World Health Organization

NEW RECOMMENDATIONS IN THE UPDATED WHO

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

POLICY BRIEF

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WHO/HIV/2016.01

Design and layout: blossoming.it

Printed by the WHO Document Production Services, Geneva, Switzerland

WHY IS WHO UPDATING ITS HEPATITIS C TREATMENT GUIDELINES?

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

The World Health Organization (WHO) issued the first *Guidelines for the screening, care and treatment of persons with hepatitis C infection* in 2014. Since then, several new medicines for the treatment of HCV infection have been introduced. Of these, daclatasvir, ledipasvir, and a combination of ombitasvir, paritaprevir and dasabuvir were added to the WHO Model List of Essential Medicines in 2015. These medicines are transforming the treatment of HCV, enabling the use of regimens that can be administered orally, are shorter in duration (as short as eight weeks), result in cure rates higher than 90%, and are associated with fewer serious adverse events (SAEs) than the previous interferon-containing regimens.

The objectives of these updated WHO Guidelines are to provide evidence-based recommendations for the treatment of persons with hepatitis C infection using, where possible, all-oral combinations of these new medicines, also called direct-acting antivirals (DAAs). The Guidelines also provide recommendations on the preferred regimens based on a patient's HCV genotype and clinical history, and assess the appropriateness of continued use of the existing medicines. The key audience for these guidelines are policy-makers in low- and middle-income countries who formulate country-specific treatment guidelines, and who plan infectious disease treatment programmes and services, in addition to those people responsible for delivering treatment. The Guidelines are appropriate for all countries, including high-income countries.

1. WHAT ARE THE NEW RECOMMENDATIONS IN THE UPDATED GUIDELINES?

1.1 Treatment with direct-acting antiviral agents

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

Strong recommendation, moderate quality of evidence

Specific subgroup consideration

For patients with HCV genotype 3 infection with cirrhosis, and patients with genotypes 5 and 6 infection with and without cirrhosis, sofosbuvir/pegylated interferon and ribavirin is still recommended as an alternative treatment option.

Treatment with DAA-based regimens have a short duration, are easy to administer (given orally), have a lower pill burden (as few as one pill/day), are very effective (sustained virological response [SVR] rates of ≥90%) and well tolerated, with few adverse events. Thus, they have the potential to be the basis for a large expansion in the number of persons treated. However, not all persons with HCV infection can be treated with DAAs alone, as pegylated interferon and/or ribavirin are needed for some genotypes.

1.2 Removal of recommendation for treatment with telaprevir or boceprevir

Boceprevir- or telaprevir-containing regimens are no longer recommended for the treatment of persons with hepatitis C infection.

Strong recommendation, moderate quality of evidence

Telaprevir and boceprevir are first-generation protease inhibitors, which when administered with pegylated interferon/ribavirin to persons infected with HCV genotype 1, result in higher SVR rates as compared with pegylated interferon and ribavirin alone. As a result, they were included in the WHO 2014 *Guidelines for the screening, care and treatment of persons with hepatitis C infection* for consideration of treatment for genotype 1 HCV infection. However, these regimens result in high rates of SAEs. Compared with the newer DAAs, the treatment effectiveness of telaprevir- or boceprevir-containing regimens is lower and adverse effects are more frequent, and thus telaprevir- or boceprevir-containing regimens are no longer recommended by WHO.

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

TABLE 1 Summary of recommended preferred regimens with treatment durations*

PATIENTS WITHOUT CIRRHOSIS

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

PATIENTS WITH CIRRHOSIS

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

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

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

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

TABLE 2 Summary of recommended alternative regimens with treatment durations*

PATIENTS WITHOUT CIRRHOSIS

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

PATIENTS WITH CIRRHOSIS

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

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

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

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

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

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

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

The updated guidelines provide recommendations on the preferred and alternative DAA regimens by HCV genotype and cirrhosis status. The selected preferred and alternative regimens provide clinicians with the choice of prescribing interferon-free regimens for everyone (except patients who have both cirrhosis and genotype 3 infection, and those infected with genotypes 5 and 6). This dramatically simplifies implementation by lessening the requirement for genotype testing and reducing the risk of treatment discontinuation due to adverse events. Unfortunately, it is not yet possible to recommend a single regimen that could be used for all patients with HCV infection regardless of HCV genotype or degree of cirrhosis and previous treatment experience. It is anticipated that improved, truly pangenotypic regimens will soon become available.

