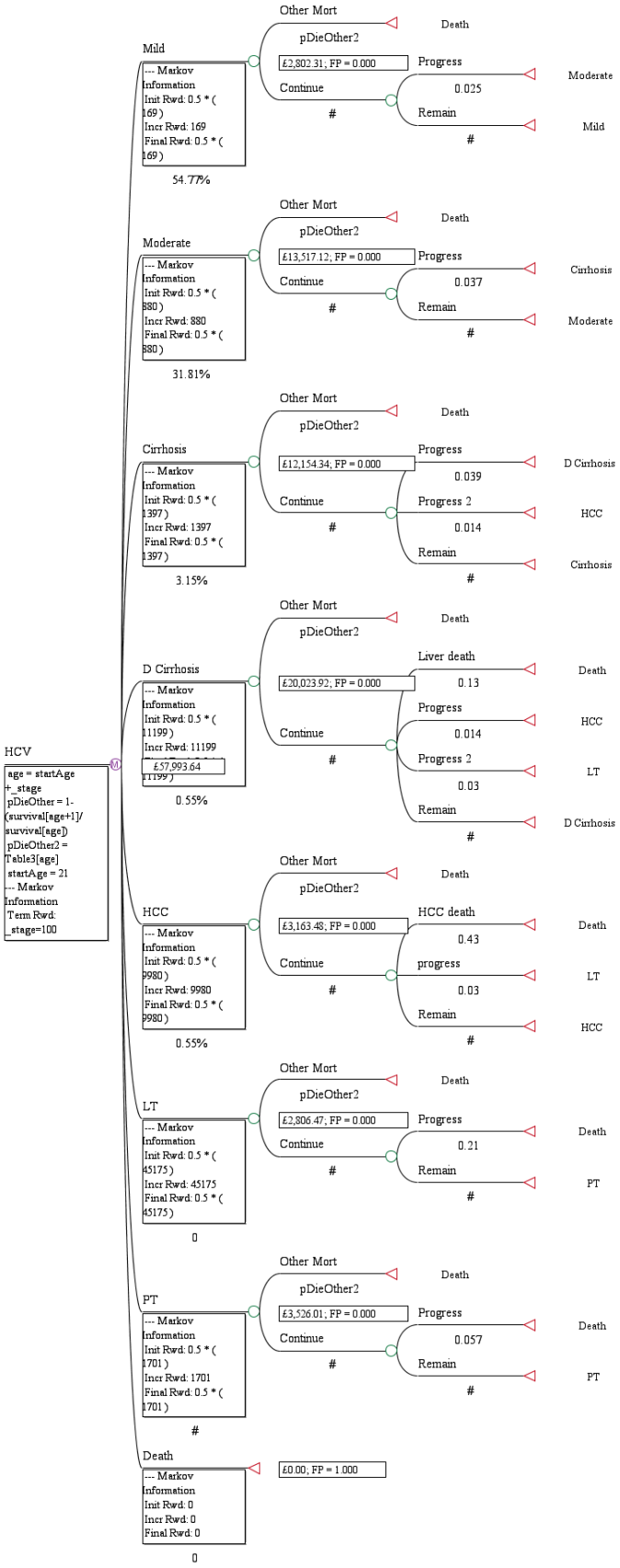
HCV state	Mean cost (in 2011, £)
Mild diagnosed	169
Moderate diagnosed	880
Cirrhosis diagnosed	1,397
Decompensated cirrhosis	11,199
Hepatocellular carcinoma	9,980
Liver transplant	33,561
Cost of care in year of liver transplant	11,614
Post transplant	1,701
Mild SVR	318
Moderate SVR	880
Cirrhosis SVR	1,397
Undiagnosed states	0

2. **What are the likely prevalence, health care costs and health utility of people in London in each stage of disease from HCV in London over the next 10, 20 and 50 years?**

Again, a Markov approach was taken to modelling the probability of a London HCV-infected population progressing through different stages of HCV disease over time. The cohort size given was 58,000, as per the LJWG estimates for HCV in London. This cohort was distributed across estimates of the current burden of chronic HCV infection at each stage of disease in London to form a baseline. There is little data available on prevalence across these stages, so a proxy has been taken from the 2015 scenario HPA prevalence estimates model(10). These estimates are mild 54.77%, moderate 31.81%, cirrhotic 3.15% and end-stage disease 1.10%. An illustration of this model is provided in figure 1a.

Assumptions regarding these rates of progression between each stage of disease are presented in table 3a, and the corresponding costs of each state, presented in table 2a above, are applied. The progression rates applied have a sound evidence base are not age-specific, and we know that the speed of HCV-related liver disease progression increases as people get older. Professional opinion suggests that this costing information is an underestimate for London, but in the absence of other costing data these NICE

Figure 1a: Markov chain of progression through HCV disease states, including cost and quality of life score



estimates were adopted. Mortality from other causes was also included in this model. Probability of mortality from other causes was calculated based on the reported finding that HCV-infected individuals have a three times greater mortality rate than the general population. This calculation therefore required an assumption of the average age of HCV-infected individuals. This was taken as the average age of initiation (21 years) since the majority of cases reported in the baseline had mild chronic HCV and were therefore considered to be relatively new initiators. The limitation of this assumption may mean that mortality from other causes is underestimated in this model.

