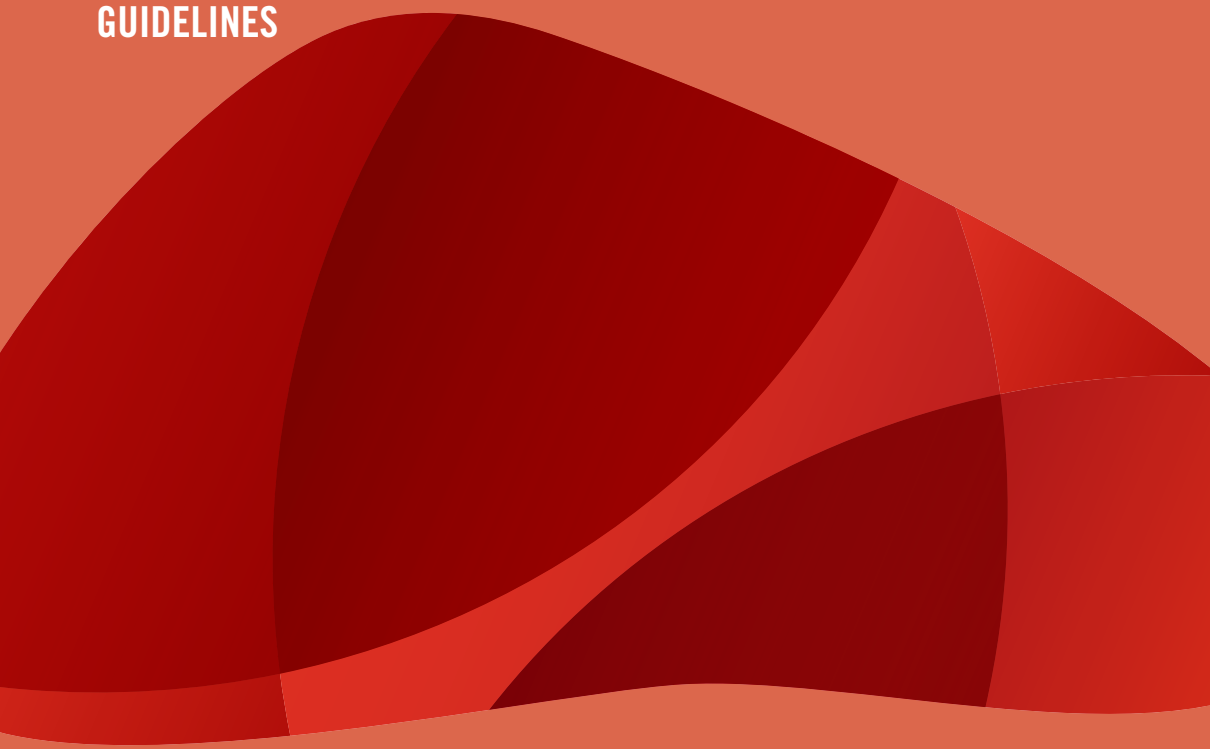
World Health Organization

GUIDELINES FOR THE SCREENING, CARE AND TREATMENT OF PERSONS WITH CHRONIC HEPATITIS C INFECTION

UPDATED VERSION
APRIL 2016

GUIDELINES



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Guidelines Development

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And for the 2014 recommendations:
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Overall coordination

Stefan Wiktor coordinated the development of these guidelines.

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ABBREVIATIONS AND ACRONYMS

AASLD	American Association for the Study of Liver Disease
ALT	alanine aminotransferase
APRI	AST-to-platelet ratio index
ART	antiretroviral therapy
ARV	antiretroviral
ASSIST	Alcohol, Smoking and Substance Involvement Screening Test
AST	aspartate aminotransferase
BCRP	breast cancer resistance protein
CI	confidence interval
CrI	credible interval
DAA	direct-acting antiviral (drug)
DDI	drug–drug interaction
EASL	European Association for the Study of the Liver
EIA	enzyme immunoassay
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
FBC	full blood count
FDA	United States Food and Drug Administration
gGT	gamma glutamyl transpeptidase
gp	glycoprotein
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
Hb	haemoglobin
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
INR	international normalized ratio
LMIC	low- and middle-income countries
mhGAP	WHO Mental Health Gap Action Programme
MSM	men who have sex with men
NAT	nucleic acid testing/test
NGO	nongovernmental organization
NNRTI	non-nucleoside reverse transcriptase inhibitor
NRTI	nucleoside reverse transcriptase inhibitor
NS5B	non-structural protein 5B (of HCV)
NS3/NS4A	non-structural protein 3/non-structural protein 4A
OR	odds ratio
OST	opioid substitution therapy

PICO	Population, Intervention, Comparison, Outcomes
PWID	people who inject drugs
RAV	resistance-associated variant
RCT	randomized controlled trial
RNA	ribonucleic acid
RR	relative risk
SAE	severe adverse event
SVR	sustained virological response
TB	tuberculosis
WHO	World Health Organization

GLOSSARY OF TERMS

Anti-HCV antibody	Presence of antibodies to hepatitis C virus (HCV) indicating history of exposure to HCV
Chronic HCV	Continued presence of HCV RNA in the blood six months or more after acquiring infection
Delayed virological response	More than 2 log reduction in HCV RNA viral load but a detectable HCV RNA level at week 12 of treatment and an undetectable HCV RNA level at week 24 of treatment
Early virological response	More than 2 log reduction in HCV RNA viral load at week 12 of treatment
Extended rapid virological response	Undetectable HCV RNA at 4 weeks (rapid) and 12 weeks (extended) after the start of treatment
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
Negative predictive value	The probability that when a person's test result is negative, they truly do not have the infection/disease. Predictive values are influenced by the prevalence of the disease in the population
Non-response	Detectable HCV RNA throughout treatment
Null response	Less than 2 log reduction in HCV RNA level by week 12 of treatment
Partial response	2 log reduction in HCV RNA by week 12 of treatment but HCV RNA remains detectable at week 24 or end of treatment
Positive predictive value	The probability that when a person's test result is positive, they truly have the infection/disease. Predictive values are influenced by the prevalence of the disease in the population
Rapid virological response	Undetectable HCV RNA in the blood at 4 weeks of treatment
Relapse	Undetectable HCV RNA in the blood at the end of treatment but detectable HCV RNA within 24 weeks of completing treatment
Sensitivity	The ability of a test to correctly identify those with the infection/disease (true positives/true positives + false negatives)
Specificity	The ability of a test to correctly identify those without the infection/disease (true negatives/true negatives + false positives)
Sustained virological response (SVR)	Undetectable HCV RNA in the blood after the end of HCV treatment, either at 12 weeks (SVR12) or at 24 weeks (SVR24)
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
Viraemic HCV	Presence of HCV RNA in the blood

EXECUTIVE SUMMARY

Globally, the morbidity and mortality attributable to hepatitis C virus (HCV) infection continues to increase. Approximately 700 000 persons die each year from HCV-related complications, which include cirrhosis, hepatocellular carcinoma (HCC) and liver failure. HCV infection can be cured by antiviral treatment; however, due to the asymptomatic nature of the disease, many infected persons are unaware of their infection and, for those who are diagnosed, access to treatment remains poor in many settings.

The field of HCV therapeutics continues to evolve rapidly and, since the World Health Organization (WHO) issued its first *Guidelines for the screening, care and treatment of persons with hepatitis C infection* in 2014, several new medicines have been approved by at least one stringent regulatory authority. These medicines, called direct-acting antivirals (DAAs), are transforming the treatment of HCV, enabling regimens that can be administered orally, are of shorter duration (as short as eight weeks), result in cure rates higher than 90%, and are associated with fewer serious adverse events than the previous interferon-containing regimens. WHO is updating its hepatitis C treatment guidelines to provide recommendations for the use of these new medicines.

The objectives of these WHO guidelines are to provide updated evidence-based recommendations for the treatment of persons with hepatitis C infection using, where possible, all DAA-only combinations. The guidelines also provide recommendations on the preferred regimens based on a patient's HCV genotype and clinical history, and assess the appropriateness of continued use of certain medicines. This document also includes existing recommendations on screening for HCV infection and care of persons infected with HCV that were first issued in 2014. The key audience for these guidelines are policy-makers in low- and middle-income countries who formulate country-specific treatment guidelines and who plan infectious disease treatment programmes and services, in addition to those people responsible for delivering treatment. The guidelines are appropriate for all countries, including high-income countries.

The guidelines were produced in line with processes described in the WHO *Handbook for guideline development,* using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) method, which provides guidance and tools to define research questions, develop an analytical framework, conduct systematic reviews, assess the overall quality of the evidence, and determine the direction and strength of the recommendations. The process involved multiple steps that included the formation of a Guidelines Development Group, and the development of a series of questions across the screening, care and treatment framework, which were structured in the PICO format (Population, Intervention, Comparison, Outcomes). Systematic reviews of the best available evidence were conducted and

the findings were assessed for quality and presented in GRADE evidence profiles. For the recommendations on preferred treatment regimens, network meta-analyses were conducted to compare the efficacy and safety of antivirals for the treatment of HCV infection. Pooled proportions for sustained virological response (SVR), severe adverse events (SAEs), treatment discontinuation and mortality rates were calculated for each regimen by genotype and previous treatment experience. In addition, a budget impact analysis was undertaken to assess the cost per patient and overall cost to treat the defined populations in selected countries.

In developing the recommendations, the Guidelines Development Group considered the evidence as well as the characteristics of each regimen, such as pill burden, frequency of drug–drug interactions, and whether they required interferon or ribavirin. Based on these considerations, preferred and alternative regimens were selected for each genotype. Decision-makers will then be able to choose from these options based on the price and availability of the medicines and the endemic HCV genotypes in their countries. To support decision-making, clinical considerations such as treatment prioritization, drug–drug interactions, monitoring for treatment response and adverse reactions, treatment in pregnancy and in those with coinfection are also covered in the guidelines, in addition to treatment considerations for specific populations.

Summary of recommendations

New recommendations (2016)

Treatment with direct-acting antiviral agents: it is recommended that DAA regimens be used for the treatment of persons with hepatitis C infection rather than regimens with pegylated interferon and ribavirin.

(Strong recommendation, moderate quality of evidence)

> *Subgroup considerations:* for patients with HCV genotype 3 infection with cirrhosis and patients with genotypes 5 and 6 infection with and without cirrhosis, an interferon-based regimen: sofosbuvir/pegylated interferon and ribavirin is still recommended as an alternative treatment option.

Removal of recommendation for treatment with telaprevir or boceprevir: the use of boceprevir- or telaprevir-containing regimens is no longer recommended for the treatment of persons with hepatitis C infection.

(Strong recommendation, moderate quality of evidence)

Preferred and alternative regimens for the treatment of persons with chronic hepatitis C virus infection:

Strength of recommendation and quality of evidence:

Genotypes 1 and 4 regimens: strong recommendation, moderate quality of evidence

Genotypes 2 and 3 regimens: strong recommendation, low quality of evidence

Genotypes 5 and 6 regimens: conditional recommendation, very low quality of evidence

Summary of recommended preferred regimens with treatment durations*

Persons without cirrhosis

	Daclatasvir/ sofosbuvir	Ledipasvir/ sofosbuvir	Sofosbuvir/ ribavirin
Genotype 1	12 weeks	12 weeks[a]	
Genotype 2			12 weeks
Genotype 3	12 weeks		24 weeks
Genotype 4	12 weeks	12 weeks	
Genotype 5		12 weeks	
Genotype 6		12 weeks	

Persons with cirrhosis

	Daclatasvir/ sofosbuvir	Daclatasvir/ sofosbuvir/ ribavirin	Ledipasvir/ sofosbuvir	Ledipasvir/ sofosbuvir / ribavirin	Sofosbuvir/ ribavirin
Genotype 1	24 weeks	12 weeks	24 weeks	12 weeks[b]	
Genotype 2					16 weeks
Genotype 3		24 weeks			
Genotype 4	24 weeks	12 weeks	24 weeks	12 weeks[b]	
Genotype 5			24 weeks	12 weeks[b]	
Genotype 6			24 weeks	12 weeks[b]	

* Treatment durations are adapted from the 2015 guidelines of the American Association for the Study of Liver Diseases (AASLD) and European Association for the Study of the Liver (EASL).

[a] Treatment may be shortened to 8 weeks in treatment-naive persons without cirrhosis if their baseline HCV RNA level is below 6 million (6.8 log) IU/mL. The duration of treatment should be shortened with caution.

[b] If platelet count <75 x 10^3/μL, then 24 weeks' treatment with ribavirin should be given.

Summary of recommended alternative regimens with treatment durations*

Persons without cirrhosis

	Simeprevir/ sofosbuvir	Daclatasvir/ sofosbuvir	Ombitasvir/ paritaprevir/ ritonavir/ dasabuvir	Ombitasvir/ paritaprevir/ ritonavir/ ribavirin	Sofosbuvir/ pegylated interferon/ ribavirin
Genotype 1	12 weeks[a]		12 weeks[b]		
Genotype 2		12 weeks			
Genotype 3					
Genotype 4	12 weeks			12 weeks	
Genotype 5					12 weeks
Genotype 6					12 weeks

* Treatment durations are adapted from 2015 AASLD and EASL guidelines.

[a] If genotype 1a-infected patient is positive for the Q80K variant, a simeprevir/sofosbuvir regimen should not be chosen.

[b] For genotype 1a-infected patients, treat with ombitasvir/paritaprevir/ritonavir/dasabuvir and ribavirin; for genotype 1b-infected patients, treat with ombitasvir/paritaprevir/ritonavir/dasabuvir.

Persons with cirrhosis

	Can be prescribed to persons with compensated or decompensated cirrhosis	These regimens should be prescribed only to persons with compensated cirrhosis because they can cause liver failure and death when prescribed to persons with decompensated cirrhosis. Therefore, they should be used only in settings where specialized care is available and where the degree of cirrhosis (compensated vs decompensated) can accurately be assessed.				
	Daclatasvir/ sofosbuvir	**Simeprevir/ sofosbuvir**	**Simeprevir/ sofosbuvir/ ribavirin**	**Ombitasvir/ paritaprevir/ ritonavir/ dasabuvir**	**Ombitasvir/ paritaprevir/ ritonavir/ ribavirin**	**Sofosbuvir/ pegylated interferon/ ribavirin**
Genotype 1		24 weeks[a]	12 weeks[a]	24 weeks[b]		
Genotype 2	12 weeks					
Genotype 3						12 weeks
Genotype 4		24 weeks	12 weeks[a]		24 weeks	
Genotype 5						12 weeks
Genotype 6						12 weeks

* Treatment durations are adapted from 2015 AASLD and EASL guidelines.

[a] If genotype 1a-infected patient is positive for the Q80K variant, a simeprevir/sofosbuvir regimen should not be chosen.

[b] For genotype 1a-infected patients, treat with ombitasvir/paritaprevir/ritonavir/dasabuvir and ribavirin for 24 weeks; for genotype 1b-infected patients, treat with ombitasvir/paritaprevir/ritonavir/dasabuvir and ribavirin for 12 weeks.

Discussion of preferred and alternative regimens

The selection of preferred and alternative regimens remains somewhat complex; however, the recommended regimens in these guidelines are a step in the direction of recommending a single regimen for all genotypes and for all patients, regardless of the degree of cirrhosis and previous treatment experience. Furthermore, the selected preferred regimens provide clinicians with the opportunity of prescribing interferon- and ribavirin-free regimens for everyone (except patients who have genotype 2 infection or both cirrhosis and genotype 3 infection). This simplifies implementation by lessening the requirement for genotype testing (in countries where a single genotype predominates) as well as reducing the risk of treatment discontinuation due to adverse events.

Despite these advances, implementation of these recommendations may not be immediate. In addition to the high prices, these medicines have not yet received regulatory approval in many countries. Clinicians in many countries are not aware of the availability of these medicines. These recommendations provide policy-makers with a framework for initiating the implementation of therapies, with the potential for wide-scale provision of treatment, on account of high efficacy and less need for medical testing and interventions before, during and after treatment.

Existing recommendations (from the 2014 guidelines document)

Screening to identify persons with HCV infection: it is recommended that HCV serology testing be offered to individuals who are part of a population with high HCV prevalence or who have a history of HCV risk exposure/behaviour.

(Strong recommendation, moderate quality of evidence)

When to confirm the diagnosis of chronic HCV infection: it is suggested that nucleic acid testing (NAT) for the detection of HCV ribonucleic acid (RNA) be performed directly following a positive HCV serological test to establish the diagnosis of chronic HCV infection, in addition to NAT for HCV RNA as part of the assessment for starting treatment for HCV infection.

(Conditional recommendation, very low quality of evidence)

Screening for alcohol use and counselling to reduce moderate and high levels of alcohol intake: 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: in resource-limited settings, it is suggested that the aminotransferase/platelet ratio index (APRI) or FIB-4 test be used for the assessment of hepatic fibrosis rather than other noninvasive tests that require more resources such as elastography or FibroTest.

(Conditional recommendation, low quality of evidence)

Assessing for HCV treatment: all adults and children with chronic HCV infection, including people who inject drugs, should be assessed for antiviral treatment.

(Strong recommendation, moderate quality of evidence)

Treatment with pegylated interferon and ribavirin: pegylated interferon in combination with ribavirin is recommended for the treatment of chronic HCV infection rather than standard non-pegylated interferon with ribavirin.

(Strong recommendation, moderate quality of evidence)

1. SCOPE AND OBJECTIVES

The objective of these guidelines is to provide evidence-based recommendations on screening for, and the care and treatment of, persons with chronic hepatitis c virus (HCV) infection. They are primarily intended to provide a framework for the development or strengthening of hepatitis C treatment programmes. This is an update to the guidelines document first issued by the World Health Organization (WHO) in April 2014 *(1)*, which were the first WHO guidelines on hepatitis treatment. The document includes new recommendations for the treatment of HCV infection, as well as recommendations that are unchanged from the 2014 document regarding the diagnosis of persons with HCV infection, clinical management of HCV infection, including alcohol-reduction counselling and assessment of liver fibrosis. The 2014 guidelines included recommendations for treatment with pegylated interferon and ribavirin, boceprevir, simeprevir, sofosbuvir and telaprevir. Since April 2014, several new, oral direct-acting antiviral (DAA) medicines have been approved by at least one stringent regulatory authority. These include asunaprevir, daclatasvir, ledipasvir, and a combination of ombitasvir, paritaprevir and dasabuvir. These medicines, with the exception of asunaprevir, were added to the WHO Model list of essential medicines in 2015 *(2)*. The guidelines are now updated to include new recommendations on the use of these DAAs.

Advances in drug development are revolutionizing HCV treatment. Most importantly, the availability of several DAAs allows their use in combination, which obviates the need for interferon. It is important that persons managing hepatitis treatment programmes and clinicians have guidance on the appropriate use of these medicines. Thus, in addition to recommendations on screening and care, the objective of these guidelines is to provide recommendations on the use of the new medicines, specifically to recommend "preferred" combinations of medicines to be used, depending on the viral genotype and other clinical factors.

WHO guidance on the use of these medicines will help policy-makers decide whether to include them in national formularies. Furthermore, by accelerating the introduction of DAAs in countries, they will complement other WHO mechanisms to promote access to these medicines. These include the prequalification of generic formulations of DAAs and the provision of technical assistance to country health officials.

1.1 Target audience

Although the recommendations from these guidelines apply to all countries, the key audience for these guidelines is policy-makers in ministries of

health working in low- and middle-income countries (LMIC), who formulate country-specific treatment guidelines, and plan infectious disease treatment programmes and services. The recommendations are intended to be used by government officials as the basis for developing national hepatitis policies, plans and treatment guidelines. For countries with existing national plans/programmes, these guidelines can serve as a basis for updating national hepatitis treatment guidelines in order to decide which medicines to include in national formularies and which regimens to use. In addition, persons working in nongovernmental organizations (NGOs) that organize hepatitis C treatment services can use the guidelines to inform the necessary elements of the treatment services. The guidelines are also intended to be helpful for clinicians who treat patients with HCV.

1.2 Scope of the guidelines

Although most of the recommendations deal with treatment issues, recommendations related to screening and care are included to reinforce the importance of the continuum of care that is a key element of the clinical management HCV infection. Each of these topics is complex and includes many dimensions that could not be assessed by the Guidelines Development Group. In the screening section, there is no discussion on the selection of laboratory tests; in the care section, the Group only assessed one intervention (alcohol reduction counselling), and in the area of treatment, there are no recommendations regarding the management of complications of HCV, including cirrhosis and hepatocellular carcinoma (HCC).

1.3 Related guidelines

These guidelines are intended to complement existing guidance on the primary prevention of HCV and other bloodborne viruses transmissions 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 specifically relevant to the management of those infected with HCV can be found in the following documents:

- *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection*. Geneva: WHO; 2016 *(3)*
- *Guidelines for the prevention, care and treatment of persons with hepatitis B infection*. Geneva: WHO; 2015 *(4)*
- *Guidance on prevention of viral hepatitis B and C among people who inject drugs*. Geneva: WHO; 2012 *(5)*

2. BACKGROUND

2.1 Epidemiology

Reliable epidemiological data are essential for planning health programmes and facilitating the scaling up of hepatitis C treatment. It is important to know the number of persons infected with and dying from HCV-related liver disease, the prevalence of HCV-related morbidity, and the distribution of genotypes and fibrosis stages. This is because the selection of DAA treatments can depend upon the genotype, and the presence or absence of cirrhosis, while the urgency with which to initiate treatment depends largely on the degree of liver fibrosis. Unfortunately, estimates of these key epidemiological parameters are limited by the lack of data from some parts of the world.

2.1.1 Burden of HCV infection and mortality

The number of deaths per year due to HCV-related diseases continues to increase. According to estimates from the Global Burden of Disease study, the number of deaths due to hepatitis C was 333 000 in 1990, 499 000 in 2010 and 704 000 in 2013 *(6, 7)*. The increase in number of deaths reflects the high incidence of hepatitis C during the mid-twentieth century, which is thought to have increased dramatically starting in the 1940s due to the expanded use of parenteral procedures and injection drug use *(8)*. The incidence declined in the 1990s following the discovery of the HCV, resulting in the introduction of screening of blood for HCV, improvements in infection control and safer injection practices among PWID. Despite the declining incidence, a large number of persons who were infected 30–60 years ago are now dying from HCV-related cirrhosis and HCC, as these complications often take decades to develop. The increase in the number of deaths is projected to continue for several more decades unless treatment is scaled up considerably *(9)*. Some countries are also experiencing a recent resurgence of HCV infection among young PWID and HIV-infected men who have sex with men (MSM) *(10, 11)*.

More recent analyses of the global prevalence of HCV indicate that there may be fewer persons living with HCV infection than previously estimated. In 2013, a systematic review concluded that there were 185 million persons with a history of HCV infection (presence of anti-HCV antibody) *(12)*. Of those, an estimated 130–150 million may be chronically infected (HCV-RNA positive). A more recent systematic review that excluded older studies estimated that 110 million persons are HCV-antibody positive and 80 million have chronic infection (Table 2.1) *(13)*. This lower estimate may be explained by a declining incidence as well as improved diagnostic serological

tests for HCV, resulting in fewer false-positive results. If correct, this lower burden of disease would mean that the overall number of persons needing HCV treatment would be lower than previously thought; nevertheless, the number of people needing treatment remains high. There are also improved estimations of the prevalence of HCV in Africa. A systematic review of studies from Africa showed a prevalence of HCV of 2.98%, with a higher prevalence observed in studies from west Africa and lower in studies from south-east Africa *(14)*. The variability in estimates may be due in part to the lack of data from many countries, and the selection of populations for testing that are not representative of the general population.

TABLE 2.1 Estimated prevalence of HCV infection by Global Burden of Disease regions *(13)*

Regions	Anti-HCV prevalence (CI)[a]	Viraemic HCV prevalence (CI)[b]	Viraemic rate	2013 population (millions)	Anti-HCV infected (millions)	Viraemic HCV infected (millions)
Asia Pacific, high income	1.1% (0.5–1.7%)	0.8% (0.4–1.2%)	74%	182	2.0 (0.9–3.0)	1.5 (0.6–2.2)
Asia, Central	5.4% (3.5–6.8%)	2.3% (1.5–3.0%)	43%	84	4.5 (2.9–5.7)	1.9 (1.3–2.5)
Asia, East	1.2% (0.4–1.8%)	0.7% (0.3–1.1%)	60%	1434	16.6 (6.3–25.3)	10.0 (3.9–15.1)
Asia, South	1.1% (0.7–1.5%)	0.9% (0.5–1.2%)	81%	1650	18.8 (11.3–24.5)	15.2 (8.9–19.8)
Asia, Southeast	1.0% (0.8–1.8%)	0.7% (0.5–1.1%)	63%	635	6.6 (5.3–11.3)	4.2 (3.4–7.2)
Australasia	1.4% (1.0–1.5%)	1.0% (0.8–1.1%)	75%	28	0.4 (0.3–0.4)	0.3 (0.2–0.3)
Caribbean	0.8% (0.2–1.3%)	0.6% (0.1–0.9%)	70%	39	0.3 (0.1–0.5)	0.2 (0.0–0.4)
Europe, Central	1.3% (1.1–1.6%)	1.0% (0.9–1.2%)	80%	119	1.5 (1.3–1.9)	1.2 (1.1–1.5)
Europe, Eastern	3.3% (1.6–4.5%)	2.3% (1.1–3.0%)	69%	207	6.8 (3.4–9.3)	4.7 (2.4–6.3)
Europe, Western	0.9% (0.7–1.5%)	0.6% (0.5–1.0%)	70%	425	3.7 (3.0–6.3)	2.6 (2.1–4.4)
Latin America, Andean	0.9% (0.4–1.3%)	0.6% (0.3–0.9%)	70%	57	0.5 (0.2–0.7)	0.4 (0.2–0.5)
Latin America, Central	1.0% (0.8–1.4%)	0.8% (0.6–1.1%)	75%	246	2.6 (1.9–3.5)	1.9 (1.4–2.6)
Latin America, Southern	1.2% (0.5%–2.1%)	0.9% (0.4%–1.6%)	79%	62	0.8 (0.3–1.3)	0.6 (0.2–1.0)
Latin America, Tropical	1.2% (0.9–1.2%)	1.0% (0.7–1.0%)	80%	207	2.5 (1.9–2.6)	2.0 (1.5–2.1)
North Africa/ Middle East	3.1% (2.5–3.9%)	2.1% (1.7–2.6%)	66%	469	14.6 (11.9–18.2)	9.7 (7.8–12.1)
North America, high income	1.0% (1.0–1.9%)	0.8% (0.7–1.4%)	76%	355	3.7 (3.4–6.7)	2.8 (2.6–5.0)
Oceania	0.1% (0.1–0.6%)	0.1% (0.1–0.4%)	69%	10	0.0 (0.0–0.1)	0.0 (0.0–0.0)
Sub-Saharan Africa, Central	4.2% (2.4–9.2%)	2.6% (1.5–5.5%)	61%	100	4.3 (2.4–9.2)	2.6 (1.5–5.5)
Sub-Saharan Africa, East	1.0% (0.6–3.1%)	0.6% (0.4–2.0%)	62%	385	3.9 (2.4–12.1)	2.4 (1.6–7.9)
Sub-Saharan Africa, Southern	1.3% (0.8–2.5%)	0.9% (0.6–1.7%)	69%	75	1.0 (0.6–1.9)	0.7 (0.4–1.3)
Sub-Saharan Africa, West	5.3% (2.9–9.1%)	4.1% (2.3–6.7%)	77%	367	19.3 (10.5–33.3)	14.9 (8.5–24.6)
Other	1.9% (1.0–3.4%)	1.3% (0.7–2.4%)	69%	27	0.5 (0.3–0.9)	0.4 (0.2–0.7)
Total	**1.6% (1.3–2.1%)**	**1.1% (0.9–1.4%)**	**70%**	**7162**	**114.9 (91.9–148.7)**	**80.2 (64.4–102.9)**

[a] Presence of antibody indicating exposure to HCV
[b] Presence of RNA indicating chronic HCV infection

Because of shared routes of transmission, certain groups, in particular PWID, have high rates of coinfection with HIV and HCV; however, there are no reliable estimates of the global prevalence of HIV/HCV coinfection. A frequently cited article states that 4 million persons are coinfected; however, this estimate is not based on a systematic review of data. Recent reviews of the literature indicate that the prevalence of coinfection may be lower than previously thought. One analysis indicates that 2.3 million persons may be coinfected globally, while an analysis from Africa estimated that 5.7% of persons with HIV were coinfected with HCV *(14, 15)*. It is worth noting that the prevalence of coinfection is generally lower in settings where the primary route of HIV transmission is not through injection drug use.

Groups at increased risk of infection with HCV are also at risk of infection with tuberculosis (TB) *(16)*, as TB is endemic in many countries where blood products are not screened routinely. TB is also the most common AIDS-defining illness and the leading cause of HIV-associated mortality.

Understanding the proportion of individuals who have advanced fibrosis is important in planning for HCV treatment services. These are the individuals who should be prioritized for HCV treatment, as they are at higher risk of developing decompensated cirrhosis and HCC. Although there are no population-based estimates for this parameter, a reasonable assumption is that between 10% and 30% of persons with chronic HCV infection have stage F3 or F4 fibrosis.

2.1.2 Distribution of genotypes

The HCV is a small, positive-stranded RNA-enveloped virus. It has a highly variable genome, which has been classified into six distinct genotypic groups *(17)*. Existing DAA treatments are significantly more effective on certain genotypes than others; thus, it is important to know a patient's genotype prior to initiating treatment. In view of its expense and complexity, the requirement for genotyping represents a significant barrier to scaling up HCV treatment. The distribution of HCV genotypes and subgenotypes varies substantially in different parts of the world (Fig. 2.1). According to a recent review, genotype 1 is the most common, accounting for 46.2% of all HCV infections, followed by genotype 3 (30.1%). The diversity of genotypes also varies; the highest diversity is observed in China and South-East Asia, while in some countries, such as Egypt and Mongolia, almost all HCV infections are due to a single genotype *(18)*. Genotyping may not be required in countries where the epidemiological profile shows the presence of only a single HCV genotype. In the near future, pan-genotypic DAA regimens could obviate the need for genotyping, which would help facilitate the expansion of HCV treatment.

Certain groups are at higher risk of HCV infection, and estimates of the prevalence of HCV in these groups are shown in Table 2.2. The relative importance of risk factors for HCV infection varies substantially, depending on the geographical region and population studied. Greater access to HCV

testing and better surveillance are important steps to both increase the number of persons diagnosed with HCV and to improve understanding of the distribution of HCV infection in the general population and groups at increased risk.

FIGURE 2.1 Global distribution of genotypes of HCV *(18)*

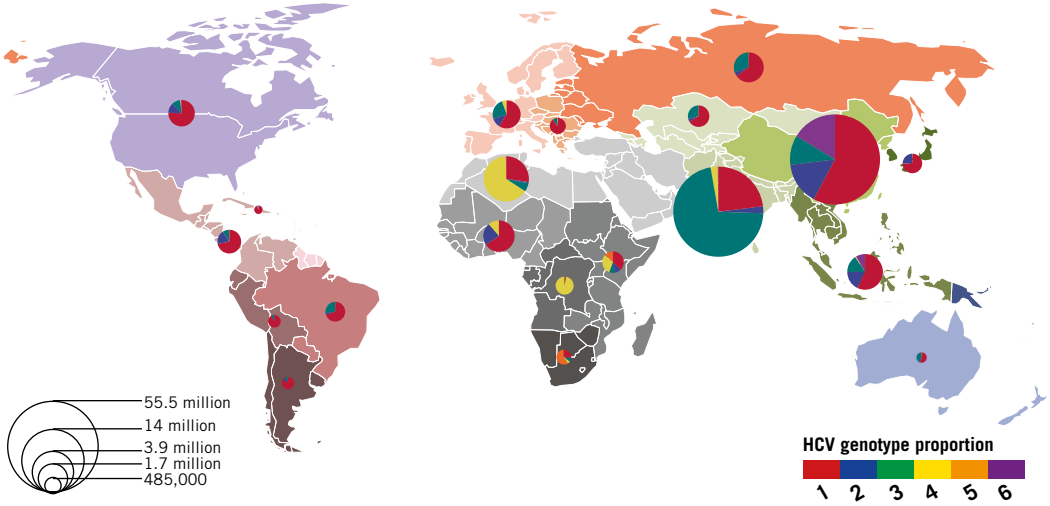


TABLE 2.2 Populations at increased risk of HCV infection

Population	Comment
Persons who inject drugs (PWID) *(19)*	PWID have the highest risk of infection. Globally, the prevalence of anti-HCV antibody is 67% among PWID.
Recipients of infected blood products or invasive procedures in health-care facilities with inadequate infection control practices *(20–30)*	Risk of HCV infection varies depending upon the frequency of medical procedures (i.e. number of injections/person/year) and level of infection control practices. A high frequency of injections and a low level of infection control can result in a high prevalence of HCV in the general population (e.g. prevalence of chronic HCV infection confirmed by nucleic acid testing was 4.0% in Egypt in 2015) *(31).*
Children born to mothers infected with HCV *(30, 32–35)*	HCV transmission risk is estimated as 4–8% among mothers without HIV infection. Transmission risk is estimated as 10.8–25% among mothers with HIV infection.
People with sexual partners who are HCV infected *(36–40)*	There is low or no risk of sexual transmission of HCV among HIV-uninfected heterosexual couples and HIV-uninfected men who have sex with men (MSM). The risk of sexual transmission is strongly linked to pre-existing HIV infection.
People with HIV infection *(40–48)*	Persons with HIV infection, in particular MSM, are at increased risk of HCV infection through unprotected sex.
People who use intranasal drugs *(49)*	Non-injecting drug use (e.g. through sharing of inhalation equipment for cocaine) is associated with a higher risk of HCV infection.
People who have had tattoos or piercings *(50)*	Tattoo recipients have higher prevalence of HCV compared with persons without tattoos (odds ratio = 2.24, 95%CI 2.01, 2.50)

2.1.3 Routes of transmission and prevention

Health-care-associated transmission

HCV infection is strongly associated with health inequity; in LMIC, infection with HCV is most commonly associated with unsafe injection practices and procedures such as renal dialysis and unscreened blood transfusions *(28, 51).* Over 16 billion injections are administered yearly around the world and 40% of these are considered to be unsafe (mainly in sub-Saharan Africa and Asia) *(52).* According to the latest WHO report on blood safety (2011), 39 countries do not routinely screen blood transfusions for bloodborne viruses *(53).* The most well-documented example of health-care-associated transmission is the generalized epidemic of HCV infection resulting from unsafe injection practices in Egypt, where HCV RNA prevalence was 14.6% in some regions in 2015 *(31)*. Persons who received untested blood products prior to the introduction of screening of blood for HCV in high-income countries were also at increased risk of infection. Universal access to safe blood transfusion requires the implementation of key strategies to ensure access to a safe and sufficient blood supply, including the implementation of 100% voluntary blood donation and 100% quality-assured testing of donated blood. WHO has developed guidelines on best practices in phlebotomy, and best practices for injections and related procedures (Table 2.3).

Transmission among people who inject drugs

In middle- and high-income countries, most HCV infections occur among people who use unsterile equipment to inject drugs and contaminated drug solutions. Of the estimated 16 million people in 148 countries who actively inject drugs, 10 million have serological evidence of HCV infection *(19)*. 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 (Tables 2.4 and 2.5) *(19, 54)*.

TABLE 2.3 WHO guidance on prevention of HCV infection in health-care settings

• Hand hygiene: including surgical hand preparation, hand-washing and use of gloves
• Safe handling and disposal of sharps and waste
• Safe cleaning of equipment
• Testing of donated blood
• Improved access to safe blood
• Training of health personnel

Sources: WHO guidelines on hand hygiene in health care. Geneva: World Health Organization; 2009 (http://apps.who.int/iris/bitstream/10665/44102/1/9789241597906_eng.pdf, accessed 10 March 2016).

Safe abortion: technical and policy guidance for health systems, second edition. Geneva: World Health Organization; 2012. (http://apps.who.int/iris/bitstream/10665/70914/1/9789241548434_eng.pdf, accessed 10 March 2016).

Universal access to safe blood transfusion. Geneva: World Health Organization; 2008 (http://www. who.int/bloodsafety/publications/UniversalAccesstoSafeBT.pdf, accessed 10 March 2016).

Blood donor selection: guidelines on assessing donor suitability for blood donation. Geneva: World Health Organization; 2012 (http://apps.who.int/iris/bitstream/10665/76724/1/9789241548519_eng.pdf, accessed 10 March 2016).

WHO guidelines on drawing blood: best practices in phlebotomy. Geneva: World Health Organization; 2010 (http://www.who.int/injection_safety/sign/drawing_blood_best/en/index.html, accessed 10 March 2016).

TABLE 2.4 WHO/UNODC/UNAIDS comprehensive package of interventions for HIV prevention, treatment and care in PWID

1.	Provision of sterile injection equipment including needles and syringes, and other drug-use paraphernalia
2.	Opioid substitution therapy and other drug-dependence treatment
3.	HIV testing and counselling
4.	Antiretroviral therapy
5.	Prevention and treatment of sexually transmitted infections
6.	Condom programmes for people who inject drugs and their sexual partners
7.	Targeted information, education and communication for people who inject drugs and their sexual partners
8.	Vaccination, diagnosis and treatment of viral hepatitis
9.	Prevention, diagnosis and treatment of tuberculosis.

UNAIDS: Joint United Nations Programme on HIV/AIDS; UNODC: United Nations Office on Drugs and Crime

Source: WHO, UNODC, UNAIDS. *Technical guide for countries to set targets for universal access to HIV prevention, treatment and care for injecting drug users. 2012 revision*. Geneva: World Health Organization; 2012 (http://www.drugsandalcohol.ie/19190/1/IDU-Technical_Guide_2012_ Revision.pdf accessed 30 January 2014).

TABLE 2.5 WHO recommendations for prevention of HCV infection among people who inject drugs*

• Offer people who inject drugs the rapid hepatitis B vaccination regimen.
• Offer people who inject drugs incentives to increase uptake and complete the hepatitis B vaccination schedule.
• Implement sterile needle and syringe programmes that also provide low dead-space syringes for distribution to people who inject drugs.
• Offer peer interventions to people who inject drugs to reduce the incidence of viral hepatitis.
• Offer opioid substitution therapy to treat opioid dependence, reduce HCV risk behaviour and transmission through injecting drug use, and increase adherence to HCV treatment.
• Integrate the treatment of opioid dependence with medical services for hepatitis.

* in addition to the interventions described in Table 2.4

Sources: Guidance on prevention of viral hepatitis B and C among people who inject drugs. Geneva: World Health Organization; 2012 (http://apps.who.int/iris/bitstream/10665/75357/1/9789241504041_ eng.pdf, accessed 10 March 2016).

WHO guidelines for the psychosocially assisted pharmacological treatment of opioid dependence. Geneva: World Health Organization; 2009 (http://www.who.int/substance_abuse/publications/ opioid_dependence_guidelines.pdf, accessed 10 March 2016).

