Joint working to treat hepatitis C in hard-to-reach patients who are co-infected: a case study example

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Introduction

As a result of shared routes of transmission, at least one quarter of people living with HIV globally are also infected with hepatitis C (HCV) [1] and the rate of co-infection in the UK is estimated to be approximately 9% [2]. Hepatitis C does not have an effect on HIV progression [3], but despite advances in treatment, patients who are co-infected with HIV and HC are still at higher risk of developing liver cirrhosis [4]. In addition to this, the progression of liver fibrosis in co-infected patients is more rapid than in those who are mono-infected [4]. Successful eradication of HCV is believed to reduce the incidence of hepatocellular carcinoma, slow the progress to liver cirrhosis, and decrease liver-disease-related mortality [5]. Because of these independent risk factors, treatment for hepatitis C in co-infected patients should be a priority [6].

In recent years, there have been significant advances in treatment for hepatitis C, including advances in treatments for those who are co-infected with HIV. Treatment was previously pegylated interferon alfa 2a and ribavirin therapy, lasting 48 weeks. Side effects included flu like symptoms, pancytopenia, GI upset, weight loss, alopecia, sleep disturbance, depression and irritability [4]. In addition to this, patients co-infected with HIV and HCV had only a 20–50% success rate [7]. A combination of poor success rates and a myriad of side effects led to a poor uptake of treatment and a high discontinuation rate [4].

However, since 2011, there have been dramatic improvements to both the safety and side-effect profile, and more importantly, the success rates of treatment, rising to over 95% [4]. This is true of both patients with nil liver disease and compensated cirrhosis [8]. The new generation of treatments are known as directly acting antivirals (DAAs) and work by inhibiting several of the nonstructural proteins that are integral to HCV replication and function. People co-infected with HIV and HCV had poor response rates to interferon treatment, but this is no longer the case using DAAs. Studies have shown that the cure rates are as high as those for HCV mono-infected individuals, and they do not experience any worse side-effects [9].

As the safety of hepatitis C treatment has improved, the need for treatment to take place in a hospital environment has lessened. Increasingly, hard-to-reach patients are being treated successfully in the community [10] and this case study highlights an example of treating a patient who has HIV and HCV, and is hard-to-reach in terms of not attending the clinic for specialist review.

Treatment guidelines

The American Association for the Study of Liver Diseases (AASLD) 2018 guidelines recommend that the same treatments are applied to co-infected and mono-infected individuals, but with an emphasis on further monitoring and management of drug–drug interactions. They also recommend that any antiviral switches should be done in collaboration with an HIV consultant and preferably a specialist pharmacist [6]. Any interruption of HIV therapy to allow HCV treatment to go ahead is not recommended as HIV suppression needs to be maintained and is of absolute importance; HIV treatment interruption can lead to an increased risk of cardiovascular events, as demonstrated in the SMART study [11], and increased risk of fibrosis progression and hepatic-related events [12]. Prior to any switching, previous treatment history, viral response to treatments, resistance profiles and drug tolerance all need to be considered to ensure the most efficacious treatment is given to suppress any HIV activity. Switching an HIV regimen does have risks and patients are generally anxious about any new potential side effects or viral rebound.

The British HIV Association (BHIVA) 2013 guideline recommends that patients with co-infection should be looked after by clinicians who are experienced in both HIV and HCV, and those patients with advance liver disease should be treated by liver specialists in centres that manage these complications [13].

A group of representatives from the British Viral Hepatitis Group, British Association of Study of Liver, British HIV Association, British Infection of the Liver and the Clinical Virology Network met in June 2017 to produce national guidelines that reflected best practice in using DAAs, particularly considering different commissioning decisions in England, regarding individual trusts' prescribing policies [14].

Recommendations included:

- NHS England considers commissioning a pan-genotypic regimen for use in the community for

treatment-naive patients who are not cirrhotic to avoid the need for genotype tests and facilitate rapid access to care.
- Ribavirin to be avoided when possible.
- First-line choice for treatment naive non-cirrhotic patients treated in the community or prison regardless of genotype should be a ribavirin-free course for 8 weeks. Lastly, therapy should take potential drug–drug interactions into account and continual assessments should be carried out to monitor these.

Treatment criteria in NHS Lothian are based on National Clinical Guidelines published in 2017 by Healthcare Improvement Scotland and NHS National Services Scotland. They outline that all treatment naive and treatment experienced patients irrespective of genotype or liver disease progression are eligible for DAA treatments, with priority being given to those patients with more advanced disease and co-infection [15].

