

Training workshop on screening, diagnosis and treatment of hepatitis B and C

Session 15

Clinical management of HCV infection (including case studies) Part I

Learning objectives

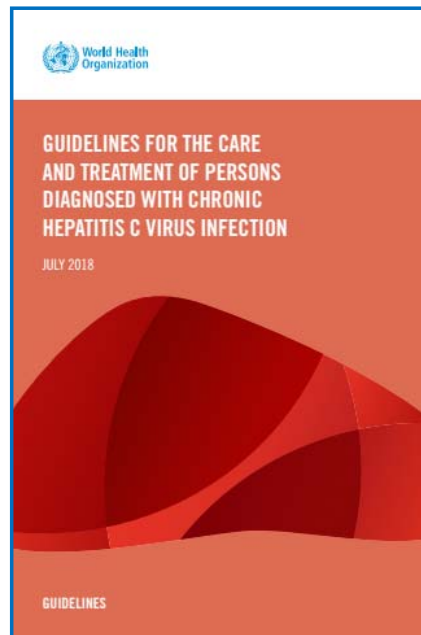
At the end of this session, participants would know the following:

- How to clinically assess HCV-infected persons
- Appropriate laboratory investigations needed for assessment
- Direct-acting antiviral drugs available for treating HCV infection
- Various treatment strategies recommended for HCV infection
- Identify the appropriate treatment strategy for individual patients with HCV infection.



The objectives of this session are to provide participants with the knowledge needed for the assessment and interpretation of relevant laboratory investigations, and selection and execution of the appropriate treatment strategy for an HCV-infected person in a real-life scenario.

WHO Guidelines for HCV treatment



Latest guidelines:
Released July 2018



This session is based on the HCV guidelines launched by WHO. The most recent WHO HCV guidelines were published at 2018.

Antibodies: what is it?

- Antibodies are part of immune response
- Specific antibodies are formed against a particular pathogen and may remain for life and be protective, example:
 - Measles is a viral disease which provides lifelong immunity
 - Anti-measles antibody remains positive for life
- In HCV, anti-HCV antibodies are form after HCV viral infection and remains in the serum even after clearance of the virus
- Detected through anti-HCV tests



First – a recap on antibodies

As a part of the host's innate immune response, antibodies are formed in our body against any pathogenic invasion. Once a specific antibody is formed against a particular pathogen, it remains in the body for the rest of the host's life and protects them against a second attack by the same pathogen. A classic example is measles, which is a viral disease and the antibodies, developed either after natural infection or vaccination, protect the host for life. Hence, the presence of antibodies does not signify active infection but only indicates that there has been previous exposure.

Similarly, after HCV infection, anti-HCV antibodies are formed, which remain circulating in the serum after clearance of the virus.

To identify an HCV-infected person, we are using an anti-HCV antibody test (but not an antigen test) to identify those who might still be having active HCV infection. This is in contrast to hepatitis B virus where we test a person for HBsAg (which is an antigen), which indicates ongoing active hepatitis B infection.

We must explain to patients about the perpetual persistence of anti-HCV even after successful treatment. This should be documented in his/her health records.

Assessment of a person with HCV infection

In a patient with HCV infection, the following issues may need consideration:

1. Infection: acute or chronic
2. Infection: active or resolved
3. Assess liver fibrosis and function
 - cirrhosis versus no cirrhosis (fibrosis assessment)
 - compensated versus decompensated cirrhosis
4. Other associated factors that influence treatment
 - comorbidities
 - pregnancy
 - drug–drug interactions.



While evaluating a patient with an anti-HCV positive result, the physician needs to know the answers to four questions:

- (i) whether the infection is still active or has already been resolved;
- (ii) if active, then whether the infection is acute or chronic;
- (iii) whether the patient has developed cirrhosis, either compensated or decompensated, or not; and
- (iv) whether there are any other associated conditions that could affect the treatment regimen or its outcome.

Acute versus chronic infection

	Acute	Chronic
Duration	<6 months	>6 months
Significance	A proportion of persons will clear the infection spontaneously (i.e. without any treatment)	Once chronic, most of the persons are unlikely to clear the infection
Need for treatment	Usually, no treatment is indicated	Treatment advisable

Laboratory tests do not permit this distinction
(except if a person was recently tested to be negative and has then become positive)



The duration of acute infection is less than 6 months. A proportion of persons will clear the infection spontaneously (i.e. without any treatment).

Usually, no treatment is indicated for acute hepatitis C.

If the HCV infection continues for more than 6 months, it is labelled as chronic HCV infection. Once the infection becomes chronic, most persons are unlikely to clear the infection and hence treatment is advisable.

However, laboratory tests do not help in distinguishing between acute and chronic HCV infection; except if a person was recently tested to be negative and has then become positive.

HCV infection: acute vs chronic

- HCV infection can be **suspected/assumed** to be acute if a person has had a possible exposure in the past 6 months
 - blood transfusion
 - unsafe injections
 - medical procedures, e.g. haemodialysis
 - surgery
 - sexual (rare).
- However,
 - a person with a recent risk factor may have pre-existing infection
 - no risk factor may be identified in many acute HCV cases.



It is very difficult to identify acute HCV infection because HCV infection does not produce clinical jaundice or any other specific signs or symptoms. In the majority of cases, the diagnosis of acute HCV is based on assumptions. Most commonly, the diagnosis of acute HCV is suspected in people who were known to be anti-HCV negative and had exposure to a risk factor for HCV in the past six months and were recently found to be anti-HCV positive.

These assumptions may not be accurate all the time.

Acute HCV infection

- Diagnosis difficult
- A person with HCV infection and one of the following:
 - recent change in anti-HCV antibody/HCV RNA status (from -ve to +ve)
 - recent jaundice or ALT >10 x ULN (beginning <20 weeks ago)

Hajarizadeh B, Grebely J, Dore GJ. Case definitions for acute hepatitis C virus infection: a systematic review. J Hepatol. 2012 Dec;57(6):1349-60.



As of now, we do not have any universally accepted definition of acute HCV infection. In the literature, several definitions have been used for the diagnosis of acute HCV. Based on a systematic review of the available literature search, the most acceptable definition of acute HCV infection is given here: recent (within six months) change in anti-HCV antibody or HCV RNA serostatus (from negative to positive status) associated with clinical jaundice or ALT elevation of more than 10 times the normal.

HCV infection: active vs resolved

Definition

- Active = virus is still present in the host
- Resolved = no virus in the host
(immune system has cleared the infection)

If the virus is still circulating in the host blood then it is called active infection.

HCV infection: active vs resolved

Definition

- Active = virus is still present in the host
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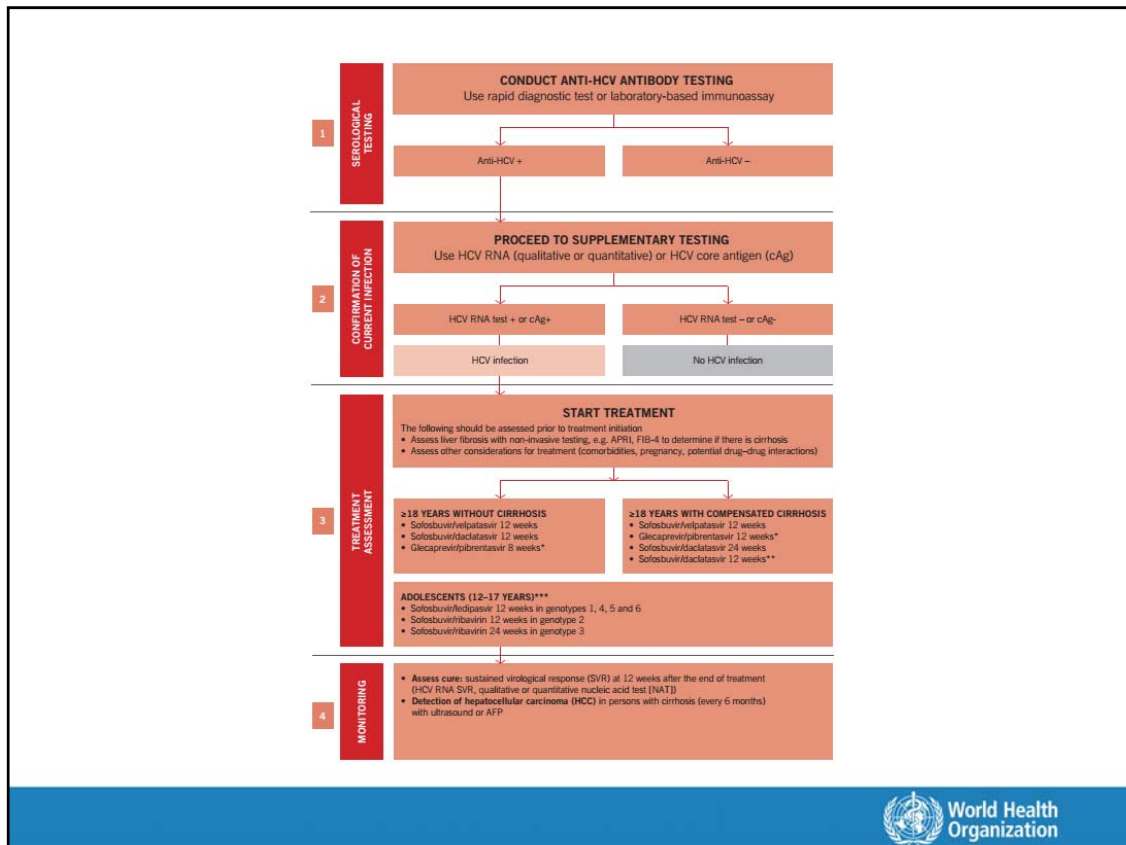
Laboratory diagnosis

