NATIONAL CONSENSUS PRACTICE GUIDELINES

Diagnosis, Management and Prevention of Hepatitis C in Pakistan 2017

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We acknowledge that many references, recommendations, tables, figures and other text material is adopted from AASLD, APASL, ACG, WGO, and EASL guideline for diagnosis and management of Hepatitis C. We try to follow the international rules and ethics. However, in some sections, this was not possible because of lack of published research in our country. There were also language issues that can cause confusion in understanding of guidelines. We hope that authors, editors and publishers of these guidelines, understand these limitations. However, if there is any concern, we will be pleased to rectify that.

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Aims and Objectives:

Since the advent of direct acting antiviral agents, there is a revolutionary change in the management of HCV infection. Newer drugs with different mechanism of action are being introduced and are expected to be available in coming few months in Pakistan as well. The main purpose of the guideline is to review and induct the latest research in field of HCV infection in Pakistani perspective so that our healthcare professionals can apply the new recommendations in timely and judicial manner.

Target groups of guidelines are general physicians treating hepatitis C, hepatologists and gastroenterologists. Other beneficiaries of these guidelines are public health institutions of Pakistan, which provide free treatment to deserving patients under National Hepatitis Prevention and Control Program and Pakistan Bait-ul-Mal Program.

Methodology:

These guidelines are based on the review of National consensus practice guidelines: Diagnosis, Management and Prevention of Hepatitis C Pakistan 2009. Published data in National and International Journals searched with the help of Google search and pub med, and 2015–16 guidelines of HCV by AASLD, EASL, APASL and WHO.

Local studies are preferably added with references to enhance the Pakistani perspective. Evidence was also taken from published studies. Recommendations have been based upon evidence from national publications on the subject and scientific presentations at national liver meeting as well from experts' personal experience and opinion.

LIST OF ABBREVIATIONS

AASLD	American Association for the Study of Liver Diseases
ALT	Alanine Aminotransferase
CHC	Chronic Hepatitis C
CKD	Chronic Kidney Disease
CLD	Chronic Liver Disease
CrCl	Creatinine Clearance
CYP	Cytochrome P
DAA	Direct Acting Antiviral
DCV	Daclatasvir
EASL	European Association for the Study of the Liver
ESRD	End Stage Renal Disease
ETR	End of Treatment Response
FDA	Food and Drug Administration
GFR	Glomerular Filtration Rate
HBsAg	Hepatitis B Surface Antigen
HBV	Hepatitis B Virus
HCC	Hepatocellular Carcinoma
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
IFN	Interferon
IV	Intra Venous
KPK	Khyber Pakhtunkhwa
LDV	Ledipasvir
NS5B	Nonstructural protein 5B
PEG	Pegylated interferon
RBV	Ribavirin
RNA	Ribonucleic acid
RVR	Rapid Virologic Response
SMV	Simeprevir
SOF	Sofosbuvir
SVR	Sustained VirologicResponse
VRVR	Very Rapid Virologic Response
WHO	World Health Organization

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1. INTRODUCTION

Hepatitis C virus infection is a global health problem and is the main cause of chronic liver disease worldwide. Almost 170 million people are infected with HCV globally.[1] Large number of persons who are infected will develop cirrhosis with liver failure and HCC.

In Pakistan HCV sero-prevalence is about 6.7% whereas the adult viremic prevalence is 5.8%, making Pakistan the 2nd country with the highest viremic infection in the world.[2] Pakistan with population of 190 million, about 10 million people are infected with hepatitis C virus.[3] With chronicity rate of 55–85% a large majority these individuals are going to develop cirrhosis and HCC unless diagnosed and tested under a National program[4]. Use of IFN based therapy was standard of care therapy for chronic hepatitis C patients in the country. With advent of new DAAs since 2011 the treatment of hepatitis C is revolutionized causing a dire need to update the recommendations for therapy.

Unsafe injection practice, unsterilized medical equipment and unscreened blood transfusion are the commonest mode of transmission for hepatitis C in Pakistan[4]. So there is a dire need to not only treat hepatitis C but study and compile the national data on exact epidemiology, risk factors and treatment responses of different regimens used in past to treat hepatitis C patients.

The present guidelines are aims to address these referenced issues and formulate a comprehensive consensus guideline for the prevention and treatment of hepatitis C in Pakistan.

1.1 Disease Definition

Any disease due to HCV, i.e., acute hepatitis, chronic hepatitis, cirrhosis, HCC, and extra hepatic manifestations is included in the definition.

1.2 Prevalence of Hepatitis C in Pakistan

Collecting and comparing health data across the country is a way to describe health problems, identify trends and help decision-makers to set priorities. The global epidemiology of Hepatitis C is well established. But HCV epidemiology in Pakistan is not well documented. Mostly the data is from hospital-based studies because there is a dearth of community-based studies. A National Survey of Hepatitis published in 2010 have shown a national prevalence rate of 4.8%.[5] The present paper summarizes the available data on the epidemiology of Hepatitis C virus since the first report of its recognition in 1992.

The literature search revealed 166 published studies during index period. The years of publication of these studies is shown in table-1. More than three quarter of the studies (80.7%) were carried out between the periods 2001–2015.

Table-1: Distribution of studies by year of Publication

Year of Publication	Number	Percent
2011–2015	38	**22.9**
2006–2010	33	**19.8**
2001–2005	63	**37.9**
1996–2000	24	**14.4**
1995 and earlier	8	**4.8**
Total	**166**	**100.0**

The geographical distribution showed that the maximum number of studies (42) were from Punjab, followed by Sindh (33), KPK (28), Islamabad (11), Northern areas/Azad Kashmir (5) and Balochistan (2).

1.2.1 Community Prevalence

Thirty studies dealt with sero-prevalence of HCV in general population (Table-2).[6-29] Majority of these studies (93.33%) dated 2000 to 2015. Only two studies were conducted in nineties.[6,7] Total number of persons examined during these studies was 111,926.

Unfortunately, there was no study from any major city of Balochistan or interior Sind. The prevalence ranged from 0.4% in Karachi to 23.8% in Gujranwala and Rahim Yar Khan.[6,12] The mean prevalence was 5.7% (95% CI: 5.1–6.3)

1.2.2 Sero-Prevalence in Healthy Blood Donors

Analysis of data from 0.6 million voluntary blood donors, which included 26 published studies from various regions of Pakistan, revealed a cumulative prevalence of 4.1%, ranging from as low as 0.13% to as high as 6%, as displayed in table-3.[30-58] Hasan Abbas Zaheer *et al* reported a prevalence of 3.26% in voluntary blood donors by analysing 160376 individuals (age range 18–60 years).[58]

Prevalence of anti HCV antibodies in professional blood donors has been reported to as high as 20% by Hamid S *et al*. Mujeeb S *et al* reported 30% combined prevalence of HBV/HCV/HIV among paid blood donors.[33,49]

Table-2: Sero-Prevalence of HCV in general population

Author	Year	Place	Number	Anti HCV (%)	Reference
Agboatwala *et al*	1994	Karachi	258	0.4	**6**
Luby	1997	Hafizabad	313	6.5	**7**
Aslam	2001	Lahore	488	16.0	**8**
Aslam	2001	Gujranwala	1,922	23.8	**8**
Khan	2004	Mardan	700	9.0	**9**
Khokhar	2004	Islamabad	47,538	5.3	**10**
Muhammad	2005	Buner	16,400	4.6	**11**
Farooq *et al*	2005	Khuzdar	665	3.3	**12**
Fayyaz *et al*	2006	Bahawalpur	2,086	6.3	**13**
Tariq & Janjua	2006	Rawalpindi	15,550	3.7	**14**
Jafri *et al*	2006	Karachi	3,533	1.6	**15**
Ahmad *et al*	2007	Faisalabad	300	16.0	**16**
Butt & Amin	2008	Rawalpindi	5,707	1.7	**17**
Khan *et al*	2008	Azad Kashmir	245	3.3	**18**
Idrees *et al*	2008	Lahore	6,817	14.6	**19**
Muhammad Umar *et al*	2009	Rawalpindi	1004391	11.52	**20**
Shahid Jamil *et al*	2010	Mansehra	67	10.3	**21**
Shoaib Khan *et al*	2011	Southern KPK	850	3.27	**22**
M. Ilyas et ai	2011	Gujranwala	58	2.32	**23**
Zafar Majeed *et al*	2012	Rahim Yar Khan	476	23.8	**24**
Farukh Naheed	2012	Karachi	46	8.6	**25**
Abida Arshad *et al*	2012	Mardan	22	3.66	**26**
M. Ikram Anwar *et al*	2013	Lahore	210	4.9	**27**
M. Tahir Mehr	2013	Peshawar	185	3.98	**28**
M. Ilyas	2015	Gujranwala	44	5.16	**29**

Table-3: Sero-Prevalence of HCV in blood donors

Author	Year	Place	Number	Anti HCV (%)	Reference
Kakepoto *et al*	1996	Karachi	16,705	1.2	**30**
Bhatti *et al*	1996	Rawalpindi	760	4.8	**31**
Lone *et al*	1999	Lahore	186	4.3	**32**
Mujeeb	2000	Karachi	612	0.5	**33**
Tanwani & Ahmad	2000	Islamabad	1345	12.5	**34**
DBTU	2001	Rawalpindi	20,500	5.0	**35**
PBTS	2001	Lahore	120,000	2.3	**36**
Ryas *et al*	2001	Rawalpindi	1,885	4.7	**37**
Ahmed *et al*	2001	Karachi	1,410	4.4	**38**
Ahmad *et al*	2002	Lahore	5,789	4.9	**39**
Khattak *et al*	2002	Rawalpindi	103,858	4.0	**40**
Fayyaz *et al*	2002	Bahawalpur	345	5.6	**41**
Mumtaz *et al*	2002	Rawalpindi	553	6.2	**42**
Akhtar *et al*	2004	Karachi	351,309	1.8	**43**
Ahmad *et al*	2004	Peshawar	4,000	2.2	**44**
Mahmood *et al*	2004	Multan	6,000	0.3	**45**
Sirhindi	2006	Lahore	18,216	4.2	**46**
Khan	2006	Bahawalpur	27,938	2.5	**47**
Aziz	2006	Skardu	850	1.1	**48**
Mujeeb *et al*	2006	Karachi	7,325	3.6	**49**
Azam	2007	Karachi	688	4.4	**50**
Ishaq *et al*	2007	Thatta	310	1.3	**51**
Bhatti *et al*	2007	Karachi	94,177	4.2	**52**
Khattak *et al*	2008	Peshawar	1,131	4.1	**53**
Mujeeb & Pearce	2008	Karachi	5,345	7.5	**54**
Chaudhary *et al*	2008	Rawalpindi	1,428	2.5	**55**
Najib U Khan *et al*	2011	KPK & FATA	7148	1.89	**56**
M. Umair *et al*	2012	AJK	8927	2.5	**57**
Hasan Abbas *et al*	2014	Islamabad	160376	3.26	**58**

1.2.3 Sero-Prevalence in High Risk Groups[59]

- Healthcare workers 5.5%
- Hemodialysis patients 38.8%
- Thalassemia patients 47.2%

1.2.4 Burden of HCV Related Liver Disease

A hospital based Pakistani mortality analysis conducted in 2002 noted that 7% in hospital deaths were caused by liver disease like viral hepatitis (1.53%), liver cancer (0.48%), and chronic disease of liver (5.46%).[60] Eight years' data from a tertiary care hospital showed that 17–22% deaths were due to liver disease caused by HBV and HCV infections.[61]

Sero-prevalence of hepatitis C in chronic liver disease patients is variable in four provinces and different regions of Pakistan. Burden of chronic liver disease clearly seems to be increasing in Pakistan. In studies done before 1997, 16.6% chronic liver disease patients were anti HCV positive, while in recent studies 60–70% of chronic liver disease patients are anti HCV positive.[2,62–65]

1.2.5 Prevalence of HCV in Hepatocellular Carcinoma Patients

Prevalence of HCC in cirrhotics ranges from 3.7–16.7%. Data published up to 1997, showed 50–60% HBsAg and 10–25% anti HCV positivity, in HCC cases.[66–70] A paradigm shift from hepatitis B to HCV infection was noted after 1998. Cumulative analysis of fourteen studies from different regions of Pakistan after 2000 showed 50–80% anti HCV and 20-30% HBsAg positivity in HCC patients.[71–80]

1.2.6 Sero-Prevalence of HCV in Pregnant Women

Pregnancy is not considered as a risk factor of acquiring HCV infection; however more exposure to gynaecological procedures and interventions during delivery may increase chances of acquiring HCV infection in our scenario. Sero-positivity of HCV in pregnant women ranges from 3–10.8%.[81–90]

1.2.7 Sero-Prevalence of HCV in Children

Children have low sero-positivity of HCV which range from 0.4–4.09% as displayed in table-4.[7,15,48,91-94]

Table-4: Sero-prevalence of HCV in children

Author (Year)	Region	No	HCV	Reference
Khan HI (1996)	Lahore	538	4%	91
Luby S (1997)	Hafizabad	-	2%	7
Frank M (1999)	Lahore	-	1.30%	48
Hussain M (2001)	Peshawar (Haemophilia)	40	25.00%	92
Mohammad J (2003)	Peshawar (Thalassemia)	80	36.25%	93
Jafri SW (2006)	Karachi	3533	1.60%	15
Shahid Nazir (2014)	Lahore (Thalassemia)	200	41%	94

Table-5: Prevalence of genotype 3 of HCV in Pakistan population[92,96,97,103–112]

Author (Year)	Location	Population	Prevalence*	Ref
Tong (1996)	Liverpool, UK	CHC±HCC	100% (15/15)	102
Zuberi SJ (2002)	Karachi	CHC & ALT	80% (171/215)	97
Ansari (2002)	Karachi	CHC	78% (198/255)	96
Khokhar N (2003)	Islamabad	CHC & ALT	83% (241/292)	92
Shaikh W (2003)	Larkana	CHC/Cirrhosis	100% (48/48)	103
Arif Hussain (2011)	Karachi	CHC	85.8% (392/457)	104
Sajjad Ashraf (2012)	Islamabad	CHC	91% (222/244)	105
Taj M.Khan (2014)	D.I.Khan	CHC	68.7% (369/537)	106
Amna Rasheed (2014)	Lahore	CHC	81.7% (400/489)	107
M. Waqar (2014)	Karachi	CHC	61.6% (231/375)	108
Shail Baig (2014)	Jamshoro	CHC	72.9% (78/107)	109
Shamim Saleha (2014)	Bannu	Seroprevalance	59% (65/110)	110
Faizan Younus (2015)	Rawalpindi	CHC	87% (142/163)	111
Abdul Majeed Akhter (2016)	Lahore	IV drug abusers	75% (65/87)	112

1.2.8 HCV genotype in Pakistan

Cumulative data from published Pakistani studies revealed that in Pakistani patients commonest genotype type is 3 (80%), followed by un-typeable (16–18%) and type 1 (6%).[95–112]

Nasar Khan published data from all over Pakistan in 2014 suggesting genotype 3a (39.4%) as the most prevalent genotype but the data from KPK showed 2a the most prevalent genotype (43.4%).[113]

1.3 Risk Factors for HCV Transmission in Pakistan

Hepatitis C can be transmitted through various routes, most common route is parenteral, and however non-parenteral transmissions can also occur, i.e., perinatal transmission, sexual exposure, and household contacts. In Pakistan injection use and treatment with un-sterilized equipments is major cause of nosocomial HCV transmission.

