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SHC & ME DEPARTMENT

Primary & Secondary Healthcare Department

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PROVINCIAL HCV TREATMENT GUIDELINES FOR PUNJAB

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INTRODUCTION

Viral Hepatitis B & C is a global problem and a major challenge for all public health departments. It is estimated that yearly approximately 1.4 million persons die from different types of viral hepatitis. In Pakistan, the 2008 National survey showed 5% prevalence of hepatitis C virus (HCV) infection, affecting over 8 million people. From the PMRC survey of 2008 to Punjab Bureau of Statistics survey 2018 the HCV problem in Punjab has increased from 6.7% to 8.9% though HBV situation has improved from 2.4 to 2 %. Pakistan now stands as the highest HCV prevalence country in the world and Punjab being the most populace province bears the maximum burden of HBV & HCV. Being a silent killer, HCV virus causes chronic liver disease in large majority of people who remain unaware of their infection and progress to cirrhosis and its complications ultimately leading to thousands of early deaths.

Although Punjab Government has been trying to control the disease through its prevention and treatment strategies but the impact was limited as the diagnosis and treatment of HCV & HBV was very cumbersome and expensive coupled with poor response to interferon. In management of Hepatitis C viral infections, the development of pan genotypic direct acting antivirals (DAAs) has brought a paradigm shift. The challenge remains to treat as many patients suffering from hepatitis as possible through "test and treat strategy' and prevent further spread of disease by 'educate, risk behaviours modification and vaccinate strategy'. Since Pakistan is producing the world's cheapest DAAs, with an over 95% response, therefore there was a great need to revise our HCV guidelines. Upon the request of the Ministry of National Health Services, Regulation and Coordination (NHSRC) and Technical Advisory Group (TAG) for the prevention and control of viral hepatitis in Pakistan, the HCV guidelines were updated in 2018 through the technical assistance of WHO. Since Punjab is running the biggest hepatitis control programme of the country, hence there was a need to update the guidelines for better guidance to the treating physicians in the province.

Punjab has the widest and well integrated network of providing treatment facilities to patients suffering from hepatitis through more than 145 hepatitis clinics in various hospitals attached with Primary and Secondary Health Department and Specialized healthcare & medical Education department. Punjab hepatitis control programme is using a uniform EMR for integration, avoidance of overlaps and devising common strategies. The purchase processes and diagnostics are centralized to ensure uniformity and continuity of care.

The Hepatitis management guidelines have been revised with the intention to "treat all" persons having the disease irrespective of their disease status. The testing and treatment algorithm has been simplified to such an extent that all expensive and unnecessary tests like genotype have been removed and recommendations have been made using the local evidence. The guidelines are primarily focusing on their use by the members of provincial hepatitis control programme and physicians in public and private health care settings including the general practitioners.

These guidelines need to be disseminated to the hepatitis clinics of provincial health departments, partner hospitals, departments, NGO's and the private sector for wider use with trainings of health care providers where required. Universal testing and treatment of HCV at all levels of health care is the need of the day if Pakistan has to achieve hepatitis elimination targets of 2030.

We remain committed to eliminating hepatitis C by 2030.

Barrister	**Captain ®**	**Professor**
Nabeel Awan	**Muhammad Usman**	**Ghias Un Nabi Tayyab**

Provincial HCV Treatment Guidelines for Punjab

1. BACKGROUND

Global estimates show that about 71 million people are infected with hepatitis C virus (HCV) and out of these almost 399,000 die each year.[1] Once infected, the disease has no specific signs or symptoms, therefore majority progress to chronic liver disease.[2] Almost one third of chronically infected liver disease cases may progress to liver cirrhosis and later hepatocellular carcinoma.[3] Previously many people who have been diagnosed could not undergo treatment due to access and affordability issues but the scenario is changing since Direct Acting Anti virals (DAAs) with their high efficacy (SVR rates more than 90 percent) have become available and affordable in many countries including Pakistan.[4]

The first national hepatitis prevalence survey for Pakistan was done in 2008, and it reported a 5% prevalence of HCV antibodies in the general population (8 million people). The disease prevalence was highest in Punjab (6.7%).[5] A serosurvey was done by Bureau of Statistics, Punjab in 2017-18, which showed a rise in the HCV prevalence to 8.9%. If these figures are taken as National figures, it is estimated that almost 14 million cases have HCV infection and one third i.e. 5 million will go into chronic disease and its complications leading to death.

The HCV testing and treatment guidelines have been based on WHO and EASL guidelines, local data, international literature and national guidelines on the management of HCV and have used a combination of low costs but internationally acceptable tests and treatment strategies with appropriate durations assigned for patients suffering from an uncomplicated disease as well as advanced fibrosis.

2. INTRODUCTION

The first national treatment guidelines for hepatitis C were developed by Pakistan Society of Gastroenterology in 2004.[6] Second guidelines for treatment of hepatitis were developed by the Prime Minister's Programme for Prevention and Control of Hepatitis in Pakistan, 2005.[7] Then the National Technical Advisory Group (TAG) on viral hepatitis developed the "Guidelines for the treatment of persons with chronic hepatitis C infection; 2016". The need for these new guidelines was felt due to introduction of novel testing and treatments that have become available for HCV screening and treatment.

