

Review

Hepatitis C: recent advances and practical management

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ABSTRACT

Hepatitis B virus and hepatitis C virus (HCV) remain leading causes of disability and premature death worldwide. In May 2016, the UK, as a member of the World Health Assembly, adopted the Global Health Sector Strategy and its targets to eliminate viral hepatitis as a public health threat by 2030. In pursuit of this goal, there have been a number of recent advances in viral hepatitis care. Perhaps most notable is the availability of short courses of all-oral curative direct acting antivirals for hepatitis C. However, while access to treatment has been scaled up across the UK, an estimated 93 000 people were still living with HCV at the end of 2021 of which three-quarters remained unaware of their infection.

This review article will summarise key advances in hepatitis C treatment and prevention and provide a practical approach to the management of individuals living with hepatitis C infection.

INTRODUCTION

There were an estimated 1.34 million deaths from viral hepatitis (47% hepatitis B virus (HBV), 48% hepatitis C virus (HCV), 5% hepatitis A and E viruses) worldwide in 2015 due to acute infection, chronic liver disease (720 000 due to cirrhosis) and primary liver cancer (470 000 due to hepatocellular carcinoma (HCC)).¹ In response to the viral hepatitis pandemic, the first global health sector strategy on viral hepatitis was launched in 2016 and committed to eliminate viral hepatitis as a public health threat by 2030, defined as a 65% reduction in mortality and 90% reduction in new infections compared with a 2015 baseline. In pursuit of this goal, there have been a number of recent advances in viral hepatitis care. Perhaps most notable is the availability of short courses of all-oral, well-tolerated direct acting antivirals (DAA) that result in hepatitis C cure in over 90% of individuals regardless of hepatitis C genotype and stage of liver disease.

Key points

- ⇒ Hepatitis C virus (HCV) remains a leading cause of morbidity and premature death worldwide.
- ⇒ Injecting drug use remains the most important risk factor for HCV acquisition across the UK.
- ⇒ Almost three-quarters of individuals living with chronic HCV remain unaware of their infection.
- ⇒ Short courses of all-oral direct acting antivirals achieve cure in >90% of people regardless of genotype and stage of liver disease.
- ⇒ The UK is on track to eliminate HCV as a public health threat by 2030.

EPIDEMIOLOGY

In the UK, the estimated chronic prevalence of HCV has declined by 47.2% since 2015.² This largely reflects improved access to curative treatment, the UK Health and Security Agency reporting 58 850 treatment initiations between tax years 2015–2016 and 2020–2021 in England alone.³ At the current rate of reduction, the UK should be on track to achieve an 80% reduction in chronic HCV prevalence by 2030 (table 1). However, an estimated 92 900 people continued to live with HCV in the UK at the end of 2021.² Almost three-quarters of those still living with chronic HCV remained unaware of their infection and access to testing and treatment has not yet fully recovered following the COVID-19 pandemic. If the UK is to achieve and maintain HCV elimination, more needs to be done to prevent new infections and reinfections.

HCV is bloodborne and most infections worldwide are acquired through unsafe healthcare procedures or injection practices. Injecting drug use remains the most important risk factor for HCV acquisition across the UK but an increased risk of HCV acquisition has also been reported in



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Table 1 UK progress towards the WHO 2020 impact targets^{2 5}

Impact target (by 2020)	UK status
30% reduction in new cases of chronic HCV infections	47.2% reduction in new cases of chronic HCV infections (to 2021)=achieved 43.3% reduction in new cases of chronic HCV in the general population and 55.1% in people who inject drugs in England (to 2021)
10% reduction in HCV-related deaths	31.3% reduction in HCV-related deaths=achieved 30.8% reduction in England 25% reduction in Northern Ireland 36.7% reduction in Scotland 25% reduction in Wales
Annual absolute HCV-related mortality rate of ≤2 per 100 000 population	0.48 per 100 000 population=achieved 0.47 per 100 000 population in England 0.19 per 100 000 population in Northern Ireland 0.70 per 100 000 population in Scotland 0.63 per 100 000 population in Wales

HCV, hepatitis C virus.

- ▶ People who have been in prison or other secure and detained settings.
- ▶ People who have experienced homelessness.
- ▶ People with close links to countries where HCV is endemic (for practical purposes this includes all countries in Africa, Asia, the Caribbean, Central and South America, Eastern and Southern Europe, the Middle East and the Pacific islands).⁴
- ▶ People who received blood prior to 1 September 1991 or National Health Service (NHS) blood products prior to 1986.
- ▶ People who have had occupational exposure to HCV, for example, via needle stick injury.