1.3.1 Injection Use

According to WHO data Pakistan has highest rate of injection per person per year (0.9–8.5 per person/year). Most of these injections have been administered by un-sterilized, contaminated, non-disposable syringes in previous 20 years.[105,114–117]

Different studies have reported unsafe injection use as route of HCV transmission in 20–100% HCV infected patients. In many of these patients however, more than one risk factor was present.[104,118–121]

1.3.2 Intravenous Drug Use

Most frequent mode of transmission of HCV in United States is through sharing of drug-injecting equipment among IV drug users. According to National assessment study on drug abuse in Pakistan, conducted in 2000, it was estimated that about 60,000 drug addicts were using drugs through injections.[122] This is a significant group, which may be exposed to hepatitis B and C viruses and HIV. Sero-prevalence of hepatitis B and C were however not mentioned in this study.

Shahid Abbasi along with his colleagues conducted a study amongst 300 IV drug abusers in Quetta and found that 134 (44.7%) were anti HCV antibodies positive.[123] Abdul Majeed Akhter determined the Anti HCV prevalence of 36.09% in 241 IV drug abusers from Lahore.[112]

In another meta-analysis where 562 IV drug abusers were analysed, anti-HCV prevalence was 87.01%.[20]

1.3.3 Transmission through Dental Treatment

Transmission of HCV can occur via improper handling and cleaning of dental instruments. There is no definite data available with statistical authenticity regarding dental treatment as risk factor for HCV transmission. Analysis of published studies show that history of dental treatment (once or more than one time) is present in 10–60% of HCV infected persons. Many of these however have other risk factors like therapeutic injections and minor surgical procedures[37,120,124–132]

1.3.4 Transmission through Sharps

Barbers shaving, ear and nose piercing, tattooing and non-sterile surgical and dental practices of unqualified health care workers (quacks) are other important risk factors for HCV transmission. In a study by Janjua reuse of used razor was noted in 46% of infected persons.[133] Ghias *et al* in their study demonstrated that 11% of the patients with HCV infection had history of sharps injury.[130] Zulfikar conducted a study amongst health care workers and showed an Odds ratio of 6 for needle stick injury and an odds ratio of 5.7 for recapping the needle.[134]

1.3.5 Transfusion Associated Hepatitis C infection

Transmission of HCV through blood transfusion is a major cause of all chronic HCV infections in Asia. History of blood transfusion has been noted in 11.1–83.5% Pakistani chronic liver disease patients. In multi transfused thalassemia major children 56.8% anti HCV antibody positivity has been noted.[120,130,131,135,136]

1.3.6 Intrafamilial Transmission

Few studies are available in this regard. 4.34% spouses of HCV infected persons were noted to be anti HCV positive by Irfan *et al*. In another study, 31.8% of parents, 38.2% of brothers and 5.1% spouses of HCV related chronic liver disease patients were positive.[137,138]

1.4 Response Rate of Interferon plus Ribavirin Therapy in Chronic Hepatitis C Patients

Literature review reveals limited published data regarding interferon therapy in Pakistani population. 71–89.42% ETR and 50–86.3% SVR using conventional IFN has been reported in different studies as shown in table 6.[139–155]

Table-6: End treatment response and sustained virological response with standard interferon and ribavirin combination therapy

Author (Year)	Place	Number	ETR%	SVR%	Ref
Hussain AB (2000)	Rawalpindi	204	72.40	-	139
Shaikh WM (2002)	Larkana	82	71	65.40	140
Farooqi JI (2002)	Peshawar	183	88	82.61	141
Khokhar N (2002)	Islamabad	100	83.00	79.50	142
Niaz A (2003)	Rawalpindi	60	75.00	-	143
Hussain AB (2004)	Rawalpindi	279	86.50	76	144
Muhammad N (2004)	Buner	350	85.14	78.85	145
Farooqi RJ (2005)	Swat	33	M=77.27 F= 81.81	M= 61.18 F= 72.27	146
Farooqi JI (2005)	Peshawar	65	M=86.04 F= 86.36	M= 81.39 F= 86.36	147
Sarwar S (2005)	Lahore	55	-	56.30	148
Ahmed A (2009)	Swat	117	89.42	71.21	149
Batool U (2006)	Islamabad	250	81.00	58.90	150
Khan AA (2009)	Lahore	721	84	72.7	151
Umar M (2008)	Rawalpindi	300	75	50	152
Aziz H (2011)		616		63.5	153
Ahmed F (2011)		829	74	63	154
Akram M (2011)	Lahore	86		53.5	155

As far as Pegalated Interferon and Ribavirin is concerned data suggests a 69.7–84.9% ETR and 57.6–82.2% SVR in Pakistani population as displayed in table-7.[156–166]

Table-7: End Treatment response and sustained virological response with pegylated interferon and ribavirin combination therapy

Author (Year)	Place	Number	ETR%	SVR%	Ref
Butt AS (2009)		66	69.7	57.6	156
Aziz H (2011)		403		74.7	157
Aziz H (2012)		426		75.1	158
Shafi S (2011)	Rawalpindi	44	75	-	159
Ali I (2011)	Kohat	27		74.07	160
Gill U (2013)	Islamabad	236		82.2	161
Umar M (2014)	Rawalpindi	352	74.1		162
Qureshi MS (2014)	Islamabad	220	84.92	63.31	163
Jadoon SA (2014)	Abbotabad	170	73.5		164
Aziz H (2014)	Islamabad	105		68.6	165
Sarwar S (2015)	Lahore	154	81.7	72.1	166

The rates are further reduced for non-responders/relapsers. Faiqa Fateen *et al* conducted a study on 132 non-responder/relapse patients and showed a SVR for genotype 3a to be 27%.[167]

Similarly Zaigham Abbas conducted a study in Karachi. He included 44 patients who were either failure or non-responders to Pegylated Interferons and then treated with consensus Interferons. The data suggested an ETR of 43.1% and SVR of 27.3%.[168]

1.5 Response Rate of Direct Acting Antivirals (DAAs) in Chronic Hepatitis C Patients

To date there is no published data regarding response of direct acting antivirals in Pakistan. Data of 66 patients from Centre for liver and digestive diseases, Holyfamily Hospital, Rawalpindi, who were treated with Sofosbuvir and Ribavirin suggests a RVR of about 94.4%.[169]

Another study showed a ETR of 94% and SVR 82% respectively showing comparable results.[170] A multicentre RESiP study including 1147 patients from 8 different centres in Pakistan showed a SVR12 of 93% using Sofosbuvir and RBV for 24 weeks. Treatment naïve non-cirrhotics showed a SVR of 97%, treatment experienced non-cirrhotics 94%, treatment naïve cirrhotics 89% and treatment experienced cirrhotics 86% respectively.[171]

1.6 Implications of Cost of Antiviral Therapy (DAA)

Six months of treatment with PEG/Ribavirin costs around $ 1200 in Pakistan. Conventional interferon with ribavirin cost around $ 300. The cost of laboratory tests and doctor fee has to be added accordingly.

With the availability of generic DAAs since 2016 the cost of 12 week and 24-week treatment is reasonably low and affordable. The cost of using generic sofosbuvir and RBV is $300 whereas Sofosbuvir + Daclatasvir is $1200. This price is expected to decrease further in near future.

Availability of generic DAAs in Pakistan have made the all oral antiviral therapy cheaper for patients of chronic Hepatitis C.

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SECTION-II

2. WHO SHOULD BE SCREENED, WHEN AND HOW?

The principles of screening are that, there is a suitable disease, that there is suitable test, suitable program and it's a good use of resource. The disease must be serious, be detectable before serious consequences occur and a better outcome occurs if cured. The test must be safe, accurate, acceptable and cost-effective. The program must reach those at risk, have a good follow-up and be efficient. It must be a good use of resources.

The cost of an antibody screening test in Pakistan is between 800–1000 rupees (8–10 USD). Considering the above arguments to be valid, we recommend screening of following:

A. All people if at high risk should have one time screening. The high-risk group of population includes the following:[1–5]

- Person who had received transfusion of blood or blood products at any time
- Person who had surgical procedures/operations
- Females during antenatal check up
- Female with interventional deliveries
- Anyone who has had injections with used or glass syringe
- Person with commercial/ barber shaving
- Person who had dental treatment
- Person who had history of nose/ear piercing or tattooing.
- Healthcare workers
- Household contacts of HCV infected patients
- Family members of HCV infected patients
- Sex workers
- Sexual partner of HCV infected patients
- Multi-transfused thalassemics and hemophilics
- Dialysis patients
- Children born to HCV infected mother.
- Intravenous drug users
- Persons with abnormal unexplained aminotransferase level
- Prisoners
- Person with organ transplant
- Person with HIV infection
- Healthy Liver Donor

B. Persons with ongoing exposure e.g. IV drug abusers should be screened on annual basis.

2.1. How to Screen

Exposure to HCV is diagnosed by testing for specific antibodies using enzyme linked immunoassay (ELISA). Presence of HCV antibody shows that person has been infected with HCV virus but does not indicate whether infection is acute, chronic or has resolved.

Antibodies might not be detectable in first few weeks after initial infection, known as window period or if patient is immunocompromised. Antibody levels may decrease or become undetectable in patients with resolution of infection over years. Sometimes these antibodies persist throughout life.[6–8] If Anti HCV antibodies are positive, the person must undergo HCV RNA testing. The testing sequence for identifying current HCV infection is shown in figure-1.

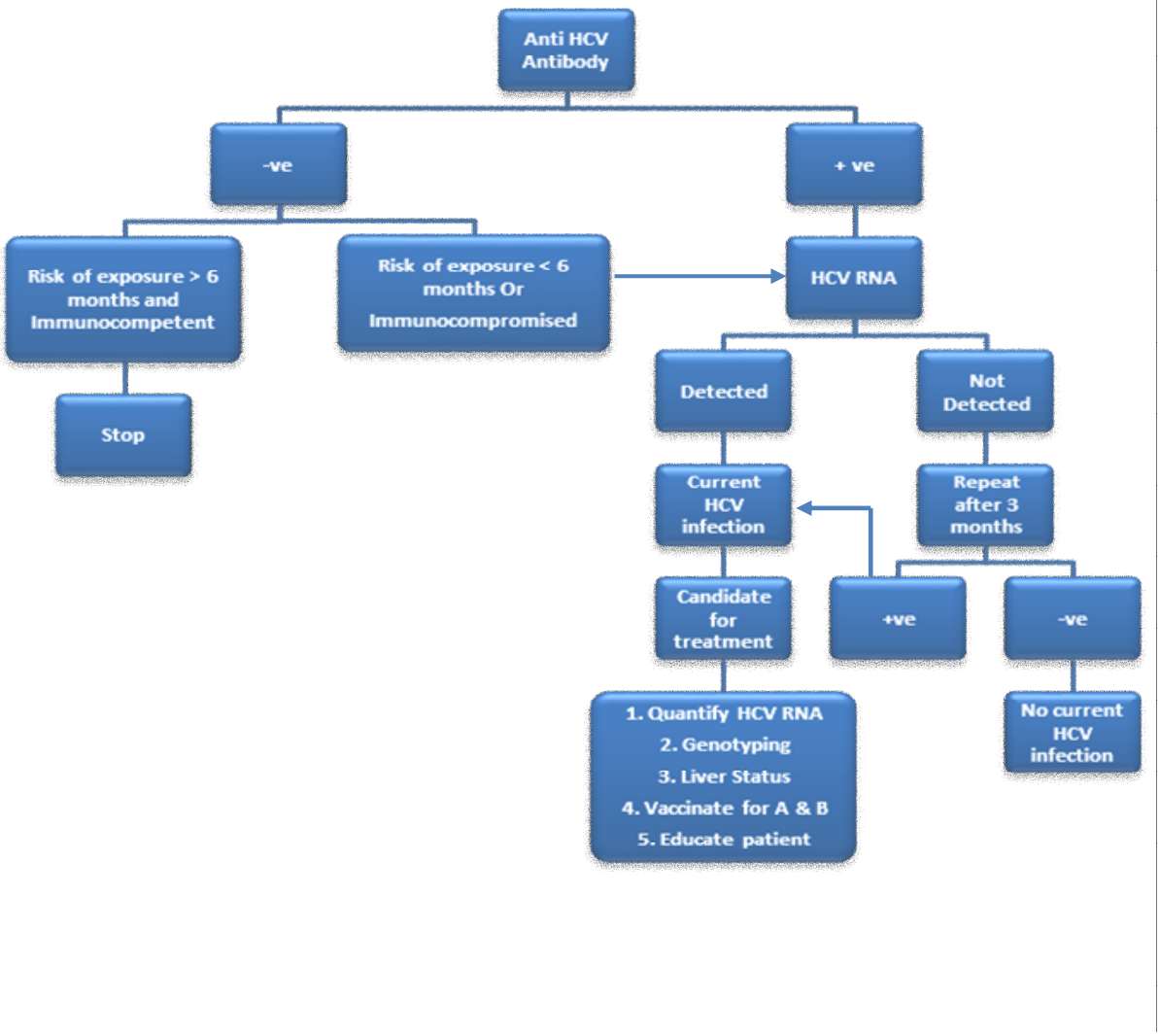

Figure-1: Testing sequence for identifying current HCV infection and recommendations

3. DIAGNOSIS OF HEPATITIS C VIRUS INFECTION

The diagnosis of hepatitis C infection depends upon test of HCV antibodies, HCV RNA and liver biopsy. Anti HCV testing is important for determining exposure to virus but does not identify whether the patient has current infection. This information can be provided by testing HCV RNA. The timing of test for Anti HCV antibodies and HCV RNA differentiate between acute hepatitis C and chronic hepatitis C.[9] It is also important to categorize the different stages of resolution of HCV infection. In initial 3–6 months HCV antibodies are usually negative and diagnosis of acute hepatitis is done by positive HCV RNA.