The Provincial Technical Working Group (TWG) has recommended that this document will remain a dynamic guideline that would require frequent revisions based on upcoming treatment regimens worldwide. Therefore, in November 2018 a National Consultation Workshop was held to update the "Guidelines for the treatment of persons with chronic hepatitis C infection; 2016" according to the latest testing and treatment regimens available in the country. These guidelines have been named as "Guidelines for the treatment of persons with chronic hepatitis C infection; 2019". Since each provincial programme is working under the new system after devolution and has its own strengths and weaknesses hence the task was assigned to the committee initially in 2019 and then later on in 2020 for upgradation and revision of local public health practices and evidence aligned with updated national guidelines issued by Ministry of National Health Services Regulations and Coordination (NHSR& C).

The objective of these guidelines is to provide evidence-based recommendations on cascade of care; registration, screening, testing, enrolment in treatment for persons infected with HCV infection. 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.

In the screening section, the guidelines would focus on using certified/standardized Rapid Diagnostic Tests (RDT) to screen patients.

The treatment duration will be determined on the basis of the amino-transferase/platelet ratio index (APRI) score.

3. METHODOLOGY

A Technical Working Group (TWG), Punjab that was nominated by the Provincial Government and endorsed by steering

committee on viral hepatitis, has updated provincial HCV Treatment Guidelines. Provincial TWG comprised of gastroenterologists, clinicians and public health experts from national and provincial health departments, academic and research institutions, civil society organizations (CSOs) and patient groups.

The technical working group in its meeting noted that last guidelines were adapted from WHO guidelines. The group discussed the WHO, EASL and AASLD guidelines and a detailed comparative point to point discussion was carried out and suggestions were made keeping in view the on ground limitation of resources and finanaces. Based on these discussions the task was assigned to a core group to make a provisional draft of the guidelines. The provisional draft was presented in TWG and detailed point to point discussion was done again and amendments were suggested in the draft. The draft was shared after the suggested changes with the whole group through E mails and thus a consensus document was approved.

4. RECOMMENDATIONS ON SCREENING

4.1 Populations with High HCV Prevalence

- Since Punjab is a high prevalence area with figures > 5 % of total population, hence mass screening is warranted.
- Persons with past or present history of taking more than four therapeutic injections per year
- Persons with past history of any surgery including gynaecological and dental treatment
- Persons with past history of blood transfusion
- Persons with past history of admission in health care setting
- People who inject drugs (PWID)
- Men who have sex with men (MSM)
- Partners and family members of HCV index cases

4.2 Screening to Identify Persons with HCV Infection

- HCV serological testing shall be expanded to all parts of Punjab to detect HCV positive patients in the population and link them to cascade of care.
- Testing shall be offered to all populations but prioritized in high risk population of the country.
- To test for serological evidence of past or present infection in adults, adolescents and children (>18 months of age)[1] HCV serological assay using a rapid diagnostic test with WHO prequalified (RDT) that meet minimum safety, quality and performance standards (with regard to both analytical and clinical sensitivity and specificity).

1. HCV infection can be confirmed in children less than 18 months only by virological assays to detect HCV RNA, because transplacental maternal antibodies remain in the child's bloodstream up until 18 months of age, making test results from serology assays ambiguous.

In Pakistan, many people remain un-diagnosed until they develop complications of cirrhosis like variceal bleeding, ascites or encephalopathy or terminal liver cancer. Often at this point, liver injury is difficult to revert and virus-clearing treatments may not be optimally effective but still effective enough to be offered a treatment as this may reduce the disease burden and reduce the chance of disease transmission to healthy contacts. It is therefore important to identify patients earlier in the course of disease. Keeping in mind the huge burden of disease in Punjab, it is strongly recommended that anti HCV testing should be offered to all individuals and screening should be available at all health care public and private health facilities to enroll as many patients as possible for enlistment in to cascade of care.

4.3 When and how to Confirm Diagnosis of Chronic HCV Infection

- All anti HCV positive persons shall be confirmed using Nucleic acid testing (NAT) i-e Real Time PCR for detection of HCV

RNA unless they give history of anti HCV treatment along with documented evidence of NAT negative.

◆ With the use of pangenotypic regimens, genotype testing is no more required before starting the treatment.

◆ PCR facility will be provided by Hepatitis Control Programme (HCP) Punjab. Sample collection, transportation, testing and reporting mechanism will be provided to the center separately.

