World Health Organization

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

APRIL 2014

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APPENDICES

All appendices will be made available on the WHO, HIV website, along with the entire report.

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ABBREVIATIONS AND ACRONYMS

3TC	lamivudine
AASLD	American Association for the Study of Liver Diseases
ABC	abacavir
ALT	alanine aminotransferase
AST	aspartate aminotransferase
APRI	aminotransferase/platelet ratio index
ART	antiretroviral therapy
ARV	antiretroviral
ASSIST	Alcohol, Smoking and Substance Involvement Screening Test
AUDIT	Alcohol Use Disorders Identification Test
AZT	zidovudine
BHIVA	British HIV Association
CD4	cluster of differentiation 4
CI	confidence interval
CUPIC	Compassionate Use of Protease Inhibitors in Viral C Cirrhosis (study)
d4T	stavudine
DAA	direct-acting antiviral (drug)
ddI	didanosine
DVR	delayed virological response
EASL	European Association for the Study of the Liver
EIA	enzyme immunoassay
EOT	end of treatment
eRVR	extended rapid virological response
ES	effect size
FBC	full blood count
FDA	(US) Food and Drug Administration
FTC	emtricitabine
gGT	gamma glutamyl transpeptidase
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HAV	hepatitis A virus
HBV	hepatitis B virus
HCV	hepatitis C virus
IFN	interferon
INR	international normalized ratio
mhGAP	WHO Mental Health Gap Action Programme

MSM	men who have sex with men
NAT	nucleic acid testing
NNRTI	non-nucleoside reverse transcriptase inhibitor
NRTI	nucleoside reverse transcriptase inhibitor
NS5B	non-structural protein 5B (of HCV)
NVP	nevirapine
OR	odds ratio
OST	opioid substitution therapy
PCR	polymerase chain reaction
PEG-IFN	pegylated interferon
PI	protease inhibitor
PICO	population, intervention, comparison, outcomes
PWID	people who inject drugs
RAL	raltegravir
RNA	ribonucleic acid
RBV	ribavirin
RCT	randomized controlled trial
RR	relative risk
RTV or r	ritonavir
RVR	rapid virological response
SVR	sustained virological response
TB	tuberculosis
TDF	tenofovir
UNAIDS	Joint United Nations Programme on HIV/AIDS
UNODC	United Nations Office on Drugs and Crime
WHO	World Health Organization
WHO GHP	WHO Global Hepatitis Programme

GLOSSARY OF TERMS

Acute HCV	Presence of HCV within six months of acquiring infection
Chronic HCV	Continued presence of HCV six months or more after acquiring infection
Delayed virological response (DVR)	More than 2 log decline 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 (EVR)	More than 2 log reduction in HCV RNA viral load at week 12 of treatment
Extended rapid virological response (eRVR)	Undetectable HCV RNA 4 weeks (rapid) and 12 weeks (extended) after the start of treatment
GRADE	Grading of Recommendations Assessment, Development and Evaluation
Negative predictive value	The probability that when a person's test result is negative, they truly do not have the infection/disease
Non-response	Detectable HCV RNA throughout treatment
Null response	Less than 2 log drop in HCV RNA level by week 12 of treatment
Partial response	2 log drop 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 (RVR)	Undetectable HCV RNA 4 weeks after the start of treatment
Relapse	Undetectable HCV RNA at the end of treatment but detectable HCV RNA within 24 weeks of completing treatment
Sensitivity of a test	The ability of a test to correctly identify those with the infection/ disease. (True positives / true positives + false negatives)
Specificity of a test	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 three or six months after the end of treatment
Viral breakthrough	Undetectable HCV RNA during treatment followed by detectable HCV RNA during treatment

EXECUTIVE SUMMARY

Background

According to recent estimates, more than 185 million people around the world have been infected with the hepatitis C virus (HCV), of whom 350 000 die each year. One third of those who become chronically infected are predicted to develop liver cirrhosis or hepatocellular carcinoma. Despite the high prevalence of disease, most people infected with the virus are unaware of their infection. For many who have been diagnosed, treatment remains unavailable. Treatment is successful in the majority of persons treated, and treatment success rates among patients treated in low- and middle-income countries are similar to those in high-income countries.

These are the first guidelines dealing with hepatitis C treatment produced by the World Health Organization (WHO) and complement existing guidance on the prevention of transmission of bloodborne viruses, including HCV. They are intended for policy-makers, government officials, and others working in low- and middle-income countries who are developing programmes for the screening, care and treatment of persons with HCV infection. These guidelines serve as a framework that can allow the expansion of clinical services to patients with HCV infection, as they provide key recommendations in these areas and discuss considerations for implementation. The guidelines are also intended for health-care providers who care for persons with HCV infection in low- and middle-countries and provide them guidance in the management of patients infected with HCV.

Hepatitis C infection differs from other chronic viral infections, notably HIV infection, in that it can be cured by treatment. Several medicines are available to treat persons infected with HCV, and cure rates have steadily improved with the introduction of newer medicines. The field of HCV therapeutics is evolving rapidly, and a number of compounds are in various stages of development. These new compounds can cure more than 90% of persons with HCV infection and are effective against genotypes that were previously difficult to treat. Currently licensed treatments for HCV infection include pegylated and standard interferon alpha (IFN), ribavirin (RBV), the protease inhibitors boceprevir, telaprevir and simeprevir; and the NS5B nucleotide polymerase inhibitor inhibitor sofosbuvir. It is expected that in the next few years, a number of additional antiviral compounds will be licensed. This guidance includes recommendations for all medicines approved as of December 2013, and will be updated periodically as new compounds become available for use.

These guidelines were produced following the standard process for developing WHO guidelines as described in the WHO Handbook for Guideline Development, 2012. The development process followed 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; Appendix 1). Systematic reviews of the best available evidence were conducted and the findings were assessed for quality and presented in GRADE evidence profiles (Appendices 2-4). Existing national and international guidelines were also evaluated and, where necessary, comprehensive reviews and technical reports obtained (Appendix 5). The final recommendations were agreed upon by consensus during a meeting of the Guidelines Development Group in June 2013.

By the time of the June 2013 meeting, it was clear that two additional medicines, simeprevir and sofosbuvir, would likely be approved in at least one country (the United States) prior to the release of these guidelines; therefore, it was decided to include recommendations for their use as well. Using the same approach as for all the recommendations in these guidelines, additional systematic reviews were commissioned, and evidence profiles and decision-making tables were prepared. These were reviewed by the Guidelines Development Group during a web-based meeting that took place in December 2013, and recommendations were developed for the use of simeprevir and sofosbuvir. The final version of the document was approved by the WHO Guidelines Review Committee.

Summary of recommendations

Recommendations on screening for HCV infection

1. *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)

2. *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)

Recommendations on care of people infected with HCV

3. *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)

4. *Assessing degree of liver fibrosis and cirrhosis:* In resource-limited settings, it is suggested that the aminotransferase/platelet ratio index (APRI) or FIB4 tests be used for the assessment of hepatic fibrosis rather than other non-invasive tests that require more resources such as elastography or Fibrotest. (Conditional recommendation, low quality of evidence)

Recommendations on treatment of HCV infection

5. *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)

6. *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)

7. *Treatment with telaprevir or boceprevir:* Treatment with the direct-acting antivirals telaprevir or boceprevir, given in combination with pegylated interferon and ribavirin, is suggested for genotype 1 chronic HCV infection rather than pegylated interferon and ribavirin alone. (Conditional recommendation, moderate quality of evidence)

8. *Treatment with sofosbuvir:* Sofosbuvir, given in combination with ribavirin with or without pegylated interferon (depending on the HCV genotype), is recommended in genotypes 1, 2, 3 and 4 HCV infection rather than pegylated interferon and ribavirin alone (or no treatment for persons who cannot tolerate interferon). (Strong recommendation, high quality of evidence)

9. *Treatment with simeprevir:* Simeprevir, given in combination with pegylated interferon and ribavirin, is recommended for persons with genotype 1b HCV infection and for persons with genotype 1a HCV infection without the Q80K polymorphism rather than pegylated interferon and ribavirin alone. (Strong recommendation, high quality of evidence)

Note: Recommendations 8 and 9 were made without taking resource use into consideration, as pricing information was not available for any country other than the United States at the time this recommendation was formulated.

HCV screening

Screening for HCV infection requires an initial serologic screening test followed by an HCV RNA test (either quantitative or qualitative) to confirm the presence of viraemia, and therefore chronic infection, as 15–45% of those initially infected will spontaneously clear the virus, usually within six months of acquiring the infection. Persons who do not clear HCV within six months are defined as having chronic HCV infection and are diagnosed either during routine screening or when they develop symptoms of HCV-associated liver disease. Those at risk of infection include people undergoing medical procedures (such as the transfusion of infected blood or blood products, renal dialysis, reuse of syringes, catheters, needles and other medical equipment) in a clinical setting with substandard infection control practices, people who inject drugs using contaminated injection equipment and paraphernalia, and those who have used intranasal drugs or undergone cosmetic procedures (such as tattooing and body piercing). Sexual partners of people infected with HCV may become infected, although the risk is very low in heterosexual couples. Those at higher risk include HIV-infected men who have sex with men as well as others infected with HIV and infants born to mothers with HCV infection. The relative importance of these risk factors varies substantially, depending on the geographical location and population studied.

WHO recommends that HCV serology testing be performed on individuals who are part of a population with high HCV seroprevalence or who have a history of HCV risk exposure and/or behaviour, rather than at the time of presentation with symptomatic disease. The application of this recommendation will require taking into consideration which populations meet these criteria. In some countries with a high seroprevalence of HCV or low level of infection control, HCV testing might be recommended for the general population. Clearly, this would have significant resource implications.

In addition, it is suggested that NAT for HCV RNA be performed directly following an HCV seropositive test result to establish a definitive diagnosis of HCV infection in addition to the use of NAT as part of the evaluation for treatment eligibility. Earlier testing for the detection of RNA allows those patients who have spontaneously cleared the virus to know that they have resolved the infection and facilitates earlier identification of persons who require treatment.

Persons at risk of HCV are also likely to be at risk for other bloodborne viruses, including hepatitis B virus (HBV) and HIV. Related WHO guidance recommends screening at-risk groups for these viruses also (*see* section 2.4).

Care of patients infected with HCV

Decades can pass between the time of acquiring HCV infection and the development of HCV-related liver disease such as cirrhosis. During that time, it is important for clinicians to monitor and manage hepatic diseases due to other causes as well as the extrahepatic manifestations of HCV infection, including insulin resistance and diabetes. Addressing co-morbidities such as high body mass index and smoking is also important, as are measures to avoid reinfection through ensuring the availability of safe blood transfusions and sterile medical equipment. Of these various conditions or behaviours, the Guidelines Development Group assessed the value of conducting alcohol screening and behavioural interventions to limit alcohol intake. Alcohol use can accelerate the progression of HCV-related cirrhosis. Alcohol use in persons with HCV varies considerably in different geographical regions and in different risk groups. WHO now recommends that a brief alcohol intake assessment be conducted for all persons with HCV infection, followed by the offer of a behavioural alcohol reduction intervention in persons with moderate-to-high alcohol intake. The Guidelines Development Group proposed that the WHO ASSIST (Alcohol, Smoking and Substance Involvement Screening Test) package 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.

Transmission of HCV through the sharing of contaminated injecting equipment among persons who inject drugs is the leading route of HCV transmission in some countries. Therefore, reducing this risk of transmission is an essential component of patient care. WHO recommends a comprehensive package of harm reduction interventions, which comprise nine activities specifically for people who inject drugs.[a]

Previous WHO guidance exists regarding vaccination for hepatitis A virus (HAV) and HBV (acquisition of HAV or HBV may lead to more severe liver disease in HCV-infected individuals). Screening and testing for co-morbidities among people who use drugs is crucial for informing treatment plans (drug–drug interactions, potential hepatotoxicity, among others).

a. Advice on interventions for individuals using alcohol, injected and non-injected drugs is available at http://www.who.int/substance_abuse. The elements of the comprehensive package are described in: Technical guide for countries to set targets for universal access to HIV prevention, treatment and care for injecting drug users, 2012 revision. http://www.who.int/hiv/pub/idu/targets_universal_access/en/

Assessment of liver fibrosis

Deciding when to initiate therapy for HCV infection is challenging and requires reliable assessment of the degree of liver fibrosis. For many years, liver biopsy was considered to be the gold standard for staging the degree of fibrosis, but this test is expensive, associated with a risk of complications including bleeding, and requires careful histological interpretation. In view of these considerations, the Guidelines Development Group assumed that liver biopsy was not a viable option in many of the countries where these guidelines would be used. Rather, it was assumed that non-invasive tests would be used. Non-invasive measures of hepatic fibrosis include indices based on combinations of blood tests (e.g. APRI, Fibrotest, FIB4), and an ultrasound-based technique called transient elastography. These tests perform less well than liver biopsy and can be difficult to interpret as there are different cut-off values for different fibrosis stages. The equipment for transient elastography is also very expensive. Based on a systematic review of the performance of these tests and taking cost into consideration, the APRI and FIB4 tests were considered by the Guidelines Development Group to be more suitable for resource-limited settings than more expensive options such as transient elastography. However, if transient elastography is available and the cost of the test is not a barrier to its use, it is also recommended.

Patients with less advanced fibrosis respond better to treatment, while those with more advanced disease are at higher risk of developing cirrhosis and hepatocellular carcinoma. Therefore, recommendations regarding whom to treat are based on the balance between the benefits (cure and resulting lower risk of cirrhosis and hepatocellular carcinoma) and the potential harms (drug toxicity and cost). In most countries where these guidelines will be applied, treatment availability will be limited, and patients will need to be prioritized for treatment. In view of this, patients with advanced fibrosis and cirrhosis (METAVIR stages F3 and F4) should be prioritized for treatment as they are at higher risk of developing cirrhosis and hepatocellular carcinoma. If resources permit, then persons with less advanced fibrosis (METAVIR stages F1 and F2) could also be considered for treatment.

Treatment of hepatitis C

Because of the high cost of treatment, the requirement for sophisticated laboratory testing to monitor treatment response, and the high rate of adverse events to existing medications (interferon and ribavirin), the number of persons receiving treatment for HCV is very low in most low- and middle-income countries. Furthermore, even in many high-income countries, treatment is often denied to persons in certain groups, notably those who are current or former drug injectors. In some countries, standard interferon (IFN) continues to be used because of

its lower cost, despite evidence that it is less effective than pegylated interferon (PEG-IFN). To address these considerations, the Guidelines Development Group assessed the benefits of treatment for HCV and made recommendations regarding existing medicines. Four topics were considered with regard to treatment for HCV: (i) the utility of treatment versus no treatment; (ii) the efficacy of PEG-IFN versus standard IFN (in combination with ribavirin [RBV]); (iii) the efficacy of the direct-acting antivirals telaprevir, boceprevir and simeprevir in combination with PEG-IFN and RBV for those with genotype 1 infection; and (iv) the efficacy of sofosbuvir in combination with RBV or PEG-IFN/RBV for genotypes 1–4.

The evidence of effectiveness of different IFN types (IFN or PEG-FN) in combination with RBV compared with placebo showed a clear benefit of treatment versus placebo in achieving sustained virological response, including in children, HIV-infected individuals and people who inject drugs. Therefore, WHO recommends that all adults and children with chronic HCV infection, including people who inject drugs, should be assessed for receiving treatment for HCV.