How were these regimens selected?

The recommendations were produced using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) method. Systematic reviews and network meta-analyses were conducted using evidence from all available clinical trials to assess the comparative efficacy and safety of antivirals for the treatment of HCV infection. Pooled proportions for SVR, SAEs, and treatment discontinuation and mortality rates were calculated for each regimen by genotype, stage of disease (with cirrhosis or without cirrhosis) and previous treatment experience.

The acceptability of different regimens from a patient's perspective was classified as "high", "moderate" and "low" depending on the requirement of ribavirin or interferon, the number of doses/day and the frequency of drug–drug interactions. Preferred regimens were those that had high efficacy and safety, and had a dosage schedule that was highly acceptable. Safe and effective regimens with moderate or low acceptability were classified as "alternative regimens". Based on this, decision-makers are then able to choose from these preferred options based on local price, availability and feasibility of use.

Implementation considerations

DAA-only therapy is easier to administer and requires less patient monitoring than interferon-containing therapy; therefore, it could be administered in non-specialized clinical settings such as primary-care clinics by health cadres such as primary-care doctors. This would lead to the availability of treatment in a wider range of settings, including those with populations such as people who inject drugs (PWID) and migrants, who are at high risk of infection but who have difficulty in accessing treatment services. As the recommended regimens vary by genotype, genotyping is still required except perhaps in countries where a single genotype predominates. However, other health system requirements, such as the need for laboratory monitoring, will be reduced because the treatment duration is shorter and the need for laboratory monitoring is less intense than with interferon-containing regimens due to less frequent adverse reactions to the medicines.

Cost and budget impact of implementing treatment with new DAAs

Initial prices of DAAs were prohibitively high. However, the prices of DAAs are falling in a number of countries as a result of price negotiations with the manufacturers, and through the introduction and registration of generic medicines. As a result of these lower prices, budget impact analyses demonstrate that in some countries, expanding access to treatment using interferon-free regimens will be less costly and result in better rates of cure than if traditional pegylated interferon-based regimens are used.

2. PRIORITIZATION

A key question in implementing these recommendations is who should receive treatment. WHO is not making a recommendation regarding this, but guidelines of other organizations (e.g. AASLD and EASL) now recommend that all persons with HCV infection should receive treatment. Despite this, the scaling up of treatment is likely to remain restricted in many countries because of the continued high prices of medicines and lack of health-care infrastructure (e.g. lack of laboratory capacity or trained health-care workers). Policy-makers will be faced with the challenge of how to prioritize treatment given limited resources. Therefore, it is important to have a framework to help policy-makers decide who to prioritize for treatment.

Two broad criteria can be used to prioritize treatment: (i) minimizing mortality and morbidity by prioritizing those people with advanced HCV-related liver disease or who have factors that make them more likely to progress to cirrhosis; and (ii) maximizing the prevention benefit by prioritizing people at highest risk of transmitting HCV infection, for example, PWID. These factors are summarized below to assist policy-makers in making decisions on how best to prioritize treatment allocation.

Factors to be considered in prioritizing treatment

- Increased risk of death:
  - advanced fibrosis and cirrhosis
  - post-liver transplantation
- Risk of accelerated fibrosis:
  - coinfection with either HIV or hepatitis B virus (HBV)
  - metabolic syndrome
- Extrahepatic manifestations and evidence of end-organ damage
  - debilitating fatigue
  - vasculitis and lymphoproliferative disorders
- Significant psychosocial morbidity (due to stigma, discrimination, fear of transmission to others)
- Maximizing reduction in incidence:
  - PWID
  - men who have sex with men (MSM)
  - prisoners
  - sex workers
  - women with childbearing potential
  - health-care workers

3. PLANS FOR UPDATING

The interim guidelines will be updated regularly as more medicines become available and new evidence is published. The updated *Guidelines for the screening, care and treatment of persons with hepatitis C infection*, which will include these new recommendations in addition to recommendations on screening and care, will be released in April 2016.

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WHO/HIV/2016.01