TABLE 2.6 WHO guidance on prevention of sexual transmission of HCV infection

• Promotion of correct and consistent condom use
• Routine testing of sex workers in high-prevalence settings
• Integrated action to eliminate discrimination and gender violence, and increased access to medical and social services for vulnerable persons

Sources: Prevention and treatment of HIV and other sexually transmitted infections for sex workers in low- and middle-income countries: recommendations for a public health approach. Geneva: World Health Organization; 2012 (http://apps.who.int/iris/bitstream/10665/77745/1/9789241504744_eng.pdf, accessed 11 March 2016).

Prevention and treatment of HIV and other sexually transmitted infections among men who have sex with men and transgender people. Geneva: World Health Organization, Department of HIV/AIDS; 2011 (http://www.who.int/hiv/pub/guidelines/msm_guidelines2011/en/, accessed 11 March 2016).

Mother-to-child transmission

The risk of transmission of HCV from a mother to her child occurs in 4–8% of births to women with HCV infection, and in 10.8–25% of births to women with HIV and HCV coinfection (Table 2.2) *(30, 32–35).* There are no proven interventions to reduce this risk of transmission.

Sexual transmission

Sexual transmission of HCV occurs infrequently in heterosexual couples *(55).* It is more common in HIV-positive persons, particularly in MSM *(56).* In several recent outbreaks of HCV infection among MSM in Europe, Australia and the United States, transmission has been linked to sexual exposure as well as potentially to underreported use of non-injecting recreational drugs *(57, 58).* HIV-infected heterosexual partners of HCV-infected people are also more likely to acquire HCV; this may be due to sexual transmission or other exposure to blood or due to unreported injection or non-injection drug use, such as sharing of straws for inhaling cocaine *(57).* Table 2.6 provides guidance on preventing the sexual transmission of HCV infection.

Other

Other routes of transmission of HCV include intranasal drug use and other modes of bloodborne transmission, such as acquisition by health-care workers, cosmetic procedures (such as tattooing and body piercing), scarification and circumcision procedures *(50, 59).*

2.1.4 Coinfections

HIV and HCV coinfection

HIV and HCV have common routes of transmission, and it is estimated that, globally, 2.3 million persons are coinfected with these two viruses *(15).* With the widespread use of antiretroviral therapy (ART), which reduces the risk of HIV-associated opportunistic infections, HCV-related liver disease has started to overtake AIDS-defining illnesses as a leading cause of death in some high-income countries *(60).* HIV and HCV coinfection is discussed further in section 9.2.

HBV and HCV coinfection

Hepatitis B virus (HBV) and HCV coinfection is commonly found in HBV-endemic countries in Asia, sub-Saharan Africa and South America. Up to 25% of HCV-infected persons may be coinfected with HBV in some areas *(61–66).* HBV and HCV coinfection is discussed further in section 9.6.

Tuberculosis and HCV coinfection

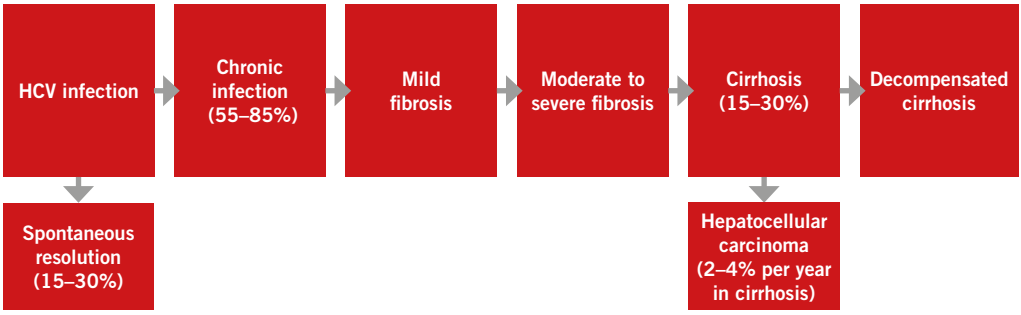
Groups at increased risk of infection with HCV are also at risk of infection with TB. TB is endemic in many countries where blood products are not screened

routinely. TB is the most common AIDS-defining illness and the leading cause of HIV-associated mortality. PWID are more at risk of developing TB, regardless of their HIV status. Among PWID who develop TB, two out of three will have anti-HCV antibodies. People who live with HIV and inject drugs have a two- to sixfold increased risk of developing TB compared with non-injectors. Prisoners, who have a high risk of acquiring HCV, are also at increased risk of coinfection with TB; incarceration is associated with a 23 times higher risk of TB than in the general population *(67, 68).* Appropriate care for persons being considered for HCV treatment would include screening for active TB, as the co-management of such persons needs sound clinical judgement and the provision of treatment that takes into consideration the side-effects and interactions of the drugs used to treat HIV, TB and viral hepatitis. TB and HCV coinfection is discussed further in section 9.7.

2.1.5 Natural history of HCV infection

HCV causes both acute and chronic hepatitis. Chronic infection with HCV is usually clinically silent, and is only very rarely associated with life-threatening disease. Spontaneous clearance of acute HCV infection occurs within six months of infection in 15–45% of infected individuals in the absence of treatment. Almost all the remaining 55–85% of persons will harbour HCV for the rest of their lives (if not treated) and are considered to have chronic HCV infection. Anti-HCV antibodies develop as part of acute infection and persist throughout life. In persons who have anti-HCV antibodies, a nucleic acid test (NAT) for HCV RNA, which detects the presence of the virus, is needed to confirm the diagnosis of chronic HCV infection *(69, 70).*

FIGURE 2.2 Natural history of HCV infection



Left untreated, chronic HCV infection can cause liver cirrhosis, liver failure and HCC (Fig. 2.2). Of those with chronic HCV infection, the risk of cirrhosis of the liver is 15–30% within 20 years *(71–73).* The risk of HCC in persons with cirrhosis is approximately 2–4% per year *(74).*

Patients with cirrhosis can be classified as either having compensated or decompensated cirrhosis *(75).* The Child–Turcotte–Pugh Classification System *(76)* is a scoring system for liver disease severity. Based on clinical and laboratory criteria, patients are classified as Class A, B, or C. Those with class C have the most severe liver disease (Table 2.7). Treatment with some HCV medicines is contraindicated among persons with Child–Pugh Class B and C.

The risk of cirrhosis and HCC varies, depending upon certain patient characteristics or behaviours. For example, men, persons who consume excess alcohol, persons with hepatitis B or HIV coinfection and immunosuppressed individuals are all at higher risk of developing cirrhosis or HCC *(77).* Disease associated with HCV infection is not confined to the liver. Extrahepatic manifestations of HCV include cryoglobulinaemia, glomerulonephritis, thyroiditis and Sjögren's syndrome, insulin resistance, type 2 diabetes, and skin disorders such as porphyria cutanea tarda and lichen planus. Persons with chronic HCV infection are more likely to develop cognitive dysfunction, fatigue and depression *(78).* These outcomes may be associated with replication of the virus in the brain; however, the causal link between these manifestations and chronic HCV infection is not certain *(79).*

TABLE 2.7 Child–Turcotte–Pugh score (Child–Pugh score)

Points	1	2	3
Encephalopathy	None	Minimal (grade 1 or 2)	Advanced (grade 3 or 4)
Ascites	Absent	Controlled	Refractory
Total bilirubin (μmol/L) (mg/dL)	<34 (<2)	34–51 (2–3)	>51 (>3)
Albumin (g/dL)	>3.5	2.8–3.5	<2.8
Prothrombin time (seconds) or PT-INR	<4 or <1.7	4–6 or 1.7–2.3	>6 or >2.3

PT-INR; prothrombin time international normalized ratio
Child–Pugh Class A: 5–6 points
Child–Pugh Class B: 7–9 points
Child–Pugh Class C: 10–15 points

2.1.6 Natural history of HIV/HCV coinfection

Coinfection with HIV adversely affects the course of HCV infection, and coinfected persons, particularly those with advanced immunodeficiency (CD4 count <200 cells/mm^3), have significantly accelerated progression of liver disease to cirrhosis, decompensated liver cirrhosis and HCC than HCV-monoinfected persons *(80–83).* In high-income countries, HCV-associated liver disease has become a leading cause of death in people living with HIV in the era of combination ART *(60, 84, 85)*, accounting for around 47% of deaths in one series from the United States.

It remains unclear whether HCV infection accelerates HIV disease progression, as determined by AIDS-related events or death *(86).* Two large European cohorts have shown that after ART initiation, CD4 recovery was impaired in HIV/HCV-coinfected persons when compared to those infected with HIV alone. HIV/HCV-coinfected persons also demonstrated more rapid HIV disease progression compared to those who were HIV-infected alone, and had impaired recovery of CD4 cells. However, other studies have shown no such differences in response *(86–90).* 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 linked to HCV infection *(91, 92).* In persons with HIV infection, HCC tends to occur at a younger age and within a shorter time period *(93).*

2.2 Screening for HCV infection

Screening for HCV infection is done using HCV serological testing. If positive, a NAT for HCV RNA is needed to confirm chronic HCV infection. Several screening assays have been evaluated by WHO, and sensitivity, specificity, and positive and negative predictive values are available. It is important to consider the possibility of infection with other bloodborne viruses in persons infected with HCV, and to offer screening for HBV and HIV in addition to HCV. Screening for other infections, for example TB, is also indicated in some groups at risk, such as people living with HIV, prisoners and PWID. WHO guidance on testing for hepatitis B and hepatitis C will be released in 2016.

2.3 Care of patients with HCV infection

The spectrum of disease in persons infected with HCV extends from mild fibrosis to cirrhosis and HCC. Compensated cirrhosis may progress over time to decompensated cirrhosis associated with ascites, oesophageal and gastric varices, and eventually to liver failure, renal failure and sepsis, all of which are life-threatening. HCC may also occur at a rate of 2–4% per year in persons with cirrhosis *(74)*. The diagnosis of decompensated liver disease is based on both clinical examination and laboratory monitoring, and therefore a careful medical examination of patients must be made prior to commencing therapy. The stage of disease may be assessed by liver biopsy or by using a variety of non-invasive methods. These are discussed further in section 6.2.

Staging of HCV infection is important as it identifies patients with advanced disease, a group that requires enhanced monitoring and prioritization for treatment before the onset of decompensated cirrhosis. In many high-income countries, all persons with chronic HCV infection who do not have a contraindication for therapy are considered to be suitable for treatment (although many are not able to access treatment because of eligibility restrictions placed by third-party payers to reduce costs). In LMIC, where access to treatment is limited, the stage of fibrosis may be used to prioritize treatment for patients with more advanced disease (e.g. patients with cirrhosis or those with ≥F2 fibrosis).

Persons infected with HCV often have other comorbidities such as HBV, HIV, TB and substance use. Related WHO guidance is available for PWID and for those infected with HIV (*see* section 1.3). Excessive alcohol use is common in some populations infected with HCV and can accelerate disease progression. WHO guidance on alcohol reduction is discussed in detail in section 6.1.

2.4 Treatment of HCV infection

In the decades following the discovery of the HCV in 1989, treatment of persons with HCV infection became possible. The first treatment for HCV was based on interferon-alpha, which is a cytokine released by host cells in the presence of a pathogen. When administered by subcutaneous injection, it inhibited the replication of HCV and modulated the immune response against liver cells infected with HCV *(94)*.

The addition of ribavirin, which is a nucleoside inhibitor with an unclear mechanism of action against HCV, increased cure rates. The addition of polyethylene glycol to the interferon, through a process known as pegylation, extends the half-life of interferon. However, pegylated interferon/ribavirin regimens were poorly tolerated, associated with severe adverse effects and resulted in cure rates of between 40% and 65%, depending on the patient's genotype, presence of cirrhosis, HIV status and previous treatment experience. A dramatic improvement in HCV therapy followed the introduction of oral medicines that directly inhibited the replication cycle of HCV. These medicines, called direct-acting antivirals (DAAs), target three important regions within the HCV genome: NS3/4A protease, NS5A and NS5B RNA-dependent polymerase. These medicines have led to higher sustained virological responses (SVRs) than interferon-based regimens, are shorter in treatment duration, are orally administered and have fewer side-effects. Individual DAAs vary in therapeutic efficacy, genotypic efficacy, adverse events and drug–drug interactions (DDIs), and must be used in combination with at least one other DAA *(95)*.

The first-generation DAAs that were marketed were the protease inhibitors boceprevir and telaprevir, which were co-administered with interferon and ribavirin. However, they were only effective in treating patients with genotype 1 infection; moreover, they caused frequent and sometime severe side-effects, particularly among persons with more advanced disease *(94)*. Second-generation DAAs have higher rates of SVR, are safer and can be used in combinations that obviate the need for interferon and ribavirin. Thus, these are referred to as "interferon-free" treatment regimens. The combination of two or three subclasses of these DAAs have demonstrated excellent efficacy in general, although cure rates among certain patient subgroups are lower *(95)*.

As of October 2015, eight separate DAAs (*see* Table 2.8) have been approved for the treatment of persons with HCV infection.

TABLE 2.8 Classes of DAAs licenced for the treatment of HCV (as of October 2015)

Protease (NS3/4A) inhibitors	NS5A inhibitors	Polymerase (NS5B) inhibitor, nucleos(t)ide analogue	Polymerase (NS5B) inhibitor, non-nucleoside analogue
Asunaprevir	Daclatasvir	Sofosbuvir	Dasabuvir
Paritaprevir	Ledipasvir		
Simeprevir	Ombitasvir		

Asunaprevir

Asunaprevir is a protease inhibitor and is used in conjunction with daclatasvir mainly in patients with genotype 1b infection.

Daclatasvir

Daclatasvir is an NS5A inhibitor that has been evaluated as a daily regimen in combination with sofosbuvir with or without weight-adjusted dosing of ribavirin in patients infected with genotypes 1–4. Daclatasvir has demonstrated safety and efficacy when combined with sofosbuvir, including in patients with

decompensated liver disease, post-liver transplantation and HIV/HCV coinfection *(96)*, and can be used without dose adjustments in people with renal insufficiency *(97)*. While daclatasvir has very few DDIs and can be safely administered with opioid substitution therapy (OST), some dose adjustments are needed when it is prescribed to persons on ART for HIV.

Ledipasvir

Ledipasvir is an NS5A inhibitor that is administered with sofosbuvir. It has demonstrated good efficacy when used in patients infected with genotypes 1, 4, 5 and 6, and in the setting of decompensated liver disease. It has few DDIs but an important consideration is that ledipasvir requires low gastric pH for absorption and therefore should be carefully administered with acid suppression therapies, which may reduce absorption. Certain HIV antiretroviral (ARV) regimens should be used with caution, in particular, regimens containing tenofovir in combination with certain other ARVs.

Paritaprevir (ritonavir boosted), ombitasvir and dasabuvir

Paritaprevir, a protease inhibitor boosted with ritonavir, and ombitasvir, an NS5A inhibitor, are effective for the treatment of persons infected with genotype 4 HCV *(98)*. In patients infected with genotype 1, ombitasvir administered with the NS5B inhibitor dasabuvir is required *(99)*. Important considerations include monitoring for increases in liver enzymes (termed alanine aminotransferase [ALT] flares) in the first few weeks of treatment, the addition of ribavirin for those infected with genotype 1a subtype, differing treatment durations according to subtype and presence of cirrhosis, and relatively high pill burden with twice-daily dosing. Numerous DDIs need to be considered prior to treatment commencement. As ritonavir is also used to treat HIV infection, it is important that patients with HIV infection be identified and combination ART initiated to achieve HIV suppression before starting this regimen. Otherwise, HIV resistance to ritonavir may develop. No dose adjustments are required in patients with renal impairment. In October 2015, the United States Food and Drug Administration (FDA) issued a drug safety warning that treatment with ombitasvir/paritaprevir/ritonavir is contraindicated in patients with underlying advanced liver disease (i.e. Child–Pugh Class B and C cirrhosis) because it can cause serious liver injury *(100)*.

Simeprevir

Simeprevir is a second-generation protease inhibitor that is effective in patients with genotypes 1 and 4 infection, except those with genotype 1a-associated Q80K polymorphisms *(101)*. Simeprevir can be used with OST (methadone and buprenorphine) but has some important DDIs including with HIV medications, and is not recommended in patients with moderate or severe hepatic impairment (Child–Pugh Class B and C) because of substantial increases in simeprevir levels in these patients.

Sofosbuvir

Sofosbuvir is an HCV-specific nucleotide analogue inhibitor of NS5B and has

demonstrated pan-genotypic antiviral activity with a high barrier to resistance *(102)*. It has been shown to be effective for infections with genotypes 1–6 in numerous settings in combination with other antivirals. Its use is limited to patients with an estimated glomerular filtration rate (eGFR) >30 mL/min/1.73 m^2 as safety has not been established in severe renal impairment or during haemodialysis. It has few DDIs and does not interact with OST or with many of the HIV medications, including ritonavir-boosted protease inhibitors.

DAAs approved, or that are likely to be approved, in 2016

Grazoprevir and elbasvir

Grazoprevir (MK-5172) is a protease inhibitor and elbasvir (MK-8742) is an NS5A inhibitor that was approved by FDA in January 2016. The regimen is effective against genotypes 1, 4 and 6. At the time of the Guidelines Development Group meeting, initial available data suggested that this combination demonstrates efficacy in a variety of situations, including in those with HIV coinfection, and stages 4 and 5 chronic kidney disease (including patients undergoing dialysis). Recent data suggest that some populations may not benefit from the combination of grazoprevir and elbasvir. The presence of baseline NS5A resistance, which occurs in about 12% of patients, led to a marked decrease in SVR compared to those without baseline resistance in genotype 1a-infected patients (69% vs 96%, respectively) *(103)*. This combination has not been considered in these guidelines as it had not received stringent regulatory approval at the time of the Guidelines Development Group meeting.

GS-5816 (velpatasvir) and GS-9857

GS-5816 (velpatasvir) is an NS5A inhibitor and GS-9857 is a protease inhibitor. Clinical study data with velpatasvir and sofosbuvir ± GS-9857 are currently ongoing, with preliminary data suggesting that they will provide good efficacy and safety. Phase 3 data suggest a strong potential for a pan-genotype regimen when using co-formulated fixed-dose sofosbuvir and velpatasvir *(104–106)*. This combination has not been considered in these guidelines as it had not received stringent regulatory approval at the time of the Guidelines Development Group meeting.

2.5 Access to and price of direct-acting antivirals

The introduction of DAA therapy has resulted in an increase in the number of persons treated; however, almost of all of this increase has occurred in high-income countries. The sales of the most widely used DAA, sofosbuvir, have increased from US$ 140 million in the fourth quarter of 2014 to US$ 1.3 billion in the second quarter of 2015. Ninety-six per cent of all sales (from launch up until the end of the second quarter of 2015) occurred in the United States and Europe *(107)*.

When DAA therapy was introduced in the United States in 2013, the wholesale acquisition drug price to treat one person was US$ 84 000. Prices in the United States have since come down as a result of negotiated discounts, but still exceed

US$ 50 000 per patient. The high prices have led third-party payers to implement strict treatment eligibility criteria.

A number of countries have obtained access to DAA therapy at much lower prices due to direct negotiations with the manufacturers and by the introduction of generic medicines. An encouraging development is the licensing agreements signed between originator and generic manufacturers, which have resulted in much lower prices. For example, generic formulations of sofosbuvir are coming to the market at a price below US$ 900/patient for 12 weeks of treatment, with anecdotal reports of even lower prices (e.g. US$ 500/patient for 12 weeks) in India *(108)*. The availability of generic medicines from different manufacturers would permit different DAAs to be combined. However, this is made difficult because some of the manufacturers have not yet negotiated licensing agreements.

A different dynamic presents itself in upper–middle-income countries. As these countries are viewed as having market potential, they are mostly excluded from the license agreements and have to explore other options to procure these treatments at affordable prices. The approach to date has been based on tiered pricing, whereby government representatives negotiate a sales price directly with the manufacturers. An example is Brazil, where the price for 12 weeks of sofosbuvir is approximately US$ 6900 *(109)*. Although tiered pricing results in lower prices as compared with high-income countries, the negotiated prices are higher than those seen where generics are available *(110)* and may be unaffordable in view of the high disease burden in some of these countries. Other options include compulsory licensing as well as the use of other flexibilities available under the World Trade Organization Agreement on Trade-Related Aspects of Intellectual Property Rights *(111)*.

In addition to the high prices of the medicines, several other barriers limit the expansion of HCV therapy in many countries. These are summarized in Table 2.9.

TABLE 2.9 Health systems barriers to HCV treatment access

A number of technical, logistical and financial challenges must be overcome for the expansion of HCV treatment services.
HCV testing: most persons with HCV infection remain undiagnosed and few have access to HCV testing. Increased investments in HCV testing services are needed. National testing policies are also needed to target approaches based on the best assessment of the prevalence of HCV infection so that testing services reach high-prevalence groups in the general population and in key populations.
Laboratory capacity: the current diagnosis and clinical management of HCV infection requires sophisticated laboratory capacity to diagnose the presence of chronic infection, the viral genotype, and assess the degree of liver fibrosis. In many low-income countries, there are few laboratories that can perform these tests. DAA therapy provides an opportunity to simplify the laboratory requirements, as combinations of these medicines will, in the future, be effective against all genotypes, thus obviating the need for genotyping. DAAs are also much safer, thus reducing the complexity of monitoring for adverse events.
Health systems: currently, HCV therapy is provided in specialized centres by hepatologists or other subspecialists. For HCV therapy to be expanded, it will need to be administered by general practitioners and other health-care workers in primary-care clinics. To do this, clinics will need to be equipped suitably, and many more health-care workers will need training in the clinical management of HCV infection.

3. GUIDING PRINCIPLES

The overarching objective of WHO is to achieve the highest possible level of health for all people. These guidelines have been developed with this principle in mind and that of the United Nations Universal Declaration of Human Rights *(112).* People infected with HCV are commonly subject to discrimination and stigma, and it is thus essential that these guidelines and policies derived from them incorporate basic human rights, including the right to confidentiality and informed decision-making when considering whether to be screened and treated for HCV infection.

3.1 Human rights

The protection of human rights for all persons infected with HCV is a central precept of these guidelines. People with HCV infection frequently come from vulnerable groups because of low socioeconomic status, poor access to appropriate health care, or because they belong to groups that are marginalized or stigmatized such as PWID or prisoners. Thus, screening for HCV must not be used as a means to discriminate against those testing positive, for example, by denying them employment or education. The promotion of human rights and equity in access to testing and treatment are guiding principles central to these guidelines.

3.2 Access to health care

Target 3.8 of the Sustainable Development Goals is to *achieve universal health coverage, including financial risk protection, access to quality essential health-care services and access to safe, effective, quality and affordable essential medicines and vaccines for all (113) .* Access to health care is a basic human right and applies equally to men, women and children, regardless of gender, race, sexual preference, socioeconomic status or behavioural practices, including drug use. Policy-makers should ensure that antidiscrimination laws protect vulnerable groups and confidentiality principles, as outlined in the Declaration of Geneva, 2006 *(114).*

3.3 Service provision

Providing quality screening, care and treatment for persons with HCV infection requires involvement of appropriately trained individuals as well as facilities suitable for the regular monitoring of patients, especially those on therapy. Facility requirements for providing treatment for HCV infection will depend on the setting, but will always require access to appropriate laboratory facilities for monitoring the toxicity and efficacy of treatment, and adequate supplies

of medication (including refrigeration facilities for pegylated interferon). Operating testing services under quality management systems is essential for the provision of quality testing results. The protection of confidentiality and a non-coercive approach are fundamental principles of good clinical practice. Acceptability of services is a vital component of health care, and service delivery should ideally involve patient-representative organizations and peer-support groups.

3.4 Integrated health care

Persons infected with HCV often require additional health care. Rates of depression in HCV-infected populations are high, opioid dependency is common in PWID, and persons coinfected with HIV require additional treatment. Prisoners or people with a history of incarceration such as PWID have high rates of HCV infection and may be at risk of infection with TB in many settings, in particular, multidrug-resistant TB. Screening for comorbidity is therefore an important consideration in patients who will be screened and potentially treated for HCV infection. Integration of health-care services requires adaptation to the services available in individual countries. Consultation with and involvement of community organizations (including drug-user organizations) is central to the principle of integrated health care.

3.5 Public health approach

In accordance with WHO guidance on HIV since 2002 *(115),* these guidelines are based on a public health approach to scaling up the use of antiviral treatment for HCV infection. The public health approach seeks to ensure the widest possible access to high-quality services at the population level, based on simplified and standardized approaches, and to strike a balance between implementing the best-proven standard of care and what is feasible on a large scale in resource-limited settings.

4. METHODS

4.1 Updating the existing guidelines

WHO issued the first *Guidelines for the screening, care and treatment of persons with hepatitis C infection* in 2014 *(1).* Since then, several new medicines, called direct-acting antivirals (DAAs), have been introduced for the treatment of HCV infection. Of these, daclatasvir, ledipasvir, and a combination of ombitasvir, paritaprevir and dasabuvir were added to the WHO Model List of Essential Medicines in 2015 *(2).* Following this, WHO has undertaken a new guideline development process in order to provide updated evidence-based recommendations for the treatment of persons with HCV infection using, where possible, all-oral combinations of DAAs. These new recommendations put forward preferred regimens based on a patient's HCV genotype and clinical history, and assess the appropriateness of continued use of the existing medicines. In addition to these new recommendations, this current guideline also brings forward recommendations on screening and care from the 2014 guidelines, and those treatment recommendations from the 2014 guideline that remain applicable. This section provides details specifically for the development of the new 2016 recommendations. Information pertaining to the development of the prior (2014) recommendations can be found in the 2014 guideline *(1).*

4.2 WHO guideline development process

These WHO guidelines were produced following the recommendations for standard guidelines, as described in the WHO *Handbook for guidelines development (116)*. The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework was followed for this process *(117)*. 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 persons living with HCV infection, advocacy groups, researchers and clinicians. Group membership also sought to achieve geographical representation and gender balance. A guidelines development proposal was submitted to the WHO Guidelines Review Committee and approved in April 2015. The Steering Committee proposed potential topics for developing recommendations and formulated these in the PICO format (PICO: Population, Intervention, Comparison, Outcomes). Patient-important outcomes were also identified for each PICO question. These were discussed and agreed upon by the Guidelines Development Group during several web-enabled conference calls (web Appendix 1, 2016). Outcomes were ranked by the Group members based

on their importance to the patient population. Members of the Guidelines Development Group held a meeting in June 2015.

Systematic reviews and meta-analyses were undertaken to assess the comparative safety and efficacy of treatment regimens. The quality of the evidence was assessed and either rated down or up based on the following criteria: *rated down* based on (i) risk of bias (using the Cochrane Risk of Bias assessment tool); (ii) inconsistency or heterogeneity; (iii) indirectness (addressing a different population than the one under consideration or estimates based on only indirect comparisons); or (iv) imprecision. Conversely, the quality of the evidence was *rated up* if the effect size was large, defined as at least a 10% difference in SVR rate between regimens. We did not rate down for publication bias because unpublished data were obtained directly from the manufacturers of antiviral drugs. Based on the rating of the available evidence, the quality of evidence was categorized as high, moderate, low or very low (Table 4.1).

TABLE 4.1 GRADE categories of quality of evidence *(118)*

• High: We are very confident that the true effect lies close to that of the estimate of the effect.
• Moderate: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
• Low: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
• Very low: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of the effect.

4.3 Formulation of recommendations

At the June 2015 meeting of the Guidelines Development Group, for each of the PICO questions, the results of the systematic reviews and network meta-analyses were presented, and the evidence profiles and decision-making tables were reviewed to ensure that there was understanding of and agreement on the scoring criteria. Recommendations were then formulated based on the overall quality of the evidence, in addition to the balance between benefits and harms, values and preferences, and resource implications. Members of the Guidelines Development Group assessed these through discussions. The strength of recommendations was rated as either strong (the panel was confident that the benefits of the intervention outweighed the risks) or conditional (the panel considered that the benefits of the intervention probably outweighed the risks). The principal factors that determine the direction and strength of a recommendation are the confidence in the estimates of effect of the evaluated evidence, values and preferences related to the outcomes of the intervention, the balance of benefits and harms, and resource implications. Recommendations were then formulated and the wording finalized by the entire group. After all of the comments and questions from members of the Guidelines Development Group were addressed, to document consensus, the Chair asked Group members whether they agreed with the recommendation. If

there was no disagreement then the recommendation was considered final. All Group members agreed with all the recommendations. Implementation needs were subsequently evaluated, and areas and topics requiring further research identified. At the meetings, declarations of interest were reported according to WHO standard requirements (web Appendix 6, 2016).

After the Guidelines Development Group meeting in June 2015, new evidence became available which affected the recommendations. This included new data related to the treatment of persons with genotypes 2 and 3 infection, which were presented at the annual meeting of the American Association for the Study of Liver Diseases (AASLD) in November 2015 and a Drug Warning issued by FDA in October 2015 about the use of ombitasvir/paritaprevir/dasabuvir among persons with cirrhosis. These data were incorporated into an updated meta-analysis, and reviewed during two web-enabled meetings that were held in November and December 2015. During these meetings, an additional alternative regimen was proposed for genotype 2 infection and a change was proposed in the recommended regimen for genotype 3 infection. Members of the Guidelines Development Group were asked to submit an email indicating their agreement with the wording of the two new recommendations to confirm consensus. All Group members agreed with the recommendations. The results of those discussions are summarized in the decision-making tables (web Appendix 5, 2016).

A draft of the guidelines document was prepared and circulated to members of the Guidelines Development Group and WHO Steering Committee. Suggested changes were incorporated into a second draft. If the comments were not clear, reviewers were contacted and asked to provide clarification. The second draft was circulated to the external peer reviewers and the draft document revised to address their comments. Suggested changes made by peer reviewers to the wording of the recommendations or suggested modifications to the scope of the document were not considered.

4.4 Roles

The Guidelines Development Group – formulated the PICO questions, reviewed the evidence profiles and decision-making tables, formulated and agreed upon the wording of the recommendations, and reviewed drafts of the guidelines document.

The peer reviewers – reviewed the draft guidelines document, and provided comments and suggested editorial changes.

The guideline methodologist – ensured that the GRADE framework was appropriately applied throughout the guidelines development process. This included the 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.

4.5 Declarations of interest

In accordance with WHO policy, all potential members of the Guidelines Development Group were required to complete and submit a WHO Declaration of Interest form and brief biography. The biographies were posted for comment on the WHO website. The Steering Committee reviewed and assessed the declarations submitted by each member and agreed on an approach to assess potential conflicts of interest. This approach was discussed with a staff member of the WHO Compliance and Risk Management and Ethics Department. Individuals from civil society organizations whose organizations received most of their funding from private (primarily pharmaceutical) companies and individuals who had received honoraria that exceeded US$ 5000/year from pharmaceutical companies (the WHO threshold for categorizing financial interests as "significant") were classified as having conflicts of interest. Their participation in the Guidelines Development Group was classified as "restricted". This meant that these Group members contributed to the development of PICO questions and provided technical expertise in reviewing the evidence summaries but did not participate in the formulation of recommendations. Group members whose participation was "restricted" were Charles Gore, Francesco Negro and Jürgen Rockstroh (web Appendix 6, 2016).

4.6 Evidence that informed the recommendations

Systematic reviews and meta-analyses were undertaken to address the research questions and patient-important outcomes. Criteria for inclusion and exclusion of literature (e.g. study design, sample size, duration of follow up) for the reviews were based on the evidence needed and available to answer the research questions. Existing national and international guidelines were also evaluated and, where necessary, comprehensive reviews and technical reports obtained. For the 2014 guidelines, systematic reviews were externally commissioned through the Burnet Institute, Australia and Glasgow Caledonian University/ Health Protection Scotland. For the new 2016 recommendations, systematic reviews were commissioned through Global Evaluative Sciences, Vancouver, Canada. Reviews were conducted to identify clinical trials that evaluated the medicines of interest. The manufacturers of the DAAs of interest (AbbVie, BMS, Gilead and Janssen) were contacted and asked to provide any additional data from clinical trials. Search strategies and summaries of evidence are available in web Appendix 2, 2016.

To complement the evidence from clinical trials, principal investigators of observational cohort studies that followed individuals receiving DAA treatment were asked to contribute their most recent data on rates of SVR, serious adverse events (SAEs), and treatment discontinuation due to adverse events. Published and unpublished data from the HCV-TARGET *(119)*, HEPAVIH *(120, 121)* and HEPATHER *(122)* studies were reviewed (web Appendix 7, 2016).

4.6.1 Network meta-analysis

A particular challenge in evaluating clinical trial results for DAAs is that many of the trials were conducted as single-arm studies without a comparator arm. This means that there were only limited data that allowed the direct evaluation of the safety and efficacy of one regimen compared with another. This prevented the direct comparison of outcomes using a pair-wise meta-analysis (web Appendix 2, 2016).

To address this limitation, a network meta-analysis was conducted, which is a statistical approach that combines direct and indirect evidence to optimize the use of available evidence and to permit comparisons of interventions that have not been compared directly *(123)*. This approach involves creating a network of results by treatment regimen and provides an estimate of effect sizes for all possible pair-wise comparisons, whether or not they have been compared head-to-head in a randomized controlled trial (RCT). Network meta-analysis is a recognized approach for guideline development; guidance on how to assess evidence from network meta-analyses has recently been issued by the GRADE Working Group and was followed during the development of these guidelines *(124)*.

The analysis had three components. The first was a systematic review of publications reporting on the outcomes of clinical trials of DAAs as described above, as well as clinical trial data provided by manufacturers. In the second part, key outcome variables (i.e. SVR, SAEs, treatment discontinuation and mortality rates) from these clinical trials were entered into a network meta-analysis model; for each treatment regimen, these results were stratified by genotype and previous treatment experience. Third, to address the lack of comparator arms in most studies, a synthetic or simulated comparator arm was created *(125)*. To do this, the average outcome values of the pegylated interferon/ribavirin arms in comparative trials were used to simulate a virtual pegylated interferon/ribavirin control arm. Thus, application of the network meta-analysis methodology was possible within datasets containing no comparative arms, thereby increasing the available data pool that could be studied. As antiviral regimens for HCV can differ in treatment length, use of ribavirin, etc., different regimens using the same medicines were grouped into one regimen. As cirrhosis affects treatment outcomes, separate analyses were conducted, one adjusting for the proportion of patients with cirrhosis in the individual studies and the other a non-adjusted analysis. Both analyses produced similar results, thus only the unadjusted analysis was used throughout.

Only the regimens of interest were included in the analysis. This was defined as medicines that had received regulatory approval from FDA or the European Medicines Agency (EMA). Asunaprevir was also included, as it has received regulatory approval in a number of countries. Because genotypes 1 and 4 are expected to have comparable treatment outcomes, these genotypes were combined (Table 4.2 and 4.3). Genotypes 2 and 3 were analysed separately, as were genotypes 5 and 6. For genotypes 2, 3, 5 and 6, the evidence was limited and therefore the network meta-analysis approach was not possible. For these genotypes, the direct, pooled outcomes of individual studies were assessed.

Summary of studies included in the network meta-analysis

TABLE 4.2 Summary of studies for treatment-naive genotypes 1 and 4 included in the network meta-analysis

Combined regimens	No. of patients (no. of arms)	Pooled proportions of SVR, % *(95% confidence interval)*	Individual regimens	No. of patients (no. of arms)	Pooled proportions of SVR, % (95% confidence interval)
Pegylated-interferon/ribavirin (PR)	1564 (16)	46.86 (41.87, 51.86)	PR 1–48	1564 (16)	46.86 (41.87, 51.86)
Telaprevir (TVR) + PR	641 (7)	76.47 (70.21, 82.74)	TVR + PR 1–12, PR 13–48	117 (2)	65.30 (50.21, 80.39)
			TVR + PR 1–12, PR 13–24 or PR 13–48**	524 (5)	78.71 (74.28, 83.13)
Boceprevir (BOC) + PR	901 (4)	66.43 (61.81, 71.05)	PR 1–4, BOC + PR 5–48	533 (3)	63.32 (58.39, 68.24)
			PR 1–4, BOC + PR 5–28 or BOC + PR 5–36, PR 37–48	368 (1)	68.08 (61.73, 74.42)
Simeprevir (SMV) + PR	686 (5)	80.51 (77.54, 83.47)	SMV + PR 1–12, PR 13–24*	633 (4)	80.61 (77.53, 83.69)
			SMV + PR 1–12, PR 13–48	53 (1)	79.25 (68.33, 90.16)
SMV + sofosbuvir (SOF)	40 (4)	97.32 (90.35, 100.00)	SMV + SOF 1–12	7 (1)	85.71 (59.79, 100.00)
			SMV + SOF 1–24	8 (1)	100.00 (85.03, 100.00)
			SMV + SOF + R 1–12	12 (1)	91.67 (76.03, 100.00)
			SMV + SOF + R 1–24	13 (1)	100 (90.28, 100.00)
SOF + PR	464 (3)	90.18 (87.48, 92.89)	SOF + PR 1–12	344 (2)	89.55 (86.31, 92.78)
			SOF + PR 1–24	120 (1)	91.67 (86.72, 96.61)
SOF + R	390 (9)	77.26 (67.98, 86.54)	SOF + R 1–24	390 (9)	77.26 (67.98, 86.54)
SOF + ledipasvir (LDV)	1028 (8)	97.65 (96.03, 99.26)	SOF + LDV 1–8	221 (2)	94.06 (91.04, 97.08)
			SOF + LDV 1–12	563 (5)	98.56 (96.91, 100.00)
			SOF + LDV 1–24	212 (1)	97.70 (95.70, 99.69)
Daclatasvir (DCV) + SOF	195 (5)	98.35 (96.14, 100.00)	DCV + SOF 1–12	125 (2)	98.40 (94.91, 100.00)
			DCV + SOF 1–24	14 (1)	100.00 (90.92, 100.00)
			DCV + SOF + R 1–12	41 (1)	95.12 (88.53, 100.00)
			DCV + SOF + R 1–24	15 (1)	100.00 (91.47, 100.00)
DCV + asunaprevir (ASV) ***	265 (2)	83.07 (75.99, 90.15)	DCV + ASV 1–24	265 (2)	83.07 (75.99, 90.15)
Ombitasvir (OMB) + paritaprevir/ritonavir (PAR)/r ± dasabuvir (DSV)	1399 (8)	96.99 (95.19, 98.78)	OMB + PAR/r + DSV 1–12	414 (2)	94.86 (86.25, 100.00)
			OMB + PAR/r + DSV + R 1–12	869 (4)	97.20 (94.75, 99.65)
			OMB + PAR/r + DSV + R 1–24	74 (1)	94.59 (89.44, 99.75)
			OMB + PAR/r + R 1–12	42 (1)	100.00 (96.80, 100.00)
			OMB + PAR/r + R 1–24**	--	--

*No trial assessed this exact regimen in this population. These data represent SMV + PR 1–12, PR 13–24 or PR 13–48.
**No trial assessed this exact regimen in this population.
***Although this regimen is not EMA or FDA approved, it was included because it is of interest in some settings.
ASV: asunaprevir; BOC: boceprevir; DSV: dasabuvir; DCV: daclatasvir; LDV: ledipasvir; OMB: ombitasvir; PAR/r: paritaprevir/ritonavir; PR: pegylated interferon/ribavirin; R: ribavirin; SOF: sofosbuvir; SMV: simeprevir; TVR: telaprevir

TABLE 4.3 Summary of studies for treatment-experienced genotypes 1 and 4 included in the network meta-analysis

Combined regimens	No. of patients (no. of arms)	Pooled proportions of SVR, % *(95% confidence interval)*	Individual regimens	No. of patients (no. of arms)	Pooled proportions of SVR, % (95% confidence interval)
Pegylated-interferon/ribavirin (PR)	592 (6)	21.70 (15.19, 28.20)	PR 1–48	592 (6)	21.70 (15.19, 28.20)
Telaprevir (TVR) + PR	650 (2)	59.37 (49.97, 68.78)	TVR + PR 1–12, PR 13–48	650 (2)	59.37 (49.97, 68.78)
			TVR + PR 1–12, PR 13–24 or PR 13–48**	--	--
Boceprevir (BOC) + PR	457 (3)	63.13 (58.49, 67.77)	PR 1–4, BOC + PR 5–48	295 (2)	65.44 (60.02, 70.87)
			PR 1–4, BOC + PR 5–36 or BOC + PR 5–36, PR 37–48	162 (1)	58.64 (51.06, 66.23)
			PR 1–4, BOC + PR 5–36, PR 37–48**	--	--
Simeprevir (SMV) + PR	830 (5)	64.93 (52.21, 77.66)	SMV + PR 1–12, PR 13–24*	332 (2)	68.71 (46.90, 90.52)
			SMV + PR 1–12, PR 13–48	492 (3)	61.53 (50.95, 72.12)
SMV + sofosbuvir (SOF)	127 (8)	93.96 (89.65, 98.27)	SMV + SOF 1–12	21 (2)	95.66 (89.38, 100.00)
			SMV + SOF 1–24	23 (2)	83.97 (72.82, 95.11)
			SMV + SOF + R 1–12	42 (2)	95.58 (94.82, 100.00)
			SMV + SOF + R 1–24	41 (2)	83.97 (72.82, 95.11)
SOF + PR	--	--	SOF + PR 1–12**	--	--
			SOF + PR 1–24**	--	--
SOF + R	49 (2)	75.46 (53.94, 96.98)	SOF + R 1–24	49 (2)	75.46 (53.94, 96.98)
SOF + ledipasvir (LDV)	412 (6)	97.88 (95.64, 100.00)	SOF + LDV 1–12	226 (4)	95.57 (89.61, 100.00)
			SOF + LDV 1–24	186 (2)	98.74 (97.14, 100.00)
Daclatasvir (DCV) + SOF	87 (3)	98.10 (94.82, 100.00)	DCV + SOF 1–12	46 (1)	97.83 (93.61, 100.00)
			DCV + SOF 1–24	21 (1)	100 (93.77, 100.00)
			DCV + SOF + R 1–12**	--	--
			DCV + SOF + R 1–24	20 (1)	95.00 (85.45, 100.00)
DCV + asunaprevir (ASV)	233 (2)	62.85 (15.23, 100.00)	DCV + ASV 1–24	233 (2)	62.85 (15.23, 100.00)
Ombitasvir (OMB) + paritaprevir/ritonavir (PAR)/r ± dasabuvir (DSV)	745 (6)	97.26 (94.98, 99.54)	OMB + PAR/r + DAS 1–12	91 (1)	100.00 (98.50, 100.00)
			OMB + PAR/r + DAS + R 1–12	507 (3)	95.02 (91.85, 98.20)
			OMB + PAR/r + DAS + R 1–24	98 (1)	96.94 (93.53, 100.00)
			OMB + PAR/r + R 1–12	49 (1)	100.00 (97.24, 100.00)
			OMB + PAR/r + R 1–24**	--	--

*No trial assessed this exact regimen in this population. These data represent SMV + PR 1–12, PR 13–24 or PR 13–48.
**No trial assessed this exact regimen in this population.
***Although this regimen is not EMA or FDA approved, it was included because it is of interest in some settings.

