Disclaimer: The content presented in this booklet is solely for informational purposes. While Cipla makes every effort to present accurate and reliable information, Cipla does not endorse, warrant, or assume any legal liability or responsibility for the accuracy or completeness of any information provided. Cipla hereby disclaims all warranties regarding the contents of these materials, including without limitation all warranties of title, non-infringement, merchantability, and fitness for a particular purpose. Any advice regarding the management of the medical condition is totally in the discreet of the physician. No part of this may be reproduced, transmitted or stored in any form or by any means either mechanically or electronically.

Cipla Ltd. Regd. Office Cipla House,
Peninsula Business Park, Ganpatrao Kadam Marg,
Lower Parel, Mumbai - 400 013

For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only.

HCV MANAGEMENT SERIES

Cipla

Issue 2

Management of Treatment-naïve and Treatment-experienced HCV Patients

PREFACE

Treatment for hepatitis C is necessary, since a cure (sustained virologic response; SVR) is possible. Moreover, SVR is associated with improved benefits, including a decrease in liver inflammation, regression of fibrosis in most cases, and resolution of cirrhosis in almost half of the cases. Among the latter group, portal hypertension and other clinical manifestations of advanced liver disease also improve.

The therapy for hepatitis C is rapidly evolving from conventional interferons (IFNs) to the radicalizing, oral directly acting antivirals (DAAs).

Peg-interferon (peg-IFN) and ribavirin encompassed the conventional therapy for chronic hepatitis C. However, injectable therapy and low cure rates, accompanied by numerous side effects, limited the therapy.

The advent of sofosbuvir, a non-structural 5B (NS5B) protein inhibitor, has created a revolution, making headway for the development of newer all oral DAAs and bringing in a new era of hepatitis C treatment with all–oral DAAs. However, IFNs and ribavirin still form a part of sofosbuvir-based regimens and additionally, some groups have emerged as “difficult-to-treat” with sofosbuvir-based regimens.

This has prompted the addition of a second DAA to sofosbuvir-based regimens, anticipating a better response in these patients and leading to the development of newer DAAs, i.e., the NS5A inhibitors, daclatasvir, ledipasvir and velpatasvir, as an add-on to sofosbuvir.

These new DAAs have brought in an era of all-oral regimens to treat HCV, thus, obviating the need for injectables such as peg-IFN.

This booklet gives an overview of the treatment evolution, treatment approaches and recommendations for treatment-naïve and treatment-experienced hepatitis C patients.

CONTENTS

1. CONVENTIONAL THERAPY FOR CHRONIC HEPATITIS C

The therapy of chronic hepatitis C has evolved vastly beginning from the interferons (IFNs), cytokines produced by nucleated cells in response to viruses to the IFN-free, all-oral hepatitis C combination regimen today, using directly acting antiviral (DAA) agents.

HCV therapy began with the introduction of standard IFN or plain IFN, which was administered parenterally at least three times per week at a dose of 3 MIU. However, it associated with multiple adverse effects. Due to the suboptimal antiviral potency of standard IFN, SVR rates were generally less than 20%. This led to the addition of ribavirin, an antiviral used in combination with IFN therapy, anticipating a better response.

Ribavirin is a synthetic nucleoside antagonist that is active against a broad range of viruses and blocks the initiation and elongation of RNA fragments by inhibiting the synthesis of viral proteins. However, the mechanism by which it inhibits HCV RNA in combination therapy with IFN has not been established. Further studies focused on combining standard IFN with ribavirin and these studies showed improved SVR rates of 40–50% in HCV genotype 1 and 60-70% in HCV genotypes 2 and 3. In addition, ribavirin use was found to be associated with reduced relapse rates.

However, using ribavirin alone as a monotherapy for hepatitis C is not recommended, as the synergism when ribavirin combined with IFN is responsible for antiviral activity. Also, ribavirin has several adverse side effects such as hemolytic anemia. Other frequent side effects of ribavirin include pruritus, rash and indigestion, loss of appetite, nausea, headache, fatigue and teratogenic effects.

The next milestone in conventional therapy has been the development of modified IFNs or pegylated IFNs (peg-IFN). Due to limitations in the effectiveness of IFN alfa due to its rapid systemic clearance and short plasma elimination half-life of about 8 hours, pegylated subcutaneous formulations of IFN alfa have been developed, which are produced by the covalent attachment of recombinant IFN alfa to branched 40 kDa or 12 kDa peg moieties.

Peg-IFN alfa-2b has a linear 12 kDa PEG chain covalently attached primarily to histidine-34 of IFN alfa-2b via an unstable urethane bond that is subject to hydrolysis once injected, releasing native IFN alfa-2b. The branched 40 kDa PEG chain of peg-IFN alfa-2a is covalently attached via stable amide bonds to lysine residues of IFN alfa-2a, and circulates as an intact molecule. Consequently, peg-IFN alfa-2a has a very restricted volume of distribution, longer half-life and reduced clearance compared with native IFN alfa-2a, and can be given once weekly independent of body weight.

Peg-IFN alfa-2b has a shorter half-life in serum than peg-IFN alfa-2a and requires body weight-based dosing. Thus, the two peg-IFNs have different pharmacokinetic profiles needing different doses

The development of peg-IFN improved the pharmacokinetics of IFN, allowing more convenient dosing intervals and resulting in higher SVR (Fig. 1).

The development of conventional IFN therapy is explained in Fig.1. As shown, IFN monotherapy presented SVR rates of merely around 6–22%. Addition of ribavirin to IFN has shown about 33–36% SVR rates in genotype 1 patients and 61–79% in genotype 2 and 3 patients, respectively. The addition of peg-IFN has improved the SVR rates in HCV genotype 2 and 3 patients to 76–82%. However, genotype 1 has showed low SVRs of around 42–46%.

