

# GUIDELINES FOR THE CARE AND TREATMENT OF PERSONS DIAGNOSED WITH CHRONIC HEPATITIS C VIRUS INFECTION

JULY 2018





World Health  
Organization

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Guidelines for the care and treatment of persons diagnosed with chronic hepatitis C virus infection

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# ABBREVIATIONS AND ACRONYMS

AASLD	American Association for the Study of Liver Disease
Ab	antibody
AE	adverse event
ALT	alanine aminotransferase
anti-HBc	antibody to hepatitis B core antigen
APRI	AST-to-platelet ratio index
ART	antiretroviral therapy
ARV	antiretroviral
AST	aspartate aminotransferase
CI	confidence interval
DAA	direct-acting antiviral (medicine)
DBS	dried blood spot
DDI	drug–drug interaction
EASL	European Association for the Study of the Liver
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
FBC	full blood count
FDA	United States Food and Drug Administration
FDC	fixed-dose combination
FIB-4	fibrosis-4 index for liver fibrosis
GHP	Global Hepatitis Programme
GHSS	Global Health Sector Strategy (on viral hepatitis)
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HIC	high-income country
HIV	human immunodeficiency virus
LMICs	low- and middle-income countries
MSF	Médecins Sans Frontières or Doctors Without Borders
MSM	men who have sex with men
NAT	nucleic acid testing/test
NS5B	non-structural protein 5B (of HCV)
NS3/NS4A	non-structural protein 3/non-structural protein 4A (of HCV)

NSP	needle–syringe programme
OR	odds ratio
OST	opioid substitution therapy
PEG-IFN	pegylated interferon
PICO	Population, Intervention, Comparison, Outcomes
PWID	people who inject drugs
RBV	ribavirin
RCT	randomized controlled trial
RDT	rapid diagnostic test
RNA	ribonucleic acid
RR	relative risk
SAE	severe adverse event
STI	sexually transmitted infection
SVR12	sustained virological response at 12 weeks post-treatment
TB	tuberculosis
UK	United Kingdom
USA	United States of America
WHO	World Health Organization
WTO	World Trade Organization

# GLOSSARY OF TERMS

New HCV infection	A new infection with HCV that may or may not be symptomatic
Acute HCV infection	A new infection with HCV that leads to acute symptoms
Anti-HCV antibody	Presence of antibodies to hepatitis C virus (HCV), which is a biomarker of past or present infection
Chronic HCV infection	Continued infection six months or more after acquiring HCV infection
Cirrhosis	Extensive liver scarring secondary to prolonged inflammation of the liver (F4 in the METAVIR scoring system)
Compensated cirrhosis	Cirrhosis usually without liver-related symptoms
Decompensated cirrhosis	Cirrhosis with the development of symptomatic complications, including ascites or variceal bleeding
GRADE	Grading of Recommendations Assessment, Development and Evaluation (GRADE) is an approach used to assess the quality of a body of evidence, and to develop and report recommendations
Hepatitis B core antibody (anti-HBc)	Antibody to HBV core protein. Anti-HBc antibodies are non-neutralizing antibodies and are detected in both recent and chronic infection
HCV infection	Active replication of HCV in the body The biomarker of HCV infection is the presence of HCV RNA in the blood
Pangenotypic	Activity and effectiveness of antiviral medicine against all major HCV genotypes
Relapse	Undetectable HCV RNA in the blood at the end of treatment but detectable HCV RNA within 24 weeks of completing treatment
Spontaneous viral clearance	Clearance of HCV infection without treatment
Sustained virological response (12)	Undetectable HCV RNA in the blood 12 weeks after treatment completion. SVR 12 is considered equivalent to a cure for HCV infection
Viral breakthrough	Undetectable HCV RNA in the blood during treatment followed by detectable HCV RNA during treatment, which is not caused by a new HCV infection

# EXECUTIVE SUMMARY

## Background

WHO estimates that in 2015, 71 million persons were living with chronic hepatitis C virus (HCV) infection worldwide and that 399 000 died from cirrhosis or hepatocellular carcinoma caused by HCV infection. In May 2016, the World Health Assembly endorsed the Global Health Sector Strategy (GHSS) on viral hepatitis, which proposes to eliminate viral hepatitis as a public health threat by 2030 (90% reduction in incidence and 65% reduction in mortality). Elimination of viral hepatitis as a public health threat requires 90% of those infected to be diagnosed and 80% of those diagnosed to be treated.

## Rationale

Since the last update to the *Guidelines* was issued in 2016, three key developments have prompted changes in terms of when to treat and what treatments to use. First, the use of safe and highly effective direct-acting antiviral (DAA) regimens for all persons improves the balance of benefits and harms of treating persons with little or no fibrosis, supporting a strategy of treating all persons with chronic HCV infection, rather than reserving treatment for persons with more advanced disease. Second, since 2016, several new, pangenotypic DAA medicines have been approved by at least one stringent regulatory authority, reducing the need for genotyping to guide treatment decisions. Third, the continued substantial reduction in the price of DAAs has enabled treatment to be rolled out rapidly in a number of low- and middle-income countries.

## Scope

These guidelines aim to provide evidence-based recommendations on the care and treatment of persons diagnosed with chronic HCV infection. They update the care and treatment section of the WHO *Guidelines for the screening, care and treatment of persons with hepatitis C infection* issued in April 2016. The 2017 *Guidelines on hepatitis B and C testing* update the screening section.

## Audience

These guidelines are intended for government officials to use as the basis for developing national hepatitis policies, plans and treatment guidelines. These include country programme managers and health-care providers responsible for planning and implementing hepatitis care and treatment programmes, particularly in low- and middle-income countries.

## Methods

WHO developed these guidelines in accordance with procedures established by its Guidelines Review Committee. Systematic reviews were undertaken to assess the safety and efficacy of treatment regimens in adults, to examine the morbidity and mortality from extrahepatic manifestations in persons with HCV infection and to review the literature on cost-effectiveness. In addition, modelling was carried out. A regionally representative and multidisciplinary Guidelines Development Group met in September 2017 to formulate the recommendations, using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach. This included an assessment of the quality of evidence (high, moderate, low or very low), consideration of the overall balance of benefits and harms (at individual and population levels), patient/health worker values and preferences, resource use, cost-effectiveness, and consideration of feasibility and effectiveness across a variety of resource-limited settings.

## Summary of the new recommendations

### When to start treatment in adults and adolescents

**WHO recommends offering treatment to all individuals diagnosed with HCV infection who are 12 years of age or older,<sup>1</sup> irrespective of disease stage** (*Strong recommendation, moderate quality of evidence*)

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<sup>1</sup> With the exception of pregnant women

## What treatment to use for adults and adolescents

**WHO recommends the use of pangenotypic DAA regimens for the treatment of persons with chronic HCV infection aged 18 years and above.<sup>2</sup>**

*(Conditional recommendation, moderate quality of evidence)*

**In adolescents aged 12–17 years or weighing at least 35 kg with chronic HCV infection, WHO recommends:**

- sofosbuvir/ledipasvir for 12 weeks in genotypes 1, 4, 5 and 6
- sofosbuvir/ribavirin for 12 weeks in genotype 2
- sofosbuvir/ribavirin for 24 weeks in genotype 3.

*(Strong recommendation/very low quality of evidence)*

## Pangenotypic regimens currently available for use in adults 18 years of age or older

For adults without cirrhosis, the following pangenotypic regimens can be used:

- Sofosbuvir/velpatasvir 12 weeks
- Sofosbuvir/daclatasvir 12 weeks
- Glecaprevir/pibrentasvir 8 weeks<sup>3</sup>

For adults with compensated cirrhosis, the following pangenotypic regimens can be used:

- Sofosbuvir/velpatasvir 12 weeks
- Glecaprevir/pibrentasvir 12 weeks<sup>3</sup>
- Sofosbuvir/daclatasvir 24 weeks
- Sofosbuvir/daclatasvir 12 weeks<sup>4</sup>

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2 The Guidelines Development Group defined pangenotypic regimens as those leading to a SVR rate >85% across all six major HCV genotypes.

3 Persons with HCV genotype 3 infection who have received interferon and/or ribavirin in the past should be treated for 16 weeks.

4 May be considered in countries where genotype distribution is known and genotype 3 prevalence is <5%.



## Treatment of children 0–12 years of age

In children aged less than 12 years with chronic HCV infection, WHO recommends:

- **deferring treatment until 12 years of age**  
*(conditional recommendation, very low quality of evidence)*
- **treatment with interferon-based regimens should no longer be used**  
*(strong recommendation, very low quality of evidence)<sup>5</sup>*

## Clinical considerations

### General clinical considerations

- The use of pangenotypic regimens obviates the need for genotyping before treatment initiation.
- In resource-limited settings, WHO recommends that the assessment of liver fibrosis should be performed using non-invasive tests (e.g. aspartate/platelet ratio index (APRI) score or FIB-4 test, see existing recommendations, p. xvii). This can determine if there is cirrhosis before initiation of treatment.
- There are a few contraindications to using pangenotypic DAAs together with other medicines.
- DAAs are well tolerated, with only minor side-effects. Therefore, the frequency of routine laboratory toxicity monitoring can be limited to a blood specimen at the start and end of treatment.
- Following completion of DAA treatment, sustained virological response (SVR) at 12 weeks after the end of treatment is used to determine treatment outcomes (See existing recommendations, p. xvii).

### HIV/HCV coinfection

- Persons with HIV/HCV coinfection are at a higher risk for progression of fibrosis and were included in the list of persons prioritized for treatment since the 2014 WHO treatment guidelines. Treatment for HCV infection needs to consider drug–drug interactions with antiretroviral medications.

### HBV/HCV coinfection

- Persons with HBV/HCV coinfection are at risk for HBV reactivation during and following HCV treatment. An assessment for HBV treatment eligibility with initiation of HBV treatment for those eligible may prevent HBV reactivation during HCV treatment.

<sup>5</sup> Prior to approval of DAAs for children aged <12 years of age, exceptional treatment with interferon + ribavirin may be considered for children with genotype 2 or 3 infection and severe liver disease. This may include children at higher risk of progressive disease, such as with HIV coinfection, thalassaemia major and survivors of childhood cancer.

### Cirrhosis

- Persons with cirrhosis, including those who have achieved SVR, may be regularly screened for hepatocellular carcinoma (HCC).

### Chronic kidney disease

- Data are insufficient on the safety and efficacy of sofosbuvir-based regimens in persons with severe renal impairment. Glecaprevir/pibrentasvir is effective against infection with all six major genotypes in persons with chronic kidney disease.

### TB/HCV coinfection

- In persons with TB/HCV coinfection, treatment for active TB is considered before treatment of HCV infection. TB/HCV-coinfected persons treated for TB are at an increased risk of hepatotoxicity.

### Retreatment after DAA treatment failure

- Currently, only one pangenotypic DAA regimen, sofosbuvir/velpatasvir/voxilaprevir, is approved by a stringent regulatory authority for the retreatment of persons who have previously failed DAA treatment.
- Investigations of a failure to achieve SVR with DAA therapy includes re-examination of adherence and of potential drug–drug interactions.

## Simplified service delivery models

An eight-point approach to service delivery supports implementation of the clinical recommendations for Treat All and adoption of pangenotypic DAA regimens:

1. Comprehensive national planning for the elimination of HCV infection;
2. Simple and standardized algorithms across the continuum of care;
3. Integration of hepatitis testing, care and treatment with other services;
4. Strategies to strengthen linkage from testing to care, treatment and prevention;
5. Decentralized services, supported by task-sharing;
6. Community engagement and peer support to address stigma and discrimination, and reach vulnerable or disadvantaged communities;
7. Efficient procurement and supply management of medicines and diagnostics;
8. Data systems to monitor the quality of individual care and the cascade of care.

## Public health considerations in specific populations

Five population groups (people who inject drugs [PWID], people in prisons or other closed settings, men who have sex with men, sex workers and indigenous populations) require specific public health approaches because of one or more of the following specific issues: high incidence, high prevalence, stigma, discrimination, criminalization or vulnerability, and difficulties in accessing services.

## Summary of the existing WHO recommendations

### Who to test for HCV infection? (2017 testing guidelines) (3)

**1. Focused testing in most-affected populations.** In all settings (and regardless of whether delivered through facility- or community-based testing), it is recommended that serological testing for HCV antibody (anti-HCV)<sup>1</sup> be offered with linkage to prevention, care and treatment services to the following individuals:

- Adults and adolescents from populations most affected by HCV infection<sup>2</sup> (i.e. who are either part of a population with high HCV seroprevalence or who have a history of exposure and/or high-risk behaviours for HCV infection);
- Adults, adolescents and children with a clinical suspicion of chronic viral hepatitis<sup>3</sup> (i.e. symptoms, signs, laboratory markers).

*(Strong recommendation, low quality of evidence)*

*Note: Periodic retesting using HCV nucleic acid tests (NAT) should be considered for those with ongoing risk of acquisition or reinfection.*

**2. General population testing.** In settings with a  $\geq 2\%$  or  $\geq 5\%$ <sup>4</sup> HCV antibody seroprevalence in the general population, it is recommended that all adults have access to and be offered HCV serological testing with linkage to prevention, care and treatment services.

General population testing approaches should make use of existing community- or facility-based testing opportunities or programmes such as HIV or TB clinics, drug treatment services and antenatal clinics.<sup>5</sup>

*(Conditional recommendation, low quality of evidence)*

**3. Birth cohort testing.** This approach may be applied to specific identified birth cohorts of older persons at higher risk of infection<sup>6</sup> and morbidity within populations that have an overall lower general prevalence.

*(Conditional recommendation, low quality of evidence)*

1 This may include fourth-generation combined antibody/antigen assays.

2 Includes those who are either part of a population with higher seroprevalence (e.g. some mobile/migrant populations from high/intermediate endemic countries, and certain indigenous populations) or who have a history of exposure or high-risk behaviours for HCV infection (e.g. PWID, people in prisons and other closed settings, men who have sex with men and sex workers, and HIV-infected persons, children of mothers with chronic HCV infection especially if HIV-coinfected).

3 Features that may indicate underlying chronic HCV infection include clinical evidence of existing liver disease, such as cirrhosis or hepatocellular carcinoma (HCC), or where there is unexplained liver disease, including abnormal liver function tests or liver ultrasound.

4 A threshold of  $\geq 2\%$  or  $\geq 5\%$  seroprevalence was based on several published thresholds of intermediate and high seroprevalence. The threshold used will depend on other country considerations and epidemiological context.

5 Routine testing of pregnant women for HCV infection is currently not recommended.

6 Because of historical exposure to unscreened or inadequately screened blood products and/or poor injection safety.

## How to test for chronic HCV infection and monitor treatment response? (2017 testing guidelines) (3)

**1. Which serological assay to use?** To test for serological evidence of past or present infection in adults, adolescents and children (>18 months of age),<sup>1</sup> an HCV serological assay (antibody or antibody/antigen) using either a rapid diagnostic test (RDT) or laboratory-based immunoassay formats<sup>2</sup> that meet minimum safety, quality and performance standards<sup>3</sup> (with regard to both analytical and clinical sensitivity and specificity) is recommended.

- In settings where there is limited access to laboratory infrastructure and testing, and/or in populations where access to rapid testing would facilitate linkage to care and treatment, RDTs are recommended.

*(Strong recommendation, low/moderate quality of evidence)*

**2. Serological testing strategies.** In adults and children older than 18 months, a single serological assay for initial detection of serological evidence of past or present infection is recommended prior to supplementary nucleic acid testing (NAT) for evidence of viraemic infection.

*(Conditional recommendation, low quality of evidence)*

### 3. Detection of viraemic infection

- Directly following a reactive HCV antibody serological test result, the use of quantitative or qualitative NAT for detection of HCV RNA is recommended as the preferred strategy to diagnose viraemic infection.

*(Strong recommendation, moderate/low quality of evidence)*

- An assay to detect HCV core (p22) antigen, which has comparable clinical sensitivity to NAT, is an alternative to NAT to diagnose viraemic infection.

*(Conditional recommendation, moderate quality of evidence)<sup>4</sup>*

### 4. Assessment of HCV treatment response

- Nucleic acid testing for qualitative or quantitative detection of HCV RNA should be used as the test of cure at 12 or 24 weeks (i.e. sustained virological response [SVR12 or SVR24]) after completion of antiviral treatment.

*(Conditional recommendation, moderate/low quality of evidence)*

1 HCV infection can be confirmed in children under 18 months only by virological assays to detect HCV RNA, because transplacental maternal antibodies remain in the child's bloodstream up until 18 months of age, making test results from serology assays ambiguous.

