Indian National Association for Study of the Liver (INASL) Guidance for Antiviral Therapy Against HCV Infection: Update 2016

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India contributes significantly to the global burden of HCV. While the nucleoside NS5B inhibitor sofosbuvir became available in the Indian market in March 2015, the other directly acting agents (DAAs), Ledipasvir and Daclatasvir, have only recently become available in the India. The introduction of these DAA in India at a relatively affordable price has led to great optimism about prospects of cure for these patients as not only will they provide higher efficacy, but combination DAAs as all-oral regimen will result in lower side effects than were seen with pegylated interferon alfa and ribavirin therapy. Availability of these newer DAAs has necessitated revision of INASL guidelines for the treatment of HCV published in 2015. Current considerations for the treatment of HCV in India include the poorer response of genotype 3, nonavailability of many of the DAAs recommended by other guidelines and the cost of therapy. The availability of combination DAA therapy has simplified therapy of HCV with decreased reliance of evaluation for monitoring viral kinetics or drug related side effects. (J Clin Exp Hepatol 2016;6:119–145)

There have been revolutionary changes in the management of chronic hepatitis C (CH-C) over the last few years. Pegylated interferon alfa (Peg-IFNα) plus ribavirin (RBV) therapy, which till the recent past was the standard of care, has been eclipsed by the arrival of newer directly acting antiviral agents (DAAs). Not only do the DAAs have better efficacy, they are also associated with lower side effects, have better tolerability, a shorter duration of therapy, and have simpler administration.

In the recent guidelines issued by the American Association for the study of Liver Diseases (AASLD), in collaboration with the Infectious Diseases Society of America[1] and the European Association for Study of the Liver z (EASL),[2] the role of Peg-IFNα/RBV therapy in the management of HCV has been relegated to second-line, backup status. These newer guidelines, however, cannot be implemented in India as many of the recommended drugs are yet to be marketed in India. Other considerations for the treatment of HCV in India are a predominance of

Keywords: hepatitis C virus, chronic hepatitis, HCV, antiviral therapy
Available online: 2 July 2016
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Abbreviations: ALT: alanine aminotransferase; ANC: absolute neutrophil count; anti-HCV: antibody to HCV; AST: aspartate aminotransferase; CH-C: chronic hepatitis C; CTP: Child-Turcotte-Pugh; DAA: directly acting antiviral agents; DCV: daclatasvir; EIA: enzyme immunoassay; ESRD: end-stage renal disease; EVR: early virological response; FCH: fibrosing cholestatic hepatitis; GT: genotype; HCV: hepatitis C virus; HCWs: healthcare workers; HIV: human immunodeficiency virus; INASL: Indian National Association for Study of the Liver; IU: international units; LDV: ledipasvir; LT: liver transplantation; NSI: needlestick injury; NS: nonstructural protein; PCR: polymerase chain reaction; Peg-IFNα: pegylated interferon alfa; RBV: ribavirin; RVR: rapid virological response; SOF: sofosbuvir; SVR: sustained virological response; ULN: upper limit of normal
http://dx.doi.org/10.1016/j.jceh.2016.07.001

genotype (GT)-3 and the considerations of the cost of management of HCV.

The Indian National Association for Study of the Liver (INASL) had previously reviewed the epidemiology of HCV in India[3] and formulated the guidelines for HCV in India relevant to the available therapy in India. The initial guidelines were based on Peg-IFNα/RBV therapy.[4] Following the availability of the nucleoside NS5B inhibitor sofosbuvir (SOF) in India with effect from March 2015, INASL had revised the guidance for antiviral therapy against HCV.[5] However, while SOF was the sole DAA in the Indian market, efficacy of the all-oral regimen (SOF/RBV) was limited. Now with the arrival of two new DAAs [NS5A replication complex inhibitors, ledipasvir (LDV) and daclatasvir (DCV)] in the Indian market in December 2015, the recommendations for management of CH-C must accordingly change.

The availability of these newer DAAs is an exciting development in the management of HCV in India. Not only will they provide higher efficacy, but combination DAAs as all-oral regimen will also obviate the reliance on Peg-IFNα/RBV therapy, which had significant side effects.

EVALUATION OF HCV IN THE ERA OF DAA

With Peg-IFNα/RBV therapy, there is a high reliance on laboratory monitoring not only for monitoring the side effects of therapy but also for efficacy and decision for duration of therapy. Repeated testing of HCV RNA for viral kinetics was done to look for rapid virologic response (RVR, undetectable HCV RNA after 4 weeks of treatment) and early virologic response (negative HCV RNA at 12 weeks), which are predictors of sustained virologic response (SVR). However, unlike Peg-IFNα-based therapy, with DAA, there is limited role for repeated HCV RNA testing for RVR or EVR for residual viremia and response-guided therapy. The need for repeated viral load testing for response-guided therapy is obviated, as is the frequent blood sampling for monitoring adverse effects. This simplification of antiviral therapy for HCV and lower laboratory requirements are an advantage in resource-constrained settings.[6]

Diagnosis of HCV Infection

Antibodies to hepatitis C (anti-HCV antibodies) are the screening test for HCV infection. However, these antibodies may be negative early in acute HCV infection, in immunosuppressed individuals, or years after resolution of HCV infection.[7,8] Hence, in patients with suspected acute hepatitis C, HIV infection, organ transplant recipients, and in patients on immunosuppressive drugs, HCV RNA may be required for the diagnosis of HCV infection if anti-HCV is negative.

Anti-HCV antibodies only indicate prior exposure to HCV infection and detection of active viral replication by either HCV core-antigen (HCV core-Ag) or HCV RNA testing is needed to differentiate between active and resolved HCV infection. Traditionally, HCV RNA testing has been used for this purpose and for following the response to antiviral therapy. A simpler alternative to HCV RNA testing is the estimation of HCV core-Ag, a protein with highly conserved sequence, by enzyme immunoassays.[9] Newer, more sensitive assays of HCV core-Ag have now become available. Automated platforms, such as Abbott Architect®, are able to rapidly perform anti-HCV and HCV core-Ag together in a short period of time. The major advantages of HCV core-Ag testing are that it is simple to perform, does not require highly skilled manpower, is cheaper, and can be performed at the same time as the anti-HCV test. HCV core-Ag testing has been shown to be valuable in detection of active HCV infection, HCV infection in seronegative hemodialysis patients, early treatment monitoring, and as a cost-effective alternative to nucleic acid technology for the identification of blood donors in the preseroconversion window.[10–14]

The arrival of DAAs has reduced the need for pretreatment viral load measurement. Detection of HCV replication prior to therapy and its absence 12 weeks after end-of-therapy may be sufficient for diagnosis and monitoring of the treatment. HCV core-Ag may be useful in resource-limited settings and provides smaller laboratories with the capacity to detect active HCV infection where HCV RNA testing may not be feasible.[15] Algorithms incorporating HCV core-Ag testing have been proposed for the evaluation and management of patients with chronic hepatitis C (CH-C).[16,17] However, further evaluation of HCV core-Ag testing is required to guide its use in the management of CH-C in the absence of HCV RNA testing.

Assessment Prior to Treatment

Prior to starting treatment, the following evaluation should be done:

- A detailed history and physical examination is essential, including history of alcohol consumption and drug abuse. Cardiac, pulmonary, and psychiatric evaluations should be done, if indicated.
- Baseline tests include complete hemogram and liver biochemistry [alanine aminotransferase (ALT), aspartate aminotransferase (AST) alkaline phosphatase, bilirubin, gamma-glutamyl transpeptidase (GGT), prothrombin time or INR, albumin], renal function tests, and thyroid function tests.
- Investigations for viral coinfections: Hepatitis B surface antigen, anti-HIV.
- Evaluation for other causes: The causal relationship between HCV infection and liver disease should be established and tests for additional etiologic factors may be done as indicated, e.g., antimitochondrial antibodies, antinuclear antibodies, anti-smooth muscle antibodies, serum ceruloplasmin, serum ferritin, etc.
- Serum HCV RNA (quantitative) and HCV genotyping.
- Cardiac, pulmonary, and psychiatric evaluations, if indicated.
- In women of childbearing age, urine pregnancy test should be done.

- IL28B genotyping cannot be recommended for routine use. IL28B polymorphisms have a relationship with the spontaneous clearance of acute HCV infection and the response to treatment with Peg-IFNα-based therapy.[18] In the DAA era, interleukin (IL) 28B testing may be relevant only when DAAs are used in combination with Peg-IFNα and RBV. In the NEUTRINO trial, treatment-naive GT-1, 4, 5, and 6 patients who were treated for 12 weeks with SOF with Peg-IFNα/RBV, non-CC IL28B GT (SVR 12: 87% vs. 98%), and cirrhosis (80% vs. 92%) were significantly associated with reduced response on multivariate analysis.[19]
- Detection of liver fibrosis and cirrhosis: Though liver biopsy remains the 'gold standard,' liver cirrhosis is usually diagnosed on the basis of a combination of clinical, biochemical, sonographic, and endoscopic criteria. This approach is reliable for detecting compensated cirrhosis with portal hypertension but not in the absence of portal hypertension. The increasing use of liver stiffness measurements using techniques such as transient elastography (Fibroscan™), acoustic radiation force impulse (ARFI) and shear wave elastography (SWE) allows detection of cirrhosis without portal hypertension, a subset which was earlier included in the 'no cirrhosis' group. Transient elastography has been used as a diagnostic method to rule out cirrhosis with reasonable accuracy. ARFI and batteries of biochemical tests used for detection of fibrosis, such as aspartate transaminase-platelet ratio index (APRI) or FIB-4, are not widely validated or have lower diagnostic accuracy. In the Peg-IFNα/RBV era, assessment of hepatic fibrosis and staging of the disease was considered to be important for deciding whether or not to initiate therapy in HCV infection. In the present era of combination DAA therapy with high cure rates even in patients with advanced fibrosis and compensated cirrhosis, the role of fibrosis assessment is becoming less important for making the decision to initiate therapy. However, since presence of liver cirrhosis results in lower SVR rates and higher relapse rates even after DAAs, determination of degree of fibrosis remains important before retreatment after relapse following Peg-IFNα or DAA-based therapy for deciding on duration of therapy, addition of RBV with some regimens [e.g. SOF/DCV for GT-3 liver cirrhosis], and for planning HCC surveillance.

Goals and Endpoints of Therapy

The goal of therapy is to cure HCV, thereby preventing development of cirrhosis and hepatocellular carcinoma. The assay of choice to measure level of HCV RNA is the real-time PCR-based assay with a lower limit of detection of ≤15 IU/ml. With Peg-IFNα-based therapy, sustained viral response (SVR) was considered as the absence of detectable virus 24 weeks after the completion of therapy (SVR24). Recent data suggest that absence of detectable virus at 12 weeks after completion of therapy (SVR12) with DAA-based regimens is concordant with SVR24.[20] The concordance of SVR4 with SVR24 and SVR12 has also been suggested with SOF therapy.[21]

AVAILABLE ANTIVIRAL DRUGS FOR HCV IN INDIA

Many newer DAA are in clinical use in other parts of the world and others are at different stages of development. These include nonstructural protein 3/4A protease inhibitors (NS3/4A PI), NS5A replication complex inhibitors (NS5B-RCI), and NS5B polymerase inhibitors [both nucleoside (NPI) and non-nucleoside (NNPI)]. Combination therapy with Peg-IFNα/RBV was the standard of care in India till SOF was introduced in March 2015 and, more recently, LDV and DCV were launched in December 2015. The present version of guidance for antiviral therapy against HCV infection in India will focus on the role of the available DAAs in treatment of the dominant GTs in India (GT-3 followed by GT-1).

Peglylated Interferon Alfa (Peg-IFNα)

Peg-IFNα is available as Peg-IFNα2a, which is used at a dose of 180 μg/week, and Peg-IFNα2b, which is used at a dose of 1.5 μg/kg/week. Peg-IFNα-related side effects, which need frequent dose adjustments and use of growth factors, are anemia and low white cell and platelet counts. Other side effects are flu-like symptoms, fatigue, depression, sleep disorder, irritability, dyspnea, headache, injection-site reaction, autoimmune reactions, hearing and visual disturbances, interstitial lung disease, and thyroid function abnormalities. Peg-IFNα should be used with caution in patients with advanced cirrhosis as hepatic decompensation may occur.

Ribavirin (RBV)

RBV is available as 200 mg tablets and the recommended dosage is weight based (1000 mg/day if body weight <75 kg, 1200 mg/day if body weight >75 kg). The significant side effect of RBV is anemia. RBV dose should be adjusted downward by 200 mg decrements if hemoglobin level drops below 10 g/dl and it should be stopped if hemoglobin level falls below 8.5 g/dl. Women of childbearing potential and/or their male partners must use an effective form of contraception during treatment and for a period of 6 months after the treatment has concluded, since significant teratogenic and/or embryocidal effects have been demonstrated in all animal species exposed to RBV.