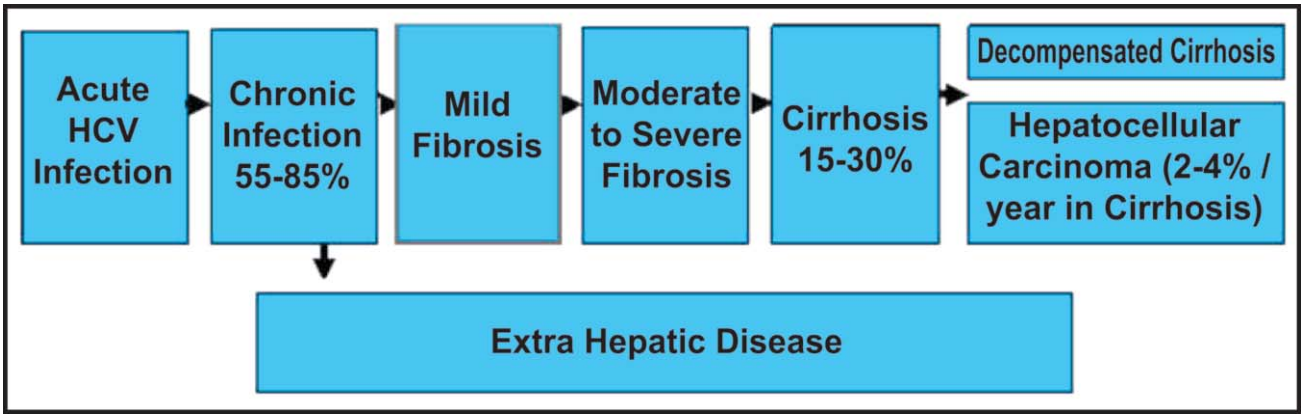


Figure1: Natural History of HCV.

5. RECOMMENDATIONS ON CARE OF PEOPLE INFECTED WITH HCV

◆ All anti HCV positive patients should be checked for HBV, HIV (preferably), tuberculosis, diabetes mellitus, current medication list, renal impairment, blood dyscraisas, pregnancy and lactation.

◆ All HCV should be tested for HBV and those who are negative will be vaccinated against HBV if not already vaccinated

◆ All HCV cases should be questioned for alcohol intake.

◆ All HCV positives should be informed on how to avoid disease transmission to others.

◆ Close contacts of HCV patients will undergo mandatory HCV testing using WHO prequalified RDT.

In many persons having chronic HCV infection, co-morbidities like diabetes may be found which may be treated simultaneously. Similarly, certain health conditions and behaviours can accelerate the disease progression and liver damage. These include alcohol consumption and obesity. Although no clear data about the consumption of alcohol in HCV patients is available in Pakistan, but anecdotal evidence suggests that its use is not very uncommon. Heavy intake of alcohol (210 and 560 gms/week) doubles the risk of cirrhosis.[8]

Co-infection with HBV or HIV is often associated with poor prognosis.[9] Patients with obesity and metabolic syndrome due to underlying insulin resistance are more prone to have non-alcoholic fatty liver disease (NAFLD) which is a risk factor for the progression of fibrosis in HCV positive cases.[10] Therefore HCV infected patients who are overweight/obese (BMI 25kg/m^2 or more) should be counseled for weight reduction via diet, exercise, other medical therapies including hypolipidaemic drugs such as statins.

6. ASSESSMENT OF PERSONS WITH HCV INFECTION PRIOR TO TREATMENT

Clinical assessment

◆ All HCV RNA positive cases shall be assessed for the degree of liver fibrosis to decide the duration of treatment through use of APRI score and tissue elastography (in selected cases).

◆ This recommendation was formulated assuming that liver biopsy is not a feasible option.

◆ Pretreatment evaluation for the risk of adverse events and length of treatment is based on the person's clinical co morbidities, previous drug exposures, concomitant medications and knowledge of treatment regimen to be administered.

◆ Women of childbearing age willbe offered pregnancy testing if last menstural period (LMP) is delayed and will be informed about the lack of available data on the safety and efficacy of DAAs during pregnancy.

◆ Patients getting pregnant while on treatment may continue the Ribavirin free regimens.

6.1 Baseline labs Assessment

◆ Blood Counts

◆ Liver Function Tests (Bilirubin, ALT, AST, ALP, Albumin)

◆ Serum Creatinine

◆ Random Blood Glucose

◆ Prothrombin Time(PT) / International Normalized Ratio(INR)

6.2 Assessing The Degree of Liver Fibrosis and Cirrhosis to Decide Regimine and Duration of Treatment

Since, liver biopsy is invasive and has complications; therefore, non-invasive methods are recommended to estimate liver fibrosis. These include APRI test or Fib4. Other non-invasive tests like liver elastography or fibroscan may be more accurate than APRI or Fib4 but their high cost prohibits their wider use in the resource poor countries.[11]

In resource-limited settings, before starting the DAAs, liver fibrosis shall be assessed using non-invasive tests (e.g. Aspartate aminotransferase/Platelet Ratio Index (APRI) score to determine the presence of cirrhosis to decide the duration of therapy and have been validated in several studies for its specificity and sensitivity.

Other non-invasive tests that require more resources such as Shear wave or Transient elastography shall be used in selected cases as discussed under and facility shall be available at specialized healthcare setups.