If a re-infection is suspected, after spontaneous or previously treated viral clearance, testing HCV-RNA is the recommended initial test as the anti-HCV test is expected to be positive.

In patients with Anti-HCV positive but HCV RNA negative testing, a repeat HCV RNA should be performed 3 months later to confirm true convalescence.

Persons with Anti-HCV positive and persistent HCV RNA negative should be counselled that they don't have evidence of active HCV infection and don't need treatment.

3.1. Qualitative HCV RNA Assays

HCV RNA assay is performed to document viremia. Qualitative HCV RNA is more sensitive to detect viremia as compared to quantitative assays.[10]

3.2. Quantitative HCV RNA Assays

These assays determine the quantity of HCV RNA using amplification techniques. Results are reported in international units to standardize data and same quantitative tests should be used while on therapy to avoid confusion, because dynamic ranges differ and results can be difficult to compare between assays.

Quantitative HCV RNA should be tested before the start of antiviral therapy to document the baseline viral load. Sensitive assays as low as 15 IU/ml are recommended internationally[11].

3.3. HCV Antigen

The first HCV core antigen test was developed in 2000 but it was unable to gain popularity because of its less sensitivity and high cost. A positive core antigen confirms replication and can be one of the treatment indications.[12] Although much sensitive core assay is now available but AASLD[13] and EASL[11] guidelines don't recommend it.

3.4. HCV Genotyping

Hepatitis C virus has more than six genotypes and many quasi species. Genotype I and non-I had different response to antiviral therapy. According to international guidelines genotyping is mandatory before start of therapy of hepatitis C.[14]

Reported data had shown in Pakistan 80–85% cases of HCV infection are genotype 3a[15].

3.5. IL28B

IL28B gene has got an immune response against hepatitis c and its genotype cc has got a good response when treated with Pegylated interferon+Ribavirin especially for genotype 1.[16,17] Aziz H. *et al* and Farooqi JI *et al* in their two separate studies have proved that HCV-infected patients from Pakistani population carrying homozygous cc have a higher chance of SVR.[18,19]

As the new DAAs has a very high response rate so AASLD[13] and EASL[11] suggest that IL28B genotyping has no role in the treatment of HCV infection with these new DAAs.

3.6. Liver Status

Evaluation for Liver Disease Severity is recommended for all HCV infected patients either by using liver biopsy, imaging techniques, or non-invasive markers so that appropriate decisions should be made regarding HCV treatment.

3.6.1. Liver Biopsy:

Role of liver biopsy in management of chronic hepatitis C is debatable. The objective to perform liver biopsy is to assess the degree of necro-inflammation and fibrosis, so the severity of liver injury and progression of liver disease can be determined. The grade defines the extent of inflammation and stage assesses the extent of fibrosis. There are many scoring systems of liver histology.[20]

The histopathological features normally predict not only the progression of disease but also the urgency of treatment. Patients with milder degree of fibrosis generally respond more favourably to treatment than do patients with more advanced fibrosis like bridging fibrosis and cirrhosis. However, the patients with milder

disease can be observed without treatment and patients with fibrosis stage 3 or 4 need to be treated earlier. This can be a cost-effective approach used as selection criteria while offering free treatment to chronic hepatitis C patients in government health institutions.

Secondly, patients of HCV infection who are difficult to treat like non-responders, relapsers and having co morbid conditions like renal failure, diabetes mellitus and suspected NASH, preferably need liver biopsy before the start of treatment to assess the prognosis and predict response to treatment. Generally, these patients had low SVR and more side effects.

Although liver biopsy is considered "Gold Standard" for defining liver disease status, this procedure has its disadvantages and limitations including pain, bleeding, perforation and mortality 2 – 3.3/1000. Biopsy sample represent 1/50,000 to 1/100,000 of entire liver and intra observer error rate in staging of fibrosis is up to 20%.[21–27]

Ten to fifteen portal tracts are required in reliably reporting both the inflammation grades and stages of fibrosis as compared to the size of liver biopsy core in patients with hepatitis C infection.[28]

3.6.2. Imaging

- Ultrasound is an important non-invasive investigation to detect cirrhosis, portal hypertension, HCC and other co morbid conditions like fatty liver.
- CT scan and MRI are usually not required in routine in patients with chronic hepatitis C.

3.6.3. Fibro scan and Non-invasive Marker

Hepatic fibrosis develops in almost all patients with chronic liver injury due to Hepatitis B and C virus infections. The degree of hepatic fibrosis increases with age and occurs more in males as compared to females.

Transient Elastography is a new non-invasive bedside tool that uses ultrasound and low frequency waves to measure liver elasticity for diagnosis and quantifications of hepatic fibrosis (by measuring liver stiffness) in patient with chronic liver disease.

Recent studies have demonstrated that fibro scan combined with other non-invasive serum markers is a sensitive alternative for liver biopsy. The amount of fibrosis can be quantified very easily and reliably in more than 95% of the patients. The liver stiffness measurements and fibrosis score correlate well with more extensive fibrosis (F>3) or cirrhosis.[30–32]

In a study by Shahzad Ashraf *et al* five statistically significant non-invasive markers including bilirubin, Gamma glutamyl transferase, Hyaluronic acid, alpha 2 macroglobulin, and platelets were evaluated to determine a fibro score that proved to be a useful tool in determining different stages of liver fibrosis.[33]

According to AASLD[13] and EASL[11] guidelines, liver disease severity should be assessed by methods which are non-invasive. Liver biopsy should only be considered when there is uncertainty or possibility of additional aetiologies. Therefore, fibro scan has now a key role in evaluating such patients.

3.7. Patient Education

a. Everyone with HCV infection should be educated regarding the transmission of HCV to others.
b. Abstinence from alcohol should be advised to all the patients with HCV infection to avoid alcohol related liver insult.
c. All persons with HCV who are overweight (BMI > 25 kg/m^2) should be counselled for measures to reduce weight including diet, exercise and medications as NAFLD also increases the chances of progression of fibrosis in these patients.

3.8. Patient Vaccination

Vaccination for hepatitis A and hepatitis B should be considered in all persons susceptible to HCV infection.

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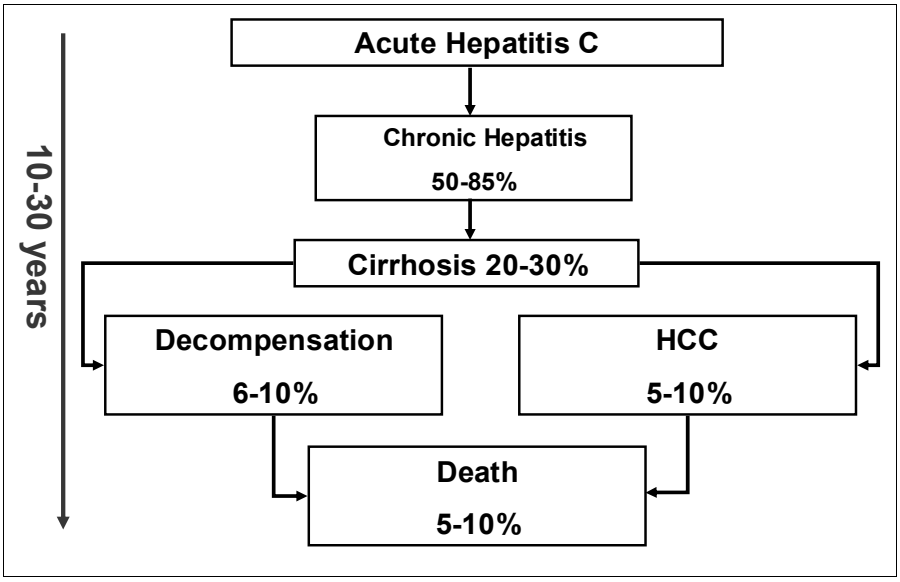
SECTION-III

4. WHAT HAPPENS TO PATIENTS INFECTED WITH HCV INFECTION (NATURAL HISTORY)

It is difficult to study the natural history of HCV infection because of multiple factors; 1) mostly HCV infection is asymptomatic, 2) difficult to ascertain exact time of acquisition of infection, 3) progression of disease is slow, and 4) data collected from different group of patients e.g., communities, healthy blood donors, patients attending liver clinics, post transfusion cohort, and persons with multiple risk factors cannot be generalized to whole country or whole population. The retrospective and prospective studies which were focused on natural history of HCV infection had many limitations because of confounding factors affecting the natural history of HCV infection.[1–3]

There is no study on long term outcomes of HCV infection in Pakistan. The vast majority of HCV infected patients are asymptomatic and have slow progressive disease. 15–20% patients will become jaundiced. Of those who become chronically infected, 20% become cirrhotic at 20 years and of those with cirrhosis, 4% per annum will decompensate, 5% per annum will develop cancer and survival then depends on availability of resection or transplantation.[4,5]



Natural History of Hepatitis C

5. ASSESSMENT AND MONITORING

Assessment of HCV infected patients before treatment, during treatment and after treatment is separately discussed as under. The following recommendations are adapted in accordance to EASL[1] and AASLD[2] guidelines:

5.1. Pre-Treatment Assessment

Prior to start of DAAs following should be assessed:

- Other liver diseases which can adversely affect liver status like Hepatitis B infection, HIV, alcoholism, autoimmunity, metabolic liver diseases or hepato-toxic drugs should be searched and appropriate measures should be taken to reduce the risks. Factors associated with accelerated fibrosis progression are tabulated in table-1.
- Degree of hepatic fibrosis using non-invasive measures. Liver biopsy can be considered when there is possibility of additional aetiology.
- A sensitive assay (≤15 IU/ml) based quantification of HCV RNA.
- HCV genotyping
- Drug history for drug-drug interaction.

5.1.1. Recommendations for Pre-treatment investigations:

1. Complete blood count (CBC), Liver function tests (LFT), Serum Albumin, INR, GFR and TSH (if IFN regimen is planned) should be performed within 12 weeks of start of therapy.
2. Quantitative PCR and genotyping anytime before start of therapy.
3. Women of child bearing age group intended to receive Ribavirin as part of their therapy must undergo pregnancy testing before start of therapy.

5.2. On-Treatment Assessment:

Following recommendations are made for patients receiving HCV treatment during their therapy:

1. Ensure compliance either by clinical visits or telephonically. Ask for any adverse event. Also, advice regarding drug-drug interaction.
2. For patients with child bearing age group intended to receive RBV or female partners of men receiving RBV should not conceive during and six months' post therapy.
3. CBC, serum Creatinine, GFR and LFTs should be performed at 4 weeks of treatment. CBC can be performed more frequently in patients receiving RBV if clinically indicated.
4. TSH should be performed at 12 weeks for those patients receiving IFN.
5. Quantitative PCR at 4th week of treatment and then 12 weeks after treatment is mandatory. If no financial restraints, then additional PCR can be planned at the end of treatment and then 24 weeks after treatment.

5.2.1. When to stop the treatment because of side effects:

1. A 10-fold or more rise in ALT at 4 weeks of therapy
2. A less than 10-fold rise in ALT with one of the following
   a. Patient symptomatic (nausea, vomiting, weakness)
   b. Jaundice
   c. A rise in Bilirubin, ALP or INR
3. A less than 10-fold rise in ALT and patient is asymptomatic, repeat ALT at 6 weeks; if persistently high can consider stopping therapy.

5.2.2. When to stop treatment due to efficacy:

If PCR is detectable at 4 weeks of treatment, repeat PCR at 6 weeks of treatment

1. If PCR RNA is 10 folds (1 $\log_{10}$ IU/ml) greater than baseline discontinue the treatment.
2. If PCR RNA is positive but less than 10 folds of baseline there is insufficient data regarding that but we recommend completion of treatment till further evidence based recommendations are available.
3. If PCR RNA is negative treatment should be continued.

Table-1: Risk Factors causing accelerated fibrosis

Host related modifiable	Host related non-modifiable	Viral related
Alcohol consumption	Fibrosis Stage	Genotype 3
Non-Alcoholic fatty liver disease	Inflammation grade	Co infection with HBV
Obesity	Older age	Co infection with HIV
Insulin resistance	Male sex	
	Organ transplant	

5.3. Post-Treatment Assessment

5.3.1. For patients who fail to respond to treatment

1. LFTs, CBC, INR every 6 months to 1 year for assessment of disease progression.
2. HCC surveillance for patients with advanced fibrosis (Metavir F3F4)
3. Using USG every 6 months' Endoscopic surveillance for varices in case of cirrhotic patients
4. Retreatment evaluation once an effective alternative treatment is available.

