Screening, Treatment, and Pharmacologic Considerations for Patients with Hepatitis C Virus (HCV)

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Disclosures (Past 12 Months)

- James Hanje, MD, FAASLD:
  - Intercept Pharmaceuticals, Inc.
  - Salix Pharmaceuticals, Inc.

- Kenneth Barga, PharmD, BCPS, BCACP:
  - None

Learning Objectives

1. Review epidemiology, etiology, and pathophysiology of Hepatitis C viral infections.
2. Differentiate between patients with Hepatitis C who may be safely treated in the community versus those that require hepatology referral.
3. Review AASLD-IDSA guideline recommendations for the management of Hepatitis C.
4. Assess literature surrounding the two primary medications used in the community: sofosbuvir-velpatasvir (Epclusa®) and glecaprevir-pibrentasvir (Mavyret®).
5. Discuss the drug acquisition process and follow-up needs.

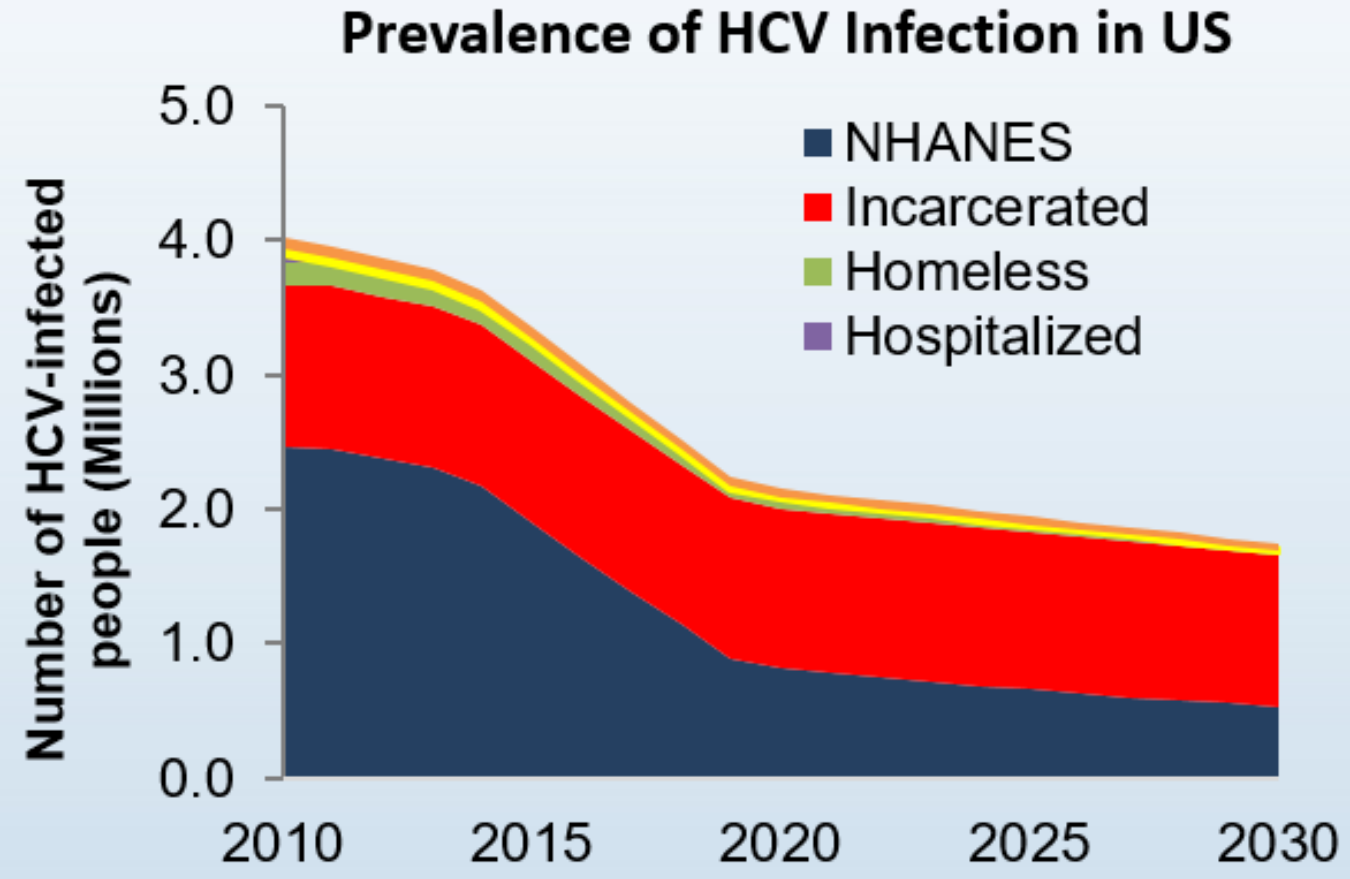
Epidemiology

- Centers for Disease Control & Prevention (CDC):
  - Incidence (2019): ~57,500 cases/year
  - Prevalence (2013-2016): ~2.4 million patients
  - Most Common Genotypes: 1a, 1b, 2, and 3

- World Health Organization (WHO):
  - Incidence: ~1.5 million cases/year
  - Prevalence: ~58 million patients
  - Mortality (2019): ~290,000 deaths

Data collected from:
- Centers for Disease Control & Prevention's National Center for HIV, Viral Hepatitis, STD, and TB Prevention (https://www.cdc.gov/hepatitis/hcv/hcvfaq.htm#a11)
- World Health Organization (https://www.who.int/news-room/fact-sheets/detail/hepatitis-c)

Prevalence of HCV in the United States: Simulation Model Including Non-NHANES Population