Table 3a: HCV disease progression estimates, per year

Transition	Mean probability	Of 1000 people in the initial state, how many progress to the next state
Mild to moderate	0.025	25
Moderate to cirrhosis	0.037	37
Cirrhosis to decompensated cirrhosis	0.039	39
Cirrhosis/decompensated cirrhosis to HCC	0.014	14
Decompensated cirrhosis/HCC to LT	0.030	30
Decompensated cirrhosis to death	0.130	130
HCC to death	0.430	430
LT to death	0.210	210
Post-transplant to death	0.057	57

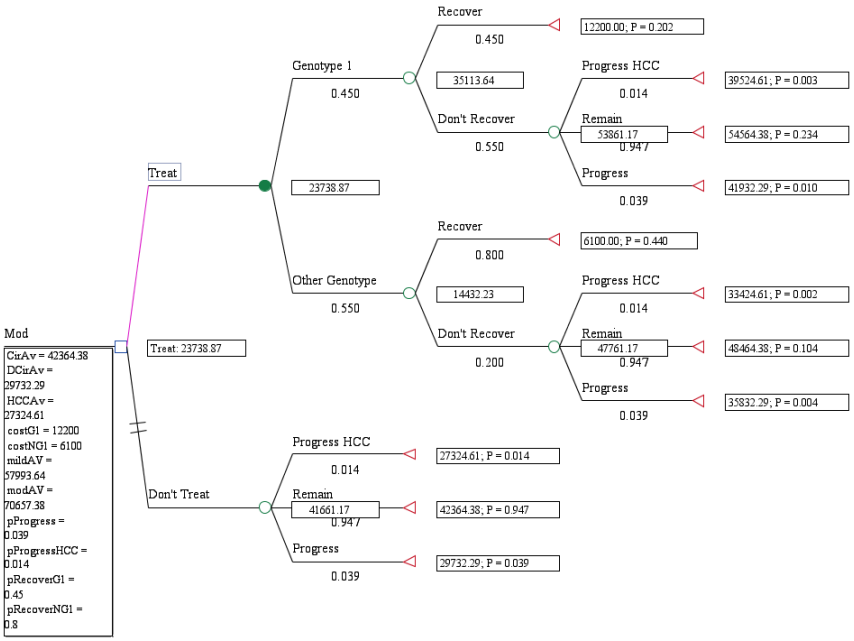
The parameters in the economic model were projected forward over 10, 20 and 50 years to calculate the number of people who will be in each stage of the disease after this period of time. These projections assumed a static cohort with no new entrants (i.e. no new people becoming infected over this time). These projections enabled a calculation of the average time spent by HCV-infected people in each stage of the disease and average life expectancy. These findings were applied first to the annual cost to the health service of each stage of disease to obtain an average cost of having HCV, with 0% treatment. They were then applied to the health utility states provided in the recent NICE cost-effectiveness report(5) of 0.77 (mild), 0.66 (moderate), 0.55 (cirrhosis), 0.45 (decompensated cirrhosis), 0.45 (hepatocellular carcinoma), 0.45 (liver transplant) and 0.67 (post-liver transplant). These applications are subject to ecological fallacy and care must be taken not to apply average costs and health utility at the individual level. The London cohort of 58,000 is sufficiently large to have suitable application at the population level. It could equally be applied to borough-level reports.

3. What are the relative costs of treatment and non-treatment for HCV in the London cohort?

A Markov chain was created to map the probabilities of an HCV-infected individual having genotype 1 or another genotype (as this has implications for treatment costs), of being treated and of achieving SVR following treatment, see figure 2a. Costs of each scenario were then applied, as per table 2a, with the addition of costs of treatment. It should be noted that most studies assume some continued health care costs following SVR and these are not accounted for in this model, which will have the effect of falsely inflating the cost-effectiveness of treatment(46). The scenario incorporated both HCV genotype 1 with 45% SVR and a cost of £12,200 for treatment (excluding protease inhibitors because of the complexities involved in their administration), and all other genotypes were grouped together at 80% SVR and £6,100 cost of treatment. The relative prevalence was taken as 45% for genotype 1 and 55% for all other

genotypes. The treatment costs only factor in drug costs. There are two reasons for this: first this was considered a counterbalance to the costs of no treatment which are considered an underestimate for London, and secondly the service configurations in London are so diverse that the service costs would differ considerably. Any projected savings from the model can therefore be employed within the service to cover administrative costs, etc.

