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FOREWORD

Globally viral hepatitis affects a large population and it is estimated that yearly approximately **1.4 million** persons die from different types of viral hepatitis. In Pakistan, the 2005 National survey showed 5% prevalence of **hepatitis C virus** (HCV) infection, affecting over **8 million** people. The 2018 survey of Punjab province showed that the HCV prevalence now is 9%. Taking Punjab's prevalence as the national figures, Pakistan now stands as the highest HCV prevalence country in the world. 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.

Previously the diagnosis and treatment of HCV was very cumbersome and expensive coupled with poor response to interferon. Since the development of pan genotypic direct acting antivirals (DAAs), the diagnosis and treatment of HCV has become so simple that even a paramedic can treat it. Credit should be given to WHO, whose team was very instrumental in revising their HCV guidelines in 2018. 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, Regulations 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.

The HCV 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, viral quantification and fibroscan have been removed and recommendations have been made using the local evidence. The guidelines are primarily focusing on their use by the 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 provincial health departments 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**.

It is my pleasure to extend my sincere thanks to TAG, Pakistan Health Research Council (PHRC), WHO, Technical Working Groups (TWGs), provincial health departments and all colleagues who devoted their time and expertise in the discussions that lead to the development of these national HCV guidelines.

Dr Zafar Mirza
Special Assistant on Health to the Prime Minister
Ministry of National Health Services, Regulations and Coordination (NHSRC) Islamabad

EXECUTIVE MESSAGE

Since many years, Pakistan is facing an epidemic of Hepatitis C Virus (HCV). The provincial hepatitis prevention and control programmes have the mandate to prevent and control this disease using National HCV guidelines. Unfortunately,interferon based therapy had poor response and multiple side effects making treatment compliance an issue.

The introduction of direct-acting antivirals (DAAs) has revolutionized the treatment of HCV globally including Pakistan, where a hard-to-treat genotype of the virus is encountered. Initially genotype specific DAAs were introduced whose cure rates were around 85-90%. Later pangenotypic DAAs have been introduced which work on all genotypes equally with a cure rate now exceeding 95-98%. Since the introduction of DAAs, interferon use in HCV has become obsolete and even ribavirin has been removed from the treatment plan of non cirrhosis cases. Its use is now limited to decompensated cirrhosis only.

Presently there are many pharmaceutical companies in Pakistan that are producing generic pangenotypic DAAs. The most cost effective combination is Sofosbuvir and Declatasvir given as two separate tablets once a day for 12 weeks in non cirrhosis and 24 weeks in cirrhosis. Velpatasvir is another pangenotypic drug with one tablet having two molecules i.e. sofosbuvir + velaptasvir. This is more expensive but has a 2% higher cure rate as compared to the former combination. Present guidelines give a choice to the treating physician to choose between different combinations but for the provincial programmes, the cheaper version is recommended. This decision was adopted due to the large number of cases which will have to be treated annually to achieve elimination by **2030**.

Some other DAAs are also available in other countries,which have higher cure rates with a shorter duration of therapy and minimal resistance. Efforts are being made to procure these drugs for Pakistan at affordable rates, for treating the millions of HCV cases.

Keeping in view the latest treatment scenarios and contextual settings of Pakistan where we have limited resources and a huge disease burden, the HCV testing has also been tailored to be specific yet cost effective. The expensive tests like genotyping of the virus, quantification of the virus and the liver biopsy or fibroscans have been removed as one drug works on all genotypes irrespective of the viral load. This approach has made testing and treatment so easy that even a general practitioner sitting in a remote area with limited access to tests can start the treatment.

The guidelines also have separate sections for treating patients having dual infections like HCV and TB, HCV and HBV, HCV and HIV/AIDS, HCV and Chronic Renal Failure. As these are co-infections, therefore it is recommended that liver specialists in collaboration with the respective programme like TB or HIV/ AIDS may treat the patient jointly. These guidelines will be modified as and when the new test and treatment becomes available.

These HCV testing and treatment guidelines have been revised through a collaborative work of many Pakistani and international partners like MSF, CDC and WHO. I would like to thank all of them for undertaking this important task of revising the testing and treatment guidelines within a very short span of time.