Assessment of the liver fibrosis shall be made by using noninvasive test, the APRI score (Figure-2) with the interpretation of the test as per table. An online calculator is available in the software of Hepatitis Control programme (HCP) Punjab for patient registration of the programme. Table-2 summarizes the cut-off values for the detection of cirrhosis. This information will allow clinicians to decide on the appropriate pangenotypic treatment duration and inclusion of Ribavirin in the regimen. A staging strategy that uses a combination of two cut off values will be used. If APRI score <1, it will be labeled as absence of cirrhosis and if the APRI score is >2, it will be labeled as cirrhosis. If the patient has value in between 1 and 2, an alternative testing in the form of fibro scan/transient elastography will be done and the facility will be available in the nearest autonomous Medical Institute (AMI) attached hepatitis clinics.

Figure-2:

APRI = [{AST (IU/L)/ AST_ULN (IU/L)}×100]/ platelet count (10^9/L)
FIB4= age (yr) x AST(IU/L)/platelet count (109/L x [ALT(IU/L)1/2]

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

Table-2: Low and high cut-off values for the detection of significant fibrosis and cirrhosis.

	Low cut-off	In determinate	High cut-off
APRI score	<1.0	1 - 2	>2.0
Stage of disease/action	Treat as non Cirrhosis	Needs Elastography	Treat as Cirrhosis

These non-invasive tests are recommended to be used for deciding the duration of DAAs. All patients without cirrhosis will receive 12 weeks of therapy while those with cirrhosis will receive 24 weeks therapy.[11,12]

In Pakistan, where the cost of screening and treatment is expensive and access to health facilities is a serious issue, it is recommended that APRI score will be used to assess the degree of fibrosis. Due to low literacy rates in Pakistan, many people do not know their correct age. Fib4 is dependent on exact age; therefore in such cases APRI is preferred over Fib4. Blood tests that are used to calculate APRI are cheap and widely available throughout the country.[11]

7. RECOMMENDATIONS FOR TREATMENT

Treatment in adults and adolescents

◆ All individuals (except for pregnant or lactating women) diagnosed with HCV infection who are 12 years of age or older, irrespective of disease stage should be offered treatment.

◆ All persons with chronic HCV irrespective of their disease status will be prioritized for treatment.

◆ Direct Acting Antiviral Agents (DAAs) Sofosbuvir and Daclatasvir without Ribavirin for 12 weeks will be treatment of choice in all cases without cirrhosis.

Patients with cirrhosis will be treated with Sofosbuvir, Daclatasvir and Ribavirin for 24 weeks[13]

Treatment in children

◆ All children 6 years and older or weighing at least 37 pounds (17kg) without cirrhosis will be treated with Sofosbuvir and Velpatasvir for 12 weeks

◆ All children 6 years and older or weighing at least 37 pounds (17kg) with cirrhosis will be treated with Sofosbuvir, Velpatasvir and Ribavirin for 12 weeks. Chances of having significant fibrosis because of HCV in this age group (6-12) are very remote and an additional pathology must be excluded.[16]

7.1 Rationale for Selection of HCV Treatment

Ever since the availability of pan genotypic DAAs, there is no need to check the genotype to decide the drug combinations.

7.2 Treatment Decisions

Treatment with DAAs shall be given to all patients who have a detectable HCV RNA. The treatment regimens are described in Table-3.[11-13]

Table-3: Treatment Regimens.

Type of Patients	Preferred Treatment	Treatment facility
All HCV RNA positive patient without cirrhosis	**Sofosbuvir** 400 mg one tablet (after breakfast once a day) for 12 weeks **Plus** **Daclatasvir** 60 mg one tablet (after breakfast once a day) for 12 weeks	All centers
Patients with Cirrhosis*	**Sofosbuvir** 400 mg one tablet (after breakfast once a day) for 24 weeks **Plus** **Daclatasvir** 60 mg one tablet (after breakfast once a day) for 24 weeks **Plus** **Ribavirin** (1000 mg in 2 divided doses for <75 kg and 1200 mg in 2 or 3 divided doses for >75 kg) for 24 weeks	Hepatitis clinics at AMI's under Specialised Health Care and Medical Education (SHC & ME)

* These patients will be screened for oesophageal varices and HCC surveillance with alpha-fetoprotein and ultrasound abdomen every 6 months and in case of decompensation all the complications will be managed at tertiary care hospitals and will be listed for liver transplant.

8. CLINICAL CONSIDERATIONS

8.1 Contraindications to Treatment

◆ Although considered safe, all pregnant women and lactating mothers shall not receive DAA due to their possible adverse effects on the foetus and excretion in the breast milk. Therefore, sexually active women of child bearing age and their male partners must be counseled to use contraception during and for 6 months after therapy.[11-13]

◆ In case patient becomes pregnant during, treatment medicines except Ribavirin are to be continued for the course of treatment

◆ Pregnant patients with advanced DCLD will be offered termination of pregnancy in consultation with obstetrician

◆ Ribavirin is only to be used in cirrhosis including those with decompensation.