2 Laboratory-based immunoassays include enzyme immunoassay (EIA), chemoluminescence immunoassay (CLIA) and electrochemoluminescence assay (ECL).

3 Assays should meet minimum acceptance criteria of either WHO prequalification of in vitro diagnostics (IVDs) or a stringent regulatory review for IVDs. All IVDs should be used in accordance with manufacturers' instructions, and where possible at testing sites enrolled in a national or international external quality assessment scheme.

4 A lower level of analytical sensitivity can be considered if an assay is able to improve access (i.e. an assay that can be used at the point of care or is suitable for dried blood spot [DBS] specimens) and/or affordability. An assay with a limit of detection of 3000 IU/mL or lower would be acceptable and would identify 95% of those with viraemic infection, based on the available data.

### **Screening for alcohol use and counselling to reduce moderate and high levels of alcohol intake (2016 treatment guidelines) (2)**

An alcohol intake assessment is recommended for all persons with HCV infection followed by the offer of a behavioural alcohol reduction intervention for persons with moderate-to-high alcohol intake.

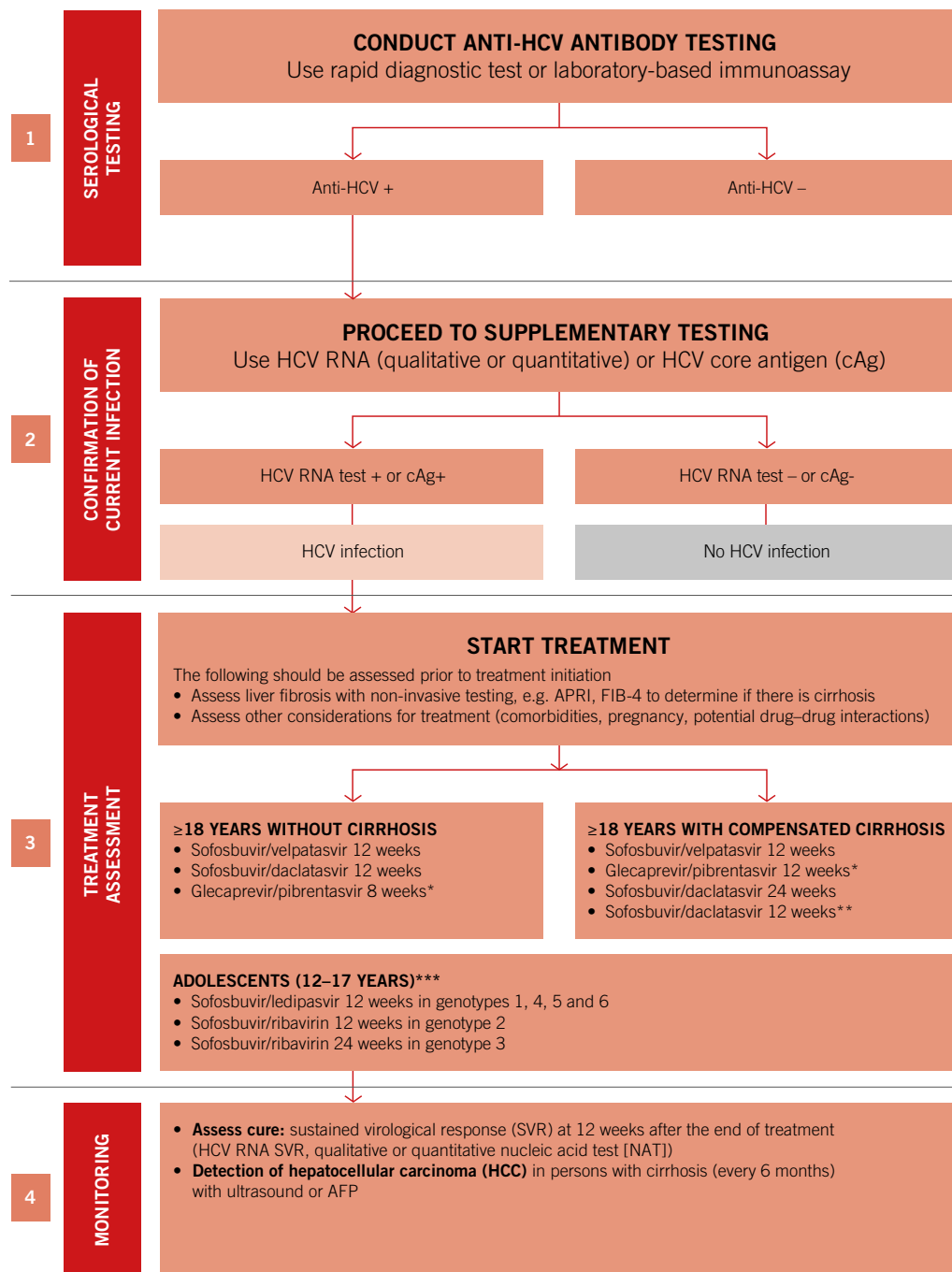
*(Strong recommendation, moderate quality of evidence)*

### **Assessing degree of liver fibrosis and cirrhosis (2016 treatment guidelines) (2)**

In resource-limited settings, it is suggested that the aminotransferase/platelet ratio index (APRI) or FIB-4 tests be used for the assessment of hepatic fibrosis rather than other non-invasive tests that require more resources such as elastography or FibroTest.

*(Conditional recommendation, low quality of evidence)*

## Summary algorithm for the diagnosis, treatment and monitoring of chronic HCV infection in adults and adolescents



\* Persons with HCV genotype 3 infection who have received interferon and/or ribavirin in the past should be treated for 16 weeks.

\*\* May be considered in countries where genotype distribution is known and genotype 3 prevalence is <5%.

\*\*\* Treatment in adolescents at this time still requires genotyping to identify the appropriate regimen.

AFP: alpha fetoprotein, APRI: aspartate-to-platelet ratio index, FIB-4: fibrosis stage

# CHAPTER 1. SCOPE AND OBJECTIVES

## 1.1 Objectives

The objective of these guidelines is to provide updated evidence-based recommendations on the care and treatment of persons with chronic hepatitis C virus (HCV) infection in terms of when to treat and what treatment to use in children, adolescents and adults.

## 1.2 New developments and rationale for an update of the guidelines

In 2014, WHO published its first *Guidelines for the screening, care and treatment of persons with HCV infection* (1). The care and treatment component of the 2014 *Guidelines* were updated a first time in 2016 (2) and a second time with the present guidelines. In parallel, the 2017 *Guidelines* on testing for viral hepatitis recommended which approaches to use in terms of who to test and how to test (3).

*The 2016 Guidelines for the screening, care and treatment of persons with HCV infection* recommended DAA regimens for the treatment of persons with HCV infection (2). While all HCV-infected persons could be considered for treatment, the *Guidelines* also highlighted key factors to consider in prioritizing treatment (i) for those likely to derive the greatest individual benefit, or (ii) in populations deriving the greatest treatment benefit from limiting HCV transmission. Those with the highest risk of mortality and morbidity include those at risk of accelerated fibrosis, metabolic syndrome and extrahepatic manifestations. Those for whom treatment could lead to a reduction in incidence included PWID, HIV-infected MSM, prisoners, sex workers and health-care workers.

Since the *2016 Guidelines for the screening, care and treatment of persons with HCV infection*, three key developments prompted changes in terms of when to treat and what treatment to use:

1. **The generalized use of safe and highly effective direct-acting antiviral (DAA) medicine regimens for all persons improves the balance of benefits to harms of treating persons with little or no fibrosis**, supporting a strategy of treating all persons with chronic HCV infection, rather than reserving treatment for persons with more advanced disease. Prior to 2014, HCV treatment involved the use of interferon-based regimens with generally low rates of cure, long duration of therapy and substantial toxicities. The introduction of highly

effective and well tolerated short-course oral DAA therapy that can cure HCV infection with high rates of sustained virological response (SVR) within weeks transformed the treatment landscape for persons with chronic HCV infection. Since the 2016 *Guidelines*, DAA regimens have continued to improve.

- 2. Several new, pangenotypic DAA medicines have been approved by at least one stringent regulatory authority**, reducing the need for genotyping to guide treatment decisions. Pangenotypic DAA combination regimens approved by the United States Food and Drug Administration (FDA) and European Medicines Agency (EMA) include sofosbuvir/velpatasvir, sofosbuvir/velpatasvir/voxilaprevir and glecaprevir/pibrentasvir. These regimens achieve high treatment efficacy across all six major HCV genotypes, including in those with cirrhosis or HIV coinfection. In addition, the Guidelines Development Group considered sofosbuvir/daclatasvir, commonly used in LMICs, as a pangenotypic regimen, based on all the available evidence from clinical trials and observational studies in different settings.
- 3. The continued substantial reduction in the price of DAA regimens has enabled treatment to be rolled out** rapidly in a number of low- and middle-income countries (LMICs) (4).

Together, these three factors have shifted the balance of benefits and risks in favour of treating all persons with chronic HCV infection with pangenotypic regimens.

### 1.3 Target audience

Although the recommendations included in these guidelines apply to all countries, the key audience for these guidelines is policy-makers in ministries of health in LMICs. The recommendations are intended for government officials to use as the basis for developing national hepatitis policies, plans and treatment guidelines. For countries with existing national plans/programmes, these guidelines can guide updates of national hepatitis treatment guidelines and for deciding which medicines to use. In addition, implementing partners can use the guidelines to inform the design and implementation of treatment services. The guidelines are also intended to be helpful for clinicians who treat HCV-infected persons.

### 1.4 Scope of the guidelines

The recommendations in these guidelines address treatment issues. However recommendations related to prevention, testing and care are referred to in order to reinforce the importance of the continuum of care (including identification of infected persons) that is a key element of the clinical management of HCV infection. The management of acute HCV infection was not included in the scope of work for these guidelines.



## 1.5 Related guidelines

These guidelines are intended to complement existing guidance on the primary prevention of HCV and other bloodborne viruses by improving blood and injection safety, and health care for people who inject drugs (PWID) and other vulnerable groups, including those living with HIV.

Additional guidance relevant to the prevention, care and treatment of those infected with HCV can be found in the following documents:

- *Consolidated guidelines on HIV prevention, diagnosis, treatment and care for key populations*. Geneva: WHO; 2016 update (5)
- *Guidelines for the prevention, care and treatment of persons with hepatitis B infection*. Geneva: WHO; 2015 (6)
- *WHO guideline on the use of safety-engineered syringes for intramuscular, intradermal and subcutaneous injections in health-care settings*. Geneva: WHO; 2016 (7)
- *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection*. Geneva: WHO; 2016 (8)
- *Guidelines on hepatitis B and C testing*. Geneva: WHO; 2017 (3)

## 1.6 Guiding principles

The following principles have informed the development of these guidelines and should guide the implementation of the recommendations.

- The guidelines will contribute to realizing the Sustainable Development Goals through achieving key global and national hepatitis goals.
- The guidelines are based on a public health approach to scaling up the use of antiviral treatment for HCV infection along the continuum of hepatitis prevention, care and treatment.
- Implementation of the guidelines need to be accompanied by efforts to promote and protect the human rights of people who need hepatitis services, including ensuring informed consent, preventing stigma and discrimination in the provision of services and promoting gender equity.
- Implementation of the recommendations in these guidelines should be informed by local context, including HCV epidemiology and prevalence of other comorbidities, availability of resources, the organization and capacity of the health system and anticipated cost-effectiveness.

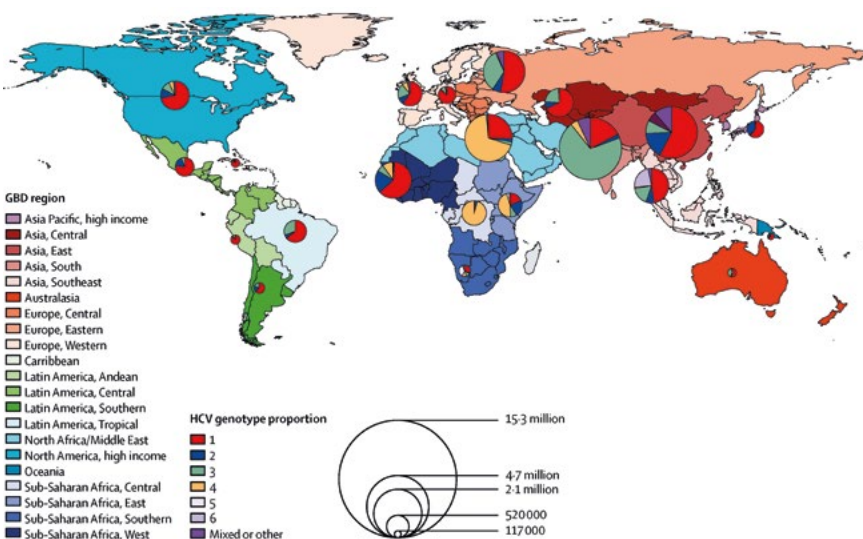
# CHAPTER 2. BACKGROUND

## 2.1 The challenge of HCV elimination

WHO estimated that in 2015, 71 million persons were living with chronic HCV infection worldwide (global prevalence: 1%) and that 399 000 had died from cirrhosis or hepatocellular carcinoma (HCC) (9). Aside from the burden of HCV infection secondary to liver-related sequelae, HCV causes an additional burden through comorbidities among persons with HCV infection, including depression, diabetes mellitus and chronic renal disease. A proportion of these morbidities is directly attributable to HCV and is therefore referred to as extrahepatic manifestations. These manifestations are likely to be affected by treatment (see Chapter 4 and Fig. 2.2). The World Health Assembly recognized that viral hepatitis is a major public health problem and passed two initial resolutions in 2010 (10) and 2014 (11).

WHO estimated that in 2015, 1.75 million new HCV infections occurred, mostly because of injecting drug use and unsafe health care (9). Worldwide, HCV infection may be caused by one of six major HCV genotypes (Fig. 2.1) (12). However, in many countries, the genotype distribution remains unknown (13).

**FIG. 2.1** Worldwide distribution of HCV genotypes



Source: The Polaris Observatory HCV Collaborators. Global prevalence and genotype distribution of hepatitis C virus infection in 2015: a modelling study. *Lancet Gastroenterol Hepatol.* 2017;2:161–76.

Disclaimer: This map is reproduced as originally published.

In May 2016, the World Health Assembly endorsed the Global Health Sector Strategy (GHSS) for 2016–2021 on viral hepatitis (HBV and HCV infection), which proposes to eliminate viral hepatitis as a public health threat by 2030. Elimination is defined as a 90% reduction in new chronic infections and a 65% reduction in mortality compared with the 2015 baseline (14). To reach these targets, the GHSS recommends scaling up currently available prevention interventions and introducing newer programmatic components, such as testing and treatment. Elimination of HCV infection as a public health threat requires diagnosing 90% of those infected and treating 80% of those diagnosed. However, in 2015, there were large deficits in achieving these service coverage objectives. Of the 71 million persons with HCV infection, 14 million (20%) had been diagnosed (a 70% gap), and of the 14 million diagnosed, 1.1 million (7%) had been started on treatment (a 73% gap) (9).

### 2.1.1 Natural history of HCV infection

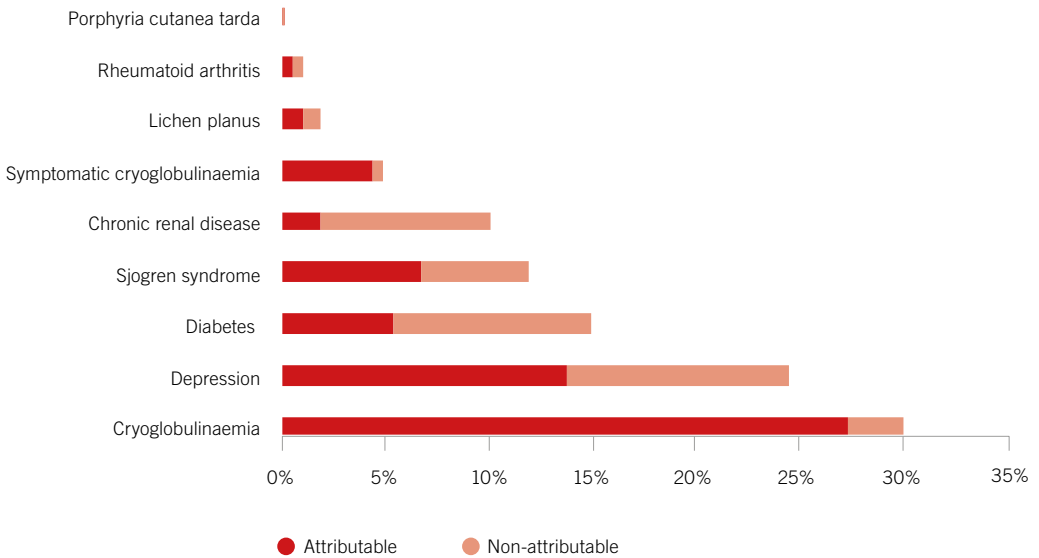
#### Hepatitis

HCV infection causes both acute and chronic hepatitis. Incident infection is associated with early symptoms in about 20% of persons. Spontaneous clearance occurs within six months of infection in 15–45% of infected individuals in the absence of treatment. The remaining 55–85% develop chronic infection, which can lead to progressive fibrosis and cirrhosis. The risk of cirrhosis ranges from 15% to 30% after 20 years of infection with HCV (15–17). Initially, cirrhosis may be compensated. Decompensation may occur later, leading to variceal haemorrhages, ascites or encephalopathy (18). Each year, approximately 1–3% of persons with cirrhosis progress to hepatocellular carcinoma (HCC) (19). The risk of progression to cirrhosis and HCC varies according to the person's characteristics and behaviours. Alcohol use, HBV or HIV coinfection and immunosuppression due to any cause increase the risk of developing cirrhosis or HCC (20).

