INTRODUCTION

Approximately 160-180 million people have chronic hepatitis C infection worldwide\textsuperscript{1}. An estimated 4.9% of the general population is infected with HCV in Pakistan\textsuperscript{2}, which roughly equals to 10 million people today. Ninety percent cases are genotype 3. True prevalence is elusive due to the asymptomatic nature of the HCV infection and lack of surveillance infrastructure in our country. Pakistan has the highest number of people with active HCV infection of all countries except China in the world, but unlike China the total number of infections in Pakistan is not declining\textsuperscript{3}.

The treatment of chronic hepatitis C (CHC) has undergone revolutionary change with the availability of direct acting antiviral agents (DAAs) in 2011. The pace of introduction of new DAAs and related data is so rapid that every 6-12 months new clinical practice guidelines are published by international liver societies. Therefore to keep our healthcare professionals timely updated with latest therapeutic options for HCV, Pakistan Society of Hepatology (PSH) has launched this "living document" which will be updated frequently as new DAAs and related data become available.

TARGET AUDIENCE

All healthcare professionals, healthcare institutions and healthcare authorities involved in providing and delivering treatment for patients with HCV in Pakistan.

METHODOLOGY

This Clinical Practice Guidance is based on latest international guidelines on HCV management\textsuperscript{4-6}, local experience\textsuperscript{7} and available DAAs in Pakistan.

As per international protocol, available regimens have been classified as below:

- **Recommended**: These are effective (chances of SVR12 90% or above), high eligibility and tolerability and few side-effects profile, shorter duration of therapy and low pill burden. These are sub classified into:
  - Preferred having most of the characteristics mentioned above
  - Alternate almost equally effective but inferior to above in terms of eligibility, tolerability and/or duration of therapy.

- **Not Recommended**: These are less effective (chances of SVR12 less than 90%), with low eligibility and tolerability and increased side-effects profile, longer duration of therapy and higher pill burden.

These guidelines discuss only those DAAs, which are currently available or expected to become available in near future for clinical practice in Pakistan. These include:

- **Sofosbuvir + Ribavirin**
• **Sofosbuvir + Daclatasvir ± Ribavirin**
• **Sofosbuvir/Ledipasvir ± Ribavirin**
• **Sofosbuvir/Velpatasvir ± Ribavirin**
• **Sofosbuvir/Velpatasvir/Voxilaprevir**

**Virology and Natural History of HCV**

Hepatitis C virus (HCV) was identified as a cause of Non-A, Non-B (NANB) hepatitis in 1989\(^8,9\). Hepatitis C virus belongs to the Hepacivirus genus within the Flaviviridae family. It is an enveloped single stranded positive sense, 9.6 kb and about 50 nm in diameter RNA virus. It is a blood-borne virus and the most common sources include unsafe injection practices, blood transfusion, unsterilized or inadequately sterilized medical equipment and vertical transmission from mother to child and the sexual contact. Hepatitis C virus has 6 major genotypes with variable global distribution: genotypes 1 is mostly found in USA and Europe, genotype 3 mostly in Southeast Asia, genotype 4 mostly in Middle East, Egypt and Central Africa, genotype 5 almost exclusively in South Africa and genotype 2 almost equally across the world. The incubation period for HCV is 2 weeks to 6 months.

By and large, hepatitis C infection exhibits “80:20 rule”:

- 80% acute hepatitis C patients are asymptomatic and 20% symptomatic.
- Out of symptomatic patients, 80% patients have mild symptoms with mildly raised liver enzymes and 20% have significant symptoms with significantly raised liver enzymes.
- Out of these acute hepatitis C patients, 80% progress into chronic hepatitis and 20% recover spontaneously within 6 months of acquiring infection.
- Out of chronic hepatitis C patients, 80% remain stable and 20% develop cirrhosis with life threatening complications like hepatic encephalopathy, variceal bleeding, ascites and hepatorenal syndrome and certainly fatal hepatocellular carcinoma until identified and treated early in its course.

**Diagnosis of HCV Infection**

Two sets of tests are required to diagnose and confirm HCV infection, as described below:

- **First-line diagnostic test:** Anti-HCV antibody is the first test to find out if a patient has infection of HCV or not. In many regions of Pakistan, anti-HCV is checked by Immunoassay Chromatography Test (ICT) method, which has questionable sensitivity. It is recommended that anti-HCV should be determined by Enzyme-linked Immunoassays (ELISA) method.

- **Second-line diagnostic test(s):** After anti-HCV is found to be reactive, HCV infection is confirmed by two types of tests:
  - **HCV-RNA PCR:** It’s the most widely used second-line test to confirm the presence of active HCV infection. HCV RNA should be determined by a sensitive molecular assay (lower limit of detection of <15 IU/ml).
  - **HCV core antigen:** It’s not widely used in clinical practice. It’s a surrogate marker of HCV replication, but its detection assays are less...
sensitive than HCV RNA assays (lower limit of detection equivalent to approximately 500 to 3000 HCV RNA IU/ml, depending on the HCV genotype\textsuperscript{10,11}.

- **Interpretation of results:** These can be interpreted as follows:
  - **Anti-HCV [+], but PCR [-]:** It suggests recovered case of HCV infection. In case of no therapy in past, it may be a case of “spontaneously recovered case of HCV”; HCV-RNA PCR must be repeated after 3-6 months to confirm recovered status.
  - **Anti-HCV [-], but PCR [+]:** It suggests suspected case of “acute hepatitis C” or immunocompromised state. Acute hepatitis C can be suspected if: i) recent source of transmission is identifiable, ii) recent onset jaundice, iii) serum ALT >10 times the upper limit of normal, and iv) appearance of anti-HCV within following 2 months period.
  - **Both anti-HCV & PCR [+]:** It suggests chronic HCV infection and warrants anti-viral therapy until and unless contraindicated.

**ANTI-HCV THERAPY**

**Goal of therapy:** - Therapy is given to eradicate HCV infection and thus:

1. To prevent hepatic cirrhosis in patients without cirrhosis.
2. To reduce the rate of decompensation, risk of HCC, and death in patients with cirrhosis.

**Indication of therapy:** - Every patient with positive PCR must be treated, except where:

- Therapy is contraindicated, and/or
- Therapy is not tolerated, and/or
- There is poor life expectancy.

**Endpoint of therapy** is undetectable HCV RNA in a sensitive assay (<15 IU/ml) 12 weeks after the end of therapy (SVR-12).

**General principle of therapy** is that all treatment-naïve and -experienced patients should be considered for therapy. Severity of liver disease has pivotal role in selecting patients for therapy, as explained below:

- **Patient with no or mild disease (<F2):** Antiviral therapy may safely be delayed, if there is some genuine reason.

- **Patient with significant fibrosis (≥F2):** Antiviral therapy needs to be initiated in the absence of absolute contraindication(s).

- **Patient with decompensated cirrhosis:** In these patients (CTP class B and C, Table-1) antiviral therapy should not be withheld until there is absolute contraindication. Such patient must be referred to highly experienced HCV treatment provider (ideally in a liver transplant center) at earliest.
Table – 1: Child-Turcotte-Pugh Classification

**Scoring:** The score employs five clinical measures of liver disease. Each measure is scored 1-3, with 3 indicating most severe derangement

<table>
<thead>
<tr>
<th>Measure</th>
<th>1 Point</th>
<th>2 Points</th>
<th>3 Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Bilirubin, mg/dL</td>
<td>&lt;2</td>
<td>2 – 3</td>
<td>&gt;3</td>
</tr>
<tr>
<td>Serum Albumin, g/dL</td>
<td>&gt;3.5</td>
<td>2.8 – 3.5</td>
<td>&lt;2.8</td>
</tr>
<tr>
<td>PT-INR</td>
<td>&lt;1.7</td>
<td>1.71 – 2.3</td>
<td>&gt;2.3</td>
</tr>
<tr>
<td>Ascites</td>
<td>None</td>
<td>Mild</td>
<td>Moderate to Severe</td>
</tr>
<tr>
<td>Hepatic Encephalopathy</td>
<td>None</td>
<td>Grade I-II (or suppressed with medication)</td>
<td>Grade III-IV (Refractory)</td>
</tr>
</tbody>
</table>

**Interpretation:** Chronic liver disease is classified into Child-Pugh class A to C, employing the added score from above

<table>
<thead>
<tr>
<th>Points</th>
<th>Class</th>
<th>1-year survival</th>
<th>2-years survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-6</td>
<td>A</td>
<td>100%</td>
<td>85%</td>
</tr>
<tr>
<td>7-9</td>
<td>B</td>
<td>81%</td>
<td>57%</td>
</tr>
<tr>
<td>10-15</td>
<td>C</td>
<td>45%</td>
<td>35%</td>
</tr>
</tbody>
</table>

PT-INR = Prothrombin Time and International Normalized Ratio

**Anti-HCV Drugs Available in Pakistan In 2017:**
As against US and Europe, only following drugs are available here in Pakistan:
- **Sofosbuvir:** It is the freely available DAA in Pakistan.
- **Daclatasvir:** It is the freely available DAA in Pakistan.
- **Sofosbuvir/Ledipasvir:** It’s a combo-pill and available on patients’ demand.
- **Sofosbuvir/Velpatasvir:** It’s a combo-pill and available on patients’ demand.
- **Sofosbuvir/Velpatasvir/Voxilaprevir:** It’s recently FDA approved combo-pill for DAAs-experienced cases and hopefully to become available here in Pakistan on patients’ demand.

Table-2 summarizes indications of these drugs and table-3 summarizes dosages of these drugs. Rest of the DAAs has not been mentioned in these Guidelines.

**Table – 2: Anti-HCV drugs available in Pakistan**

<table>
<thead>
<tr>
<th>Options</th>
<th>Indications</th>
<th>Genotypes</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOF/VEL ± RBV</td>
<td>Initial &amp; recommended therapy</td>
<td>1,2,3,4,5,6</td>
</tr>
<tr>
<td>SOF+DCV ± RBV</td>
<td>Initial &amp; recommended therapy</td>
<td>1,2,3,4,5,6</td>
</tr>
<tr>
<td>SOF/LDV ± RBV</td>
<td>Initial &amp; recommended therapy</td>
<td>1,4,5,6</td>
</tr>
<tr>
<td>SOF+RBV</td>
<td>Initial but alternate therapy</td>
<td>2,3</td>
</tr>
<tr>
<td>SOF/VEL/VOX</td>
<td>Repeat therapy for DAAs-experienced patients only</td>
<td>1,2,3,4,5,6</td>
</tr>
</tbody>
</table>

SOF=Sofosbuvir, VEL=Velpatasvir, DCV=Daclatasvir, LDV=Ledipasvir, VOX=Voxilaprevir, RBV=Ribavirin
Table – 3: Therapeutic dosages of these drugs (For Adults)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOF (400 mg)/VEL (100 mg)</td>
<td>In a single dose for 12/24 weeks</td>
</tr>
<tr>
<td>SOF (400 mg)+DCV (60 mg)</td>
<td>In a single dose for 12/24 weeks</td>
</tr>
<tr>
<td>SOF (400 mg)/LDV (90 mg)</td>
<td>In a single dose for 12/24 weeks</td>
</tr>
<tr>
<td>SOF (400 mg)</td>
<td>In a single dose for 12/24 weeks</td>
</tr>
<tr>
<td>SOF (400 mg)/VEL (100 mg)/VOX (100 mg)</td>
<td>In a single dose for 12 weeks</td>
</tr>
<tr>
<td>RBV</td>
<td>For &lt;75 kg: 1000 mg in divided doses</td>
</tr>
<tr>
<td></td>
<td>For &gt;75 kg: 1200 mg in divided doses</td>
</tr>
</tbody>
</table>

SOF=Sofosbuvir, VEL=Velpatasvir, DCV=Daclatasvir, LDV=Ledipasvir, VOX=Voxilaprevir, RBV=Ribavirin

Table-4 summarizes different Phase II, III and IV studies, which established the efficacy and safety of different DAAs in HCV infection and on the basis of which clinical approval was granted to these DAAs.