Sofosbuvir (SOF)

SOF is a first-in-class pangenotypic nucleoside polymerase inhibitor, which suppresses all HCV GTs at low MICs. It is an analog of cytidine, a pyrimidine nucleotide, and inhibits viral RNA-dependent RNA polymerase (RDRP) encoded by the NS5B region of the viral genome. It is a prodrug that undergoes intracellular metabolism in the hepatocytes to the active form (GS-461203), which acts as a chain terminator. It is available as a 400 mg capsule and is given once a day. Its primary metabolite, GS-331007, is inactive and undergoes renal excretion. The drug is therefore not recommended in patients with severe renal impairment [estimated glomerular filtration rate (eGFR) <30 mL/min]. The

common adverse effects of SOF in combination with RBV are fatigue, headache, nausea, insomnia, and anemia. SOF is substrate for and is transported by P-glycoprotein (P-gp), and since P-gp inducers, including anticonvulsants (carbamazepine, oxcarbazepine, phenobarbital, phenytoin), antimycobacterials (rifabutin, rifampin), HIV protease inhibitors (tipranavir/ritonavir), and herbal supplements (St. John's wort), decrease its plasma levels, SOF is not recommended for coadministration with them. Coadministration of SOF with amiodarone is contraindicated due to serious risk of symptomatic bradycardia.

Ledipasvir (LDV)

The nonstructural protein 5A (NS5A) is needed for the formation of the HCV replication complex involving mRNA, RDRP, and amino acids. The NS5A replication complex inhibitor LDV is most active against GT-1 and -4 and has a high MIC for GT-3 HCV.

If the patient is using acid suppressing medications, LDV should be administered simultaneously with H_2RA or PPI and at least 4 hours after antacids, since its solubility decreases as gastric pH increases. It is excreted unchanged in the feces, with approximately 1% eliminated in the urine and is safe in patients with renal and hepatic impairment. It has little effect on CYP450 enzymes but is a substrate and weak inhibitor of P-gp and BCRP (breast cancer resistance protein). Coadministration with P-gp inducers should be avoided, since this reduces LDV levels, while concurrent administration with P-gp and BCRP substrates should be avoided, since LDV can increase their levels. P-gp substrates include immunosuppressant (cyclosporine, tacrolimus, methotrexate, and rivaroxaban), statins (atorvastatin, lovastatin, pravastatin, and simvastatin), antineoplastics (colchicine), calcium channel blockers (diltiazem and verapamil), and digoxin. BRCP substrates include nucleoside analog reverse transcriptase inhibitors (NRTIs; lamivudine, zidovudine), statins (pravastatin and rosuvastatin), methotrexate, and ciprofloxacin. LDV is suitable for use in postliver transplant patients, since it does not interact with immunosuppressants like cyclosporine and tacrolimus.

Daclatasvir (DCV)

DCV is a first-in-class, pangenotypic NS 5A replication complex inhibitor (NS5A RCI) with a low-to-moderate genetic barrier to resistance that has been used against GT-1 as well as GT-3 infections. It is available as a 60 mg capsule and is given once per day. Dose of the drug does not need to be adjusted in the presence of renal or liver failure. However, since DCV is a substrate and a very weak inducer of CYP3A4 as well as a substrate and inhibitor of P-gp, it needs dose adjustment when used with potent inducers and inhibitors of these enzymes, many of which are used in antiretroviral therapy (ART). When used with CYP3A4 inducers (e.g. efavirenz, etravirine, etc.), a 90 mg dose of DCV has been recommended.[22] When used with potent CYP3A4 inhibitors (e.g. ritonavir-boosted atazanavir), a 30 mg dose of DCV has been recommended. However, its interactions with specific ART drugs and regimens are being studied and dose modification recommendations are being finalized.[23] Table 1 highlights drug–drug interactions between DAA and some commonly prescribed medications. The University of Liverpool website, www.hep-druginteractions.org, is a valuable resource for screening for DDI with DAA.

Resistance to DAAs

HCV Replication, Quasispecies, and Resistance-Associated Variants

The 9.6 kb positive single-stranded RNA virus genome of the hepatitis C virus (HCV) encodes a single 3100 amino acid long polyprotein, which is cleaved during post-translational processing into four structural proteins (C, E1, E2, and p) and six nonstructural proteins (NS2, NS3, NS4A, NS4B, NS5A, and NS5B). HCV has a high genetic variability with seven GTs that have a sequence variability of up to 20 percent. NS5B RDRP is highly error prone. Due to high daily production of more than 10^{12} virions, high mutation rate, and poor ability to repair RDRP errors, there is a large variability in viral sequences within the same patient, resulting in numerous quasispecies.[24,25] DAA targets are nonstructural proteins, especially the NS3-NS4A protease, NS5A replication complex, and NS5B polymerase. Some of the numerous variants in the vast HCV pool confer resistance to various DAAs and are termed resistance-associated variants (RAVs). RAVs can be detected by population sequencing (detects variants that form up to space 15% of viral population), clonal sequencing (variants up to 5%), or ultradeep pyrosequencing (Next Generation sequencing; picks up variants up to 0.5–1%).[26]

Genetic Barrier to Antiviral DAAs and Viral Fitness

Genetic barrier to resistance for directly acting antiviral agents (DAA) is decided by number and type of base pair mutation[s] needed to produce amino acid substitution[s] that confer resistance to the agent.[26,27] Replication fitness refers to relative capacity of a viral variant to replicate in a given environment.[25] Though resistance profiles of currently available DAAs have been identified, there are no established standardized commercial assays for testing for resistance.[28]

Significance of RAVs

RAVs are associated with resistance to DAAs and are important with regard to potency of antiviral regimens. RAVs maybe present at baseline in treatment-naive patients or may be treatment-emergent, as seen in patients with treatment failure. Treatment-emergent RAVs are noted with all DAA classes, most commonly with NS5A

Table 1 Drug–Drug Interactions Between HCV DAAs and Some Common Drugs.

	Sofosbuvir	Daclatasvir	Sofosbuvir plus ledipasvir
Immunosuppressants			
Azathioprine	No interaction	No interaction	No interaction
Cyclosporine	No interaction	No interaction	Potential interaction
Etanercept	No interaction	No interaction	No interaction
Everolimus	No interaction	Potential interaction	Potential interaction
Mycophenolate	No interaction	No interaction	No interaction
Sirolimus	No interaction	No interaction	Potential interaction
Tacrolimus	No interaction	No interaction	Potential interaction
Antiretrovirals			
Zidovudine	No interaction	No interaction	No interaction
Tenofovir	No interaction	No interaction	Potential interaction
Lamivudine	No interaction	No interaction	No interaction
Efavirenz	No interaction	Potential interaction	Potential interaction
Nevirapine	No interaction	Potential interaction	No interaction
Abacavir	No interaction	No interaction	No interaction
Didanosine	No interaction	No interaction	No interaction
Stavudine	No interaction	No interaction	No interaction
Lipid lowering drugs			
Statins	No interaction	Potential interaction	Potential interaction
Fibrates	No interaction	No interaction	No interaction
CNS drugs			
Antidepressants	No interaction	No interaction	No interaction
Antipsychotics	No interaction	No interaction	No interaction
CVS drugs			
Amiodarone	Severe interaction	Severe interaction	Severe interaction
Digoxin	No interaction	Potential interaction	Potential interaction
Flecainide	No interaction	No interaction	No interaction
Clopidogrel	No interaction	Potential interaction	No interaction
Dabigatran	No interaction	Potential interaction	Potential interaction
Beta-blockers	No interaction	No interaction	No interaction
Amlodipine	No interaction	Potential interaction	Potential interaction
Diltiazem	No interaction	Potential interaction	Potential interaction
Nifedipine	No interaction	Potential interaction	No interaction
Enalapril	No interaction	No interaction	No interaction

inhibitors (NS5A-I) but only rarely with NS5B inhibitors (NS5B-I), especially nucleoside inhibitors like SOF. Libraries of RAVs have been accumulated by identifying substitutions observed in variants isolated and sequenced from treated patients who experienced on- or post-treatment virologic failure.[26] Most RAVs are quickly lost in the absence of DAAs and detection of RAVs does not necessarily preclude successful treatment, especially with SOF.[28] Treatment-emergent RAVs induced by NS3-4A protease inhibitors (NS3-4A PIs) have low replication efficiency and disappear over 9 to 18 months; however, NS5A-I treatment-emergent RAVs are persistent, being detected up to 2 years or more after end-of-therapy, and pose a clinical challenge when planning re-treatment with regimens including DCV or LDV.[4] RAV testing is not indicated in treatment-naive patients as its utility is not established and it is not commercially available. More data are required to establish whether testing for NS5A-I RAVs before planning retreatment improves the choice of regimen and provides any therapeutic benefit.

Important NS5A-I and NS5B-I RAVs

NS3-4A PI-associated RAVs are not discussed, since this class of drugs is not marketed in India yet.

NS5A-I-Associated RAVs

Daclatasvir: Data are available mainly regarding GT-1 and GT-4 RAVs; information about GT-3-related RAVs with DCV is very scarce. In GT-1a-infected patients who did not achieve SVR, NS5A amino acid substitutions most commonly observed were M28T, Q30E/H/R, L31M, H58D, and Y93H/N. Among patients infected with GT-1b who failed to achieve SVR, substitutions most commonly observed were L31M/V and Y93H, while in GT-4-infected patients it was Q30H/S.

Ledipasvir: Q30E/R, L31M, and Y93C/H/N were the substitutions most commonly observed in GT-1a-infected patients who did not achieve SVR, while in GT-1b-infected patients it was Y93H.

The most troublesome NS5A-I RAVs are those linked with GT-1a, and to the Y93 position, they have been shown to confer over 14,000-fold resistance to DCV and LDV in replicon models. Other difficult RAVs, which confer >100-fold resistance, are M 28, Q30, L31, and H58 substitutions, alone or in conjunction with Y93 substitutions.[26]

Retreatment of Patients with NS5A-I RAVs

Lower SVR rates have been reported in GT-1 patients with RAVs compared with those without RAVs following retreatment with SOF/LDV for 24 weeks in those who relapsed after SOF/LDV for 8–12 weeks. Options for retreatment are limited and consist of extending duration of therapy from 12 to 24 weeks, adding RBV or including Peg-IFNα in the retreatment regimen. Successful retreatment has been reported with all these strategies in preliminary studies.[29]

NS5B-I RAVs

Sofosbuvir: The S282T substitution was first reported in a patient with GT-2 infection who received SOF monotherapy. The S282T variant was found to be replication unfit and the infection was easily cured with SOF/RBV for 12 weeks. Treatment-emergent L159F and V321A RAVs have been reported in GT-3 patients who failed to achieve SVR; however, these variants conferred only a 1.2- to 1.6-fold increased resistance to SOF in vitro, which may not be sufficient to confer virologic resistance in vivo. Further investigations are underway. Baseline C316N/H/F variants have been reported in six patients infected with GT 1b who experienced treatment failure and in one GT-1a patient who experienced relapse while on treatment; however, more studies are needed to assess role of this substitution in resistance to SOF.[26]

Results of Sofosbuvir and Ribavirin Therapy in Management of Chronic Hepatitis C

Genotype 1

There are limited data to recommend the use of SOF and RBV therapy for GT- 1. Six trials have addressed the issue of SOF and RBV therapy, with or without Peg-IFNα, in the management of GT- 1. These include the NIH SPARE, [30] ELECTRON,[31] NEUTRINO,[19] QUANTUM,[32] ATOMIC,[33] and PROTON[34] trials. All the trials enrolled treatment-naive patients of GT-1, except for the one arm of treatment-experienced GT-1 patients in the ELECTRON trial (n = 10). Data of use of SOF and RBV used alone without Peg-IFNα are available from the NIH SPARE, ELECTRON, and the QUANTUM trials.

Treatment-naive genotype 1: The NIH SPARE trial exclusively studied the role of non-Peg-IFNα-based regime of SOF and RBV in GT-1 patients. In the NIH SPARE trial, Osinusi et al.[30] evaluated the role of SOF and RBV in 60 treatment-naive patients with HCV GT-1 with unfavorable characteristics (e.g. African American race and advanced fibrosis). In the proof-of-concept part of the study, 9/10 (90%) patients with early-to-moderate liver fibrosis treated with SOF (400 mg daily) plus weight-based RBV for 24 weeks achieved SVR. In part 2 of the trial, 50 patients with all stages of liver fibrosis were randomized to receive 400 mg SOF with either weight-based RBV or low-dose RBV (600 mg daily) for 24 weeks. However, results of the study were dismal. SVR24 was seen in only 68% (17/25) in the weight-based RBV group and 48% (12/25) in the low-dose RBV group.

The ELECTRON study included both treatment-naive (n = 25) and treatment-experienced (n = 10) patients with chronic HCV GT-1 who were treated with SOF and RBV for 12 weeks. SVR was achieved in 84% (21/25) of treatment-naive patients.[31]

However, in the QUANTUM study, which included 38 treatment-naive HCV GT-1 patients randomized into 12 or 24 weeks of treatment with SOF and RBV, the response rate was only 50%, with 53% (10/19) in the 12-week arm and 47% (9/19) in the 24-week arm achieving SVR.[32]

Treatment-experienced genotype 1: In the ELECTRON trial, unlike in treatment-naive patients, results of SOF and RBV therapy were dismal in treatment-experienced patients, with only 10% (1/10) achieving SVR. [31]

Genotype 1 with advanced fibrosis and cirrhosis: In the NIH SPARE trial, 7 of the 13 participants (54%) with advanced liver fibrosis treated in this study relapsed including all 4 patients with cirrhosis.[30]

SOF used as a single DAA along with RBV has poor results for GT-1 HCV infection. The results of SOF and RBV therapy in prior treatment failures and in cirrhotics are even worse. Considering the excellent treatment response of regimens combining DAAs, it is no surprise that the current guidelines do not recommend use of the SOF/RBV combination in the treatment of GT-1 CH-C.