#### Extrahepatic manifestations

HCV infection can lead to extrahepatic manifestations (21). Among HCV-infected persons, the three most common comorbidities are depression (24%), diabetes mellitus (15%) and chronic renal disease (10%). A proportion of these morbidities is directly attributable to HCV and is therefore referred to as extrahepatic manifestations (Fig. 2.2). Extrahepatic manifestations are likely to be affected by treatment (in red in Fig. 2.2, for example, only 37% of diabetes among HCV-infected persons would be attributable to HCV infection). The prevalence of these extrahepatic manifestations is usually independent of the degree of liver fibrosis (22, 23).

**FIG. 2.2** Prevalence of comorbidities among persons with HCV infection, including the fraction that is attributable to HCV infection (calculated on the basis of Younossi et al. 2016, using attributable fractions among those exposed)



### 2.1.2 Natural history of HIV/HCV coinfection

Coinfection with HIV adversely affects the course of HCV infection. Coinfected persons, particularly those with advanced immunodeficiency (CD4 count  $<200$  cells/mm<sup>3</sup>), have significantly accelerated progression to cirrhosis, decompensated cirrhosis and HCC compared to HCV-monoinfected persons (24–26). In high-income countries (HICs), HCV-associated liver disease has become a leading cause of death in people living with HIV, accounting for almost half (47%) of the deaths in the United States (27, 28). It is unclear whether HCV infection accelerates HIV disease progression, but after initiation of antiretroviral therapy (ART), CD4 recovery is impaired in HIV/HCV-coinfected persons when compared to those with HIV monoinfection (29, 30). HIV/HCV-coinfected persons have demonstrated more rapid HIV disease progression compared to those who were HIV-infected alone in some but not all studies (31–33). Assessment of the impact of HCV infection on HIV disease progression may be confounded by the negative health consequences of injecting drug use, which is strongly associated with HCV infection (34, 35). In persons with HIV coinfection, HCC tends to occur at a younger age and within a shorter time period (36, 37).

### 2.1.3 Routes of transmission

#### Health-care-associated transmission

In countries where infection control measures are insufficient, HCV infection is associated with unsafe injection practices and procedures such as renal dialysis, surgery, dental care and unscreened blood transfusions (38–41). Worldwide, in 2010, 5% of health-care injections were given with unsterilized, reused injection devices (42) and unsafe injections were estimated to lead to 315 000 new HCV infections each year (43). In addition, excessive use of injections to administer medications is a matter of concern (44). Coupled with poor injection practices, overuse of injections further increases HCV transmission. This persisting driver of transmission needs to be addressed through safer health care, introduction of reuse-prevention devices (45) and a reduction in unnecessary health-care injections.

#### Transmission among people who inject drugs

Globally, injection drug use may account for 23% of new HCV infections; 8% of current HCV infections are among PWID (9). PWID infected with HCV are at increased risk of all-cause mortality, reflecting the combined role of injecting drug use, low socioeconomic status, poor access to health care and environmental factors (46, 47).

#### Other modes of transmission

Other modes of HCV transmission include mother-to-child transmission, which affects 4–8% of children born to women with HCV infection and 10.8–25% of children born to women with HIV/HCV coinfection (48), other percutaneous procedures, such as tattooing and body piercing (49), and needlestick injuries in health-care workers (50, 51). Sexual transmission of HCV occurs infrequently in heterosexual couples. However, it is more frequent in HIV-positive persons, particularly in men who have sex with men (MSM) (52).

## 2.2 Direct-acting antivirals

As of May 2018, the FDA or the EMA had approved 13 direct-acting antivirals from four classes (see Table 2.1), and several fixed-dose combination (FDC) DAAs for the treatment of persons with HCV infection.

**TABLE 2.1** Direct-acting antivirals (DAAs) according to class

NS3/4A (protease) inhibitors	NS5A inhibitors	NS5B polymerase inhibitor (nucleotide analogue)	NS5B polymerase inhibitor (non-nucleoside analogue)
Glecaprevir	Daclatasvir	Sofosbuvir	Dasabuvir
Voxilaprevir	Velpatasvir		
Grazoprevir	Ledipasvir		
Paritaprevir	Ombitasvir		
Simeprevir	Pibrentasvir		
	Elbasvir		

### 2.2.1 Summary of the currently available pangenotypic DAA combinations

DAAs are considered pangenotypic when they achieve high treatment efficacy across all six major HCV genotypes.

#### Sofosbuvir/velpatasvir

Sofosbuvir/velpatasvir is an FDC of a pangenotypic NS5A inhibitor and sofosbuvir. It was approved both by the FDA and EMA in 2016. In clinical trials, it is associated with good efficacy in infections with genotypes 1–6, HIV/HCV coinfection, persons on opioid substitution therapy (OST) and persons with compensated or decompensated cirrhosis (53–57).

#### Sofosbuvir/velpatasvir/voxilaprevir

Sofosbuvir/velpatasvir/voxilaprevir is generally considered for use in the retreatment of HCV-infected persons who previously failed a DAA regimen (see *also* section 5.2.6 on retreatment of persons with DAA failure); however, in some HICs it is also registered for treatment-naïve HCV-infected persons.

### Glecaprevir/pibrentasvir

Glecaprevir/pibrentasvir is an FDC containing a pangenotypic NS3/4A protease inhibitor with a pangenotypic NS5A inhibitor that was approved by the FDA and EMA in 2017. In clinical trials, glecaprevir/pibrentasvir suggest good efficacy in infections with genotypes 1–6, compensated cirrhosis, including in persons with renal insufficiency and end-stage renal disease (58–64). It is contraindicated in persons with decompensated cirrhosis (Child–Pugh Class C).

### Sofosbuvir/daclatasvir

Daclatasvir, an NS5A inhibitor that has been evaluated with sofosbuvir, was approved by the EMA in 2014 and by the FDA in 2015. Clinical trials reported good efficacy of the combination of daclatasvir and sofosbuvir in infections with genotypes 1–4, persons with decompensated liver disease, liver transplant recipients and those with HIV/HCV coinfection (65–68). Recent data suggest that the combination of sofosbuvir/daclatasvir is also effective in infections with genotypes 5 and 6 (69) (Médecins Sans Frontières [MSF] demonstration project, manuscript in preparation).

### Other DAA regimens

Additional evidence being generated may indicate in the future that other DAA regimens (e.g. sofosbuvir/ravidasvir) are pangenotypic or that existing pangenotypic DAA regimens can be used in more populations (e.g. children and adolescents <18 years of age).

## 2.3 Access to direct-acting antivirals

DAAs for HCV infections have been initially sold at a very high price, limiting access. Opportunities to access low-price generic medicines are increasing, particularly in LMICs (4). (See Strategies for more efficient procurement and supply management of medicines and diagnostics in section 6.7, Table 6.2.)

# CHAPTER 3. METHODS

## 3.1 WHO guidelines development process

These WHO guidelines were produced by following the recommendations for standard guidelines, as described in the WHO *Handbook for guideline development* (70). The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework was followed (71). A WHO Steering Committee was constituted, which included individuals with relevant expertise from different WHO departments. This Committee oversaw the entire guidelines development process.

A Guidelines Development Group was constituted to ensure representation from various stakeholder groups, including members of organizations that represent patients' groups, advocacy groups, researchers and clinicians. Group members were also selected to achieve geographical representation and gender balance.

Systematic reviews were undertaken to assess the safety and efficacy of treatment regimens in adults and children, to examine the morbidity and mortality from extrahepatic manifestations in persons with HCV infection and to review the literature on cost-effectiveness. In addition, modelling was carried out. Outcomes were ranked by the Guidelines Development Group based on their importance to the patient population. Members of the Group met in Geneva in September 2017.

## 3.2 Formulation of recommendations

At the Guidelines Development Group meeting, the results of the systematic reviews, meta-analyses and complementary information were presented, and the evidence profiles and decision-making tables were reviewed to ensure that there was understanding and agreement on the scoring criteria. See Web annexes 3.1, 3.2 and 8 for the reviews and Web annexes 1, 2 and 6 for the decision-making tables. The GRADE method was used to rate the certainty of the evidence and determine the strength of the recommendations. The strength of the recommendations was rated as either strong (the panel was confident that the desirable effects of the intervention outweighed the undesirable effects) or conditional (the panel considered that the desirable effects of the intervention probably outweighed the undesirable effects). The certainty of evidence supporting each recommendation was graded as high, moderate, low or very low. Recommendations were then formulated by members of the Guidelines Development Group through discussions based on the certainty of the evidence, the balance of benefits and harms,



considerations of values and preferences, resource use and the feasibility of carrying out the intervention (72). The Chairs and methodologist worked to reach consensus during the meeting. After addressing all comments and questions from members of the Group, the Chair asked Group members whether they agreed with the recommendations to document consensus. All Group members agreed with all the recommendations. Implementation needs were subsequently evaluated, and areas and topics requiring further research identified.

The draft guidelines was reviewed by the Guidelines Development Group and an external review group.

### 3.3 Roles

*The Guidelines Development Group* formulated the questions on population, intervention, comparison, outcomes (PICO), reviewed the evidence profiles and decision-making tables, composed and agreed upon the wording of the recommendations, and reviewed drafts of the guidelines document.

*The guidelines methodologist* ensured that the GRADE framework was appropriately applied throughout the guidelines development process. This included formulation of the PICO questions, ensuring the comprehensiveness and quality of the systematic reviews, and preparation of evidence profiles and decision-making tables. The methodologist also provided guidance to the Guidelines Development Group in formulating the wording and strength of the recommendations.

*The External Review Group* reviewed the draft guidelines document and provided critical feedback.

### 3.4 Declarations of interest and management of conflicts of interest

In accordance with WHO policy, all external contributors to the guidelines, including members of the Guidelines Development Group and the External Review Group, completed a WHO declaration of interest form (see Annexes 1 and 2, pages 80 and 83). A brief biography of each member of the Guidelines Development Group was posted on the web. The biographies of the Group members are available on <http://www.who.int/hepatitis/news-events/gdg-hepatitis-c/en/>. The Steering Committee reviewed and assessed the declarations submitted by each member and agreed on an approach to assess potential conflicts of interest, which they discussed with a staff member of the WHO Compliance and Risk Management and Ethics Department. At the meeting, declarations of interest were reported according to WHO standard requirements.

Individuals from organizations that had received significant funding from private (primarily pharmaceutical) companies and individual researchers or clinicians who had received honoraria above US\$ 5000 from pharmaceutical companies were considered to have a conflict of interest, and their participation in the Guidelines Development Group was classified as restricted. The Group members whose participation was restricted were Charles Gore, Francesco Negro, Jurgen Rockstroh and Alexander Thompson. These individuals contributed to the development of the PICO questions and provided technical expertise in reviewing the evidence summaries but were excluded from participation in the discussion, voting and formulation of the recommendations (see Annex 1, page 80).

The declarations of interest forms from members of the External Review Group were reviewed in accordance with the WHO guidelines development policy. Any conflicts of interest identified were considered when interpreting comments from External Review Group members during the external review process. The external reviewers could not and did not make changes in the recommendations (see Annex 2, page 83).

### **3.5 Dissemination and updating of the guidelines**

The Global Hepatitis Programme Secretariat will disseminate the guidelines through WHO regional offices to WHO country offices and Ministries of Health, as well as to key international, regional and national collaborating centres, civil society organizations and national programmes. In addition, the guidelines will be made accessible on the WHO website with links to other United Nations and related websites.

The successful implementation of the recommendations in these guidelines will depend on a well-planned and appropriate process of adaptation and integration into relevant regional and national strategies. It is a process that will be determined by available resources, existing enabling policies and practices, and levels of support from partner agencies, nongovernmental organizations (NGOs) and civil society.

Implementation of these guidelines can be measured by the number of countries that incorporate them into their national treatment programmes and actual treatment onset rates in countries, which is part of the cascade of care. With respect to policy uptake, the Global Hepatitis Programme (GHP) conducted a country profile survey in 2016/2017. With respect to the cascade of care, GHP has set up a monitoring and evaluation framework (73) and led a process to generate initial estimates for 2015 (9) and 2016 (4). In 2018, GHP will be setting up a

new system of routine reporting to obtain yearly updates on these two levels of indicators. This new system will be instrumental in measuring how much these guidelines are resulting in impact at country level.

The Guidelines Development Group recognized that the field of hepatitis treatment is evolving rapidly. New data are expected for the treatment of HCV-infected adolescents and children in the coming year; therefore, it is anticipated that an update will be needed in 2020.

## **3.6 Evidence that informed the recommendations**

Systematic reviews, meta-analyses, modelling, cost-effectiveness analyses, values and preferences and a feasibility survey were undertaken to support the process of formulating recommendations and identifying patient-important outcomes. Existing national and international guidelines were also evaluated.

### **3.6.1 Systematic reviews and meta-analyses**

For the recommendation to Treat All persons diagnosed with HCV infection, WHO commissioned a systematic review and meta-analyses of morbidity and mortality from extrahepatic manifestations in persons with HCV infection (74).

For the updated recommendations on treatment with DAAs, a systematic review was conducted. The manufacturers of the DAAs of interest (AbbVie and Gilead) were contacted to provide any additional data from clinical trials. To complement evidence from clinical trials, observational cohort studies that followed individuals receiving DAA treatment were taken into account. In addition, Médecins Sans Frontières (MSF) contributed data from their treatment programmes in South Africa and Cambodia. Search strategies and summaries of evidence are available in Web annexes 2, 3.1 and 3.2.

The decision-making table to inform treatment decisions of HCV-infected adolescents and children under the age of 18 years is available in Web annex 6.

### **3.6.2 Modelling**

Modelling was carried out to predict the expected impact of HCV treatment on the incidence of new HCV infections. Existing national and subnational models were used to estimate the prevention impact by treating a fixed number of HCV infections in various regions (see Web annex 4).

### **3.6.3 Feasibility survey**

An online feasibility survey was conducted to assess programmatic and personal experiences of introducing a Treat All recommendation. The online survey was sent to members of the Guidelines Development Group, who distributed the survey within their networks. The survey was completed by 10 programme managers, 145 health-care providers and 112 people living with HCV infection. The questionnaire focused on experiences and the perceived challenges of a Treat All recommendation, as well as suggested solutions provided by the participants (see Web annex 7).

### **3.6.4 Cost–effectiveness analyses**

WHO commissioned a systematic review of the cost–effectiveness literature to evaluate the cost–effectiveness and population health outcomes of a Treat All scenario compared to a more restricted set of access policies (75).

### **3.6.5 Values and preferences**

To provide information on values and preferences, a stakeholder survey was conducted and the literature reviewed to determine which characteristics of a treatment regimen are important from the patient's perspective (see Web annex 7).

# CHAPTER 4. RECOMMENDATIONS

## 4.1 Treatment with direct-acting antiviral agents: when to start treatment

### New recommendation

WHO recommends offering treatment to all individuals diagnosed with HCV infection who are 12 years of age or older,<sup>1</sup> irrespective of disease stage. (*Strong recommendation, moderate quality of evidence*)

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1 With the exception of pregnant women

### 4.1.1 Summary of the evidence

#### **Treating HCV infection is beneficial for all HCV-infected persons**

DAA's have been on the market since 2013, which means that there are no trials available that compared persons with HCV infection treated early with those treated late in terms of clinical outcomes. The Guidelines Development Group therefore examined the evidence of the benefit of treating all persons with HCV infection, irrespective of the stage of liver disease.