A systematic review of PEG-IFN versus standard IFN showed that PEG-IFN with RBV is superior to standard IFN with RBV, and increases the likelihood of a sustained virological response without increasing the side-effect profile. WHO recommends that PEG-IFN in combination with RBV be used for the treatment of chronic HCV infection rather than standard IFN with RBV.

The Guidelines Development Group recommends that persons with genotype 1 HCV infection should be considered for treatment with the currently approved direct-acting antivirals (telaprevir, boceprevir or simeprevir), given in combination with PEG-IFN and RBV rather than only PEG-IFN and RBV. Genotyping is therefore indicated prior to selecting the appropriate regimen. In addition, persons with genotype 1a HCV infection treated with simeprevir/PEG-IFN/RBV require testing for the absence of the Q80K mutation, as this significantly reduces the efficacy of treatment with this combination.

The Guidelines Development Group also recommends that persons with genotypes 1, 2, 3 or 4 HCV infection should be considered for treatment with sofosbuvir and RBV with or without PEG-IFN, depending on the genotype.

It is difficult to recommend one of these medicines over another as the only available data for the direct-acting agents are from drug registration trials; thus, there are no studies comparing the outcomes of one medicine versus another. Furthermore, data on safety of the newer compounds are also limited because of the small number of persons who have taken these medicines. As the manufacturers of the newer medicines had not fixed the price of these medicines, at the time of the development of these guidelines. For most countries, it is not possible to take cost into consideration while making treatment recommendations. Finally, it is likely

that in many countries, PEG-IFN and RBV will be the only available medicines for the next several years as the newer medicines have not been approved or licensed in most countries. This process can take more than one year.

There are a number of other considerations that are important elements of treatment for HCV. These include the need for genotype and Q80K mutation testing, decisions related to duration of treatment, frequency of monitoring and contraindications of treatment. Because of the number and complexity of these parameters, they were not evaluated by the Guidelines Development Group and no recommendations were made. Rather, the following statements reflect either the standard of care or product registration information.

- As the selection of medicines and duration of treatment depends on the HCV genotype, determining genotype is important, as is the determination of Q80K mutation if treatment with simeprevir is being considered.

- Accepted standards for treatment indicate that persons infected with genotypes 1 and 4 are treated with PEG-IFN/RBV for 48–72 weeks, while those infected with genotypes 2 and 3 are treated with PEG-IFN/RBV for 24–48 weeks. The longer treatment durations are recommended for persons with advanced fibrosis or cirrhosis (F3 and F4), those coinfected with HIV and in those with a slow early virological response. In addition, persons with genotype 1 infection and an extended rapid virological response may be treated with a shortened course of 24 weeks of PEG-IFN/RBV.

- Persons treated with direct-acting antivirals require different durations of treatment, depending on the genotype and previous response to treatment, as discussed further in Chapter 7.

- Interferon-containing regimens are contraindicated in persons with decompensated cirrhosis because of the risk of accelerated decompensation. These persons do require follow up of liver function and monitoring for hepatocellular carcinoma. Consideration of liver transplant for such patients can be made in settings where this is available. Treatment is also contraindicated in pregnant women due to the risk of fetal abnormalities from the use of RBV. For this reason, women of childbearing age and their partners are advised to use two forms of contraception (including a barrier method) during and for six months after the end of treatment.

- HCV treatments require regular monitoring for toxicity and efficacy. Side-effects range from mild to life threatening, and are detected by laboratory monitoring and on clinical review.

Issues related to treatment access

The aim of these guidelines is to facilitate the introduction and expansion of treatment services for persons with HCV infection, particularly in low- and middle-income countries. As discussed throughout this document, a number of technical, logistical, and financial challenges must be overcome for this to become a reality.

HCV screening

Most persons with HCV infection remain undiagnosed and few have access to HCV testing. National testing policies are needed as are increased investments in hepatitis C screening services based on the best assessment of the prevalence of HCV infection in the general population and in key populations.

Laboratory capacity

The diagnosis and clinical management of HCV infection requires sophisticated laboratory capacity. Diagnosing HCV infections requires serologic testing followed by NAT to confirm the presence of chronic infection. Assessment for treatment requires NAT to measure HCV viral load and to determine HCV genotype, and if the use of simeprevir is being considered, the detection of the Q80K mutation. In many low-income countries there are no laboratories that can perform these tests. Even in countries where this capacity exists, it is available only in some large cities, and the tests are very expensive. The new direct-acting agents provide an opportunity to simplify the laboratory requirements for HCV therapy as combinations of these medicines will be effective against all genotypes, thus obviating the need for genotyping, and much safer, thus reducing the complexity of monitoring for adverse events.

Health systems

Currently, HCV therapy is provided in specialized centers by hepatologists or other subspecialists. For HCV therapy to be expanded, it will need to be administered by general-practice physicians and other health care workers in primary-care clinics. To accomplish this, clinics will need to be equipped and many more health care workers will need training in the clinical management of HCV infection.

Selection of patients for treatment

A critical question is who needs HCV treatment. This decision is complicated as it is made while taking into consideration the health of the patient, in particular the degree of fibrosis or cirrhosis, as well as the cost, safety, and efficacy of the medicines. Based on these considerations, currently patients with more advanced fibrosis and cirrhosis (METAVIR F3 and F4 stages) should be prioritized for treatment. However, there are no population-based data to indicate how many persons meet these criteria. Furthermore, this prioritization may change, as safer and more effective medicines become available, assuming that they are affordable.

Price of medicines

HCV treatment is expensive. Prices range from US$ 2 000 in Egypt for 48-weeks of PEG/IFN RBV to as much as US$84 000 in the US for a single 12-week course of sofosbuvir. At these prices, these treatments will remain unaffordable for most persons who need treatment. A concerted effort is needed to reduce the price of HCV medicines. The experience with HIV, where the price of antiretrovirals was reduced by nearly a hundred fold through the introduction of generic drugs, has shown that the key to achieving low prices for medicines is to use a multipronged approach. This can include voluntary licensing (where the patent owner licenses the medicine to generics-producing companies or a patent pool), tiered pricing (where the manufacturer sets different prices for different countries based on their income level and disease burden), and compulsory licensing (where a national government grants a license to companies producing generic drugs or importing the product). National governments, international agencies, donors, civil-society organizations, and the pharmaceutical industry will need to work together to help assure that hepatitis C treatment is affordable and accessible for all those who need treatment.

1. SCOPE AND OBJECTIVES

Introduction and objectives

Most of the existing guidelines for the treatment of hepatitis C have been developed by specialist medical organizations and relate to the treatment of persons living in high-income countries. There are no evidence-based treatment guidelines that focus on persons living in low- and middle-income countries. In addition, these are the first WHO guidelines dealing with the topics of screening and management of HCV infection. The objective of these guidelines is to provide evidence-based recommendations on screening for HCV infection, and the care and treatment of persons with HCV infection. These guidelines are meant to provide a framework for the development or strengthening of hepatitis C treatment programmes in low- and middle-income countries. 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 of 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.

Target audience

These guidelines are primarily targeted at policy-makers in ministries of health working in low- and middle-income countries who formulate country-specific treatment guidelines and who plan infectious diseases treatment programmes. These guidelines are intended to assist officials as they develop national hepatitis C treatment plans and policy, and guideline documents. In addition, it is anticipated that nongovernmental agencies and health professionals organizing treatment and screening services for hepatitis C will use the guidelines to define the necessary elements of such services. These guidelines will also be a useful resource for clinicians who manage persons with HCV infection.

Related WHO materials and guidelines

These are the first WHO guidelines on the screening, care and treatment of persons with HCV infection. They are intended to complement existing guidance on the primary prevention of HCV and other bloodborne viruses by improving blood and injection safety, and health care for people who inject drugs (PWID) and other vulnerable groups, including those living with HIV (*see* section 2.4 for related WHO guidelines).

This guidelines document will be revised in 2016. Because a number of new medicines are expected to become available in the meantime, WHO will issue interim guidance twelve months after publication of these guidelines to provide recommendations regarding newly approved medicines.

2. BACKGROUND

2.1 Epidemiology of hepatitis C

According to recent estimates, more than 185 million people around the world have been infected with HCV, of whom 350 000 die each year.[1,2] Most people infected with the virus are unaware of their infection and, for many who have been diagnosed, treatment remains unavailable.[3] Treatment is successful in the majority of persons treated, and treatment success rates among persons treated in low- and middle-income countries are similar to those in high-income countries.[4] One third of those who become chronically infected are predicted to develop liver cirrhosis or hepatocellular carcinoma.[5]

The prevalence of hepatitis C infection varies substantially around the world (Table 2.1). When countries are grouped into Global Burden of Disease regions, the estimated prevalence of HCV infection is highest in Central and East Asia and in the North Africa/Middle East regions. In view of the larger populations in Asia, the South Asia and East Asia regions have by far the largest number of persons living with HCV infection.

TABLE 2.1 Global seroprevalence of HCV by region

Region	Prevalence (%)	Estimated number of people infected
Asia Pacific	1.4	>2.4 million
Central Asia	3.8	>2.9 million
East Asia	3.7	>50 million
South Asia	3.4	>50 million
South-East Asia	2.0	>11 million
Australasia	2.7	>0.6 million
Caribbean	2.1	>0.7 million
Central Europe	2.4	>2.9 million
Eastern Europe	2.9	>6.2 million
Western Europe	2.4	>10 million

Andean Latin America	2.0	>1.0 million
Central Latin America	1.6	>3.4 million
Southern Latin America	1.6	>0.9 million
Tropical Latin America	1.2	>2.3 million
North Africa/Middle East	3.6	>15 million
North America	1.3	>4.4 million
Oceania	2.6	>0.2 million
Central sub-Saharan Africa	2.3	>1.9 million
East sub-Saharan Africa	2.0	>6.1 million
South sub-Saharan Africa	2.1	>1.4 million
West sub-Saharan Africa	2.8	>8.4 million

Source: Adapted from Mohd Hanafiah et al., 2013[1]

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.

2.1.1 Routes of transmission

TABLE 2.2 Populations at increased risk of HCV infection

Population	Comment
Persons who inject drugs[6]	PWID have the highest risk of infection: Globally, the prevalence of HCV is 67% among PWID.
Recipients of infected blood products or invasive procedures in health-care facilities with inadequate infection control practices[7-16]	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. High frequency of injections and low level of infection control can result in high prevalence of HCV in the general population (e.g. prevalence of chronic HCV infection confirmed by nucleic acid testing was 9.8% in Egypt in 2008)
Children born to mothers infected with HCV[17, 18]	HCV transmission risk is estimated as 4–8% among mothers without HIV infection Transmission risk is estimated as 17-25% among mothers with HIV infection

People with sexual partners who are HCV-infected[19,20-23]	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[23-31]	Persons with HIV infection, in particular MSM, are at increased risk of HCV infection through unprotected sex.
People who have used intranasal drugs[32]	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[33]	Tattoo recipients have higher prevalence of HCV compared with persons without tattoos (odds ratio = 2.24, 95%CI 2.01,2.50)

Health-care associated transmission

Hepatitis C virus infection is strongly associated with health inequity; in low- and middle-income countries, infection with HCV is most commonly associated with unsafe injection practices and procedures such as renal dialysis and unscreened blood transfusions.[15,34] Between 8 and 12 billion injections are administered yearly around the world and 50% of these are considered to be unsafe (mainly in sub-Saharan Africa and Asia).[35] In low- and middle-income countries, infection with HCV is frequently associated with unsafe injection practices and unscreened (or inadequately screened) blood transfusions. According to the latest WHO report on blood safety (2011), 39 countries do not routinely screen blood transfusions for bloodborne viruses.[36] 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 prevalence is 25% in some regions.[8] Persons who received untested blood products prior to the introduction of screening of blood for HCV in high-income countries are also at risk. 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.[37]

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 are infected with HCV.[6] PWID infected with HCV are at increased risk of all-cause mortality, reflecting the role of injecting drug use, low socioeconomic status, poor access to health care and environmental factors.[38]

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 17–25% of births to women with HIV and HCV coinfection (Table 2.2).[17,18]

Sexual transmission

Sexual transmission of HCV occurs infrequently in heterosexual couples.[39] It is more common in HIV-positive persons, particularly in men who have sex with men (MSM).[40] In several recent outbreaks of HCV infection among MSM in Europe, Australia and the US, transmission has been linked to sexual exposure as well as potentially to underreported use of non-injecting recreational drugs.[41,42] 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.[41]

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.[33,43]

2.1.2 Coinfections

HIV and HCV coinfection

HIV and HCV have common routes of transmission, and it is estimated that, globally, 4–5 million persons are coinfected with these two viruses.[44] 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.[45]

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.[46-51] HBV and HCV coinfection is discussed further in Chapter 9.

Tuberculosis and HCV coinfection

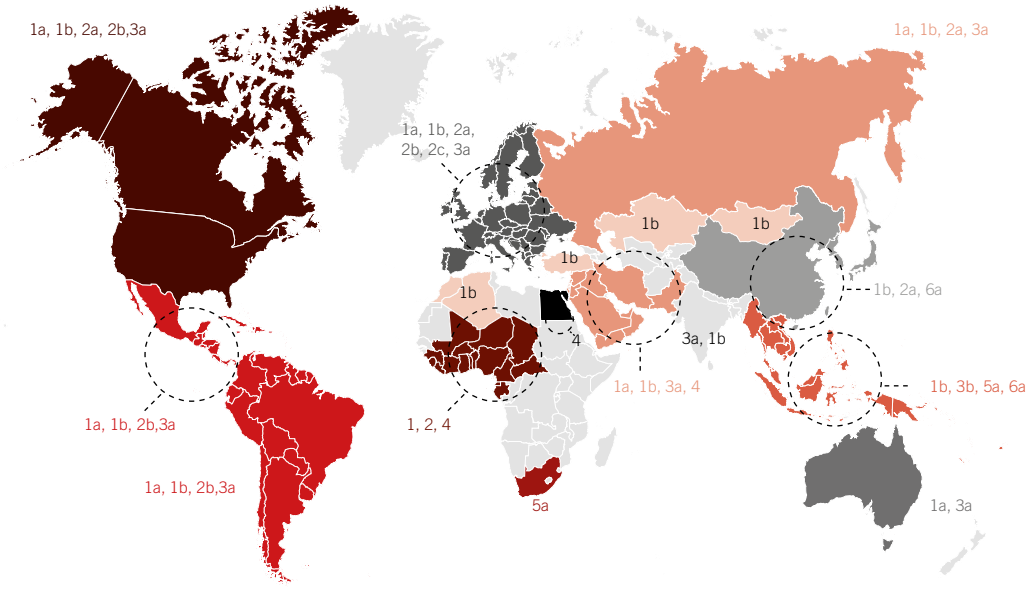
Groups at increased risk of infection with HCV are also at risk of infection with tuberculosis (TB). TB is endemic in many countries where blood products are not screened routinely. TB is the most common AIDS-defining illness and the leading cause of HIV-associated mortality. PWID are more at risk of developing TB, regardless of their HIV status. Among PWID who develop TB, two out of three will have 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.[52,53] Appropriate care for persons being considered for hepatitis C 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.