Table – 4: Summary of published data evidence

<table>
<thead>
<tr>
<th>Regimens</th>
<th>Studies</th>
<th>Genotypes</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOF/VEL ± RBV</td>
<td>ASTRAL-1&lt;sup&gt;12&lt;/sup&gt;</td>
<td>1,2,4,5,6</td>
</tr>
<tr>
<td></td>
<td>ASTRAL-2&lt;sup&gt;13&lt;/sup&gt;</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>ASTRAL-3&lt;sup&gt;17&lt;/sup&gt;</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>ASTRAL-4&lt;sup&gt;14&lt;/sup&gt;</td>
<td>1-6 (CTP-B &amp; C)</td>
</tr>
<tr>
<td>SOF+DCV ± RBV</td>
<td>ALLY-1&lt;sup&gt;15&lt;/sup&gt;</td>
<td>1,3</td>
</tr>
<tr>
<td></td>
<td>ALLY-2&lt;sup&gt;16&lt;/sup&gt;</td>
<td>1,2,3,4</td>
</tr>
<tr>
<td></td>
<td>ALLY-3&lt;sup&gt;17&lt;/sup&gt;</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>ALLY-3+&lt;sup&gt;18&lt;/sup&gt;</td>
<td>3</td>
</tr>
<tr>
<td>SOF/LDV ± RBV</td>
<td>ION-1&lt;sup&gt;19&lt;/sup&gt;, -2, -3, -4&lt;sup&gt;22&lt;/sup&gt;</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>SOLAR-1&lt;sup&gt;23&lt;/sup&gt;</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>SYNERGY-&lt;sup&gt;24&lt;/sup&gt;</td>
<td>4</td>
</tr>
<tr>
<td>SOF+RBV</td>
<td>VALENCE&lt;sup&gt;25&lt;/sup&gt;</td>
<td>2,3</td>
</tr>
<tr>
<td></td>
<td>BOSON&lt;sup&gt;26&lt;/sup&gt;</td>
<td>2,3</td>
</tr>
<tr>
<td></td>
<td>RESiP&lt;sup&gt;7&lt;/sup&gt;</td>
<td>1-6</td>
</tr>
<tr>
<td>SOF/VEL/VOX</td>
<td>POLARIS-1&lt;sup&gt;27&lt;/sup&gt;, -2&lt;sup&gt;28&lt;/sup&gt;</td>
<td>1-6</td>
</tr>
<tr>
<td></td>
<td>POLARIS-3&lt;sup&gt;28&lt;/sup&gt;</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>POLARIS-4&lt;sup&gt;27&lt;/sup&gt;</td>
<td>1-4</td>
</tr>
</tbody>
</table>

SOF=Sofosbuvir, VEL=Velpatasvir, DCV=Daclatasvir, LDV=Ledipasvir, VOX=Voxilaprevir, RBV=Ribavirin

**Sofosbuvir/Velpatasvir:**

**Genotype 1** – In phase III ASTRAL-1 trial<sup>12</sup>, patients with genotype-1 were treated with the fixed-dose combination of sofosbuvir and velpatasvir for 12 weeks without ribavirin. Patients’ population included: 66% treatment-naïve, 34% treatment-
experienced (44% of whom were exposed to previous DAA), and 22% with cirrhosis. Following SVR12 was observed:
- 98% (206/210) in patients with genotype 1a
- 99% (117/118) in patients with genotype 1b

**Genotype 2** – In phase III ASTRAL-2 trial\(^{13}\), patients with genotype-2 were treated with the fixed-dose combination of sofosbuvir and velpatasvir for 12 weeks without ribavirin. Patients’ population included: 86% treatment-naive, 14% treatment-experienced and 14% with cirrhosis. SVR12 was observed in 99% (133/134).

**Genotype 3** – In phase III ASTRAL-3 trial\(^{13}\), patients with genotype-3 were treated with the fixed-dose combination of sofosbuvir and velpatasvir for 12 weeks without ribavirin. Patients’ population included: 74% treatment-naive, 26% treatment-experienced and 29% with cirrhosis. Following SVR12 was observed:
- 98% (160/163) in treatment-naive patients without cirrhosis
- 93% (40/43) in treatment-naive patients with compensated cirrhosis
- 91% (31/34) in treatment-experienced patients without cirrhosis
- 89% (33/37) in treatment-experienced patients with compensated cirrhosis
- 97% (225/231) in patients without NS5A RASs at baseline
- 88% (38/43) in those with detectable NS5A RASs at baseline (present in 16% of cases)

**Genotype 4** – In phase III ASTRAL-1 trial\(^{12}\), patients with genotype-4 were treated with the fixed-dose combination of sofosbuvir and velpatasvir for 12 weeks without ribavirin. Patients’ population included: 55% treatment-naive, 45% treatment-experienced and 23% with cirrhosis. SVR12 was observed in 100% (4/4).

**Genotype 5** – In phase III ASTRAL-1 trial\(^{12}\), patients with genotype-5 were treated with the fixed-dose combination of sofosbuvir and velpatasvir for 12 weeks without ribavirin. Patients’ population included: 69% treatment-naive, 31% treatment-experienced and 14% with cirrhosis. SVR12 was observed in 97% (34/35).

**Genotype 6** – In phase III ASTRAL-1 trial\(^{12}\), patients with genotype-6 were treated with the fixed-dose combination of sofosbuvir and velpatasvir for 12 weeks without ribavirin. Patients’ population included: 93% treatment-naive, 17% treatment-experienced and 15% with cirrhosis. SVR12 was observed in 100% (44/41).

**Sofosbuvir and Daclatasvir:**

**Genotype 1** – One Phase IIb\(^{29}\) and two Phase III trials ALLY-1\(^{15}\) and ALLY-2\(^{16}\) were conducted on patients with HCV genotype-1 infection:

**Phase IIb trial\(^{29}\)** was conducted on patients with HCV genotype-1 infection with the combination of sofosbuvir and daclatasvir with and without ribavirin. Following SVR12 was observed:
- Treatment naïve Patients:
  - 98% (40/41) after 12 weeks of therapy without ribavirin.
  - 100% (14/14) after 24 weeks of therapy without ribavirin.
  - 100% (15/15) after 24 weeks of therapy with ribavirin.
- Treatment-experienced patients who did not respond to the combination of pegylated IFN-a, and either telaprevir or boceprevir:
  - 100% (21/21) after 24 weeks of therapy without ribavirin.
  - 90.48% (19/21) after 24 weeks of therapy with ribavirin.
ALLY-2 trial\textsuperscript{16}, was conducted on patients on treatment for HIV as well. All patients were treated with the combination of sofosbuvir and daclatasvir for 12 weeks without ribavirin. The dose of daclatasvir was adjusted to 30 mg in patients receiving ritonavir-boosted HIV protease inhibitors. An SVR12 was observed in 96\% (100/104) in genotype 1a- and 100\% (23/23) in genotype 1b-infected patients.

In ALLY-1 trial\textsuperscript{15}, 91\% (10/11) of patients with compensated cirrhosis achieved SVR12.

Genotype 2 – Phase III ALLY-2 trial\textsuperscript{16}—was conducted on patients with HCV genotype-2 infection. All patients were treated with the combination of sofosbuvir and daclatasvir for 12 weeks without ribavirin. An SVR12 was observed in 100\% (11/11) in treatment-naïve and 100\% (2/2) in treatment-experienced patients.

Genotype 3 – One Phase IIb trial\textsuperscript{29} and two Phase III trials ALLY-3\textsuperscript{17} and ALLY-3+\textsuperscript{18}, were conducted on patients with HCV genotype-3 infection:

In Phase IIb trial\textsuperscript{29}, the SVR12 was achieved in 89\% (16/18) treatment naïve non-cirrhotic patients with HCV genotype 3 with combination of sofosbuvir and daclatasvir without ribavirin for 24 weeks.

In ALLY-3 trial\textsuperscript{17}, patients were treated for 12 weeks with the combination of sofosbuvir and daclatasvir, without ribavirin. The SVR12 rates were:
- 97\% (73/75) in treatment-naïve non-cirrhotic patients
- 58\% (11/19) in treatment-naïve cirrhotic patients
- 94\% (32/34) in treatment-experienced non-cirrhotic patients
- 69\% (9/13) in treatment-experienced cirrhotic patients

In ALLY-3+ trial\textsuperscript{18}, following SVR12 rates were reported:
- 100\% (6/6) in patients with advanced fibrosis (METAVIR score F3) after 12 weeks of sofosbuvir and daclatasvir with ribavirin
- 100\% (8/8) in patients with advanced fibrosis (METAVIR score F3) after 16 weeks of sofosbuvir and daclatasvir with ribavirin
- 83\% (15/18) in patients with cirrhosis after 12 weeks of sofosbuvir and daclatasvir with ribavirin
- 89\% (16/18) in patients with cirrhosis after 16 weeks of sofosbuvir and daclatasvir with ribavirin
- 88\% (14/16) in patients with treatment-experienced cirrhosis after 12 weeks of sofosbuvir and daclatasvir with ribavirin
- 86\% (12/14) in patients with treatment-experienced cirrhosis after 16 weeks of sofosbuvir and daclatasvir with ribavirin

Genotype 4 – Very little data is available in HCV genotype 4: only 4 patients in ALLY-1 trial\textsuperscript{15} and 3 patients in ALLY-2 trial\textsuperscript{16} (all achieved SVR12).

Genotype 5 & 6 – No data is available from clinical trials for these rare genotypes.

Ledipasvir/Sofosbuvir:
Genotype 1 – Four Phase III trials ION-1\textsuperscript{19}, ION-2\textsuperscript{20}, ION-3\textsuperscript{21} and ION-4\textsuperscript{22} were conducted on patients with HCV genotype-1 infection:

In ION-1 trial\textsuperscript{19}, treatment-naïve patients (16\% with compensated cirrhosis) were treated. Following SVR12 was observed:
- 99% (211/214) after 12 weeks of the fixed-dose combination of ledipasvir and sofosbuvir without ribavirin.
- 97% (211/217) after 12 weeks of the fixed-dose combination of ledipasvir and sofosbuvir with ribavirin.
- 98% (212/217) after 24 weeks of the fixed-dose combination of ledipasvir and sofosbuvir without ribavirin.
- 99% (215/217) after 24 weeks of the fixed-dose combination of ledipasvir and sofosbuvir with ribavirin.