**Treatment with DAAs leads to high rates of SVR.** Systematic reviews of the effectiveness of DAAs for the treatment of chronic HCV infection indicate that SVR rates generally exceed 90%, except for those with the most advanced stages of cirrhosis (76) and persons infected with HCV genotype 3.

#### **SVR is associated with reduced mortality from liver diseases and reduced risk of progression to HCC.**

A 2017 systematic review and meta-analysis indicated that HCV-infected persons with SVR following treatment had an 87% reduction in liver-related mortality, an 80% reduction in the incidence of HCC, and a 75% reduction in all-cause mortality (77) compared to HCV-infected persons who did not reach SVR. Many of these studies used older interferon-based treatment. Studies that considered only DAAs also indicate a reduction in mortality from liver diseases and HCC (78). DAAs would have a larger impact than interferon-based treatment overall because of a higher SVR rate.

**SVR is associated with improvement of extrahepatic manifestations.** A systematic review and meta-analysis concluded that SVR reduced extrahepatic mortality (pooled odds ratio [OR]: 0.44, 95% confidence interval [CI]: 0.3–0.7). SVR was also associated with better outcomes related to cryoglobulinaemia (pooled OR: 21, 95% CI: 6.7–64.1) and lymphoproliferative diseases (pooled OR: 6.5, 95% CI: 2–20.9), and decreased risk of major cardiovascular adverse events (pooled OR: 0.37, 95% CI: 0.2–0.6), incidence of de novo type 2 diabetes (pooled OR: 0.27, 95% CI: 0.2–0.4), depression (pooled OR: 0.59, 95% CI: 0.1–3.1), arthralgia (pooled OR: 0.86, 95% CI: 0.5–1.5) and fatigue (pooled OR: 0.52, 95% CI: 0.3–0.9) (74).

**Treatment of adolescents is highly effective and well tolerated.** Although advanced disease is uncommon among adolescents, a systematic review of two studies on the use of DAA regimens in adolescents >12 years of age indicated high SVR and excellent tolerance (see section 4.3). DAA treatment has also been reported to improve impaired cognitive functioning, educational attainment and well-being (79, 80).

**Treating all HCV-infected persons modestly reduces the risk of transmission.** Globally, treating persons without any prioritization by risk or age group or by disease stage points to a modest effect of treatment as prevention. Modelling in 82 countries distributed across all regions indicates that treating persons with HCV infection without any prioritization by risk or age group or by disease stage would prevent around 0.57 infections over 20 years for each person treated (see Web annex 4). However, this prevention benefit is highly variable across countries and WHO regions. Two main country-level factors influence the number of infections averted per person treated: the population growth rate, the HCV prevalence among PWID in their country (the contribution of injection drug use to the epidemic).

First, the number of infections averted per treatment increases with increasing population growth, suggesting that LMICs with higher population growth rates have the potential to achieve more prevention benefits through Treat All than high-income countries.

Second, the number of infections averted per treatment decreases when injection drug use accounts for a substantial proportion of new infections, and the prevalence of HCV infection among PWID is high (prevalence >60%). In these epidemic scenarios, there are high rates of reinfection when PWID are treated while limited prevention benefit is achieved through treating other individuals who do not inject drugs. For treatment to achieve prevention benefits in these “concentrated epidemic” scenarios, HCV treatment needs to be given at higher rates (e.g. about 5% of infections need to be treated per year in Australia) and reinfection risks need to be reduced through scaling up comprehensive, effective harm reduction measures, such as needle and syringe programmes (NSPs) and OST (see Web annex 4).

## 4.1.2 Rationale for the recommendation

### Balance of benefits versus harms of treating all HCV-infected persons

#### Benefits

**Treatment of all patients has the potential to prevent more liver-related morbidity.** A systematic review with meta-analysis and meta-regression estimated that the prevalence of cirrhosis at 20 years after the initial infection was 16% (14–19%) for all studies, ranging from 7% (4–12%) to 18% (16–21%) according to the types of studies and recruitment of individuals (15). Treating all persons diagnosed with HCV infection would prevent a large proportion of these avoidable complications. However, when expanding from treating persons with fibrosis to treating all HCV-infected persons, the additional gain in terms of years of life saved would occur further away in the future.

**Extrahepatic manifestations are common and their occurrence is usually independent of liver fibrosis.** Persons infected with HCV may suffer from comorbidities, including common extrahepatic manifestations (Fig. 2.2, Chapter 2.1.1).

**Treatment of adolescents results in high SVR rates and is well tolerated.** Early treatment also reduces the onset of cirrhosis and HCC (81–83), potentially reducing downstream costs of care (84, 85). Cure following DAA treatment may improve impaired cognitive functioning, educational attainment and well-being (79, 80). Cure enables adolescents to live free of a socially stigmatizing infection.

**Treating all will facilitate a public health approach to implementation.** Treating all persons diagnosed with HCV infection will simplify clinical decision-making and patient management. Staging can be simplified and limited to the use of non-invasive methods to identify persons with cirrhosis. Most HCV-infected persons will be able to start treatment immediately, reducing the potential for loss to follow up that occurs when there are delays in starting treatment for HCV (86) as well as HIV disease (87). Simplifying disease stage assessment and laboratory investigations also facilitates treatment by non-specialized health-care workers, a critical strategy for providing treatment at scale (88–90). Task-sharing with non-specialist providers has increased access to HIV testing and ART (91–93).

#### Potential harms

**Treating more HCV-infected persons could lead to more side-effects.** DAAs have an excellent safety profile, particularly when compared with interferon therapy (76). In an approach where more apparently healthy persons will be treated with DAAs once prioritization for severity of liver disease is removed, the occurrence of rare side-effects that have not been identified during post-marketing surveillance is theoretically possible (94). However, such events are unlikely, given the clinical experience of using these medicines to date (76).

**Treating hepatitis B virus (HBV)/HCV-coinfected persons can lead to HBV reactivation.** Persons with HBV infection (hepatitis B surface antigen [HBsAg]-positive) who are treated for HCV infection are at risk for reactivation of HBV infection (95). Persons who are HBsAg positive may need to be treated for HBV before they are treated for HCV (see section 5.2.2, Persons with HBV/HCV coinfection). The risk of reactivation among persons who are anti-hepatitis B core antibody (HBcAb) positive but HBsAg negative is very low (96). Deferring treatment of such persons because of concerns of HBV reactivation needs to be balanced against the risk of morbidity and mortality from untreated HCV infection.

**Treat All may lead to a perception that scaling up access to harm reduction is unnecessary.** As treating all persons with HCV infection has an effect on incidence, there is a possibility that some stakeholders may underestimate the continued need for high-coverage harm reduction interventions for PWID. Harm reduction remains a critical component of the comprehensive package of interventions for PWID alongside treatment (see Web annex 4).

#### Values and preferences

Four studies were identified that assessed patient preferences related to HCV treatment (97–100). The most important patient-relevant outcome was overall treatment efficacy followed by risk of adverse events. Of 112 people living with HCV infection who responded to an online feasibility survey carried out by WHO, nearly all favoured a Treat All policy and advocated for universal access to treatment for all those with HCV infection (see Web annex 7).

While there is clear support for a Treat All policy among people living with HCV infection, 18% of respondents expressed some concern about acceptability among HCV-infected persons without fibrosis or with mild fibrosis. This finding underscores the need for careful messaging to help HCV-infected persons understand the benefits of early treatment.

Health-care workers highly value cure for persons with HCV infection and expressed a preference for simplified patient management algorithms.

Programme managers understand that cure of more individuals through a Treat All policy will lead to progress towards elimination, and that simplifying the staging step with the use of serum biomarkers facilitates implementation and task-sharing (88–90, 101). Programme managers expressed a preference for strategies that represent cost-effective use of the resources available. Therefore, they would benefit from cost-effectiveness analyses that describe the relation between the cost incurred in the short term versus the savings in the future because of prevented sequelae of HCV infection and onward transmission (102, 103).



### Feasibility and acceptability

An online feasibility survey among 145 health-care providers indicated that 45% of respondents already had a Treat All policy at their place of work. Nearly all perceived it as feasible and desirable (see Web annex 7).

Experience from HIV suggests that widening treatment access is feasible. In September 2015, WHO released guidance recommending Treat All for HIV-positive individuals (8). By the end of 2017, more than 70% of LMICs and almost all HICs had adopted the Treat All policy, demonstrating a high level of acceptability of this recommendation by policy-makers (104). Despite initial concerns about health system capacity to meet the demands of a Treat All approach, no major increase in medication stock-outs or other essential supplies have been reported during this period.

### Equity and human rights

Therapeutic guidelines that restrict an individual's access to HCV treatment when cure rates are high and adverse events are rare raise ethical challenges (105). Many HCV-infected persons from groups that are marginalized or stigmatized such as PWID, MSM, prisoners or migrants have poor access to health care. Progress towards a Treat All approach with equity in access regardless of age, risk group or stage of disease would help overcome some of the obstacles to access among these populations. Concerns that mandatory or coercive approaches might be used among highly affected marginalized populations highlight the importance of adequate information, informed consent, appropriate health worker training and rights-based legal frameworks to facilitate access.

### Resource considerations

**DAAs are cost effective or cost-saving.** In general, in many countries, DAAs are cost effective or cost-saving for the large majority of subgroups (defined in terms of prior treatment experience, fibrosis stage and HCV genotype). Most published cost-effectiveness analyses do not include HCV transmission or the risk of reinfection. This omission may result in underestimating or overestimating the benefits of treatment (75).

**Expanding treatment to the general population is cost effective.** When applying country-specific willingness-to-pay thresholds, several studies from HICs and Egypt reported that expanding treatment in the general population is cost effective, though it may require substantial short-term payments to cover the cost of treatment. The cost-effectiveness of treatment expansion for individuals above 65 years of age with mild fibrosis is highly sensitive to treatment price and, in some settings, where prices remain relatively high, may not be cost effective (75).

**Treating PWID along with provision of harm reduction interventions is cost effective.** It is generally cost effective to treat HCV-infected PWID, but cost-effectiveness is influenced by the potential for preventing new infections and by the risk of reinfection. Some studies also estimate that intensified case-finding in this group is cost effective along with treatment scale up, that treatment of all PWID was cost effective compared to delaying treatment until progression to a later stage of fibrosis, and that treatment can be cost effective even in a declining epidemic. However, in settings with a high burden of HCV infection among PWID, the cost-effectiveness of preventing onward transmission via treatment is diminished by the high probability of reinfection in case of inadequate access to harm reduction programmes. This underscores the need for concurrent, high-coverage HCV prevention interventions with highly effective and cost-effective harm reduction programmes (75).

**Treating incarcerated individuals is cost effective.** Studies from the United States of America (USA), Australia and the United Kingdom (UK) reported that it is generally cost effective to treat incarcerated individuals who are HCV infected (3). Testing upon entry to prisons can be cost effective if there is linkage to treatment that can be completed in prison or after release through continuity of care. Similar to the findings in PWID communities, concurrent investments in HCV prevention programmes complement investments in HCV treatment and make HCV treatment more cost effective by reducing the probability of reinfection (75).

**Budget implications.** While DAAs are cost effective and/or cost-saving for the treatment of HCV infection, the short-term budget implications will depend on (i) the price of the medications and (ii) the size of the population to be treated (the latter being also affected by testing and linkage activities in the population). On the one hand, treating all will increase the budget impact. On the other hand, the Treat All policy should lead to price reductions as it will increase the volume of medicines purchased (see section 6.7 on Strategies for more efficient procurement and supply management of medicines and diagnostics and Table 6.2). To finance the treatment of all persons with HCV through a universal health coverage approach, a two-step approach is proposed.

- **Improving efficiencies and reducing costs.** This can be done through the choice of high-impact interventions, simplified management and price reduction strategies for key commodities, including medicines, and improved service delivery, as has been demonstrated for other infectious diseases (106). The calculation for cost-effectiveness may be used to back-calculate the pricing level that DAAs should reach to be cost effective or cost-saving within a horizon that has been defined by those that finance the health sector (e.g. health insurance, national social security scheme, Ministry of Health); see the hepatitis C calculator (<http://www.hepccalculator.org/>).

- **Identifying innovative financing solutions.** This can be done through both external and domestic funding, and innovative and fair budget allocation (107).

### 4.1.3 Implementation considerations

- Transitioning from a clinical prioritization approach to a Treat All approach requires planning with respect to the eight good principles of health-care service delivery (see Chapter 6 for service delivery models (88–90)).
- The implementation and budget impact of a recommendation to treat all persons diagnosed with HCV infection need to be considered in the context of testing activities that identify more individuals to be treated.
- If the budget impact of immediately implementing a Treat All recommendation is not affordable in the short term, national programmes may consider allocating resources preferentially to individuals at higher risk of hepatic and extrahepatic morbidity and mortality.
- Treatment of PWID needs to be integrated with harm reduction services to prevent reinfections, particularly in settings where the prevalence of HCV infection exceeds 60% in PWID.
- Persons with HBV infection (HBsAg positive) may need to be treated for HBV before they are treated for HCV.

### 4.1.4 Research gaps

- Long-term clinical studies of persons with early-stage HCV treated with DAAs.
- Post-marketing surveillance for adverse events and drug resistance with expansion of antiviral treatment.
- Cost–effectiveness and budget impact studies in a variety of settings.
- Monitoring the impact of expansion of DAA treatment on the incidence of HCV infection, especially in populations such as PWID and MSM.

## 4.2 Treatment of adults with direct-acting antiviral agents: what treatment to use

### New recommendation

WHO recommends the use of pangenotypic DAA regimens for the treatment of persons with chronic HCV infection aged 18 years and above<sup>1</sup> (*Conditional recommendation, moderate quality of evidence*).

1 Pangenotypic is defined as an SVR rate >85% across all six major HCV genotypes

### 4.2.1 Summary of the evidence

**TABLE 4.1** Currently available pangenotypic DAAs for the treatment of HCV-infected persons without cirrhosis

HCV-infected persons without cirrhosis		
glecaprevir/ pibrentasvir	sofosbuvir/ daclatasvir	sofosbuvir/ velpatasvir
8 weeks <sup>1</sup>	12 weeks	12 weeks

1 Persons with HCV genotype 3 infection who have received interferon and/or ribavirin in the past should be treated for 16 weeks.

#### Evidence that pangenotypic DAAs are effective in HCV infection

A WHO-commissioned systematic review identified 142 clinical studies that evaluated the safety and efficacy of various FDA- and EMA-approved DAA regimens. These included sofosbuvir/velpatasvir, glecaprevir/pibrentasvir, sofosbuvir/daclatasvir, daclatasvir/asunaprevir, elbasvir/grazoprevir, ledipasvir/sofosbuvir, paritaprevir/ritonavir/ombitasvir/dasabuvir, sofosbuvir/velpatasvir/voxilaprevir, sofosbuvir/daclatasvir/ribavirin, sofosbuvir/ribavirin. The complete evidence summaries for each of the regimens can be found in Web annex 3.1, 3.2 and 8, with a short summary below.

#### Pangenotypic DAAs in HCV-infected adults without cirrhosis

##### *Sofosbuvir/velpatasvir*

In combined treatment-naïve and treatment-experienced persons treated with sofosbuvir/velpatasvir, the pooled SVR rates exceeded 96% (92–100%) for all six major genotypes, except for genotype 3 (SVR rate: 89%, 85–93%) (see Web annex 8 Table 4, page 17).

### *Glecaprevir/pibrentasvir*

In combined treatment-naive and treatment-experienced persons treated with glecaprevir/pibrentasvir, pooled SVR rates exceeded 94% (89–100%) for infections with all six major genotypes. For the relatively rare genotype 5, two persons treated reached SVR (see Web annex 8 Table 2, page 4).

### *Sofosbuvir/daclatasvir*

In combined treatment-naive and treatment-experienced persons treated with sofosbuvir/daclatasvir, the pooled SVR rates exceeded 92% for infection with genotypes 1, 2, 3 and 4. Data from an observational study (manuscript in preparation, MSF demonstration project) provided information on the less commonly reported genotypes 5 and 6. A total of eight persons with genotype 5 and 123 persons with genotype 6 infection were treated with sofosbuvir/daclatasvir for 12 weeks. SVR rates were, respectively, 88% and 94% for genotypes 5 and 6 (see Web annex 8 Table 3, page 10).

