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Hepatitis C: Pathophysiology & Treatment

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March 10, 2022

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Hepatitis C Virus (HCV)

- Affects >1.9 million people living in the United States
- Transmitted through contaminated blood, sexual contact, perinatal exposure
  - Sharing needles, blood transfusion, organ transplant
- Acute: first 6 months after virus exposure
  - 50-90% develop chronic infection
- Complications: cirrhosis and hepatocellular carcinoma (HCC)
- Leading indication for liver transplant

Holmes JA, Chung RT. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 11th edition. Elsevier, Inc.;2021.

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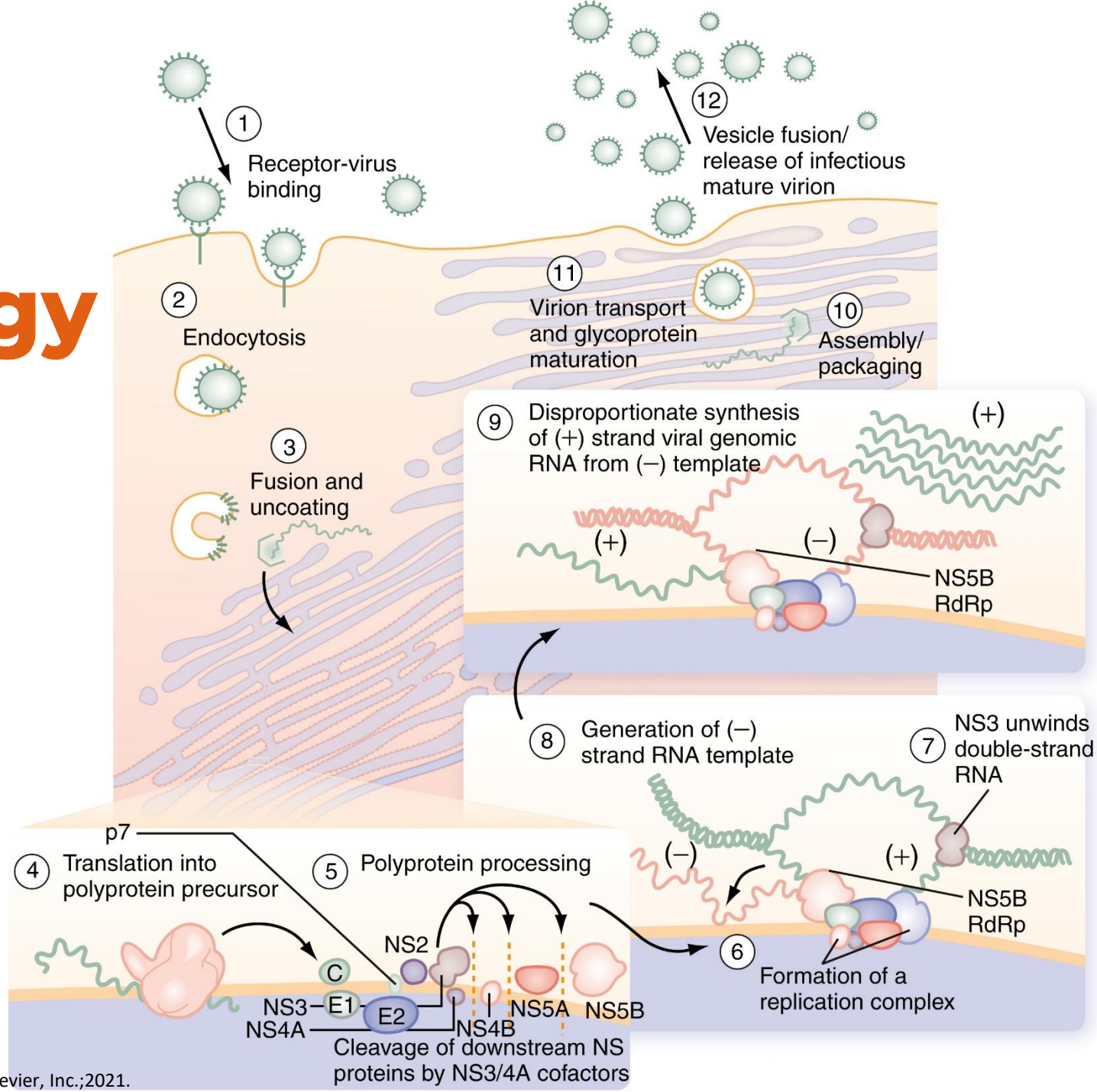
HCV Pathophysiology

- Single-stranded RNA virus
- Hepatocytes = major site of viral replication



Holmes JA, Chung RT. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 11th edition. Elsevier, Inc.;2021.

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HCV Genotype

- High mutational rate leading to genetic variation
- Mixed-genotype indicates coinfection with more than one HCV virus
- Geographic variations exist & genotype 3 is most severe

Genotype	Prevalence in US (%)
1a	46
1b	26
2	11
3	9
4	<8
5	<8
6	<8

Holmes JA, Chung RT. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 11th edition. Elsevier, Inc.;2021.

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Clinical Presentation

- Primarily asymptomatic
- Advanced hepatic fibrosis: fatigue, vague abdominal pain, depression

Holmes JA, Chung RT. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 11th edition. Elsevier, Inc.;2021.

