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Hepatitis C: current treatments, emerging therapies and tackling health inequities on the path to global elimination ☆

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ABSTRACT

Hepatitis C virus (HCV) remains a significant global health challenge, affecting an estimated 50 million people. In most cases, infection becomes chronic, with long-term risks including liver cirrhosis and hepatocellular carcinoma. Beyond hepatic complications, many individuals experience non-specific symptoms such as fatigue and cognitive impairment, which can significantly impact daily functioning. The introduction of direct-acting antivirals has transformed HCV management, offering cure rates above 95% with minimal side effects. However, HCV continues to disproportionately affect marginalised groups, including people who inject drugs, migrants, and those experiencing homelessness. With targeted support and inclusive care pathways, these populations can be effectively treated. In this review, we examine the latest developments in HCV care, including current treatment protocols, emerging clinical trial data, and future directions – particularly the pursuit of a preventative vaccine. Achieving HCV elimination will require not only continued therapeutic innovation, but also a commitment to equality and equity in healthcare delivery.

Background

Hepatitis C virus (HCV) is a blood-borne virus (BBV), affecting millions globally with high morbidity and mortality. Once infected, the majority develop chronic infection and, without treatment, this leads to the development of fibrosis, complications of cirrhosis and end-stage liver disease over 3–4 decades. People with HCV-induced cirrhosis are at increased risk of liver cancer and the risk persists even with viral clearance. Although infection prior to the development of cirrhosis is often referred to as 'asymptomatic', quality of life assessments and careful questioning shows that infected people have a variety of non-specific symptoms, including fatigue and difficulty in concentrating ('brain fog'), which usually improve with effective treatment.[1]

Epidemiology

Globally, it is estimated that at least 50 million people are affected by HCV, with around 1 million new infections every year.[2] Effective directly-acting antivirals (DAAs) may allow global elimination of HCV as a public health hazard if the drugs are widely deployed. The World Health Organization (WHO) has called for global elimination. However, at the end of 2022, only 12.5 million people had received HCV curative treatment. Six countries – Pakistan, India, China, Russia, USA and Indonesia – represent 50% of HCV cases globally, with relatively limited access to curative treatments,[2] and the number of cases is predicted to rise, with around 1.4 million new cases by 2040.[3] Ongoing transmission of HCV in countries without elimination programmes is likely to lead to significant increases in disease morbidity and mortality and make the global elimination target ineffective.

The risk of HCV transmission and acquisition is predominately via percutaneous blood exposure, due to either injecting drug use (which is common in the developed world) or medical procedures with transfusion of unscreened blood/blood products or reuse of unsterilised needles and surgical instruments in developing countries. In contrast to hepatitis B virus (HBV), the risk of infection by vertical transmission from mother to child or through sexual activity is low, except in people living with HCV having unprotected sexual intercourse with men.[4]

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Table 1
Directly Acting Anti-viral (DAAs) mechanism of action, types and genotype targets.

Directly acting anti-viral (DAA) class	Name of drug and genotype	Mechanism of action	Barrier to resistance
NS5B polymerase inhibitor (nucleotide analogue)	Sofosbuvir – G1 – G6	Targets the NS5B polymerase, an enzyme responsible for post-translational processing for viral RNA replication	High
NS5B polymerase inhibitor (non-nucleotide analogue)	Dasabuvir – G1		Low
NS5A inhibitors	Velpatasvir – G1- G6 Ledipasvir – G1 Daclatasvir – G3 Ombitasvir – G1 Pibrentasvir – G1 - G6 Elbasvir – G1, G4	Targets the NS5A protein, which plays a role in viral replication and assembly.	Low
NS3/4A protease inhibitors	Voxilaprevir – G1 - G6 Simepravir – G1, G4 Glecaprevir - G1 - G6 Paritaprevir – G1, G4 Grazoprevir – G1, G3, G4	Targets the NS3/4A protease, an enzyme essential for viral replication.	Intermediate

Pathogen

HCV is a single-stranded, positive-sense, enveloped RNA hepacivirus from the family *Flaviviridae* whose genome encodes a polyprotein producing structural (core, envelope glycoproteins [E1, E2]) and non-structural (NS) proteins (NS1–NS3, NS4A, NS4B, NS5A and NS5B). Of clinical importance are the NS3 serine-like protease, NS5A and NS5B polymerase proteins, as these are targets for antiviral drugs.

There are six common HCV genotypes (G1–G6), which have different geographic origins.[5] Genotype 1 (G1a and 1b) predominates globally (44% of all infections) and is the commonest genotype in Europe, North and Latin America. This is followed by G3 (25%) which predominates in South Asia (Pakistan, India, Bangladesh) and Australasia, G4 (15%) in Egypt and North Africa, G2 (9.1%) in West Africa, G6 (5.4%) with less than 1% of G5.[5,6] Due to the viral diversity of HCV, post-cure HCV seropositivity does not preclude future reinfection and people can be reinfected with another genotype.

