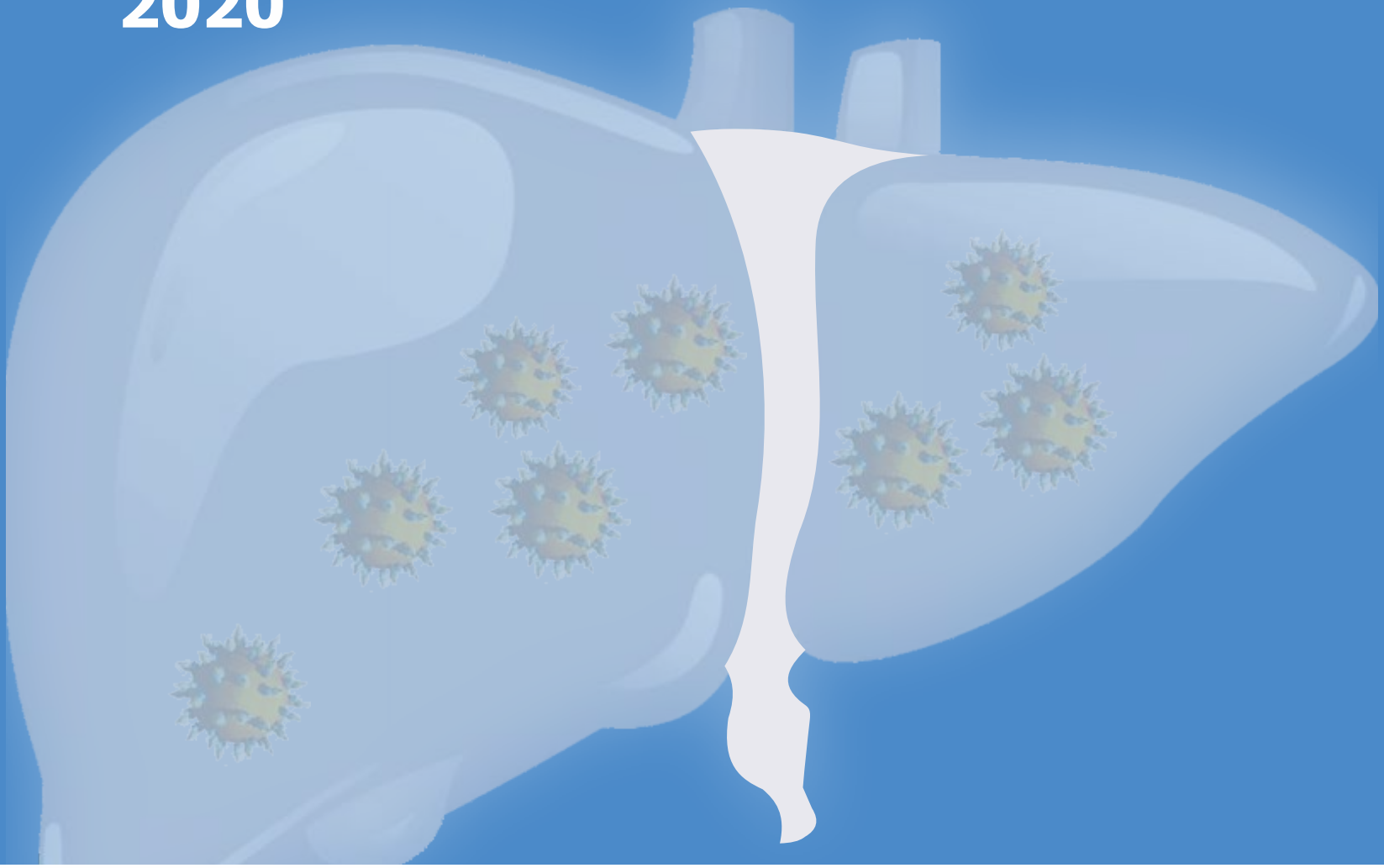
GUIDELINES FOR THE TREATMENT OF THE PERSONS WITH CHRONIC HEPATITIS C INFECTION

PAKISTAN
2020



Government of Pakistan
Ministry of National Health Services,
Regulations & Coordination

World Health Organization

Updated Pakistan HCV Treatment Guidelines

Contents

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Many professionals from a range of backgrounds and specialties have contributed to the development of these guidelines. We are sincerely grateful for their time and support.

Guidelines Development Group

The Chair of the Guideline Development Groups was Dr. Huma Qureshi, National Focal Person on hepatitis for government of Pakistan.