2.2 Hepatitis C virus

The hepatitis C virus is a small, positive-stranded RNA-enveloped virus that is approximately 9.6 kb in length. The genetic sequence was first characterized in 1989,[54] placing the virus in the Hepacivirus genus within the Flaviviridae family.[55,56] It has a highly variable genome and multiple genotypes and subgenotypes.[57] The distribution of HCV genotypes and subgenotypes varies substantially in different parts of the world (Figure 2.1). Some genotypes are easier to treat and, thus, the duration of and recommended medicines for therapy vary by genotype. For this reason, determining a patient's genotype is important to appropriately tailor therapy. It is possible that this advice may change when antiviral agents that are active against all genotypes (referred to as pangenotypic) are licensed.

FIGURE 2.1 Global distribution of genotypes of HCV



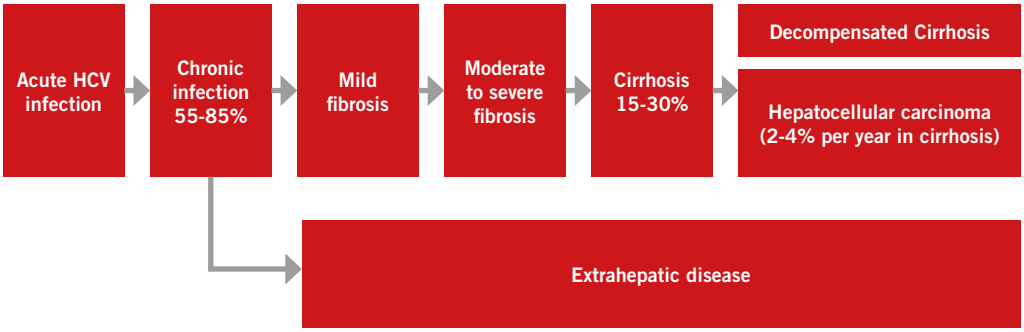
Source: Hussain Z. Genomic heterogeneity of hepatitis viruses (A–E): role in clinical implications and treatment. In: Serviddeo G, editor. Practical management of chronic viral hepatitis. Rijeka, Croatia: InTech; 2013. (www.intechopen.com/books/practical-management-of-chronic-viral-hepatitis/genomic-heterogeneity-of-hepatitis-viruses-a-e-role-in-clinical-implications-and-treatment, accessed 10 February 2014).

2.3 Natural history of HCV infection

Hepatitis C virus causes both acute and chronic infection. Acute HCV infection is defined as the presence of HCV within six months of exposure to and infection with HCV. It 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 virus, is needed to confirm the diagnosis of chronic HCV infection.[58,59]

Left untreated, chronic HCV infection can cause liver cirrhosis, liver failure and hepatocellular carcinoma (HCC; Figure 2.2). Of those with chronic HCV infection, the risk of cirrhosis of the liver is 15–30% within 20 years.[60,61,62] The risk of HCC in persons with cirrhosis is approximately 2–4% per year.[63]

FIGURE 2.2 Natural history of HCV infection



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.[64] Disease associated with HCV is not confined to the liver. Extrahepatic manifestations of HCV include cryoglobulinaemia, glomerulonephritis, thyroiditis and Sjögren syndrome, insulin resistance, type-2 diabetes mellitus, 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.[65] 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.[66]

Natural history of HIV/HCV coinfection

Coinfection with HIV adversely affects the course of HCV infection, and coinfected persons have a significantly accelerated progression of liver disease to cirrhosis, decompensated liver cirrhosis and HCC than HCV-monoinfected persons, particularly those with advanced immunodeficiency (CD4 count <200 cells/mm^3).[67-70] In high-income countries, death due to HCV-associated liver disease has become a leading cause of death in people living with HIV in the era of combination ART,[45,71,72] 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.[73] 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 an impaired recovery of CD4 cells. However, other studies have shown no such differences in response.[73-77] 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.[78,79] In persons with HIV infection, HCC tends to occur at a younger age and within a shorter time period.[80]

2.4 Prevention of HCV infection

In the absence of a vaccine for hepatitis C, prevention of HCV infection depends upon reducing the risk of exposure to the virus. This is challenging because of the various routes of transmission and the different populations that are affected. Globally, most HCV infections occur in health-care settings as a result of inadequate infection control procedures, for example, the reuse of injection equipment. HCV infections in health-care settings also occur through the transfusion of blood that has not been screened for HCV antibodies. WHO has published guidelines with recommendations to prevent health-care associated HCV infection (Table 2.3).

PWID are at great risk of HCV infection through the use of contaminated injection equipment as well as non-injection drug use. WHO, United Nations Office on Drugs and Crime (UNODC), and the Joint United Nations Programme on HIV/AIDS (UNAIDS) have developed a set of nine core interventions for the prevention, care and treatment of HIV infection among PWID (Table 2.4). These interventions are also relevant for the prevention and management of viral hepatitis in this population. In addition, WHO has developed guidelines with recommendations for preventing transmission of viral hepatitis among PWID (Table 2.5).

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

Focus of guidance documents:
• 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

References

WHO guidelines on hand hygiene in health care. Geneva: World Health Organization; 2009. (http://whqlibdoc.who.int/publications/2009/9789241597906_eng.pdf, accessed 20 January 2014).

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 20 January 2014).

Universal access to safe blood transfusion. Geneva: World Health Organization; 2008. (http://www.who.int/bloodsafety/publications/UniversalAccesstoSafeBT.pdf, accessed 20 January 2014).

Blood donor selection: guidelines on assessing donor suitability for blood donation. Geneva: World Health Organization; 2012. (http://www.who.int/bloodsafety/publications/bts_guideline_donor_suitability/en/index.html 2012, accessed 20 January 2014).

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 20 January 2014).

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

Interventions
1. Needle and syringe programmes including other drug-using 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.

References

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, in addition to interventions described in Table 2.4

Recommendations
• Offer people who inject drugs the rapid hepatitis B vaccination regimen. • Offer people who inject drugs incentives to increase uptake and completion of 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 treatment of opioid dependence with medical services for hepatitis.
References 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 20 January 2014). 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 20 January 2014).

The risk of sexual transmission of HCV varies depending on the type of exposure. The risk is lowest among heterosexual couples and highest among MSM with HIV coinfection. Existing guidelines for prevention of HCV infection through sexual exposure are listed in Table 2.6.

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

Focus of guidance documents:
• Promotion of correct and consistent condom use • Routine screening of sex workers in high-prevalence settings • Integrated action to eliminate discrimination and gender violence and to increase access to medical and social services for vulnerable persons
References 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 20 January 2014). 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 20 January 2014).

Prevention of mother-to-child transmission of HCV is difficult as there are no proven interventions to reduce this risk. Neither mode of delivery nor breastfeeding are reliably linked with transmission. The development of effective drugs against HCV that can be given safely during pregnancy might be a future option.

2.5 Screening for HCV infection

Screening for HCV infection is done using HCV serological testing. If positive, a NAT for HCV RNA assay is needed to confirm chronic HCV infection. Several screening assays have been evaluated by WHO, and sensitivity, specificity, and positive and negative predictive value results are available.[81] It is important to consider the possibility of infection with other bloodborne viruses in persons 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.

2.6 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. 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 Chapter 6.2.

Staging of HCV infection is important as it results in the identification of 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 persons with mild-to-moderate disease may elect to wait for newer, less toxic and more efficacious medicines). In low- and middle-income countries, 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).

Patients infected with HCV often have other co-morbidities such as HBV, HIV, TB and substance use. Related WHO guidance is available for persons who inject

drugs and for those infected with HIV (*see* section 2.4). Excessive alcohol use is common in some populations infected with HCV and can accelerate disease. WHO guidance on alcohol reduction is discussed in detail in Chapter 6.1.

2.7 Treatment of patients with HCV infection

HCV is a now a curable disease, and advances in HCV therapy have resulted in steadily higher cure rates. Identification and treatment of chronic HCV infection has a prevention benefit, as persons who are cured of HCV cannot transmit the virus to others. HCV cure is also beneficial for the patient's health, as it reduces the risk of development of HCC among persons at all stages of fibrosis by >75%.[82,83] At the time of writing (December 2013), six drugs are licensed for the treatment of HCV – standard interferon (IFN) or pegylated interferon alpha (PEG-IFN), ribavirin (RBV), the protease inhibitors (PIs) boceprevir, simeprevir and telaprevir, and the nucleotide analog polymerase inhibitor sofosbuvir. The limitations of treatment include high cost, the need for sophisticated laboratory tests and trained clinicians, as well as the limited efficacy and high toxicity of some of the medicines. It is anticipated that the number of medicines for the treatment of HCV will expand rapidly over the coming years, and WHO plans to periodically update these guidelines to include newly licensed drugs.

Before treatment for HCV can be commenced, it is necessary to genotype the virus as different genotypes require different types and durations of treatment, and the protease inhibitors boceprevir, simeprevir and telaprevir are licensed only for genotype 1 infection. Current therapy for genotype 1 infection is a combination of PEG-IFN, RBV and a PI or nucleotide polymerase inhibitor, which results in high rates of sustained virological response (SVR; a negative HCV RNA test three or six months after the end of treatment).[84-87] Dual therapy with PEG-IFN and RBV or sofosbuvir with RBV is used for genotypes 2 and 3 infections.[88,89] Patients with genotype 4 infection treated with treated with sofosbuvir, PEG-IFN and RBV have similar response rates when compared with genotype 1-infected individuals. Small studies of genotypes 5- and 6-infected patients have shown similar SVR rates to genotypes 2- and 3-infected ones.[90,91] Larger studies in these groups are required to confirm these results and to identify predictors of response or non-response to treatment.

Treatment with some HCV medicines may result in marked side-effects and therefore careful patient assessment and close monitoring is required.[92,93,94]

2.8 Cost–effectiveness of treatment

Among the major hurdles in setting up a treatment service for patients with HCV are the high cost of medications, need for regular monitoring, setting up, running

and maintaining appropriate facilities, and assuring adequate numbers and training of staff. The benefits of instituting treatment programmes include the benefit to individual patients as well as the potential reduction of transmission of infection from treated persons who are no longer infected with HCV.

In high-income settings, HCV treatment with PEG-IFN/RBV and with PEG-IFN/RBV and telaprevir or boceprevir has been evaluated as being cost–effective.[95,96] PEG-IFN and RBV treatment in current PWID has also been shown to be cost–effective in high-income settings, despite the potential risk of reinfection, and may be even more cost–effective than treatin≤g those with lower risks of transmission to others.[97,98] HCV case-finding and treatment in specialist drug dependency services has also been shown to be cost–effective. 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.[97]

In low- and middle-income countries, data on cost–effectiveness are limited but have been evaluated in some settings, for example, in Egypt and Viet Nam.[99,100] Where the availability of medication is restricted, treatment of persons with more advanced disease may be the most cost–effective strategy.[100]

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.[101] 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

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.[102]

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 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 PEG-IFN). 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 co-morbidity is therefore an important consideration in patients who will be screened and potentially treated for HCV. 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.

4. METHODS

WHO guideline development process

These WHO guidelines were produced following the recommendations for standard guidelines as described in the WHO Handbook for guideline development, 2012.[103] The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework was followed for this process.[104] A Guidelines Development Group was formed with care taken to ensure representation from various stakeholder groups, including members of organizations that represent persons living with HCV infection and PWID, advocacy groups, academicians, researchers, clinicians, and programme managers. Geographical representation and gender balance were also important considerations in selecting Group members. Following an initial scoping and planning process, a meeting was held by members of the Guidelines Development Group in December 2012 in order to formulate questions and determine patient-important outcomes. These were selected with an emphasis on answering questions most applicable to low- and middle-income settings and did not include questions already addressed by existing WHO guidance (for example, guidance already formulated for PWID). Each member of the Group initially nominated at least three issues, which they felt were essential for inclusion in WHO guidance. These were discussed in working groups and a preliminary ranking was formulated. The group then arrived at a consensus on the seven most important questions across the screening, care and treatment framework. These questions were structured in PICO format (Population, Intervention, Comparison, Outcomes; Appendix 1) and patient-important outcomes were identified for each research question. These outcomes were refined and ranked based on their importance to the patient population.[105] The guidelines methodologists further refined the research questions.

Systematic reviews and meta-analyses of the primary literature were commissioned 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 (Appendix 5). Search strategies and summaries of evidence are available in Appendix 3. Systematic reviews were externally commissioned through the Burnet Institute, Australia and Glasgow Caledonian University/ Health Protection Scotland, UK.

The quality of the evidence was assessed and either rated down or rated up based on the following criteria: rated down based on (i) risk of bias (using the Cochrane Risk of Bias assessment tool) including publication bias; (ii) inconsistency or heterogeneity; (iii) indirectness (addressing a different population than the one under consideration); or (iv) imprecision. Conversely, the quality of the evidence was rated up if it met any of three criteria: (i) large effect size; (ii) dose–response; or (iii) plausible residual confounders (i.e. when biases from a study might be reducing the estimated apparent intervention effect). Based on the rating of the available evidence, the quality of evidence was categorized as high, moderate, low or very low (Table 4.1). Summaries of the quality of evidence to address each outcome were entered in the GRADE profiler software (GRADEpro 3.6,) (Appendix 2).

TABLE 4.1 GRADE categories of quality of evidence[106]

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

At the June 2013 meeting of the Guidelines Development Group, for each of the PICO questions, the results of the systematic reviews 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. These were assessed through discussions among members of the Guidelines Development Group. 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 results of those discussions are summarized in the decision-making tables (Appendix 4). Recommendations were then formulated and the wording finalized by the entire group. Implementation needs were subsequently evaluated and areas and topics requiring further research identified. At both meetings, declarations of interest were reported according to WHO standard requirements.

At the June 2013 meeting of the Guidelines Development Group, presentations were made by external experts on fibrosis assessment and cost–effectiveness of fibrosis assessment tests (Louise Longworth and Emmanuel Tsochatzis), cost–effectiveness of treatment in low- and middle-income settings (Yazdan Yazdapanah), treatment of PWID (Natasha Martin) and frequency of laboratory monitoring during therapy (Emma Thomson). Resource use was considered based on the available evidence and presentations from invited external expert speakers.

The final recommendations were agreed on by consensus during a face-to-face meeting in June 2013. After all of the comments and questions from members of the Guidelines Development Group were addressed, to document consensus, the Chairs asked each Group member individually whether he/she agreed with the recommendation. For all of the recommendations, there was unanimous agreement of Group members.

The intended scope of these guidelines was to include all HCV medicines that had received regulatory approval in at least one country. At its meeting in June 2013, the Guidelines Development Group considered that two new medicines (simeprevir and sofosbuvir) were likely to gain approval by at least one national regulatory body prior to the release of the guidelines and agreed that, if this was the case, recommendations should be formulated concerning their use. Systematic reviews for sofosbuvir and simeprevir were conducted by the same individuals who had done the other reviews and included peer-reviewed articles, conference abstracts, and data submitted to the US Food and Drug Administration (FDA) as part of the drug registration applications. Evidence profiles and decision-making tables were prepared using the same methods as for the other recommendations, and these were reviewed and recommendations formulated during a web-based meeting that was held in December 2013. 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.

A draft document was prepared and circulated to the members of the Guidelines Development Group and the WHO Steering Committee. Suggested changes were incorporated into subsequent drafts. If comments were not clear, reviewers were contacted to provide clarification. Thereafter, a draft was circulated to

the external peer reviewers and the draft document furher revised to address their comments. Suggested changes to the wording of the recommendations or suggested modifications to the scope of the document were not considered, but otherwise there were no comments that suggested conflicting changes.

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.

