Increasing treatment uptake to eradicate hepatitis C infection

In 2016, the World Health Organization set itself the goal of eliminating viral hepatitis – which causes an estimated 1.34 million deaths every year (Bit.ly/WHAViralHep) – by 2030 (WHO, 2016a). The plan is to:

- Reduce the mortality rate by 65%;
- Increase access to treatment from 1% to 80% of infected people;
- Reduce transmission by 90% (WHO, 2017).

If these targets are achieved, an estimated 7.1 million lives will have been saved (WHO, 2016a). Hepatitis C virus (HCV) is one of the major culprits in the spreading of viral hepatitis; NHS England recently announced plans to be the first country to eliminate it, aiming to do so at least five years ahead of WHO’s goal of 2030 (NHSE, 2018). To achieve elimination, healthcare providers need to increase uptake of HCV treatment by identifying people with existing infection and engaging with hard-to-reach patients. This article describes how Queen Elizabeth Hospital Birmingham is addressing the challenge by re-engaging with patients lost to follow-up and to engage with local drug users and prison inmates.

Abstract
Viral hepatitis is a major cause of death across the world and hepatitis C virus infection represents a large share of the burden. Curing hepatitis C has become more feasible since the emergence of direct-acting antivirals, which have cure rates of >95%. NHS England has set up a national network of treatment services and, since February 2017, treatment has been available to all infected patients, regardless of genotype and liver fibrosis staging. Today the challenge is not so much how to treat patients, but how to identify them in the first place, as many are not known to health services. This is because they are unaware of their infection, they do not feel they need treatment, do not know about the new treatments available, or they belong to hard-to-reach groups such as homeless people, prisoners and injecting drug users. This article looks at the methods used at Queen Elizabeth Hospital Birmingham to re-engage with patients lost to follow-up and to engage with local drug users and prison inmates.

Key points
- The World Health Organization aims to eradicate viral hepatitis by 2030
- Hepatitis C virus infection is often asymptomatic so people who are infected may not realise
- With the emergence of direct-acting antivirals, cure for all patients is within reach
- Services need to actively engage with patients lost to follow-up and hard-to-reach groups such as prisoners, homeless people and injecting drug users
- Collaboration between services is needed to work towards prevention, testing and treatment

In 2016, the World Health Organization set itself the goal of eliminating viral hepatitis – which causes an estimated 1.34 million deaths every year (Bit.ly/WHAViralHep) – by 2030 (WHO, 2016a). Hepatitis C virus (HCV) is one of the major culprits in the spreading of viral hepatitis; NHS England recently announced plans to be the first country to eliminate it, aiming to do so at least five years ahead of WHO’s goal of 2030 (NHSE, 2018). To achieve elimination, healthcare providers need to increase uptake of HCV treatment by identifying people with existing infection and engaging with hard-to-reach patients. This article describes how Queen Elizabeth Hospital Birmingham is addressing the challenge by identifying known patients lost to services and identifying new ones.

HCV infection
There are different types of viral hepatitis, hepatitis C being one of the most common. Previously known as ‘non-A, non-B hepatitis’, hepatitis C was discovered in 1989 (Dudley, 2009). The different HCV mutations are grouped into six genotypes, which often correlate with a geographical area:

- Genotype 1 is common in the Western world;
- Genotype 3 is more common in Asia;
- Genotype 5 is most often found in South Africa.

Treatment will vary according to genotype (Jack, 2014).
Effects of HCV infection
The term ‘hepatitis’ means inflammation of the liver cells – or hepatocytes. HCV infects hepatocytes and prevents them from functioning properly, which leads to the liver becoming inflamed. This inflammation, known as fibrosis, is reversible if its cause is removed or eliminated. If inflammation and damage continue, the amount of fibrosis increases and eventually leads to cirrhosis, resulting in permanent scarring. Some patients infected with HCV may not develop cirrhosis for 15-20 years, but heavy drinking and co-infection with HIV and/or hepatitis B virus are known to accelerate the process (Boesecke and Wasmuth, 2014).

Diagnosis
The suspicion of HCV infection often arises because routine blood tests (measuring levels of aspartate transaminase and alanine transaminase) reveal abnormal liver function. Further blood tests are undertaken to see whether hepatitis C antibodies are present, which will show in the blood within 2-3 months of infection. However, antibodies will also be present if the patient has been infected in the past and has either seroconverted or been treated and cured, so a third blood test is needed to diagnose current infection. This uses the polymerase chain reaction, which shows the reproduction and amount of HCV in the blood.