Chatwal, et al. The Liver Meeting, 2017. #989

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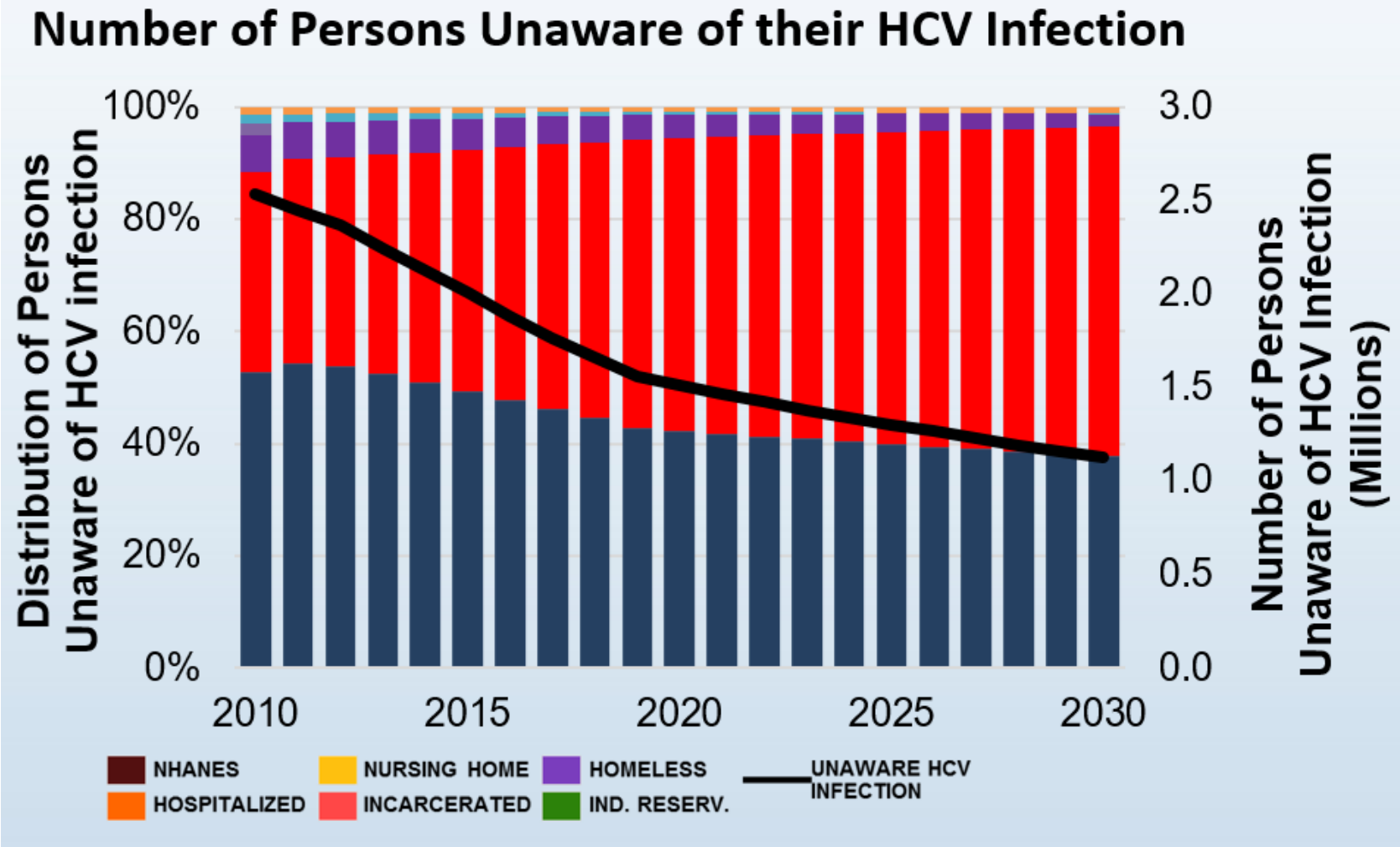

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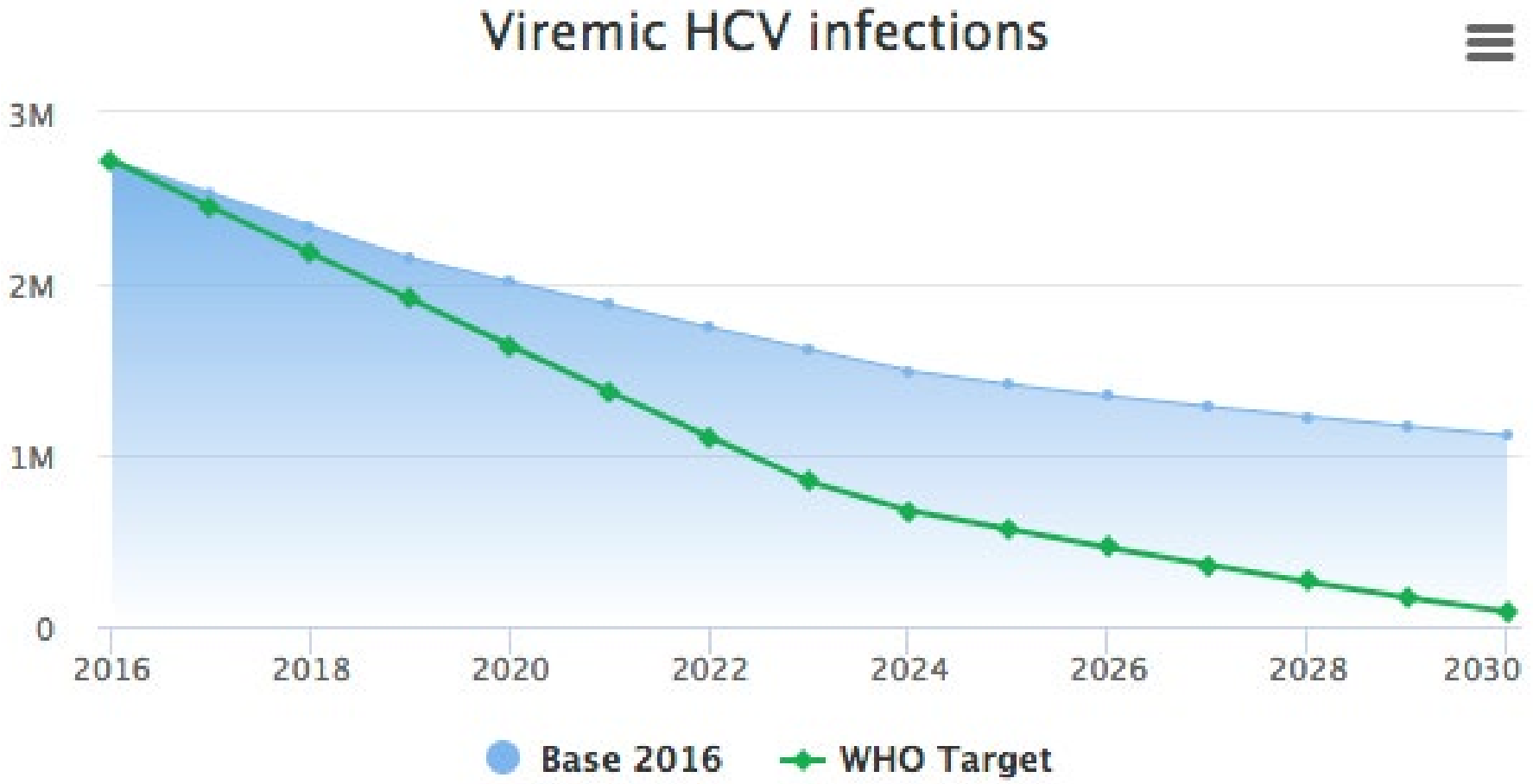
Road to Elimination