5.3.2. For patients who achieve SVR

1. For patients with F0-F2 fibrosis same recommendations as if they were never infected with HCV.
2. For patients with F3F4 fibrosis twice yearly USG is recommended for HCC surveillance.
3. Baseline endoscopic surveillance in case of cirrhotic patients and if varices found they should be treated and followed in the standard way.
4. If persistently abnormal LFTs despite SVR other causes of liver disease should be assessed

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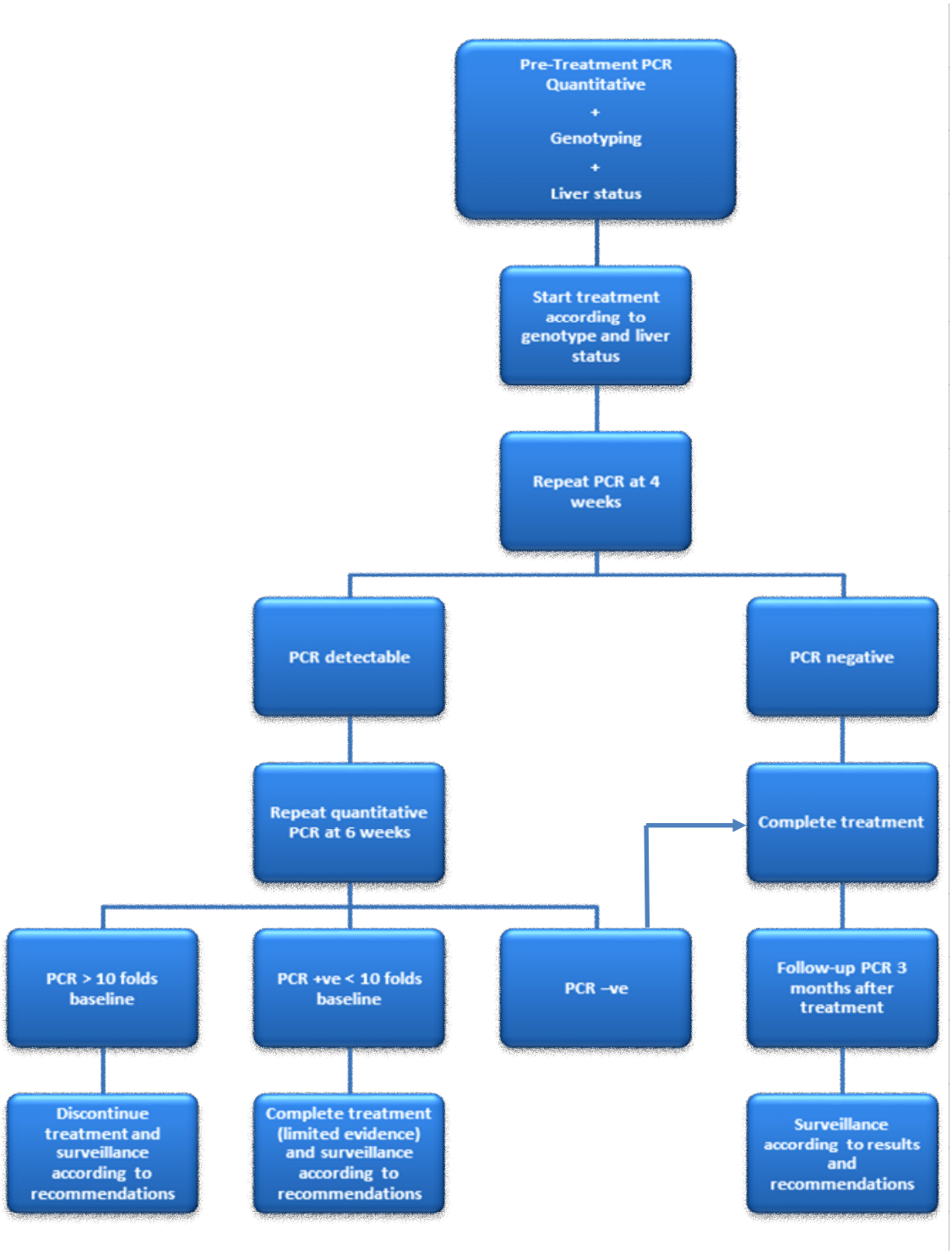
Assessment and Monitoring of patients undergoing HCV therapy



6. CONTRAINDICATIONS AND INDICATIONS TO HCV THERAPY

6.1. Contraindications to HCV therapy

6.1.1. Interferon and Ribavirin therapy[1,2]

Following are few absolute contraindications for the use of Interferon and Ribavirin. They include:

- History of severe depression or psychosis
- Uncontrolled seizures
- Decompensated liver disease
- Pregnancy (RBV)
- Renal failure (RBV)
- Severe cardiac disease (RBV)

The relative contraindications for Interferon and Ribavirin are:

- Uncontrolled DM
- Uncontrolled HTN
- Retinopathy
- Psoriasis
- Active autoimmune diseases
- Symptomatic cardiac disease or severe vascular disease
- Anaemia/ischemic vascular disease

In addition to these contraindications, special caution is required if interferon is administered in the following circumstances:

- Neutropenia (neutrophil count <1500 cells/ mm^3)
- Thrombocytopenia (platelet count <90,000/mm^3)
- Organ transplantation (e.g. Kidney Transplant)
- History of autoimmune disease
- Presence of thyroid auto antibodies

6.1.2. DAA Therapy

There is no absolute contra-indication to the DAAs which are approved so far. For patients with severe renal disease Sofosbuvir should be used with extreme caution as this aspect is still under investigation[3].

6.1.2.1. Drug-Drug Interaction:

Although there is no specific contraindication to DAAs in general but their pharmacological interaction should be kept in mind before prescribing them. Like Sofosbuvir cannot be co-administered with Amiodarone.

Similarly, Daclatasvir if prescribed with atorvastatin needs dose adjustment. As detailed discussion is beyond the scope of this article therefore for more drug-drug interactions we recommend EASL/AASLD guidelines.[3,4]

6.2. When and in Whom to Initiate HCV Therapy

All patients with chronic HCV infection should receive therapy except patients with short life expectancy due to severe co-morbid condition. Patients who are at high risk for liver related complications should be preferred for immediate treatment. They include the following[3]:

1. Patients with advanced fibrosis having Metavir stage F3
2. Patients with compensated cirrhosis having Metavir stage F4
3. Patients with liver transplant
4. Patients with severe extra hepatic complications like vasculitis, cryoglobulinemia causing end organ damage, glomerulonephritis/nephrotic syndrome causing significant proteinuria.

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7. DEFINITION OF RESPONSE

Before start of specific therapies, desired endpoint of treatment of HCV infection must be defined. Desired endpoint of therapy is viral clearance of HCV infection by achieving SVR. Different treatment responses are defined as follow.[6–12]:

Very Rapid Virological Response (VRVR): HCV RNA negative at 1st week of treatment by a sensitive PCR based quantitative assay (<15 IU/ml)

Rapid Virological Response (RVR): HCV RNA negative at treatment week 4 by a sensitive PCR based quantitative assay

End-of-treatment response (ETR): HCV RNA negative by a sensitive test at the end of treatment

Sustained virological response (SVR): HCV RNA negative at 12 weeks (SVR12) or 24 weeks (SVR24) after stopping of treatment

Breakthrough: Reappearance of HCV RNA in serum while still on therapy

Relapse: Reappearance of HCV RNA in serum after discontinuation of therapy (after achieving ETR)

Non – Responder: Failure to clear HCV RNA from serum after completion of therapy

Null Responder*: increase in HCV RNA by >1 $\log_{10}$IU/ml as compared to baseline after 6 weeks of therapy

Partial responder*: increase in HCV RNA but <1 $\log_{10}$IU/ml as compared to baseline after 6 weeks of therapy

(*concept adapted from AASLD guidelines for DAAs[12])

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SECTION-IV

8. TREATMENT OF HEPATITIS C

DAAs have become the main stay of HCV treatment in the various international HCV guidelines. Multiple studies showed the efficacy and safety of different regimens of DAAs used in treatment of HCV. The overall sustained virologic response (SVR) was more than 90% with different regimens in multiple phase IV randomized control trials[1,2]. With the advent of direct acting antivirals (DAAs) the whole scenario of Hepatitis C treatment has been revolutionized. New and new drugs are being introduced in this regard and the recommended regimens are continuously evolving to improve the treatment outcomes.

8.1. Treatment Objectives and Endpoints

The goal of therapy against hepatitis C virus infection is to prevent liver cirrhosis and its decompensation, HCC, decreasing its rate of transmission, severe extra-hepatic manifestations and death. These goals are achieved by eradication of virus. Patients who achieve SVR have clearance of virus in 99.9% of cases[3].

With the approval of IFN free treatment regimens, many patients who were previously unable to get HCV treatment can now be offered the therapy. Majority of them are those having advanced fibrosis and decompensated cirrhosis.

In cirrhosis, eradicating HCV will reduce the decompensation rate, the risk for HCC and the need for liver transplantation. However the surveillance of HCC in such patients should be continued.

The treatment endpoint should be an undetectable HCV RNA by using a sensitive assay (≤15 IU/ml) at 12 weeks (SVR12) post therapy[1].

Before starting antiviral therapy, all patients should be explained about,

- The natural history of disease and liver related complications
- Chances and success of all categories of treatments available
- Adverse effects of the available treatments and supportive treatment if needed e.g. Ethyropoietin, Thrombopoietin, CSF (Colony stimulating factor)
- Cost of the available treatments and cost of supportive treatment when required.

8.2. Direct Acting Antiviral Agents for treatment of Hepatitis C patients

8.2.1. Sofosbuvir

In Dec 2013 and Jan 2014, FDA approved second generation DAAs for the treatment of chronic hepatitis genotype 1 infection, which is the most prevalent genotype and considered to be difficult to treat genotype. The first one is Sofosbuvir (SOF) which is a NS5B polymerase inhibitor. The first trial using SOF/RBV was the ELECTRON study. This showed a SVR in 84% of 25 treatment naïve patients after 24 week of therapy (SVR 24).[4,5] In the subsequent study regimen consisting of SOF/RBV for 24 weeks in 60 naïve genotype 1 patients with poor prognostic factors like black, ccIL28B and viral load more than 800,000 IU/ml, the SVR 24 rates were 68%.[5] In ELECTRON study SOF/RBV was used in genotype 2 and 3 patients without cirrhosis and 100% achieved SVR24.[6] In the FISSION trial SOF/RBV for 12 weeks in 499 naïve patients, SVR12 rates were 97% for genotype 2 HCV patients. In Genotype 3 patients the SVR12 rates were 56% only.[7] Similarly in POSITRON trial SVR 24 rate after 24 weeks of treatment were 61% for genotype 3 and 93% for genotype 2 respectively.[8] In FUSSION Trial, similar results were achieved showing poor SVR rates of 62% for patients infected with genotype 3.

8.2.2. Sofosbuvir and Ledipasvir (Harvoni)

FDA approved in October 2014, the first all oral IFN free combination therapy of DAAs for chronic HCV genotype I infection. Sofosbuvir 400 mg a NS5B polymerase inhibitor combined with Ledipasvir (LDV) 90 mg a NS5A inhibitor. This is a single pill under the trade name Harvoni. The ION study phase III trial inducted 1952 patients with genotype I infection, 1512 were naïve and 224 had compensated cirrhosis. According to the results reported, treatment with 12 weeks for non cirrhotic or 24 weeks treatment for cirrhotic regardless of previous therapy or concurrent use of RBV showed SVR 12 rate of 93–97.7 %.[9,10] Similarly in LONESTAR trial, the SVR 12 rates were 100% with 8 or 12 weeks of therapy with or without RBV irrespective of previous treatment with Bocepravir or Telepravir or presence or absence of compensated cirrhosis.[11,12] Sofosbuvir/Ledipasvir without RBV is the therapy of choice for genotype 1 HCV infection patients with minimal side effects.

8.2.3. Daclatasvir + Sofosbuvir

Daclatasvir is NS5A inhibitor that has potent pan-genotype activity. Sulbowashi *et al* reported in a phase II trial which includes non cirrhotic treatment naïve patients as well as previously treated patients with PEG/Protease inhibitor. All patients underwent treatment with Daclatasvir and Sofosbuvir with or without RBV for 24 weeks. The SVR 12 rates were 98%.[13,14] Another study by Chayama k from Japan used a combination of Daclatasvir plus Asunaprevir. The SVR 24 rates were 87.4% for PEG ineligible patients and 80.5% for previously PEG non Responders.[15]

8.2.4. Simeprevir + Sofosbuvir

Simepravir (SMV) is a second generation protease inhibitor. FDA approved its use with PEG+RBV for genotype 1 treatment.[16] Three major studies QUEST study, PROMISE Study and ASPIRE study using SMV+PEG/RBV in all categories patients: Treatment naïve, treatment experienced and null responders, showed a SVR 12 of 80% (Cirrhotics showed a lower SVR rate of 60–65%).[17–19] The AASLD guidelines recommended Simepravir & Sofosbuvir combination as first line option for genotype 1 interferon ineligible patients and PEG/RBV non responders.

In the phase 2 Cosmos study SVR 12 was 96% regardless of patients with cirrhosis, length of treatment (12 vs 24 week) and with or without Ribavirin. However, prolonged therapy for 24 weeks is recommended in cirrhotic patients by AASLD guidelines.[20] In another study, Sarene V reported SVR 12 of 91% in patients with Child class A and SVR 12 of 73% in Child class B/C respectively.[21] Simepravir has minor side effects e.g Headache, Fatigue and Insomnia.

8.2.5. 3D Regimen

This is a potent, all oral combination of three DAA including ABT 450; a Protease Inhibitor boosted with Ritonavir, Dasabuvir ABT 333, a non nucleoside RNA polymerase inhibitor and Ombitasvir ABT 267 a NS5A inhibitor. The AVIATOR trial results showed the treatment naïve patients who were treated with 3D regimen plus RBV had SVR 24 of 88–94% in response to 8–12 weeks of treatment. SVR 12 of 89% was achieved in non RBV group.[22]

8.2.6. *Paritaprevir* + Dasabuvir / *Ombitasvir*+ R*itonavir* (Viekira pak)

This is one of the recent and most potent combination of all oral IFN free regimen used for the treatment of genotype 1 HCV infection. SAPPHIRE – I and II studies are multi centre randomized double blinded placebo controlled studies with above DAAs plus Ribavirin and showed a SVR12 which was achieved in 95–98% of the patients with genotype I. Commonly reported side effects with this combination were headache, nausea and fatigue only. 1% of the patients discontinue drugs due to these side effects.[23-26]

8.2.7. Sofosbuvir + Velpatasvir

This is one of the most recent FDA approved pangenotype combination available as trade name Epclusa.[27] Feld JJ *et al* in a phase 3 trial used this combination for 12 weeks and showed a SVR12 of 99% in patients with genotype 1,2,4,5 and 6.[28] ASTRAL-3 trial showed a SVR12 of 95% in genotype 3 patients treated with Sofosbuvir+Velpatasvir for 12 weeks.[29] Curry MP *et al* in another trial used this combination in decompensated patients and the SVR12 was 83% in patients who used the combination for 12 weeks, 86% who used it for 24 weeks and 94% in patients who used the combination along with Ribavirin for 12 weeks.[30]

8.2.8. Grazoprevir + Elbasvir

C-Worthy phase II trials have shown a SVR12 of 98% in genotype 1 patients using this combination for 12 weeks[31]. A SVR12 of 97% has been established in patients having co-infection with HIV when the combination is used along with Ribavirin[32]. Currently FDA has approved this combination for genotype 1 and 4 only[33].