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HCV Testing

Recommendations for One-Time Hepatitis C Testing	
RECOMMENDED	RATING ⓘ
One-time, routine, opt out HCV testing is recommended for all individuals aged 18 years or older.	I, B
One-time HCV testing should be performed for all persons less than 18 years old with activities, exposures, or conditions or circumstances associated with an increased risk of HCV infection (see below).	I, B
Prenatal HCV testing as part of routine prenatal care is recommended with each pregnancy.	I, B
Periodic repeat HCV testing should be offered to all persons with activities, exposures, or conditions or circumstances associated with an increased risk of HCV exposure (see below).	IIa, C
Annual HCV testing is recommended for all persons who inject drugs, for HIV-infected men who have unprotected sex with men, and men who have sex with men taking pre-exposure prophylaxis (PrEP).	IIa, C

Risk Activities

- Injection drug use (current or ever, including those who injected only once)
- Intranasal illicit drug use
- Use of glass crack pipes
- Male engagement in sex with men
- Engagement in chem sex (defined as the intentional combining of sex with the use of particular nonprescription drugs in order to facilitate or enhance the sexual encounter [Bourne, 2015])

Risk Exposures

- Persons on long-term hemodialysis (ever)
- Persons with percutaneous/parenteral exposures in an unregulated setting
- Healthcare, emergency medical, and public safety workers after needlestick, sharps, or mucosal exposure to HCV-infected blood
- Children born to HCV-infected women
- Recipients of a prior transfusion or organ transplant, including persons who:
  - Were notified that they received blood from a donor who later tested positive for HCV
  - Received a transfusion of blood or blood components, or underwent an organ transplant before July 1992
  - Received clotting factor concentrates produced before 1987
- Persons who were ever incarcerated

Other Conditions and Circumstances

- HIV infection
- Sexually active persons about to start pre-exposure prophylaxis (PrEP) for HIV
- Chronic liver disease and/or chronic hepatitis, including unexplained elevated alanine aminotransferase (ALT) levels
- Solid organ donors (living and deceased) and solid organ transplant recipients

AASLD-IDSA. Recommendations for testing, managing, and treating hepatitis C. http://www.hcvguidelines.org.

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HCV Testing (cont.)

- HCV-antibody testing
- HCV RNA polymerase chain reaction (PCR)
- Quantitative HCV-RNA prior to treatment initiation to document baseline level of viremia
- HCV genotype
- Cirrhosis assessment via liver fibrosis (Fibroscan or Fibrotest)
- Prior treatment history

- HCV-antibody testing likely to be positive once exposed; HCV RNA by PCR helps determine if current (active) infection

Holmes JA, Chung RT. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 11th edition. Elsevier, Inc.;2021.

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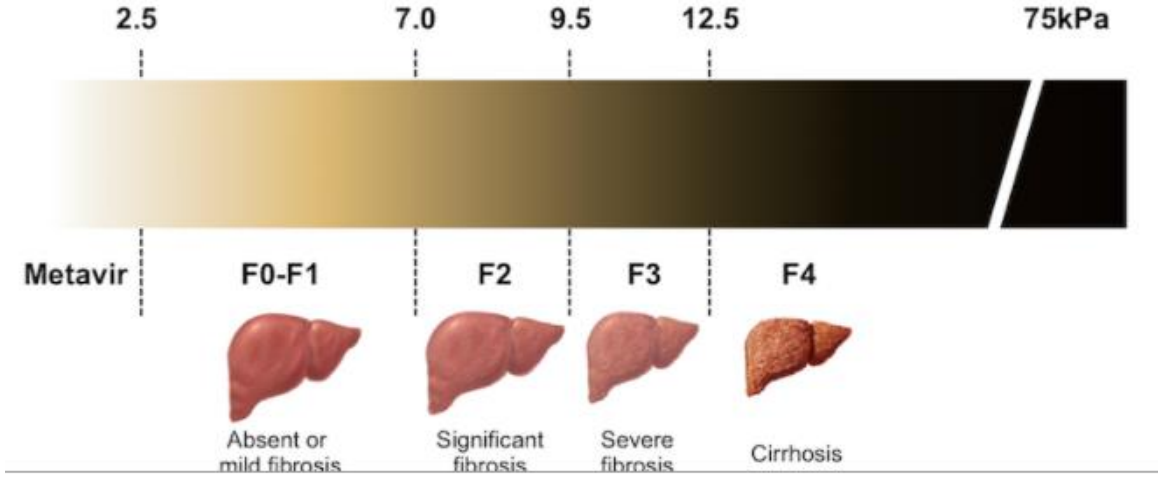
HCV Testing (cont.)

- Cirrhosis assessment via liver fibrosis (Fibroscan or Fibrotest)



- If F4, calculate Child-Pugh Score to determine cirrhotic state
  - Compensated or decompensated

https://www.medgadget.com/2019/09/using-fibroscan-in-the-clinic-interview-with-dr-stephen-a-harrison.html
https://www.hepatitisc.uw.edu/go/evaluation-staging-monitoring/evaluation-staging/core-concept/all

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HCV Treatment

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Treatment Goals

- Eradicate virus
- Prevent progression of liver disease and death
- Prevent hepatocellular carcinoma
- Achieve sustained virologic response (SVR) at week 12 post-treatment
  - Surrogate marker – aim to have absence of detectable virus in blood

