

# Hepatitis C

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Hepatitis C is a global health problem, and an estimated 71·1 million individuals are chronically infected with hepatitis C virus (HCV). The global incidence of HCV was 23·7 cases per 100 000 population (95% uncertainty interval 21·3–28·7) in 2015, with an estimated 1·75 million new HCV infections diagnosed in 2015. Globally, the most common infections are with HCV genotypes 1 (44% of cases), 3 (25% of cases), and 4 (15% of cases). HCV transmission is most commonly associated with direct percutaneous exposure to blood, via blood transfusions, health-care-related injections, and injecting drug use. Key high-risk populations include people who inject drugs, men who have sex with men, and prisoners. Approximately 10–20% of individuals who are chronically infected with HCV develop complications, such as cirrhosis, liver failure, and hepatocellular carcinoma over a period of 20–30 years. Direct-acting antiviral therapy is now curative, but it is estimated that only 20% of individuals with hepatitis C know their diagnosis, and only 15% of those with known hepatitis C have been treated. Increased diagnosis and linkage to care through universal access to affordable point-of-care diagnostics and pangenotypic direct-acting antiviral therapy is essential to achieve the WHO 2030 elimination targets.

## Introduction

Persistent infection with hepatitis C virus (HCV) is a leading cause of chronic liver disease, resulting in 475 000 deaths in 2015.<sup>1</sup> The estimated global HCV prevalence in 2015 was 1·0% (95% uncertainty interval [UI] 0·8–1·1), aggregating to 71·1 million viraemic individuals (95% UI 62·5–79·4) infected with HCV.<sup>1,2</sup>

In 2016, WHO adopted a global hepatitis strategy to eliminate viral hepatitis as a public health threat by 2030, with ambitious targets: a 90% reduction in incident cases of hepatitis B and C and a 65% reduction in mortality.<sup>3</sup> To reach these targets, 80% of treatment-eligible individuals with chronic hepatitis B virus (HBV) and HCV need access to care.

Unfortunately, only around 14 million (20%) people who were estimated to be infected with HCV in 2016 were diagnosed, 1·76 million (13%) people were treated, and 1·51 million (86%) of those treated were given direct-acting antivirals (DAAs).<sup>1</sup> Between 2016 and 2017, the number of people infected with HCV who were treated increased from 1·76 million to 2·10 million, with the greatest increase occurring in middle-income countries. It is of concern that only 12 of 194 countries were on track to meet the 2030 WHO elimination targets in June, 2018. Screening, diagnosis, facilitated linkage to care, and sustainable access to affordable DAA regimens are all fundamental to achieve the WHO 2030 elimination targets.

## Epidemiology

### Overview

Globally, 80% of all HCV infections occur in 31 countries, with six countries (China, Pakistan, Nigeria, Egypt, India, and Russia) accounting for greater than 50% of all infections.<sup>2</sup> Prevalence data in many countries remains of low quality and requires constant reappraisal.<sup>2</sup>

An estimated 1·75 million new HCV infections (95% UI 1·57–2·12) occurred in 2015. Hepatitis C incidence is highest in the WHO European and Eastern

Mediterranean regions. In 2015, an incidence of 61·8 cases per 100 000 people (50·3–66·0) was reported in the European region, versus 62·5 cases per 100 000 people (55·6–65·2) in the Eastern Mediterranean region.<sup>1</sup> The bimodal age distribution of HCV infection in the global population reflects the higher prevalence of infection in both older (aged >50 years) and younger (aged 20–40 years) individuals. The injecting opioid epidemic is the predominant driver of new infections in the younger population. Approximately 2·3 million people are co-infected with HCV and HIV, with prevalence notably higher in men who have sex with men (MSM) and in people who inject drugs (PWID).<sup>4</sup> Approximately 3·5 million children are infected with HCV.

### Global genotype distribution

Thus far, eight confirmed HCV genotypes and 86 subtypes have been reported (figure).<sup>2,5</sup> 44% of infections with HCV worldwide and 60% of HCV infections in high-income and middle-income countries are of genotype 1. Around a third of genotype 1 infections occur in east Asia.

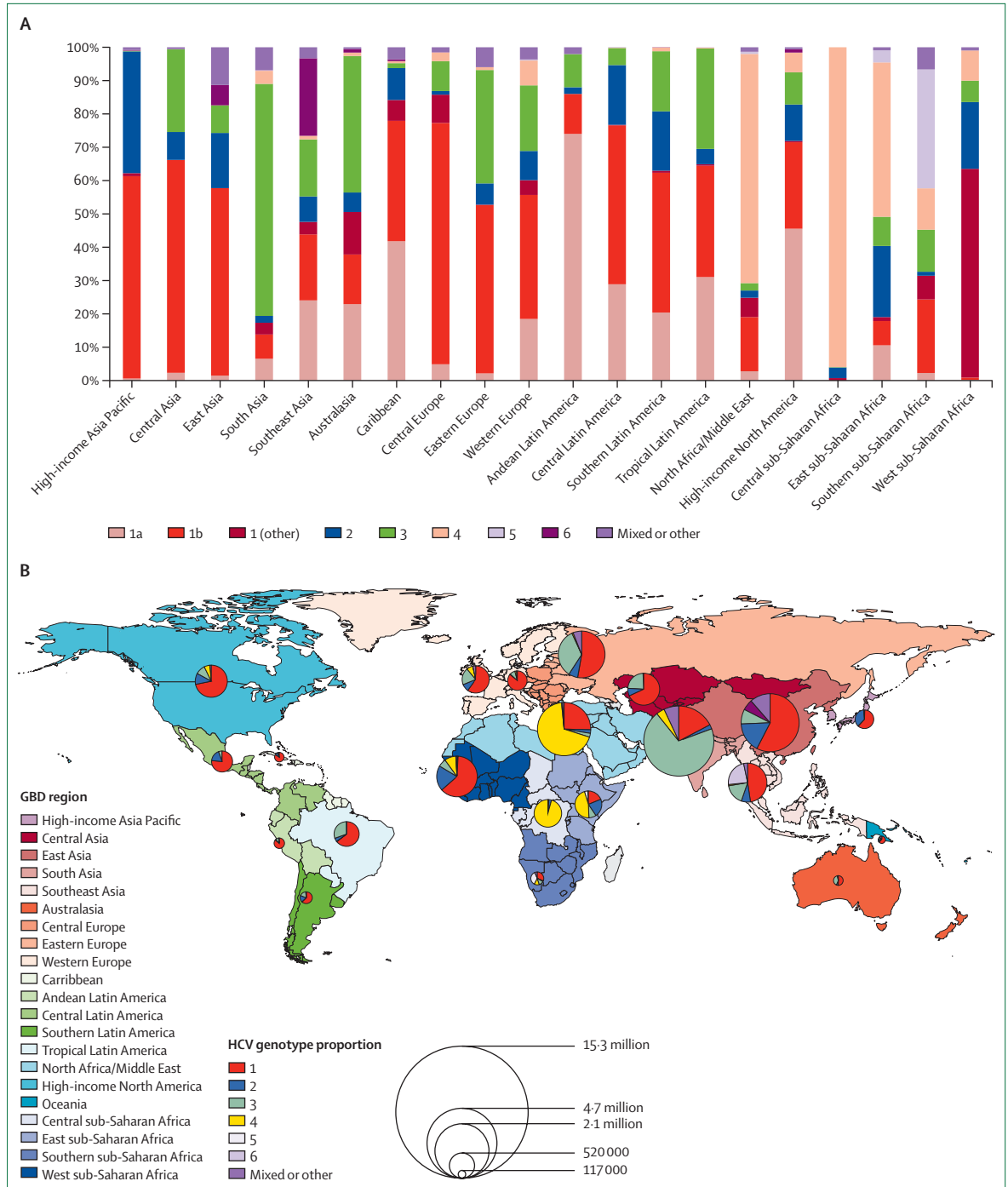
### Search strategy and selection criteria