In ION-3 trial\textsuperscript{21}, treatment-naïve patients (13% with compensated cirrhosis) were treated. Following SVR12 was observed:
- 94% (202/215) after 8 weeks of the fixed-dose combination of ledipasvir and sofosbuvir without ribavirin.
- 93% (201/216) after 8 weeks of the fixed-dose combination of ledipasvir and sofosbuvir with ribavirin.
- 95% (205/216) after 12 weeks of the fixed-dose combination of ledipasvir and sofosbuvir without ribavirin.
- 97% (119/123) after 8 weeks of the fixed-dose combination of ledipasvir and sofosbuvir without ribavirin in patients with an HCV RNA level <6 million (6.8 Log) IU/ml at baseline on post-hoc analysis. Later on similar results were found in many real-world studies from Europe and the United States:\textsuperscript{30} 95% (251/263) in the TRIO cohort, 97% (150/154) in the HCV TARGET cohort, 97% (155/159) in the GECCO cohort, 99% (127/128) in the IFI cohort, and 98% (47/48) in the VA-Ohio cohort.

In ION-2 trial\textsuperscript{20}, treatment-experienced patients (20% with compensated cirrhosis) were treated. These patients were previously treated with pegylated IFN-a and ribavirin, or pegylated IFN-a, ribavirin and either telaprevir or boceprevir. Following SVR12 was observed:
- 94% (102/109) after 12 weeks of the fixed-dose combination of ledipasvir and sofosbuvir without ribavirin.
- 96% (107/111) after 12 weeks of the fixed-dose combination of ledipasvir and sofosbuvir with ribavirin.

ION-4 trial\textsuperscript{22}, was conducted on patients on treatment for HIV as well (45% treatment-naïve, 55% treatment-experienced – 36% DAAs, and 20% with cirrhosis). All patients were treated with the fixed-dose combination of sofosbuvir and velpatasvir for 12 weeks without ribavirin. SVR12 was observed in 96% (314/327).

Patients with compensated cirrhosis:\textsuperscript{31} An integrated analysis of 513 genotype 1 patients with compensated cirrhosis treated with the fixed-dose combination of ledipasvir and sofosbuvir, with or without ribavirin, in different Phase II and III studies showed:
- Overall SVR12 rates of 95% (305/322) after 12 weeks and 98% (188/191) after 24 weeks of therapy.
- Neither treatment duration nor ribavirin had an impact on SVR12 in treatment-naïve patients (SVR12 rates between 96% and 100%).
- In contrast, in treatment-experienced patients, the SVR12 rates were 90% after 12 weeks without ribavirin, 96% after 12 weeks with ribavirin, 98% after 24 weeks without ribavirin, and 100% after 24 weeks with ribavirin.
- A platelet count <75 x 10\textsuperscript{3}/μL was associated with a lower rate of SVR among treatment-experienced patients (based on 28 patients).
- In the SIRIUS study\textsuperscript{32}, in treatment-experienced patients (pegylated IFN-a, ribavirin and either telaprevir or boceprevir), SVR12 was achieved in 96% (74/77) with 12 weeks of the fixed-dose combination of sofosbuvir and ledipasvir with ribavirin and 97% (75/77) with 24 weeks of the same combination without ribavirin.
Genotype 4 – Two trials SYNERGY\(^2^4\) and one phase II trial\(^2^2\) were conducted on patients with HCV genotype-4 infection:
- In SYNERGY trial\(^2^3\), 95% (20/21) SVR\(^{12}\) was achieved after 12 weeks of the fixed-dose combination of ledipasvir and sofosbuvir without ribavirin.
- In one phase II trial\(^2^2\), 96% (21/22) SVR\(^{12}\) was achieved after 12 weeks of the fixed-dose combination of ledipasvir and sofosbuvir without ribavirin in treatment-naïve patients and 91% (20/22) SVR\(^{12}\) in treatment-experienced patients.

Genotype 5 & 6 – In Phase II trial\(^3^4\) patients with HCV genotype-5 and 6 infections were treated with 12 weeks of the fixed-dose combination of ledipasvir and sofosbuvir without ribavirin:
- HCV genotype-5 infection (41 patients treatment-naïve and treatment-experienced, with 9 patients with cirrhosis) with SVR\(^{12}\) in 95% (39/41).
- HCV genotype-6 infection (25 patients with treatment-naïve and treatment-experienced) with SVR\(^{12}\) in 96% (24/25).

Sofosbuvir and Ribavirin:

Genotype 2 – Phase III VALENCE trials\(^2^5\) was conducted on patients with HCV genotype-2 infection. All patients were treated with the combination of sofosbuvir and ribavirin for 12 weeks. Following SVR\(^{12}\) rates were reported:
- 97% (29/30) in treatment-naïve and non-cirrhotics
- 100% (2/2) in treatment-naïve and cirrhotics
- 94% (30/32) in treatment-experienced and non-cirrhotics
- 78% (7/9) in treatment-experienced and cirrhotics

Genotype 3 – Phase III VALENCE\(^2^5\) & BOSON\(^2^6\), and Phase IV RESiP\(^7\) trials were conducted on patients with HCV genotype-3 infection. All patients were treated with the combination of sofosbuvir and ribavirin for 24 weeks.

In VALENCE trial\(^2^5\) following SVR\(^{12}\) rates were reported:
- 95% (87/92) in treatment-naïve and non-cirrhotics
- 92% (12/13) in treatment-naïve and cirrhotics
- 87% (85/98) in treatment-experienced and non-cirrhotics
- 62% (29/47) in treatment-experienced and cirrhotics

In BOSON trial\(^2^6\) following SVR\(^{12}\) rates were reported:
- 90% (65/72) in treatment-naïve and non-cirrhotics
- 82% (18/22) in treatment-naïve and cirrhotics
- 84% (44/54) in treatment-experienced and non-cirrhotics
- 77% (26/34) in treatment-experienced and cirrhotics

In RESiP trial\(^7\) following SVR\(^{12}\) rates were reported:
- 97% (426/438) in treatment-naïve and non-cirrhotics
- 89% (263/294) in treatment-naïve and cirrhotics
- 94% (194/207) in treatment-experienced and non-cirrhotics
- 86% (179/208) in treatment-experienced and cirrhotics

Sofosbuvir/Velpatasvir/Voxilaprevir:
Four Phase III clinical studies (POLARIS-1\(^2^7\), -2\(^2^8\), -3\(^2^8\) and -4\(^2^7\)) were conducted to evaluate the efficacy and safety of fixed-dose combination of SOF/VEL/VOX without RBV in the treatment of chronic hepatitis C patients. POLARIS-2-\&-3\(^2^8\) were conducted on DAAs-naïve patients and POLARIS-1-\&-4\(^2^7\) were conducted on DAAs-experienced patients.
In POLARIS-1\textsuperscript{27}, patients with HCV genotype 1-6 infection who had previously received a regimen containing an NS5A inhibitor were included. Overall SVR12 was achieved in 96% patients with 12 weeks therapy:
- 99% (140/142) in patients with normal liver
- 93% (113/121) in patients with compensated cirrhosis

In POLARIS-4\textsuperscript{27}, patients with HCV genotype 1-4 infection who had previously received a DAA regimen but not an NS5A inhibitor were included. Overall SVR12 was achieved in 98% patients with 12 weeks therapy:
- 98% (96/98) in patients with normal liver
- 98% (82/84) in patients with compensated cirrhosis

**PRE-TREATMENT PHASE**

When HCV therapy is indicated, it is mandatory to do evaluate for important baseline factors, as shown below, to select best available regimen for the patient:

![Diagram of pretreatment assessment for anti-HCV therapy]

**Figure-1:** Pretreatment assessment for anti-HCV therapy

**Virological assessment of HCV:** - It includes:
- HCV RNA quantification by a sensitive assay (lower limit of detection of <15 IU/ml)
- HCV genotyping prior to initiation of antiviral treatment to determine the choice and duration of therapy

**Previous HCV Treatment:** - It is important to know status of previous anti-HCV therapy, and accordingly patients can be classified into one of the followings:
1) Treatment naïve
2) Interferon experienced but DAAs naïve
3) DAAs experienced irrespective of Interferon therapy

**Assessment of liver status:** - Chronic hepatitis C is essentially characterized by varying degree of hepatic fibrosis. In the absence of effective treatment, the fibrosis increases in severity from F1 to F4 grade and ultimately results in development of liver cirrhosis. Therefore, liver disease severity should be assessed prior to therapy. Identifying patients with cirrhosis is of particular importance, as their prognosis is altered and their treatment regimen may be adapted. Fibrosis stage should be assessed as follows:

- **Step-1:** Clinical picture like ascites, splenomegaly, peripheral stigmata of chronic liver disease on physical examination, previous history of hepatic encephalopathy, variceal bleeding, ascites, etc.

- **Step-2:** In case of no obvious clinical features of liver cirrhosis and any clue in history, abdominal ultrasound should be done to look for possible signs of cirrhosis and associated portal hypertension, like:
  - Coarse parenchyma of liver
  - Splenomegaly
  - Dilated portal vein
  - Ascites

- **Step-3:** In case of normal ultrasound findings, Transient Elastography (TE) and/or couple of indices may assess liver fibrosis.
  - **Transient Elastography (TE)** by FibroScan is currently recommended to use for liver stiffness measurement (LSM) in chronic hepatitis C, as it has high sensitivity in identifying patients with significant fibrosis (≥F2) and no fibrosis (<F2).
  - **APRI and Fib-4** are two indices based on ratio of simple laboratory variables like serum ALT, AST, Platelets count and age and available online and as smartphone Apps, and have high sensitivity in identifying patients with significant fibrosis (≥F2) and no fibrosis (<F2), like TE.

- **Liver Biopsy** is not indicated as an assessment tool for liver fibrosis unless to look for potential additional etiologies.

**Baseline RAVs:** Currently it’s not recommended to screen for presence of baseline RAVs, but it may become in clinical practice in future. Nevertheless we need to understand drug resistance concepts and terminology for selecting effective HCV therapy with DAAs:
• **Resistance Associated Substitution (RAS):** Amino acid change in a viral protein, which leads to a decrease in the susceptibility of the virus to inhibitory activity of the drug.

• **Resistance Associated Variant (RAV):** Genetic variant strain of the virus, which has one or more resistance associated substitutions.

• **Genetic Barrier to Resistance:** Multiple factors, which together determine the speed of selection of viral variants resistant to the DAAs.

• **Viral Fitness:** the ability of the virus to survive and propagate under particular conditions (e.g. under inhibitory activity of the drug).