Symptoms
Many people with HCV infection remain asymptomatic, so it is likely that many are unaware of their infection (Maghlaoui, 2012). However, one in four will show symptoms within six months; these may include:

- Fatigue;
- Depression;
- Headaches;
- Itching;
- Muscle pains;
- Confusion or, as the Hepatitis C Trust has referred to it: ‘brain fog’ (Bit.ly/HepCTrustSymptoms).

Such symptoms occur in a variety of conditions so there is a risk of misdiagnosis. As the condition and related liver damage progress, symptoms will worsen. Patients may experience splenomegaly and portal hypertension, which increases the risk of varices and bleeding. Other long-term symptoms include:

- Ascites;
- Jaundice;
- Hepatic encephalopathy (British Liver Trust, 2016).

Viral transmission
Viral hepatitis is blood borne, so HCV transmission via infected blood can result from:

- Poor medical and dental infection control;
- The sharing of infected needles among injecting drug users;
- A lack of infection control precautions in tattoo and piercing parlours.

The virus can also be transmitted through contaminated blood products used for transfusion, as happened in the UK (and other countries) before 1991.

Another possible route of transmission is unprotected sexual intercourse with an infected partner. The risk of sexual transmission is low in heterosexual couples but higher in men who have sex with men (British Liver Trust, 2015).

Who needs treatment?
In 20% of cases, HCV is cleared from the body without treatment. The remaining 80% of patients will develop chronic HCV infection and require treatment; cure is defined as having reached a sustained virologic response (SVR). In the UK, an estimated 200,000 people have chronic HCV infection; many are from disadvantaged backgrounds – people living in poverty, homeless people, injecting drug users – or are in prison (Public Health England, 2017), where infection rates with blood-borne viruses among inmates are increasing.

Preventing transmission
Drug services work to encourage safer needle practices by providing needle exchange services to injecting drug users. Health professionals advise people who are found to be HCV-positive to avoid sharing razors or toothbrushes, and teach them how to clean blood spillages.

Safer sex practices and only having piercings and tattoos from reputable services are two further keys to the prevention of HCV transmission (British Liver Trust, 2013).

A sea change in treatment
Direct-acting antivirals
The way HCV infection is treated has changed dramatically over the past few years. This is mostly due to the emergence of new drugs called direct-acting antivirals (DAAs), which NHSE started commissioning in June 2014. These drugs are taken orally, which simplifies treatment; traditional dual-treatment regimens – still commonly prescribed until very recently – involved a weekly subcutaneous injection of pegylated interferon (peg-IFN) combined with an oral antiviral medication such as ribavirin, both of which carried a high risk of side-effects. DAA regimens have better side-effect profiles, shorter treatment courses and much higher cure rates (>95%) (Vine et al, 2015).

Today, there is a wide range of DAAs marketed in the UK in different combinations. They include:

- Daclatasvir;
- Dasabuvir;
- Grazoprevir;
- Elbasvir;
- Ledipasvir;
- Ombitasvir;
- Paritaprevir;
- Ritonavir;
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- Sofosbuvir;
- Velpatasvir.

All of these have been approved by the National Institute for Health and Care Excellence.

Operational delivery networks

In August 2015, NHSE set up 22 operational delivery networks (ODNs) across England to oversee the implementation and running of a national hepatitis C treatment service (Bit.ly/HepCODNs) that would ensure access to treatment for all, including prisoners and people with chaotic lifestyles. However, ODNs were still prioritise patients with cirrhosis.

In April 2016, in line with PHE data on local epidemiology, NHSE set a target of 10,000 patients to be treated in England during the financial year 2016/17. Each ODN was allocated its own target of patients to treat, which was linked to a Commissioning for Quality and Innovation (CQUIN) scheme. Not only did ODNs have to aim to treat all patients with first-line treatment, but they also risked incurring a financial penalty if they did not reach their target. The CQUIN scheme also required enhanced data collection, participation in clinical trials and improved services for patients (NHSE, 2016a).

Extending DAA regimens

At the beginning of 2016, patients without cirrhosis became eligible for the new all-oral DAA regimens, except for genotype 3 patients, which led to many becoming disengaged from health services and lost to follow-up.