Studies that were not analysed by network meta-analysis

Treatment-naive genotypes 2 and 3

As genotypes 2 and 3 have variable responses to different DAAs, we attempted to analyse separately the outcomes for these genotypes; however, many clinical studies reported combined outcomes for these two genotypes. In the event that results were not available for each genotype separately, data on the combined genotypes were used to assess rates of treatment discontinuation due to adverse events and SAEs. Furthermore, if data were not available for treatment-naive and treatment-experienced patients separately, the combined data were used. Because of the scarcity of and heterogeneity in the data, it was not possible to construct a network meta-analysis model to conduct indirect comparisons between treatments and data were summarized as pooled proportions.

Genotype 2
Ten study arms provided data on SVR, four study arms on treatment discontinuation due to adverse events and SAEs, and two study arms provided data on mortality. DAA regimens that were evaluated included daclatasvir/sofosbuvir ± ribavirin, and sofosbuvir/ribavirin.

Genotype 3
Nine study arms providing data on SVR among patients with genotype 3 were included. Of these, seven study arms provided data on treatment discontinuation due to adverse events, and four on SAEs and mortality. DAA regimens that were evaluated included daclatasvir/sofosbuvir ± ribavirin, sofosbuvir/pegylated interferon/ribavirin and sofosbuvir/ribavirin.

Treatment-experienced genotypes 2 and 3

Similar to studies in treatment-naive patients, outcomes for genotypes 2 and 3 were relatively few in number and were reported together in many cases. Where possible, they were analysed separately.

Genotype 2
Seven study arms provided data on SVR using the regimens of interest. Four study arms provided data on treatment discontinuation due to adverse events and three on SAEs, and two study arms on mortality. DAA regimens that were evaluated included daclatasvir/sofosbuvir ± ribavirin and sofosbuvir/ribavirin.

Genotype 3
Twelve study arms provided data on SVR, and three study arms provided data on treatment discontinuation due to adverse events, SAEs and mortality. DAA regimens that were evaluated included daclatasvir/sofosbuvir ± ribavirin, sofosbuvir/pegylated interferon/ribavirin, and sofosbuvir/ribavirin.

Treatment-naive and -experienced genotypes 5 and 6

Four study arms with a total of 77 treatment-naive and treatment-experienced

patients with genotypes 5 and 6 infections were evaluated for sofosbuvir/pegylated interferon/ribavirin and ledipasvir/sofosbuvir.

4.6.2 Budget impact analysis

We conducted a budget impact analysis to assess the cost per patient and overall cost to treat a defined population in Brazil, Mongolia and Ukraine (web Appendix 3, 2016). These countries were selected as they represented a range of epidemic and health system responses of middle-income countries. We were not able to include an African country due to lack of data on HCV epidemiology and health costs. For each country, proportions were estimated of the total number of persons with HCV infection and the proportion who had been diagnosed. Treatment costs were estimated taking into consideration different genotypes, prior treatment experience and presence of cirrhosis. Two different treatment regimens were compared – treating all patients with pegylated interferon/ribavirin versus treating with DAAs using combinations of daclatasvir, ledipasvir, ribavirin and sofosbuvir, depending on the genotype distribution in the countries. Costs were estimated for drug treatment as well as laboratory monitoring. Drug prices used were from an informal survey of key individuals in the selected countries *(109)*. This information was used by the Guidelines Development Group to compare the cost of implementing the recommended DAA regimens as compared with interferon-based regimens that remain the standard of care in many countries.

4.6.3 Values and preferences

To provide information on values and preferences, we assessed what characteristics of a treatment regimen were rated as important from a patient's perspective (web Appendix 4, 2016). To do this, we identified studies that dealt with this topic by searching MEDLINE using terms for hepatitis C virus infection, antiviral therapy, and patient preferences or patient values. We also reviewed reference lists of relevant articles to identify additional studies. Four studies were identified that assessed patient preferences related to HCV treatment. From these studies, the most important patient-relevant outcome was overall efficacy (likelihood of cure) followed by risk of adverse events. Other factors related to the regimens that were considered important from a patient's perspective included frequency of dosing, need for injections and, to a lesser extent, duration of therapy.

This information was used by the Guidelines Development Group to formulate the recommendations and to identify the preferred and alternative regimens. This delineation between preferred and alternative regimens was made based on efficacy and safety, as well as on the regimen-specific characteristics that were related to patient-relevant outcomes and preferences. To assist in this determination, Group members rated the acceptability of the different HCV treatment regimens. Regimens that included pegylated interferon were rated as having "low acceptability", and regimens that included ribavirin were rated as having "moderate acceptability". Other factors that resulted in a "moderate" rating included the need for multiple daily dosing, frequency of DDIs and laboratory monitoring. Regimens not requiring pegylated interferon or ribavirin and that had once-daily dosing and few DDIs were classified as having "high acceptability". Only regimens with high and moderate acceptability were selected as preferred regimens.

5. RECOMMENDATIONS ON SCREENING

5.1 Screening to identify persons with HCV infection

Existing recommendation from 2014

It is recommended that HCV serology testing be offered to individuals who are part of a population with high HCV seroprevalence or who have a history of HCV risk exposure/ behaviour.

Strong recommendation, moderate quality of evidence

Note: Information on WHO prequalified serological diagnostic tests for hepatitis C infection are regularly updated at: http://www.who.int/diagnostics_laboratory/evaluations/PQ_list/en

5.1.1 Background

In many countries, people have very limited access to HCV testing and thus remain undiagnosed until they present at a health centre with symptoms of cirrhosis or HCC *(126)*. Testing at this time is referred to as "symptomatic testing". At this point, HCV-induced liver damage is often advanced and therapy may be contraindicated. Therefore, it is critical to identify approaches that will lead to a diagnosis of chronic HCV infection earlier in the course of disease. The 2014 Guidelines Development Group considered the value of risk group-based and prevalence-based approaches. These approaches, where testing is based on whether a person belongs to a group that practises behaviours that place them at risk of HCV infection or belongs to a population of known high HCV prevalence, are recommended in many high-income countries *(127, 128)*. The difficulty in considering these approaches is that the relative importance of risk factors and history of behaviours linked to HCV infection vary substantially, depending on the geographical setting and population studied (Table 5.1). In 2016, WHO will issue testing guidelines that will provide more comprehensive recommendations on testing for hepatitis B and C, including testing strategies (i.e. whom to test).

5.1.2 Evidence

A systematic review was conducted to examine the effectiveness of interventions to promote HCV testing before persons develop symptoms of liver damage due to HCV infection. Outcomes assessed included the number of HCV tests carried out, the number of seropositive cases detected, the number of referrals to a specialist, the number commencing treatment for HCV, disease progression, SVR, quality of life and all-cause mortality (web Appendix 3, 2014).

Sixteen studies were reviewed; five RCTs, four non-RCTs, three before/after studies

TABLE 5.1 Populations with a high HCV prevalence or who have a history of HCV risk exposure/behaviour

• Persons who have received medical or dental interventions in health-care settings where infection control practices are substandard
• Persons who have received blood transfusions prior to the time when serological testing of blood donors for HCV was initiated or in countries where serological testing of blood donations for HCV is not routinely performed
• People who inject drugs (PWID)
• Persons who have had tattoos, body piercing or scarification procedures done where infection control practices are substandard
• Children born to mothers infected with HCV
• Persons with HIV infection
• Persons who use/have used intranasal drugs
• Prisoners and previously incarcerated persons

and four time-series analyses. Of these, 12 studies reported on practitioner-based targeted HCV testing interventions. The interventions that were evaluated included awareness-raising of practitioners through in-service training sessions or mailed information, provision of additional clinic staff, routine offer of testing to all patients, or placing reminders in medical records. Four studies reported on media-/information-based targeted HCV testing interventions, such as invitations to information sessions for care providers, leaflets or posters on HCV testing for use in service settings, and TV/radio awareness-raising campaigns.

Practitioner-based targeted HCV testing approaches were found to be more effective than media-/information-based targeted approaches in increasing the number of people being tested, detecting anti-HCV antibody-positive cases, and the number of attendances and referrals to specialist care. This evidence was rated as being of moderate quality because of inconsistency and imprecision of the relative risks (RRs).

A targeted approach to testing increased HCV testing uptake compared to no targeted intervention (RR 2.9, 95% confidence interval [CI] 2.0, 4.2). A practitioner-based approach to targeted testing increased both the number of people tested for HCV and the number who tested seropositive for HCV (RR 3.5, 95% CI 2.5, 4.8; and RR 2.3, 95% CI 1.5, 3.6, respectively). A media-/information-based approach to targeted testing was, however, less effective than practitioner-based measures in increasing the number of people tested for HCV and the number who tested seropositive (RR 1.5, 95% CI 0.7, 3.0; and RR 1.3, 95% CI 1.0, 1.6, respectively). Targeted testing versus no targeted testing was associated with increased referrals to a specialist (RR 3.0; 95% CI 1.8, 5.1) and increased attendance at specialist appointments (RR 3.7; 95% CI 1.9, 7.0).

Although testing interventions were associated with an increase in the uptake of HCV treatment, this did not result in an increased likelihood of SVR or reduced mortality. This is possibly due to the short period of follow up in most studies. Although there was no direct evidence showing that targeted testing resulted in reduced mortality, it was felt that this was likely to occur based on an increased referral and treatment rate,

and that longer-term studies would be likely to show this effect.

5.1.3 Rationale for the recommendation

The summary of evidence demonstrated that practitioner-based and media-based interventions are effective in increasing the uptake of testing, identifying HCV-infected persons and referring them to care. However, the approaches to achieve these results were different in the studies that were evaluated. Therefore, the 2014 Guidelines Development Group could not recommend a specific intervention to increase the uptake of HCV testing. Instead, the Group recommended a more general approach of focusing testing efforts on persons who belong to populations with a known high prevalence of HCV or who have a history of behaviours that place them at risk for HCV infection (Table 5.1). In some countries where unsafe injection practices and invasive medical procedures are common, much of the general population would be considered to be "of known high prevalence". The identification of approaches to implement this recommendation will vary, based on the composition of the high-prevalence groups in a country, as well as the availability of resources, and clinical and outreach testing services.

Balance of benefits and harms

Targeted testing of persons belonging to risk groups and those with high HCV prevalence is likely to increase the number of HCV-infected people identified, referred to a specialist and provided access to treatment, resulting in a higher likelihood of treatment success. An additional benefit is that knowing one's HCV infection status provides the opportunity to reduce transmission to others by avoiding behaviours such as sharing of injection equipment that place others at risk of HCV infection. Potential undesirable outcomes were not assessed in the studies that were reviewed, but the 2014 Guidelines Development Group recognized that persons with HCV infection can face stigma, discrimination and potential loss of employment and health benefits. Thus, it is vital that testing is voluntary and that confidentiality be maintained as part of the approaches to enhance testing. Members of the 2014 Guidelines Development Group also expressed concern that persons with HCV infection identified through enhanced screening efforts in LMIC might not have access to care and treatment. Despite these concerns, the 2014 Guidelines Development Group felt that persons have the right to know their HCV status, and an increase in the number of persons who are aware of their diagnosis could lead to an increased demand for treatment. The 2014 Guidelines Development Group concluded that the desirable outcomes outweighed the undesirable outcomes. WHO is currently developing separate screening and testing guidelines for hepatitis B and C, which will address many of these issues in greater detail.

Values and preferences

In populations where HCV infection is higher in groups that are marginalized (e.g. PWID), targeted HCV testing that is linked to prevention and treatment services could lead to reductions in health disparities. Assuming that screening efforts were conducted taking into consideration the elements of lack of coercion,

confidentiality, cultural sensitivity, and linkage to health services, the 2014 Guidelines Development Group felt that screening would be acceptable to the affected groups.

Resource considerations

Moving away from symptomatic testing as the primary strategy for diagnosis of infected persons to a model that targets screening of specific high-risk or high-prevalence populations will require additional resources, including medical training, staffing and equipment for phlebotomy, counselling and serological screening. Furthermore, a positive HCV serology test result needs additional testing to confirm the presence of chronic infection (*see* section 5.2). Monitoring of laboratory and clinical facilities are additionally required to ensure high standards of practice. Targeted testing has different costs associated with different settings – if HCV is prevalent in the general population, a substantial screening effort would be indicated and would result in significant costs. Members of the 2014 Guidelines Development Group emphasized the importance of assuring access to treatment following screening. The 2014 Guidelines Development Group agreed that the infrastructure for both screening and treatment is necessary for screening to have an impact on key outcomes, including quality of life and mortality; therefore, resources put into screening need to be matched with increased resources for treatment.

5.1.4 Implementation

The implementation of this recommendation will require an assessment of the epidemiology of HCV in a specific country or region seeking to expand testing. This is difficult, as many countries have no or very little data on the prevalence of HCV infection. Two approaches are taken in high-income countries to expand HCV testing. The first is to specify the risk groups for testing, while a second approach recommended in the United States is to define demographic groups using age criteria *(127, 128).* Risk group identification is challenging because many individuals do not wish to acknowledge behaviours that are stigmatized, such as drug use.

In either case, successful implementation would require developing a national HCV testing policy with suggestions for implementation. Considerable resources are needed to purchase test kits, train health-care workers and laboratory staff, and implement quality assurance programmes. Another challenge is to ensure that patients who are diagnosed are referred for appropriate care. This would include evaluation for therapy, provision of lifestyle advice to reduce progression of liver disease (for example, by reducing alcohol intake), as well as measures taken to prevent transmission.

5.1.5 Considerations in persons with HIV/HCV coinfection

In the United States and western Europe, it is recommended that all persons with HIV infection be screened for HCV at the time of enrolment into HIV care,

and that those who are not infected with HCV but practise behaviours that place them at risk for HCV infection, such as injection drug use, be retested annually. Rates of HCV infection in persons with HIV infection are higher than in the general population, but vary widely by country.

5.1.6 Research questions

There is a lack of direct evidence that HCV testing interventions positively affect treatment outcomes and HCV-related morbidity and mortality. Further research in this area focusing on the longer-term outcomes of testing interventions for HCV would be useful, particularly in low-income settings. Operational research is needed to evaluate different approaches to increase the reach and uptake of screening services, particularly among marginalized populations and in low-income settings.

5.2 When to confirm a diagnosis of chronic HCV infection

Existing recommendation from 2014

It is suggested that nucleic acid testing for the detection of HCV RNA be performed directly following a positive HCV serological test to establish the diagnosis of chronic HCV infection, in addition to nucleic acid testing for HCV RNA as part of the assessment for starting treatment for HCV infection.

Conditional recommendation, very low quality of evidence

5.2.1 Background

Approximately 15–45% of persons who are infected with HCV will spontaneously clear the infection *(69, 70, 129, 130)*. These persons are HCV seropositive but are no longer infected with HCV. A NAT for HCV RNA, which detects the presence of the virus, is needed to distinguish persons with chronic HCV infection from those who have cleared the infection. It is therefore the standard of care to carry out a NAT for HCV RNA for persons who are found to be anti-HCV antibody positive. A NAT for HCV RNA is also important prior to commencing and during treatment to assess the response to treatment *(131, 132)*. The 2014 Guidelines Development Group felt it important to assess whether, in addition to a NAT for HCV RNA prior to initiation of treatment, there is a benefit to confirming the presence of chronic HCV infection directly following a positive HCV serological test result. In 2016, WHO will issue testing guidelines that will provide additional information on this question, including the value of HCV core antigen testing as an alternative to NAT.

5.2.2 Evidence

A systematic review was conducted to compare whether there was a benefit to performing a NAT for HCV RNA directly following a positive serological test result (called "immediate testing") as compared with testing carried out at the time of assessment for antiviral therapy (called "delayed testing") (web Appendix 3, 2014). Outcomes assessed included the number of cases of HCV transmission, the number achieving SVR, the number of cases of decompensated liver disease and HCC, mortality and quality of life.

Eight articles were obtained for full-text appraisal *(133–140).* No study matched the complete inclusion criteria as all of them lacked a comparison arm and were primarily designed to address other research questions; thus, the quality of evidence was graded as very low. As the aims were different, these studies did not directly report on the outcomes of interest specified in the PICO question.

Therefore, no studies were included for qualitative or quantitative assessment, and in the absence of any directly relevant studies, neither narrative synthesis nor meta-analysis could be performed. To address this data gap, a broadened search was conducted of systematic reviews, comment papers and other types of studies to capture relevant studies relating to the timing of NAT, including comparisons of NAT at any time versus no NAT. This also yielded no citations of primary studies or systematic reviews.

Articles were then analysed for indirect evidence related to the question. There was indirect evidence showing that NAT for HCV RNA is underutilized in populations in which it is indicated *(136, 138, 139, 141)*. Rongey et al. found that NAT for HCV RNA among a cohort of anti-HCV-positive United States veterans was more likely to be carried out in patients with abnormal transaminases, in those with non-HCV hepatitis, and those with decompensated liver disease, while those aged over 65 years and PWID were significantly less likely to be tested for HCV RNA *(136).*

5.2.3 Rationale for the recommendation

Balance of benefits and harms

In the absence of direct or indirect evidence from the systematic reviews, members of the 2014 Guidelines Development Group discussed the implications of not conducting an immediate NAT for HCV RNA. These included labelling persons as being infected with HCV when, in fact, they had spontaneously cleared the infection. Such individuals could unnecessarily face stigma and discrimination, including difficulties with employment and procuring health services. Knowing whether someone has chronic HCV infection allows health staff to provide prevention messages to protect the infected individual (e.g. alcohol reduction counselling) as well as the health of their family or contacts (e.g. PWID networks) by informing them of methods to reduce the risk of transmission of HCV. Knowing someone's HCV status provides an opportunity to link him or her with appropriate care.

A potential harm of knowing one's HCV infection status is the psychological stress related to having a life-threatening infection, particularly if HCV treatment is not available. Despite this, the expert opinion of the 2014 Guidelines Development Group was that the benefits of immediate testing versus delayed testing outweighed the potential harms.

Values and preferences

Immediate testing was considered likely to be acceptable to key stakeholders. Patients with resolved HCV infection following spontaneous clearance would be reassured and those who learn of their infection can take steps to protect

their health and that of others.

Resource considerations

The resources required for NAT for HCV RNA were, however, considered to be substantial. The cost of the test is high, ranging from US$ 30 to US$ 200 per test. Furthermore, the laboratory equipment is expensive and requires technicians with specialized training. As the infrastructure for immediate NAT is also needed for HCV viral load testing (quantitative HCV RNA) to commence and monitor treatment for HCV, the incremental cost of implementing this recommendation would be associated with additional reagent cost and technician time, and the cost of repeat testing before initiation of treatment. Therefore, although an increase in cost associated with earlier testing was considered to be likely, the 2014 Guidelines Development Group considered that the incremental cost was smaller than the net benefit, and immediate NAT was considered to be feasible in countries where pre-treatment NAT is already being performed.

5.2.4 Implementation

The 2014 Guidelines Development Group emphasized that HCV testing should be voluntary, the results of the test should be confidential and that referral for treatment should be considered in all persons with detectable HCV RNA. Laboratories should operate within a quality-assurance framework, which is essential for accurate testing results. The possibility of reinfection with HCV after spontaneous clearance or successful treatment was considered, and persons with undetectable HCV RNA but who are still at active risk (e.g. current PWID) should be advised to get retested.

5.2.5 Considerations among persons with HIV/HCV coinfection

Persons who are infected with both HIV and HCV can have false-negative HCV serological test results. This may occur in up to 6% of persons with HIV who undergo testing using a second-generation anti-HCV enzyme immunoassay (EIA) *(142, 143),* but may occur more often among persons with advanced immunosuppression due to HIV and during early HCV infection *(144, 145).* As the range of CD4 counts in persons with a false-negative anti-HCV antibody test was so different in the various studies, it was not possible to suggest a specific CD4 cut-off level below which all those with a negative anti-HCV antibody test should have HCV RNA testing performed. The influence of HIV status on the detection of anti-HCV antibody is reviewed in the forthcoming hepatitis B and C testing guideline.

5.2.6 Research questions

Further research into the optimal timing of NAT for HCV RNA is warranted to compare the effect of immediate testing with delayed testing on patient outcomes, including HCV transmission, morbidity, mortality and quality of life. Research evaluation is needed of novel laboratory techniques that would allow confirmation of HCV infection without the need for expensive laboratory equipment or trained personnel.

6. RECOMMENDATIONS ON CARE OF PEOPLE INFECTED WITH HCV

6.1 Screening for alcohol use and counselling to reduce moderate and high levels of alcohol intake

Existing recommendation from 2014

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

Note: The WHO Alcohol, Smoking and Substance Involvement Screening Test (ASSIST) *(146)* screening questionnaire can be used to quantify the level of alcohol intake as low, moderate or high, based on the responses to eight screening questions that assess the frequency of use and presence of alcohol-associated problems.

6.1.1 Background

In many persons with chronic HCV infection, decades can pass between the time they acquire infection and when they develop fibrosis and cirrhosis. During that time, there are health conditions and behaviours that can accelerate the progression of liver damage, including alcohol consumption and obesity. The 2014 Guidelines Development Group assessed various interventions that slow the rate of liver damage among persons with HCV infection and decided to evaluate interventions to reduce alcohol intake because alcohol consumption is common, has been shown to accelerate the progression of liver disease among people with HCV infection *(147)* and it was felt that persons with HCV infection would be amenable to such measures. Reducing the use of cannabis in persons with HCV infection was discussed by the 2014 Guidelines Development Group but was not considered as part of a systematic review process due to a paucity of data and conflicting reports on any association with progression of liver disease *(148)*.

A heavy intake of alcohol, of between 210 and 560 g/week (a glass of wine or can of beer contains 10–14 g alcohol), doubles the risk of cirrhosis, and even moderate alcohol consumption can be detrimental *(149)*. The purpose of the systematic review was to investigate the effectiveness of behavioural interventions to reduce alcohol intake among people with HCV infection, in terms of HCV infection treatment outcomes, progression of liver disease and quality of life.

Alcohol use in persons with HCV varies considerably in different geographical regions and in different risk groups. Many countries have no published prevalence rates of alcohol use in persons with HCV infection. Some countries, such as Egypt and Saudi Arabia, report extremely low or negligible alcohol use in persons with

HCV infection *(149, 150)*. Considerably higher alcohol use is found in other countries, especially among PWID and prisoners. In China, the majority of PWID in one region was found to use alcohol regularly prior to starting injecting drug use *(151)*. In one study from Russia, 26–30% of PWID drank moderate-to-heavy amounts of alcohol *(152)*. In Brazil, HCV-infected youth offenders had high rates of alcohol use *(153)* and in a study among Nigerian prisoners, 59% with HCV infection also drank alcohol *(154)*. Alcohol intake has also been found to be high in other groups of persons with HCV infection; 37% of male and 9% of female commercial plasma donors infected with HCV in Guan, China were found to drink >40 g of alcohol per day *(155)*. In view of these figures, the 2014 Guidelines Development Group considered that even in countries where alcohol intake is low among the general population, alcohol reduction advice might have an impact.

6.1.2 Evidence

A systematic review was conducted of studies examining a brief behavioural alcohol reduction intervention versus no behavioural intervention for persons with HCV infection. The outcomes considered were reduction or cessation of alcohol intake, SVR, liver fibrosis, decompensated liver cirrhosis, HCC, quality of life and mortality (web Appendix 3, 2014).

Five trials were identified that met the PICO criteria for assessment; two RCTs *(156, 157)* and three cohort studies *(158–160)*. These studies evaluated different interventions and used different measures of alcohol intake. The interventions that were evaluated included four sessions of motivational enhancement therapy, six two-hour group counselling sessions, 24-week integrated alcohol reduction and health-promotion counselling, and two studies with a single "brief" counselling session. These studies provided some evidence that alcohol reduction interventions can reduce alcohol consumption among people with moderate-to-high alcohol intake living with chronic HCV infection. However, the evidence was graded as being of moderate quality because of considerable heterogeneity in the intervention and comparison groups, and measures of alcohol intake across these studies.

There are more studies evaluating brief alcohol reduction counselling among HCV-uninfected persons. A Cochrane review conducted by Kaner et al. *(161)* found that among 5860 hazardous or dependent drinkers followed in 22 studies, screening for HCV followed by a brief intervention (compared with no intervention) significantly reduced mean weekly alcohol consumption of 313 g per week by 38 g per week. Klimas et al. *(162)* investigated the efficacy of psychosocial interventions for drinkers who concurrently used illicit drugs. Among 594 participants across four studies, alcohol-focused interventions resulted in significant reductions in alcohol consumption at 3 months (RR 0.32) and 9 months (RR 0.16) compared to treatment as usual. The quality of the evidence overall was considered to be moderate as there was variability in the type of interventions. Although these studies were conducted among persons without HCV infection, the 2014 Guidelines Development Group felt that the benefits demonstrated in these studies would apply to persons with HCV infection. One limitation is that most of the studies included in

these reviews were from North America and Europe; thus, it is uncertain how generalizable they are to other parts of the world.

6.1.3 Rationale for the recommendation

In summary, the 2014 Guidelines Development Group concluded that there was evidence of moderate quality that alcohol reduction interventions would reduce alcohol consumption among persons with chronic HCV infection who consume moderate-to-large amounts of alcohol. Although there are no data on whether longer-term important outcomes, including treatment response, morbidity, mortality and quality of life, are affected by alcohol reduction interventions, the opinion of the Group was that these outcomes are likely to be improved. The 2014 Guidelines Development Group also felt that this intervention would be acceptable to key stakeholders.

Balance of benefits and harms

The evidence in favour of an alcohol reduction intervention was considered to be of moderate quality and the likelihood of undesirable effects minimal. However, the relevance of this advice is likely to be context specific and countries with low alcohol use may not wish to commit as much time and resources to carrying out alcohol reduction interventions as other countries.

Values and preferences

An intervention delivered in the context of a liver health assessment was felt to be acceptable to persons with HCV infection, assuming that confidentiality was maintained. Regarding equity, members of the 2014 Guidelines Development Group felt that alcohol use should not preclude treatment for HCV.

Resource considerations

The principal costs of implementing a brief alcohol reduction intervention were considered to be related to the training of clinicians and counsellors, and the additional time required to deliver counselling. Nevertheless, a brief 5–10 minute alcohol reduction intervention was considered to be unlikely to substantially increase costs and would be likely to be feasible to implement in most health-care settings.

6.1.4 Implementation

An important challenge to implementing a brief alcohol reduction intervention is deciding on which approach to consider. The 2014 Guidelines Development Group proposed that the WHO ASSIST *(146)* would be an appropriate framework to design alcohol screening and reduction interventions because it is evidence based, proposes a standardized approach, and is aimed at the primary health-care level. The ASSIST package includes tools for carrying out an assessment of the level of intake of alcohol and other substances, and instructions on implementing a brief counselling intervention.

The elements of the ASSIST approach are outlined in Table 6.1 and include the administration of a questionnaire regarding the use of alcohol and other substances, classification of the level of consumption and, if needed, alcohol-reduction counselling or referral.

This approach is more fully described in the WHO Mental Health Gap Action Programme (mhGAP) guidelines for mental health, neurological and substance use disorders in non-specialized settings in LMIC *(163).*

6.1.5 Research questions

Additional research is required to fully assess the impact of a brief behavioural intervention such as the ASSIST intervention on other outcomes, including morbidity, mortality and quality of life, particularly in different geographical settings. Measuring alcohol consumption is complex and different instruments are used across studies, making comparisons and synthesis of the evidence difficult. Future research should consider using validated and standardized tools for measuring alcohol consumption where possible. Operational research is needed to evaluate approaches that integrate alcohol screening and counselling in different geographical settings.

TABLE 6.1 ASSIST – The Alcohol, Smoking and Substance Involvement Screening Test *(146)*

The ASSIST package has been developed in response to the public health burden associated with psychoactive substance use worldwide. It is designed for use in primary health-care settings to assess levels of dependence and to detect harmful substance use in non-dependent persons. The ASSIST approach is designed to be cross-culturally effective.

The elements of the ASSIST package are described in three manuals:

1. *The ASSIST screening test: a manual for use in primary care*
2. *The ASSIST-linked brief intervention for hazardous and harmful substance use: a manual for use in primary care*
3. *Self-help strategies for cutting down or stopping substance use: a guide*.

The elements of the ASSIST approach are:

- a screening questionnaire that takes 5–10 minutes and can be administered in primary health-care settings;
- determination of the "risk score" based on the questionnaire, which allows the patient to be categorized according to risk. The categories determine the intervention type, as follows:
  - lower risk means no treatment is needed;
  - moderate risk calls for a brief intervention;
  - high risk leads to referral to a specialist for assessment and treatment.

The brief intervention manual assists health-care workers in conducting a simple brief intervention for patients at risk.

The self-help guide is a resource for the patient to use to help change substance-use behaviour.

6.2 Assessing the degree of liver fibrosis and cirrhosis

Existing recommendation from 2014

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.

6.2.1 Background

Assessing the degree of liver fibrosis is an important step in the clinical management of persons with HCV infection. Although HCV treatment should be considered for all persons with HCV infection, as indicated in section 10.1, persons with cirrhosis should be prioritized for treatment because they are at increased risk of HCC and death due to liver failure. Furthermore, the selection of treatment regimens can depend on the presence or absence of cirrhosis. Thus, the 2014 Guidelines Development Group felt it important to identify low-cost, effective methods of assessing the degree of fibrosis, which would be widely available in LMIC.

Liver biopsy is considered the gold standard method for fibrosis assessment, but it is not widely used in low-income countries because of its high cost, invasiveness, patient discomfort, risk of complications, as well as the need for expert histological interpretation. Several liver biopsy-scoring systems have been developed, of which the METAVIR system is most widely used (Table 6.2).

TABLE 6.2 METAVIR liver biopsy scoring system *(164)*

METAVIR stage	F0	F1	F2	F3	F4
Definition	No fibrosis	Portal fibrosis without septa	Portal fibrosis with septa	Numerous septa without cirrhosis	Cirrhosis

A variety of non-invasive fibrosis tests based on blood indices and imaging modalities are now available, which may be more suitable for LMIC (Table 6.3). These include serum tests such as the aminotransferase/platelet ratio index (APRI), FIB-4 scores, which measure indirect markers of fibrosis such as ALT, aspartate aminotransferase (AST) and platelet count (Fig. 6.1); tests that should be available at all clinics treating patients with HCV infection. Other serum tests such as FibroTest measure direct markers of fibrosis such as haptoglobin. These tests are patented, must be performed in laboratories that meet certain quality standards, and are thus more expensive and less readily available. Not all of these tests can assess all stages of fibrosis as

well as cirrhosis. For example, FIB-4 was evaluated only for the diagnosis of significant fibrosis (METAVIR stage ≥F2), while APRI was validated for the diagnosis of both significant fibrosis and cirrhosis. More recently, new techniques have been developed that are based on ultrasound technology and assess the degree of fibrosis and cirrhosis by measuring liver stiffness. Of these, transient elastography, which is performed with FibroScan® (Echosens, Paris) has been the most widely evaluated. Characteristics that limit the use of transient elastography include the high cost of the equipment, the need for regular recalibration, trained operators and the lack of validated cut-off values for specific fibrosis stages.

TABLE 6.3 Selected non-invasive tests to assess liver fibrosis *(75, 164–169)*

Test	Components	Requirements	Cost
APRI	AST, platelets	Simple serum and haematology tests	+
FIB-4	Age, AST, ALT, platelets	Simple serum and haematology tests	+
FibroTest	gGT, haptoglobin, bilirubin, A1 apolipoprotein, α2-macroglobulin	Specialized tests. Testing at designated laboratories	++
FibroScan®	Transient elastography	Dedicated equipment	+++

APRI: aminotransferase/platelet ratio index; ALT: alanine aminotransferase; AST: aspartate aminotransferase; gGT: gamma glutamyl transpeptidase

FIGURE 6.1 APRI and FIB-4 formulas

APRI = [(AST (IU/L)/ AST_ULN (IU/L))×100]/ platelet count (10^9/L)
FIB-4= age (yr) x AST (IU/L)/platelet count (10^9/L) x [ALT (IU/L)$^{1/2}$]

ALT: alanine aminotransferase; AST: aspartate aminotransferase; IU: international unit; ULN: upper limit of normal

6.2.2 Evidence

The PICO question for this recommendation was based on two assumptions. First, that liver biopsy would not be available for the reasons listed above, and second, that all sites would have access to the laboratory tests needed to calculate APRI and FIB-4 indices. Thus, the results of the systematic reviews were analysed to assess the benefit of more complex and expensive tests (e.g. FibroTest or FibroScan®) compared with APRI and FIB-4 (web Appendix 3, 2014). A systematic review was conducted to evaluate the diagnostic accuracy of non-invasive fibrosis assessment tests in adult patients with chronic HCV infection. The systematic review included full papers and abstracts, without language restrictions, which (i) evaluated non-invasive tests for the staging of liver fibrosis using liver biopsy as the reference standard, (ii) reported on the data necessary to calculate the true-positive, false-positive, true-negative and false-negative diagnostic results of the non-invasive tests based on a defined index test cut-off point, and (iii) had a maximum of six months of elapsed time between the liver biopsy and the index test. For data synthesis and analysis, the histological scores used in individual studies were

transformed to the METAVIR staging system. Significant fibrosis (METAVIR stage ≥F2) and cirrhosis (F4) were assessed as outcome variables. Overall, the quality of evidence was found to be low, primarily because of potential bias due to the absence of predetermined index test cut-offs for diagnosing specific fibrosis stages, and low or unreported quality of liver biopsy samples. Summary sensitivity and specificity results and relevant confidence intervals are available in web Appendix 3, 2014.

Non-invasive tests provide a numerical value, while histological staging of liver biopsies yields descriptive, semi-quantitative categories. For the non-invasive tests, thresholds exist that correlate with specific histological stages and, in the cases of APRI and FIB-4, these cut-offs have been validated. APRI and FIB-4 have two cut-off values for diagnosing specific fibrosis stages, as the use of a single cut-off would result in suboptimal sensitivity and specificity: a high cut-off with high specificity (i.e. fewer false-positive results) and a low cut-off with high sensitivity (i.e. fewer false-negative results). A staging strategy that uses a combination of these two values uses the low cut-off to rule out the presence of a particular stage of fibrosis and the high cut-off to confirm that the patient has fibrosis that is greater than or equal to a particular stage (e.g. ≥F2). However, a number of patients will fall in the indeterminate range of test results (i.e. their score will be between the low and the high cut-off) and such patients will need either alternative testing or future retesting. Transient elastography uses a single cut-off; however, there are no uniformly established and validated cut-offs for specific fibrosis stages. Therefore, reported sensitivities and specificities of FibroScan® are probably overestimated. The established high and low cut-off values of the APRI and FIB-4 tests along with a range of the most commonly reported cut-offs of FibroScan® for diagnosing ≥F2 stage fibrosis and cirrhosis are presented in Table 6.4. The summary sensitivity and specificity of these tests and FibroScan® for the detection of significant fibrosis (≥F2 stage) and cirrhosis (F4 stage) are listed in Table 6.5.

Having established the sensitivity and specificity of the non-invasive tests compared with liver biopsy as the reference test (Table 6.5), the 2014 Guidelines Development Group considered the comparative performance of the non-invasive tests. For this analysis, APRI and FibroScan® were selected to illustrate clinical trade-offs, as these tests can assess both F2 and F4 cut-offs (i.e. F0–1 vs F2–4; and F0–3 vs F4).

