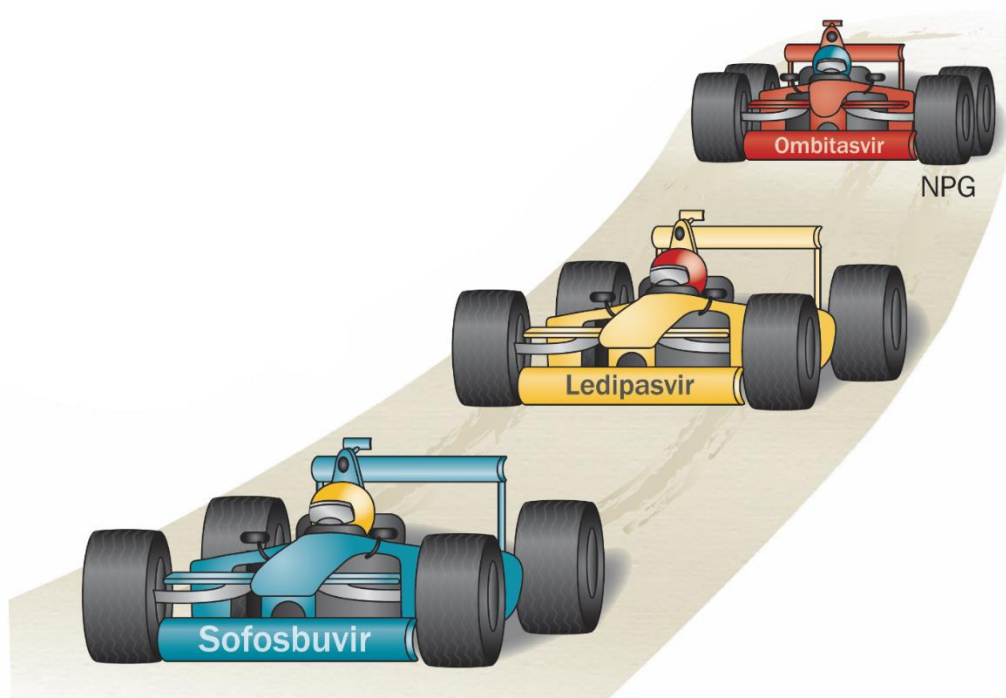


Interferon-free Treatments for Chronic Hepatitis C Genotype 1 Infection



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Learning Objectives

1. Describe the life cycle of hepatitis C virus (HCV) and its mechanism of chronic infection.
2. Explain the challenges in management of chronic hepatitis C.
3. Discuss the role of interferon-free treatments for chronic hepatitis C.
4. Evaluate the evidence for appropriate selection of therapy for patients with various risk factors.

Introduction

- A. The hepatitis C virus (HCV) was discovered in 1989.²
- B. Prior to the discovery, it was shown in the mid-1970's that most post-transfusion cases of hepatitis were not due to either the hepatitis A or B virus, thus giving it its initial name, "non-A non-B hepatitis".³
- C. HCV is a leading cause of chronic hepatitis, cirrhosis, and liver cancer and a primary indication for liver transplantation in the Western world.⁴

Epidemiology

- A. As many as 185 million persons are chronically infected with HCV worldwide and approximately 3.4 million to 4.4 million individuals in the United States.^{5,6}
- B. Spontaneous clearance of chronic hepatitis C is relatively rare, but can occur.⁷
- C. Approximately 18-34% of acutely infected HCV patients naturally clear the virus, but the majority of infected patients will progress to chronic infection (without treatment), 25% of whom will develop cirrhosis over 25-30 years, and 25% of patients with cirrhosis will develop hepatocellular carcinoma (HCC) and/or decompensated liver disease.^{5,7}
 - a. New data suggest patients may experience a more rapid progression of liver fibrosis and accelerated time to development of cirrhosis than previously thought (within 5 to 10 years of infection).⁸
 - b. New data also suggest that once cirrhosis develops, the disease appears to stabilize, and the development of hepatic decompensation in the first 10 years is infrequent.⁸
- D. Approximately 30% of cases of cirrhosis and 25% of HCC worldwide are due to HCV infection.⁹
- E. Globally, more than 350,000 people die annually from liver disease caused by HCV.¹⁰

HCV Genotypes

- A. There are seven major HCV genotypes (~30% sequence divergence) whose prevalence varies geographically, with disease association largely similar across genotypes.^{11,12}
- B. Genotype 1 accounts for the majority of infections in North America, South America, Japan, and Europe.⁴
- C. Genotype 2 is mostly prevalent in Europe, United States, and Central Africa.¹¹
- D. Genotype 3 is prevalent in Southeast Asia.¹¹
- E. Each genotype is grouped into a number of subtypes (~20% sequence divergence).¹¹
- F. Subtype 1a predominates in the United States and subtype 1b predominates in Europe, Japan, and China.¹³⁻¹⁵

Table 1: Prevalence of HCV Genotypes in the United States^{5,16}

HCV genotype	Prevalence of HCV	Geographic Location
1a	36-55%	United States
1b	23-25%	Europe, Japan, and China
2	13-16%	Europe, United States, and Central Africa
3	8-13%	Southeast Asia
4	1-2%	Middle East and Northern Africa
5	< 1%	South Africa
6	< 1%	Southeast Asia
7	< 1%	Unknown

Transmission

- A. HCV RNA (ribonucleic acid) can be detected in blood, saliva, tears, seminal fluid, ascitic fluid, and cerebrospinal fluid.¹⁷⁻¹⁹
- B. Risk factors for transmission include injection-drug use (60%), blood transfusion before 1992, high lifetime number of sexual partners, and iatrogenic transmission, including through dialysis.⁴
- C. Vertical transmission is likely the primary transmission route among children, with more than 1 in 20 children delivered by HCV-infected mothers infected.²⁰

Screening

- A. Widespread screening of blood products and universal precautions were adopted in 1992.
- B. It is estimated that only half of HCV infected individuals have been tested and diagnosed in the U.S.²¹
- C. Who should be screened?
 - a. Persons born between 1945 and 1965.
 - b. Persons with risk behaviors
 - Injection-drug use.
 - Intranasal illicit drug use.
 - c. Persons at risk of exposure:
 - Long-term hemodialysis.
 - Getting a tattoo in an unregulated setting.
 - Healthcare, emergency medical, and public safety workers after needle sticks, sharps, or mucosal exposures to HCV-infected blood.
 - Children born to HCV-infected women.
 - Prior recipients of transfusions or organ transplants.
 - Persons who were ever incarcerated.
 - d. Persons with other medical conditions
 - HIV infection.
 - Unexplained chronic liver disease.
 - Chronic hepatitis.
- D. It takes 2-26 weeks after HCV exposure for acute hepatitis C to develop. HCV RNA can be detected in blood as early as 1 week after exposure.^{22,23}
- E. Second- and third-generation enzyme immunoassays (EIAs) can detect anti-HCV IgG as early as 10 weeks after exposure. Results must be confirmed by either a recombinant immunoblot antibody assay (RIBA) or nucleic acid testing (NAC) to detect HCV RNA.²³
- F. The majority of patients are typically positive for HCV RNA and anti-HCV IgG at presentation, making it difficult to distinguish between acute and chronic infection.²³
- G. An anti-HCV test is recommended for HCV testing, and if the result is positive, current infection should be confirmed by a sensitive RNA test.
- H. Quantitative HCV RNA testing is recommended prior to the initiation of antiviral therapy to document the baseline viral load.
- I. Testing for HCV genotype is recommended to guide selection of the most appropriate antiviral regimen.