We searched MEDLINE and PubMed for studies published between Jan 1, 2016, and July 31, 2019, with the search terms “HCV” or “hepatitis C virus”, and “epidemiology”, “key populations”, “natural history”, “extrahepatic manifestations”, “HIV-HCV co-infection”, “HBV-HCV co-infection”, “screening and diagnosis”, “point-of-care diagnostics”, “linkage to care”, “direct acting antivirals and hepatocellular carcinoma”, “HCV positive donors”, “direct acting antivirals and organ transplantation” or “direct acting antiviral therapy”, “generics”, “vaccines”, or “modelling studies”. Most of the articles selected were published within the last 3 years, and all articles were published in English. However, we did not exclude commonly referenced and highly regarded older publications.

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**Figure: HCV genotype distribution**  
HCV genotype distribution by GBD region (A) and genotype proportion and total number of infections (represented by size of circle) in GBD regions (B). Reproduced from Polaris Observatory HCV Collaborators<sup>2</sup> by permission of Elsevier. HCV=hepatitis C virus. GBD=Global Burden of Disease.

Genotype 3 infections are more common in lower-middle-income countries (LMICs) than in high-income, upper-middle-income, and low-income countries, and they account for 25% of all HCV infections; around 75% of infections with HCV genotype 3 occur in south Asia.

Genotype 4 infections constitute 15% of all HCV infections and they are most common in north Africa and the Middle East.<sup>2</sup> Genotype 2 and 6 infections occur largely in east Asia.<sup>6</sup> Genotypes 5, 7, and 8 comprise less than 1% of global HCV infections, with most cases

	Formulation	Dosage
<b>Pangenotypic drugs or drug combinations</b>		
Sofosbuvir (NS5B polymerase inhibitor)	Tablets containing 400 mg sofosbuvir	One tablet once daily
Daclatasvir (NS5A inhibitor)	Tablets containing 60 mg daclatasvir	One tablet once daily
Sofosbuvir (NS5B polymerase inhibitor) and velpatasvir (NS5A inhibitor)	Tablets containing 400 mg sofosbuvir and 100 mg velpatasvir	One tablet once daily
Sofosbuvir (NS5B polymerase inhibitor) and daclatasvir (NS5A inhibitor)	Tablets containing 400 mg sofosbuvir and 60 mg daclatasvir	One tablet once daily
Sofosbuvir (NS5B polymerase inhibitor), velpatasvir (NS5A inhibitor), and voxilaprevir (NS3/4A protease inhibitor)	Tablets containing 400 mg sofosbuvir, 100 mg velpatasvir, and 100 mg voxilaprevir	One tablet once daily
Glecaprevir (NS3-4A protease inhibitor) and pibrentasvir (NS5A inhibitor)	Tablets containing 100 mg glecaprevir and 40 mg pibrentasvir	Three tablets once daily
<b>Genotype-specific drugs or drug combinations</b>		
Sofosbuvir (NS5B polymerase inhibitor) and ledipasvir (NS5A inhibitor) for genotypes 1, 4, 5, and 6	Tablets containing 400 mg sofosbuvir and 90 mg ledipasvir	One tablet once daily
Grazoprevir (NS3/4A protease inhibitor) and elbasvir (NS5A inhibitor) for genotypes 1, 4, and 6	Tablets containing 100 mg grazoprevir and 50 mg elbasvir	One tablet once daily
NS=non-structural protein.		

**Table 1: Hepatitis C virus and direct-acting antiviral classes, formulations, and dosages**

originating in southern and central sub-Saharan Africa.<sup>6</sup> HCV genotypes and subtypes respond differently to available therapies (table 1).<sup>7</sup>

### Transmission

HCV transmission typically requires direct percutaneous exposure to blood via blood transfusions, health-care-related parenteral administrations, or injecting drug use.<sup>1,8,9</sup>

Unsafe medical practices, particularly in LMICs, are a key risk factor underpinning the high HCV prevalence (ie, a national HCV prevalence of >1%) in Egypt,<sup>10</sup> India,<sup>11</sup> and other parts of Asia.<sup>2,12</sup> Iatrogenic transmission, caused by poor infection control and inadequate screening of blood and blood product donations to ensure safety of blood supplies, remains a risk in some LMICs.<sup>13</sup> PWID represent a continuing reservoir of the hepatitis C epidemic worldwide.<sup>14</sup> PWID and iatrogenic transmission are the most common sources of hepatitis C in Pakistan, Georgia, and parts of India.<sup>15-17</sup>

Sexual transmission of HCV has emerged as a risk factor for HCV infection since 2000, particularly in HIV-positive MSM in Europe, north America, and Asia.<sup>18</sup> Concomitant injecting drug use in HIV-positive MSM further increases their risk of contracting HCV.<sup>19</sup> The likelihood of contracting HCV and HIV is also increased by behavioural risk factors, such as receptive intercourse without a condom, fisting, and group sex, and biological risk factors, such as concurrent ulcerative sexually transmissible infections and individuals with HIV infection and a high HCV viral load.<sup>20</sup> Incident infection in HIV-negative MSM remains infrequent but it is most commonly associated with injecting drug use. Increasing the uptake of pre-exposure prophylaxis by HIV-negative MSM might increase the risk of HCV infection.<sup>21</sup>

Apart from in cases of co-infection with HIV, sexual transmission of HCV is rarely observed in serodiscordant

couples. In a study<sup>22</sup> of monogamous heterosexual couples, attributable HCV prevalence was estimated at 0·6%, based on genotype concordance.

Mother-to-infant transmission occurs from 6% of mono-infected mothers and 11% of mothers with HCV and HIV co-infection to their newborn babies.<sup>23</sup> The mode of delivery and type of feeding do not influence vertical transmission in mono-infected women. Other reported routes include tattooing and traditional scarification, which are attributable risk factors in some sub-Saharan African countries.<sup>24</sup> Renal haemodialysis units with suboptimal universal precautions and prisons (which encompass several routes of transmission) also pose transmission risks.<sup>25</sup>

### Key populations

#### Prevention

Primary prevention interventions for HCV remain paramount,<sup>26</sup> and strengthening of health systems is essential.<sup>1</sup> Screening of blood supplies, safe injections, reducing unnecessary parenteral medications, staff training, and proper waste management all prevent iatrogenic transmission.<sup>9</sup>

Harm-reduction interventions, including needle and syringe programmes and the provision of opioid substitution therapy, reduce the incidence of primary infection and reinfection among PWID.<sup>27</sup> Despite data showing the efficacy and cost-effectiveness of opioid substitution therapy and needle and syringe programmes, these strategies remain illegal, unavailable, or are limited in scale in some countries.<sup>28,29</sup> The criminalisation of drugs reduces access to opioid substitution therapy, needle and syringe programmes, and DAA therapy by PWID. Only 60 of more than 10 000 prisons worldwide provide needle and syringe programmes, and 52 countries provide opioid substitution therapy in prisons.<sup>30,31</sup> Behavioural interventions have been shown to prevent HCV transmission in MSM.<sup>32</sup> A HCV transmission model

parameterised with data from the Swiss HIV Cohort<sup>32</sup> has shown that reducing high-risk behaviour associated with HCV transmission would be the most effective intervention for controlling the HCV epidemic in MSM infected with HIV, even if this was not accompanied by an increase in treatment uptake or efficacy.