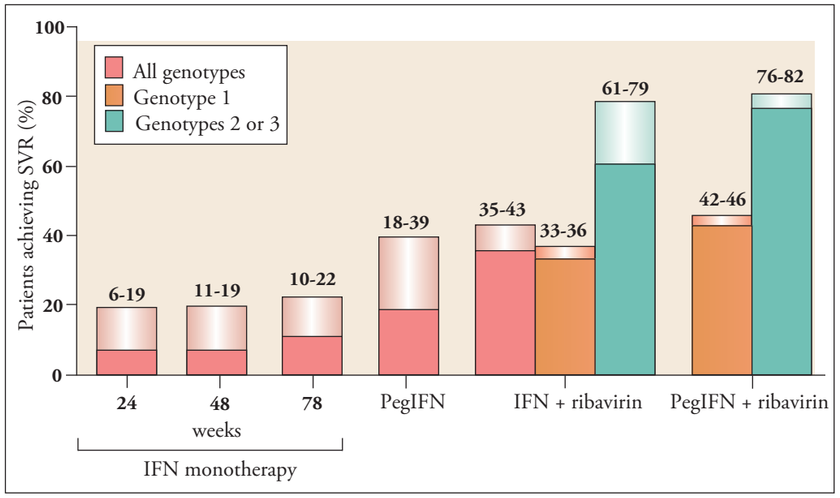

Fig. 1: Development of Conventional HCV Therapy

The numbers above the columns, and the paler shaded area of the columns, represent the ranges of SVR reported in the literature for each treatment or patient population.
Adapted from: *Nature Reviews Drug Discovery 2007; 6: 991-1000.*

Peg-IFN alfa-2b is dosed according to body weight (1.5 µg/kg once weekly), while the larger peg-IFN alfa-2a is given as a fixed dose of 180 µg once weekly.

Ribavirin should be administered as per the body weight of the patient.

Thereby, the peg-IFN and ribavirin combination has been the US Food and Drug Administration (FDA)-approved regimen for the treatment of hepatitis C, as mentioned in Table 1.

Table 1: Conventional Dual-Regimen Antiviral Treatment for Chronic HCV in Adults

Generic Name	Recommended Dose	Recommended Dose in Renal or Hepatic Dysfunction
Peg-IFN alfa-2a	180 mcg SC once weekly	CrCl <30 mL/min:135 mcg SC once weekly Hemodialysis: 135 mcg SC once weekly
Peg-IFN alfa-2b	1.5 mc/kg SC once weekly	CrCl 30–50 mL/min: reduce dose by 25% CrCl 10–29 mL/min: reduce dose by 50%
Ribavirin	**Genotype 1 or 4** <65 kg: 800 mg PO daily in two divided doses 65–85 kg: 1,000 mg PO daily in two divided doses >85–105 kg: 1,200 mg PO daily in two divided doses >105 kg: 1,400 mg PO daily in two divided doses Genotype 2 or 3 800 PO daily in two divided doses	CrCl 30–50 mL/min: 200 mg PO daily, alternating with 400 mg PO daily CrCl <30 mL/min: 200 mg PO daily

CrCl, creatinine clearance; SC: subcutaneous; PO: oral

Contraindications to IFN/Ribavirin or Peg-IFN/Ribavirin Therapy

The peg-IFN/ribavirin therapy is accompanied by various side effects.

Peg-IFN: Fatigue, fever, depression, insomnia, cytopenias, and alopecia

Ribavirin: Hemolytic anemia, cardiotoxicity, renal failure, risk of fetal malformation

Conventional therapy may not be tolerated by all HCV patients. Hence, various absolute and relative contraindications exist for peg-IFN and ribavirin usage as stated below.

The various absolute contraindications include

- uncontrolled depression, psychosis or epilepsy;
- pregnant women or couples unwilling to comply with adequate contraception;
- severe concurrent medical diseases;
- comorbidities, including retinal disease, autoimmune thyroid disease; and,
- decompensated liver disease

Relative contraindications include abnormal hematological parameters (hemoglobin <10.0 g/dL, baseline neutrophil count <1,500/mm^3, or a baseline platelet count <90,000/mm^3), serum creatinine >1.5 mg/dl, significant coronary artery disease and untreated thyroid disease, previous intolerance or hypersensitivity to IFN alfa and age >70 years. Therapy can be individualized on a case-to-case basis in elderly patients.

Other Limitations with Peg-IFN/Ribavirin-based Regimens

1. Efficacy and inter-patient variability

- **a.** Peg-IFN and ribavirin regimens demonstrated reduced efficacy, with SVR rates of only 40–50% in HCV genotype 1 patients.
- **b.** Since, the combination shows effect by modulating the host immune respones, several patient-related factors lead to varied effects amongst patients:
  - **i.** Response to IFN and attainment of SVR depends on some of the host genetic factors such as race, IL28B gene polymorphisms, with responses in the order IL28BCC>IL28BCT>IL28BTT.
  - **ii.** Efficacy is reduced in patients with IL28B non-CC genotypes and Black race.

2. Patient compliance

- **a.** Long duration of therapy of about 48 weeks in some patients, accompanied by several side effects.
- **b.** Injectable formulation of peg-IFNs and high pill burden of oral ribavirin, warranting multiple administrations.

These factors have led to the development of alternative options, DAAs for the treatment of hepatitis C.

2. DAAs FOR CHRONIC HEPATITIS C

The limitations of IFN-based therapies have prompted the development of DAAs.

DAAs are molecules that target specific nonstructural proteins of the virus and result in disruption of viral replication and infection. There are three main classes of DAAs, which are defined by their mechanism of action and therapeutic target. (Fig. 2)

The three main classes are as below:

1. Nonstructural proteins 3/4A (NS3/4A) protease inhibitors (PIs)
2. NS5B nucleoside polymerase inhibitors (NPIs) and non-nucleoside polymerase inhibitors (NNPIs)
3. NS5A inhibitors

Additionally, there exists another class of antivirals called host-targeting agents, which interfere with the cellular factors involved in viral replication. They target many cellular host factors that are required for HCV viral entry and replication such as scavenger receptor-BI (SR-BI), 3-hydroxy-3-methyl-glutaryl-CoA reductase (HMG CoA reductase), cyclophilin A (CypA), fatty acid synthase (FAS) and miRNA-122.