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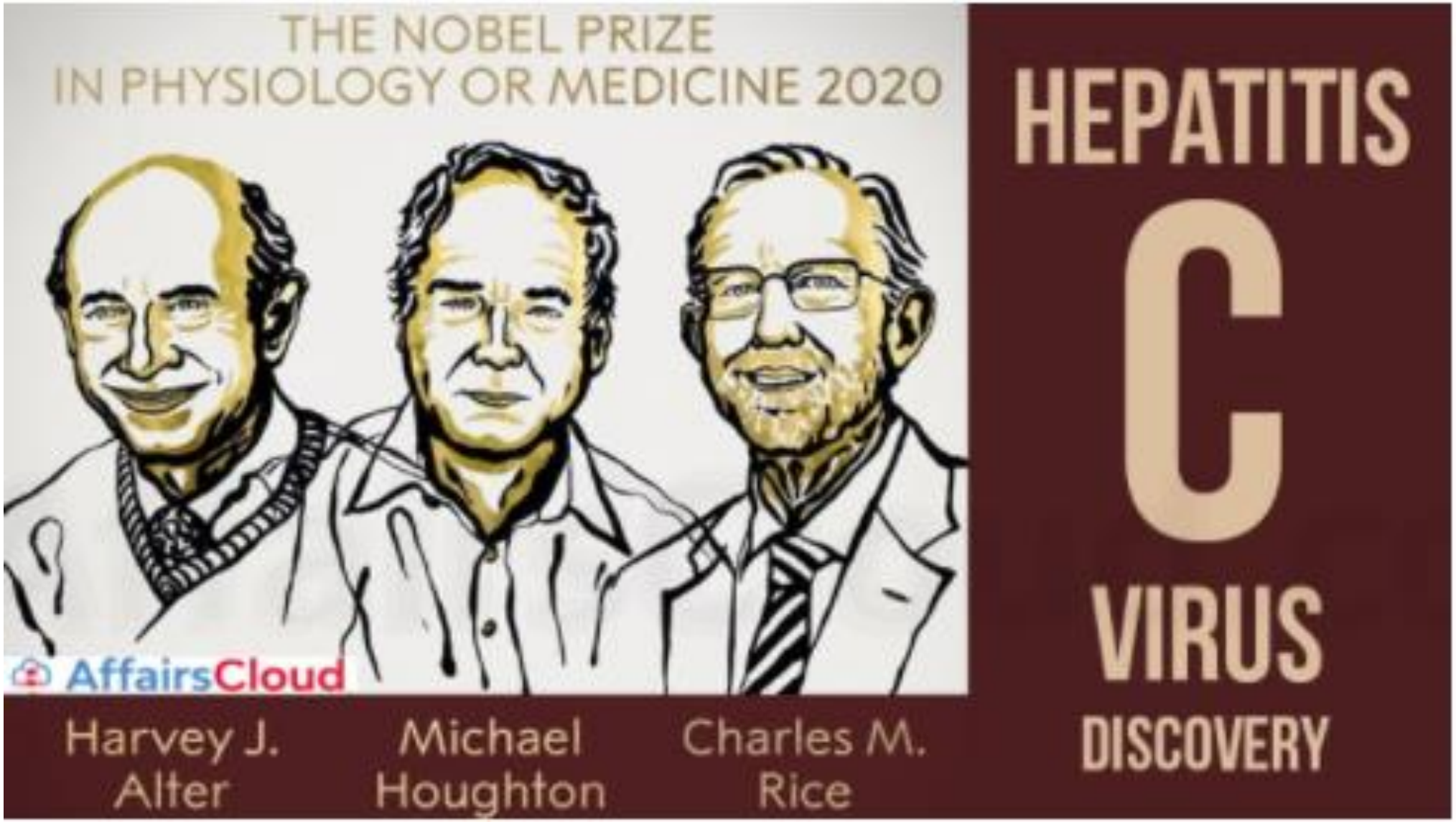

https://affairscloud.com/harvey-j-alter-charles-m-rice-michael-houghton-won-2020-nobel-prize-in-physiology-or-medicine-for-discovering-the-hepatitis-c-virus/