- Active = serum HCV RNA +ve
- Resolved = serum HCV RNA –ve

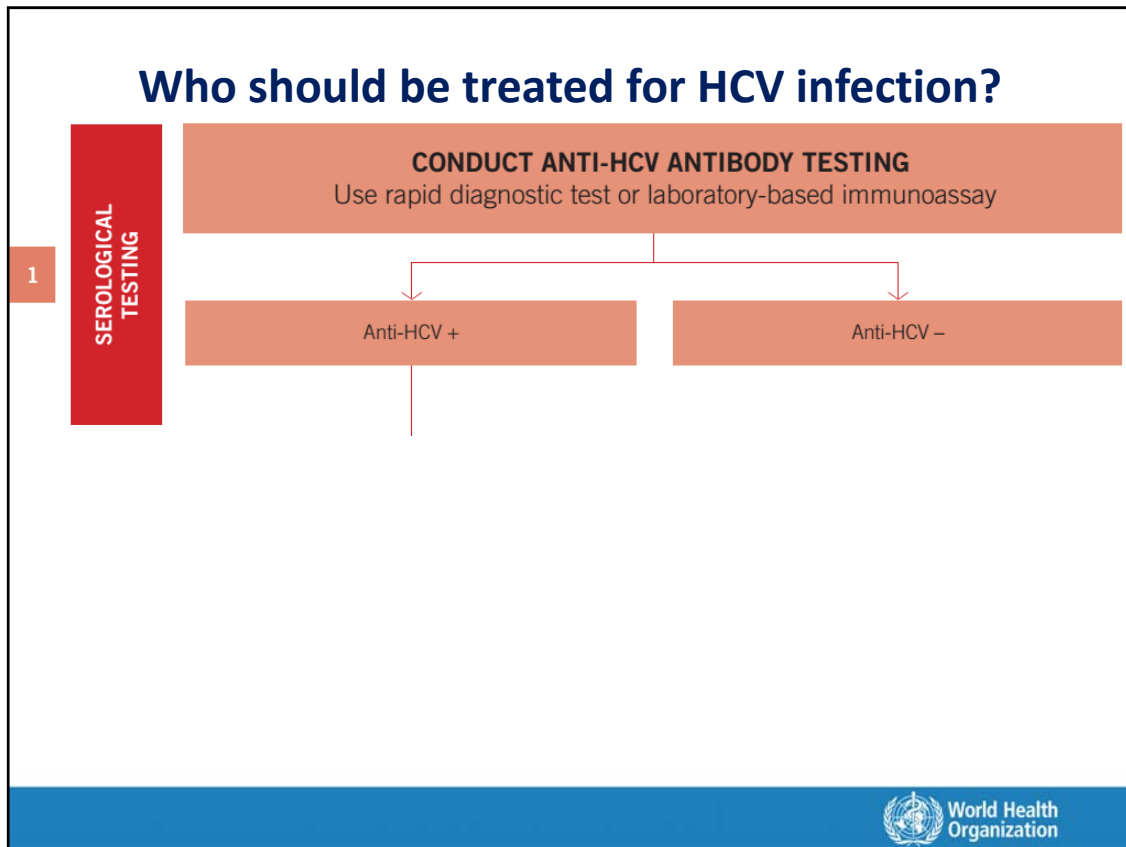
All persons with active HCV infection should be considered for treatment



Active infection is diagnosed by the presence of HCV RNA in the serum and all those with active HCV infection, regardless of the level of viraemia, should be treated.

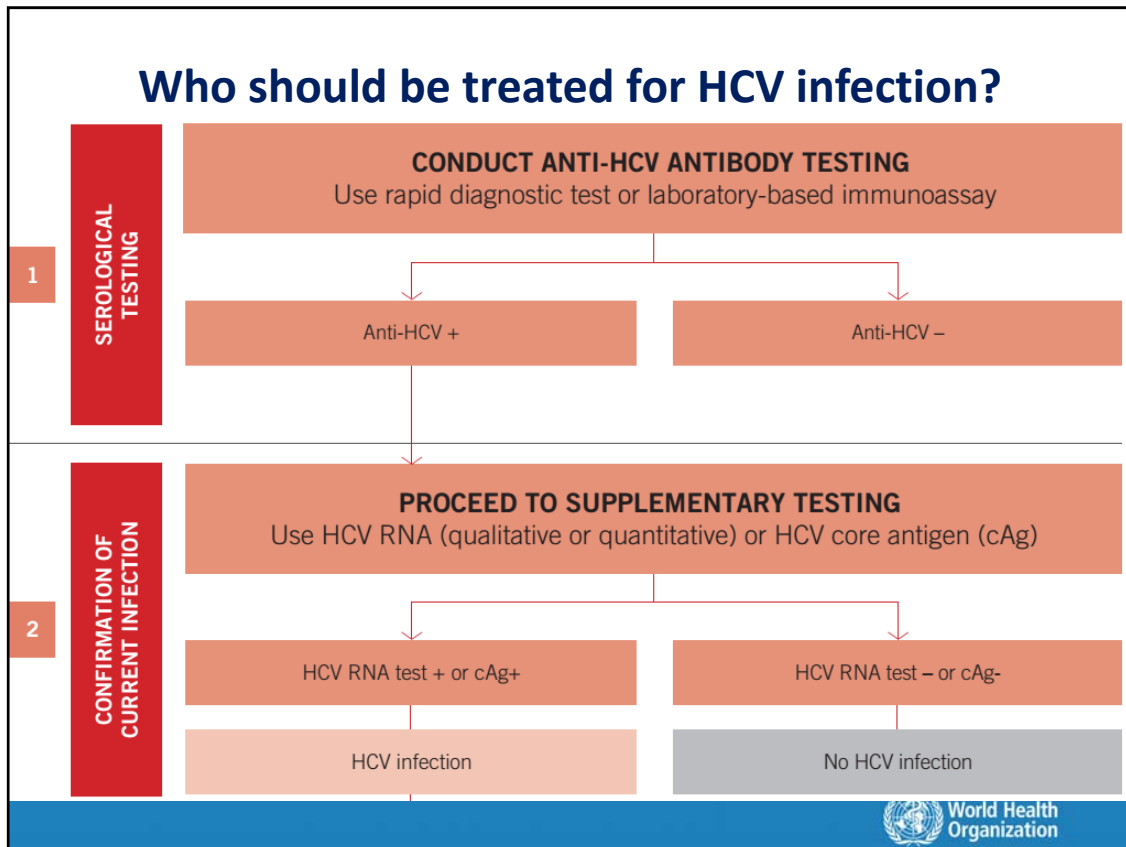


The slide shows a summary algorithm for the diagnosis, treatment and monitoring of chronic HCV infection.



At the first stage, serological testing such as anti-HCV antibody testing should be conducted.

When it is positive, we should go to the next stage.



At the second stage, supplementary testing such as HCV RNA or cAg should be tested. When it is positive, we can confirm current HCV infection.

Who should be treated for HCV infection?

All patients (≥ 12 years of age) with detectable HCV RNA

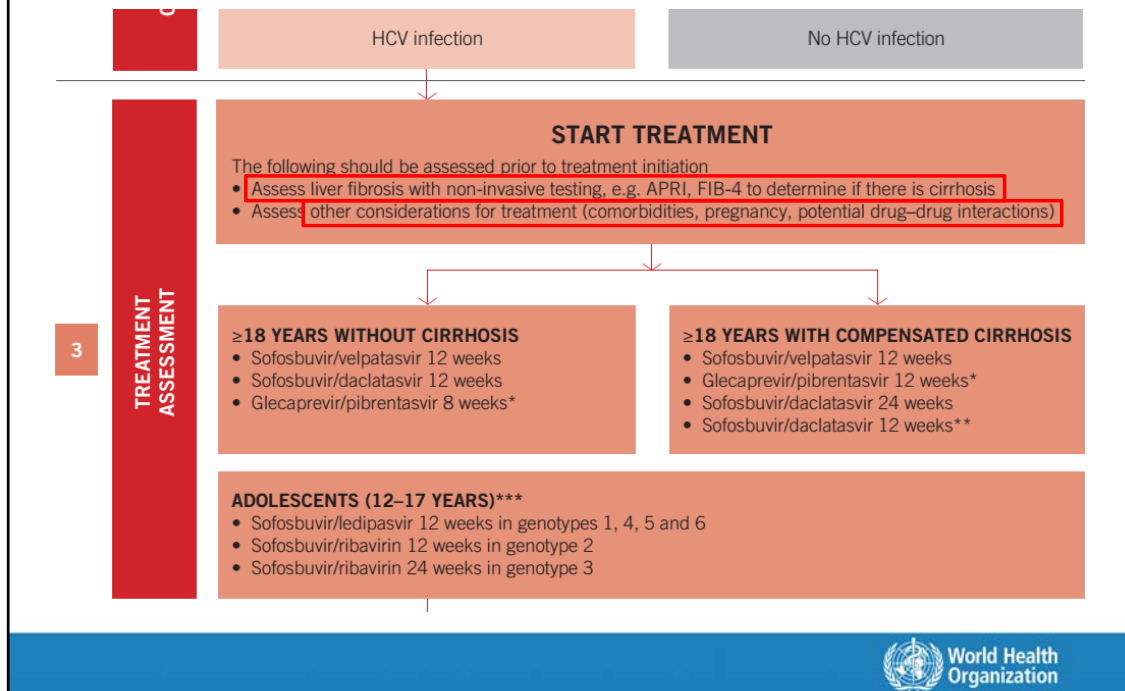
(Drugs are currently not approved for use at age < 12 years)

(Also, only some drugs are approved in the 12–17 years age group)



At present, HCV treatment is permitted for patients aged 12 years or more because drugs are not approved for use in children below 12 years of age. They are likely to be approved soon (clinical trials ongoing for use of drugs among younger age groups).

