Hepatitis C

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Case

- 55-year-old male, type 2 diabetes, hypertension, comes for a routine checkup to the office.
- Should he get tested for Hepatitis C?

Hepatitis C: Background

- Prevalence:
- >1% of the US population (3-4 million) has Chronic Hepatitis C
- Peak prevalence :
  - (4.3%)in persons born between 1945- 1965
  - IVDU
- Screen adults at risk for HCV infection PLUS
- Screen adults born 1945 through 1965
  - One-time testing for HCV without prior ascertainment of HCV risk factor
- *Smith BD et al. MMWR Morb Mortal Wkly Rep. 2012;61:1-32.*

Those at "Risk"

- **Risk behaviors**
  - Injection-drug or Intranasal illicit drug use
- **Risk exposures**
  - Persons on long-term hemodialysis (ever)
  - Persons with percutaneous/parenteral exposures
  - Needlesticks, sharps, or mucosal exposures to HCV-infected blood
  - Children born to HCV-infected women
  - Prior recipients of transfusions or organ transplants, including persons who:
    - Received a transfusion of blood/blood components, or underwent an transplant before July '92
    - Received clotting factor concentrates produced before 1987
  - Persons who were ever incarcerated
- **Other considerations**
  - HIV infection
  - Sexually active persons about to start PrEP for HIV
  - Unexplained chronic liver disease and/or chronic hepatitis including elevated alanine aminotransferase levels
  - Solid organ donors (deceased and living)

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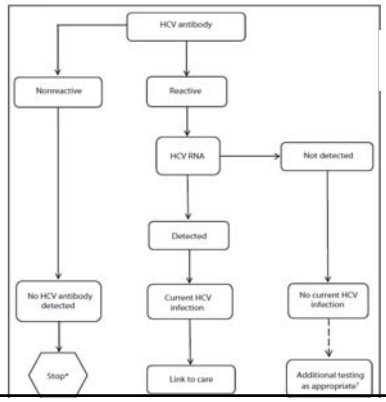
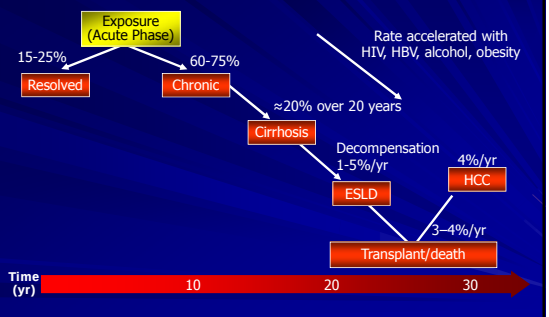
HCVguidelines.org

FIGURE. Recommended testing sequence for identifying current hepatitis C virus (HCV infection



MMWR / May 10, 2013

Natural History of HCV Infection



HCC = hepatocellular carcinoma
ESLD = end-stage liver disease

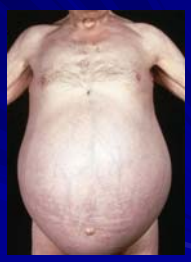
Modified from Di Bisceglie A, et al. *Hepatology*. 2000;31:1014-1018.

P-DS-D-041

Ascites is usually the first sign of liver decompensation

Other clues:

- Thrombocytopenia
- Anemia
- Hypoalbuminemia
- Coagulopathy
- SBP
- Variceal bleeding
- Encephalopathy
- Asterixis



Pre-treatment Evaluation

- HIV Antibody
- Hepatitis A Total Antibody
- Hepatitis B
  - HBc Ab- total
  - HBsAg
  - HBsAb- quantitative
- CBC, CMP
- HCV Genotype
  - And subtype
- HCV RNA
- HCV treatment history
- Liver staging
- Baseline Resistance Testing
  - (Only where indicated)
- Ultrasound
  - To R/O HCC in advanced fibrosis
- *(Urine toxicology)*
- *(Mental health/Adherence)*

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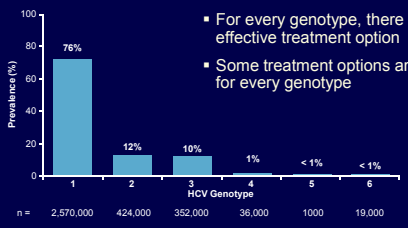
Distribution of Hepatitis C Virus by Genotype in the US



- For every genotype, there is an effective treatment option
- Some treatment options are effective for every genotype

Messina JP, et al. Hepatology. 2015;61:77-87.