Finally, in February 2017, NHSE made DAA regimens available to all patients infected with HCV, regardless of genotype or liver fibrosis staging. The number of patients to treat in 2017/18 was increased by a quarter, with a corresponding increase in funding for the drugs, so 12,500 patients could be treated with an excellent chance of cure (Vine et al, 2015). The primary aim was to continue engaging with patients, particularly those without cirrhosis who could now be offered an all-oral treatment regimen (NHSE, 2016b).

Change of focus

DAA regimens are still relatively new, and took time to be made available to all patients – as a result there are still many misconceptions and still much misinformation among patients. Many do not know that interferon is no longer used and has now been replaced by safer and more-efficient drugs.

For health professionals, the ability to treat all patients – and potentially cure many of them – is encouraging. However, a number of barriers make it challenging to ensure people with HCV infection receive treatment. For example, many may not be aware they are infected (Thursz, 2017), while those without cirrhosis may not feel ill, so not see the importance of treatment.

Some might not want treatment because they are unaware of the advantages of all-oral regimens, while others may have chaotic lifestyles that are unconducive to treatment, even though the new regimens are much easier to follow than previous ones. Some may be aware of their HCV status but have never been referred for treatment by their GP.

The focus needs to move from simply treating patients who are known or found to be infected, to proactively identifying people who are infected but are not known to, or engaged with, health services.

Engaging with patients

One key question is: how do you re-engage with patients who have been lost to follow-up? At the hepatology department at Queen Elizabeth Hospital Birmingham, we have an extensive database of patients known to have HCV infection. In June 2016, we started using the database to try to reconnect with those with whom we had lost contact, with a view to offering them treatment with DAA regimens.

Phase 1

In a first phase, we identified 31 patients with cirrhosis who had not attended more than two clinic appointments with us. For 19 of them, we wrote to the consultant and/or clinical nurse specialist who had cared for them in local hospitals, asking for an update. We
obtained a good response: of the 19 patients, 16 had either been treated – and many cured – or were still being treated (Fig 1).

We wrote to the GPs of the other 12 patients; we received no response to nine of the letters, two had been addressed to the wrong GP due to patients changing GPs but GP systems not being updated, and one patient was tracked down and wanted to be treated. The patient was offered an appointment to see a CNS, but did not attend that appointment and contact was lost again.

**Phase 2**

In the second phase, as DAAs became more widely available to patients with cirrhosis, we turned our attention to those who did not have cirrhosis. We sent out 22 letters, and made one phone call, to local consultants and CNSs (Fig 2). This time, due to the low response rate from previous letters to GPs, patients who had not been seen at a local hospital were contacted directly, rather than through their GPs. We sent them a letter inviting them to attend a nurse-led consultation at our hospital. In total, 17 letters were sent, but only five patients took up the offer of an appointment. Of these five people, only two started treatment: one of these patients was cured, the other did not return for SVR.

Of the 17 letters:
- Two were returned as having a wrong address;
- One patient cancelled the appointment that had been made;
- One patient was an inpatient elsewhere;
- Eight patients did not respond;
- Five patients attended the appointment; of which:
  - Two did not want treatment;
  - Three were booked in for treatment, but one did not attend.

We also contacted patients directly by telephone. So far we have contacted an additional 11 patients in this way, with the following results:
- Five calls were not responded to;
- Two outpatient appointments have been made;
- One patient is serving a prison sentence;
- One patient is being treated at their local hospital;
- Two patients have been referred to their local hospital.

This work is ongoing.

**Phase 3**

Since February 2017, when DAA regimens became accessible to all genotype 3 patients, we have been trying to re-engage with all our genotype 3 patients. In this third phase, we contacted 29 patients with cirrhosis (Fig 3) and 43 patients without cirrhosis (Fig 4).

Patients who had not been seen recently were contacted by telephone and informed of the new treatments. A small number of patients were already due for outpatient appointments; the CNSs ensured we discussed their cases at our weekly multidisciplinary team meeting and the new treatments were explained to them at their appointments. There were a few patients we were unable to contact.

We also had, in our database, 10 genotype 3 post-transplant patients who had not yet been treated or had not achieved an SVR with traditional dual therapy. They were also contacted by telephone, or ‘caught’ at outpatient appointments that had already been planned, and informed of the changes in treatment regimens. Of these 10 patients:
- One was living abroad;
- Two had already been treated elsewhere;
- Three had treatment planned at their local hospital;
- Four were referred for treatment locally.