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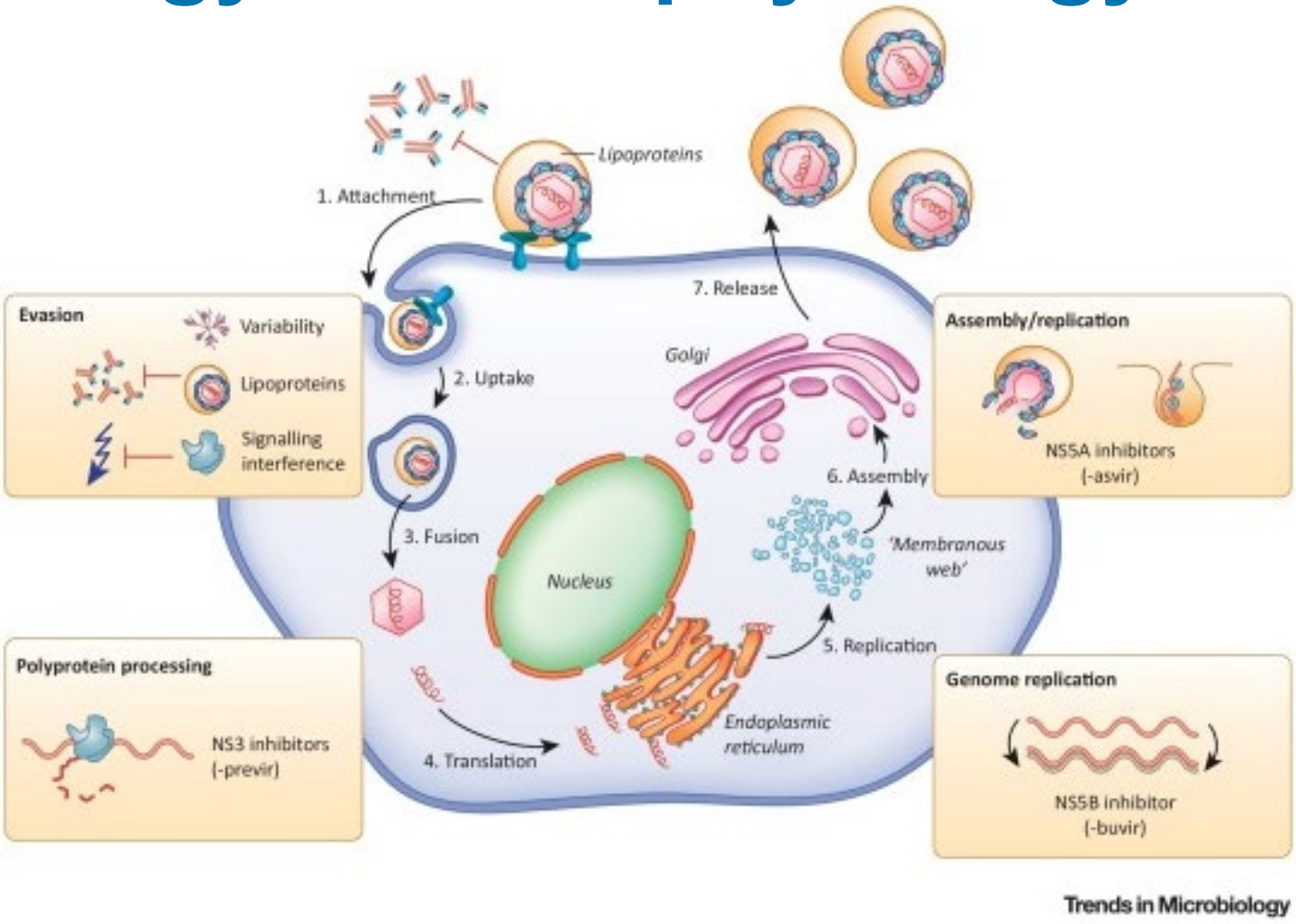
Etiology & Pathophysiology



Pietschmann T & Brown RJP. Hepatitis C Virus. *Trends in Microbiology*. 2019;27(4):P379-380. DOI: https://doi.org/10.1016/j.tim.2019.01.001

Extrahepatic Manifestations

- Dermatologic:
  - Porphyria cutanea tarda
  - Leukocytoclastic vasculitis
  - Lichen planus
- Hematologic:
  - Mixed cryoglobulinemia
- Renal:
  - Glomerulonephritis

Community's Role in HCV Management

Screen Patients

Manage Risk Factors

Differentiate Between Primary Care-Eligible Patients vs Referrals

Link Patients to Specialized Care

Screening: Who Should Be Screened?