Slide credit: clinicaloptions.com

Staging Liver Fibrosis

Clinical or Laboratory Tests			Imaging
Invasive[1]	Simple[1]	Complex[2]	Elastography[3]
▪ Liver biopsy	▪ AST-to-platelet ratio index ▪ FIB-4 index	▪ *FibroSure*	▪ VCTE *FibroScan* ▪ MR elastography ▪ ARFI

Serum based tests have good predictive value for excluding cirrhosis
Poor specificities for mild to moderate liver disease

1. AASLD/IDSA. HCV Guidelines. April 2017. 2. EASL, et al. J Hepatol. 2015;63:237-264. 3. Barr RG, et al. Radiology. 2015;276:845-861.

Slide credit: clinicaloptions.com

Non-invasive evaluation of liver damage

FIBROSURE:

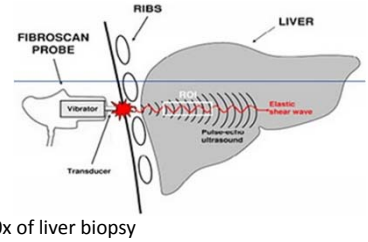
A blood test that uses an algorithm to generate a measure of fibrosis and necroinflammatory activity in the liver :

1. α2-macroglobulin
2. haptoglobin
3. apolipoprotein A1
4. bilirubin
5. γ-glutamyl transpeptidase (GGT)
6. ALT 7.patient's age and gender

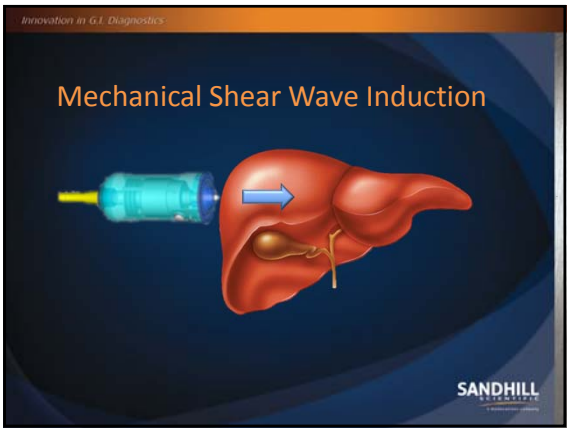
Advanced fibrosis : Sensitivity- 85%, Specificity - 60%

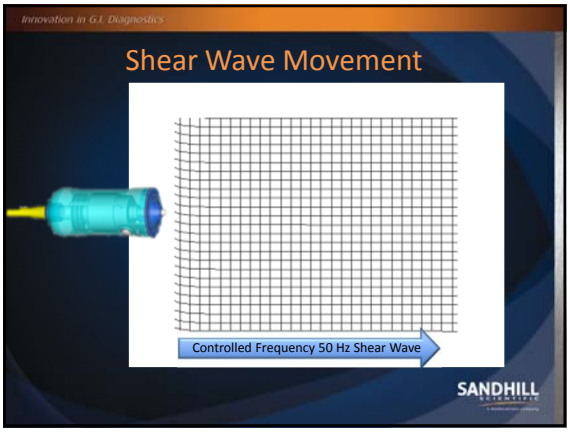
Score > 0.75 is consistent with cirrhosis

Non-Invasive, Transient Elastography



- Sample size 100x of liver biopsy
- Scored in kPascals, range 2.5-75 (normal is 5.5 kPa)
- Best for F4 (>12.5 has a 90% probability of cirrhosis) and absence of significant fibrosis (<7.3 kPa)
- Potentially confounded by: obesity, ascites, inflammation, alcohol intake, food ingestion