Figure 2a: Markov chain of impact of treatment on populations with moderate liver disease from HCV, including treatment and non-treatment costs



A marginal analysis was conducted on the level of treatment for people in each disease state, at increments of 10% from 0-100%. Costs of treatment were then weighed against costs of HCV if the patient remains untreated, taking into account patients who are treated but do not achieve SVR who will still incur the other costs of HCV. Costs of any co-morbidities were not included in this analysis. Costs presented are all HCV-related costs accrued over a lifetime. Therefore costs presented in the model may appear higher for lack of disease progression but this is largely due to the lower life expectancy of progressing disease. Retreatment rates are considered to be negligible and are therefore not included in the model.

There are two major limitations to the assumptions applied in this model: a fixed SVR rate has been applied to treatment of all ages and stages of HCV-related liver disease, and discounting has not been employed. Firstly, more advanced disease and disease in older age groups has lower success rates of treatment. Simplifying assumptions (non-age- and stage-specific-rates) will result in more high-risk patients being predicted to achieve SVR than is realistic, skewing results. This is particularly true of people with compensated cirrhosis, where the assumed SVRs from treatment are over-estimates. Secondly, NICE recommends that all cost-effectiveness studies employ discounting in order to compensate for current-time preference for returns on investment. The greatest benefit of treatment occurs in the future but the cost of treatment is immediately incurred in full. Economic analysis that incorporates discounting will

therefore make annual adjustments to reduce these longer terms gains reflective of the opportunity cost involved. Since discounting is not used in this study, its findings are likely to more optimistic of the value of treatment than comparable studies.

Results

1. **How can we most efficiently affect the testing and treatment pathway to increase the number of HCV-infected patients in treatment?**

Taking the assumptions cited above as the baseline scenario, if all former PWID are offered testing 46 will complete treatment each year, and 23 will complete treatment if half are offered testing. It would cost approximately £452,500 per year for all former PWID to be offered testing, taking into account the drop-out rates for each step of the pathway.

If all current PWID are offered testing through drug treatment services, 41 will complete treatment each year despite a much lower cohort than former IDUs. 21 will complete treatment if half are offered testing each year. We know current rates of testing being offered are already high among people in contact with drug treatment services. It would cost £781,500 per year for all current PWID in London to be offered testing in drug treatment services, considering the drop-out rates for each step in the pathway. This is considerably higher than in general practice due to the high initial uptake rates but greater rates of drop-out later in the pathway.

Table 4a: Impact of OFAT sensitivity analysis on numbers completing treatment and testing costs among former PWID tested in the general practice setting across London

	Positive result to referral to specialist services		Referral to attendance at specialist services		Positive RNA result to initiate treatment		Initiate treatment to >80% compliance and completion of treatment	
	No. complete treatment	Test costs	No. complete treatment	Test costs	No. complete treatment	Test costs	No. complete treatment	Test costs
Baseline	46	£452,500	46	£452,500	46	£452,500	46	£452,500
20%	14	£298,000	12	£360,000	167	£452,500	14	£452,500
40%	28	£365,000	24	£392,000	335	£452,500	28	£452,500
60%	42	£432,000	36	£423,500	502	£452,500	42	£452,500
80%	56	£499,000	48	£455,500	670	£452,500	56	£452,500
100%	70	£566,000	60	£487,500	837	£452,500	70	£452,500

The progression from being RNA positive to initiating treatment was, unsurprisingly, the most sensitive to change as the progression rates are so low among both former and current PWID. The relative increases of each step in the pathway and resultant costs at baseline and 20%, 40%, 60%, 80% and 100% scenarios are provided both for the GP setting, (table 4a,) and the drug treatment services setting, (table 5a).

Table 5a: Impact of OFAT sensitivity analysis on numbers completing treatment and testing costs among current PWID tested in drug treatment services across London

	Positive result to referral to specialist services		Referral to attendance at specialist services		Positive RNA result to initiate treatment		Initiate treatment to >80% compliance and completion of treatment	
	No. complete treatment	Test costs	No. complete treatment	Test costs	No. complete treatment	Test costs	No. complete treatment	Test costs
Baseline	41	£781,500	41	£781,500	41	£781,500	41	£781,500
20%	19	£647,000	17	£717,000	150	£781,500	12	£781,500
40%	39	£766,000	35	£764,000	299	£781,500	25	£781,500
60%	58	£885,000	52	£811,000	449	£781,500	37	£781,500
80%	77	£1004,000	69	£858,000	598	£781,500	50	£781,500
100%	97	£1123,000	87	£905,000	748	£781,500	62	£781,500

2. **What are the likely prevalence, health care costs and health utility of people in London in each stage of disease from HCV in London over the next 10, 20 and 50 years?**

If no treatment takes place, the average number of years that an HCV-infected person will live is 45 years from the point of infection. The average age of initiation is 21 years, and therefore average life expectancy is 66 years. With an average health utility of 0.67 (weighted for time spent in each disease state), the equivalent QALYs for people living to 66 years is 44 QALYs. At a population level, the average cost to the health service of having HCV and not receiving treatment is £58,000 over a lifetime. This does not include any costs incurred for any co-morbidities.