Clinical Manifestations

- A. Acute Hepatitis C²⁴
 - a. Usually asymptomatic (70-85%)
 - b. Malaise
 - c. Jaundice
 - d. Influenza-like symptoms
 - e. Elevated aminotransferase levels

- B. Chronic Hepatitis C
 - a. Usually asymptomatic
 - b. Alanine transaminase (ALT) levels typically fluctuate independent of symptoms, while serum HCV RNA levels remain fairly constant.²⁵
 - c. Insulin resistance²⁶
 - d. Steatosis²⁷
 - e. Symptoms of decompensated cirrhosis: esophageal varices, ascites, coagulopathy, encephalopathy, or hepatocellular carcinoma (HCC).
- C. Extrahepatic Manifestations²⁶
 - a. Cryoglobulinemia
 - b. Vasculitis
 - c. Porphyria cutanea tarda
 - d. Membranous glomerulonephritis

Virology

- A. HCV, an enveloped flavivirus, is a positive sense viral ribonucleic acid (RNA).⁴
- B. The viral RNA utilizes the hepatocyte ribosomes for translation. The resulting polyprotein undergoes proteolytic cleavage to ten polypeptides, each with distinct functions.²⁷
- C. There are three structural proteins. The two envelope glycoproteins are targets of host antibody response and the core protein interacts with progeny viral genomes for assembly of the virus.²⁸
- D. The nonstructural proteins NS2, NS3, NS4A, NS4B, NS5A, and NS5B form a complex with viral RNA to initiate viral replication in a cytoplasmic membranous structure.^{27,28}

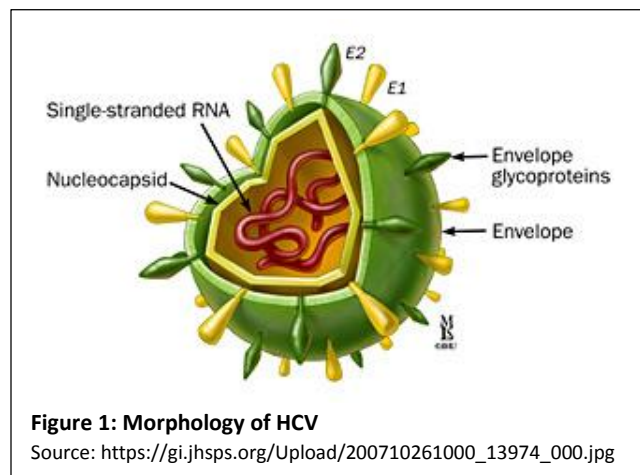


Figure 1: Morphology of HCV

Source: https://gi.jhsps.org/Upload/200710261000_13974_000.jpg

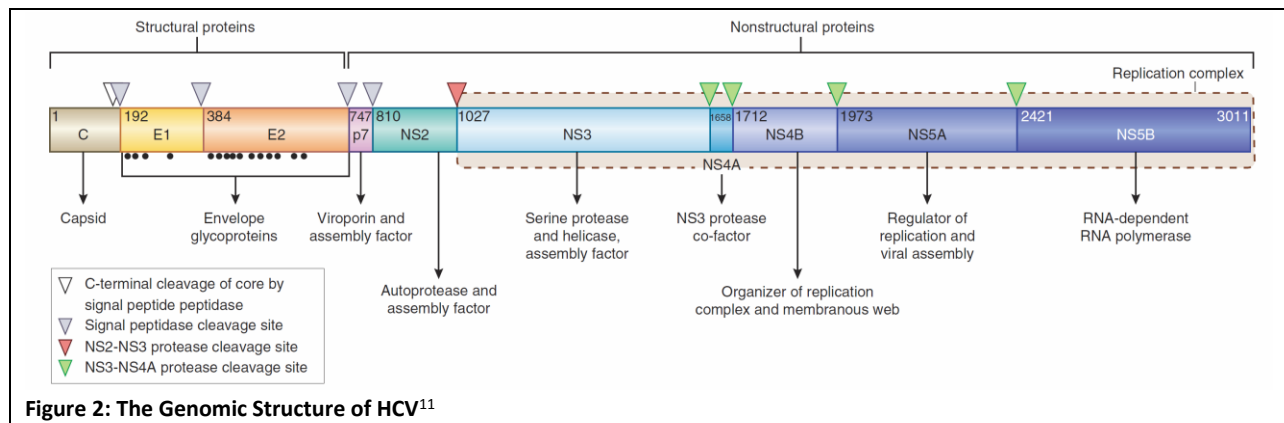
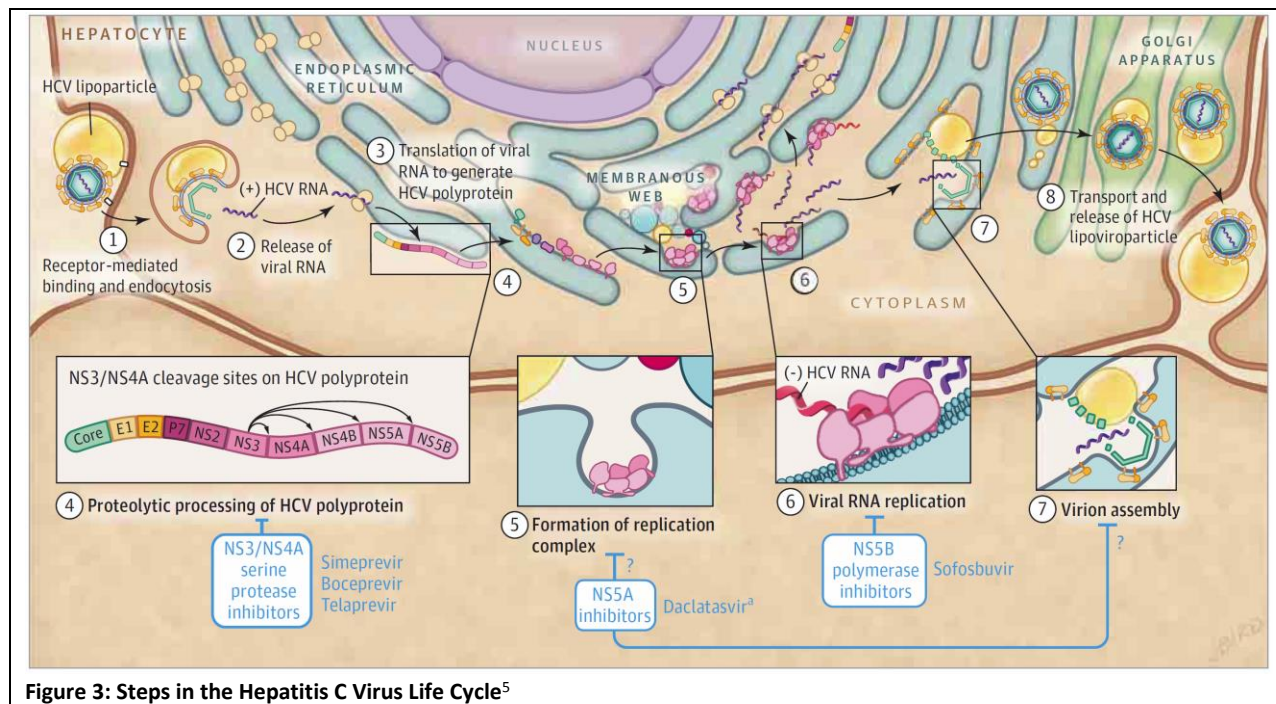


Figure 2: The Genomic Structure of HCV¹¹

HCV Life Cycle

Step 1: Cell entry¹¹

- A. HCV virions exist as lipoviroparticles (LVPs) and associate with low-density and very-low-density lipoproteins (LDL and VLDL).
- B. Uptake is by endocytosis, and fusion, which requires a low pH, is probably encountered in endosomes.