8.2 Absolute Contraindications

Following are the absolute contraindications for RBV:

◆ Pregnancy

◆ Breastfeeding

◆ Life expectancy < 6 months due to extra hepatic cause

◆ Severe concurrent medical disease

◆ Poorly controlled cardiac failure

◆ Age less than 2 years

◆ Hypersensitivity to drugs

9. ASSESSMENT OF TREATMENT RESPONSE

◆ NAT i-e Real Time PCR for detection of HCV RNA should be used as the test of cure at 12 weeks (i.e. sustained virological response [SVR12]) after completion of antiviral treatment.

◆ NAT testing is not required during or at the end of treatment.

10. MONITORING FOR SIDE EFFECTS

◆ All DAAs are safe and have no major side effects; therefore except for those patients who are receiving ribavirn based DAA treatment, there is no need to monitor them for side effects.

◆ RBV causes haemolytic anaemia and is teratogenic. Persons with cirrhosis are at high risk of serious adverse events (40-57%), particularly anaemia, infection and renal worsening.[14,15] Monitoring during treatment with RBV is therefore recommended at regular intervals.

Table-4: Monitoring during treatment.

Time	DAA alone	DAA + Ribavirin	In all cases
	Full blood count, renal, liver function	Full blood count, renal, liver function	PCR QL for HCV RNA
Baseline	✓	✓	✓
Week 2	X	✓	X
Week 6	X	✓	X
Week 12	X	✓	X
End of treatment	X	✓	X
Week 12 after end of treatment	✓	✓	✓

Table-5: Follow up of registered HCV cases.
On routine follow-up visits according to the schedule given above, for each patient:

Clinically assess for:	■ Adherence to drug intake ■ Anaemia; ascites; reported complaints/ side effects ■ Known co-morbidity: HTN/CVD, DM, renal impairment etc
Investigate for:	■ CBC (leukocyte and platelet count) ■ ALT (altered: male ≥30; female ≥ 20 years ■ Known co-morbidity - as required e.g. RBG;proteinuria (if renal dysfunction)
Prescribe and dispense drugs:	■ One month of anti-HCV drugs; ◆ Hb. 8.5 - 10 g/dl: reduce RBV to 600mg/day; monitor fortnightly ◆ Hb. < 8.5; stop RBV ■ Drug for co-morbidity, as per programme/hospital practice ■ HBV vaccine shot, as schedule
Educate patient	■ Counsel on adherence; also prevention ■ Update the HCP recommended records
Monitoring visit:	■ If cirrhotic: assess for de-compensation; do albumin, bilirubin and coagulation (INR) ■ If anaemia or renal impairment: check Hb. and proteinuria
Refer if:	■ De-compensation or signs of deterioration

Treatment will be offered to all individuals diagnosed with HCV infection who are 12 years of age or older (with exception of pregnant and lactating women) irrespective of disease stage.

A. Children 6-12 years with hepatitis C will be treated with Sofosbuvir and Velpatasvir with or without Ribavirin depending on presence or absence of cirrhosis.

B. Selected cases with severe liver disease, children at higher risk of progressive disease, such as with HIV co-infection, thalassaemia major and survivors of childhood cancer should be referred to AMIs attached Hepatitis clinics.

11. CONSIDERATIONS FOR SPECIFIC POPULATIONS

Specialist care needs to address the additional needs of special populations of patients, including persons with liver cirrhosis, children and adolescents, chronic renal failure patients, patients who inject drugs (PWID) and persons co-infected with (or at risk for infection with) HBV,TB and HIV.