Genotypes 2

Across all trials, SOF and RBV therapy has resulted in excellent SVR rates in GT-2. In the FISSION trial, SVR rate

was 97% in among treatment-naive GT-2 patients, being similar in those with [91% (10/11)] and without cirrhosis [98% (58/59)].[19]

In the POSITRON trial, SVR rate was 93% (101/109) among IFN-unwilling, ineligible, or intolerant GT-2 patients.[35] In the FUSION trial, among treatment-experienced GT-2 patients, SVR rates were better, with 16 weeks of therapy (94%) than after 12 weeks (86%). This was also the case in GT- 2 patients with cirrhosis; SVR rates were better after 16 weeks of therapy (78%; 7/9) than after 12 weeks (60%; 6/10). This observation indicated that cirrhotic patients might need therapy for more than 12 weeks.[35]

In the VALENCE trial, among patients with GT- 2 HCV treated for 12 weeks with SOF and RBV, SVR rate was 93% (68/73), being 94% (59/63) without and 82% (9/11) with cirrhosis. According to treatment experience, SVR rate was 97% (29/30) in treatment-naive noncirrhotic patients, 100% (2/2) in treatment-naive cirrhotic patients, 91% (30/33) in treatment-experienced noncirrhotic patients, and 88% (7/8) in treatment-experienced cirrhotic patients.[36]

The BOSON study has reinforced these results. In a cohort of 32 treatment-experienced GT-2 cirrhotic patients, SVR rates were 87% (13/15) after 16 weeks of SOF/RBV therapy and 100% (17/17) after 24 weeks.[37]

Genotype 3

The main evidence of SOF and RBV therapy in GT-3 has come from the FISSION,[19] (treatment-naive HCV, interferon-eligible), POSITRON[35] (treatment-naive and treatment-experienced HCV, people who were ineligible for interferon or intolerant to it or unwilling to have it), FUSION[35](treatment-experienced HCV), the VALENCE[28] (treatment-naive and treatment-experienced)], an arm in the ELECTRON trial,[31] and the BOSON trial.[37]

Treatment-naive genotype 3: The FISSION trial compared results of 12 weeks of SOF and RBV therapy with that of 24 weeks Peg-IFNα and RBV in treatment-naive HCV patients. The SVR in GT-3 patients was 53% with SOF and RBV therapy, which were much lower than that for GT-2 (SVR 97%).[19]

The POSITRON trial included treatment-naive patients who would not or could not take Peg-IFNα. SVR rate of 12 weeks of SOF and RBV therapy in GT-3 was 61% (101/109).[35]

The VALENCE trial was initially started with 12 weeks of SOF and RBV therapy for GT-2 and 3 HCV. On the basis of emerging data from phase-3 trials indicating that patients with HCV GT-3 infection had higher response rates when they were treated for 16 weeks, as compared with 12 weeks, the study was unblinded and treatment for all patients with genotype 3 infection was extended to 24 weeks. The SVR rate with 24 weeks of therapy for GT-3 in treatment-naive HCV patients was 94%, while that for 12 weeks of therapy was only 27%.[36]

Treatment-experienced genotype 3: The FUSION trial was designed to assess the benefit of extending duration of treatment in patients who had failed previous therapy. This phase-3 trial compared SOF/RBV for 12 weeks with SOF/RBV for 16 weeks in treatment-experienced patients with GT-2 or 3 HCV infection. Only 19 of 64 (30%) GT-3 patients achieved an SVR12 with SOF/RBV for 12 weeks, which improved to 39/63 (62%) in the 16-week group. [35]

The phase-3 VALENCE trial included 419 patients (261 with GT-3) and explored results of extending treatment with SOF/RBV to 24 weeks in GT-3 patients. There was improvement in SVR 12 rates in the treatment-experienced noncirrhotic patients (87%). This study has established the paradigm that GT-3 patients need 24 weeks of SOF/RBV.[36]

Genotype 3 with cirrhosis: The SVR rates of 12-week therapy with SOF and RBV therapy in HCV-related cirrhosis in the FISSION and POSITRON trials were 47% and 21%, respectively. [19,35] In the FUSION trial, the SVR rate in cirrhotics with 12-week therapy was 61%, while that with 16-week therapy was 85%. [35] In the VALENCE trial, the SVR rates were 91% and 68% among those without and those with cirrhosis, respectively. [36] These data show that even 24 weeks of therapy with SOF/RBV is suboptimal in patients with liver cirrhosis.

Genotypes 4, 5, and 6

In the Egyptian ancestry trial, Ruane et al.[38] enrolled 30 treatment-naive and 30 previously treated GT- 4 patients who were treated for 12 weeks (n = 31) or 24 weeks (n = 29) with SOF and RBV. SVR12 was achieved in 68% of patients in the 12-week group and in 93% of patients in the 24-week group. Doss et al.[39] have also reported their results in 103 treatment-naive or -experienced HCV GT 4 Egyptian patients. SVR12 rates were 90% (46/51) with 24 weeks and 77% (40/52) with 12 weeks of SOF and RBV therapy. Patients with cirrhosis at baseline had lower rates of SVR12 (63% for 12 weeks and 78% for 24 weeks) than those without cirrhosis (80% for 12 weeks and 93% for 24 weeks). Data on GT- 5 and 6 are scarce.

Results of Peg-IFNα with Sofosbuvir and RBV in Management of Chronic Hepatitis C

Genotype 1

Treatment-naive patients: The PROTON,[34] ATOMIC,[33] and NEUTRINO[19] trials showed that adding SOF to standard Peg-IFNα/RBV therapy in treatment-naive patients improved SVR rates in GT-1 CH-C.

In the ATOMIC trial, 316 GT-1 patients were randomized to receive SOF 400 mg plus Peg-IFNα/RBV for 12 weeks or 24 weeks or for 12 weeks followed by 12 weeks of either SOF monotherapy or SOF plus RBV. The SVR rates in all three cohorts ranged from 87% to 89%.[33]

In the NEUTRINO, treatment-naive GT-1, 4, 5, and 6 patients were treated for 12 weeks with SOF plus

Peg-IFNα/RBV. Among GT-1 patients, the overall SVR12 was 89% (259/291); it was 92% (207/225) for subtype 1a and 82% (54/66) for subtype 1b.[19]

The PROTON trial is the only trial in which the duration of therapy was guided by the patient response. In this trial, 122 patients with HCV GT-1 were randomized to receive SOF 400 mg or 200 mg for 12 weeks plus Peg-IFNα/RBV for 24 or 48 weeks (response-guided) or placebo for 12 weeks plus Peg-IFNα/RBV for 48 weeks. The SVR rates were 91% and 90%, respectively in the SOF cohorts.[34]

Treatment-naive cirrhosis: In the NEUTRINO study, presence of cirrhosis was associated with significantly reduced SVR rates (80% vs. 92%).[19]

In another study, Pearlman et al.[40] have evaluated the results of 12 weeks of SOF plus Peg-IFNα/RBV compared to SOF and simeprevir therapy in GT-1a HCV-related Child A cirrhotics. Though lower than the results in the SOF/simeprevir cohort, SVR rate was a respectable 75% with SOF/Peg-IFNα/RBV in this difficult-to-treat group.

Treatment-experienced patients: US Food and Drug Administration had predicted that 78% of patients who failed previous therapy with Peg-IFNα/RBV would achieve an SVR with the triple combination of Peg-IFNα/RBV and SOF.[41]

Some information on the treatment-experienced subset of GT-1 CH-C patients is available from the initial results of this regimen reported in two large US real-life cohorts, the HCV TARGET 2.0[42] and the TRIO study.[43] In HCV TARGET 2.0, SVR4 was 85% (140/164; 55% in treatment-naive and 45% in treatment-experienced) and was higher among noncirrhotics (90%; 114/127) than in patients with cirrhosis (70%; 26/37). [42] In the TRIO real-life study, SVR12 was 81% among treatment-naive patients and was similar among noncirrhotics (81%; 112/138) and cirrhotics (81%; 25/31). However, among treatment-experienced patients, SVR12 was achieved in 77% (30/39) without cirrhosis but in only 62% (53/85) with cirrhosis.[43]

Genotype 2

The excellent results of SOF/RBV therapy in treatment-naive GT-2 patients leave little role for addition of Peg-IFNα in this subgroup. The BOSON study has evaluated the role of treatment-experienced patients with cirrhosis and HCV GT-2 infection. Rates of SVR12 among patients with GT-2 HCV were 87% and 100%, for those receiving 16 and 24 weeks of SOF/RBV, respectively, and 94% for those receiving SOF and Peg-IFNα/RBV for 12 weeks.[37]

Genotype 3

The triple regimen of SOF plus Peg-IFNα/RBV has been shown to have a response rate of 90–100% of treatment-naive patients with GT-3 CH-C in PROTON and ELECTRON trials. Moreover, in LONESTAR 2 trial, this combination has been shown to have 83% SVR rate in treatment-experienced patients with similar results in cirrhotics.[44] Esteban et al.[45] have shown that patients who do not achieve SVR with SOF and RBV therapy achieved SVR in 91% (20/22) of cases after this triple-therapy regimen.

The BOSON study re-emphasized the role of triple therapy of SOF plus Peg-IFNα/RBV. The BOSON trial included 279 treatment-naive and 265 treatment-experienced patients with HCV GT-3 infection who were randomly assigned to groups given SOF/RBV for 16 weeks, SOF/RBV for 24 weeks, or SOF with Peg-IFNα/RBV for 12 weeks. Rates of SVR12 among patients with GT-3 HCV were 71% and 84% in those receiving 16 and 24 weeks of SOF and RBV, respectively, and 93% in those receiving SOF with Peg-IFNα/RBV.[37]

The EASL guidelines give the option of triple therapy with SOF and Peg-IFNα/RBV in GT-3 especially mentioning its value in cirrhotics and treatment failures.[2] The AASLD guidelines recommend SOF and Peg-IFNα/RBV therapy for 12 weeks as one of the first-line regimen in HCV GT-3.[1]

Results of Ledipasvir and Sofosbuvir Therapy in Management of Chronic Hepatitis C

LDV is a NS5A inhibitor, which is available as a fixed-dose combination of 90 mg LDV along with 400 mg SOF. The recommended dose is 1 tablet daily. This combination is marketed for treatment of GT-1, 3, and 4 only.

Genotype 1

The phase-3 trials of role of LDV/SOF in HCV GT-1 include the ION-1, ION-2, and ION-3 trials. The ION-1 trial[46] (865 treatment-naive GT-1 patients including cirrhotics) evaluated 12- vs. 24-week therapies and the need for RBV with LDV/SOF treatment. SVR12 was 97–99% across all arms, irrespective of cirrhosis, RBV administration, or duration of therapy.

The ION 2-study[47] evaluated the role of LDV/SOF (12 weeks or 24 weeks, with or without RBV) in nonresponders to prior Peg-IFNα/RBV therapy. In noncirrhotics, SVR was 98%. In cirrhotics, SVR was 94% with LDV/SOF alone, and 100% after treatment with LDV/SOF and RBV. In the cirrhotics, higher SVR rates were achieved with 24-week therapy compared to 12-week therapy. This study established the role of 12 weeks of treatment, with 24 weeks of treatment without RBV in treatment-experienced HCV patients with cirrhosis.

The ION-3 study[48] (647 treatment-naive noncirrhotic patients) evaluated the role of further shortening the duration of LDV/SOF therapy (12 weeks vs. 8 weeks, with or without RBV), while SVR rates were 93 to 95% across all arms. However, for patients with HCV RNA of more than 6 million international Units (IU)/ml, relapse rates were higher with 8-week therapy compared to 12-week therapy in the RBV free arms.

Reddy et al.[49] have evaluated the role of LDV/SOF, with and without RBV for 12 or 24 weeks in 513 treatment-naive

and treatment-experienced patients with GT-1 HCV and compensated cirrhosis. SVR12 rates did not vary greatly with treatment duration (95% of patients receiving 12 weeks and 98% of patients receiving 24 weeks of treatment), or with addition of RBV (95% of patients receiving LDV/SOF alone and 97% of those who received LDV/SOF plus RBV). However, previously treated patients receiving 12 weeks of LDV/SOF without RBV had an SVR12 rate of 90%. The relatively lower SVR in treatment-experienced patients treated with 12 weeks of LDV/SOF raises the question of whether these patients would benefit from adding RBV or extending treatment duration to 24 weeks.

Genotype 3

There are limited data on the efficacy of LDV/SOF therapy in HCV GT-3. Gane et al.[50] evaluated the efficacy of LDV/SOF regimens with or without RBV for 12 weeks in GT-3 and 6 patients. The treatment-naive patients were randomized to receive LDV/SOF with or without RBV for 12 weeks, whereas the treatment-experienced patients were treated with LDV/SOF and RBV for 12 weeks. In patients treated with LDV/SOF and RBV, SVR12 rates were 100% and 82% in treatment-naive and -experienced patients, respectively. However, in the treatment-naive individuals treated with LDV/SOF without RBV, SVR rates were only 64%. These data suggest that RBV cannot be omitted from regimen containing LDV/SOF without a considerable loss of efficacy.[51] The data available on use of LDV/SOF in GT-3 are however limited and this regimen cannot be recommended until further data are available.