Dr Allah Bakhsh Malik
Secretary
Ministry of National Health Services, Regulations and Coordination (NHSRC) Islamabad

MESSAGE
WHO Representative in Pakistan

WHO estimates that in 2015, **71 million** persons were living with chronic **hepatitis C virus** (HCV) infection worldwide and that 399,000 died from cirrhosis or hepatocellular carcinoma caused by HCV infection. While, the Eastern Mediterranean Region (EMR) continues to have the highest prevalence of viral hepatitis C globally, more than 15 million people in the region are currently chronically infected with hepatitis C and 80% of the regional burden of these infections lies in Egypt and Pakistan.

In May 2016, the World Health Assembly endorsed the Global Health Sector Strategy (GHSS) on Viral Hepatitis, which proposed to eliminate viral hepatitis as a public health threat by **2030** (90% reduction in incidence and 65% reduction in mortality). Elimination of viral hepatitis as a public health threat requires 90% of those infected to be diagnosed and 80% of those diagnosed to be treated.

WHO recommends use of safe and highly effective direct-acting antiviral (DAA) regimens for all persons for improving the balance of benefits and harms of treating persons with little or no fibrosis, supporting a strategy of treating all persons with chronic HCV infection, rather than reserving treatment for persons with more advanced disease. Several new, pangenotypic DAA medicines have been approved, reducing the need for genotyping to guide treatment decisions. The continued substantial reduction in the price of DAAs has enabled treatment to be rolled out rapidly in a number of low- and middle income countries.

WHO introduced 'Guidelines for care and treatment of persons diagnosed with chronic Hepatitis C virus infection' in 2017 with the aim to provide evidence-based recommendations on the care and treatment of persons diagnosed with chronic HCV infection. These guidelines are intended for government officials to use as the basis for developing national hepatitis policies, plans and treatment guidelines. These include country programme managers and health-care providers responsible for planning and implementing hepatitis care and treatment programmes, particularly in low- and middle-income countries.

I appreciate efforts of national Technical Working group (TWG) for adaptation and introducing locally representative guidelines for management of all persons having hepatitis C, irrespective of the disease status.

I wish you all, including the provincial department of health and private sector for an effective implementation of the guideline for expansion and decentralization of Hepatitis C treatment services in the country.

Dr Palitha Mahipala
WHO Representative and Health of Mission
Pakistan

GUIDELINES

Pakistan National HCV Treatment Guidelines

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Abstract

Objective: The guidelines are being published locally for a wider readership and usage.

Methods: These guidelines have been updated by a Technical Working Group (TWG) that was nominated by the respective Federal and Provincial Governments and endorsed by Technical Advisory Group (TAG) on viral hepatitis. The National and 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.

Summary of recommendation: 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 tested for anti HCV using one of the WHO prequalified test.

- If found reactive, they should undergo viral detection using HCV RNA or HCV antigen.
- Treatment is recommended with Sofosbuvir and Daclatasvir as 1st line treatment or Velpatasvir as 2nd line treatment.
- In compensated cirrhosis, give Sofosbuvir and Daclatasvir for 24 weeks or Velpatasvir for 12 weeks.
- The decompensated cirrhosis cases should be referred to gastroenterologists.
- With the use of pan genotypic regimens, genotype testing and viral load testing is no more required before starting the treatment.
- Before starting the DAAs, liver fibrosis should be assessed using non-invasive tests (e.g. aminotransferase /Platelet Ratio Index (APRI) score or FIB-4 test to determine the presence of cirrhosis to decide the duration of therapy.
- DAAs are generally well tolerated, with only minor side-effects. Therefore, the frequency of routine laboratory testing for monitoring the side effects of drugs are reduced to a blood test at the start of treatment and no testing in between.
- Following the completion of DAA treatment, Sustained Virologic Response (SVR) at 12 weeks after the completion of treatment is used to determine the treatment outcome.

Keywords: Hepatitis C, Guidelines, Sofosbuvir, Daclatasvir, DAA. (JPMA 74: S-4 [Suppl. 7]; 2024)

Introduction

The first national treatment guidelines for hepatitis B and C were developed by Pakistan Society of Gastroenterology.[1] Second guidelines for treatment of hepatitis were developed by the Prime Minister's Programme for Prevention and Control of Hepatitis in Pakistan in 2005.[2] The National Technical Working Group (TAG) on viral hepatitis developed the "Guidelines for the treatment of persons with chronic hepatitis C infection in 2016.[3] The need for these new guidelines was felt due to introduction of new testing and treatments that have become available for HCV screening and treatment.