Step 2: Release of viral RNA¹¹

- A. The low pH environment of endosomes results in uncoating of the virion and the release of viral RNA into the cytoplasm.

Step 3: Translation of viral RNA by RNA polymerase¹¹

- A. Translation is initiated in rough endoplasmic reticulum (ER).
- B. miR-122 is a microRNA that is expressed abundantly in the liver and binds to viral RNA to facilitate translation as well as replication.^{27,29} miR-122 binding has a stimulatory effect on translation and also protects uncapped HCV RNA from degradation.^{30,31}

Step 4: Polyprotein processing¹¹

- A. The resulting HCV polyprotein is co- and post-translationally cleaved by cellular proteases and the viral NS2/3 and NS3/4A proteases to release ten HCV proteins (Figure 4).

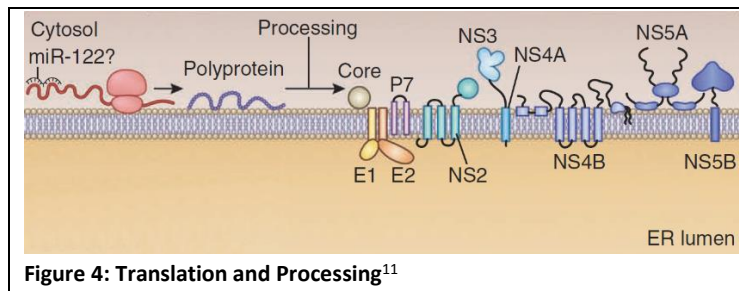


Figure 4: Translation and Processing¹¹

Step 5: Formation of replication complex¹¹

- A. The HCV replicase complex consists of NS3, NS4A, NS4B, NS5A, and the RNA-dependent RNA polymerase NS5B.
- B. NS3 protein possesses serine protease activity and is an RNA helicase.
- C. NS4A protein is a cofactor for the NS3 protease. It anchors the NS3/4A complex to membranes and also interacts with NS5A in the replicase complex.
- D. NS5A protein has RNA binding activity and is important in the assembly of the replication complex.^{27,32}
- E. NS5B protein is the catalytic core of the replicase complex.
- F. Cholesterol and fatty acid biosynthesis are important to HCV replication, for forming membrane-associated RNA replication complexes.

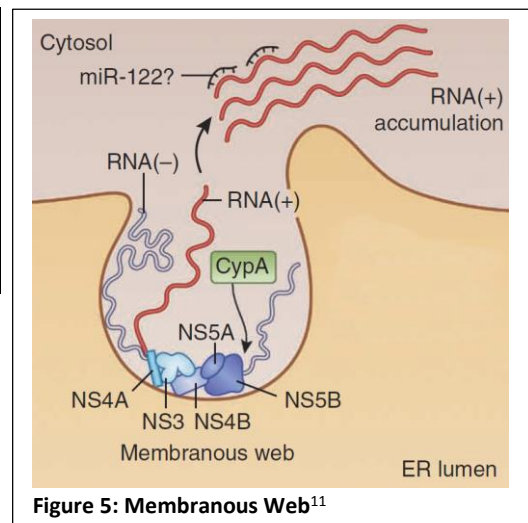


Figure 5: Membranous Web¹¹

Step 6: Viral RNA replication¹¹

- A. The replicase complex recognizes the positive-strand RNA and synthesizes a negative-strand copy, which serves as template for replication.³³
- B. The helicase, NS3, separates the nascent and template RNA strands, unwinding local RNA secondary structures.

Step 7: Virion assembly¹¹

- A. Assembly of HCV requires close interactions with lipid droplets and lipoprotein metabolism.^{27,34}
- B. NS2 coordinates virion assembly through interactions with the glycoproteins, p7, NS3, and NS5A.

Step 8: Release¹¹

- A. Mature virus is released from cells through the Golgi apparatus as lipoviral particles.^{27,35}

Pathogenesis

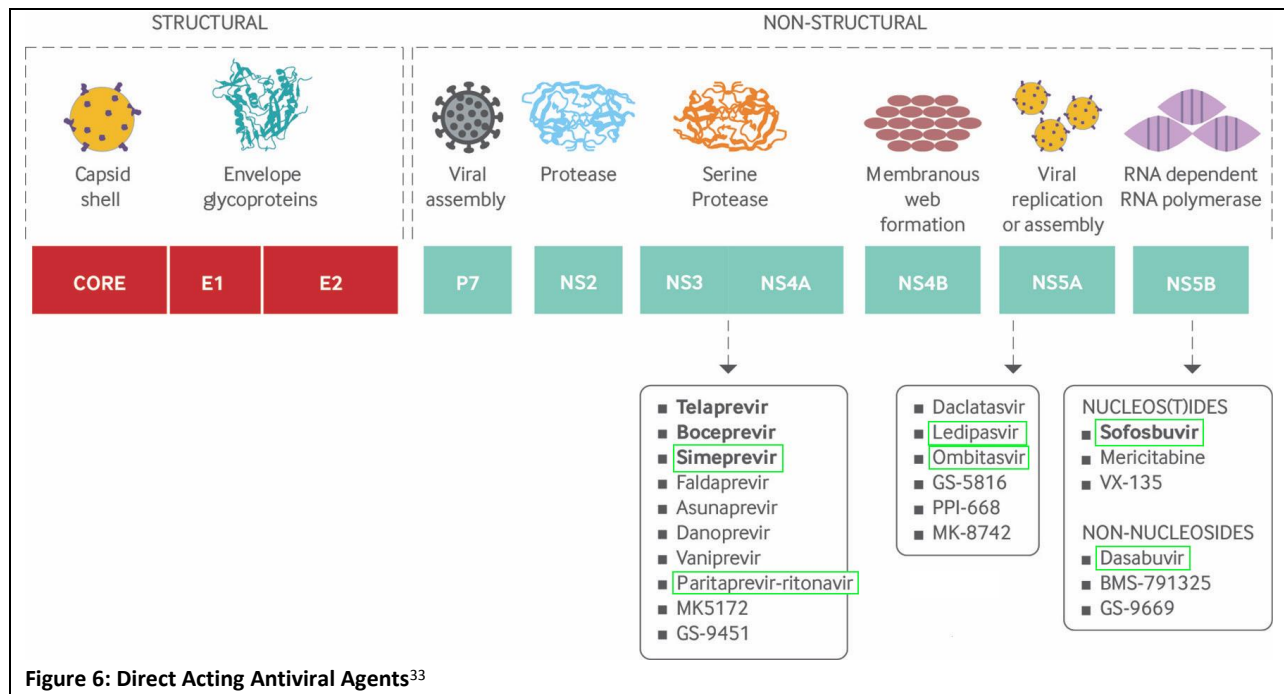
- A. HCV infects predominantly hepatocytes and has the ability to evade the host immune response.^{27,36}
- B. The mechanisms for the persistence of HCV infection and its pathogenesis are not well understood.³⁷
- C. HCV is not directly cytopathic. The hepatic lesions result from the immune recognition and destruction of infected hepatocytes. The continuous necroinflammatory process, inefficient for clearing viral infection, is probably the main cause of the progressive fibrosis.³⁷

