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Medical Guidelines

# Recommendations for Diagnosis, Treatment & Monitoring of Chronic HCV Infection in Adults

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## Introduction

### Objectives

Aim of present recommendations is to optimize Hepatitis C related patient care informed by best available evidence and broad consensus to improve clinical and public health outcomes. The aim is to provide recommendations that are relevant for the confined regional epidemiology of hepatitis C infection as well as healthcare delivery mechanism in Pakistan.

These recommendations are adapted from World Health Organization (WHO) guide for hepatitis C virus infection targeted particularly for low and middle income countries (LMICs), presenting high burden of disease while treatment is readily available and costs of direct-acting antivirals (DAAs) are on the decline.

### Target audience

HCV treatment pathway can now be simplified to diagnostic algorithms and easily replicated by non-specialists in diverse settings to diagnose, assess and treat HCV infection. Therefore, these recommendations are intended to present as reference to healthcare professionals who offer or implement diagnostics and medication to individuals suffering from hepatitis C.

### Scope

This document supports clinical practice by making recommendations on the screening, assessment, evaluation, and management of clinically stable HCV-infected persons.

## Background

### HCV Disease Burden and Elimination Targets

Infection with hepatitis C virus causes liver disease, which leads to the complications comprising hepatocellular carcinoma and liver cirrhosis. The global burden with hepatitis C has significant impact, distressing about 71 million people and responsible for 400,00 annual demises associated with its complications.[1,2]

In 2016, the WHO adopted the first Global health sector strategy on viral hepatitis that aims to eliminate hepatitis C virus by 2030. The elimination targets include treatment of 80% of those eligible with direct-acting antivirals (DAAs), reduction of 90% in incidence of new infections and 65% in liver-related mortality.

Pakistan comprise the second most highest global burden of hepatitis C infection, with an estimated prevalence of 6% nationwide.[3] Regardless of the provision of generic DAAs in the country, Pakistan managed to reduce the cost of treatment but failing to decline burden of hepatitis C.

One of the reasons for overwhelming disease burden of HCV in Pakistan is the lack of a complete, nationwide screening program which may find and track infected persons who require treatment. To decrease the burden of disease and attain the goal of HCV elimination in Pakistan, large-scale screening to identify the missing millions along with timely initiation of treatment is required. There is a need of prompt action at central level to take ownership and implement policies and sponsor programs to facilitate a mass screening and treatment effort.

## Ordinary History of HCV

Both chronic and acute hepatitis may be caused by hepatitis C. In 15-45% of infected individuals, extemporaneous clearance from acute infection from hepatitis C infection takes six months from infection in the absence of treatment. Estimates show an overall 55-85% of people who get infected with hepatitis C may develop chronic infection which is usually clinically

silent.[3]

Immune response develops anti-HCV antibodies as a result of acute infection and these antibodies may persist for life. This is the reason behind the people presenting anti-HCV need confirmation of chronic HCV infection through test such as a polymerase chain reaction using nucleic acid of HCV RNA, which indicates the existence of active virus.

Complications of chronic infection with HCV include decompensated liver diseas, liver cirrhosis and leads to hepatocellular carcinoma among untreated individuals (Fig. 1). Probability of risk of liver cirrhosis among chronic HCV patients ranges from 15-30% in upcoming 20 years.[4,5,6] Similarly, risk of hepatocellular carcinoma ranges 2-4% annually.[7]

Classification of liver cirrhosis consists of decompensated and compensated where former type is defined as cirrhosis consisting at least one symptom of ascites, jaundice, or encephalopathy.[4]

Once patients with liver cirrhosis develop decompensated disease, early mortality risk increases sharply.

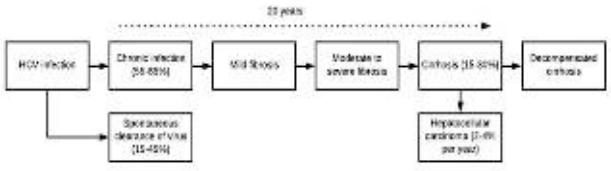

**Figure 1:** *Natural History of HCV Infection*

Disease associated with HCV infection can also cause a spectrum of systemic manifestations including cryoglobulinemia, thyroiditis, glomerulonephritis, Sjogren syndrome, type 2 diabetes, insulin resistance and skin problems like lichen planus and porphyria cutanea.[5]

### Risk Factors for HCV Transmission in Pakistan

Risk factors that drive transmission of HCV in Pakistan is different from advanced countries where transmission is more prevalent in certain high-risk groups such as IDUs.[6] Other important risk factors in the developed world include blood transfusions, body piercing, sex with IDUs, prisons and needle stick injuries.