The reduction in HCV prevalence among people who inject drugs is thought to be due to improved treatment coverage and not harm reduction. Reinfection is currently thought to occur in 4% of treated individuals.⁵

Sexual transmission of HCV among heterosexual couples is extremely rare with an estimated maximum incidence rate of 0.07% per year (95% CI 0.01% to 0.13%) or approximately one transmission per 190 000 sexual contacts.⁶ However, since 2000, a global epidemic of recently acquired HCV has been described among HIV positive gay, bisexual and other men who have sex with men, driven by per mucosal and parenteral transmissions. Both behavioural (receptive condomless anal sex, traumatic sex including sex in a group environment, sharing of sex toys, use of recreational drugs during sex) and biological (concurrent sexually transmitted infections (STIs), especially ulcerative conditions such as lymphogranuloma venereum and syphilis) risk factors have been identified.

ASSESSMENT

Traditionally, HCV infection has been classified as acute (the first 6 months of infection) or chronic (absence of spontaneous clearance of HCV within the first 6 months of infection) (figure 1).^{7 8} However, acute HCV usually has no notable symptoms and

remains subclinical. Precise timing of infection is often therefore difficult to establish. The term ‘recently acquired’ HCV is now preferred and is defined by the presence of anti-HCV antibodies, HCV RNA and/or HCV core antigen that were not detectable in previous samples up to 12 months prior.⁸ In practice, historical results are often unavailable and antiviral treatment in the early phase of infection is thought to be both cost-effective and important in interrupting the chain of transmission.

Anti-HCV antibodies remain detectable after successful antiviral treatment or spontaneous HCV clearance.⁸ HCV reinfection is diagnosed by detection of HCV RNA by molecular testing or HCV core antigen.

Screening for HCV infection

Screening algorithms for HCV infection mainly adopt a two-step approach. Initial testing is based on the detection of anti-HCV antibodies. Either enzyme immunoassays or rapid diagnostic tests (RDTs) can be used to screen for anti-HCV antibodies.⁸ RDTs can use serum and plasma, fingerprick whole blood or oral fluid and can facilitate testing at room temperature without the need for venepuncture or extensive training.

Ongoing viraemia in anti-HCV antibody positive individuals is confirmed by the presence of HCV RNA by a molecular assay or HCV core antigen.⁸ Most NHS laboratories now perform reflex RNA testing on the sample obtained for antibody testing. This substantially increases the proportion of HCV antibody-positive patients who are tested for viraemia and subsequently linked to care. HCV core antigen is a surrogate marker of HCV replication and can be used to diagnose acute or chronic infection. However, HCV core antigen assays are less sensitive than HCV RNA molecular testing assays and confirmation of viraemia by testing for HCV core antigen is not recommended on dried blood spot samples due to insufficient sensitivity.