Considerations for treatment



In the third phase, we should conduct treatment assessment.

Before treatment, we should assess for liver fibrosis with non-invasive testing such as APRI, FIB-4 to determine if there is cirrhosis and assess other considerations for treatment such as comorbidities, pregnancy and potential drug–drug interactions.

Liver fibrosis: cirrhosis versus no cirrhosis

- Chronic HCV infection can lead to progressive liver fibrosis.
- Degree of fibrosis can be identified by liver biopsy and is classified as F0 to F4 (using the METAVIR staging system).
- Cirrhosis (or F4 fibrosis) indicates **extensive liver scarring** secondary to prolonged inflammation of the liver, and is associated with **a high risk of serious complications**.

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

Chronic viral hepatitis induces liver fibrosis. The severity of liver fibrosis is a continuous process. For ease of understanding and communication, the severity of liver fibrosis is graded into five grades from no fibrosis (called F0) to cirrhosis (called F4).

From the HCV management and prognosis point of view, in every patient, the physician needs to determine whether the fibrosis has progressed to the stage of cirrhosis or not. Those with cirrhosis need a longer duration of treatment, addition of ribavirin, lower chance of response, higher risk for relapse, and lifelong monitoring and follow up (after successful antiviral treatment and virus eradication) for hepatocellular carcinoma.

Diagnosis of cirrhosis

- Clinical features
- Indirect tests
 - haemogram, especially platelet count
 - biochemical tests: ALT, AST, albumin
 - **composite measures**
 - **FIB-4, APRI, Fibrotest**
- Imaging
 - **ultrasound**
- Specialized tests
 - endoscopy for varices
 - **liver stiffness (transient elastography)**



The presence of cirrhosis can be identified with a combination of clinical findings (oedema, ascites, variceal bleed, hepatic encephalopathy), haemogram (which may show pancytopenia; the platelets are the first to show a reduction in number), liver function tests (low serum albumin and composite scores such as APRI, FIB-4), ultrasound abdomen (nodular and shrunken liver, dilated portal vein, splenomegaly, etc), and endoscopy (for oesophageal and gastric varices).

If available, liver stiffness measurement (transient elastography) could also help in diagnosing cirrhosis.

Cirrhosis versus no cirrhosis

	Components	Requirements	Co st
APRI	AST, platelets	Simple serum and haematology test	+
FIB-4	Age, AST, ALT, platelets		
FibroTest	GGT, haptoglobin, bilirubin, apoprotein A1, α2-macroglobulin	Specialized tests at designated laboratories	++
FibroScan [®]	Transient elastography	Dedicated equipment	++ +
AST	aspartate aminotransferase		
ALT	alanine aminotransferase		
GGT	gamma glutamyl transpeptidase		
APRI	aspartate aminotransferase-to-platelet ratio index		
FIB-4	fibrosis-4 score		



There are a few composite scores that have been validated for the diagnosis of cirrhosis. The calculation of these scores requires a few simple laboratory parameters. The most commonly used scores are APRI, FIB-4, and FibroTest.

Among these composite scores, APRI (AST-to-platelets ratio index) is the one that is the most extensively studied, validated and used. The widespread acceptability of APRI is contributed by several of its qualities such as use of easily available parameters, ease of calculation without a calculator, and extensive validation in various populations across the grades of fibrosis.

These composite scores, other than APRI, have limitations such as the need for an uncommon laboratory variable, calculator or computer-based calculation or need of a specific instrument.

FibroScan is one of the newer devices that has been used for fibrosis assessment. This is an ultrasound-like machine that non-invasively measures liver fibrosis. It is easy to use and can be repeated frequently. The major limitation of the FibroScan is its huge cost and need for a dedicated person to maintain the quality of fibrosis assessment.

APRI: cirrhosis versus no cirrhosis

- In resource-constrained settings, two cut-off values help in treatment prioritization.
- Values above the high cut-off
 - high probability of cirrhosis
- Values below the lower cut-off
 - high certainty that there is no cirrhosis
- Between the two cut-offs
 - Cirrhosis possible but not very certain



APRI and FIB-4 are the two most commonly used composite measures of liver fibrosis. These two indices could easily be calculated with simple laboratory parameters. Hence, WHO has recommended their use for fibrosis assessment. APRI is the most widely used.

These indices are useful in determining the presence or absence of liver cirrhosis. These indices have limited roles in differentiating between the various grades of fibrosis such as F1 versus F2 fibrosis.

In the era of DAAs, for patient management and follow up, we need to know whether cirrhosis is absent or present but we do not need to know the grade of fibrosis if cirrhosis is absent.

For each of these indices, WHO recommended two cut-off levels to define cirrhosis: (i) lower cut-off value which has a high sensitivity (means detects true positive) to detect cirrhosis if it is present and (ii) upper cut-off value, which is more specific for diagnosing cirrhosis.

Values above the high cut-off indicate a high probability of having cirrhosis; any value below the low cut-off value indicates a very low probability of having cirrhosis.

These two cut-offs may be used in resource-constrained countries where anti-HCV treatment is prioritized on the basis of severity of fibrosis; in such places, those with scores above the higher cut-off will receive treatment on a priority and those with a score below the lower cut-off will not be treated. Those with score between the low and high cut-off values could either be monitored at regular intervals for disease progression or could be treated if resources become available.

Compensated versus decompensated cirrhosis

- **Compensated cirrhosis**

Cirrhosis usually without liver-related symptoms or signs

- **Decompensated cirrhosis**

Cirrhosis with the development of symptomatic complications

Another important step in the management of a cirrhosis patient is to decide whether the cirrhosis has progressed to the stage of decompensation or not.

Compensated versus decompensated cirrhosis

- **Compensated cirrhosis**

Cirrhosis usually without liver-related symptoms or signs

- **Decompensated cirrhosis**

Cirrhosis with the development of symptomatic complications

- ascites
- hepatic encephalopathy
- total bilirubin $>2.5 \times \text{ULN}$ + prolonged prothrombin time (>3 second prolongation or $\text{INR} >1.5$)
- variceal bleed

- Indicates the presence of advanced liver disease



Decompensation is defined by the presence of clinical symptoms due to cirrhosis or portal hypertension such as ascites, variceal bleed, hepatic encephalopathy and jaundice.

Severity of liver dysfunction

Methods	Parameters assessed
Child–Pugh–Turcotte (CTP) score/class	Clinical evaluation: ascites encephalopathy Serum bilirubin Serum albumin Prothrombin time (INR)
Model for End-stage Liver Disease (MELD)	Serum bilirubin Prothrombin time (INR) Serum creatinine

We can assess the severity of liver dysfunction by 2 methods:

First, the Child–Pugh–Turcotte (CTP) score assesses disease severity on the basis of parameters that are determined by clinical evaluation such as ascites and encephalopathy. Serum bilirubin, serum albumin, and prothrombin time (INR) should be estimated as well. Hence this score is a relatively subjective score.

Model for End-stage Liver Disease (MELD) assesses serum bilirubin, prothrombin time (INR) and serum creatinine.

Child–Pugh–Turcotte Score

Child-Turcotte-Pugh Classification for Severity of Cirrhosis			
Clinical and Lab Criteria	Points*		
	1	2	3
Encephalopathy	None	Grade 1 or 2	Grade 3 or 4
Ascites	None	Mild to moderate (diuretic responsive)	Severe (diuretic refractory)
Bilirubin (mg/dL)	< 2	2-3	>3
Albumin (g/dL)	> 3.5	2.8-3.5	<2.8
Prothrombin time Seconds prolonged or International normalized ratio	<4 <1.7	4-6 1.7-2.3	>6 >2.3
*Child-Turcotte-Pugh Class obtained by adding score for each parameter (total points)			
Class A = 5 to 6 points			
Class B = 7 to 9 points			
Class C = 10 to 15 points			

In terms of the Child–Pugh–Turcotte Score, we can divide each clinical and laboratory parameter criteria into three grades.

As a result, the CTP score ranges between 5 and 15.

Class A is 5 to 6 points, class B is from 7 to 9 points, and class C is from 10 to 15 points.

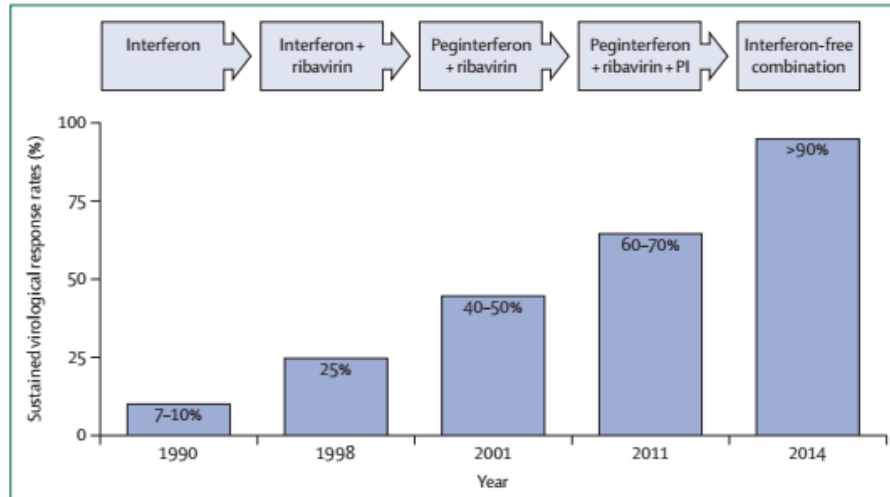
Why treat HCV infection?