One-Time Testing

- ALL patients ≥18 years
- Patients <18 years with associated circumstances that increase HCV risk
- Prenatal assessment with EACH pregnancy

Repeat Testing

- *Annual:* IVDM
- *Annual:* MSM (HIV-infected or taking PrEP)
- *Periodic:* All other persons with continued, associated circumstances that increase HCV risk

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Risk Factors

- **Intravenous drug misuse**
- Intranasal drug use, glass crack pipes
- Receipt of:
  - Blood products (prior to 1992)
  - Clotting factor concentrates (prior to 1987)
  - Long-term hemodialysis
- Healthcare needle-stick injuries
- Perinatal transmission
- Incarceration
- Percutaneous or parenteral exposures in an unregulated setting (ie. garage tattoos)
- Men who have sex with men

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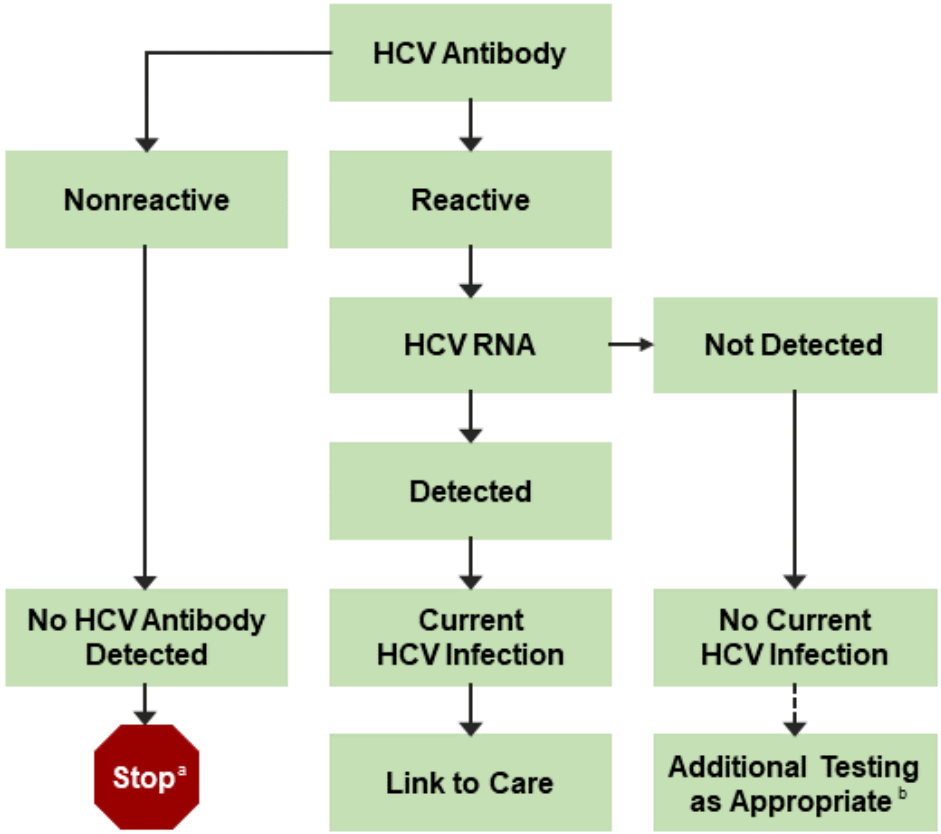
Screening: Interpretation



[a]For persons who might have been exposed to HCV within the past 6 months, testing for HCV RNA or follow-up testing for HCV Ab should be performed. For persons who are immunocompromised, testing for HCV RNA should be performed.
[b]To differentiate past, resolved HCV infection from biologic false positivity for HCV Ab, testing with another HCV Ab Assay can be considered. Repeat HCV RNA testing if the person tested is suspected to have had HCV exposure within the past 6 months or has clinical evidence of HCV disease, or if there is concern regarding the handling or storage of the test specimen.

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Who Should Manage HCV?

Eligible for Treatment in Primary Care Settings	Hepatology Referral Required
Patients must meet ALL of the following criteria: - Adults (≥18 years of age) - Chronic, treatment-naïve HCV of any genotype (1-6) - Little to no evidence of advanced liver disease determined by fibrotic staging (≤F2). Although the American Association for the Study of Liver Diseases (AASLD) and the Infectious Disease Society of America (IDSA) states patients with compensated cirrhosis may be treated in primary care settings, it is recommended to refer patients with advanced liver disease (≥F3) to hepatology as routine, specialized care is required.	Patients with one or more of the following criteria: - Prior HCV treatment - Advanced liver disease evidenced by fibrotic staging (≥F3) - HIV or HBsAg positive - Pregnant and/or breastfeeding mothers - Known or suspected hepatocellular carcinoma - Prior liver transplantation Patients are assumed to have cirrhosis if indicated by the following: - Transient elastography indicating cirrhosis (ie. FibroScan Stiffness >12.5 kPa) - Noninvasive serologic tests above proprietary cutoffs indicating cirrhosis (ie. FibroSure, FibroTest) - Clinical evidence of cirrhosis (ie. Liver nodularity and/or splenomegaly on imaging, platelet count <150,000/mm^3, etc.) - Prior liver biopsy showing cirrhosis