TABLE 6.4 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)	Transient elastography (FibroScan®)
Significant fibrosis (METAVIR ≥F2)	0.5	1.5	1.45	3.25	7–8.5 kPa
Cirrhosis (METAVIR F4)	1.0	2.0	-	-	11–14 kPa

APRI: aminotransferase/platelet ratio index; kPa: kilopascal

TABLE 6.5 Summary of sensitivity and specificity of APRI, FIB-4 and FibroScan® for the detection of advanced fibrosis and cirrhosis (all values are percentages)

		APRI (low cut-off)	APRI (high cut-off)	FIB-4 (low cut-off)	FIB-4 (high cut-off)	Transient elastography
Significant fibrosis (METAVIR ≥F2)	Sensitivity (95% CI)	82 (77–86)	39 (32–47)	89 (79–95)	59 (43–73)	79 (74–84)
	Specificity (95% CI)	57 (49–65)	92 (89–94)	42 (25–61)	74 (56–87)	83 (77–88)
Cirrhosis (METAVIR F4)	Sensitivity 95% CI)	77 (73–81)	48 (41–56)	–	–	89 (84–92)
	Specificity (95% CI)	78 (74–81)	94 (91–95)	–	–	91 (89–93)

APRI: aminotransferase/platelet ratio index

A strategy that uses a combination of the high and low cut-off values was assessed. Using this strategy, patients with values above the APRI high cut-off value would be prioritized for treatment as they have a high probability (94%) of having F4 cirrhosis. For patients with an APRI score below the low cut-off value, treatment could be deferred as they have a very low probability (18%) of having advanced fibrosis (F2 fibrosis or higher) and could thus be reassured and reassessed periodically. Those patients with APRI values between the low and high cut-off values could either be retested every one or two years or, if resources are available, could be treated.

A number of caveats were considered. First, the APRI scoring system may be less reliable in persons with HIV due to the possibility of thrombocytopenia associated with HIV infection rather than cirrhosis. However, HIV-related thrombocytopenia would result in a higher APRI score, and thus earlier treatment. Although this was not assessed in the current analysis, a meta-analysis showed that the diagnostic accuracy of APRI did not significantly differ between HCV-monoinfected and HCV/HIV-coinfected patients *(170)*. Theoretically, the FIB-4 test could also be affected by thrombocytopenia but this scoring system was first evaluated in patients with HIV and was found to perform well *(171)*. Transient elastography values may be artificially increased by a number of factors, including acute liver inflammation, liver congestion (e.g. cardiac failure), a recent meal, amyloidosis and cholestasis. Moreover, the lack of validated cut-offs for the diagnosis of specific stages of fibrosis could hinder the interpretation of the test results.

6.2.3 Rationale for the recommendation

The use of non-invasive monitoring was considered by the 2014 Guidelines Development Group to be preferable to invasive testing, particularly in LMIC, as liver biopsy is an expensive and invasive procedure associated with patient discomfort, a small risk of serious bleeding and requires specialist histological examination for accurate staging. On the basis of the results of the systematic review discussed above, the Group considered that APRI, FIB-4 and transient elastography were the most useful tests for assessing the stage of liver disease. The advantage of APRI as compared with FIB-4 is that it is validated for the diagnosis of F4 fibrosis, and would thus be useful for identifying persons at

greatest risk of morbidity who, therefore, could be prioritized for treatment. It was also recommended that persons who tested negative for significant fibrosis and/or cirrhosis could be retested periodically, and could thus be treated if their APRI or FIB-4 indices increased.

Balance of benefits and harms

The principal undesirable outcomes of this recommendation would be due to treatment decisions based on either a false-positive or false-negative APRI or FIB-4 test result. A false-positive test result would lead to a patient being potentially treated earlier than necessary, which would expose him or her to the risk of harm from drug-related side-effects and would also increase resource use. A false-negative result would mean that a person who needs treatment would not receive it, resulting in the possibility that the person would develop cirrhosis or HCC that could potentially have been prevented by treatment for HCV. Despite this, the potential increase in treatment availability resulting from increased access to low-cost, non-invasive monitoring and reduced risk of adverse events from liver biopsy was felt to outweigh the potential harms of false-positive and false-negative case identification.

Values and preferences

APRI and FIB-4 tests require only phlebotomy; thus, the 2014 Guidelines Development Group felt that these tests would be acceptable to patients. Similarly, transient elastography is non-invasive and thus would probably be acceptable.

Resource considerations

The lower cost of the serum-based non-invasive tests was the most important factor that drove the recommendation. The blood tests that are needed to calculate APRI and FIB-4 scores are inexpensive and would be available at health facilities providing treatment for HCV infection, as they are also needed to monitor patients before and after the commencement of treatment. In contrast, the cost of acquiring, running and maintaining a transient elastography machine such as the FibroScan® is very high. The cost of a fixed machine is US$ 100 000 and for a portable one it is US$ 30 000. The cost of yearly maintenance is US$ 4700. For these reasons, the use of transient elastography was considered to be not feasible in most LMIC.

6.2.4 Implementation considerations

The calculation of the APRI score should be easy to implement as it relies on tests that are available in most clinics. Evaluation of the results is more challenging because of the need to assess two cut-off values. However, the above-mentioned strategy provides an approach that should be feasible and will allow clinicians to decide who should be treated. As persons with advanced fibrosis and cirrhosis (METAVIR F3 and F4 stages) are at the highest risk of dying from complications of HCV infection, they need to be prioritized for treatment. If resources allow, treatment of persons with less advanced stages of cirrhosis could be considered.

7. RECOMMENDATIONS ON TREATMENT

7.1 Assessment for HCV treatment

Existing recommendation from 2014

All adults and children with chronic HCV infection, including people who inject drugs, should be assessed for antiviral treatment.

Strong recommendation, moderate quality of evidence

7.1.1 Background

Over the past two decades, the success of treatment for HCV infection as measured by SVR has steadily increased. Early treatments with standard interferon resulted in SVR rates of 30–60%, depending on the genotype. The introduction of pegylated interferon increased SVR rates to 40–70%, and the more recent introduction of DAAs increased the SVR rate for genotype 1 from 40% to more than 90%. Despite these advances, very few persons in LMIC have been treated for HCV infection. The reasons for this are many and include the high cost of treatment, requirement for expensive laboratory equipment and tests to evaluate eligibility for and response to treatment, and lack of health-care workers trained in administering treatment for HCV infection. Regimens based on pegylated interferon and ribavirin also result in high rates of adverse events, which can be debilitating and even life threatening. Thus, the 2014 Guidelines Development Group felt it important to evaluate the relevant evidence of the benefits and harms of treatment versus no treatment of HCV infection.

7.1.2 Evidence

A systematic review was conducted to investigate the utility of treatment versus no treatment for HCV infection in adults and children. The outcome measures were rates of SVR, decompensated liver disease, HCC, liver-related and all-cause mortality, treatment-related adverse events leading to discontinuation, and quality of life (web Appendix 3, 2014).

Fourteen systematic reviews were included in the final synthesis. Six reviews reported data comparing interferon to placebo *(172–177)*, and six combined and compared different types of interferon (standard interferon or pegylated interferon) to placebo *(178–183).* No studies were available comparing placebo to treatment regimens that included DAAs, as the standard of care at the time of institution of DAA-based therapy was treatment with pegylated interferon and ribavirin. One review evaluated ribavirin monotherapy against placebo *(184).* All

reviews of interferon, pegylated interferon or ribavirin versus placebo were RCTs that used appropriate meta-analytical methods with no significant indirectness or imprecision, and thus contained high-quality evidence according to the GRADE criteria.

The systematic reviews of effectiveness of different interferon types (interferon or pegylated interferon), in combination with ribavirin compared with placebo showed a clear benefit of treatment versus placebo in achieving SVR. The effects of pegylated interferon/ribavirin on HCC, liver-related morbidity and all-cause mortality were inconsistent or statistically non-significant. One study comparing ribavirin with placebo showed no significant beneficial effect of ribavirin in achieving SVR, reducing all-cause mortality or improving the quality of life *(184).*

The systematic reviews showed that the most common adverse events were flu-like syndromes, depression due to interferon and anaemia due to ribavirin. The frequency of discontinuation of treatment approached 20% in one study of patients being evaluated for liver transplantation compared with 0% among placebo recipients *(179).*

One systematic review, including four RCTs and 31 non-randomized studies on the virological outcomes and adverse effects of treatment among children, showed that treatment success rates with interferon-based regimens are similar in children and adults *(174)*. The overall SVR rate for pegylated interferon and ribavirin was 30–100%, which is comparable to SVR rates seen in adults. Adverse effects were primarily flu-like symptoms and neutropenia. Data were insufficient to assess the applicability of stopping therapy at week 12 if there was less than a 2 log reduction in HCV RNA, or the efficacy of shortening treatment duration to 24 weeks in children with genotypes 2 and 3 infection.

In studies conducted among persons with HIV coinfection, there were 110 more cases of treatment discontinuation and 830 more cases of flu-like symptoms per 1000 persons treated than among persons receiving placebo. Studies showing the benefit of therapy among persons with HIV/HCV coinfection are described in section 9.2.

PWID are excluded from most clinical trials; thus, data on the benefits of treatment among them come from observational studies. A systematic review of treatment outcomes among PWID (both former and current users), of whom approximately half were concurrently injecting drugs, demonstrated an SVR of 56% (37% for genotypes 1 and 4, and 67% for genotypes 2 and 3), a treatment discontinuation rate of 22% and a high level of drug adherence. These outcomes were similar to those observed among non-drug users *(185)*. In addition, economic modelling data evaluating the cost–effectiveness of treating HCV infection among PWID was considered by the 2014 Guidelines Development Group. In this group, treatment was considered to be cost–effective in a variety of settings. Additional benefits of treating PWID are that treatment for HCV infection may prevent transmission and reduce the prevalence of HCV infection in this population *(186, 187).*

7.1.3 Rationale for the recommendation

Balance of benefits and harms

Interferon-based therapy, whether using standard or pegylated interferon, increases the likelihood of SVR. Although the studies assessed were not able to show a survival or quality-of-life benefit from achieving SVR, other studies with longer periods of follow up have shown this link *(188).* There is evidence, primarily from observational studies, for the efficacy of treatment for HCV infection among PWID, including those who continue to inject drugs during treatment. Treatment for HCV infection is also effective among persons coinfected with HIV.

The risk of adverse events from interferon-based therapy for HCV infection is high, with many persons discontinuing therapy due to adverse reactions. The most significant risks are depression, increased risk of severe infection and anaemia. In addition, a flu-like syndrome occurs frequently among persons receiving interferon-based therapy. Additional harms that were considered were the financial burden placed on patients who are required to pay for the expensive and lengthy treatment. Despite this, in view of the substantial morbidity and mortality from untreated HCV infection, the 2014 Guidelines Development Group concluded that the benefits of treatment clearly outweighed the potential harms. The Group considered that the risk of harms would be reduced with the introduction of the new DAAs, which have shorter durations of therapy and more favourable safety profiles.

Values and preferences

Many persons who are eligible for HCV treatment are reluctant to be treated because of the fear of adverse events due to the medications, particularly pegylated interferon. This reluctance is likely to lessen with the introduction of medicines that are safer and easier to administer.

Resource considerations

The cost of treatment for HCV infection is high. A treatment regimen of pegylated interferon plus ribavirin costs between US$ 2000 and US$ 28 000 per person *(189).* This wide range in prices reflects the success in some countries of negotiating with the manufacturers for price reductions. Treatment for HCV requires the clinical and laboratory infrastructure for follow up and monitoring on therapy; therefore, the feasibility of providing treatment is challenging. Several middle-income countries have successfully expanded treatment for HCV. Egypt provides the most impressive example where more than 300 000 persons living with HCV have been treated as of March 2016. Treatment is also delivered in several other LMIC such as Brazil, China, India and Pakistan. An economic analysis based on data from Egypt indicated that treating patients with more advanced disease (METAVIR F4) was considered more cost–effective than treating patients with less advanced fibrosis *(190).* Economic evaluations indicate that HCV treatment for PWID is cost–effective and may be more so in

some scenarios than treating those with no ongoing risk of infection, because transmission of HCV infection may be averted. These model projections also show that scaling up treatment for HCV could be critical to reducing the prevalence of HCV infection among PWID *(186, 187, 191, 192)*.

7.1.4 Research questions

Operational research is needed to assess different models of care. This could include evaluation of task shifting and integration of HCV treatment services with other clinical services, such as those in TB or HIV clinics. Also, it would be important to evaluate ways of providing treatment services to groups that are marginalized such as PWID and who find standard clinical services difficult to access.

7.2 Treatment with direct-acting antiviral agents

New recommendation

It is recommended that DAA regimens be used for the treatment of persons with hepatitis C infection rather than regimens with pegylated interferon/ribavirin.

Subgroup considerations: **for patients with HCV genotype 3 infection with cirrhosis, and patients with genotypes 5 and 6 infection with and without cirrhosis, an interferon-based regimen – sofosbuvir/pegylated interferon/ribavirin – is still recommended as an alternative treatment option (*see* Rationale for the recommendation).**

Strong recommendation, moderate quality of evidence

7.2.1 Background

Since the issuance of the first WHO guidelines for the treatment of persons with HCV infection in April 2014, several new medicines have received regulatory approval, and evidence from clinical studies and observational cohorts demonstrate the safety and efficacy of regimens using these new medicines. These treatment regimens (some of which include pegylated interferon and/or ribavirin) have a short treatment duration (usually 12 weeks), are easy to administer (as few as one pill/day), are very effective (SVR rates of ≥90%), and well tolerated with few adverse events. They have the potential to be the basis for a large expansion in the number of persons treated. The Guidelines Development Group felt that it was important to assess whether there was sufficient evidence to recommend the new DAA medicines in preference to treatments based on pegylated interferon.

7.2.2 Evidence

The systematic review (web Appendix 2, 2016) identified 204 studies that evaluated the safety and efficacy of various DAA-based regimens and an independent search found two additional studies. Studies conducted among patients infected with

genotype 1 or 4 were entered into a network meta-analysis to generate indirect, pooled estimates of SVR, treatment discontinuation and SAE and mortality rates. Because of the lack of data on genotypes 2, 3, 5 and 6, a network meta-analysis was not possible, and direct, pooled estimates of SVR, treatment discontinuation and SAE and mortality rates were calculated. In the network meta-analysis, the outcomes among patients treated with DAAs were compared with outcomes among patients treated with pegylated interferon/ribavirin.

The approach taken to grading the evidence was a modification of the standard GRADE approach, in that the evidence from the studies was considered as high quality even though these were not RCTs. This was because the studies were conducted following strict study protocols (i.e. with defined inclusion and exclusion criteria, pre-defined outcomes and very low loss-to-follow-up rates). Also, despite the lack of a control arm in most of the studies, the efficacy and safety of the comparator treatment (interferon and ribavirin) are well established from many earlier trials. The strength of evidence was then lowered because of indirectness (use of network meta-analysis) and risk of bias (single-arm studies). Because of the large effect size, the quality of the evidence was raised such that the final assessment was for moderate-quality evidence.

In treatment-naive patients with genotype 1 or 4 infection treated with pegylated interferon/ribavirin, the pooled SVR rate was 46.9% (95% credible interval [CrI]: 41.9–51.9%). For patients treated with regimens that combined pegylated interferon/ribavirin with a DAA, the pooled SVR rates were between 66.4% and 90.2%. In patients treated with a single DAA/ribavirin, the pooled SVR rate was 77.3%, and for DAA regimens, the pooled SVR rates were all higher than 96%, with the exception of asunaprevir/daclatasvir (SVR rate 83.1%) (Fig. 7.1). Similar results were observed in treatment-experienced patients, where interferon-based therapies achieved SVR rates of 21.7–64.9%, while DAA therapies had SVR rates of between 94% and 98.1%, with the exception of asunaprevir/daclatasvir (SVR rate 62.9%) (Fig. 7.2).

Treatment discontinuation due to adverse events occurred in 2.1–13.6% of treatment-naive patients with genotype 1 or 4 infection treated with regimens containing pegylated interferon, and between 0.1% and 1.5% of patients treated with all-DAA regimens, with the exception of asunaprevir/daclatasvir (5.2%) (Figs 7.3). SAEs occurred in 2.6–10.9% of patients treated with interferon-based regimens as compared with 0.9–2.2% of patients treated with DAA regimens, with the exception of asunaprevir/daclatasvir (8.3%) (Fig. 7.5). Similar results were observed in treatment-experienced patients with genotype 1 or 4 infection (Fig. 7.4 and 7.6).

Fewer studies were conducted among patients with genotypes 2, 3, 5 and 6 infections, but the available data showed similar results as among those infected with genotypes 1 and 4, with higher SVR rates and lower discontinuation and SAE rates among patients treated with DAA regimens.

Data from observational studies were used to provide information where data from clinical studies were limited (web Appendix 7, 2016). A total of 440

FIGURE 7.1 Pooled proportions of sustained virological response rates in treatment-naive hepatitis C genotypes 1 and 4 populations

Regimen	No. patients	Proportion (95% CI)
PR	1564	46.86 (41.87, 51.86)
TVR + PR	641	76.47 (70.21, 82.74)
BOC + PR	901	66.43 (61.81, 71.05)
SMV + PR	686	80.51 (77.54, 83.47)
SOF + PR	464	90.18 (87.48, 92.89)
SOF + R	390	77.26 (67.98, 86.54)
SOF + LDV	1028	97.65 (96.03, 99.26)
DCV + SOF	195	98.35 (96.14, 100.00)
SMV + SOF	40	97.32 (90.35, 100.00)
DCV + ASV	265	83.07 (75.99, 90.15)
OMB + PAR/r	1399	96.99 (95.19, 98.78)

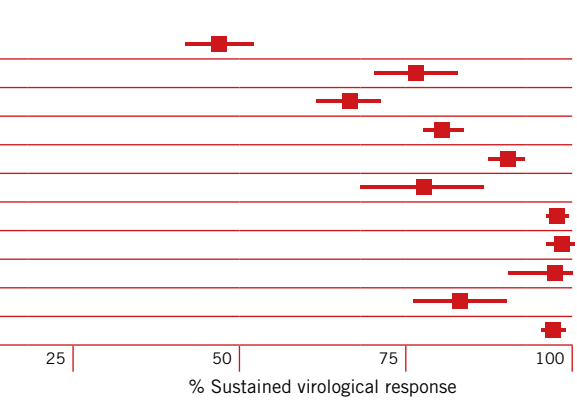


FIGURE 7.2 Pooled proportions of sustained virological response rates in treatment-experienced hepatitis C genotypes 1 and 4 populations

Regimen	No. patients	Proportion (95% CI)
PR	592	21.70 (15.19, 28.20)
TVR + PR	650	59.37 (49.97, 68.78)
BOC + PR	457	63.13 (58.49, 67.77)
SMV + PR	830	64.93 (52.21, 77.66)
SOF + R	49	75.46 (53.94, 96.98)
SOF + LDV	412	97.88 (95.64, 100.00)
DCV + SOF	87	98.10 (94.82, 100.00)
SMV + SOF	127	93.96 (89.65, 98.27)
DCV + ASV	233	62.85 (15.23, 100.00)
OMB + PAR/r	745	97.26 (94.98, 99.54)

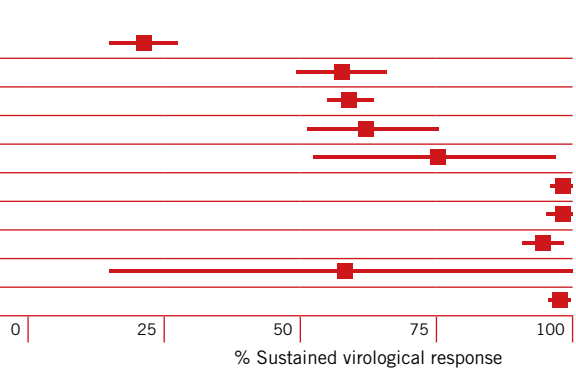
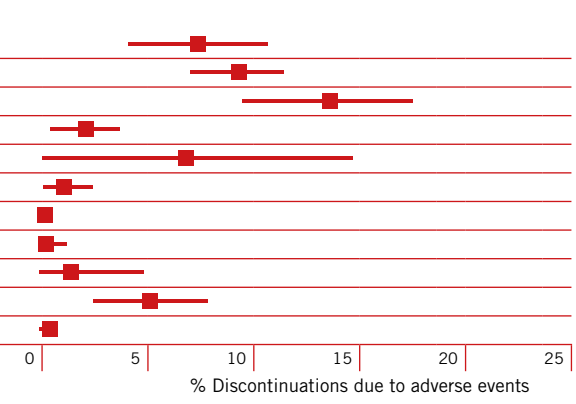


FIGURE 7.3 Pooled proportions of rates of discontinuation due to adverse events in treatment-naive hepatitis C genotypes 1 and 4 populations

Regimen	No. patients	Proportion (95% CI)
PR	1566	7.42 (4.17, 10.68)
TVR + PR	641	9.34 (7.09, 11.59)
BOC + PR	901	13.64 (9.74, 17.53)
SMV + PR	704	2.09 (0.49, 3.68)
SOF + PR	504	6.84 (0.00, 14.66)
SOF + R	411	1.12 (0.00, 2.40)
SOF + LDV	1122	0.15 (0.00, 0.52)
DCV + SOF	212	0.05 (0.00, 1.21)
SMV + SOF	87	1.47 (0.00, 4.90)
DCV + ASV	265	5.20 (2.53, 7.88)
OMB + PAR/r	1619	0.42 (0.00, 0.87)



PR: pegylated interferon/ribavirin
TVR + PR: telaprevir/pegylated interferon/ribavirin
BOC + PR: boceprevir/pegylated interferon/ribavirin
SMV + PR: simeprevir/pegylated interferon/ribavirin
SOF + PR: sofosbuvir/pegylated interferon/ribavirin
R + SOF: ritonavir/sofosbuvir
LDV + SOF: ledipasvir/sofosbuvir
DCV + SOF: daclatasvir/sofosbuvir
SMV + SOF: simeprevir/sofosbuvir
ASV + DCV: asunaprevir/daclatasvir
OMB + PAR/r: ombitasvir/paritaprevir/ritonavir ± dasabuvir

FIGURE 7.4 Pooled proportions of rates of discontinuation due to adverse events in treatment-experienced hepatitis C genotypes 1 and 4 populations

Regimen	No. patients	Proportion (95% CI)
PR	592	3.25 (0.75, 5.76)
TVR + PR	650	8.26 (0.00, 22.70)
BOC + PR	457	12.09 (7.03, 17.15)
SMV + PR	811	0.58 (0.00, 1.58)
SOF + R	69	4.21 (0.00, 8.95)
SOF + LDV	495	0.00 (0.00, 0.56)
DCV + SOF	93	0.00 (0.00, 2.25)
SMV + SOF	167	1.45 (0.00, 3.94)
DCV + ASV	233	4.66 (1.89, 7.43)
OMB + PAR/r	912	1.04 (0.30, 1.77)

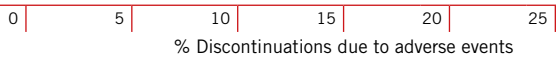


FIGURE 7.5 Pooled proportions of rates of serious adverse events in treatment-naive hepatitis C genotypes 1 and 4 populations

Regimen	No. patients	Proportion (95% CI)
PR	1540	7.67 (6.34, 8.99)
TVR + PR	641	7.11 (3.73, 10.50)
BOC + PR	901	10.89 (7.43, 14.35)
SMV + PR	811	4.85 (3.38, 6.33)
SOF + PR	504	2.62 (0.11, 5.13)
SOF + R	268	3.19 (0.38, 6.00)
SOF + LDV	1122	2.24 (0.76, 3.71)
DCV + SOF	183	0.92 (0.00, 2.49)
SMV + SOF	87	2.24 (0.00. 6.56)
DCV + ASV	265	8.33 (1.02, 15.65)
OMB + PAR/r	1619	2.18 (1.01, 3.35)

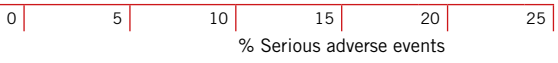
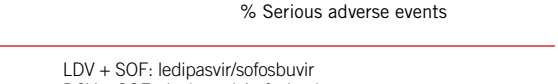


FIGURE 7.6 Pooled proportions of rates of serious adverse events in treatment-experienced hepatitis C genotypes 1 and 4 populations

Regimen	No. patients	Proportion (95% CI)
PR	592	6.95 (4.91, 8.99)
TVR + PR	650	10.23 (6.53, 13.93)
BOC + PR	457	12.18 (9.19, 15.18)
SMV + PR	918	4.65 (2.28, 7.02)
SOF + R	69	12.68 (4.85, 20.51)
SOF + LDV	495	2.92 (0.26, 5.57)
DCV + SOF	93	3.22 (0.00, 7.25)
SMV + SOF	167	0.77 (0.00, 3.20)
DCV + ASV	233	5.45 (2.47, 8.43)
OMB + PAR/r	912	2.68 (1.10, 4.26)



PR: pegylated interferon/ribavirin
TVR + PR: telaprevir/pegylated interferon/ribavirin
BOC + PR: boceprevir/pegylated interferon/ribavirin
SMV + PR: simeprevir/pegylated interferon/ribavirin
SOF + PR: sofosbuvir/pegylated interferon/ribavirin
R + SOF: ritonavir/sofosbuvir
LDV + SOF: ledipasvir/sofosbuvir
DCV + SOF: daclatasvir/sofosbuvir
SMV + SOF: simeprevir/sofosbuvir
ASV + DCV: asunaprevir/daclatasvir
OMB + PAR/r: ombitasvir/paritaprevir/ritonavir ± dasabuvir

patients with genotype 2 infection were treated with sofosbuvir/ribavirin. In these patients, SVR was achieved in 70–92% of treatment-naive patients and 70–93.5% of treatment-experienced persons. These results are in alignment with those from the clinical studies described above.

In these observational cohorts, 82 persons with genotype 3 infection were treated with sofosbuvir/daclatasvir for 12 or 24 weeks. When stratified by prior treatment experience, presence of cirrhosis and use of ribavirin, the overall numbers in each group were small (less than 38 per group). However, all persons without cirrhosis who were treatment naive and treated with daclatasvir/sofosbuvir ± ribavirin achieved SVR. In those who did not have cirrhosis and were treatment experienced, addition of ribavirin improved SVR rates from 89% to 100%. Among those with both prior treatment experience and cirrhosis, the addition of ribavirin increased SVR rates from 73.7% to 89.5%. These outcomes are better than those with pegylated interferon and ribavirin. Few results were available for patients with genotype 3 infection taking sofosbuvir/pegylated interferon/ribavirin. This treatment resulted in SVR rates of 100% in treatment-naive persons without cirrhosis, 82% in treatment-naive persons with cirrhosis, 85% in treatment-experienced persons without cirrhosis, and 77% in treatment-experienced persons with cirrhosis.

Data were available for a total of 77 persons infected with genotypes 5 or 6 who were treated with either sofosbuvir/pegylated interferon/ribavirin, or ledipasvir/sofosbuvir. The SVR rates were 100% with sofosbuvir/pegylated interferon/ribavirin and ≥95% with ledipasvir/sofosbuvir.

7.2.3 Rationale for the recommendation

Balance of benefits and harms

The Guidelines Development Group concluded that there was moderate-quality evidence that DAA regimens are superior to regimens that include pegylated interferon. In addition to the strength of the evidence, this recommendation was considered “strong” because the potential benefits of higher SVR rates and lower rates of SAEs and treatment discontinuation outweighed the potential harms. From a values and preferences perspective, DAA regimens are likely to be preferred by patients for these reasons, and because of their ease of administration and shorter duration of treatment. Furthermore, with the declining prices of medicines, DAA therapy is less expensive than interferon-based therapy in many countries. Finally, administering DAA therapy is easier than interferon-based therapy, which favours its implementation.

The Guidelines Development Group acknowledges that there remains a limited role for pegylated interferon and ribavirin in certain specific scenarios where currently data are limited in supporting DAA-only therapies. Specifically, these apply to persons infected with genotype 3 with compensated liver cirrhosis where, based on clinical study results, sofosbuvir/pegylated interferon/ribavirin confer the highest chance of SVR. Likewise, the lack of data on the use of DAAs among patients with genotypes 5 and 6 infection, sofosbuvir/pegylated interferon/ribavirin is recommended as an alternative regimen for these genotypes.

Values and preferences

As mentioned earlier, for patients, the likelihoods of a cure and lack of adverse events are the most important considerations related to treatment regimens, though patients also value factors such as not requiring injections and shorter courses of treatment. Thus, DAA therapy is likely to be acceptable to patients as it leads to higher cure rates, is shorter in duration, easier to administer, and leads to fewer adverse events.

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 patients with DAAs requires fewer health system costs as compared with interferon-based treatment because the treatment durations are shorter, and laboratory tests required and adverse events are fewer.

As for drug prices, these are variable and dynamic. The prices of DAAs are extremely high in high-income countries. Despite this, cost–effectiveness studies done in high-income countries indicate that the cost–effectiveness of DAA therapy is generally below the willingness-to-pay threshold of these countries. Few cost–effectiveness studies have been conducted in LMIC. Patients in low-income countries can benefit from low-cost generic formulations where licensing agreements have been signed with companies that manufacture generic medicines. Other countries negotiate tiered prices directly with the manufacturers. Because of these price arrangements, the price of DAA therapy is actually lower than interferon-based therapy in countries such as Mongolia and Ukraine (Table 7.1). Although the price of DAA therapy is higher in Brazil, when viewed from the perspective of price per SVR, the difference between interferon-based and DAA-based therapy is small (Tables 7.2).

Even with favourable prices of medicines, the budget impact of treating all patients already diagnosed with chronic HCV infection will be considerable. Table 7.3 presents the budget impact for Brazil, Mongolia and Ukraine. In Brazil, the overall cost would exceed US$ 3 billion. In Ukraine, the corresponding figure is nearly US$ 1.2 billion, and US$ 101 million in Mongolia.

7.2.4 Implementation

The experience of using DAAs in the United States, western Europe and Egypt demonstrates the feasibility of widening access to HCV treatment with the use of DAAs. In other related examples, notably HIV, wide-scale access to therapies in all income settings has been demonstrated to be feasible. Because of less intensive monitoring requirements, indirect on-treatment costs related to laboratory monitoring will be lower when compared to those with pegylated interferon and ribavirin.

As DAA therapy is easier to administer and requires less patient monitoring, lower-level health cadres (e.g. primary-care doctors or nurses) could administer

TABLE 7.1 Cost of drug per four weeks of HCV medication in Brazil, Mongolia and Ukraine (2015 US$)

Drug		Ribavirin ($)	Pegylated interferon ($)	Sofosbuvir ($)	Ledipasvir/ sofosbuvir ($)	Daclatasvir ($)
Country	Brazil	26.63	455.18[a]	2 300.00	3149.00	849.00
	Mongolia	26.63	455.18[a]	300.00	400.00	512.00
	Ukraine	21.19	118.00[a]	300.00	812.00	512.00

Source: Budget impact analysis (web Appendix 3, 2016)

[a] *Note:* pegylated interferon-based regimens generally have a duration of 48 weeks as compared with 12 or 24 weeks for DAA regimens.

TABLE 7.2 Estimated cost per patient (CPP) and cost per SVR (CPSVR) of selected DAA regimens in Brazil, Mongolia, Ukraine (2015 US$)

	Pegylated interferon/ribavirin		All DAAs	
	CPP ($)	CPSVR ($)	CPP ($)	CPSVR ($)
Brazil	5 368	10 733	10 831	11 312
Mongolia	7 036	15 316	1 709	1 739
Ukraine	3 173	6 150	2 953	3 097

Source: Budget impact analysis (web Appendix 3, 2016)

TABLE 7.3 Estimated total cost of treating all persons diagnosed with chronic HCV infection in Brazil, Mongolia, Ukraine (2015 US$) with DAA regimens

	No. of persons with chronic HCV infection	No. of persons diagnosed	No. achieving SVR	Drug cost (US$)	Other cost (US$)	Total cost (US$)
Brazil	2 036 570	314 934	299 734	3 324 524 944	65 984 876	3 390 509 821
Mongolia	198 764	59 629	58 249	81 417 808	19 897 906	101 315 714
Ukraine	1 024 858	410 783	387 365	972 405 729	227 160 446	1 199 566 175

Source: Number of persons with chronic HCV infection based on reference *(13)* and diagnosed based on reference *(9)*.

it. This would lead to the availability of treatment in more settings, including those for populations such as PWID and migrants, who are at high risk of infection but who have difficulty in accessing treatment services.

7.2.5 Research questions

1. More data are required in specific subpopulations, including those with severe renal impairment (i.e. eGFR <30 mL/min/1.73 m^2 and on haemodialysis), persons under the age of 18 years, pregnant women, and those coinfected with HBV.

2. More data are needed to identify predictive factors to select persons who could be treated for shorter durations of therapy.

3. To date, there are limited data on cost–effectiveness evaluation in LMIC using DAAs. These data may prove beneficial in aiding policy-makers with decision-making on resource allocation for DAAs.

4. Emerging evidence suggests that NS5A resistance may result in lower SVR rates; however, the clinical importance of resistance is not known.

5. More studies are needed to help guide treatment decisions following treatment failure, and what second- or third-line strategies should be advocated.

6. Regional registries in LMIC would help provide currently missing data for "real-world" outcomes in these settings.

7. Algorithms with simplified approaches to screening, treatment and monitoring for chronic HCV infection should be evaluated for use in primary-care settings.

8. Research is required on the development of a vaccine for primary prevention of HCV infection.

9. More studies are needed on the co-management of chronic HCV infection and active TB.

7.3 Removal of recommendation for treatment with telaprevir or boceprevir

New recommendation

The use of boceprevir- or telaprevir-containing regimens is no longer recommended for the treatment of persons with hepatitis C infection.

Strong recommendation, moderate quality of evidence

7.3.1 Background

Telaprevir and boceprevir are first-generation protease inhibitors, which when administered with pegylated interferon/ribavirin to persons infected with HCV genotype 1, result in higher SVR rates as compared with pegylated interferon and ribavirin alone. As a result, they were included in the WHO 2014 HCV guidelines for consideration of treatment for genotype 1 HCV infection. However, these regimens result in high rates of SAEs, including adverse events related to interferon and ribavirin, as well as those related to telaprevir and boceprevir. Compared with the newer DAAs, the treatment effectiveness of telaprevir- or boceprevir-containing regimens is lower and adverse effects are more frequent. In particular, patients with advanced disease, such as those with a platelet count <100 000/mm^3 and albumin <35 g/L at baseline (envisaged to be a significant proportion of patients treated in the initial phases in many countries) are more likely to die or to have severe infection or decompensation *(193)*. While these medicines may still be marketed in certain countries, the manufacturers have decided to withdraw them from most high-income countries. Furthermore, these medicines are no longer recommended by either the 2015 guidelines by EASL or AASLD *(194, 195)*.

7.3.2 Evidence

The systematic review identified seven study arms that evaluated telaprevir and four study arms that evaluated boceprevir in genotype 1 or 4 HCV infection. From the network meta-analysis, the SVR rates were lower for treatment-naive (76.5%; 95% CrI 70.2, 82.7%) and treatment-experienced (59.4%; 95% CrI 50.0%, 68.8%) patients treated with telaprevir/pegylated interferon/ribavirin compared with patients treated with regimens of DAA combinations, all of which produced SVR rates >90% for both treatment-naive and -experienced patients (Fig. 7.1 and 7.2). The results were similar for boceprevir/pegylated interferon/ribavirin. The risk differences in SVRs between boceprevir- and telaprevir-containing regimens and newer DAA regimens were all statistically significant. Higher rates of discontinuation (range 8.3–13.6%) and SAEs (range 7.1–12.2%) were observed among treatment-naive and -experienced patients treated with telaprevir- and boceprevir-containing regimens than among patients treated with all-DAA regimens (range 0.0–6.8% for discontinuation and range 0.9–12.7% for SAEs) (Fig. 7.3 to 7.6). The factors affecting the quality of the evidence were indirectness and risk of bias; thus, the evidence was considered to be of moderate quality.

7.3.3 Rationale for the recommendation

Balance of benefits and harms

The balance of benefits and harms favoured treatment with newer DAA regimens over treatment with boceprevir or telaprevir because of higher rates of SVR, and lower rates of adverse events and treatment discontinuation. The regimen durations with boceprevir and telaprevir are also longer and require the co-administration of interferon; therefore, they are unlikely to be preferred by patients. Using newer DAAs that do not require interferon rather than continuing to use telaprevir and boceprevir should be associated with significant benefits and no harms.

Values and preferences

Boceprevir- and telaprevir-based regimens are associated with higher rates of adverse events and lower efficacy than the newer DAA therapies. The regimens are longer in treatment duration, require weekly injections, and more intensive laboratory monitoring. They are therefore unlikely to be acceptable to patients in the presence of better options (i.e. newer DAAs).

Resource considerations

DAAs require a shorter duration of therapy, have fewer monitoring requirements and are less likely to incur costs of managing side-effects when compared with treatment with boceprevir- or telaprevir-based regimens. Because of the shorter treatment duration and in countries where the price of newer DAAs has been reduced, 8–12 weeks of treatment with newer DAAs should be less expensive than treatment with boceprevir- or telaprevir-based regimens. In the long run, treatment with newer DAAs with appropriately negotiated pricing is envisaged to require fewer resources than treatment with boceprevir- or telaprevir-based regimens.

7.3.4 Implementation

As discussed in section 7.2, avoiding the use of pegylated interferon/ribavirin and not having to manage frequent SAEs related to both interferon, and boceprevir and telaprevir will facilitate the implementation of HCV treatment. To ensure that these medicines are no longer prescribed, national medicines agencies should consider removing telaprevir and boceprevir from national formularies and treatment guidelines/protocols.

7.4 Preferred and alternative regimens for the treatment of persons with chronic hepatitis C virus infection

New recommendation

For persons with HCV genotype 1 infection without and with cirrhosis, treatment with ledipasvir/sofosbuvir with/without ribavirin or daclatasvir/sofosbuvir with/without ribavirin is recommended.

Alternative recommended treatment regimens for persons with genotype 1 infection without and with cirrhosis is simeprevir/sofosbuvir with/without ribavirin or ombitasvir/paritaprevir/ritonavir/dasabuvir with/without ribavirin.

Strong recommendation, moderate quality of evidence

New recommendation

For persons with HCV genotype 2 infection without and with cirrhosis, treatment with sofosbuvir/ribavirin is recommended.

The alternative recommended regimen is daclatasvir/sofosbuvir.

Strong recommendation, low quality of evidence

New recommendation

For persons with HCV genotype 3 infection without cirrhosis, treatment with daclatasvir/sofosbuvir or sofosbuvir/ribavirin is recommended.

For persons with HCV genotype 3 infection with cirrhosis, treatment with daclatasvir/sofosbuvir/ribavirin is recommended.

The alternative suggested regimen for persons with HCV genotype 3 infection with cirrhosis is sofosbuvir with pegylated interferon/ribavirin.