Drug–drug interactions

In the era of directly acting antivirals (DAAs) for treatment of HCV, the efficacy and adverse events rates when treating co-infected patients are similar to those seen when treating HCV mono-infected patients [9]. It is vitally important to remain vigilant regarding potential complex drug–drug interactions that could occur between DAAs and highly active antiviral therapy (HAART) and it may be that HIV therapy needs to be switched prior to commencing treatment for HCV [16].

Case study

Background

DM is a 45-year-old man who has a diagnosis of both HIV and hepatitis C (HCV), genotype one (G1) of >15 years. DM previously was infected with hepatitis B (HBV) but cleared this virus, leaving him hepatitis B core positive, surface antigen negative. He is stable on his antiretroviral (ARV) therapy and has no issues with adherence but does not attend outpatient clinic due to low mood and severe social anxiety. In terms of medication adherence, DM believes 'nurse knows best' – knowing very little about the medication he takes but trusting expert opinion. His HIV nurse specialist visits him at home and he has an excellent relationship with his GP, and his local pharmacy knows him well. He has previously declined treatment for HCV due to the need for frequent monitoring and hospital appointments before, during and after treatment.

As we have highlighted earlier, previous treatments for HCV were arduous, both physically and mentally, and DM has friends who have experienced challenging side effects, only for the treatment to fail, so he has refused to consider taking treatment to eradicate his HCV for many years.

In terms of other physical health issues, recent blood tests indicated an ongoing decrease in renal function. Extra-hepatic manifestations of HCV can include cryoglobulinemia but tests for this proved negative. He is hypertensive and has been prescribed both an ACE inhibitor, ramipril, and a calcium channel blocker, amlodipine (Box 1).

Box 1. Patient history

- HIV
- Hepatitis C
- Hepatitis B core positive, surface antigen negative
- Depression and anxiety
- Decreasing renal function

HCV:

- Assessment fibroscan 8.0kPa (F2)
- Abdominal ultrasound normal
- FIB4 1.1*

Medication:

- Nevirapine one tablet every 12 hours
- Raltegravir one tablet every 12 hours
- Lamivudine one tablet every 24 hours
- Ramipril 2.5 mg daily
- Amlodipine 10 mg daily

*FIB4: fibrosis scoring system combining patient age, platelet count and transaminase levels. 1.1 score indicates no cirrhosis.

Reactivation of hepatitis B

As mentioned in Box 1, DM had previously been infected with HBV, which he had then cleared, leaving him hepatitis B core antibody positive (HbcAb pos). Lamb reinforces the importance of monitoring for reactivation during any treatment with a DAA [8]. Hepatitis C is the dominant virus of the two; therefore, a patient can be exposed to reactivation once the hepatitis C virus is no longer prevalent [17]. In line with this evidence, best practice dictates that HBV DNA levels are monitored during and immediately after therapy [13]. Liver function tests are part of normal treatment monitoring, but specific care would be taken in reviewing transaminase levels.

Treatment regime

As mentioned earlier, all treatment options are now interferon free. According to best practice and local policy to treat non-cirrhotic G1 patients [15], DM was to be treated with an 8-week course of glecaprevir/pibrentasvir (Maviret) [18] – three tablets once daily. Maviret consists of a combination of a pangenotypic NS3/4A protease inhibitor: glecaprevir, and a pangenotypic NS5A inhibitor: pibrentasvir [19]. In terms of interactions with anti-retrovirals, Maviret should not be prescribed in conjunction with atazanavir, ritonavir-containing antiretroviral regimens, efavirenz, or etravirine [16]. The safety and efficacy of Maviret was evaluated in the phase 3, multi centre EXPEDITION-2 study [20]. This study included both cirrhotic and non-cirrhotic patients, treated for 8 weeks with a daily fixed dose of glecaprevir/pibrentasvir 300/120 mg and showed a sustained virological response at week 12 of 98%.

Treatment assessment and monitoring

As standard of care, HIV patients who have not received treatment for their HCV are highlighted by the blood

borne virus (BBV) team to the HIV team. By working together, nurse specialists from both teams try to elicit reasons for their non-attendance and assess any challenges to treatment. During a recent appointment with DM, the HIV nurse specialist discussed the excellent safety profile of new drug regimens for HCV that would minimise the need for frequent invasive monitoring. Using a multidisciplinary approach, the HIV nurse specialist, BBV nurse specialist and GP practice arranged assessment, treatment and any monitoring required to be carried out in the community. Excellent communication between community and hospital-based services are key to maintain patient safety and the benefits of this approach were made clear during the treatment of this patient.

