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Summarized

The changing landscape of treatment in hepatitis C and the impact on patients

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The development of new therapeutic agents is set to transform the treatment of hepatitis C over the coming years. For many patients, these treatments offer fewer and less severe side effects, a shorter treatment duration, a less complex regimen and dramatically improved rates of success compared to current interferon-based treatments. With the arrival of these new treatments, what role will patients play in managing their condition? And what types of support will they need to achieve the best results?

To address these unknowns, we spoke with people living with hepatitis C, interviewed experts and reviewed the latest adherence research in this therapeutic area.

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Executive summary

Currently, while treatment offers the possibility of cure, the majority of people living with hepatitis C (HCV) do not receive treatment...

There are several reasons for this: many people remain undiagnosed, some are not eligible for treatment and others decline. For those who initiate treatment, good outcomes are dependent on a high level of adherence to a demanding regimen. Missed doses and non-completion of treatments for HCV compromise efficacy and pose a threat to health and wellbeing.

Predictors of non-adherence identified in the literature include current drug use, psychiatric problems, depression and experience of intolerable side effects. Features of the healthcare system, such as physician expertise, may also play a role.

There have been few evaluations of strategies to facilitate adherence among patients receiving treatments for HCV. Components of promising interventions have included the provision of information about treatment and side effects and telephone follow-up. Innovative interventions in other clinical areas include cognitive behavioural approaches and peer support. To facilitate the success of treatments for HCV, the systematic development and evaluation of tailored interventions to address factors known to impact on adherence is now a priority.

> "Adherence is critical and we need to be on top of that. The new drugs are expensive and there is the possibility that the virus could become resistant if adherence is sub-optimal, so we will need to support people to take the medication"
>
> **Professor David Goldberg**
> **Health Protection Scotland**

Introduction

Hepatitis C (HCV) is a virus carried in the blood that predominantly affects the liver. The worldwide prevalence of HCV has been estimated at about 3% (>170 million people), with approximately 3-4 million new infections and 350,000 deaths from the virus each year.[1,2] The virus is transmitted through infected blood, most commonly through intravenous drug use. There is currently no vaccine for HCV. Approximately 20% of people infected with HCV spontaneously clear the virus within the first six months, but the majority go on to develop chronic HCV. Often people are unaware of the infection as it is usually asymptomatic. However, it can lead to serious liver disease, with high levels of morbidity and mortality.[3] Of those who are chronically infected, 60-70% develop chronic liver disease, 5-20% develop cirrhosis of the liver and 1-5% die from cirrhosis or liver cancer.[2] HCV therefore poses a major global burden, with infected individuals experiencing increased healthcare utilisation, greater work impairment and lower health-related quality of life than non-infected individuals.[4] Treatment can prevent these complications by suppressing the virus to undetectable levels.

There are at least six genotypes of HCV, each of which responds differently to treatment.[2] Successful treatment results in sustained virological response (SVR), where the virus cannot be detected in the blood six months after the end of treatment. Until 2011, the recommended treatment for HCV was weekly subcutaneous injections of pegylated interferon and daily ribavirin tablets, leading to SVR in approximately 50% of patients.[5] Recent guidelines recommend the addition of a protease inhibitor (boceprevir or telaprevir) for the treatment of patients with HCV genotype[1,6] significantly increasing the likelihood of SVR.[7,8]

Despite the existence of potentially effective drug therapy, less than half the patients with HCV receive treatment.[9,10] Patients may be excluded from treatment because of coexisting medical conditions – indeed the majority of patients with HCV have at least one comorbidity.[10] Others may decline or fail to initiate recommended treatment.[11] Common reasons for declining include a lack of symptoms,[12] and anticipated side effects[13] – interferon-based treatments are associated with debilitating gastrointestinal and flu-like symptoms, depression, fatigue, headache, irritability and insomnia.[14] Once started, a high level of adherence is required.[15,16] Treatment is more likely to lead to SVR if patients take 80% or more of their treatment for the prescribed duration.[16,17] A recent review reported mean adherence levels of 74-100%.[18] However, levels of adherence to ribavirin tend to decline over time[19] and early discontinuation of treatment is common, with studies indicating that 30-60% patients do not complete their prescribed course.[11,16,20,21] The most common reason for discontinuation of treatment is intolerance of side effects.[11,22]

New drugs are set to revolutionise the treatment of HCV, offering vastly improved efficacy, reduced treatment duration, and fewer side effects.[23] A recent trial reported that over 95% of patients achieved SVR after just eight weeks of treatment.[24]

Professor David Goldberg, who leads Health Protection Scotland's hepatitis C programme, predicted that uptake and adherence to hepatitis C treatment would dramatically increase with the introduction of these new interferon-free treatments, but stressed the continued importance of supporting patients with adherence.

"Adherence is critical and we need to be on top of that," he says. "The new drugs are expensive and there is the possibility that the virus could become resistant if adherence is sub-optimal, so we will need to support people to take the medication."