Almost 71 million people around the world are infected with HCV, of whom 399,000 die each year.[4] Most people infected with the virus are unaware of their infection and, for many who have been diagnosed; treatment remains unavailable.[5,6] One third of those who become chronically infected progress to develop liver cirrhosis and later hepatocellular carcinoma.[7] The highest prevalence of HCV chronic viraemic infection (10%) was recorded in Egypt in 2008 but with the launch of a very active hepatitis programme, its prevalence has come down to 7% (HCV RNA positive in 2015).[8]

The 2005 National hepatitis survey showed that Pakistan has the highest prevalence (5%) of HCV, while population wise, China has the largest number of people infected with

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Table-1: Population at increased risk of HCV in Pakistan.

Population	Risk
Population frequently using therapeutic injections.[47]	Risk of HCV infection depends on the frequency of therapeutic injections. Pakistan has the highest number of therapeutic injections i.e.(13 injections/person/year).[23]
Population frequently visiting health care facilities to seek medical help.	Local studies reported inadequate infection control practices in health care settings.[48]
Population receiving improperly screened blood and its products.[4,49-53]	In Pakistan, seroprevalence of HCV ranges from 1.5 - 3.3% in healthy blood donors.[54-56]
Partners and family members of HCV index cases.[57-59]	Local study reported HCV positivity of 38% in the spouses of index cases.[60]
Patients with evidence of liver disease or abnormal liver function.[61]	A large population with chronic liver disease and abnormal LFTs have HCV infection.[62,63]
People Who Inject Drugs (PWID).[64]	National prevalence of HCV is 91.7% among PWID.[65]
People with multiple sexual partners who are HCV infected.[57,66,67]	There is negligible to low risk of transmission of HCV in stable sexual relationships (marital life). The risk increases with increasing number of partners, among men having sex with men(MSM), and in those with concomitant STIs.
People who have had tattoos or piercing.[68]	Local studies reported tattooing and skin piercing as risk factors for HCV.[69,70]
Barbers, beauty parlors, circumcision.[71]	Unsterilized equipment at barbers, beauty parlors, during head shave at birth and circumcision are also risk factors for HCV.[72-74]

HCV followed by Pakistan, where almost 10 million general population have HCV infection.[9,10] The 2005 survey showed that Punjab province had the highest HCV prevalence of 6.5%. In 2017-2018, a serosurvey was undertaken by the Punjab Province and it showed 8.9 % HCV prevalence.[11] If this is taken as the national prevalence, there are almost 14 million HCV cases in Pakistan. A study reported HCV prevalence as high as 25.7% in Gilgit Baltistan province.[12] Various risk factors for the transmission of HCV have been identified and reported in Pakistan. These are shown in Table 1:

Over 80% HCV infected people in Pakistan have genotype.[3,13,14] In a longitudinal study (2000-2009), the HCV genotype distribution was determined in all the four provinces of Pakistan from a 20,552 consecutive HCV RNA positive patient's sample. The analysis showed that 85 .1 % were genotype 3(74.2% 3a, 10.9% 3b and 0.24% 3c), 4.3% were genotype 1 (3.3% 1a, 0.83% 1b and 0.24% 1c), 2.3 % were genotype 2 (2.1% 2a, 0.23% 2b, 0.01% with 2c), 0.5% were genotype 4, 0.06% were 5a and 6a each while 4.7% were with mixed-genotype infection.[15] Molecular analysis of HCV isolates (n=1537) from different geographical region of Punjab showed 88% of genotype 3a while other were Ia (3.5%) followed by 3b (3.0%), Ib (0.8%), and 2a (1.0%) while in 3.6% had mixed genotypes.[16]

Hepatitis C virus causes both acute and chronic infections. Acute HCV infections defined as the presence of HCV within six months of exposure with HCV. It is usually clinically silent and is very rarely associated with life threatening disease. Spontaneous clearance of acute HCV infection occurs within six months of infection in 15-45% of infected individuals in the absence of treatment. Almost all the remaining 55-85% of persons will harbour HCV for the rest of their lives (if not treated) and are considered to have chronic HCV infection. Anti-HCV antibodies develop as part of acute infection and persist throughout life. In persons who have anti-HCV antibodies, a nucleic acid test (NAT) for HCV RNA, which detects the virus, is needed to confirm the diagnosis of chronic HCV infection.[17,18] If left untreated, chronic HCV infection can cause liver cirrhosis, liver failure and hepatocellular carcinoma (HCC). Of those with chronic HCV infection, the risk of liver cirrhosis is 15-30% over 20 years.[19-21] The risk of HCC in persons with cirrhosis is approximately 2-4% per year.[22]