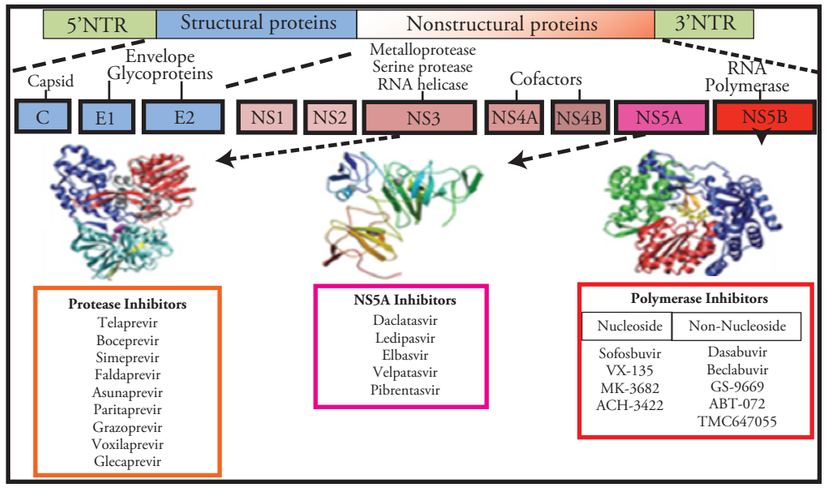

Fig. 2: Classes of DAAs and Their Therapeutic Target Site

Adapted from: *Liver Int. 2012; 32 Suppl 1:88-102.*

A. Nonstructural proteins 3/4A (NS3/4A) protease inhibitors (PIs)

NS3/4A PIs are the first DAAs introduced for the treatment of HCV. The era of PIs started with the introduction of telaprevir and boceprevir, which even posed to be the first DAAs approved for HCV. These DAAs were approved by the US-FDA and Europe for the treatment of HCV genotype 1.

Combined with peg-IFN and ribavirin, these drugs increased the chance of cure for treatment-naïve genotype 1 HCV patients by 30% (SVR rates of 73% and 67%, respectively). However, these were accompanied by some limitations.

These drugs were not effective in 25% HCV treatment-naïve genotype 1 patients and 71% of patients who did not respond to previous IFN-based treatment. These drugs could not be used as monotherapy because of the rapid development of virological breakthrough. They were, additionally, accompanied by complicated dosing regimens, with 8-hourly dosing, specific dietary requirements and care regarding drug interactions, and additional toxicity, particularly cytopenias and rashes. So, the tolerability from the patient perspective was challenging when combined with peg-IFN and ribavirin.

This led to the development of a second wave of first generation NS3/4A PIs. These include simeprevir, approved in November 2013 in the United States and in May 2014 in the European Union, for the treatment of HCV genotype 1. Others drugs of this class include asunaprevir, paritaprevir, etc. They have an edge over telaprevir and boceprevir with once- or twice-daily dosing; active against at least genotypes 1, and 4. Better SVR rates were observed when simeprevir was added to peg-IFN plus ribavirin compared to those of peg-IFN plus ribavirin alone in treatment-naïve and previously treated patients.

In November 2014, the US-FDA approved an all-oral regimen of simeprevir plus sofosbuvir for treatment-naïve or treatment-experienced patients. Simeprevir when given with sofosbuvir has shown SVR rates of 88–97% in treatment-naïve and 79–95% in treatment-experienced HCV genotype 1 patients in the Phase 3 clinical trials. Further, drawbacks like low barrier to resistance and extensive cross-resistance among PIs have limited the use of PIs.

To address these issues, the second generation of protease inhibitors were introduced, overcoming the limitations of resistance, thus presenting a high barrier to resistance than the first-generation drugs. In addition, some of these drugs may have pan-genotypic action, including those with genotype 3. Examples of this class include grazoprevir, glecaprevir and voxilaprevir.

These drugs are not meant to be administered alone and are recommended with other DAAs like NS5A and/or NS5B inhibitors.

B. NS5B nucleoside polymerase inhibitors (NPIs) and non-nucleoside polymerase inhibitors (NNPIs)

These two classes of drugs, **NPIs** and **NNPIs** help prevent HCV RNA replication. The **NPI** class interacts directly with the catalytic site of NS5B and, by being incorporated into the elongating HCV RNA, act as chain terminators of RNA synthesis. In contrast, **NNPIs** bind to sites outside the catalytic site and inhibit NS5B function by changing the conformation of the active site.

They have **good efficacy** and **high barrier to resistance** because the viral variants they select are not fit enough to replicate at high levels *in vitro* or *in vivo.*

Sofosbuvir is a prototype drug of this class and has brought about a revolution in the therapy of hepatitis C, with SVRs of around 90% across all genotypes.

However, sofosbuvir is not recommended for monotherapy, and needs to be administered along with one or more of these medicinal agents: ribavirin, peg-IFN, PIs or NS5A inhibitors.

Sofosbuvir can be administered in the following regimens:

1. **Sofosbuvir (400 mg) daily + Ribavirin (Weight-based*) daily ----not recommended currently**
2. **Sofosbuvir (400 mg) daily + Peg-IFN (Peg-IFN alfa-2a: 180 µg/week or Peg-IFN alfa-2b: 1.5 µg/kg/week) + Ribavirin (Weight-based*) daily---------- not recommended currently**
3. **Sofosbuvir + NS3/4A Inhibitors**
   - Sofosbuvir (400 mg) daily+ Simeprevir (150 mg) daily
4. **Sofosbuvir + NS5A inhibitors**
   - Ledipasvir-Sofosbuvir FDC (90/400 mg) once daily
   - Sofosbuvir (400 mg) daily + Daclatasvir (60 mg) daily
   - Sofosbuvir - Velpatasvir FDC (400/100 mg) once daily
5. **Sofosbuvir + NS5A inhibitors+ NS3/4A inhibitors**
   - Sofosbuvir - Velpatasvir - Voxilaprevir FDC (400/100/100 mg) once daily

* Dose of ribavirin is weight-based (<75 kg = 1,000 mg and ≥75 kg = 1,200 mg). The daily dose of ribavirin is administered orally in two divided doses with food. Patients with renal impairment (CrCl ≤50 mL/min) require ribavirin dose reduction.

C. NS5A inhibitors

NS5A inhibitors are chemical compounds that target the HCV-encoded NS5A gene product—a rather enigmatic non-enzymatic protein, which is essential for viral genome replication and virus assembly. It is a key modulator of the HCV life cycle but its exact functions are unknown.

Although their exact mechanism of action remains unknown, NS5A-proteins probably function by

A. Regulating HCV replication and host–cell interactions as an essential component of the viral replication complex; and,
B. Inhibiting virus assembly and secretion from cells.

These agents are meant to be administered in in combination with either NS3/4A PIs or NS5B NPIs.