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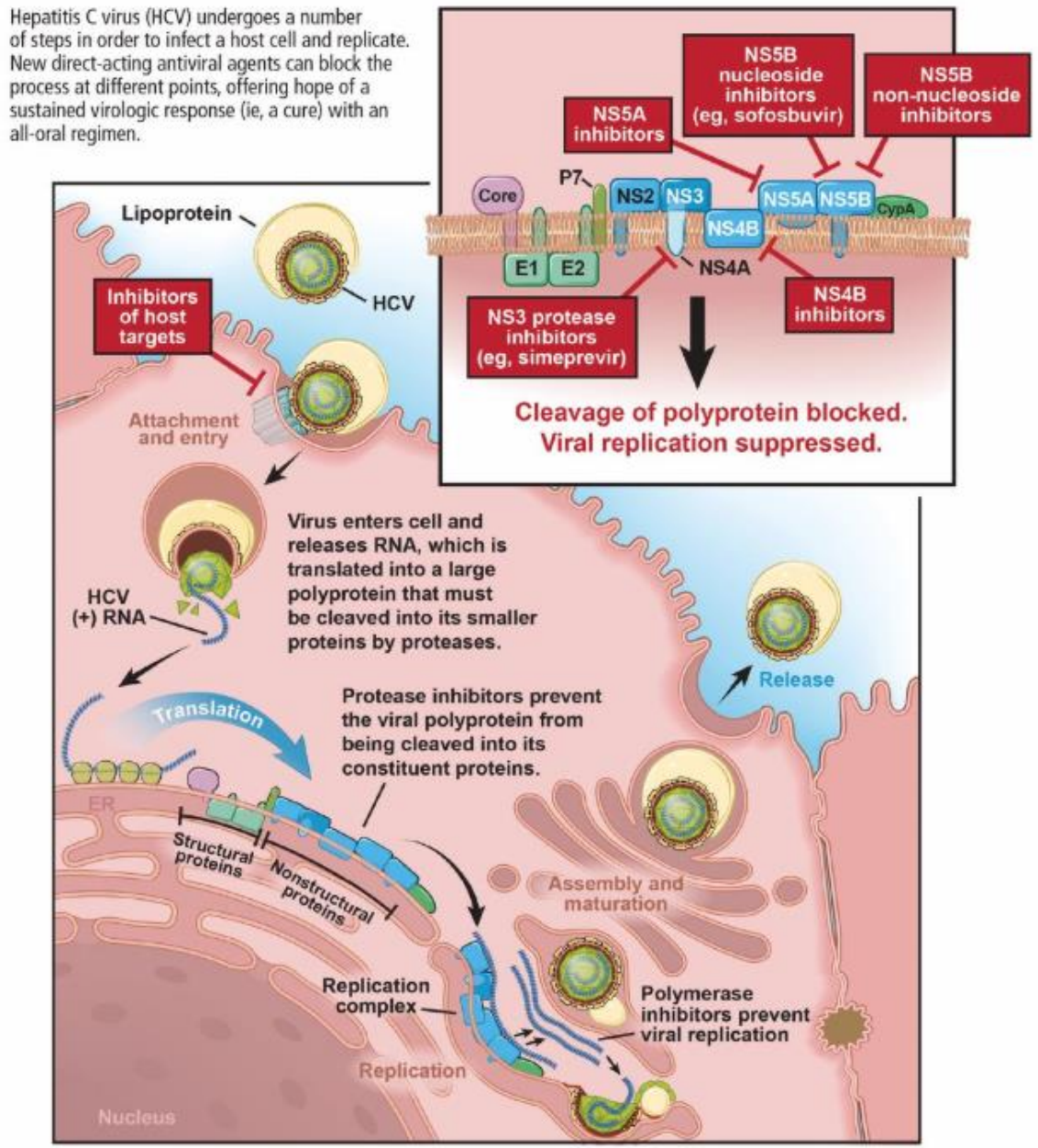
Blocking the HCV life cycle



Dugum M et al. *Cleve Clin J Med*. 2014;81(3):159-172.

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Class	Mechanism of Action	Medications
NS3/4A protease inhibitor	Prevents cleavage of HCV-encoded polyprotein (into mature forms of NS3, NS4A, NS5A, NS5B proteins), essential for viral replication	Gleca**previr** Grazoprevir Voxilaprevir Paritaprevir Simeprevir
First generation NS5A inhibitor	Potent antiviral activity against HCV NS5A (essential for viral replication and virion assembly)	Daclat**asvir** Ledipasvir Ombitasvir
Second generation NS5A inhibitor		Pibrentasvir Elbasvir Velpatasvir
NS5B polymerase inhibitor	Metabolized to active uridine analog triphosphate and acts as chain terminator for NS5B polymerase	Sofo**sbuvir**

AASLD-IDSA. Recommendations for testing, managing, and treating hepatitis C. http://www.hcvguidelines.org.

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Hepatitis B Reactivation – Black Box Warning

- Test for current or prior HBV infection
- If HBV not treated, may result in reactivation and lead to fulminant hepatitis, hepatic failure, and death
- Measure hepatitis B surface antigen (HBsAg) and hepatitis B core antibody (anti-HBc) before initiating HCV treatment
- Risk in HBsAg positive and in those HBsAg negative + anti-HBc positive
- In those with serologic evidence, monitor for clinical and lab signs of hepatitis flare or HBV reactivation (increase in aminotransferase levels, bilirubin levels)

AASLD-IDSA. Recommendations for testing, managing, and treating hepatitis C. http://www.hcvguidelines.org.

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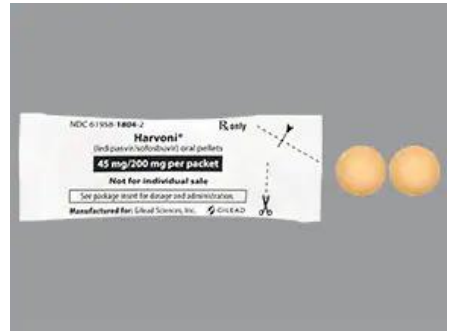
Ledipasvir/sofosbuvir [Harvoni]

- Patients ≥ 3 years old
- Once-daily tablet (adults)
- Tablets or pellets depending on weight-based dosing (children)

Body Weight (kg)	Dosing of HARVONI Tablets or Oral Pellets	HARVONI Daily Dose
at least 35	one 90 mg/400 mg tablet once daily or two 45 mg/200 mg tablets once daily or two 45 mg/200 mg packets of pellets once daily	90 mg/400 mg per day
17 to less than 35	one 45 mg/200 mg tablet once daily or one 45 mg/200 mg packet of pellets once daily	45 mg/200 mg per day
less than17	one 33.75 mg/150 mg packet of pellets once daily	33.75 mg/150 mg per day



  - Pellets must be swallowed whole
  - Can be sprinkled into non-acidic soft food at or below room temperature and consumed within 30 minutes of mixing

- No dose adjustments for renal impairment including end stage renal disease (ESRD)
  - No safety data in pediatric population

Harvoni [package insert]. U.S. Food and Drug Administration website. https://www.gilead.com/~/media/files/pdfs/medicines/liver-disease/harvoni/harvoni_pi.pdf. Revised 3/2020.

