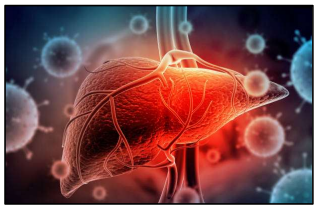
Hepatitis C Treatment and Access in Michigan:

Presentation to Western Michigan Society of Health-System Pharmacists



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Presentation adapted from original by Jonathan Cohn, MD and Gretchen Newman, MD

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Disclosures

No relevant personal financial relationships within the past 24 months

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Overview of Presentation

- HCV Epidemiology
- Disease states caused by HCV
- HCV Treatment

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Hepatitis C Epidemiology

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Hepatitis C

- RNA virus of the flavivirus family, discovered in 1988
- Prior to this was known as “non-A, non-B hepatitis”
- 6 major genotypes (1-6)
- 70% of cases in the US are genotype 1

Dr. Gretchen Snoeyenbos-Newman; CDC

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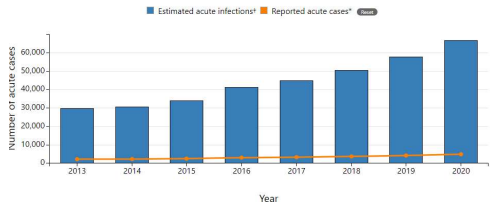
Number of reported cases* of acute hepatitis C virus infection and estimated infections† — United States, 2013-2020



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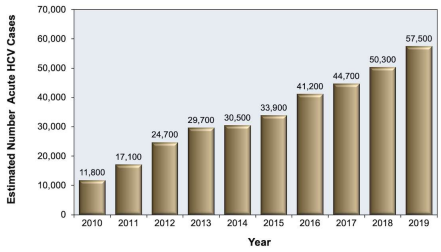
HCV incidence is rising



Source: Centers for Disease Control and Prevention (CDC). 2019 Viral Hepatitis Surveillance Report—Hepatitis C. Published May 2021.

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HCV Acquisition

- Injection drug use – 60% of all cases of HCV
  - 20-30% of PWID acquire HCV in their first year, 50% by 5 years
- Non-injection drug use – controversial (surrogate?)
- Sexual exposure – controversial
  - MSM – especially with HIV coinfection, chemsex, etc
- Chronic HD
- Receipt of blood products prior to 1992
- Perinatal
- Transplantation
- Household contact
- Tattoos and Piercing

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Risk Factors of HCV acquisition

- Most common blood-borne illness in the US
- Up to 45% of persons with HCV infection do not report exposure
  - After careful questioning, many identify IDU

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Route of Transmission prior to 1992

- In the 1970s and 1980s >50% of new cases of HCV were due to blood products or organs

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Injection Drug Use

- Accounts for >60% of all new cases of HCV
- 20-30% of PWID will become infected within 2 years of starting on inject drugs
- 50% of PWID will become infected within 5 years
- Risk is highest with direct needle sharing, but persists with sharing of works

https://medicalxpress.com/news/2018-07-hepatitis-vaccine-transmission-people-drugs.html

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Injection Drug Use

- Increase in HCV among young PWID
- Driven by opioid epidemic
- Several common factors
  - Age under 30
  - White race
  - Non-urban residence
  - Use of oral Rx opiates prior to using heroin
- Rates highest in central Appalachian region

https://www.totalaccessgroup.com/stericup_colored.html

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Non-Injection Drug Use

Available on amazon…

- The role of non-injection drug use is controversial
- Most likely through sharing straws
- Drugs that cause sores or erosion of nasal mucosa
- ie. Cocaine

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Sexual Exposure

- Controversial
- Monogamous heterosexual couples show transmission <1% per year
- MSM transmission has been reported
  - Risk factors include
    - HIV co-infection
    - Chemsex
    - Sexual practices that result in rectal bleeding or damage to the mucosa (eg fisting, use of sex toys)

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Perinatal Transmission

- Risk of transmission is about 6%
- Risk is highest when there is viremia
- Women co-infected with HIV have twofold higher risk
- Risk via breastfeeding is negligible

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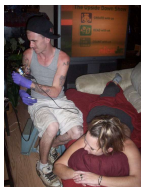
Household Contacts/Tattoos

- Possible but unlikely
- Don't share toothbrushes, razors
- Professional tattoo artists – negligible
- Kitchen magician…higher