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Steering Committee and Overall coordination

The following members formed the Guidelines Steering Committee and performed the overall coordination:

Dr. Huma Qureshi, Dr. Safdar Kamal Pasha (National Professional Officer, WHO) and Dr. Hassan Mahmood (National Consultant, WHO)

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 prevalence, Pakistan now stands as the highest HCV prevelance 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 program 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 tesing and treatment of HCV at all levels of health care is the need of the day if Pakistan has to achieve hepatitis elmimination tragets 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
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EXECUTIVE MESSAGE

Since many years, Pakistan is facing an epidemic of Hepatitis C Virus (HCV). The provincial hepatitis prevention and control programs 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 revolutionalised the treatment of HCV globally including in Pakistan where we have a hard-to-treat genotype of the virus. Initially genotype specific DAAs were introduced whose cure rates were around 85-90%. Later pangeotypic 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 removed for the treatment of non cirrhosis cases while its use is 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 is one tablet having two molecules i.e. sofosbuvir + velaptasvir. This is more expensive but has a 2% higher cure rates as compared to former combination. Present guidelines give a choice to the treating physician to choose between different combinations but for the provincial programs, the cheaper version is recommended, keeping in view the large number of cases that have to be treated yearly to achieve elimination by 2030.

Some other DAAs are also available out side Pakistan that has higher cure rates with shorter duration of therapy and minimal resisitance. Efforts are being made to get these drugs in Pakistan at much affordable rates for the treatment of millions of HCV cases.

Keeping in view the latest treatment scenarios and contextual settings of Pakistan where we have limited resources and 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 program like TB or HIV/AIDS may treat the patient jointly. These guidelines will be modified as new test and treatment become 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 guidleines within a very short span of time.

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

MESSAGE BY 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, with 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

EXECUTIVE SUMMARY

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. Once infected, the disease has no specific signs or symptoms, therefore majority progress to chronic liver disease. Almost a third of chronically infected cases progress to liver cirrhosis and hepatocellular carcinoma. Previously many people who had been diagnosed could not undergo treatment due to access and afforadability issues but the scenario has changed since DAAs became available and affordable in many countries including Pakistan.

The first hepatitis prevalence survey for Pakistan was done in 2005, 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%). A serosurvey was done for Punjab province in 2017-18 which showed a rise in the HCV prevalence to 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 revised using a combination of low cost bare minimum tests along with usage of highly effective oral medications for a short time. These guidelines have been mostly adapted from World Health Organization (WHO) 2018 guidelines along with evidence collected from local literature.

The users of these HCV testing and treatment guidelines shall be the provincial program managers and their identified physicians in different health-care settings. The general physiscians and the private practitioners can also use them for the treatment of their cases. The guidelines have list of DAAs that are available in Pakistan and also identify the most cost effective and efficacious combination for common use. Newer drugs are on way and shall be included as they become available in Pakistan.

Key recommendations

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.
- In adults aged 18 years and above, pangenotypic DAAs should be used for the treatment of chronic HCV infection.
- Adolescents (12–17 years) having chronic HCV infection, should be given one of the following combinations:
    - Sofosbuvir/ribavirin for 24 weeks in genotype 3.
    - Sofosbuvir/ledipasvir for 12 weeks in genotypes 1, 4, 5 and 6
    - Sofosbuvir/ribavirin for 12 weeks in genotype 2

Treatment in adults 18 years or above: Pangenotypic regimens should be used.

- Patients having no cirrhosis can be given one of the following pangenotypic regimens:
    - Sofosbuvir+Daclatasvir 12 weeks
    - Sofosbuvir+Velpatasvir 12 weeks
- Adults with compensated cirrhosis can be given one of the following pangenotypic regimens:
    - Sofosbuvir+Daclatasvir 24 weeks
    - Sofosbuvir+Velpatasvir 12 weeks
    - Add weight-based Ribavirin in above treatment regimens for treatment experienced patients
- Adults with decompensated cirrhosis should be referred to gastroenterologists. They can be given one of the following pangenotypic regimens:
    - Sofosbuvir+Velpatasvir 24 weeks
    - Sofosbuvir+Daclatasvir+Ribavirin 24 weeks
    - Sofosbuvir+Velpatasvir +Ribavirin 24 weeks [1]

Treatment of children 0–12 years of age

- In children aged less than 12 years having chronic HCV infection, it is recommended to defer thetreatment until 12 years of age
- Treatment with interferon-based regimens should no longer be used

[1] If patent is already treatment experienced

Clinical considerations for HCV patients in Pakistan

- With the use of pangenotypic regimens, genotype testing and viral load testing is no more required before starting the treatment.
- In resource-limited settings, 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.