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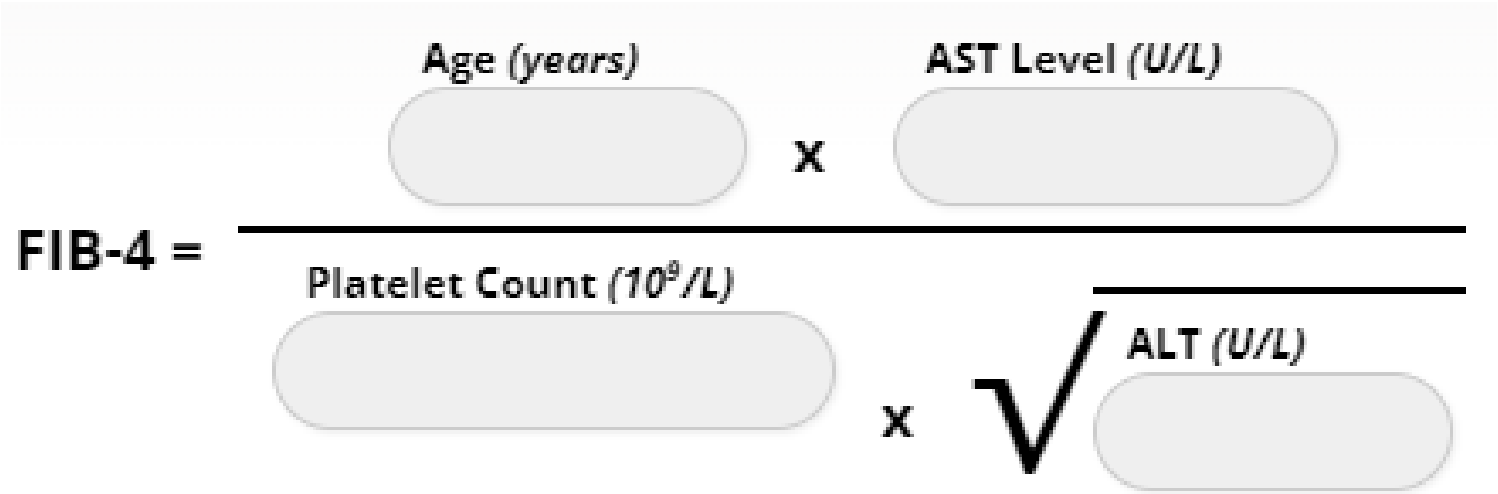
Pre-Treatment: Cirrhosis Assessment

Pre-Treatment Assessment for Patients with UNKNOWN Cirrhosis*	Presumed Cirrhosis (Interpretation)
FIB-4 Score[a]	>3.25
Transient Elastography (ie. FibroScan)	FibroScan Stiffness >12.5kPa
Noninvasive Serologic Tests (ie. FibroSure)	Value above proprietary cutoffs indicating cirrhosis
Liver Biopsy	Cirrhosis found on biopsy
Clinical Evidence of Cirrhosis	Liver nodularity and/or splenomegaly on imaging, Platelet count <150,000/mm^3, etc.

*Only one of these five means of cirrhosis assessment are required.
[a]FIB-4 Score <1.45 indicates a lack of cirrhosis with 86% certainty.

Pre-Treatment Assessment for Patients with KNOWN Cirrhosis
Calculated Child-Turcotte-Pugh (CTP) Score
Liver Ultrasound (≤6 months)

Pre-Treatment: FIB-4 Score



Interpretation:

- FIB-4 <1.45: 90% negative predictive value of advanced fibrosis
- FIB-4 >3.25: 65% positive predictive value of advanced fibrosis

FIB-4 IS NOT REQUIRED FOR PATIENTS WITH KNOWN CIRRHOSIS.

Pre-Treatment: Additional Assessments

- Reconcile medications
- Identify potential drug-drug interactions
- Educate patient regarding:
  - HCV and risks associated with not treating
  - Risk factor management / reinfection prevention
  - Treatment (if appropriate)

Pre-Treatment: Lab Monitoring

Within Three Months of Initiating Treatment
Complete Blood Count (CBC)
Hepatic Function Panel
Calculated Glomerular Filtration Rate (eGFR)
International Normalized Ratio (INR)*
Any Time Prior to Initiating Antiviral Therapy
Quantitative HCV RNA
HIV Antigen/Antibody Test
Hepatitis B Surface Antigen Test
HCV Genotype (if treating with sofosbuvir/velpatasvir)*
Before Initiating Antiviral Therapy
Serum Pregnancy Testing (women of childbearing age)

*Recommendations may vary in those with advanced fibrosis/cirrhosis.

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Who Should Be Treated?

- Do NOT Treat:
  - Short life expectancy (≤12 months) that cannot be remediated by HCV resolution
  - Liver transplant candidate
- Do Treat:

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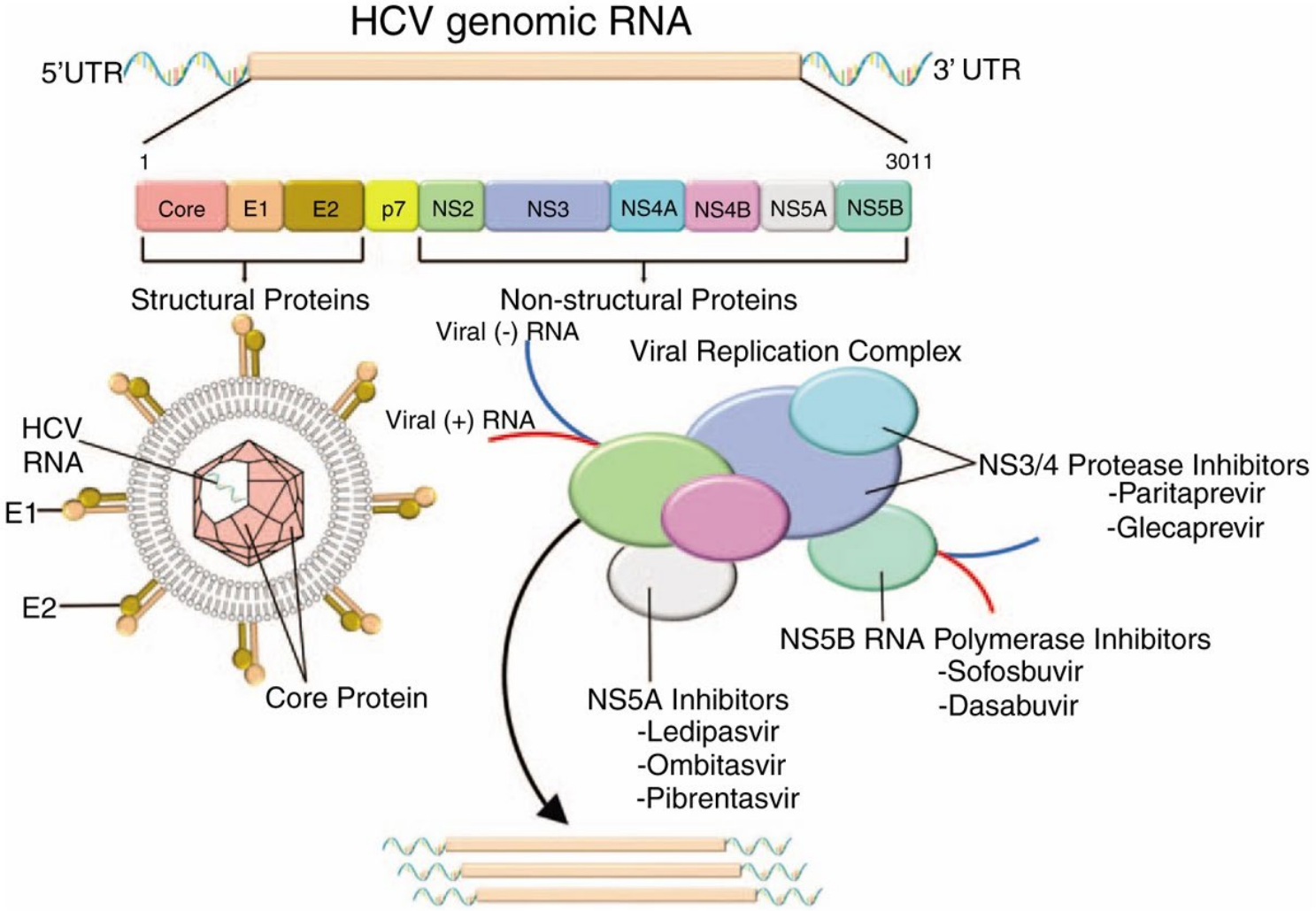
Direct-Acting Antivirals: Mechanism of Action