Daclatasvir was the first NS5A HCV inhibitor to be introduced. Ledipasvir is another clinically important NS5A inhibitor, given in combination with NS5B inhibitor, sofosbuvir, as a fixed-dose combination (FDC) (HCV genotypes 1, 4, 5 and 6). Daclatasvir (60 mg) in combination with sofosbuvir (400 mg) is an US-FDA approved NS5A/NS5B regimen for HCV (HCV genotypes 1 and 3).

However, they are accompanied by certain drawbacks. They are active against all HCV genotypes, but some of them are less active against genotypes 2 and 3. They can select resistant viruses *in vivo*—especially those with substitutions at NS5A positions Q30, L31, and Y93. Hence, they are never recommended for monotherapy and must be given in combination with NS3/4A protease inhibitors and/or NS5B polymerase inhibitors.

Second-generation NS5A inhibitors recently introduced include elbasvir, pibrentasvir and velpatasvir. Sofosbuvir-velpatasvir FDC has been approved as a pangenotypic regimen in all HCV genotypes (1-6).

Thus, owing to the introduction of DAAs, HCV therapy has undergone a paradigm transition from IFN-dependent to IFN-free all-oral DAA regimens with improved SVR rates.

3. SOFOSBUVIR: A REVOLUTION IN THE MANAGEMENT OF HEPATITIS C

The introduction of sofosbuvir has been a significant development in the HCV therapy. It targets the NS5B polymerase, which plays an important role in RNA replication. Inhibition of this enzyme results in suppression of HCV replication and life cycle. Sofosbuvir was approved by the US-FDA in December 2013 for treatment of chronic hepatitis C infection genotypes 1, 2, 3, and 4 as part of a combination antiviral regimen, including those with hepatocellular carcinoma meeting the Milan criteria (awaiting liver transplantation) to prevent HCV recurrence and those with HCV/HIV-1 co-infection.

Sofosbuvir treatment regimens and duration are dependent on both viral genotype and patient population. The recommended dose of sofosbuvir is 400 mg once daily to be taken with other DAAs with or without weight-based ribavirin. This has helped to shorten the earlier 24-48 weeks of therapy to 12-24 weeks.

Approval for sofosbuvir was based on the results of some Phase 3 studies that evaluated 12 weeks of treatment with the drug combined with either ribavirin or ribavirin plus peg-IFN alfa. Three of these studies evaluated sofosbuvir plus ribavirin in genotype 2 or 3 patients who were either treatment-naïve, treatment-experienced or peg-IFN-intolerant, -ineligible or -unwilling. The fourth study evaluated sofosbuvir in combination with peg-IFN/ribavirin in treatment-naïve patients with genotypes 1, 4, 5 or 6.

In these studies, sofosbuvir-based therapy was found to be superior to historical controls or to placebo, based on the proportion of patients who had a SVR12 after completing therapy.

Based on these trials, it was observed that patients with genotypes 1 and 4 who were treated with 12-week therapy of sofosbuvir achieved more than 90% SVR12 (NEUTRINO study). In addition, patients with genotype 2 achieved over 90% SVR12 with all-oral therapy of sofosbuvir and ribavirin for 12 weeks. In patients with genotype 3, 24 weeks of sofosbuvir and ribavirin is recommended based on 85% SVR12 observed with this regimen in one key Phase 3 trial, VALENCE.

Sofosbuvir has shown high SVR12 rates in HCV-infected special populations like those with HCV/HIV-1 co-infection and in post-liver transplant patients to treat HCV post-liver transplant or preventing recurrence post-liver transplant. In HCV/HIV-1 co-infected patients with limited options for HCV treatment earlier, 12-week and 24-week dual therapies of sofosbuvir-ribavirin have shown high SVR12 rates of around 85-90%.

Such high SVR12 rates with a good tolerance to the therapy across the HCV population were not observed with conventional therapies before. Moreover, in all these studies, sofosbuvir had reasonable safety profile, without any serious adverse effects attributed to sofosbuvir. Most of the adverse events were related to ribavirin or peg-IFN.

In all Phase 3 studies, no viral resistance to sofosbuvir was detected among patients who relapsed following completion of therapy. In addition, high SVR12 rates were seen in patients who failed earlier treatments with peg-IFN and ribavirin-based regimens. This indicates that sofosbuvir has a high barrier to resistance.

However, the IFN-based regimens are no longer recommended in the international HCV guidelines, at least as first-line therapy for treatment-naïve patients, as they are inferior to IFN-free oral DAA combinations in terms of both their safety and tolerability profiles.

The development of sofosbuvir has paved the way for development of newer DAAs for HCV therapy. The development of all-oral DAAs for the treatment of HCV started with the approval of simeprevir administered with sofosbuvir for the treatment of chronic HCV genotype 1. Simeprevir (150 mg) when given with 400 mg sofosbuvir, for 12–24 weeks has resulted in SVR rates ranging from 85–90% in HCV genotype 1 patient. However, response rates are significantly affected by the presence of baseline NS5A resistance-associated variants especially the Q80K polymorphism. The presence of Q80K polymorphism results in lower response in these patients. This limitation urged the development of NS5A inhibitors.

The NS5A inhibitor ledipasvir, when added to sofosbuvir is a significant advancement towards an all-oral DAA therapy for HCV genotype 1. The FDC of ledipasvir-sofosbuvir (in the dose of 90 mg/400 mg, respectively) is approved by the US-FDA for HCV genotype 1, 4, 5 or 6.

The ledipasvir-sofosbuvir FDC has shown excellent efficacy with SVR12 rates in HCV genotype 1 patients: 99% in treatment-naïve patients, 94–99% in treatment-experienced patients, and 86–99% in cirrhotic patients. It has also produced very good results in different subgroups of patients regardless of patient ethnicity or host genetic factors. The combination therapy was well tolerated as shown in various studies.

Hence, the introduction of the ledipasvir-sofosbuvir FDC provides a new IFN- and ribavirin-free one pill once a day treatment option in HCV genotype 1.

Although, sofosbuvir-based regimens have shown good efficacy across all the genotypes, genotype 3 has emerged as relatively difficult-to-treat, warranting a second DAA to be added to sofosbuvir for treatment. This led to the development of daclatasvir, a NS5A inhibitor, which inhibits viral production, virion assembly or secretion from the infected cells. It is administered along with sofosbuvir. The two drugs in combination act synergistically to eradicate the infection.