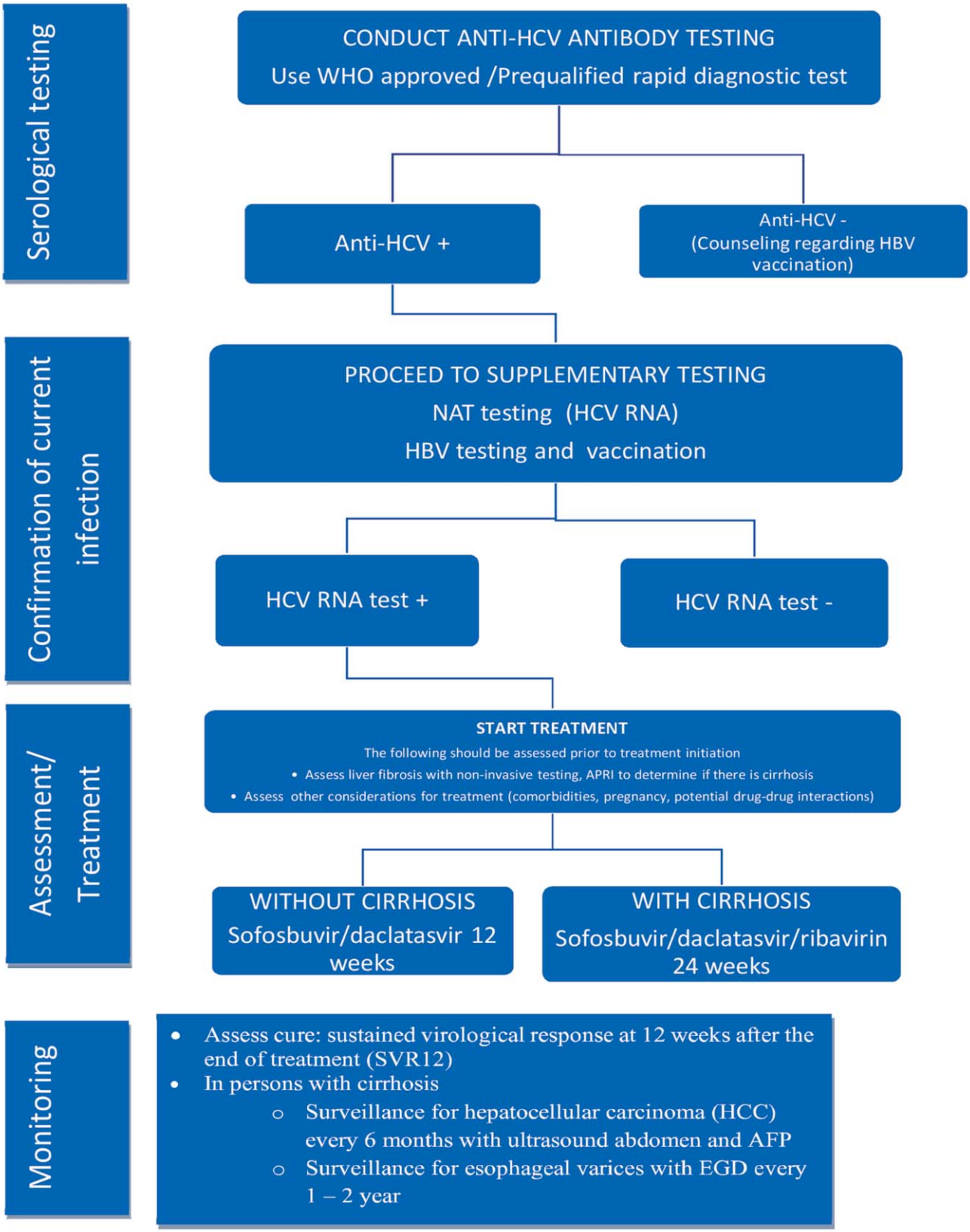
11.1 Patients with decompensated cirrhosis[17-20]

◆ Patients with decompensated (Child-Pugh B or C) cirrhosis shall be treated in regional centers of expertise at the nearby Autonomous Medical Institute Hepatitis Clinic and close monitoring during therapy is required. The therapy may be stopped in case of worsening decompensation during treatment.

◆ Patients with decompensated (Child-Pugh B or C) cirrhosis, without HCC, awaiting liver transplantation with a MELD score <18-20 shall be treated prior to liver transplantation. Treatment should be initiated as soon as possible in order to complete a full treatment course before transplantation and assess the effect of SVR on liver function, because significant improvement in liver function may occur in selected cases to the extent of avoiding the need for liver transplant.

◆ Patients with decompensated (Child-Pugh B or C) cirrhosis, without HCC, awaiting liver transplantation with a MELD score <18-20 can be treated with Sofosbuvir, Daclatasvir, with daily weight-based Ribavirin (1,000 or 1,200 mg in patients <75 kg or ≥75 kg, respectively) for 24 weeks (Ribavirin should be started with an initial lowest tolerated dose (200-400 mg per day) and the dose subsequently adjusted depending on tolerance).

◆ The higher risk of adverse events reported in patients with decompensated cirrhosis awaiting liver transplantation


Serological testing
CONDUCT ANTI-HCV ANTIBODY TESTING
Use WHO approved /Prequalified rapid diagnostic test
Anti-HCV +
Anti-HCV -
(Counseling regarding HBV vaccination)
Confirmation of current infection
PROCEED TO SUPPLEMENTARY TESTING
NAT testing (HCV RNA)
HBV testing and vaccination
HCV RNA test +
HCV RNA test -
Assessment/ Treatment
START TREATMENT
The following should be assessed prior to treatment initiation
• Assess liver fibrosis with non-invasive testing, APRI to determine if there is cirrhosis
• Assess other considerations for treatment (comorbidities, pregnancy, potential drug-drug interactions)
WITHOUT CIRRHOSIS
Sofosbuvir/daclatasvir 12 weeks
WITH CIRRHOSIS
Sofosbuvir/daclatasvir/ribavirin 24 weeks
Monitoring
• Assess cure: sustained virological response at 12 weeks after the end of treatment (SVR12)
• In persons with cirrhosis
o Surveillance for hepatocellular carcinoma (HCC) every 6 months with ultrasound abdomen and AFP
o Surveillance for esophageal varices with EGD every 1 – 2 year

necessitates appropriately frequent clinical and laboratory assessments during and after HCV therapy.