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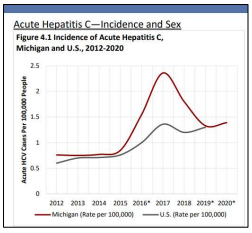
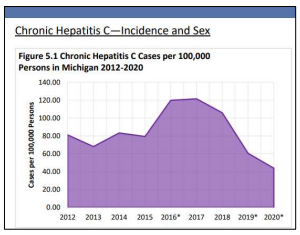
Hepatitis C In Michigan





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Understanding Disease States Caused by Hepatitis C

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Natural History of HCV Infection

- 55-85% of people infected with HCV will develop chronic HCV
- More likely to clear in:
  - Younger persons
  - Women
  - Non-Black persons
  - Persons with symptomatic acute infection
  - Persons without HIV co-infection

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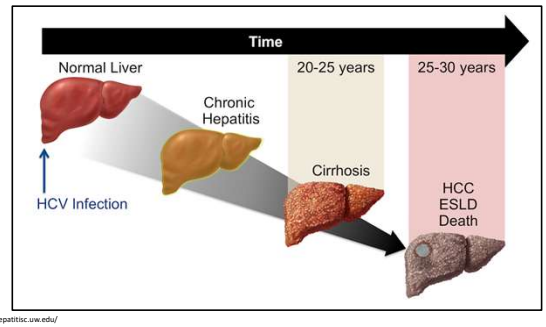
The Natural History of the Disease



https://www.hepatitisc.uw.edu/

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Question!

- Who should be screened for HCV?

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Who do you screen? - Recommendations

USPSTF, CDC & AASLD:

- Universal screening once in lifetime for all people 18+ (USPSTF – 18-79)

CDC:

- During every pregnancy
- All adults at least once
- Routine (annual) screening for those with ongoing risks:
  - People who inject drugs
  - Persons on hemodialysis
- Anyone who asks for a test

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Who do you screen? – Recommendations

AASLD:

- One-time HCV testing should be performed for all persons younger than 18 years old with behaviors, exposures, or conditions or circumstances associated with an increased risk of HCV infection. (I, B)
  - AASLD/IDSA adds: Persons under 18 with risk exposures
  - AASLD/IDSA adds: MSM with HIV
- Routine screening should be offered to all persons with behaviors, exposures, or conditions or circumstances associated with an increased risk of HCV exposure. (IIa, C)
- Annual HCV testing for all persons who inject drugs and for men with human immunodeficiency virus (HIV) infection who have unprotected sex with men. (IIa, C)

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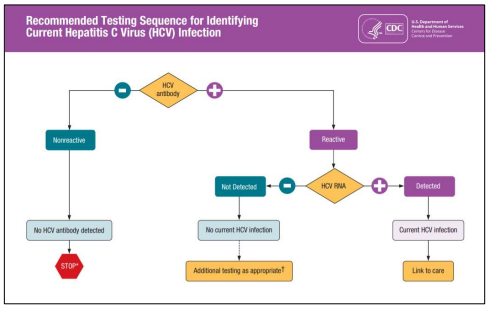
HCV Diagnostic Testing



Some laboratories offer reflex testing: a sample positive for hepatitis C antibody is automatically tested for HCV RNA without obtaining another sample

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Acute HCV Infection

- 20-50% of acute HCV infections clear in 6 months and rarely after 6 months
- AASLD/IDSA recommends treatment of acute infection
  - Uses current treatment regimens
  - Low toxicity, high efficacy, avoidance of any liver damage
  - May reduce HCV transmission
- Diagnosing acute HCV infection
  - Known or likely exposure
  - Baseline HCV Ab and RNA negative within 48 hours of exposure
  - Symptomatic hepatitis or increased ALT AST bilirubin
  - Development of HCV RNA
  - HCV antibody positive after ≥6 weeks of infection

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Case 1

35yo woman with dx of chronic HCV.

What do you need to know?

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HCV Baseline Assessment: Focused History

- Prior HCV diagnosis?
- Was there prior HCV treatment?
- Review symptoms of liver decompensation or portal hypertension
  - History of decompensated cirrhosis requires referral to a specialist for treatment
- HBV, HIV, pregnancy require consultation for HCV treatment
  - YOU are that consultant
- Update the medication list including supplements
  - Is glecaprevir/pibrentasvir (Mavyret) compatible?
- What was the presumed route of HCV acquisition and are their ongoing potential exposures?
  - Opportunity for drug or alcohol treatment or HIV/STD testing and treatment
- What is patient's experience with medication adherence?
  - Planning intensity of monitoring on treatment

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Case 1

- Prior HCV diagnosis? No.
- Was there prior HCV treatment? n/a
- Review symptoms of liver decompensation or portal hypertension: None
  - History of decompensated cirrhosis requires referral to a specialist for treatment
- HBV, HIV, pregnancy require consultation for HCV treatment: None
- Update the medication list including supplements: she takes no meds
  - Is Mavyret compatible?
- What was the presumed route of HCV acquisition and are their ongoing potential exposures? IDU, currently using
- What is patient's experience with medication adherence? Recently completed a course of oral antibiotics for pyomyositis without problems

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Now what?