#### *Treatment as prevention: breaking the cycle of infection*

Treatment as prevention has shown benefits in achieving microelimination of HCV in prison settings and rural villages in Egypt and has enabled HCV to be almost eradicated in Iceland.<sup>33,34</sup> Additionally, the incidence, prevalence, and sequelae of hepatitis C have been reduced in several countries, including Scotland,<sup>35</sup> Portugal,<sup>36</sup> and Egypt.<sup>37</sup> The success of treatment as prevention depends on treatment coverage<sup>38,39</sup> and benefits from the rapid scale-up of DAA therapy.<sup>40,41</sup> Primary community-based prevention efforts should accompany treatment as prevention to reduce HCV incidence and reinfection.<sup>27,41-43</sup>

#### *Reinfection*

The reported rate of HCV reinfection among current PWID is 3.1 reinfections per 100 person-years (incidence rate ratio [IRR] 6.7, 95% CI 1.9–23.5), whereas the reported reinfection rate among former PWID is 1.4 reinfections per 100 person-years (3.7, 1.1–12.9). The reinfection rates among recent and former PWID are higher than those for who do not inject drugs (0.3 reinfections per 100 person-years [1.0]) and are highest in individuals co-infected with HIV (5.7 reinfections per 100 person-years [1.6, 0.8–3.3]).<sup>44</sup> Reinfection in high-risk populations (PWID and HIV-infected MSM) is an important obstacle in HCV elimination. Harm-reduction programmes and behavioural interventions are essential components of successful microelimination programmes. Repeat treatment of reinfections is crucial to prevent ongoing transmission.

### Natural history

#### **Progression of liver disease with HCV infection**

75–80% of individuals develop chronic infection after exposure to HCV; however, some surveys report a lower incidence. Cirrhosis and hepatic decompensation, which has an annualised risk of 2–5%, can develop as a result of chronic HCV infection. 15–20% of people with liver disease die during the first year following decompensation.<sup>45</sup>

#### **Acute hepatitis C**

Acute hepatitis C infection is typically anicteric, and less than 25% of cases are clinically apparent. Symptoms, if present, become apparent 2–26 weeks after HCV exposure, and the acute illness lasts 2–12 weeks. Hepatitis C antibodies emerge within 12 weeks of infection; HCV RNA is detectable before anti-HCV seroconversion. A diagnosis of acute HCV after suspected exposure is confirmed with a positive HCV RNA test. Fulminant

hepatitis is rare (<1%), and associated chronic hepatitis B infection, HIV co-infection, and concomitant immunosuppression are risk factors for the development of this condition.<sup>45</sup>

HCV clearance following acute infection is associated with favourable *IFNL3* (previously known as IL28B) genetic polymorphisms, being female, high alanine aminotransaminase concentrations, jaundice, a rapid decrease in HCV RNA concentrations, and high blood concentrations of interferon  $\gamma$ -induced protein-10 concentrations.<sup>46</sup> Detectable HCV RNA at 12 weeks after exposure predicts chronicity of hepatitis C and indicates a requirement for treatment to prevent ongoing transmission in high-risk groups.<sup>47</sup> The HepNet Acute HCV IV study<sup>48</sup> included patients with acute HCV genotype 1 monoinfection, who were treated with ledipasvir-sofosbuvir for 6 weeks. A sustained virological response (SVR) at 12 weeks after discontinuation of therapy (SVR12) was achieved in 100% of patients. Short-duration treatment for acute HCV can be considered in high-risk populations (eg, PWID and MSM) to reduce transmission. The current recommendation for short-duration treatment is 8 weeks, although the ideal duration and timing of treatment initiation has not been fully established.<sup>49-51</sup>

#### **Chronic hepatitis C**

Around 10–20% of individuals with chronic HCV infection develop complications, including decompensated cirrhosis and hepatocellular carcinoma, over a period of 20–30 years. Disease progression is accelerated by higher age of acquisition, being male, obesity, high alcohol consumption, HIV co-infection, and immunosuppression.<sup>52</sup> The 5-year risk of developing hepatocellular carcinoma ranges from 1% in people with no liver fibrosis to 13% in those with cirrhosis.<sup>53</sup> Other factors, such as hepatitis B co-infection, having diabetes, hepatic steatosis, infection with HCV genotype 3, high alcohol consumption, advanced age, lower platelet counts, being male, and possibly genetic factors, also increase an individual's risk of developing hepatocellular carcinoma.<sup>45</sup>

#### **Extrahepatic manifestations**

The quality of life of patients with chronic HCV is lower than that of the general population. Extrahepatic manifestations and immune-related or inflammatory-related events occur in up to 75% of individuals with chronic HCV. These sequelae include mixed cryoglobulinaemia vasculitis, atherosclerotic cardiovascular disease, renal disease (type 1 membranoproliferative glomerulonephritis, focal segmental glomerulosclerosis, and interstitial nephritis), type 2 diabetes, lymphoproliferative disease (non-Hodgkin lymphoma and hepatosplenic T-cell lymphoma), skin disease (porphyria cutanea tarda and lichen planus), thyroid disease (Hashimoto's thyroiditis and Graves' disease), and eye disease (Mooren's ulcers and Sjögren's syndrome).<sup>54</sup>

## Screening and linkage to care

### Screening

Screening and linkage to treatment are fundamental prerequisites of the WHO elimination goals.<sup>55</sup> Screening approaches vary by country, and although they are guided by HCV prevalence and dominant transmission routes, the approaches can be universal or targeted (eg, screening based on birth cohort or risk factors), or a combination of the two. WHO guidelines<sup>55,56</sup> recommend that serological testing for HCV be offered to individuals in a population with high HCV prevalence or to those who have a history of HCV risk exposure. The US Centers for Disease Control and Prevention support a single HCV screening for people born between 1945 and 1965 (the so-called baby boomers), since sentinel surveys indicate that 75% of adults infected with HCV in the USA are within this birth cohort. These recommendations have been updated and strengthened to include targeted screening of at-risk groups, including individuals with at least one risk factor (panel 1).<sup>57</sup> Targeted screening would need to be directed at wider ranges of birth cohorts in Europe (1940–85), and in the Middle East and Asia (1925–95) compared with the USA.<sup>58</sup> Rates of opioid injection, particularly injection of prescription opioid pain relievers and heroin, have increased with the rate of hepatitis C infection among younger Americans (aged 18–39 years) between 2004 and 2014.<sup>59</sup> Birth-cohort screening has not taken the hepatitis C epidemic in these young opioid injection users into account, and will need to be addressed. Screening of PWID, prisoners, sex workers, MSM, the homeless, and immigrants from Africa or Asia requires reinforcement.<sup>60</sup> The scaling up of screening obligates access to affordable point-of-care diagnostics with consequent unrestricted linkage to affordable DAA therapy, particularly in LMICs. However, political, cultural, financial, and geographical barriers, which are all augmented by poor awareness and fragmented multipayer or health insurance systems, together with the burden of self-payment, can prevent access to affordable point-of-care diagnostics. Nevertheless, screening has been considered to be good value for money at specific willingness-to-pay thresholds.<sup>61,62</sup>