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Ledipasvir/sofosbuvir [Harvoni]

- Indications:
  - Genotype 1, 4, 5, 6 w/out cirrhosis or w/ compensated cirrhosis
  - Genotype 1 with decompensated cirrhosis + ribavirin
  - Genotype 1 or 4 s/p liver transplant without cirrhosis or w/ compensated cirrhosis + ribavirin

- ADR: headache, fatigue, asthenia

Harvoni [package insert]. U.S. Food and Drug Administration website. https://www.gilead.com/~/media/files/pdfs/medicines/liver-disease/harvoni/harvoni_pi.pdf. Revised 3/2020.

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Ledipasvir/sofosbuvir [Harvoni] - Interactions

- Amiodarone = fatal cardiac arrest; bradycardia (may occur up to 2 weeks after initiating HCV treatment)
- P-gp inducers may decrease plasma concentrations
- Antacids = decrease ledipasvir concentration
  - Separate administration by 4 hours
- H2-receptor antagonist = administer with or 12 hours apart
  - Famotidine 40 mg PO twice daily is max dose
- Proton pump inhibitors = administer with under fasting conditions
  - Omeprazole 20 mg PO daily is max dose
- Anticonvulsants, antimycobacterials, HIV antiretrovirals, HMG-CoA reductase inhibitors (statins)

Harvoni [package insert]. U.S. Food and Drug Administration website. https://www.gilead.com/~/media/files/pdfs/medicines/liver-disease/harvoni/harvoni_pi.pdf. Revised 3/2020.

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Sofosbuvir/Velpatasvir [Epclusa]

- Patients >6 years old or weighing at least 17 kg
- Tablets

Body Weight (kg)	Dosing of EPCLUSA	EPCLUSA Daily Dose
at least 30	one 400 mg/100 mg tablet once daily or two 200 mg/50 mg tablets once daily	400 mg/100 mg per day
17 to less than 30	one 200 mg/50 mg tablet once daily	200 mg/50 mg per day

- No dose adjustments for renal impairment including end stage renal disease (ESRD)
  - No safety data in decompensated cirrhosis or pediatric patients

Epclusa [package insert]. U.S. Food and Drug Administration website. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/208341s014lbl.pdf. Revised 3/2020.

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Sofosbuvir/Velpatasvir [Epclusa]

- Pangenotypic (covers all genotype)
- ADR: headache and fatigue

Epclusa [package insert]. U.S. Food and Drug Administration website. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/208341s014lbl.pdf. Revised 3/2020.

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Sofosbuvir/Velpatasvir [Epclusa] – Interactions

- Amiodarone = fatal cardiac arrest; bradycardia (may occur up to 2 weeks after initiating HCV treatment)
- P-gp and/or moderate to potent inducers of CYP2B6, CYP2C8, or CYP3A4 may decrease plasma concentrations of sofosbuvir and/or velpatasvir
- Antacids = decrease velpatasvir concentration
  - Separate administration by 4 hours
- H2-receptor antagonist = administer with or 12 hours apart
  - Famotidine 40 mg PO twice daily is max dose
- Proton pump inhibitors = AVOID. If medically necessary, take sofosbuvir/velpatasvir with meal and 4 hours before omeprazole 20 mg PO daily
  - No other proton pump inhibitor has been studied

Epclusa [package insert]. U.S. Food and Drug Administration website. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/208341s014lbl.pdf. Revised 3/2020.

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Glecaprevir/pibrentasvir [Mavyret]

- Patients ≥ 3 years old
- Three tablets daily (adults)
- Tablets or pellets depending on weight-based dosing (children)

Body Weight (kg) or Age (yrs)	Daily Dose of glecaprevir/pibrentasvir	Dosing of MAVYRET
Less than 20 kg	150 mg/60 mg per day	Three 50 mg/20 mg packets of oral pellets once daily
20 kg to less than 30 kg	200 mg/80 mg per day	Four 50 mg/20 mg packets of oral pellets once daily
30 kg to less than 45 kg	250 mg/100 mg per day	Five 50 mg/20 mg packets of oral pellets once daily
45 kg and greater OR 12 years of age and older	300 mg/120 mg per day	Three 100 mg/40 mg **tablets** once daily[1] (see Recommended Dosage in Adults)

- Must be taken with food
  - Pellets should be sprinkled on small amount of soft food with low water content that can be swallowed whole (e.g., peanut butter, cream cheese, Greek yogurt)

Mavyret [package insert]. U.S. Food and Drug Administration website. https://www.rxabbvie.com/pdf/mavyret_pi.pdf. Revised 6/2021.

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Glecaprevir/pibrentasvir [Mavyret]

- Contraindicated in:
  - Moderate to severe hepatic impairment (Child Pugh B or C) or those with history of prior hepatic decompensation
  - Coadministration with atazanavir or rifampin
- Pangenotypic (covers all genotype)
- ADR: headache, fatigue

Mavyret [package insert]. U.S. Food and Drug Administration website. https://www.rxabbvie.com/pdf/mavyret_pi.pdf. Revised 6/2021.

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Glecaprevir/pibrentasvir [Mavyret] - Interactions

- P-gp/CYP3A4 inducer can decrease glecaprevir/pibrentasvir plasma concentrations
- Coadministration with ethinyl estradiol-containing products may increase risk of ALT elevations
- Coadministration with HMG-CoA reductase inhibitors can increase statin concentrations
  - Dose reduction
  - Consider use of lower dose
  - Avoid atorvastatin, lovastatin, and simvastatin

Mavyret [package insert]. U.S. Food and Drug Administration website. https://www.rxabbvie.com/pdf/mavyret_pi.pdf. Revised 6/2021.