In Pakistan, the major risk factors arise from poor infection control practices in health care settings. It is demonstrated by several studies that HCV transmission in Pakistan is attributed to unnecessary use and reuse of injections, unsafe medical/dental/surgical procedures, use of contaminated razors by barbers, body piercings, transfusion of unscreened blood and needle stick injuries (NSI).[7]

## Recommendations

### HCV testing

Diagnosis of HCV is completed in two steps:

1. Initially testing for screening is advised by anti-HCV antibodies through serological testing that finds individuals infected with virus.
2. Chronic infection with HCV is confirmed by combination of anti-HCV positive antibodies, detection of HCV RNA by nucleic acid test, or presence o of core antigen (cAg) assay.

## Screening

Many persons with HCV infection remain undiagnosed due to the asymptomatic nature of chronic infection and limited access to testing and thus seek healthcare only when symptoms of decompensated cirrhosis or HCC have developed. At this point, significant liver damage has occurred, which is largely irreversible and may lead to complications despite a cure. This signifies the need for active case finding in areas with high disease burden.

HCV screening using RDTs is recommended for, and should be offered to all individuals in Pakistan according to the following WHO guidelines:

- Serological testing of HCV is offered to each person among population with high sero-prevalence or amongst high risk groups of HCV exposure.
- Serological evidence of prior or present infection with HCV is tested among children, adolescents and adults with a complete assay of HCV serology including antigen and antibody testing using rapid chromatographic techniques or lab based immunoassay to meet minimum recommended standards of safety, quality and performance.
- In healthcare settings having diminished access to diagnostics and laboratory testing, and/or specific populations in which linkage to treatment

**Table 1:** *List of WHO-prequalified HCV RDT*

| Year prequalified | Type of assay | Product name | Manufacturer | Manufacturing site |
|---|---|---|---|---|
| **2016** | HCV RDT | SD Bioline HCV | Standard Diagnostics, Inc. | Giheung-gui, Republic of Korea |
| **2017** | HCV RDT | OraQuick HCV Rapid Antibody Test Kit | OraSure Technologies, Inc. | Bethlehem, USA |
| **2019** | HCV RDT | Rapid Anti-HCV test | InTec PRODUCTS, INC | Xiamen, China |

and care is based on rapid testing are also preceded for treatment.

The use of RDTs over comes the barriers of multiple follow-up appointments, extended turnaround interval, elevated cost and existence of specialized equipment and skilled personnel. RDTs enable simplification and decentralization of testing with comparable sensitivities and specificities to laboratory-based assays.

Several screening tests have been evaluated and prequalified by WHO and are approved for professional use. (Table I)

## Confirmation of Active Infection

Individuals reported positive for anti HCV screening test must advised for NAT to detect viral RNA to establish definite diagnosis of chronic infection. Serum HCV RNA detects viral RNA in serum and confirms the presence of an ongoing infection. Thus chronic HCV patients are differentiated from people who have cleared from infection earlier.

People presenting HCV antibodies on screening test but remain undetectable by NAT must be reassured that they do not have hepatitis C infection and that they have spontaneously cleared the virus.

Core antigen assay for HCV is considered to be the quicker, easy and affordable replacement of NAT for HCV, being used to confirm active infection with HCV. Further HCV core Ag may be diagnosed in the blood within 2 weeks after exposure which is very much earlier as compared to antibody testing which requires around 10 weeks to become detecatbale after exposure.[9,10,11]

## Clinical Assessment

### Baseline labs

- Blood Counts (Hemoglobin, Platelet count)
- Liver Function tests (Bilirubin*, ALT, AST, albumin*)
- Prothrombin time (PT) / International Normalized Ratio (INR)*
- Serum Creatinine

*If suspicion of decompensated liver disease

Pregnancy testing must be offered to the women of childbearing age, if last menstrual period (LMP) is delayed and cognized regarding the deficient available data on the efficacy and safety of DAAs in duration of pregnancy.[12]

### Assessment of liver cirrhosis

All HCV RNA positive cases shall be assessed for the degree of liver fibrosis using non-invasive methods. These include biochemical markers of fibrosis (i.e., FIB4 or aspartate transaminase to platelet ratio index [APRI] score) or transient elastography.[13]

The determination of the extent of hepatic fibrosis is important as it identifies patients with advanced disease who require enhanced monitoring and appropriate treatment regimen. The assessment of decompensated hepatic disease is founded equally on laboratory monitoring and clinical examination, consequently a keen medical examination of suspects should be the priority for commencement of therapy.