### Rapid diagnostic and point-of-care testing

A positive anti-HCV screening test result from a quality-assured laboratory-based immunoassay or rapid diagnostic test requires subsequent verification of the presence of HCV RNA or HCV core antigen (HCVcAg) in serum to confirm viraemia. Assays with a lower HCV RNA detection limit of less than 15 IU/mL are advised. HCVcAg tests with a lower detection limit of 500–3000 IU/mL are potentially useful as single-step diagnostic assays in LMICs.<sup>63</sup> Elimination of viral hepatitis requires an affordable, point-of-care, rapid diagnostic test, to facilitate test and treat programmes. Tests with a target limit of detection of approximately 1000 IU/mL or higher will identify the majority of viraemic infections.<sup>64</sup> Rapid diagnostic tests use either

### Panel 1: Targeted hepatitis C virus (HCV) risk screening

Individuals are considered at risk for HCV if they:

- have ever injected drugs, including those who have previously injected drugs but do not consider themselves drug users
- have received clotting factor concentrates, blood, and blood products before the country of residence adopted safe screening protocols and practices
- have received blood from a donor who later tested positive for HCV infection
- have required haemodialysis
- have persistently abnormal serum alanine aminotransferase levels
- were born to a mother with HCV antibodies
- have HIV or who are co-infected with HIV and hepatitis B virus
- have had a percutaneous needle-stick injury or have had mucosal exposure to HCV-positive blood (eg, health-care, emergency medical, and public safety workers) or
- are a man who has sex with other men, is HIV-positive, or is using pre-exposure prophylaxis

fingerprick capillary whole blood or oral crevicular fluid (eg, the OraQuick HCV test; OraSure Technologies, Bethlehem, PA, USA). Dried blood spot testing with fingerprick capillary whole blood has been used for anti-HCV, HCV RNA, HCVcAg, and genotype testing.<sup>65,66</sup> WHO have prequalified two point-of-care HCV antibody tests (SD Bioline HCV test; Abbott Diagnostics, Lake Forest, IL, USA) and the OraQuick HCV Rapid Antibody Test), which are as effective as third-generation ELISA immunoassays. Xpert HCV Viral Load (Cepheid; Cepheid, Sunnyvale, CA, USA) is the only WHO pre-qualified HCV RNA quantification test with a linear range of less than 10–100 000 000 IU/mL.

## Treatment

### Effectiveness of therapy

The primary goal of therapy is to achieve undetectable HCV RNA—or an SVR—12 weeks (SVR12) or 24 weeks (SVR24) after the end of therapy, and is judged on the basis of a sensitive molecular assay with an acceptable lower limit of quantification.<sup>67</sup> Concordance between SVR12 and SVR24 surpasses 99%.<sup>67</sup> If a less sensitive HCV RNA test method or HCVcAg is used, SVR24 should be confirmed.<sup>51,63</sup> SVR is associated with improved liver-related and all-cause morbidity and mortality, and it is also associated with improvements in quality of life, and cardiovascular, renal, and metabolic diseases.<sup>68,69</sup> Although the risk of hepatocellular carcinoma is reduced in people with advanced fibrosis and cirrhosis, those with advanced fibrosis (ie, those with a METAVIR score of  $\geq$ F3<sup>70</sup>) or cirrhosis require continued surveillance for hepatocellular carcinoma.<sup>71</sup>

### Who should be treated?

The two major liver societies (the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver) agree in recommending that all treatment-naïve and treatment-experienced individuals who are infected with HCV

should be offered treatment. The only exceptions to this recommendation are in people with a life expectancy of 1 year or less and those whose disease is not remediable either by DAA therapy or liver transplantation.<sup>51,72</sup> Treatment should be expedited in patients with substantial fibrosis (a METAVIR score of F2 or F3) or cirrhosis (a METAVIR score of F4), high-risk populations, those with extrahepatic manifestations, and recipients of liver transplants. Women of childbearing age who are trying to conceive and patients receiving haemodialysis should access treatment as a priority.

Interferon-free DAA regimens are the primary treatment option and, where possible, ribavirin should be omitted. Standard DAA regimens are appropriate for both treatment-naïve and treatment-experienced individuals (patients who have received pegylated interferon and ribavirin; pegylated interferon, ribavirin, and sofosbuvir; or sofosbuvir and ribavirin regimens).<sup>51,72</sup>

#### Assessing liver fibrosis

Staging fibrosis to measure cirrhosis is important for determining the potential duration and choice of DAA regimen, and the need for surveillance for hepatocellular carcinoma and endoscopy after therapy. Liver biopsy is costly, invasive, subject to sampling error and inter-reader variability, and is impractical for rapid linkage to care. Non-invasive methods to stage liver fibrosis, such as serum biomarkers or liver stiffness measurement (LSM), are preferred. These non-invasive methods include: vibration-controlled transient elastography (eg, FibroScan, Echosens, Paris, France), for which the suggested cutoffs are 10.0 kPa for F3 and at least 12.5 kPa for F4;<sup>73</sup> shearwave elastography (eg, Aixplorer; SuperSonic Imagine, Aix-en-Provence, France), for which the suggested cutoffs are 9 kPa for F3 and greater than 13 kPa for F4; and acoustic radiation force impulse elastography, for which the cutoffs are 1.60–2.17 m/s for F3 and 2.19–2.67 m/s for F4. Postprandial determinations, high alanine aminotransferase concentrations, hepatic congestion, or obesity can influence the results. The cost of LSM technology means that this procedure can be unaffordable in many LMICs.

Biomarkers offer a more cost-effective, simple, and readily available alternative to staging liver fibrosis, which is important for enabling hepatitis C treatment in primary care clinics, especially in LMICs. The aspartate aminotransferase-to-platelet ratio index (APRI) and fibrosis-4 scores can be derived from readily available tests.<sup>74</sup> The FibroTest (also known as FibroSure in the USA) biochemical test is a commercial assay.<sup>75</sup> Optimal cutoff values for APRI and fibrosis-4 scores stratified by aspartate aminotransferase concentrations have been proposed to predict cirrhosis,<sup>76</sup> and cutoff values for advanced fibrosis (F3) or cirrhosis (F4) have been validated. Fibrosis biomarkers and LSM are effective in confirming or excluding cirrhosis. Combining different serum biomarker tests, or biomarker tests with LSM

improves the accuracy of findings.<sup>74</sup> Globally, the APRI score is a commonly used initial fibrosis screen (a score of  $\geq 1$  indicates possible liver fibrosis, and a score of  $\geq 2$  indicates cirrhosis).