Resistance develops because of two unique features of HCV biology. These are:
1. High mutation rate – one error is introduced per HCV particle produced
2. High virus production – more than $10^{12}$ HCV particles are produced per day

Because of these two features, $8.7 \times 10^{10}$ viruses with single mutation and $4.2 \times 10^9$ viruses with double mutations are produced each day. All possible single and double mutants are generated several times per day. Some are unviable and are eliminated; some may confer resistance.

It has been found that in treatment naïve patients, baseline contains wild type (sensitive) variants and resistant variants. If therapy suppresses DAAs-resistant variants, SVR is achieved but if therapy fails to suppress DAAs-resistant variants, breakthrough, relapse and even non-response happen. RAVs are of three types:
- NS3/4 Protease Inhibitors associated RAVs
- NS5A Inhibitors associated RAVs
- NS5B Inhibitors associated RAVs

Therefore we need to combine ≥ 2 drug classes to increase resistance barriers, which may depend upon drugs combination and genotype (subtype). Genetic barrier can be measured by fold change in IC50 values. IC50 is defined as half maximal inhibitory concentration (drug concentration required to inhibit 50% of the biochemical activity in vitro).

Three methods are available to detect RAVs. These are:
1. Direct (population) sequencing with 10-20% sensitivity
2. Cloning-sequencing with 5-10% sensitivity
3. Next Generation Sequencing (NGS) or Deep Sequencing with <1% sensitivity

The first method is relatively simple, reliable and may be used in clinical diagnostic laboratories. Other two are only for research laboratories.

Clinical utility of RASs is determined by multiple factors: IC50 fold change, combination, patients’ population, and treatment regimen. For example:
- RAS testing is most likely not required in populations and regimens with SVR >99%.
- RAS testing is most likely clinically useful and cost-effective in populations and regimens with suboptimal SVR <90%. These include treatment-experienced patients, cirrhosis, and combination with DAAs with low genetic barrier.
- RAS testing may become mandatory in patients who did not respond to DAAs therapy.

Looking for HBV/HIV co-infections: As HBV and HIV have similar modes of transmission as HCV; therefore HBV/HCV co-infection and HCV/HIV co-infection is not uncommon in clinical practice. HBV is more common than HIV in our country. We have 4.9% prevalence of HCV and 2.5% prevalence of HBV in our general population\textsuperscript{11}. Therefore all CHC patients must be screened for hepatitis B virus (HBV) by testing HBsAg by ELISA.

If HBsAg is found to be “Reactive” by ELISA, HBV-DNA quantitative PCR, HBeAg & anti-HBe, along-with anti-HDV should be tested, to determine whether HBV infection is active or not, and to look for concomitant hepatitis D virus (HDV) infection.

Looking for comorbid conditions: There are many co-morbid conditions, which aid to the progression of liver disease, therefore it is mandatory to look for these and treat them before starting AVT. These conditions include:
- Chronic Kidney Disease (CKD)
- Nonalcoholic steatohepatitis (NASH)
- Diabetes mellitus (DM)
- Ischemic Heart Disease (IHD)
- Drug induced liver injury (DILI)
- Autoimmune disorders
- Hemochromatosis
- Alcohol

Pharmacokinetics Profile: PK is defined as the study of the time course of drug absorption, distribution, metabolism, and excretion. Pharmacokinetic profile of any drug determines the safety and efficacy of therapy in an individual patient and therefore must be considered before prescribing DAAs therapy in HCV patient. For example: sofosbuvir is mostly excreted via kidneys and has limitations to be used in patients with GFR <30.

Drug-Drug Interaction: DAAs has interactions with other drugs where the dose may be increased or decreased; therefore its important to know about all drugs patient is already taking and before prescribing new drug in a patient already using DAAs. For example, the dose of daclatasvir may need to increase or decrease when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively.

Kindly visit University of Liverpool website \url{http://www.hep-druginteractions.com} or refer to University of Liverpool smartphone App-Liverpool HEP iChart for comprehensive list of such drug-drug interactions in addition to drug’s information leaflet by manufacturing company.

Counseling of Patients before initiation of HCV Therapy:
It is mandatory to educate and counsel all patients on the following aspects, before starting them on AVT:
**General aspects of HCV infection:** These include
- Natural course of HCV
- Disease status of the patient
- Alleviating of baseless worries and misbelieves associated with suffering from HCV infection
- Screening of other family members for HCV and HBV
- The measures to prevent spread of HCV to other family members and community
- Emphasis on good nutrition, avoidance of any dietary restrictions. The only avoidance is that of smoking and alcohol.

**Important aspects of HCV treatment:** These include
- The aims of AVT
- Common side-effects of AVT and general measures to cope with these
- Proper schedule of AVT
- Adherence to AVT
- Regular follow-ups and monitoring for safety and efficacy of AVT
- Use of double contraceptive methods including condoms

**TREATMENT PHASE**

Treatment of hepatitis C patients will be discussed in two sections:

1. **“General Populations”:** These include:
   - DAAs Naïve
     - Interferon Naïve
       - Patients with normal liver (Class-I)
       - Patients with compensated cirrhosis (Class-II)
     - Interferon Experienced
       - Patients with normal liver (Class-III)
       - Patients with compensated cirrhosis (Class-IV)
   - DAAs Experienced
     - Patients with normal liver (Class-V)
     - Patients with compensated cirrhosis (Class-VI)

*Patients with normal liver:* In these patients, there is no eligibility and/or tolerability issue; rather these are straightforward cases and must be started on anti-HCV treatment, until it’s relatively contraindicated like pregnancy, lactation, and hypersensitivity to anti-HCV drug(s); or patient not willing for anti-HCV therapy or want to delay it for some peculiar reasons.

*Patients with compensated cirrhosis:* In general, patients with compensated cirrhosis only have mild hepatic impairment (CTP-class A, Table-1) and do not have jaundice, ascites, variceal hemorrhage, or hepatic encephalopathy.

*Goals of Therapy* can be divided into three:
- **Immediate:** to achieve an SVR, since subsequent liver benefit is closely linked to obtaining an SVR.
- **Intermediate-term:** to decrease the patient’s risk of developing hepatic decompensation.
- **Long-term:** to diminish the risk of developing hepatitis C-related hepatocellular cancer and death.
During treatment, it is important to avoid therapy-induced hepatic decompensation in these patients.

2. **“Special Populations”:** These include:
   - Decompensated cirrhosis
   - HCC
   - Liver transplantation
   - Co-infections like HBV and/or HIV
   - Co-morbidities like chronic kidney disease, hemoglobinopathies
   - Adolescent and pediatric age group
   - Acute hepatitis C.

In treating these patients, following peculiar issues need to be kept in mind:
   - Eligibility for HCV therapy
   - Tolerability of HCV therapy
   - Drugs dosages and/or duration may need to be altered
   - More frequent and extra monitoring is warranted in such patients.

These will be further discussed individually with each category of such patients.

**Genotype-1:**
Treatment options depend upon subtype, as summarized below in table-5 &- 6:

### Table – 5: Available therapeutic options for genotype-1a in Pakistan

<table>
<thead>
<tr>
<th>DAAs Naive</th>
<th>Interferon Naive</th>
<th>Interferon Experienced</th>
<th>DAAs Experienced</th>
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<td>SOF/VEL</td>
<td>SOF/VEL/VOX</td>
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<td>SOF+DCV+RBV</td>
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<td></td>
<td>SOF/LDV</td>
<td>SOF/LDV+RBV</td>
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<tr>
<td></td>
<td>NL</td>
<td>LC-A</td>
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<tbody>
<tr>
<td>SOF/VEL</td>
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<tr>
<td>SOF+DCV</td>
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<tr>
<td>SOF/LDV</td>
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</table>

**Table – 6: Available therapeutic options for genotype-1b in Pakistan**

<table>
<thead>
<tr>
<th>DAAs Naive</th>
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<th>Interferon Experienced</th>
<th>DAAs Experienced</th>
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<td>SOF/VEL</td>
<td>SOF/VEL/VOX</td>
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<td>SOF+DCV</td>
<td>SOF+DCV+RBV</td>
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<td></td>
<td>SOF/LDV</td>
<td>SOF/LDV+RBV</td>
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<tr>
<td></td>
<td>NL</td>
<td>LC-A</td>
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<table>
<thead>
<tr>
<th>DAAs Experienced</th>
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<tbody>
<tr>
<td>SOF/VEL</td>
</tr>
<tr>
<td>SOF+DCV</td>
</tr>
<tr>
<td>SOF/LDV</td>
</tr>
</tbody>
</table>

**Table notes:**
- NL = Normal Liver, LC-A= Liver Cirrhosis CTP- Class A
- SOF= Sofosbuvir, VEL= Velpatasvir, DCV= Daclatasvir,
- LDV= Ledipasvir, VOX= Voxilaprevir, RBV= Ribavirin, W= Weeks
Sofosbuvir/Velpatasvir
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) without ribavirin for 12 weeks, in Class I-IV of both subtypes

Sofosbuvir and Daclatasvir
- **Genotype-1a Class I & II, and Genotype-1b Class I-IV:** Daily combination of daclatasvir (60 mg) plus sofosbuvir (400 mg) without ribavirin for 12 weeks
- **Genotype-1a Class II & IV:** Two regimens:
  - Daily combination of daclatasvir (60 mg) plus sofosbuvir (400 mg) with weight-based ribavirin for 12 weeks
  - Daily combination of daclatasvir (60 mg) plus sofosbuvir (400 mg) without ribavirin for 24 weeks, if ribavirin ineligible or not tolerated.