Daclatasvir when administered with sofosbuvir for 12 weeks has shown excellent efficacy in HCV genotype 3 patients. SVR12 rates of 94–97% were achieved in non-cirrhotic, treatment-experienced and treatment-naïve HCV genotype 3 patients,

respectively. Increased SVR rates were achieved in clinical trials, compared to the earlier regimens, with peg-IFN and ribavirin, as well as sofosbuvir- and ribavirin-based dual regimens, especially in treatment-experienced HCV genotype 3 patients.

Daclatasvir with sofosbuvir is an US-FDA-approved regimen for treatment-naïve and treatment-experienced patients with HCV genotypes 1 and 3.

Sofosbuvir-velpatasvir is the first, pangenotypic, once-daily, oral FDC to be approved by US-FDA for treating adults with HCV genotypes 1-6. It can be in both treatment-naïve and treatment-experienced patients without cirrhosis as well as those with compensated and decompensated cirrhosis. The recommended dosage of sofosbuvir-velpatasvir FDC (400 mg/100 mg) is one tablet taken once daily for 12 weeks in patients without cirrhosis and compensated cirrhosis. In patients with decompensated cirrhosis, the same regimen is recommended with ribavirin. These recommendations are uniform regardless of the genotype and prior HCV treatment experience.

Sofosbuvir-velpatasvir FDC for 12 weeks has resulted in overall SVR rates of 98%-100% in treatment-naïve and treatment-experienced HCV genotype 1-6 patients without cirrhosis or compensated cirrhosis. In HCV patients with decompensated cirrhosis, 12-24-week therapy of the FDC with or without ribavirin resulted in SVR rates ranging from 86%-94%. It has been found to be safe and tolerable across the HCV population.

The approval of sofosbuvir-based therapies with daclatasvir, ledipasvir and velpatasvir has further revolutionized HCV therapy, bringing in the trend of peg-IFN-free all-oral regimens. Moreover, a shortened therapy period of 12–24 weeks with improved SVR rates of above 90% is a great leap ahead in the development of HCV therapy (Fig. 3). Most recently a triple fixed drug combination of sofosbuvir-velpatasvir-voxilaprevir (400/100/100 mg) has been approved by the US-FDA as a second-line regimen in treatment of adult patients with chronic HCV infection without cirrhosis or with compensated cirrhosis (Child-Pugh A) who have genotype 1, 2, 3, 4, 5, or 6 infection and have previously been treated with an HCV regimen containing an NS5A inhibitor or genotype 1a or 3 infection and have previously been treated with an HCV regimen containing sofosbuvir without an NS5A inhibitor.

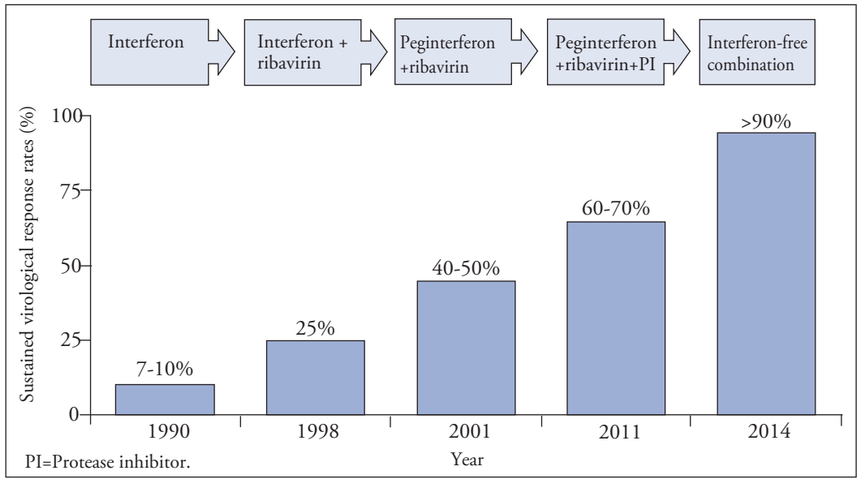

Fig. 3: Revolution in the Management of Hepatitis C from IFN-based to IFN-Free Regimens. Adapted from: *Lancet 2015; 385: 1124–35.*

Besides sofosbuvir containing regimens, other US-FDA approved non-sofosbuvir containing regimens include the Abbvie 3D regimen (Viekira Pak) which contains three new drugs—ombitasvir, paritaprevir (boosted with ritonavir) and dasabuvir approved for use in HCV genotype 1 with SVR12 rates of 91%–100% in patients including those considered difficult to treat. The Abbvie 2D regimen with ombitasvir, paritaprevir (boosted with ritonavir) is approved for use in HCV genotype 4.

Grazoprevir-elbasvir FDC (100/50 mg) is indicated with or without ribavirin for the treatment of chronic HCV genotypes 1 or 4 infection. Recently the US-FDA has also approved glecaprevir-pibrentasvir FDC (3 tablets once daily each containing glecaprevir 100 mg and pibrentasvir 40 mg) as a firstline treatment of HCV genotype 1, 2, 3, 4, 5 or 6 infection without cirrhosis or with compensated cirrhosis (Child-Pugh A) and as a second line agent for patients with HCV genotype 1 infection, who previously have been treated with a regimen containing an HCV NS5A inhibitor or an NS3/4A PI, but not both.

4. GUIDELINE RECOMMENDATIONS FOR THE TREATMENT OF HEPATITIS C

Guidelines devised by the American Association for the Study of Liver Disease (AASLD) (updated in April 2017) and European Association for the Study of Liver (EASL) (updated in March 2016) as well as the Indian National Association for the Study of Liver (INASL) (updated in September 2016) recommend strategies for the management of hepatitis C.

Treatment for hepatitis C is recommended for all groups, since cure is possible. However, these guidelines recommend prioritization of treatment in some patient groups.

- According to the AASLD guidelines, antiviral treatment is recommended for all patients with chronic HCV infection, except those with limited life expectancy due to non-hepatic causes.
- If resources limit the ability to treat all infected patients immediately as recommended, then it is most appropriate to treat those at greatest risk of disease complications before treating those with less advanced diseases.
- The AASLD recognizes certain patient groups who pose a risk for transmitting HCV and in whom treatment may reduce transmission (Table 2).