#### HCV genotype testing

The HCV genotype, treatment history, and severity of liver disease collectively determine the optimal DAA regimen for an individual. Pangenotypic DAA regimens preclude the need for expensive genotype testing, and with prices of less than US\$60 per cure in some countries,<sup>77</sup> these regimens simplify drug procurement and supply chains. Differentiating HCV subtypes is warranted if treatment is specified by subtype. Reliable genotyping assays (preferably those that detect the core-coding regions or the NS5B-coding regions of HCV) are required.<sup>78</sup>

#### Role of HCV resistance testing

Basic population (Sanger sequencing) or deep sequencing can be done to detect resistance to DAAs, but the availability of these assays is scarce. Some commercial HCV resistance testing assays (all of which are Sanger sequencing-based) are available, but these assays are not standardised.<sup>79</sup> Several treatment regimens are more successful in patients with a baseline resistance-associated substitution (RAS). The American Association for the Study of Liver Diseases recommends baseline testing for the non-structural protein-5A (NS5A) Tyr93His RAS (commonly referred to as Y93H) in genotype 3 cirrhotic patients. If the NS5A Tyr93His RAS is present, ribavirin should be added to the sofosbuvir–velpatasvir regimen, or the sofosbuvir–velpatasvir–voxilaprevir regimen should be used to maintain a SVR of greater than 95%.<sup>72</sup> Similar guidance for baseline RAS assessment exists if using elbasvir–grazoprevir for patients with genotype 1a HCV infections. Where available, RAS testing should guide individualised choice of retreatment regimens, especially if NS5A inhibitors were previously used. However, given the efficacy of new triple combination salvage regimens, RAS testing might not be required.<sup>72</sup>

#### Mechanisms of action of DAAs

HCV is a positive-strand RNA virus encoding a single polyprotein, which is subsequently cleaved by cellular and viral proteases into three N-terminal structural proteins and seven non-structural proteins. DAAs target the NS3/4A serine protease, the NS5A replicase and assembly moiety, and the NS5B RNA-dependent polymerase.<sup>80</sup> Early limitations of first-generation NS3 protease inhibitors, including class-specific adverse effects and a low genetic barrier, have been overcome by second-generation and third-generation pangenotypic protease inhibitors. Protease inhibitors include the suffix, -previr. NS5A inhibitors target the NS5A multifunctional protein, which has no enzymatic activity but has dual

mechanisms of action, including replication of the genomic RNA, and assembly of virus particles. NS5A inhibitors are potent inhibitors of HCV replication (at picomolar concentrations); however, they can select for NS5A resistance variants. NS5A inhibitors include the suffix, -asvir. Two subclasses of NS5B inhibitors have been developed: an allosteric non-nucleoside inhibitor (dasabuvir) that binds to the enzyme to block its catalytic activity, and the nucleotide sofosbuvir, a nucleoside analogue chain terminator. Sofosbuvir confers a high barrier to resistance. NS5B polymerase inhibitors include the suffix, -buvir.

### Choice of DAA regimen

#### Overview

The range of DAA regimens, dosages, and drug formulations for non-cirrhotic or compensated cirrhotic, treatment-naïve or treatment-experienced, HCV-monoinfected individuals are shown in tables 1 and 2. Several groups, including WHO, provided updated guidance on HCV treatment in 2018.<sup>51,72,78</sup> The chosen DAA regimen is primarily dependent upon available virological data, accessibility, and cost.<sup>77,78</sup> Similarly, the choice between originator drugs or cheaper generic drugs depends on access and availability. Enough data now support the equal efficacy of originator and generic therapies.<sup>81,82</sup>

#### Sofosbuvir–velpatasvir

Sofosbuvir–velpatasvir is an effective pangenotypic regimen with real-world experience and supporting data from a series of ASTRAL registration studies.<sup>83,84</sup> 95–100% of patients with genotype 1–6 infections given sofosbuvir and velpatasvir for 12 weeks achieved SVR12.<sup>85–87</sup> Of those with genotype 3 disease, 91% of treatment-experienced patients without cirrhosis and 89% of treatment-experienced patients with cirrhosis achieved an SVR12.<sup>88</sup> Impaired responses to sofosbuvir–velpatasvir were seen in patients with baseline NS5A RASs (84–88%) compared with patients without baseline RASs (97%).<sup>84</sup> A controlled trial of sofosbuvir–velpatasvir showed a benefit of ribavirin in patients with baseline NS5A Tyr93His RASs. If RAS testing is unavailable, ribavirin should be added to the regimen for patients with genotype 3 infections that have cirrhosis, or an alternative combination of sofosbuvir–velpatasvir–voxilaprevir is recommended.<sup>89</sup>

#### Sofosbuvir–ledipasvir

Sofosbuvir–ledipasvir is a specific regimen for patients with genotype 1, 4, 5 and 6 infections. The ION-1 to ION-4 studies,<sup>90–94</sup> pooled data analyses, and real-world data support the efficacy of this regimen, with reported SVRs in 94–99% of participants. Post-hoc analysis and real-world studies indicate that 8 weeks of treatment is sufficient for treatment-naïve patients without cirrhosis.<sup>91–93</sup> Similarly high proportions of patients who were co-infected with genotype 1 or 4 and HIV achieved

an SVR.<sup>94</sup> Less data have been accrued in patients infected with genotypes 4, 5, and 6, but the proportion attaining SVR is similar.<sup>95–97</sup> Ledipasvir has reduced in-vitro activity against genotype 6e, but there are some data to show that this activity does not affect the SVR12.<sup>98</sup> Newer non-1a and non-1b subtypes, genotype 4r subtypes reported in sub-Saharan Africa, and the genotype 3b subtype, contain resistance-associated polymorphisms at positions 28–32 in the NS5A region that reduce susceptibility to first-generation NS5A inhibitors, including ledipasvir and daclatasvir. In a Rwandan study<sup>99</sup> of patients infected with genotype 1 and genotype 4 HCV, 56% of patients with genotype 4r, which was present in 16% of study participants, attained an SVR12. Data from the French DAA treatment programme suggests a similar result.<sup>100</sup> The optimal regimen for these distinct subtypes is uncertain.<sup>101</sup> Use of second-generation NS5A inhibitors with an additional protease inhibitor might be required for patients with non-1a and non-1b subtypes and genotype 4r HCV infections.<sup>100,102</sup>

#### Sofosbuvir–daclatasvir

Generic sofosbuvir and daclatasvir are widely used in LMICs. A phase 2b<sup>103</sup> and phase 3<sup>104</sup> trial in treatment-naïve and treatment-experienced patients who were monoinfected with genotypes 1–4 or co-infected with HIV were given sofosbuvir–daclatasvir for 12 or 24 weeks with or without ribavirin. The results showed similar proportions of patients achieving SVR12 (>95%) in monoinfected and HIV co-infected patients. Lower proportions of patients achieving SVR12 were found in those with more advanced disease and in treatment-naïve and treatment-experienced patients with HCV genotype 3 and cirrhosis.<sup>105,106</sup> Data from observational studies<sup>107,108</sup> found that 88% of patients with genotype 5 and 92% of those with genotype 6 who were administered this regimen achieved SVR12. Extensive real-world data from Egypt show high efficacy of the sofosbuvir–daclatasvir regimen for genotype 4a infections.<sup>109</sup> Despite the low cost of the generic regimen, efficacy of this first-generation NS5A inhibitor in patients infected with non-1a, non-1b, non-4a or non-4d subtypes might be similarly less effective.