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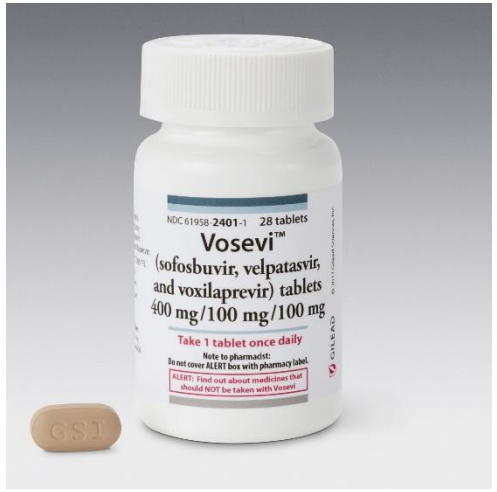
Sofosbuvir + velpatasvir + voxilaprevir [Vosevi]



- Adult patients
- 1 tablet by mouth daily with food x 12 weeks
- Not indicated in moderate to severe hepatic renal impairment (Child Pugh B or C)

Vosevi [package insert]. U.S. Food and Drug Administration website. https://www.gilead.com/~/media/Files/pdfs/medicines/liver-disease/vosevi/vosevi_pi.pdf. Revised 11/2019.

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Sofosbuvir + velpatasvir + voxilaprevir [Vosevi]

- Indications:
  - Without cirrhosis or compensated cirrhosis
  - Genotype 1, 2, 3, 4, 5, 6 with prior treatment containing NS5A inhibitor
  - Genotype 1a or 3 with prior treatment containing sofosbuvir without NS5A inhibitor

- ADR: Headache, fatigue, diarrhea, nausea

Vosevi [package insert]. U.S. Food and Drug Administration website. https://www.gilead.com/~/media/Files/pdfs/medicines/liver-disease/vosevi/vosevi_pi.pdf. Revised 11/2019.

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Sofosbuvir + velpatasvir + voxilaprevir [Vosevi] – Interactions

- Amiodarone = fatal cardiac arrest; bradycardia (may occur up to 2 weeks after initiating HCV treatment)
- P-gp and/or moderate to potent inducers of CYP2B6, CYP2C8, or CYP3A4 may decrease plasma concentrations of sofosbuvir + velpatasvir + voxilaprevir
- Antacids = decrease velpatasvir concentration
  - Separate administration by 4 hours
- H2-receptor antagonist = administer with or 12 hours apart
  - Famotidine 40 mg PO twice daily is max dose
- Proton pump inhibitors = administer with using omeprazole 20 mg PO daily max
  - No other proton pump inhibitor has been studied
- Anticoagulants, anticonvulsants, antimycobacterials, antiretrovirals, HMG-CoA reductase inhibitors

Vosevi [package insert]. U.S. Food and Drug Administration website. https://www.gilead.com/~/media/Files/pdfs/medicines/liver-disease/vosevi/vosevi_pi.pdf. Revised 11/2019.

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Ribavirin

- Used in combination with decompensated cirrhosis and in certain clinical scenarios (e.g., genotype 3 with prior sofosbuvir-based treatment failure)
- Weight-based, split-dosing and administered with food

Body Weight (kg)	Oral Ribavirin Daily Dosage[a]
less than 47	15 mg per kg per day (divided dose AM and PM)
47–49	600 mg per day (1 x 200 mg AM, 2 x 200 mg PM)
50–65	800 mg per day (2 x 200 mg AM, 2 x 200 mg PM)
66–80	1,000 mg per day (2 x 200 mg AM, 3 x 200 mg PM)
greater than 80	1,200 mg per day (3 x 200 mg AM, 3 x 200 mg PM)

- ADR: anemia, cough, insomnia, dyspnea, pruritus, rash, nausea

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Selecting the Right HCV Treatment

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Factors to Consider

1. HCV treatment history (naïve or experienced)
2. Cirrhosis (none, compensated, decompensated)
3. HCV genotype
4. Medication reconciliation (including herbal/dietary supplements) & potential drug interactions
5. Access to food
6. Adherence (one vs. three tablets; duration – 8 vs. 12 weeks)
7. Past medical history (e.g., transplant, human immunodeficiency virus)