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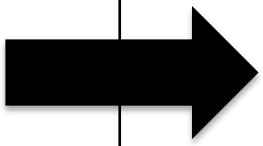
Available Direct-Acting Antivirals

Medication Class: NS3/4A Protease Inhibitors
Glecaprevir
Grazoprevir
Voxilaprevir
Medication Class: NS5A Inhibitors
Elbasvir
Ledipasvir
Pibrentasvir
Velpatasvir
Medication Class: NS5B Inhibitors
Sofosbuvir
Medication Class: Purine Nucleoside Analog
Ribavirin



Generic Name (Abbreviation)	Brand Name
Elbasvir-Grazoprevir (EBR-GZR)	Zepatier®
Glecaprevir-Pibrentasvir (GLE-PIB)	Mavyret®
Ledipasvir-Sofosbuvir (LDV-SOF)	Harvoni®
Ribavirin (RBV)	Copegus®, Rebetol®, Ribasphere®
Sofosbuvir (SOF)	Sovaldi®
Sofosbuvir-Velpatasvir (SOF-VEL)	Epclusa®
Sofosbuvir-Velpatasvir-Voxilaprevir (SOF-VEL-VOX)	Vosevi®

Treatment Options in Community Settings

Generic Name (Abbreviation)	Brand Name	Medication Class(es)	Genotypes Covered	Cirrhosis	Dose	Duration*
Glecaprevir-Pibrentasvir (GLE-PIB)	Mavyret®	NS3/4A PI (Glecaprevir) NS5A Inhibitor (Pibrentasvir)	Pan-Genotypic	With (compensated) or without	300-120mg once daily with food[a]	8 weeks
Sofosbuvir-Velpatasvir (SOF-VEL)	Epclusa®	NS5B Inhibitor (Sofosbuvir) NS5A Inhibitor (Velpatasvir)	Pan-Genotypic[b]	With or without	400-100mg once daily	12 weeks

*Duration of therapy assumes treatment-naïve, chronic HCV with either compensated cirrhosis or no cirrhosis at baseline.
[a]To achieve a dose equivalent to 300-120mg, patients will need to take three tablets per dose.
[b]Patients with genotype 3 require baseline NS5A resistance-associated substitution (RAS) testing. Those without Y93H can be treated with 12 weeks of sofosbuvir/velpatasvir.

- Renal Considerations: None
- Hepatic Considerations:
  - GLE-PIB: Contraindicated in Child-Pugh Class B-C
  - SOF-VEL: None

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Primary Literature: GLE-PIB

Trial	N	Population*	Follow-Up	Primary Outcome(s)
SURVEYOR-1	147	Treatment-naïve or -experienced (PegIFN/RBV) adults (<70yo) with chronic HCV (genotypes 1 and 4-6) without cirrhosis	24 weeks post-treatment	SVR12: - 12-week treatment (1 and 4-6): 97-100% and 100% - 8-week treatment with GLE 300mg-120mg (1): 97-98%
SURVEYOR-2	302	Treatment-naïve or -experienced (PegIFN/RBV) adults (<70yo) with chronic HCV (genotypes 2 and 3) without cirrhosis	24 weeks post-treatment	SVR12 - 12-week treatment (2 and 3): 96-100% and 83-94% - 8-week treatment with GLE 300mg-120mg (2 and 3): 97-98%
EXPEDITION-1	146	Treatment-naïve or -experienced (PegIFN/RBV/SOF+RBV) adults with chronic HCV (genotypes 1, 2, 4-6) with compensated cirrhosis	24 weeks post-treatment	SVR12 - Overall: 99% (CI: 98-100%)

*Patients with co-infecting HBV, HIV, or ≥1 HCV genotype were excluded.