8.2.9. Treatment recommendations of DAAs by genotype

After reviewing all the DAAs in previous section, final recommendations are made as per HCV genotype infection in Chronic Hep C patients. These recommendations are in light of AASLD[2] and EASL[1] guidelines along with literature and data from different studies and different authors. For simplification first option, second option and third option system is adopted where the first option is with best results considering rate of achieving SVR, short duration of therapy and all oral regimen.

8.2.10. Management of HCV infection for treatment Naïve or Relapser patients

These are the patients who haven't been treated before at all or if treated previously, have achieved undetectable viral load with IFN/RBV therapy once but relapsed after achieving ETR.

1. Genotype 1:
   i. Recommendation I:
      Elbasvir (50 mg) + Grazoprevir(100 mg) daily for 12 weeks.
   ii. Recommendation II:

Velpatasvir (100 mg) + Sofosbuvir (400 mg) daily for 12 weeks

iii. Recommendation III:
Daclatasvir (60 mg) + Sofosbuvir (400 mg) daily for 12 weeks

iv. Recommendation IV:
Ledipasvir (90 mg) + Sofosbuvir (400 mg) daily for 12 weeks

v. Recommendation V:
Paritaprevir (150 mg) + Ritonavir (100 mg) + Ombitasvir (25 mg) + twice-daily Dasabuvir (250 mg) + weight based RBV for 12 weeks. The same regimen can be used without RBV for genotype 1b.

vi. Recommendation VI:
Sofosbuvir (400 mg) + Simeprevir (150 mg) for 12 weeks

2. Genotype 2:
   i. Recommendation I:
   Velpatasvir (100 mg) +Sofosbuvir (400 mg) daily for 12 weeks
   ii. Recommendation II:
   Daclatasvir (60 mg)+Sofosbuvir (400 mg) daily for 12 weeks
   iii. Recommendation III:
   Sofosbuvir (400 mg) + weight-based RBV for 12 weeks
3. Genotype 3:
   i. Recommendation I:
   Daclatasvir (60 mg) + Sofosbuvir (400 mg) daily for 12 weeks
   ii. Recommendation II:
   Velpatasvir (100 mg) + Sofosbuvir (400 mg) daily for 12 weeks
   iii. Recommendation III:
   Sofosbuvir (400 mg) + weight-based RBV + weekly PEG-IFN for 12 weeks
   This Regimen is for those patients who are *IFN eligible*.
   iv. Recommendation IV:
   Sofosbuvir (400 mg) + weight-based RBV for 24 weeks.
   This Regimen cab be considered in patients who are IFN ineligible.

4. Genotype 4:
   i. Recommendation I:
   Paritaprevir (150 mg) + Ritonavir (100 mg)+Ombitasvir (25 mg) + weight-based RBV for 12 weeks.
   ii. Recommendation II:
   Velpatasvir (100 mg) + Sofosbuvir (400 mg) daily for 12 weeks
   iii. Recommendation III:
   Elbasvir (50 mg) + Grazoprevir (100 mg) daily for 12 weeks.
   iv. Recommendation IV:
   Ledipasvir (90 mg) + Sofosbuvir (400 mg) for 12 weeks
5. Genotype 5 or 6:
   i. Recommendation I:
   Velpatasvir (100 mg) + Sofosbuvir (400 mg) daily for 12 weeks
   ii. Recommendation II:
   Ledipasvir (90 mg) + Sofosbuvir (400 mg) for 12 weeks.

8.2.11. Management of HCV infection for treatment Failure patients

As we have entered into the era of DAAs, despite a good response there is quite some number of patients who don't respond to the DAAs. Therefore in this section we have separately categorized the patients into IFN/RBV failures and SOF/RBV failures.

8.2.11.1. Management of HCV infection for treatment Failure patients who are IFN/RBV experienced in the past:

This category includes the patients who have already received IFN/RBV for Hepatitis C but either they were partial responders or didn't respond at all. Partial responders by definition are the patients with viral load clearance of ≥ 2 $\log_{10}$ IU/ml but their virus remains detectable at 24 weeks or by the end of treatment.

1. Genotype 1:
   i. Recommendation I:
   Elbasvir (50 mg) + grazoprevir (100 mg) daily for 12 weeks.
   ii. Recommendation II:
   Velpatasvir (100 mg) + Sofosbuvir (400 mg) daily for 12 weeks.
   iii. Recommendation III:
   Daclatasvir (60 mg) + Sofosbuvir (400 mg) daily for 12 weeks.
   iv. Recommendation IV:
   Ledipasvir (90 mg) + Sofosbuvir (400 mg) for 12 weeks
   v. Recommendation V:
   Paritaprevir (150 mg) + Ritonavir (100 mg) + Ombitasvir (25 mg) + twice-daily Dasabuvir (250 mg) + weight based RBV for 12 weeks.
   For Genotype 1b patients RBV can be avoided.
   vi. Recommendation IV:
   Sofosbuvir (400 mg) + Simeprevir (150 mg) for 12 weeks.

2. Genotype 2:
   i. Recommendation I:

Velpatasvir (100 mg) +Sofosbuvir (400 mg) daily for 12 weeks.

ii. Recommendation II:
Daclatasvir (60 mg) + Sofosbuvir (400 mg) daily for 12 weeks.

iii. Recommendation III:
Sofosbuvir (400 mg) + weight-based RBV for 16 weeks or 24 weeks whereas SOF (400 mg) + weight-based RBV + weekly PEG-IFN for 12 weeks is only for IFN eligible's.

3. Genotype 3:
   i. Recommendation I:
   Daclatasvir (60 mg) + Sofosbuvir (400 mg) daily for 12 weeks.
   ii. Recommendation II:
   Velpatasvir (100 mg) + Sofosbuvir (400 mg) daily for 12 weeks.
   iii. Recommendation III:
   Sofosbuvir (400 mg) + weight-based RBV + weekly PEG-IFN for 12 weeks
   This Regimen is for those patients who are IFN eligible. Although no more recommended by AASLD but in resource poor countries like Pakistan where genotype 3 is prevalent, it should be considered till new combinations are available.
4. Genotype 4:
   i. Recommendation I:
   Paritaprevir (150 mg) + Ritonavir (100 mg) + Ombitasvir (25 mg) + weight-based RBV for 12 weeks.
   ii. Recommendation II:
   Sofosbuvir (400 mg) + velpatasvir (100 mg) daily for 12 weeks.
   iii. Recommendation III:
   Elbasvir (50 mg) + grazoprevir(100 mg) + weight baised RBV daily for 16 weeks.
   iv. Recommendation IV:
   Ledipasvir (90 mg) + Sofosbuvir (400 mg) for 12 weeks.

5. Genotype 5 or 6:
   i. Recommendation I:
   ii. Ledipasvir (90 mg) + Sofosbuvir (400 mg) for 12 weeks.
   iii. Recommendation II:
   Sofosbuvir (400 mg) + velpatasvir (100 mg) daily for 12 weeks.

8.2.11.2. Management of HCV infection for treatment Failure patients who are SOF/RBV with or without PEG-IFN treated in the past:

This category includes the patients who have already received SOF/RBV ± PEG-IFN for Hepatitis C but either they were partial responders or didn't respond at all. Partial responders by definition are the patients whose viral load increases but <1 $\log_{10}$IU/ml as compared to baseline after 6 weeks of therapy.

1. Genotype 1:
   i. Recommendation I:
   Ledipasvir (90 mg) + Sofosbuvir (400 mg) with weight based RBV for 12 weeks for non-cirrhotics and 24 weeks for cirrhotics.
   ii. Recommendation II:
   Daclatasvir (60 mg) + Sofosbuvir (400 mg) with weight based RBV for 12 weeks for non-cirrhotics and 24 weeks for cirrhotics.
2. Genotype 2:
   i. Recommendation I:
   Velpatasvir (100 mg) + Sofosbuvir (400 mg) with RBV daily for 12 weeks irrespective of cirrhosis.
   ii. Recommendation II:
   Daclatasvir (60 mg) + Sofosbuvir (400 mg) with or without RBV daily for 24 weeks irrespective of cirrhosis.
3. Genotype 3:
   i. Recommendation I:
   Daclatasvir (60 mg) + Sofosbuvir (400 mg) + weight based RBV daily for 24 weeks irrespective of cirrhosis.
   ii. Recommendation II:
   Velpatasvir (100 mg) + Sofosbuvir (400 mg) + weight based RBV daily for 12 weeks irrespective of cirrhosis.
4. Genotype 4:
   i. Recommendation I:
   Ledipasvir (90 mg) + Sofosbuvir (400 mg) with weight based RBV for 12 weeks for non-cirrhotics and 24 weeks for cirrhotics.
   ii. Recommendation II:
   Daclatasvir (60 mg) + Sofosbuvir (400 mg) with weight based RBV for 12 weeks for non-cirrhotics and 24 weeks for cirrhotics.
   iii. Recommendation I:
   Paritaprevir (150 mg) + Ritonavir (100 mg) + Ombitasvir (25 mg) + weight-based RBV for 12 weeks for non-cirrhotics and 24 weeks for cirrhotics.

5. Genotype 5 or 6:
   i. Recommendation I:
   Ledipasvir (90 mg) + Sofosbuvir (400 mg) with weight based RBV for 12 weeks for non-cirrhotics and 24 weeks for cirrhotics.
   ii. Recommendation II:
   Daclatasvir (60 mg) + Sofosbuvir (400 mg) with weight based RBV for 12 weeks for non-cirrhotics and 24 weeks for cirrhotics.

Table-1: Treatment Failures who experienced SOF based regimen in past

Genotype	Options	Non-Cirrhotics	Cirrhotics
1,5 or 6	**I**	ledipasvir (90 mg)/SOF (400 mg) + wt based RBV for 12 weeks	ledipasvir (90 mg)/SOF (400 mg) + wt based RBV for 24 weeks
	II	Daclatasvir (60mg)/ sofosbuvir (400 mg) + wt based RBV for 12 weeks	Daclatasvir (60mg)/ sofosbuvir (400 mg) + wt based RBV for 24 weeks
2 or 3	**I**	SOF (400 mg) / velpatasvir (100 mg) + weight based RBV for 12 weeks.	SOF (400 mg) / velpatasvir (100 mg) + weight based RBV for 12 weeks.
	II	Daclatasvir (60mg)/ sofosbuvir (400 mg) ± RBV for 24 weeks	Daclatasvir (60mg)/ sofosbuvir (400 mg) ± RBV for 24 weeks
4	**I**	ledipasvir (90 mg)/SOF (400 mg) + wt based RBV for 12 weeks	ledipasvir (90 mg)/SOF (400 mg) + wt based RBV for 24 weeks
	II	Daclatasvir (60mg)/ sofosbuvir (400 mg) + wt based RBV for 12 weeks	Daclatasvir (60mg)/ sofosbuvir (400 mg) + wt based RBV for 24 weeks
	III	Paritaprevir (150 mg) + Ritonavir (100 mg) + Ombitasvir (25 mg) + weight-based RBV for 12 weeks.	Paritaprevir (150 mg) + Ritonavir (100 mg) + Ombitasvir (25 mg) + weight-based RBV for 24 weeks

8.3. Treatment of Patient with Acute Hepatitis C

Acute hepatitis C is difficult to diagnose in asymptomatic patients, especially when exact time of acquisition is not definite. In acute hepatitis C patient two issues need to be addressed. Firstly when to start the therapy and secondly what should be the regimen and duration of therapy.

In one meta-analysis of 16 studies, the outcome of the group offered early therapy in acute hepatitis was superior to the group of patients who were observed for spontaneous clearance. In another study, the early therapy with higher doses of conventional IFN achieved the SVR of 85–100%. The dose of conventional IFN was 5-10 million units/day for 12 weeks. Peg IFN with a dose of 1.2–1.3 mg/kg weekly was another choice because of convenient dose schedule but had a higher cost.[34–39]

A study by Deterding showed that delayed treatment is as effective as immediate treatment. Furthermore, delayed treatment can reduce the possibility of unnecessary treatment in those patients who can spontaneously clear their virus without any treatment, but close monitoring is required in these cases.[40]

With the new DAAs having better efficacy and safety the argument of early treatment has become relatively weaker. So the new recommendations are:

- Regular Laboratory monitoring with HCV RNA is recommended at least for 6 months to determine spontaneous clearance.
- Counseling is required to patients with acute HCV infection to avoid hepatotoxic drugs (eg, Acetaminophen) and alcohol. They should also take precautionary measures to reduce the risk of transmitting their disease to others.
- Early treatment can only be considered in special circumstances like in people who are at risk of transmitting the disease to others(e.g. IV drug abusers, Surgeons), patients already suffering from advanced liver disease due to some other reason, and those in which chances of being lost to follow-up are more. Even in these patients one should at least wait for 12–16 weeks before starting therapy.
- The therapy for acute HCV infection if indicated can be done using DAAs with the same regimens as for chronic disease.
- Prophylactic therapy is not recommended in needle stick injuries as the infectivity rate is very low.

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8.4. DAA Regimens for Compensated Cirrhosis

The use of over one and a half decade of PEG/RBV therapy did not lead to the cure of large number of HCV infected population. This is not only because of low efficacy but also a significant number of patients are not eligible for PEG/RBV combination due to decompensated cirrhosis, low platelets, intolerance and side effects of therapy. The special population was just waiting for new data in these special groups and recommendations of the experts for the use of DAAs in this large number of population. With advent of highly effective therapy of DAAs since 2014, advance fibrosis and cirrhosis is considered an important prognostic factor in determining the SVR[1]. Recent studies with DAA have promising results in this group of patient.[2]

Genotype I Compensated Cirrhotic Patients

Considering low SVR rate and poor tolerance for PEG/RBV in cirrhotic patients, the all oral DDAs is an ideal treatment option, having pan genotypic effect and excellent safety profile. 1st phase-II COSMOS study by Lawitz E *et al* showed SVR rate of 94–100% in genotype-I of cirrhotic patients by using SOF+SIM for 12 and 24 weeks with and without RBV.[3]

Another study in cirrhotic patients with Child Pugh class A where SVR12 rate of 95% is achieved by using SIM+SOF for 12 weeks.[4] Afdhal N and Zeuzem S, in ION -2 Study showed a SVR_{12} of 86% in treatment experienced cirrhotics with SOF and Ledipasvir combination and 98% for 24 weeks duration.[5–7] In the LONESTAR study, Lawitz E reported >95% SVR in genotype-1 cirrhotics as well as in protease inhibitor failure patients with SVR of 100%.[8]

The SIRUS study evaluated the patients who participated in LUPIC study and reported the Genotype I cirrhotic, who failed Protease Inhibitor triple therapy, achieved a SVR of 96% with combination of SOF and Ledipasvir.