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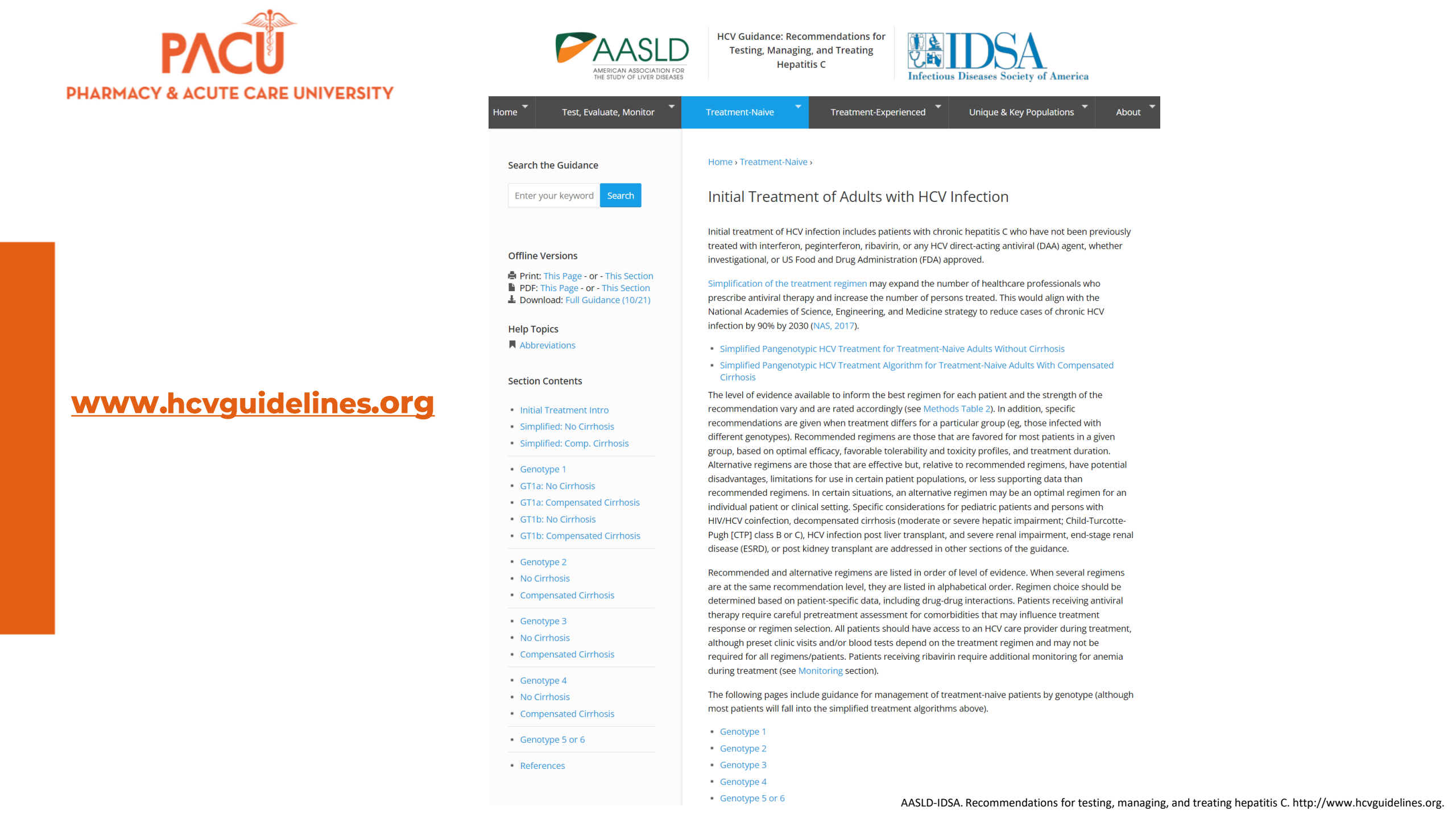

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HS

- 50 year old male with treatment-naïve HCV genotype 1A without cirrhosis

PMHx –
Opioid use disorder (in remission)
Obesity

Social Hx –
Alcohol: n/a
Tobacco: 1 PPD smoker x 10 years
IVDU: clean x 5 months – relapsed 1/2019 after 9 years sobriety

OTC/herbals/mineral supplements – denies

Drug Interactions – none

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Pertinent Labs –

	3/4/22
Hgb	17
Hct	49.9
Platelets	165
INR	1.01
Serum creatinine	0.83
eGFR	112
ALT	64
AST	37
Albumin	4.3
Tbili	0.3
HCV Viral Load	4,030

HIV: non-reactive

Hep B Core (3/4/22) – non-reactive
Hep B Antigen (3/4/22) – non-reactive
Hep B Surface Antibody (3/4/22) – 1.42

Pertinent Imaging/Procedures -
Fibroscan (1/3/22) – F2 – c/w moderate portal fibrosis with septa

US Abdomen (1/15/22) –no focal solid mass or dilated intrahepatic ducts. No findings suggestive of cirrhosis.

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Potential Treatment Options

Treatment-Naive Genotype 1a Without Cirrhosis

Recommended and alternative regimens listed by evidence level and alphabetically for: Treatment-Naive Genotype 1a Patients Without Cirrhosis		
RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)[a]	8 weeks	I, A
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg)	12 weeks	I, A
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for patients who are HIV-uninfected and whose HCV RNA level is <6 million IU/mL	8 weeks	I, B
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks	I, A
ALTERNATIVE	DURATION	RATING
Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg)	12 weeks	I, A
[a] Dosing is 3 coformulated tablets (glecaprevir [100 mg]/pibrentasvir [40 mg]) taken once daily. Please refer to the prescribing information.		