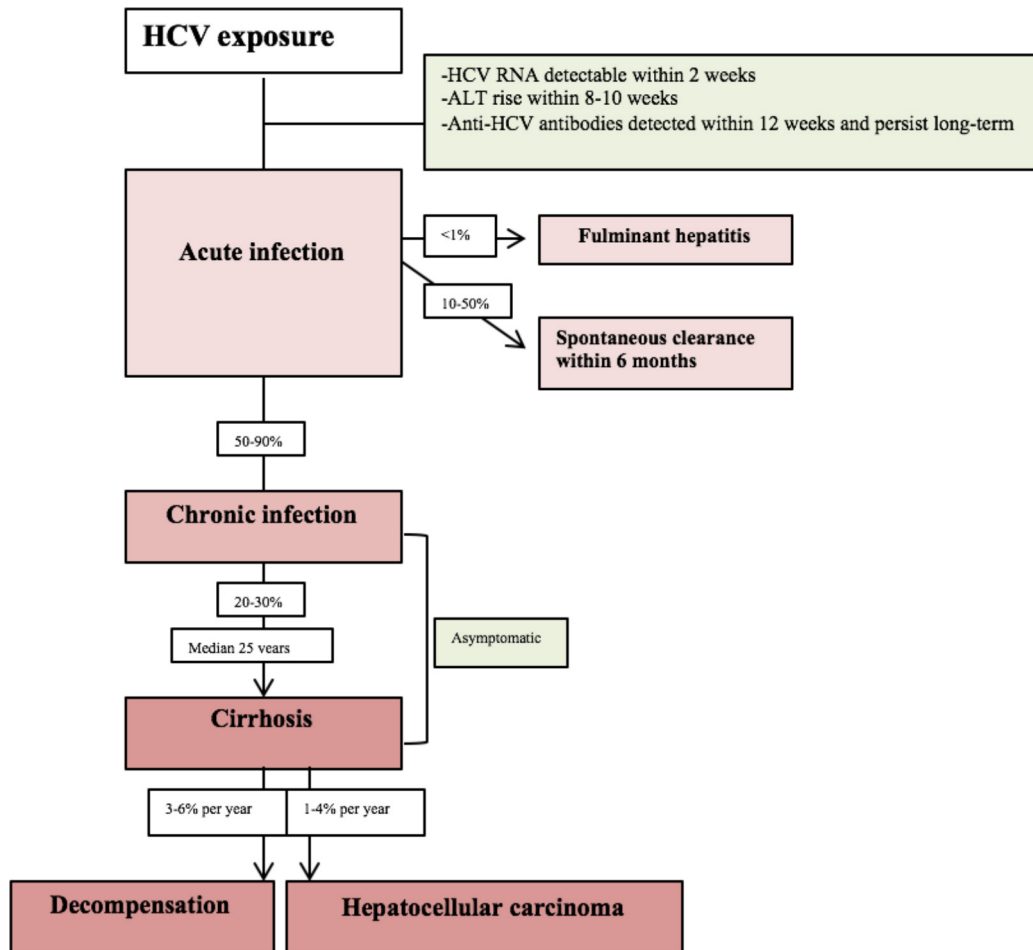


Figure 1 Overview of the natural history of HCV. ALT, alanine transaminase; HCV, hepatitis C virus.

Test outcome	Interpretation
HCV antibody not detected/negative	No prior exposure to HCV, hepatitis C negative.
HCV antibody detected/positive	Presumptive diagnosis of acute or chronic hepatitis C or past hepatitis C (either spontaneously cleared or cured with treatment).
HCV antibody detected/positive HCV RNA detected	Current HCV infection (acute or chronic hepatitis C infection or hepatitis C reinfection).
HCV antibody detected/positive HCV RNA not detected	No current HCV infection. Past hepatitis C (either spontaneously cleared or cured with treatment). False positive hepatitis C antibody test is more often seen in persons who have a low risk of infection.
HCV antibody not detected/negative HCV RNA detected	Current HCV infection (acute or chronic hepatitis C infection or hepatitis C reinfection). False negative hepatitis C antibody test associated with HIV, renal dialysis, organ transplantation and immunosuppression.
HCV, hepatitis C virus.	

Interpretation of HCV diagnostic tests are summarised in [table 2](#).

HCV genotype and resistance testing

Current antiviral combinations eradicate HCV in the majority of patients regardless of genotype. However, determination of HCV genotype remains useful and has remained a current requirement of commissioning for the majority of patients treated in the UK.⁸ Distinct subtypes of genotypes 1–8 are known to carry natural polymorphisms that confer inherent resistance to non-structural protein 5A (NS5A) inhibitors and have demonstrated suboptimal cure rates.⁹ These include genotypes 1l, 4r, 3g, 6u and 6v. While these subtypes remain uncommon in the UK and Europe, they are highly prevalent in regions of Africa and Asia. Analysis of samples from patients born in Africa enrolled in the HCV Research UK cohort determined full-length viral genomic sequences for 26 known subtypes and 5 previously unidentified isolates covering 5 genotypes.¹⁰ While the overall sustained virological response (SVR) rate was high (93%), treatment failure was associated with sofosbuvir/ledipasvir treatment of 1l or 4r infection. If accurate genotyping is not available or may

delay or limit access to treatment, we would recommend against the use of ledipasvir but a pan-genotypic regimen could be safely used in migrants from this region.

Access to resistance testing is limited and there remains no standardisation in the techniques, interpretation and reporting of tests. DAAs achieve high cure rates and can be effective in the presence of detectable resistance-associated substitutions at baseline, therefore, routine testing is not recommended prior to treatment in DAA-naïve individuals.⁸ However, we increasingly see individuals who have either interrupted treatment or completed treatment but not undergone repeat testing to confirm cure. In these individuals, genotyping and resistance testing can be helpful in diagnosing reinfection and determining further treatment courses.