Strong recommendation, low quality of evidence

New recommendation

For persons with HCV genotype 4 infection without and with cirrhosis, treatment with ledipasvir/sofosbuvir with/without ribavirin or daclatasvir/sofosbuvir with/without ribavirin is recommended.

Alternative recommended treatment regimens for genotype 4 infection without and with cirrhosis is simeprevir/sofosbuvir with/without ribavirin or ombitasvir/paritaprevir/ritonavir with ribavirin.

Strong recommendation; moderate quality of evidence

New recommendation

For persons with HCV genotype 5 or 6 infection without and with cirrhosis, treatment with ledipasvir/sofosbuvir is recommended.

The alternative recommended regimen is sofosbuvir/pegylated interferon/ribavirin.

Conditional recommendation, very low quality of evidence

Regimens with daclatasvir, ledipasvir and sofosbuvir can be prescribed to patients without cirrhosis as well as those with compensated and decompensated cirrhosis.

Regimens with paritaprevir, simeprevir and pegylated interferon can be prescribed to persons without cirrhosis or with compensated cirrhosis but not to persons with decompensated cirrhosis because they can cause liver failure and death in these persons. Therefore, if prescribed to persons with cirrhosis, they should be used only in settings where specialized care is available and where the degree of cirrhosis (compensated vs decompensated) can accurately be assessed.

Table 7.4 provides a summary of the recommended preferred and alternative regimens for treatment of HCV infection with each genotype. Tables 7.5 and 7.6 give the recommended preferred and alternative treatment durations in persons with and without cirrhosis, respectively. There was insufficient evidence to be able to formulate recommendations regarding specific treatment durations. Rather, a summary of existing treatment-duration recommendations from the 2015 AASLD and EASL guidelines is presented in Tables 7.5 and 7.6. Where the recommendations differed between these two guidelines, the regimen with fewer options (e.g. "ribavirin 12 weeks" rather than "ribavirin 12 or 24 weeks") was selected.

TABLE 7.4 Recommended preferred and alternative regimens with quality of evidence and strength of recommendation

	Preferred	Alternative	Strength of recommendation	Quality of evidence
Genotype 1 without cirrhosis	Daclatasvir/sofosbuvir or ledipasvir/sofosbuvir	Simeprevir/sofosbuvir or ombitasvir/paritaprevir/ritonavir/ dasabuvir ± ribavirin	Strong	Moderate
Genotype 1 with cirrhosis	Daclatasvir/sofosbuvir ± ribavirin or ledipasvir/ sofosbuvir ± ribavirin	Simeprevir/sofosbuvir ± ribavirin or ombitasvir/paritaprevir/ritonavir/ dasabuvir ± ribavirin		
Genotype 2 with and without cirrhosis	Sofosbuvir/ribavirin	Daclatasvir/sofosbuvir	Strong	Low
Genotype 3 without cirrhosis	Daclatasvir/sofosbuvir or sofosbuvir/ribavirin		Strong	Low
Genotype 3 with cirrhosis	Daclatasvir/sofosbuvir / ribavirin	Sofosbuvir/pegylated interferon/ ribavirin		
Genotype 4 without cirrhosis	Daclatasvir/sofosbuvir or ledipasvir/sofosbuvir	Simeprevir/sofosbuvir or ombitasvir/ paritaprevir/ritonavir /ribavirin	Strong	Moderate
Genotype 4 with cirrhosis	Daclatasvir/sofosbuvir ± ribavirin or ledipasvir/ sofosbuvir ± ribavirin	Simeprevir/sofosbuvir ± ribavirin or ombitasvir/paritaprevir/ritonavir /ribavirin		
Genotype 5 or 6 with and without cirrhosis	Ledipasvir/sofosbuvir	Sofosbuvir/pegylated interferon/ ribavirin	Conditional	Very low

TABLE 7.5 Summary of recommended preferred regimens with treatment durations*

Persons without cirrhosis

	Daclatasvir/ sofosbuvir	Ledipasvir/ sofosbuvir	Sofosbuvir/ ribavirin
Genotype 1	12 weeks	12 weeks[a]	
Genotype 2			12 weeks
Genotype 3	12 weeks		24 weeks
Genotype 4	12 weeks	12 weeks	
Genotype 5		12 weeks	
Genotype 6		12 weeks	

Persons with cirrhosis

	Daclatasvir/ sofosbuvir	Daclatasvir/ sofosbuvir/ ribavirin	Ledipasvir/ sofosbuvir	Ledipasvir/ sofosbuvir / ribavirin	Sofosbuvir/ ribavirin
Genotype 1	24 weeks	12 weeks	24 weeks	12 weeks[b]	
Genotype 2					16 weeks
Genotype 3		24 weeks			
Genotype 4	24 weeks	12 weeks	24 weeks	12 weeks[b]	
Genotype 5			24 weeks	12 weeks[b]	
Genotype 6			24 weeks	12 weeks[b]	

* Treatment durations are adapted from the 2015 guidelines of the American Association for the Study of Liver Diseases (AASLD) and European Association for the Study of the Liver (EASL).

[a] Treatment may be shortened to 8 weeks in treatment-naive persons without cirrhosis if their baseline HCV RNA level is below 6 million (6.8 log) IU/mL. The duration of treatment should be shortened with caution.

[b] If platelet count <75 x 10^3/μL, then 24 weeks' treatment with ribavirin should be given.

TABLE 7. 6 Summary of recommended alternative regimens with treatment durations*

Persons without cirrhosis

	Simeprevir/ sofosbuvir	Daclatasvir/ sofosbuvir	Ombitasvir/ paritaprevir/ ritonavir/ dasabuvir	Ombitasvir/ paritaprevir/ ritonavir/ ribavirin	Sofosbuvir/ pegylated interferon/ ribavirin
Genotype 1	12 weeks[a]		12 weeks[b]		
Genotype 2		12 weeks			
Genotype 3					
Genotype 4	12 weeks			12 weeks	
Genotype 5					12 weeks
Genotype 6					12 weeks

* Treatment durations are adapted from 2015 AASLD and EASL guidelines.

[a] If genotype 1a-infected patient is positive for the Q80K variant, a simeprevir/sofosbuvir regimen should not be chosen.

[b] For genotype 1a-infected patients, treat with ombitasvir/paritaprevir/ritonavir/dasabuvir and ribavirin; for genotype 1b-infected patients, treat with ombitasvir/paritaprevir/ritonavir/dasabuvir.

Persons with cirrhosis

	Can be prescribed to persons with compensated or decompensated cirrhosis	These regimens should be prescribed only to persons with compensated cirrhosis because they can cause liver failure and death when prescribed to persons with decompensated cirrhosis. Therefore, they should be used only in settings where specialized care is available and where the degree of cirrhosis (compensated vs decompensated) can accurately be assessed.				
	Daclatasvir/ sofosbuvir	**Simeprevir/ sofosbuvir**	**Simeprevir/ sofosbuvir/ ribavirin**	**Ombitasvir/ paritaprevir/ ritonavir/ dasabuvir**	**Ombitasvir/ paritaprevir/ ritonavir/ ribavirin**	**Sofosbuvir/ pegylated interferon/ ribavirin**
Genotype 1		24 weeks[a]	12 weeks[a]	24 weeks[b]		
Genotype 2	12 weeks					
Genotype 3						12 weeks
Genotype 4		24 weeks	12 weeks[a]		24 weeks	
Genotype 5						12 weeks
Genotype 6						12 weeks

* Treatment durations are adapted from the 2015 AASLD and EASL guidelines.

[a] If genotype 1a-infected patient is positive for the Q80K variant, a simeprevir/sofosbuvir regimen should not be chosen.

[b] For genotype 1a-infected patients, treat with ombitasvir/paritaprevir/ritonavir/dasabuvir and ribavirin for 24 weeks; for genotype 1b-infected patients, treat with ombitasvir/paritaprevir/ritonavir/dasabuvir and ribavirin for 12 weeks.

7.4.1 Background

Since the first WHO hepatitis C treatment guidelines were issued in 2014, several new DAA regimens have gained regulatory approval. These regimens have been studied in different combinations and among different patient groups (i.e. by genotype, treatment experience, presence/absence of cirrhosis and coinfection). As a result, different treatment regimens are indicated for different patient groups. This profusion of regimens results in confusion among health-care workers as to which treatment should be prescribed for which patient. With the move toward all-DAA-based therapy, the Guidelines Development Group felt it important that guidance be provided as to which regimens were preferred for the various genotypes and patient groups.

7.4.2 Evidence

Genotypes 1 and 4

Numerous studies evaluated the efficacy of DAA regimens among treatment-naive and -experienced patients with genotypes 1 and 4 infection (Fig. 7.1 to 7.6; web Appendix 2, 2016). Of these, daclatasvir/sofosbuvir, ombitasvir/paritaprevir/ritonavir ± dasabuvir, ledipasvir/sofosbuvir, and simeprevir/sofosbuvir all resulted in SVR rates of >96% in treatment-naive patients with genotype 1 infection. An SVR rate of 46.9% was obtained for pegylated interferon/ribavirin, 77.3% for sofosbuvir/ribavirin, 80.5% for simeprevir/pegylated interferon/ribavirin, and 83.1% for asunaprevir/daclatasvir. The results were similar among treatment-experienced patients, where the CrIs for the DAA regimens were overlapping, and thus were

statistically indistinguishable. Results were also similar for rates of treatment discontinuation and SAEs, where all the DAA regimens had comparable outcomes to each other.

The Guidelines Development Group recommended specific preferred regimens among those that performed similarly, based on their safety and efficacy, acceptability to patients, complexity of regimens, need for subgenotyping, and likely important DDIs. Based on these criteria, daclatasvir/sofosbuvir and ledipasvir/sofosbuvir are considered preferred regimens.

For persons without cirrhosis, simeprevir/sofosbuvir and ombitasvir/paritaprevir/ritonavir ± dasabuvir were listed as alternative choices because of the need for Q80K testing prior to simeprevir therapy and, for ombitasvir/paritaprevir/ritonavir, the need for twice-daily dosing and frequency of DDIs. Also, ombitasvir/paritaprevir/ritonavir ± dasabuvir could lead to HIV ARV resistance if prescribed to persons with undiagnosed HIV infection who would unwittingly be prescribed single-drug HIV treatment (i.e. ritonavir).

The protease inhibitors simeprevir and paritaprevir as well as pegylated interferon pose an additional concern. When prescribed to patients with decompensated cirrhosis, they can precipitate liver failure and death. For this reason, according to the FDA and EMA, these medicines can be used among persons with compensated cirrhosis (Child–Pugh Class A) but are contraindicated for individuals with decompensated cirrhosis (Child–Pugh Class B and C). Therefore, they should be used only in settings where specialized care is available and where the degree of cirrhosis (compensated vs decompensated) can be accurately assessed.

Genotype 2

In the systematic review, 17 study arms evaluated treatment outcomes among treatment-naive and -experienced patients with genotype 2 infection. DAA regimens that were evaluated included sofosbuvir/ribavirin, and daclatasvir/sofosbuvir ± ribavirin. Because of the scarcity of data, a network meta-analysis model was not possible; thus, comparisons are based on direct pooled SVR rates (web Appendix 2, 2016). The pooled SVR rate for treatment-naive patients treated with sofosbuvir/ribavirin was 94.5% (95% CI 91.9%, 96.6%) and with pegylated interferon/ribavirin it was 78.3% (95% CI 68.6%, 86.7%). The pooled SVR rate for treatment-experienced patients treated with sofosbuvir/ribavirin for 12 weeks was 91.0% (95% CI 85.7%, 95.1%) and 24 weeks was 88.0% (95% CI 74.7%, 96.8%). A total of 21 patients were in the three daclatasvir/sofosbuvir study arms (19 treatment-naive and 2 treatment-experienced), all of whom achieved SVR *(196, 197)*. One additional study provided data on daclatasvir/sofosbuvir/ribavirin among five patients who were either treatment-naive or -experienced. Of these, 80% (95% CI 28.4%, 99.5%) achieved SVR. The rate of discontinuation due to adverse events was ≤0.05%, the rate of SAEs was ≤0.03%, and the mortality rate was zero among both treatment-naive and -experienced patients with genotype 2 infection.

Genotype 3

Twenty-one study arms evaluated different DAA regimens among patients with genotype 3 infection. Despite different treatment durations, among treatment-naive patients, the pooled SVR rates were comparable: for patients treated with sofosbuvir/ribavirin 92.2% (95% CI 88.1%, 95.5%), sofosbuvir/pegylated interferon/ribavirin 93.3% (95% CI 83.4%, 99.0%), or daclatasvir/sofosbuvir 12 weeks 90.1% (95% CI 83.0%, 95.0%) and daclatasvir/sofosbuvir 24 weeks 100.0% (95% CI 90.7%, 99.8%)(web Appendix 2, 2016). The pooled SVR rate for daclatasvir/sofosbuvir/ribavirin among treatment-experienced patients was 91.5% (95%CI 85.6%, 97.4%) for treatment duration 12 weeks and 16 weeks. In persons with cirrhosis, to date, clinical trial data demonstrate limited support for DAA-only regimens. Daclatasvir/sofosbuvir for 12 weeks without ribavirin results in an SVR rate of 62.2% (95%CI 46.6%, 77.8%), sofosbuvir/ribavirin for 24 weeks has an SVR rate of 77.7% (95%CI 69.9%, 85.5%) in persons with cirrhosis *(198, 199)*. Discontinuation rates were the highest (10.4%) among treatment-naive patients treated with pegylated interferon/ribavirin for 24 weeks, followed by 5.0% among treatment-experienced persons treated for 24 weeks with sofosbuvir/ribavirin. The discontinuation rate of DAA regimens was ≤0.03%. The rate of SAEs was ≤0.04% for treatment-naive persons but was higher in treatment-experienced patients, 0.01–9.4%. The mortality was zero in all study arms.

Genotypes 5 and 6

Four studies consisting of 77 patients assessed treatment efficacy among patients infected with HCV genotypes 5 and 6. The first study assessed sofosbuvir/pegylated interferon/ribavirin in five treatment-naive genotype 6 patients and all achieved SVR *(200)*. The second study arm assessed sofosbuvir/pegylated interferon/ribavirin in five treatment-naive genotype 6 patients and one treatment-naive genotype 5 patient and all achieved SVR *(201)*. One study provided data for 21 treatment-naive and 20 treatment-experienced patients infected with genotype 5, while another study included 25 treatment-naive and -experienced patients infected with genotype 6 who were treated with 12 weeks of ledipasvir/sofosbuvir. SVRs in both studies were ≥95% *(202, 203)*. Outcomes in patients infected with genotypes 5 and 6 appear consistent with outcomes for patients with genotypes 1 and 4 (although there are no data evaluating the use of ombitasvir/paritaprevir/ritonavir ± dasabuvir). As such, the limited data from clinical trials supporting the use of ledipasvir/sofosbuvir in patients infected with genotypes 5 and 6 show comparable results to those of patients infected with genotypes 1 and 4, which lends support for its use as first-line therapy. However, given the paucity of data, the Guidelines Development Group also advocates the use of sofosbuvir/pegylated interferon/ribavirin as alternative regimens. In settings where first-line recommended regimens are not yet available, during the period of transition to more optimal regimens, use of sofosbuvir/ribavirin or sofosbuvir/pegylated interferon/ribavirin can be considered.

7.4.3 Rationale for the recommendation

Balance of benefits and harms

The preferred regimens were selected based on evidence of higher cure rates, lower rates of adverse events, and ease of administration, compared with other regimens. With the exception of patients with cirrhosis infected with genotypes 3, 5 and 6, the Guidelines Development Group was able to identify preferred or alternative regimens that do not require pegylated interferon and ribavirin. These two medicines have much higher toxicity than the DAAs; thus, the benefits of using the selected regimens outweigh the harms, leading to strong recommendations for most of the selected regimens, including for genotypes 2 and 3, where the strength of evidence was considered low. The Guidelines Development Group felt that a strong recommendation was warranted because the benefits of the recommended all-DAA regimens greatly outweighed the harms, because patients are likely to greatly prefer the DAA regimens, and because the newer regimens are now less expensive than interferon-based regimens in many countries.

Values and preferences

The selected regimens are likely to be acceptable to patients because of their high efficacy and safety, and ease of use. The preferred regimens are all oral, taken for a relatively short duration, and once per day.

Resource considerations

The Guidelines Development Group recognizes that at the time of writing of these guidelines, there are substantial intercountry variations in the price and availability of these regimens. Among the recommended regimens, daclatasvir/sofosbuvir and ledipasvir/sofosbuvir are the preferred or alternative regimens for all of the genotypes except for patients with genotype 3 infection with cirrhosis. The medicines for these two regimens are included in voluntary licensing agreements signed between the originator companies and generics companies. Daclatasvir/sofosbuvir and ledipasvir/sofosbuvir are already available in generic formulations in some countries. The introduction of generic formulations results in lower prices; the price for a 12-week regimen of generic sofosbuvir is reported to be less than US$ 500/patient in India *(204).* Wide-scale implementation of HCV treatment will be facilitated by this rapid reduction in the price of DAAs.

7.4.4 Implementation

The ideal situation vis-à-vis regimen selection would be to have a single regimen for all genotypes and for all patients, regardless of their degree of cirrhosis and previous treatment experience. The recommended regimens in these guidelines are a significant step in that direction. Furthermore, the selected preferred regimens provide clinicians with the opportunity of prescribing interferon- and ribavirin-free regimens for everyone (except

patients who have genotype 2 infection or both cirrhosis and genotype 3 infection). This simplifies implementation by lessening the requirement for genotype testing (in countries where a single genotype predominates) as well as reducing the risk of treatment discontinuation due to adverse events.

The Guidelines Development Group recognizes that despite these advances, implementation of the recommendations may not be immediate. In addition to the high prices, these medicines have not yet received regulatory approval in many countries. Clinicians in many countries are not aware of the availability of these medicines. It is hoped that these recommendations will provide policy-makers with a framework for initiating the implementation of therapies with the potential for wide-scale provision of treatment, on account of high efficacy and less need for medical testing and interventions before, during and after treatment.

7.4.5 Research questions

1. More clinical study and observational data are required on treatment outcomes with DAAs in patients infected with genotypes 2, 3, 5 and 6 in order to provide more robust guidance.

2. Data supporting DAA-only therapies are limited in patients infected with genotype 3, particularly in those with cirrhosis. Further data on current regimens, especially daclatasvir/sofosbuvir/ribavirin for 12 weeks, as well as newer second-generation DAAs, are required to address this unmet need.

7.5 Treatment with pegylated interferon and ribavirin

Existing recommendation from 2014

Pegylated interferon in combination with ribavirin is recommended for the treatment of chronic HCV infection rather than standard non-pegylated interferon with ribavirin.

Strong recommendation, moderate quality of evidence

Note: In settings where access to treatment for HCV infection is limited, priority for treatment should be given to patients with advanced fibrosis and cirrhosis (METAVIR stages F3 and F4).

7.5.1 Background

Although the treatment for HCV infection is moving away from the use of interferon, it is still the only recommended medicine for children and adolescents and, as an alternative regimen, for certain genotypes. When treatment regimens include interferon, the pegylated formulation is the accepted standard of care in high-income countries because it has a longer half-life, resulting in the need for less frequent injections and because it results in higher SVR rates than standard interferon. Despite this, standard interferon continues to be used in some LMIC because it is much less expensive than pegylated interferon. The 2014 Guidelines Development Group felt that it

was important to analyse the evidence and provide a clear recommendation on which form of interferon was preferable.

7.5.2 Evidence

A systematic review was conducted to assess the efficacy of pegylated interferon/ribavirin versus interferon/ribavirin in treatment-naive adults and children with chronic HCV infection. Outcomes assessed were SVR, decompensated liver disease, HCC, all-cause mortality, adverse events and quality of life (web Appendix 3, 2014).

Twenty-five articles were included in the analysis, and evidence for the outcome of SVR from these studies was considered to be of high quality due to the precision and consistency of the results, and the low risk of bias. The available evidence indicated that the use of pegylated interferon/ribavirin is more effective at achieving SVR among people with chronic HCV compared with standard interferon/ribavirin (RR 0.81; 95% CI 0.76, 0.86). The anticipated absolute effect estimates that 661 per 1000 persons treated with standard interferon would fail to reach SVR (which equates to an SVR of 33.9%) while 535 per 1000 persons would fail to reach SVR with pegylated interferon (which equates to an SVR of 46.5%). The increased efficacy of pegylated interferon was observed in infection with genotype 1 and non-genotype 1, in persons with and without cirrhosis, and in treatment-naive and -experienced individuals.

The studies found no difference in treatment discontinuation rates due to adverse events when comparing pegylated interferon versus standard interferon. The data on adverse events were evaluated as being of moderate quality and revealed no significant difference in the rate of study termination due to adverse events among patients administered pegylated interferon versus standard interferon. Limited data were available on some outcomes, including liver-related mortality, hepatic decompensation and HCC. From the data available, 14 fewer cases of HCC per 1000 cases occurred with pegylated interferon (baseline 21 per 1000), 3 fewer cases of hepatic decompensation (from 17 per 1000) and 5 fewer cases of liver-related mortality (from 15 per 1000). One more patient per 1000 terminated treatment due to adverse events (from 118 per 1000).

Three studies have been carried out in persons with HIV/HCV coinfection *(205–207).* The ACTG 5071, RIBAVIC and APRICOT studies compared standard interferon and ribavirin with pegylated interferon and ribavirin. In the APRICOT study, the SVR rate was significantly higher in those who received pegylated interferon and rivabirin than in those who received standard interferon and ribavirin, and reached 62% in genotype 2 or 3 infection but only 29% in genotype 1 infection. In the RIBAVIC study, SVR rates were higher in the pegylated interferon and ribavirin arms (27% versus 20%) but lower than in APRICOT; this was likely to have been related to a very high treatment discontinuation rate (42%). In the ACTG 5071 study, overall, SVR rates for genoptypes 1 and non-1 combined were 27% and

12%, respectively. Treatment discontinuation rates were also higher in the standard interferon arm.

7.5.3 Rationale for the recommendation

Balance of benefits and harms

The 2014 Guidelines Development Group concluded that there is high-quality evidence that pegylated interferon and ribavirin are more effective than standard interferon and ribavirin. Furthermore, there was no difference in the rates of adverse events or longer-term outcomes. Therefore, the 2014 Guidelines Development Group felt that the benefits of pegylated interferon versus standard interferon clearly outweighed the risks.

Values and preferences

The option was considered to be likely to be acceptable to patients as pegylated interferon is easier to administer. It requires less frequent injections than standard interferon and is associated with a substantially higher chance of SVR without an increase in side-effects.

Resource considerations

The reason that standard interferon continues to be used in some countries is because it is less expensive than pegylated interferon. The principal barrier to more extensive use of pegylated interferon is its high cost. Pegylated interferon is manufactured by a limited number of companies, and the cost of a 48-week regimen of pegylated interferon and ribavirin varies between US$ 2000 in Egypt and US$ 28 000 in Viet Nam. Modelling has shown that treatment of patients with compensated cirrhosis is cost–effective in this context *(190).* Feasibility is likely to vary substantially in different clinical settings. Treatment requires clinical infrastructure for follow up and monitoring on therapy, but has been successfully rolled out in several LMIC. In particular, Egypt has made treatment available to a large number of patients.

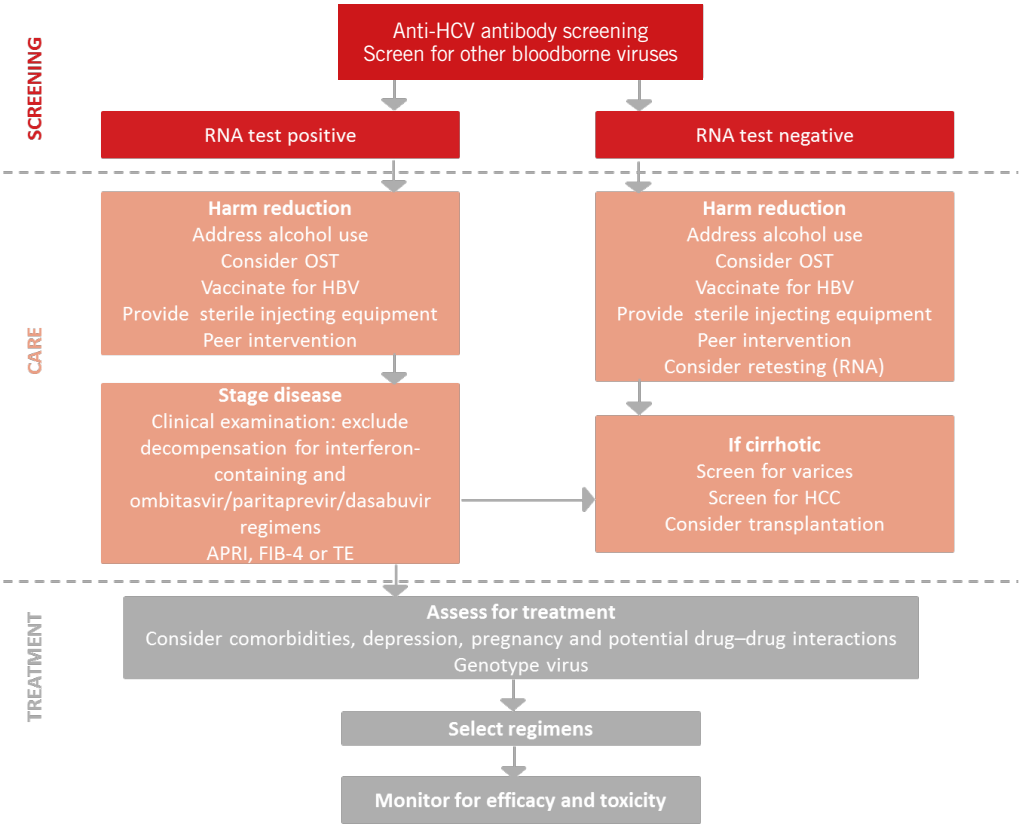
7.5.4 Implementation

The recommended duration of treatment varies, depending on combination with DAAs, the genotype, stage of disease, coinfection with HIV and initial response to treatment. Furthermore, pegylated interferon is recommended only for children older than 2 years of age.

8. CLINICAL CONSIDERATIONS

A number of clinical considerations are important for the management of persons with chronic HCV infection. These will influence the selection of a specific treatment regimen and how patients will be monitored for side-effects. Because of the complexity of the questions involved, the 2014 Guidelines Development Group did not formally assess these types of considerations. Rather, existing recommendations, guidelines and package insert guidance were reviewed and discussed. These are presented here to assist policy-makers and clinicians in identifying factors that may affect treatment choices. These should be considered in conjunction with the recommended treatment regimens covered in Chapter 7 and considerations for specific populations covered in Chapter 9. A typical patient treatment pathway is shown in Fig. 8.1.

FIGURE 8.1 Patient treatment pathway



APRI: aminotransferase/platelet ratio index; HBV: hepatitis B virus; HCC: hepatocellular carcinoma; HCV: hepatitis C virus; OST: opioid substitution therapy; TE: transient elastography

8.1 Clinical assessment of patients prior to treatment

Pre-treatment evaluation of the risk of adverse events should be based on the patient's clinical details, concomitant medications, and knowledge of treatment regimen to be administered. The potential for DDIs should be assessed before treatment, and a regimen that has a low risk of DDI selected. Standard laboratory tests that are assessed prior to treatment initiation include a full blood count (FBC), international normalized ratio (INR), renal function and liver function tests: ALT, AST, bilirubin, albumin and alkaline phosphatase. In patients undergoing treatment with interferon, thyroid function tests and fundoscopy should also be performed before treatment.

8.1.1 Genotype testing

In most countries, there is a mix of HCV genotypes among persons with chronic HCV infection (*see* Fig. 2.1). The 2016 Guidelines provide recommendations on the preferred and alternative DAA regimens by HCV genotype. Therefore, knowing a patient's genotype is still important for determining the most appropriate treatment regimen. Genotyping is usually carried out following sequencing of the 5'UTR (untranslated region) or of the NS5B region of the HCV genome. Genotype determination, however, is expensive and not available in all settings. Where genotype information is unavailable, pragmatic decision-making may be required, taking into account the common genotypes circulating in the affected population. However, this advice would only be practicable in countries such as Egypt or Mongolia, where almost all persons are infected with a single genotype.

Q80K mutation testing

A reduction in the efficacy of treatment with simeprevir occurs in persons with genotype 1a HCV infection with NS3 Q80K polymorphism. Therefore, patients need to be tested for the presence of this polymorphism prior to prescribing simeprevir and to consider alternative therapy if it is detected. This test is expensive and is not widely available in LMIC.

IL28B testing

IL28B testing is useful in predicting the response to interferon therapy. Favourable genotypes include the CC genotype at rs12979860, TT at rs8099917 and AA at rs12980275 *(208, 209)*. However, this test is not helpful in predicting response to DAA therapy, and thus is no longer part of the pre-treatment evaluation.

8.1.2 Contraindications to treatment

There are many contraindications to interferon- and ribavirin-based therapy, including depression, decompensated cirrhosis, and comorbidities. However, DAA therapy has many fewer contraindications, and thus can be used in a wider range of persons. Tables 8.1–8.3 list these conditions, which are based on product labels and the guidelines of the 2015 guidelines of the AASLD and EASL. *(194,*

195). Some of the DAAs can be used in persons with decompensated cirrhosis. However, this condition remains a contraindication for the use of simeprevir and combined ombvitasvir/paritaprevir/dasabuvir/ritonavir or ombitasvir/paritaprevir/ritonavir as well as pegylated interferon and ribavirin. Pregnant women should not receive ribavirin as it causes fetal malformations. Because of this risk, sexually active women of childbearing age and their male partners are counselled to use double contraception (including condoms with spermicide) during and for six months after therapy. Many persons treated with interferon will develop depression; interferon-containing regimens are contraindicated in those with uncontrolled depression, psychosis or epilepsy. There are reports of suicide among persons receiving interferon therapy and therefore careful patient selection is required in persons with depression.

TABLE 8.1 Therapy with direct-acting antivirals: contraindications/warnings

Drug	Contraindication/warning
Ledipasvir/sofosbuvir	• Amiodarone co-administration • P-glycoprotein (gp) inducers • Renal failure (eGFR <30 mL/min/1.73 m^2)
Daclatasvir	• Drugs inducing or inhibiting CYP3A
Sofosbuvir	• Amiodarone co-administration (caution also with beta-blockers) • Renal failure (eGFR <30 mL/min/1.73 m^2)
Ombitasvir/dasabuvir/paritaprevir/ritonavir or ombitasvir/dasabuvir/ritonavir	• Child–Pugh Class B and C cirrhosis • Drugs inducing or inhibiting CYP3A or CYP2C8 • Hypersensitivity to any component including ritonavir • Untreated HIV-1 infection because ritonavir can lead to antiretroviral drug resistance
Simeprevir	• Child–Pugh Class B and C cirrhosis • CYP3A interaction

Source: Based on product label information and the 2015 AASLD and EASL guidelines *(194, 195)*.
eGFR: estimated glomerular filtration rate; gp: glycoprotein

TABLE 8.2 Contraindications to therapy with ribavirin

Absolute contraindications
• Pregnancy or unwillingness to use contraception • Breastfeeding women • Severe concurrent medical disease, including severe infections • Poorly controlled cardiac failure • Chronic obstructive pulmonary disease • Previous ribavirin hypersensitivity • Co-administration of didanosine
Relative contraindications
• Abnormal haematological indices: - Hb <10 g/dL - Neutrophil count <1.5x10^9/L - Platelet count <90x10^9/L • Serum creatinine >1.5 mg/dL • Haemoglobinopathies (sickle cell disease or thalassaemia) • Significant coronary artery disease

Source: Based on product label information and the 2015 AASLD and EASL guidelines *(194, 195)*.

TABLE 8.3 Contraindications to the use of pegylated interferon

Absolute contraindications
• Uncontrolled depression or psychosis • Uncontrolled epilepsy • Uncontrolled autoimmune disease • Decompensated cirrhosis • Pregnancy or unwillingness to use contraception • Breastfeeding women • Severe concurrent medical disease, including severe infections • Poorly controlled hypertension • Poorly controlled cardiac failure • Poorly controlled diabetes • Solid organ transplant (except liver transplant recipients) • Chronic obstructive pulmonary disease • Age less than 2 years • Previous interferon hypersensitivity • Co-administration of didanosine
Relative contraindications
• Abnormal haematological indices: - Hb <10 g/dL - Neutrophil count $<1.5 \times 10^9$/L - Platelet count $<90 \times 10^9$/L • Serum creatinine >1.5 mg/dL • Haemoglobinopathies (sickle cell disease or thalassaemia) • Significant coronary artery disease • Untreated thyroid disease • Ophthalmological disease • Colitis • Pancreatitis

Source: Based on product label information and the 2015 AASLD and EASL guidelines *(194, 195)*.

8.2 Monitoring for adverse events

Monitoring guidance for the detection of adverse events to HCV treatment has largely been based on the experience of interferon and ribavirin therapy. A technical report on monitoring during treatment was carried out as part of the guidelines development process in 2014 (web Appendix 5, 2014). Newer interferon-free regimens are much better tolerated by patients, as they have fewer adverse events and thus less need for early discontinuation of therapy. Therefore, the frequency of routine laboratory monitoring may be reduced; however, there remains the need for laboratory monitoring in patients with cirrhosis, those with significant comorbidities and those treated with ribavirin therapy. Although this approach is being evaluated, no data are yet available to allow for absolute recommendations. A summary monitoring schedule framework for the treatment of patients that is based on expert opinion is shown in Table 8.4. If blood parameters become abnormal on therapy, increased monitoring and dose adjustment may be required.

Clinical judgement based on the patient's clinical details such as presence of HIV coinfection, cirrhosis or renal impairment, potential DDIs and clinical well-being during treatment may necessitate more frequent monitoring than the schedule illustrated in Table 8.4. Indirect hyperbilirunaemia can occur in patients taking regimens containing protease inhibitors (simeprevir, paritaprevir and asunaprevir), especially if combined with ribavirin. This is usually transient and decreases with continued treatment.

TABLE 8.4 Framework for the frequency of monitoring patients undergoing HCV therapy based on type of regimen

Time	DAA alone			DAA + ribavirin			DAA + pegylated interferon + ribavirin			
	FBC, renal, liver function	Adherence, side-effects	HCV RNA	FBC, renal, liver functions	Adherence, side-effects	HCV RNA	FBC, creatinine, ALT	Thyroid function	Adherence, side-effects	HCV RNA
Baseline	X		X	X		X	X	X		X
Week 1				X	X		X		X	
Week 2				X	X		X		X	
Week 4	X	X		X	X		X		X	
Week 8				X	X		X		X	
Week 12				X	X		X	X	X	
Week 12 after end of treatment			X	X		X	X	X		X
Week 24 after end of treatment										X

ALT: alanine aminotransferase; DAA: direct-acting antiviral; FBC: full blood count

8.2.1 Regimens containing DAAs

New DAA regimens appear to be well tolerated by patients in both clinical studies and "real-world" observational studies. Certain regimens have been shown to be safe for use in patients with decompensated liver cirrhosis and those who have undergone liver transplantation. However, close monitoring is required in these patients and it is recommended that such regimens be undertaken only in units with the expertise to manage these patients and treat complications if they arise.

Daclatasvir

The common adverse reactions associated with this drug are fatigue, headache and nausea, seen in studies that have either used the drug in combination with sofosbuvir with or without ribavirin *(197)*, or with interferon and ribavirin *(210)*.

Ombitasvir/paritaprevir/ritonavir and dasabuvir

SAEs with this regimen occurred in <2.5% of cases and the treatment discontinuation rate was <2% in phase 3 clinical studies. Pruritus was the most common side-effect attributable to this regimen; however, patients also experienced fatigue, nausea and insomnia in regimens in which ribavirin was co-administered.

Asymptomatic serum ALT elevations, without an increase in serum bilirubin, were noted in the first four weeks of treatment but resolved without intervention or need for DAA discontinuation. This was most common in patients using estrogen therapy concomitantly. Transient unconjugated bilirubinaemia was noted in patients also receiving ribavirin, related to the inhibition of OATP1B1 and OATP1B3 bilirubin transporters by ritonavir. An increase in total bilirubin was observed more often in patients with liver cirrhosis.

Simeprevir

A reduction in the efficacy of treatment with simeprevir was observed in persons infected with HCV genotype 1a who had NS3 Q80K polymorphism. The simeprevir drug label therefore includes a recommendation to screen for the presence of this variant polymorphism prior to beginning therapy and to consider alternative therapy if the Q80K strain is detected. This test is expensive and not widely available in LMIC.

Patients taking simeprevir may experience mild-to-moderate rashes and photosensitivity, which may be more pronounced in people of east Asian ancestry. Phase 3 clinical studies showed that rates of SAEs were low (≤6%) when simeprevir was used with either interferon or sofosbuvir *(101, 211)*. Some limited data from real-life cohorts suggest that patients with an eGFR <46 mL/min/1.73 m^2 who are treated with sofosbuvir and simeprevir may be more likely to develop adverse events *(119).* Common adverse effects are fatigue, headache, nausea, insomnia and pruritus.

Sofosbuvir with or without ledipasvir

Both drugs have been well tolerated by patients, both in clinical study and "real-life" settings. Sofosbuvir with interferon and ribavirin for 12 weeks appears to be reasonably well accepted by patients, with low rates of discontinuation in clinical studies. In all these regimens, fatigue, headache, insomnia and nausea are the most common adverse events reported. Recent evidence has emerged of significant bradyarrhythmias associated with sofosbuvir in patients also taking amiodarone and therefore it is contraindicated in these patients. Sofosbuvir is renally excreted and is also not recommended in those with eGFR <30 mL/min/1.73 m^2 or those with end-stage renal failure.

8.2.2 Regimens containing interferon

Therapy with interferon causes a number of side-effects, some of which can be life threatening. Patients should be regularly assessed, and warned to be

vigilant for features of depression, irritability, severe fatigue, sleeping disorders, retinopathy and skin reactions. It is advised to discuss important side-effects with the family, as patients may tend to underreport or to ignore early signs of depression. Dose reduction or treatment cessation should be considered, as well as the administration of antidepressants if there is depression.

Haematological side-effects include neutropenia, thrombocytopenia, lymphopenia and anaemia. These parameters should be assessed at weeks 1, 2 and 4 of therapy. Depending on the clinical situation, lengthening the intervals between assessments from 4- to 8-weekly can be considered thereafter. The dose of interferon should be reduced if the neutrophil count falls below 750/mm^3, or the platelet count falls below 50 000/mm^3. Treatment should be stopped if the neutrophil count falls below 500/mm^3 or the platelet count below 25 000/mm^3. When the neutrophil or platelet counts rise from those levels, treatment can be restarted at a lower dose. These interruptions should be as brief as possible and a switch to interferon-free regimens, if available, should be considered in patients who cannot tolerate interferon.