Ledipasvir/Sofosbuvir
- **Genotype-1a Class I & II, and Genotype-1b Class I-IV:** Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) without ribavirin for 12 weeks
- **Genotype-1a Class II & IV:** Two regimens:
  - Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) with weight-based ribavirin for 12 weeks
  - Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) without ribavirin for 24 weeks, if ribavirin ineligible or not tolerated.
- **Genotype-1a and -1b Class I with viral load <6 million IU/mL:** Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) without ribavirin for 8 weeks

Sofosbuvir/Velpatasvir/Voxilaprevir
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/Voxilaprevir (100mg) without ribavirin for 12 weeks, in class V & VI of both subtypes

**Genotype 2:**
Treatment options are summarized below in table-7:

**Table – 7: Available therapeutic options for genotype-2 in Pakistan**

<table>
<thead>
<tr>
<th>DAAs Naive</th>
<th>Interferon Experienced</th>
<th>DAAs Experienced</th>
</tr>
</thead>
<tbody>
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<td>Interferon Naive</td>
<td>Interferon Experienced</td>
<td>DAAs Experienced</td>
</tr>
<tr>
<td>(I) NL</td>
<td>(II) LC-A</td>
<td>(III) NL</td>
</tr>
<tr>
<td>SOF/VEL</td>
<td>SOF/VEL</td>
<td>SOF/VEL</td>
</tr>
<tr>
<td>SOF+DCV</td>
<td>SOF+DCV</td>
<td>SOF+DCV</td>
</tr>
<tr>
<td>SOF+RBV</td>
<td>SOF+RBV</td>
<td></td>
</tr>
</tbody>
</table>

NL= Normal Liver, LC-A= Liver Cirrhosis CTP-Class A, SOF=Sofosbuvir, VEL=Velpatasvir, DCV=Daclatasvir, VOX=Voxilaprevir, RBV=Ribavirin, W= Weeks

**Sofosbuvir/Velpatasvir**
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) without ribavirin for 12 weeks, in Class I-IV
**Sofosbuvir and Daclatasvir**
Daily combination of daclatasvir (60 mg) plus sofosbuvir (400 mg) without ribavirin for 12 weeks, in class I-IV

**Sofosbuvir and Ribavirin**
Daily combination of sofosbuvir (400 mg) and weight-based ribavirin for 12 weeks (as an alternate option in Class-I), and 16 weeks (as an alternate option in Class-III)

**Sofosbuvir/Velpatasvir/Voxilaprevir**
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/Voxilaprevir (100mg) without ribavirin for 12 weeks, in class V & VI

**Genotype 3:**
Treatment options are summarized below in table-8:

**Table – 8: Available therapeutic options for genotype-3 in Pakistan**

<table>
<thead>
<tr>
<th>DAAs Naïve</th>
<th>Interferon Naïve</th>
<th>Interferon Experienced</th>
<th>DAAs Experienced</th>
</tr>
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<tbody>
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<td>(II) LC-A</td>
<td>(III) NL</td>
<td>(IV) LC-A</td>
</tr>
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<td>SOF/VEL</td>
<td>SOF/VEL+RBV</td>
<td>SOF/VEL+RBV</td>
<td>SOF/VEL+RBV</td>
</tr>
<tr>
<td>SOF+DCV</td>
<td>SOF+DCV+RBV</td>
<td>SOF+DCV+RBV</td>
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<td>SOF+RBV</td>
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</tbody>
</table>

NL= Normal Liver, LC-A= Liver Cirrhosis CTP-Class A, SOF=Sofosbuvir, VEL=Velpatasvir, DCV=Daclatasvir, VOX=Voxilaprevir, RBV= Ribavirin, W= Weeks

**Sofosbuvir/Velpatasvir**
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) without ribavirin for 12 weeks (in Class-I), and with weight-based ribavirin for 12 weeks (in Class-II-IV)

**Sofosbuvir and Daclatasvir**
Daily combination of daclatasvir (60 mg) plus sofosbuvir (400 mg) without ribavirin for 12 weeks (in Class-I), and with weight-based ribavirin for 12 weeks (in Class-III) and 24 weeks (in Class-II & IV)

**Sofosbuvir and Ribavirin**
Daily combination of sofosbuvir (400 mg) and weight-based ribavirin for 24 weeks, in Class-I & III (as an alternate option)

**Sofosbuvir/Velpatasvir/Voxilaprevir**
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/Voxilaprevir (100mg) without ribavirin for 12 weeks, in class V & VI
Genotype 4:
Treatment options are summarized below in table-9:

Table – 9: Available therapeutic options for genotype-4 in Pakistan

<table>
<thead>
<tr>
<th>DAAAs Naïve</th>
<th>Interferon Naïve</th>
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<tr>
<td>SOF/VEL</td>
<td>SOF/VEL</td>
<td>SOF/VEL</td>
<td>SOF/VEL/VOX</td>
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<tr>
<td>SOF+DCV</td>
<td>SOF+DCV</td>
<td>SOF+DCV+RBV</td>
<td>SOF+DCV+RBV</td>
</tr>
<tr>
<td>SOF/LDV</td>
<td>SOF/LDV</td>
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**Sofosbuvir/Velpatasvir**
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) without ribavirin for 12 weeks, in Class I-IV

**Sofosbuvir and Daclatasvir**
- **Class I & II**: Daily combination of daclatasvir (60 mg) plus sofosbuvir (400 mg) without ribavirin for 12 weeks
- **Class III & IV**: Two regimens:
  o Daily combination of daclatasvir (60 mg) plus sofosbuvir (400 mg) with weight-based ribavirin for 12 weeks
  o Daily combination of daclatasvir (60 mg) plus sofosbuvir (400 mg) without ribavirin for 24 weeks, if ribavirin ineligible or not tolerated (as an alternate option).

**Ledipasvir/Sofosbuvir**
- **Class I & II**: Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) without ribavirin for 12 weeks
- **Class III & IV**: Two regimens:
  o Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) with weight-based ribavirin for 12 weeks
  o Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) without ribavirin for 24 weeks, if ribavirin ineligible or not tolerated (as an alternate option).

**Sofosbuvir/Velpatasvir/Voxilaprevir**
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/Voxilaprevir (100mg) without ribavirin for 12 weeks, in class V & VI

Genotype 5 & 6:
Treatment options are summarized below in table-10:
Table – 10: Available therapeutic options for genotype-5 & -6 in Pakistan

<table>
<thead>
<tr>
<th>DAAs Naive</th>
<th>DAAs Experienced</th>
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<tbody>
<tr>
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<td>SOF/LDV</td>
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</tbody>
</table>

NL = Normal Liver, LC-A= Liver Cirrhosis CTP-Class A, SOF=Sofosbuvir, VEL=Velpatasvir, DCV=Daclatasvir, LDV=Ledipasvir, VOX=Voxilaprevir, RBV= Ribavirin, W= Weeks

Sofosbuvir/Velpatasvir
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) without ribavirin for 12 weeks, in Class I-IV

Sofosbuvir and Daclatasvir
- **Class I & II:** Daily combination of daclatasvir (60 mg) plus sofosbuvir (400 mg) without ribavirin for 12 weeks
- **Class III & IV:** Two regimens:
  - Daily combination of daclatasvir (60 mg) plus sofosbuvir (400 mg) with weight-based ribavirin for 12 weeks
  - Daily combination of daclatasvir (60 mg) plus sofosbuvir (400 mg) without ribavirin for 24 weeks, if ribavirin ineligible or not tolerated (as an alternate option).

Ledipasvir/Sofosbuvir
- **Class I & II:** Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) without ribavirin for 12 weeks
- **Class III & IV:** Two regimens:
  - Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) with weight-based ribavirin for 12 weeks
  - Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) without ribavirin for 24 weeks, if ribavirin ineligible or not tolerated (as an alternate option).

Sofosbuvir/Velpatasvir/Voxilaprevir
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/Voxilaprevir (100mg) without ribavirin for 12 weeks, in class V & VI

**Monitoring During Treatment with DAAs**

1. First follow-up 2 weeks after start of treatment with CBC, Creatinine and LFTs.
2. Second and subsequent follow-ups every 4 weeks with CBC, Creatinine and LFTs till the treatment finishes.
3. Amiodarone should not be co-administrated with any Sofosbuvir containing regimen.
4. Drug-Drug Interactions: Help may be taken from online (http://www.hep-druginteractions.org/) and mobile applications (Liverpool HEP iChart) to look for interaction of DAAs with other drugs.

5. HCV RNA by PCR (Qualitative) or HCV Core Antigen test week 4 and end of treatment. Non-availability of these viral markers should not be a bar to treatment.

6. HCV RNA by PCR (Qualitative) or HCV Core Antigen test week 12 and 24-48 weeks after end of treatment to assess SVR.

Follow-up after treatment with DAAs for those who achieved SVR

It depends upon the liver status of the patient:

- **In patients with no significant fibrosis (F0, F1 & F2):** Serum ALT and HCV RNA should be retested at 24 and then 48 weeks. If PCRs remain negative and serum ALT remains within normal limits, no further monitoring is warranted.

- **In patients with significant fibrosis (F3 & F4):** long-term monitoring is required:
  - Serum ALT and qualitative PCR after week 24-48 after stopping treatment
  - Ultrasound and serum alpha-fetoproteins (AFP) should be done every 6 months as surveillance for HCC.
  - Endoscopic screening for varices at 6-12 monthly intervals.

Follow-up after treatment with DAAs for those who did not achieve SVR

1. Evaluation for retreatment every 6 months as effective alternative treatments become available
2. In the absence of retreatment:
   - **In patients with no significant fibrosis (F0, F1 & F2):** APRI, Fib-4 and ultrasound every 6 months to assess disease progression.
   - **In patients with significant fibrosis (F3 & F4):** long-term monitoring is required:
     - Ultrasound and serum alpha-fetoproteins (AFP) should be done every 6 months as surveillance for HCC.
     - Endoscopic screening for varices at 6-12 monthly intervals.

**TREATMENT OF SPECIAL POPULATIONS**

This section describes treatment of chronic hepatitis C patients with decompensated cirrhosis, hepatocellular carcinoma (HCC), liver transplantation, co-infections, co-morbidities, adolescent and pediatric age group and acute hepatitis C. As mentioned early, these patients have many peculiar issues in their management. For example:

- Eligibility and/or tolerability regarding anti-HCV therapy
- Dosages and/or duration of anti-HCV drugs need to be altered
- More frequent and extra monitoring is warranted
Patients with Decompensated Cirrhosis (CTP-Class B & C):

Patients are considered to have decompensated cirrhosis if they develop any of the following complications: jaundice, variceal bleeding, ascites or encephalopathy. The treatment of patients with decompensated cirrhosis (CTP-class B or C, Table-1) is extremely complex since most of these patients will require liver transplantation for long-term survival. The goal of treatment for patients with decompensated cirrhosis differs based on whether the patient is a candidate for liver transplantation or not:

- For patients who are not a candidate for transplantation, therapy is given to achieve an SVR, with the hope that some degree of liver fibrosis will reverse as a result of therapy and the patient could stabilize or improve their clinical condition.
- For patients who are candidates for liver transplantation, therapy is given to eradicate HCV infection prior to liver transplantation to prevent infection of liver graft and thus improve post-transplantation outcomes.

Treatment of hepatitis C in patients with decompensated cirrhosis is extremely challenging and sparse data exists in this patient population. Only highly experienced hepatitis C medical providers should perform treatment of hepatitis C in these patients.

**Sofosbuvir/Velpatasvir:** Phase III ASTRAL-4 trial\(^{14}\) was conducted on patients with HCV genotype-1 to -4 infection (all CTP-class B cirrhosis). Patients were randomized to receive the fixed-dose combination of sofosbuvir and velpatasvir for 12 weeks without ribavirin, for 12 weeks with weight-based dosed ribavirin, or for 24 weeks without ribavirin.

- Following SVR12 rates were observed:

<table>
<thead>
<tr>
<th>Genotype</th>
<th>SOF/VEL x 12W</th>
<th>SOF/VEL+RBV x 12W</th>
<th>SOF/VEL x 24W</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>88% (44/50)</td>
<td>94% (51/54)</td>
<td>93% (51/55)</td>
</tr>
<tr>
<td>1b</td>
<td>89% (16/18)</td>
<td>100% (14/14)</td>
<td>88% (14/16)</td>
</tr>
<tr>
<td>2</td>
<td>100% (4/4)</td>
<td>100% (4/4)</td>
<td>75% (3/4)</td>
</tr>
<tr>
<td>3</td>
<td>50% (7/14)</td>
<td>85% (11/13)</td>
<td>50% (6/12)</td>
</tr>
<tr>
<td>4</td>
<td>100% (4/4)</td>
<td>100% (2/2)</td>
<td>100% (2/2)</td>
</tr>
</tbody>
</table>

- Following change in MELD score was observed at week 12 post-treatment:
  - In patients who had baseline MELD score <15
    o 51% (114/223) had an improved MELD score
    o 22% (49/223) had no change in their MELD score, and
    o 27% (60/223) worsened MELD score
  - In patients who had a baseline MELD score >15
    o 81.5% (22/27) had an improved MELD score,
    o 11.1% (3/27) had no change in their MELD score, and
    o 7.4% (2/27) worsened MELD score.