Genotype 4

The role of LDV/SOF combination in HCV GT-4 has been established by Abergel et al.[52] and the SYNERGY trial,[53] both of which reported SVR12 of 95% with 12 weeks of LDV/SOF therapy.

Results of Daclatasvir and Sofosbuvir Therapy in Management of Chronic Hepatitis C

DCV is an NS5A inhibitor, which is administered in a standard oral dose of 60 mg/day. It is currently recommended in combination with SOF (with or without RBV) or Peg-IFNα/RBV.

Genotype 1

Sulkowski et al.[54] evaluated the role of DCV/SOF with or without RBV in HCV in the AI444-040 trial. In part 1 of the trial, 88 treatment-naive patients (44 with GT-1 and 44 with GT-2 or 3) were treated with DCV/SOF, with or without weight-based RBV for 24 weeks. The study was later expanded (part 2) to include an additional 123 patients with GT-1 who were randomly assigned to a therapy with DCV/SOF, with or without RBV for 12 weeks (for 82 treatment-naive patients) or 24 weeks (for 41 who had prior treatment failure with telaprevir or boceprevir-based regimens). Among patients with GT-1 infection, 98% of previously untreated patients (n = 126) and 98% of previous nonresponders to HCV protease inhibitors (n = 41) had SVR after the end-of-therapy.

In the COMMAND-1 trial,[55] treatment-naive HCV GT-1 and 4 patients were treated with DCV (or placebo) plus Peg-IFNα/RBV. The study design consisted of three arms: Peg-IFNα/RBV plus DCV 20 mg, DCV 60 mg, or placebo. The SVR12 rates were 65% in the DCV 20 mg arm (95/147), 90% in the 60 mg arm (88/146), and 36% (26/72) in the placebo arm.

The ALLY-2 trial[23] assessed the role of DCV/SOF in HCV/HIV coinfection. Treatment-naive patients were randomly assigned to receive either 12 weeks or 8 weeks of DCV/SOF therapy, while previously treated patients were treated for 12 weeks. SVR was seen in 96.4% who were treated for 12 weeks and in 75.6% who were treated for 8 weeks in treatment-naive patients and in 97.7% who were treated for 12 weeks among previously treated patients.

Genotype 2

High SVR rates have been reported with DCV/SOF for 12 and 24 weeks in GT-2 HCV.[23,54] While SOF/RBV therapy has excellent efficacy in HCV GT-2, many patients may not be able to tolerate RBV. These patients may benefit from combination therapy with DCV and SOF. Mangia et al.[56] showed the efficacy of DCV/SOF therapy in RBV-intolerant patients. Their study supports the use of DCV/SOF therapy for 12 weeks in noncirrhotics or 24 weeks in cirrhotic GT- 2 patients who cannot tolerate RBV, including those with decompensated disease.

Genotype 3

The recommendation for use of DCV/SOF in HCV GT-3 is based on the ALLY-3 study,[57] which included treatment-naive (n = 101) and treatment-experienced (n = 51) patients, who were treated with DCV/SOF therapy for 12 weeks. SVR12 rates were 90% (91 of 101) and 86% (44 of 51) in treatment-naive and treatment-experienced patients, respectively. SVR12 rates were higher in patients without cirrhosis (96%) than in those with cirrhosis (63%).

Genotype 4

In the Command-4 trial,[58] GT-4 patients were treated with DCV (or placebo) plus Peg-IFNα/RBV. The treatment arm had a response-guided strategy and treatment was stopped at 24 weeks if HCV RNA was undetectable at weeks 4 and 12 (79% of the DCV arm); the remainder and the placebo arm received 48 weeks of Peg-IFNα/RBV. The SVR12 rates were 82% for the DCV arm versus 43% for the placebo arm.

THERAPY OF CHRONIC HEPATITIS C IN INDIA

Except for SOF, DCV, and LDV, the other DAA recommended by the AASLD[1] and EASL[3] guidelines are not

available in India. Hence, these guidelines are not applicable to the Indian scenario. The predominance of GT-3 is another issue to be considered in the management of HCV in India.

Indications for Therapy

All patients with active HCV infection who have evidence of viral replication and no contraindications to therapy should be considered for treatment. Patients in urgent need of treatment are those with advanced fibrosis (Fibrosis score F3 or F4) or significant extrahepatic manifestations (symptomatic cryoglobulinemia or HCV immune complexes nephropathy). Antiviral treatment decision for patients with HCV infection should not be based only on alanine aminotransferase (ALT) values, as significant liver disease may exist even in patients with persistently normal ALT.[59]

Patients with CHC fall into standard categories, based on presence or absence of cirrhosis and previous treatment status, or into special categories, which need separate discussion. Standard categories include either treatment-naive patients or treatment-experienced patients, who may be with and without liver cirrhosis. The special categories include coinfections with HIV or HBV, dual etiologies like obesity/nonalcoholic fatty liver disease, and immune-compromised patients like postliver transplant, postrenal transplant, and miscellaneous category like renal failure or thalassemia. Since the efficacy of treatment regimen differs in these different categories, assessment for presence or absence of liver cirrhosis plays a major role in predicting outcome of therapy for CHC.

Contraindication to Peg-IFNα/RBV or DAA Therapy

Absolute contraindications to Peg-IFNα therapy include decompensated liver disease [Child-Turcotte Pugh (CTP) score ≥7], uncontrolled depression, psychosis, epilepsy, uncontrolled autoimmune disease including retinal disease and autoimmune thyroid disease, pregnancy or planning pregnancy, and severe concurrent medical disease like poorly controlled hypertension, diabetes mellitus, heart failure, and chronic obstructive pulmonary disease.

Relative contraindications to Peg-IFNα therapy include abnormal hematological parameters (Hb < 10.0 gm/dl, baseline neutrophil count <1500/μL, or a baseline platelet count <90,000/μL); serum creatinine >1.5 mg/dl; significant coronary artery disease and untreated thyroid disease; previous intolerance or hypersensitivity to IFNα and age >70 years. Therapy can be individualized on case-to-case basis in elderly patients.

SOF therapy is contraindicated in patients with severe renal impairment [estimated glomerular filtration rate (eGFR) <30 mL/min]. Drug interactions with DAA especially with highly active antiretroviral therapy (HAART) may be a contraindication to use of specific DAA.

Monitoring During Treatment

Monitoring during treatment is aimed at the following: (i) monitoring for treatment efficacy and (ii) monitoring for adverse effects of treatment.

Patients on Peg-IFNα/RBV therapy are followed at 2 weeks and subsequently every 4 weeks till completion of therapy. At each visit, patients should be assessed for assessment of side effects like flu-like symptoms, fatigue, depression, sleeping disorder, irritability, dyspnea, headache, and injection-site reaction. Patients should be assessed for infections, autoimmune reactions, hearing and visual disturbances, and interstitial lung disease. Need for contraception should be emphasized. Complete blood count should be done at 1, 2, and 4 weeks and every 4 weeks thereafter. Liver biochemistry and renal function should be done every 4 weeks. Thyroid function should be done every 12 weeks. HCV RNA testing should be done at baseline, at 4 weeks, at 12 weeks (end-of-treatment), and 12 weeks after the end-of-therapy.

Patients on DAA therapy with RBV should be monitored for anemia with hemoglobin testing every week for the first four weeks and then monthly till end-of-therapy. If hemoglobin drops, RBV dose may have to be modified as discussed earlier.

Patients on DAA therapy without Peg-IFN or RBV should be monitored every 4 weeks with hemogram and liver function tests. HCV RNA monitoring should be done at baseline, end-of-therapy, and 12 weeks after completion of therapy for SVR12. End-of-therapy testing should be optional, since it does not play a role in decision-making and suffers from the drawback that patients may think they are cured and there may be poor compliance with SVR12 testing. Hence the need for SVR12 testing should be emphasized to the patients. Patients on SOF should have monitoring of renal functions and patients on DAA should have monitoring for possible drug interactions.

Post-Treatment Follow-Up

Patients who achieve SVR12 can be retested for ALT and HCV RNA at 48 weeks post-treatment. Patients who are negative can be taken as cured. Thyroid function should be assessed after 1 year of therapy with Peg-IFNα/RBV. Patients with cirrhosis need surveillance for HCC and portal hypertension.

Treatment Recommendations for Chronic Hepatitis C

Management of Genotype 1

GT-1 has been more difficult to treat with poorer response to Peg-IFNα/RBV therapy. With availability of DAA in the Indian market, there is no role of Peg-IFNα/RBV therapy in GT-1. In GT-1 HCV-infected patients without cirrhosis, the recommended regimen, irrespective of GT-1a or 1b, is the fixed-dose formulation of SOF (400 mg) and LDV (90 mg) for 12 weeks or SOF (400 mg) and DCV

(60 mg) for 12 weeks. While either regimen can be used in patients without cirrhosis, for patients with cirrhosis, SOF and LDV for 12 weeks should be the preferable regimen.

There are inadequate data on the use of DCV and SOF in cirrhotic patients with GT-1, though the compassionate use program in Europe has shown that cirrhotic patients with GT-1 may benefit from extension of therapy to 24 weeks. In case the regimen of SOF and DCV is used, weight-based RBV (1000 mg if weight <75 kg and 1200 mg if >75 kg, as tolerated) should be added and the treatment duration should be increased to 24 weeks.

Management of Genotype 2

Considering the excellent response to SOF therapy in GT-2, the recommended therapy for GT- 2 is SOF plus RBV for 12 weeks. Use of SOF and DCV combination therapy should be reserved for patients who are intolerant to RBV. In patients with cirrhosis, therapy for GT-2 should be extended to 16 weeks.

Management of Genotype 3

As has been highlighted earlier, unlike GT-2, GT-3 is not really an "easy-to-treat" GT. The data from India had shown that the response rates to Peg-IFNα/RBV therapy in GT-3 may be lower than that reported for GT- 2/3 from the west.[60,61]

Patients with GT-3 should be treated either with SOF plus DCV for 12 weeks or the triple therapy of SOF plus Peg-IFNα/RBV for 12 weeks. SOF and weight-based RBV therapy should be recommended only in the unlikely event of a patient being unwilling/intolerant to DCV.

In patients with compensated cirrhosis, the first-line regimen should be SOF and DCV with weight-based RBV (1000 mg if weight <75 kg and 1200 mg if >75 kg, as tolerated) and the treatment duration should be increased to 24 weeks. The alternative regimen in this group is the triple-therapy regimen, SOF plus Peg-IFNα/RBV for 12 weeks. SOF and RBV without DCV or Peg-IFNα should not be recommended.

Management of Other Genotypes

There are recent reports of GT-4 from India. The preferred treatment option for GT-4 is SOF plus LDV for 12 weeks. The alternative regimens for this GT are SOF plus Peg-IFNα/RBV for 12 weeks or SOF plus weight-based RBV for 24 weeks.

GT-5 and 6 are rare in India and should be managed with SOF plus LDV for 12 weeks. An alternate regimen for this group is triple therapy with SOF plus Peg-IFNα/RBV.

GT wise recommendations for management of CH-C in India are given in Table 2.

Management of HCV in Special Situations

Decompensated Cirrhosis

The aim of treatment of hepatitis C in decompensated cirrhotic population is to: (a) eradicate circulating HCV by achieving SVR12, i.e., make the patient aviremic; (b) stabilize or improve liver function; (c) improve portal hypertension and prevent or mitigate sequelae such as HCC; (d) reverse decompensation such that liver transplant may be deferred or avoided; and (e) accomplish the above safely.

Peg-IFNα/RBV-based treatment regimen had poor tolerability and limited efficacy in patients with decompensated liver disease. SVR rates even when using a low accelerating dose IFNα regimen were around 25%.[62] Importantly, only a small fraction of the HCV-infected decompensated cirrhotics were eligible for IFNα-based therapy. Peg-IFNα/RBV could be given only to patients with patients with reasonable liver functions [CTP $\leq$ 7, Model for End-Stage Liver Disease (MELD $\leq$ 18)], or in patients with HCC with good liver functions awaiting liver transplantation (LT). In patients with more advanced disease, IFNα-based therapy can result in serious adverse events such as bacterial infections, cytopenias, and worsening decompensation. The arrival of DAA has made it possible to treat patients with decompensated cirrhosis using interferon-free regimens before and after LT. However, patients with decompensated cirrhosis may not tolerate DAAs, especially in the presence of impaired renal function.

Improvement in liver function, reversal of decompensation, and making the patient aviremic: Initial evidence for improvement in liver function in decompensated cirrhosis came from Afdhal,[63] who showed that 48 weeks treatment with SOF/RBV gave SVR12 rate of 72% and led to significant improvement in ascites, encephalopathy, CTP, and MELD scores in the majority. However, only Child's status A and B patients were included; there were no Child's C patients in this trial.