Screening for HCV-related liver disease

Screening for liver disease is recommended in all individuals with chronic HCV infection.⁸ The gold standard for assessing fibrosis and inflammation is liver biopsy. However, biopsy has largely been replaced by non-invasive tests due to the procedural risk of biopsy, sampling error and high cost. Measurement of transient elastography by fibroscan is the preferred method providing an immediate, non-invasive, highly reproducible and validated assessment of fibrosis stage. A median stiffness cut-off of 10 kPa has 62% positive predictive value and 89% negative predictive value for advanced fibrosis ($\geq F3$), with 72% sensitivity and 80% specificity.⁸ Alternatives to elastography, where venepuncture is possible, include serum markers such as aspartate transferase (AST) to platelet ratio index (APRI) and Fibrosis-4 (FIB-4). The formula for APRI is $(AST \text{ in IU/L}) / (AST \text{ upper limit of normal in IU/L}) / (\text{platelets in } 10^9/L)$. Data from meta-analysis suggest

a threshold of 1 has a sensitivity of 76% and specificity of 72% for cirrhosis.¹¹ The formula for FIB-4 score is $(age \times AST) / (\text{platelets} \times \sqrt{ALT})$. A score > 3.25 indicates cirrhosis. Both APRI and FIB-4 have demonstrated good performance in detecting patients without liver fibrosis as well as satisfactory performance in detecting significant fibrosis, compared with fibroscan.¹²

Additional screening

Individuals tested for HCV should be offered screening for HBV (hepatitis B surface antigen) and HIV (HIV antigen/antibody) due to their common routes of transmission.⁸ Testing for Hepatitis A antibodies is also recommended. Hepatitis A and hepatitis B vaccination should be offered to individuals who test negative and are not immune. An STI screen is recommended in people who may have acquired HCV sexually.

TREATMENT

All individuals with recently acquired or chronic HCV should be offered HCV treatment with DAAs. Local treatment pathways vary, but all patients with detectable HCV RNA should be referred directly to their local specialist team without delay.

Direct acting antivirals

DAAs are standard of care for treatment of HCV. They interrupt replication by inhibiting HCV non-structural proteins, namely NS3/4A (protease inhibitors, PIs), NS5A (NS5A inhibitors) and NS5B inhibitors (polymerase inhibitors). DAA combinations available for use in the UK are summarised in table 3.⁸

There are few contraindications to DAA treatment but genotype (if known), presence or absence of cirrhosis, potential for drug–drug interactions and comorbidities are important considerations in

Table 3 DAA combinations used in the treatment of recently acquired and chronic HCV infection

Product	Components		Polymerase inhibitor	Administration	Duration of treatment	Most common adverse effects
	NS5A inhibitor	Protease inhibitor				
Pan-genotypic (G1–6) drug combinations						
Epclusa	Velpatasvir 100 mg	–	Sofosbuvir 400 mg	1 tablet once daily	12 weeks	Headache Fatigue
Maviret	Pibrentasvir 40 mg	Glecaprevir 100 mg	–	3 tablets once daily	8 weeks 12 weeks (if treatment experienced and cirrhotic)	Gastrointestinal symptoms (nausea, diarrhoea)
Genotype-specific (G1 or G4) drug combinations						
Harvoni	Ledipasvir 90 mg	–	Sofosbuvir 400 mg	1 tablet once daily	8–12 weeks	
Zepatier	Elbasvir 50 mg	Grazoprevir 100 mg	–	1 tablet once daily	12 weeks	
Retreatment after first-line DAA failure						
Vosevi	Velpatasvir 100 mg	Voxilaprevir 100 mg	Sofosbuvir 400 mg	1 tablet once daily	12 weeks	

DAA, direct acting antiviral.

treatment selection. They are generally well tolerated, with few adverse effects. A full and detailed drug history should be obtained prior to treatment including prescribed medications, over-the-counter remedies, herbal supplements and illicit drugs. Drug–drug interactions should be checked. The University of Liverpool online interaction checker (www.hep-druginteractions.org) is a useful clinical resource.^{8 13}

Examples of significant drug–drug interactions and comorbidities commonly encountered in clinical practice can be found in online supplemental material.^{8 13 14}