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 entacavir to prevent HBV reactivation during HCV treatment.

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.

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.

Patients with Liver Cirrhosis

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

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 pangenotypic therapy in persons having chronic kidney disease. This medicine is not currently available in Pakistan.

Retreatment after DAA treatment failure

Currently, only one pangenotypic 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.

Implementation of the guidelines

Using an eight-point service delivery approach will ease the implemention of the recommendations to Treat All using pangenotypic DAA regimens:

1. Comprehensive national hepatitis strategic planning for the elimination of HCV infection;
2. Simple and standardized algorithms across the continuum of care;
3. Integration of hepatitis testing, care and treatment with other services;
4. Strategies to strengthen linkage from testing to care, treatment and prevention;
5. Decentralized services, supported by task-sharing;
6. Community engagement and peer support to address stigma and discrimination, and reach vulnerable or disadvantaged communities;
7. Efficient procurement and supply management of medicines and diagnostics;
8. Data systems to monitor the quality of individual care and the cascade of care.

Testing of Chronic HCV Infection and Monitoring of Treatment Response

Serological assay to use

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.

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.

Detection of viraemic infection

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

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

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.

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.

1. INTRODUCTION

The first national treatment guidelines for hepatitis B and C were developed by Pakistan Society of Gasterentrology [1]. Second guidelines for treatment of hepatitis were developed by the Prime Minister's Program for Prevention and Control of Hepatitis in Pakistan, 2005 [2]. Then the National Technical Working Group (TAG) on viral hepatitis developed the "Guidelines for the treatment of persons with chronic hepatitis C infection; 2016" [3]. 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 Technical Working Group (TWG) has recommended that this document will remain a dynamic guideline that would require frequent revisons 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; 2020"

The objective of these guidelines is to provide evidence-based recommendations on screening, care and 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 continumof care.

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

In treatment section, the guidelines focus on genotype 3 and 1. The treatment duration is determined on the basis of the amino-transferase/platelet ratio index (APRI) or FIB 4 score.

1.1 Target Audience

The target audiences for national HCV treatment guidelines are doctors (medical officers) specially 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 programs like TB, HIV along with gastroenterologists. In these cases referral to specialized care in tertiary care hospitals is recommended.

To achieve these objectives, the TWG has intentionally kept these guidelines simple and focused to cater the needs of the identified target audience.

1.2Epidemiology of Hepatitis C

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 havebeen 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 prevalence of hepatitis C infection varies substantially around the world. When countries are grouped into Global Burden of Disease regions, the estimated prevalence of HCV infection is highest in Central and East Asia andin the North Africa/Middle East region [5]. In view of the larger populations in Asia,the South Asia and East Asia regions have by far the largest number of personsliving with HCV infection. The highest prevalence of HCV chronic viraemic infection (10%) was recorded in Egypt in 2008 but with the launch of a very active hepatitis program, 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 HCV followed by Pakistan, where almost 10 million general populations 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 Pakisan. A study reported HCV prevalence as high as 25.7% in Gilgit Baltistan province [12]

1.3Population at increase risk of HCV in Pakistan

Various risk factors for HCV transmission of HCV have been identified and reported in Pakistan. These are shown in Table-1.

Table-1: Population at increase risk of HCV in Pakistan

Population	Risk
Population frequently using therapeutic injections [13]	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)[,14]
Population frequently visiting health care facilities to seek medical help.	Local studies reported inadequate infection control practices in health care settings

	especially in public sector facilities and in rural areas and informal health sector [15,16,17]
Population receiving unscreened blood and its products[14,18,19,20,21,22].	In Pakistan, seroprevalence of HCV ranges from 1.5 - 3.3% in healthy blood donors [23,24,25,26].
Partners and family members of HCV index cases [27,28]	Local study reported HCV positivity of 38% in the spouses of index cases [29]
Patients with evidence of liver disease or abnormal liver function [30]	A large population with chronic liver disease and abnormal LFTs have HCV infection. [31, 32]
People Who Inject Drugs (PWID) [33].	National prevalence of HCV is 91.7% among PWID [34].
People with multiple sexual partners who are HCV infected[26,35,36]	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 [37]	Local studies reported tattooing and skin piercing as risk factors for HCV [38,39]
Barbers, beauty parlors, circumcision[40]	Unsterilized equipment at barbers, beauty parlors, during head shave at birth and circumcision are also risk factorsfor HCV [41,42,43]

1.4 Hepatitis C Virus

The hepatitis C virus is a small, positive-stranded RNA-enveloped virus that is approximately 9.6 Kb in length. The genetic sequence was first characterized in 1989, placing the virus in the Hepacivirus genus within the Flaviviridae family [44,45,46]. It has a highly variable genome and multiple genotypes and subgenotypes[47]. Six genotype of HCV have been identified and each genotype has different sub type whose prevalence varies in the world. Few genotypes are more prevalent in certain areas as compared to others like HCV subtype 1a is more common in South America, Europe, and Australia while subtype 1b is mostly recorded in North America and Europe. HCV genotype 3 is the second mostabundant HCV type in the world and especially in Pakistan [48, 49].