**Ledipasvir/Sofosbuvir:** Phase II SOLAR-1 trial\(^{23}\) was conducted on patients with HCV genotype-1 and 4 infection (CTP-class B & C cirrhosis). Patients were randomized to receive the fixed-dose combination of ledipasvir and sofosbuvir with ribavirin for 12 or 24 weeks. Ribavirin was started at 600 mg/day and then escalated as tolerated up to maximum of 1200 mg/day. Following SVR12 rates were observed:
CTP-class | LDV/SOF+RBV x 12W | LDV/SOF+RBV x 24W  
---|---|---  
B | 87% (26/30) | 89% (24/27)  
C | 86% (19/22) | 87% (20/23)  

Phase II SOLAR-2 trial\(^{35}\) was conducted on patients with HCV genotype-1 and 4 infection (CTP-class B & C cirrhosis). Patients were randomized to receive the fixed-dose combination of ledipasvir and sofosbuvir with ribavirin for 12 or 24 weeks. Ribavirin was started at 600 mg/day and then escalated as tolerated up to maximum of 1200 mg/day. Following SVR12 rates were observed:

CTP-class | LDV/SOF+RBV x 12W | LDV/SOF+RBV x 24W  
---|---|---  
B | 87% (20/23) | 96% (22/23)  
C | 85% (17/20) | 78% (18/23)  

The MELD and Child-Pugh scores improved in approximately half of treated.

In a real-world study\(^{36}\) based on the United Kingdom early access program, patients with decompensated cirrhosis infected with HCV genotype 1 were treated with fixed-dose combination of ledipasvir and sofosbuvir, with or without ribavirin, for 12 weeks. The SVR12 rates were:

- 85% (11/13) in patients treated with ledipasvir and sofosbuvir without ribavirin
- 91% (136/149) in patients treated with ledipasvir and sofosbuvir with ribavirin

**Sofosbuvir and Daclatasvir:** In a real-world study\(^{36}\) based on the United Kingdom early access program, patients with decompensated cirrhosis infected with HCV genotype 1 and 3 were treated with combination of sofosbuvir and daclatasvir, with or without ribavirin, for 12 weeks. The SVR12 rates were:

- Genotype-1  
  - 50% (2/4) in patients treated with sofosbuvir and daclatasvir without ribavirin  
  - 88% (30/34) in patients treated with sofosbuvir and daclatasvir with ribavirin
- Genotype-3  
  - 60% (3/5) in patients treated with sofosbuvir and daclatasvir without ribavirin  
  - 71% (75/105) in patients treated with sofosbuvir and daclatasvir with ribavirin

Approximately one third of patients improved their MELD scores, one third had no change, and one third suffered deteriorating liver function 12 weeks after treatment. Improvement in MELD score was more frequent in treated than in untreated patients.

**Indication:** All patients with decompensated cirrhosis must be treated with anti-viral therapy if they are found to be PCR positive, until and unless contraindicated.

**Contraindications:** Anti-viral therapy is contraindicated in these patients in the following conditions:

1. HCC in CTP-class C cirrhosis
2. Low life-expectancy because of liver and/or other comorbidities

**CTP-class C cirrhosis:** Simple principle of anti-HCV therapy in CTP-class C is

- Patient with HCC (irrespective of No & Size) – No AVT
- Patient without HCC:
  - MELD score <18-20 = AVT and then LT
○ MELD score >18-20 = LT and then AVT

**Therapeutic Options:** Currently following options are available for HCV-related decompensated cirrhosis:

- **Sofosbuvir/Velpatasvir ± Ribavirin**
  - **Sofosbuvir and Daclatasvir ± Ribavirin**
- **Ledipasvir/Sofosbuvir ± Ribavirin**

**Sofosbuvir/Velpatasvir ± Ribavirin:** It’s indicated in all genotypes-1 to 6, irrespective of previous treatment status, with two regimens as described below:

- Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) with weight-based ribavirin for 12 weeks. Low initial dose of ribavirin (600 mg) is recommended for patients with CTP class C.
- In case of ribavirin ineligible patients, daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) without ribavirin for 24 weeks.

**Sofosbuvir and daclatasvir ± Ribavirin:** It’s indicated in all genotypes-1 to 6, irrespective of previous treatment status, with two regimens as described below:

- Daily daclatasvir (60 mg) plus sofosbuvir (400 mg) with weight-based ribavirin for 12 weeks for genotype 1, 2, 4, 5, 6 and 24 weeks for genotype 3. Low initial dose of ribavirin (600 mg) is recommended for patients with CTP class C.
- In case of ribavirin ineligible patients, daily daclatasvir (60 mg) plus sofosbuvir (400 mg) without ribavirin for 24 weeks.

**Ledipasvir/Sofosbuvir ± Ribavirin:** It’s indicated in genotypes-1, 4, 5 and 6, irrespective of previous treatment status, with two regimens as described below:

- Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) with weight-based ribavirin for 12 weeks. Low initial dose of ribavirin (600 mg) is recommended for patients with CTP class C.
- In case of ribavirin ineligible patients, daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) without ribavirin for 24 weeks.

**Patients with Hepatocellular carcinoma (HCC):**

Hepatitis C virus infection is a major cause of hepatocellular carcinoma worldwide. Interferon has been the major antiviral treatment, yielding viral clearance in approximately half of patients. New direct-acting antivirals substantially improved the cure rate to above 90%. Cancer risk persists even after 10 years of viral cure, and thus a clinical strategy for its monitoring is urgently needed. Several risk-predictive host factors, e.g., advanced liver fibrosis, older age, accompanying metabolic diseases such as diabetes, persisting hepatic inflammation, and elevated alpha-fetoprotein, as well as viral factors, e.g., core protein variants and genotype 3, have been reported. Indeed, a molecular signature in the liver has been associated with cancer risk even after viral cure.\(^{36}\)

Recently, some concerns have been raised about the possible increased risk of neoplastic recurrence after DAA therapy particularly in cirrhotic patients with previously cured HCC. DAA treatment is not associated with HCC recurrence after
viral clearance in patients with HCV-related cirrhosis and no previous history of HCC\textsuperscript{37}.

These different studies bring no strong evidence for an increased risk of HCC occurrence in “HCC naïve” patients treated by DAA. However, the persistent risk of HCC development strongly justifies HCC screening after viral clearance in patients with HCV related cirrhosis\textsuperscript{38}.

\textbf{HCV Therapy:} depends upon the category of patient:

1. Patient treated successfully for HCC in past: HCV therapy should be initiated as per routine guidance depending upon genotype and other baseline factors. Close monitoring during and after therapy for HCC is recommended.
2. Patient presented with HCC:
   a. Recurrent HCC after previous treatment
   b. New HCC before initiating HCV therapy
   HCV therapy depends upon the BCLC\textsuperscript{39} stage of HCC (Figure-2):
      - If HCC can be cured, HCV therapy should be initiated even before subjecting to HCC curative therapy. Liver transplantation remains the treatment of choice for HCC in such patient.
      - HCV therapy should be deferred if HCC cannot be cured.
3. Patient who develops HCC during HCV therapy: HCV therapy should be continued and HCC should be treated promptly so it is cured in its early stage. Liver transplantation remains the treatment of choice for HCC in such patient.

Figure-2: Staging and Treatment of HCC @ BCLC
Patients with Liver Transplantation:

Post-transplant Phase is characterized by following factors:

**Immunosuppressant (IS) Therapy:** Most commonly used IS drugs are:
- Prednisolone during initial 3 months
- Tacrolimus (Tac) alone or in combination of Mycophenolate Mofetyl (MMF), and Cyclosporin A (CsA) at times, started on first post-transplant day and given life-long to prevent graft-rejection.

**Renal Function:** Renal dysfunction is frequent after LT either due to early postoperative complications such as acute tubular necrosis or as a result of long-term exposure to calcineurin inhibitors (CNI). HCV-related kidney injury, diabetes and hypertension are other possible factors impairing kidney function. This is why the majority of LT recipients present a 30% GFR decline after one year from LT and a 15–20% prevalence of severe renal impairment (eGFR <30 ml/min) after 5 years\(^40\).

**Co-morbid conditions:** like diabetes mellitus, hypertension, dyslipidemia, etc. which require drugs in addition to IS drugs.

**Post-liver transplant HCV infection:** HCV infection invariably recurs in patients with detectable HCV RNA at the time of liver transplantation. HCV RNA can be detected as early as a few hours post-transplant and HCV graft re-infection subsequently leads to symptomatic HCV hepatitis between 1 and 4 months post-LT, with variable clinical patterns\(^41,42\).

The natural course of HCV infection is significantly accelerated in LT recipients when compared to immunocompetent individuals, with 15 to 30% of the patients progressing to cirrhosis within 5 years after LT, and approximately 50% developing liver failure shortly thereafter. A subset of patients (2–9%) may develop fibrosing cholestatic hepatitis (FCH), which is defined by progressive cholestasis, very high HCV RNA levels, hepatocyte ballooning and rapid progression to graft failure\(^45-47\).

**HCV Therapy:** This includes two types of scenarios: Pre-Transplant and Post-Transplant

- **Patients with an indication for liver transplantation:** HCV therapy should be given to all patients awaiting liver transplantation to make them HCV-RNA PCR negative at least 30 days prior to transplantation to prevent graft infection.
- **Patients with post-liver transplantation recurrence of HCV infection:** HCV therapy should be given to all patients after liver transplantation to make them HCV-RNA PCR negative as all studies have shown a beneficial impact of HCV clearance on liver function and patient survival post-liver transplantation. Two types of post-LT therapy is possible:
  - Very early or early DAA treatment, before biochemical manifestations of HCV recurrence develop i.e. *pre-emptive therapy*.
Later treatment initiated in response to biochemical and histopathological evidence of HCV recurrence, i.e. *clinically oriented treatment*. Currently this is the recommended approach: Initiation of DAA therapy between 3 and 6 months post-LT.

**Drug-Drug Interactions (DDIs):** Life-long IS therapy and many other drugs to treat various co-morbidities such as diabetes mellitus, hypertension, dyslipidemia etc. result in DDI with DAAs. Renal dysfunction is another common problem after LT, which limits the use of SOF.

- SOF+DCV, SOF/LDV have no significant DDIs with any IS and antimetabolites. However, potential interactions with Everolimus may require additional monitoring. No data are available regarding possible interactions between SOF/VEL and major IS.
- Possible DDI between DAA and other frequently prescribed drugs should be considered, particularly when antifungal agents, cardiovascular drugs, statins and central nervous system (CNS) drugs are administered simultaneously.