Guideline methodologists 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 preparing evidence profiles and decision-making tables. The methodologists also provided guidance to the Guidelines Development Group in the formulation of the wording and strength of the recommendations.

Declarations of interest

In accordance with WHO policy, all members of the Guidelines Development Group were required to complete and submit a WHO Declaration of Interests form. The Secretariat then reviewed and assessed the declarations submitted by each member and presented a summary to the Guidelines Development Group.

Individuals from civil society organizations whose organizations received most of their funding from private (primarily pharmaceutical) companies or individuals who received honoraria from such companies were classified as having potential conflicts of interest. These persons were partially excluded from the Guidelines Development Group by not participating in the formulation of recommendations. These Group members contributed to the development of PICO questions, and provided technical expertise in reviewing the evidence summaries. Persons who were partially excluded were: Vladimir Chulanov, Charles Gore, Anna Lok, Masashi Mizokami and Manal El-Sayed.

5. RECOMMENDATIONS ON SCREENING

5.1 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 seroprevalence or who have a history of HCV risk exposure/ behaviour.

Strong recommendation, moderate quality of evidence

Notes: The WHO list of prequalified serological diagnostic tests for hepatitis C infection are available at. http://www.who.int/diagnostics_laboratory/evaluations/en/hcv_rep1.pdf and http://www.who.int/diagnostics_laboratory/evaluations/en/hcv_rep2.pdf

This list will be updated in 2014.

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 liver cancer.[107] 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 Guidelines Development Group considered the value of a risk group-based and prevalence-based approach. 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.[108,109] 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).

TABLE 5.1 Populations with 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
- Persons 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 have used intranasal drugs
- Prisoners and previously incarcerated persons

Summary of the 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.

Sixteen studies were reviewed; five randomized controlled trials (RCTs), four non-randomized controlled trials, three before/after studies and four time-series analyses (Appendix 3). 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 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% 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.

Rationale for the recommendation

The summary of evidence demonstrated that practitioner-based and media-based interventions are effective in increasing uptake of testing, identifying HCV-infected individuals and referring them to care. However, the approaches to achieve these results were different in the studies that were evaluated. Therefore, the 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 of 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 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 approaches to enhance testing. Members of the Guidelines Development Group also expressed concern that persons with HCV identified through enhanced screening efforts in low- and middle-income countries might not have access to care and treatment. Despite these concerns, the 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 Guidelines Development Group concluded that the desirable outcomes outweighed the undesirable outcomes. WHO is 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 above-mentioned elements (lack of coercion, confidentiality, cultural sensitivity, linkage to health services), the Guidelines Development Group felt that screening would be acceptable by 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 Guidelines Development Group emphasized the importance of assuring access to treatment following screening. The 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.

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 US is to define demographic groups using age criteria.[108,109] 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.

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 practice 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.

Research gaps

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

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

Background

Approximately 15–45% of persons who are infected with HCV will spontaneously clear the infection.[58,59] These persons are HCV seropositive but are no longer infected with HCV. A nucleic acid test (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 standard of care to carry out a NAT for HCV RNA for persons who are found to be HCV antibody positive. A NAT for HCV RNA is also important prior to commencing and during treatment to assess the response to treatment.[110-112] The 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.

Summary of the evidence

A systematic review was conducted to compare whether there was a benefit to performing an HCV-RNA NAT 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") (Appendix 3). 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. [113-120] 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 study types 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 HCV-RNA NAT is underutilized in populations in which it is indicated.[116,118-120] Rongey found that HCV-RNA NAT among a cohort of anti-HCV-positive US 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.[116]

Rationale for the recommendation

Balance of benefits and harms: In the absence of direct or indirect evidence from the systematic reviews, members of the Guidelines Development Group discussed the implications of not conducting an immediate HCV-RNA NAT. 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 Guidelines Development Group panel 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$ 30–200 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 to implement 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 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.

Implementation

The 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 be retested.

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),[121,122] but may occur more often among persons with advanced immunosuppression due to HIV and during early HCV infection.[123,124] As the range of CD4 counts in persons with a false-negative HCV antibody test were 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 HCV antibody test should have HCV RNA testing performed.

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 evaluations are 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

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 ASSIST[141] 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

Background

In many persons with chronic HCV infection, decades can pass between the time of 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 Guidelines Development Group assessed various interventions that slow the rate of liver damage among persons with HCV 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[125] and it was felt that persons with HCV infection would be amenable to such measures. Reducing the use of cannabis in persons with HCV was discussed by the 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.[126]

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.[127] The purpose of the systematic review was to investigate the effectiveness of behavioural interventions to reduce alcohol intake among people with HCV, in terms of HCV treatment outcomes, liver disease progression 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 HCV-infected individuals. Some countries, such as Egypt and Saudi Arabia, report extremely low or negligible alcohol use in persons with HCV.[127,128] 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.[129] In one study from Russia, 26–30% of PWID drank moderate-to-heavy amounts of alcohol.[130] In Brazil, HCV-infected youth offenders had high rates of alcohol use[131] and in a study among Nigerian prisoners, 59% with HCV also drank alcohol.[132] Alcohol intake has also been found to be high in other groups of HCV-infected individuals; 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.[113,b] In view of these figures, the Guidelines Development Group considered that even in countries where alcohol intake is low among the general population, alcohol reduction advice might have an impact.

Evidence

A systematic review was conducted of studies examining a brief behavioural alcohol reduction intervention versus no behavioural intervention for HCV-infected individuals. The outcomes considered were reduction or cessation of alcohol intake, SVR, liver fibrosis, decompensated liver cirrhosis, HCC, quality of life and mortality.

Five trials were identified that met the PICO criteria for assessment (Appendix 3); two RCTs[134,135] and three cohort studies.[136-138] 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. However, the evidence

b. Further information collected by WHO on alcohol use by country is available online: http://www.who.int/substance_abuse/publications/global_alcohol_report/profiles/.

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 individuals. A Cochrane review conducted by Kaner et al.[139] found that among 5 860 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.[140] 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 since there was variability in the type of interventions. Although these studies were conducted among persons without HCV infection, the 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.

Rationale for the recommendation

In summary, the 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 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 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.

Implementation

An important challenge to implementing a brief alcohol reduction intervention is deciding on which approach to consider. The Guidelines Development Group proposed that the WHO ASSIST (Alcohol, Smoking and Substance Involvement Screening Test) package[141] 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 low- and middle-income countries.[142]

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 of integrating alcohol screening and counselling in different geographical settings.

TABLE 5.1 ASSIST – The Alcohol, Smoking and Substance Involvement Screening Test[141]

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 are as follows:
  - lower risk means no treatment is needed
  - moderate risk calls for a brief intervention
  - high risk leads to referral to a for specialist 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

In resource-limited settings, it is suggested that aminotransferase/platelet ratio index (APRI) or FIB4 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 FIB4, may be preferable in settings where the equipment is available and the cost of the test is not a barrier to testing.

Background

Decisions regarding treatment initiation for HCV are based on a patient's degree of fibrosis and the balance between the likelihood of cure versus that of serious side-effects from the treatment. Patients with less advanced fibrosis respond better to HCV treatment, with a higher SVR rate. However, some of these individuals would never progress to cirrhosis, and thus are unnecessarily exposed to potentially toxic drugs. On the other hand, individuals with more advanced fibrosis and compensated cirrhosis respond less well to treatment, with a lower SVR rate. If they do achieve SVR, they benefit more than persons with less advanced cirrhosis as they are at much higher risk of dying from advanced liver disease if they do not receive treatment. According to guidelines developed for high-income countries, therapy should be considered for all persons with chronic HCV infection.[110,111] In lower-income countries, where the availability of treatment can be severely restricted, prioritizing, or even limiting, treatment to those persons at highest risk of morbidity and mortality may be necessary. Thus, the Guidelines Development Group felt it important to identify low-cost, effective methods of assessing the degree of fibrosis that would be widely available in low- and middle-income countries.

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[143]

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 low- and middle-income countries (Table 6.3). These include serum tests such as the APRI, FIB4 scores, which measure indirect markers of fibrosis such as alanine aminotransferase (ALT), aspartate aminotransferase (AST) and platelet count (Figure 6.1); tests that should be available at all clinics treating patients with HCV. 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, FIB4 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.

FIGURE 6.1 APRI and FIB4 formulas

APRI = [{AST (IU/L)/ AST_ULN (IU/L)}×100]/ platelet count (10^9/L)

FIB4= 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

TABLE 6.3 Selected non-invasive tests to assess liver fibrosis [143-148]

Test	Components	Requirements	Cost
APRI	AST, platelets	Simple serum and haematology tests	+
FIB4	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

Summary of 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 FIB4 indices. Thus, the results of systematic reviews were analysed to assess the benefit of more complex and expensive tests (e.g. Fibrotest or Fibroscan) compared with APRI and FIB4. A systematic review was conducted to evaluate the diagnostic accuracy of non-invasive fibrosis assessment tests in adult patients with chronic HCV infection (Appendix 3). The systematic review included full papers and abstracts, without language restrictions, which: (i) evaluated non-invasive tests in 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 Appendix 3.

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 FIB4, these cut-offs have been validated. APRI and FIB4 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 FIB4 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 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 cirrhosis and fibrosis

	APRI (low cut-off)	APRI (high cut-off)	FIB4 (low cut-off)	FIB4 (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, FIB4 and Fibroscan for the detection of advanced cirrhosis and fibrosis (all values are percentages)

		APRI (low cut-off)	APRI (high cut-off)	FIB4 (low cut-off)	FIB4 (high cut-off)	Transient elastography (Fibroscan)
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; kPa kilopascal

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 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.[149] Theoretically, the FIB4 test could also be affected by thrombocytopenia but this scoring system was first evaluated in patients with HIV and was found to perform well.[150] 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.

Rationale for the recommendation

The use of non-invasive monitoring was considered by the Guidelines Development Group to be preferable to invasive testing, particularly in low- and middle-income countries, 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, FIB4 and transient elastography were the most useful tests for assessing the stage of liver disease. The advantage of APRI as compared with FIB4 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 FIB4 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 FIB4 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 FIB4 tests require only phlebotomy; thus, the 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 FIB4 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$ 4 700. For these reasons, the use of transient elastography was considered to be not feasible in most low- and middle-income countries.

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 highest risk of dying from complications of HCV, 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

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

Background

Over the past two decades, the success of treatment for HCV infection as measured by SVR has steadily increased. Early treatments with standard IFN resulted in SVR rates of 30–60% depending on the genotype. The introduction of PEG-IFN increased SVR rates to 40–70%, and the more recent introduction of direct-acting antivirals (DAAs) increased the SVR rate for genotype 1 from 40% to greater than 90%. Despite these advances, very few persons in low- and middle-income countries 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 PEG-IFN and RBV also result in high rates of adverse events, which can be debilitating and even life threatening. Thus, the Guidelines Development Group felt it important to evaluate the relevant evidence of the benefits and harms of treatment versus no treatment of HCV infection.

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.

Fourteen systematic reviews were included in the final synthesis (Appendix 3). Six reviews reported data comparing IFN to placebo[151-156] and six combined and compared different types of IFN (standard IFN or PEG-IFN) to placebo.[157-162] No studies were available comparing placebo to triple therapy (PEG-IFN, RBV and a PI) as the standard of care at the time of institution of triple therapy was dual therapy with PEG-IFN and RBV. One review evaluated RBV monotherapy against placebo.[163] All reviews of IFN, PEG-IFN or RBV 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 analysis showed that IFN was superior to placebo in achieving SVR. The effects of IFN on HCC, liver-related morbidity and all-cause mortality were inconsistent or statistically non-significant. No studies were found that reported quality-of-life changes with IFN versus placebo.

The systematic reviews of effectiveness of different interferon types (IFN or PEG-IFN), in combination with RBV compared with placebo showed a clear benefit of treatment versus placebo in achieving SVR. There were inconsistent or statistically non-significant effects of PEG-IFN/RBV on HCC, liver-related morbidity and all-cause mortality. One study comparing RBV with placebo showed no significant beneficial effect of RBV in achieving SVR, reducing all-cause mortality or quality of life.[163]

The systematic reviews showed that the most common adverse events were flu-like syndromes and depression due to IFN and anaemia due to RBV. The frequency of discontinuation of treatment approached 20% in one study of patients being evaluated for liver transplants compared with 0% among placebo recipients.[158]

Treatment success rates are similar in adults and children, although fewer studies have been carried out in children.[153] One systematic review reported on the virological outcomes and adverse effects of treatment among children.[153] This review included four RCTs and 31 non-randomized studies. The overall SVR rate for PEG-IFN and RBV 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 drop 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 treatment discontinuations and 830 more cases of flu-like symptoms per 1 000

persons treated than among persons receiving placebo. Studies showing the benefit of therapy among persons with HIV/HCV coinfection are described in Section 7.2.

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 1/4 and 67% in genotypes 2/3), a treatment discontinuation rate of 22% and a high level of drug adherence. These outcomes were similar to those observed among non-drug users.[164] In addition, economic modelling data evaluating the cost–effectiveness of treating HCV infection among PWID was considered by the Guidelines Development Group. In this group, treatment was considered to be cost–effective in a variety of settings. Additional benefits of treating PWID is that treatment for HCV infection may prevent transmission and reduce prevalence of HCV infection in this population.[98,99]

Rationale for the recommendation

Balance of benefits and harms: IFN-based therapy, whether using standard or PEG-IFN, 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.[165] 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 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 IFN-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 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 treatment are reluctant to be treated because of the fear of adverse events due to the medications, particularly PEG-IFN. 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 PEG-IFN plus RBV costs between US$ 2 000 and US$ 28 000 per person.[166] 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. Treatment is also delivered in several other low- and middle-income countries 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.[100] Economic evaluations indicate that treatment for PWID is cost–effective and may be more cost–effective 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 chronic HCV prevalence among PWID[98,99] (Chapter 8: Monitoring).

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 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

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).

Background

All genotypes of HCV respond to and repetition with RBV and either standard IFN or PEG-IFN. PEG-IFN 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. Despite this, standard IFN continues to be used in some low- and middle-income countries because it is much less expensive than PEG-IFN. The Guidelines Development Group felt that it was important to analyse the evidence and provide a clear recommendation on which form of IFN was preferable.

Evidence

A systematic review was conducted to assess the efficacy of PEG-IFN and RBV versus IFN and RBV 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.

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 PEG-IFN and RBV is more effective at achieving SVR among people with chronic HCV compared with standard IFN and RBV (RR 0.81; 95% CI 0.76, 0.86). The anticipated absolute effect estimates that 661 per 1 000 persons treated with standard IFN would fail to reach SVR (which equates to an SVR of 33.9%) while 535 per 1 000 persons would fail to reach SVR with PEG-IFN (which equates to an SVR of 46.5%) (Appendix 3). Increased efficacy of PEG-IFN 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 PEG-IFN versus standard IFN. 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 PEG-IFN versus standard IFN. 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 1 000 occurred with PEG-IFN (baseline 21 per 1 000), 3 fewer cases of hepatic decompensation (from 17 per 1 000) and 5 fewer cases of liver-related mortality (from 15 per 1 000). One more patient per 1 000 terminated treatment due to adverse events (from 118 per 1 000).

Three studies have been carried out in persons with HIV/HCV coinfection.[167-169] The ACTG 5071, RIBAVIC and APRICOT studies compared standard IFN and RBV with PEG-IFN and RBV. In the APRICOT study, the SVR rate was significantly higher in those who received PEG-IFN and RBV than in those who received standard IFN and RBV, 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 PEG-IFN and RBV 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 IFN arm.