Over 80% HCV infected people in Pakistan have genotype 3 [50, 51]. 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 patients sample. The analysis showed that 85.1% were genotype 3

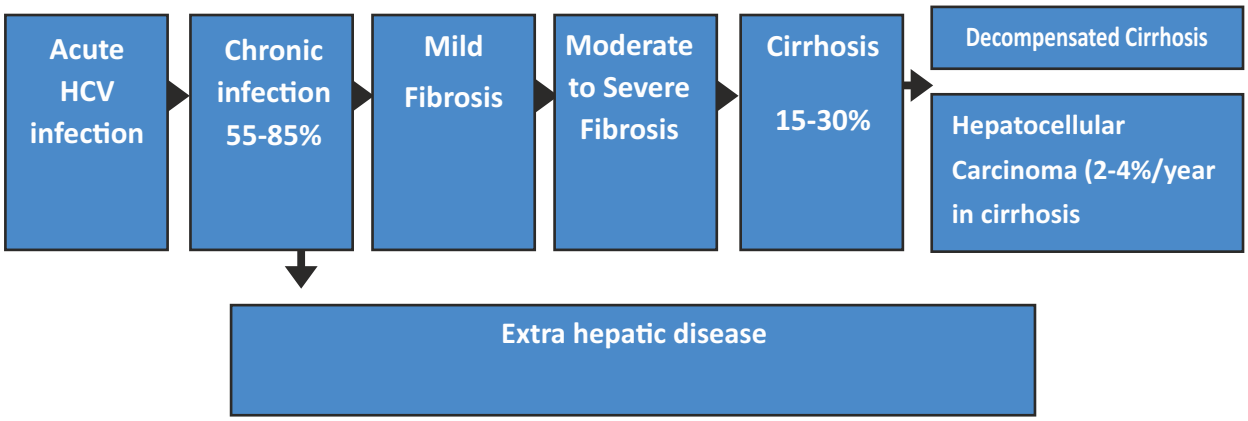
(74.2% 3a, 10.9% 3b and 0.24% 3c), 4.3% were genotype 1 (3.3% 1a, 0.83% 1b and 0.24% 1c), 2.3 % were genotype 2 (2.1% 2a, 0.23% 2b, 0.01% with 2c), 0.5% were genotype 4, 0.06% were 5a and 6a each while 4.7% were with mixed-genotype infection[52].Similarly in another study, the molecular analysis of HCV isolates (n=1537) from different geographical region of Punjab showed 88% of genotype 3a while other were 1a (3.5%) followed by 3b (3.0%), 1b (0.8%), and 2a (1.0%) while in 3.6% had mixed genotype[53].

1.5 Natural History of HCV Infection

Hepatitis C virus causes both acute and chronic infections. Acute HCV infectionis defined as the presence of HCV within six months of exposurewith 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 HCVinfection. 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 [54,55].

Left untreated, chronic HCV infection can cause liver cirrhosis, liver failure and hepatocellular carcinoma (HCC) (Figure-1). Of those with chronic HCV infection, the risk of liver cirrhosis is 15–30% over 20 years [56, 57, 58]. The risk of HCC in persons with cirrhosis is approximately 2–4% per year [59].

Figure 1: Natural Histroy of HCV infection



The risk of cirrhosis and HCC varies depending upon certain patient characteristics or behaviours. For example, persons who consume excess alcohol, persons coinfected with hepatitis B or HIV and immune suppressed individuals are at a higher risk of developing cirrhosis or HCC. Disease associatedwith HCV is not confined to the liver. Extrahepatic manifestations of HCV include cryoglobulinaemia, glomerulonephritis, thyroiditis and Sjögren syndrome, insulin resistance, type-2 diabetes mellitus, and

skin disorders such as porphyria cutaneatarda and lichen planus. Persons with chronic HCV infection are more likely to develop cognitive dysfunction, fatigue and depression[60].These outcomes maybe associated with replication of the virus in the brain; however, the causal link between these manifestations and chronic HCV infection is not certain[61].