Fibroscan Interpretation

Table 1 Recommended values for different stage of fibrosis

Disease	F0–F1 (Kpa)	F2 (Kpa)	F3 (kpa)	F4 (kpa)
Hepatitis B	≤6.0	≥6.0	≥9.0	≥12.0
Hepatitis C	≤7.0	≥7.0	≥9.5	≥12.0
HCV–HIV coinfection	≤7.0	≤10	≥11.0	≥14.0
Cholestatic liver disease	≤7.0	≥7.5	≥10.0	≥17.0
NAFLD/NASH	≤7.0	≥7.5	≤10	≥14.0

Ensure Hepatitis B testing is complete

- Evaluation prior to HCV treatment- CHECK ALL THREE
  - HBsAg
  - Hepatitis B c antibody (anti-HBc)- Total antibody or IgG
  - Hepatitis B surface antibody (anti-HBs)
- If a patient is HBsAg +-- check HBV DNA prior to DAA therapy
- If isolated anti-HBc positive- monitor every 4 weeks while on DAA therapy
- There have been a few cases of Hepatitis B "flare ups" while on HCV treatment

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http://www.fda.gov/DrugsDrugSafety/ucm522032.htm

Baseline Resistance Testing

- 10-15% of HCV GT 1-infected patients **without** prior exposure to NS5A inhibitors will have detectable HCV NS5A RAVs
- Baseline NS5A RAVs - strongest pre-treatment predictors of treatment outcome
  - 28, 30, 31, **93** (and 58) are the major ones
- Testing for RAVs prior to treatment is recommended in **select situations.**
  - **Elbasvir/Grazoprevir in GT1a- Check for NS5A RAS**
  - **Treatment failure with DAAs- Check for NS5A RAS**
  - **GT3- considering Sofosbuvir/velpatasvir** or daclatasvir/sof- check for NS5A RAS- **mainly Y93H**
  - **Genotype 1a + Cirrhosis and planning a ledipasvir/sofosbuvir–based regimen**
  - Simeprevir in GT1a and cirrhosis- Check for NS34A RAS

Zeuzem S et al. Predictors of Response to Grazoprevir/Elbasvir Among HCV Genotype 1 (GT1)-Infected Patients.Liver Diseases (AASLD). November 13-17, 2015c; San Francisco, CA.

Case continued

- Patient is:
  - Treatment naïve
  - HIV -negative
  - Hepatitis B serologies -negative
  - Hepatitis C viral load -1.6 million
  - HCV genotype- 1a
  - **Fibroscan- Metavir F3 (Metavir ≥ F3 is considered as advanced fibrosis/cirrhosis)**
  - Creatinine clearance- normal
  - Ultrasound- no liver lesions

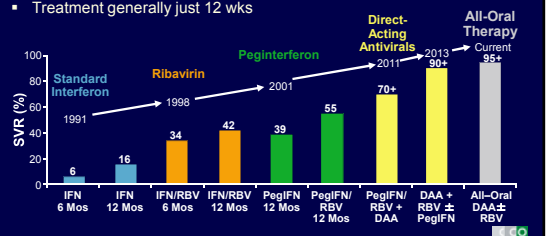
Recommendations for When and in Whom to Initiate HCV Treatment

- **Treatment is recommended for all pts with chronic hepatitis C infection**
  - Exception: life expectancy likely to be short despite treatment or transplantation

AASLD-IDSA. HCV Guidelines 2016.