Rationale for the recommendation

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

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

Resource considerations: The reason that standard IFN continues to be used in some countries is because it is less expensive than PEG-IFN. The principal barrier to more extensive use of PEG-IFN is its high cost. PEG-IFN is manufactured by a limited number of companies, and the cost of a 48-week regimen of PEG-IFN and RBV varies between US$ 2 000 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.[100] 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 low- and middle-income countries. In particular, Egypt has made treatment available to large numbers of patients.

Implementation

The recommended duration of treatment varies, depending on the genotype, stage of disease, coinfection with HIV and initial response to treatment. Furthermore, PEG-IFN is recommended only for children older than two years of age. Additional considerations regarding adjustment of duration of therapy based on genotype, and monitoring for side-effects and efficacy are discussed in Chapter 8.

Duration of treatment for HCV

In persons with HCV monoinfection as well as those with HIV/HCV coinfection, PEG-IFN and RBV are recommended for 48 weeks in those with genotype 1 infection (this can be extended to 72 weeks in those with a delayed virological response or shortened to 24 weeks in those with a rapid virological response). In persons with HCV monoinfection with genotypes 2 or 3, 24 weeks of treatment is recommended (unless the patient has cirrhosis or HIV coinfection, when treatment extension to 48 weeks may be considered). Treatment should be discontinued in persons who have failed to achieve at least a 2 log drop in HCV RNA below baseline by 12 weeks of therapy, since SVR is unlikely to be achieved.[168]

Research questions

There is a lack of research examining the safety and efficacy of PEG-IFN versus standard IFN in low- and middle-income countries and among persons with HIV/HCV coinfection who have genotypes 2 or 3 infection. Testing of different treatment delivery models, including decentralized models that may rely in part on community-based services, was also considered an important area for research by the Guidelines Development Group.

7.3 Treatment with telaprevir or boceprevir

Treatment with telaprevir or boceprevir, given in combination with pegylated interferon and ribavirin, is suggested for genotype 1 chronic hepatitis C infection rather than pegylated interferon and ribavirin alone.

Conditional recommendation, moderate quality of evidence

Treatment regimens

- Treatment duration of telaprevir/PEG-IFN/RBV for treatment-naive patients is 24–48 weeks depending on the response to treatment (telaprevir is given for 12 weeks only).
- Treatment duration of boceprevir/PEG-IFN/RBV in treatment-naive patients is 28–48 weeks depending on the response to treatment.
- Treatment duration in previously treated patients varies by previous response to treatment.

Background

The PIs boceprevir and telaprevir, used in combination with PEG-IFN and RBV, have substantially increased SVR rates in persons with genotype 1 HCV infection.[84,85,170] These PIs have limited activity against other genotypes and are therefore licensed for use only in persons infected with HCV genotype 1. The availability of newer DAAs for HCV will expand rapidly over the coming years and the treatment guidelines will be updated accordingly as these are licensed for use; these have a broader spectrum of activity and are likely to be suitable for non-genotype 1 infections. The use of PIs adds substantial costs to treatment regimens and increases the likelihood of adverse events and thus the need for frequent monitoring for side-effects. Current administration schedules are discussed in Chapter 8: Monitoring.

Evidence

A systematic review of the DAAs telaprevir and boceprevir versus PEG-IFN/RBV alone for adults with chronic genotype 1 HCV infection provided high-quality evidence for the outcome of SVR; DAA/PEG-IFN/RBV would result in 315 per 1 000 fewer virological failures compared with PEG-IFN/RBV given alone

(baseline failure rate 643 per 1 000). Triple therapy was found to be effective in persons with both mild and advanced liver fibrosis.

The incidence of side-effects was higher in persons treated with triple therapy and there was moderate-quality evidence that the inclusion of a PI increased the treatment discontinuation rate from a baseline of 95 cases per 1 000 by 17 additional cases per 1 000. In addition, there was high-quality evidence that a PI given with PEG-IFN and RBV was associated with 41 additional cases of grade 3 or 4 anaemia (Hb <8.5 g/dL) per 1 000 persons (baseline with IFN and RBV only: 22 cases of anaemia per 1 000 persons). Evidence of an increase in cases of grade 3 or 4 neutropenia was moderate and increased the risk from 174 cases per 1 000 by 106 additional cases per 1 000. Deaths occurred less frequently, however, in persons treated with a PI (from 6 deaths per 1000 to 3 deaths per 1 000). The CUPIC (Compassionate Use of Protease Inhibitors in Viral C Cirrhosis) study[171] revealed a higher risk of side-effects in treatment-experienced persons with compensated cirrhosis. Among 497 persons who completed at least 16 weeks of treatment with PEG-IFN/RBV and either telaprevir or boceprevir, 40% of patients developed a serious adverse event and 11.7% had to stop therapy. Those patients with a starting serum albumin level of <35 g/L or a platelet count ≤100 x10^9/L were at highest risk.[172]

The use of DAAs has been inadequately studied in children as they were excluded from the phase III studies of boceprevir and telaprevir.[84,85] Boceprevir and telaprevir are approved only for adults (>18 years of age).

Triple therapy with boceprevir or telaprevir and PEG-IFN/RBV is currently being tested in HIV-positive patients in phase III clinical trials. A major potential problem is that of drug–drug interactions (*see* Table 8.3). Both boceprevir and telaprevir are inhibitors of CYP3A4, which mediates many drug metabolic pathways and therefore any potential interaction must be carefully evaluated before commencing treatment.[c] Boceprevir has been been evaluated in HIV-positive individuals who were either not on ART or were treated with two nucleoside reverse transcriptase inhibitors (NRTI)s plus one of the following agents: efavirenz, raltegravir, lopinavir/ritonavir, atazanavir/ritonavir or darunavir/ritonavir. Data from these studies has led to the FDA recommendation that efavirenz and PIs should not be used with boceprevir but that raltegravir can be co-prescribed. Telaprevir is currently in phase III trials in patients receiving a dual NRTI backbone plus one of efavirenz (telaprevir must be given in a higher dose), raltegravir or atazanavir/ritonavir. Further studies exploring the potential for drug–drug interactions between ART

c. A useful resource for searching for drug–drug interactions can be found at the following website: http://www.hep-druginteractions.org.

regimens and newer compounds under development for the treatment of HCV are eagerly awaited and phase III trials of simeprevir, faldaprevir, and the NS5A inhibitor daclatasvir are under way among persons with HIV infection.

Rationale for the recommendation

Balance of benefits and harms: The consideration of the Guidelines Development Group was that the addition of telaprevir or boceprevir to a PEG-IFN and RBV-based regimen provided the benefit of an increased likelihood of SVR. Persons treated with these DAAs had an estimated SVR almost twice that of persons receiving only PEG-IFN and RBV. However, these two DAAs also considerably increased the likelihood of harms, in particular, anaemia and neutropenia. The use of these medicines among persons with more advanced liver disease resulted in high rates of treatment discontinuation. Despite this, the Guidelines Development Group concluded that the benefit of increased SVR outweighed the increased risk of side-effects, and that triple therapy for genotype 1 HCV infection was preferable to dual therapy.

Values and preferences: The inclusion of a DAA to a PEG-IFN and RBV-based regimen was considered to be likely to be acceptable due to the substantially higher chance of SVR. The considerable risk of adverse events would be a deterrent to individuals, particularly as safer medicines are now available. No difficulties were anticipated in relation to unforeseen consequences or cultural contexts. Some difficulty in obtaining high-fat meals for cultural reasons, for example during Ramadan, was considered by the Group but it was thought likely that stakeholders would approve use in the context of medical illness.

Resource considerations: The resources required to treat patients with a PI in addition to PEG-IFN/RBV include treatment costs and the costs associated with increased frequency of laboratory and clinical monitoring. An important barrier to the use of boceprevir and telaprevir is their high cost (US$ 55 000 and US$ 37 000, respectively, in the United Kingdom for a single course of treatment), in addition to the cost of PEG-IFN/RBV.[95,96] Additional costs are related to the need for greater frequency of monitoring for and treatment of adverse events while using these medicines. In high-income settings, an assessment by the National Institute for Health and Clinical Excellence in the UK evaluated DAAs as being cost–effective.[95,96] For patients with mild disease (METAVIR F0–F1), the incremental cost was considered to be small relative to the net benefit. For more advanced disease (F4), due to the increased risk of severe adverse events, this was considered to be less certain and would be likely to require increased monitoring, particularly for evidence of anaemia.

Feasibility is variable in different infrastructure and health-care service settings. While DAA therapy is associated with a marked increase in SVR rate, it is also associated with an increase in the incidence of adverse reactions. Monitoring for these adverse reactions does not require different laboratory tests from those used to monitor IFN and RBV therapy, but does require more frequent clinic visits (primarily to assess rash) and laboratory tests (primarily to assess anaemia). Thus, policy-makers will need to consider the impact on the health system of these additional tests and visits.

Athough persons with more advanced disease have more side-effects and a lower chance of SVR, the potential benefits of achieving SVR are significantly higher. The availability of enhanced monitoring is likely to be highly context-specific in low- and middle-income countries. In countries that can afford triple therapy, it was considered by the Group that it should be feasible to also fund appropriate monitoring.

Implementation

First-generation triple therapy should be given in centres where appropriate clinical and laboratory monitoring can be carried out and where experienced clinicians are available for advice. The availability and cost of first-generation DAAs varies in different countries and is likely to affect the feasibility of roll-out, especially in low-income settings. The duration of therapy is dependent on treatment response and previous response to antiviral therapy (*see* Section 8.2).

HCV/HIV-coinfected persons treated with PEG-IFN/RBV and a first-generation PI who require HIV therapy should be treated with compatible ART (Table 8.3). They require regular monitoring of CD4 counts during treatment.[173]

Research questions

Data on the use of first-generation DAAs in children is an important area for future research. Improvements in virological response may lead to improvements in liver-related morbidity and mortality. However, there are no direct data available from studies to make definite conclusions about longer-term outcomes. Data are also missing on the use of these medicines in low- and middle-income countries.

7.4 Introduction to recommendations concerning sofosbuvir and simeprevir

A number of new medicines to treat HCV infection are in various stages of development. Treatment duration with these medicines is shorter (12–24 weeks) and is associated with fewer side-effects. Some can be administered without IFN and, in some clinical trials, have shown SVR rates of more than 90%. On 22 November 2013, the FDA approved simeprevir and on 5 December 2013, it approved sofosbuvir. On 16 January 2014, the European Medicines Agency approved sofosbuvir for use in the European Union.

7.5 Treatment with sofosbuvir

Sofosbuvir, given in combination with ribavirin with or without pegylated interferon (depending on the HCV genotype), is recommended in genotypes 1, 2, 3 and 4 HCV infection rather than pegylated interferon and ribavirin alone (or no treatment for persons who cannot tolerate interferon).

Strong recommendation, high quality of evidence. This recommendation was made without taking resource use into consideration, as pricing information was not available for any country other than the United States at the time this recommendation was formulated.

Treatment regimens

- For infection with HCV genotypes 1 and 4, sofosbuvir/RBV/PEG-IFN may be given for 12 weeks.
- In persons with genotype 1 infection who are IFN intolerant, sofosbuvir/RBV may be given for 24 weeks, but this regimen will result in substantially lower SVR rates than a PEG-IFN-containing regimen.
- For infection with HCV genotype 2, sofosbuvir/RBV may be given for 12 weeks.
- For infection with HCV genotype 3, sofosbuvir/RBV may be given for 24 weeks or PEG-IFN/RBV/sofosbuvir may be given for 12 weeks.

Background

Sofosbuvir is an HCV viral polymerase nucleotide inhibitor. When used in combination with RBV alone or RBV in combination with PEG-IFN, it is associated with high SVR rates in persons infected with HCV genotypes 1, 2, 3 and 4. At present, treatment with sofosbuvir and RBV is the only all-oral IFN-free treatment available for HCV infection. Eventually, this medicine, whether combined with RBV or other DAAs, may greatly facilitate treatment for HCV and its use may be expanded to health facilities with less sophisticated infrastructure. This medicine is approved for use in North America and Europe, and according to its manufacturer (Gilead Sciences), the wholesale price in the US for a single 12-week regimen is US$ 84 000, which equates to US$ 1 000 per pill.

Evidence

Evidence was considered for trials of sofosbuvir given either with RBV or with RBV/PEG-IFN for infection with HCV genotypes 1, 2, 3 and 4. Only limited data were available for efficacy in persons infected with HCV genotypes 5 or 6.

Data from two studies were reviewed to assess the benefit of 12 weeks of sofosbuvir/PEG-IFN/RBV for treatment-naive persons infected with genotypes 1 and 4.[89,174] Neither study included patients who were treated only with PEG-IFN/RBV (one was a single-arm study and the other compared sofosbuvir/PEG-IFN/RBV to placebo). To assess the treatment benefit of sofosbuvir, a conservative comparator SVR estimate of 65% for PEG-IFN/RBV was assumed.[86] Despite the lack of a direct comparator arm, the quality of evidence for achieving an SVR was considered to be high because of a very large effect size and evidence of a clear dose–response effect (Appendix 4). The combined SVR rate among persons treated with sofosbuvir/PEG-IFN/RBV was 90.3%, and persons receiving this regimen had 253 fewer failures at achieving SVR per 1 000 persons treated than did persons treated with PEG-IFN/RBV. Based on one placebo-controlled trial, the risk of sofosbuvir-associated adverse events leading to treatment discontinuation was estimated to be similar to that among placebo recipients (quality of evidence downgraded to moderate due to imprecision).

No data were available regarding the use of sofosbuvir-based regimens among persons with genotype 1 infection who had been previously treated with PEG-IFN/RBV.

An assessment was made of the oral IFN-free regimen sofosbuvir and RBV given for 24 weeks in genotype 1 infection in treatment-naive persons versus no treatment (assuming IFN intolerance or contraindication).[87] As above, the quality of evidence for efficacy for achieving SVR was considered to be of high quality despite the lack of a direct comparator arm in the studies considered because of a very large effect size and evidence of a clear dose–response effect. The use of RBV/sofosbuvir

therapy was associated with 745 fewer SVR failures per 1 000 people treated as, in the single placebo-controlled study where this was evaluated, all patients with HCV infection in the placebo group failed to achieve an SVR. Despite the lack of direct comparisons between the two regimens, 12 weeks of sofosbuvir with PEG-IFN and RBV results in higher SVR rates than 24 weeks without PEG/IFN.

For persons with genotype 2 infection, the use of 12 weeks of sofosbuvir/RBV versus no treatment was assessed for treatment-naive and -experienced persons. Five single-arm cohorts were considered,[87,88,89,175,176] and 918 fewer SVR failures per 1 000 persons treated (which corresponds to an SVR of 91.8%) was estimated versus 1 000 failures per 1 000 untreated individuals (high quality of evidence, as above).