2. METHODOLOGY

These National HCV Treatment Guideliens 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 the guidelines using local evidence and adapting WHO guidelines.Based on those inputs,the revised draft was shared with all the experts and partners in Eighth TAG meeting held on February 28, 2020. The inputs of the experts were incorporated in the final draft and the updated guidelines were finalized and launched in April 2020.

3. RECOMMENDATIONS ON SCREENING

3.1 Screening to Identify Persons with HCV Infection

1. HCV serological testing shall be expanded to all parts of Pakistan to detect HCV positive patients in the population and link them to treatment.
2. Testing shall be offered to all populations of the country.
3. WHO prequalified rapid test for anti HCV that is available in Pakistan is SD Bioline

Note: The list of WHO prequalified serological diagnostic tests for hepatitis C infection areavailable at NACP website [34].

In Pakistan, many people remain un-diagnosed until they they develop complications of cirrhosis like variceal bleeding, ascites or encephalopathy or terminal liver cancer [62]. Often at this point, liver injury is difficult to revert and virus clearing treatments might not be that effective. It is therefore important to identify patients earlier in the course of disease. 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.

3.2Populations with High HCV Prevalence

1. Persons with past or present history of taking more than 4therapeutic injectonsper year [14]
2. Persons with past history of any surgery including gynaecological and dental treatment
3. Persons with past history of blood transfusion
4. Persons with past history of admission in health care setting
5. People who inject drugs (PWID)
6. Men who have sex with men (MSM)
7. 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 sex with males (MSM). Places from where infection can spread include barbers, tattooing, beauty parlors and ear/ nose piercing.

3.3 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 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 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 positive anti HCV test to establish the diagnosis of chronic HCVinfection and initiate treatment.

According to the natural history of disease, approximately 15–45% of persons who are infected with HCV will spontaneously clear the infection [54, 63]. These persons will continue to be anti HCV positive for life but they are not infected. Virus dectection is confirmed by the detection of HCV RNA or HCV antigen, therefore this test is needed to distinguish persons with chronic HCV infectionfrom those who have cleared the infection. HCV RNA is also used to ensure viral clearance after treatment. [64,65,66]. 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.

4. RECOMMENDATIONS ON CARE OF PEOPLE INFECTED WITH HCV

1. All anti HCV positive patients should be checked for HBV
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.

Certain health conditions and behaviors 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 anecodotal evidence suggests that its use is not very uncommon. Heavy intake of alcohol (210 and 560 gms/week) doubles the risk of cirrhosis [67].

Co-infection with HBV or HIV is often associated with poor prognosis [68]. Interlinakages and coordination mechanisms should be developed with HIV control programs to treat HIV and HBV and HCV coninfections. 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[69].Therefore HCV infected patients who are overweight/obese (BMI 25 kg/m^2 or more) should be counselled for weight reduction via diet, execise, other medical therapies including hypolipidemic drugs such as statins.

5. ASSESSING THE DEGREE OF LIVER FIBROSIS AND CIRRHOSIS TO DECIDE DURATION OF TREATMENT

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

Note: This recommendation was formulated assuming that liver biopsy is not a feasibleoption. Fibroscan, 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]

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

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]

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]

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*

5.1How to calculate the duration of DAAs therapy with APRI.

For all patient who have an APRI of <1.5, the duration of therapy will be 12 weeks. For all patients having and 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. [3.70,71]

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 andreassessed 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.

6. RECOMMENDATIONS FOR TREATMENT

1. All persons with chronic HCV infection, irrespective of their disease status, will be prioritized for treatment.
2. Direct Acting Antiviral Agents (DAAs) without Ribavirin will be treatment of choice in all cases without cirrhosis.

Background

Over the past two decades, the cure of HCV infection with DAAs as measured by SVR has been found to be > 95% thus making them the treatment of choice for all HCV cases. Treatment of HCV with PEG-IFN is obsolete now.[71] Pan-genotypic DAAs have further reduced the use of ribavirin to only those having either advanced cirrhosis or decompensated disease.[71]

6.1Rationale for Selection of HCV Treatment

Since the availability of pan genotypic DAAs there is no need to check the genotype or viral load to decide the durg combinations.