In 2014 Poordad F *et al* published in NEJM the results of TURQUOISE-2 study showing that combination of Paritaprevir / Ritonavir / Ombitasvir and Dasabuvir with RBV for 12 or 24 weeks in Genotype 1 Naïve and treatment experienced cirrhotics. The SVR_{12} rate was 92–96% respectively.[9] The common side effects of all these regimens include fatigue, insomnia and headache.

i. Recommendation I:
Elbasvir(50 mg) + grazoprevir(100 mg) daily for 12 weeks. For cirrhotic patients RBV can be added as an alternative regimen, but the duration needs to be extended for 16 weeks.
ii. Recommendation II:
Sofosbuvir (400 mg) + velpatasvir (100 mg) daily for 12 weeks.
iii. Recommendation III:
Daclatasvir (60 mg) + Sofosbuvir (400 mg)±weight based Ribavirin daily for 24 weeks. The regimen is only recommended for treatment failure patients who used IFN & Ribavirin in past.
iv. Recommendation IV:
Ledipasvir (90 mg) + Sofosbuvir (400 mg).
For treatment Naïve patients/Relapsers the regimen is given for 12 weeks. For treatment failure either the duration is increased for 24 weeks or weight based RBV is to be added for 12 weeks (Ia or Ib) or 24 weeks (Ia only).
The RBV based 24 week treatment can also be used for Sofosbuvir + RBV failure candidates.
v. Recommendation V:
Paritaprevir (150 mg) + Ritonavir (100 mg) + Ombitasvir (25 mg) + twice-daily dasabuvir (250 mg) + weight based RBV.
The regimen is recommended for 24 weeks for patients who are Genotype 1a whereas for Genotype Ib same regimen without RBV is given for 12 weeks.
vi. Recommendation VI:
Sofosbuvir (400 mg) + Simeprevir (150 mg) + RBV for for 12 weeks and if the regimen is to be used without RBV the duration can be extended to 24 weeks.

Genotype 2 and 3 Compensated Cirrhotic Patients

Genotype 2 & 3 cirrhosis is prevalent in Indian sub-continent. Limited studies are done for these genotype because most of trials were in USA where genotype I is more prevalent. Genotype 2 is considered easy to treat genotype even with PEG/RBV with 80–90% SVR rate but genotype 3 is considered a difficult to treat genotype not only with PEG/RBV combination but also with different regimens of all oral DAAs.

The FISSION study using SOF+RBV in genotype 2 naïve cirrhotic patients showed SVR rate of 100% and in previously treated patients a SVR rate of 78% with 12 weeks duration therapy[10,11].

The FUSION study of treatment experience patients for 12 vs 16 weeks duration did not show any extra benefit for extended treatment.[12]

In genotype 3 naïve cirrhotic patients VALENCE study using combination of SOF/RBV for 24 weeks showed SVR_{12} of 92% and SVR_{12} of 62% in treatment experienced cirrhotic patient. However

prolongation of therapy to 24 weeks improves the SVR_{12} to 73%.[13] In another study (ALLY 3) the combination of SOF + Daclatasvir for 12 weeks showed a SVR of 58% in naïve and 69% in treatment failure genotype 3 cirrhotic patients.[14]

Genotype 2:

i. Recommendation I:
Sofosbuvir (400 mg) + daclatasvir (60 mg) daily for 16 to 24 weeks. For patients who have experienced SOF/RBV combination in the past RBV can be added in the regimen and it should be extended for 24 weeks.
ii. Recommendation II:
Sofosbuvir (400 mg) + velpatasvir (100 mg) daily for 12 weeks. For patients who have experienced SOF/RBV combination in the past RBV should be added in the regimen and it should be extended for 24 weeks.
iii. Recommendation III:
Sofosbuvir (400 mg) + weight-based RBV for 16 weeks. For treatment failures regimen can be extended to 24 weeks as well. If the treatment failure patients are IFN eligible then adding weekly PEG-IFN can reduce the duration to 12 weeks as well. Although this regimen is no longer recommended by AASLD but it can be practiced till the availability of above mentioned drugs in certain part of the world.

Genotype 3:

i. Recommendation I
Daclatasvir (60 mg) + sofosbuvir (400 mg) ± weight based RBV daily for 24 weeks. This Regimen is also recommended for patients with treatment failure who have used IFN + RBV or Sofosbuvir + RBV in past but RBV must be added then.
ii. Recommendation II:
Sofosbuvir (400 mg) + velpatasvir (100 mg) daily for 12 weeks. For treatment failures RBV should be added to the regimen.
iii. Recommendation III:
Sofosbuvir (400 mg) + weight-based RBV + weekly PEG-IFN for 12 weeks but for IFN ineligible patients SOF (400 mg) + weight-based RBV can be used for 24 weeks. Although this regimen is no longer recommended by AASLD but it can be practiced till the availability of above mentioned regimens in certain part of the world.

Genotype 4 Compensated Cirrhotic Patients

The consensus treatment guidelines recommend PEG IFN + DDA for treatment of Genotype 4 patient in chronic hepatitis and cirrhosis. Most of the data is for PEG IFN ineligible patients. In Egypt genotype 4 cirrhotic patients treated with SOF + RBV for 24 weeks showed a SVR rate of 100%.[15] In NIAID SYNERGY study patients with genotype 4 having adverse fibrosis treated with Ledipasvir and SOF for 12 weeks with SVR rate of 95%.[16]

EASL guidelines 2014 preliminary recommended Daclatasvir + SOF + RBV as well as Paritoprevir/ Omlistasvir/ for the treatment of genotype 4 cirrhotic patients for 24 weeks.[15]

i. Recommendation I:
Paritaprevir (150 mg) + Ritonavir (100 mg) + Ombitasvir (25 mg) + weight-based RBV for 12 weeks.
ii. Recommendation II:
Sofosbuvir (400 mg) + velpatasvir (100 mg) daily for 12 weeks.
iii. Recommendation III:
Elbasvir(50 mg) + grazoprevir(100 mg) for 12 weeks but for treatment failures weight baised RBV should be added for 16 weeks.
iv. Recommendation IV:
Ledipasvir (90 mg) + Sofosbuvir (400 mg) for 12 weeks. For treatment failures RBV should be added to the regimen.

Genotype 5 and 6 Compensated Cirrhotic Patients

There are limited studies available for genotype 5 or 6. Only very small number of patients of genotype 5 or 6 are reported from NEUTRINO study using Sofosbuvir and all patients achieved 100% SVR rate [10]. However ASSLD guidelines recommend Sofosbuvir + Ledipasvir for 12 weeks.[17,18]

i. Recommendation I:
Ledipasvir (90 mg) + Sofosbuvir (400 mg) for 12 weeks.
ii. Recommendation II:

Sofosbuvir (400 mg) + velpatasvir (100 mg) daily for 12 weeks.

8.5. Treatment of HCV infection in special populations

8.5.1. Management of HCV infection in patients with Decompensated Cirrhosis

Before the advent of DAAs, treatment of HCV was out of question for decompensated patients as IFN based regimens can worsen the Liver status. Whether eradicating HCV in decompensated patients will have a long term beneficial effect is not known yet, but on short term basis.

It reduces the need for liver transplant in this group of population. In Solar 1 phase II trial, the combination of Ledipasvir, Sofosbuvir, and Ribavirin for 12 weeks achieved high rates of SVR12 in patients with advance disease, including decompensated cirrhosis before and after liver transplantation.[19]

According to AASLD 2016 guidelines the patients with Decompensated Cirrhosis who are

candidates for liver transplant should be managed in a specialized centre whereas the recommended Regimens for patients with Decompensated Cirrhosis not candidates for liver transplant including patients with hepatocelular carcinoma are as follows:

Genotype 1 or 4:

i. Recommendation I:
Daclatasvir (60 mg) + Sofosbuvir (400 mg) + RBV (initial dose of 600 mg, increased as tolerated) for 12 weeks. For RBV ineligible patients the regimen can be extended for 24 weeks without RBV.

ii. Recommendation II:
Velpatasvir (100 mg) + Sofosbuvir (400 mg) + RBV (initial dose of 600 mg, increased as tolerated) for 12 weeks. For RBV ineligible patients the regimen can be extended for 24 weeks without RBV.

iii. Recommendation III:
Ledipasvir (90 mg) + Sofosbuvir (400 mg) + RBV (initial dose of 600 mg, increased as tolerated) for 12 weeks. For RBV ineligible patients the regimen can be extended for 24 weeks without RBV.

Genotype 2 or 3:

i. Recommendation I:
Daclatasvir (60 mg) + Sofosbuvir (400 mg) + RBV (initial dose of 600 mg, increased as tolerated) for 12 weeks

ii. Recommendation II:
Sofosbuvir (400 mg) + Velpatasvir (100 mg) + weight-based RBV for 12 weeks.

8.5.2. Management of HCV infection in patients with Renal Impairment:

IFN therapy in patients with renal impairment has high rates of adverse events and poor tolerance. Although studies in CKD patients suggest a SVR of about 30–40% with IFN monotherapy and 50–60% when used in combination with RBV, but the dropout rate is as high as 50%.[20–23]

DAAs could be used with much ease in patients with renal impairment. Although the data is limited but the results are promising. Gane *et al*. treated 10 patients with severe renal disease having HCV related CLD with SOF200mg/RBV200mg and showed SVR12 of 40% with good tolerance.[24].

i. Mild to moderate Renal impairment(CrCl ≥30ml/min):

No dose adjustment is required for Sofosbuvir, Simeprevir, Daclatasvir, fixed-dose combination of Ledipasvir (90 mg)/Sofosbuvir (400 mg), fixed dose combination of Velpatasvir(100 mg)/Sofosbuvir(400 mg) or fixed-dose combination of Paritaprevir (150 mg)/Ritonavir (100 mg)/Ombitasvir (25 mg) plus twice-daily dosed Dasabuvir (250 mg) in patients with mild to moderate renal impairment. Whereas PEG and RBV need dose adjustment, according to GFR, in patients with moderate renal impairment (CrCl 30-50 ml/min). PEG (2a) 180 µg; PEG (2b) 1 µg/kg or 25% reduction & Ribavirin 200mg and 400 mg alternating doses every other day is recommended.

ii. Severe Renal impairment (CrCl <30 ml/min):

Standard dose of Simeprevir is used in patients with severe renal impairment whereas Sofosbuvir is contraindicated in patients with CrCl<30 ml/min. Preliminary data suggests that no dose adjustment is required with Ledipasvir, Ritonavir, Ombitasvir and Dasabuvir in patients with severe renal impairment.[25,26] Dose adjustment according to GFR is required for PEG/RBV. PEG (2a) 135µg; PEG (2b) 1µg/kg or 50% reduction & Ribavirin 200mg/day is recommended.

iii. End Stage renal disease/Haemodialysis:

Elbasvir and Grazoprevir can safely be used in this group of patients with genotype 1 or 4. No data is available so far regarding the use of Sofosbuvir and Simeprevir so their use is not recommended in patients with End Stage renal disease or patients on hemodialysis. However, Daclatasvir can be used in ESRD without dose adjustment.[27] GFR adjusted doses of PEG/RBV can be given in these patients. Therefore PEG (2a) 135µg; PEG(2b) 1µg/kg or 50% reduction & Ribavirin 200mg/day is still recommended for Genotype 2,3, 5 and 6 or where Elbasvir, Grazoprevir are not available.

Recommended DAAs according to Creatinine Clearance (CrCl)

CrCl (mL/min)	Data available for the use of Standard doses of DAAs	Limited Data available	Data not available
>50	SOF, SIM, DCV, LDV, Paritaprevir, Ombitasvir, Dasabuvir, Velpatasvir, Elbasvir, Grazoprevir		
30–50	SOF, SIM, DCV, LDV, Paritaprevir, Ombitasvir, Dsabuvir, Velpatasvir, Elbasvir, Grazoprevir		
<30	SIM, Elbasvir, Grazoprevir	SOF, DCV, Paritaprevir, ombitasvir, Dasabuvir,	LDV, Velpatasvir
ESRD/HD	Elbasvir, Grazoprevir	SOF, SIM, DCV, Paritaprevir, Ombitasvir, Dasabuvir,	LDV, Velpatasvir

SOF: Sofosbuvir, SIM: Simeprevir, DCV: Daclatasvir, LDV: Ledipasvir

iv. Patients with Renal Transplant:

IFN based treatment in renal transplant patients who are already immune-compromised, are disappointing because of non-satisfactory SVR, patient's intolerability and possibility of graft rejection. Although most recent studies don't show significant acute allograft rejection (AAR). Sanai FM *et al* used PEG/RBV in 32 post renal transplant patients for 48 weeks and none of the patients showed AAR but the SVR was only about 37.5% and 12.5% patients discontinued the treatment.[28]

With the advent of DAAs, IFN free regimens should be opted for post renal transplant patients. Boceprevir and Telaprevir are inhibitors of CYP3A enzymes and regimens with these drugs interact with immunosuppresents like Cyclosporine and Tacrolimus used in renal transplant patients.[29–31]

Sofosbuvir does not undergo CYP3A metabolism and can easily be used in patients with renal transplant whereas Daclatasvir although metabolized by CYP3A but there is no clinical evidence of CYP3A inhibition or induction[31]. Simeprevir is a mild CYP3A inhibitor and a weak drug-drug interaction may be observed with immunosuppressant agents.[32]

8.5.3. Management of HCV infection in patients with Liver Transplant (LT):

In patients with Hepatitis C, undergoing LT 40% develop Hepatitis C related cirrhosis within 10 years of transplant[31] and it is a described fact that progression of liver fibrosis is faster after liver transplant so early viral eradication is the best way to improve patient survival.[33,34] The PEG-IFN/RBV based treatment for 48 weeks showed a SVR of about 30% with drug withdrawal of 27.6% due to severe side effects.[35] Another study by Tim Zimmermann *et al* of 26 post LT patients showed that PEG/RBV treatment for 48 weeks was relatively safe and tolerable but only 19% patients showed SVR.[36]

With the advent of DAAs, there seems to be a breakthrough for liver transplant patients. In TARGET study SOF & SIM ± RBV was given to 68 liver transplant recipients showing SVR4 of 94% in non-cirrhotics and 86% in cirrhotic.[37] In SOLAR I trial Ledipasvir & SOF given to post transplant patients for 24 weeks showed a SVR12 of 98% for F_0-F_3 patients, 96% for Child class A, 83% for child class B and 67% for Child class C post transplant cirrhosis.[38]

DAA interaction with immunosuppressant drugs should also be kept in mind before starting treatment in Liver transplant patients. SIM interacts with cyclosporine but not with Tacrolimus or Sirolimus. The combination of Ritonavir boosted Paritaprevir, Ombitasvir and Dasabuvir also interacts with both Cyclosporine and Tacrolimus. Sofosbuvir and Daclatasvir on the other hand seems to have no interaction with immunosuppressant drugs.[39]

According to the AASLD guidelines 2015, the patients developing recurrent HCV infection in post LT including those with compensated cirrhosis is as under:

1. Genotype 1 or 4:
   i. Recommendation I:
   Daclatasvir (60 mg) + Sofosbuvir (400 mg) + RBV (initial dose of 600 mg, increased as tolerated) for 12 weeks
   ii. Recommendation II:
   Daily fixed-dose combination of Ledipasvir (90 mg)/Sofosbuvir (400 mg) with weight based RBV for 12 for weeks. For decompensated cirrhosis patients RBV should be started with low initial dosage.
   iii. Recommendation III:
   Daily fixed-dose combination of Ledipasvir (90 mg)/Sofosbuvir (400 mg) for 24 weeks for RBV intolerant or ineligible.
   iv. Recommendation IV:
   Daclatasvir (60 mg) + Sofosbuvir (400 mg) for 24 weeks for RBV ineligible patients.