Efficacy of SOF/LDV in GT-1 or 4 HCV-related decompensated cirrhosis treated prior to liver transplantation has been evaluated in the SOLAR-1 and SOLAR-2 trials carried out in US and Europe, respectively. In the SOLAR-1 trial, 108 patients with HCV-related decompensated cirrhosis (59 CTP-B, 49 CTP-C) were randomized to receive 12 or 24 weeks of SOF/LDV/RBV. SVR12 was achieved in 86–89% patients; the rate was similar among patients with CTP class B and C regardless of duration of therapy. MELD as well as CTP scores improved in the majority of the patients in both arms, while bilirubin and albumin levels improved significantly in CTP B but not in CTP C patients. A number of patients showed improvement in control of ascites and grade of encephalopathy; one patient improved to the extent that he was delisted from transplant list. All but one patient in this study had MELD score less than 20; hence, these results should not be extrapolated to patients with high MELD scores.[64] In the SOLAR-2 study, which included 107 patients with decompensated cirrhosis treated before liver transplant, SVR12 was achieved in 87% in the 12-week treatment group and 89% in the 24-week treatment group.[65] These studies have shown that

Table 2 INASL Guidance for Treatment of Chronic Hepatitis C.

Genotype	Scenario	Treatment regimen
1	Recommended regimen for genotype 1a or 1b	• SOF (400 mg) + LDV (90 mg) × 12 weeks • SOF (400 mg) + DCV (60 mg) × 12 weeks
	For patients with cirrhosis	• SOF (400 mg) + LDV (90 mg) × 24 weeks • SOF (400 mg) + LDV (90 mg) + weight-based RBV[a] for 12 weeks • SOF (400 mg) + DCV (60 mg) × 24 weeks • SOF (400 mg) + DCV (60 mg) + weight-based RBV[a] for 12 weeks
2	Recommended regimen	• SOF (400 mg) + weight-based RBV × 12 weeks
	Alternative regimen for RBV-intolerant patients	• SOF (400 mg) + DCV (60 mg) × 12 weeks
	For patients with cirrhosis	• Increase treatment duration to 16 weeks
	Alternative regimen in cirrhotics	• SOF (400 mg) + DCV (60 mg) × 12 weeks
3	Recommended regimen	• SOF (400 mg) + DCV (60 mg) × 12 weeks • SOF (400 mg) + weight based[a] RBV × 24 weeks
	For patients with cirrhosis	• SOF (400 mg) + DCV (60 mg) + weight based[a] RBV × 24 weeks
	Alternative regimen in compensated cirrhotics	• SOF (400 mg) + Peg-IFNα weekly + weight based[a] RBV × 12 weeks
4	Recommended regimen	• SOF (400 mg) + LDV (90 mg) × 12 weeks
	Alternative regimen	• SOF (400 mg) + Peg-IFNα weekly + weight based[a] RBV × 12 weeks • SOF (400 mg) + weight based[a] RBV × 24 weeks
	For patients with cirrhosis	• SOF (400 mg) + LDV (90 mg) × 24 weeks • SOF (400 mg) + LDV (90 mg) + weight-based RBV[a] for 12 weeks
5 & 6	Recommended regimen	• SOF (400 mg) + LDV (90 mg) × 12 weeks
	Alternative regimen	• SOF (400 mg) + Peg-IFNα weekly + weight based RBV[a] × 12 weeks
	For patients with cirrhosis	• SOF (400 mg) + LDV (90 mg) × 24 weeks • SOF (400 mg) + LDV (90 mg) + weight-based RBV[a] for 12 weeks

DCV, daclatasvir; LDV, ledipasvir; Peg-IFNα, pegylated interferonα; RBV, ribavirin; SOF, sofosbuvir.
[a]Weight-based RBV (1000 mg if weight <75 kg and 1200 mg if >75 kg, as tolerated).

SVR12 rates were comparable for 12 or 24 weeks of therapy with SOF/LDV/RBV.

Similar data were recently published by Foster et al. (NHS England Expanded Access Program). When SOF in combination with either LDV or DCV with or without RBV was given to 467 patients with decompensated cirrhosis (CTP score ≥ 7), SVR 12 was obtained in 91% (209 of 231) of GT-1 patients but in only 69% (132 of 192) of GT-3 patients. SOF/LDV/RBV regimen fared better in GT-1 patients, while SOF/DCV/RBV regimen did better in GT-3 patients, though statistical significance was not reached in either case. Use of RBV increased SVR rates in both regimens. On multivariate analysis, baseline factors predicting virologic failure included GT-3, BMI > 30 kg/m^2, and detectable HCV RNA at week 2 of therapy. Overall, adverse outcomes were more common in patients with a higher baseline MELD score, low serum albumin (<3.5 gm/dl), higher age (>65 years), and low serum sodium values (<135 mEq/L).[66]

The recent open-label ALLY-1 study also reported better results in GT-1 than in GT-3 among 60 decompensated HCV cirrhotic patients (76% GT-1; 20% CTP-A, 53% CTP-B, and 27% CTP-C) treated with SOF/DCV/RBV for 12 weeks. SVR12 rate was higher in CTP-B (30/32; 94%) than in CTP-C patients (9/16; 56%). As in most trials studying decompensated cirrhotics, the initial dose of RBV was 600 mg/day, and this was gradually escalated up to 1000 mg/day based on creatinine clearance values, as well as the hemoglobin values.[67]

In the French early access program (EAP), SOF and DCV, with or without RBV, were given for 12 or 24 weeks. For SOF/DCV, SVR rate was higher in patients treated for 24 weeks rather than 12 weeks. Extending treatment to 24 weeks and use of RBV were both significantly associated with SVR, whereas cirrhosis emerged as the main predictor for treatment failure.[68] These data reinforce the need for addition of RBV in the DCV and SOF regimen. For cirrhotic patients, treatment should be extended to 24 weeks and/or RBV should be added to the 12-week treatment regimen.

Improvement in portal hypertension: Evidence for the improvement of PH is preliminary. The effect on portal pressure of curing HCV infection in patients with HCV-related cirrhosis has been reported in two trials. Afdhal enrolled 50 patients with baseline HVPG >6 mm Hg who were treated with SOF and RBV for 48 weeks; 33 of these had HVPG ≥12 mm Hg at baseline and a paired HVPG

after treatment. Eight patients (24%) had a >20% fall in HVPG, in 4 of whom it dropped to a value of <12 mm Hg.[63] Mandorfer et al.[69] studied 56 patients with cirrhosis in whom HVPG was measured before starting treatment with SOF with RBV or DCV or SMV (simeprevir) for 12–24 weeks. Forty-one (73%) of these patients had a baseline HVPG >10 mm Hg. However, post-treatment HVPG levels were not reported; instead, this study reported an improvement in liver stiffness and platelet counts as surrogate markers for improvement in portal pressure.

While regression of advanced F4 fibrosis and even histological cirrhosis has been documented in CH-C after SVR, reversal of advanced cirrhosis with distortion of microvasculature and portal hypertension has not been documented so far and appears unlikely.[70] Further studies are required to show whether HCV eradication is effective to such an extent that patients can be removed from the waiting list. However, currently available data of delisting from the LT list are scarce.[71]

Pretransplant treatment of HCV infection: While treatment of HCV in patients listed for transplant had been shown to prevent or decrease HCV recurrence after transplant, even in the pre-DAA era, the advent of DAAs has greatly simplified treatment of HCV of patients listed for liver transplant. Curry et al.[72] demonstrated that SOF and RBV given before LT resulted in good post-transplant virological response (PTVR) and prevented HCV recurrence. They evaluated 61 patients with HCV-related cirrhosis and HCC, predominantly GT-1 or 4, who received SOF/RBV for up to 48 weeks before LT. In this study, 75% of the patients were CTP grade A and in all cases MELD score was <15. HCV RNA was undetectable at the time of LT in 43 of 46 (90%) undergoing LT and remained undetectable at 12 weeks after liver transplantation (PTVR12) in 70% (30/43) cases, indicating an absence of hepatitis C recurrence. Recurrence related inversely to period for which HCV RNA had remained undetectable before LT. Patients in whom HCV RNA had been undetectable for >30 days before LT had 95% chance of achieving PTVR12.

Safety: Safety issues have been addressed in SOLAR-1 and 2 trials as well as NHS EAP study group.[64–66] In the SOLAR-1 and 2 trials, the most common grade 3/4 adverse effects seen in the decompensated patients were an increase in serum bilirubin and a decrease in lymphocyte count. In the SOLAR-1 trial, anemia was noted in 39% who dropped their hemoglobin values to less than 10 gm/dl; in 13%, it dropped to below 8.5 gm/dl. Blood transfusion or erythropoietin was used in 15% of the cases in this trial. Thirteen patients in the SOLAR-1 trial (6 in the pre-LT cohort) and 17 in SOLAR-2 (5 in pre-LT cohort) died, primarily due to worsening of hepatic decompensation, sepsis, and multiorgan dysfunction syndrome (MODS).

In the NHS EAP study, 6% of the patients discontinued treatment due to adverse effects, while seven patients died during the course of the trial. A hemoglobin value of <8 gm/dl was seen in 5% of the cases. Acute kidney injury, defined by an increase in serum creatinine value by 1.5 times from baseline value was seen in 3% cases.[66]

Recommendations

1. SOF-based regimens are safe to use in decompensated cirrhosis patients with MELD ≤20. Currently, data are insufficient to recommend the use of these drugs in patients with high MELD scores [MELD > 20], especially in those likely to undergo LT.
2. Patients with HCV-related decompensated cirrhosis with MELD <21 should be treated with SOF-based regimens while waiting for LT.
3. Patients on DDLT waiting list should be put on treatment while waiting, but they should receive the transplant as soon as an organ is available, irrespective of the viral status of patient at that time, in view of high SVR rates with treatment after transplant. Even after becoming aviremic, there may not be a significant improvement in their liver disease severity scores, so they should remain active on LT list.
4. Patients who have a living donor LT option available should be initiated on antiviral treatment at centers with the expertise to treat these patients. Some of these patients may improve significantly and come off the LT waitlist. Should the patient deteriorate, urgent LT can be offered.

The recommended treatment regimens for patients with decompensated cirrhosis are shown in Table 3.

Management of HCV Infection After Liver Transplant (LT)

Post-transplantation HCV recurrence is universal and graftreinfection can lead to graft fibrosis, cirrhosis, and decompensation. Successful therapy has been shown to have a positive impact on both graft and patient survival.[73] As compared to the nontransplant population, HCV disease progression post-transplantation is accelerated. The response rate to antiviral therapy with Peg-IFNα with or without RBV is lower in the transplant population.[74–76] Also post-transplant patients have relatively more side effects and poor tolerance to combination antivirals. The arrival of DAA allows IFNα-free treatment regimen in HCV-infected liver transplant recipients (LTR). Encouraging initial results were reported with the SOF/RBV combination, while more recently, excellent results have been noted with combination DAA therapy.

Charlton et al.[77] have shown that SOF and RBV combination therapy for 24 weeks is an effective and well-tolerated interferon-free treatment for post-transplantation HCV infection. They treated 40 patients of postliver transplant HCV with SOF and RBV for 24 weeks. The HCV GT was 1 in 85% and bridging fibrosis/cirrhosis was present in 63%. They found an SVR12 of 70%. The beneficial effect of SOF and RBV therapy in postliver transplant scenario has also been demonstrated in other studies.[42,78]

In the SOLAR-1 study, SOF/LDV/RBV for 12 or 24 weeks was evaluated in 223 LTRs.[64] These predominantly GT-1 patients included 50% (n = 111) with METAVIR score of F0-3, 23% (n = 51) with CPT-A cirrhosis, 23% (n = 52)

Table 3 Recommended HCV Treatment Regimen for Patients with Decompensated Cirrhosis.

Genotype	Recommended regimen
1 & 4	• SOF + LDV + RBV (initial dose of 600 mg, increased as tolerated) × 12 weeks • SOF + DCV + RBV (initial dose of 600 mg, increased as tolerated) × 12 weeks **Alternative regimen for RBV-intolerant patients** • SOF + DCV × 24 weeks • SOF + LDV × 12 weeks
2	• SOF + DCV + RBV (initial dose of 600 mg, increased as tolerated) × 12 weeks
3	• SOF + DCV + RBV (initial dose of 600 mg, increased as tolerated) × 24 weeks **Alternative regimen** • SOF + RBV (initial dose of 600 mg, increased as tolerated) for up to 48 weeks

DCV, daclatasvir (60 mg); LDV, ledipasvir (90 mg); RBV, Ribavirin; SOF, sofosbuvir

with CPT-B cirrhosis, and 4% (n = 9) with CPT-C cirrhosis. SVR12 was achieved in 96% of patients with F0-3 fibrosis, 96% with CPT A cirrhosis, and 81% with CPT B and C cirrhosis. Seven patients died in the study, but this was not attributable to the study drugs. In the European SOLAR-2 trial, SVR12 was achieved in 95% patients with F0-3 fibrosis and 98% with CPT-A cirrhosis.[65]

An uncommon complication of post-LT HCV recurrence is a condition called fibrosing cholestatic hepatitis (FCH). Till DAAs became available, this condition was associated with a very high mortality. However, as shown in the SOLAR-1 (6 cases) and SOLAR-2 trials (5 cases), all patients achieved SVR12 with the SOF/LDV/RBV regimen. There was no drug-to-drug interaction with any of the immunosuppressive agents in these trial.[64,65]

In the recent open-label ALLY-1 study, SOF/DCV RBV for 12 weeks was examined in LT recipients with recurrent HCV infection (n = 53, 41 GT-1 and 11 GT-3 patients). SVR12 was achieved in 50 out of 53 patients (94%). Even though cyclosporine increases the DCV exposure with a 40% increase in AUC_{0-24}, this is not of much clinical consequence. Therefore, the standard immunosuppression does not need any change with the DAAs described in this review.[67]

The efficacy and safety data for DCV-based all-oral antiviral therapy in LT has been shown by Fontana et al.[79] in 97 cases after LT [(DCV/SOF (n = 77), DCV/simeprevir (n = 18), and DCV/SOF/simeprevir (n = 2)]. Overall, 35% of the patients received RBV. Majority of the patients had HCV GT-1 infection. The overall SVR12 rate was 87%. SVR rates were significantly higher with DCV/SOF than with DCV/simeprevir (91% vs 72%; P = 0.047).