Four studies were considered in which treatment-naive or -experienced persons with genotype 3 infection were treated with 12 weeks of sofosbuvir/RBV.[87-89,176] An estimated 487 fewer SVR failures per 1 000 were predicted in those treated for 12 weeks but heterogeneity was present due to much lower SVR rates in treatment-experienced patients. In contrast, prolonging treatment to 24 weeks for this group resulted in an estimated 850 fewer SVR failures in those treated with 24 weeks of sofosbuvir/RBV (high quality of evidence). The use of PEG-IFN/RBV/sofosbuvir for 12 weeks versus RBV/sofosbuvir for 24 weeks was predicted to result in 233 fewer SVR failures per 1 000 but 16 more adverse events per 1 000 (very low quality of evidence due to imprecision and indirect comparisons). This analysis included one study with a high prevalence of cirrhosis in the patients.[177]

Rationale for the recommendation

Balance of benefits and harms: The Guidelines Development Group concluded that the benefits of using sofosbuvir far outweighed the risks. The efficacy of sofosbuvir either with RBV alone or RBV and PEG-IFN resulted in much higher SVR rates and a low rate of sofosbuvir-associated adverse events. Persons infected with HCV genotypes 1 and 2 could benefit from a shorter duration of PEG-IFN, and those infected with HCV genotypes 2 and 3 could avoid the difficulties and toxicities associated with PEG-IFN altogether. No significant adverse events were identified in the clinical trials. The Group noted that these results are based on a small number of studies with relatively few participants (a total of approximately 3 000 persons have received sofosbuvir in the various phases 2 and 3 registration trials of sofosbuvir). Although the data were obtained from trials conducted in North America and Europe, they did include some persons of Asian or African origin. No differences in treatment response or safety profile were noted in these persons. The Group also noted that these studies do not include several important subgroups, in particular, treatment-experienced patients with genotype 1 HCV infection and very little data are available for patients with HCV genotype 5 and 6.

Values and preferences: The Group felt that sofosbuvir would be acceptable to patients because of the higher expected SVR rate and the convenience of a shorter treatment course. Patients with genotype 2 or 3 infection would also benefit from an oral-only regimen with few side-effects. For patients with genotype 1 or 4 infections, however, the acceptability may be lowered by the fact that sofosbuvir must be administered with RBV and PEG-IFN, thereby exposing patients to the inconvenience of IFN injections and the toxicity of these two medicines.

Resource considerations: At the time of the meeting of the Guidelines Development Group, pricing information for sofosbuvir was available only from the US where the price for a single 12-week regimen is US$ 84 000. Clearly, the current high price of the medicine will be a significant barrier to its use in all countries. The manufacturer has stated that it "is developing a hepatitis C treatment access programme, focusing on those countries with the greatest HCV burden". However, few details are yet available.[178] Thus, policy-makers might be reluctant to approve the use of the medicine in their country in view of its high price.

For the medicine to be used in other countries, it must be registered with the national drug regulatory agency. This process can take 1–2 years. It will be important for national and international agencies, civil society organizations and pharmaceutical companies to work together to assure rapid approval of this medicine and that it is available at an affordable price.

Implementation

The Guidelines Development Group felt that implementation strategies would be similar for treatment programmes using sofosbuvir in addition to PEG-IFN/RBV treatment regimens as compared with those using PEG-IFN/RBV alone. RBV/sofosbuvir regimens would probably be easier to implement because the complexities of administering IFN could be avoided in infection with some genotypes, the course of treatment is shorter than PEG-IFN/RBV regimens for all genotypes, and monitoring for adverse reactions would be less complex.

Research questions

Evaluation of sofosbuvir in patients who had prior IFN-treatment failure is lacking. The efficacy of sofosbuvir in patients with low levels of adherence requires evaluation In addition, the efficacy of sofosbuvir in patients with genotype 5 and 6 needs further study.

In February 2014, Gilead Sciences announced that it would license sofosbuvir to four generics manufacturers for sale in 60 low-income countries. In March 2014, the manufacturer announced that in Egypt it would market sofosbuvir for US$900 for a 12-week regimen.

7.6 Treatment with simeprevir

Simeprevir, given in combination with pegylated interferon and ribavirin, is recommended for persons with HCV genotype 1b infection and for persons with HCV genotype 1a infection without the Q80K polymorphism rather than pegylated interferon and ribavirin alone.

Strong recommendation, high quality of evidence. This recommendation was made without taking resource use into consideration, as pricing information was not available for any country other than the United States at the time this recommendation was formulated.

Treatment regimens

- Simprevir in combination with PEG-IFN/RBV is given for 12 weeks followed by an additional 12 weeks of PEG-INF/RBV for a total of 24 weeks treatment for all treatment-naive and prior relapsed patients (including those with cirrhosis).
- Prior non-responder patients (including partial or null-responders) should undergo an additional 36 weeks of PEG-INF/RBV for a total of 48 weeks of treatment.
- HCV RNA should be monitored and treatment discontinued if it is >25 IU/mL at weeks 4, 12 or 24.

Background

The simeprevir is associated with high SVR rates when given in combination with PEG-IFN/RBV for treatment-naive and -experienced patients with HCV genotype 1 infection. For the time being, the medicine is approved for use only in the US and Canada, according to its manufacturer (Janssen Pharmaceuticals), the wholesale price in the US for a single 12-week regimen is US$ 66 000.

Evidence

Data were considered from four RCTs comparing simeprevir/RBV/PEG-IFN with PEG-IFN/RBV in persons with chronic HCV infection.[86,179-181] The combined SVR rate for patients treated with simeprevir/RBV/PEG-IFN was 79.2%, and for patients treated with PEG-IFN/RBV it was 45.6% (Appendix 4). This difference would result in 332 fewer SVR failures per 1 000 persons treated (high quality of evidence) and two more serious adverse events per 1 000 persons treated (moderate quality of evidence due to imprecision). Persons with genotype 1a infection with the Q80K mutation (approximately 30% of patients in the included studies) were found to have SVR rates similar to those who received PEG-IFN

and RBV only. And therefore simeprevir is not recommended for persons infected with genotype 1a infection in which the Q80K mutation has been detected. The analysis did not include persons infected with HIV but one single-arm study was available and showed an SVR rate of 74%, similar to that reported in RCTs in HIV-negative individuals.[182]

Rationale for the recommendation

Balance of benefits and harms: The Guidelines Development Group concluded that the benefits of simeprevir were considerable in view of the shorter duration of therapy, the much higher SVR, and the low rate of side-effects. The Group considered that the total number of patients treated with this medicine is small, and that the trials were conducted primarily in Europe and North America. These trials did include persons of Asian and African origin who responded similarly to other persons. Taking into consideration all of these factors (the high SVR rate, shorter duration of treatment and favourable safety profile), the Guidelines Development Group felt that the benefits clearly outweighed the risks.

Values and preferences: It was felt that this medicine would be acceptable to patients because of the shorter duration of therapy and the expectation of a higher SVR. However, the acceptability may be lowered by the fact that it must be administered with RBV and PEG-IFN, thereby exposing patients to the inconvenience of IFN injections and the toxicity of these two medicines. Simeprevir sometimes causes photosensitivity, and the resulting rash may also reduce acceptability.

Resource considerations: At the time of the meeting of the Guidelines Development Group, simeprevir was approved for use only in North America where the wholesale price for a single treatment costs approximately US$ 66 000. The anticipated high cost of simeprevir in other countries is likely to be a significant barrier to its use. Policy-makers might be reluctant to introduce simeprevir into national treatment programmes in view of its high price.

Implementation

Although simeprevir results in high SVR rates, the fact that it is administered with PEG-IFN and RBV means that frequent monitoring for side-effects is necessary. Also, since the Q80K mutation reduces the efficacy of simeprevir, patients must be tested for the presence of this mutation prior to treatment. The availability of this test may be limited in many countries.

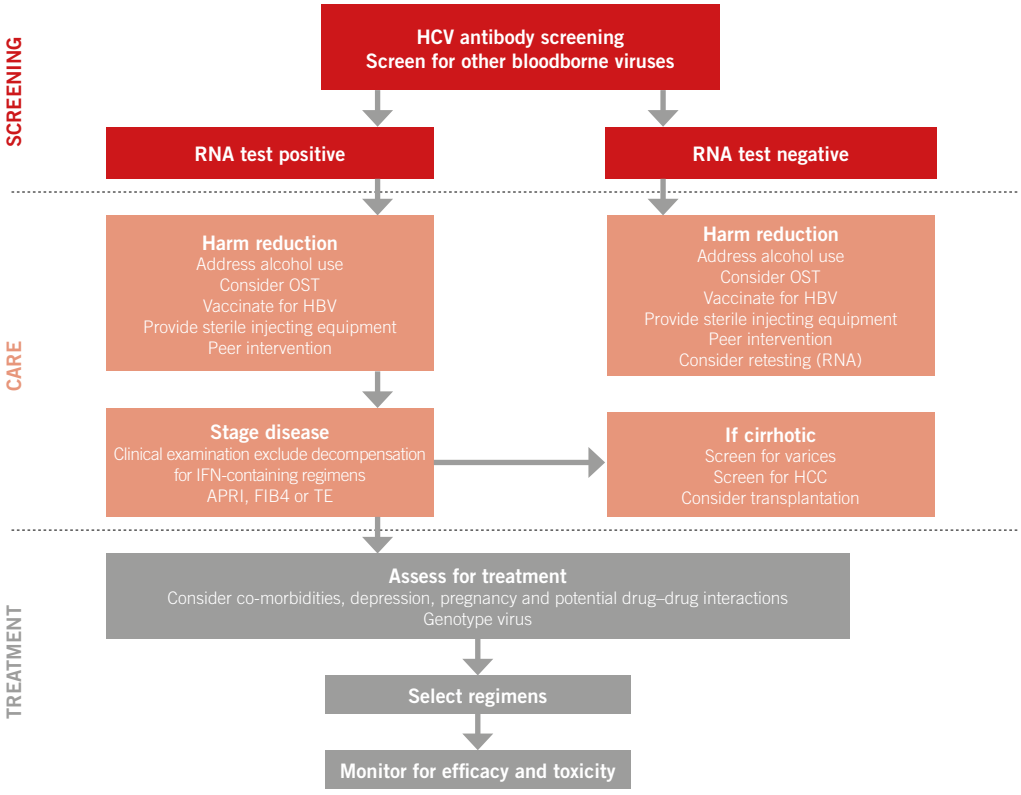
Research questions

Combinations of different DAAs not requiring the use of PEG-IFN are being tested in clinical trials. The use of simeprevir in genotype 4 infection also requires further evaluation.

8. CLINICAL CONSIDERATIONS

A number of clinical considerations are important for the management of persons with chronic HCV infection. Some of these have been included in the Recommendations discussed in Chapter 7. Because of the complexity of the questions involved, the Guidelines Development Group did not formally assess a number of additional considerations. Rather, existing recommendations, guidelines and package insert guidance were reviewed and discussed. These are presented here to assist policy-makers and medical professionals in considering the essential components of a treatment service for HCV infection. A typical patient treatment pathway is shown in Figure 8.1.

FIGURE 8.1 Patient treatment pathway



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

Genotype testing

In most countries, there is a mix of HCV genotypes among persons with chronic HCV infection (*see* Figure 2.1). Certain medicines for treating HCV (e.g. boceprevir, telaprevir and simeprevir) are active only against specific genotypes, while the duration of treatment with other medicines needs to be adjusted based on the genotype. Therefore, knowing a patient's genotype is important to determine 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. This advice would only be practicable in countries such as Egypt, where almost all persons are infected with a single genotype.

Q80K mutation testing

A reduction in the efficacy of treatment with simeprevir was observed in persons with genotype 1a hepatitis C virus where the NS3 Q80K polymorphism was present. The simeprevir drug label therefore includes a recommendation to screen for the presence of this strain prior to beginning therapy and to consider alternative therapy if the Q80K strain is detected. This test is expensive and is not widely available in low- and middle-income countries.

IL28B testing

A number of polymorphisms within the IFN (IL28B) gene have been associated with the likelihood of response to treatment. Favourable genotypes include the CC genotype at rs12979860, TT at rs8099917 and AA at rs12980275.[183,184] These polymorphisms of the IL28B gene are strongly associated with race/ethnicity. Favourable genotypes are more likely to be found in some East Asian and white populations.

Implementing treatment programmes for HCV infection in resource-limited settings does not require the use of prognostic marker tests (e.g. IL28B testing) for predicting treatment response; when available, they are prognostically useful but the absence of availability of these tests should not delay initiation of treatment programmes.

Contraindications to treatment

Treatment for hepatitis C is contraindicated in persons with a number of conditions. Table 8.1 lists these conditions, which are based on the guidelines of

the American Association for the Study of Liver Diseases (AASLD) and European Association for the Study of the Liver (EASL). Treatment of persons who have decompensated cirrhosis (Child–Pugh B or above) with IFN or PEG-IFN is risky, as such persons can develop life-threatening infections and accelerated decompensation leading to death. Pregnant women should not receive RBV 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 IFN will develop depression; in those with pre-existing depression, it can become more severe. There are reports of suicide among persons receiving IFN therapy and therefore careful patient selection is required in persons with depression.

TABLE 8.1 Contraindications to PEG-IFN/RBV therapy

Absolute contraindications
• Uncontrolled depression or psychosis • Uncontrolled epilepsy • Uncontrolled autoimmune disease • Decompensated cirrhosis (Child–Pugh ≥B7 or B6 in HCV/HIV coinfection) • 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 • Hypersensitivity to drugs used to treat HCV
Relative contraindications
• Abnormal haematological indices: - Hb <13 g/dL in men or <12 g/dL in women - 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 • Untreated thyroid disease

Source: Based on guidelines of the American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of Liver Disease (EASL)

Monitoring for adverse reactions and treatment response

Monitoring of persons on treatment for HCV is required in order to prevent and manage toxicity, and to assess the efficacy of treatment. The application of stopping rules when a patient is unlikely to respond to therapy allows the cessation of potentially toxic and expensive therapy. Side-effects range from mild to life threatening, and are detected by laboratory monitoring and on clinical review. Contraindications to therapy are shown in Table 8.1. A technical report on monitoring during treatment was carried out as part of the guidelines development process (Appendix 5). A summary of recommended sampling time points for monitoring is shown in Table 8.2.