The number of people in London projected to be in each stage of disease over time is presented in table 6a. These projections are applied to the costs associated with each stage of disease in order to provide costs to the health service, in that year only, of HCV without any treatment. Costs are seen to go down over time, as more people will have died in that time. It should be noted, however, that in real terms new people will enter this cohort so the costs will continue to increase.

Table 6a: Projections of disease progression in London over 10, 20, and 50 years and related in-year costs of HCV with no treatment.

	Mild	Moderate	Cirrhosis	D Cirrhosis	HCC	LT	PT	Death	In-year costs
2013	31767	18450	1827	319	319	0	5319	0	**£4.0m**
2023	24543	18550	6511	971	197	32	3063	4134	**£4.9m**
2033	18880	17189	8981	1693	308	58	1968	8924	**£5.9m**
2063	7321	9330	7789	1805	297	63	998	30397	**£4.8m**

3. **What are the relative costs of treatment and non-treatment for HCV in the London cohort?**

Taking into account the different treatment costs and SVR rates for each genotype, the average lifetime costs of treatment were £29,700 for mild disease, £33,700 for moderate disease and £23,700 for

cirrhosis. The lifetime costs of no treatment were £58,300 for mild disease, £69,600 for moderate disease and £41,700 for cirrhosis. The respective remaining life expectancy for each of these disease states is 45, 34 and 17 years accounting for why cirrhosis treatment is the cheapest form. We have already discussed how the assumptions of SVR following treatment for people with cirrhosis are over-estimated and therefore will underestimate the costs of treatment in this group. While those who do not achieve SVR after treatment will be in a more severe stage of disease, they will have fewer years of life remaining in which health care costs are incurred. The average cost per year is £1,300, £2,100 and £2,500 for mild, moderate disease and cirrhosis respectively, demonstrating the increasing costs of disease progression.

It is always cheaper to treat as there is the option of full recovery, in which case there are no further HCV-related costs incurred in this model. As already shown, there are often ongoing costs of monitoring and care following successful treatment, which are not included here. Additionally, costs of monitoring and care are often also incurred prior to treatment, sometimes for several years until an appropriate time to initiate treatment is reached. These costs are also not included in this analysis.

The average lifetime savings from treating someone for HCV are £28,600 if they are treated while they have mild disease, £35,900 if they are treated while they have moderate disease and £18,000 if treated while they are cirrhotic. Based on this analysis it is most cost-effective to treat people with moderate disease. Table 7a illustrates the marginal cost analysis of different rates of treatment for people with moderate disease.

Table 7a: Marginal analysis of average lifetime costs for people with moderate liver disease from HCV at different levels of treatment.

Proportion of people receiving treatment	Average cost per population head, at this level of treatment	Average saving per population head, at this level of treatment
0.00%	£69,610.54	£0.00
10.00%	£66,022.56	£3,587.98
20.00%	£62,434.59	£7,175.95
30.00%	£58,846.61	£10,763.93
40.00%	£55,258.63	£14,351.91
50.00%	£51,670.66	£17,939.89
60.00%	£48,082.68	£21,527.86
70.00%	£44,494.70	£25,115.84
80.00%	£40,906.72	£28,703.82
90.00%	£37,318.75	£32,291.79
100.00%	£33,730.77	£35,879.77

The greater the level of treatment, the greater potential there is for savings in the health system. In the knowledge that treatment levels are currently very low (<3-4%), a conservative estimate can be made for potential savings if this level of treatment is increased to 10% in each London Borough, see table 8a. The estimated savings would double if 20% treatment were achieved among the HCV-infected population. The HCV prevalence estimates applied here are based on HPA data(10).

Table 8a: Total HCV-related costs to health service, and potential savings from treating 10% of infected population compared to 0%, for each London Borough