#### Glecaprevir–pibrentasvir

The SURVEYOR-I, SURVEYOR-II, the ENDURANCE (1, 2, 3, 5, and 6), CERTAIN-2, and the EXPEDITION (2 and 8) clinical trials<sup>110,111</sup> have shown more than 97% efficacy of the pangenotypic protease inhibitor, glecaprevir, and the NS5A inhibitor, pibrentasvir. Real-world data<sup>112</sup> show that 96.7% of patients without cirrhosis achieved SVR12 with 8 weeks of treatment, but only when treatment-experienced patients with genotype 3 infections were excluded. In the ENDURANCE-3 trial, SVR12 was attained by 95% of people following 8 weeks of treatment in treatment-naïve patients without cirrhosis who were infected with genotype 3.<sup>113</sup> Treatment-naïve or

	Sofosbuvir–velpatasvir (weeks)	Sofosbuvir–ledipasvir (weeks)	Sofosbuvir–daclatasvir (weeks)	Glecaprevir–pibrentasvir (weeks)	Grazoprevir–elbasvir (weeks)
<b>Patients without cirrhosis*</b>					
Genotype 1a					
Naive	12	8–12†	12	8	12‡
Experienced	12	12§	12	8	12‡
Genotype 1b					
Naive	12	8–12†	12	8	8 or 12¶
Experienced	12	12	12	8	12
Genotype 2					
Naive	12	..	12	8	..
Experienced	12	..	12	8	..
Genotype 3					
Naive	12	..	12	8	..
Experienced	12	..	12	12	..
Genotype 4					
Naive	12	12	12	8	12‡
Experienced	12	12§	12	8	..
Genotype 5					
Naive	12	12	12	8	..
Experienced	12	12§	12	8	..
Genotype 6					
Naive	12	12	12	8	..
Experienced	12	12§	12	8	..
<b>Patients with compensated cirrhosis   **</b>					
Genotype 1a					
Naive	12	12	12	12	12‡
Experienced	12	12	12	12	12‡
Genotype 1b					
Naive	12	12	12	12	12
Experienced	12	12	12	12	12
Genotype 2					
Naive	12	..	12	12	..
Experienced	12	..	12	12	..
Genotype 3					
Naive	12††	..	12	12	..
Experienced	12††	..	12	16	..
Genotype 4					
Naive	12	12	12	12	12‡
Experienced	12	12	12	12	..
Genotype 5					
Naive	12	12	12	12	..
Experienced	12	12	12	12	..
Genotype 6					
Naive	12	12	12	12	..
Experienced	12	12	12	12	..

Sofosbuvir–velpatasvir, sofosbuvir–daclatasvir, and glecaprevir–pibrentasvir are pangenotypic regimens. Treatment-experienced HCV monoinfected patients include those previously treated with pegylated interferon and ribavirin, or pegylated interferon, ribavirin, and sofosbuvir, and patients treated with sofosbuvir plus ribavirin. HCV=hepatitis C virus. \*As per WHO guidance for sofosbuvir–daclatasvir, if the patient is treatment-experienced, consider addition of ribavirin (applies to all genotypes). †8 weeks if the HCV RNA is <6 000 000 IU/mL and the patient is HIV-negative and not black. ‡For genotype 1a, or if genotype 1 subtyping has not been done, only use this regimen if HCV RNA is <800 000 IU/mL; the same viral load threshold applies to genotype 4 infections. §Requires incorporation of weight-based ribavirin dosing. ¶Data support 8 weeks if the patient has a METAVIR fibrosis score of F0–F2, and 12 weeks if the score is F3. ||For the sofosbuvir–ledipasvir regimen, consider adding weight-based ribavirin dosing for patients with compensated cirrhosis or who are treatment-experienced (applies to all genotypes). \*\*As per WHO guidance for sofosbuvir–daclatasvir, consider adding ribavirin if the patient has compensated cirrhosis or is treatment-experienced (applies to all genotypes). ††Consider sofosbuvir–velpatasvir–voxilaprevir as an alternative if resistance-associated substitution testing is not available, or add weight-based ribavirin dosing to sofosbuvir–velpatasvir regimen.

**Table 2: Direct-acting antiviral therapy regimens and duration of therapy for treatment-naïve or treatment-experienced patients who are monoinfected with HCV, classified by HCV genotype**



treatment-experienced patients without cirrhosis can be given glecaprevir–pibrentasvir for 8 weeks, and treatment-naïve patients with cirrhosis can be given glecaprevir–pibrentasvir for 12 weeks. 95% treatment-naïve patients without cirrhosis and who were infected with genotype 3 attained a SVR12 following 8 weeks of therapy. However, in a pooled analysis, 78% of patients with baseline NS5A A30K RASs achieved an SVR12. Despite this observation, the SVR12 was not influenced by the presence of the Tyr93His RAS.<sup>114</sup> A pooled analysis<sup>114</sup> suggests that treatment with glecaprevir–pibrentasvir for 16 weeks is optimal for treatment-experienced patients with cirrhosis and who are infected with genotype 3.

#### *Grazoprevir–elbasvir*

Grazoprevir and elbasvir are only given to patients with genotype 1, 4, and 6 infections.<sup>115</sup> After 12 weeks of grazoprevir–elbasvir treatment in patients with genotype 1b infections, 97% of patients showed an SVR.<sup>116</sup> Scant data support 8 weeks of therapy in patients with genotype 1b infections and a fibrosis score of F2 or lower.<sup>117</sup> The presence of baseline RASs or HCV RNA concentrations greater than 800 000 IU/mL markedly reduced the proportion of patients attaining SVR12 in those infected with genotype 1a, whereas cirrhosis did not influence the proportion of patients infected with either genotype 1 subtype who achieved SVR12. However, 100% of patients infected with genotype 1a responded to 16 weeks of treatment with grazoprevir–elbasvir plus ribavirin.<sup>118</sup> Data from the C-EDGE treatment-naïve trial<sup>119</sup> supports treatment with elbasvir–grazoprevir for 12 weeks in treatment-naïve patients, with or without cirrhosis, who are infected with genotype 4. RAS testing remains the most accurate way of assessing the benefit from 12 weeks of therapy.

#### *Sofosbuvir–velpatasvir–voxilaprevir*

Sofosbuvir–velpatasvir–voxilaprevir is a pangenotypic regimen that is prescribed predominantly for retreatment of DAA treatment-experienced patients because of its demonstrable efficacy in patients after 12 weeks of treatment in the POLARIS trials.<sup>120,121</sup> As a ribavirin-free treatment alternative to sofosbuvir–velpatasvir in treatment-naïve or treatment-experienced patients infected with genotype 3, 12 weeks of sofosbuvir–velpatasvir–voxilaprevir therapy can also be considered.

## Treatment of special populations

### HCV–HIV co-infection

HCV–HIV co-infection increases the likelihood of progression to advanced liver fibrosis and cirrhosis and increases the risk of hepatocellular carcinoma. However, more than 95% of patients who are monoinfected with HCV or co-infected with HCV attain SVR following 8–12 weeks of DAA therapy.<sup>122</sup> Potential complex drug–drug interactions between DAAs and antiretroviral therapy should be assessed before therapy is given.

### HCV–HBV co-infection

HCV is often the dominant driver of chronic inflammatory activity in patients who are co-infected with HCV and HBV. In such patients, HBV DNA concentrations are usually low, but HBV reactivation can occur during or after HCV clearance. A meta-analysis<sup>123</sup> showed that the pooled proportion of patients with HBV reactivation was 24% (95% CI 19–30) in HBsAg-positive patients versus 1.4% (0.8–2.4) in patients with a resolved HBV infection. Therefore, HBsAg, anti-hepatitis B core antibody, and anti-hepatitis B surface antibody testing is recommended before DAA therapy is given. If the HBsAg test is positive, concurrent HBV nucleoside analogue therapy is advised. Treatment should be continued for 12 weeks after DAA therapy, and patients should be monitored after HBV nucleoside analogue therapy is stopped. Serum alanine aminotransferase concentrations should be carefully monitored in HBsAg-negative patients that are anti-HBc antibody-positive.<sup>51</sup>

### Chronic kidney disease

In patients with mild to moderate renal impairment (estimated glomerular filtration rate  $\geq 30$  mL/min per 1.73 m<sup>2</sup>), no DAA dose adjustments are necessary. However, in patients with an estimated glomerular filtration rate of less than 30 mL/min per 1.73 m<sup>2</sup>, or in those with end-stage renal disease, it is preferable to use glecaprevir–pibrentasvir for 8 or 12 weeks in patients infected with genotypes 1–6,<sup>124</sup> or to use elbasvir–grazoprevir for 12 weeks in patients infected with genotypes 1 and 4.<sup>125,126</sup> The major metabolite of sofosbuvir, GS-331007, accumulates during renal impairment. Sofosbuvir has not been conclusively shown to worsen renal function, but it is not licensed for patients with stage 4 or stage 5 chronic kidney disease. Candidates for renal transplantation should be treated with a suitable DAA regimen, and the timing of treatment is dependent on liver disease stage and whether the kidney donor is HCV-positive.