- Who can prescribe HCV treatment covered by Michigan Medicaid?
- What are the limitations of prescribing?
- Who is eligible for HCV treatment?
- What is the preferred medication?

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Which Medicaid enrollees are eligible for streamlined HCV treatment with glecaprevir/pibrentasvir?

- **Persons 12 years and older, not pregnant, with active hepatitis C**
  - Hepatitis C RNA present in blood samples
  - Other medications available for 3-12 year olds
  - Defer treatment in pregnant and lactating women
- **Persons whose medications do not have important glecaprevir/pibrentasvir drug-drug interactions**
  - Medicaid patients requiring a different hepatitis C drug will need a prior authorization; the PA does not include a specialist nor a sobriety requirement

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While most patients can be treated in primary care, some should be referred to a specialist

- **Patients who should be referred to a specialist or co-managed with a specialist:**
  - Patients with prior hepatitis C treatment failure
  - Patient with active hepatitis B: Hep B Surface antigen **OR** isolated Hep B Core total antibody
  - Active HIV infection
  - Persons with decompensated cirrhosis
  - Prior liver transplant or other organ transplant
  - Liver cancer
- For most of these patients, primary care providers are the specialist!

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Ok, fine I am treating her!

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Pretreatment Assessment: Labs

- Within 6 months of starting treatment
  - CBC
  - LFTs
  - GFR
  - Calculate FIB-4 and complete any further cirrhosis assessment
- Any time prior to starting DAA
  - HCV viral load and Genotype*
  - HIV testing
  - HepB SA
- Before starting DAA
  - Pregnancy testing

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2020 AASLD Recommendations for Treatment Naïve Patients

Genotype	1	2	3	4	5	6
Treatment naïve, non-cirrhotic or compensated cirrhosis	Epclusa Mavyret Harvoni# Zepatier	Epclusa Mavyret	Epclusa* Mavyret Vosevi	Epclusa Mavyret Harvoni Zepatier	Epclusa Mavyret Harvoni	Epclusa Mavyret Harvoni

Epclusa (12 weeks) and Mavyret (8 weeks) are pangenotypic medications indicated for no cirrhosis or compensated cirrhosis
*AASLD recommends adding ribavirin to Epclusa when treating persons with GT3, compensated cirrhosis and Y93H RAS. Vosevi may also be used for this situation.
#Harvoni is effective in GT 1, non-cirrhotic, without HIV co-infection, with HCV RNA <6 million, for 8 weeks

www.hcvguidelines.org

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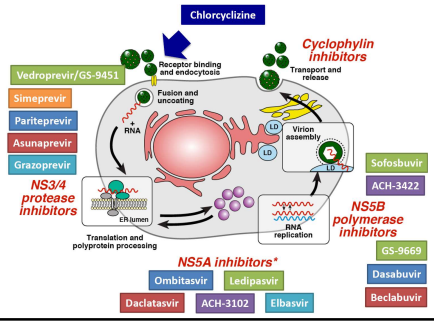
HCV replication provides multiple potential targets for drug treatment:

Three enzyme systems targeted with currently licensed medications



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HCV combination formulations inhibit multiple HCV enzyme systems

	NS3/4A serine protease inhibitors	NS5A replication complex inhibitors	NS5B nucleotide polymerase inhibitors	NS5B non-nucleoside polymerase inhibitors
	Inhibit protein cleavage	Mechanism unclear	Chain termination	Block active site
Harvoni		ledipasvir	sofosbuvir	
Epclusa		velpatasvir	sofosbuvir	
Vosevi (for reRx)	voxilaprevir	velpatasvir	sofosbuvir	
Zepatier	grazoprevir	elbasvir		
Mavyret	glecaprevir	pibrentasvir		
Viekira Pak (+/- ribavirin)	paritaprevir/ ritonavir	ombitasvir		dasabuvir