## Pangenotypic DAAs in HCV-infected adults with compensated cirrhosis

**TABLE 4.2** Current available pangenotypic DAAs for the treatment of HCV-infected persons with compensated cirrhosis

HCV-infected persons with compensated cirrhosis			
glecaprevir/ pibrentasvir	sofosbuvir/ daclatasvir	sofosbuvir/ daclatasvir	sofosbuvir/ velpatasvir
12 weeks <sup>1</sup>	24 weeks	12 weeks may be considered in countries where genotype 3 distribution is known and prevalence is <5% <sup>2</sup>	12 weeks

1 Persons with HCV genotype 3 infection who have received interferon and/or ribavirin in the past should be treated for 16 weeks.

2 In a population of persons with cirrhosis where 5% of persons would be infected with genotype 3 HCV, the SVR would be 80% in the 5% infected with genotype 3 and 93% in the 95% infected with other genotypes, leading to an overall SVR rate of  $(0.05 \times 0.80) + (0.93 \times 0.95) = 92\%$ .

### *Sofosbuvir/velpatasvir*

In combined treatment-naive and treatment-experienced persons with cirrhosis treated with sofosbuvir/velpatasvir for 12 weeks, the pooled SVR rates in those infected with genotypes 1, 2 and 4 were 90%, 86% and 88%, respectively. The pooled SVR rate in genotype 3 infection was 97% in treatment-naive persons and 90% in treatment-experienced persons. An additional study (published after the systematic review inclusion period ended) (108) reported SVR rates of 100% for both genotype 5 (N= 13) and genotype 6 (N = 20) after 12 weeks of treatment (see Web annex 3.1 Tables 40–42, page 46).

*Glecaprevir/pibrentasvir*

In combined treatment-naive and treatment-experienced persons with compensated cirrhosis treated with glecaprevir/pibrentasvir for 12 weeks, SVR rates exceeded 94% for infection with genotypes 1, 2, 3, 4 and 6. Two persons treated for infection with genotype 5 reached SVR (see Web annex 3.1 Table 35, page 43).

*Sofosbuvir/daclatasvir*

In combined treatment-naive and treatment-experienced persons with compensated cirrhosis treated with sofosbuvir/daclatasvir for 12 weeks, the pooled SVR rates exceeded 93% for infection with genotypes 1 and 2. SVR rates for infection with genotype 3 were low, ranging from 79% to 82%. However, after 24 weeks of treatment, SVR rates increased to 90%. Data from an observational study (manuscript in preparation, MSF demonstration project) provided information on genotypes 5 and 6, and real-world data from Egypt provided information on genotype 4 (101). One cirrhotic person with genotype 5 infection treated with sofosbuvir/daclatasvir for 12 weeks reached SVR. Among 185 cirrhotic persons with genotype 6 infection treated with sofosbuvir/daclatasvir for 12 weeks, 92% reached SVR. Cirrhotic persons with genotype 4 infection had SVR rates that exceeded 98% after 12 weeks of treatment (101) (see Web annex 3.1 Tables 29–31, page 39).

**Safety of pangenotypic DAAs**

Treatment discontinuation due to adverse events was very low in persons without and with cirrhosis in the regimens discussed above (<1%). Similar results were observed in treatment-naive and treatment-experienced persons (see Web annex 3.1 Tables 58–60, page 58).

**4.2.2 Rationale for the recommendation**

The Guidelines Development Group made an overall conditional recommendation to use pangenotypic DAA regimens for the treatment of HCV infection. The Group acknowledged that the potential clinical benefits of pangenotypic regimens are similar to those of non-pangenotypic regimens. However, pangenotypic DAAs present an opportunity to simplify the care pathway by removing the need for expensive genotyping and so simplifying procurement and supply chains. These regimens offer a major opportunity to facilitate treatment expansion worldwide. These factors shift the balance of benefits and harms in favour of the use of pangenotypic regimens, leading to a conditional recommendation.

The Guidelines Development Group acknowledged that there are countries where pangenotypic formulations may not yet be approved or available. In addition, there are countries where the HCV epidemic is almost entirely caused by one genotype, and where national hepatitis programmes successfully use a non-pangenotypic DAA regimen such as sofosbuvir/ledipasvir. In these cases and when treating adolescents, there remains a role for non-pangenotypic DAAs while national programmes transition to using pangenotypic regimens. Consequently, non-pangenotypic DAAs listed in Web annex 5 may be used during a transition phase.

### Balance of benefits and harms

The use of pangenotypic regimens removes the need for genotyping. This simplifies medicine procurement and supply chains, may reduce costs and loss to follow up after diagnosis. Potential harms include the development of rare long-term side-effects of these recently approved medicines, which may not have been identified during post-marketing surveillance, and the potential overtreatment of persons treated with sofosbuvir/daclatasvir if persons are treated for 24 weeks in the absence of genotyping.

### Values and preferences and acceptability

Four identified studies investigated the preferences of HCV-infected persons regarding HCV treatment regimens. For persons infected with HCV, the likelihood of a cure and the lack of adverse events are the most important considerations related to treatment regimens, though factors such as a shorter (e.g. 8-week) course of treatment were also valued (97–100). Therefore, use of pangenotypic regimens would be acceptable.

### Resource considerations

The resources required to administer HCV therapy can be broadly divided into health system costs (e.g. laboratory and personnel) and the price of medicines. Treating persons with pangenotypic DAAs incurs fewer health system costs as it removes expensive genotyping, which requires specialist laboratories and personnel, saving up to US\$ 200 per test in LMICs. The Guidelines Development Group recognizes, however, that access to pangenotypic DAA regimens remains limited in many LMICs (see Chapter 6, Table 6.2). Prices for sofosbuvir/velpatasvir and glecaprevir/pibrentasvir are still higher than the older DAA combinations, but it is expected that prices will substantially decrease as the volume of use increases and access policies for HCV-infected persons living in LMICs are optimized.

### Feasibility

The WHO progress report on access to hepatitis C treatment points to the feasibility of widening access to HCV treatment with the use of pangenotypic DAAs (4).

## Equity

Simplifying the care pathway by using pangenotypic regimens could improve equity and help improve access to populations that currently do not have access to HCV treatment.

### 4.2.3 Implementation considerations

Countries need to plan for transitioning to the use of pangenotypic DAA regimens. The speed of transition may depend on the prevalence of HCV infection, the distribution of HCV genotypes and how effective their current DAA regimens are in treating infection with these genotypes. (For key steps to implementation, see section 6.7.)

### 4.2.4 Research gaps

- More data on the efficacy and safety of pangenotypic regimens are required in specific subpopulations, including those with severe renal impairment, persons under the age of 18 years and pregnant women.
- Predictive factors for selecting persons who could be treated for a shorter duration.
- Data on the cost–effectiveness of pangenotypic DAAs in LMICs.
- The clinical importance of NS5A resistance.
- Data on treatment failure and the relation with rare HCV genotypes.

## 4.3 Treatment of adolescents (12–17 years) and deferral of treatment in children (<12 years of age)

### New recommendation

#### What treatment to use

**In adolescents aged 12–17 years or weighing at least 35 kg with chronic HCV,\* WHO recommends:**

- **sofosbuvir/ledipasvir for 12 weeks\*\* in genotypes 1, 4, 5 and 6** (*strong recommendation, very low quality of evidence*)
- **sofosbuvir/ribavirin for 12 weeks in genotype 2** (*strong recommendation, very low quality of evidence*)
- **sofosbuvir/ribavirin for 24 weeks in genotype 3** (*strong recommendation, very low quality of evidence*).

\* In those without cirrhosis or with only compensated cirrhosis

\*\* Treatment for 24 weeks in those who are treatment experienced and with compensated cirrhosis



**In children aged less than 12 years with chronic hepatitis C,\* WHO recommends:**

- **deferring treatment until 12 years of age\*\*** (*conditional recommendation, low quality of evidence*)
- **treatment with interferon-based regimens should no longer be used\*** (*strong recommendation, very low quality of evidence*).

\* In those without cirrhosis or with only compensated cirrhosis

\*\*Prior to approval of DAAs for children aged <12 years of age, exceptional treatment with interferon + ribavirin may be considered for children with genotype 2 or 3 infection and severe liver disease. This may include children at higher risk of progressive disease, such as with HIV coinfection, thalassaemia major and survivors of childhood cancer.

### 4.3.1 Background

To date, the global response to the HCV epidemic focused on the adult HCV-infected population. Compared with adults, there are major gaps in data and evidence to inform management practices and policies in adolescents and children.

Prior to regulatory approval of DAA's for use in children, the standard of care of adolescents and children infected with HCV was dual therapy with pegylated-interferon and ribavirin for 24 weeks for genotypes 2 and 3, and 48 weeks for genotypes 1 and 4 (109–117). This combination resulted in an SVR rate of around 52% in children infected with HCV genotypes 1 and 4, and 89% in those infected with HCV genotypes 2 and 3 (109, 110, 112, 114), but was associated with significant side-effects.

In 2017, two DAA regimens (sofosbuvir/ledipasvir and sofosbuvir/ribavirin) received regulatory approval from FDA and EMA for use in adolescents ( $\geq 12$  years) (118, 119). Trials are ongoing to evaluate pangenotypic DAA regimens in both adolescents ( $\geq 12$  years) and children (aged 6–11 years). As of June 2018, in those younger than 12 years, the only licensed treatment options remain interferon with ribavirin as DAAs are not yet approved for use in younger children, and the Guidelines Development Group therefore formulated separate recommendations for adolescents and children. None of the recommended pangenotypic DAAs in these current guidelines (sofosbuvir/daclatasvir or sofosbuvir/velpatasvir) are yet approved for use in either adolescents and children, but this is anticipated in 2019, which would represent a major opportunity to advance treatment access (120, 121).

### 4.3.2 Summary of the evidence

The main evidence base to support treatment recommendations in adolescents aged 12 or more years were the two studies used for regulatory approval of the regimens (118, 119), and the extensive evidence base from DAA trials in adults.

#### Adolescents (12–17 years)

The regulatory approval by the FDA and EMA in April and June 2017, respectively, of the use of a fixed-dose combination of sofosbuvir/ledipasvir for genotype 1-infected adolescents aged 12–17 years old or weighing  $\geq 35$  kg, and sofosbuvir/ribavirin for those infected with HCV genotype 2 or 3 was based on the extensive data in adults of high rates of cure and low rates of toxicity, and two studies of pharmacokinetics, efficacy and safety in adolescents (118, 119). In one study, 100 genotype 1 HCV-infected treatment-naïve and -experienced adolescents were treated with sofosbuvir/ledipasvir as a single tablet once daily for 12 weeks (118). The SVR was 98% with good tolerability. A second study evaluated the use of sofosbuvir and weight-based ribavirin for 12 weeks in 52 adolescents with genotype 2 or 3 infection (119). SVR rates were 100% (13/13) in genotype 2 and 97% (38/39) in persons with genotype 3. No serious adverse effects leading to treatment discontinuation or significant abnormalities in laboratory results were reported. This study also reported an improvement in health-related quality of life following SVR (122), particularly in social functioning and school performance domains.

#### Children (6–12 years)

Currently, the only licensed, approved treatment option for children younger than 12 years is pegylated-interferon  $\alpha$ -2a or -2b injections with twice-daily ribavirin tablets, for 24 to 48 weeks depending on the HCV genotype (109–117). In genotype 1, the SVR of pegylated-interferon/ribavirin is suboptimal compared to DAAs; and only 52% in those with HCV genotype 1 and 4, but 89% in genotypes 2 and 3 (109–111, 114). Pegylated-interferon and ribavirin are associated with significant side-effects, and potentially irreversible post-therapy side-effects, such as thyroid disease, type 1 diabetes, ophthalmological complications and growth impairment (112, 114, 123–127). None of the DAAs are approved yet for use in children aged less than 12 years. There are two ongoing studies of half-dose sofosbuvir/ledipasvir in 90 treatment-naïve or -experienced children aged 6 to 12 years infected with HCV genotypes 1, 3 and 4, and sofosbuvir plus ribavirin in children aged 6 to 12 years (120).

### 4.3.3 Rationale for the recommendations

#### Balance of benefits and harms

Among the Guidelines Development Group there was consensus that the overall goal of treatment in adolescence and childhood is to prevent HCV-associated liver damage and extrahepatic manifestations, together with the potential to achieve an HCV-free generation through earlier treatment.

#### Treat adolescents $\geq 12$ years or weighing at least 35 kg (without cirrhosis or with only compensated cirrhosis) with sofosbuvir/ledipasvir and sofosbuvir/ribavirin

The Guidelines Development Group recommended that all chronically HCV infected adolescents should be offered treatment with the current FDA- and EMA-approved regimens of sofosbuvir/ledipasvir and sofosbuvir/ribavirin. Data on DAA therapy in HCV-infected adolescents is limited. The recommendation was based on both indirect evidence from adult treatment studies (discussed in Chapter 4.2, see Web annexes 3.1 and 3.2) and two published trials in adolescents (*118*, *119*) of specific recommended regimens (sofosbuvir/ledipasvir and sofosbuvir/ribavirin) used for regulatory approval by the EMA and FDA that showed high efficacy and safety rates and pharmacokinetic equivalence. A systematic review and meta-analysis comparing DAAs with pegylated-interferon in adolescents (*128*) also confirmed higher efficacy and tolerability of oral short-course DAA treatments when compared to interferon therapy in adolescents and children. This recommendation was therefore strong despite the low quality of evidence specific to adolescents.

The Guidelines Development Group recognized that the recommended regimens had limitations.

1. These regimens are not pangenotypic and therefore genotyping will still be required. Pangenotypic DAA regimens would be preferable in settings with a range of genotypes. DAAs under evaluation in adolescents include sofosbuvir/velpatasvir, sofosbuvir/daclatasvir and glecaprevir/pibrentasvir.
2. There remains limited data on treatment in those with cirrhosis, but recommendations include those with compensated cirrhosis. In those who are treatment experienced and with compensated cirrhosis, treatment for 24 weeks is recommended.
3. Use of a ribavirin-based regimen requires haematological monitoring. Ribavirin is also teratogenic and contraindicated in pregnancy. This is important as adolescents are more likely to have unplanned pregnancies. Extreme care must be taken to avoid pregnancy during therapy and for 6 months after completion of therapy, as well as in partners of HCV-infected men who are taking ribavirin therapy.

4. Sofosbuvir with ribavirin is a suboptimal regimen for persons with genotype 3 infection, especially if they have cirrhosis. The Guidelines Development Group noted that the EMA indicates that sofosbuvir/ledipasvir can be considered for use in some persons infected with genotype 3, and so a potential off-label use of sofosbuvir/ledipasvir plus ribavirin is a possible option for adolescents with genotype 3 HCV infection.

### **Deferral of treatment in children until 12 years**

In children less than 12 years, the Guidelines Development Group recommended that treatment be deferred until they either reach 12 years or until DAA regimens are approved for those less than 12 years. Interferon-based regimens should no longer be used for either adolescents or children (except in situations where there is no alternative). The Guidelines Development Group recognized that the benefits of deferral far outweigh the small risk of progression of liver fibrosis during childhood, and the unpredictable rapid development of advanced liver disease in a few children (83, 129).

The key reasons for the current conditional recommendation to defer HCV treatment in children aged less than 12 years were as follows:

1. **The low frequency of HCV-related liver disease in childhood.** Only a small number of children experience significant morbidity that would benefit from early treatment.
2. **The only available and approved regimen for this age group is pegylated-interferon/ribavirin.** This regimen has an overall low efficacy, a prolonged treatment duration (6–12 months), an inconvenient administration route (via injection), significant side-effects and high costs.
3. New, highly effective short-course oral pangenotypic DAA regimens are likely to become available for children <12 years in 2019.

### **Treatment with interferon should not be used**

The key reasons for the current strong recommendation that interferon should not be used in children aged less than 12 years despite the very low quality of evidence were as follows:

1. **The issues with interferon-containing regimens and ribavirin in children.** These include long duration of treatment, limited efficacy and burdensome side-effects, including high rates of flu-like symptoms and haematological complications (anaemia, leukopenia and neutropenia), and several potentially irreversible side-effects, such as thyroid disease, type 1 diabetes, ophthalmological complications and impaired growth (112, 114, 123–127).

2. **The imminent arrival of alternative DAA options.** Preliminary trial data show much higher efficacy and safety of DAAs in children less than 12 years compared to interferon, as observed for adults and adolescents.
3. **The low availability of interferon.** Interferon is increasingly less available, especially in LMICs. It requires a cold chain, which makes delivery to scale less feasible.