8.2.3 Regimens containing ribavirin

Most of the recommended regimens do not require the addition of ribavirin. However, in certain situations, particularly when treating persons with cirrhosis, ribavirin may be required to optimize efficacy, shorten treatment duration and thereby cost, and possibly reduce the risk of selection of resistance-associated variants (RAVs). Administration of ribavirin is complicated because it should be taken with food and causes a predictable, dose-dependent haemolytic anaemia. Therefore, it should not be administered to patients with anaemia or those with blood disorders such as thalassaemia. Moreover, patients with cirrhosis, cardiovascular disease, pulmonary disease, renal impairment and all those older than 60 years of age need close monitoring when treated with ribavirin-containing regimens. Dose reductions may be required (*see* text bow below). Careful clinical evaluation of patients before and during treatment is important to identify those in need of closer monitoring.

Dose adjustment of ribavirin

Anaemia is a common, predictable side-effect of ribavirin therapy and dose adjustment is often required. Patients whose haemoglobin (Hb) level falls below 10 g/dL should have their ribavirin dose reduced from 800–1200 mg/day (depending on the patient's weight and HCV genotype) to 600 mg/day. A patient whose Hb level falls below 8.5 g/dL should discontinue ribavirin therapy. For patients with a history of stable cardiovascular disease, dose reduction of ribavirin is required if the Hb decreases by ≥2 g/dL during any 4-week period. In addition, for these patients, if the Hb remains <12 g/dL after 4 weeks on a reduced dose, the patient should discontinue combination therapy.

The dose of ribavirin in patients with renal failure must also be adjusted; patients with an eGFR <50 mL/min/1.73 m^2 should not be treated with ribavirin and those on dialysis must have the dose lowered to 200 mg per day or take it three times per week. Increased monitoring is required in this group.

Among patients with decompensated cirrhosis, ribavirin dosing should either be weight-based or started at an initial dose of 600 mg and increased as tolerated.

Ribavirin is teratogenic and thus cannot be used during pregnancy. Women of childbearing age must avoid pregnancy by using at least two reliable forms of contraception. Ribavirin also has a long half-life; thus, pregnancy must be prevented for at least 6 months after the end of ribavirin therapy. Providers have a responsibility to ensure that their patients and male partners can access and use reliable contraception.

8.3 Drug–drug interactions

It is not within the scope of this guideline to address all DDIs. However, it is important for clinicians to consider potential DDIs in choosing regimens, as DDIs vary both in number and clinical significance, depending on the medicines prescribed. Thus, it is strongly recommended that prescribers 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 drugs. An overview of some of the more significant interactions is given below.

8.3.1 Sofosbuvir

Sofosbuvir co-administered with amiodarone in combination with another DAA may result in serious symptomatic bradycardia. Drugs that are intestinal P-gp inducers (e.g. rifampicin, carbamazepine, St John's wort) may alter the concentrations of sofosbuvir. Sofosbuvir is generally safe when administered with HIV medications, although co-administration with tipranavir/ritonavir may reduce concentrations of sofosbuvir.

8.3.2 Simeprevir

Simeprevir mildly inhibits CYP1A2, CYP3A4, OATP1B3 and P-gp pathways. It therefore has some important DDIs with cardiac drugs, statins, anticonvulsants, antibiotics, HIV drugs and herbal remedies.

8.3.3 Daclatasvir

Daclatasvir is affected by moderate or strong inducers of CYP3A, and has DDIs with certain antibiotics, antifungals, cardiac drugs, statins and some HIV medications, for which dose adjustment may be required.

8.3.4 Ledipasvir

Ledipasvir is an inhibitor of P-gp and breast cancer resistance protein (BCRP). Co-administration with ledipasvir/sofosbuvir and amiodarone may result in serious symptomatic bradycardia. Gastric acid-reducing agents should also be used with caution as they reduce concentrations of ledipasvir. Ledipasvir is safe for use with many HIV medications but should be avoided in those taking tipranavir/ritonavir. Other important drugs that should be avoided include simeprevir, St John's wort and rosuvastatin.

8.3.5 Ombitasvir, paritaprevir, ritonavir and dasabuvir

This regimen has numerous DDIs, mainly on account of the combination with ritonavir. As for all the other drugs mentioned above, it is strongly advised that prescribers carefully pre-assess potential DDIs and stop or switch medications that are likely to interact. Recreational drug use, for example, with benzodiazepines, may also be associated with potentially life-threatening interactions.

8.3.6 Antiretroviral therapy in persons with HIV/HCV coinfection

In 2015, WHO updated its HIV treatment recommendations to recommend treatment for all persons living with HIV regardless of WHO clinical stage or CD4 cell count *(3).* The choice of ART for persons with coinfection is the same as for those with HIV alone. However, persons coinfected with HIV are at higher risk of developing side-effects of HCV therapy, and should be monitored more closely. Before starting HCV therapy, careful consideration of DDIs is essential. Where DDIs are likely, ARV drug substitutions should be made before commencement of HCV therapy. It is particularly important to be aware of HIV infection when considering ritonavir-based therapies (i.e. paritaprevir) in order to avoid single-drug therapy of HIV infection, which could lead to drug resistance to ARVs. Table 8.5 summarizes the first-line ART regimens and Table 8.6 summarizes the DDIs between HIV ART medicines and HCV medicines.

TABLE 8.5 Summary of first-line ART regimens for adults, adolescents, pregnant and breastfeeding women and children

Category of patients	Preferred first-line regimens	Alternative first-line regimens
Adults	TDF + 3TC (or FTC) + EFV	AZT + 3TC + EFV (or NVP)
		TDF + 3TC (or FTC) + DTG[a]
		TDF + 3TC (or FTC) + EFV400[a]
		TDF + 3TC (or FTC) + NVP
Pregnant/ breastfeeding women	TDF + 3TC (or FTC) + EFV	AZT + 3TC + EFV (or NVP)
		TDF + 3TC (or FTC) + NVP
Adolescents	TDF + 3TC (or FTC) + EFV	AZT + 3TC + EFV (or NVP)
		TDF (or ABC) + 3TC (or FTC) + DTG
		TDF (or ABC) + 3TC (or FTC) + EFV400[a]
		TDF (or ABC) + 3TC (or FTC) + NVP
Children aged 3 to 10 years of age	ABC + 3TC + EFV	ABC + 3TC + NVP
		AZT + 3TC + EFV (or NVP)
		TDF + 3TC (or FTC) + EFV (or NVP)
Children younger than 3 years of age	ABC or AZT + 3TC + LPV/r	ABC or AZT + 3TC + NVP

Source: Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. WHO, 2015 *(3)* 3TC: lamivudine; ABC: abacavir; AZT: zidovudine; DTG: dolutegravir, EFV: efavirenz; EFV400: EFV at lower dose (400 mg/day); FTC: emtricitabine; LPV: lopinavir; NVP: nevirapine; r: ritonavir; TDF: tenofovir.

[a] Safety and efficacy data on use of DTG and EFV400 in pregnant women, people with HIV/TB coinfection, and children and adolescents younger than 12 years of age are not yet available

TABLE 8.6 Drug–drug interactions between co-administered HCV and HIV treatment

HIV antiviral drugs	Daclatasvir	Ledipasvir/ sofosbuvir	Ombitasvir/ paritaprevir/ ritonabir	Ombitasvir/ paritaprevir/ ritonabir/ dasabuvir	Simeprevir	Sofosbuvir	Pegylated interferon	Ribavirin
Nucleoside reverse transcriptase inhibitors (NRTIs)								
Abacavir (ABC)	◆	◆	◆	◆	◆	◆	■	■
Emtricitabine (FTC)	◆	◆	◆	◆	◆	◆	■	■
Lamivudine (3TC)	◆	◆	◆	◆	◆	◆	■	■
Tenofovir (TDF)	◆	■	◆	◆	◆	◆	■	■
Zidovudine (AZT)	◆	◆	◆	◆	◆	◆	●	●
HIV entry/integrase inhibitor								
Dolutegravir (DTG)	◆	◆	◆	◆	◆	◆	◆	◆
Non-nucleoside reverse transcriptase inhibitors (NNRTIs)								
Efavirenz (EFV)	■	■	●	●	●	◆	◆	◆
Nevirapine (NVP)	■	◆	●	●	●	◆	◆	◆
Protease inhibitor								
Lopinavir	◆	◆	●	●	●	◆	◆	◆
Ritonavir	■	◆	●	●	●	◆	◆	◆

Source: University of Liverpool hepatitis drug interactions webpage (http://www.hep-druginteractions.org/)

● These drugs should not be co-administered
■ Potential interaction
◆ No clinically significant interaction expected

8.4 Monitoring for treatment response

Treatment with interferon-based regimens required frequent monitoring of HCV RNA levels. This was necessary to decide whether (a) treatment should be stopped when there was an absence of viral clearance at certain time points (termed "treatment futility"); or (b) treatment duration could be shortened based on a rapid reduction in viral load (termed "rapid viral response"). These issues are not relevant with the newer DAAs, because of the relative infrequency of viral breakthrough and because the rate of viral load decline does not correlate with SVR. In fact, in most persons treated with DAAs, the viral load is undetectable 4 weeks after treatment initiation. This provides an important opportunity to reduce the frequency of laboratory monitoring. In view of the high cost and relative unavailability of HCV RNA testing, this would be an important factor in facilitating the expansion of HCV treatment in LMIC.

Among patients treated with DAA regimens, HCV RNA level is sometimes tested in the first 2–4 weeks of treatment to monitor treatment adherence but there is no evidence that this practice improves treatment outcomes. Following completion of treatment, SVR at 12 weeks after completion of treatment is the benchmark for assessing treatment outcome in DAA-based regimens. In countries where testing for HCV RNA is difficult or too costly, and where sequencing for RAVs is not feasible, it could be considered feasible to do HCV monitoring at reduced time points. A suggested simplified monitoring schedule is listed in Table 8.4.

Considerations for simplification of treatment monitoring

Table 8.4 is an illustrative example of how DAA regimens can allow for reduced monitoring compared with previous interferon-based regimens. At baseline, safety monitoring such as FBC, clotting screen, liver and kidney function tests should be performed. In the context of DAA regimens where there are no "futility rules", it is conceivable that expensive pre-treatment HCV viral load testing would not need to be repeated as long as there was evidence that the individual had undergone viral load testing in the past 6 months to confirm the presence of chronic hepatitis C (i.e. presence of quantifiable viral load for more than 6 months).

The combination of ombitasvir, paritaprevir and dasabuvir is associated with clinically uneventful ALT flares in the first 4 weeks in approximately 1% of patients. It is good practice to monitor liver function tests in this period; the drug should be discontinued if the ALT level is >10 times the upper limit of normal *(212)*. Other DAA regimens without the use of ribavirin can in general be given without the need for regular monitoring tests but close clinical evaluation for any side-effects is essential. Careful pretreatment clinical assessment of the patient's comorbidities, drug history and overall health are essential in order to identify which patients are likely to require closer monitoring.

Regimens that include ribavirin are associated with more frequent adverse events, particularly anaemia. Patients with chronic renal disease (eGFR <50 mL/min/1.73 m^2) should be treated with caution as ribavirin-related side-effects, particularly anaemia, tend to be more common and severe. However, in general and in patients with chronic renal disease, renal function should be closely monitored. In general, patients who do not have significant comorbidities and have no pretreatment anaemia are likely to tolerate 12 weeks of DAA and ribavirin well. If asymptomatic, the Hb could be checked at week 4 and repeated only if clinically indicated.

The current standard of cure in clinical trials and practice is a negative viral load at 12 weeks after treatment (SVR12). This replaces the post-treatment viral load testing traditionally done at 4, 12 and 24 weeks after the end of treatment. The value of a test result at week 4 is limited, as a repeat test is required at week 12. Likewise, the 24-week test (SVR24) is of marginal value, as the likelihood of relapse past week 12 in DAA-based regimens is very small. There is increasing interest in testing for RAVs, but the clinical importance of RAVs remains unclear, and this test is not available in most LMIC. Therefore, it is conceivable that a single HCV viral load estimation be performed at any time point between 12 and 24 weeks post treatment to confirm successful eradication of the virus.

9. SPECIAL CONSIDERATIONS FOR SPECIFIC POPULATIONS

9.1 People who inject drugs

Injecting drug use is prevalent in many countries around the world, affecting people in low-, middle- and high-income countries. Globally, approximately 67% of PWID have evidence of HCV infection (i.e. anti-HCV antibodies); 10 million of 16 million people in 148 countries *(19).* PWID are at increased risk of HCV-related disease and transmission, as well as for all-cause morbidity and mortality, and therefore require specialized care *(54)* and should be considered as a priority for HCV treatment. In reality, many PWID with HCV infection are unaware that they are infected and HCV treatment rates among them are very low *(213).* This is due to a number of reasons, including the criminalization of drug use, as well as discrimination and stigma in health-care settings.

When caring for PWID, the central tenets of respect and non-discrimination should be followed, and additional adherence and psychological support given as required.

9.1.1 Screening

As a population with a high prevalence of HCV infection, all PWID should be offered screening for HCV as an integral component of a comprehensive package of harm reduction interventions. Repeated screening is required in individuals at ongoing risk of reinfection, and the possibility of reinfection after spontaneous clearance or successful treatment should also be considered. Those who have been previously infected should be retested using RNA testing, as the antibody remains positive after the first infection. Potential reinfection should not be an argument to withhold treatment from PWID.

HCV case-finding and treatment in specialist drug dependency services has also been shown to be cost–effective in high-income settings. The higher the treatment rates, the more cost–effective HCV case-finding becomes, as more of those identified will be treated, and a greater population impact would be seen *(186)*. Screening for HBV and HIV is also recommended in PWID.

9.1.2 Care

Treatment of HCV in PWID requires integration of services, as other health-care needs, including treatment for HIV and TB as well as drug and alcohol

dependency, are often also present. Harm reduction strategies, including the provision of OST and sterile injection equipment, are required in order to prevent acquisition of HCV and other bloodborne viruses such as HBV and HIV.

At all times, avoidance of discrimination or stigmatization of PWID is essential. Care should be given only with informed consent. Moreover, acceptability of services is a vital component of health care, and peer interventions may help with reducing injecting drug use and promoting safer injection practices. Guidance on brief behavioural interventions is available as part of the WHO ASSIST package *(146).* PWID are at risk of infection with HBV and should be vaccinated using the rapid vaccination regimen, as described in other WHO guidance *(5)*. Needle and syringe programmes should also provide sterile needles and syringes with low dead space to PWID.

Concurrent infection with HIV and/or TB is common in PWID and these require additional consideration, as discussed in sections 9.2 and 9.7.

9.1.3 Treatment

Treatment for HCV infection is both efficacious and cost–effective in PWID *(214–216)* and therefore WHO recommends that all adults and children with chronic HCV infection, including PWID, should be assessed for antiviral treatment. Treatment is also an effective prevention measure, as persons cured of HCV infection do not transmit the virus *(186, 187, 217)*.

Increasing treatment rates among PWID will require novel approaches, such as testing and diagnosing more PWID, linking individuals to HCV care, and increasing treatment uptake, adherence and rates of successful treatment *(218)*. Coordination with and integration of HCV treatment services with needle and syringe programmes or drug dependency services are being evaluated to facilitate access to HCV treatment among PWID.

Successful strategies to increase HCV testing and diagnosis among PWID include free counselling and testing, point-of care testing and monitoring, as well as risk-based assessment and counselling. In addition, screening for and assessment of liver disease through transient elastography (e.g. FibroScan®) is a very useful strategy to increase linkage to care and identify patients most in need of treatment. Care models based on case management and peer support may additionally increase linkage to care and adherence to treatment in this population.

PWID treated with pegylated interferon/ribavirin have outcomes similar to those among non-PWID, but there are few data on the success of DAAs among PWID. A recent report of a clinical study of grazoprevir and elbasvir (which received FDA approval in January 2016) among PWID receiving OST documented a 4-week SVR of 96%, despite the fact that 79% of the subjects had illicit drugs detected in urine screens conducted during therapy *(219)*.

This supports the use of DAA-based therapy among PWID, even for those who are active users of illicit drugs.

Consideration must be given to potential DDIs – between both prescribed and non-prescribed drugs (*see* section 8.3).

9.2 Persons with HIV/HCV coinfection

Persons with HIV/HCV coinfection generally have more rapid progression of liver fibrosis, especially those with a CD4 cell count of <200 cells/mm^3 *(80–82, 220)*. Furthermore, even among patients in whom ART leads to successful control of HIV infection (i.e. undetectable HIV viral load), the risk of hepatic decompensation among coinfected patients is higher than among patients with HCV monoinfection *(221)*. For these reasons, all persons with HIV/HCV coinfection should be considered for HCV treatment.

Treating such patients in the past with interferon and ribavirin combination therapy was very difficult, as many patients had to discontinue treatment due to side-effects such as depression or weight loss as well as severe anaemia, thrombocytopenia and neutropenia. Furthermore, SVR rates in patients with coinfection were lower than among HCV-monoinfected patients.

Outcomes of HCV therapy with DAAs in persons with HIV coinfection are comparable to those with HCV monoinfection. Thus, DAA therapy has substantially simplified the treatment of persons with HIV and HCV coinfection. There are fewer DDIs between DAAs and ARV medicines, and SVR rates with DAA-based therapy among persons with HIV coinfection are higher than 95%, even for those with prior HCV treatment failure or advanced fibrosis. Therefore, there is no longer a need to consider HIV/HCV-coinfected patients as a special, difficult-to treat patient population. The need to check for DDIs between HIV and HCV medications, however, needs to be emphasized (*see also* section 8.3, Table 8.6).

It is advisable to first initiate treatment for HIV and achieve HIV suppression before starting HCV treatment, although there are some circumstances where it may make sense to treat HCV infection first and then initiate therapy for HIV *(222)*. This could include persons with moderate-to-severe fibrosis at risk of rapid liver disease progression if the HIV infection is not associated with significant immunosuppression at the time of treatment. Also, in view of the short duration of HCV treatment, the risk of DDIs between HCV and HIV medicines and the increased risk of ART-related hepatotoxicity in the presence of HCV infection, treating HCV infection first can simplify subsequent ART depending on the regimen available locally. Persons coinfected with HIV are at higher risk of developing side-effects of HCV therapy, and should be monitored more closely. Before starting HCV therapy, careful consideration of DDIs is essential (*see* section 8.3). Where DDIs are likely, ARV drug substitutions should be made before commencement of HCV therapy. It is particularly important to be aware of HIV infection when considering ritonavir-

based therapies (such as paritaprevir/ombitasvir/dasabuvir) in order to avoid single-drug treatment of HIV infection, which could lead to drug resistance to ARVs. Given that many countries will not have access to a wide range of HCV therapies and may have limited opportunities for re-treatment, it is critical that coinfected patients be carefully assessed and any drug interactions that may either reduce efficacy or increase the risk of side-effects avoided.

Potential harmful effects of ARV drugs include their hepatotoxic effects. Several studies have shown that hepatotoxicity as a result of ART may be worsened in the presence of concomitant HCV infection *(223–225)*. However, the highest rates of hepatotoxicity have been observed with ARV drugs that are no longer commonly used or recommended, including stavudine (d4T), didanosine (ddI) *(226)*, nevirapine (NVP) or full-dose ritonavir (600 mg twice a day) *(227).* For most HIV/HCV-coinfected persons, including those with cirrhosis, the benefits of ART outweigh concerns regarding drug-induced liver injury.

Raised liver enzymes may be the result of ART-induced drug toxicity and/or opportunistic infections, making interpretation of liver enzyme elevations more problematic than for patients with HCV infection alone. ALT and AST should be monitored at 1 month after ART initiation and then every 3–6 months. A significant elevation of AST/ALT may prompt careful evaluation for other causes of liver function impairment (e.g. alcoholic hepatitis, hepatobiliary disease), and may require short-term interruption of the ART regimen or specific drug suspected of causing the elevation.

9.2.1 Monitoring of therapy in persons with HIV/HCV coinfecion

Ledipasvir/sofosbuvir may be given with all ARVs. However, due to an increase in tenofovir concentrations when a pharmacokinetic enhancer (ritonavir or cobicistat) is present in an ARV regimen, these combinations should be used with frequent renal monitoring if other alternatives are not available. Tenofovir concentration is also increased in efavirenz-containing regimens and caution with regard to renal monitoring is also required.

Interferon-based regimens are associated with a reversible CD4 decline (average 140 cells/mm^3) and a high rate of treatment discontinuation due to side-effects (25% of patients in the APRICOT study) *(207).* CD4 count monitoring is therefore recommended in coinfected persons on treatment. A higher risk of haematological suppression is also present in persons with HIV infection; these are important dose-limiting side-effects, especially with co-administration of certain ARV drugs.

Monitoring during interferon and ribavirin treatment with or without protease inhibitor therapy is therefore recommended at multiple time points (Table 8.4). Additional time points may be required for persons with evidence of side-effects and in persons at highest risk (for example, persons with cirrhosis and HIV, and those on protease inhibitor therapy). Additional monitoring of liver function is recommended in persons with cirrhosis, including albumin,

bilirubin and coagulation tests. Persons with evidence of neutropenia, thrombocytopenia and anaemia require 1–2-weekly monitoring.

9.3 Children and adolescents

The United Nations Convention on the Rights of the Child defines a child as an individual below the age of 18 years *(228)*; WHO defines an adolescent as a person between the ages of 10 and 19 years. In countries where adults have a high prevalence of HCV infection, an increased prevalence in children can also be expected. This rate is substantially higher in certain subgroups, such as those exposed to medical intervention. Iatrogenic transmission has been reported in hospitals *(229)*. The reduction of HCV transmission in health-care settings is a priority (strategies for reduction in HCV transmission as part of medical care are summarized in Table 2.3). Seroprevalence rates of 10–20% have been reported among children who have been treated in hospital for malignancy, renal failure requiring haemodialysis, extracorporeal membrane oxygenation and those who have undergone surgical procedures *(230–235)*.

9.3.1 Screening

Targeted screening is indicated for children who have had medical interventions or who have received blood products in countries where screening of blood is not carried out routinely or where medical equipment is inadequately sterilized. Children born to mothers with HCV infection are also at risk; the risk of vertical (mother-to-child) transmission is approximately 4-8% and is substantially higher in infants born to HIV-infected mothers (10.8–25%) *(30, 32–35)*.

9.3.2 Care

Integrated health care is a key aspect of child health-care provision. Linkage is necessary with maternal and child health services, primary care, services for PWID and, if required, referral for HIV care and treatment.

9.3.3 Treatment

None of the DAAs have been approved for use among children; thus, the only approved treatment for children remains pegylated interferon/ribavirin, which is recommended for children older than 2 years. Clinical trials are urgently needed to provide the necessary safety and efficacy data to allow regulatory approval of DAAs among children. The product literature for pegylated interferon reports that paediatric subjects treated with ribavirin combination therapy had a delay in weight and height increases after 48 weeks of therapy compared with baseline. However, by the end of 2 years of follow up, most subjects had returned to baseline normative growth curve percentiles for weight and height (mean weight-for-age percentile was 64% at baseline and 60% at 2 years' post-treatment; mean height percentile was 54% at baseline and 56% at 2 years' post-treatment).

9.4 Persons with cirrhosis

The spectrum of disease in those infected with HCV extends from mild fibrosis to compensated then decompensated cirrhosis and HCC. Between 15% and 30% of persons infected with HCV will go on to develop cirrhosis of the liver within 20 years and a proportion of these will progress to HCC. The risk is markedly increased in those who consume excess alcohol *(149)* and in those coinfected with HBV and/or HIV, particularly those who do not have access to ART *(71, 72)*. Persons with cirrhosis have the least time available for treatment, the most to lose and much to gain from achieving SVR. Treatment of HCV infection should be commenced before the onset of decompensated disease because medical management is more complicated and some HCV medicines can precipitate liver failure and death if administered at this stage.

Regular clinical examination and monitoring of serum bilirubin, albumin and coagulation profile *(134)* are necessary in persons with cirrhosis on interferon-based treatment in order to detect decompensated disease. The treatment of such persons with interferon-containing regimens carries a higher risk of serious side-effects, and the use of haemopoietic factors is recommended in settings where these are available *(132)*.

Use of certain DAA regimens among persons with cirrhosis has been shown to be both safe and efficacious, especially in those with compensated disease. The addition of ribavirin to treatment increases the risk of SAEs, most notably those related to anaemia, and requires additional monitoring. Simeprevir and ombitasvir/paritaprevir/ritonavir/dasabuvir are not approved for use in patients with decompensated liver disease. Daclatasvir, ledipasvir and sofosbuvir have been studied in persons with decompensated cirrhosis and their use has been demonstrated to be both feasible and effective. However, a proportion of patients with decompensated liver disease will deteriorate on treatment and currently there are no pretreatment predictors to identify these patients. Therefore, treatment of patients with decompensated liver cirrhosis should be considered only in centres with the expertise to manage complications and ideally where access to liver transplantation is available.

Assessment and follow up for the progression of disease and for evidence of HCC is an essential part of the care of persons with HCV-related cirrhosis. Compensated cirrhosis may also progress over time to decompensated cirrhosis associated with ascites, oesophageal and gastric varices, and eventually to liver failure, renal failure and sepsis, all of which are life threatening. The diagnosis of decompensated liver disease is based on both laboratory and clinical assessment, and therefore a careful medical examination of patients must be made before starting treatment. Persons with cirrhosis (including those who have achieved an SVR) should be screened for HCC with six-monthly ultrasound examination and α-fetoprotein estimation, and should have endoscopy every 1–2 years to exclude oesophageal varices *(132)*.

9.5 Persons with chronic kidney disease

There is an unmet need for DAA treatment in patients with severe renal disease (eGFR <30 mL/min/1.73 m^2) and those requiring haemodialysis. Sofosbuvir, which is used in many approved regimens, does not have the safety and efficacy data to support its use in these situations. Preliminary pharmacokinetic and clinical study data suggest that the use of ombitasvir/paritaprevir/ritonavir and dasabuvir is feasible and the early results suggest possible efficacy *(236)*. Future regimens are also looking at addressing this unmet need.

Both ribavirin and pegylated interferon require dose adjustment in persons with renal failure. Pegylated interferon α2a is cleared by the liver and pegylated interferon α2b via the kidneys. While a theoretical accumulation of pegylated interferon α2b could occur in persons on haemodialysis, no differences have been reported clinically *(225, 227)*.

In persons with severe renal disease (eGFR <30 mL/min/1.73 m^2), including those on haemodialysis, a reduced dose of pegylated interferon α2a 135 µg once a week is recommended. The dose of ribavirin must also be decreased as the risk of anaemia-related adverse events is high.

In persons with renal impairment receiving chronic haemodialysis, ribavirin may be administered at a dose of 200 mg daily or 200 mg every other day. Plasma ribavirin is removed by haemodialysis with an extraction ratio of approximately 50%.

Patients receiving ARV drugs in combination with tenofovir and sofosbuvir may require enhanced renal monitoring (*see* section 9.2).

9.6 Persons with HBV/HCV coinfection

It is important to check for the presence of HBV infection before starting HCV treatment. HBV and HCV coinfection may result in an accelerated disease course; HCV is considered to be the main driver of disease. Persons coinfected with HBV and HCV can be treated with antiviral therapy for HCV; SVR rates are likely to be similar to those in HCV-monoinfected persons *(66, 237)*. During treatment and after HCV clearance, there is a risk of reactivation of HBV, and this may require treatment with concurrent anti-HBV antiviral therapy *(224)*. DDIs must be checked before initiating treatment. Telbivudine, in particular, may be associated with a higher risk of neuropathy if given with interferon-containing regimens. For more information, see the WHO *Guidelines for the prevention, care and treatment of persons with hepatitis B infection (4)*.

9.7 Persons with TB/HCV coinfection

People at increased risk of infection with HCV are also often at increased risk of infection with TB. Therefore, screening for active TB should be part of the clinical evaluation of patients being considered for HCV treatment. WHO recommends a four-symptom screening algorithm to rule out active TB *(238)*. If the patient does not have any one of the following symptoms – current cough, fever, weight loss or night sweats – TB can be reasonably excluded; otherwise, the patient should undergo further investigations for TB or other diseases.

Most of the DAAs interact with metabolic pathways in the liver, which increases and/or decreases the drug level of DAAs when co-administered with antimicrobial medicines such as rifabutin, rifampin and rifapentine *(239, 240)*. Therefore, concurrent treatment of HCV infection and TB should be avoided. Active TB should generally be treated before commencing therapy for HCV. Furthermore, in persons with HCV infection being treated for TB, it is important to monitor liver function tests, as the risk of antimycobacterial-induced hepatotoxicity is higher in patients with TB/HCV coinfection than in those with TB monoinfection, although the risk of severe hepatotoxicity is rare *(241)*.

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 coinfected with HCV, HIV and TB, but such cases need sound clinical judgement in order to reduce the additive side-effects, pill burden and DDIs. Clinicians need to be aware of the risk of reactivation of TB if the person, particularly if HIV coinfected, receives interferon-based therapy, as interferon-based therapy could increase the incidence of active TB *(16)*. Baseline liver function tests for individuals with chronic liver disease are encouraged prior to initiating treatment for latent TB infection. For individuals with abnormal baseline test results, routine periodic laboratory testing should be carried out during the treatment of latent TB infection *(242)*.

10. OPERATIONAL AND IMPLEMENTATION ISSUES

Until recently, HCV therapy required lengthy treatment with pegylated interferon and ribavirin, with suboptimal rates of success and high rates of SAEs. Thus, treatment was often reserved for patients with advanced fibrosis and cirrhosis, for whom the risk of adverse events was outweighed by the potential benefits of a cure. When DAAs were introduced in high-income countries, treatment eligibility was also very restricted based on disease severity or other factors in order to minimize the budgetary impact *(243)*. This dynamic is now changing for several reasons. First, the price of DAAs is falling in some countries. Second, there is a better understanding of the benefits of early treatment of HCV infection, prior to the development of fibrosis. Recent studies show that patients who achieve SVR tend to have improvements in liver inflammation and fibrosis *(244)*, and also in work-based productivity *(245)* and quality of life *(246, 247)*. SVR is also associated with improved extrahepatic manifestations independent of the stage of the underlying liver disease. Finally, the new DAAs are much safer and produce high cure rates. For these reasons, eligibility criteria are becoming more liberal, and some countries are expanding their HCV treatment programmes so that they can treat virtually all people with HCV infection and "eliminate" HCV in their populations.

Despite these developments, in most countries, treatment allocation will initially be very restricted because of the high price of medicines and lack of laboratories and health-care infrastructure. Therefore, a framework to help policy-makers decide whom to prioritize for treatment is important.

TABLE 10.1 Factors to be considered in prioritizing who receives treatment

- Increased risk of death:
  - advanced HCV-related liver disease (METAVIR score F3–F4)
  - treatment after liver transplantation
- Risk of accelerated fibrosis:
  - coinfection with either HIV or HBV
  - high level of alcohol use
- Metabolic syndrome, extrahepatic manifestations and evidence of end-organ damage:
  - debilitating fatigue
  - significant psychosocial morbidity (due to stigma, discrimination, fear of transmission to others)
- Maximizing reduction in incidence:
  - PWID
  - MSM with HIV
  - prisoners
  - sex workers
  - women with childbearing potential
  - health-care workers.

Allocation of costly medicines is a perennial challenge that has complex ethical and economic implications. Various principles have been proposed, including morally relevant values such as treating people equally, giving priority to the worst off and saving the most lives *(248)*. As in most countries, treatment will be rationed based on the availability of resources; this may mean prioritizing treatment for "high-risk" populations. The scope of this section is to aid policy-makers by providing a guidance framework to aid decision-making processes for the initial stages of implementing HCV treatment strategies.

Two broad criteria can be used to prioritize treatment – minimizing mortality and morbidity by prioritizing those people with advanced HCV-related liver disease or who have factors that make them more likely to progress to cirrhosis; and maximizing the prevention benefit by prioritizing people at highest risk of transmitting HCV infection, for example, PWID.

10.1 Factors to be considered in prioritizing who receives treatment

10.1.1 Increased risk of death

Advanced HCV-related liver disease (METAVIR score F3–F4)

Patients with advanced fibrosis and cirrhosis are at increased risk of death, mainly due to complications of cirrhosis and HCC, but also all-cause mortality *(249, 250)*. Successful treatment is associated with reduced complications and liver-related morality *(251, 252)*. A paradigm shift in the treatment of HCV is the emergence of efficacious, tolerable and safe interferon-free DAA regimens suitable for patients with advanced cirrhosis *(253)*.

Analysis of data on effectiveness from three LMIC – Egypt, Thailand and Côte d'Ivoire (HCV prevalence 14.7%, 2.2% and 3%, respectively) – suggested that, given a limited number of treatment slots, treatment with DAA regimens among persons with F3–F4 disease would result in an increase in life-years saved of 16.7% in Egypt, 22% in Thailand and 13.1% in Côte d'Ivoire when compared with treating persons with F2–F4 disease *(254, 255)*.

It should be recognized that a small proportion of patients with decompensated cirrhosis appear to deteriorate during treatment. Clinical management of these patients is challenging, as it is difficult to predict which patients will experience this deterioration. Therefore, treatment of HCV infection should be considered only under close supervision of specialist teams with experience in treating and managing complications.

Treatment after liver transplantation

Treatment of patients following liver transplantation improves the chances of long-term liver graft survival. Following liver transplantation, more than

95% of the grafted livers will become reinfected with HCV and typically fibrosis develops more rapidly *(256).*

Retransplantation in patients with HCV is complicated by poorer outcomes compared to retransplantation done for other causes, and therefore the goal would be to treat before the development of cirrhosis in the grafted liver *(257)*.

Treatment with interferon and ribavirin after transplantation is feasible but the chances of SVR are generally low *(258)*. Newer DAA therapies are advantageous, with reduced DDIs, better tolerability and improved SVR rates *(259, 260)*.

10.1.2 Risk of accelerated fibrosis

Coinfection with HIV

According to the existing HIV treatment guidelines *(3)*, all patients coinfected with HIV should be considered for HCV treatment. Approximately 2.3 million people are believed to be coinfected with HIV globally *(15)*. HIV coinfection is associated with more rapid progression of liver fibrosis *(80, 261)*. Patients with HIV coinfection have reduced access to liver transplantation and outcomes are poor. Thus, treatment may be beneficial at earlier stages of liver disease.

Many patients with HIV coinfection are already on treatment for HIV and therefore easy to access. SVR rates with interferon-based therapies against HCV are lower in HIV-coinfected patients compared with HCV-monoinfected patients. However, when treated with DAAs, SVR rates are comparable among patients with mono- and coinfection. DDIs in patients on ART for HIV are important and should be carefully considered prior to DAA dosing.

Coinfection with HBV

Persons with HBV coinfection should also be prioritized for treatment of HCV due to an increased risk of progression of liver fibrosis and HCC, independent of the development of cirrhosis *(262)*. Globally, up to 10% of patients with HCV are coinfected with HBV *(263)*. Treatment of each virus should be undertaken as in patients with monoinfection.

Metabolic syndrome

In patients with HCV, obesity and the metabolic syndrome are associated with progression of liver disease and increased risk of HCC *(264)*. Furthermore, HCV appears to be strongly associated with type 2 diabetes and insulin resistance *(265, 266)*. Treating HCV infection in persons with diabetes results in a lower incidence of renal and cardiovascular complications as compared to untreated controls *(267)*.

Patients with type 2 diabetes and insulin resistance have an impaired response to interferon-based therapy *(268).*

10.1.3 Extrahepatic manifestations of chronic HCV infection

Fatigue

Most persons with HCV have no symptoms; however, some exhibit serious and sometimes debilitating symptoms related to HCV infection and may benefit strongly from treatment. Fatigue is a common symptom, which in most cases does not preclude activities of daily living but does impact negatively on quality of life *(269)*. Improvement of these symptoms has been demonstrated after SVR *(270)*. Quality-of-life assessments following treatment with DAA regimens in patients within phase 3 clinical studies demonstrated improvement in fatigue and projected an increase in societal economic benefit *(245, 247)*.

Vasculitis and lymphoproliferative disorders

Cryoglobulinaemia and lymphoproliferative disorders are associated with HCV infection *(271)*, and can be improved or resolved following HCV cure *(272)*. Patients with these conditions are therefore considered a priority for treatment. Cryoglobulins are frequently present among HCV-infected patients. However, a proportion develops evidence of end-organ damage such as renal disease, peripheral neuropathy, arthropathy, and peripheral and central nervous system vasculitis. Treatment with interferon is feasible; however, it can mimic the manifestations of cryoglobulinaemia *(273, 274)*. Renal disease, commonly membranoproliferative glomerulonephritis, can be improved with treatment of HCV, with reversal of proteinuria and the nephrotic syndrome *(275)*.

10.1.4 Maximizing reduction in incidence

People who inject drugs and others with an increased risk of transmission

PWID who engage in drug consumption-related risk behaviours and HIV-positive MSM who engage in high-risk sexual practices have a high incidence of HCV infection and, through those behaviours, can transmit the virus to others. While increasing awareness about the disease and measures to reduce risk are important, only HCV treatment can reduce the current prevalence among these populations. Persons who achieve cure are no longer at risk of onward transmission of HCV.

Mathematical models suggest that even a modest increase in treatment coverage can result in reductions in HCV prevalence *(186, 187, 191, 192)*. These models also demonstrate that the prevention effect of HCV treatment is increased if it is combined with harm reduction services such as OST, and needle and syringe programmes. According to systematic reviews of interferon-based regimens, PWID have equivalent treatment efficacy and adherence as non-PWID *(185, 276)*. While fears remain regarding HCV reinfection in PWID populations, studies suggest that reinfection rates in successfully treated patients are low, assuming that treatment is combined with other harm reduction measures *(185, 277)*.

Significant increases in the incidence of HCV have been reported in HIV-positive MSM in Europe, the United States, Australia and Asia, with reinfection rates in

this population of between 6% and 33% *(278)*. Treating MSM could lead to a reduction in transmission risk.

Mother-to-child transmission

Mother-to-child transmission from monoinfected mothers occurs in 4–8% of infants and from mothers coinfected with HIV in 10.8–25% of infants *(30, 32–35)*. Unlike with HBV and HIV, there are no interventions to reduce this risk of vertical HCV transmission during pregnancy *(279)*. Treatment currently cannot be recommended during pregnancy, especially with ribavirin-based regimens, and also because of the lack of data for the new DAA regimens. Successful treatment of women infected with HCV prior to pregnancy is the only measure that can negate any risk of mother-to-child transmission of HCV.

Incarcerated populations

Among incarcerated populations, HCV incidence is high and HCV prevalence can be as high as 60%, primarily because many prisoners are PWID *(280)*. In the United Kingdom, it is estimated that treatment is cost–effective, and in fact, results in health-care savings *(281)*.

Major barriers related to the management of interferon-based therapies in these institutions preclude adequate treatment, as does the high turnover and movement of incarcerated individuals with poor linkage to care. Shorter, more tolerable treatment regimens with less monitoring needs may help circumvent these issues.

Haemodialysis

Nosocomial transmission events remain an important cause of HCV transmission. Persons on haemodialysis are particularly prone to infection, with length of time on dialysis increasing the risk of HCV acquisition *(282)*. Improved education and strict universal precautions can drastically reduce the risk of nosocomial transmission among dialysis patients but still, particularly in resource-limited settings, this practice is not always optimally adhered to. HCV infection also has a negative impact on graft survival post renal transplantation *(283)*.