- Delay the progression of cirrhosis
- Reduce the incidence of hepatocellular carcinoma
- Improve the quality of life
- Improve long-term survival (reduce death)
- Potentially, reduce transmission



As of now, every person with active HCV infection should be treated because successful HCV treatment confers several advantages on the host such as delay in the progression of fibrosis, reduced risk for HCC, improvement in the quality of life and survival. Successful HCV treatment may even cause regression of the liver fibrosis. Because person-to-person HCV transmission is relatively uncommon, hence HCV treatment plays a limited role in preventing HCV transmission.

Evolution of HCV treatment over time



This slide shows the evolution of HCV treatment over time.

In the 1990s, interferon and ribavirin were the only medications to treat HCV. The sustained virological response (SVR) rate was only 7–25%.

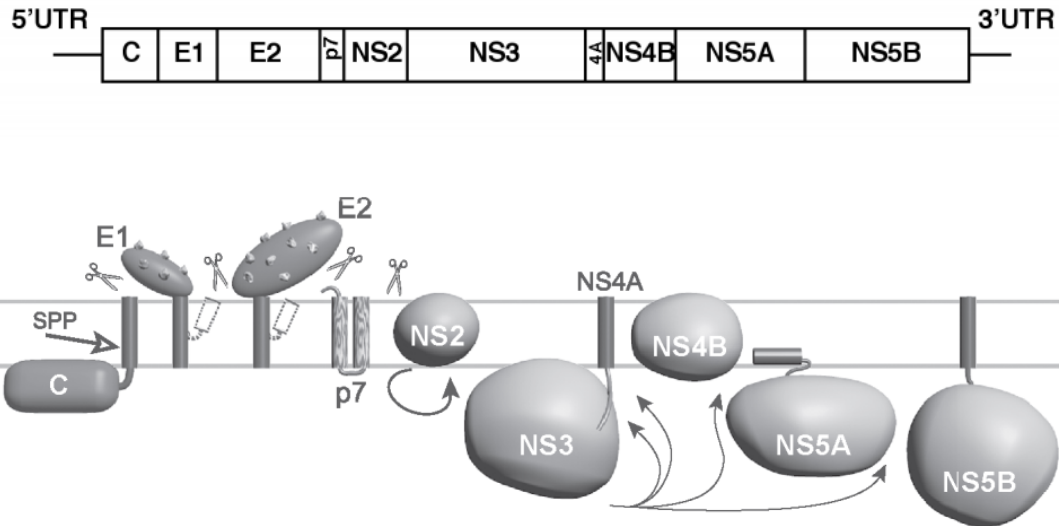
In the 2000s, pegylated interferon was available, therefore, the SVR rate increased to 40–50%.

In the beginning of the 2010s, protease inhibitors were developed and became available. The SVR rate was 60–70%.

Interferon-free combinations were innovative and greatly increased the SVR rate to over 90%.

HCV genome

A) Hepatitis C virus



Hepatitis C virus has a positive-sense single-stranded RNA genome. The genome consists of a single open reading frame that is about 10 000 nucleotide bases long. This single open reading frame is translated to produce a single protein product, which is then further processed to produce smaller active proteins. This is why on publicly available databases, such as that of the European Bioinformatic Institute, the viral proteome consists of only 2 proteins.

At the 5' and 3' ends of the RNA are the untranslated regions (UTRs), which are not translated into proteins but are important for translation and replication of the viral RNA. The 5' UTR has a ribosome binding site or internal ribosome entry site that initiates the translation of a very long protein containing about 3,000 amino acids. The core domain of the HCV internal ribosome entry site (IRES) contains a four-way helical junction that is integrated within a predicted pseudoknot. The conformation of this core domain constrains the open reading frame's orientation for positioning on the 40S ribosomal subunit. The large pre-protein is later cleaved by cellular and viral proteases into 10 smaller proteins that allow viral replication within the host cell, or assemble into mature viral particles. Structural proteins made by the hepatitis C virus include core protein, E1 and E2; nonstructural proteins include NS2, NS3, NS4A, NS4B, NS5A and NS5B.

Direct-acting antiviral drugs (DAAs)

DAAs = drugs that specifically act against hepatitis C virus

Three groups, depending on the mechanism of action

NS3 protease inhibitors	(....previr)	simeprevir
NS5B inhibitors	(....buvir)	sofosbuvir
NS5A inhibitors	(....asvir)	daclatasvir

All the oral anti-HCV drugs, which are called DAAs and are used today, can be categorized into three groups. Each of these drugs inhibits a specific non-structured protein of the virus. The names of these drugs are difficult to remember and hence their names are provided with specific suffixes such asprevir.....buvir and.....asvir at the end of their names.

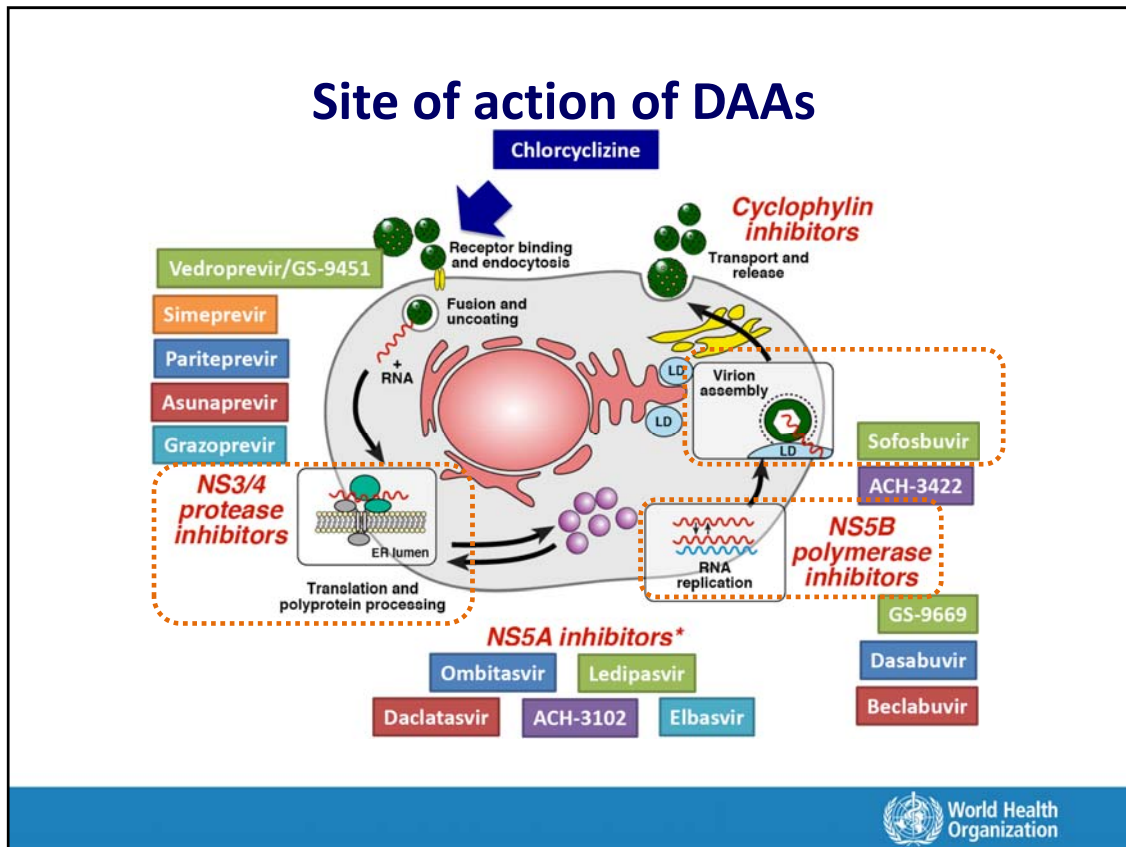
HCV infection: common treatment regimens

- Interferon-based **Not recommended**
 - Pegylated interferon plus ribavirin
 - Pegylated interferon plus ribavirin plus sofosbuvir
- Interferon-free, DAA-based treatment **Recommended**

NS5B inhibitor (e.g. sofosbuvir/dasabuvir)	+	NS3 inhibitor (e.g. glecaprevir)
		NS5A inhibitor (e.g. ledipasvir/daclatasvir)
		Both of the above

Till a couple of years ago, HCV infection was treated with pegylated interferon but now pegylated interferon is not used for HCV treatment.

Among the currently available oral drugs, NS5B inhibitors, mainly sofosbuvir, forms the backbone and is used in combination with drugs from one or both remaining groups of DAAs.



There are 4 targets on the hepatitis C virus that DAA medications attack to destroy the virus.

Each DAA medication attacks one of these targets; combination DAA tablets attack more than one target.

DAA medications are classified based on which mechanism they use against HCV.

Recognizing the DAA medication classes becomes particularly important when re-treating a patient for HCV who has been previously treated with DAA-based therapy.