TABLE 8.2 Monitoring time points recommended by the American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of Liver Disease (EASL) and drug-registration literature

	TOXICITY			EFFICACY				
Time	FBC, creatinine, ALT	Thyroid function	Adherence, side effects	IFN/ RBV	IFN/ RBV TEL	IFN/ RBV BOC	IFN/ RBV SMV	IFN/ RBV SOF
● Week 0	X	X	X	X	X	X	X	X
● Week 1[a]	X		X					
● Week 2[a]	X		X					
● Week 4	X		X	X	X	X	X	X
● Week 8	X		X			X		
● Week12 EOT[b]	X	X	X	X	X	X	X	X
● Week24 EOT[c]	X	X	X	X	X	X	X	X
● Week 36	X	X	X			X	X	
● Week48 EOT[d]	X	X	X	X	X	X	X	X[d]
● Week 12 after EOT	X		X					
● Week 24 after EOT	X		X	X	X	X	X	X

Incidence of side -effects red highest - yellow lowest

a Time points recommended in EASL but not AASLD guidelines. Additional monitoring is required 1–2 weekly in patients with moderate-to-severe anaemia, thrombocytopenia or neutropenia.

b EOT at 12 weeks is applicable only for patients treated with sofosbuvir.

c EOT: end of treatment depending on genotype, response to treatment, presence of cirrhosis or HIV coinfection

d Sofosbuvir EOT at 48 weeks may be considered in patients with cirrhosis awaiting liver transplant

ALT alanine aminotransferase; BOC boceprevir; FBC full blood count; IFN interferon; RBV ribavirin; TEL telaprevir; SMV simeprevir; SOF sofosbuvir; EOT end of treatment

8.1 Monitoring for toxicity

The side-effect profile of IFN (and PEG-IFN) includes depression, fatigue, flu-like symptoms, neutropenia, thrombocytopenia, anaemia, thyroid imbalance (hyper- or hypothyroidism), lowered absolute CD4+ T cell count in HIV-positive persons, alopecia, arthralgia, anorexia, pneumonitis, and ophthalmological disorders including retinopathy, retinal haemorrhages, cotton wool spots, papilloedema, optic neuropathy and retinal artery or vein obstruction (an eye examination is recommended prior to starting IFN therapy). There may also be marked interactions with other medications in patients with co-morbidity. RBV can cause haemolytic anaemia and is teratogenic. The addition of the PIs boceprevir or telaprevir for genotype 1 infection substantially increases the efficacy of treatment but also increases the likelihood of side-effects. Telaprevir may cause skin reactions, which range from mild to severe, as well as anal discomfort and itching. Boceprevir is associated with dysgeusia (an altered sense of taste) and may also occasionally be associated with rash. Simeprevir is associated with photosensitivity. In addition, an increased incidence of neutropenia, anaemia and thrombocytopenia has been observed in patients receiving triple (with boceprevir or telaprevir) rather than dual therapy. Persons with cirrhosis are at high risk of serious adverse events (40–57%), particularly anaemia and infection.[171,172] Monitoring during treatment with IFN and RBV with or without PI therapy is therefore recommended at multiple time points (Table 8.2). Monitoring at additional time points is required for persons with evidence of side-effects and in persons at highest risk (for example, persons with cirrhosis and HIV coinfection, and those on PI therapy). Additional monitoring of liver function is recommended in persons with cirrhosis, including albumin, bilirubin and coagulation (international normalized ratio [INR]). Patients with evidence of neutropenia, thrombocytopenia and anaemia require 1–2-weekly monitoring.

HCV/HIV coinfection

In persons with HCV/HIV coinfection, IFN-based treatment is 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).[169] A serious concern was that liver failure occurred and was fatal in 6/14 patients. This was associated with cirrhosis with Child–Pugh scores of 5 or more at baseline and didanosine (ddI)-containing regimens.[185] For this reason, ddI and stavudine (d4T) are contraindicated in patients receiving IFN/RBV therapy. More recent studies have shown fewer side-effects as such combinations are now avoided. Depression rates as high as 40% have been recorded when treating patients coinfected with HIV and HCV with IFN therapy. There are also reports of marked weight loss.[186] Severe anaemia, thrombocytopenia and neutropenia are important dose-limiting factors when treating coinfected patients.

Persons coinfected with HCV/HIV treated with PEG-IFN/RBV with or without a PI or sofosbuvir who require treatment for HIV should receive compatible ART (Table 8.3).[177] It is recommended that treating practitioners check potential interactions online as these are frequently updated (http://www.hep-druginteractions.org).

TABLE 8.3 Drug–drug interactions in HIV and HCV treatment

HIV NRTIs	Boceprevir	Telaprevir	Peg-IFN alfa	Ribavirin
Abacavir	◆	■	■	■
Didanosine	◆	◆	■	●
Emitricitabine	◆	◆	■	■
Stavudine	◆	◆	■	■
Zidovudine	■	■	●	●
HIV Protease Inhibitors	**Boceprevir**	**Telaprevir**	**Peg-IFN alfa**	**Ribavirin**
Atazanavir	■	■	◆	■
Darunavir	■	■	◆	◆
Fosamprenavir	■	■	◆	◆
Indinavir	■	■	◆	◆
Lopinavir	■	■	◆	◆
Nelfinavir	■	■	◆	◆
Ritonavir	■	■	◆	◆
Saquinavir	■	■	◆	◆
Tipranavir	■	■	◆	◆
HIV NNRTIs	**Boceprevir**	**Telaprevir**	**Peg-IFN alfa**	**Ribavirin**
Delavirdine	■	■	◆	◆
Efavirenz	■	■	◆	◆
Etravirine	■	◆	◆	◆
Nevirapine	■	■	◆	◆
Rilpivirine	◆	◆	◆	◆
HIV Entry/Integrase	**Boceprevir**	**Telaprevir**	**Peg-IFN alfa**	**Ribavirin**
Elvitegravir/cobicistat	■	■	◆	◆
Maraviroc	■	■	◆	◆
Raltegravir	◆	◆	◆	◆

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

Source: adapted from http://www.hep-druginteractions.org

Liver cirrhosis

The CUPIC study[171,172] found a very high risk of side-effects in treatment-experienced patients with compensated cirrhosis treated with PEG-IFN, RBV and either boceprevir or telaprevir. Among patients who received at least 16 weeks of treatment, 40% of patients developed a serious adverse event and 11.7% had to cease therapy. Six patients died; five from severe infection and one from oesophageal variceal haemorrhage. Hepatic decompensation occurred in 2.4% of patients (manifesting as ascites, encephalopathy or variceal bleeding).

8.2 Dose modification

Recommendations for dose modification based on abnormal haematological parameters are summarized below and in Table 8.4, based on the relevant product literature.[187,188]

TABLE 8.4 Dose modifications recommended in the product literature for pegylated interferon and ribavirin

	Reduce IFN dose	Discontinue IFN
Neutrophil count	At <0.75 cells x10^9/L reduce to 135 µg PEG-IFNα2a. At <0.75 cells x10^9/L PEG-IFNα2b should be reduced in increments of 0.5 µg/kg/week, e.g. from 1.5 µg/kg/week to 1 µg/kg/week and then if required to 0.5 µg/kg/week.	At <0.5 cells x10^9/L PEG-IFNα2a treatment should be suspended until neutrophils reach >1.0 cells x10^9/L Reinstitute at a dose of 90 µg and monitor. At <0.5 cells x10^9/L PEG-IFNα2b should be permanently discontinued.
Platelets	25–50 cells x10^9/L reduce dose of IFN to 90 µg or reduce PEG-IFNα2b as above.	<25 cells x10^9/L discontinue PEG-IFNα2a and PEG-IFNα2b.
Haemoglobin	When Hb <10 g/dL reduce RBV to 600 mg/day when given with PEG-IFNα2a. When Hb <10 g/dL, the starting dose of RBV should be reduced sequentially by 200 mg when given with PEG-IFNα2b (unless starting dose is 1 400 mg when reduction should be to 1 000 mg).	Discontinue PEG-IFN permanently if Hb is <8.5 g/dL.

Dose adjustment of ribavirin

Anaemia is a common side-effect of RBV therapy and dose adjustment is often required. Patients whose haemoglobin (Hb) level falls below 10 g/dL should have their RBV dose reduced. A patient whose Hb level falls below 8.5 g/dL should discontinue therapy. For patients with a history of stable cardiovascular disease, RBV dose reduction 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 RBV in patients with renal failure must also be adjusted; patients with creatinine clearance <50 mL/min should not be treated with RBV 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.

Dose adjustment of interferon

Discontinuation of PEG-IFNα2b is recommended if the Hb is <8.5 g/dL (or <12 g/dL after 4 weeks of dose reduction in patients with cardiac failure), total white blood cell count <1.0 x 10^9/L, neutrophil count <0.5 x 10^9/L, platelet count <25 x 10^9/L in patients with genotype 1 infection or <50 x 10^9/L in those with non-genotype 1 infection, bilirubin (direct) 2.5 x upper limit of normal, total bilirubin (>4 mg/dL for >4 weeks), creatinine >2.0 mg/dL or ALT/AST 2 x baseline and >10 x upper limit of normal.

Discontinuation of PEG-IFNα2a is recommended if the platelet count is <25 x 10^9/L, Hb <8.5 g/L or the Hb is <12 g/dL despite 4 weeks of dose adjustment in patients with cardiac failure.

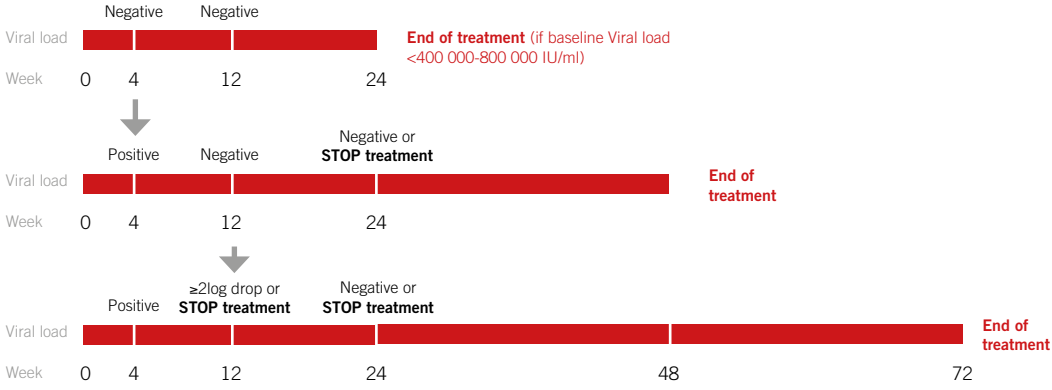
In patients with end-stage renal disease (creatinine clearance 20–40 mL/min), a starting dose of PEG-IFNα2a of 135 µg once a week should be used.

8.3 Monitoring for efficacy

Stopping rules and recommended duration of treatment depends on the stage of disease (cirrhosis versus mild-to-moderate disease), previous treatment failure response (null response, partial response or relapse), genotype and on the results of HCV viral load testing while on treatment (Figure 8.2). Treatment recommendations on stopping rules and monitoring for efficacy are illustrated further in Appendix 5 for persons with genotype 1 infection receiving PEG-IFN/RBV and either boceprevir or telaprevir. Longer treatment regimens may be given in slow virological responders and persons with HIV or cirrhosis. For example, in the PRESCO study, higher weight-based dosing of RBV was used and treatment duration was extended from 48 to 72 weeks. This improved the SVR rate in genotype 1-infected HIV-positive persons (53% versus 31%).[189] Premature

treatment discontinuation was common, however, and occurred in 45% in the prolonged treatment arm (2.6% due to severe anaemia). Extension of treatment duration from 24 to 48 weeks in genotype 2/3 infection also resulted in a higher SVR rate (82% versus 67%).

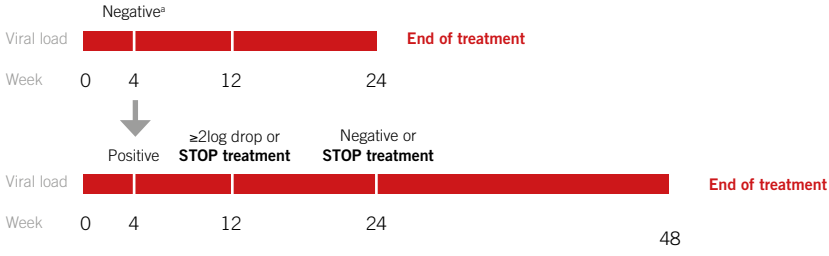
FIGURE 8.2A Duration of pegylated interferon and ribavirin therapy for infection with HCV genotypes 1 and 4



PEG-INF/RBV

PEG-IFN and RBV used in combination to treat genotypes 1 and 4 chronic HCV infection may be given for varying durations depending on treatment response. If the viral load drops less than 2 log at 12 weeks or is detectable at 24 weeks of therapy, treatment should be stopped. An extended rapid virological response (eRVR) is associated with a high likelihood of SVR and therefore a reduced treatment duration of 24 weeks can be considered if the baseline viral load is <400 000–800 000 IU/mL. Conversely, if patients have a slow virological response with a detectable viral load at 12 weeks of treatment (and a ≥2 log drop) with a negative viral load at week 24 (delayed virological response; DVR), a prolonged 72-week course of therapy can be considered.

FIGURE 8.2B Duration of pegylated interferon and ribavirin therapy for genotypes 2, 3, 5 and 6



PEG-INF/RBV

Pegylated IFN and RBV used in combination to treat chronic HCV infection with genotypes 2, 3, 5 and 6 may be given for varying durations depending on treatment response. If the viral load drops by less than 2 log at 12 weeks or is detectable at 24 weeks of therapy, treatment should be stopped. An extended rapid virological response (eRVR) is associated with a high likelihood of SVR and therefore a reduced treatment duration of 24 weeks can be considered. Conversely, if patients have a slow virological response with a detectable viral load at 12 weeks of treatment (and a ≥2 log drop) with a negative viral load at week 24 (delayed virological response; DVR), a prolonged 48-week course of therapy can be considered.

a. A shortened course of 12–16 weeks of therapy may be considered in patients with HCV genotypes 2 and 3 and an RVR (there is a slight reduction in final SVR rates).

9. SPECIAL CONSIDERATIONS FOR SPECIFIC POPULATIONS

Specialist care needs to address the additional needs of special populations of patients, including PWID, persons coinfected with (or at risk for infection with) HIV, children and adolescents, and those with cirrhosis.

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. Approximately 67% of PWID are infected with HCV; 10 million of 16 million people in 148 countries.[6] PWID are at increased risk of HCV-related disease and all-cause morbidity and mortality, and therefore require specialized care.[38] Related guidance is summarized below, and in section 2.4 and Figure 8.1. When caring for PWID, the central tenets of respect and non-discrimination should be followed, and additional adherence and psychological support given as required.

Screening

As an integral component of a comprehensive package of harm reduction interventions, WHO recommends targeted HCV screening of PWID as a population with a high prevalence of infection. Repeated screening is required in individuals at ongoing risk, 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. 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 could be seen.[97] Screening for HBV and HIV is also recommended in PWID.

Care

Treatment of HCV in PWID requires integration of services, as other health-care needs are often also present. Dependency on opiates or other substances may be present and alcohol excess is also a common problem in PWID. Harm reduction strategies are required in order to prevent acquisition of 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.

Drug dependency services may be required for the provision of opioid substitution therapy and sterile injection equipment. In addition, alcohol reduction strategies may be required and HIV treatment may also be necessary. 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.[d] Guidance on brief behavioural interventions is available as part of the WHO ASSIST package.

PWID are at risk of infection with HBV and should be vaccinated using the rapid vaccination regimen, as described in other WHO guidance.[190] Needle and syringe programmes should also provide sterile needles and syringes with low dead space to PWID. It is also suggested that peer interventions be offered to PWID to reduce the incidence of viral hepatitis.

Treatment

Treatment for HCV infection is both efficacious and cost–effective in PWID[164,191,192] and therefore WHO recommends that all adults and children with chronic HCV infection, including PWID, should be assessed for antiviral treatment. Treatment may also be effective as prevention, due to a reduction in transmission.[97,98,99]

Consideration must be given to potential drug–drug interactions – between both prescribed and non-prescribed drugs.[e] Methadone levels may be decreased in persons treated with PEG-IFN/RBV, for example. Although this interaction is usually subclinical, monitoring for symptoms of withdrawal is recommended.

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

9.2 Persons with HIV and HCV coinfection

Coinfection with HIV and HCV poses a challenge because of the large number of persons affected, the negative impact of HIV on the natural history of HCV infection, and the therapeutic challenges of dealing with interactions between the drugs used for treating HIV and HCV infections.