**Tackling barriers to treatment**

The other burning question to ask is: how do you engage with hard-to-reach patients and persuade them to take up treatment? For groups such as prisoners, homeless people and injecting drug users, treatment in hospital is nigh on impossible. Prison services often cannot take inmates to outpatient appointments, while injecting drug users and the homeless face barriers such as:

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**Fig 3. Outcomes for genotype 3 patients with cirrhosis (n = 29)***

- Patient in prison
- Did not want treatment
- Treatment booked
- Treatment planned at local hospital
- Outpatient appointment planned at UHB
- Started treatment
- Unable to contact
- Deceased
- Other health issues

***Patients contacted by phone or at pre-planned outpatient appointment. †At the time of project hepatocellular carcinoma treatment took priority.

UHB = University Hospitals Birmingham.

**Fig 4. Outcomes for genotype 3 patients without cirrhosis (n = 43)***

- Treatment planned at local hospital
- Started treatment
- Treatment booked
- Did not attend for treatment†
- Did not want treatment
- Unable to have treatment due to other health issues
- Outpatient appointment planned at UHB
- Patient in prison
- Unable to contact

***Patients contacted by telephone or at pre-planned outpatient appointment. †At the time of project hepatocellular carcinoma treatment took priority, and patients with end-stage renal failure could not have the available treatment for hepatitis C.

UHB = University Hospitals Birmingham.
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- Financial constraints;
- A distrust of health services;
- Chaotic lifestyles.

As a result, very few come forward for testing and treatment (Grebely et al, 2017).

Injecting drug users

In parallel with our work trying to reconnect with patients who lost to follow-up, in September 2015 we set up an outreach service to bring treatment to patients. A local GP practice allowed us to hold a clinic for patients who received methadone prescriptions at the surgery and had hepatitis C infection. The purpose of the clinic was to enable patients to meet a consultant to discuss HCV treatment and have fibrosis staging and blood tests, thereby reducing the number of outpatient appointments and the travel requirements they would need if they decided to proceed.

Forty-four patients were invited to meet a consultant; if they decided to proceed with treatment, they would meet the CNS again to start the process. Of these:
- Sixteen patients attended the appointment with the consultant;
- Twelve were treated and have now achieved an SVR;
- Three did not attend their appointment with the CNS;
- One has been referred to a local hospital.

We also started seeing service users at a local drug service where they pick up their methadone or buprenorphine prescriptions. The service is in the centre of Birmingham, so it is easily accessible.

So far, we have seen 74 patients who had been referred to us from a range of sources; 73 consultant appointments have been offered (one service user has died in the mean time). At the time of writing, 42 appointment dates have passed, of which 21 (50%) have been attended. For seven patients who were being seen in hospital it was found that it was more appropriate for them to receive treatment at the local drug service. In total, 28 patients were booked in with a CNS to start treatment. Of these:
- Eighteen have begun treatment (eight are awaiting their SVR result and 10 are still on treatment);
- Three did not attend for treatment;
- Two are booked for a future date;
- Five are waiting to find out their genotype so treatment can be planned.

Prison inmates

Our local prison is another place where we are trying to establish an in-reach service, with many obstacles to overcome. For example, prisoners are often moved around between prisons, and a ‘medical hold’, which prevents them from being transferred for medical reasons, is no longer likely to be granted. In fact, one patient on treatment has since been transferred without their medication.

Gaining access for healthcare workers, obtaining authorisation to bring medication into prison and going through security procedures can take time (NICE, 2017). It has taken our consultant three years to obtain access to the local prison for the team.

Two clinics have taken place so far, with further clinics planned. So far, 10 prisoners have been seen:
- Two had already been treated for HCV infection but had not been given an SVR result, so their status was checked;
- One has started treatment;
- One has been released and is planning to be treated at the hospital;
- Six are waiting genotyping results so treatment can be planned.

Conclusion

There is no single solution to tackling HCV infection, and our experience at Birmingham shows how difficult it can be to track down former patients and identify and engage new ones. NHS Scotland has increased the target number of patients to be treated in 2018/19 to 15,000. This gives treatment centres in England a great opportunity to focus on engaging or re-engaging with patients.

Hospital departments need to work closely with drug services, public health teams, outreach clinics and general practices to identify newly diagnosed and undiagnosed patients (PHE, 2017). Public awareness needs to increase so the risk of transmission can be lowered. Better public awareness will also mean better uptake of testing, leading to more people being diagnosed and treated. Prevention will help to reduce new transmissions, but there will remain a high number of people already infected who will need treatment – once they are identified (WHO, 2016b). NT

References


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