DAA regimens as per WHO Guidelines

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

- Fixed-dose combinations
 - sofosbuvir + ledipasvir
 - sofosbuvir + velpatasvir
 - sofosbuvir + daclatasvir (also separately)

Other drugs

- Ribavirin (in combination with DAAs)

WHO recommends the use of the following DAAs for HCV treatment in different combinations.

Treatment regimens for HCV infection: WHO

Choice of the HCV treatment regimen depends on

- Patient's age
- Virus genotype
 - genotype-dependent regimens
 - pangenotypic regimens
- Cirrhosis or no cirrhosis



For every person who needs treatment for HCV infection, infection management will require information on age of the patient, genotype of the virus circulating in the host, and presence or absence of cirrhosis.

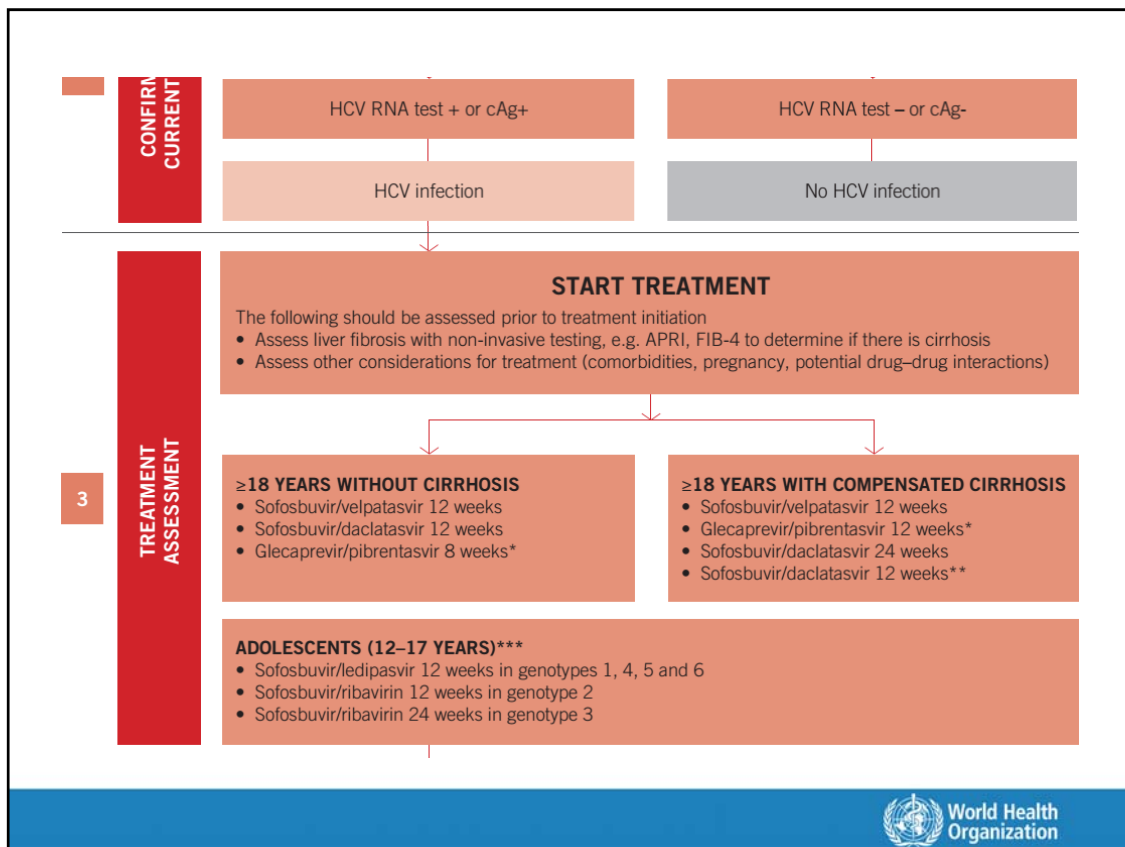
General rules for DAA-based treatment

- Genotype
 - 1, 4, 5 and 6 Similar treatment
 - 2 “Easy to treat”
 - 3 “Difficult to treat”
- If cirrhosis is present
 - longer duration (24 weeks) of treatment
 - addition of ribavirin may provide additional benefit
 - higher response rate
 - shorter duration
 - higher risk of complications and need for monitoring during Rx
 - higher risk of relapse

Earlier in the era of pegylated interferon, genotype 3 infection was considered difficult to treat.

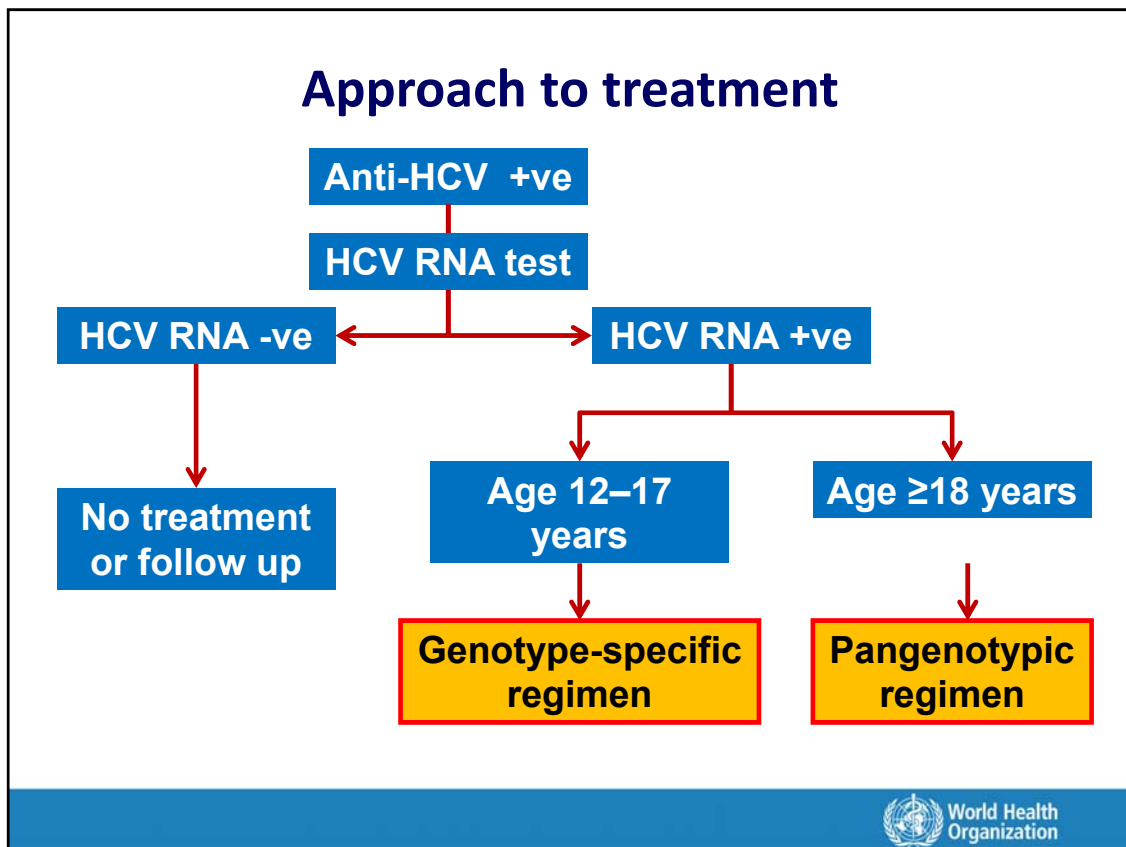
But in the present era of DAAs this is not true because DAAs are highly effective against genotype 3 as well.

A HCV-infected person with cirrhosis needs a longer duration of treatment, may require ribavirin to either enhance the response or to reduce the duration of treatment, and will require lifelong monitoring for the complications of cirrhosis such as HCC after successful treatment.