Table 2: Persons with Risk of HCV Transmission or in Whom Treatment May Reduce Transmission

• Men who have sex with men with high-risk sexual practices
• Active injection- drug users
• Incarcerated persons
• Persons on long-term hemodialysis
• HCV-infected women of childbearing potential wishing to get pregnant
• Infected health care workers who perform exposure-prone procedures

According to the EASL 2016 guidelines, following are the priorities and treatment indications:

- All treatment-naïve and treatment-experienced patients with compensated or decompensated chronic liver disease related to HCV, who are willing to be treated and who have no contraindications to treatment, must be considered for therapy.
- Treatment must be considered without delay in patients with significant fibrosis (METAVIR score F2 or F3) or cirrhosis (METAVIR score F4), including decompensated cirrhosis; patients with clinically significant extrahepatic manifestations (e.g. symptomatic vasculitis associated with HCV-related mixed cryoglobulinaemia HCV immune complex-related nephropathy and non-Hodgkin B cell lymphoma); patients with HCV recurrence after liver transplantation; patients at risk of a rapid evolution of liver disease due to concurrent comorbidities (non-liver solid organ or stem cell transplant recipients, diabetes); and individuals at risk of transmitting HCV (active injection drug users, men who have sex with men with high-risk sexual practices, women of childbearing age who wish to get pregnant, haemodialysis patients, incarcerated individuals).
- Patients with decompensated cirrhosis and an indication for liver transplantation with a MELD score ≥18–20 will benefit from transplantation first and antiviral treatment after transplantation, because the probability of significant liver function improvement and delisting is low. If the waiting time before transplantation expected to be more than six months, these patients can be treated or their HCV infection.

Treatment is not recommended in patients with limited life expectancy due to non-liver-related comorbidities.

Treatment recommendations by the AASLD and EASL are made considering the newer DAAs, viz., ledipasvir, daclatasvir, velpatasvir, elbasvir, grazoprevir, simeprevir, voxilaprevir and ritonavir-boosted paritaprevir, ombitasvir and dasabuvir.

Although newer DAAs such as velpatasvir are approved in the Indian scenario, the INASL guidelines released in 2016 have, yet, not updated the recommendations with this DAA. The INASL (2016) recommendations are as under.

Table 3: INASL Guidance (2016) for Treatment of Chronic Hepatitis C

HCV Genotype 1	
Recommended Regimen	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) + RBV[a]: 12 weeks
	SOF (400 mg) + LDV (90 mg): 24 weeks
	SOF (400 mg) + DCV (60 mg): 24 weeks
	SOF (400 mg) + DCV (60 mg) + RBV[a]: 12 weeks

HCV Genotype 2	
Recommended regimen	SOF (400 mg) + weight-based RBV[a]: 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

HCV Genotype 3	
Recommended regimen	SOF (400 mg) + DCV (60 mg): 12 weeks
	SOF (400 mg) + RBV[a]: 24 weeks
For patients with cirrhosis	SOF (400 mg) + DCV (60 mg) + RBV[a]: 24 weeks
Alternative regimen in compensated cirrhotics	SOF (400 mg) + Peg-IFN-α weekly + RBV[a]:12 weeks

HCV Genotype 4	
Recommended Regimen	SOF (400 mg) + LDV (90 mg) : 12 weeks
Alternative regimen	SOF (400 mg) + Peg-IFN-α weekly + RBV[a]: 12 weeks SOF (400 mg) + RBV[a]: 24 weeks
For patients with cirrhosis	SOF (400 mg) + LDV (90 mg): 24 weeks SOF (400 mg) + LDV (90 mg) + RBV[a]: for 12 weeks

HCV Genotype 5 and 6	
Recommended Regimen	SOF (400 mg) + LDV (90 mg): 12 weeks
Alternative regimen	SOF (400 mg) + Peg-IFN-α weekly + RBV [a]: 12 weeks
For patients with cirrhosis	SOF (400 mg) + LDV (90 mg): 24 weeks SOF (400 mg) + LDV (90 mg) + RBV[a] : 12 weeks

Abbreviations: DCV, daclatasvir; LDV, ledipasvir; Peg-IFN, pegylated interferon alfa; RBV, ribavirin; SOF, sofosbuvir.
[a]Weight-based RBV (1000 mg if weight <75 kg and 1200 mg if ≥75 kg, as tolerated).

The AASLD (April 2017) recommendations are as under.

Table 4: AASLD Guideline Recommendations for Treatment-naïve HCV Patients (2017)

Genotype	Treatment	Duration
1 a	Ledipasvir + Sofosbuvir FDC	12 weeks (no cirrhosis/cirrhosis) 8 weeks (no cirrhosis; non-black, HIV-uninfected, and HCV RNA level <6 million IU/mL)
	Paritaprevir/Ritonavir + Ombitasvir FDC + Dasabuvir as part of an extended-release regimen or plus twice-daily dosed dasabuvir +Ribavirin	12 weeks (no cirrhosis) 24 weeks (cirrhosis) (Alternative)
	Sofosbuvir + Simeprevir	12 weeks (no cirrhosis)
	Sofosbuvir + Simeprevir +/- Ribavirin	24 weeks (cirrhosis) (Alternative) (without Q80K mutation)
	Elbasvir + Grazoprevir FDC	12 weeks (no cirrhosis/cirrhosis)
	Elbasvir + Grazoprevir FDC + Ribavirin	16 weeks (cirrhotic and non-cirrhotic with baseline NS5A RAVS for elbasvir) (Alternative)
	Sofosbuvir + Velpatasvir FDC	12 weeks (no cirrhosis/cirrhosis)
	Daclatasvir + Sofosbuvir Daclatasvir + Sofosbuvir +/- Ribavirin	12 weeks (no cirrhosis) 24 weeks (cirrhosis) (Alternative)