**There are no sources in the current document.**

Transient elastography can be used which have satisfactory sensitivity and specificity but its higher cost limits wider use in resource-limited settings. An abdominal ultrasound can be observed to recognize the possible existence of focal lesions and cirrhosis in the liver of suspicious cases of malignancy.

## APRI

An easy and low cost method known to be the APRI score, being described as a substitute for the assessment of structural variations in chronic HCV infection. This score is based on serological markers which present good specificity and sensitivity together along high predictive value.

$$\textbf{APRI} = \frac{\dfrac{\text{AST Level (IU/L)}}{\text{AST (Upper Limit of Normal) (IU/L)}}}{\text{Platelet Count } (10^9/\text{L})} \times \textbf{100}$$

**Figure 2:** *Formula for the Calculation of APRI Score*

**Interpretation:** An APRI score of >1.0 has high specificity and sensitivity in prediction of cirrhosis.[14] The lower the APRI score (< 0.5), A bigger negative predictive value (along capability of ruling out cirrhosis) and the greater value (>1.5) denotes higher positive predictive value (and capable to rule in cirrhosis), while mid-range values are less helpful.[15]

### FIB-4

FIB-4 is a non-invasive and inexpensive measure for the assessment of liver fibrosis.

$$\textbf{FIB-4} = \frac{\text{Age (years)} \times \text{AST Level (U/L)}}{\text{Platelet count } (10^9/\text{L}) \times \sqrt{\text{ALT (U/L)}}}$$

**Figure 3:** *Formula for the Calculation of FIB-4 score*

**Interpretation:** FIB-4 score of <1.45 rules out advanced fibrosis. In contrast, a FIB-4 score of >3.25 would has a 97% specificity for advanced fibrosis.[16]

### Child-Turcotte-Pugh (CTP) classification

The Child–Pugh Score (Table 2) is a scoring system

to assess the prognosis of chronic liver disease particularly in patients with liver cirrhosis. It uses five parameters to classify disease stage. Each parameter is scored from 1-3, with 3 indicating most severe derangement. Five parameters provide points to sum up for categorization of patients into A, B, or C classes of Child-Pugh score. Researches comprising cirrhotic patients predict that "Child-Pugh score" can assess the risk of mortality 3 months, 1 & 2 year survival. Survival rate of cirrhotic patients for two years has been calculated by Child-Turcotte-Pugh score and remained to be 90% for class A, 70% for B anad 35% for class C.[17]

Few of the regimens in treatment of HCV are contraindicated amongst the decompensated patients or classified as B and C with Child-Pugh thus, the classification helps to guide subsequent management plans.

**Table 2:** *Child-Turcotte-Pugh (CTP) Classification*

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

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

## Decompensated liver disease

Fractions of patients of decompensated hepatic disease can deteriorate by the treatment and there are no predictors to recognize such cases at present. That's why the treatment of decompensated cirrhotic patients considered in ideal conditions with specialist care in centers with the expertise for close monitoring and management of complications can be ensured.

### Treatment of adults with DAAs

The main purpose of HCV treatment remains to eliminate and prevent complications of hepatic and extra hepatic nature with ultimate improvement in probable survival. Treatment should be offered to all patients detected to have HCV infection, aged 12 years or above irrespective of gender and stage of disease.[16] The following regimens are easily available in Pakistan:

- Patients having no cirrhosis can be given one of the following pan genotypic regimens:
  - o Sofosbuvir + Daclatasvir for 12 weeks
  - o Sofosbuvir + Velpatasvir for 12 weeks
- Patients with compensated cirrhosis can be given one of the following pan genotypic regimens:
  - o Sofosbuvir + Daclatasvir for 24 weeks
  - o Sofosbuvir + Velpatasvir for 12 weeks