Treatment of HCV Genotype 1 Infection

- A. Several definitions are used when monitoring patients
- a. Sustained virologic response (SVR)
 - SVR24 – Historic endpoint
 - Undetectable serum HCV RNA or <25 IU/mL 24 weeks after treatment completed.
 - SVR12^{38,39} – Current endpoint
 - Undetectable serum HCV RNA or <25 IU/mL 12 weeks after treatment completed.
 - 98% positive predictive value (PPV).
 - 99% negative predictive value (NPV).
 - b. Null response – a decrease in HCV RNA level of <2 log IU/mL at week 12.
 - c. Partial response – a decrease in HCV RNA level of ≥2 log IU/mL but a detectable level at the end of treatment.
 - d. Virologic breakthrough – a detectable HCV RNA level while on treatment after previously undetectable.
 - e. Relapse – an undetectable level of HCV RNA during treatment but a detectable level after stopping treatment.
- B. Indirect-acting treatments (Table A1 & A2 in appendix)
- a. Historic treatments
 1. Interferon monotherapy.
 2. Interferon plus ribavirin combination.
 3. Peginterferon plus ribavirin combination.
 - b. Challenges with historic treatments
 1. Poor response associated with cirrhosis, IL28B genotype, black race, HIV coinfection, steatosis, and insulin resistance.⁴⁰⁻⁴⁵
 2. Long duration of therapy 48 weeks.
 3. Severe adverse effects such as flu-like symptoms, depression, and anemia.
 4. Subcutaneous injection as administration route of peginterferon alfa.
 5. Poor adherence.
 6. IFN-ineligibility.
 - c. Direct cost of historic treatments
 - Peginterferon alfa-2a is approximately \$867 per 180 mcg dose, approximately \$10,404 for a 12-week supply, \$20,808 for a 24-week supply, and \$41,616 for a 48-week supply (per Red Book®).
 - Ribavirin 200 mg cap price varies, \$550 to \$850 for 12 weeks of treatment, \$1100 to \$1700 for 48 weeks of treatment (per Red Book®).

C. Direct Acting Antiviral Agents

a. Emergence of direct-acting antiviral (DAA) agents since 2011.



b. Treatment Strategies using DAAs:

- Interferon-sparing therapy (Table A6 in appendix)
 - Addition of a DAA to IFN and RBV will shorten the duration of therapy.
- Interferon-free therapy
 - Combination of two or more DAAs will eliminate the need for PegIFN therapy.
- Ribavirin-free therapy
 - Combination of certain DAAs will eliminate the need for RBV therapy.
- Shorter duration of therapy
 - Cost-effective therapy

c. The First Wave of First Generation Protease Inhibitors (Table A3 in appendix)

- The first two direct-acting antiviral (DAA) agents that were approved, **telaprevir** and **boceprevir**, are inhibitors of the NS3/4A protease.⁴⁶
- The addition of a protease inhibitor to the backbone of peginterferon and ribavirin boosts rates of SVR from about 45% to approximately 75% among treatment-naïve patients with HCV genotype 1.⁶
- In treatment-experienced patients, rates of SVR of 69-88% among prior relapsers, 40-59% among partial responders, and 29-33% among null responders.^{47,48}
- Limitations of this class include rapid emergence of viral resistance, need for a response-guided therapy management, lack of pangenotypic coverage, additional adverse events, drug-drug interactions, pill burden, and contraindications.^{40,47,49}
- The use of telaprevir or boceprevir is no longer recommended by AASLD and IDSA guidelines.**

- d. Currently available direct-acting antiviral agents
 - First Generation NS3/4A Protease Inhibitors (Table A3 in appendix)
 - Second wave: **simeprevir, paritaprevir**
 - NS5B Polymerase Inhibitors: (Table A4 in appendix)
 - Nucleotide Analogue: **sofosbuvir**
 - Non-nucleoside: **dasabuvir**
 - NS5A Inhibitors: (Table A5 in appendix)
 - First generation: **ledipasvir, ombitasvir**
- e. Emerging direct-acting antiviral agents
 - Second Generation NS3/4A Protease Inhibitor
 - **Grazoprevir**
 - NS5B Polymerase Inhibitor
 - Non-nucleoside: **ABT-072**
 - NS5A Inhibitors:
 - First generation: **daclatasvir**
 - Second generation: **elbasvir**

Sofosbuvir and Simeprevir Combination

- A. Sofosbuvir (Sovaldi®) – by Gilead Sciences
 - a. Mechanism of action
 - Sofosbuvir is an inhibitor of the HCV NS5B RNA-dependent RNA polymerase, which is essential for viral replication.
 - b. Adverse effects profile
 - Fatigue and headache (≥20%)
 - Pancytopenia and depression (<1%)
 - c. Resistance profile
 - High barrier to resistance
 - d. Renal impairment
 - No dose recommendation can be given for patients with severe renal impairment (estimated Glomerular Filtration Rate (eGFR) <30 mL/min/1.73m²).
 - e. Drug interactions
 - Sofosbuvir is a substrate of P-glycoprotein (P-gp) and and breast cancer resistance protein (BCRP).
 - Drugs that are potent P-gp inducers in the intestine may significantly decrease sofosbuvir plasma concentrations and may lead to a reduced therapeutic effect of sofosbuvir.
 - Sofosbuvir may be co-administered with P-gp and/or BCRP inhibitors.
- B. Simeprevir (Olysio®) – by Janssen
 - a. Mechanism of action
 - Simeprevir is an inhibitor of the HCV NS3/4A protease which is essential for viral replication.
 - Macrocyclic peptide mimetic that non-covalently binds to NS3/4A protease.
 - b. Adverse effects profile
 - Fatigue (25%), headache (21%), nausea (21%), insomnia (14%), pruritus (11%), rash (11%), and photosensitivity (7%) during 12 weeks.
 - Dizziness (16%), and diarrhea (16%) during 24 weeks.
 - c. Resistance⁵⁰
 - Low barrier to resistance.

- Extensive cross-resistance with telaprevir and boceprevir.
- d. Drug interactions
- Simeprevir is a substrate of CYP3.
 - Co-administration of simeprevir with substances that are moderate or strong inducers or inhibitors of CYP3A is not recommended.
 - Simeprevir mildly inhibits CYP1A2 activity and intestinal CYP3A4 activity, but does not affect hepatic CYP3A4 activity.
 - Simeprevir inhibits OATP1B1/3 and P-gp transporters.
- C. FDA-approved dosing
- a. 12 weeks of simeprevir 150 mg po daily with food plus sofosbuvir 400 mg po daily for treatment-naïve and treatment-experienced patients without cirrhosis.
 - b. 24 weeks of simeprevir 150 mg po daily with food plus sofosbuvir 400 mg po daily for treatment-naïve and treatment-experienced patients with cirrhosis.
- D. Cost
- a. Sofosbuvir 400 mg cap is \$1000 per pill, \$84,000 for 12 weeks of treatment, and \$168,000 for 24 weeks of treatment (per Red Book®).
 - b. Simeprevir 150 mg cap is ~\$800 per pill, \$67,200 for 12 weeks of treatment, and \$134,400 for 24 weeks of treatment (per Red Book®).
- E. Efficacy (Table 3)