Understanding the reasons for non-adherence is essential for the development of effective interventions to support patients taking HCV treatment.

350,000
people die a year from the hepatitis C virus

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Insights from the experts

Samantha May, Head of Support Services at the Hepatitis C Trust (UK) speaks about the treatment issues facing people diagnosed with HCV. Samantha told us about the challenges of taking the standard interferon and ribavirin treatment for HCV

"On a practical level, it means lots of hospital appointments and that can be tough for people who are working, have families or live rurally. Then there are the side effects... it can get to the point where you're so tired it's hard to get out of a chair on some days. So obviously that has a real impact on people's ability to work or just go about their day. It's also daunting in terms of the timescale – often it's a 48-week treatment, so it's a big commitment."

Samantha talked about the hope offered by the new treatments on the horizon, but also how that made current treatment decisions more complex:

"Just around the corner, we have new treatments that only have to be taken for three months, have high success rates and will be well tolerated, so it's a much more complicated decision now that people are facing – whether to wait that little bit longer, or whether to take what's on offer now."

One of the advantages of the interferon-free treatments will be no more need for injections:

"This will normalise the treatment. Having to take interferon by injection has been a barrier for a lot of people, whereas taking a couple of pills is much more doable."

Given the challenges and complexities of treatment, Samantha emphasised the need for patient support.

"In the past, support hasn't been good, but it has got a lot better now. For example, some nurses will provide patients with a mobile number so they can get in contact in between appointments. And one of the drug companies provides a telephone link for patients to a general nurse, to provide information and support 24/7."

The value of peer support was particularly highlighted:

"I think for anyone with hepatitis C, because of the nature of it and the stigma attached to it, it's so important to be linked in to other patients. Being able to speak to somebody who has done the same treatment can take a lot of the fear out of it – and give you tips for managing it."

Professor David Goldberg, who leads Health Protection Scotland's Hepatitis C programme talked to us about the likely impact of new treatments on adherence:

From physician- to patient-driven care:

"Treatment for hepatitis C is currently physician-led – doctors are driving the effort to get people diagnosed, assessed and treated. That's partly because many of the people who have the virus also have other problems, so hepatitis C isn't always the priority for them. Furthermore, the perception is – rightly – that treatment is difficult and it doesn't always work. With the new therapies coming on line, much of the demand for treatment will come from the patients. They will hear it's much easier to take, more effective, has fewer side effects and can be taken without disrupting one's work. This shift in dynamic will result in greater compliance throughout the patient pathway."

Patient insights

Fi spoke to us about what it is like to have hepatitis C and her decision, to date, not to take treatment. Her primary reason for declining treatment was the strong likelihood of side effects, in particular depression and alopecia

She was optimistic that future treatments would have fewer side effects.

CONCERNS ABOUT SIDE EFFECTS

My mental health has been a whole lot better in the past five years, but it would still be a huge concern to me to do anything that was pretty much guaranteed to cause depression... there is bound to come a point when there are treatments available that are going to be far less difficult for me, with my particular health concerns.

Fi talked about the importance of accurate information to enable people to make informed decisions about treatment:

LACK OF INFORMATION ABOUT HEPATITIS C AND TREATMENT

It was left to me to read up on it – to find out what the deal was, to find out what it would mean to me, to find out what the side effects were, to find out the odds of the treatment working. I was merely told 'you have treatment or you die'... There was no way that I was going to go ahead without knowing what I was signing up for.

She described how she uses information from regular liver biopsies to determine her need for treatment:

LACK OF PERCEIVED NEED FOR TREATMENT

The results of the biopsy were that, for sure, my liver had hepatitis C – but the level of damage was really quite negligible. I wasn't going to drop dead tomorrow... I've continued to have regular biopsies and have made an agreement that if at any point my doctor says to me, 'look, there are some pretty severe changes going on here,' I will hold my hands up and say 'OK, let's do treatment'.

Caspar spoke to us about his experiences of treatment for HCV. He is coming to the end of a six-month course of treatment with weekly interferon injections and twice daily ribavirin tablets

Feedback from blood tests has given Caspar confidence that his treatment will be successful:

PERCEIVED TREATMENT EFFICACY

From week four of treatment it had cleared up. The nurse said there's an 80% chance that it won't come back after treatment, which is good. Hopefully I will be better and can just get on with my life.

Caspar described experiencing persistent, severe, side effects from his treatment:

SIDE EFFECTS

I've been really, really moody – my temperament has been up and down every day basically. It's made me really depressed, which I'm starting to get over now without extra tablets. I've lost my appetite and lost quite a bit of weight since I've been on the tablets... It makes me feel tired all the time as well, all I want to do is sleep. Sometimes it makes me feel sick... It has made my hair thin, really thin and it's started to come out, which is quite concerning.

Side effects have had significant impact on Caspar's day-to-day life:

IMPACT ON DAILY LIFE

My life has been put on hold. It's hard to find a job when you're on the treatment. It's had really big financial effects.