#### Values and preferences and acceptability

Curative, short-course (e.g. 12-week) oral DAA treatment is highly acceptable to adolescents and children, as well as their parents or caregivers (80), because of the likelihood of a cure, and minimal side-effects compared to interferon injections. Cure will enable adolescents and children to live free of a socially stigmatizing infection.

#### Resource considerations

Treatment of adolescents (and in the future children <12 years) may avoid the higher costs associated with treating adults with advanced liver disease and related complications. Deferring treatment until children reach 12 years and can be treated with DAAs (or until approval of DAAs in younger children), has the potential to reduce costs, as interferon is more expensive.

#### Equity

The approval of DAAs for use in adolescents is a major opportunity to advance treatment access and cure to a vulnerable group that will benefit from early treatment.

### 4.3.4 Implementation considerations

A major constraint to implementation of these recommendations is that few LMICs have included adolescents and children in their national testing and treatment guidelines, so most remain undiagnosed. All countries should include testing for adolescents and children, and treatment for adolescents in their national guidelines, based on the recommendations of the 2017 WHO testing guidelines (3). This includes focused testing of adolescents from populations most affected by HCV infection (e.g. PWID, MSM, HIV-infected persons, children of mothers with chronic HCV infection, especially if HIV-coinfected) and those with a clinical suspicion of viral hepatitis. The age of consent for testing varies across countries, and this can pose barriers to adolescents' access to services. Engaging adolescents in testing and treatment should be based on adolescent-friendly services.

### 4.3.5 Research gaps

- Evaluation of short-course pangenotypic regimens in adolescents and children, and retreatment options for children who experience DAA failure.
- Estimates of prevalence and burden in adolescents and children to inform needs.
- Cohort studies to examine clinical outcomes of chronic HCV that is vertically acquired and in childhood to guide indications for treatment initiation in younger children.
- Follow-up studies to examine the impact of DAA treatment on growth, cognitive function, educational attainment and quality of life among children.

# CHAPTER 5. CLINICAL CONSIDERATIONS

The three considerations (boxes below) are existing formal WHO recommendations that address alcohol intake, fibrosis assessment and treatment response assessment.

## *Existing recommendation from the 2016 HCV treatment guidelines (2)*

An alcohol intake assessment is recommended for all persons with HCV infection followed by the offer of a behavioural alcohol reduction intervention for persons with moderate-to-high alcohol intake. *(Strong recommendation, moderate quality of evidence)*

## *Existing recommendation from the 2016 HCV treatment guidelines (2)*

In resource-limited settings, it is suggested that aminotransferase/platelet ratio index (APRI) or FIB-4 be used for the assessment of hepatic fibrosis rather than other non-invasive tests that require more resources such as elastography or FibroTest.

*(Conditional recommendation, low quality of evidence)*

*Note:* This recommendation was formulated assuming that liver biopsy was not a feasible option. FibroScan®, which is more accurate than APRI and FIB-4, may be preferable in settings where the equipment is available and the cost of the test is not a barrier to testing.

## *Existing recommendation from the 2017 hepatitis B and C testing guidelines (3)*

Nucleic acid testing for qualitative or quantitative detection of HCV RNA should be used as test of cure at 12 or 24 weeks (i.e. sustained virological response [SVR12 or SVR24]) after completion of antiviral treatment. *(Conditional recommendation, moderate/low quality of evidence)*

All other considerations discussed in this chapter are based on good practice principles.

## 5.1 Clinical assessment of persons with HCV infection prior to treatment

Pretreatment evaluation of the risk of adverse events is based on the person's clinical information, concomitant medications and knowledge of treatment regimen to be administered. Women of childbearing age may be offered pregnancy testing and are informed about the lack of available data on the safety and efficacy of DAAs during pregnancy. In addition, in 2016, WHO recommended an alcohol intake assessment before initiating treatment and a fibrosis assessment using noninvasive tests such as the APRI score or FIB-4 test (formula in Fig. 5.1) to determine if there is cirrhosis (2). An online calculator is available at <http://www.hepatitisc.uw.edu/page/clinical-calculators>. Tables 5.1 and 5.2 summarize the cut-off values for the detection of significant fibrosis and cirrhosis, and the sensitivity and specificity of the APRI score and FIB-4 test when using these cut-offs. This information will allow clinicians to decide on the appropriate treatment duration of the pangenotypic regimen of their choice based on the absence or presence of cirrhosis. The treatment duration of the recommended pangenotypic regimens sofosbuvir/daclatasvir and glecaprevir/pibrentasvir depends on the absence or presence of cirrhosis.

**FIG. 5.1** APRI and FIB-4 formulas

$$\text{APRI} = [(\text{AST (IU/L)}/\text{AST\_ULN (IU/L)}) \times 100] / \text{platelet count (10}^9\text{/L)}$$

$$\text{FIB-4} = \text{age (years)} \times \text{AST (IU/L)} / \text{platelet count (10}^9\text{/L)} \times [\text{ALT (IU/L)}]^{1/2}$$

APRI: aminotransferase/platelet ratio index; ALT: alanine aminotransferase; AST: aspartate aminotransferase; IU: international unit; ULN: upper limit of normal

**TABLE 5.1** Low and high cut-off values for the detection of significant fibrosis and cirrhosis

	APRI (low cut-off)	APRI (high cut-off)	FIB-4 (low cut-off)	FIB-4 (high cut-off)
<b>Significant fibrosis (METAVIR ≥F2)</b>	0.5	1.5	1.45	3.25
<b>Cirrhosis (METAVIR F4)</b>	1.0	2.0	–	–



**TABLE 5.2** Sensitivity and specificity of APRI and FIB-4 for the detection of advanced fibrosis and cirrhosis

		APRI (low cut-off)	APRI (high cut-off)	FIB-4 (low cut-off)	FIB-4 (high cut-off)
<b>Significant fibrosis (METAVIR <math>\geq</math>F2)</b>	Sensitivity (95% CI)	82 (77–86)	39 (32–47)	89 (79–95)	59 (43–73)
	Specificity (95% CI)	57 (49–65)	92 (89–94)	42 (25–61)	74 (56–87)
<b>Cirrhosis (METAVIR F4)</b>	Sensitivity (95% CI)	77 (73–81)	48 (41–56)	–	–
	Specificity (95% CI)	78 (74–81)	94 (91–95)	–	–

### 5.1.1 Drug–drug interactions

Drug–drug interactions (DDIs) for DAA regimens vary both in number and clinical significance, depending on the medicines prescribed. Commonly prescribed medicines that may lead to DDIs include proton pump inhibitors, statins, antidepressants and antiretrovirals (ARVs) for HIV (now recommended for all HIV-infected persons, regardless of CD4 count) (130). The association between recommended pangenotypic regimens and efavirenz is either contraindicated (in the case of sofosbuvir/velpatasvir and glecaprevir/pibrentasvir) or requires dose adjustment (in the case of sofosbuvir/daclatasvir). Table 5.3 summarizes the DDIs between WHO-recommended HIV ARV medicines and HCV medicines. Where DDIs are likely, ARV substitutions may be considered before initiating HCV therapy. Prescribers may consult the University of Liverpool webpage on hepatitis drug interactions (<http://www.hep-druginteractions.org/>) prior to prescribing, as details of interactions are frequently updated. This website includes details of interactions with prescribed and non-prescribed medicines.

**TABLE 5.3** Drug–drug interactions between antiretrovirals and direct-acting antivirals

DAA	ABC	ATZ/r	DRV/r	DTG	EFV	LPV/r	NVP	RAL	TDF	TAF	ZDV	XTC
Daclatasvir	Green	Adjust dose	Green	Green	Adjust dose	Green	Red	Green	Green	Green	Green	Green
Glecaprevir/ pibrentasvir	Green	Red	Red	Green	Red	Red	Red	Green	Green	Green	Green	Green
Sofosbuvir	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green
Sofosbuvir/ ledipasvir	Green	Monitor for renal toxicity when used with TDF	Monitor for renal toxicity when used with TDF	Green	Monitor for renal toxicity when used with TDF	Monitor for renal toxicity when used with TDF	Green	Green	Monitor for renal toxicity when used with EFV or boosted protease inhibitor	Green	Green	Green
Sofosbuvir/ velpatasvir	Green	Monitor for renal toxicity when used with TDF	Monitor for renal toxicity when used with TDF	Green	Red	Monitor for renal toxicity when used with TDF	Red	Green	Monitor for renal toxicity	Green	Green	Green

Red = do not co-administer

Yellow = possible toxicity/interaction/dose adjustment, as specified

Green = no interaction; can be co-administered

ABC: abacavir; ATZ/r: atazanavir/ritonavir; DRV/r: darunavir/ritonavir; DTG: dolutegravir; EFV: efavirenz; LPV/r: lopinavir/r; NVP: nevirapine; RAL: raltegravir; ZDV: zidovudine; TDF: tenofovir disoproxil fumarate; XTC: emtricitabine/lamivudine; TAF: tenofovir alafenamide

### 5.1.2 Monitoring for treatment toxicity

In general, DAAs are well tolerated by persons with HCV infection, with only minor side-effects. The American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver (EASL) recommend a monitoring schedule that includes baseline, week 4 and week 12 after the end of treatment (131, 132). The Guidelines Development Group proposed to simplify this schedule as the most common adverse events of DAAs are minor and include fatigue, headache, insomnia and nausea. The Guidelines Development Group proposed that the frequency of routine laboratory monitoring be limited to a baseline and end-of-treatment specimen (see summary monitoring schedule framework for the treatment of persons with HCV infection based on expert opinion in Table 5.4).

Additional laboratory monitoring is necessary in persons treated with ribavirin. Ribavirin is taken with food and causes a predictable, dose-dependent haemolytic anaemia. It is contraindicated in persons with anaemia or those with blood disorders such as thalassaemia. Finally, HIV coinfection, HBV coinfection (see sections 5.2.1 and 5.2.2), cirrhosis or renal impairment, potential DDIs and ill-health may also necessitate more frequent monitoring than proposed in Table 5.4.

### 5.1.3 Monitoring for treatment response

In 2017, WHO recommended that following completion of DAA treatment, SVR should be assessed at 12 weeks after the end of treatment using HCV RNA NAT (3).

**TABLE 5.4** Monitoring framework before and during DAA treatment

Time	DAA alone	DAA + ribavirin <sup>a</sup>
	Full blood count, renal, liver function	Full blood count, renal, liver function
<b>Baseline</b>	X <sup>b</sup>	X
<b>Week 4</b>		X
<b>Week 12 after end of treatment</b>	X	X

<sup>a</sup> Recommended treatment for adolescents with genotypes 2 and 3 HCV infection

<sup>b</sup> If Hb >10 g/dL then no need to check again at week 4

## 5.2 Clinical considerations for specific populations

### 5.2.1 Persons with HIV/HCV coinfection

Persons with HIV/HCV coinfection generally have more rapid disease progression than monoinfected persons (133, 134). Even among persons in whom ART leads to successful control of HIV infection (i.e. undetectable HIV viral load), the risk of hepatic decompensation among coinfecting persons is higher than among persons with HCV monoinfection (135, 136). For these reasons, since 2014, the WHO *Guidelines* listed persons with HIV/HCV coinfection among those to be prioritized for HCV treatment (1).

HCV treatment outcomes with DAAs are comparable in persons with HIV/HCV coinfection to those with HCV monoinfection (137). Because DAAs are safe and effective for people with HIV/HCV, there is no longer any need to consider them as a special or difficult-to-treat population. However, there are important DDIs with pangenotypic HCV regimens and ART. Therefore, checking for DDIs between HIV and HCV medications needs to be emphasized (see also section 5.1.1 and Table 5.3).

## 5.2.2 Persons with HBV/HCV coinfection

There are no global prevalence data on HBV/HCV coinfection, but various studies have reported that 3–18% of people who are HBsAg positive are also HCV infected (138). HBV/HCV coinfection is more likely among PWID and persons living in areas where both viruses are endemic (138). Coinfection with HBV and HCV increases the risk for HCC, although the reasons for this are not well understood (139, 140).

In 2016, the FDA issued a warning about the risk of HBV reactivation during DAA treatment (defined as >1000 IU/mL increase in HBV DNA or detection of HBsAg in a person who was previously negative) based on 29 case reports (95). Even though HBV reactivation appears rare, individuals may be considered for HBV testing before initiating HCV treatment (131, 141). Persons with HBV/HCV coinfection may be assessed for eligibility for HBV treatment and, if needed, started on HBV treatment before starting HCV treatment (131, 141). Persons with advanced disease may be considered for monitoring at regular intervals for HBV reactivation during HCV treatment. The risk of reactivation among persons who are anti-HBc positive but HBsAg negative is very low (142–144).

## 5.2.3 Persons with cirrhosis

The risk of cirrhosis is increased in those who consume excess alcohol (145), and in those coinfecting with HBV and/or HIV (133, 135, 136, 139), particularly those who are not receiving ART (146). To determine if fibrosis or cirrhosis is present, WHO recommends the use of non-invasive tests such as the APRI score or the FIB-4 test (see section 5.1) (2).

### Management of compensated cirrhosis

Assessment and follow up for progression of disease and evidence of HCC is an essential part of the care of persons with HCV-related cirrhosis. Persons with cirrhosis (including those who have achieved SVR) may be considered for HCC screening with six-monthly ultrasound examinations and/or alpha-fetoprotein estimation (131, 141), and endoscopy every 1–2 years to exclude oesophageal varices (147).

### Management of decompensated cirrhosis

Diagnosis of decompensated liver disease is based on both laboratory and clinical assessment. A proportion of persons with decompensated liver disease will deteriorate on treatment and currently there are no predictors to identify these persons. Therefore, treatment of persons with decompensated cirrhosis ideally takes place in centres with the expertise to manage complications and where access to liver transplantation is available.

Daclatasvir, velpatasvir and sofosbuvir have been studied in persons with decompensated cirrhosis and their use has been demonstrated to be generally safe and effective. In contrast, regimens that include an HCV protease inhibitor (e.g. glecaprevir/pibrentasvir) are not approved for use in persons with decompensated liver disease.

### 5.2.4 Persons with chronic kidney disease

Glecaprevir/pibrentasvir have been shown to be effective and safe in persons with chronic kidney disease and HCV infection with all six major HCV genotypes (63). However, in 2018, there is limited availability in LMICs of this regimen, hence as an interim measure where genotype appropriate, consideration could be given to those combinations previously recommended in the WHO 2016 HCV treatment guidelines (2) and listed in Web annex 5 as safe in persons with grades 4 and 5 chronic kidney disease.

Sofosbuvir-based regimens do not have the safety and efficacy data to support their use in persons with chronic kidney failure grades 4 and 5, i.e. severe renal impairment (estimated glomerular filtration rate [eGFR] <30 mL/min/1.73 m<sup>2</sup>).

### 5.2.5 Persons with TB/HCV coinfection

Persons at increased risk of infection with HCV may also be at increased risk of infection with TB. Therefore, the clinical evaluation of persons being considered for HCV treatment can include screening for active TB. A four-symptom screening algorithm exists to rule out active TB (148). If the person does not have any one of the following symptoms – current cough, fever, weight loss or night sweats – TB can be reasonably excluded; otherwise, the person must undergo further investigations for TB or other diseases.

Most of the DAAs interact with metabolic pathways in the liver, which increases or decreases the level of DAAs when co-administered with commonly used rifamycins such as rifabutin, rifampin and rifapentine (149–151). Therefore, concurrent treatment of HCV infection and TB must be avoided. Active TB involves a risk of secondary transmission and that can be life-threatening in a shorter time frame than HCV. Thus, TB is usually treated before HCV. In persons with HCV infection treated for TB, the risk of antimycobacterial-induced hepatotoxicity is higher than in those with TB mono-infection, although the risk of severe hepatotoxicity is rare (152). Monitoring liver function tests detects hepatotoxicity early.

Concurrent treatment of HCV infection and multidrug-resistant TB is particularly complicated because of many DDIs between DAAs and second-line antimicrobials. There are limited data on the management of persons coinfecting with HCV, HIV and TB. Specialist referral may be needed to reduce the additive side-effects, pill burden and DDIs.

### 5.2.6 Retreatment of persons with failure of DAA therapy

With DAAs, SVR rates generally exceed 90% across all HCV genotypes (76). Even if all of the 71 million persons with HCV infection were to gain access to DAA therapy, an estimated 2–5 million of them would not be expected to achieve SVR, and would need effective retreatment. Persons who do not achieve SVR after DAA treatment have limited options for retreatment. An appropriate, highly effective initial treatment regimen helps avoiding the dilemma of limited retreatment options. Examination of adherence and potential DDIs may guide decisions when persons fail DAA therapy.