**Table 3:** *Pangenotypic Regimens Currently Available for use in Adults 18 Years of Age or Older*

| Type of patient | Regimen | Duration |
|---|---|---|
| **No evidence of cirrhosis** | Sofosbuvir + Daclatasvir | 12 weeks |
| | Sofosbuvir + Velpatasvir | 12 weeks |
| **Compensated cirrhosis** | Sofosbuvir + Daclatasvir | 24 weeks |
| | Sofosbuvir + Velpatasvir | 12 weeks |

### Monitoring of Therapeutic Response

Polymerase chain reaction to test viral RNA for quantitative and/or qualitative detection of HCV genome must be utilized to declare the patient as cure at 12 weeks (i.e. sustained virological response) following antiviral treatment completion.

### Retreatment of Chronic Hepatitis C Non-responders

SVR rates after appropriate treatment with DAA generally exceed 90% across all HCV genotypes.[18] Patients fail to achieve sustained virological response after DAA left with fewer choices for further treatment. A suitable, effective treatment regimen at initiation may be helpful to avoide the dilemma of limitations in treatment choices.

Based on drug regimens available in Pakistan, the following options can be considered for those who have not responded to first line treatment:

- Adults with no cirrhosis who have failed treatment can be given one of the following regimens:
  - o Sofosbuvir + Daclatasvir for 24 weeks
  - o Sofosbuvir + Velpatasvir for 24 weeks
- Adults with cirrhosis who have failed treatment can be given one of the following regimens:
  - o Sofosbuvir + Daclatasvir + Ribavirin for 24 weeks
  - o Sofosbuvir + Velpatasvir + Ribavirin for 24 weeks

**Algorithm for Management of Chronic HCV Infection**

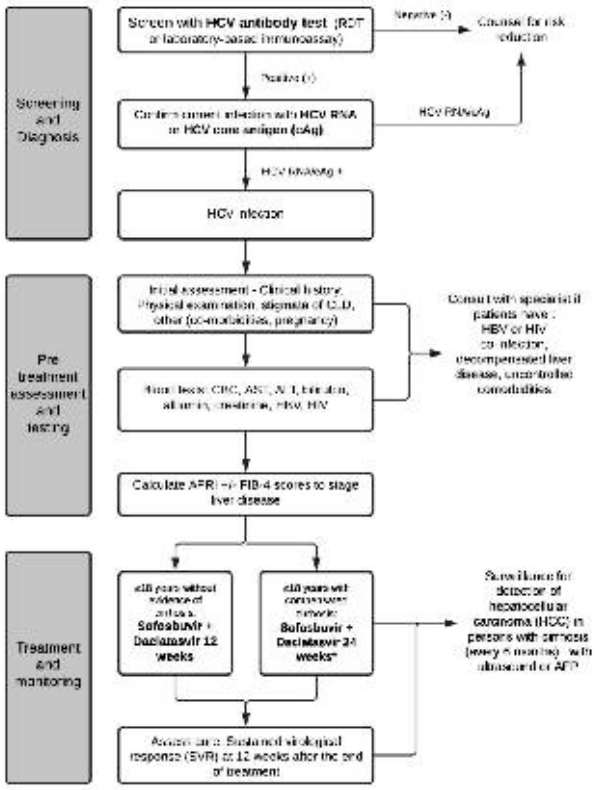


**Figure 4:** *Summary Algorithm for the Diagnosis, Treatment and Monitoring of Chronic HCV Infection In Adults*

## Glossary

| | |
|---|---|
| **Anti-HCV antibody** | Presence of antibodies to hepatitis C virus (HCV), which is a biomarker of past or present infection |
| **Chronic HCV infection** | Continued infection six months or more after acquiring HCV infection |
| **Cirrhosis** | Extensive liver scarring secondary to prolonged inflammation of the liver (F4 in the METAVIR scoring system) |
| **Compensated cirrhosis** | Cirrhosis usually without liver-related symptoms |
| **Decompensated cirrhosis** | Cirrhosis with the development of symptomatic complications, including ascites or variceal bleeding |
| **Pan genotypic** | An SVR rate >85% across all six major HCV genotypes |
| **Spontaneous viral clearance** | Clearance of HCV infection without treatment |
| **SVR 12** | Undetectable HCV RNA in the blood 12 weeks after treatment completion. SVR 12 is considered equivalent to a cure for HCV infection |

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