Diagnosis

HCV infection is usually asymptomatic, with a small proportion of patients developing a non-specific febrile illness with fatigue. Additionally, patients with acute HCV may develop jaundice and right upper quadrant pain, but hepatic failure is very rare. A proportion of people spontaneously clear the virus, but most develop chronic infection.

HCV is diagnosed by testing for HCV antibody (anti-HCV-Ab) or HCV core antigen (HCV-Ag) using ELISA assays, which confirms exposure, but HCV RNA testing by nucleic acid detection is required to confirm infection. Since liver function tests fluctuate during infection and may be persistently normal in some people, the presence of normal liver function tests does not exclude infection and anyone with antibodies/antigen against HCV must undergo HCV RNA testing to exclude viraemia. Once HCV RNA is confirmed, further testing to establish the viral genotype and the extent of the liver damage, by non-invasive fibroscan assessment or blood test-based algorithms (eg the APRI score) is useful,[7] but such testing is not essential. For many individuals, rapid access to treatment once infection is confirmed is preferable to prolonged pre-treatment assessment that may lead to curative opportunities being lost. Treatment options do not change with the diagnosis of cirrhosis, but post-treatment follow-up is modified (see later). However, in poorly engaged populations it is preferable to have undiagnosed cirrhosis and cured HCV rather than formally diagnosed cirrhosis with a disengaged patient who has not been treated. Careful clinical judgement is required to determine the optimal pre-treatment work-up for patients, but it is the authors' view that over-treatment and under-investigation is always preferable to under-treatment and comprehensive assessment, and this approach is recommended by the World Health Organization (WHO).[2] For mobile populations, HCV testing can be performed via point-of-care testing (POCT) or via dried-blood spot (DBS) testing.[8] More could be achieved to develop this area of novel outreach testing programmes and settings across the world, particularly in marginalised communities.[9]

Treatment

As HCV is an RNA virus, the aim is for cure, in contrast to HBV and HIV (DNA-based retroviruses), in which viral suppression is the goal. Trials confirm that people with undetectable HCV RNA 12 weeks after the end of therapy are very unlikely to relapse, leading to this metric being used for the definition of treatment success (Sustained Virological Response at 12 weeks [SVR12]).[10] Virological cure improves symptoms in most patients and reduces the risk of disease progression and development of liver cancer, although in those with cirrhosis the risk of malignancy persists, leading to recommendations that such people should be screened for liver cancer by 6-monthly ultrasound scans along with alpha feto-protein assessments.[11]

Pre-2011, the main treatment for HCV was injectable interferon (IFN)-based regimens, which were poorly tolerated with a SVR of 40% with IFN and 54% with long acting (pegylated)-IFN and ribavirin (RBV) use. Pegylated-IFN+RBV was the mainstay of treatment from 2001 to 2011, until the advent of the first generation of DAAs with NS3/4A protease inhibitors (bocepavir and telaprevir). However, these were adjuncts to the use of pegylated-IFN with associated side effects, with imperfect response rates and primarily limited to HCV-G1 infection.

With the need for IFN-free and oral therapy, HCV research accelerated, with landmark trials (COSMOS and HALLMARK-DUAL trials)[12,13] demonstrating SVR rates of greater than 90%. These studies utilised newer DAA agents incorporating sofosbuvir (NS5B nucleotide polymerase inhibitor) and simeprevir (NS3/4A protease inhibitor) and asunaprevir with daclatasvir, respectively. These studies demonstrated that combinations of two or more highly effective antiviral agents for several months would lead to virological cure and paved the way for the development of current single-tablet regimens for 8–12 weeks. These extraordinarily effective therapies are virtually side effect free and have few contra-indications to their use. The current regimens are summarised in Table 1. In people with decompensated cirrhosis, protease inhibitors are contraindicated and these drugs should also be used with caution in people receiving some additional medications (particularly some anti-retrovirals) as drug–drug interactions have been observed. The non-protease-based treatments have few interactions, but care with amiodarone and some anticonvulsants is required.

With these efficacious treatments, hepatology and infectious disease (ID) guidelines globally have recommended their widespread use, and

Table 2
National Institute for Health and Care Excellence (NICE) guidelines for management of HCV.