Currently, there is one pangenotypic regimen approved for the retreatment of persons who have been previously treated with any combination of DAAs. This is the FDC of sofosbuvir, velpatasvir and the protease inhibitor voxilaprevir (153, 154). In two clinical trials of sofosbuvir/velpatasvir/voxilaprevir, more than 300 persons, 46% with cirrhosis, were treated for 12 weeks. The triple DAA regimen was highly effective for persons who did not reach an SVR with DAA-containing regimens. SVR rates ranged from 93% to 99%, with the lowest rate in persons with genotype 3 infection and cirrhosis (155). Sofosbuvir/velpatasvir/voxilaprevir cannot be used in persons with Child–Pugh Class B or C cirrhosis or renal failure. The combination of glecaprevir/pibrentasvir has been approved for retreatment in patients who have failed sofosbuvir-containing regimens and those who have failed treatment with either a protease inhibitor or an NS5A inhibitor (but not both). In the absence of these regimens, expert consultation suggests that extending the initial DAA therapy to 16 or 24 weeks, while at the same time reinforcing adherence, may be an alternative option for retreatment.

# CHAPTER 6. SIMPLIFIED SERVICE DELIVERY FOR A PUBLIC HEALTH APPROACH TO TESTING, CARE AND TREATMENT FOR HCV INFECTION

## Background

In 2016, WHO estimated that only 13% of persons diagnosed with HCV infection had initiated treatment (4). This chapter provides a summary of eight key good practice approaches to service delivery across the continuum of care to support implementation of the clinical recommendations for Treat All and use of pangenotypic regimens. These would help countries improve access to effective hepatitis services (Box 6.1).

### Box 6.1. Good practice principles for health service delivery

1. **Comprehensive national planning for the elimination of HCV infection** based on local epidemiological context, existing health-care infrastructure, current coverage of testing, treatment and prevention, and available financial or human resources
2. **Simple and standardized algorithms** across the continuum of care from testing, linkage to care and treatment
3. **Strategies to strengthen linkage from testing to care**, treatment and prevention
4. **Integration of hepatitis testing, care and treatment with other services** (e.g. HIV services) to increase the efficiency and reach of hepatitis services
5. **Decentralized** testing and treatment services at primary health facilities or harm reduction sites to promote access to care. This is facilitated by two approaches:
  - 5a. **task-sharing**, supported by training and mentoring of health-care workers and peer workers;
  - 5b. **a differentiated care** strategy to assess level-of-care needs, with specialist referral as appropriate for those with complex problems.
6. **Community engagement and peer support** to promote access to services and linkage to the continuum of care, which includes addressing stigma and discrimination
7. **Strategies for more efficient procurement and supply management** of quality-assured, affordable medicines and diagnostics
8. **Data systems to monitor the quality of individual care and coverage** at key steps along the continuum or cascade of care at the population level.

## 6.1 National planning for HCV elimination

In 2015, WHO published a manual to guide national programme managers in developing or strengthening national viral hepatitis plans (156). The manual is aligned with a health systems approach to disease planning and supports an evidence-based decision-making process. It includes a template for a national hepatitis plan that covers prevention, testing and treatment within the framework of universal health coverage principles and other planning tools. National stakeholders should also use the plan to agree on the service coverage targets for the interventions towards achievement of elimination.

## 6.2 Simple standardized algorithms

A simplified algorithm is given for testing, treatment and monitoring with five key steps that can be adapted for use at the national level (see summary algorithm in the Executive summary).

## 6.3 Strategies to strengthen linkage from testing to care

Multiple factors may hinder successful uptake of testing and linkage to care, treatment and prevention. These include patient-level factors (e.g. mental health issues, substance abuse, misinformation, depression, lack of social or family support, fear of disclosure and housing instability), as well as structural or economic factors (e.g. stigma and discrimination, high cost of care, distance from care sites, transportation costs and long waiting times at the facility) (157). Optimizing the impact of effective treatment and prevention will require interventions to both expand the uptake of testing and improve linkage to confirmatory viral load testing and uptake of treatment.

*The 2017 WHO Guidelines on hepatitis B and C testing* recommended that all facility- and community-based hepatitis testing services adopt and implement strategies to enhance uptake of testing and linkage to care (*strong recommendation, moderate quality of evidence*) (3). In particular, the following evidence-based interventions should be considered to promote uptake of hepatitis testing and linkage to care and treatment initiation (*conditional recommendation*):

- trained peer and lay health worker support in community-based settings (*moderate quality of evidence*);
- clinician reminders to prompt provider-initiated, facility-based HCV testing in settings that have electronic records or analogous reminder systems (*very low quality of evidence*);



- provision of hepatitis testing as part of integrated services within a single facility, especially mental health/substance use (*very low quality of evidence*);
- dried blood spot (DBS) specimens for NAT ± serology in some settings (*low/moderate quality of evidence*).

Other approaches that may be considered to promote linkage include (8)

- **on-site single rapid diagnostic test (RDT)** with same-day results;
- **reflex laboratory-based virological NAT** of positive serology samples;
- **providing assistance with transport** if the treatment centre is far from the testing site.

Specific policies can improve and monitor linkages between hepatitis testing and prevention, treatment and care services. Interventions that impact on multiple steps along the care continuum will generally be more resource efficient.

## 6.4 Integrated testing, care and treatment

The goal of programme collaboration is to create integrated delivery systems that can facilitate access to hepatitis testing, treatment and other health services. There are three types of potential service integration:

1. providing testing for HCV infection in different settings (e.g. in HIV/ART, TB, sexually transmitted infection [STI] or antenatal clinics);
2. integrating the diagnosis of hepatitis with diagnostic platforms and laboratory services used for other infections;
3. integrated service delivery of care, prevention and treatment (e.g. HCV care at harm reduction or HIV sites).

### 6.4.1 Providing testing for HCV infection in different settings

WHO already recommends integration of HIV testing into a range of other clinical services, such as services for TB, HIV/ART, maternal and child health, sexual and reproductive health (STI clinics), mental health and harm reduction programmes, migrant and refugee services, and in prisons (158). Integrating HCV and HIV testing will be particularly important in populations with high-risk behaviours for both infections, such as PWID, MSM and incarcerated persons who have a high prevalence of both HIV and HCV infection (159).

The primary purpose of integration is to make HBV, HCV and HIV testing more convenient for people coming to health facilities, and so expand the reach and uptake of viral hepatitis testing. For the HCV-infected person, integration of hepatitis testing into other health services may facilitate addressing other health needs at the same time, thereby saving time and money. For the health system, integration may reduce duplication of services and improve coordination (e.g. in stock management of diagnostic assays).

#### **6.4.2 Integrating the diagnosis of hepatitis with diagnostic platforms and laboratory services used for other infections**

##### **Combination integrated multidisease serological tests**

The use of combination integrated blood- or oral-based multidisease assays allow for integrated testing of HIV, HBV and HCV. Using a single specimen improves the efficiency of testing programmes, especially in populations with a high prevalence of HIV/HCV or HBV/HCV coinfection. While not yet fully validated, preliminary results of these combination assays appear promising (160).

##### **Shared use of HIV or TB multidisease platforms for HCV viral load testing**

The introduction of multidisease testing devices (also known as polyvalent testing platforms) brings new opportunities for collaboration and integration, and can both increase access as well as provide significant system efficiencies, with cost-savings. Countries with existing multidisease platforms for HIV viral load or TB testing or those that are planning for their introduction can consider collaboration and integration of HCV viral load testing (161). This includes both high-throughput laboratory-based instruments for HIV viral load measurement and point-of-care instruments such as GeneXpert for HIV and TB.

#### **6.4.3 Integrated service delivery of care, prevention and treatment**

Increased access and rapid scale up of HCV treatment and care will require a significant change in the way that services are delivered. Where possible, HCV services (testing and DAA treatment) can integrate the public health system. In many cases, this integration goes down to primary health-care facilities. It makes use of existing HIV and harm reduction services (OST and/or needle exchange programmes) or prison health services to increase access, especially for PWID. Existing WHO guidance on delivery of effective OST programmes is available (5). Continuity of prevention and care is needed to ensure ongoing harm reduction measures and avoid reinfection, especially among PWID and MSM. Integration of services means not only provision of related services at a single setting, but also linking reporting systems to share information between settings and providers.

## 6.5 Decentralized services

Decentralization of services refers to service delivery at peripheral health facilities, community-based venues and locations beyond hospital sites, bringing care nearer to patients' homes. This may reduce transportation costs and waiting time experienced at central hospitals and, as a result, improve linkage to treatment and follow up. In high HIV-burden LMICs, the decentralization of HIV treatment services was a key factor in successful global scale up, improving uptake of both testing and treatment, and reducing loss to follow up (162, 163). In contrast, delivery of viral hepatitis testing and treatment has until recently generally relied on specialist-led centralized care models in hospital settings (164, 165). Decentralization of testing services will require access to quality-assured RDTs or collection and analysis of DBS specimens, good specimen referral networks, enhanced connectivity for return of results, and an electronic results system. Decentralized provision of care and treatment will be facilitated by use of a simplified algorithm (see summary algorithm in the Executive summary), access to pangenotypic regimens and a programme of staff training and supervision. There are now several examples of successful models of decentralized viral hepatitis testing and treatment services emerging in high-burden countries, including Mongolia and Egypt. Decentralization of services, however, may not always be appropriate for all settings, or acceptable to all clients, and the relative benefits should be assessed according to the context. Key requirements to deliver effective decentralized care are described below.

### 6.5.1 Task-sharing

Many countries affected by HCV infection face shortages of trained health workers and specialists in hepatitis management. Task-sharing is a pragmatic response to shortages of the health workforce to support decentralized care. It is strongly recommended by WHO in HIV care based on a comprehensive evidence base and has been widely adopted to expand access to HIV testing and treatment globally (91, 166). Effective task-sharing with non-specialists or nurses requires provision of appropriate training at the decentralized site, and access to additional support or referral to tertiary or specialist sites for more complex cases.

### 6.5.2 Differentiated HCV care and treatment

Currently, the majority of HCV care and treatment during this early phase of scale up is facility based, and not differentiated according to individual needs. Differentiated care is defined as a client-centred approach that simplifies and adapts services across the cascade, in ways that both serve the needs better of

those with more complex problems requiring prompt or specialized clinical care but also relieves overburdened hepatitis clinics in central hospitals. Based on an evidence-based differentiated care framework recommended by WHO and widely adopted in HIV treatment and care programmes, a similar approach is proposed to support decentralized management of HCV infection.

Broadly, three groups of HCV-infected persons with specific needs can be identified. Table 6.1 summarizes these three groups, their anticipated care needs, the most appropriate setting to deliver care and the type of provider needed. The majority of persons with HCV will have early-stage liver disease; they can be treated at facility level or potentially even in the community. Only a small proportion will require more intensive clinical or psychosocial support. However, this will vary considerably according to the epidemic profile of the country, and the maturity of the treatment response and diagnosis rate.

1. **Persons clinically well and stable:** this represents the majority of persons diagnosed, and includes those with no evidence of cirrhosis, serious comorbidities, mental health issues or active drug use; and the ability to comprehend issues of adherence and prevention messages.
2. **Persons requiring more intensive clinical support:** this includes persons presenting to care with advanced liver disease or serious comorbidities, previous treatment failure that requires either a more intensive or fast-tracked clinical and care package to manage life-threatening clinical problems and initiate treatment with more intensive monitoring.
3. **Persons requiring more intensive psychosocial/mental health support, or intercultural or language support:** this may include those with mental health issues, PWID, those with alcohol misuse, or adolescents requiring additional support and counselling. Migrant populations and Indigenous Peoples may also require more intensive intercultural or language support.

**TABLE 6.1** Potential differentiated care needs and approaches to viral hepatitis

Who? HCV-infected persons category	What? Care needs	Where? Site	By whom? Caregiver
<b>Clinically well and stable</b>	<b>Standard care package:</b> counselling, adherence support, treatment initiation and monitoring	Facility-based, including primary care or community-based settings, and mobile/outreach	Physician or nurse
<b>Advanced liver disease or serious comorbidities, hepatocellular cancer (HCC), previous treatment failure</b>	<b>Requiring more intensive clinical support and follow up:</b> management of liver-related complications (e.g. variceal bleed, ascites, encephalopathy, HCC treatment)	Facility-based – hospital	Physician
<b>Mental health issues, people who inject drugs or engage in alcohol misuse, adolescents, migrants</b>	<b>Requiring more intensive psychosocial/ mental health support, or intercultural and language support</b>	Can be facility-based or community-based, harm reduction site	Physician and counsellor/peer support

## 6.6 Community engagement and peer support, including addressing stigma and discrimination in the general population

Peer-led interventions have been effective in increasing access, care and treatment, and supporting adherence to treatment, for both hepatitis and other infectious diseases particularly for marginalized population groups such as PWID (3, 167). In addition to providing services, peers can act as role models and offer non-judgemental support that may contribute to reducing stigma and improving the acceptability of services.

## 6.7 Strategies for more efficient procurement and supply management of medicines and diagnostics

Access to DAAs for hepatitis C has improved since their initial registration in 2013 (Table 6.2). In 2017, 62% of those infected with HCV lived in countries where generic medicines could be procured. Countries that made use of this possibility and registered multiple medicines from different manufacturers managed to achieve a major reduction in prices (4). However, initial progress in access to DAAs has been mostly for the sofosbuvir/ledipasvir and sofosbuvir/daclatasvir combinations (Table 6.2). Of these, sofosbuvir/daclatasvir is a pangenotypic regimen. With respect to the other two pangenotypic regimens, the innovator company has announced an access programme for sofosbuvir/velpatasvir. No information is available for glecaprevir/pibrentasvir.

Key steps to increase the availability of DAA and diagnostics at country level include the following (4):

1. **Selecting products:** formulating national testing and treatment guidelines that specify which medicines and diagnostic assays should be used. WHO-prequalified products are listed at: [http://www.who.int/diagnostics\\_laboratory/evaluations/PQ\\_list/en/](http://www.who.int/diagnostics_laboratory/evaluations/PQ_list/en/)  
[http://www.who.int/medicines/news/2017/1st\\_generic-hepCprequalified\\_active\\_ingredient/en/](http://www.who.int/medicines/news/2017/1st_generic-hepCprequalified_active_ingredient/en/)
2. **Determining whether generic medicines are available in the country:** if DAAs are not protected by a patent or if the country is included in the respective license agreement, procurement of generic medicines from various sources is possible. Otherwise, the country needs to enter into price negotiations with the originator company or if this does not yield satisfactory results, use the flexibilities contained in the World Trade Organization (WTO) Agreement on Trade Related Intellectual Property Rights (4).
3. **Registration and inclusion in the national essential medicines list:** DAAs need to be registered with the national regulatory authority and included in the national essential medicines list. If access to generic medicines is possible, registration of products from as many manufacturers as possible will increase competition and lower prices.
4. **Quantification and forecasting of demand for commodities:** to estimate the volume of products required to meet programme demand, managers need to estimate the size of the infected population in need of treatment and the expected rate of scale up for testing and treatment activities.

5. **Procurement of commodities:** procurement mechanisms can include (i) a competitive tendering process in case of registration of multiple manufacturers of generic medicines or (ii) price/volume negotiation with the originators if generic medicines cannot be procured. A pooled procurement mechanism (e.g. Strategic Fund of the Pan American Health Organization) is another option for economies of scale in procurement of commodities, including diagnostics.

WHO tools are also available to estimate the cost-effectiveness of HCV treatment in individual countries (<http://tool.hepccalculator.org/>) and to procure diagnostics. ([http://www.who.int/diagnostics\\_laboratory/publications/procurement/en/](http://www.who.int/diagnostics_laboratory/publications/procurement/en/)).

**TABLE 6.2** Characteristics of available pangenotypic and non-pangenotypic DAAs

	Pangenotypic regimens			Sofosbuvir/ ledipasvir
	Sofosbuvir/ velpatasvir	Sofosbuvir/ daclatasvir	Glecaprevir/ pibrentasvir	
<b>Efficacy in infection with HCV genotypes 1–6</b>	Pangenotypic	Pangenotypic	Pangenotypic	Genotype dependent
<b>Tolerability</b>	High	High	High	High
<b>Registration status in low- and middle-income countries</b>	Very low	Low	Very low	Low
<b>Access plans in low- and middle-income countries</b>	In development	Large number of countries included in voluntary license agreements	No information available	Large proportion of countries included in voluntary license agreements
<b>Acceptability by health providers</b>	Highest	Highest	Highest	High
<b>Health system costs (genotyping; laboratory; personnel)</b>	Low	Low	Low	High

## 6.8 Data systems for monitoring the quality and cascade of care

WHO has developed a monitoring and evaluation framework to enable Member States to report on hepatitis elimination (73). Three indicators address the cascade of care, including the proportion of infected persons diagnosed (core indicator C6b), treatment initiation rate (core indicator C7b) and the proportion of those treated who are cured (C8b). In an initial assessment phase, triangulation of data from different sources may be used to generate an initial estimate of the three core indicators of the cascade of care. In the longer term, estimating the indicators of the cascade of care requires a database of HCV-infected persons based on simple individuals' records. Such databases can be integrated with those used to monitor HIV and/or TB treatment as appropriate.