Borough	HCV prevalence	Total HCV-related costs at 10% treatment rate (including costs of 90% non-treatment)	Potential savings from treating 10%, compared to 0% of infected population
Barking and Dagenham	979	£64,700,000	£3,500,000
Barnet	1560	£103,000,000	£5,600,000
Bexley	1061	£70,100,000	£3,800,000
Brent Teaching	1721	£113,600,000	£6,200,000
Bromley	1598	£105,500,000	£5,700,000
Camden	3028	£199,900,000	£10,900,000
City and Hackney	1449	£95,700,000	£5,200,000
Croydon	2413	£159,300,000	£8,700,000
Ealing	1758	£116,100,000	£6,300,000
Enfield	1771	£116,900,000	£6,400,000
Greenwich	1705	£112,500,000	£6,100,000
Hammersmith and Fulham	1478	£97,600,000	£5,300,000
Haringey Teaching	1707	£112,700,000	£6,100,000
Harrow	1074	£70,900,000	£3,900,000
Havering	1066	£70,400,000	£3,800,000
Hillingdon	1397	£92,200,000	£5,000,000
Hounslow	1206	£79,600,000	£4,300,000
Islington	2473	£163,300,000	£8,900,000
Kensington and Chelsea	1570	£103,600,000	£5,600,000
Kingston	927	£61,200,000	£3,300,000
Lambeth	2690	£177,600,000	£9,700,000
Lewisham	2043	£134,900,000	£7,300,000
Newham	1659	£109,500,000	£6,000,000
Redbridge	1470	£97,100,000	£5,300,000
Richmond and Twickenham	1246	£82,300,000	£4,500,000
Southwark	2627	£173,500,000	£9,400,000
Sutton and Merton	2378	£157,000,000	£8,500,000
Tower Hamlets	1870	£123,500,000	£6,700,000
Waltham Forest	1197	£79,000,000	£4,300,000
Wandsworth	1810	£119,500,000	£6,500,000
Westminster	2212	£146,000,000	£7,900,000
London	**58000**	**£3,829,300,000**	**£208,100,000**

Interpretation

The analysis above demonstrates that it is always cheaper to treat HCV-infected people than to allow their disease to progress unchecked. According to this model, a conservative objective of increasing treatment to 10% of infected people would result in £200million savings over the lifetime of this cohort,

and a more challenging goal of 20% treatment coverage would result in £400million savings across London. These savings are not inconsiderable, and in reality are likely to be much greater.

The difficulty this poses for Commissioners is that the costs of treatment must be found now and then the savings are realised later. It was stated above that whilst the costs of non-treatment were considered to be underestimates, the cost of treatment only factored in drug costs. The costs of administrative, structural and clinical costs could be found from the projected savings. While the considerable savings outlined for each borough in table 8a would cover these costs comfortably, the fact remains that the savings have yet to be realised. In this context, 'savings' can be a misleading term, however, and 'avoided cost' is a more accurate description. Ultimately, upfront investment is required to achieve these outcomes and willingness to do this will depend on a number of factors including existing service infrastructure in each locality, local priorities to reduce health inequalities and to reduce premature mortality from liver disease, and willingness to work with and invest in this client group.

If there is a commitment to invest in this area, the question remains as how best to go about this. From this analysis we can see that treating all stages of disease from mild to cirrhotic is cost effective, the most cost effective being moderate liver disease. Consideration of the testing to treatment pathway for general practice and drug treatment services showed the latter to be more costly due to the higher uptake of antibody tests followed by a greater drop-out rate further along the pathway before treatment is initiated. These additional costs must factor in two important factors: the additional factors related to a positive diagnosis of HCV and the higher overall conversion rate in this population. The additional factors to consider are whether a positive HCV diagnosis causes current PWID to adopt safer injecting practices, thus reducing risk of transmission, and whether it may serve as a trigger to reduce or stop injecting. Similar numbers of HCV-positive people were completing treatment despite the former PWID population being over three times larger than the current PWID cohort. Focussing on improving the drug treatment services pathway is therefore a more cost-effective approach than general practice testing.

Improving the proportion of patients referred to specialist hepatology services who then go on to initiate treatment would have by far the greatest impact on numbers completing treatment, and therefore SVR, even if only a small increase were achieved. Otherwise, increasing the number of referrals from drug treatment services has the next greatest impact on treatment completion.

Appendix B: Survey to Commissioners

1. What is the name of the Local Authority/ies on whose behalf you commission drug treatment services?

2. If you are happy to be contacted in relation to your responses to this survey, please could you provide your name and contact details

3. Do you have a documented patient pathway for PWID and HCV for your borough, from testing through to discharge from treatment? If yes, please could you provide a copy to abigail.knight@inwl.nhs.uk

4. Please could you list all the Drug Service Providers you commission in your area?

5. Please could you list all the GP shared care providers that you commission in your area?

6. Please could you list all the needle exchange providers who also offer any blood borne virus (BBV) services in your area?

7. Please could you list any other services you commission related to blood borne viruses in PWID?

8. For each of the below BBV service areas, please indicate which are offered by each type of service provider (please tick as many boxes as apply):

	Offered by drug treatment services	Offered by GP shared care	Offered by needle exchange programmes	Offered by another service, please name
HCV rapid blood spot testing				
HCV RNA testing				
HBV blood test screening				
HBV vaccination				
Liver Function Tests				
HCV treatment				
Holistic assessment, including housing status, social needs, MH needs				
Mental health assessment and support				
Alcohol extended brief intervention				
Key worker support for HCV				
Peer support groups for HCV				
Other (please specify)				

9. What mechanisms do you have in place in your local area to ensure that patients referred for HCV treatment attend the appropriate treatment services?