Genotype	Treatment	Duration
1b	Ledipasvir + Sofosbuvir FDC	12 weeks (no cirrhosis/cirrhosis) 8 weeks (no cirrhosis; non-black, HIV-uninfected, and whose HCV RNA level is <6 million IU/mL)
	Paritaprevir/Ritonavir + Ombitasvir + Dasabuvir FDC as part of an extended-release regimen or plus twice-daily dosed dasabuvir	12 weeks (no cirrhosis/cirrhosis)
	Sofosbuvir + Simeprevir Sofosbuvir + Simeprevir +/- Ribavirin	12 weeks (no cirrhosis) 24 weeks (cirrhosis) (Alternative)
	Daclatasvir + Sofosbuvir Daclatasvir + Sofosbuvir +/- Ribavirin	12 weeks (no cirrhosis) 24 weeks (cirrhosis) (Alternative)
	Elbasvir + Grazoprevir FDC	12 weeks (no cirrhosis/cirrhosis)
	Sofosbuvir + Velpatasvir FDC	12 weeks (no cirrhosis/cirrhosis)
2	Sofosbuvir + Velpatasvir FDC	12 weeks (no cirrhosis/cirrhosis)
	Daclatasvir + Sofosbuvir	12 weeks (no cirrhosis)(Alternative) 16-24 weeks (cirrhosis)
3	Daclatasvir + Sofosbuvir Daclatasvir + Sofosbuvir + Ribavirin	12 weeks (no cirrhosis) 24 weeks (cirrhosis)
	Sofosbuvir + Velpatasvir FDC	12 weeks (no cirrhosis/cirrhosis)

Genotype	Treatment	Duration
4	Sofosbuvir + Velpatasvir FDC	12 weeks (no cirrhosis/cirrhosis)
	Ledipasvir + Sofosbuvir FDC	12 weeks (no cirrhosis/cirrhosis)
	Paritaprevir/Ritonavir + Ombitasvir FDC + Ribavirin	12 weeks (no cirrhosis/cirrhosis)
	Elbasvir + Grazoprevir FDC	12 weeks (no cirrhosis/cirrhosis)
5 or 6	Ledipasvir + Sofosbuvir FDC	12 weeks (no cirrhosis/cirrhosis)
	Sofosbuvir + Velpatasvir FDC	12 weeks (no cirrhosis/cirrhosis)

NOTE: The dose of daclatasvir may need to increase or decrease when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. Please refer to the prescribing information.

Table 5: AASLD Guideline Recommendations for Treatment-experienced HCV Patients (2017)

Genotype	Treatment	Duration
1 a/1b	Daclatasvir + Sofosbuvir Daclatasvir + Sofosbuvir+/- Ribavirin	12 weeks (no cirrhosis) 24 weeks (cirrhosis) (Alternative)
	Ledipasvir + Sofosbuvir Ledipasvir + Sofosbuvir+ Ribavirin	12 weeks (no cirrhosis) 24 weeks (cirrhosis) (Alternative) 12 weeks (cirrhosis)

Genotype	Treatment	Duration
	Paritaprevir/ Ritonavir + Ombitasvir FDC + Dasabuvir as part of an extended-release regimen or plus twice daily dosed dasabuvir +Ribavirin	12 weeks (no cirrhosis) 24 weeks (cirrhosis) (Alternative)----1a
	Paritaprevir/ Ritonavir + Ombitasvir FDC + Dasabuvir as part of an extended-release regimen or plus twice -daily dosed dasabuvir	12 weeks (cirrhosis)-----1b
	Sofosbuvir + Simeprevir Sofosbuvir + Simeprevir +/- Ribavirin	12 weeks (no cirrhosis) 24 weeks (cirrhosis) (Alternative)
	Elbasvir + Grazoprevir FDC Elbasvir + Grazoprevir FDC + Ribavirin	12 weeks (no cirrhosis/cirrhosis) 16 weeks (cirrhotic and non-cirrhotic with baseline NS5A RAVS for elbasvir) (Alternative)
	Sofosbuvir + Velpatasvir FDC	12 weeks (no cirrhosis/cirrhosis)
2	Sofosbuvir + Velpatasvir FDC Sofosbuvir + Velpatasvir FDC + Ribavirin	12 weeks (no cirrhosis/cirrhosis) 12 weeks (Sofosbuvir Plus Ribavirin Treatment-experienced)
	Daclatasvir + Sofosbuvir Daclatasvir + Sofosbuvir+/- Ribavirin	12 weeks (no cirrhosis) (Alternative) 16-24 weeks (cirrhosis) (Alternative) 24 weeks (Sofosbuvir Plus Ribavirin Treatment-experienced)

Genotype	Treatment	Duration
3	Daclatasvir + Sofosbuvir Daclatasvir + Sofosbuvir + Ribavirin	12 weeks (no cirrhosis) 24 weeks (cirrhosis) (Alternative)/ Sofosbuvir-based treatment-experienced
	Sofosbuvir + Velpatasvir FDC Sofosbuvir + Velpatasvir FDC + Ribavirin	12 weeks (no cirrhosis) 12 weeks (cirrhosis)
	Elbasvir + Grazoprevir FDC Elbasvir + Grazoprevir FDC + Sofosbuvir +/- Ribavirin	12 weeks (cirrhosis) 12-16 weeks (Sofosbuvir Plus Ribavirin Treatment-experienced)
4	Sofosbuvir + Velpatasvir FDC	12 weeks (no cirrhosis/cirrhosis)
	Ledipasvir + Sofosbuvir FDC + Ribavirin Ledipasvir + Sofosbuvir FDC	12 weeks (no cirrhosis/cirrhosis) 24 weeks (cirrhosis) (Alternative)
	Paritaprevir/Ritonavir + Ombitasvir FDC + Ribavirin	12 weeks (no cirrhosis/cirrhosis)
	Elbasvir + Grazoprevir FDC Elbasvir + Grazoprevir FDC + Ribavirin	12 weeks (no cirrhosis/cirrhosis) ..... prior virologic relapse 16 weeks (no cirrhosis/cirrhosis) … prior on-treatment virologic failure
5 or 6	Ledipasvir + Sofosbuvir FDC	12 weeks (no cirrhosis/cirrhosis)
	Sofosbuvir + Velpatasvir FDC	12 weeks (no cirrhosis/cirrhosis)

There are other recommendations based on the unique patient profiles such as HIV-HCV co-infection, liver transplant and HCV-chronic kidney disease (CKD) patients which have not been dealt in this issue.

Recommendations for treatment monitoring in the era of DAAs

For treatment monitoring in the era of DAAs, the INASL guidelines recommend the following:

- Patients 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.
- Patients on sofosbuvir should have monitoring of renal functions and patients on DAA should have monitoring for possible drug interactions.
- Patients with cirrhosis need surveillance for HCC and portal hypertension

The AASLD guidelines recommend quantitative HCV viral load testing after 4 weeks of therapy and at 12 weeks following completion of therapy. In addition, they also state that antiviral drug therapy should not be interrupted or discontinued if HCV RNA levels are not performed or available during treatment.