Table 3: COSMOS Phase 2 trial⁵¹

Objective				
To determine the efficacy and safety of combined simeprevir and sofosbuvir, with or without ribavirin, in patients who had previously not responded to or not received therapy with peginterferon and ribavirin.				
Patients				
Total No.	167 (40 TN and 127 TE)			
Genotype 1a	78% (45% with Q80K polymorphism)			
Genotype 1b	22% (0% with Q80K polymorphism)			
Cirrhosis	25%			
Design				
Enrollment Period	Nov 2011 to Jan 2014			
Study Type	Phase 2			
Randomization	Randomized, 2:1:2:1			
Blinding	Open-label			
Centers	23 centers in USA			
Primary Endpoint	SVR12			
Interventions				
Treatment Regimens	A: SMV+SOF+RBV for 24 weeks B: SMV+SOF for 24 weeks C: SMV+SOF+RBV for 12 weeks D: SMV+SOF for 12 weeks			
Results				
	A	B	C	D
SVR12 (Overall)	87% (47/54)	97% (30/31)	94% (51/54)	93% (26/28)
Cirrhosis - TN	100% (3/3)	100% (6/6)	100% (6/6)	67% (2/3)
Cirrhosis - TE	90% (9/10)	100% (4/4)	80% (4/5)	100% (4/4)
Genotype 1a (Q80K)	86% (83%)	100% (100%)	93% (88%)	91% (89%)
Genotype 1b	91%	88%	100%	95%
Relapse – TN	0%	0%	1 patient	1 patient
Relapse – TE	1 patient	0%	2 patients	1 patient

Resistance	At the time of relapse, five of the six had developed resistance-associated mutations to simeprevir in NS3, but none to sofosbuvir.
Adverse Effects	The most common AEs were fatigue in 52 (31%) patients, headache in 33 (20%), and nausea in 26 (16%), but none of these was deemed to be clinically important.
Reviewer's Conclusion	
COSMOS had a great four-arm design, examining both duration of therapy and the need for RBV. It included a variety of patients with unfavorable characteristics to respond to historic treatments. In non-cirrhotic patients, 12 weeks of SMV+SOF without RBV seems to be effective in both TN and TE patients. In cirrhotic patients, use of ribavirin, duration of treatment, or use of previous treatment did not seem to have an effect on the results, but the sample size was very small. This regimen was also effective in patients infected with genotype 1 Q80K polymorphism. Patient characteristics historically associated with poor response did not have an effect on the results.	
Bottom-line	
SMV+SOF for 12 weeks is effective in TN and TE patients without cirrhosis at a cost of ~\$150,000. This option seems to be effective in patients with cirrhosis as well. However, the guidelines recommend 24 weeks of treatment until the results of phase 3 trials become available.	
RBV = ribavirin; SMV = simeprevir; SOF = sofosbuvir; SVR = sustained virologic response; TN = treatment-naïve; TE = treatment-experienced.	

Sofosbuvir and Ledipasvir Combination

- A. Sofosbuvir-ledipasvir (Harvoni®) – by Gilead Sciences
- B. Ledipasvir
 - a. Mechanism of action – dual mechanism⁵⁰
 - It binds to domain 1 of the HCV NS5A protein and blocks its ability to regulate HCV replication within the replication complex.
 - It also inhibits assembly and release of viral particles.
 - b. Adverse effects profile
 - Fatigue and headache (>10%).
 - Nausea, diarrhea, and insomnia.
 - Bilirubin and lipase elevations.
 - c. Resistance⁵⁰
 - Low barrier to resistance.
 - d. Drug interactions
 - Ledipasvir is a substrate of drug transporters P-gp and BCRP.
 - Co-administration of ledipasvir with P-gp inducers is not recommended.
 - Ledipasvir is an inhibitor of the drug transporters P-gp and breast cancer resistance protein (BCRP).
- C. FDA-approved dosing
 - a. 12 weeks of sofosbuvir 400 mg po daily plus ledipasvir 90 mg po daily for treatment-naïve and treatment-experienced patients without cirrhosis.
 - b. 12 weeks of sofosbuvir 400 mg po daily plus ledipasvir 90 mg po daily for treatment-naïve patients with cirrhosis.
 - c. 24 weeks of sofosbuvir 400 mg po daily plus ledipasvir 90 mg po daily for treatment-experienced patients with cirrhosis.

- d. 8 weeks of sofosbuvir 400 mg po daily plus ledipasvir 90 mg po daily for treatment-naive patients without cirrhosis who have pre-treatment HCV RNA less than 6 million IU/mL.
- D. Cost
 - a. Ledipasvir-sofosbuvir is \$1125 per pill, \$63,000 for 8 weeks, \$94,500 for 12 weeks, and \$189,000 for 24 weeks (per Red Book®).
- E. Efficacy (Table 4)

Table 4: ION trials for sofosbuvir-ledipasvir ± ribavirin

Trial	ION-1 ⁵²				ION-2 ⁵³				ION-3 ⁵⁴		
Patients											
Total No.	865, TN				440, TE				647, TN		
Genotype 1a	67%				79%				80%		
Genotype 1b	32%				21%				20%		
Cirrhosis	16%				20%				0%		
Design											
Enrollment Period	Oct 2012 to May 2013				Jan to Feb 2013				May to Jun 2013		
Study Type	Phase 3				Phase 3				Phase 3**		
Randomization	Randomized				Randomized				Randomized		
Blinding	Open-label				Open-label				Open-label		
Centers	Multicenter, USA & EU				Multicenter, USA				Multicenter, USA		
Primary Endpoint	SVR12				SVR12				SVR12		
Interventions											
Treatment Regimens	A: SOF+LDV for 12 weeks B: SOF+LDV+RBV for 12 weeks C: SOF+LDV for 24 weeks D: SOF+LDV+RBV for 24 weeks							A: SOF+LDV for 8 weeks B: SOF+LDV+RBV for 8 weeks C: SOF+LDV for 12 weeks			
Results											
	A	B	C	D	A	B	C	D	A	B	C
SVR12 (Overall)	99%	97%*	98%	99%	94%	96%	99%	99%	94%	93%	95%
Cirrhosis	97%	100%	97%	100%	86%	82%	100%	100%	---		
Genotype 1a	99%	100%	100%	100%	95%	96%	99%	99%	93%	92%	95%
Genotype 1b	100%	100%	97%	100%	87%	100%	100%	100%	98%	96%	98%
Relapsers	---				95%	97%	100%	98%	---		
Non-responders	---				92%	96%	98%	100%	---		
Relapse	A: 1 pt w/ C B: 0% C: 1 pt w/ C D: 0%				A: 6% B: 4% C: 0% D: 0%				A: 5% B: 4% C: 1%		
Resistance	2 pts with relapse had NS5A-resistant variants at baseline. No resistance to sofosbuvir.				6 of 11 pts with relapse had NS5A-resistant variants at baseline, but all 11 at the time of relapse.				15 of 23 pts with relapse had NS5A-resistant variants at the time of relapse, 9 of which had the variants at baseline. No resistance to sofosbuvir was detected.		
Adverse Effects	Fatigue, headache, insomnia, and nausea; higher in RBV arms				Fatigue, nausea, insomnia, arthralgia, cough, rash, irritability, dyspnea, and anemia; higher in RBV arms				Fatigue, headache, and nausea; higher in RBV arm.		

Reviewer's Conclusion

ION trials had a great multi-arm design, evaluating both duration of therapy and the need for RBV. They included a variety of patients with unfavorable characteristics to respond to historic treatments. 12 weeks of SOF+LDV without RBV is effective in all TN patients, with or without cirrhosis. 12 weeks of SOF+LDV without RBV is effective in TE patients without cirrhosis and 24 weeks is effective in TE patients with cirrhosis; RBV has no additional benefits. In TN patients without cirrhosis, 8 weeks of SOF+LDV without RBV is effective but is associated with increased rate of relapse, mostly in genotype 1a; RBV has no additional benefits. Patient characteristics historically associated with poor response did not have an effect on the results.