### Paediatric populations

Cirrhosis and hepatocellular carcinoma are uncommon in children; however, co-factors, such as thalassaemia-associated iron overload, HIV co-infection, and obesity can contribute to advancing fibrosis.<sup>127</sup> HCV therapy has proven to be safe and effective in adolescents aged 12–17 years and who weigh more than 35 kg. Data support 12 weeks of sofosbuvir–ledipasvir for adolescents infected with genotypes 1, 4, 5, and 6, and sofosbuvir–ribavirin for adolescents infected with genotype 2 (for 12 weeks) or genotype 3 (for 24 weeks).<sup>51</sup> The US Food and Drug Administration has approved glecaprevir–pibrentasvir for the treatment of genotype 1–6-infected adolescents with or without compensated cirrhosis. Treatment duration depends on treatment history, HCV genotype, and whether the patient has cirrhosis. The US

Food and Drug Administration has approved the use of sofosbuvir–ledipasvir for children aged 3 years and older who have genotype 1, 4, 5, and 6 HCV infections.

#### Decompensated cirrhosis and liver transplantation

HCV recurrence is certain in patients with detectable HCV RNA at the time of liver transplantation. If recurrent HCV is not treated, there is a risk that the recipient will develop fibrosing cholestatic hepatitis and accelerated graft failure.<sup>128</sup> Over the past decade, liver transplants for end-stage HCV disease have decreased by more than 30%. HCV-positive recipients of liver transplants have similar 3-year graft survival rates as non-HCV recipients.<sup>129</sup> The timing of DAA therapy in patients awaiting a liver transplantation remains controversial, since only 20% of treated patients on the waiting list for transplants are delisted within 1 year of stopping DAA therapy.<sup>130–132</sup> Centre-specific factors, such as anticipated time to transplantation, access to related living donors, and availability of anti-HCV-positive donors influence the timing of DAA therapy either before or after transplantation. Protease inhibitor-based regimens should be avoided because of the risk of hepatic decompensation.<sup>133</sup>

Achieving SVR can improve model for end-stage liver disease (MELD) scores and indirectly reduce the need for liver transplantation. However, MELD score improvements without an associated improvement in quality of life is potentially disadvantageous. The consensus opinion is that patients with MELD scores of less than 20 and with no clinically significant ascites or encephalopathy, or both, are more likely to be removed from the liver transplant waiting list after DAA therapy than patients with MELD scores of more than 20. A score based on five baseline factors—the body-mass index, encephalopathy, ascites, serum alanine aminotransferase, and albumin (BE3A)—identifies patients with decompensated cirrhosis who will benefit from DAA therapy.<sup>134</sup> Patients with decompensated cirrhosis who have MELD scores of 18–20 or higher, will benefit from transplantation first and DAA therapy after transplantation.<sup>135</sup> However, if a patient is on the liver transplant waiting list for more than 6 months, they should be considered for DAA therapy first.

#### Solid organ transplantation

DAA therapy is safe and effective after transplantation, and a similar proportion of patients achieve an SVR12 (without an increased risk of rejection) as those who do not receive an organ transplant. DAA therapy should be initiated when the patient receiving an organ transplant has stabilised. Drug–drug interactions occur between protease inhibitor-containing DAAs and immunosuppressive drugs, such as calcineurin inhibitors and mTOR inhibitors, and potential drug–drug interactions between NS5A inhibitors and everolimus can occur.<sup>136</sup> After 12 weeks of treatment with sofosbuvir–velpatasvir, 96% of liver transplant recipients (n=79) infected with

genotype 1–4 HCV achieved an SVR12.<sup>137</sup> After 12 weeks of glecaprevir–pibrentasvir treatment, 98% of liver (n=80) or kidney (n=20) transplant recipients with genotype 1–6 infections achieved SVR12.<sup>138</sup> Treatment with ledipasvir–sofosbuvir for 12 or 24 weeks achieved 100% SVR12 in renal transplant recipients (n=117) with genotype 1 and 4 infections.<sup>139</sup>

#### Pregnancy

Women of childbearing age who are infected with HCV have a lower chance of livebirths, and a greater risk of infertility, gestational diabetes, pre-eclampsia, and miscarriage compared with those women that are not infected with HCV. The risk of these adverse events is reduced by early HCV suppression.<sup>140</sup> Few data have been published on the safety or efficacy of DAA in pregnancy, and treatment is therefore delayed until after delivery. Data from a phase 1 trial<sup>141</sup> shows no increased risk of adverse events in women given sofosbuvir–ledipasvir in the third trimester relative to pregnant women who are not infected with HCV.

#### Controversies, ongoing research, and the future of treatment

##### DAA therapy and risk of hepatocellular carcinoma

The effect of achieving SVR following DAA therapy on the risk of hepatocellular carcinoma occurrence and recurrence has been controversial.<sup>142</sup> A systematic review and meta-analysis<sup>143</sup> compared the risk of the occurrence and recurrence of hepatocellular carcinoma in 41 studies (n=13 875 patients); of these, 26 studies analysed de-novo occurrence of hepatocellular carcinoma (17 studies with interferon and nine studies that used DAAs), and 17 analysed the recurrence of hepatocellular carcinoma (seven studies that used interferon and ten studies with DAA). This analysis found an occurrence of hepatocellular carcinoma of 1.14 cases per 100 person-years (95% CI 0.86–1.52) in interferon and 2.96 cases per 100 person-years (1.76–4.96) in studies with DAAs. The analysis found a recurrence of hepatocellular carcinoma of 9.21 cases per 100 person-years (7.18–11.81) in studies that used interferon and 12.16 cases per 100 person-years (5.00–29.58) in studies with DAAs. In a meta-regression study,<sup>143</sup> DAA therapy was not associated with higher occurrence of hepatocellular carcinoma (rate ratio [RR] 0.68, 95% CI 0.18–2.55; p=0.55) or recurrence (0.62, 0.11–3.45; p=0.56) after adjusting for follow-up and age. Similar to interferon, DAAs reduced individual risk by 63%. There is evidence that the risk of de-novo hepatocellular carcinoma is reduced after SVR, and that the risk of recurrence is not increased after DAA therapy. However, all patients with cirrhosis should receive standard surveillance for hepatocellular carcinoma after achieving SVR.<sup>144</sup> The American Gastroenterological Association recommends deferring DAA therapy for 4–6 months to confirm response to therapy for hepatocellular carcinoma.<sup>145</sup>

The mechanisms of de-novo or recurrent hepatic carcinogenesis associated with HCV infection are unclear. Molecular and genetic mechanisms, and the potential failure of immune surveillance involved in the occurrence and recurrence of hepatocellular carcinoma, are discussed (appendix pp 1–3).<sup>142,146–152</sup>

### The use of HCV-positive donors

The use of HCV-positive organ donors potentially expands the donor pool, increases access to transplantation when wait times are long, and is cost-effective.<sup>153,154</sup> Transmission will occur if the donor is viraemic but, given that almost 100% SVR can be achieved with DAAs after transplantation, HCV-positive organs can be considered for HCV-positive and HCV-negative recipients.<sup>155,156</sup> The use of HCV-positive donors requires detailed informed consent about the risk of developing HCV-induced fibrosing cholestatic hepatitis and membranous nephropathy and it requires histological assessment of liver graft quality and assured early access to DAA therapy.