**General Principles of Post-LT HCV Therapy:**

- SOF+DCV, SOF/VEL can be given safely in combination with any IS therapy due to no or minimal DDI.
- Since SOF/LDV moderately affects CNI/mTOR metabolism, the blood levels of IS drugs should be monitored.
- Any other drug co-administered with DAAs after LT should be checked for possible DDI, such as antifungal agents, antibiotics, cardiovascular drugs, CNS drugs, recreational drugs and even hormonal treatments.
- Arrhythmia frequently occurs after LT, therefore patients treated with DAAs should be closely monitored for this. Amiodarone should be avoided.
- The issue of an increased risk of rejection following HCV clearance is of concern but needs to be evaluated in properly designed studies. In the meantime, close monitoring of CNI/mTOR is recommended, particularly at the end of DAA therapy when the cessation of DDIs and the improved metabolic capacity of the liver may alter the exposure to various IS.

**Efficacy of Post-LT HCV Therapy:** It depends upon liver status as described below:

- **Normal Liver & Compensated Cirrhosis:** In patients with mild fibrosis stages and compensated cirrhosis (CTP-class A), SVR was achieved in more than 90% of patients, with a good safety profile. In the SOLAR-1 study, the combination of SOF/LDV+RBV (1,000–1,200 mg) given to patients with genotype 1 or 4 infection, resulted in SVR12 rates higher than 90%, irrespective of treatment duration (12 or 24 weeks).
- ** Decompensated Cirrhosis:** In patients with decompensated cirrhosis after LT, the SVR rates were 10% to 30% lower than what is generally observed in patients without decompensation. In the SOLAR-2 study post-LT SVR was 95% and 100% in patients treated for 12 and 24 weeks respectively.

- **Fibrosing Cholestatic Hepatitis (FCH):** In the French multicenter cohort CUPILT, SVR12 rates of 88% and 100% were obtained in patients with strictly defined severe forms of FCH treated with SOF+RBV or SOF+DCV±RBV (600 mg increased as tolerated) for 24 weeks. There was no graft loss at the end of follow-up and a significant improvement in liver graft
function was constantly observed.

**Post-LT Therapeutic Options:** Currently following options are preferred for post-transplant recurrent HCV infection:
- **Sofosbuvir and Daclatasvir ± Ribavirin**
- **Ledipasvir/Sofosbuvir ± Ribavirin**
- **Sofosbuvir/Velpatasvir ± Ribavirin**

**Sofosbuvir and daclatasvir ± Ribavirin:** It’s indicated in all genotypes-1 to 6, irrespective of previous treatment status, with two regimens as described below:
- Daily daclatasvir (60 mg) plus sofosbuvir (400 mg) with ribavirin (initial low dose of 600 mg, increased as tolerated) for 12 weeks.
- In case of ribavirin ineligible patients, daily daclatasvir (60 mg) plus sofosbuvir (400 mg) without ribavirin for 24 weeks.

**Ledipasvir/Sofosbuvir ± Ribavirin:** It's indicated in genotypes-1, 4, 5 and 6, irrespective of previous treatment status, with two regimens as described below:
- Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) with weight-based ribavirin for 12 weeks.
- In case of ribavirin ineligible patients, daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) without ribavirin for 24 weeks.

**Sofosbuvir/Velpatasvir ± Ribavirin:** Though no published data are available to date; SOF/VEL seems to be the most appropriate option in all genotypes-1 to 6, irrespective of previous treatment status, with two regimens as described below:
- Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) with weight-based ribavirin for 12 weeks. Low initial dose of ribavirin (600 mg) is recommended for patients with CTP class C.
- In case of ribavirin ineligible patients, daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) without ribavirin for 24 weeks.

**Patients with HBV co-infection:**

In patients with HCV-HBV coinfection, there are four possibilities:
1. Both infections active
2. Both infections inactive
3. HCV active and HBV inactive
4. HCV inactive and HBV active

Scenario-3 is the most common one where the HBV DNA level is often low or undetectable, although it may fluctuate widely.

As both infections have the same route of transmission, therefore it’s mandatory to test all hepatitis C patients for HBsAg and anti-HBc antibody before starting them on DAAs:
- In case, HBsAg and/or anti-HBc antibody is positive, it should be followed by HBV DNA PCR and anti-HDV antibody
- In case, anti-HDV antibody is positive, it should be followed by HDV RNA PCR

Treatment of BC-coinfection depends upon activity of both infections, as described in Table-11, below:
Table-11: Treatment of HBV-HCV co-infections:

<table>
<thead>
<tr>
<th>HCV-PCR</th>
<th>HBV-PCR</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Detected</td>
<td>Not detected</td>
<td>Treat as HCV mono-infected patient. There is a potential risk of HBV reactivation during or after HCV clearance; therefore close monitoring is warranted.</td>
</tr>
<tr>
<td>Not Detected</td>
<td>Detected</td>
<td>Nucleoside/nucleotide analogue therapy as per standard guidelines</td>
</tr>
<tr>
<td>Detected</td>
<td>Detected</td>
<td>Treat both infections with DAAs and Nucleoside/nucleotide analogue therapies combined. #</td>
</tr>
<tr>
<td>Not Detected</td>
<td>Not Detected</td>
<td>No antiviral therapy Surveillance monitoring is warranted.</td>
</tr>
</tbody>
</table>

Note: - If HDV RNA PCR is positive; it should be treated as per standard guidelines

*Occult Hepatitis B, if HBsAg is negative and anti-HBc antibody is positive

# Renal monitoring is warranted when using Tenofovir with SOF/VEL or LDV/SOF

Patients with HIV co-infection:

Following points should be kept in mind while treating these patients:6

2. Don’t interrupt antiretroviral treatment to allow HCV therapy.
3. If antiretroviral drug needs to be switched to another agent, it should be done in collaboration with the HIV practitioner.
4. Sofosbuvir/Velpatasvir:
   a. Should NOT be used with efavirenz, etravirine, or nevirapine.
   b. When used Tenofovir, renal monitoring is mandatory. It should be stopped in those with eGFR below 60 mL/min.
5. Ledipasvir/Sofosbuvir:
   a. Should NOT be used with cobicistat-boosted regimens.
   b. When used Tenofovir, renal monitoring is mandatory. It should be reduced or replaced in those with eGFR below 60 mL/min.
6. Daclatasvir:
   a. Dose should be decreased to 30 mg daily with atazanavir
   b. Dose should be increased to 90 mg daily with efavirenz or etravirine
7. Ribavirin should NOT be used with didanosine, stavudine, or zidovudine.

Patients with Chronic Kidney Disease (CKD):

The kidney is important for the catabolism and/or filtration of sofosbuvir and ribavirin, and therefore, reduced doses are warranted in patients with reduced kidney functioning. Sofosbuvir is extensively metabolized in the liver to form the
pharmacologically active nucleoside analog triphosphate GS-461203. The kidneys eliminate almost 80% of the drug.

Patients with CKD can be divided into two main categories: pre-renal transplant patients, and post-renal transplant patients.

**Pre-renal transplant patients:** Dosage depends upon eGFR of these patients (Table-12):
- **DAAs:** Regarding DAAs, patients can be divided into two broad categories:
  - *Patients with CrCl > 30 mL/min.1.73m^2* – no dose adjustments are necessary for the combinations of sofosbuvir, velpatasvir, daclatasvir and ledipasvir in such patients.
  - *Patients with CrCl < 30 mL/min.1.73m^2* – Data on the safety and efficacy of sofosbuvir-based regimens are lacking in such patients. Therefore appropriate therapeutic dose of sofosbuvir is not established and therefore sofosbuvir-free regimens should be preferred whenever possible; but if no sofosbuvir-free regimen is available (as for genotypes 2 and 3 in particular), the risks vs. the benefit of sofosbuvir-based regimens should be carefully weighed:
    - If there is no significant liver fibrosis on elastography or liver biopsy, these patients should be encouraged to undergo kidney transplant and hepatitis C may be taken care of after renal transplant with Sofosbuvir and ribavirin.
    - If treatment is urgent, informed consent from the patient regarding “Off-Label” use of sofosbuvir must be taken. Close monitoring is required and treatment should be rapidly interrupted if the renal function deteriorates. For patients on dialysis, the optimal timing of treatment is an important consideration, i.e. pre- or post-renal transplantation if they are candidates for renal transplantation, or the risks vs. the benefit if renal transplantation is not possible.
- **Ribavirin:** Regarding RBV, patients can be divided into four broad categories:
  - *Patients with CrCl > 50 mL/min.1.73m^2* – no dose adjustments are necessary for ribavirin in such patients. Normal dosage is 1000 mg for up to 75 kg body weight and 1200 mg for >75 kg body weight, in divided doses.
  - *Patients with CrCl 30-50 mL/min.1.73m^2* – ribavirin should be given in alternate doses: 400mg alternating with 200mg/day in such patients.
  - *Patients with CrCl 15-30 mL/min.1.73m^2* – ribavirin should be given in 200mg/day in such patients.
  - *Patients with CrCl < 15 mL/min.1.73m^2* – ribavirin should be given in 200 mg/every other day or 200 mg thrice weekly after hemodialysis.

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

**Post-renal transplant patients:** Patients acquiring HCV after renal transplant fare better than those acquiring HCV while on hemodialysis. Patient infected with HCV (before renal transplant) have worse patient and allograft survival as compared to
uninfected patients. Post-renal transplant HCV infection should be treated as per guidelines described above in the section of liver transplant.

Table-12: Therapeutic dosages for anti-HCV drugs in patients with chronic kidney disease

<table>
<thead>
<tr>
<th>Renal Impairment</th>
<th>CrCl (eGFR Level)</th>
<th>Ribavirin</th>
<th>DAAs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage-1</td>
<td>Normal</td>
<td>≥ 80 mL/min/1.73 m²</td>
<td>1200 mg &gt;75Kg body weight</td>
</tr>
<tr>
<td>Stage-2</td>
<td>Mild</td>
<td>50-80 mL/min/1.73 m²</td>
<td>1000 mg &lt;75Kg body weight</td>
</tr>
<tr>
<td>Stage-3</td>
<td>Moderate</td>
<td>30-50 mL/min/1.73 m²</td>
<td>400 mg alternating with 200 mg per day</td>
</tr>
<tr>
<td>Stage-4</td>
<td>Severe</td>
<td>15-30 mL/min/1.73 m²</td>
<td>200 mg daily</td>
</tr>
<tr>
<td>Stage-5</td>
<td>ESRD/HD</td>
<td>&lt; 15 mL/min/1.73 m²</td>
<td>200 mg every other day</td>
</tr>
</tbody>
</table>

CrCl = Creatinine Clearance, eGFR = Estimated Glomerular Filtration rate, ESRD = End-Stage Renal Disease, HD = Hemodialysis, SOF=Sofosbuvir, VEL=Velpatasvir, DCV=Daclatasvir, LDV=Ledipasvir, RBV=Ribavirin

CHC Patients with Hemoglobinopathies:

The most frequent hemoglobinopathy associated with chronic hepatitis C is thalassemia major, followed by sickle cell anemia and thalassemia minor. Thalassemia major is characterized by a more rapid course of liver disease because of the concurrent iron overload. Following points should be kept in mind while treating these patients:

1. The indications for HCV therapy are the same in patients with and without hemoglobinopathies.
2. Ribavirin-based therapy should not be given to patients with a hemoglobin level less than 7 g/dL.
3. When the use of RBV is needed, careful monitoring is recommended, and blood transfusions may be required.