Nearly Everyone With HCV Can Now Be Treated Successfully

- Very high SVR rates; therapies highly tolerable
- All-oral therapy for almost every pt
- Treatment generally just 12 wks



Slide credit: clinicaloptions.com

Directly Acting Antivirals

- **Sofosbuvir/Velpatasvir (Epclusa)**
- **Sofosbuvir/Velpatasvir/ Voxilaprevir (Vosevi)**
- **Glecaprevir/Pibrentasvir (Mavyret)**
- **Sofosbuvir/Ledipasvir (Harvoni)**
- **Elbasvir/Grazoprevir (Zepatier)**
- **Ombitasvir,paritaprevir,ritonavir and dasabuvir (Viekira Pak)**
- Daclatasvir (NS5A inhibitor, has to be given with another drug like Sofosbuvir

Available co-formulated DAAs

Sofosbuvir/Ledipasvir (Harvoni) (Approved October 2014)

- Fixed-dose combination
  - Sofosbuvir (400 mg)- NS5B polymerase inhibitor
  - Ledipasvir (90 mg) - HCV NS5A inhibitor
- Oral, once-daily
- Treatment naïve patients:
- Genotypes 1, 4, 5, 6

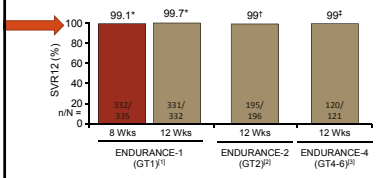
Sofosbuvir/ledipasvir [package insert].

Glecaprevir/ Pibrentasvir (Mavyret)

- Coformulated into single tablet
  - Glecaprevir 300mg/ Pibrentasvir 120mg= target dose
  - Formulated as Glecaprevir 100mg/Pibrentasvir 40mg
  - 3 pills a day
- Approved August 2017:
- Minimal side effects
- Treatment naïve patients
  - For Genotypes 1-6 without cirrhosis or mild cirrhosis
  - Patients with moderate to severe kidney disease and on dialysis.
- Treatment experienced patients
  - Who have been previously treated with a regimen either containing an NS5A inhibitor or an NS3/4A protease inhibitor but not both.

Mavyret® treatment naïve studies: ENDURANCE-1, -2, -4 : Efficacy of GLE/PIB for GT1, 2, 4, 5, 6 HCV

SVR > 99% regardless of GT or duration of therapy



1 case of on-treatment virologic failure at Day 29 in pt with GT1a HCV infection

*ITT-PS analysis: included all pts receiving ≥ 1 dose of study drug; excluded pts with HIV coinfection or SOF experience.
†ITT analysis: excluded pts with SOF experience. ‡ITT analysis.

1. Zeuzem S, et al. AASLD 2016. Abstract 253. 2. Kowdley KV, et al. AASLD 2016. Abstract 73. 3. Asselah T, et al. AASLD 2016. Abstract 114.

Slide credit clinicaloptions.com

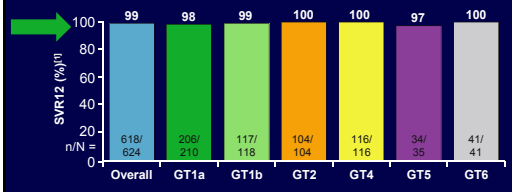
Sofosbuvir/Velpatasvir

(Approved July 2016)

- EPCLUSA :Fixed-dose combination of
  - Sofosbuvir (400 mg)- NS5B polymerase inhibitor
  - Velpatasvir (100 mg) - HCV NS5A inhibitor
- Indicated for the treatment of adult patients with
  - Chronic HCV genotype 1, 2, 3, 4, 5, or 6
    - Without cirrhosis or with compensated cirrhosis
    - With decompensated cirrhosis in combination with ribavirin
  - Baseline resistance testing required only when treating GT 3
- Recommended dosage: One tablet taken orally once daily with or without food

ASTRAL-1: SOF/VEL for 12 Wks in GT1, 2, 4, 5, 6 Pts With and Without Cirrhosis

- 19% cirrhosis, 32% treatment experienced
- SVR > 97% regardless of genotype



1. Feld JJ, et al. N Engl J Med. 2015;373:2599-2607.
2. Foster GR, et al. N Engl J Med. 2015;373:2608-2617.

Slide credit: clinicaloptions.com

Zepatier

- Fixed-dose combination product
  - Elbasvir (50 mg) - NS5A inhibitor
  - Grazoprevir (100 mg)- NS3/4A protease inhibitor
- Indication: Genotypes 1 or 4 infection in adults (with or without ribavirin)
- Recommended dosage: One tablet once daily

Sofosbuvir/Velpatasvir/Voxilaprevir Approved July 2017

Fixed dose combination:

Sofosbuvir (400mg)- NS5B polymerase inhibitor

Velpatasvir(100mg)-NS5A inhibitor

Voxilaprevir(100mg)- HCV NS3/4A protease

Indications:

Treatment experienced patients :

GT 1, 2, 3, 4, 5, or 6 previously been treated with an HCV regimen containing an NS5A inhibitor.