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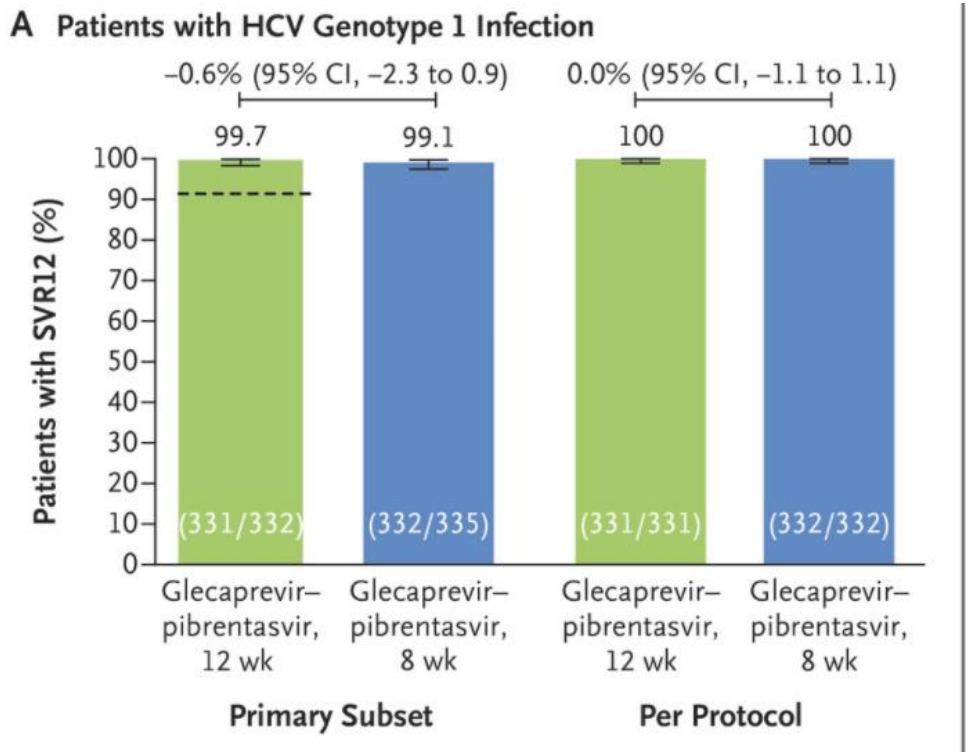
Glecaprevir/Pibrentasvir Data

- ENDURANCE-1
  - Phase 3 randomized trial of HCV genotype-1 patients without cirrhosis on glecaprevir-pibrentasvir for 8 (n=351) or 12 (n=352) weeks



- 8 week treatment duration was non-inferior to 12 weeks
- One patient experienced on-treatment virologic failure
- Similar safety profile across both treatment duration with headaches and fatigue being most common
- No patients discontinued treatment due to side effects
- No documented relapse in either study arm

Zeuzem S et al. *N Engl J Med*. 2018;378(4):354-369.

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Ledipasvir/Sofosbuvir Data

- ION-1
  - Phase 3 randomized trial of HCV genotype-1 patients ± cirrhosis on ledipasvir/sofosbuvir OR ledipasvir/sofosbuvir + ribavirin x 12 weeks, ledipasvir-sofosbuvir OR ledipasvir-sofosbuvir + ribavirin x 24 weeks

Table 2. Response during and after Treatment.

Response	12-Wk Regimen		24-Wk Regimen	
	LDV–SOF (N=214)	LDV–SOF + RBV (N=217)	LDV–SOF (N=217)	LDV–SOF + RBV (N=217)
HCV RNA <25 IU/ml				
During treatment — no./total no. (%)*				
At week 2	174/213 (82)	181/217 (83)	179/216 (83)	180/217 (83)
At week 4	213/213 (100)	215/217 (99)	216/216 (100)	217/217 (100)
At week 12	213/213 (100)	214/214 (100)	213/214 (>99)	216/216 (100)
After end of treatment — no. (%)				
At week 4	211 (99)	213 (98)	215 (99)	215 (99)
At week 12	211 (99)	211 (97)	212 (98)	215 (99)
Virologic failure during treatment — no.	0	0	1	0
Relapse — no.	1	0	1	0
Lost to follow-up — no.	2	4	2	2
Withdrew consent — no.	0	2	1	0

* Data shown are for patients for whom HCV RNA results were available.

- No difference in SVR12 rate between those with cirrhosis (97%) vs. without cirrhosis (98%)
- Most common side effects were fatigue, headache, insomnia, nausea

Afdhal N et al. *N Engl J Med*. 2014;370(20):1889-1898.

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Ledipasvir/Sofosbuvir Data

- ION-3
  - Phase 3 randomized trial of HCV genotype-1 patients without cirrhosis on ledipasvir/sofosbuvir OR ledipasvir/sofosbuvir + ribavirin x 8 weeks, ledipasvir-sofosbuvir x 12 weeks

Table 2. Response during and after Treatment.

Response	LDV–SOF for 8 Wk (N=215)	LDV–SOF + RBV for 8 Wk (N=216)	LDV–SOF for 12 Wk (N=216)
HCV RNA <25 IU/ml			
During treatment period — no./total no. (%)*			
At wk 2	190/215 (88)	195/214 (91)	197/216 (91)
At wk 4	215/215 (100)	211/213 (99)	216/216 (100)
After end of treatment — no. (%)			
At wk 4	207 (96)	205 (95)	208 (96)
At wk 12	202 (94)	201 (93)	206 (95)
Virologic failure during treatment — no.	0	0	0
Relapse in patients with HCV RNA <25 IU/ml at end of treatment — no. (%)	11 (5)	9 (4)	3 (1)
Lost to follow-up — no.	1	5	7
Withdrew consent — no.	1	1	0

* Data shown are for patients for whom HCV RNA results were available.

- SVR12 rates of 93-95% across all study arms
- Higher relapse rates with 8 week tx noticed in those who had baseline HCV RNA level <6 million IU/mL
- Most common side effects were fatigue, headache, and nausea

Kowdley KV et al. *N Engl J Med*. 2014;370(20):1879-1888.

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Back to HS

- What treatment option do you select and why?

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Feel free to email me at shubhat10@gmail.com if any further questions! Thank you!

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Hepatitis C: Pathophysiology & Treatment

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March 10, 2022