◆ Patients with decompensated cirrhosis without HCC awaiting liver transplantation with a MELD score ≥18-20 should be transplanted first, without antiviral treatment. HCV infection should be treated after liver transplantation.

◆ Patients with decompensated cirrhosis without HCC awaiting liver transplantation with a MELD score ≥18-20 can be treated before transplantation if the there is delay in transplant list of more than 6 months, depending on the local situation. Every possible attempt should be made to treat the patients waiting Liver transplantation with the available treatment options.

11.2 Persons with co-infections

11.2.1 Persons with HCV/HBV co-infection.[19,20]

◆ HBV and HCV co-infection may result in an accelerated disease course; HCV is considered to be the main driver of disease.[21,22]

There is potential risk of HVB reactivation during or after clearance of HCV.[23]

◆ Patients with HCV/HBV co infection should be treated in regional centers of expertise at the nearby Autonomous Medical Institute Hepatitis Clinic if the APRI score is >2.

◆ Patients with HBV-HCV co infection should be treated with the same anti-HCV regimens, following the same rules as HCV mono infected patients.

◆ Patients co-infected with HCV and HBV fulfilling the standard criteria for HBV treatment should receive nucleoside/nucleotide analogue treatment.

◆ Patients who are HBs antigen-positive should receive nucleoside/nucleotide analogue prophylaxis at least until week 12 post anti-HCV therapy and be monitored monthly if HBV treatment is stopped.

◆ In patients who are HBs antigen-negative but anti-HBc antibody-positive, serum ALT levels should be monitored monthly, HBs antigen and HBV DNA should be tested if ALT levels do not normalize or rise during or after anti-HCV therapy, and nucleoside/nucleotide analogue therapy should be initiated if HBs antigen and/or HBV DNA are present.

◆ HBs antigen-negative, anti-HBc antibody-positive patients undergoing anti-HCV treatment should be monitored monthly for ALT and tested for HBs antigen and HBV DNA in case of ALT elevation.

11.2.2 HCV/HIV co-infection

◆ These cases should be referred to specialized HIV treatment centers of the department and treatment shall be started in consultation with HIV centers by the hepatitis center of the respective AMI.

◆ Co-infection with HIV and HCV poses a challenge because of large number of affected persons, negative impact of HIV on the natural history of HCV infection, and the therapeutic challenges of dealing with drug interactions that are used for these diseases.

◆ 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 co-infection.[24] As the management of these infections is complex, it is advisable to provide treatment in an integrated fashion by involving HIV/AIDS programme which shall provide all medications free of cost to the patient along with regular monitoring and testing while for HCV a clinician familiar with HCV treatment may be involved.

11.3 Patient with HCV/ Tuberculosis co infection

◆ Each patitent with HCV should be screened for active tuberculosis in the presence of suggestive symptoms.

◆ Active tuberculosis should be treated first, concurrent treatment of HCV infection and TB must be avoided.

◆ These patients shall be monitored at AMI attached teaching hepatitis clinics.

◆ Patients with tuberculosis/HCV co infection can be treated in primary care clinics if the APRI score is <1 with stable LFTs, while patients with APRI score is >1 should be treated at regional centers of expertise at the nearby Autonomous Medical Institute Hepatitis Clinic and close monitoring during therapy is required.

◆ Persons at increased risk of infection with HCV may also be at increased risk if infection with TB. Therefore, the clinical evaluation of persons being considered for HCV treatment can include screening for active TB. A four-symptom screening algorithm exists to rule out active TB. If the person does not have any one of the following symptoms — current cough, fever, weight loss or night sweats, TB can be reasonably excluded; otherwise, the person must undergo further investigations for TB or other diseases.[25] In case of active Tuberculosis and with viraemic HCV, the management of Tuberculosis takes priority status and HCV may be treated after the successful completion of Anti Tuberculosis drugs.

◆ Most of the DAAs interact with metabolic pathways in the liver, which increases or decreases the level of DAAs when co-administered with commonly used rifamycins such as rifabutin, rifampin and rifapentine. Therefore, concurrent treatment of HCV infection and TB must be avoided. In persons with HCV infection treated for TB, the risk of antimycobacterial-induced hepatotoxicity is higher than in those with TB monoinfection, although the risk of severe hepatotoxicity is rare. Monitoring liver function tests detects hepatotoxicity early.[26]

11.4 Patients with renal impairment including haemodialysis[20,27,28]

◆ GFR will be calculated using Cockcroft formula as under:

Creatinine clearance (male) = ([140-age] × weight in kg)/ (serum Creatinine × 72)

Creatinine clearance (female) = CrCl (male) × 0.85

◆ Patients with renal impairment including haemodialysis should be treated in regional centers of expertise at the nearby Autonomous Medical Institute attached Hepatitis Clinics and close monitoring during therapy is required, with the possibility of stopping therapy with evidence of worsening renal function during treatment.