2. Genotype 2:
   i. Recommendation I:
   Daclatasvir (60 mg) + Sofosbuvir (400 mg) + RBV (initial dose of 600 mg, increased as tolerated) for 12 weeks
   ii. Recommendation II:
   SOF 400mg daily + weight based RBV for 24 weeks. This regimen with low initial RBV can be used in decompensated liver disease.
   iii. Recommendation III:
   Daclatasvir (60 mg) + Sofosbuvir (400 mg) for 24 weeks. This regimen is recommended for patients who are RBV intolerant or ineligible.
3. Genotype 3:
   i. Recommendation I:
   Daclatasvir (60 mg) + Sofosbuvir (400 mg) + RBV (initial dose of 600 mg, increased as tolerated) for 12 weeks
   ii. Recommendation II:
   Daclatasvir (60 mg) + Sofosbuvir (400 mg) for 24 weeks. This regimen is recommended

for patients who are RBV intolerant or ineligible.

iii. Recommendation III:

Daily Sofosbuvir (400 mg) and weight-based RBV for 24 weeks. Although no more recommended by AASLD but in resource poor countries the regimen can be considered till availability of Daclatasvir.

8.5.4. Management of HCV infection in Paediatric Population:

There are different schools of thought regarding Hep C treatment in children. As the natural course of Chronic Hepatitis C infection is slow, the treatment can be deferred till adolescence. But adolescent and young adult age group is thought to be care free and less treatment compliant.

The AASLD yet recommends only Interferon's along with RBV in paediatric population where PEG IFN is thought to be superior to conventional IFN in children as well.[40] PEG IFN α 2b given at a dose of 60 μg/m^2/week, whereas PEG IFN α 2a given at a dose of 180μg/1.73m^2/week along with RBV at a dose of 15 mg/kg/day. For genotype 1 or 4 the combination is given for 48 weeks and for genotype 2 or 3 it is given for 24 weeks.

Paediatric response to IFN/RBV therapy in HCV infection is 36–57% SVR for genotype 1, 84–100% for genotype 2, 3 and 50–80% for genotype 4. Whereas the side effect profile of IFN/RBV in children includes flu-like symptoms, fever, leucopoenia, headaches, abdominal pain, loss of appetite, diarrhoea and psychiatric effects.[41–45]

Due to the side effects and low SVR especially in genotype 1 in children the use of DAAs needs consideration. Two trials sponsored by Gilead Sciences are in phase 2 evaluating the efficacy and safety of Ledipasvir and Sofosbuvir for genotype 1 and Sofosbuvir and RBV for genotype 2 & 3 respectively. Excellent efficacy of new DAAs in adult population has encouraged scientists to evaluate the drugs in adolescent population. Pharmacokinetics and safety profile of sofosbuvir and ledipasvir/sofosbuvir has been evaluated in children from 12–17 year age group and comparable results have been established in this age group[46]. But more in-depth trials are required for the approval of these DAAs in children.

8.5.5. Management of HCV infection in IV Drug Abusers:

As IV drug use is a major risk factor for Hep C transmission so IV drug abusers are an important group of patients in which the treatment for Hep C needs consideration. These patients are thought difficult to treat because of social reasons and life styles. These patients are generally excluded from therapy because of lack of tolerability and compliance.[40] Esther J. Aspinall *et al* in a Meta-analysis showed in 314 IV drug abusers a SVR of 54% in all genotypes.[47] Barbara Zanini *et al* in a study on CHC IV drug abusers showed an 80% adherence rate to therapy when a treatment was offered to 49 patients.[48] Thus the IV drug abusers having Hep C related CLD can be managed successfully with standard therapy therefore same regimens are recommended as for general population.

8.5.6. Management of HCV/HBV co-infection:

In patients with HCV/HBV co-infection it is usually hepatitis C replication that causes chronic active liver disease. Therefore HCV is treated on the same lines as recommended for the general population. But one should keep in mind that there is always a potential risk of HBV reactivation during or after HCV treatment.[49] In such cases simultaneous HBV treatment with nucleoside/nucleotide analogues can be started. Drug-drug interactions has to be kept in mind before prescribing therapy. E.g. the concomitant use of Simepravir and Tenofovir needs much frequent renal function tests monitoring. Co-administration of ledipasvir with tenofovir is not recommended in patients with Creatinine clearance <60 mL/min.

8.5.7. Management of HCV infection in Thalassemia patients:

As evident from section I, there is a strong association between HCV infection and Thalassemia in Pakistan. Before the advent of DAAs treatment with PEG-IFN and Ribavirin was often withheld as both these drugs are associated with anaemia.

Although currently data for the safety of DAAs in thalassemia patients is lacking but evidence based studies are in progress. As there is no obvious contraindication to these DAAs in thalassemia patients one should consider using IFN and Ribavirin free regimens in these thalassemia patients.

Table: Recommended Regimens for the treatment of HCV in different Genotypes

Genotype	Regimens	Treatment Naïve or Relapsers		Treatment Failures	
		Without Cirrhosis	**With Cirrhosis**	**Without cirrhosis**	**With cirrhosis**
1a	I	Elbasvir (50 mg)/ grazoprevir (100 mg) for 12 weeks.		Elbasvir (50 mg)/ grazoprevir (100 mg) for 12 weeks.	
	II	Sofosbuvir (400 mg) / velpatasvir (100 mg) for 12 weeks.		Sofosbuvir (400 mg) / velpatasvir (100 mg) for 12 weeks.	
	III	Daclatasvir 60mg)/Sofosbuvir (400 mg) for 12 weeks	Daclatasvir (60mg)/Sofosbuvir (400 mg) ± weight based RBV for 24 weeks	Daclatasvir (60mg)/Sofosbuvir (400 mg) for 12 weeks	Daclatasvir (60mg)/Sofosbuvir (400 mg) ± weight based RBV for 24 weeks
	IV	Ledipasvir (90 mg)/Sofosbuvir (400 mg) for 12 weeks		Ledipasvir (90 mg)/Sofosbuvir (400 mg) for 12 weeks or + RBV(for SOF/RBV failure cases)*	Ledipasvir (90 mg)/sofosbuvir (400 mg) + weight based RBV for 12 weeks (24 weeks for SOF/RBV failure cases)* or without RBV for 24 weeks
	V	Paritaprevir (150 mg)/Ritonavir (100 mg)/Ombitasvir (25 mg) plus twice-daily dosed Dasabuvir (250 mg) and weight based RBV for 12 weeks	Paritaprevir (150 mg)/Ritonavir (100 mg)/Ombitasvir (25 mg) plus twice-daily dosed Dasabuvir (250 mg) and weight based RBV for 24 weeks	Paritaprevir (150 mg)/Ritonavir (100 mg)/Ombitasvir (25 mg) plus twice-daily Dasabuvir (250 mg) and weight-based RBV for 12 weeks	Paritaprevir (150 mg)/Ritonavir (100 mg)/Ombitasvir (25 mg) plus twice-daily dosed Dasabuvir (250 mg) and weight-based RBV for 24 weeks
	VI	Sofosbuvir (400 mg) plus Simeprevir (150 mg) for 12 weeks	Sofosbuvir (400 mg) plus Simeprevir (150 mg) ± RBV for 24 weeks	Sofosbuvir (400 mg) plus Simeprevir (150 mg) for 12 weeks	Sofosbuvir (400 mg) plus Simeprevir (150 mg) ± RBV for 24 weeks
1b	I	Elbasvir (50 mg)/ grazoprevir (100 mg) for 12 weeks.		Elbasvir (50 mg)/ grazoprevir (100 mg) for 12 weeks.	
	II	Sofosbuvir (400 mg) / velpatasvir (100 mg) for 12 weeks.		Sofosbuvir (400 mg) / velpatasvir (100 mg) for 12 weeks.	
	III	Daclatasvir(60mg)/Sofosbuvir (400 mg) for 12 weeks	Daclatasvir(60mg)/Sofosbuvir (400 mg) ± weight based RBV for 24 weeks	Daclatasvir (60mg)/Sofosbuvir (400 mg) for 12 weeks	Daclatasvir (60mg)/Sofosbuvir (400 mg) ± weight based RBV for 24 weeks
	IV	Ledipasvir (90 mg)/Sofosbuvir (400 mg) for 12 weeks		Ledipasvir (90 mg)/Sofosbuvir (400 mg) for 12 weeks or + RBV(for SOF/RBV failure cases)*	Ledipasvir (90 mg)/sofosbuvir (400 mg) + weight based RBV for 12 weeks (24 weeks for SOF/RBV failure cases)* or without RBV for 24 weeks
	V	Paritaprevir (150 mg)/Ritonavir (100 mg)/Ombitasvir(25 mg) plus twice-daily dosed Dasabuvir (250 mg) for 12 weeks		Paritaprevir (150 mg)/Ritonavir (100 mg)/Ombitasvir (25 mg) plus twice-daily dosed Dasabuvir (250 mg) for 12 weeks	
	IV	Sofosbuvir (400 mg) plus Simeprevir (150 mg) for 12 weeks	Sofosbuvir (400 mg) plus Simeprevir (150 mg) ± RBV for 24 weeks	Sofosbuvir (400 mg) plus Simeprevir (150 mg) for 12 weeks.	Sofosbuvir (400 mg) plus Simeprevir (150 mg) ± RBV for 24 weeks

2	I	Sofosbuvir (400 mg) / velpatasvir (100 mg) for 12 weeks.		Sofosbuvir (400 mg) / velpatasvir (100 mg) for 12 weeks. (Add RBV for 12 weeks for SOF/RBV experienced)*	
	II	Daclatasvir (60mg)/Sofosbuvir (400 mg) for 12 weeks	Daclatasvir (60 mg) /Sofosbuvir (400 mg) for 1624 weeks	Daclatasvir (60mg)/Sofosbuvir (400 mg) for 12 weeks (Add RBV for 24 weeks for SOF/RBV experienced)*	Daclatasvir (60mg)/Sofosbuvir (400 mg) for 16–24 weeks (Add RBV for 24 weeks for SOF/RBV experienced)*
	III	Sofosbuvir (400 mg) and weight-based RBV for 12 weeks	Sofosbuvir (400 mg) and weight-based RBV for 16 weeks	Sofosbuvir (400 mg) and weight-based RBV for 16 or 24 weeks (IFN ineligible patients) Sofosbuvir (400 mg) and weight-based RBV + weekly PEG-INF for 12 weeks (IFN eligible patients)	
3	I	Sofosbuvir (400 mg) / velpatasvir (100 mg) for 12 weeks.		SOF(400 mg) / velpatasvir (100 mg) for 12 weeks.(Add RBV for 12 weeks for SOF/RBV experienced)*	SOF (400 mg) / velpatasvir (100 mg) + weight-based RBV for 12 weeks*
	II	Daclatasvir(60mg)/Sofosbuvir (400 mg) for 12 weeks	Daclatasvir (60mg)/ sofosbuvir (400 mg) ± weight based RBV for 24 weeks	Daclatasvir (60mg)/ sofosbuvir (400 mg) for 12 weeks. (Add RBV for 24 weeks for SOF/RBV experienced)*	Daclatasvir (60mg)/ sofosbuvir (400 mg) + weight based RBV for 24 weeks*
	III	Sofosbuvir (400 mg) and weight-based RBV + weekly PEG-INF for 12 weeks(IFN eligible patients) Sofosbuvir (400 mg) and weight-based RBV for 24 weeks(IFN ineligible patients)		Sofosbuvir (400 mg) and weight-based RBV plus weekly PEG-IFN for 12 weeks (IFN eligible)	
4	I	Paritaprevir (150 mg)/Ritonavir (100 mg)/Ombitasvir (25 mg) and weight-based RBV for 12 weeks		Paritaprevir (150 mg)/Ritonavir (100 mg)/Ombitasvir (25 mg) and weight-based RBV for 12 weeks*	Paritaprevir (150 mg)/Ritonavir (100 mg)/Ombitasvir (25 mg) and weight-based RBV for 12 weeks(extend for 24 weeks for SOF/RBV experienced)*
	II	Sofosbuvir (400 mg) / velpatasvir (100 mg) for 12 weeks.		Sofosbuvir (400 mg) / velpatasvir (100 mg) for 12 weeks.	
	III	Elbasvir (50 mg)/ grazoprevir (100 mg) for 12 weeks.		Elbasvir (50 mg)/ grazoprevir (100 mg) for 16 weeks.	
	IV	Ledipasvir (90 mg)/Sofosbuvir (400 mg) for 12 weeks		Ledipasvir (90 mg)/Sofosbuvir (400 mg) for 12 weeks (Add RBV for SOF/RBV experienced)*	Ledipasvir (90 mg)/sofosbuvir (400 mg) + RBV for 12 weeks (extend for 24 weeks for SOF/RBV experienced)*
	V	Sofosbuvir (400 mg) and weight-based RBV for 24 weeks.		Sofosbuvir (400 mg) and weight-based RBV plus weekly PEG-IFN for 12 weeks(IFN eligible) or Sofosbuvir (400 mg) and weight-based RBV for 24 weeks(IFN ineligible)	
5 or 6	I	Ledipasvir (90 mg)/Sofosbuvir (400 mg) for 12 weeks.		Ledipasvir (90 mg)/Sofosbuvir (400 mg) for 12 weeks (Add RBV for SOF/RBV experienced)*	Ledipasvir (90 mg)/Sofosbuvir (400 mg) for 12 weeks (add RBV and extend for 24 weeks for SOF/RBV experienced)*
	II	Sofosbuvir (400 mg) / velpatasvir (100 mg) for 12 weeks.		Sofosbuvir (400 mg) / velpatasvir (100 mg) for 12 weeks.	