Bottom-line

SOF+LDV for 8 weeks is effective in TN patients without cirrhosis at a cost of ~\$63,000. SOF+LDV for 12 weeks is effective in TN patients with cirrhosis and TE patients without cirrhosis at a cost of ~\$94,500. SOF+LDV for 24 weeks is effective in TE patients with cirrhosis at a cost of ~\$189,000.

*100% if excluding patients who withdrew consent

**Non-inferiority trial

RBV = ribavirin; SOF = sofosbuvir; LDV = ledipasvir; R = relapsers; NR = non-responders; C = cirrhosis; TN = treatment-naïve; TE = treatment-experienced.

Paritaprevir/r-Ombitasvir and Dasabuvir (3D) Combination

A. Paritaprevir-ritonavir – by Abbvie

a. Mechanism of action

- Paritaprevir is an inhibitor of the HCV NS3/4A protease which is necessary for the proteolytic cleavage of the HCV encoded polyprotein (into mature forms of the NS3, NS4A, NS4B, NS5A, and NS5B proteins) and is essential for viral replication.
- Ritonavir is a CYP3A4 inhibitor that acts as a pharmacokinetic booster for paritaprevir, increasing its plasma concentration.

b. Resistance

- Low barrier to resistance.⁵⁰

c. Drug interactions

- Paritaprevir is a substrate of CYP3A and P-gp.
- Paritaprevir is an inhibitor of UGT1A1, OATP1B1, OATP1B3, and BCRP.
- Ritonavir is an inhibitor of CYP3A4 and BCRP.
- Co-administration of 3D with strong inhibitors of CYP3A may increase paritaprevir and ritonavir concentrations.

B. Ombitasvir

a. Mechanism of action

- Ombitasvir is an inhibitor of HCV NS5A, which is essential for viral RNA replication and virion assembly.

b. Resistance

- Low barrier to resistance.⁵⁰

c. Drug interactions

- Ombitasvir is a substrate of P-gp.
- Ombitasvir is an inhibitor of UGT1A1.

C. Dasabuvir

a. Mechanism of action

- Dasabuvir is a non-nucleoside inhibitor of the HCV RNA-dependent RNA polymerase encoded by the NS5B gene, which is essential for replication of the viral genome.
- It binds to 1 of 4 allosteric sites at the surface of the enzyme. By altering the conformation of the polymerase, it blocks its catalytic function, thereby indirectly blocking RNA replication.⁵⁰

- b. Resistance
 - Low barrier to resistance.⁵⁰
- c. Drug interactions
 - Dasabuvir is a substrate of P-gp.
 - Dasabuvir is an inhibitor of UGT1A1 and BCRP.
 - Dasabuvir is primarily metabolized by CYP2C8 enzymes.
- D. Adverse effects profile
 - a. With ribavirin: fatigue, nausea, pruritus, other skin reactions, insomnia and asthenia (>10%).
 - b. Without ribavirin: nausea, pruritus and insomnia (>5%).
- E. Hepatic impairment
 - a. This combination is not recommended in patients with moderate hepatic impairment (Child-Pugh B).
 - b. It is contraindicated in patients with severe hepatic impairment (Child-Pugh C).
- F. FDA-approved dosing
 - a. 12 weeks of PTVr+OBV+DSV for treatment of genotype 1b without cirrhosis.
 - b. 12 weeks of PTVr+OBV+DSV plus RBV for treatment of genotype 1a without cirrhosis or genotype 1b with cirrhosis.
 - c. 24 weeks of PTVr+OBV+DSV plus RBV for treatment of genotype 1a with cirrhosis.
 - d. Recommended dosage: Two ombitasvir, paritaprevir, ritonavir 12.5/75/50 mg tablets once daily (in the morning) and one dasabuvir 250 mg tablet twice daily (morning and evening) with a meal without regard to fat or calorie content.
- G. Cost
 - a. \$83,319 for 12 weeks.
 - b. Ribavirin 200 mg cap price varies, \$550 to \$850 for 12 weeks of treatment, \$1100 to \$1700 for 48 weeks of treatment (per Red Book®).
- H. Efficacy (Table)

Table 5: PEARL III and IV trials⁵⁵

Trial	PEARL III	PEARL IV		
Objective	To examine the efficacy and safety of 3D (PTVr+OBV+DSV) regimen in previously untreated patients with HCV genotype 1 infection and no cirrhosis.			
Patients				
Total No.	419, treatment-naïve	305, treatment-naïve		
Genotype 1a	0%	100%		
Genotype 1b	100%	0%		
Cirrhosis	0%	0%		
Design				
Study Period	Dec 2012 to Aug 2014	Mar 2013 to Sep 2014		
Study Type	Phase 3			
Randomization	Randomized			
Blinding	Double-blind			
Centers	Multi-center, USA, EU, and Russia	North America and UK		
Primary Endpoint	SVR12			
Interventions				
Treatment Regimen	A: PTVr+OBV+DSV+RBV for 12 weeks B: PTVr+OBV+DSV for 12 weeks			
Results	A	B	A	B
SVR12	99.5%	99%	97%	90%
Relapse	0%	0%	1% (1 patient)	5% (10 patients)
Failure during treatment	0.5% (1 patient)	0%	1% (1 patient)	2.9% (6 patients)

Resistance	No significant predictors of virologic failure.	All 18 patients who had virologic failure had at least one resistance-associated variant.
Adverse Effects	The most common adverse events were headache and fatigue. In both studies, adverse events were more frequently reported in the groups receiving antiviral regimens that contained ribavirin.	
Reviewer's Conclusion		
PEARL III and IV trials examined the need for addition of RBV to 12 weeks of treatment with the 3D regimen in TN patients without cirrhosis. They included a variety of patients with unfavorable characteristics to respond to historic treatments. 12 weeks of PTVr+OBV+DSV without RBV is effective in TN patients without cirrhosis infected with genotype 1b. In TN patients without cirrhosis infected with genotype 1a, however, the addition of RBV improves relapse and virologic failure during treatment. Patient characteristics historically associated with poor response did not have an effect on the results.		
Bottom-line		
PTVr+OBV+DSV for 12 weeks is effective in TN patients without cirrhosis infected with genotype 1b at a cost of ~\$83,319. PTVr+OBV+DSV+RBV for 12 weeks is effective in TN patients without cirrhosis infected with genotype 1a at a cost of ~\$84,169.		
DSV = dasabuvir; OBV = ombitasvir; PTVr = paritaprevir/ritonavir; RBV = ribavirin; TN = treatment-naïve; SVR = sustained virologic response.		