The target audiences for national HCV treatment guidelines are doctors (medical officers) especially those trained and working at secondary level health facilities in public sector health facilities. While in private sector, the target audience is the general practitioners (GP) providing healthcare services at the doorstep of the patients. However, in case of complications such as end stage liver disease (decompensated cirrhosis, hepatocellular carcinoma) or co-infections (HCV/HBV, HCV/HBV/HDV, HCV/HIV, HCV /TB), the patient would be jointly treated by the programmes like TB, HIV along with gastroenterologists. In these cases, referral to specialized care in tertiary care hospitals is recommended.

Methods

These National HCV Treatment Guidelines have been updated by a Technical Working Group (TWG) that was nominated by the respective Federal and Provincial Governments and endorsed by Technical Advisory Group (TAG) on viral hepatitis. The National and 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. A National Consultation workshop was held in November 2018 where TWG and all the stakeholders gave their inputs into the revision of HCV guidelines using local evidence and adapting WHO guidelines. Based on those inputs, the revised draft was shared with all the experts and partners in the Eighth TAG meeting held on February 28, 2020. The recommendations of the experts were incorporated in the final draft and the updated guidelines were finalized and launched in April 2020.

Results

Screening to Identify Persons with HCV Infection:

- HCV serological testing shall be expanded to all parts of Pakistan to detect HCV positive patients in the population and link them to treatment.
- Testing shall be offered to all populations of the country.
- The WHO prequalified rapid test for anti HCV, available in Pakistan, is SD bioline, Intec and Biosensor.

Keeping the huge burden of disease in Pakistan it is strongly recommended that anti HCV testing should be offered to all individuals. Screening should be available at all health care public and private health facilities.

Populations with High HCV Prevalence:

- Persons with past or present history of taking more than 5 therapeutic injections per year.[23]
- 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.

In Pakistan, the major risk factors for the spread of HCV include unsafe blood transfusions, reuse of syringes for therapeutic injections and improperly sterilized invasive medical devices. Special high risk populations include people who inject drugs (PWID), people having HIV/AIDS and males who have sex with males (MSM). Places from where infection can spread include barbers, tattooing, beauty parlours and ear/ nose piercing centres.

When and how to confirm diagnosis of Chronic HCV Infection:

1. Initial diagnosis shall be made on rapid test.
2. Active HCV infection shall be confirmed using Nucleic Acid Test (NAT or RNA) either through RT PCR or GeneXpert or HCV antigen.
3. Qualitative HCV RNA or HCV antigen shall be used to initiate Direct Acting Antivirals.

Currently WHO has approved three tests and any one of them can be used to confirm active HCV disease. These include HCV RNA using a RT PCR, HCV RNA using a GeneXpert and HCV antigen. It is recommended that the HCV RNA or HCV antigen test may be performed following a reactive anti HCV test to establish the diagnosis of chronic HCV infection and initiate treatment. Virus detection is confirmed by the detection of HCV RNA or HCV antigen. HCV RNA is also used to ensure viral clearance after treatment.[24-27] With the pan-genotypic DAAs, no genotyping is required and only qualitative HCV RNA is recommended because the duration of treatment remains the same irrespective of the quantity of viral load.

METAVIR Stage	F0	F1	F2	F3	F4
Definition	No Fibrosis	Portal Fibrosis without septa	Portal Fibrosis with septa	Numerous septa without cirrhosis	Cirrhosis

Recommendations on care of people infected with HCV:

1. All anti HCV positive patients should be checked for HBsAg.
2. All HCV cases that are negative for HBsAg should be vaccinated against HBV.
3. All HCV cases should be questioned for alcohol intake.
4. All HCV positives should be informed on how to avoid disease transmission to others.

Assessing the degree of liver fibrosis and cirrhosis to decide duration of treatment:

All HCV RNA positives cases should be assessed for the degree of liver fibrosis to decide the duration of treatment through use of APRI or FIB4 test.

Note: This recommendation was formulated assuming that liver biopsy is not a feasible option. Fibro scan, which is more accurate than APRI and FIB4, may be preferable in settings where equipment is available and the cost of the test is not a barrier to testing.