GT 1a or 3 infection and have previously been treated with an HCV regimen containing sofosbuvir without an NS5A inhibitor.

Case summary

- Patient is:
  - Treatment naïve
  - HIV -negative
  - Hepatitis B serologies -negative
  - Hepatitis C viral load -10,000,000
  - HCV genotype- 1a
  - **Fibroscan- Metavir F3 (Metavir ≥ F3 is considered as cirrhosis)**
  - Creatinine clearance- normal
  - Ultrasound- normal

Next Step?

- Go to HCVguidelines.org
- This is a regularly updated website that gives testing, linkage and treatment recommendations
- **Ensure there are no drug-drug interactions**

Recommended and alternative regimens listed by evidence level and alphabetically for:

Treatment-Naive Genotype 1a Patients With Compensated Cirrhosis[a]

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) for patients without baseline NS5A RASs[b] for elbasvir	12 weeks	I, A
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)[c]	12 weeks	I, A
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg)	12 weeks	I, A
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) with weight-based ribavirin for patients with baseline NS5A RASs[b] for elbasvir	16 weeks	IIa, B

[a] For decompensated cirrhosis, please refer to the appropriate section.
[b] Includes genotype 1a resistance-associated substitutions at amino acid positions 28, 30, 31, or 93 known to confer antiviral resistance.
[c] This is a 3-tablet coformulation. Please refer to the prescribing information.

Recommended monitoring during antiviral therapy

- At 4 weeks and as clinically indicated
  - CBC, calculated GFR, LFT.
  - Monitor CBC more closely if on RBV
- Quantitative HCV viral load testing
  - At 4 weeks
  - At the end of RX (optional)
  - 12 weeks after completion of therapy

Vaccination

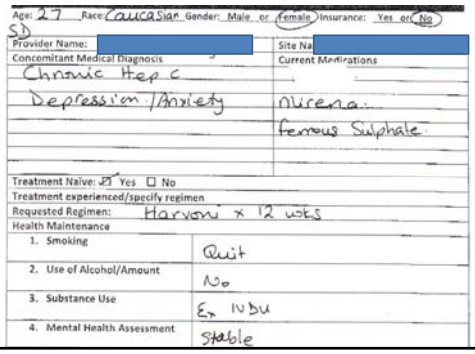
- Hepatitis A Vaccine
- Hepatitis B vaccine
  - Protection ~30-50% dose 1; 75% - 2; 96% - 3; lower in older, immunosuppressive illnesses (e.g., HIV, chronic liver diseases, diabetes), obese, smokers
- Other age appropriate vaccinations

http://www.fda.gov/Drugs/DrugSafety/ucm522932.htm

Appropriate Follow Up

- Follow-up for sustained virological response (SVR) of high importance
  - HCV Viral Load 12 weeks after finishing treatment
  - HCV Viral Load 24-48 weeks after finishing treatment
- appropriate screening for cirrhotic patients
- Counseling on re-infection

Case 1



Age: 27 Race: Caucasian Gender: Male or Female Insurance: Yes or No
SJ
Provider Name: Site Na
Concomitant Medical Diagnosis: Chronic Hep C; Depression/Anxiety
Current Medications: Mirena; ferrous Sulphate
Treatment Naive: ☑ Yes ☐ No
Treatment experienced/specify regimen
Requested Regimen: Harvoni x 12 wks
Health Maintenance