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Glecaprevir/pibrentasvir

- 3 tablets PO QD for 8 weeks
- Carton with one month supply contains:
  - 4 weekly cartons which contain
  - 7 daily wallets which contain
  - 3 tablets

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Monitoring on glecaprevir/pibrentasvir

- On Treatment
  - None for most patients
  - Hypoglycemia for patients on diabetes meds
  - INR for patients on warfarin
- Visits or telehealth can be scheduled as needed for patient support, assessment of symptoms, or new meds

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Assessment of Cure – SVR achievement

- 12 weeks after treatment
  - HCV RNA
  - LFTs
- Follow up after achieving SVR
  - No liver-related follow up
  - Continue to test for new infection based on risk factors
- Follow up if NO SVR
  - Refer to specialist for re-treatment (that is you, we will discuss at a later date)
  - Assess disease progression q6-12months with CBC, LFTs, INR

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Same patient…

But her FIB-4 >3.25

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Assessing Liver Fibrosis

- Streamlined assessment for cirrhosis:
  - FIB-4: calculated from age, AST, ALT, and platelet count
    - >3.25 considered cirrhosis
  - Current or prior clinical evidence of cirrhosis:
    - Prior commercial lab test result of F4 (F4 fibrosis=cirrhosis)
    - Prior elastography result >12.5 kPa
    - Nodular liver or splenomegaly on ultrasound
    - Platelet count <150,000
    - Prior liver biopsy showing cirrhosis
- Commercial blood tests of liver fibrosis give more specific results
  - (FibroSure, FibroTest, FibroMetric, etc.)
- Elastography
- Liver ultrasound has poor sensitivity for cirrhosis but is used to screen for hepatocellular cancer

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Assessing Cirrhosis: Child-Turcotte-Pugh (CTP) Score

	1 points	2 points	3 points
Albumin g/dl	>3.8	3.5-2.8	<2.8
Bilirubin mg/dl	< 2	2-3	>3
INR	<1.7	1.7-2.3	>2.3
Ascites	None	Moderate (diuretic responsive)	Severe
Encephalopathy	None	Mild-Moderate (grade 1-2)	Severe (grade 3-4)

Class A: 5-6 points, compensated, 2 yr survival 85%
Class B: 7-9 points, decompensated, 2 yr survival 57%
Class C: ≥ 10 points, decompensated, 2 yr survival 35%

Child-Turcotte-Pugh (CTP) Calculator - Clinical Calculators - Hepatitis C Online (uw.edu)

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Management of Cirrhosis

- Can treat adults who never had liver decompensation with glecaprevir/pibrentasvir for 8 weeks for any genotype
- Refer patients who have or had ***decompensated liver disease*** to hepatologist or liver transplant specialist

Surveillance for hepatocellular cancer
- Liver ultrasound prior to treatment to assess for ascites and HCC, repeat every 6 months after treatment
- Alpha-feto-protein (AFP) in addition is optional

AASLD HCC guidelines 2018

Assessment for portal hypertension
- EGD for surveillance for varices
- No EGD is necessary if:
  - Elastography result <20 kPa
    and
  - Platelet count ≥ 150,000

AASLD Portal Hypertension guidelines 2017

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Monitoring on glecaprevir/pibrentasvir: Cirrhosis

- On Treatment
  - Monitor liver enzymes as decompensation may occur (rare)
    - Refer to GI for worsening liver-ness
  - Hypoglycemia for patients on diabetes meds
  - INR for patients on warfarin
- Visits or telehealth can be scheduled as needed for patient support, assessment of sx, or new meds

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Same patient…

But she takes medicines

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Assessing Drug Interactions

Check for interactions with all the medications and supplements

- Liverpool University Drug Interaction Checker
  - Website: Liverpool HEP Interactions (hep-druginteractions.org)
  - Smartphone app: Hep iChart
- AASLD/IDSA website: hcvguidelines.org
- Manufacturer's Full Prescribing Information

- Glecaprevir/pibrentasvir is known to be safe with buprenorphine, methadone, and naloxone and is expected to be safe with naltrexone.
- Sofosbuvir/velpatasvir is known to be safe with methadone and expected to be safe with buprenorphine, naloxone and naltrexone.