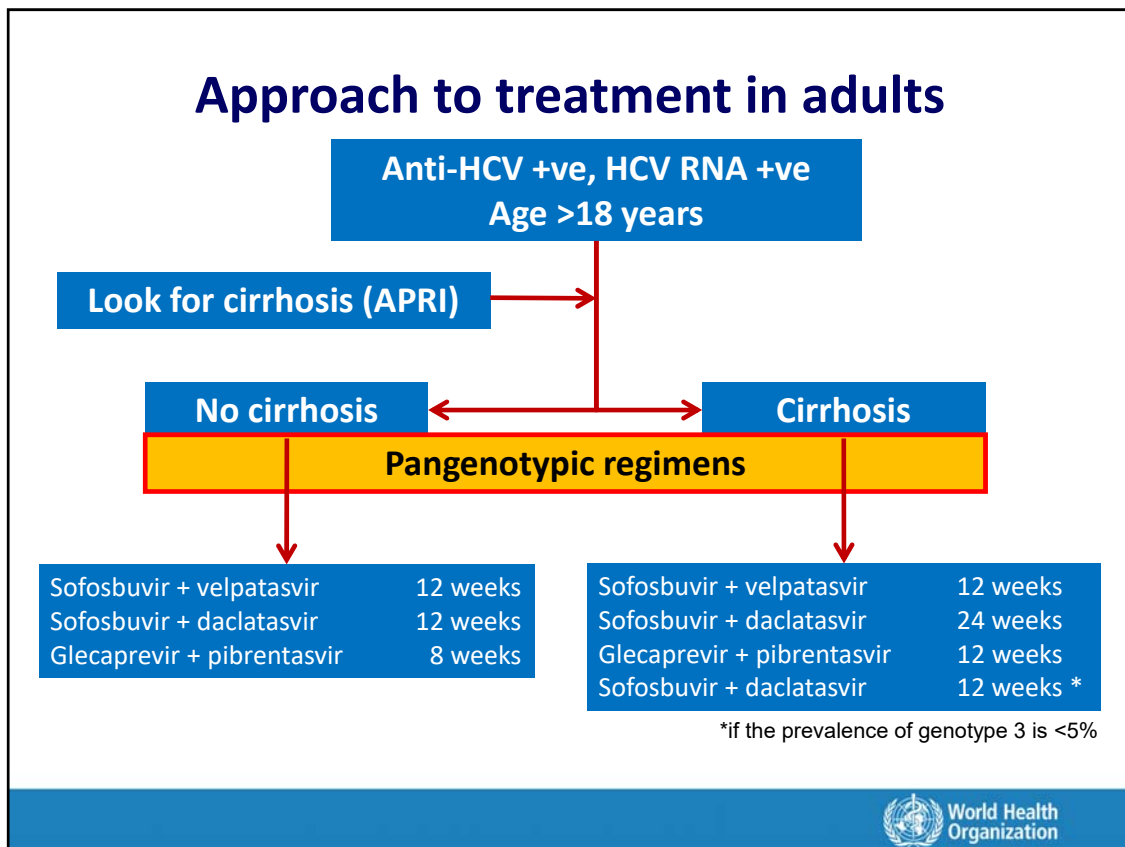


We should divide treatment into 3 groups, those over 18 years with and without cirrhosis, i.e. those 12–17 years old.

In the current guideline, treatment among the 3 groups is different.

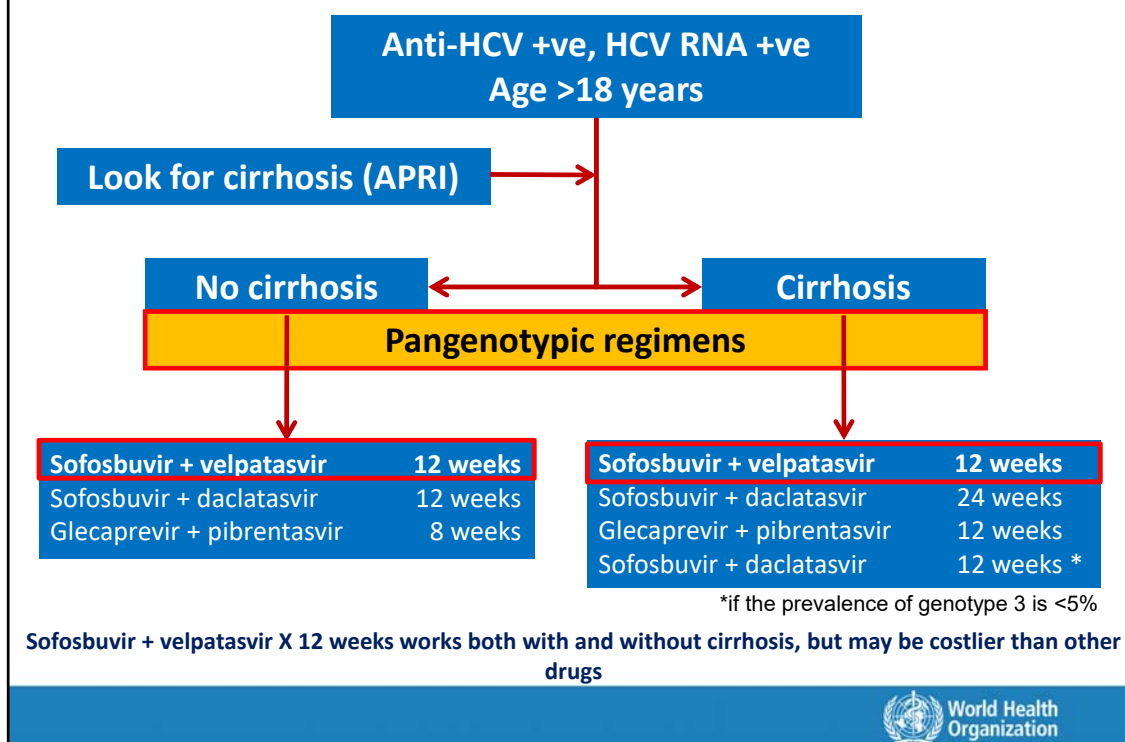


For patients who are HCV RNA positive, only genotypic-specific regimen is available for those aged 12–17 years, and pangenotypic regimen can be applicable for those over 18 years.

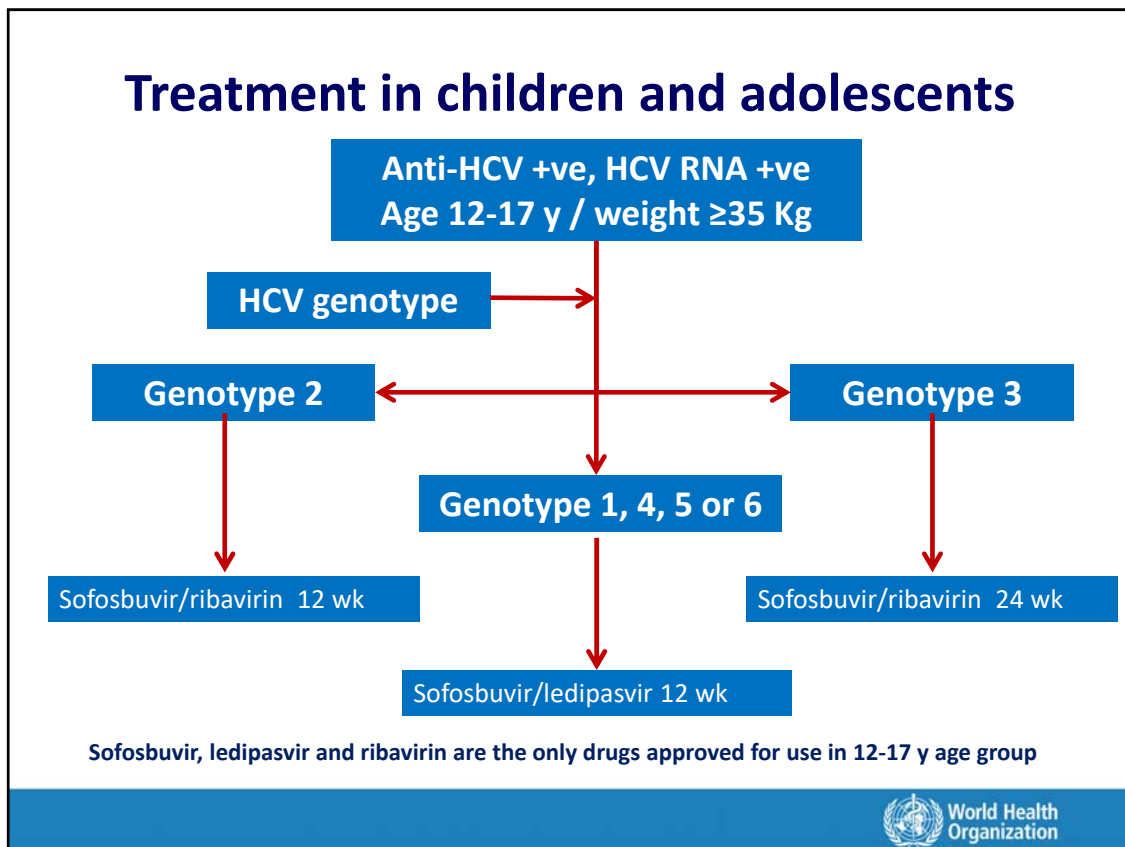


For a patient over 18 years, we should evaluate the patient for the status of cirrhosis. Whether cirrhosis is present or absent, a pangenotypic regimen is applicable, however, the treatment duration is different in each group.

Approach to treatment in adults



Sofosbuvir and velpatasvir for 12 weeks works both with and without cirrhosis, but may be costlier than the other drugs.



As we have discussed a while ago, only genotypic specific regimen is available for age 12-17 years.

We should check HCV genotype and choose the regimen corresponding the genotype.

This is because Sofosbuvir, ledipasvir and ribavirin are the only drugs approved for use in 12-17 y age group.

Pre-treatment assessment

- Clinical features Cirrhosis
 Decompensation
- Laboratory Haemogram
 Liver function tests
 Creatinine
- Fibrosis/cirrhosis Non-invasive fibrosis assessment
 FibroScan: if available
 UGI endoscopy, if needed
- HCV RNA
- HCV genotype Only if age 12–17 years



The evaluation of a patient, regardless of the pathogen (e.g. HCV in this case), includes two components: first, investigations to diagnose the condition, identify the pathogen and decide specific chemotherapeutic agents (e.g. Widal test and blood culture with antibacterial sensitivity in a patient with suspected enteric fever; HCV RNA and HCV genotype in an anti-HCV-positive person); second; the investigation to identify and assess adverse effects in the form of complications because of the identified pathogen (e.g. to evaluate every HIV-positive person for tuberculosis).

To assess the pathogen here, we need HCV RNA and HCV genotyping if the age is between 12 and 17 years; these tests should only be done if the administration of anti-HCV treatment is a possibility because these are very costly tests and may cost around US\$ 1500 in a non-public-funded setting.

Assessment for liver disease severity due to HCV is needed in every person regardless of treatment; these investigations include haemogram, LFT, ultrasound abdomen and endoscopic examination.