Patients with adolescent and pediatric age group:

Till early 2017, no enough data was available on use of DAAs in adolescent and pediatric age group, and peg-IFN+RBV remained the only therapy for below 18 years of age, as shown below:

- PRG-IFNα-2b (1.5 μg/Kg per week) in combination with RBV (15mg/kg per day) for age 3 years and older
- PEG-IFNα-2a (100 μg/m² per week) in combination with RBV (15mg/kg per day) for children aged 5 years and older

Adolescent age group: On 7th April 2017, FDA approved sofosbuvir with ribavirin and ledipasvir/sofosbuvir with or without ribavirin to treat hepatitis C virus in adolescent age group (12 to 17 years). Details are given below:

- Sofosbuvir is indicated for the treatment of chronic HCV genotype 2 or 3 infection in pediatric patients 12 years of age and older or weighing at least 35
kg without cirrhosis or with compensated cirrhosis for use in combination with ribavirin. The recommended dosage of sofosbuvir is one 400 mg tablet taken orally once daily with or without food in combination with ribavirin for 12 weeks (genotype-2) and 24 weeks (genotype-3).

- **Ledipasvir/Sofosbuvir** is indicated for the treatment of pediatric patients 12 years of age and older or weighing at least 35 kg with HCV genotype 1, 4, 5, or 6 infection without cirrhosis or with compensated cirrhosis. The recommended dosage of Ledipasvir/Sofosbuvir is one tablet (90 mg ledipasvir and 400 mg sofosbuvir) taken orally once daily with or without food for 12 weeks (24 weeks in case of genotype-1, treatment-experienced with compensated cirrhosis).

- **Ribavirin** is given weight-based and orally in two divided doses with food, as detailed out in Table-13:

Table-13: Ribavirin dose in 13-17 years old patients

<table>
<thead>
<tr>
<th>Body Weight</th>
<th>Daily Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>35 – 46 Kg</td>
<td>15mg/Kg/day in 2 divided doses</td>
</tr>
<tr>
<td>47 – 49 Kg</td>
<td>600 mg/day in 2 divided doses</td>
</tr>
<tr>
<td>50 – 65 Kg</td>
<td>800 mg/day in 2 divided doses</td>
</tr>
<tr>
<td>66 – 80 Kg</td>
<td>1000 mg/day in 2 divided doses</td>
</tr>
<tr>
<td>More than 80 Kg</td>
<td>1200 mg/day in 2 divided doses</td>
</tr>
</tbody>
</table>

**Pediatric age group:** Till date, DAAs are not recommended below 12 years of age. In EASL-2017, Karen F. Murray, et al\(^5\) found half-strength LDV/SOF (45/200 mg) safe and tolerable in children aged between 6 and 12 years. The overall SVR rates were excellent with only one genotype-1a child with cirrhosis relapse. This creates possibility of DAAs use in pediatric age group as well in 2018 or so.

**Patients with Acute Hepatitis C:**

Most patients with acute hepatitis C are asymptomatic and 50-90% patients progress to the chronic phase. Therefore, patients with acute hepatitis C should be considered for antiviral therapy in order to prevent progression to chronic hepatitis C\(^5\).

**Spontaneous Recovery:** Symptomatic disease with jaundice, female gender, a young age, and genetic polymorphisms in the region upstream of the IL28B (recently renamed IFN lambda-3, IFNL3) gene have been associated with spontaneous viral clearance, but none of these parameters accurately predicts spontaneous resolution at the individual level.

**Timing of HCV Therapy:** The ideal time point for starting therapy has not been firmly established. The more rationale timing may be:

- Elevated serum ALT, with or without clinical symptoms
- With no elevated serum ALT, after 12 weeks of acquiring acute infection
HCV Therapy: It includes following regimens:
- Sofosbuvir/Velpatasvir (all genotypes) without ribavirin for 8 weeks
- Sofosbuvir and Daclatasvir (all genotypes) without ribavirin for 8 weeks
- Ledipasvir/Sofosbuvir (genotypes 1, 4, 5 and 6) without ribavirin for 8 weeks
  o Patients with acute hepatitis C and HIV coinfection and/or a baseline HCV RNA level >1 million IU/ml (6.0 log IU/ml) may need to be treated for 12 weeks with the same combination regimens.

Efficacy: SVR should be assessed at 12 and 24 weeks post-treatment, because late relapses have been reported. High SVR rates (>90%) have been reported.

Prophylaxis: There is no indication for antiviral therapy as post-exposure prophylaxis in the absence of documented HCV transmission.

HOW TO ERADICATE HCV FROM PAKISTAN

Viral eradication has remained a persistent public health challenge across the world except smallpox and polio. Smallpox was successfully eradicated from the world by 1979 and now polio is almost eradicated except 3 countries\(^{33,54}\); and unfortunately Pakistan is among these 3 countries where polio still exists. Eradication of these two viral infections became possible mostly because of vaccine that reduced transmission and curtailed new infections. Unfortunately we don’t have any vaccine available against HCV till date, and even if it had been available to us, it would have been very difficult to solely depend upon this, as we haven’t been able to eradicate polio from our country despite the free availability of its effective vaccine, because of our local factors.

Whether we can eradicate HCV from our country or not, depends upon the proper understanding of the dynamics of the problem:

- Identified number of patients with active HCV infection is the tip of iceberg; accounting for less than 20% of the total patients pool existing at any given time; which in turn is determined by entry of newly HCV acquired cases and exit of treated and cured HCV cases from this pool.

- Eradication of HCV is only possible if we block entry of new cases and ideally increase exit of treated and cured cases.

- Before 2015, only interferon and ribavirin were the available therapeutic options for patients with chronic hepatitis C with an average success rate of 60%-70%; but for the last 3 years oral antiviral drugs are now available in Pakistan. All these oral drugs have therapeutic efficacy of more than 95% in easy to treat cases.

- Another good news is that the price of sofosbuvir is very low as compared to the original price of these drugs. Excellent efficacy and low pricing brings hope to extinct greater number of HCV cases from the existing pool of active infection.

Therefore we need to adopt a multifaceted national policy to become able to successfully eradicate HCV from our country. Our intervention strategies should include:
1. Prevention of spread of HCV to others
2. Successful treatment of known cases of active HCV
3. Screening for unidentified cases of HCV

Prevention: In 2015, on Center for Disease Assessment (CDA) platform with Homie Razavi, local expert panel including myself reviewed local and international publications as well as analyzed local data. We found that 230,000 new cases occur and 85,000 patients are treated each year; resulting in constant expansion of the HCV pool. Injections have been found to be the greatest risk factor for spread of HCV in our country, followed by surgical instruments and unscreened blood transfusions. Other known risk factors play a minor role. Therefore we need to limit the number of unnecessary injections use and advocate the use of new disposable syringes every time injection needs to be given. We need to address this issue at different levels starting from government level to healthcare institutions to healthcare workers to general public. Government needs to make legislation about mandatory disposable syringes, safe blood transfusions and safe surgical procedures. Healthcare institutions need to implement policy of hepatitis free surgical and instrumental interventions and safe hospital waste disposal. Healthcare workers need to adopt safe procedures and advocate hepatitis C prevention strategies in the public. There is a great responsibility on public as well especially barbers, beauticians, professional personnel involved in ear piercing etc. to adopt hepatitis free strategies. We need to create public awareness in rural as well as urban areas particularly with high prevalence of HCV. We may use electronic and social media as well as lectures and videos in schools, colleges and universities. We may use platform of madrassas, religious speeches in mosque, public messages by public celebrities, public leaders and scholars.

Treatment: In our country, HCV treatment is mostly via “out of pocket” approach by patients. Most of our patients belong to low socio-economic group and find difficult to afford anti-HCV treatment and related investigations. Since 2005, we have patients support program run by government but till date it has not achieved its targets. We need to ensure treatment to each and every diagnosed case of hepatitis C in our country; if unable to afford treatment by himself/herself; then via patients support program. We need to motivate philanthropists, social organizations and NGOs to come forward and help in providing free treatment to poor patients with HCV. We need to negotiate with pharmaceutical companies to provide subsidized anti-HCV drugs to these poor patients. We need to ensure proper and complete anti-HCV treatment to patients with proper follow-up and in time treatment of those who fail to respond to initial antiviral treatment. We need to ensure quality of anti-HCV drugs and proper prescription of these drugs. Not only the drugs, we need to train healthcare personnel at all levels to educate and train on protocols of these new drugs in form of refresher courses and CME activities. We need national guidelines on hepatitis C by our liver societies, which must be freely available to all concerned.

Screening: Because of the asymptomatic nature of HCV infection, almost 80% of HCV-positive people are unaware of their infection and therefore remain unidentified reservoirs for further transmission in the family and community. Therefore it is important to plan national hepatitis screening program, which should be properly funded, well coordinated and multi-phased as explained below:

- Mass Screening: It should have 3 phases:
  - In first phase, high-risk people need to be screened. These include
family members of HCV patients, those who need regular blood transfusions or hemodialysis; those who have underwent surgery and dental extraction, IV drug abusers and sex-workers, etc.

- In second phase, people residing in areas with high prevalence of HCV.
- In third phase, rest of the general population need to be screened.

**Mandatory Screening**: This includes:

- At the time of blood donation
- At the time of surgery or other interventional procedure
- At the time of admission to school
- At the time of employment
- At the time of making NIC and passport

During devising screening strategy, we need to ensure proper budgeting of the project, quality screening methods, proper counseling and awareness, and then adopting “go to person and screen” rather than “come and get screened” policy. It must be realized that screening must be followed by effective treatment and it brings responsibility to the screening authority and body to ensure effective treatment of HCV accordingly.

Fortunately we have national hepatitis control and treatment program in our country since 2005; it was run by Federal government as “Prime-Minister” program from 2005 to 2010 and since 2010 it is run as “Provincial Hepatitis Program” by all provinces. It is important to understand that we need to work on all the above mentioned three aspects to ensure eradication of hepatitis C from Pakistan, which is otherwise going to engulf all our resources in years to come.

**AREAS FOR FUTURE RESEARCH**

Safety, tolerability and efficacy of DAAs in:

- Decompensated cirrhosis
- Post-liver transplant scenario
- Chronic kidney disease
- HBV-HCV coinfection
- Pediatric population
- Risk of HCC
REFERENCES

Daclatasvir with sofosbuvir and ribavirin for hepatitis C virus infection with advanced cirrhosis or post-liver transplantation recurrence. Hepatology 2016; 63:1493–1505.


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