1. Smoking	Quit
2. Use of Alcohol/Amount	No
3. Substance Use	Ex IVDU
4. Mental Health Assessment	Stable

Case 1

5. Pregnancy/Contraception	Currently breastfeeding. Diagnosed during pregnancy (first trimester)				
Laboratory Tests and date tested 1/30/18					
HCV Genotype	1a	ALT	54	Creatinine	0.8
HCV Quantitative RNA	12,000	AST	26	Platelet Count	180
HIV Antibody	Neg	Total Bilirubin	0.3	Hemoglobin	13.0

GFR 864

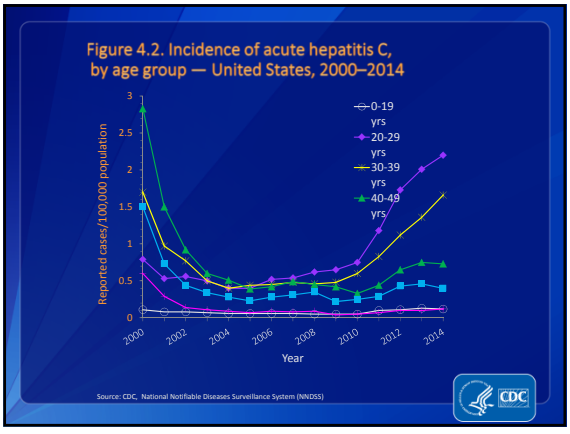
Staging of Liver Disease		
Test Performed	Date	Findings/Results
Liver Biopsy		
Ultrasound	3/17/2017	No evidence of cirrhosis
HCV Fibrosure Assay	01/30/18	F0
Transient Elastography		

APRI: 0.413
FIB4: 0.53
Other Information: PT/INR: 10.5/1.0 ALB: 4.1

HB_sAg
HB_sAb: 550
HB_cTotal

Case 2 Summary

- 27 year old
- Diagnosed during pregnancy, currently breast-feeding
- Hep C characteristics:
  - GT1a, F0, creatinine normal, HCV viral load 12,000, Treatment naïve
- **Considerations:**
  - Should all pregnant women be screened for hepatitis C?
  - Could this patient have acute hepatitis C?



Screening in Pregnancy

- Screening not yet routine
- Prevalence of HCV infection among U.S. women giving birth doubled from 2009-2014.
- C- section- not needed
- HCV not transmitted through breast milk
- Rate of vertical transmission - 6%
  - (11% if the mother is co-infected with HIV)
    - HCV RNA is the appropriate test to test infants.
  - Risk factors that increase the possibility of HCV vertical transmission
    - HIV coinfection, IVDU, elevated maternal HCV viral load
    - Reports of spontaneous clearance of HCV after pregnancy

Hashem M, et al. Spontaneous viral load decline and clearance of chronic HCV in post partum women with a favorable IL28B allele. Clinical Infectious Diseases. 2017

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HCVguidelines.org

Acute HCV infection

- Acute infection is usually asymptomatic
- Clearance usually happens in 12 weeks
- Acute HCV infection
  - Viral-host interactions lead to marked virologic fluctuations
  - **Low levels of viremia (< 10,000) are frequently observed**
  - ALT > 7X upper limit of normal
- Chronic HCV
  - stable HCV-RNA levels that vary by approximately 0.5 log

- ***Improving the Diagnosis of Acute Hepatitis C Infection using Expanded Viral Load Criteria;*** *Barbara H. McGovern, Clin Infect Dis. 2009 Oct 1; 49(7): 1051–1060.*

Recommendations

- Young age, low viral load, could suggest acute infection
- Repeat HCV RNA, genotype, HIV antibody in 12 weeks.
- Reassess risk factors for infection/reinfection.