Pan-genotype or genotype-specific	Regimen – generic and [brand] name	Genotype	Cirrhosis status	Duration (weeks)	Untreated (naïve)	Treated (treatment experienced)
Pan-genotype	Sofosbuvir–velpatasvir [Epclusa]	1 2 3 4–6 1–6	With or without compensated cirrhosis Without cirrhosis Compensated cirrhosis (± RBV) With or without compensated cirrhosis Decompensated cirrhosis (± RBV)	12	Recommended	
	Sofosbuvir–velpatasvir–voxilaprevir [Vosevi]	1–6 3	With or without compensated cirrhosis	12 8	Not recommended Recommended	Recommended
Genotype-specific	Ledipasvir–sofosbuvir [Harvoni]	1	Without cirrhosis	8 12	Recommended Not recommended	Not licensed Recommended
			With compensated cirrhosis	12	Recommended	Recommended (if criteria met)[a]
		4	Without cirrhosis	12	Not recommended	Recommended
			With compensated cirrhosis	12	Recommended	Recommended (if criteria met)[a]
	Ombitasvir–paritaprevir–ritonavir [Viekirax] with dasabuvir [Exviera] and ribavirin	1a 1b	Without cirrhosis With compensated cirrhosis With or without compensated cirrhosis	12 24 12	Recommended	
	Ombitasvir–paritaprevir–ritonavir [Viekirax] with ribavirin	4				
	Elbasvir–grazoprevir [Zepatier]	1a 1b 4	With or without compensated cirrhosis	12–16[b] 12 12–16[c]	Recommended	

[a] Criteria for treatment recommendation in compensated cirrhosis:
- Child–Pugh class A.
- Platelet count ≥ 75,000/mm^3.
- No portal hypertension.
- No history of HCV-associated decompensation.
- No prior treatment with an NS5A inhibitor.

[b] Consider elbasvir–grazoprevir plus ribavirin for 16 weeks in people with a baseline hepatitis C virus RNA level of more than 800,000 IU/ml or specific NS5A polymorphisms causing at least a 5-fold reduction in activity of elbasvir.

[c] Consider elbasvir-grazoprevir plus ribavirin for 16 weeks in people with a baseline hepatitis C virus RNA level of more than 800,000 IU/ml.

the National Health Service (NHS – the publicly funded healthcare system) in England being guided by its National Institute for Health and Care Excellence (NICE) guidelines (Table 2). NICE guidelines recommend that all people who acquire HCV should be initiated on DAA therapy with the goal of treatment to cure HCV.

Impact of health inequalities in HCV elimination target

Global organisations differ as to their viewpoints of HCV treatment with some preferring a virologically focused treatment regimen based on HCV-genotype.[14] While other organisations endorse a population-health approach to ensure a pan-genotypic regimen, which can also be used with point-of-care testing. The public-health approach ensures prompt treatment for disadvantaged and stigmatised populations such as people who inject drugs (PWID), people in prison settings, coastal communities[15] and people experiencing homelessness. Such underserved communities, which are often marginalised, can be readily accessed with appropriate service design (including in-reach prison services, peer support for the vulnerable). Recent work from NHS England confirms the massive reduction in morbidity when disadvantaged communities are targeted in this way.[16] With England on track to achieve HCV elimination,[17] it marks a significant achievement in reducing health inequalities. This progress is due to a nationally coordinated elimination programme led by the NHS, which has improved diagnosis and management of HCV. With treatment delivered directly to patients wherever they are, this has led to reduced morbidity and mortality from HCV.[17] In addition to health improvement, HCV elimination also leads to positive health economic impacts in both Global North[18] and Global South settings.[19]

Future of HCV – hope for a vaccine

Although treatment is effective with SVR rates of >95%, there are concerns that in high prevalence communities with limited access to therapy – such as people living in countries with limited resources or countries that do not prioritise treatment for disadvantaged ongoing transmission – will reduce the effectiveness of global elimination programmes.

To address this unmet need, future research in HCV is being expanded to develop novel vaccines to reduce the primary acquisition of HCV. Current HCV vaccine candidates utilise recombinant envelope glycoproteins E1 and E2 with an adjuvant (ClinicalTrials.gov NCT00500747), T-cell based (ClinicalTrials.gov NCT01070407) and an mRNA E1 and modified E2.[20] As acute HCV is asymptomatic, there is difficultly finding potential HCV vaccine candidates. With the high efficacy of DAAs and HCV being safely treated, it may be necessary to develop a human challenge model, which are deemed safe, akin to other infectious diseases to properly assess the efficacy of an HCV vaccine.[21]

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Hamzah Z. Farooq: Writing – review & editing, Writing – original draft, Validation, Funding acquisition, Data curation, Conceptualization. **Graham R. Foster:** Writing – review & editing, Writing – original draft, Validation, Supervision, Resources, Conceptualization.

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