Outcome of interest

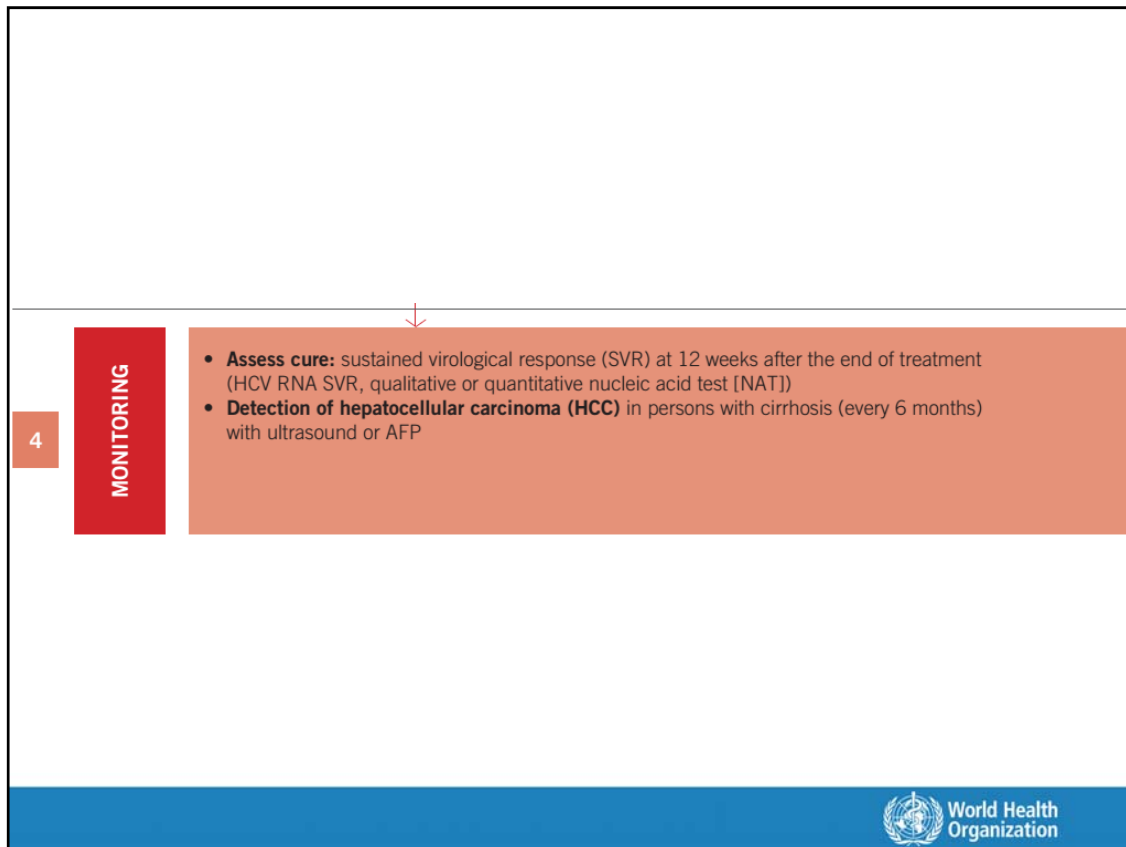
- **Sustained virological response at 12 weeks post-treatment**
- SVR12
- Undetectable HCV RNA at 12 weeks after stopping drugs
 - No cirrhosis ~95–98%
 - Cirrhosis ~80–90%

The success of DAA-based anti-HCV treatment is assessed by the sustained virological response rate after 12 weeks of stopping the treatment, which is also known as SVR12. SVR12 is achieved in 95–98% of people without cirrhosis but the rate is reduced to 80–90% in the presence of cirrhosis.

Drug interactions/warnings with DAA use

Drugs	Contraindication/warning
Sofosbuvir (SOF)	<ul style="list-style-type: none"> • Amiodarone co-administration • Renal failure (eGFR <30 mL/min/1.73m²)
Daclatasvir (DCV)	<ul style="list-style-type: none"> • Drugs that induce or inhibit activity of CYP3A
Ribavirin (RBV)	<ul style="list-style-type: none"> • Pregnancy or unwillingness to use contraception, breastfeeding • Severe concurrent medical disease (cardiac failure, COPD) • Co-administration of didanosine

We should pay attention to drug interactions and warnings with DAA use. A few of the most important interactions are described here.



In the final phase, we should conduct monitoring.

Assessing cure is necessary. We should make sure to confirm SVR 12.

In addition, even though we can confirm SVR, detection of HCC is necessary in persons with cirrhosis. Therefore, we should conduct ultrasound or AFP in every 6 months.

Monitoring while on HCV treatment

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

^a Recommended treatment for adolescents with genotypes 2 and 3 HCV infection

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

This slide shows how to monitor a person while on HCV treatment.

We should monitor full blood count, renal and liver functions at baseline and week 12 after the end of treatment.

In addition, these should be monitored at week 4, as well patients who take ribavirin or whose haemoglobin is under 10 g/dL.

Monitoring

- **While on treatment: all patients**
 - Adherence, toxicities
 - Haemoglobin, TLC, platelets (only with IFN or RBV)
 - Liver function tests (esp. if cirrhosis)
 - Creatinine
- **12 weeks after completion of treatment: all patients**
 - Treatment response: HCV RNA (12 weeks after completion)
- **On follow up after SVR: only in those with cirrhosis**
 - Hepatocellular carcinoma
 - Portal hypertension



During treatment, every patient should be monitored for drug compliance, tolerance and toxicities, if any.

After stopping treatment everyone will need an HCV RNA assay for SVR12.

After achieving SVR12, non-cirrhotic patients need no further follow up but those with cirrhosis will need lifelong follow up for cirrhosis-related complications such as HCC, varices, hepatic encephalopathy, etc.

Summary

- Acute infection is difficult to diagnosis. Spontaneous clearance is possible. Hence, if identified/suspected, it may be useful to wait.
- All persons aged >12 years with detectable HCV RNA need treatment.
- Before treatment, evaluate for cirrhosis and decompensation.
- The treatment regimen depends on person's age and cirrhosis status.
- DAAs have an excellent response and are free of adverse effects
- Sustained virological response at 12 weeks post-treatment implies cure and no further testing is needed.
- Persons with decompensated cirrhosis need closer monitoring during treatment.
- Persons with cirrhosis need follow-up for hepatocellular carcinoma



Acute infection with HCV is occasionally diagnosed and may clear spontaneously in a proportion of patients.

All those aged >12 years with active HCV infection should be treated according to the recommended treatment regimens.

Currently available DAAs are highly effective and safe, and the majority of those treated will achieve SVR12.

In the absence of cirrhosis, a person does not need any follow up after achieving SVR12.

HCV and HIV coinfection


- In patients receiving ART that has been modified to accommodate HCV treatment, HIV load should be measured within 2 to 8 weeks after changing HIV therapy to confirm the effectiveness of the new regimen.
- Clinicians should wait at least 2 weeks after ART modification before initiating an HCV DAA regimen.
- Clinicians should also wait for at least 2 weeks before resuming the original ART regimen after a patient completes the HCV DAA regimen.
- The prolonged half-life of some HIV and HCV drugs poses a potential risk of drug–drug interactions if a regimen is resumed soon after ART modification or HCV treatment completion.



In the era of DAA use, HIV/HCV-coinfected people are not considered to be a “difficult-to-treat” group because in HCV/HIV-coinfected persons the treatment regimens, durations and the response (which is measured as SVR12) are similar to those with HCV mono-infection.

In an HIV-coinfected person, drug-to-drug interactions between antiretroviral and anti-HCV drugs are very important and this may need some modification in treatment regimens.

A few important aspects should be kept in mind while dealing with an HCV/HIV-coinfected person. A few patients on antiretroviral drugs may need a change in ART regimen before starting anti-HCV drugs. In such patients, the efficacy of ART should be ensured before starting anti-HCV drugs; anti-HCV treatment should be started after at least 2 weeks of ART modification; ART should be reinstituted or modified to the pre-HCV treatment regimens after 2 weeks of stopping anti-HCV drugs.


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Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV

Home > Guidelines > Adult and Adolescent ARV > Hepatitis C Virus/HIV Coinfection

The information in the brief version is excerpted directly from the full-text guidelines. The brief version is a compilation of the tables and boxed recommendations.

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Considerations for Antiretroviral Use in Patients with Coinfections

Hepatitis C Virus/HIV Coinfection

Last Updated: October 25, 2018, Last Reviewed: October 25, 2018

- All people with HIV should be screened for hepatitis C virus (HCV) infection.
- Patients at high risk of HCV infection should be screened annually and whenever incident HCV infection is suspected.
- Antiretroviral therapy (ART) may slow the progression of liver disease by preserving or restoring immune function and reducing HIV-related immune activation and inflammation.
- The benefits of ART outweigh concerns regarding drug-induced liver injury. Therefore, ART should be initiated in all patients with HCV/HIV coinfection, regardless of CD4 T lymphocyte cell count.
- Initial ART regimens that are recommended for most patients with HCV/HIV coinfection are the same as those recommended for individuals without HCV infection. However, when treatment for both HIV and HCV is indicated, the ART and HCV treatment regimens should be selected with special consideration for potential drug–drug interactions and overlapping toxicities.
- All patients with HCV/HIV coinfection should be evaluated for HCV therapy, which includes having their liver fibrosis stage assessed to inform the length of their therapy and subsequent risk of hepatocellular carcinoma and liver disease complications.


World Health Organization

These are a few other important points that need mention in this presentation.