Recommendations

1. Combination oral DAA therapy with SOF/LDV for GT-1 is safe and highly effective for recurrent post-LT HCV infection.
2. SOF/DCV has been shown to have high efficacy for post-LT recurrent HCV and does not interact with immunosuppressants.
3. The optimal timing to initiate therapy is the first 6-12 months post LT, when the patient would have absent/low stage of fibrosis. Treatment should be offered when the LT recipient has a stable allograft function and is on stable immunosuppression dosages, with no recent acute cellular rejections and renal dysfunction. Combination therapy must be initiated before decompensation.[80]
4. The available data underline the importance of inclusion of RBV in treatment regimens for difficult-to-treat population, as exemplified by GT-3 cirrhosis.

The recommended treatment regimens for patients who develop recurrent HCV after LT are shown in Table 4.

Management of HCV in HIV Coinfection

The advances in management of patients with acquired immunodeficiency syndrome (AIDS) with highly effective antiretroviral therapy (HAART) have changed the clinical profile of patients with HIV infection. Longevity has increased and AIDS-related illnesses are no longer the major cause of death. Liver disease has become a growing concern in HIV/AIDS and is the leading cause of death in patients with HIV.[81,82] In the D:A:D study, viral hepatitis was the commonest cause of death (84% of liver-related deaths and 11% of all-cause mortality). Hepatitis C was the most common viral hepatitis coinfection seen in HIV.[83]

The high prevalence of HCV infection in HIV is not surprising considering the shared routes of transmission. The prevalence of HCV coinfection in HIV depends on the patient's risk factor for HIV acquisition.[81] The prevalence rates of HIV-HCV coinfection vary from 10% among those with high-risk sexual behavior to 90% with injection drug use.[84] Exposure to contaminated blood or blood products is the most efficient method of transmission of HCV, while perinatal and vertical transmission is less efficient.[85] Sexual transmission of HCV infection is more efficient in presence of ulcerative sexually transmitted infections and homosexual practices.[86] Unlike the west, where 30% of HIV-infected individuals are coinfected with HCV,[87] in India there is higher heterosexual transmission and transmission by needle sharing in injection drug use is lower. These factors may account for the differences in HIV coinfection in India.

The prevalence of HCV in HIV-infected persons has ranged between 1.3% and 8.3% with a higher prevalence in southern India than that in northern India.[88–93] A high

Table 4 Recommended HCV Treatment Regimen for Patients with Recurrent HCV After Liver Transplantation.

Genotype	Regimen
1 & 4	**Recommended regimen** • SOF + LDV + RBV (initial dose of 600 mg, increased as tolerated) × 12 weeks • SOF + DCV + RBV (initial dose of 600 mg, increased as tolerated) × 12 weeks **Alternative regimen for RBV-intolerant patients** • SOF + DCV × 24 weeks • LDV + SOF × 24 weeks
2	**Recommended regimen** • SOF + DCV + RBV (initial dose of 600 mg, increased as tolerated) × 12 weeks • SOF + RBV (initial dose of 600 mg, increased as tolerated) × 24 weeks **Treatment regimen for RBV-intolerant patients** • SOF + DCV × 24 weeks
3	**Recommended regimen** • SOF + DCV + RBV (initial dose of 600 mg, increased as tolerated) × 12 weeks **Alternative regimen** • SOF + RBV (initial dose of 600 mg, increased as tolerated) × 24 weeks **Treatment regimen for RBV-intolerant patients** • SOF + DCV × 24 weeks

DCV, daclatasvir (60 mg); LDV, ledipasvir (90 mg); RBV, Ribavirin; SOF, sofosbuvir

prevalence of HCV and HIV coinfection has been found in intravenous drug users ranging from 13.2% to 86%.[94–97]

HIV-infected patients with HCV coinfection have a faster progression to AIDS and slower CD4+ recovery than patients with HIV infection alone as was shown in the Swiss Cohort study.[98] There is a better immunological response to HAART in HIV-infected patients without HCV than in the coinfected patients.[99]

With increasing longevity in HIV-infected individuals, HCV-related chronic liver disease and hepatocellular carcinoma have become major causes of mortality in HCV-HIV coinfected patients.[83,100,101] Studies have shown that chronic hepatitis C patients with HIV infection have a worse prognosis as compared to those without HIV.[102–107]

Coinfection with HIV and HCV is associated with a lower rate of spontaneous HCV RNA clearance.[108] There is an increased rate of fibrosis in HIV and HCV coinfected patients, with an accelerated progression of HCV-related liver disease.[109] Cirrhosis develops 12–16 years earlier in patients coinfected with HIV and HCV than in those infected with HCV alone.[110] The median survival of decompensated cirrhosis in patients with HIV and HCV coinfection is only 13 months.[111]

With newer developments in the management of both HIV as well as HCV, the natural history of HCV and HIV coinfection is likely to change and might resemble HCV monoinfected patients.[112] With the introduction of DAA against HCV, the mechanism of action of HCV therapies has shifted from immune-regulation by PEG-IFNα/RBV therapy to direct viral inhibition.[113] The SVR of HCV in HIV coinfected patients appears to be comparable to monoinfected patients.[114] HAART is now more effective, and the older drugs like didanosine and stavudine, which were associated with hepatic fibrosis, are now not being prescribed. Moreover, the treatment threshold of starting HAART has changed to higher CD4+ count levels. As a result, HIV-infected patients are treated earlier with more effective and less hepatotoxic HAART. This leads to earlier control of viremia and rise in CD4+ counts, which are likely to slow the progression of fibrosis in these patients.

All HCV patients should be tested for HCV antibodies by enzyme-linked immunosorbent assay (ELISA). However, ELISA antibody test for HCV can be false negative in HIV patients with low CD4 counts. In patients with negative antibody test, repeat tests should be recommended yearly as patients may have ongoing risks of transmission like high-risk sexual behavior or illicit drug use. In patients with elevated liver enzyme, HCV infection can be confirmed by testing for HCV RNA.

In the pre-DAA era, the SVR of therapy of HCV with PEG-IFNα and RBV were lower in HIV coinfected patients, and were 17% and 29%, as shown in the RIBAVIC and APRICOT trials, respectively.[115,116] The advent of newer drugs for HCV has resulted in a marked improvement in the treatment outcomes in patients with HIV coinfection and has closed the SVR gap between the HCV monoinfected and coinfected patients.

Current guidelines for management of HCV recommend that patients with and without HIV coinfection be treated with the same HCV regimens.[1,2] One notable exception in the setting of HCV and HIV coinfection is that PEG-IFNα therapy is not recommended due to its adverse effects and poor response rates. Of the DAA recommended by international guidelines, only DCV, LDV, and SOF are available in India. The other recommended DAA, simeprevir and the '3D' regimen consisting of paritaprevir (NS3/4A protease

inhibitor) boosted with ritonavir, ombitasvir (NS5A replication complex inhibitor), and dasabuvir (non-nucleoside NS5B polymerase inhibitor), are not available in India.

Drug interactions need to be considered before starting any treatment for HIV and HCV concurrently. There is also a concern that with increasing complexity of treatment regimen for both HCV as well as HIV, the overall adherence to medication may decrease.[117] Treatment interruption in HCV and HIV coinfected individuals is not recommended. Therapy interruption has been shown to be associated with progression of liver fibrosis[118] besides significantly increased risk of opportunistic infections and death.[119,120] Initiation of HCV therapy along with HAART requires a thorough understanding of drug–drug interactions between antiretroviral therapies to treat HIV and DAA medications to treat HCV.

Antiretroviral drug switching may be required to allow for compatible DAA. It has been shown that a majority of coinfected patients may need to switch to antiretroviral therapy to accommodate DAA for treatment of HCV.[121] Antiretroviral agents with minimal drug–drug interactions include integrase strand transfer inhibitors such as raltegravir or dolutegravir, or the non-nucleoside reverse transcriptase inhibitor, rilpivirine. A switch to raltegravir has been shown to improve antiviral-associated hepatotoxicity in individuals coinfected with HIV and hepatitis C.[122]

Daclatasvir in HCV and HIV coinfection: DCV is a CYP3A4 substrate and is susceptible to drug interactions with drugs that may induce or suppress this enzyme. The dosage needs to be reduced to 30 mg/day with strong CYP3A4 inhibitors (ritonavir-boosted atazanavir, bocepravir, telprevir, cobicistat, ketoconazole, and clarithromycin). On the other hand, DCV dose needs to be increased to 90 mg when it is administered with inducers of CYP3A4 (efavirenz and etravirine).[22]

The safety and efficacy of DCV and SOF therapy in HCV and HIV coinfection has been shown in the ALLY-2 trial, which had evaluated a 12-week vs. 8-week regimen in GT-1 to 4 in treatment-naive (n = 151) and treatment-experienced (n = 52) HIV and HCV coinfected patients. The study showed a SVR at 12 weeks (SVR12) of 96% with 12-week combination therapy, but in case of 8-week therapy, the SVR12 was only 76%.[23]

Many HCV and HIV coinfected patients may be on antiretroviral agents, which may not allow recommended DAA regimen to be used. Switching of HAART may be associated with a risk of viral breakthrough.[123] In case of concern of drug resistance to antiretroviral drugs, use of DCV and SOF therapy may be optimal as it is compatible with most antiretroviral regimens and a switch of antiretroviral regimen may be avoided. DCV and SOF therapy is associated with significantly higher SVR12 rate and lower rate of discontinuation due to adverse effects than SOF and RBV in patients coinfected with HIV and HCV.[124]

Ledipasvir in HCV and HIV coinfection: LDV increases drug levels of tenofovir and should be avoided in patients with creatinine clearance less than 60 mL/min. Ritonavir-boosted protease inhibitors potentiate this effect on tenofovir levels and LDV should be avoided. Cobicistat levels are also significantly increased with LDV and elvitegravir and cobicistat combination should be avoided in LDV/SOF therapy.

The safety and efficacy of LDV/SOF was evaluated in the ERADICATE study where 50 HCV and HIV coinfected patients without cirrhosis were treated with a 98% SVR12.[125] The ION-4 study studied 335 treatment-naive and treatment-experienced patients and reported an overall SVR12 of 96%.[126] There are no data of shortened 8-week duration therapy of LDV/SOF in HCV and HIV coinfection.

Sofosbuvir in HCV and HIV coinfection: SOF is a nucleoside NS5B polymerase inhibitor given at a dose of 400 mg once a day in combination with RBV, DCV, or LDV. SOF is not metabolized by cytochrome P450 enzymes and has no significant drug–drug interactions with antiviral drugs. SOF is transported by P-glycoprotein (P-gp) and its drug levels can be reduced by P-gp-inducers. It is therefore not recommended for use with tipranavir because of its potential to induce P-gp.

The PHOTON-1 and -2 studies were conducted to evaluate the use of SOF/RBV therapy in HCV and HIV coinfection. In the PHOTON-1 study, a 24-week treatment course was given to all patients with HCV GT-1 and to treatment-experienced patients with HCV GT-2 or 3; treatment-naive patients with HCV GT- 2 or 3 received a 12-week treatment course. For treatment-naive patients, the SVR12 rates were 76% with GT-1, 88% with GT-2, and 67% with GT-3. In treatment-experienced patients, SVR12 rates in GT- 2 and 3 were 92 and 94%, respectively. Treatment-experienced patients with GT-2 had a 92% SVR12 rate and those with GT-3 had a 94% SVR12 rate.[127]

In the PHOTON-2 study, a 24-week treatment course was given to all patients with HCV GT-1, 3, or 4 and treatment-experienced patients with GT- 2, whereas treatment-naive with HCV GT-2 received 12 weeks of treatment. The SVR12 rates were 85% in GT-1, 88% in GT-2, 89% in GT-3, and 84% in GT-4. The treatment responses were similar in the treatment-naive and treatment-experienced patients.[128]

Ribavirin in HCV and HIV coinfection: Concomitant use RBV with didanosine or stavudine is contraindicated as it can cause dangerous drug interactions resulting in mitochondrial toxicity, lactic acidosis, and pancreatitis.[129] RBV is also not recommended for use in zidovudine due to increased rates of anemia.[130]

The salient drug interactions of drugs for HCV with HAART and recommended modifications are given in Table 5.

Table 5 Salient Drug Interactions of Drugs for HCV with HAART.