He described the importance of good coping skills, support and belief in the efficacy of treatment for persisting with treatment in the face of side effects:

COPING

I've just got on with it, even if I've felt really rough I've just got on with the day, unless I've felt really, really bad and then I've just stayed in bed... A couple of times I've felt like giving the treatment up but my partner keeps me going, and the fact that there's a light at the end of the tunnel.

He said that getting into a good routine helped him to take his medication:

ADHERENCE

I've got myself into a good routine with it, just take it and then just get on with the day, if I can do that. I think out of the whole course I've only missed one lot [of tablets] and that was because I had a drink the night before – I was slightly hungover and I didn't want to take them in case they interacted with the alcohol that was in my system.

Predictors of non-adherence

A recent systematic review[18] reported on 13 studies exploring adherence to dual therapy (interferon/ribavirin). Three additional studies identified factors associated with early discontinuation of treatment.[11,22,25] Table 1 shows the key determinants of non-adherence identified in the literature and categorised according to the Capability, Opportunity and Motivation model of Behaviour (COM-B)[26].

The most frequently identified predictors of non-adherence were related to comorbidity, including psychiatric diagnosis and active drug use.[18] Interestingly, higher rates of adherence were found in patients who had comorbid HIV infection than those who were HIV negative.

Research into adherence to treatment for other long-term conditions highlights the key role of patients' beliefs about illness and treatment,[27] yet this has not been explored in the HCV literature.

Table 1 : predictors of non-adherence or treatment discontinuation

Factors associated with non-adherence to HCV treatments	
Capability	Active drug use during treatment[18]
Opportunity	Shorter transport time to medical centre[18] No private insurance[22] Lack of employment[22] Increased pill burden[18] Limited provider experience[25]
Motivation	Absence of HIV co-infection[18] Persistent side effects/treatment intolerance[11,22] More severe disease[18] Treatment naïve[25] Depression[18,22] Psychiatric diagnosis at baseline[18]

The findings of research to date suggest that adherence and persistence with treatment may be enhanced by interventions which:

- Optimise the management of side effects[28]
- Provide a strong patient support network including specialist nurses[28] and peer support[29]
- Facilitate the detection and optimal management of depression[18,22]
- Provide appropriate support for patients who use drugs or have comorbid conditions[18,30]

The approval of new treatments is likely to spark renewed interest in patient adherence to treatments for HCV over the coming years.

Interventions that work

A recent systematic review[31] identified five interventions that enhanced adherence with HCV treatment.[32-36] A simple regimen-level intervention, which involved reducing the pill burden of ribavirin, resulted in significantly increased adherence and persistence with treatment.[32]

Four studies reported increased adherence to HCV treatment following patient-level interventions.[33-36]

These interventions included:

- Patient education provided by a healthcare professional other than the physician[33]
- Personalised nursing support via the telephone, plus mailed educational materials and motivational letters throughout treatment[34]
- A multidisciplinary intervention for patients with a history of substance abuse, including education about HCV and psychological support[36]
- Regular nurse-led education to evaluate and understand HCV and side effects[35]

The final study also found a significant effect of the intervention on virological response.

Three further interventions did not significantly impact adherence. These were a system-level intervention comparing a specialist pharmacy with standard retail pharmacies,[37] plus two side-effect management interventions, both of which aimed to prevent depression in patients undergoing interferon-based treatment.[38,39]

One study researched patients' preferences for future interventions. Patients wanted more frequent telephone contact with healthcare professionals and the availability of peer support from others with HCV treatment experience.[29] Peer-support interventions have shown promise in enhancing adherence among HIV positive drug users.[40] The development of interventions to enhance adherence may also be guided by the emerging field of behavioural economics, which recognises that life gets in the way of rational decision making.[41] Such interventions might include motivation-enhancing prompts and financial incentives.

Concluding statements

- **Current treatments for HCV are challenging, as a result of debilitating side effects, lengthy treatment duration and complex regimens.**
- **Recent years have seen dramatic advances in the development of new treatments for HCV, with several new drugs in the pipeline. The introduction of these treatments will offer significant benefits to patients, including vastly improved effectiveness, less complex treatment regimens, shorter duration of treatment and increased patient choice.**
- **It is anticipated that HCV treatment will shift from being physician-led (whereby doctors drive the effort to get people diagnosed and treated) to patient-led, with people actively seeking diagnosis and treatment. This is likely to have a major impact on uptake and adherence.**
- **Despite the high prevalence of comorbidity among people with HCV, the way in which this impacts on adherence to treatment has received little attention. More research is required in order to develop strategies to support patients with multiple health concerns.**
- **The development of effective strategies to support patients taking treatment for HCV remains a priority.**

> "It is anticipated that HCV treatment will shift from being physician-led (whereby doctors drive the effort to get people diagnosed and treated) to patient-led, with people actively seeking diagnosis and treatment"

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