Treatment options remain limited for patients with severe renal disease, an eGFR <30 mL/min/1.73 m^2 and those on haemodialysis. The dose of ribavirin should be reduced and careful monitoring done for anaemia. DDIs should be carefully considered.

Health-care workers

Health-care workers with evidence of active viral replication (in the United States >10^4 genome equivalents/mL) are restricted from performing procedures prone to exposure *(284)*. Successful treatment would therefore eliminate any risk of transmission to patients and increase the availability of health-care workers for more wide-ranging clinical activities.

10.2 Service planning

Service planning requires an estimation of the local burden of disease, and an assessment of the availability of resources and infrastructure for rolling out treatment. National programmes are required to plan screening and treatment strategies. At present, many countries have poor documentation of the prevalence of infection; this is particularly the case in low-income countries.

The Global policy report on the prevention and control of viral hepatitis, 2013 provides country-specific information on policies and structures already in place to combat viral hepatitis *(126)*. Building on these policies and structures will be necessary to increase the availability of treatment for those infected. Estimates of how many people are likely to be affected may be made by assessing populations at high risk as well as previously documented prevalence and incidence rates. Regular sentinel screening of targeted populations using serology and NAT is therefore required to facilitate service planning and is the first step in increasing access to care and treatment for hepatitis C. Improvements in molecular tools for rapid screening, including dried blood spot and oral fluid testing, as well as polyvalent platforms for NAT, would increase the number of infected patients identified. They would also allow the expansion of screening services into the field as well as among difficult-to-access populations such as PWID. Integration of HCV screening with HIV, HBV and TB screening services may be suitable in many settings as the routes of transmission are common.

A central barrier to treatment roll-out is cost – this includes the cost of medicines, taxes, import charges, appropriate medical facilities and staff, as well as diagnostic and monitoring facilities. Negotiation on drug costs is required and prioritization of particular groups, for example, patients with advanced liver disease (≥F2 disease or, in more constrained settings, F4) may be required. Integration of services, for example, diagnostic and treatment facilities, may help to minimize costs and is likely to facilitate treatment delivery. Task-shifting is the process of sharing clinical management responsibilities with trained personnel such as nurses, clinical officers and pharmacists. Such personnel should have access to consultations with specialized team members as necessary and are likely to require training in order to facilitate adequate health-care delivery. Sourcing of medication and negotiation on pricing at a central level (using pooled procurement) may also minimize costs. Patent coverage and the availability of prequalified biosimilar agents or generic formulations is another central consideration – this is likely to be of key importance as new DAAs are licensed.

Clinical and laboratory facilities for screening and monitoring patients on treatment are an essential component of health-care provision. The development and implementation of simpler methods to assess HCV viral load and genotype as well as for the tests needed to monitor drug toxicity are important to increase accessibility of treatment in less well-resourced settings. Point-of-care HCV viral load testing may be required in some settings in order to facilitate appropriate treatment. Pharmacy facilities and drug storage space, including refrigeration space for interferon, should be included in the planning of new treatment centres. Sourcing and distribution planning is also required. The registration of new drugs in individual Member States may be time consuming and will require adequate planning.

10.3 Service delivery

The key programmatic components of service delivery are adequate clinic infrastructure, laboratory and diagnostic services, reliable drug supply, human resources (doctors, nurses, trained persons to provide psychological support), a referral system, monitoring and evaluation, and civil society participation. Improving access to treatment requires the identification of infected patients. Implementation of screening for HCV therefore needs to be prioritized and targeted screening of high-risk populations carried out. Subsequently, persons with HCV infection require access to medical facilities for treatment, with ongoing follow up and monitoring for toxicity and efficacy. Integration with pre-existing services such as those already established for HIV would be of added value.

Service delivery may be achieved more readily by providing standardized, simplified treatment regimens at a population level. Decentralized service delivery has already enabled the treatment of large numbers of people infected with HIV. Service delivery should make use of simplified operational guidelines, training materials and approaches to clinical decision-making, as well as limited formularies. An initial clinical assessment is essential prior to commencing therapy in order to assess the presence of pre-morbid conditions that may rule out or delay treatment such as severe intercurrent illnesses, for example, TB, decompensated cirrhosis or pregnancy. A psychological assessment at this time and evaluation for potential DDIs are also essential. Disease education, patient preparation for side-effects while on treatment, support and appropriate informed pre- and post-test counselling are required. Access to appropriate diagnostic facilities for toxicity and efficacy monitoring is of critical importance and could be facilitated by utilizing the same or similar platforms currently being rolled out for HIV *(285)*.

For treatment, standardized regimens should be used in combination with simplified clinical decision-making tools and standardized monitoring. Minimum packages for care and treatment require to be formulated locally, and treatment and monitoring algorithms developed. Such algorithms should include information on when to start therapy, when to stop, follow up, side-effects and management flow sheets. Management of DDIs is important, particularly in those coinfected with HIV. Monitoring and evaluation of centres treating persons for HCV is an essential component of appropriate management. Implementation of standard registers for tracking progress, such as those developed for use in TB treatment programmes, will allow monitoring and evaluation of progress after roll-out of treatment for HCV. Increased supervision of sites is likely to be important during the early stages of treatment roll-out. Other guidance on the delivery of treatment for HCV to people in LMIC has been developed by Médecins Sans Frontières *(189)*.

10.4 Concerns of infringement of patient rights due to implementation of anti-diversion measures

In response to calls to make expensive, life-saving medicines more readily available in LMIC, pharmaceutical companies have applied measures such

as voluntary licensing, tiered pricing and direct negotiations with national governments. These measures result in significantly lower prices in some countries, primarily LMIC, than those charged for the same medicines in other, primarily high-income countries. Such large price discrepancies and lack of access to affordable medicines increase the risk of product diversion from countries where treatment is less expensive to countries where it is more expensive. Pharmaceutical companies, national treatment programmes and private distributors thus implement what are called anti-diversion measures. These practices were first introduced to control the resale of ARVs for HIV *(286)*. Possible specific measures include product packaging that is specific to the treatment programme, different trade names, different colour of tablets and electronic tracking tools. Concerns have been raised about some additionally stringent anti-diversion measures that have been implemented in relation to the new HCV treatments. Current reported practices to control the individual diversion of medicines include the following:

- distribution of medicines with bar codes that include some patient information;
- access to medicines provided on a named patient basis with proof of identification;
- requiring proof of residence and citizenship before providing access to medication;
- photographing the patient when he/she picks up the first bottle of medicine;
- distribution of a limited (e.g. 2 weeks or 1 month) supply of medicine at a time with the requirement that empty medicine bottles be brought or sent back in exchange for new bottle(s);
- requiring documentation of a negative viral load result if a patient fails to return an empty bottle of medicine (to prove that the patient has been taking the medicine rather than having sold it).

Preventing diversion of medicines is a legitimate concern of pharmaceutical companies and treatment programme managers, as well as hospital staff. However, it is important that anti-diversion measures operate within the bounds of medical ethics. These include the following:

- Confidentiality of patient information – access to patient-identifying information should be restricted to health-care providers caring for the patient;
- Autonomy – patients have a right to make decisions about their health care, including stopping treatment if they so choose;
- Privileged physician–patient interaction: treatment decisions should be made by health-care workers providing care to a patient;
- Proportionality – anti-diversion measures should not put an undue burden on patients, health-care workers and treatment programmes;
- Non-discrimination – anti-diversion measures should not directly or indirectly restrict access to care for vulnerable and marginalized communities such as refugees, PWID, migrants, homeless persons or those with unstable living arrangements.

11. DISSEMINATION AND UPDATING OF THE GUIDELINES

These guidelines will be launched at the annual meeting of the European Association for the Study of the Liver (April 2016). Following the launch, the Global Hepatitis Programme Secretariat will identify suitable international venues to present and distribute the recommendations. The guidelines will also be disseminated through WHO regional offices to WHO country offices and Ministries of Health where possible, as well as to key international, regional and national collaborating centres, civil society organizations and national programmes. In addition, the guidelines will be 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 and organizations.

Implementation of these guidelines can be measured by the number of countries that have incorporated them in their national treatment programmes. Ideally, the impact of the guidelines would be measured by monitoring the number of persons treated for HCV and the number cured. Currently, no monitoring system exists that can collect this information on a national level.

As indicated in section 2.4, new DAAs will acquire regulatory approval within months following the release of these guidelines, and the generics landscape and drug-pricing structures will continue to change. WHO will issue new guidance approximately 12–18 months after publication of these guidelines to provide recommendations relevant to the new treatment landscape.

REFERENCES

1. Guidelines for the screening, care and treatment of persons with hepatitis C infection. Geneva: World Health Organization; 2014 (http://apps.who.int/iris/bitstream/10665/111747/1/9789241548755_eng.pdf?ua=1&ua=1, accessed 18 December 2015).

2. 19th WHO Model list of essential medicines Geneva: World Health Organization; 2015 (http://www.who.int/medicines/publications/essentialmedicines/EML2015_8-May-15.pdf, accessed 29 September 2015).

3. Consolidated guidelines on the use of antiretrovirals for treating and preventing HIV infection. Geneva: World Health Organization; In press.

4. Guidelines for the prevention, care and treatment of persons with hepatitis B infection. Geneva: World Health Organization; 2015 (http://apps.who.int/iris/bitstream/10665/154590/1/9789241549059_eng.pdf?ua=1&ua=1, accessed 18 December 2015).

5. Guidance on prevention of viral hepatitis B and C among people who inject drugs. Geneva: World Health Organization; 2012 (http://apps.who.int/iris/bitstream/10665/75357/1/9789241504041_eng.pdf?ua=1, accessed 18 December 2015).

6. Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012;380(9859):2095–128.

7. GBD Mortality and Causes of Death Collaborators. Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet. 2014;385(9963):117–71.

8. Magiorkinis G, Magiorkinis E, Paraskevis D, Ho SY, Shapiro B, Pybus OG, et al. The global spread of hepatitis C virus 1a and 1b: a phylodynamic and phylogeographic analysis. PLoS Med. 2009;6(12):e1000198.

9. Razavi H, Waked I, Sarrazin C, Myers RP, Idilman R, Calinas F, et al. The present and future disease burden of hepatitis C virus (HCV) infection with today's treatment paradigm. J Viral Hepatitis. 2014;21 (Suppl 1):34–59.

10. Community outbreak of HIV infection linked to injection drug use of

oxymorphone — Indiana, 2015. Morbid Mortal Wkly Rep (MMWR). 2015;64(16):434–44.

11. Wandeler G, Schlauri M, Jaquier ME, Rohrbach J, Metzner KJ, Fehr J, et al. Incident hepatitis C virus infections in the Swiss HIV Cohort Study: changes in treatment uptake and outcomes between 1991 and 2013. Open Forum Infect Dis. 2015;2(1). doi: 10.1093/ofid/ofv026.

12. Mohd Hanafiah K, Groeger J, Flaxman AD, Wiersma ST. Global epidemiology of hepatitis C virus infection: new estimates of age-specific antibody to HCV seroprevalence. Hepatology. 2013;57(4):1333–42.

13. Gower E, Estes C, Blach S, Razavi-Shearer K, Razavi H. Global epidemiology and genotype distribution of the hepatitis C virus infection. J Hepatol. 2014;61(1 Suppl):S45–57.

14. Rao VB, Johari N, du Cros P, Messina J, Ford N, Cooke GS. Hepatitis C seroprevalence and HIV co-infection in sub-Saharan Africa: a systematic review and meta-analysis. Lancet Infect Dis. 2015;15(7):819–24.

15. Platt L, Easterbrook P, Gower E, McDonald B, Sabin K, McGowan C, et al. Prevalence and burden of HCV co-infection in people living with HIV: a global systematic review and meta-analysis. Lancet Infect Dis. published online 24 February 2016; DOI: http://dx.doi.org/10.1016/S1473-3099(15)00485-5 (http://www.thelancet.com/pdfs/journals/laninf/PIIS1473-3099%2815%2900485-5.pdf, accessed 21 March 2016).

16. Lin SY, Chen TC, Lu PL, Lin CY, Lin WR, Yang YH, et al. Incidence rates of tuberculosis in chronic hepatitis C infected patients with or without interferon based therapy: a population-based cohort study in Taiwan. BMC Infect Dis. 2014;14:705.

17. Simmonds P. Reconstructing the origins of human hepatitis viruses. Philos Trans R Soc Lond B Biol Sci. 2001;356(1411):1013–26.

18. Messina JP, Humphreys I, Flaxman A, Brown A, Cooke GS, Pybus OG, et al. Global distribution and prevalence of hepatitis C virus genotypes. Hepatology. 2015;61(1):77–87.

19. Nelson PK, Mathers BM, Cowie B, Hagan H, Des Jarlais D, Horyniak D, et al. Global epidemiology of hepatitis B and hepatitis C in people who inject drugs: results of systematic reviews. Lancet. 2011;378(9791):571–83.

20. Shepard CW, Finelli L, Alter MJ. Global epidemiology of hepatitis C virus infection. Lancet Infect Dis. 2005;5(9):558–67.

21. Frank C, Mohamed MK, Strickland GT, Lavanchy D, Arthur RR, Magder LS, et al. The role of parenteral antischistosomal therapy in the spread of hepatitis C virus in Egypt. Lancet. 2000;355(9207):887–91.

22. Singh S, Dwivedi SN, Sood R, Wali JP. Hepatitis B, C and human immunodeficiency virus infections in multiply-injected kala-azar patients in Delhi. Scand J Infect Dis. 2000;32(1):3–6.

23. Marx MA, Murugavel KG, Sivaram S, Balakrishnan P, Steinhoff M, Anand S, et al. The association of health-care use and hepatitis C virus infection in a random sample of urban slum community residents in southern India. Am J Trop Med Hyg. 2003;68(2):258–62.

24. Wang CS, Chang TT, Chou P. Differences in risk factors for being either a hepatitis B carrier or anti-hepatitis C+ in a hepatoma-hyperendemic area in rural Taiwan. J Clin Epidemiol. 1998;51(9):733–8.

25. Ho MS, Hsu CP, Yuh Y, King CC, Tsai JF. High rate of hepatitis C virus infection in an isolated community: persistent hyperendemicity or period-related phenomena? J Med Virol. 1997;52(4):370–6.

26. Lin CC, Hwang SJ, Chiou ST, Kuan CL, Chen LW, Lee TC, et al. The prevalence and risk factors analysis of serum antibody to hepatitis C virus in the elders in northeast Taiwan. J Chin Med Assoc. 2003;66(2):103–8.

27. Saxena R, Thakur V, Sood B, Guptan RC, Gururaja S, Sarin SK. Transfusion-associated hepatitis in a tertiary referral hospital in India. A prospective study. Vox Sang. 1999;77(1):6–10.

28. Candotti D, Sarkodie F, Allain JP. Residual risk of transfusion in Ghana. Br J Haematol. 2001;113(1):37–9.

29. El-Zanaty F, Way A. Egypt demographic and health survey, 2008. Final report. In: Measure DHS. Cairo, Egypt: Ministry of Health, El-Zanaty and Associates and Macro International: 2009 (http://dhsprogram.com/pubs/pdf/fr220/fr220.pdf, accessed 20 January 2016).

30. Thomas DL, Villano SA, Riester KA, Hershow R, Mofenson LM, Landesman SH, et al. Perinatal transmission of hepatitis C virus from human immunodeficiency virus type 1-infected mothers. Women and Infants Transmission Study. J Infect Dis. 1998;177(6):1480–8.

31. Egypt Health Issues Survey 2015. Cairo: Egypt and Rockville, Maryland, USA: and Ministry of Health and ICF International; 2015 (https://dhsprogram.com/pubs/pdf/FR313/FR313.pdf, accessed 7 March 2016).

32. Benova L, Mohamoud YA, Calvert C, Abu-Raddad LJ. Vertical transmission of hepatitis C virus: systematic review and meta-analysis. Clin Infect Dis. 2014;59(6):765–73.

33. Mast EE, Hwang LY, Seto DS, Nolte FS, Nainan OV, Wurtzel H, et al. Risk factors for perinatal transmission of hepatitis C virus (HCV) and the natural history of HCV infection acquired in infancy. J Infect Dis. 2005;192(11):1880–9.

34. Selvapatt N, Ward T, Bailey H, Bennett H, Thorne C, See LM, et al. Is antenatal screening for hepatitis C virus cost effective? A decade's experience at a London centre. J Hepatol. 2015;63(4):797–804.

35. Floreani A. Hepatitis C and pregnancy. World J Gastroenterol. 2013;19(40):6714–20.

36. Terrault NA, Dodge JL, Murphy EL, Tavis JE, Kiss A, Levin TR, et al. Sexual transmission of hepatitis C virus among monogamous heterosexual couples: The HCV partners study. Hepatology. 2013;57(3):881–9.

37. Valadez JJ, Berendes S, Jeffery C, Thomson J, Ben Othman H, Danon L, et al. Filling the knowledge gap: measuring HIV prevalence and risk factors among men who have sex with men and female sex workers in Tripoli, Libya. PLos One. 2013;8(6).

38. Tseng YT, Sun HY, Chang SY, Wu CH, Liu WC, Wu PY, et al. Seroprevalence of hepatitis virus infection in men who have sex with men aged 18–40 years in Taiwan. J Formos Med Assoc. 2012;111(8):431–8.

39. Price H, Gilson R, Mercey D, Copas A, Parry J, Nardone A, et al. Hepatitis C in men who have sex with men in London – a community survey. HIV Med. 2013;14(9):578–80.

40. Tohme RA, Holmberg S. Is sexual contact a major mode of hepatitis C virus transmission? Hepatology. 2010;52(4):1497–505.

41. Karuru JW, Lule GN, Joshi M, Anzala O. Prevalence of HCV and HCV/HIV co-infection among in-patients at the Kenyatta National Hospital. East Afr Med J. 2005;82(4):170–2.

42. Quaranta JF, Delaney SR, Alleman S, Cassuto JP, Dellamonica P, Allain JP. Prevalence of antibody to hepatitis C virus (HCV) in HIV-1-infected patients (nice SEROCO cohort). J Med Virol. 1994;42(1):29–32.

43. Sherman KE, Rouster SD, Chung RT, Rajicic N. Hepatitis C virus prevalence among patients infected with human immunodeficiency virus: a cross-sectional analysis of the US adult AIDS Clinical Trials Group. Clin Infect Dis. 2002;34(6):831–7.

44. Rauch A, Rickenbach M, Weber R, Hirschel B, Tarr PE, Bucher HC, et al. Unsafe sex and increased incidence of hepatitis C virus infection among HIV-infected men who have sex with men: The Swiss HIV Cohort Study. Clin Infect Dis. 2005;41(3):395–402.

45. D'Oliveira A, Voirin N, Allard R, Peyramond D, Chidiac C, Touraine JL, et al. Prevalence and sexual risk of hepatitis C virus infection when human immunodeficiency virus was acquired through sexual intercourse among patients of the Lyon University Hospitals, France, 1992–2002. J Viral

Hepat. 2005;12(3):330–2.

46. Vandelli C, Renzo F, Romano L, Tisminetzky S, De Palma M, Stroffolini T, et al. Lack of evidence of sexual transmission of hepatitis C among monogamous couples: results of a 10-year prospective follow-up study. Am J Gastroenterol. 2004;99(5):855–9.

47. Eyster ME, Alter HJ, Aledort LM, Quan S, Hatzakis A, Goedert JJ. Heterosexual co-transmission of hepatitis C virus (HCV) and human immunodeficiency virus (HIV). Ann Intern Med. 1991;115(10):764–8.

48. Taylor LE, Swan T, Mayer KH. HIV coinfection with hepatitis C virus: evolving epidemiology and treatment paradigms. Clin Infect Dis. 2012;55 (Suppl 1):S33–42.

49. Scheinmann R, Hagan H, Lelutiu-Weinberger C, Stern R, Des Jarlais DC, Flom PL, et al. Non-injection drug use and hepatitis C virus: a systematic review. Drug Alcohol Depend. 2007;89(1):1–12.

50. Jafari S, Copes R, Baharlou S, Etminan M, Buxton J. Tattooing and the risk of transmission of hepatitis C: a systematic review and meta-analysis. Int J Infect Dis. 2010;14(11):E928–E940.

51. de Oliveira T, Pybus OG, Rambaut A, Salemi M, Cassol S, Ciccozzi M, et al. Molecular epidemiology – HIV-1 and HCV sequences from Libyan outbreak. Nature. 2006;444(7121):836–7.

52. Kane A, Lloyd J, Zaffran M, Simonsen L, Kane M. Transmission of hepatitis B, hepatitis C and human immunodeficiency viruses through unsafe injections in the developing world: model-based regional estimates. Bull World Health Organ. 1999;77(10):801–7.

53. Global database on blood safety. In: Blood transfusion safety [webpage]. Geneva: World Health Organization; 2011 (http://www.who.int/bloodsafety/global_database/en/, accessed 10 March 2016).

54. Tillmann HL, Thursz M. Hepatitis C virus infection – its role in pathogenesis. J Infect Dis. 2007;195(2):168–70.

55. Marincovich B, Castilla J, del Romero J, Garcia S, Hernando V, Raposo M, et al. Absence of hepatitis C virus transmission in a prospective cohort of heterosexual serodiscordant couples. Sex Transm Infect. 2003;79(2):160–2.

56. Danta M, Brown D, Bhagani S, Pybus OG, Sabin CA, Nelson M, et al. Recent epidemic of acute hepatitis C virus in HIV-positive men who have sex with men linked to high-risk sexual behaviours. AIDS. 2007;21(8):983–91.

57. van de Laar T, Pybus O, Bruisten S, Brown D, Nelson M, Bhagani S, et al. Evidence of a large, international network of HCV transmission in HIV-positive

men who have sex with men. Gastroenterology. 2009;136(5):1609–17.

58. Fierer DS, Uriel AJ, Carriero DC, Klepper A, Dieterich DT, Mullen MP, et al. Liver fibrosis during an outbreak of acute hepatitis C virus infection in HIV-infected men: a prospective cohort study. J Infect Dis. 2008;198(5):683–6.

59. Karmochkine M, Carrat F, Dos Santos O, Cacoub P, Raguin G. A case–control study of risk factors for hepatitis C infection in patients with unexplained routes of infection. J Viral Hepat. 2006;13(11):775–82.

60. Bica I, McGovern B, Dhar R, Stone D, McGowan K, Scheib R, et al. Increasing mortality due to end-stage liver disease in patients with human immunodeficiency virus infection. Clin Infect Dis. 2001;32(3):492–7.

61. Crespo J, Lozano JL, Delacruz F, Rodrigo L, Rodriguez M, Sanmiguel G, et al. Prevalence and significance of hepatitis-C viremia in chronic active hepatitis-B. Am J Gastroenterol. 1994;89(8):1147–51.

62. Pontisso P, Ruvoletto MG, Fattovich G, Chemello L, Gallorini A, Ruol A, et al. Clinical and virological profiles in patients with multiple hepatitis-virus infections. Gastroenterology. 1993;105(5):1529–33.

63. Liu CJ, Liou JM, Chen DS, Chen PJ. Natural course and treatment of dual hepatitis B virus and hepatitis C virus infections. J Formos Med Assoc. 2005;104(11):783–91.

64. Di Marco V, Lo Iacono O, Camma C, Vaccaro A, Giunta M, Martorana G, et al. The long-term course of chronic hepatitis B. Hepatology. 1999;30(1):257–64.

65. Kaur S, Rybicki L, Bacon BR, Gollan JL, Rustgi VK, Carey WD. Performance characteristics and results of a large-scale screening program for viral hepatitis and risk factors associated with exposure to viral hepatitis B and C: results of the national hepatitis screening survey. Hepatology. 1996;24(5):979–86.

66. Potthoff A, Manns MP, Wedemeyer H. Treatment of HBV/HCV coinfection. Expert Opin Pharmacother. 2010;11(6):919–28.

67. Getahun H, Gunneberg C, Sculier D, Verster A, Raviglione M. Tuberculosis and HIV in people who inject drugs: evidence for action for tuberculosis, HIV, prison and harm reduction services. Curr Opin HIV AIDS. 2012;7(4):345–53.

68. Getahun H, Baddeley A, Raviglione M. Managing tuberculosis in people who use and inject illicit drugs. Bull World Health Organ. 2013;91(2):154–6.

69. Thomson EC, Fleming VM, Main J, Klenerman P, Weber J, Eliahoo J, et al. Predicting spontaneous clearance of acute hepatitis C virus in a large cohort of HIV-1-infected men. Gut. 2011;60(6):837–45.

70. Gerlach JT, Diepolder HM, Zachoval R, Gruener NH, Jung MC, Ulsenheimer A, et al. Acute hepatitis C: high rate of both spontaneous and treatment-induced viral clearance. Gastroenterology. 2003;125(1):80–8.

71. Tong MJ, Elfarra NS, Reikes AR, Co RL. Clinical outcomes after transfusion-associated hepatitis-C. N Engl J Med. 1995;332(22):1463–6.

72. Tremolada F, Casarin C, Alberti A, Drago C, Tagger A, Ribero ML, et al. Long-term follow-up of non-A, non-B (type C) post-transfusion hepatitis. J Hepatol. 1992;16(3):273–81.

73. Thein HH, Yi Q, Dore GJ, Krahn MD. Estimation of stage-specific fibrosis progression rates in chronic hepatitis C virus infection: a meta-analysis and meta-regression. Hepatology. 2008;48(2):418–31.

74. El-Serag HB, Rudolph KL. Hepatocellular carcinoma: epidemiology and molecular carcinogenesis. Gastroenterology. 2007;132(7):2557–76.

75. Bedossa P, Poynard T. An algorithm for the grading of activity in chronic hepatitis C. The METAVIR Cooperative Study Group. Hepatology. 1996;24(2):289–93.

76. Durand F, Valla D. Assessment of prognosis of cirrhosis. Semin Liver Dis. 2008;28(1):110–22.

77. Freeman AJ, Law MG, Kaldor JM, Dore GJ. Predicting progression to cirrhosis in chronic hepatitis C virus infection. J Viral Hepat. 2003;10(4):285–93.

78. Fletcher NF, McKeating JA. Hepatitis C virus and the brain. J Viral Hepat. 2012;19(5):301–6.

79. Forton DM, Karayiannis P, Mahmud N, Taylor-Robinson SD, Thomas HC. Identification of unique hepatitis C virus quasispecies in the central nervous system and comparative analysis of internal translational efficiency of brain, liver, and serum variants. J Virol. 2004;78(10):5170–83.

80. Benhamou Y, Bochet M, Di Martino V, Charlotte F, Azria F, Coutellier A, et al. Liver fibrosis progression in human immunodeficiency virus and hepatitis C virus coinfected patients. The Multivirc Group. Hepatology. 1999;30(4):1054–8.

81. Di Martino V, Rufat P, Boyer N, Renard P, Degos F, Martinot-Peignoux M, et al. The influence of human immunodeficiency virus coinfection on chronic hepatitis C in injection drug users: a long-term retrospective cohort study. Hepatology. 2001;34(6):1193–9.

82. Graham CS, Baden LR, Yu E, Mrus JM, Carnie J, Heeren T, et al. Influence of human immunodeficiency virus infection on the course of hepatitis C virus infection: a meta-analysis. Clin Infect Dis. 2001;33(4):562–9.

83. Pineda JA, Romero-Gomez M, Diaz-Garcia F, Giron-Gonzalez JA, Montero JL, Torre-Cisneros J, et al. HIV coinfection shortens the survival of patients with hepatitis C virus-related decompensated cirrhosis. Hepatology. 2005;41(4):779–89.

84. Cohen MH, French AL, Benning L, Kovacs A, Anastos K, Young M, et al. Causes of death among women with human immunodeficiency virus infection in the era of combination antiretroviral therapy. Am J Med. 2002;113(2):91–8.

85. Martin-Carbonero L, Sanchez-Somolinos M, Garcia-Samaniego J, Nunez MJ, Valencia ME, Gonzalez-Lahoz J, et al. Reduction in liver-related hospital admissions and deaths in HIV-infected patients since the year 2002. J Viral Hepat. 2006;13(12):851–7.

86. Greub G, Ledergerber B, Battegay M, Grob P, Perrin L, Furrer H, et al. Clinical progression, survival, and immune recovery during antiretroviral therapy in patients with HIV-1 and hepatitis C virus coinfection: the Swiss HIV Cohort Study. Lancet. 2000;356(9244):1800–5.

87. De Luca A, Bugarini R, Lepri AC, Puoti M, Girardi E, Antinori A, et al. Coinfection with hepatitis viruses and outcome of initial antiretroviral regimens in previously naive HIV-infected subjects. Arch Intern Med. 2002;162(18):2125–32.

88. Law WP, Duncombe CJ, Mahanontharit A, Boyd MA, Ruxrungtham K, Lange JMA, et al. Impact of viral hepatitis co-infection on response to antiretroviral therapy and HIV disease progression in the HIV-NAT cohort. AIDS. 2004;18(8):1169–77.

89. Rancinan C, Neau D, Saves M, Lawson-Ayayi S, Bonnet F, Mercie P, et al. Is hepatitis C virus co-infection associated with survival in HIV-infected patients treated by combination antiretroviral therapy? AIDS. 2002;16(10):1357–62.

90. Tedaldi EM, Baker RK, Moorman AC, Alzola CF, Furhrer J, McCabe RE, et al. Influence of coinfection with hepatitis C virus on morbidity and mortality due to human immunodeficiency virus infection in the era of highly active antiretroviral therapy. Clin Infect Dis. 2003;36(3):363–7.

91. Vlahov D, Graham N, Hoover D, Flynn C, Bartlett JG, Margolick JB, et al. Prognostic indicators for AIDS and infectious disease death in HIV-infected injection drug users – plasma viral load and CD4(+) cell count. JAMA. 1998;279(1):35–40.

92. Celentano DD, Vlahov D, Cohn S, Shadle VM, Obasanjo O, Moore RD. Self-reported antiretroviral therapy in injection drug users. JAMA. 1998;280(6):544–6.

93. Garcia-Samaniego J, Rodriguez M, Berenguer J, Rodriguez-Rosado R, Carbo

J, Asensi V, et al. Hepatocellular carcinoma in HIV-infected patients with chronic hepatitis C. Am J Gastroenterol. 2001;96(1):179–83.

94. Parekh PJ, Shiffman ML. The role of interferon in the new era of hepatitis C treatments. Expert Rev Gastroenterol Hepatol. 2014;8(6):649–56.

95. Schinazi R, Halfon P, Marcellin P, Asselah T. HCV direct-acting antiviral agents: the best interferon-free combinations. Liver Int. 2014;34 (Suppl 1):69–78.

96. Wyles DL, Ruane PJ, Sulkowski MS, Dieterich D, Luetkemeyer A, Morgan TR, et al. Daclatasvir plus sofosbuvir for HCV in patients coinfected with HIV-1. N Engl J Med. 2015;373(8):714–25.

97. Poordad F, Schiff ER, Vierling JM, Landis C, Fontana RJ, Yang R, et al. Daclatasvir with sofosbuvir and ribavirin for HCV infection with advanced cirrhosis or post-liver transplant recurrence. Hepatology. published online 7 March 2016;. doi: 10.1002/hep.28446.

98. Hezode C, Asselah T, Reddy KR, Hassanein T, Berenguer M, Fleischer-Stepniewska K, et al. Ombitasvir plus paritaprevir plus ritonavir with or without ribavirin in treatment-naive and treatment-experienced patients with genotype 4 chronic hepatitis C virus infection (PEARL-I): a randomised, open-label trial. Lancet. 2015;385(9986):2502–9.

99. Feld JJ, Kowdley KV, Coakley E, Sigal S, Nelson DR, Crawford D, et al. Treatment of HCV with ABT-450/r-ombitasvir and dasabuvir with ribavirin. N Engl J Med. 2014;370(17):1594–603.

100. United States Food and Drug Administration Drug Safety Communication: FDA warns of serious liver injury risk with hepatitis C treatments Viekira Pak and Technivie. [Press release]. 22 October 2015 (http://www.fda.gov/Drugs/DrugSafety/ucm468634.htm, accessed 22 March 2016).

101. Jacobson IM, Dore GJ, Foster GR, Fried MW, Radu M, Rafalsky VV, et al. Simeprevir with pegylated interferon alfa 2a plus ribavirin in treatment-naive patients with chronic hepatitis C virus genotype 1 infection (QUEST-1): a phase 3, randomised, double-blind, placebo-controlled trial. Lancet. 2014;384(9941):403–13.

102. Sofia MJ, Bao D, Chang W, Du J, Nagarathnam D, Rachakonda S, et al. Discovery of a beta-d-2'-deoxy-2'-alpha-fluoro-2'-beta-C-methyluridine nucleotide prodrug (PSI-7977) for the treatment of hepatitis C virus. J Med Chem. 2010;53(19):7202–18.

103. Black S, Pak I, Ingravallo P, McMonagle P, Chase R, Shaughnessy M, et al. editors. Resistance analysis of virologic failures in hepatitis C genotype 1-infected patients treated with grazoprevir + elbasvir ± ribavirin: the C-WORTHY Study. In: 2015 International Liver Congress: 50th Annual

Meeting of the European Association for the Study of the Liver (EASL). Vienna, 22–26 April 2015.

104. Feld JJ, Jacobson IM, Hezode C, Asselah T, Ruane PJ, Gruener N, et al. Sofosbuvir and velpatasvir for HCV genotype 1, 2, 4, 5, and 6 infection. N Engl J Med. 2015;373 (27):2599–607.

105. Foster GR, Afdhal N, Roberts SK, Brau N, Gane EJ, Pianko S, et al. Sofosbuvir and velpatasvir for HCV genotype 2 and 3 infection. N Engl J Med. 2015;373(27):2608–17.

106. Curry MP, O'Leary JG, Bzowej N, Muir AJ, Korenblat KM, Fenkel JM, et al. Sofosbuvir and velpatasvir for HCV in patients with decompensated cirrhosis. N Engl J Med. 2015;373(27):2618–28.

107. UNITAID. Hepatitis C medicines: technology and market landscape – update. Geneva: WHO; 2015 (http://unitaid.org/images/marketdynamics/publications/Hepatitis_C_Medicines_Technology_and_Market_Landscape__Update.pdf, accessed 18 December 2015).

108. Hill A, Simmons B, Gotham D, Fortunak J. Rapid reductions in prices for generic sofosbuvir and daclatasvir to treat hepatitis C. J Virus Erad. 2016;2:28–31.

109. Andrieux-Meyer I, Cohn J, de Araujo ES, Hamid SS. Disparity in market prices for hepatitis C virus direct-acting drugs. Lancet Glob Health. 2015;3(11):e676–7.

110. Moon S, Jambert E, Childs M, von Schoen-Angerer T. A win-win solution? A critical analysis of tiered pricing to improve access to medicines in developing countries. Glob Health. 2011;7:39.

111. World Trade Organization Agreement on Trade-Related Aspects of Intellectual Property Rights. Morocco: World Trade Organization; 1994 (https://www.wto.org/english/docs_e/legal_e/27-trips.pdf, accessed 18 December 2015).

112. The Universal Declaration of Human Rights. Geneva: United Nations; 1948 (http://www.un.org/en/documents/udhr/index.shtml, accessed 21 January 2016).

113. Sustainable Development Goals. Geneva: United Nations; 2015 (https://sustainabledevelopment.un.org/?menu=1300, accessed 7 March 2016).

114. Declaration of Geneva. Geneva: 2006 (http://www.wma.net/en/30publications/10policies/g1/index.html, 21 January 2016).

115. Gilks CF, Crowley S, Ekpini R, Gove S, Perriens J, Souteyrand Y, et al. The WHO public-health approach to antiretroviral treatment against HIV in resource-limited settings. Lancet. 2006;368(9534):505–10.

116. Handbook for guidelines development. Geneva: World Health Organization;

2014 (http://www.who.int/kms/handbook_2nd_ed.pdf, accessed 21 January 2016).

117. Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, et al. GRADE guidelines: 1. Introduction – GRADE evidence profiles and summary of findings tables. J Clin Epidemiol. 2011;64(4):383–94.

118. Balshem H, Helfand M, Schunemann HJ, Oxman AD, Kunz R, Brozek J, et al. GRADE guidelines: 3. Rating the quality of evidence. J Clin Epidemiol. 2011;64(4):401–6.

119. Gordon SC, Muir AJ, Lim JK, Pearlman B, Argo CK, Ramani A, et al. Safety profile of boceprevir and telaprevir in chronic hepatitis C: real world experience from HCV-TARGET. J Hepatol. 2015;62(2):286–93.

120. Sogni P, Gilbert C, Lacombe K, Piroth L, Rosenthal E, Dominguez S, et al. Safety and efficacy of all-oral DAA regimens in HIV/HCV coinfected cirrhotic patients from the prospective ANRS CO13 HEPAVIH cohort. In: 2015 International Liver Congress: 50th Annual Meeting of the European Association for the Study of the Liver. Vienna, 22–26 April 2015 [Abstract LP20].

121. Salmon D, Lacombe K, Esterle L, Gilbert C, Piroth L, Bani-Sadr F, et al. Use of oral DAA-based regimens in HIV-HCV co-infected patients in a real life setting – interim analysis from the ANRS CO13 HEPAVIH cohort. In: 8th International AIDS Society (IAS) Conference on HIV Pathogenesis, Treatment and Prevention, Vancouver, 19–22 July 2015 [Poster no. TULBPE09].

122. Pol S, Bourliere M, Lucier S, De Ledinghen V, Zoulim F, Dorival-Mouly C, et al.; on behalf of the HEPATHER Study Group. Safety and efficacy of the combination daclatasvir-sofosbuvir in HCV genotype 1-mono-infected patients from the French Observational Cohort ANRS CO22 HEPATHER. J Hepatol. 2015;62(Suppl 2):S258–9.

123. Mills EJ, Ioannidis JP, Thorlund K, Schunemann HJ, Puhan MA, Guyatt GH. How to use an article reporting a multiple treatment comparison meta-analysis. JAMA. 2012;308(12):1246–53.

124. Puhan MA, Schunemann HJ, Murad MH, Li T, Brignardello-Petersen R, Singh JA, et al. A GRADE Working Group approach for rating the quality of treatment effect estimates from network meta-analysis. BMJ. 2014;349:g5630.

125. Druyts E, Kanters S, Toor K, Thorlund K, Mills EJ. The use of single-arm evidence in the comparative efficacy of interferon-free antivirals for treatment-naive hepatitis C genotype 1. Value Health. 2015;18(7):A576.

126. Global policy report on the prevention and control of viral hepatitis in WHO Member States. Geneva: WHO; 2013 (http://apps.who.int/iris/bitstream/10665/85397/1/9789241564632_eng.pdf, accessed 21 January 2016).

127. Hepatitis B and C: ways to promote and offer testing to people at increased risk of infection. London: NICE; 2012 (http://www.nice.org.uk/nicemedia/live/14003/61863/61863.pdf, accessed 21 January 2016).

128. Smith BD, Morgan RL, Beckett GA, Falck-Ytter Y, Holtzman D, Teo C-G, et al. Recommendations for the identification of chronic hepatitis C virus infection among persons born during 1945–1965. Morbid Mortal Wkly Rep (MMWR). 2012;61(RR04):1–18. Errata in Morbid Mortal Wkly Rep (MMWR). 2012; 61(43):886.