The gold standard for evaluating liver fibrosis is liver biopsy which is calculated in terms of METAVIR Score (0-4) that shows the amount of hepatic collagen. It can also help to assess the severity of liver inflammation and hepatic steatosis.[3]

However, 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 are more accurate tests than APRI or Fib4 but their high cost prohibits their wider use in the country.[3] 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.[3]

$$\text{APRI} = \frac{\left[\left\{\frac{AST\ \frac{\text{IU}}{\text{L}}}{AST_{ULN}\left(\frac{IU}{L}\right)}\right\}\right.}{Platelet\ Count\ \left(\frac{10^9}{L}\right)} \text{ X } 100$$

$$\text{FIB4} = \frac{\text{Age (years) x AST } \left(\frac{\text{IU}}{\text{L}}\right)}{Platelet\ Count\ \left(\frac{10^9}{L}\right) X\ ALT\ \left(\frac{IU}{L}\right) 1/2]}$$

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 or FIB4 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 or Fib4 are platelets and AST which are cheap and widely available throughout the country.[3] **Formula for calculating APRI is given below.**[28] Comparison between Fib 4 and APRI is given in table 2.

Where;
ALT = Alanine Aminotransferase
AST = Aspartate Aminotransferase
IU = International Unit

Table-2: APRI& FIB4 Scores.

APRI Score	FIB4 Score	Staging of Fibrosis & Cirrhosis
<0.5	<1.45	No Fibrosis These patients have a very low probability (18%) of having advanced fibrosis (F2 fibrosis or higher) and could thus be reassured and reassessed periodically
0.5-1.5	1.45 -3.25	Significant Fibrosis These patients could be retested every one or two years
>1.5	>3.25	Cirrhosis These patients have a high probability (94%) of having F4 cirrhosis.

ULN = Upper limit of Normal

How to calculate the duration of DAAs therapy with APRI:

All patients who have an APRI of <1.5, the duration of therapy will be 12 weeks. For all patients having an APRI of>1.5 the duration of therapy will be 24 weeks. All decompensated cases will also receive 24 weeks DAAs but shall be treated by a specialist (Table 2).[29]

Recommendations for treatment:

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

Table-3: Treatment regimens.

Type of Patients	Preferred Treatment	Alternate Treatment
All HCVRNA positive patient without cirrhosis	Sofosbuvir 400 mg one tablet (after breakfast once a day) for 12 weeks + Daclatasvir 60 mg one tablet (after breakfast once a day) for 12 weeks	Fixed dose combination of Sofosbuvir and Velpatasvir one tablet (combination of Sofosbuvir 400 mg and velpatasvir 100mg) after breakfast for 12 weeks
Treatment Naive Patients with Compensated Cirrhosis	Sofosbuvir 400 mg one tablet (after breakfast once a day) for 24 weeks + Daclatasvir 60 mg one tablet (after breakfast once a day) for 24 weeks	Fixed dose combination of Sofosbuvir and Velpatasvir one tablet (combination of Sofosbuvir 400 mg and velpatasvir 100mg) after breakfast for 12 weeks
Treatment Experienced Patients with Compensated Cirrhosis	Sofosbuvir 400 mg one tablet (after breakfast once a day) for 24 weeks + Daclatasvir 60 mg one tablet (after breakfast once a day) for 24 weeks + 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	Fixed dose combination of Sofosbuvir and Velpatasvir one tablet (combination of Sofosbuvir 400 mg and velpatasvir 100mg) after breakfast for 12 weeks + Ribavirin (1000 mg in 2 divided doses for <75 kg and 1200 mg in 2 or 3 divided doses for >75 kg) for 12 weeks
Treatment Naive Patients with Decompensated Cirrhosis*	Fixed dose combination of Sofosbuvir and Velpatasvir one tablet (combination of Sofosbuvir 400 mg and velpatasvir 100mg) after breakfast for 24 weeks	Sofosbuvir 400 mg one tablet (after breakfast once a day) for 24 weeks + Daclatasvir 60 mg one tablet (after breakfast once a day) for 24 weeks + 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
Treatment Experienced Patients with Decompensated Cirrhosis*	Fixed dose combination of Sofosbuvir and Velpatasvir one tablet (combination of Sofosbuvir 400 mg and Velpatasvir 100mg) after breakfast for 24 weeks + Ribavirin (1000 mg in 2 divided doses for <7 5 kg and 1200 mg in 2 or 3 divided doses for >75 kg) for 24 weeks	

* Patients with decompensated cirrhosis should be managed by gastroenterologists.