Table 6: TURQUOISE-II trial⁵⁶

Objective				
To evaluate the efficacy and safety of 3D regimen in previously untreated and previously treated patients with HCV genotype 1 infection and compensated cirrhosis.				
Patients				
Total No.	380 (160 TN, 220 TE)			
Genotype 1a	69%			
Genotype 1b	31%			
Cirrhosis	100%			
Design				
Enrollment Period	Oct 2012 to Apr 2013			
Study Type	Phase 3			
Randomization	Randomized			
Blinding	Open-blind			
Centers	Multi-center, North America and Europe			
Primary Endpoint	SVR12			
Interventions				
Treatment Regimen	A: PTVr+OBV+DSV+RBV for 12 weeks B: PTVr+OBV+DSV+RBV for 24 weeks			
	Treatment-naïve		Treatment-experienced	
Results	A	B	A	B
SVR12 (Overall)	94%	95%	97%	100%
Genotype 1a	92%	93%	86% (65/76)	95% (62/65)
Genotype 1b	100%	100%	97% (45/46)	100%
Relapsers	---	---	97% (28/29)	100%
Partial Responders	---	---	94% (17/18)	100%
Non-responders	---	---	87% (65/75)	95%
Relapse	5 patients?	---	NR 1a: 7 patients	1 patient
Resistance	15/17 patients had resistance-associated variants in two or more of the drug targets.			

Adverse Effects	No specific adverse event led to premature discontinuation by more than one patient, and no pattern in the types of adverse events leading to discontinuation was observed.
Reviewer's Conclusion	
TURQUOISE-II evaluated the optimal duration of therapy with the 3D regimen and RBV in TN and TE patients with cirrhosis. It included a variety of patients with unfavorable characteristics to respond to historic treatments. 12 weeks of PTVr+OBV+DSV+RBV is effective in TN and TE patients with cirrhosis infected with genotype 1b and TN patients with cirrhosis infected with genotype 1a. 24 weeks of PTVr+OBV+DSV+RBV is effective in TE patients with cirrhosis infected with genotype 1a. A ribavirin-free 3D regimen was not evaluated in patients with cirrhosis. Patient characteristics historically associated with poor response did not have an effect on the results.	
Bottom-line	
PTVr+OBV+DSV+RBV for 12 weeks is effective in cirrhotic TN and TE patients with genotype 1b and cirrhotic TN patients with genotype 1a at a cost of ~\$84,169. PTVr+OBV+DSV+RBV for 24 weeks is effective in cirrhotic TE patients with genotype 1a at a cost of ~\$168,338.	
DSV = dasabuvir; OBV = ombitasvir; PTVr = paritaprevir/ritonavir; RBV = ribavirin; TN = treatment-naïve; TE = treatment-experienced; SVR = sustained virologic response.	

Emerging Treatments for HCV Genotype 1

- A. Ribavirin-free strategy
 - a. Sofosbuvir and daclatasvir combination (A1444040 Phase 2 Trial⁵⁷)
 - i. Sofosbuvir plus daclatasvir for 12 weeks in treatment-naïve patients.
 - ii. Sofosbuvir plus daclatasvir for 24 weeks in treatment-experienced patients.
- B. Nucleotide-free strategy
 - a. Grazoprevir and elbasvir combination (C-WORTHY Phase 2 Trial⁵⁸)
 - i. 12 weeks of treatment effective in treatment-naïve patients with cirrhosis.
 - ii. 12 weeks of treatment effective in treatment-experienced patients with or without cirrhosis
 - b. Beclabuvir, daclatasvir, and asunaprevir combination
 - i. Treatment for 12 weeks
- C. Shorter duration of therapy
 - a. Sofosbuvir, grazoprevir, and elbasvir combination
 - i. Treatment for 4, 6, or 8 weeks
 - b. Sofosbuvir, ledipasvir, and vedroprevir (GS-9451) combination
 - i. Treatment for 6 weeks
 - c. Sofosbuvir, beclabuvir, daclatasvir, and asunaprevir combination
 - i. Treatment for 4, 6, or 12 weeks

Monitoring

- A. Prior to starting antiviral therapy
 - a. CBC, INR, hepatic function panel, and GFR.
 - b. HCV genotype and subtype.
 - c. Quantitative HCV viral load.
 - d. Q80K as indicated for use of simeprevir.
- B. During antiviral therapy
 - a. Clinic visits or telephone contact to ensure adherence.
 - b. CBC, creatinine level, GFR, and hepatic function panel are recommended after 4 weeks of treatment and as clinically indicated.
 - i. Any 10-fold increase in alanine aminotransferase (ALT) activity at week 4 should prompt discontinuation of therapy.
 - ii. Any increase in ALT of less than 10-fold at week 4 and accompanied by any weakness, nausea, vomiting, jaundice, or increased bilirubin, alkaline phosphatase, or international normalized ratio should also prompt discontinuation of therapy.
 - iii. Asymptomatic increases in ALT of less than 10-fold elevated at week 4 should be closely monitored and repeated at week 6 and week 8.
 - c. Quantitative HCV viral load testing is recommended after 4 weeks of therapy and at 12 weeks following completion of therapy.
 - i. Antiviral drug therapy should NOT be interrupted or discontinued if HCV RNA levels are not performed or available during treatment.

Table 7: Summary of Drug Interactions

	CYP3A	CYP2C8	CYP1A2	P-gp	BCRP	UGT1A1	OATP1B1/3
SOF				SUB	SUB		
SMV	SUB/INH(intestinal)		INH	INH			INH
LDV				SUB/INH	SUB/INH		
PTV	SUB			SUB	INH	INH	INH
OBV				SUB		INH	
DSV		SUB		SUB	INH	INH	
Ritonovir	SUB/INH				INH		

SUB = substrate; INH = inhibitor; IND = inducer;
 SOF = sofosbuvir; SMV = simeprevir; LDV = ledipasvir; DSV = dasabuvir; OBV = ombitasvir; PTV = paritaprevir.

Summary and Conclusions

- A. HCV Progression
 - a. Acute infection
 - b. Chronic infection
 - c. Cirrhosis
 - d. Hepatic decompensation, HCC, and death
- B. Paradigm shift in treatment of HCV
 - a. Historic treatment with PegIFN+RBV less effective and less safe
 - b. Brief appearance of first-wave first-generation protease inhibitors
 - c. Interferon-free regimens
 - d. Ribavirin-free regimens
 - e. Shorter duration of therapy: 24 weeks → 12 weeks → 8 weeks → 6 weeks → 4 weeks
 - f. Price wars
- C. Resources for healthcare providers
 - a. IDSA-AASLD Guidelines: <http://www.hcvguidelines.org/>
 - b. Drug Interactions: <http://www.hep-druginteractions.org/>
 - c. Hepatitis C - Diagnosis, Treatment and Support: <http://hepc.liverfoundation.org/>
 - d. U.S. Department of Veterans Affairs: <http://www.hepatitis.va.gov/>

Table 8: Summary of FDA Approved Regimens

Regimen		SOF+SMV	SOF+LDV	PTVr+OBV+DSV
TN	No Cirrhosis	12 weeks	8-12 weeks	1b: 12 weeks; 1a: 12 weeks+RBV
	Cirrhosis	24 weeks	12 weeks	1b: 12 weeks+RBV; 1a: 24 weeks+RBV
TE	No Cirrhosis	12 weeks	12 weeks	1b: 12 weeks; 1a: 12 weeks+RBV
	Cirrhosis	24 weeks	24 weeks	1b: 12 weeks+RBV; 1a: 24 weeks+RBV
8 Week Treatment Cost		N/A	\$63,000	N/A
12 Week Treatment Cost		\$150,000	\$94,500	\$83,319 to \$84,169
24 Week Treatment Cost		\$300,000	\$189,000	\$168,338
SOF = sofosbuvir; SMV = simeprevir; LDV = ledipasvir; DSV = dasabuvir; OBV = ombitasvir; PTVr = paritaprevir/ritonavir; RBV = ribavirin; TN = treatment-naïve; TE = treatment-experienced.				