### Vaccines

Despite DAAs being highly effective, elimination of HCV is unlikely to be achieved by treatment alone. A vaccine remains essential to prevent transmission and reinfection in at-risk groups. HCV vaccine development remains challenging because of the complex genetic diversity of the virus, the effect of the error-prone HCV polymerase to produce dissimilar quasi-species, and an inadequate understanding of HCV immune-escape mechanisms.<sup>157</sup> Highly conserved viral epitopes are the usual target of antibody-based vaccine development. Neutralising antibodies against HCV are directed against the hypervariable region 1 of the E2 envelope protein. The heterogeneity of this region hinders development of an effective vaccine. However, induction of cross-neutralising antibodies is achievable. Several new HCV vaccines, including peptide, recombinant protein, DNA-based and vector-based vaccines, are in development.<sup>157</sup> A two-stage, phase 1/2 double-blind, randomised, placebo-controlled trial (ClinicalTrials.gov, NCT01436357) of the AdCh3NSmut1 and MVA-NSmut candidate vaccines, which were administered intramuscularly to 548 PWIDs who were not infected with HCV, showed higher rates of cell-mediated immune responses in the vaccine group than in the control group (77% vs 3%), but the same rate of chronic HCV infection (5·1%) was observed in the vaccine group versus the control group. Scientists remain optimistic about the possibility of developing a successful vaccine.

### Models to scale up prevention and treatment

Few countries have field data on HCV prevalence. Given the high cost of HCV prevalence studies, the use of modelled simulations can provide essential components to aid estimation of the number of individuals who require treatment, so that WHO elimination goals can be

reached, and the urgency and need for opportune health-system interventions can be conveyed. A dynamic transmission model of the global HCV epidemic, adjusted to 190 countries, estimated the worldwide impact of scaling up interventions that reduce transmission and improve access to treatment and screening.<sup>26</sup> Measures that reduce the risk of transmission and increase the coverage of harm reduction in PWID are estimated to prevent 14 million infections. More comprehensive packages, including prevention, screening, and treatment packages, could prevent 15 million new infections and 1·5 million deaths due to cirrhosis and hepatocellular carcinoma. As such, these packages could help countries to reach WHO incidence targets and to almost achieve the requisite reduction in mortality by 2030.

Although models can be useful, they create theoretical simulations and are restricted by uncertainty in the data and the parameters that underpin them, which could lead to underestimation or overestimation of prevalence and

See Online for appendix

## Panel 2: Future research directions

### New therapeutic framework:

- Identification of patients responding to ultrashort direct-acting antiviral (DAA) regimens who achieve rapid RNA clearance
- Development of novel and effective long-acting, nano-formulated, sustained-release, antiviral drugs

### Public health

- Updated and novel mechanisms for population estimates of prevalence and numbers of infected people
- Affordable, low-cost, WHO prequalified tests, including rapid, portable, point-of-care nucleic acid and hepatitis C virus (HCV) antigen tests
- Understanding the scale and impact of reinfection
- Understanding the characteristics of the population at risk of reinfection
- Understanding the challenge posed by distinct novel HCV subtypes in Africa, Asia, and elsewhere that could compromise DAA regimens

### Financing

- Investment framework to finance low-cost drugs, to ensure global access
- Where appropriate, inclusion of HCV in the country disease control package as part of universal health coverage and the Sustainable Development Goals
- Enriched philanthropic funding to assist agenda for global elimination

### Prevention

- Development of a pangenotypic, heterologous recombinant prophylactic vaccine
- Research priorities that address knowledge gaps in preventing and managing HCV among people who inject drugs, and in increasing linkage to community screening and care

### Scientific

- Improved understanding of host and viral genomic interactions that affect viral replication and pathogenesis
- Improved understanding of molecular mechanisms of hepatocarcinogenesis
- Biomarkers to predict residual risk of hepatocellular carcinoma after sustained virological response
- Development of immune-competent small animal models for vaccine research
- Understand the evolution of related viruses in mammalian species

the impact of an intervention. Models also do not address the practical challenges and resources necessary to successfully implement stated interventions.<sup>158</sup> Several substantive models generally stipulate that the specified targets for HCV elimination by 2030 cannot be achieved without scaling up region-appropriate treatment and sustaining it for the next decade without a decline in momentum.<sup>37</sup>

### Financing

Universal access to affordable DAAs is essential for achieving HCV elimination targets.<sup>159,160</sup> How HCV treatment is paid for in high-income and middle-income countries varies considerably. Various approaches have improved access to affordable treatment.<sup>161</sup> Payment criteria in insurance systems are still disparately decided in national and even state programmes; priorities can be restrictive and drug prices vary substantially by geographical region.<sup>162,163</sup> Many countries have made progress by use of volume-based pricing models, which form part of strategic elimination plans, and cost-saving options. Generic DAAs, manufactured by voluntary licensing instruments, are also more accessible than originator DAAs because they are cheaper. A voluntary licence is a legal contract between the original producer and generic manufacturers that permits the manufacture and sale of a patented drug, subject to licensing contracts. Voluntary licences can also be agreed via pooling mechanisms, such as the Medicines Patent Pool.<sup>164</sup> The licences help to create a balance between protecting intellectual property rights and providing a business model that facilitates entry into developing countries and markets. Notably, daclatasvir, pibrentasvir–glecaprevir, and ravidasvir, have been acquired by the Medicines Patent Pool for licensing.<sup>8,164</sup> Generic daclatasvir, sofosbuvir, ledipasvir, velpatasvir, and voxilaprevir have been manufactured through licensing agreements, allowing for substantial cost reductions.<sup>165</sup> However, whether generic pricing has thus far improved screening initiatives is unknown, and to what extent governments, rather than individuals, are meeting the costs, is unclear.

### Conclusion

HCV is a global health problem, but elimination is now possible with curative DAA therapy. Achievement of elimination will require increased diagnosis and linkage to care and universal access to affordable diagnostics and pangenotypic DAA therapy. Identifying and decriminalising key HCV-infected populations, such as PWID and MSM, and combining treatment with expansion of PWID harm reduction services, to break cycles of infection and reinfection, are essential. Upscaling blood safety programmes and reducing health-care-associated transmission remain important preventive measures in elimination programmes. Ongoing research into antiviral formulations and vaccine development, public

health implementation of viral hepatitis programmes, and innovative financing are essential (panel 2).

Achieving WHO 2030 elimination goals is possible, but it will require political will to recognise viral hepatitis as a health priority, set national elimination targets, develop costed national viral hepatitis plans with dedicated funding, and ensure universal access to therapy.

### Contributors

CWS, GMD, MH and MS contributed equally to the manuscript. CWS designed the manuscript, and all authors wrote and reviewed the manuscript. CWS was responsible for the final editing of the manuscript.

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