Note: Starred(*) recommendations are for patients with treatment failure who have used Sofosbuvir based regimens in the past

☐ Shaded options are only recommended for resource poor countries till the availability of Velpatasvir or Daclatasvir.

9. ADJUVANT THERAPY AND COMPLEMENTARY ALTERNATIVE MEDICINE

Adjuvant therapies and complementary alternative medicine (CAM) are frequently used in Pakistan for many reasons. Firstly, these drugs are economical; secondly they improve the sense of well being. The aims of adjuvant or complementary therapy in chronic HCV infection are:

- To improve SVR
- To decrease hepatic fibrosis, particularly in non-responders and relapsers
- To improve symptoms in patients who cannot afford or qualify for IFN/RBV therapy

No proposed adjuvant or complementary therapy has been shown to improve SVR or to retard fibrotic progression. Combination therapies involving Thymosin Alfa and Amantadine have been considered. Therapies that have been proven to reduce serum ALT might be considered in the absence of the effective treatment to achieve SVR. Such adjuvant therapies might include Ursodeoxycholic acid and strong Neominophagen-C (SNMC). Ofloxacin, non-steroidal anti-inflammatory drugs and Amantadine have been found to be not beneficial. Thymosin-a 1 has shown some promise alone or in combination with interferon Alfa, but larger studies are required.[50,51]

In patients with a non-response to Interferon or combination Interferon / Ribavirin therapy, vitamin E, Thymosin Alfa, interleukin-10, might be worthy of further evaluation for their effects on hepatic fibrosis and risk of hepatocellular carcinoma development.

9.1. Herbal Medicines

Chinese herbal medicines are popular alternative therapy which normalizes ALT and being anti-oxidant might have effect on hepatic fibrosis. However there are no scientific trials for these medications. While using them alone or as adjuvant therapy with antiviral drugs, patients should be monitored for hepatotoxicity, renal and pulmonary side effects.

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SECTION-V

10. HOW TO PREVENT AND CONTROL HEPATITIS C IN PAKISTAN

In Pakistan 10 million HCV infected persons are potential pool for spread of HCV infection.[1] Risk factors for transmission of hepatitis C are also different in different regions of the world. In developed countries 60-65% of patients of chronic HCV infected are IVDU. In undeveloped countries like Pakistan injudicious injections, reuse of syringes and needles, transfusion of unscreened blood and blood products, multiple transfusion in hemophilics, thalassaemic and haemodialysis patients, un-sterilized equipments used for dental treatment, surgery, endoscopic procedures, tattooing, ear & nose piercing, being house hold contact, barber shaving and mother to baby transmission are important modes of transmission.[2] It is important to know these modes of transmission of HCV infection to counsel patients regarding prevention of spread of virus to others. At mass level, it is pertinent to evolve strategies for awareness and public health education highlighting modes of transmission of HCV infection and their prevention.

In 2005, Pakistan government started National Program for Prevention and Control of Hepatitis in the country. The main component of this program is prevention by providing awareness at mass level regarding risk factors, provision of disposable syringes, free hepatitis B vaccination, waste disposal and provision of screened blood for transfusion. Public awareness and prevention is the major component of the program.

Guidelines Committee Members and Experts agreed on following strategies in prevention and control of HCV infection at individual and community level in light of the international guidelines.[3–9]

10.1 Counselling of infected person to avoid transmission of HCV

1. HCV infected person should avoid sharing tooth brush, shaving razors, blades, scissors and towels
2. HCV infected person should cover the bleeding areas to keep their blood away from others.
3. Infected person should not donate blood and body organs.
4. Counseling should be done regarding illicit drugs needle sharing.
5. Proper disposal of vomit and other body secretions of HCV patients with disinfectant e.g. bleaching powder and glutryaldehyde solution.
6. Barrier techniques are not recommended as risk for sexual transmission is very low.
7. Similarly breast feeding should not be stopped as risk of transmission is very low.

10.2 Recommendation for Prevention of HCV Infection at Community level

- Screening of blood donors with third and fourth generation EIAs must be done.
- In healthcare settings, all equipment involved in invasive procedures should be adequately cleaned and sterilized.
- Tattooists and traditional practitioners of alternative therapies should be educated regarding sterilization of equipment involved in skin penetration or mucosal breaks.
- As HCV transmission via IDU is increasing in Pakistan, so education campaigns and needle syringe programs should be implemented.
- Patients receiving surgical or dental treatment should be screened.
- Person with history of blood transfusion should have their anti HCV and HBsAg status checked.
- Hepatitis B vaccination of all chronic hepatitis C patients should be done after screening.
- Use of unnecessary injections should be discouraged as much as possible and if required disposable syringes must be used.
- Healthcare facilities should be issued certificates of good practices, if they fulfil the criteria of good practices. These certificates should be properly displayed in hospitals and shops.
- Standard protocol for needle stick injury should be implemented in all hospitals.
- Barbers, people at Parlors, Tattooists and Nose piercers should be educated regarding transmission of virus of HCV.

10.3 Occupational Health Risk

10.3.1 General Measures

- Initial and regular health screening and record of immunity.

- Incidence like needle sticks or cuts should be reported to supervisor.
- All skin lesions on hands should be covered with water proof dressing.

10.3.2 Minimal Requirement for Personal Protection

- For feco-oral route: decontamination of hands.
- For air borne route: if possible restrict non-immune staff from patient care, common surgical masks don't provide adequate protection.
- For blood borne infections: care to avoid needle stick and sharp injury, avoid recapping of needles and after use, transfer to a puncture proof container.
- To handle blood contamination material, use non-touch techniques and gloves.
- Wash hands after blood contact even if gloves are worn.
- Wash hands promptly after touching infective material (blood, body fluids, excretions, secretions, infected patients or their immediate environment and articles)
- Gloves should be used while processing blood, body fluids, excretions, secretions, and contaminated items.
- Clean up spills of infected material promptly.
- Between each patient use, disinfect or sterilize patient care equipment, supplies and linen contaminated with infective material.

10.4 Barrier Precautions

Decontamination of Hands

- Hand washing is the most effective way of preventing the transfer of bacteria between hospital personnel and patient within hospital.
- Gloves are **NOT** a substitute for hand washing. Hands should always be washed after removing gloves and also before wearing gloves.
- Social hand washing: with plain soap and water.
- Hygienic hand washing: with antiseptic detergent / Povidine iodine detergent preparation or with alcohol. 0.5 % chlorhexidine.

10.5 Healthy behaviours adaptation for prevention and Control of hepatitis

10.5.1 Health promotive & preventive behaviours for operators

Barbers / beauticians and other invasive groups (acupunturists, ear / nose pierce workers, tattooists, traditional dental healers and zangeer zani groups) must assume that all blood and body substances are potential sources of infection, so it is best to use single use disposable items on all clients / patients.

a. To make sure that all Barbers/Beauticians and Operators doing formal/informal invasive practices must be vaccinated against Hepatitis B.
b. All operators should wash their hands before attending their next client.

The following method ensures that the hands are free of germs: -

a. Remove all rings, watches and relevant jewellery
b. Wash hands gently with warm running water and avoid chapping.
c. Apply hand sanitizer/liquid soap, preferably anti-bacterial and rub hands vigorously while washing.
d. Wash all surfaces, including:
    i. backs of hand
    ii. Wrists
    iii. Between fingers
    iv. Under fingernails
e. Hands should be dried with disposable napkin/towel/tissue.
f. Turn off the water using the same towel, or with a paper with bare hands.

10.5.2 Protocols for cleaning equipment and instruments to be adopted by operators (Barbers/Beauticians and other invasive groups (Acupuncturists, Ear/Nose Pierce workers, tattooists, traditional dental healers and Zanjeer Zani groups)

a. Equipment designed not to penetrate the skin must be thoroughly cleaned prior to re-using. Thermal disinfection is preferable but if not possible it should at least be cleaned with a 70% alcohol wipe or swab.
b. Equipment must be cleaned prior to disinfection (solution of hypochlorite 1000 ppm 25 ml in one litter of water) or sterilization to remove all visible organic matter and residue, as they may inhibit the disinfection or sterilization process.
c. After using the instruments immediately put them in to the disinfection bath tub to avoid drying of debris.
d. After that rinse them in hot water (cool water if blood-soiled)
e. Wash debris from items

f. Rinse again.

10.5.2.1 Protocols of disinfection (especially to be adopted in hospital/dental surgeries)

a. All equipment must be cleaned prior to disinfection.
b. Disinfection can be achieved by chemical or thermal methods.
c. Thermal disinfection can be achieved by boiling the instruments for five minutes or more.
d. If this is not possible it must be cleaned with a 70% alcohol wipe or swab. Spirit or clear Phenolics are also suitable for wiping equipment and surfaces.
e. Chemical disinfectants are also found as chemicals in everyday use e.g Hypochlorite or household bleach. Solutions of Hypochlorite (1000 ppm 25 ml in one liter of water) can be used for disinfection.
f. Glutaraldehyde is a commercially available disinfectant and can be used to immerse instruments for disinfection.
g. Time is an important factor to take into account when using disinfectants. For most at least 30 minutes soaking time is required.
h. Reusable equipment must be stored in a clean and dry environment after disinfection.
i. The directions for the preparation, use and storage of disinfectants should be followed in true spirit.

10.5.3 Protocols to be adopted for sterilization

a. All equipment used to penetrate the skin must be sterilized.
b. Equipment can be pre-sterilized and/or single use.
c. If contact occurs between a sterile and un-sterile item, both items are to be considered un-sterile.
d. The recommended method of sterilizing is autoclaving.

10.6 SOPs for Injection Safety, Device Control and Hospital Waste Management

10.6.1 Sharp Safety

Prevention of needle stick / sharp injury

a) Take care to prevent injuries when using syringes, needles, scalpels and other sharps instrument or equipment.
b) Place used disposable syringes and needles, scalpel blades and other sharp items in a puncture resistant container with a lid that closes.
c) Such container must be located in all patient care and laboratory area where they are easily accessible to personnel working in these locations.
d) Take extra care when cleaning sharp reusable instrument or equipment.
e) Never recap or bend needle.
f) Sharp must be appropriately disinfected and or destroyed as per the national standard or guidelines.

10.6.2 Disposal of Sharp Objects

Sharp objects represent a threat for transmission of Hepatitis B, C and HIV. The following procedures must be adhered to ensure that this risk is minimized. Respective managers must ensure adherence to policy items.

b) All sharp objects must be placed in designated containers only.
c) Containers must be placed in all patient room and in convenient locations in all patient care areas.
d) If a sharp object is opened from its sterile packing and not used it still must be disposed in the said containers.
e) Normal waste must not be deposited in the sharp containers.
f) Sharp objects must not be carried around or placed in pockets while working.
g) Sharp objects must not be filled to more than $3/4^{th}$ capacity.
h) The containers should be carried out by designated persons from housekeeping and disposed-off by incineration.

10.6.3 Exposure to Hepatitis Via Needle Stick or Splash

Needles must not be recapped. If absolutely necessary, one hand technique should be used. Gloves should be used for all invasive procedures. Open wound must be covered with waterproof dressing. Protective eyewear must be worn if spray or splash is expected. If an exposure occurs the following procedure must be adopted:

1. Express any blood out of the punctured area.
2. The punctured site should be thoroughly cleaned with liberal amounts of alcohol.
3. Report the incident officially and report to your supervisor.

4. Obtain full information about the patient on whom the needle was used, especially in regard to Hepatitis B, C and HIV.
5. Report to the registrar ward (working hours) or the resident on call (after hours).
6. The registrar or the on-call resident will:

a. Categorize the exposure - High risk

- Visibly bloody needle.
- Penetration 3mm or more into the skin of the employee.
- Mucous membrane or open wound splashed with blood or bloody fluid

Low risk

- No penetration by the needle, just a graze.
- No visible blood on the needle.

b. Categorize the patient - High risk

- Known positive HIV or Hepatitis B or C
- Risk factors HIV or Hepatitis B or C

Low risk

- No risk factors HIV or Hepatitis B or C

c. Determine vaccination status of the employee against Hepatitis B

d. Order Hepatitis B / C and HIV serologies on the employee.

e. Determine or order Hepatitis B /C and HIV serologies on the patient

f. Order appropriate action (in consultation with registrar or on call consultant if necessary)

g. If the patient is HBsAg positive or is high risk for Hepatits B and the employee is anti-HBS negative:

- Hepatitis B immune globulin (HBIG) (within 24 hrs) plus a single booster of hepatitis B vaccine if the employee was vaccinated already with 3 doses of the vaccine
- Hepatitis B immune globulin (HBIG) (within 24 hrs) plus offer full 3 doses series of Hepatitis B vaccine if the employee was unvaccinated

h. If the patient is HBsAg positive or is a high-risk patient for Hepatitis B and the employee is Anti-HBS positive:

- No vaccination or HBIG

i. If the patient is HBsAg negative or a low risk patient

- No vaccination or HBIG.

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