# CHAPTER 7. PUBLIC HEALTH CONSIDERATIONS FOR SPECIFIC POPULATIONS

The two considerations in the box below are existing formal WHO recommendations that address focused testing for HBV and HCV infection and harm reduction for PWID.

## *Existing recommendation from the 2017 HBV and HCV testing guidelines (3)*

In all settings (and regardless of whether delivered through facility- or community-based testing), it is recommended that serological testing for HCV antibody (anti-HCV)<sup>1</sup> or HBsAg be offered with linkage to prevention, care and treatment services to the following individuals:

- Adults and adolescents from populations most affected by HCV infection<sup>2</sup> (i.e. who are either part of a population with high HCV seroprevalence or who have a history of exposure and/or high-risk behaviours for HCV infection);
- Adults, adolescents and children with a clinical suspicion of chronic viral hepatitis<sup>3</sup> (i.e. symptoms, signs, laboratory markers).

*(Strong recommendation, low quality of evidence)*

*Note:* Periodic retesting using HCV nucleic acid tests (NAT) should be considered for those with ongoing risk of acquisition or reinfection.

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1 This may include fourth-generation combined antibody/antigen assays.

2 Includes those who are either part of a population with higher seroprevalence (e.g. some mobile/migrant populations from high/intermediate endemic countries, and certain indigenous populations) or who have a history of exposure or high-risk behaviours for HCV infection (e.g. PWID, people in prisons and other closed settings, MSM and sex workers, and HIV-infected persons, children of mothers with chronic infection, especially if HIV-coinfected).

3 Features that may indicate underlying chronic HCV infection include clinical evidence of existing liver disease, such as cirrhosis or HCC, or where there is unexplained liver disease, including abnormal liver function tests or liver ultrasound.

*Existing recommendation from the 2016 updated guidelines on HIV prevention, diagnosis, treatment and care for key populations (5)*

All people from key populations who are dependent on opioids should be offered and have access to opioid substitution therapy.

All other considerations discussed in this chapter are based on good practice principles.

## 7.1 People who inject drugs

### 7.1.1 Background

In 2017, there were an estimated 15.6 million PWID aged 15–64 years (168). PWID are at risk for infections, including HCV infection (169), mental health issues, psychosocial challenges, contact with law enforcement agencies (170) and premature death (171).

Fifty-two per cent of PWID (95% UI: 42–62) have serological evidence of past or present HCV infection (anti-HCV positive) and 9% (95% CI: 5–13) have HBV infection (HBsAg positive) (168). However, many infected PWID are unaware of their diagnosis and few initiate treatment (172), because of criminalization, discrimination, unstable housing and stigma in health-care settings (173). Around 58% of PWID have a history of incarceration (168). PWID are also at increased risk of new HCV infection and reinfection (47, 172). They require prevention services to reduce the risk of infection and reinfection after a cure (174).

### 7.1.2 Service delivery considerations

#### Prevention services and reducing harm from injecting drug use

- **High-coverage harm reduction programmes for PWID to prevent HCV transmission and reinfection.** WHO already recommends both needle and syringe distribution and OST (5) as effective interventions for HIV prevention, but only a high coverage of these interventions also prevents HCV transmission (175) (176).
- **Education of PWID.** Harm reduction interventions educate on prevention and provide access to sterile equipment. OST reduces the frequency of injection (177), treats underlying dependence and helps to prevent overdose.
- **Access to low dead-space syringes.** NSPs make use of low dead-space syringes (178).

## Testing

**Routine targeted testing of all PWID for HCV, HBV and HIV infection** was recommended in the 2017 WHO testing guidelines (3). Testing and treatment in drug dependency services or prisons is cost effective in high-income settings (132, 179). Specific interventions improve coverage (180). Regular testing for HCV is relevant to uninfected PWID, those cured, and those who had cleared the virus spontaneously. Previously infected persons are tested directly with HCV RNA as they will remain anti-HCV positive after the first infection (181).

## Linkage and care

Following diagnosis, PWID can be referred to appropriate services. Specific interventions can improve linkage (180) to a package of care that includes treatment (182) and addresses other medical and/or psychosocial issues. Peer interventions and integrated comprehensive HCV care may increase acceptability, uptake and adherence. It can reduce injecting drug use and improve injection practices (183). See the WHO ASSIST package – guidance on brief behavioural interventions for substance use (184).

## Treatment

Limited data (185–190) indicate high SVR rates among PWID treated with DAAs for HCV infection. DDIs can take place between both prescribed and non-prescribed drugs.

## 7.2 People in prisons and other closed settings

### 7.2.1 Background

Worldwide, at any given time, an estimated 10 million people are incarcerated (191). HCV infection is more common among incarcerated persons or those who have previously spent time in correctional facilities. A meta-analysis reported a global prevalence of HCV infection of 26% among general detainees, and of 64% among detainees with a history of injecting drug use (192). Incidence was estimated at 1.4 per 100 person-years, rising to 16.4 per 100 person-years in those with a history of injecting drug use (192). Overall, 58% of PWID have a history of incarceration and 56–90% of PWID would be incarcerated at some stage (168). Criminalization of drug use may explain the frequency of HCV infection in prisons and other closed settings. One in every five prisoners is held for drug-related charges (170). Transmission continues in closed settings because of injecting drug use, tattooing (193) and possibly sexual transmission among men. However, OST is available in the prisons of only 52 countries, and only eight countries have at least one NSP within a closed setting (194).

## 7.2.2 Service delivery considerations

Prisons are an opportunity to offer prevention, testing, care and treatment services to marginalized populations that otherwise might have difficulty in accessing care.

- **Expansion of NSP and OST coverage.** The United Nations 2016 General Assembly Special Session (UNGASS) on Drugs called for non-discriminatory access to “medication-assisted therapy”, including access in prisons and other custodial settings, and suggested that national authorities consider making NSPs available in custodial settings (195).
- **Provision of DAAs in prisons.** The short duration of DAA treatment allows delivery in closed settings, including through task-sharing with nurses (196).
- **Negative consequences of testing in prison.** Mandatory or coercive testing, segregation of prisoners, and refusal of treatment have been reported.
- **Continuation of prevention, testing and treatment services available in the community during detention and vice versa.** Persons who were ever incarcerated, particularly PWID, are likely to return to prison. Health services in prisons differ from those in the community. Medical care may be interrupted because of incarceration and upon return to the community (197, 198). People receiving community-based OST, as well as treatment for HIV and HCV, suffer from these disruptions of care (199, 200).

## 7.3 Indigenous Peoples

### 7.3.1 Background

Viral hepatitis disproportionately affects Indigenous Peoples in most parts of the world (9, 201). The world’s 370 million Indigenous Peoples face displacement, dispossession, loss of livelihood, systematic racism as well as abuse and lack of recognition, threatening the sacred relation between Indigenous Peoples and their landbase. Poverty as well as large health disparities are common among Indigenous Peoples. Access to health services is often further hampered by the remoteness of their communities or language and cultural barriers. In some countries, including Canada and Australia, rates of incarceration and injecting drug use are high in Indigenous Peoples, further increasing the risk of HCV acquisition (202, 203).

### 7.3.2 Service delivery considerations

The United Nations Declaration on the Rights of Indigenous Peoples highlights several key considerations for the health of Indigenous Peoples. Indigenous Peoples have the right to be actively involved in developing and determining the health programmes that affect them, and to administer, as far as possible, such programmes through their own institutions. Indigenous Peoples also have the

right to access, without any discrimination, to all social and health services (204). Specific considerations in delivering HCV prevention, diagnosis and treatment services include:

- employing and training Indigenous staff in HCV prevention, diagnosis and treatment;
- catering to specific language or cultural needs, e.g. gender-specific service provision;
- engaging with local Indigenous representatives to gain endorsement and acceptance;
- consulting with community members to address concerns or provide information;
- engaging with the community to increase availability of treatment.

## 7.4 Men who have sex with men

### 7.4.1 Background

HCV is not commonly transmitted through unprotected sexual intercourse among monogamous heterosexual partners (205–208). However, sexual practices that cause mucosal trauma, group sex, chemSex (the practice of non-injection and injection use of certain drugs before and during sex), and the presence of HIV infection increase sexual transmission of HCV among MSM (52, 209–211). Non-injecting HIV-infected MSM populations have a high incidence of HCV infection (212). Transmission increases with unprotected receptive anal intercourse, ulcerative STI lesions and lower CD4 counts (213). The implementation of HIV pre-exposure prophylaxis (PrEP) among sexually active HIV-negative MSM was also followed by reports of a rise in HCV incidence (214).

### 7.4.2 Service delivery considerations

- **The 2017 WHO testing guidelines recommend regular HCV testing** for MSM (3). Information can be provided on modes of transmission during male-to-male sex.
- **Treatment of HCV-infected MSM with DAA.** Specific treatment of HCV/HIV-positive MSM may prevent onward transmission of HCV. Attention must be paid to DDIs with DAAs for persons on ART (see section 5.1.1).

## 7.5 Sex workers

### 7.5.1 Background

Sex workers of both genders are more likely to have HCV infection than the general population for a variety of reasons, such as higher rates of substance use and drug injecting, higher prevalence of HIV infection and more exposure to HCV (9).

### 7.5.2 Service delivery considerations

Various health and welfare needs may facilitate the engagement of sex workers in care.

- **Strategies to facilitate engagement in care.** This may include outreach, on-site testing services, peer-based interventions, and linkage to other health and welfare services.
- **Linkage and referral to appropriate services upon request where substance use, including alcohol and injecting drug use, is present.** This involves providing access to harm reduction interventions such as OST and NSP, where necessary.

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# ANNEX 1: DECLARATIONS OF INTEREST: GUIDELINES DEVELOPMENT GROUP

Name, affiliation	Country and WHO region	Employment/ consulting	Research support/ non-monetary support	Investment interests	Intellectual property	Conflicts and management plan
Saeed Sadiq Hamid (Chair) The Aga Khan University, Karachi	Pakistan Eastern Mediterranean Region	0	0	0	0	Full participation
Karla Thornton (Co-Chair) University of New Mexico	Region of the Americas	0	0	0	0	Full participation
Rakesh Aggarwal Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow	India South-East Asia Region	0	0	0	0	Full participation
Evaldo Stanislaw Affonso Araujo University of Sao Paulo, Hospital das Clinicas Infectious Diseases	Brazil Region of the Americas	Conference registration and travel support by Abbvie and MSD of US\$ 4000	0	0	0	Financial non-significant. Full participation
Anton Basenko Alliance for Public Health, Kiev	Ukraine European Region	0	0	0	0	Full participation
Roger Chou (Methodologist) Oregon Health & Science University, Portland	USA Region of the Americas	0	0	0	0	Full participation
Davaadorj Duger National University of Medical Sciences, Ulaanbaatar	Mongolia Western Pacific Region	0	0	0	0	Full participation

<b>Manal El-Sayed Ain Shams University</b>	Egypt Eastern Mediterranean Region	Travel support by Abbvie, MSD, Roche and Gilead	0	0	0	Financial non-significant. Full participation
<b>Charles Gore World Hepatitis Alliance</b>	United Kingdom European Region	Employed by Hepatitis C trust, President of World Hepatitis Alliance that receives grants and other support from BMS, Boehringer Ingelheim, Janssen, Roche, Roche diagnostics, Merck, GSK, Gilead, AbbVie, Abbott	All funding for the organization comes from these firms >US\$ 1 million	0	0	Financial significant. Restricted participation. Excluded from the discussion, voting and formulation of the treatment recommendations
<b>Azumi Ishizaki Kanazawa University, Hanoi</b>	Viet Nam Western Pacific Region	0	0	0	0	Full participation
<b>Olufunmilayo Lesi University of Lagos</b>	Nigeria African Region	0	0	0	0	Full participation
<b>Niklas Luhman Harm reduction, Hepatitis C &amp; HIV/AIDS advisor, Medecins du Monde</b>	France European Region	0	0	0	0	Full participation
<b>Constance Mukabatsinda Kigali University Teaching Hospital</b>	Rwanda African Region	0	0	0	0	Full participation
<b>Francesco Negro University Hospital of Geneva</b>	Switzerland European Region	Consulting and advisory board for Janssen-Cilag, Gilead, MSD, BMS and AbbVie of CHF 8525. Travel support to meeting by Gilead.	Gilead grant of CHF 199 000	0	0	Financial significant. Restricted participation. Excluded from the discussion, voting and formulation of the treatment recommendations
<b>David Nelson University of Florida</b>	USA Region of the Americas	0	0	0	0	Full participation

<b>Ponsiano Ocama</b> Makerere University, Kampala	Uganda African Region	0	0	0	0	0	Full participation
<b>Jurgen Rockstroh</b> University of Bonn	Germany European Region	Consulting and advisory board for Janssen-Cilag, Gilead, MSD, BMS and AbbVie. Travel support to meeting by Gilead for US\$ 12 000	Research grant for immunology in acute HCV by NEAT of US\$ 43 000 USD, Research grant for acute HCV cohort by NEAT-ID of US\$ 60 000	0	0	0	Financial significant. Restricted participation. Excluded from the formulation of the treatment recommendations
<b>Regina Tiolina Sidjabat</b> Ministry of Health, Republic of Indonesia	Indonesia South-East Asia Region	0	0	0	0	0	Full participation
<b>Khwairakpam Giten Singh</b> TreatAsia	Thailand South-East Asia Region	0	0	0	0	0	Full participation
<b>Tracy Swan</b> Hepatitis/HIV project, Treatment Action Group	USA Region of the Americas	0	0	0	0	0	Full participation
<b>Alexander Thompson</b> St Vincent's Hospital, Melbourne	Australia Western Pacific Region	Consulting and advisory board for Gilead, Merck, BMS and AbbVie for US\$ 16 000	Research grant Gilead of US\$ 4.5 million, research grant Abbvie of US\$ 580 000	0	0	0	Financial significant. Restricted participation. Excluded from the formulation of the treatment recommendations
<b>Emma Thomson</b> University of Glasgow	UK European Region	0	0	0	0	0	Full participation
<b>Lai Wei</b> Peking University Health Science Center	China Western Pacific Region	0	0	0	0	0	Full participation
<b>Stefan Wiktor</b> University of Washington, Seattle	USA Region of the Americas	0	0	0	0	0	Full participation



## ANNEX 2: DECLARATIONS OF INTEREST: EXTERNAL REVIEW GROUP

Name, affiliation	Country and WHO region	Employment/ consulting	Research support/ non-monetary support	Investment interests	Intellectual property	Conflicts and management plan
<b>Francisco Averhoff</b> Centers for Disease Control and Prevention	USA Region of the Americas	0	0	0	0	None
<b>Graham Cooke</b> Imperial College London	United Kingdom European Region	0	0	0	0	None
<b>Benjamin Cowie</b> WHO Collaborating Centre for Viral Hepatitis, Infectious Diseases, Royal Melbourne Hospital	Australia Western Pacific Region	0	0	0	0	None
<b>Sharon Hutchinson</b> Glasgow Caledonian University	United Kingdom European Region	0	0	0	0	None
<b>Maria Cassia Mendes Correa</b> Ministry of Health	Brazil Region of the Americas	0	0	0	0	None
<b>Christian Ramers</b> Clinton Health Access Initiative	USA Region of the Americas	Scientific advisory board and consulting for Gilead, Merck, BMS, Janssen and AbbVie for US\$ 85 000	Focus HCV testing grant of US\$ 164 000	0	0	Financial significant  Comments interpreted in the context of conflict of interest. No substantive changes were made based on this review.

<b>Trevor Stratton Canadian Aboriginal AIDS Network</b>	Canada Region of the Americas	Employed by Canadian Aboriginal AIDS Network of Can\$ 70 000 per year	Financial significant
			Comments interpreted in the context of conflict of interest. No substantive changes were made based on this review.
<b>Karin Timmermans Unitaid</b>	Switzerland European Region	0	None
<b>Takaji Wakita National Institute of Infectious Diseases</b>	Japan Western Pacific Region	0	None



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