◆ Patients with mild to moderate renal impairment (eGFR $\geq$30 ml/min/1.73 m^2) with HCV infection should be treated according to the general recommendations. No dose adjustments of HCV DAAs are needed, but these patients should be carefully monitored.

◆ Patients with severe renal impairment (eGFR<30 ml/min/1.73m^2) and patients with end-stage renal disease on haemodialysis should be treated in expert centers, with close monitoring by a multidisciplinary team.

◆ Sofosbuvir should be used with caution in patients with an eGFR<30ml/min/1.73 m^2 or with end-stage renal disease because no dose recommendation can currently be given for these patients.

◆ In patients receiving Ribavirin, haemoglobin levels should be carefully and frequently monitored and Ribavirin administration should be interrupted in case of severe anaemia (haemoglobin<8.5 g/dl). The use of erythropoietin and, eventually, blood transfusion, may be useful in patients with severe Ribavirin-induced anaemia.

◆ Patients with cirrhosis, and those with a contraindication or who do not tolerate Ribavirin, may benefit from 24 weeks of these therapies without Ribavirin.

◆ If treatment is urgently needed in patients with severe renal impairment (eGFR<30 ml/min/1.73 m^2) or with end-stage renal disease on haemodialysis without an indication for kidney transplantation, should receive the combination of

Sofosbuvir and Daclatasvir for 12 weeks with daily Ribavirin (200 mg/day) if the haemoglobin level is >10 g/dl at baseline, or for 24 weeks without Ribavirin. Renal function may worsen and should be carefully monitored and treatment should be interrupted immediately in case of deterioration.

◆ The risks versus benefits of treating patients with end-stage renal disease and an indication for kidney transplantation before or after renal transplantation require individual assessment.

11.5 Haemoglobinopathies

◆ HCV is more prevalent among patients with Haemoglobinopathies and there is an increased risk of rapid progression of liver disease in these patients because of iron overload.[29]

◆ Patients with Haemoglobinopathies should be treated in regional centers of expertise at the nearby Autonomous Medical Institute Hepatitis Clinic and close monitoring during therapy is required.

◆ The indications for HCV therapy are the same in patients with and without Haemoglobinopathies.

◆ Patients with Haemoglobinopathies should be treated with a Sofosbuvir and Daclatasvir for 12-24 weeks, without Ribavirin.[20]

◆ The anti-HCV regimens that can be used in patients with Haemoglobinopathies are the same as in patients without Haemoglobinopathies.

◆ When the use of Ribavirin is needed, careful monitoring is recommended, and blood transfusion support may be required.

11.6 Treatment in Children

◆ All children 6 years and older or weighing at least 37 pounds (17kg) without cirrhosis will be treated with Sofofbuvir and Velpatasvir for 12 weeks

◆ All children 6 years and older or weighing at least 37 pounds (17kg) cirrhosis will be treated with Sofofbuvir, Velpatasvir and Ribavirin for 12 weeks.[16]

11.7 Treatment failure with Sofosbuvir/Daclatasvir

Till the availability of new drugs treatment plan will be as follows:

◆ These patients should be treated with the fixed-dose combination of Sofosbuvir and Velpatasvir for 24 weeks with daily weight-based Ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively).[30]

◆ These patients will be managed only at hepatitis clinics in AMI's in consultation with expert group in steering committee.

11.8 People who inject drugs (PWID)

◆ In Pakistan a study in PWID showed a co- prevalence of HIV/HCV in 91.7% subjects.[31] Similarly a study from Lahore reported 73% co-infection.[32] PWID are at an increased risk of HCV and its related morbidity and mortality, and therefore require specialized care. When caring for PWID, the principles of respect and non-discrimination should be followed along with adherence and psychological support if required.

◆ As an integral component of a comprehensive package of harm reduction interventions, WHO recommends targeted HCV and HBV screening of PWID as a population, as they have a high prevalence of infection. Repeated

screening is required in individuals with ongoing risk, and reinfection after spontaneous clearance or successful treatment should be considered. Retesting should be done using PCR, as the antibody (anti HCV) remains positive after the first infection.

◆ Treatment of HCV in PWID requires integration of services, as other health-care needs are often also required. Care should be given only with informed consent.[33] Other health needs include opiate alcohol or other substances use, HBV and HIV infection, avoidance of discrimination or stigmatization.

◆ 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 testing and treatment may also be necessary. Acceptability of services, and peer interventions may help with reducing injecting drug use and promoting safer injection practices.

◆ PWID are at risk of infection with HBV and should be tested and vaccinated against HBV using the rapid vaccination regimen described in WHO guidelines.[34]

◆ Treatment for HCV infection is efficacious and cost effective in PWID[35,36] 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 an effective prevention, due to reduced transmission[37-39] Consideration must be given to potential drug-drug interactions between both prescribed and non-prescribed drugs.Concurrent infection with HBV, HIV and/or TB is common in PWID and these require additional consideration.[11]

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