129. Webster DP, Klenerman P, Dusheiko GM. Hepatitis C. Lancet. 2015;385(9973):1124–35.

130. Hajarizadeh B, Grebely J, Dore GJ. Epidemiology and natural history of HCV infection. Nat Rev Gastroenterol Hepatol. 2013;10(9):553–62.

131. Ghany MG, Nelson DR, Strader DB, Thomas DL, Seeff LB; American Association for Study of Liver Diseases. An update on treatment of genotype 1 chronic hepatitis C virus infection: 2011 practice guideline by the American Association for the Study of Liver Diseases. Hepatology. 2011;54(4):1433–44.

132. European Association for Study of the Liver. EASL Clinical Practice Guidelines: management of hepatitis C virus infection. J Hepatol. 2014;60(2):392–420.

133. Allison RD, Conry-Cantilena C, Koziol D, Schechterly C, Ness P, Gibble J, et al. A 25-year study of the clinical and histologic outcomes of hepatitis C virus infection and its modes of transmission in a cohort of initially asymptomatic blood donors. J Infect Dis. 2012;206(5):654–61.

134. Piasecki BA, Lewis JD, Reddy KR, Bellamy SL, Porter SB, Weinrieb RM, et al. Influence of alcohol use, race, and viral coinfections on spontaneous HCV clearance in a US veteran population. Hepatology. 2004;40(4):892–9.

135. Ohkoshi S, Tawaraya H, Kuwana K, Harada T, Watanabe M, Higuchi S, et al. A retrospective study of hepatitis-C virus carriers in a local endemic town in Japan – a possible presence of asymptomatic carrier. Dig Dis Sci. 1995;40(2):465–71.

136. Rongey CA, Kanwal F, Hoang T, Gifford AL, Asch SM. Viral RNA testing in hepatitis C antibody-positive veterans. Am J Prev Med. 2009;36(3):235–8.

137. Scott JD, McMahon BJ, Bruden D, Sullivan D, Homan C, Christensen C, et al. High rate of spontaneous negativity for hepatitis C virus RNA after establishment of chronic infection in Alaska Natives. Clin Infect Dis. 2006;42(7):945–52.

138. Sheth SD, Vera-Llonch M, Lynch J, Werther W, Rubin R. Characterization

of a cohort of incident hepatitis C patients in the US (2005–2010): comorbidities, use of medications and diagnostic tests. Gastroenterology. 2012;142(5 Suppl 1):S965.

139. Yoshino I, Kasai M. Analysis of cases of negative HCV-RNA with positive anti-HCV. Acta Hepatologica Japonica. 1996;37(8):412–16.

140. Smith BD, Yartel AK, Krauskopf K, Massoud OI, Brown KA, Fallon MB, et al. Hepatitis C virus antibody positivity and predictors among previously undiagnosed adult primary care outpatients: cross-sectional analysis of a multisite retrospective cohort study. Clin Infect Dis. 2015;60(8):1145–52.

141. Rein DB, Wagner LD, Brown KA, Fallon MB, Krauskopf K, Massoud OI, et al. Current practices of hepatitis C antibody testing and follow-up evaluation in primary care settings: a retrospective study of four large, primary care service centers. Hepatology. 2012;56:1094A.

142. Bonacini M, Lin HJ, Hollinger FB. Effect of coexisting HIV-1 infection on the diagnosis and evaluation of hepatitis C virus. J Acquir Immune Defic Syndr. 2001;26(4):340–4.

143. George SL, Gebhardt J, Klinzman D, Foster MB, Patrick KD, Schmidt WN, et al. Hepatitis C virus viremia in HIV-infected individuals with negative HCV antibody tests. J Acquir Immune Defic Syndr. 2002;31(2):154–62.

144. Thio CL, Nolt KR, Astemborski J, Vlahov D, Nelson KE, Thomas DL. Screening for hepatitis C virus in human immunodeficiency virus-infected individuals. J Clin Microbiol. 2000;38(2):575–7.

145. Thomson EC, Nastouli E, Main J, Karayiannis P, Eliahoo J, Muir D, et al. Delayed anti-HCV antibody response in HIV-positive men acutely infected with HCV. AIDS. 2009;23(1):89–93.

146. WHO ASSIST package. Geneva: World Health Organization; 2011 (http://www.who.int/substance_abuse/publications/media_assist/en/, accessed 22 March 2016).

147. Hutchinson SJ, Bird SM, Goldberg DJ. Influence of alcohol on the progression of hepatitis C virus infection: a meta-analysis. Clin Gastroenterol Hepatol. 2005;3(11):1150–9.

148. Brunet L, Moodie EE, Rollet K, Cooper C, Walmsley S, Potter M, et al. Marijuana smoking does not accelerate progression of liver disease in HIV-hepatitis C coinfection: a longitudinal cohort analysis. Clin Infect Dis. 2013;57(5):663–70.

149. Thomas DL, Astemborski J, Rai RM, Anania FA, Schaeffer M, Galai N, et al. The natural history of hepatitis C virus infection: host, viral, and environmental factors. JAMA. 2000;284(4):450–6.

150. Mughal TI, Patel SB. Hepatocellular carcinoma: a review of 140 cases. Ann Saudi Med. 1996;16(1):53–5.

151. Du WJ, Xiang YT, Wang ZM, Chi Y, Zheng Y, Luo XN, et al. Socio-demographic and clinical characteristics of 3129 heroin users in the first methadone maintenance treatment clinic in China. Drug Alcohol Depend. 2008;94(1-3):158–64.

152. Cepeda JA, Niccolai LM, Eritsyan K, Heimer R, Levina O. Moderate/heavy alcohol use and HCV infection among injection drug users in two Russian cities. Drug Alcohol Depen. 2013;132(3):571–9.

153. Fialho M, Messias M, Page-Shafer K, Farre L, Schmalb M, Pedral-Sampaio D, et al. Prevalence and risk of blood-borne and sexually transmitted viral infections in incarcerated youth in Salvador, Brazil: opportunity and obligation for intervention. AIDS Behav. 2008;12(4):S17–S24.

154. Adoga MP, Banwat EB, Forbi JC, Nimzing L, Pam CR, Gyar SD, et al. Human immunonodeficiency virus, hepatitis B virus and hepatitis C virus: sero-prevalence, co-infection and risk factors among prison inmates in Nasarawa State, Nigeria. J Infect Dev Countr. 2009;3(7):539–47.

155. Rao HY, Sun DG, Yang RF, Liu F, Wang J, Feng B, et al. Outcome of hepatitis C virus infection in Chinese paid plasma donors: a 12–19-year cohort study. J Gastroenterol Hepatol. 2012;27(3):526–32.

156. Drumright LN, Hagan H, Thomas DL, Latka MH, Golub ET, Garfein RS, et al. Predictors and effects of alcohol use on liver function among young HCV-infected injection drug users in a behavioral intervention. J Hepatol. 2011;55(1):45–52.

157. Dieperink E, Fuller B, Thuras P, McMaken K, Lenox R, Pocha C, et al. Efficacy of motivated enhancement therapy on alcohol use disorders in patients with chronic hepatitis C: a randomized controlled trial. Addiction. 2014;109(11):1869–77.

158. Dieperink E, Ho SB, Heit S, Durfee JM, Thuras P, Willenbring ML. Significant reductions in drinking following brief alcohol treatment provided in a hepatitis C clinic. Psychosomatics. 2010;51(2):149–56.

159. Proeschold-Bell RJ, Patkar AA, Naggie S, Coward L, Mannelli P, Yao J, et al. An integrated alcohol abuse and medical treatment model for patients with hepatitis C. Digest Dis Sci. 2012;57(4):1083–91.

160. Watson B, Conigrave KM, Wallace C, Whitfield JB, Wurst F, Haber PS. Hazardous alcohol consumption and other barriers to antiviral treatment among hepatitis C positive people receiving opioid maintenance treatment. Drug Alcohol Rev. 2007;26(3):231–9.

161. Kaner EFS, Dickinson HO, Beyer F, Pienaar E, Schlesinger C, Campbell F, et

al. The effectiveness of brief alcohol interventions in primary care settings: A systematic review. Drug Alcohol Rev. 2009;28(3):301–23.

162. Klimas J, Field CA, Cullen W, O'Gorman CS, Glynn LG, Keenan E, et al. Psychosocial interventions to reduce alcohol consumption in concurrent problem alcohol and illicit drug users. Cochrane Database Syst Rev. 2012;(11): CD009269.

163. mhGAP intervention guide for mental, neurological and substance use disorders in non-specialized health settings. Geneva: World Health Organization; 2010 (http://www.who.int/mental_health/publications/mhGAP_intervention_guide/en/, accessed 22 March 2016).

164. Intraobserver and interobserver variations in liver biopsy interpretation in patients with chronic hepatitis C. The French METAVIR Cooperative Study Group. Hepatology. 1994;20(1 Pt 1):15–20.

165. Scheuer PJ. Classification of chronic viral hepatitis: a need for reassessment. J Hepatol. 1991;13(3):372–4.

166. Ishak K, Baptista A, Bianchi L, Callea F, De Groote J, Gudat F, et al. Histological grading and staging of chronic hepatitis. J Hepatol. 1995;22(6):696–9.

167. Batts KP, Ludwig J. Chronic hepatitis. An update on terminology and reporting. Am J Surg Pathol. 1995;19(12):1409–17.

168. Knodell RG, Ishak KG, Black WC, Chen TS, Craig R, Kaplowitz N, et al. Formulation and application of a numerical scoring system for assessing histological activity in asymptomatic chronic active hepatitis. Hepatology. 1981;1(5):431–5.

169. Tsochatzis EA, Crossan C, Longworth L, Gurusamy K, Rodriguez-Peralvarez M, Mantzoukis K, et al. Cost-effectiveness of noninvasive liver fibrosis tests for treatment decisions in patients with chronic hepatitis C. Hepatology. 2014;60(3):832–43.

170. Lin ZH, Xin YN, Dong QJ, Wang Q, Jiang XJ, Zhan SH, et al. Performance of the aspartate aminotransferase-to-platelet ratio index for the staging of hepatitis C-related fibrosis: an updated meta-analysis. Hepatology. 2011;53(3):726–36.

171. Sterling RK, Lissen E, Clumeck N, Sola R, Correa MC, Montaner J, et al. Development of a simple noninvasive index to predict significant fibrosis in patients with HIV/HCV coinfection. Hepatology. 2006;43(6):1317–25.

172. Malaguarnera M, Restuccia S, Trovato G, Siciliano R, Motta M, Trovato BA. Interferon-α treatment in patients with chronic hepatitis C. Clin Drug Invest. 2012;9(3):141–9.

173. Myers RP, Regimbeau C, Thevenot T, Leroy V, Mathurin P, Opolon P, et

al.. 2009. Interferon for interferon naive patients with chronic hepatitis C. Cochrane Database Syst Rev. 2002(2): CD000370.

174. Hu J, Doucette K, Hartling L, Tjosvold L, Robinson J. Treatment of hepatitis C in children: a systematic review. PLoS One. 2010;5(7):e11542.

175. Koretz RL, Pleguezuelo M, Arvaniti V, Barrera Baena P, Ciria R, Gurusamy KS, et al. Interferon for interferon nonresponding and relapsing patients with chronic hepatitis C. Cochrane Database Syst Rev. 2013;(1):CD003617.

176. Tine F, Attanasio M, Russo F, Pagliaro L. A decade of trials of interferon-alpha for chronic hepatitis C. A meta-regression analysis. Contemp Clin Trials. 2005;26(2):179–210.

177. Carithers RL Jr, Emerson SS. Therapy of hepatitis C: meta-analysis of interferon alfa-2b trials. Hepatology. 1997;26(3 Suppl 1):83S–88S.

178. Fabrizi F, Ganeshan SV, Lunghi G, Messa P, Martin P. Antiviral therapy of hepatitis C in chronic kidney diseases: meta-analysis of controlled clinical trials. J Viral Hepat. 2008;15(8):600–6.

179. Xirouchakis E, Triantos C, Manousou P, Sigalas A, Calvaruso V, Corbani A, et al. Pegylated-interferon and ribavirin in liver transplant candidates and recipients with HCV cirrhosis: systematic review and meta-analysis of prospective controlled studies. J Viral Hepat. 2008;15(10):699–709.

180. Kimer N, Dahl EK, Gluud LL, Krag A. Antiviral therapy for prevention of hepatocellular carcinoma in chronic hepatitis C: systematic review and meta-analysis of randomised controlled trials. BMJ Open. 2012;2(5). pii: e001313.

181. Iorio A, Marchesini E, Awad T, Gluud LL. Antiviral treatment for chronic hepatitis C in patients with human immunodeficiency virus. Cochrane Database Syst Rev. 2010;(1):CD004888.

182. Hartwell D, Shepherd J. Pegylated and non-pegylated interferon-alfa and ribavirin for the treatment of mild chronic hepatitis C: a systematic review and meta-analysis. Int J Technol Assess Health Care. 2009;25(1):56–62.

183. Vezali E, Aghemo A, Colombo M. A review of the treatment of chronic hepatitis C virus infection in cirrhosis. Clin Therapeut. 2010;32(13):2117–38.

184. Brok J, Gluud LL, Gluud C. Ribavirin monotherapy for chronic hepatitis C. Cochrane Database Syst Rev. 2009;(4):CD005527.

185. Aspinall EJ, Corson S, Doyle JS, Grebely J, Hutchinson SJ, Dore GJ, et al. Treatment of hepatitis C virus infection among people who are actively injecting drugs: a systematic review and meta-analysis. Clin Infect Dis. 2013;57 (Suppl 2):S80–9.

186. Martin NK, Vickerman P, Foster GR, Hutchinson SJ, Goldberg DJ, Hickman M. Can antiviral therapy for hepatitis C reduce the prevalence of HCV among injecting drug user populations? A modeling analysis of its prevention utility. J Hepatol. 2011;54(6):1137–44.

187. Durier N, Nguyen C, White LJ. Treatment of hepatitis C as prevention: a modeling case study in Vietnam. PLos One. 2012;7(4).

188. Morgan TR, Ghany MG, Kim HY, Snow KK, Shiffman ML, De Santo JL, et al. Outcome of sustained virological responders with histologically advanced chronic hepatitis C. Hepatology. 2010;52(3):833–44.

189. Diagnosis and treatment of hepatitis C: a technical landscape. Geneva: Medecins sans Frontieres; 2013 (http://www.msfaccess.org/content/diagnosis-and-treatment-hepatitis-c-technical-landscape, accessed 21 January 2016).

190. Obach D, Deuffic-Burban S, Esmat G, Anwar WA, Dewedar S, Canva V, et al. Effectiveness and cost-effectiveness of immediate versus delayed treatment of hepatitis C virus-infected patients in a country with limited resources: the case of Egypt. Clin Infect Dis. 2014;58(8):1064–71.

191. Martin NK, Hickman M, Hutchinson SJ, Goldberg DJ, Vickerman P. Combination interventions to prevent HCV transmission among people who inject drugs: modeling the impact of antiviral treatment, needle and syringe programs, and opiate substitution therapy. Clin Infect Dis. 2013;57 (Suppl 2):S39–45.

192. Martin NK, Vickerman P, Grebely J, Hellard M, Hutchinson SJ, Lima VD, et al. Hepatitis C virus treatment for prevention among people who inject drugs: modeling treatment scale-up in the age of direct-acting antivirals. Hepatology. 2013;58(5):1598–609.

193. Hezode C, Fontaine H, Dorival C, Larrey D, Zoulim F, Canva V, et al. Triple therapy in treatment-experienced patients with HCV-cirrhosis in a multicentre cohort of the French Early Access Programme (ANRS CO20-CUPIC) - NCT01514890. J Hepatol. 2013;59(3):434–41.

194. AASLD/IDSA HCV Guidance Panel. Hepatitis C guidance: AASLD-IDSA recommendations for testing, managing, and treating adults infected with hepatitis C virus. Hepatology. 2015;62(3):932–54.

195. European Association for the Study of the Liver. EASL recomendations on treatment of hepatitis C. J Hepatol. 2015;63(1):199–236.

196. Wyles DL, Ruane PJ, Sulkowski MS, Dieterich D, Luetkemeyer A, Morgan TR, et al. Daclatasvir plus sofosbuvir for HCV in patients coinfected with HIV-1. N Engl J Med. 2015;373(8):714–25.

197. Sulkowski MS, Gardiner DF, Rodriguez-Torres M, Reddy KR, Hassanein T, Jacobson I, et al. Daclatasvir plus sofosbuvir for previously treated or

untreated chronic HCV infection. N Engl J Med. 2014;370(3):211–21.

198. Nelson DR, Cooper JN, Lalezari JP, Lawitz E, Pockros PJ, Gitlin N, et al. All-oral 12-week treatment with daclatasvir plus sofosbuvir in patients with hepatitis C virus genotype 3 infection: ALLY-3 phase III study. Hepatology. 2015;61(4):1127–35.

199. Zeuzem S, Dusheiko GM, Salupere R, Mangia A, Flisiak R, Hyland RH, et al. Sofosbuvir and ribavirin in HCV genotypes 2 and 3. N Engl J Med. 2014;370(21):1993–2001.

200. Kowdley KV, Lawitz E, Crespo I, Hassanein T, Davis MN, DeMicco M, et al. Sofosbuvir with pegylated interferon alfa-2a and ribavirin for treatment-naive patients with hepatitis C genotype-1 infection (ATOMIC): an open-label, randomised, multicentre phase 2 trial. Lancet. 2013;381(9883):2100–7.

201. Lawitz E, Mangia A, Wyles D, Rodriguez-Torres M, Hassanein T, Gordon SC, et al. Sofosbuvir for previously untreated chronic hepatitis C infection. N Engl J Med. 2013;368(20):1878–87.

202. Gane EJ, Hyland RH, An D, Svarovskaia E, Pang PS, Brainard D, et al. Efficacy of ledipasvir and sofosbuvir, with or without ribavirin, for 12 weeks in patients with HCV genotype 3 or 6 infection. Gastroenterology. 2015;149(6):1454–61 e1.

203. Abergel A, Asselah T, Metivier S, Kersey K, Jiang D, Mo H, et al. Ledipasvir-sofosbuvir in patients with hepatitis C virus genotype 5 infection: an open-label, multicentre, single-arm, phase 2 study. Lancet Infect Dis. published online 20 January 2016. pii: S1473-3099(15)00529-0. doi: 10.1016/S1473-3099(15)00529-0.

204. Hill AG, Gotham D, Cooke G, Bhagani S, Andrieux-Meyer I, Cohn J. Analysis of minimum target prices for production of entecavir to treat hepatitis B in high- and low-income countries. J Virus Erad. 2015;1:103–110.

205. Carrat F, Bani-Sadr F, Pol S, Rosenthal E, Lunel-Fabiani F, Benzekri A, et al. Pegylated interferon alfa-2b vs standard interferon alfa-2b, plus ribavirin, for chronic hepatitis C in HIV-infected patients: a randomized controlled trial. JAMA. 2004;292(23):2839–48.

206. Chung RT, Andersen J, Volberding P, Robbins GK, Liu T, Sherman KE, et al. Peginterferon alfa-2a plus ribavirin versus interferon alfa-2a plus ribavirin for chronic hepatitis C in HIV-coinfected persons. N Engl J Med. 2004;351(5):451–9.

207. Torriani FJ, Rodriguez-Torres M, Rockstroh JK, Lissen E, Gonzalez-Garcia J, Lazzarin A, et al. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection in HIV-infected patients. N Engl J Med. 2004;351(5):438–50.

208. Tanaka Y, Nishida N, Sugiyama M, Kurosaki M, Matsuura K, Sakamoto N, et al. Genome-wide association of IL28B with response to pegylated interferon-alpha and ribavirin therapy for chronic hepatitis C. Nat Genet. 2009;41(10):1105–9.

209. Thomas DL, Thio CL, Martin MP, Qi Y, Ge D, O'Huigin C, et al. Genetic variation in IL28B and spontaneous clearance of hepatitis C virus. Nature. 2009;461(7265):798–801.

210. Dore GJ, Lawitz E, Hezode C, Shafran SD, Ramji A, Tatum HA, et al. Daclatasvir plus peginterferon and ribavirin is noninferior to peginterferon and ribavirin alone, and reduces the duration of treatment for HCV genotype 2 or 3 infection. Gastroenterology. 2015;148(2):355–66.e1.

211. Lawitz E, Sulkowski MS, Ghalib R, Rodriguez-Torres M, Younossi ZM, Corregidor A, et al. Simeprevir plus sofosbuvir, with or without ribavirin, to treat chronic infection with hepatitis C virus genotype 1 in non-responders to pegylated interferon and ribavirin and treatment-naive patients: the COSMOS randomised study. Lancet. 2014;384(9956):1756–65.

212. Abbvie Viekira Pak: drug product label. 2015 (http://www.rxabbvie.com/pdf/viekirapak_pi.pdf, accessed 22 March 2016).

213. Grebely J, Dore GJ. Can hepatitis C virus infection be eradicated in people who inject drugs? Antivir Res. 2014;104:62–72.

214. Aspinall EJ, Corson S, Doyle JS, Grebely J, Hutchinson SJ, Dore GJ, et al. Treatment of hepatitis C virus infection among people who are actively injecting drugs: a systematic review and meta-analysis. Clin Infect Dis. 2013;57 Suppl 2:S80–9.

215. Visconti AJ, Doyle JS, Weir A, Shiell AM, Hellard ME. Assessing the cost-effectiveness of treating chronic hepatitis C virus in people who inject drugs in Australia. J Gastroenterol Hepatol. 2013;28(4):707–16.

216. Thein HH, Yi Q, Dore GJ, Krahn MD. Natural history of hepatitis C virus infection in HIV-infected individuals and the impact of HIV in the era of highly active antiretroviral therapy: a meta-analysis. AIDS. 2008;22(15):1979–91.

217. Martin NK, Vickerman P, Miners A, Foster GR, Hutchinson SJ, Goldberg DJ, et al. Cost-effectiveness of hepatitis C virus antiviral treatment for injection drug user populations. Hepatology. 2012;55(1):49–57.

218. Grebely J, Bruggmann P, Treloar C, Byrne J, Rhodes T, Dore GJ, et al. Expanding access to prevention, care and treatment for hepatitis C virus infection among people who inject drugs. Int J Drug Policy. 2015;26(10):893–8.

219. Dore G, Altice F, Litwin AH, Dalgard O, Gane EJ, Shibolet O, et al. C-EDGE CO-STAR: Efficacy of grazoprevir and elbasvir in persons who inject drugs

(PWID) receiving opioid agonist therapy. In: AASLD Liver Meeting 2015, San Francisco, 13–17 November 2015 [Abstract 40] (http://www.aasld.org/sites/default/files/2015SupplementFULLTEXT.pdf, accessed 22 March 2016).

220. Mohsen AH, Easterbrook PJ, Taylor C, Portmann B, Kulasegaram R, Murad S, et al. Impact of human immunodeficiency virus (HIV) infection on the progression of liver fibrosis in hepatitis C virus infected patients. Gut. 2003;52(7):1035–40.

221. Lo Re V 3rd, Kallan MJ, Tate JP, Localio AR, Lim JK, Goetz MB, et al. Hepatic decompensation in antiretroviral-treated patients co-infected with HIV and hepatitis C virus compared with hepatitis C virus-monoinfected patients: a cohort study. Ann Intern Med. 2014;160(6):369–79.

222. Cooper CL, Klein MB. HIV/hepatitis C virus coinfection management: changing guidelines and changing paradigms. HIV Med. 2014;15(10):621–4.

223. den Brinker M, Wit FW, Wertheim-van Dillen PM, Jurriaans S, Weel J, van Leeuwen R, et al. Hepatitis B and C virus co-infection and the risk for hepatotoxicity of highly active antiretroviral therapy in HIV-1 infection. AIDS. 2000;14(18):2895–902.

224. Sulkowski MS, Mehta SH, Chaisson RE, Thomas DL, Moore RD. Hepatotoxicity associated with protease inhibitor-based antiretroviral regimens with or without concurrent ritonavir. AIDS. 2004;18(17):2277–84.

225. Sulkowski MS, Thomas DL, Mehta SH, Chaisson RE, Moore RD. Hepatotoxicity associated with nevirapine or efavirenz-containing antiretroviral therapy: role of hepatitis C and B infections. Hepatology. 2002;35(1):182–9.

226. Noureddin M, Ghany MG. Pharmacokinetics and pharmacodynamics of peginterferon and ribavirin: implications for clinical efficacy in the treatment of chronic hepatitis C. Gastroenterol Clin North Am. 2010;39(3):649–58.

227. Nunez M. Clinical syndromes and consequences of antiretroviral-related hepatotoxicity. Hepatology. 2010;52(3):1143–55.

228. The United Nations Convention on the Rights of the Child. Geneva: The United Nations; 1992 (http://www.unicef.org/crc/files/Rights_overview.pdf, accessed 16 December 2015).

229. Thursz M, Fontanet A. HCV transmission in industrialized countries and resource-constrained areas. Nat Rev Gastroenterol Hepatol. 2014;11(1):28–35.

230. Locasciulli A, Gornati G, Tagger A, Ribero ML, Cavalletto D, Cavalletto L, et al. Hepatitis C virus infection and chronic liver disease in children with leukemia in long-term remission. Blood. 1991;78(6):1619–22.

231. Rossetti F, Cesaro S, Pizzocchero P, Cadrobbi P, Guido M, Zanesco L.

Chronic hepatitis B surface antigen-negative hepatitis after treatment of malignancy. J Pediatr. 1992;121(1):39–43.

232. Jonas MM, Zilleruelo GE, LaRue SI, Abitbol C, Strauss J, Lu Y. Hepatitis C infection in a pediatric dialysis population. Pediatrics. 1992;89(4 Pt 2):707–9.

233. Greco M, Cristiano K, Leozappa G, Rapicetta M, Rizzoni G. Hepatitis C infection in children and adolescents on haemodialysis and after renal transplant. Pediatr Nephrol. 1993;7(4):424–7.

234. Nelson SP, Jonas MM. Hepatitis C infection in children who received extracorporeal membrane oxygenation. J Pediatr Surg. 1996;31(5):644–8.

235. Ni YH, Chang MH, Lue HC, Hsu HY, Wang MJ, Chen PJ, et al. Posttransfusion hepatitis C virus infection in children. J Pediatr. 1994;124(5 Pt 1):709–13.

236. Pockros PJ, Reddy KR, Mantry PS, Cohen E, Bennett M, Sulkowski MS, et al. Efficacy of direct-acting antiviral combination for patients with HCV genotype 1 infection and severe renal impairment of end-stage renal disease. Gastroenterology. 2016; published online 11 March 2016. pii: S0016-5085(16)00326-7. doi: 10.1053/j.gastro.2016.02.078. [Epub ahead of print]

237. Potthoff A, Wedemeyer H, Boecher WO, Berg T, Zeuzem S, Arnold J, et al. The HEP-NET B/C co-infection trial: a prospective multicenter study to investigate the efficacy of pegylated interferon-alpha2b and ribavirin in patients with HBV/HCV co-infection. J Hepatol. 2008;49(5):688–94.

238. Systematic screening for active tuberculosis: principles and recommendations. Geneva: World Health Organization; 2013 (http://www.who.int/tb/tbscreening/en/, accessed 22 March 2016).

239. Dick TB, Lindberg LS, Ramirez DD, Charlton MR. A clinician's guide to drug-drug interactions with direct-acting antiviral agents for the treatment of hepatitis C viral infection. Hepatology. 2016;63:634.

240. Hill L. Hepatitis C virus direct-acting antiviral drug interactions and use in renal and hepatic impairment. Top Antivir Med. 2015;23(2):92–6.

241. Lomtadze N, Kupreishvili L, Salakaia A, Vashakidze S, Sharvadze L, Kempker RR, et al. Hepatitis C virus co-infection increases the risk of anti-tuberculosis drug-induced hepatotoxicity among patients with pulmonary tuberculosis. PLoS One. 2013;8(12):e83892.

242. Guidelines on the management of latent tuberculosis infection. Geneva: World Health Organization; 2015 (http://www.who.int/tb/publications/ltbi_document_page/en/, accessed 22 March 2016).

243. Barua S, Greenwald R, Grebely J, Dore GJ, Swan T, Taylor LE.

Restrictions for Medicaid reimbursement of sofosbuvir for the treatment of hepatitis C virus infection in the United States. Ann Intern Med. 2015;163(3):215–23.

244. Poynard T, McHutchison J, Manns M, Trepo C, Lindsay K, Goodman Z, et al. Impact of pegylated interferon alfa-2b and ribavirin on liver fibrosis in patients with chronic hepatitis C. Gastroenterology. 2002;122(5):1303–13.

245. Younossi ZM, Stepanova M, Afdhal N, Kowdley KV, Zeuzem S, Henry L, et al. Improvement of health-related quality of life and work productivity in chronic hepatitis C patients with early and advanced fibrosis treated with ledipasvir and sofosbuvir. J Hepatol. 2015;63(2):337–45.

246. Neary MP, Cort S, Bayliss MS, Ware JE Jr. Sustained virologic response is associated with improved health-related quality of life in relapsed chronic hepatitis C patients. Semin Liver Dis. 1999;19 (Suppl 1):77–85.

247. Smith-Palmer J, Cerri K, Valentine W. Achieving sustained virologic response in hepatitis C: a systematic review of the clinical, economic and quality of life benefits. BMC Infect Dis. 2015;15:19.

248. Persad G, Wertheimer A, Emanuel EJ. Principles for allocation of scarce medical interventions. Lancet. 2009;373(9661):423–31.

249. Everson GT, Hoefs JC, Seeff LB, Bonkovsky HL, Naishadham D, Shiffman ML, et al. Impact of disease severity on outcome of antiviral therapy for chronic hepatitis C: lessons from the HALT-C trial. Hepatology. 2006;44(6):1675–84.

250. Di Bisceglie AM, Shiffman ML, Everson GT, Lindsay KL, Everhart JE, Wright EC, et al. Prolonged therapy of advanced chronic hepatitis C with low-dose peginterferon. N Engl J Med. 2008;359(23):2429–41.

251. Berenguer J, Alvarez-Pellicer J, Martin PM, Lopez-Aldeguer J, Von-Wichmann MA, Quereda C, et al. Sustained virological response to interferon plus ribavirin reduces liver-related complications and mortality in patients coinfected with human immunodeficiency virus and hepatitis C virus. Hepatology. 2009;50(2):407–13.

252. Morgan RL, Baack B, Smith BD, Yartel A, Pitasi M, Falck-Ytter Y. Eradication of hepatitis C virus infection and the development of hepatocellular carcinoma: a meta-analysis of observational studies. Ann Intern Med. 2013;158(5 Pt 1):329–37.

253. Bourliere M, Bronowicki JP, de Ledinghen V, Hezode C, Zoulim F, Mathurin P, et al. Ledipasvir–sofosbuvir with or without ribavirin to treat patients with HCV genotype 1 infection and cirrhosis non-responsive to previous protease-inhibitor therapy: a randomised, double-blind, phase 2 trial (SIRIUS). Lancet Infect Dis. 2015;15(4):397–404.

254. Obach D, Yazdanpanah Y, Esmat G, Avihingsanon A, Dewedar S, Durier N, et al. How to optimize hepatitis C virus treatment impact on life years saved in resource-constrained countries. Hepatology. 2015;62(1):31–9.

255. van der Meer AJ, Veldt BJ, Feld JJ, Wedemeyer H, Dufour JF, Lammert F, et al. Association between sustained virological response and all-cause mortality among patients with chronic hepatitis C and advanced hepatic fibrosis. JAMA. 2012;308(24):2584–93.

256. Berenguer M. Natural history of recurrent hepatitis C. Liver Transplant. 2002;8(10 Suppl 1):S14–18.

257. Roayaie S, Schiano TD, Thung SN, Emre SH, Fishbein TM, Miller CM, et al. Results of retransplantation for recurrent hepatitis C. Hepatology. 2003;38(6):1428–36.

258. Rodriguez-Luna H, Khatib A, Sharma P, De Petris G, Williams JW, Ortiz J, et al. Treatment of recurrent hepatitis C infection after liver transplantation with combination of pegylated interferon alpha2b and ribavirin: an open-label series. Transplantation. 2004;77(2):190–4.

259. Kwo PY, Mantry PS, Coakley E, Te HS, Vargas HE, Brown R Jr, et al. An interferon-free antiviral regimen for HCV after liver transplantation. N Engl J Med. 2014;371(25):2375–82.

260. Curry MP, Forns X, Chung RT, Terrault NA, Brown R Jr, Fenkel JM, et al. Sofosbuvir and ribavirin prevent recurrence of HCV infection after liver transplantation: an open-label study. Gastroenterology. 2015;148(1):100–7.

261. Konerman MA, Mehta SH, Sutcliffe CG, Vu T, Higgins Y, Torbenson MS, et al. Fibrosis progression in human immunodeficiency virus/hepatitis C virus coinfected adults: prospective analysis of 435 liver biopsy pairs. Hepatology. 2014;59(3):767–75.

262. Konstantinou D, Deutsch M. The spectrum of HBV/HCV coinfection: epidemiology, clinical characteristics, viral interactions and management. Ann Gastroenterol. 2015;28(2):221–8.

263. Chu CJ, Lee SD. Hepatitis B virus/hepatitis C virus coinfection: epidemiology, clinical features, viral interactions and treatment. J Gastroenterol Hepatol. 2008;23(4):512–20.

264. Hung CH, Wang JH, Hu TH, Chen CH, Chang KC, Yen YH, et al. Insulin resistance is associated with hepatocellular carcinoma in chronic hepatitis C infection. World J Gastroenterol. 2010;16(18):2265–71.

265. Mehta SH, Brancati FL, Sulkowski MS, Strathdee SA, Szklo M, Thomas DL. Prevalence of type 2 diabetes mellitus among persons with hepatitis C virus infection in the United States. Ann Intern Med. 2000;133(8):592–9.

266. Yoneda M, Saito S, Ikeda T, Fujita K, Mawatari H, Kirikoshi H, et al. Hepatitis C virus directly associates with insulin resistance independent of the visceral fat area in nonobese and nondiabetic patients. J Viral Hepat. 2007;14(9):600–7.

267. Hsu YC, Lin JT, Ho HJ, Kao YH, Huang YT, Hsiao NW, et al. Antiviral treatment for hepatitis C virus infection is associated with improved renal and cardiovascular outcomes in diabetic patients. Hepatology. 2014;59(4):1293–302.

268. Petta S, Camma C, Di Marco V, Alessi N, Cabibi D, Caldarella R, et al. Insulin resistance and diabetes increase fibrosis in the liver of patients with genotype 1 HCV infection. Am J Gastroenterol. 2008;103(5):1136–44.

269. Foster GR, Goldin RD, Thomas HC. Chronic hepatitis C virus infection causes a significant reduction in quality of life in the absence of cirrhosis. Hepatology. 1998;27(1):209–12.

270. Bonkovsky HL, Snow KK, Malet PF, Back-Madruga C, Fontana RJ, Sterling RK, et al. Health-related quality of life in patients with chronic hepatitis C and advanced fibrosis. J Hepatol. 2007;46(3):420–31.

271. Agnello V, Chung RT, Kaplan LM. A role for hepatitis C virus infection in type II cryoglobulinemia. N Engl J Med. 1992;327(21):1490–5.

272. Shiffman ML, Benhamou Y. Cure of HCV related liver disease. Liver Int. 2015;35 (Suppl 1):71–7.

273. Saadoun D, Resche Rigon M, Thibault V, Longuet M, Pol S, Blanc F, et al. Peg-IFN alpha/ribavirin/protease inhibitor combination in hepatitis C virus associated mixed cryoglobulinemia vasculitis: results at week 24. Ann Rheum Dis. 2014;73(5):831–7.

274. Sise ME, Bloom AK, Wisocky J, Lin MV, Gustafson JL, Lundquist AL, et al. Treatment of hepatitis C virus-associated mixed cryoglobulinemia with direct-acting antiviral agents. Hepatology. 2016;63(2):408–17.

275. Johnson RJ, Gretch DR, Yamabe H, Hart J, Bacchi CE, Hartwell P, et al. Membranoproliferative glomerulonephritis associated with hepatitis C virus infection. N Engl J Med. 1993;328(7):465–70.

276. Jafferbhoy H, Miller MH, Dunbar JK, Tait J, McLeod S, Dillon JF. Intravenous drug use: not a barrier to achieving a sustained virological response in HCV infection. J Viral Hepat. 2012;19(2):112–19.

277. Grady BP, Schinkel J, Thomas XV, Dalgard O. Hepatitis C virus reinfection following treatment among people who use drugs. Clin Infect Dis. 2013;57 (Suppl 2):S105–10.

278. Bradshaw D, Matthews G, Danta M. Sexually transmitted hepatitis C infection:

the new epidemic in MSM? Curr Opin Infect Dis. 2013;26(1):66–72.

279. Delotte J, Barjoan EM, Berrebi A, Laffont C, Benos P, Pradier C, et al. Obstetric management does not influence vertical transmission of HCV infection: results of the ALHICE group study. J Matern Fetal Neonatal Med. 2014;27(7):664–70.

280. Post JJ, Arain A, Lloyd AR. Enhancing assessment and treatment of hepatitis C in the custodial setting. Clin Infect Dis. 2013;57 (Suppl 2):S70–4.

281. Martin N Hickman M, Vickerman P. HCV screening/treatment in UK prisons can be cost-effective – is increased HCV case-finding combined with 8 or 12 week interferon-free direct-acting antiviral treatment cost effective in UK prisons? A cost utility analysis including treatment as prevention benefits. In: International Liver Congress 2015; 50th annual meeting of the European association for the Study of the Liver, Vienna, Austria, 22–26 April 2015 [Abstract 0124].

282. Fissell RB, Bragg-Gresham JL, Woods JD, Jadoul M, Gillespie B, Hedderwick SA, et al. Patterns of hepatitis C prevalence and seroconversion in hemodialysis units from three continents: the DOPPS. Kidney Int. 2004;65(6):2335–42.

283. Fabrizi F, Martin P, Dixit V, Messa P. Meta-analysis of observational studies: hepatitis C and survival after renal transplant. J Viral Hepat. 2014;21(5):314–24.

284. Henderson DK, Dembry L, Fishman NO, Grady C, Lundstrom T, Palmore TN, et al. SHEA guideline for management of healthcare workers who are infected with hepatitis B virus, hepatitis C virus, and/or human immunodeficiency virus. Infect Control Hosp Epidemiol. 2010;31(3):203–32.

285. Ford N, Kirby C, Singh K, Mills EJ, Cooke G, Kamarulzaman A, et al. Chronic hepatitis C treatment outcomes in low- and middle-income countries: a systematic review and meta-analysis. Bull World Health Organ. 2012;90(7):540–50.

286. Accelerating access initiative: widening access to care and support for people living with HIV/AIDS. Geneva: World Health Organization; 2002 (http://www.who.int/hiv/pub/prev_care/en/isbn9241210125.pdf?ua=1, accessed 18 December 2015).

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