Appendix A

Table A1: Efficacy of Historic Treatments for Genotype 1

Year	Trials	Regimen	SVR24	Relapse	Treatment
1991	HIT* ⁵⁹	IFN for 24 weeks	2-3%	~80%	Naïve
1991	HIT* ⁵⁹ , IHIT* ⁶⁰	IFN for 48 weeks	7-11%	~46%	Naïve
1998	HIT* ⁵⁹ , IHIT* ⁶⁰	IFN+RBV for 24 weeks	16-18%	~42%	Naïve
1998	HIT* ⁵⁹ , IHIT* ⁶⁰	IFN+RBV for 48 weeks	28-31%	~24%	Naïve
2001	IHIT 2001* ⁴¹	PegIFN+RBV for 48 weeks	42%	~18%	Naïve
2009	IDEAL ⁶¹	PegIFN+RBV for 48 weeks	~40%; Black: 16-26%	20-31%	Naïve

* Included genotypes 1 and other genotypes.
 IFN = interferon alfa; PegIFN = pegylated interferon alfa; RBV = ribavirin; SVR = sustained virologic response.

Table A2: Available Indirect-Acting Agents

Agent	PegIFN alfa-2a	PegIFN alfa-2b	Ribavirin
Approval Date	October 16, 2002	January 19, 2001	December 3, 2002
MOA	Bind to human type 1 IFN receptor and induce innate antiviral immune response		Inhibits HCV polymerase activity; increases mutation frequency in genomes of several RNA viruses
Dosage	180 mcg SC weekly	1.5 mcg/kg SC weekly	Wt > 75 kg: 600 mg po BID c food Wt ≤ 75 kg: 400 mg po QAM c food and 600 mg QPM c food
Pregnancy	Category C	Category C	Category X
AEs	Alopecia, pruritus, injection-site reaction, myalgia, headache, anxiety, insomnia, diarrhea, depression, fatigue	Injection-site reaction, fatigue/asthenia, headache, rigors, fevers, nausea, myalgia, anxiety	Alopecia, pruritus, injection-site reaction, myalgia, headache, anxiety, insomnia, diarrhea, depression, fatigue
BBW	Total or life-threatening neuropsychiatric, autoimmune, ischemic, infectious disorders		Hemolytic anemia; teratogenic

AE = adverse effects; BBW = black box warning; MOA = mechanism of action; PegIFN = peginterferon.

Table A3: First Generation NS3/4A Protease Inhibitors

Agent	First-wave		Second-wave	
	Boceprevir	Telaprevir	Simeprevir	Paritaprevir
Brand	Victrelis®	Incivek®	Olysio®	Viekira Pak®*
Approval Date	May 13, 2011	May 23, 2011	November 22, 2013	December 19, 2014
MOA	Linear peptide mimetics with an α -ketoamide group that covalently binds with a serine in the catalytic triad of NS3/4A protease of HCV genotype 1, resulting in inhibition of HCV replication		Macrocyclic peptide mimetic that non-covalently binds to NS3/4A protease	Inhibits NS3/4A protease
Dosage	800 mg po TID c food	1125 mg po BID c fatty food	150 mg po daily c food	150 mg po daily with 100 mg of ritonavir c food
Pregnancy	Category B	Category B	Category C	Category B
AEs	Fatigue, anemia, nausea, dysgeusia	Rash, pruritus, anemia, nausea, diarrhea, anorectal pain, dysgeusia, fatigue, vomiting	Pruritus, rash, photosensitivity, nausea, myalgia, dysgeusia	Fatigue, nausea, pruritus, other skin reactions, insomnia, and asthenia
BBW	---	Fatal and non-fatal serious skin reactions	---	---
Metabolism	CYP3A4/5, aldo-keto reductase (AKR) ⁶²	CYP3A ⁶²	CYP3A ⁶²	CYP3A4/5 Ritonavir: CYP3A, CYP2D6
Cost	~\$100/day	Discontinued	~\$800 per pill	~\$992/day
*available as a combination product with other agents; see text for details. AE = adverse effects; BBW = black box warning; MOA = mechanism of action.				

Table A4: NS5B Polymerase Inhibitors

Agent	Sofosbuvir	Dasabuvir
Brand	Sovaldi®	Viekira Pak®*
Approval Date	December 6, 2013	December 19, 2014
MOA	Inhibits replication by inhibiting HCV NS5B RNA-dependent RNA polymerase	A non-nucleoside inhibitor of the HCV RNA-dependent RNA polymerase, which is essential for replication of the viral genome
Dosage	400 mg po daily	250 mg po BID
Pregnancy	Category B	Category B
AEs	Fatigue, headache, nausea, insomnia, anemia	Fatigue, nausea, pruritus, other skin reactions, insomnia, and asthenia
Metabolism	Renal	CYP2C8, CYP3A
Cost	\$1000 per pill	~\$992/day
*available as a combination product with other agents; see text for details. AE = adverse effects; BBW = black box warning; MOA = mechanism of action.		

Table A5: NS5A Inhibitors

Agent	Ledipasvir	Ombitasvir
Brand	Harvoni®*	Viekira Pak®*
Approval Date	October 10, 2014	December 19, 2014
MOA	Bind to domain 1 of the NS5A protein and block its ability to regulate HCV replication within the replication complex. Also inhibits assembly and release of viral particles.	
Dosage	90 mg po daily	25 mg po daily
Pregnancy	Category B	Category B
AEs	Fatigue and headache (≥20%) Pancytopenia and depression (<1%)	Fatigue, nausea, pruritus, other skin reactions, insomnia, and asthenia
Metabolism	Unchanged in feces; oxidation	Amide hydrolysis
Cost	\$1125 per pill	~\$992/day

*available as a combination product with other agents; see text for details.

AE = adverse effects; BBW = black box warning; MOA = mechanism of action.

Table A6: Efficacy of Interferon-Sparing Regimens for HCV Genotype 1

Year	Trial	Regimen	SVR	Relapse	Treatment
2011	SPRINT-2 ⁴⁰	BOC+PegIFN+RBV for 24-48 weeks	NB: 67-68% B: 42-53%	NB: 8-9% B: 12-17%	Naïve
2011	RESPOND-2 ⁴⁷	BOC+PegIFN+RBV for 48 weeks	R: 69-75% PR: 40-52%	R: 15% PR: 12%	Experienced
2013	NEUTRINO ⁶³	SOF+PegIFN+RBV for 12 weeks	All: 90% C: 80%	8%	Naïve
2014	QUEST-1 ⁶⁴	SMV+PegIFN+RBV for 24-48 weeks	All: 80% 1a+Q80K : 52% C: 58% TT: 65%	9%	Naïve
2014	QUEST-2 ⁶⁵	SMV+PegIFN+RBV for 24-48 weeks	All: 81% 1a+Q80K : 75% C: 65% TT: 58%	13%	Naïve
2014	ASPIRE ^{*66}	SMV+PegIFN+RBV for 12-48 weeks	R: 77-89% PR: 48-86% NR: 38-59%	6-14%	Experienced
2014	PROMISE ⁶⁷	SMV+PegIFN+RBV for 24-48 weeks (SMV for 12 weeks)	R: 79% 1a+Q80K : 47% C: 74% TT: 65%	19%	Experienced

* Phase 2 trial.

PegIFN = pegylated interferon alfa; RBV = ribavirin; BOC = boceprevir; SOF = sofosbuvir;
B = Black; NB = non-black; R = relapsers; PR = partial responders; NR = non-responders; C = cirrhosis;
IL28B genotypes: CC, CT, TT.

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