10. Please indicate for each type of service the number of HCV tests conducted in the last available 12 month period

- Drug treatment services

- GP shared care
- Needle exchange programmes
- Alcohol extended brief interventions
- Other

11. Please provide figures for the last available 12 month period on the following for your borough(s):

- Positive HCV tests
- Number of people receiving HCV treatment
- Number of people completing HCV treatment

12. What was the source of data for question 9?

13. What is the total number of people with diagnosed HCV in your area?

14. Please indicate the payment mechanism for the BBV component of each of these types of service

	Block contract	Included within larger contract including non-BBV components	Stepped contract	Tariff	No contract
Drug service					
GP shared care					
Needle exchange programme					
Other (please specify)					

15. Please could you indicate the value of the BBV contract according to the above selected mechanism of payment?

- Drug service
- GP shared care
- Needle exchange programme
- Other

16. Is laboratory HCV testing included in this contract? If no, please indicate who you commission these services from and at what cost.

17. In what areas are there additional costs to the budget if a patient tests positive? What are these additional costs and who is responsible for them?

- Secondary care referral
- Treatment
- Follow up support
- Other

18. Is there anything you would like to add on the delivery of services for HCV in PWID?

Appendix C: Survey for Drug treatment service Providers

1. What is the name of your service?

2. What is the full address of your service?

3. What is/are the name(s) of the organisation(s) that commission your service?

4. Which London Borough(s) are covered by your service?

5. If you are happy to be contacted in relation to your responses to this survey, please could you provide your name and contact details

6. Do you have a documented patient pathway for PWID and HCV, from testing through to discharge from treatment, of which your service is part? If yes, please could you provide a copy to abigail.knight@inwl.nhs.uk

7. Where do you receive referrals from which require HCV testing and follow up? please indicate as many as apply.

- No referrals that include HCV testing and follow up
- Local GP practices
- Local needle exchanges
- Alcohol extended brief interventions
- Criminal justice services
- Self-referral
- Other (please specify)

8. Please indicate how the following blood borne virus services are delivered in relation to your service and whether information on referrals are shared with you:

	Not offered	Offered through your service	Referred to another service	If you refer to another service please tick here if you receive feedback on the outcomes of your referral (eg. patients attending appointment)
Information on harm reduction				
HCV rapid blood spot testing				
HCV RNA testing				
HBV blood test screening				
HBV vaccination				
Liver Function Tests				
HCV treatment				
Holistic assessment, including housing status, social needs, MH needs				
Mental health assessment and				

support				
Alcohol extended brief intervention				
Key worker support for HCV				
Peer support groups for HCV				
Other (please specify)				

9. What is your policy on how frequently people known to your service are offered HCV testing?

- No policy in place
- Ad hoc testing
- Offered testing on entry to the service
- Annual testing
- Testing every six months

10. Do you offer outreach services for HCV testing?

11. What are the reasons given by clients for declining testing? Please highlight as many as apply. If you are able to, please indicate the number of clients giving each reason.

- Reasons not recorded
- Fear of result
- Clients do not perceive the test as relevant to them
- Clients prefer to consider testing later
- Clients do not consider they have enough information on which to make an informed decision
- Test carried out recently and no indication of risk behaviour since that time
- Other, please state

12. What are the exclusion criteria for HCV positive patients being offered HCV treatment?

- Currently injecting drugs
- Currently using any other illegal substances
- Currently alcohol dependent
- Other BBV diagnosis
- Displays medical contraindication to interferon or ribavirin
- Mental health concerns
- Other (please specify)

13. Do you have the active involvement of a Hepatologist in your service?

14. Please can you indicate the current wte. levels of staffing in your service?

- Service Managers
- Counsellors
- Nurses
- Health Care Assistants
- Other

15. Please can you indicate the current wte. vacancies in your service?

- Service Managers
- Counsellors
- Nurses
- Health Care Assistants
- Other

16. Is there a nominated person responsible for liaising with each of the following stakeholders?

- Hepatitis treatment centres
- Prisons
- Primary care

17. Do you monitor patient satisfaction in your service, and if so what aspects do you monitor?

18. Please indicate the payment mechanism for the BBV component of each of these types of service

- Block contract (single sum to deliver all BBV services)
- Included within larger contract including non-BBV components (like a block contract but including other non-BBV services as well)
- Stepped contract (like a block contract but with a stepped increase in payment based on hitting certain productivity targets)
- Tariff (payment per client seen)
- No contract
- Other (please specify)

19. Please could you indicate the amount of funding you receive as per the type of payment mechanism indicated above, £

20. What services do you subcontract to other providers as part of your service (eg. laboratory testing)? For each, please indicate the current volume and cost of the contract.