- Direct Acting Antiviral Agents (DAAs) without Ribavirin will be treatment of choice in all cases without cirrhosis.

Pan genotypic DAAs have further reduced the use of ribavirin to only those having either advanced cirrhosis or decompensated disease.[29] Since the availability of pan genotypic DAAs there is no need to check the genotype or viral load to decide the drug combinations. Treatment with DAAs shall be given to all patients who have a detected HCV RNA. The treatment regimens are described in table 3.[3,29]

Contraindications to treatment:

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 counselled to use contraception during and for 6 months after therapy.[3,29] Ribavirin is only to be used in children less than 17 years and in advanced cirrhosis and decompensated cirrhosis.

Following are the absolute contraindications for Ribavirin:

- Pregnancy.
- Breastfeeding.
- Hypersensitivity to drug.

Monitoring for treatment response:

No monitoring of blood tests or HCV RNA is recommended during treatment if ribavirin-based therapy is not used. To check viral clearance i.e. sustained virological response (SVR) a second qualitative HCV RNA is recommended at 12 weeks after stopping the treatment.

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, subjects who inject drugs (PWID) and persons co-infected with (or at risk for infection with) HBV, TB and HIV.

Persons with liver cirrhosis:

About 15% to 30% patients develop cirrhosis of the liver over 20 years and few progress to HCC. The risk is markedly increased in those consuming alcohol or co-infected with HBV and/or HIV and do not have access to ART (antiretroviral therapy).[20,21]

Persons with compensated cirrhosis have the least time available for treatment and will gain much from achieving SVR. Treatment with DAAs must be started in these cases before decompensation starts. For cirrhotic cases receiving DAAs plus ribavirin, regular clinical examination and monitoring of blood tests is necessary to detect decompensation early. Tablet folic acid may be used 2-3 times a day to cater for haemolysis in those taking ribavirin therapy, while haemopoietic factors (erythropoietin) are recommended in severe cases where resources allow.[26]

Children and adolescents:

WHO defines a child as an individual 19 years of age or younger and an adolescent as a person between the ages of 10 and 19 years.[30] In Pakistan, approximately 2% children are infected.[31] This rate is higher in populations exposed to medical intervention. Seroprevalence rates of 10-20% have been reported among children who have been treated in hospital for malignancy, renal failure requiring haemodialysis, and after surgical procedures.[32] Targeted screening is indicated for children who have had medical interventions or who have received blood products. In children less than 12 years of age with chronic HCV infection, it is recommended to defer the treatment until 12 years of age. HCV infection (mother-to-child) is mostly seen in infants born to HIV HCV co-infected mothers (17-25%).[33,34] Integrated health care is needed especially with maternal and child health services, primary care, services for PWID and, where necessary, referral for HIV care and treatment.

Treatment success rates are similar in adults and children, though DAAs have been inadequately studied in children.[27]

People who inject drugs (PWID):

In Pakistan a study carried out by APLHIV in PWID showed a co- prevalence of HIV/HCV in 91.7% subjects.[35] PWID are at an increased risk of HCV and its related morbidity and mortality, and therefore require specialized care. WHO recommends targeted HCV and HBV screening of PWIDs. Repeated screening is required in individuals with ongoing risk and re-infection after spontaneous clearance or successful treatment should be considered. Retesting should be done using HCV RNA as the antibody (anti HCV) remains positive after the first infection.

PWID should be vaccinated using the rapid vaccination regimen described in WHO guidelines.[36] Treatment for HCV infection is efficacious and cost effective in PWID[37,38] and therefore 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.[39-41] Consideration must be given to potential drug to 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.[3]

Persons with renal impairment:

Renal function tests should be done in patients having renal impairment, as pan-genotypic DAAs require dose adjustment in these cases. Strict monitoring is required in this group. Drug interactions can be checked online at http://www.hep-druginteractions.org

Persons with Co-infections:

1-HBV and HCV co-infection:

HBV and HCV co-infection may result in an accelerated disease course; HCV is considered to be the main driver of disease. HCV in these patients can be treated with antiviral therapy and their SVR rates are similar to those of HCV mono-infected persons.[42] After HCV clearance, there is a risk of HBV reactivation and this may require treatment with anti-viral therapy like Tenofovir.[42,43] Entecavir or Tenofovir as oral therapy once a day, has high viral suppression and clearance rates and is recommended for use till clearance of HBsAg (almost lifetime).[44]

2-TB and HCV co-infection:

Severe concurrent infections like TB should be treated before starting therapy for HCV. WHO recommends regular screening of people living with HIV (including PWID) with a four-symptom screening algorithm to rule out TB. If the patient does not have any one of the following symptoms current cough, fever, weight loss or night sweats, TB can be reasonably excluded otherwise they should undergo further investigations for TB or other diseases.