Both ART and treatment for HCV infection may slow the progression of HCV-related liver disease; therefore, treating both infections is a priority for persons with HIV/HCV coinfection.[193] As the management of these infections is complex, it is advisable to provide treatment in an integrated fashion by clinicians familiar with the treatment of both infections.

d. WHO advice on interventions for individuals using alcohol and recreational drugs is available at http://www.who.int/substance_abuse.

e. Up-to-date guidance on prescribed and recreational drug interactions is available online at http://www.hep-druginteractions.org/.

Treatment of HCV infection

In HIV/HCV coinfected persons, there is more rapid progression of HCV-related liver disease, and treatment for HCV may slow the progression of hepatic fibrosis and/or delay the onset of clinical consequences of decompensated cirrhosis. Therefore, treatment of HCV is a priority for persons with HIV/HCV coinfection.

The decision to initiate treatment for HCV is more complex than in those with HCV monoinfection, as response rates are lower, risk of potential toxicities is higher and treatment is complicated by a high pill burden, overlapping toxicities, and interactions between drugs used for treating HCV and HIV. In general, clinical stabilization of HIV disease with ART is advisable prior to starting treatment for HCV, especially in persons with advanced immunosuppression (CD4 count <200 cells/mm^3). In these situations, since HCV RNA suppression is greater in coinfected persons with CD4 counts higher than 450 cells/mm^3,[194] it may be preferable to initiate ART and delay therapy for HCV until CD4 counts increase as a result of ART.

HCV infection among persons with HIV coinfection can be treated with PEG-IFN/RBV. (For comments regarding response rates and duration of treatment, *see* Section 7.1.) These persons can also be treated with PEG-IFN/RBV and boceprevir, telaprevir or simeprevir (for genotype 1 infection) and may also be treated with sofosbuvir/RBV or PEG-IFN/RBV/sofosbuvir. Persons coinfected with HCV/HIV treated with PEG-IFN/RBV with or without an additional agent (PI or sofosbuvir) who require treatment for HIV should receive compatible ART (Table 8.3).[177]

Persons with HIV require special consideration regarding the selection of an antiretroviral regimen. The safety profile in HCV/HIV-1 coinfected subjects treated with sofosbuvir is similar to that observed in HCV-monoinfected subjects. Elevated total bilirubin (grade 3 or 4) occurs extremely commonly in persons treated with sofosbuvir and atazanavir as part of the antiretroviral regimen. Tipranivir/sofosbuvir is not recommended but darunavir/ritonavir, efavirenz, emtricitabine, raltegravir, rilpivirine and tenofovir have been tested and no dose adjustment is currently recommended.

Simeprevir is not recommended to be used with several HIV treatment regimens, including cobistat, the non-nucleoside reverse transcriptase inhibitors (NNRTIs) efavirenz, nevirapine, delavirdine, etravirine and any HIV PI-containing regimen.[196]

Antiretroviral therapy in persons with HIV/HCV coinfection

In 2013, WHO updated its recommendations on the use of ART in adults, adolescents, pregnant women and children.[197] Tables 9.1 and 9.2 summarize the key recommendations on timing of ART and first-line ART regimens. These

recommendations state that ART among people coinfected with HCV should follow the same principles as in HIV monoinfection. Initiating ART regardless of CD4 cell count was not recommended because of lack of evidence regarding the benefit of ART for persons with a CD4 count higher than 500 cells/mm^3. The choice of ART for persons with coinfection is the same as for those with HIV alone. The principal recommendations of the 2013 consolidated guidelines are summarized in Table 9.1.[197]

TABLE 9.1 Summary of recommendations for when to initiate ART in adults and adolescents[197]

- As a priority, ART should be initiated in all individuals with severe or advanced HIV clinical disease (WHO clinical stage 3 or 4) and individuals with CD4 counts ≤350 cells/mm^3 (*strong recommendation, moderate-quality evidence*).
- ART should be initiated in all individuals with HIV with a CD4 count between 350 and 500 cells/mm^3 regardless of WHO clinical stage (*strong recommendation, moderate-quality evidence*).
- ART should be initiated in all individuals with HIV regardless of WHO clinical stage or CD4 count in the following situations:
  - Individuals with HIV and active TB disease (*strong recommendation, low-quality evidence*)
  - Individuals coinfected with HIV and HBV with evidence of severe chronic liver disease (*strong recommendation, low-quality evidence*)
  - Partners with HIV in serodiscordant couples should be offered ART to reduce HIV transmission to uninfected partners (*strong recommendation, high-quality evidence*)
  - Pregnant and breastfeeding women with HIV.[a]
- All children infected with HIV below five years of age, regardless of CD4 count or WHO clinical stage
  - Infants diagnosed in the first year of life (*strong recommendation, moderate-quality evidence*)
  - Children infected with HIV between one and less than five years of age (*conditional recommendation, very low-quality evidence*); severe or advanced symptomatic disease (WHO clinical stage 3 or 4) regardless of age and CD4 count (*strong recommendation, moderate-quality evidence*).

a. All pregnant and breastfeeding women infected with HIV should initiate a triple antiretroviral (ARV) regimen, which should be maintained at least for the duration of risk of mother-to-child transmission. Women meeting treatment eligibility criteria should continue lifelong ART (strong recommendation, moderate-quality evidence).

For programmatic and operational reasons, particularly in generalized epidemics, all pregnant and breastfeeding women infected with HIV should initiate ART as lifelong treatment (conditional recommendation, low-quality evidence).

In some countries, for women who are not eligible for ART for their own health, consideration can be given to stopping the ARV regimen after the period of risk for mother-to-child transmission has ceased (conditional recommendation, low-quality evidence).

TABLE 9.2 Summary of first-line ART regimens for adults, adolescents, pregnant and breastfeeding women and children[197]

First-line ART	Preferred first-line regimens	Alternative first-line regimens[a,b]
Adults and adolescents (including pregnant and breastfeeding women and adults with TB coinfection and HBV coinfection)	TDF + 3TC (or FTC) + EFV as a fixed-dose combination (*strong recommendation, moderate-quality evidence*)	AZT + 3TC + EFV AZT + 3TC + NVP TDF + 3TC (or FTC) + NVP (*strong recommendation, moderate-quality evidence*)
Children ≥3 years	ABC + 3TC + EFV	ABC + 3TC + NVP AZT + 3TC + EFV AZT + 3TC + NVP TDF + 3TC (or FTC) + EFV TDF + 3TC (or FTC) + NVP
Children <3 years	ABC (or AZT) + 3TC + LPV/r	ABC + 3TC + NVP AZT + 3TC + NVP

3TC lamivudine; ABC abacavir; ATV atazanavir; AZT zidovudine; d4T stavudine; DRV darunavir; EFV efavirenz; FTC emtricitabine; LPV lopinavir; NVP nevirapine; r ritonavir; TDF tenofovir

a. ABC or boosted PIs (ATV/r, DRV/r , LPV/r) can be used in special circumstances.

b. Countries should discontinue d4T use in first-line regimens because of its well-recognized metabolic toxicities (strong recommendation, moderate-quality evidence). For adults, using d4T as an option in first-line treatment should be discontinued and restricted to special cases in which other ARV drugs cannot be used and to the shortest time possible, with close monitoring. For children, d4T use should be restricted to situations in which there is suspected or confirmed toxicity to AZT and lack of access to ABC or TDF. The duration of therapy with this drug should be limited to the shortest time possible.

Potential harmful effects of antiretroviral (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.[198-200] 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), nevirapine (NVP) or full-dose ritonavir (RTV, 600 mg twice a day).[201] 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 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.

Drug–drug interactions in persons with HIV/HCV coinfection

Assessment of potential drug–drug interactions is of critical significance in HIV-infected persons who are about to start HCV treatment (Table 8.3). Careful consideration of such interactions is important to avoid toxicity and to ensure efficacy of the regimens used to treat both HIV and HCV in order to avoid the development of ARV resistance and to increase the likelihood of SVR. Reported interactions are updated on a regular basis and therefore consultation with a frequently updated database is strongly recommended.[f]

Interactions between NRTIs have been reported in persons treated with dual IFN/RBV-based therapy. The use of ddI, d4T and AZT is associated with an increased risk of toxicities and these drugs are therefore contraindicated.[202-205] Abacavir (ABC) can be used with RBV, but a theoretical interaction has been reported to be associated with decreased SVR rates in some[206] but not all studies;[207,208] some guidelines have recommended that the use of RBV should be weight based and dose adjusted. Tenofovir (TDF) and emtricitabine (FTC) or lamivudine (3TC)-based regimens are appropriate.

Additional drug–drug interactions must be considered when using other DAAs. If patients are commencing ART and DAAs are not being considered, standard first-line ART may be used (as long as this does not include zidovudine [AZT], d4T or ddI). Efavirenz may also be used but the dose of telaprevir must be increased. Boceprevir can be administered with raltegravir (RAL), TDF plus FTC; pharmacokinetic data also support the use of etravirine, rilpivirine and maraviroc as alternatives. Telaprevir can be used with either RAL or standard-dose RTV-boosted atazanavir; pharmacokinetic data also support etravirine, rilpivirine and maraviroc as alternatives.

Monitoring of therapy in persons with HIV/HCV coinfecion

IFN-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).[169] CD4 count monitoring is therefore recommended in coinfected persons on treatment. A higher risk of haematological suppression is also present in HIV-infected individuals; these are important dose-limiting side-effects, especially with co-administration of certain ARV drugs.

Monitoring during IFN and RBV treatment with or without PI therapy is therefore recommended at multiple time points (Table 8.2). 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 PI therapy). Additional monitoring of liver function is recommended in persons with cirrhosis, including

f. Drug interactions can be checked at the Liverpool HIV drug interaction database (www.hep-druginteractions.org).

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

9.3 Children and adolescents

WHO defines a child as an individual 19 years of age or younger and 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. In Egypt, for example, approximately 2% of children are infected.[209] This rate is substantially higher in at-risk populations, such as those exposed to medical intervention. Iatrogenic transmission has been reported in hospitals[34] and 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.[210-215] Treatment is licensed for children older than 2 years of age. The product literature for PEG-IFNα2a reports that paediatric subjects treated with RBV 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).

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 5% and is substantially higher in infants born to HIV-infected mothers (17–25%).[17,18]

Care

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

Treatment

Treatment success rates are similar in adults and children, although fewer studies have been carried out in children. In particular, the use of DAAs has been inadequately studied in children as they were excluded from the phase III studies of these medicines.[84,85] One systematic review reported on

the virological outcomes and adverse effects of IFN/RBV treatment among children.[153] This review included four RCTs and 31 non-randomized studies. The overall SVR rate for PEG-IFN and RBV was 30–100%, which is comparable to SVR rates seen in adults. Adverse effects were primarily flu-like symptoms and neutropenia.

9.4 Persons with liver cirrhosis

The spectrum of disease in those infected with HCV extends from mild fibrosis to 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[216] and in those coinfected with HBV and/or HIV, particularly those who do not have access to ART.[60,61] Persons with compensated cirrhosis have the least time available for treatment, the most to lose and much to gain from achieving SVR. Treatment of HCV infection with IFN-containing regimens must be commenced before the onset of decompensated disease as it may precipitate liver failure and death if administered at this stage.

Regular clinical examination and monitoring of serum bilirubin, albumin and blood clotting profile (INR) is necessary in persons with cirrhosis on IFN-based treatment in order to detect decompensated disease. The treatment of such persons with IFN-containing regimens carries a higher risk of serious side-effects and the use of haemopoietic factors is recommended in settings where these are available.[110]

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 a 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.[110]

9.5 Persons with HBV and TB coinfection

HBV and HCV coinfection

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 similar to those of HCV-monoinfected persons.[51,217] After HCV clearance, there is a risk of HBV reactivation and this may require treatment with concurrent anti-HBV antiviral therapy.[199,g] Telbivudine, in particular, may be associated with a higher risk of neuropathy if given with IFN-containing regimens.

TB and HCV coinfection

Severe concurrent infections such as TB should generally be treated before commencing therapy for HCV. WHO recommends regular screening of people living with HIV (including PWID) with a four-symptom screening algorithm to rule out TB. 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 they should undergo further investigations for TB or other diseases. ART should be initiated with persons with HIV-associated TB as soon as possible, regardless of CD4 count. There are limited reported data on the co-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 drug–drug interactions. Potential interactions can be checked online.[g]

9.6 Persons with renal impairment

Both ribavirin and PEG-IFN require dose adjustment in persons with renal failure, and baseline testing of renal function is required before initiating therapy. PEG-IFNα2a is cleared by the liver and PEG-IFNα2b via the kidneys. While a theoretical accumulation of PEG-IFNα2b could occur in persons with haemodialysis, no differences have been reported clinically.[200,201] Sofosbuvir is excreted by the kidney; however, there are no data regarding the safety of this medication among persons with renal impairment.

In persons with end-stage renal disease (creatinine clearance 20–40 mL/min), a reduced dose of PEG-IFNα2a 135 µg once a week is recommended. The dose of RBV must also be decreased.

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

g. Drug–drug interactions can be checked online at http://www.hep-druginteractions.org.

10. OPERATIONAL AND IMPLEMENTATION ISSUES

Scaling up access to treatment for people infected with HCV in low- and middle-income countries requires careful consideration of resource availability in individual settings. A high-income model of specialist care with a high physician-to-patient ratio and availability of advanced laboratory monitoring is not feasible in many countries and therefore service delivery plans need to be adapted accordingly. A public health care-based approach to improve access to health care for people infected with TB and HIV has been promoted by WHO and has resulted in improved health care in many resource-limited settings.[219] The roll-out of screening, care and treatment for HCV in low- and middle-income countries will require an assessment of many of the same issues already addressed by TB and HIV treatment programmes, and similar approaches are likely to be effective.

10.1 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.[107] 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 HCV. Improvements in molecular tools for rapid screening, including dried blood spot and oral fluid testing, as well as polyvalent PCR platforms, would increase the numbers 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 IFN, 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.

10.2 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 of potential drug–drug interactions 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.[4]

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 (including algorithms for the use of first- and second-generation DAAs) developed. Such algorithms should include information on when to start therapy, when to stop, follow up, side-effects and management flow sheets. Management of drug–drug interactions is important, particularly in those infected with HIV. For example, drugs such as AZT, ddI and d4T used widely in low-income settings are not recommended in persons treated with IFN and RBV. 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 low- and middle-income countries has been developed by Médecins Sans Frontières.[166]

10.3 Future considerations

The treatment landscape for HCV is in a phase of rapid transformation, and adaptations will be required as soon as new drugs are approved. Curative treatments that are more efficacious and less toxic than ever before have the potential to dramatically reduce the health and economic burdens associated with HCV infection around the world. The opportunity to address the massive HCV pandemic is now within reach and a global movement is needed to

create generalized access to HCV treatment in high-, middle- and low-income countries. This will require political will, financial investment, and support from pharmaceutical, medical and civil society organizations around the world.

10.4 Dissemination, monitoring and implementation of the Guidelines for the screening, care and treatment of persons with hepatitis C infection

The guidelines will be launched at the annual meeting of the European Society for the Study of the Liver (April 2014). The Secretariat will identify other international conference venues to present the recommendations. The Secretariat staff will work with the hepatitis points of contact in the WHO regional offices to ensure dissemination to WHO country offices and Ministries of Health as well as key international, regional and national collaborating centres (e.g. civil society, foundations, donors), and national programmes. In addition, the guidelines will be accessible on the WHO website with links to other UN/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 guidelines. This will be monitored through the biannual survey that forms the basis for the *WHO Global policy report on the prevention and control of viral hepatitis*. 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.

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