Daclatasvir	• Reduce daclatasvir dose to 30 mg/day with strong CYP3A4 inhibitors (ritonavir-boosted atazanavir, bocepravir, telprevir, and cobicistat). • Increase daclatasvir dose to 90 mg when it is administered with inducers of CYP3A4 (efavirenz and etravirine)
Ledipasvir	• Avoid with tenofovir in creatinine clearance <60 mL/min or along with ritonavir-boosted protease inhibitors. • Avoid with cobicistat/elvitegravir combination therapy
Sofosbuvir	• Not recommended for use with tipranavir
Ribavirin	• Avoid with zidovudine, didanosine or stavudine

Role of liver transplantation patients with HCV and HIV coinfection: Liver transplantation is increasingly being carried out in HIV-infected patients with good results.[131]HIV infection had no impact on recurrence of hepatocellular carcinoma (HCC) or survival after liver transplantation. In a recent Spanish study in HIV-infected patients undergoing liver transplantation for HCC, Aguero et al.[132] found that survival at 1, 3, and 5 years for HIV-infected versus non-HIV-infected patients was 88% versus 90%, 78% versus 78%, and 67% versus 73% ($P = 0.779$), respectively. There was no impact on survival or recurrence of HCC.

However, results of HCV and HIV coinfected patients undergoing liver transplantation had remained suboptimal with reported survival rates ranging between 64%-88% at 1 year and 33%-51% at 5 years.[133] Two prospective studies have shown lower patient survival and higher incidence of acute cellular rejection in HCV and HIV coinfected cohort compared to HCV monoinfected patients.[134,135] FCH and sepsis are the leading causes of death in HCV and HIV coinfected patients.[136–138] With the availability of DAA for the treatment of recurrent HCV following liver transplantation, SVR rates have improved in HCV and HIV coinfected patients.[139,140]

The indications for liver transplantation in HCV and HIV coinfected patients are similar to those for noninfected patients. The HIV-specific criteria for liver transplantation are given in Table 6. Poor prognostic factors in liver transplant in HCV and HIV coinfection included pretransplant body mass index in recipient of <21 kg/m^2 and the need for a combined liver and kidney transplant. Donor factors related to poor outcome include deceased donors aged >50 years and the use of HCV-positive donors.[141,142]

Patients with HCV and HIV coinfection have been referred to as a "special" treatment group, considering the more rapid progression of HCV-related liver disease and the poor response to therapy in the past. The availability of DAA has dramatically improved the response rate of therapy for HCV in this group. However, this group still warrants special consideration in view of the high prevalence of HCV in HIV-infected patients, reinfection following successful therapy, and the need for careful monitoring of drug interactions with HAART.[143]

Management of HCV in End-Stage Renal Failure (ESRD) and Renal Transplant Recipients

Many studies have shown that HCV infection impacts survival of patients with chronic kidney disease (CKD), those on dialysis [end-stage renal disease (ESRD)], and patients with postrenal transplant status.[144,145] In CH-C patients with ESRD, altered drug pharmacokinetics, increased susceptibility to drug-related toxicity, the requirement for renal transplantation, and a modified course of disease make their treatment difficult. Some of the other issues, which are peculiar to this population of patients, include normal or minimal elevation of transaminases, GT-1 predominance, inaccurate noninvasive assessment of hepatic fibrosis especially with transient elastography, and higher complication rate after liver biopsy.

Before the introduction of DAAs, treatment guidelines for HCV treatment in patients with CKD included use of conventional IFNα or Peg-IFNα with or without RBV depending upon the stage of CKD.[146] It has been difficult to treat CH-C in ESRD patients with IFNα/RBV due to poor tolerance of drugs, higher side effects especially anemia, high dropout rate, poor response, and the cost of treatment. In

Table 6 HIV-Specific Criteria for Liver Transplantation in HCV and HIV Coinfected Individuals.

1. Absence of untreatable diseases
• Progressive multifocal leukoencephalopathy
• Chronic intestinal cryptosporidiosis
• Multidrug-resistant systemic fungal infections
• Primary CNS lymphoma
2. Pretransplant HIV RNA suppressed on HAART to <50 copies/ml or predicted absence of HIV viremia on combined antiretroviral therapy
3. CD4+ T cell count >100/μL
4. Absence of AIDS-defining illness

addition, cost of long-term dialysis and affect on the live-related donor program were other considerations.[147,148]

Among the globally licensed drugs, SOF predominantly has renal excretion, whereas simeprevir, LDV and DCV, the fixed-dose combination of PrOD and recently licensed grazoprevir, and elbasvir combination have minimal renal excretion but there are sparse data on their safety and efficacy in patients with CKD/ESRD.

AASLD recommends that for patients with mild-to-moderate renal impairment (CrCl >30 mL/min), no dosage adjustment is required for SOF, simeprevir, fixed-dose combination of LDV/SOF, and fixed-dose combination of PrOD.[1] For patients with CrCl < 30 mL/min, treatment should be contemplated after consultation with an expert as safety and efficacy data are not available in this population. For patients who do not have cirrhosis but for whom the urgency to treat (or re-treat) is high and renal transplant is not an immediate option, fixed-dose combination of PrOD is recommended for treatment of HCV GT-1 and 4 infection in patients with ESRD. However, the recommendations for HCV GT-2, 3, 5, and 6 are the use of Peg-IFNα and dose-adjusted RBV if treatment is necessary and renal transplantation cannot be performed. [1] After the results of C-SURFER study and the recent licensing of the combination by US FDA, there may soon be addition of grazoprevir and elbasvir in the treatment of ESRD patients with GT-1 HCV infection.

All the available drugs for CHC in India (conventional IFNα or Peg-IFNα with RBV, SOF, LDV, and DCV) can be used safely in patients with mild-to-moderate renal impairment (CrCl >30 mL/min) but the options are limited for patients with CKD/ESRD (CrCl <30 mL/min) where low-dose Peg-IFNα with low-dose RBV can be used safely. The data about the safety of SOF and DCV in this subgroup are still emerging. SOF and its metabolite GS-331007 have predominantly renal excretion. Hence, SOF is not recommended in patients with CrCl < 30 mL/min. Data have started emerging regarding the use of SOF in patients with CKD/ESRD.[149] Even though HCV-TARGET real-life data on use of combination of various DAAs including SOF in various stages of CKD including patients with ESRD showed high SVR12 response rates, it was associated with higher side effects including worsening of renal functions in a quarter of the patients.[150] However, two recent studies that used combination of SOF (half dose or full dose) in combination with full dose of simeprevir have shown SOF to be safe with very high efficacy (SVR 12–99-100%) in patients with ESRD.[151,152] A recent adaptive study assessing DCV pharmacokinetics and safety in HCV-uninfected subjects with renal impairment found that even though DCV AUC concentration was higher in ESRD subjects versus controls, DCV was generally well tolerated in subjects with normal renal function and moderate or severe renal impairment.[153] Though more data would be required, two recent abstracts presented at AASLD and EASL annual meetings confirmed the safety and efficacy of SOF/DCV with or without RBV in patients with renal impairment.[154,155]

With the available data and drugs in the country, the recommendations for Indian patients of CH-C with CKD with mild-to-moderate renal impairment (CrCl >30 mL/min) thus can be to either treat these patients with the available DAA combinations (SOF, LDV, and DCV) depending upon the GT with or without RBV with no dosage adjustment or to treat them with combination of Peg-IFNα and RBV. There are limited options for patients with severe renal impairment (CrCl < 30 mL/min) and these patients can be either treated with low-dose Peg-IFNα with low-dose RBV as has been done in the past or with a combination of low-dose SOF (half tablet – 200 mg/day) with full dose of DCV for all GTs. Since LDV is available only as fixed combination in a single pill with SOF (hence would be available in half dose in a half tablet of combined pill), this combination cannot be recommended in patients of CH-C with severe renal impairment.

If cirrhosis can be excluded and an early renal transplantation is possible, the other option in patients with ESRD can be to subject these patients to renal transplantation with HCV infection and then to treat them after transplantation when the renal functions have normalized and the corticosteroids have been reduced to a minimal dose. Even though the data on the use of DAAs in the postrenal transplant setting are emerging, issues related to treating HCV after renal transplantation rather than prior to transplantation can be a minor risk of FCH and the interactions of DAAs with immunosuppressive drugs.[156]

Recommendations: Management of patients with HCV and CKD/ESRD and renal transplantation

1. IFNα and RBV-free regimens with DAAs as per the GT should be the first line of treatment for patients with mild-to-moderate renal impairment (CrCl >30 mL/min).
2. Patients with severe renal impairment (CrCl <30 mL/min) who are eligible for interferon-based treatment can be treated with conventional IFNα or Peg-IFNα (135 μg/week for Peg-IFNα2a and 1 μg/kg/week for Peg-IFNα2b) with low-dose RBV (200 mg/day).
3. For patients with severe renal impairment (CrCl <30 mL/min) who are ineligible for interferon treatment and where early renal transplantation is not a possibility, combination of DAAs [Low-dose SOF (200 mg/day) and full-dose DCV (60 mg/day)] can be considered in controlled setting irrespective of the GT.
4. IFNα and RBV-free regimens with DAAs as per the GT should be the first line of treatment for postrenal transplant patients with normal renal functions or with mild-to-moderate renal impairment (CrCl >30 mL/min).
5. IFNα treatment is not recommended in postrenal transplant patients.

Acute HCV

The majority of acute HCV infections (AHCV) do not manifest clinically. AHCV is usually diagnosed by detecting

asymptomatic elevation of serum ALT level during close follow-up of individuals exposed to a source of HCV infection such as transfusion with contaminated blood or blood products, unprotected sexual contact, or percutaneous exposure, such as needle stick injury (NSI). The most common route of exposure among healthcare workers (HCWs) is percutaneous NSI, with the risk of HCV transmission being about 0.5%[157]; it is slightly higher following injury with hollow, wide-bore needles.

Several important questions related to diagnosis, follow-up, natural history, optimal time for starting antiviral therapy, choice of antiviral drugs, and duration of therapy for AHCV infection remain unanswered. Current knowledge and understanding of natural history of AHCV infection is limited, being based on conclusions drawn from small, heterogeneous studies.[158] A systematic review of 31 longitudinal cohort studies found spontaneous viral clearance in 24% of AHCV infections,[159] which was predicted by young age, female gender, clinical hepatitis, IL-28B CC GT, nonblack race, low peak viral load, and rapid decline in viral load in the first four weeks after diagnosis. One study have shown higher rate of viral clearance in GT-3 than GT-1.[160]

Definition of acute HCV infection: Although there are no universally accepted criteria, HCV infection is considered to be acute if estimated duration of infection is less than 26 weeks.[161] Acute HCV infection should be diagnosed if

a. known absence of HCV infection (undetectable HCV RNA and/or anti-HCV antibody if ever tested) or status unknown is followed by anti-HCV antibody detection within 26 weeks of a known HCV exposure; or
b. clinical features of acute hepatitis or serum peak ALT level > 400 IU/mL (i.e. 10 times ULN) occur at anytime in the 20 weeks preceding diagnosis of HCV infection with other common causes of acute hepatitis excluded (negative IgM anti-HAV and IgM anti-HEV antibodies); or
c. asymptomatic anti-HCV antibody seroconversion with the midpoint between last negative and the first positive anti-HCV antibody or HCV RNA result lying in the preceding 26 weeks.

Testing for AHCV infection: Following HCV exposure, HCV RNA can be detected in 1–3 weeks, transaminase elevation in 4–12 weeks, and anti-HCV antibody in 6–8 weeks. Anti-HCV antibody testing is preferred over HCV RNA for postexposure follow-up after NSI to HCWs, because PCR is costly, is not widely available, and there is little urgency for early diagnosis, since CHC is now easily cured.

Antiviral therapy for AHCV infection: At present, the standard of care for acute HCV is Peg-IFNα for 24 weeks for HCV monoinfection or with oral RBV for HIV/HCV coinfection. During the Peg-IFN/RBV era, there has been some debate over the optimum timing for antiviral therapy after AHCV infection. The chance of spontaneous clearance after acute infection within 12 weeks in 24% of patients has to be balanced against higher risk of chronicity when treated after 12 weeks of infection.[162] A randomized controlled trial showed 13% higher SVR (67% versus 54%) in those who received Peg-IFN within 12 weeks of exposure.[163] However, recommendations are expected to change once results of highly effective therapy with a combination of DAAs are available.

Presently data on the use of DAAs for treating AHCV infection are lacking. Till date, only one pilot study using Telaprevir with Peg-IFN/RBV for 19 patients with acute HCV/HIV coinfection has been reported, with 84% SVR rate.[164] Results of several studies using all-oral DAA-based regimens are awaited with interest[158] and are expected to change the paradigm for treatment of acute HCV infection.

Postexposure prophylaxis: Availability of highly effective DAAs at an affordable cost is likely to encourage demands for postexposure prophylaxis (PEP) after accidental NSI from an HCV-positive source, akin to current practice for HIV infection. Presently, no data are available regarding pre-emptive, postexposure use of DAAs to prevent HCV infection. Prophylactic use of DAA in this situation is unlikely to be cost-effective given the 0.5% risk of acute HCV infection after exposure, 24% chance of natural clearance following acute infection, and curable nature of chronic infection. Close postexposure follow-up with treatment if HCV infection persists 12 weeks after detection of acute infection using a combination of potent DAAs is likely to be the best plan of action.