6.2Treatment Decisions

Treatment with DAAs shall be given to all patients who have a detected HCV RNA. The treatment regimens are described in table 3. [3, 70, 71]

Table-3: Treatment Regimens

Type of Patients	Preferred Treatment	Alternate Treatment
All HCV RNA positive patient without cirrhosis	**Sofosbuvir** 400 mg one tablet (after breakfast once a day) for 12 weeks **Plus** **Daclatasvir 6**0 mg one tablet (after breakfast once a day) for 12 weeks	**Fixed dose combination of Sofosubuvir and Velpatesvir** one tablet **(combination of Sofosbuvir** 400 mg and **velpatasvir** 100mg) after breakfast for 12 weeks

Treatment Naïve Patients with Compensated Cirrhosis	**Sofosbuvir** 400 mg one tablet (after breakfast once a day) for 24 weeks **Plus** **Daclatasvir 6**0 mg one tablet (after breakfast once a day) for 24 weeks	**Fixed dose combination of Sofosubuvir and Velpatesvir** 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 **Plus** **Daclatasvir 6**0 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	**Fixed dose combination of Sofosubuvir and Velpatesvir** one tablet **(combination of Sofosbuvir** 400 mg and **velpatasvir** 100mg) after breakfast for 12 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 12 weeks
Treatment Naïve Patients with Decompensated Cirrhosis*	**Fixed dose combination of Sofosubuvir and Velpatesvir** 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 **Plus** **Daclatasvir 6**0 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
Treatment Experienced Patients with Decompensated Cirrhosis*	**Fixed dose combination of Sofosubuvir and Velpatesvir** one tablet **(combination of Sofosbuvir** 400 mg and **velpatasvir** 100mg) after breakfast 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	
* Patients with decompensated cirrhosis should be managed by gastroenterologists		

Treatment in Children

WHO recommends that treatment of HCV in children aged less than 12 years should be deferred. Treatment with interferon-based regimens should no longer be used. Sofosbuvir/ledipasvir for 12 weeks is recommended in genotypes 1, 4, 5 and 6 but not in genotype2 and 3. Sofosbuvir/ribavirin for 12 weeks is recommended in genotype 2 and sofosbuvir/ribavirin for 24 weeks in genotype 3. [71]

7. CLINICAL CONSIDERATIONS

7.1 Contraindications to Treatment

All pregnant women and lactating mothers shall not receive DAA due to their possible adverse effects on 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. [3,70,71]

Ribavarin is only to be used in children less than 17 years and in advanced cirrhosis and decompensated cirrhosis.

Following are the absolute contraindications for RBV:

1. Pregnancy
2. Breastfeeding
3. Hypersensitivity to drugs

7.2 Monitoring for treatment response

No monitoring of blood tests or HCV RNA is recommended during treatment if ribavirin-based therapy is not used. Blood CP shall be done monthly or every 2 months to monitor the hemoglobin drop in patients receiving ribavirin-based therapy.

7.3 Monitoring for Treatment response

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 clinical response or side effects.

RBV causes haemolytic anaemia and is teratogenic. Persons with cirrhosis are at high risk of serious adverse events (40–57%), particularly anaemia and infection [72, 73]. Monitoring during treatment with RBV is therefore recommended at regular intervals (Table-3). Patients with neutropenia, thrombocytopenia and anaemia require more frequent monitoring at 1–2-weeks.

To check viral clearance i.e. Sustained Virological Response (SVR) a second qualitative HCV RNA is recomemneded at 12 weeks after stopping the treatment.

8. 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 coinfected with (or at risk for infection with) HBV, TB and HIV.

8.1 Persons with liver cirrhosis

The spectrum of disease in HCV infected cases ranges from mild fibrosis to cirrhosis and HCC. About 15% to 30% develop cirrhosis of the liver over 20 years and few progresses to HCC. The risk is markedly increased in those consuming alcohol [67] or coinfected with HBV and/or HIV and do not have access to ART. [56,57]

Persons with compensated cirrhosis have the least time available for treatment and will gain much gain from achieving SVR. Treatment with DAAs must be started in these cases before decompensation starts. For cirrhotics receiving DAAs plus ribavarin, 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 hemolysis in those taking ribavarin therapy, while haemopoietic factors (erythropoietin) is recommended in severe cases where resources allow [67].

Compensated cirrhosis may progress over time to decompensated cirrhosis which may present with ascites, edema, oesophageal and gastric varices, and eventually to liver failure, renal failure and sepsis [74]. All of these complications are life-threatening. The diagnosis of decompensated liver disease is based on both laboratory and clinical assessment. Cirrhotics (including those who have achieved a SVR) should be screened for HCC with 6 monthly ultrasound and α-fetoprotein estimation. Prophylactic beta blockers may be given in all those who have a portal vein diameter of over 1.3cms to prevent variceal bleeding.