21. Which organisation conducts your laboratory tests for each of the following?

- HCV Ab tests
- HCV RNA tests

22. What is the total number of people who inject drugs known to your service?

23. What is the total number of HCV positive people known to your service?

24. How many HCV tests have been offered in the last 12 month period?

25. How many HCV tests have been performed in the last 12 month period?

26. How many HCV positive results have there been in the last 12 month period?

27. How many HCV positive patients have started treatment in your service in the last 12 month period?

28. How many HCV positive patients have completed treatment in your service in the last 12 month period?

29. How many HCV positive patients have been referred to secondary care for treatment in the last 12 month period?

30. How many HCV positive patients have started treatment in secondary care in the last 12 month period?

31. How many HCV positive patients completed treatment in secondary care in the last 12 month period?

32. How many people who inject drugs were given a hepatitis A vaccine in the last 12 month period?

33. How many people who inject drugs were given a hepatitis B vaccine in the last 12 month period?

34. How many staff members have completed the RCGP Certificate in the Detection, Management of Hepatitis B and C in Primary Care?

35. How many staff members have completed an alternative qualification or training in hepatitis management? Please state what.

36. Is there anything you would like to add on the delivery of services for HCV in people who inject drugs?

Appendix D: Abridged Analysis of HCV Testing and Diagnostic Methods, North East North Central London Health Protection Unit

Nixon G. *Draft HCV Scoping Project for Islington.* NENCL HPU, 2012 (unpublished)

Methods of HCV Testing

Table 1: Costs, accuracy and other considerations of currently available HCV antibody tests

Test	Cost	Sensitivity / Specificity	Notes
Concateno DBS (email communication with Dr Amin Sharif, Concateno)	Kit and screen handling charge - £9.98 HCV Antibody - £8.55 (confirmation done using HCV RNA assay). HCV RNA £38.00	Sensitivity 98%, specificity 100%	Assay validation - sensitivity / specificity as tested on 50 positive and 50 negative samples. However the performance on weak positives (using traditional serology method) was not demonstrated in data provided. In addition, validation did not replicate 'real life' conditions in that blood spots artificially made from plasma/serum samples and then kept in fridge until testing (as opposed to simulating conditions as in postal system). Concateno state that assays not suitable for diagnostic purposes, but should be used as 'presumptive evidence'. Reports also state that a venous blood sample is needed to confirm results. Although HCV RNA test currently cheaper than Manchester, because an antibody confirmation step is not used, it is possible that more samples are tested for HCV RNA than would be using the Manchester assay. No data provided on thresholds for HCV RNA detection.
Concateno Oral fluid (as above)		Sensitivity 90%	Sensitivity of 90% is quite low to use as a diagnostic test. May be useful for patients who are needle-phobic since it has been reported that those false negatives detected by this method represent those who have cleared infection and have waning antibody levels; however, convincing data regarding this is not currently available (personal communication with Professor John Parry, HPA). This assay will soon be withdrawn.
HPA Manchester DBS (email communication with Professor Paul Klapper)	Kit - £7.70 HCV Antibody - £3.74 (confirmation - £6.90)	sensitivity 98% specificity 99.99% (because they always confirm reactive result with the second assay)	Assay validation - 130 samples of blood known to be negative and a minimum of 60 samples known to be positive, including weak positives. Laboratory performed thorough stability testing in order to make sure each of the analytes survived on the paper during transit to the laboratory. A confirmatory assay is used to confirm reactivity. The laboratory is fully CPA accredited and the details can be found on the CPA website. The assays used are CE marked for whole blood and 'self-validated' for use on DBS.
	HCV RNA £66.22 (includes genotype)	96% sensitivity – specificity 99.99%; equates to a	Sensitivity of 500-1000 IU/ml. Currently genotype always done with HCV RNA testing, which increases costs; however, this will change in the near future so that RNA can be tested

		limit of sensitivity of about 500IU/ml	without genotype, making the assay much cheaper.
OraQuick – used on fingerstick or oral fluid	£16 per test (Invitech Ltd: £500 / for 25 tests, but 20% discount typically available)	Fingerstick – Sensitivity 99.7% Specificity 99.9% Oral fluid Sensitivity 98.1% Specificity 99.9%	This assay is CE marked for use on oral fluid and fingerprick blood (it is required to be since it is a bed-side assay); it also has FDA approval for use on fingerprick blood. This approach uses a cassette encased nitrocellulose test strip and an indirect immunoassay method. If antibodies present in the sample react with specific antigens on the strip, a line is visualised at the test zone (a control line detecting human IgG ensures a test sample has been appropriately taken and processed). The OraQuick in fact demonstrated greater sensitivity than traditional serology when tested on a panel of seroconverters, detecting HCV antibody 4.9 days before EIA. The assay has also been shown to have a PPV of 99.9% and NPV of 99.9% for fingerstick blood, and PPV of 99.3% and NPV of 99.0% for oral fluid.