All patients should be asked about social vulnerabilities and counselled on adherence prior to starting DAA therapy. Treatment interruption and reduced adherence are commonly reported due to social vulnerabilities such as homelessness and alcohol use. While treatment interruptions of less than 7 days are not thought to affect treatment outcome, for individuals that miss more than 21 consecutive days after successful completion of 28 days treatment, retesting for SVR prior to retreatment is recommended.¹⁵

Treatment outcomes

The primary goal of HCV treatment is cure, or SVR, in order to prevent liver disease, extrahepatic manifestations and death.⁸ Secondary benefits include improvement in quality of life, reduced stigma and prevention of onward HCV transmission. Cure is defined as undetectable HCV RNA in serum or plasma 12 weeks (SVR12) after the end of treatment. Repeat testing at 24 weeks post-treatment (SVR24) is no longer routinely performed given their concordance is >99%. Late relapse after SVR is rare occurring in <0.2% of individuals after 6 months of follow-up.¹⁶ SVR is generally associated with normalisation of liver enzymes, improvement in liver function and improvement or regression of liver fibrosis. The risk of HCC is significantly reduced, but not eliminated.^{8 16}

The European Association for the Study of the Liver (EASL) final update on recommendations on treatment of HCV provides a comprehensive summary of the efficacy and tolerability of DAAs in clinical trial and real-world settings.⁸ In England, 95.6% of adults treated with DAAs have achieved SVR12 (13 959/14 603; 95% CI 95.2% to 95.9%).¹⁷ Cure rates remained high regardless of liver disease stage (SVR12 in fibrosis 96.1% vs 94.2% in compensated cirrhosis and 90% in decompensated cirrhosis) and has led to a significant reduction in the proportion of liver transplant waiting list patients registered with HCV-related cirrhosis (10.5% in 2013 to 4.7% in 2016 ($p < 0.001$)) and HCC (46.4% in 2013 to 33.7% in 2016 ($p = 0.002$)).¹⁸

Treatment in patients with end-stage liver disease

Liver transplantation (LT) remains the treatment of choice for patients with decompensated cirrhosis, and for selected patients with HCC.⁸ Eradication of HCV pre-LT can stabilise or improve liver function prior to

Table 4 Recommended timing of DAA therapy

MELD score	Timing of treatment
<18–20	Treat HCV prior to transplant
≥20	Transplant then treat HCV

DAA, direct acting antiviral; HCV, hepatitis C virus.

surgery and will prevent liver graft infection, which is universal following LT. Patients treated with DAAs while active on the LT waiting list require frequent monitoring as improvement in liver function may result in delisting.¹⁹ The necessity to delist patients as a result of improved liver function post-HCV cure has been termed ‘purgatory’ as, while they may no longer meet transplant criteria, they remain at risk of decompensation, HCC and death. EASL use Model for End Stage Liver Disease score to recommend timing of DAA therapy, as illustrated in [table 4](#).⁸

The preferred treatment regimen prior to LT is sofosbuvir and velpatasvir with weight-based ribavirin for 12 weeks.⁸ For those with contraindications to or who are unable to tolerate ribavirin, sofosbuvir and velpatasvir for 24 weeks without ribavirin may be considered.

Treatment in patients with HCC

Randomised controlled trials evaluating DAAs systematically excluded patients with HCC and the benefits of DAAs in this cohort are less well defined both in terms of cure rate and in the prevention, progression and recurrence of HCC.²⁰ EASL recommends prioritisation of HCC treatment in those patients who have potentially curative disease, namely those without cirrhosis or with compensated (Child Pugh A) cirrhosis and HCC.⁸ Patients with complete response to HCC therapy should be treated for HCV in line with standard treatment recommendations. For those individuals eligible for LT, the timing of treatment is decided on a case-by-case basis through a multidisciplinary team discussion.