Epclusa and Mavyret full prescribing information; Liverpool HEP Interactions (hep-druginteractions.org)

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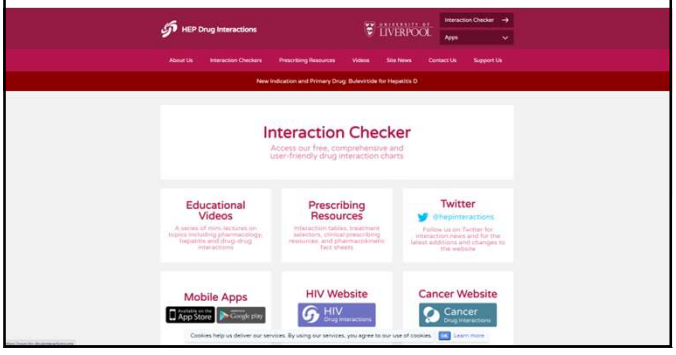
https://www.hep-druginteractions.org/



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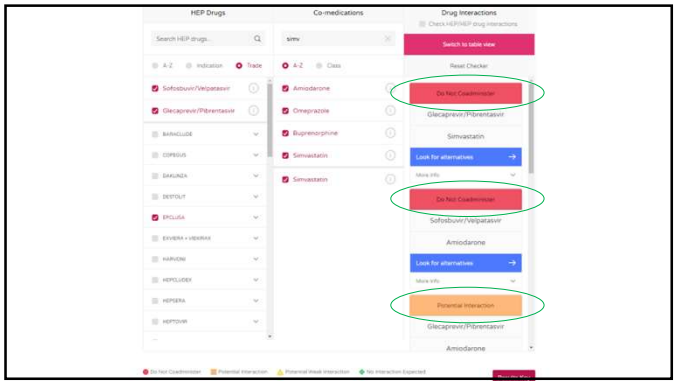

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Glecaprevir/pibrentasvir Drug-Drug interactions

- Contraindicated due to low glecaprevir/pibrentasvir levels: ***rifampin***
- Contraindicated due to high glecaprevir/pibrentasvir levels: ***PIs esp. Atazanivir***
- Not recommended due to reduced effect: ***carbamazepine, efavirenz, St. John's wort***
- Not recommended due to increased ALT on treatment: ***estrogens***
- Reduce dose or discontinue during glecaprevir/pibrentasvir treatment: ***statins***
- Increased with glecaprevir/pibrentasvir: ***Digoxin, Dabigatran***

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Streamlined HCV guidelines: glecaprevir/pibrentasvir or sofosbuvir/velpatasvir for treatment naïve patients

Similarities

- Similar effectiveness for all HCV genotypes in treatment naïve persons **without cirrhosis**
- Licensed for children ≥ 3 years of age and adults
- Similar side effects and low rates of discontinuation
- May be used with all levels of renal function and by dialysis patients
- Same concern for HBV reactivation in co-infected patients

Differences

- Dosing and formulations for children differ
- Drug interactions differ
- Use in treatment experienced persons differ
- With compensated cirrhosis need add on to sofosbuvir/velpatasvir
- Use with decompensated cirrhosis differ

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Streamlined HCV guidelines: Treatment naïve patients

glecaprevir/pibrentasvir	sofosbuvir/velpatasvir
• Glecaprevir 100 mg & pibrentasvir 40 mg tablets • 3 tablets po once daily *with food* for 8 weeks • Dosage changes for pediatric patients based on weight	• Sofosbuvir 400 mg & velpatasvir 100 mg tablets • 1 tablet po once daily for 12 weeks, *no food requirements* • Dosage changes for pediatric patients based on weight

Mavyret and Epicusa full prescribing information; hcvguidelines.org

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Streamlined HCV guidelines: Warnings and contraindications

glecaprevir/pibrentasvir	sofosbuvir/velpatasvir
• Risk of hepatitis B reactivation • Risk of hepatic decompensation/failure in patients with evidence of advanced liver disease • Cannot co-administer with atazanavir or rifampin	• Risk of hepatitis B reactivation • Bradycardia with amiodarone administration

Mavyret and Epicusa full prescribing information; hcvguidelines.org

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Streamlined HCV guidelines: Partial list of side effects

glecaprevir/pibrentasvir	sofosbuvir/velpatasvir
• Headache, fatigue (>10%) • Nausea, diarrhea (>5%) • Discontinuation rate <1% • No data in pregnancy or lactation	• Headache and fatigue (>10%) • Nausea, weakness, insomnia (>5%) • Discontinuation rate 0.2% • No data in pregnancy or lactation

Mavyret and Epicusa full prescribing information; hcvguidelines.org

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Monitoring for HBV reactivation during HCV treatment