8.2 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 [75]. In countries where adults have a high prevalence of HCV infection, an increased prevalence in children can also be expected. In Pakistan, approximately 2% children are infected [76]. 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. [77,78,79,80,81,82, 83]. In children less than 12 years of age with chronic HCV infection it is recommended to defer the treatment until 12 years of age and in adolescents aged 12–17 years or weighing at least 35 kg with chronic HCV infection,

treatment with sofosbuvir/ribavirin is recommended for 24 weeks [71]. . Targeted screening is indicated for children who have had medical interventions or who have received blood products. HCV infection (mother-to-child) is mostly seen in infants born to HIV HCV coinfected mothers (17–25%) [84,85].

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 fewer studies have been carried out in the children. DAAs have been inadequately studied in children. [86,87]

8.3 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.[89] Similarly a study from Lahore reported 73% co-infection. [90] 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 RNA, 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. [91] 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 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 vaccinated using the rapid vaccination regimen described in WHO guidelines. [92]

Treatment for HCV infection is efficacious and cost effective in PWID [93,94] 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 [95,96,97]. 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.[3]

8.4 Persons with Co-infections

8.4.1 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 monoinfected persons. [98,99] After HCV clearance, there is a risk of HBV reactivation and this may require treatment with anti-viral therapy like tenofovir. [100] Entacavir 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) [100].

8.4.2 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.

8.4.3 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[101].

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. [102] As the management of these infections is complex, it is advisable to provide treatment in an integrated fashion by involving HIV/AIDS program 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.

8.5 Persons with renal impairment

Renal function tests should be done in patients having renal imparirment 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

9. DECENTRALISATION, INTEGRATION AND OUTREACH

1. Implement and monitor nationwide elimination targets with central electronic data reporting system
2. Decentralise screening, testing and treatment to the primary health care level and involve private sector, CSOs and other partners.
3. Reduce barriers to diagnosis and treatment by integrating hepatitis services with other programs e.g. HCV, HBV, HIV and TB as one window operation for testing and treatment.
4. Integration within specialised facilities
5. Identify underserved populations and areas and bring them into loop by providing doorstep testing and treatment.
6. Engage community and empower peers for behaviour change and prevention of HCV infection

9.1 National planning

To achieve the 2030 hepatitis elimination targets, National strategic framework for 5 years has been developed with yearly testing and treatment tragets calculated along with targets for aversion of new infections. Each province should develop its action plans and cost them by involving provincial hepatitis control programs and the health departments, private sector, corporate sector, CSO's and other authorities that provide health care to the population or its employees. Yearly targets for each component should be assigned to all stakeholders while Provincial governments should undertake monitoring and evaluation of each component using WHO's M&E framework

9.1.1 Implement and monitor nationwide elimination targets with a central electronic data reporting system to monitor cascade of care

To get standardized screening, testing and treatment for the whole population and develop a cascade of care at all levels, it is important that all national, provincial and private sector health care stakeholders use the national guidelines and an electronic data entry system. Strenthening of the national and provincial hepatitis data management team would be essential to identify the gaps and undertake appropriate interventions timely.

9.2 Decentralise screening, testing and treatment and involve private sector, CSOs and other stakeholders.

WHO defines decentralisation of services as "service delivery at peripheral health facilities, community-based venues and locations beyond hospital sites, bringing care nearer to patients." [71] Devolving

service delivery to lower-level health facilities reduces transportation, wait times and opportunity costs for patients; improving linkage and adherence to treatment. In Pakistan, as over 60-70% people seek health care through private practitioners, therefore their engagement in the hepatitis program is important to divide the burden from the government. Similarly many CSOs and other stakeholders that have access to hard to reach areas and populations should also be involved in the program.

9.2.1 Decentralisation of screening

Comparative studies of WHO-prequalified rapid diagnostic tests (RDTs) available in Pakistan in 2018 have shown over 99% sensitivity and 100% specificity.[103] As RDTs are accurate, safe, and inexpensive, they are recommended for use as first-line tests for anti-HCV in almost all settings. ELISA testing is no longer recommended for use. [104,105]. In order to achieve the 2030 hepatitis elimination targets, there is a need to perform both passive and active screening of all persons aged over 12 years of age for HCV. All public and private health facilities and corporates /authorities should be involved in screening all people who visit for various reasons and put their data base and the screening results in the electroic data for easy daily count of population screened and also to avoid duplication. A unique identifier like CNIC or mobile phone may be used for this purpose. It is important that all those who test positive on screening are referred for further confirmation /diagnosis using a NAT. Proper referral should be made to the nearest identified diagnostic facility or laboratory.