There is a lack of studies evaluating the impact of DAA treatment in patients with advanced HCC. For those patients with advanced staging due to cancer-related symptoms or tumour burden, HCV eradication with DAAs is not thought to modify staging and treatment decisions should be made on a case-by-case basis.²⁰

Use of organs from HCV-positive donors in HCV-negative recipients

Despite increasing rates of organ donation and transplantation over the last few decades, the demand for organs still greatly exceeds supply and one in six patients listed for solid organ transplantation in the UK will die or become too sick for transplantation.²¹ DAAs have been shown to be safe and effective in achieving HCV clearance in transplant recipients and increasing data,

largely from America, has shown excellent outcomes of HCV-negative recipients who received HCV-positive organs.²² A 'transmit and treat' strategy seems to have been favoured with patients testing HCV viraemic post-transplantation being treated with DAAs rather than antivirals being given universally as prophylaxis. While short-term outcomes appear to be comparable for HCV-viraemic, non-viraemic and naïve donors, there is little outcome data beyond 1 year and it is still unclear if there are any lasting effects of HCV infection on the immune system or the clinical implications of treatment delay, DAA failure and relapse. In the UK, it is estimated that using organs from HCV-positive donors could result in 75 extra solid organ transplants being performed each year.²¹ Data following publication of the UK position statement on use of HCV positive organs are not yet available.

Management of patients after SVR

A recent meta-analysis estimated HCC incidence after HCV cure of 2.1 per 100 person-years among patients with cirrhosis and 0.5 per 100 person years among patients with F3 fibrosis.²³ As the risk of HCC is not abolished after SVR, all patients with cirrhosis and all those who entered surveillance prior to HCV eradication should continue to undergo liver cancer screening with ultrasound scan every 6 months.^{8 23} While the low incidence of HCC in F3 fibrosis may fall below the recommended threshold of 1.5% per year for cost-effective screening, controversy remains over this threshold which was adopted based on observational studies including mixed populations and prior to the introduction of DAAs.²³ It is likely that, in the short-term, surveillance of patients with F3 fibrosis will largely be determined by local resource.

Patients with cirrhosis should undergo surveillance for oesophageal varices by endoscopy if varices were present prior to HCV treatment or if the platelet count is below $150 \times 10^9/L$ and elastography is more than 20 kPa (in line with Baveno criteria).⁸

There is limited long-term liver outcome data to inform the management of non-cirrhotic patients achieving SVR and most of these patients will be discharged from specialist liver services. However, a number of unknowns remain including

- ▶ How fibrosis or fibrosis regression should be measured after SVR?
- ▶ How much fibrosis regression should be expected after SVR and in which patients?
- ▶ Is fibrosis regression linear over time?
- ▶ What clinical or biological factors are important in fibrosis regression?
- ▶ Is fibrosis reversion associated with reduced HCC risk?

HCV prevention

There is no vaccine to protect against HCV acquisition. In addition, there is no current recommendation for DAA treatment to be offered as postexposure

prophylaxis.⁸ Instead, prevention strategies have looked to simultaneously expand access to curative HCV treatment and harm reduction measures. However, of individuals diagnosed with chronic HCV infection in the UK between 2015 and 2020, only 74.9% were linked to treatment services of which only 67.2% initiated treatment and only 72.2% achieved cure.²⁴ Timely progression from diagnosis to treatment is paramount to break the chain of HCV transmission and treatment delays pose a major threat to elimination across the UK.

The final phase of HCV elimination will require identification and engagement of vulnerable individuals who do not access traditional healthcare systems and may be apprehensive to consider treatment.²⁵ Pathways of care will need to be based within the community and simplified to take advantage of every touch point with the individual. Examples of good practice include:

- ▶ Community based services within prisons, probation services, detention centres, pharmacies, drug treatment centres, needle exchange services and homeless shelters.
- ▶ Recruitment of peer workers with lived experience of addiction, and ideally HCV treatment, to facilitate engagement.
- ▶ Services accommodating booked and walk-in appointments and delivering face-to-face and telephone review.
- ▶ Colocation of an HCV nurse specialist or trained healthcare worker within the community location to support with education, training, liver assessment and referral to specialist liver services.
- ▶ Colocation of testing and treatment services to ensure retention of patients to treatment initiation.
- ▶ Simplified diagnostics with fingerprick blood sampling and near patient HCV RNA testing within an hour and permit immediate treatment of individuals newly diagnosed with HCV infection.

CONCLUSION

HCV infection remains a leading cause of chronic liver disease and premature death worldwide. The 194 nations of the World Health Assembly have committed to eliminate viral hepatitis as a major public health threat by 2030 as defined by a 90% reduction in new infections and 65% reduction in mortality. Progress has not been universal across or within regions but the UK has met the WHO 2020 interim elimination targets. However, to achieve and maintain HCV elimination, more needs to be done to identify and engage the most vulnerable at-risk individuals, including those with no fixed abode and those injecting drugs, and prevent new infections and reinfections.

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