Case 2

Age: 62 Race: H-A Gender: Male or (Female) Insurance: (Yes) or No

Provider Name: [redacted]	Site Name: [redacted]
Concomitant Medical Diagnosis	Current Medications
Chronic Hep C	
COPD	
HTN	
Hyperlipidemia	
Treatment Naïve: ☑ Yes ☐ No	
Treatment experienced/specify regimen	
Requested Regimen: Mavyret x 8wks, Harvoni x 12wks	

3. Substance Use	No
4. Mental Health Assessment	Stable
5. Pregnancy/Contraception	N/A

Laboratory Tests and date tested 9/18/17

HCV Genotype	1a	ALT	64	Creatinine	0.9	GFR 7674
HCV Quantitative RNA	283,768	AST	75	Platelet Count	339	
HIV Antibody	Neg	Total Bilirubin	0.3	Hemoglobin	12.4	

Staging of Liver Disease		
Test Performed	Date	Findings/Results
Liver Biopsy		
Ultrasound	11/21/17	mildly increased echogenicity - Hemangs
HCV Fibrosure Assay	9/18/17	F0
Transient Elastography		

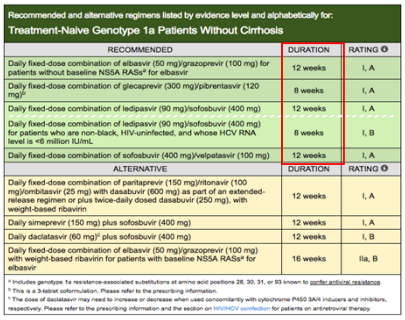
APRI: 0.632
FIB4: 1.71
Other Information PT/INR: 11.2/1.1 A:G: 4:1

HBsAg: Non reactive
HBsAb: <5
HBc Total: Reactive

Case Summary

- 62 year old African American Male
- VL 283,000, GT1a, treatment naïve, non-cirrhotic (F0)

AASLD Guidelines



Recommended and alternative regimens listed by evidence level and alphabetically for:

Treatment-Naive Genotype 1a Patients Without Cirrhosis

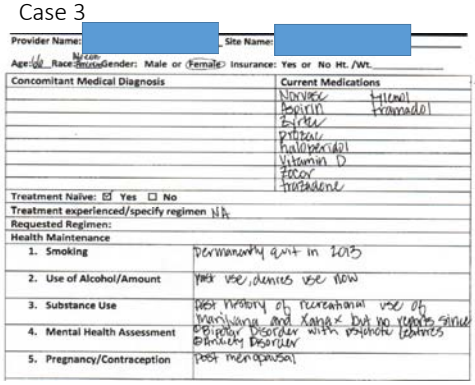
RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) for patients without baseline NS5A RAS[a] for elbasvir	12 weeks	I, A
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)[b]	8 weeks	I, A
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg)	12 weeks	I, A
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for patients who are non-black, 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 paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) with dasabuvir (600 mg) as part of an extended-release regimen or plus twice-daily dosed dasabuvir (250 mg), with weight-based ribavirin	12 weeks	I, A
Daily simeprevir (150 mg) plus sofosbuvir (400 mg)	12 weeks	I, A
Daily daclatasvir (60 mg)[c] plus sofosbuvir (400 mg)	12 weeks	I, B
Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) with weight-based ribavirin for patients with baseline NS5A RAS[a] for elbasvir	16 weeks	IIa, B

[a] Includes genotype 1a resistance-associated substitutions at amino acid positions 28, 30, 31, or 93 known to confer antiviral resistance.
[b] This is a 3-tablet coformulation. Please refer to the prescribing information.
[c] The dose of daclatasvir may need to increase or decrease when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. Please refer to the prescribing information and the section on HIV/HCV coinfection for patients on antiretroviral therapy.

Case 2-Recommendations

- ELB/GZR x 12 weeks
- GLE/PIB x 8 weeks
- SOF/LDV x 12 weeks
- SOF/VEL x 12 weeks

Case 3



Provider Name: [redacted] Site Name: [redacted]

Age: 66 Race: ~~White~~ Asian Gender: Male or (Female) Insurance: Yes or No Ht. /Wt.