Of note only one of the testing systems outlined in the table is CE marked, in line with the European Directive 98/79/EC on in vitro diagnostic medical devices, or IVD Directive (IVDD). However, it is widely recognised that the emergence of companies offering IVD testing as a service was unforeseen in the IVDD. This has led some companies offering diagnostic services to believe that their testing activities are also exempt from CE-marking. However, article 9(13) ("The provisions of this Article shall apply accordingly to any natural or legal person who manufacturers devices covered by this Directive and, without placing them on the market, puts them into service and uses them in the context of his professional activity.") of the IVDD clearly brings commercial IVD testing within the directive's scope. However, it has become clear that this requires clarification. As a result the European Commission has published a consultation on the revision of the IVDD which is likely to inform changes to the directive. Whilst some tests which are currently not CE-marked will be of high quality due to stringent internal quality control systems, the fact that these tests are not subject to any regulatory body or external quality control system, means that there is a public health risk involved with employing these assays.

Methods of HCV Diagnosis

Large numbers of methods have been investigated for this purpose. They fall into one of two main approaches:

A 'biological' approach based on the dosage of serum biomarkers of fibrosis, for example:

- Direct markers, components of extracellular matrix which forms liver fibrosis: procollagen I, procollagen III propeptide (PIIIP), transforming growth factor β1 (TGF-β1), hyaluronic acid, and combinations of direct markers, e.g. Enhanced Liver Fibrosis (ELF) test.
- Indirect markers, based on disturbance of hepatic function: alanine transaminase (ALT), aspartate transaminase (AST), Prothombin time, platelet count, Apolipoprotein A-1 (ApoA-I), Alpha-2-macroglobulin, and combinations of indirect markers, e.g. FibroTest.

A 'physical' approach based on imaging alone: Ultrasound, MRI; or measurement of liver stiffness: transient elastography (fibroscan).

It is common for ... [people with] a diagnosis of chronic HCV to decline referral to hepatology services for assessment. In such cases, blood tests taken in primary care services could provide a preliminary assessment. Studies to date have not assessed the performance of these tests in patients identified in primary care. The levels of the fibrosis markers may well vary by changes in clearance, metabolism, and excretion, and contribution from non-hepatic sources, such as bones, joints, lungs, kidneys and skin. This is significant since various concurrent problems might raise the values of these markers (e.g. [the] fibrous tissue repair process following a twisted ankle may also increase some of these values), leading to an incorrect assumption of significant fibrosis. The most appropriate test to use in the primary care setting would be one which has an excellent sensitivity and [negative predictive value] for fibrosis. Given it seems that many HCV RNA positive patients are not referred to hepatology immediately, such a test could potentially help in determining whether referral to hepatology services should not be delayed.

Some of the most intensively evaluated non-invasive methods for the assessment of liver fibrosis include:

AST to platelet count (APRI) – a simple test with reasonable accuracy, however sensitivity for fibrosis has been shown to be as low as 22-39% in some studies.

Fibrotest (combination of 5 indirect markers) – has been suggested as an alternative to liver biopsy in chronic HCV patients. Sensitivity has been reported to be 67% for significant fibrosis and 85% for cirrhosis and NPV of 78% and 100% respectively.

FibroMeter (combination of direct and indirect markers together with age) has been shown to have a sensitivity of 64% for significant fibrosis and 92% for cirrhosis, and NPV of 77% and 100% respectively, with a further study finding a sensitivity of 80% and NPV of 78%.

ELF (combination of 3 direct markers) – has been demonstrated to work well when testing a cohort with HCV who were 95% Caucasians. Sensitivity of 86% for significant fibrosis and 83% for cirrhosis has been reported with a NPV of 70% and 95% respectively. Unpublished work has shown that it does not perform well on people from Pakistan or Bangladesh with HCV.

Hepascore (combination of direct and indirect markers together with age and gender) - sensitivity of 77% for significant fibrosis and 92% for cirrhosis reported, with a NPV of 80% and 100% respectively.

FibroScan- for HCV infected patients a sensitivity of 79% for significant fibrosis and 84% for cirrhosis, and NPV of 50% and 91% respectively. A problem with this test is that a reliable result is not obtainable in as many as 22% of patients, furthermore a blood test could be offered in primary whereas a FibroScan could not.

The French authority of health recommended four tests, Fibrotest, Hepascore, FibroMeter and FibroScan for the diagnosis of liver fibrosis in adults with untreated HCV without comorbidity. Studies which compare these tests head to head on the same populations are likely to be most useful in determining which test is most suitable to a particular patient cohort: one such study suggests that FibroMeter provides the best performance. […] a paper earlier this year recording results using nine different blood tests together with FibroScan and determined that Fibrotest, interpretable Fibroscan, Fibrometer, and Hepascore perform best and similarly for diagnosis of significant fibrosis and cirrhosis. In this paper interpretable Fibroscan and Fibrometer appear to have the highest sensitivity and NPV.

Incorporating a highly sensitive blood test into referral algorithms in primary care, should be done with the caveat that the values obtained from such tests cannot be fully relied upon and does not replace or negate the need for clinical judgement by a hepatologist.

Appendix E: LJWG recommended pathway algorithm