Thus, with the introduction of all oral-DAAs to treat hepatitis C, the monitoring patterns have also undergone a change.

5. CONCLUSION

HCV infection is a global problem that leads to the development of chronic hepatitis, cirrhosis and hepatocellular carcinoma. Conventional treatment included the IFN and ribavirin combination, which has many adverse effects. With newer drugs, such as sofosbuvir, therapy for hepatitis C is undergoing a revolution. All-oral, IFN-free combinations of drugs are expected to cure more than 90% of HCV infections. With newer regimens in development, individualized therapy with shorter treatment duration may be possible in the near future.

FURTHER READING

1. Alessandra Mangia, Valeria Piazzolla. Overall efficacy and safety results of sofosbuvir-based therapies in Phase II and III studies. *Digestive and Liver Disease; 46: S179–S185.*
2. Hoofnagle J.H., Mullen K.D., Jones D.B. et al. Treatment of chronic non-A, non-B hepatitis with recombinant human alpha interferon. A preliminary report. *N Engl J Med 1986; 315:1575–8.*
3. Foster GR. Pegylated interferons for the treatment of chronic hepatitis C: phamacological and clinical differences between peginterferon-alpha-2a and pegiterferon-alpha-2b. *Drugs. 2010;70(2):147-65.*
4. Di Bisceglie A.M., Martin P., Kassianides C. et al. Recombinant interferon alfa therapy for chronic hepatitis C. A randomized, double-blind, placebo controlled trial. *N Engl J Med 1989; 321: 1506–10.*
5. Shindo M, Di Bisceglie AM, Cheung L, et al. Decrease in serum hepatitis C viral RNA during alpha-interferon therapy for chronic hepatitis C. *Ann Intern Med 1991; 115: 700–4.*
6. Poordad F., McCone J., Bacon B.R. et al. Boceprevir for untreated chronic HCV genotype 1infection. *N Engl J Med 2011; 364: 1195–206.*
7. Bacon B.R., Gordon S.C., Lawitz E. et al. Boceprevir for previously treated chronic HCV genotype 1 infection. *N Engl J Med 2011; 364: 1207–17.*
8. Hezode C., Forestier N., Dusheiko G. et al. Telaprevir and peginterferon with or without ribavirin for chronic HCV infection. *N Engl J Med 2009; 360: 1839–50.*
9. Pawlotsky J.M. New hepatitis C therapies: the toolbox, strategies, and challenges *Gastroenterology. 2014; 146 (5):1176-92.*
10. Lawitz E., Sulkowski M.S., Ghalib R. Simeprevir plus sofosbuvir, with or wit out ribavirin, to treat chronic infection with hepatitis C virus genotype 1 in non-responders to pegylated interferon and ribavirin and treatment-naive patients: the COSMOS randomised study. *Lancet. 2014; 384(9956):1756-65.*
11. Kwo P. et al. Abstract LB14. EASL - The International Liver Congress 2015-50th annual Meeting of the European association for the Study of the Liver, Vienna, Austria, April 22-26.
12. Lawitz E. et al Abstract LP04. EASL - The International Liver Congress 2015- 50th annual Meeting of the European association for the Study of the Liver, Vienna, Austria, April 22-26.
13. Jacobson I.M, Gordon S.C, Kowdley K.V. et al. Sofosbuvir for Hepatitis C Genotype 2 or 3 in Patients without Treatment Options. *N Engl J Med. 2013; 368:1867–77.*
14. Lawitz E., Mangia A, Wyles D. et al. Sofosbuvir for previously untreated chronic hepatitis C infection. *N Engl J Med. 2013; 368(20):1878–87.*
15. Zeuzem S., Dusheiko G.M., Salupereet R. et al. Sofosbuvir and Ribavirin in HCV Genotypes 2 and 3. *N Engl J Med. 2014; 370:1993–2001.*
16. Afdhal N., Zeuzem S., Kwo P. et al. Ledipasvir and sofosbuvir for untreated HCV genotype 1 infection. *N Engl J Med. 2014; 370:1889-98.*
17. Afdhal N., Reddy K.R., Nelson D.R. et al. Ledipasvir and sofosbuvir for previously treated HCV genotype 1 infection. *N Engl J Med 2014; 370:1483-93.*
18. Nelson D.R., Cooper J.N., Lalezari J.P. et al. All-oral 12-week treatment with daclatasvir plus sofosbuvir in patients with hepatitis C virus genotype 3 infection: ALLY-3 Phase III study. *Hepatology 2015; 61:1127-35.*
19. J.J. Feld, I.M. Jacobson, C. Hézode, et al. Sofosbuvir and Velpatasvir for HCV Genotype 1, 2, 4, 5, and 6 Infection. *N Engl J Med 2015; 373:2599-607.*
20. G.R. Foster, N. Afdhal, S.K. Roberts, et al. Sofosbuvir and Velpatasvir for HCV Genotype 2 and 3 Infection. *N Engl J Med 2015; 373:2608-17.*
21. Holmes JA, Thompson AJ. Interferon-free combination therapies for the treatment of hepatitis C: current insights. *Hepat Med. 2015 Nov 2;7:51-70.*
22. Lamb YN. Glecaprevir/Pibrentasvir: First Global Approval. *Drugs. 2017 Sep 19. doi: 10.1007/ s40265-017-0817-y. [Epub ahead of print]*
23. Anand A.C. Treatment of chronic hepatitis C: What is new? *Apollo Medicine 2014; 11; 93–102.*
24. Puri P., Saraswat V.A., Dhiman RK et al. Indian National Association for Study of the Liver (INASL) Guidance for Antiviral Therapy Against HCV Infection: Update 2016. *J Clin Exp Hepatol. 2016; 6: 119–145.*
25. Hepatitis C guidance: AASLD-IDSA recommendations for testing, maaging, and treating adults infected with hepatitis C virus. *http://www.hcvguidelines.org. Accessed on April 2017.*
26. Clinical Practice Guidelines. EASL Recommendations on Treatment of Hepatitis C 2016. *J Hepatol. 2017 ;66:153-194.*

NOTES