DM was keen for treatment as he believed clearing the hepatitis C virus could improve his quality of life. This belief is common for patients with other physical and mental health issues and it was important to manage his expectations.

With increased support from the multidisciplinary team (MDT), DM was able to attend the hospital for one appointment for a medical assessment and fibroscan to measure hepatic elasticity, and a local community treatment centre for an ultrasound to assess DM's liver and to exclude both cirrhosis and hepatocellular carcinoma (HCC).

DM was taking a regimen consisting of lamivudine, raltegravir and neviripine to treat HIV. Despite his aversion to attending clinic appointments, he was completely adherent to his medication and has had an undetectable viral load for many years. There were no potential interactions between his HIV antiviral medication and Maviret, consequently we were able to avoid having to switch medication, which would have increased DM's anxiety levels, and made the HCV treatment more challenging for him.

Maviret's side-effect profile is minimal – the most common side effects are headache, fatigue and nausea, and the patient was counselled to take the medication with some food to optimise absorption and prevent any nausea. Medication was prescribed by the hospital but dispensed by a local community pharmacy. DM was monitored in the community by the HIV specialist nurse and the GP, with input from the hepatitis C team as required. Blood samples to monitor HCV (PCR), liver function, blood cell counts, urea and electrolytes, coagulation and HBV DNA were obtained at weeks 0, 4 and 8 (Box 2).

Blood samples obtained 24 weeks after treatment showed a sustained virological response to treatment, i.e. a cure. Although DM was delighted that he was cured, he was disappointed at his perceived lack of improvement to his physical and psychosocial well-being.

Box 2. Treatment monitoring

Blood tests carries out at:

- week 0;
- week 4;
- week 8;
- 12 weeks post treatment; and
- 24 weeks post treatment

Discussion points

DM was very much the norm in terms of our patient population, i.e. not keen to engage with secondary care, and this had been a barrier to treatment previously. In working together, nurse specialists from both teams try to elicit reasons for their non-attendance and assess any challenges to treatment. The treatment of DM in the community rather than in the hospital was key to the success of his treatment.

There is precedence for this; project ITTREAT in England offered a 'one-stop shop' of testing through to treatment [10]. Early data suggests this to be a successful model with scope to expand the project. In terms of local approaches, hospital-based services have reached out to the community for a number of years in limited fashion. Recent moves have been made to enhance and expand this approach to provide optimum patient care. To enable DM's treatment to be successful, a multidisciplinary approach between the HIV nurse, BBV nurse and the community services was paramount, something that has previously been lacking in the care of patients with HCV [10]. Medication was prescribed by the hospital but dispensed by DM's local pharmacy. Utilising the good relationship the patient already had in place with his local pharmacy improved the patient's experience and decreased his anxiety. Using local pharmacies as part of the MDT is widely acknowledged to enhance treatment outcomes in patients with HIV [10]. The challenges of MDT- working are that it is often dependent on individuals rather than systems in place. Structural support is imperative in achieving effective collaborative working [21]. This could be true of DM's GP – he already had an excellent relationship and was well known to the GP. Perhaps if the patient had been new to the surgery, or if another GP had been approached, it may not have been as successful.

In general terms, it is clear that with the advent of easier-to-tolerate medication regimes, the rates of those accessing treatment should increase and the effort to find those lost to follow-up should be of paramount importance. GPs have a vital role to play in this and are well placed to support secondary care by improved testing and treatment in the community setting [22]. Although DM was not an injecting drug user, he was indicative of the HCV population, i.e. a poor attender of secondary care, but well engaged with his GP. GPs can access patients who would never normally attend hospital [23].

It was important to manage DM's expectations – although treatment for HCV has been shown to improve a patients' quality of life [24], physical and psychological stressors that were previously an issue, have not disappeared. However, it is important to note the increasing wealth of data that suggests treating

HCV in co-infected patients can lead to improvements both in their mental and physical health [24].

Conclusion

The successful treatment of DM demonstrated the benefits of joint working between specialist services in the hospital and services in the community. It is clear that in this case, the success was dependant on positive relationships the patient already built – both with his HIV nurse specialist and his GP. When asked, DM found the process to be relatively stress-free and the lack of contact with the hospital alleviated his anxiety. Although advanced treatments have an improved safety profile, it is evident that a thorough assessment is still vital to monitor for potential drug-drug interactions and possible barriers to treatment. Patients may require more intensive support if a switch in HIV medication is required prior to commencing HCV treatment. The advent of newer agents has led to an easier treatment course, both in side effects and monitoring, reducing barriers to eradicating HCV in our hard-to-reach co-infected population, and thereby improving their overall prognosis.

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Conflict of interest

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