3-HIV and HCV co-infection:

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.[45] 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.[46] 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.

Summary of recommendations:

- With the use of pan genotypic regimens, genotype testing and viral load testing is no more required before starting the treatment.
- Before starting the DAAs, liver fibrosis should be assessed using non-invasive tests (e.g. aminotransferase /Platelet Ratio Index (APRI) score or FIB-4 test to determine the presence of cirrhosis to decide the duration of therapy.
- DAAs are generally well tolerated, with only minor side-effects. Therefore, the frequency of routine laboratory testing for monitoring the side effects of drugs are reduced to a blood test at the start of treatment and no testing in between.
- Following the completion of DAA treatment, Sustained Virologic Response (SVR) at 12 weeks after the completion of treatment is used to determine the treatment outcome.

Treatment of patients having co-infections, advanced liver disease and retreatment after DAAs treatment.

1. Patients having HBV/HCV co-infection:

Persons with HBV /HCV co-infection are at risk for HBV reactivation during and following HCV treatment. Therefore, assess them for HBV treatment eligibility and start treatment with tenofovir or entecavir to prevent HBV reactivation during HCV treatment.

1.1. Patients having HIV/HCV co-infection:

Persons with HIV/HCV co-infection are at a higher risk for progression of fibrosis and are therefore prioritized for treatment. In these patients one needs to consider drug-drug interactions with antiretroviral medications therefore if required take an HIV expert on board.

1.2. Patients having TB/HCV co-infection:

In persons with TB/HCV co-infection, treatment for active TB should be started before treating HCV infection. These persons when treated for TB, have a higher risk of hepatotoxicity and drug to drug interaction, therefore if required, take a gastroenterologist on board and treat TB first and HCV later.

1.3. Patients having chronic kidney disease:

Data are insufficient on the safety and efficacy of sofosbuvir-based regimens in persons with severe renal impairment. Glecaprevir/pibrentasvir is an effective pan genotypic therapy in persons having chronic kidney disease. This medicine is not currently available in Pakistan.

1.4. Patients with Liver Cirrhosis:

Patients having cirrhosis, irrespective of their viral clearance should be regularly screened for hepatocellular carcinoma (HCC).

1.5. Retreatment after DAA treatment failure:

Currently, only one pan genotypic DAA regimen,

sofosbuvir/velpatasvir/ voxilaprevir, is approved for the retreatment of persons who have previously failed DAA treatment. Ensure compliance to treatment and potential drug-drug interactions while investigating treatment failure with DAA therapy.

2. Testing of Chronic HCV Infection and Monitoring of Treatment Response:

2.1. Serological assay:

To test for serological evidence of past or present infection, an HCV antibody using a rapid diagnostic test (RDT) or laboratory-based immunoassay (ELISA) is recommended.

Use of quality assured RDT is recommended in settings having limited access to laboratory infrastructure and testing, and/or in populations where access to rapid testing would facilitate linkage to care and treatment.

2.2. Serological testing strategies:

Only one single serological assay for initial detection of infection is recommended prior to Nucleic Acid Testing (NAT) for evidence of viraemic infection.

2.3. Detection of viraemia infection:

Following a reactive anti HCV test, a qualitative NAT for detection of HCV RNA is recommended to diagnose viraemia infection.

HCV core antigen has comparable clinical sensitivity to NAT, and is an alternative to NAT to diagnose viraemic infection.

2.4. Assessment of HCV treatment response:

Qualitative NAT for the detection of HCV RNA should be used to confirm cure at 12 weeks (i.e. sustained virological response (SVR12) after completion of antiviral treatment.

2.5. Assessing degree of liver fibrosis and cirrhosis:

In resource-limited settings, it is recommended to use cheaper aminotransferase/platelet ratio index (APRI) or FIB-4 tests to assess hepatic fibrosis instead of other non-invasive tests that require more resources like elastography or Fibroscan.

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