Recommendations

1. Acute HCV infection should be diagnosed as suggested above.
2. During postexposure follow-up, anti-HCV antibody rather than HCV RNA should be used for detection of fresh HCV infection.
3. Postexposure follow-up of HCWs exposed to an HCV-infected source must include the following:
   a. Baseline laboratory evaluation of the exposed person with testing for liver function, HBsAg, anti-HIV, and anti-HCV antibodies;
   b. Monitoring for clinical signs and symptoms of acute hepatitis and testing serum ALT level every month for first 12 weeks after exposure;
   c. Repeat anti-HCV antibody testing at 12 weeks and 24 weeks after exposure;
4. Those with positive result for anti-HCV antibody at 12 weeks should be provided with standard of care testing and treatment for acute HCV infection (monotherapy with Peg-IFN for 24 weeks), while those testing positive at 24 weeks should receive standard of care for chronic hepatitis C (combination of potent DAAs for 12 weeks). Treatment recommendations are likely to change once data on the use of DAAs for AHCV infection become available.

Hepatitis C in Children

Prevalence and transmission in childhood: The prevalence of hepatitis C is lower (0.31%)[165] among Indian children than among adults. Children with chronic hepatitis C (CHC) are usually well and do not have significant fibrosis. CHC is a very infrequent indication for liver

transplantation in children. The predominant mode of transmission in childhood is vertical transmission from an infected mother. About 5% of viremic mothers transmit the virus to their offspring (20% with HIV coinfection).[166] High maternal viral load (>600,000 IU/ml), invasive fetal monitoring, prolonged rupture of membranes, and fetal anoxia at the time of delivery are factors that enhance transmission.[85,167] Elective cesarean section is not required for women with HCV infection and breast-feeding does not promote transmission. However, it is prudent to avoid breast-feeding if the nipples are bleeding, if mastitis is present or if the mother is experiencing a flare of hepatitis with jaundice. The risk of transmission in households where one member has HCV infection is small (<2%).

Follow-up in children born to HCV-infected mothers: These children should be screened for vertical transmission with anti-HCV antibody testing at 18 months of age, when maternally derived antibodies have cleared, and confirmed with HCV RNA testing by PCR. Once confirmed, these children should be regularly followed for the possibility of spontaneous clearance in the first few years of life. If necessary, as in children with significant liver disease and anti-HCV seropositivity, vertical transmission can be confirmed by PCR for HCV RNA after 3 months of age; results are unreliable before this time.[168]

Natural history in children: About 7–25% of vertically infected infants clear their infection spontaneously, usually by 24 months of age.[169,170] Infection acquired during infancy progresses slowly over several decades with minimally deranged liver enzymes and minimal fibrosis, and only 5–20% develop cirrhosis after 20 years of infection. However, 2% develop cirrhosis in childhood and require liver transplantation.[169,170] Hepatocellular carcinoma due to HCV infection is extremely uncommon in childhood; only a few cases have been reported to date.[171] Extrahepatic disorders due to HCV, particularly membrano-proliferative glomerulonephritis, may occur in children although neither cryoglobulinemia nor lymphoma has yet been reported. Children with chronic hepatitis C (CHC) should be followed annually with a physical examination and blood tests for evidence of liver injury and ongoing viremia.

Treatment: Currently, DAAs are not approved for use in children and the standard of care remains Peg-IFNα/RBV. Children younger than 3 years should not be treated as they may spontaneously clear their infection. A conservative approach has generally been adopted, since progression is slow, severe disease is rare, and therapy may entail significant adverse effects.[168] Treatment with Peg-IFNα is offered only to children with significant fibrosis on biopsy, especially if infected with a favorable viral or IL 28B genotypes, and response rates are similar to adults. SVR rates of Peg-IFNα/RBV therapy in children are typically >80% for GT-2 and 3 and 40–50% for type 1. IL28 GT CC predicts a >80% response, while IL28 GT TT predicts a 30% response in GT-1 infection.[13–177] Follow-up without treatment to adulthood is a valid option, particularly in those with no evidence of significant liver fibrosis.

As of 2016, phase II/III trials of combination DAAs for children aged 3–17 years chronically infected with GT-1, 2, 3, and 4 are under way. It is expected that these trials will confirm similar efficacy of DAAs in children as in adults. In such a scenario, DAAs will replace Peg-IFNα/RBV-based regimens as the preferred treatment for pediatric chronic HCV. Practice is likely to shift from treating only children with significant liver disease and a favorable GT to treat all children as soon as infection is diagnosed, except those younger than three years of age in whom there is a significant probability of spontaneous virologic clearance.

Recommendations

1. Management of HCV-infected mother
   a. Elective cesarean section is not required for women with HCV infection and breast-feeding does not promote transmission.
   b. The child should be tested for anti-HCV antibody at 18 months or, if needed, RNA after 3 months of age.
2. Chronic HCV in children
   a. HCV in children is mainly vertically transmitted with a rate of transmission of 5%.
   b. HCV in children usually has a benign course: only ~2% children develop cirrhosis.
   c. Treating HCV in children.
3. Currently only Peg-IFNα/RBV therapy is approved for management of HCV in children
   a. Peg-IFNα/RBV therapy should be offered to children with significant liver disease.
   b. DAAs are set to be approved in children and children without significant fibrosis should be ''warehoused'' till DAAs are approved.

EVALUATION AND MANAGEMENT OF HCV INFECTION IN RESOURCE-CONSTRAINED SCENARIOS

The arrival of oral DAA combinations, which are pangenotypic, highly potent, and have a high genetic barrier to resistance, provides an unparalleled opportunity to simplify pretreatment testing and on-treatment monitoring. The need for testing all patients for various contraindications to Peg-IFNα therapy (autoimmune disease, hypothyroidism, depression, etc.), for IL28B testing, for frequent monitoring of viral loads, blood counts, thyroid functions, etc. during therapy, and, perhaps soon, even for pretreatment viral load measurement and GT testing, is likely to be obviated. Detection of HCV replication prior to therapy and its absence 12 weeks after end-of-therapy may be sufficient for diagnosis and for monitoring of treatment. The role of HCV core-antigen testing in this setting has been discussed earlier. It is a useful alternative to HCV RNA testing for detecting active HCV infection in resource-limited settings and can be carried out in smaller

laboratories where HCV RNA testing may not be feasible. However, algorithms incorporating HCV core-Ag testing proposed for the management of CH-C in the absence of HCV RNA testing require further evaluation.

In patients on DAA without Peg-IFNα, EASL guidelines recommend HCV RNA monitoring at baseline, week 3 (assessment of adherence), week 4, week 12, or 24 (end-of-treatment in patients treated for 12 or 24 weeks, respectively), and at 12 or 24 weeks after end-of-therapy.[3] However, unlike with Peg-IFNα/RBV therapy, there is little role for response-guided therapy during treatment with DAA. Recommendations for such elaborate monitoring should be reviewed, given the excellent response to antiviral therapy, given that a response-guided therapy paradigm has not yet been proposed with DAAs and that such frequent monitoring only adds to the already prohibitive cost of therapy. Hence, INASL guidelines recommend HCV RNA monitoring only at baseline and 12 weeks after completion of therapy for SVR12.

Considering the very good to excellent response to therapy with the new DAA combinations in patients across the spectrum from F0 to F3 fibrosis, fibrosis assessment may not be necessary in every patient prior to therapy. In patients with no ultrasound evidence of cirrhosis, avoiding fibrosis assessment by noninvasive means or liver biopsy would contribute to decreasing the cost of management of CH-C.

Although cost of therapy has plummeted dramatically in many resource-constrained parts of the world to levels as low as US$ 100 per month, even this low cost is too high for patients who pay out-of-pocket and for state agencies faced with huge budgetary needs, given the enormous burden of HCV disease in these regions. There is also a need to simplify patient evaluation and treatment algorithms to reduce not only costs but also complexity and enable over-stretched and over-burdened public health systems to deliver healthcare to these patients.

It has been projected that over 90% of the HCV-infected population in India has F0-F3 disease.[178] Given this scenario, it appears appropriate for public health planners to focus on a simple scenario for delivering healthcare to HCV-infected patients. Simplification of screening and testing protocols with triaging of patients into noncirrhotic and cirrhotic groups should be done. Noncirrhotic patients should be treated at primary and secondary care facilities, while patients in special groups should be managed at tertiary care facilities.

In the public health setting, the combination of SOF/DCV could be recommended as first-line therapy for all noncirrhotic chronic HCV infection in India. This combination is highly efficacious, has a high genetic barrier to resistance, is pangenotypic, being very effective in GT-3 as well as GT-1 infections that constitute over 90% of HCV infections in India, and is the cheapest DAA combination available in India. In other scenarios (among special groups, for self-funded therapy, etc.), choice of regimens should be according to recommendations made in each section above.

Close monitoring of patients treated in the public health setting should be done in order to identify those who have treatment failure. Such patients should also be channelized to specialized tertiary care centers and treated under protocol with appropriate second-line therapy.

Different states in India with a high prevalence of HCV infection have made targeted efforts for case detection, health education, and management of HCV infection. The state of Punjab in India has a high prevalence of HCV. The Punjab state government has recently launched an HCV elimination project called the Mukh Mantri Punjab Hepatitis C Relief Fund (MMPHCRF), with a corpus of INR 20 crores (approximately USD 3 million) to begin with. This scheme aims to eliminate HCV from Punjab with a combination of preventive measures and decreasing the viremic burden by treating all patients with HCV in Punjab. SOF/DCV and SOF/LDV therapy, with or without RBV, will be provided free of cost for HCV-infected patients in the state of Punjab.

As a part of this scheme, HCV GT testing is mandatory for patients with evidence of cirrhosis but is optional for the noncirrhotic patients. Considering pangenotypic efficacy of SOF/DCV therapy, this regimen is likely to be effective and economical in treating noncirrhotic patients without GT testing. Patients with cirrhosis will be managed according to their genotypes (i.e. SOF/DCV/RBV for GT-3 and SOF/LDV/RBV for GTs-1 and 4). This appears to be a cost-effective practical approach to provide therapy to HCV-infected persons with public funding. The results of the impact of this pilot project by the Punjab government are eagerly awaited before consideration for implementation in other parts of the country.

Recommendations

In cost-constrained situations, such as large-scale public healthcare delivery to HCV-infected populations, the following principles may be followed.

1. *Simplified testing:* Apart from basic tests such as hemogram, liver function test, and abdominal ultrasound, the minimum set of tests should be anti-HCV testing at baseline and HCV RNA testing at baseline and at 12 weeks after end-of-treatment in those who are positive for anti-HCV and are planned for therapy. HCV viral load testing, HCV GT testing, and fibrosis assessment may not be mandatory in noncirrhotic treatment-naive patients. Algorithms incorporating HCV core-Ag testing require further evaluation.
2. *Simplified treatment:* In the absence of GT testing, if clinical evaluation including an abdominal ultrasound does not suggest presence of liver cirrhosis, all patients should be treated with SOF/DCV for 12 weeks. This group is likely to constitute ~90% of the treatment-eligible population. Where GT testing has already been carried out, recommended regimen as per GT should be followed.
3. *Close monitoring* should ensure completion of and compliance with treatment. SVR12 testing and early identification of patients with virologic failure should be ensured.

4. *Special groups* including those with virologic failure should be managed at specialist centers, should undergo thorough evaluation, and should be treated under protocols customized for these patients.

CONCLUSIONS

There is a large burden of HCV infection in India. The current consensus on guidance for treatment of CH-C summarizes the INASL recommendations for management of HCV in India with currently approved, available drugs. Considerations for the treatment of HCV in India should include the cost of therapy, the poorer response of GT-3 as compared to GT-1, and the nonavailability of many of the DAA recommended by other guidelines. The current guidance will be updated once other newer dugs are available, more data on treatment of GT-3 HCV with newer combinations becomes available, and as 'real-life experience' of use of DAA in India accumulates.

CONFLICTS OF INTEREST

The authors have none to declare.

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DOI: https://doi.org/10.1016/j.jceh.2016.09.009

Corrigendum to "Indian National Association for Study of the Liver (INASL) guidance for antiviral therapy against HCV infection: Update 2016" [J. Clin. Exp. Hepatol. 6 (2016) 119–145]

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The authors regret for the typological error in Table 3 published in the original version of the article. The corrected version of Table 3 is given below:

The authors would like to apologise for any inconvenience caused.

Table 3 Recommended HCV Treatment Regimen for Patients with Decompensated Cirrhosis.

Genotype	Recommended regimen
1 & 4	• SOF + LDV + RBV (initial dose of 600 mg, increased as tolerated) × 12 weeks • SOF + DCV + RBV (initial dose of 600 mg, increased as tolerated) × 12 weeks **Alternative regimen for RBV-intolerant patients** • SOF + DCV × 24 weeks • SOF + LDV × 24 weeks
2	• SOF + DCV + RBV (initial dose of 600 mg, increased as tolerated) × 12 weeks
3	• SOF + DCV + RBV (initial dose of 600 mg, increased as tolerated) × 24 weeks **Alternative regimen** SOF + RBV (initial dose of 600 mg, increased as tolerated) for up to 48 weeks

DCV, daclatasvir (60 mg); LDV, ledipasvir (90 mg); RBV, Ribavirin; SOF, sofosbuvir.

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http://dx.doi.org/10.1016/j.jceh.2016.09.009