9.2.2 Decentralisation of diagnosis

It is now possible to do viral load testing at point-of-care (POC), which may reduce the need for a patient to wait and return for a confirmatory diagnosis. [106] Bringing down such barriers may translate into better patient adherence and a greater efficiency in time and resources. [107] Point-of-care testing should therefore be implemented only when appropriate and where resources allow. In the case where it is not possible or desirable to implement POC testing or to deploy equipment within decentralised setting, quantitative or qualitative (provided assay has acceptable accuracy) diagnostic analysis at centralised laboratories nearest to the decentralised site are an acceptable alternative. Over 90% cases that are diagnosed must be linked to treatment, therefore it is important that treatment site should either be within the same premises as diagnostic lab or the treating physician may be engaged with the hepatitis program to deliver medicines as per agreed protocol free of cost to the patient.

9.2.3 Decentralisation of Treatment

Since the availability of fixed drug and dose combination of pan-genotypic DAAs, it is very easy to decentralize the treatment. The present HCV treatment guidelines have been developed with the concept that they shall be used by the general practitioners. One pager of testing and treatment algorithm may be

developed and shared with all treating physicians for easy and quick reference. Several models of decentralised HCV testing and treatment service delivery have demonstrated success in high-burden countries, including Pakistan. [108] Task-sharing (by involving the general practitioners and the nurses for the treatment), use of simplified screening and treatment algorithm, and differentiation of care (serious or complicated cases are referred urgently and provided caree) are three approaches that may also facilitate the decentralisation of treatment to peripheral areas.

9.3 Reduce Barrier to diagnosis and treatment by integrading hepatitis services with other programs:

WHO recommends integrating HCV services into existing health services where possible. Integrating services reduce the overall resources required with an incremental return on investment. It also improves health equity for the population. [109] With the availability of high quality RDTs that can be used at POC by lay health workers, screening for HCV can now more easily be integrated into existing services. However, integration of HCV testing requires additional attention in linkage to care.

Service delivery	Screening and testing services	Outreach services	Diagnostic testing services
■ Primary healthcare clinic ■ Basic Health Unit ■ Rural Health Unit ■ TB Clinic ■ Drug rehabilitation clinic ■ Postnatal services ■ ART Clinics Prison health service ■ Mental health services	■ Primary healthcare clinic ■ Basic Health Unit ■ Rural Health Unit ■ Blood bank ■ Antenatal care clinic ■ HIV/ART services ■ Dental clinic ■ TB Clinics ■ Harm-reduction drop-in centre	■ Harm reduction for people who use drugs ■ TB mobile testing units ■ Maternal and child health outreach ■ Hepatitis B vaccination ■ EPI vaccination ■ Polio vaccination ■ Gender-based violence outreach ■ Street children outreach	■ GeneXpert capacity within existing TB programme
Existing healthcare services with the capacity to Integrate			

9.4 Integration within specialised facilities and dedicated out reach

Specialised and limited healthcare services such as those provided in prisons, drug rehabilitation clinics, and mental health facilities should be included. In addition, RDTs and linkage to care should be offered wherever screening and testing services are already available, even if they are not the main purpose of the facility; e.g. blood banks, dental clinics, drop-in centres for IVDUs etc. The dedicated outreach in Pakistan are shown below

Considerations for dedicated outreach in Pakistan

- Informal healthcare settings
- Haemodialysis facilities
- Thalassemia facilities
- Prisons
- Drug-rehabilitation centres
- Blood donors of unregulated blood banks
- IVDUs not in harm reduction
- Patients with known health facility-acquired transmissionhealth facility-acquired transmission
- Physically disabled
- Mentally disabled
- Untreated drug addicts
- Transgender population (Hijra)
- Sex workers
- Homeless persons
- Bonded labourers
- Migrant, displaced, and undocumented populations, including street children

9.5 Community engagement and peer support

The known risk factors for most hepatitis C infections and re-infections in Pakistan are related to behaviour and practices: unnecessary use of injections and intravenous drips for common ailments, improper indications for blood tranfusion, improperly screened blood and improper infection control at health care settings. , Community spread of disease is occurring from shaving at barber and services at parlors. Community engagement and peer-led efforts are particularly important for prevention strategies which may be the key to changing the behaviour of consumers, patients, and providers alike. [110, 111, 112, 113] . In addition to providing services, peers can act as role models and offer non-judgmental support that may contribute to reducing stigma and promote the acceptability of services.

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