Primary Literature: SOF-VEL

Trial	N	Population	Follow-Up	Primary Outcome(s)
ASTRAL-1	624	Treatment-naïve or –experienced* adults with chronic HCV (genotypes 1, 2, and 4-6) with or without compensated cirrhosis	12 weeks post-treatment	SVR12: - Overall: 99% (95% CI: 98->99%; p<0.001)
ASTRAL-2	266	Treatment-naïve or –experienced adults with chronic HCV (genotype 2) with or without compensated cirrhosis[a]	12 weeks post-treatment	SVR12: - Genotype 2: 99% (95% CI: 96-100%; p=0.02)
ASTRAL-3	552	Treatment-naïve or –experienced adults with chronic HCV (genotype 3) with or without compensated cirrhosis[a]	12 weeks post-treatment	SVR12: - Genotype 3: 95% (95% CI: 92-98%; p<0.001)

*Treatment-experienced patients included those that received previous protease inhibitor, peginterferon, and ribavirin; peginterferon and ribavirin; or nonpegylated interferon with or without ribavirin.
[a]Treatment-experienced patients included those that received interferon-containing regimens.

Drug-Drug Interactions

- Resources:
  - AASLD-IDSA HCV Guidance – “Monitoring Patients Who Are Starting HCV Treatment, Are on Treatment, or Have Completed Therapy”
    - https://www.hcvguidelines.org/evaluate/monitoring
  - University of Liverpool HEP Drug Interactions
    - https://www.hep-druginteractions.org/checker
  - AIDS Education & Training Center (AETC) Program – “HIV and HCV Drug Interactions: Quick Guides for Clinicians”
    - https://aidsetc.org/resource/hiv-and-hcv-drug-interactions-quick-guides-clinicians
  - Tertiary Drug Databases (ie. LexiComp)

Adverse Drug Events (ADEs)

- Altered Mood: Depressed, Irritable
- Asthenia
- **Fatigue**, Insomnia, Altered Sleep
- **GI Intolerances:** Nausea, Vomiting, Diarrhea
- **Headaches**
- **HBV Reactivation:**
  - Manage HBV infection in accordance with AASLD Guidelines **PRIOR TO** initiating HCV treatment.
- Skin Rash

Glecaprevir-Pibrentasvir (Mavyret) [package insert].
Sofosbuvir-Velpatasvir (Epclusa) [package insert].

Bottom Line

- Patients with acute/chronic, treatment-naïve HCV without advanced fibrosis may safely be treated in community settings.
- Screen ALL patients for HBV and HIV **BEFORE** initiating treatment.
- HCV Treatment Evolution:
  - Covered Genotypes: Pangenotypic
  - Route: Oral
  - Duration: 8-12 weeks
  - SVR Rates: High (~98%)
  - ADE: Well-tolerated
    - Fatigue, Headaches, GI Intolerances

Drug Acquisition

- Specialty Medication
  - Dispensed as 28-day supply per fill regardless of treatment duration

- Prior Authorization (PA), Peer-to-Peer, and/or Appeal
  - Modalities to Complete PA:
    - Electronic (ie. CoverMyMeds), Verbal, or Fax

Drug Acquisition

- Patient Assistance Once Approved:

Drug Coverage	Recommended Patient Assistance Paths
Commercial	Manufacturer-Sponsored Copay Card
Medicaid Only	N/A – Fully Covered
Medicare Only	National Grant Funding (ie. HealthWell Foundation) or Manufacturer-Sponsored Patient Assistance Programs (ie. AbbVie's Patient Access Support or Gilead's SupportPath)
Medicare-Medicaid Dual Eligible	N/A – Fully Covered
Uninsured	Manufacturer-Sponsored Patient Assistance Programs (ie. AbbVie's Patient Access Support or Gilead's SupportPath)

*Patients with federally-funded programs such as Veterans Affairs (VA) or Department of Defense (DOD) are generally excluded from such programs and should be directed to available resources within their overseeing organization.

On-Treatment Monitoring

- On-treatment monitoring is **NOT** recommended for most patients unless:
  - Diabetes ➔ Monitor for episodes of symptomatic hypoglycemia
  - Anticoagulation (INR) ➔ Monitor INR closely for instances of subtherapeutic INR

Pending patient/provider preference, a follow-up visit may be scheduled to provide patient support.

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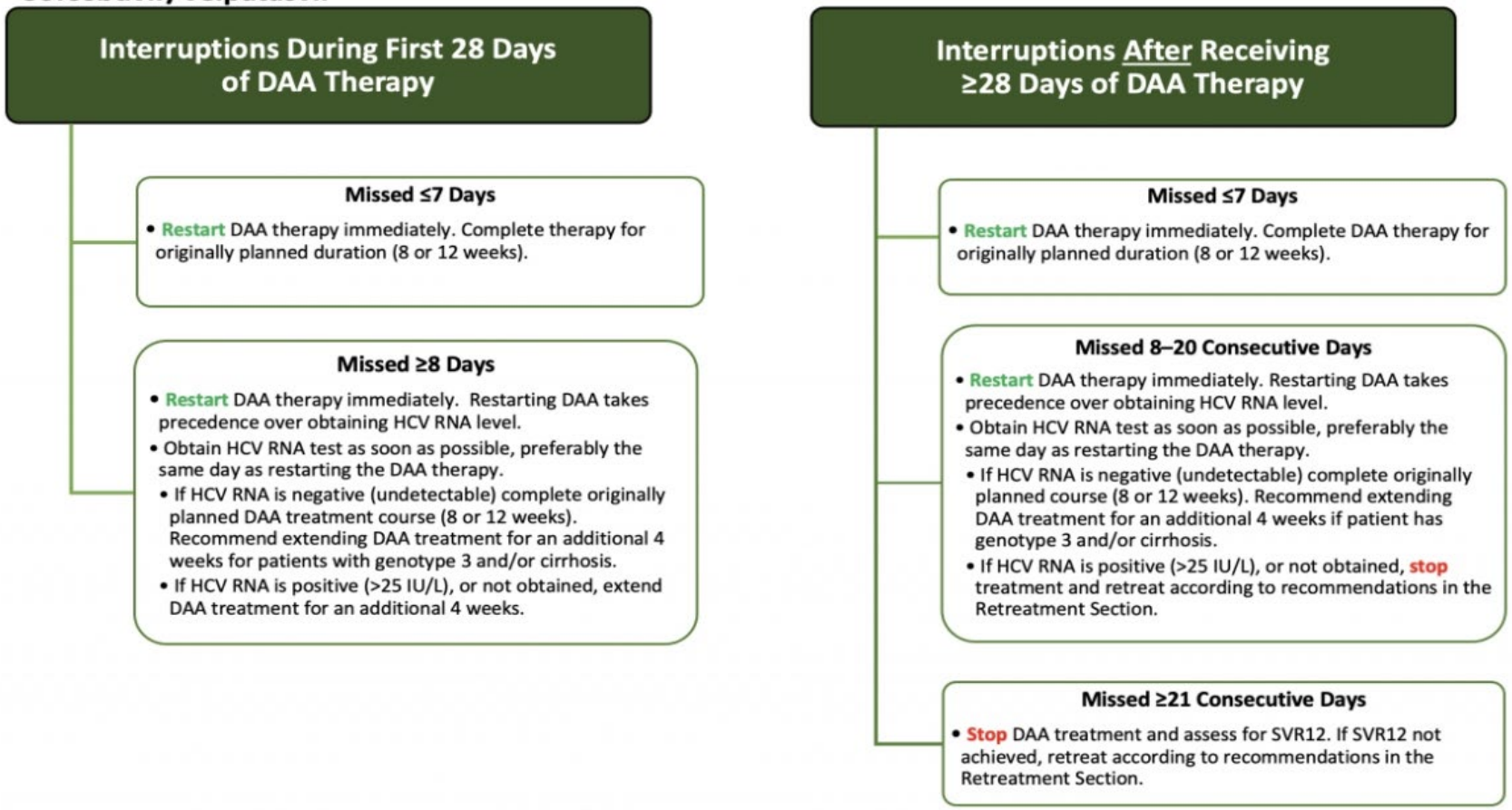
Medication Non-Compliance