Drug–drug interactions: HCV and HIV drugs

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

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

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

This slide shows the drug–drug interactions of HCV and HIV drugs. The green marks mean that no clinically significant interaction is expected, therefore, we can prescribe safely.

Practical session case-based learning



Now we will do some practice sessions.

Case 1

First case

Case 1

- A 52-year-old man presents with malaise
 - No previous illness
 - Examination: unremarkable
 - Investigations
 - ALT **64 IU/L** (normal <40)
 - AST **88 IU/L** (normal <40)
 - HBsAg Negative
 - Anti-HCV **Positive**

What further test would you order?

A 52-year-old gentleman had a few nonspecific symptoms and was detected to be anti-HCV positive.

Case 1: laboratory test results

Investigations	Values
Haemoglobin (g/dL)	11.8
Platelets (X10 ⁹ /L)	98
Total bilirubin (mg/dL)	1.2
Albumin (g/dL)	3.4
AST (IU/L)	88 (normal <40)
Prothrombin time (INR)	1.6
HCV RNA quantitative (log ₁₀ IU/mL)	7.1
Ultrasound	Coarse echotexture of liver Portal vein diameter 14 mm Splenomegaly, no ascites

His platelets were low, AST was elevated and USG abdomen showed features of chronic liver disease or cirrhosis.

Case 1: management issues

- Is treatment recommended?
- What is the stage of liver disease?
 - cirrhosis versus no cirrhosis
 - compensated versus decompensated
- What regimen should one use?
- How would you monitor the patient during treatment?
- Does the patient require follow up after achieving SVR 12?

These are the questions that we need to answer before starting treatment.

Case 1

Is treatment recommended?

HCV RNA is detectable. Hence, yes.

What is the stage of liver disease?

$$\text{APRI} = [88/40] \times 100/98 = 2.2$$

APRI >2.0 → Liver cirrhosis (compensated)

Select the preferred recommended regimen

Sofosbuvir/daclatasvir for 24 weeks

Sofosbuvir/velpatasvir for 12 weeks

Glecaprevir/pibrentasvir for 12 weeks

How should the treatment be monitored?

For efficacy and decompensation

Follow up with screening for HCC: lifelong

Case 2

Case 2

- A 45-year-old woman
- Complaints: insomnia
- No previous hospitalization
- No alcohol, tobacco and substance use
- Examination: unremarkable
- Investigations
 - Hb 12.6 g/dL
 - AST 34 IU/L (normal <40 IU/L)
 - HBsAg Negative
 - Anti-HCV **Positive**

What tests would you order?

Case 2: laboratory test results

Investigations	Values
Haemoglobin (g/dL)	9.8
Platelets (X10 ⁹ /L)	218
Total bilirubin (mg/dL)	0.8
Albumin (g/dL)	4.0
AST (IU/L)	34 (normal <40)
Prothrombin time (INR)	1.5
HCV RNA (log ₁₀ IU/mL)	6.4
Ultrasound	Liver normal size, echotexture Portal vein diameter 10 mm Spleen normal, no ascites

Case 2

What is the stage of liver disease?

$$\text{APRI} = [34/40] \times 100/218 = 85/218 = 0.4$$

APRI < 2.0 → No liver cirrhosis

Is treatment recommended?

HCV RNA is detectable.

Select the recommended preferred regimen

Sofosbuvir/daclatasvir for 12 weeks

Sofosbuvir/velpatasvir for 12 weeks

Glecaprevir/pibrentasvir for 8 weeks

What monitoring do you require?

Monitor during treatment. Ensure SVR 12.

No follow up is needed after SVR12 has been documented.

Case 3

Case 3

- 55-year-old woman
- Complaints: abdominal distension x 3 months
 - No previous hospitalization
 - No alcohol, tobacco and substance use
 - Examination: bilateral pedal oedema, splenomegaly, ascites
 - Investigations
 - Hb 10.6 g/dL
 - AST 76 IU/L (<40 IU/L)
 - HBsAg Negative
 - Anti-HCV **Positive**
- **What tests would you order?**

Case 3: Laboratory test results

Investigations	Values
Hemoglobin (g/dL)	10.8
Platelets (X10 ⁹ /L)	75
Total bilirubin (mg/dL)	1.2
Albumin (g/dL)	2.8
AST (IU/L)	96 (normal <40)
Prothrombin time (INR)	1.9
HCV RNA (log ₁₀ IU/mL)	7.1
Ultrasound	Small, shrunken, nodular liver Portal vein diameter 14 mm Splenomegaly, moderate ascites

Case 3

What is the stage of liver disease?

$$\text{APRI} = [96/40] \times 100/75 = 3.2$$

APRI >2.0 → Liver cirrhosis

Compensated or decompensated cirrhosis?

Ascites present >> decompensated cirrhosis

Is treatment recommended?

HCV RNA is detectable. Hence, yes.

Select recommended preferred regimen

Refer to a higher centre.

Case 3

What is the stage of liver disease?

$$\text{APRI} = [96/40] \times 100/75 = 3.2$$

APRI >2.0 → Liver cirrhosis

Ascites present >> **decompensated cirrhosis**

Is treatment recommended?

HCV RNA is detectable. Hence, yes.

Select the recommended preferred regimen

Refer to a higher centre.

What monitoring does she require?

Monitor **for decompensation** and efficacy (SVR 12).

Follow up with screening for **HCC – lifelong**.

Treatment: patient with advanced liver disease

- Longer treatment duration
- Need for ribavirin
- Need for supportive treatment (for ascites, varices, etc.)
- Poor drug tolerance, especially ribavirin
- Worsening of liver disease
- Poorer response Lower SVR 12
 Higher risk of relapse
- Need follow up for complications of cirrhosis, even after SVR

Case 4

- 15-year-old girl
- Incidentally detected HCV positive
- No previous hospitalization
- Examination: nno abnormality detected
- Investigations
 - Hb 12.6 g/dL
 - AST **76 IU/L** (<40 IU/L)
 - HBsAg Negative
 - Anti-HCV **Positive**
- **What tests would you order?**

Case 4: laboratory test results

Investigations	Values
Haemoglobin (g/dL)	12.6
Platelets (X10 ⁹ /L)	245
Total bilirubin (mg/dL)	0.8
Albumin (g/dL)	4.0
AST (IU/L)	76 (normal <40)
Prothrombin time (INR)	1.0
HCV RNA (log ₁₀ IU/mL)	6.4
Ultrasound	Liver normal size, echotexture Portal vein diameter 10 mm Spleen normal, no ascites

Case 4

What is the stage of liver disease?

$$\text{APRI} = [76/40] \times 100/245 = 0.80$$

APRI < 2.0 → No liver cirrhosis

Is treatment recommended?

HCV RNA is detectable.

Select the recommended preferred regimen

Case 4

- For age 12–17 years, only sofosbuvir, ledipasvir and ribavirin are approved.
- Ledipasvir is a genotype-specific drug.
- Hence, genotype testing is needed.

Case 4

What is the stage of liver disease?

$$\text{APRI} = [76/40] \times 100/245 = 0.80$$

APRI < 2.0 → No liver cirrhosis

Is treatment recommended?

HCV RNA is detectable.

Genotype = 1. Select the recommended preferred regimen

Sofosbuvir/ledipasvir for 12 weeks

What is the monitoring required?

On-treatment monitoring. Ensure SVR1 2.

No monitoring or follow up needed after SVR 12 is reached.

Review: who to treat?

When to start treatment in adults and adolescents

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

All those with active HCV infection and who are at least 12 years of age should be considered for treatment.

Review: regimen depends on age

What treatment to use for adults and adolescents

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

(Conditional recommendation, moderate quality of evidence)

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

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

(Strong recommendation/very low quality of evidence)

For adults, pangenotypic regimens are to be used while for children between 12 and 17 years, a genotype-specific regimen has to be used.

Review: regimens for adults

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

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

- Sofosbuvir/velpatasvir 12 weeks
- Sofosbuvir/daclatasvir 12 weeks
- Glecaprevir/pibrentasvir 8 weeks³

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

- Sofosbuvir/velpatasvir 12 weeks
- Glecaprevir/pibrentasvir 12 weeks³
- Sofosbuvir/daclatasvir 24 weeks
- Sofosbuvir/daclatasvir 12 weeks⁴

These are the pangenotypic regimens recommended for adults with or without cirrhosis.

Review: other considerations

- The use of pan-genotypic regimens obviates the need for genotyping before treatment initiation.
- In resource-limited settings, WHO recommends that the assessment of liver fibrosis should be performed using non-invasive tests (e.g. aspartate/platelet ratio index (APRI) score or FIB-4 test). This can determine if there is cirrhosis before initiation of treatment.
- There are a few contraindications to using pan genotypic DAAs together with other medicines.



Before starting treatment, liver fibrosis should be assessed with simple tests such as APRI or FIB-4. Pangenotypic regimens are preferred.

The DAAs have very few side-effects and need very limited monitoring while on treatment.

Treatment response should be ascertained with SVR12.

Review: other considerations

- DAAs are well tolerated, with only minor side-effects. Therefore, the frequency of routine laboratory toxicity monitoring can be limited to a blood specimen at the start and end of treatment.
- Following completion of DAA treatment, sustained virological response (SVR) at 12 weeks after the end of treatment is used to determine treatment outcomes.



Before starting treatment, liver fibrosis should be assessed with simple tests such as APRI or FIB-4. Pangenotypic regimens are preferred.

The DAAs have very few side-effects and need very limited monitoring while on treatment.

Treatment response should be ascertained with SVR12.