- Hepatitis B and C infection co-exist in about 1.5% of persons with HCV in US
- Active HCV replication may suppress hepatitis B virus (HBV) replication
- HBV reactivation has been reported in persons with HCV/HBV coinfection who were undergoing or had completed treatment with HCV direct-acting antivirals, and who were not receiving HBV antiviral therapy
- HBV reactivation → causes abrupt increase in HBV replication manifesting as a rapid increase in serum HBV DNA level and may include increases in AST and ALT.
- Some cases have resulted in fulminant hepatitis, hepatic failure and death. Cases have been reported in patients who are HBsAg positive and also in patients with serologic evidence of resolved HBV infection (i.e., HBsAg negative and anti-HBc positive)

A black box warning and this language now appears in the prescribing information of DAAs

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Monitoring for HBV reactivation during HCV treatment

- Test all patients for evidence of current or prior HBV infection by measuring **BOTH**
  - Hepatitis B surface antigen AND
  - Hepatitis B core antibody (**total**, not IgM) before initiating HCV treatment with direct acting HCV antivirals
- Persons positive for HB S Ag should also have HBV DNA (quantitative HBV viral load) measured
- We recommend referral or co-management of persons with HCV/HBV coinfection with a specialist
- Some people will require concurrent treatment for HBV
- Patients with evidence of HBV infection need monitoring of HBV DNA and/or AST & ALT during treatment and at the SVR 12 timepoint

A black box warning and this language now appears in the prescribing information of DAAs

hcvguidelines.org; Mucke M et al, Lancet/gastrohep Jan 2018 3(3):172

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Same patient…

But she is a PLHIV

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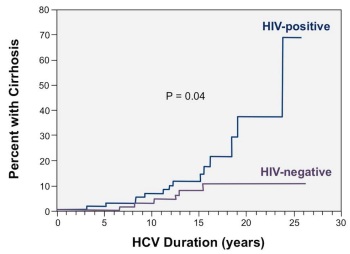
Treatment of HIV/HCV co-infection



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Major drug-drug interactions with ART

	Glecaprivir/ Pibrentasvir	Sofosbuvir/ Velpatasvir	Ledipasvir/ Sofobuvir
NRTI	✓	✓ (monitor with TDF)	✓ (monitor with TDF)
NNRTI	DOR and RPL ok Not EFV, ETR	DOR and RPL ok Not EFV, ETR	✓ (monitor with TDF)
INSTI	✓	✓	✓ (NOT)
PI	No	✓	✓ (monitor with TDF)
Boosters	Monitor when co-formulated with TDF	✓	✓ (monitor with TDF)

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Regimen Options for HCV/HIV Coinfection

Therapy	Duration without Cirrhosis	Duration with Cirrhosis
Glecaprivir/Pibrentasvir	8 weeks* *12 weeks for Genotypes 5 and 6	12 weeks
Sofosbuvir/Velpatasvir	12 weeks	12 weeks
Ledipasvir/Sofobuvir	12 weeks (data showing decreased SVR with 8 weeks)	12 weeks

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Pharmacists Treating Hepatitis C

- Action Plan for the Prevention, Care & Treatment of Viral Hepatitis prepared by DHHS, identified pharmacists as key stakeholders in the continuum of care of those living with viral hepatitis.
- The pharmacists work collaboratively with each patient's primary care provider and may independently order confirmatory laboratory tests, counsel patients, and provide other care when the physician's services aren't specifically needed.
- Many models exist using collaborative practice agreement
- Models exist at scale at VA hospitalss, IHS, Federal Bureau of Prisons, select practices in Michigan
- Pharmacists can use consult lines and ECHOs to support treatment decisions, if needed.

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MATEC Michigan HCV Resources

- Hepatitis C Clinical Decision Support
  - Fourth Tuesday of the month
  - 8:30AM-10:00AM
  - Open to all
  - Case Consult Form
- Next Date:
  - Tuesday, May 23, 2023
- Office Phone (313) 962-2000
- Email MATECmichigan@wayne.edu

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For Further Information

- MDHHS Plan on Eliminating Hepatitis C, MDHSS 2021
  - https://www.michigan.gov/documents/mdhhs/MDHHS_State_Plan_on_Eliminating_HCV_Final_Draft_720817_7.pdf
- Hepatitis C Online
  - https://www.hepatitisc.uw.edu/
- AASLD/IDSA Guidelines
  - https://www.hcvguidelines.org/
- Liverpool Hepatitis Drug Interaction Checker –
  - https://www.hep-druginteractions.org/
- Frequently Asked Questions for Providers
  - https://www.cdc.gov/hepatitis/hcv/index.htm

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