Figure 1. Recommended Management of DAA Treatment Interruptions for Treatment-Naive Patients, Without Cirrhosis or With Compensated Cirrhosis, Receiving Glecaprevir/Pibrentasvir or Sofosbuvir/Velpatasvir



DAA, direct-acting antiviral; HCV RNA, hepatitis C virus ribonucleic acid; SVR12, sustained virologic response 12 weeks after end of treatment.

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Post-Treatment: Non-Cirrhotic

POST-TREATMENT ASSESSMENT OF CURE (SVR)	FOLLOW-UP AFTER ACHIEVING VIROLOGIC CURE (SVR)	FOLLOW-UP FOR PATIENTS WHO DO *NOT* ACHIEVE A VIROLOGIC CURE
• Assessment of quantitative HCV RNA and a hepatic function panel are recommended 12 weeks or later following completion of therapy to confirm HCV RNA is undetectable (virologic cure) and transaminase normalization. • Assessment for other causes of liver disease is recommended for patients with elevated transaminase levels after achieving SVR.	• No liver-related follow-up is recommended for noncirrhotic patients who achieve SVR. • Patients with ongoing risk for HCV infection (eg, intravenous drug use or MSM engaging in unprotected sex) should be counseled about risk reduction, and tested for HCV RNA annually and whenever they develop elevated ALT, AST, or bilirubin. • Advise patients to avoid excess alcohol use.	• Patients in whom initial HCV treatment fails to achieve cure (SVR) should be evaluated for retreatment by a specialist, in accordance with AASLD/IDSA guidance. • Until retreatment occurs, assessment for disease progression every 6 to 12 months with a hepatic function panel, CBC, and INR is recommended. • Advise patients to avoid excess alcohol use.

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Post-Treatment: Cirrhotic

POST-TREATMENT ASSESSMENT OF CURE (SVR)	FOLLOW-UP AFTER ACHIEVING VIROLOGIC CURE (SVR)	FOLLOW-UP FOR PATIENTS WHO DO *NOT* ACHIEVE A VIROLOGIC CURE
• Assessment of quantitative HCV RNA and a hepatic function panel are recommended 12 weeks or later following completion of therapy to confirm HCV RNA is undetectable (virologic cure) and transaminase normalization. • Assessment for other causes of liver disease is recommended for patients with elevated transaminase levels after achieving SVR.	• Ultrasound surveillance for HCC (with or without alpha-fetoprotein testing) every 6 months is recommended for patients with cirrhosis in accordance with AASLD guidance. • Upper endoscopic surveillance for esophageal varices is recommended in accordance with AASLD guidance on portal hypertensive bleeding in cirrhosis • Patients with ongoing risk for HCV infection (eg, IV drug use or MSM engaging in unprotected sex) should be counseled about risk reduction, and tested for HCV RNA annually and whenever they develop elevated ALT, AST, or bilirubin. • Patients should abstain from alcohol to avoid progression of liver disease.	• Patients in whom initial HCV treatment fails to achieve cure (SVR) should be evaluated for retreatment by a specialist, in accordance with AASLD/IDSA guidance. • Ultrasound surveillance for hepatocellular carcinoma (with or without alpha-fetoprotein testing) every 6 months is recommended for patients with cirrhosis, in accordance with AASLD guidance. • Assessment for disease progression every 6 to 12 months with a hepatic function panel, CBC, creatinine, and INR is recommended. • Patients should abstain from alcohol to avoid progression of liver disease.

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Patient Case

RMT is a 49yoWF with a PMH significant for Chronic HCV, IVDM (sobriety x18 months), and Bipolar Disorder. Patient presents to DHFP for treatment of her chronic HCV. She is treatment-naïve with the following labs (collected ~2 weeks prior):

- HCV RNA Quant: 4,210,000 IU/mL
- HIV / HBV: (-)
- CMP: AST 63, ALT 50, eGFR WNL
- CBC: Plt 327
- Pregnancy Test: N/A (female partner)

1. Is RMT able to be safely treated in the primary care setting?
2. If so, what medication, dose, and duration would you select and why?

Questions?

How to Refer

- OhioHealth Comprehensive Liver Program:
  - Phone: 614-566-5150
  - Fax: 614-566-5153

- Ohio Gastroenterology Group:
  - Phone: 614-754-LIVR (5487)
  - Fax: 614-754-5541

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