Concomitant Medical Diagnosis	Current Medications
	Norvasc, Lipitor, Effexor, Prozac, Haldol, Vitamin D, Zocor, Trazodone, Tylenol, Tramadol

Treatment Naïve: ☑ Yes ☐ No

Treatment experienced/specify regimen N/A

Requested Regimen:

Health Maintenance

1. Smoking	Permanently quit in 2013
2. Use of Alcohol/Amount	Past use, denies use now
3. Substance Use	Past history of recreational use of Marijuana and Xanax. Pt no reports since 2014.
4. Mental Health Assessment	Bipolar disorder with psychotic features, Anxiety Disorder
5. Pregnancy/Contraception	Post menopausal

Case 3

Laboratory Tests and date tested

HCV Genotype	Type 1a (8.9.17)	ALT	35 (11.28.17)	Creatinine	1.10 (11.28.17)
HCV Quantitative RNA	6,030,284 (8.9.17)	AST	29 (11.28.17)	Platelet Count	216 (11.28.17)
HIV Antibody		Total Bilirubin	1.1 (11.28.17)	Hemoglobin	13.6 (11.28.17)

Staging of Liver Disease

Test Performed	Date	Findings/Results
Liver Biopsy		
Ultrasound		
HCV Fibrosure Assay	8.30.17	0.91 : high, cirrhosis
Transient Elastography		

Other Information

Case Summary

- 66 year African American female
- HCV characteristics:
- GT1a, F4 – Cirrhosis (Fibrosure), Treatment naïve, creatinine clearance normal, ultrasound-no mass lesions in the liver
- Clinical Questions:
  - DAA drug-interactions
  - HBV serology

Recommended and alternative regimens listed by evidence level and alphabetically for:

Treatment-Naive Genotype 1a Patients With Compensated Cirrhosis[a]

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) for patients without baseline NS5A RAS[b] for elbasvir	12 weeks	I, A
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)[c]	12 weeks	I, A
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg)	12 weeks	I, A
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) with weight-based ribavirin for patients with baseline NS5A RAS[b] for elbasvir	16 weeks	IIa, B

[a] For decompensated cirrhosis, please refer to the appropriate section.
[b] Includes genotype 1a resistance-associated substitutions at amino acid positions 28, 30, 31, or 93 known to confer antiviral resistance.
[c] This is a 3-tablet coformulation. Please refer to the prescribing information.

Drug Interactions

- **PPIs/Antaacids**
  - **Velpatasvir** and Ledipasvir:
    - AUC decreased between15-20% when administered with famotidine
    - PPIs: velpatasvir AUC lower by 26% to 55%
    - Recommendation: **Either avoid or Limit doses to those comparable to or lower than famotidine 40 mg twice daily**
- Elbasvir/Grazoprevir: okay with PPI/H2 antagonists
- Glecaprevir/Pibrentasvir: PPI/H2s OK per package insert
  - Even though decreased AUC of GLE ~20-30%

Statins:

Varies so monitor for statin toxicity

Always do a drug interaction check, amiodarone etc

AETC AIDS Education & Training Center Program Southeast

Mavyret [prescribing information]. North Chicago, IL: Abbvie Inc; August 2017.

Recommendations

- EBR/GZR x 12 weeks
  - Resistance testing needed prior to use
- GLE/PIB x 12 weeks
- SOF/LDV x 12 weeks
- SOF/VEL x 12 weeks

- Consider adjusting statin therapy
  - Discontinuation of simvastatin during DAA therapy
  - Possible switch to pravastatin

Eligibility Criteria for 8-Wk Rx

GLE/PIB[1]

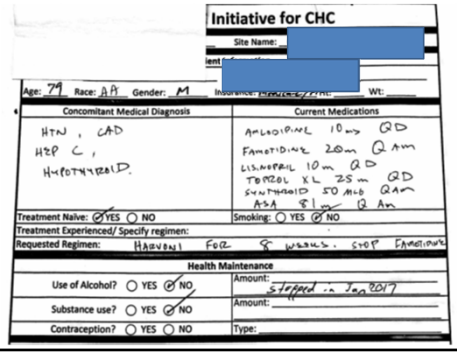
- Eligible pts must be
  - Noncirrhotic
  - Treatment-naive with GT1-6
  - No dosing adjustment needed in severe renal impairment
    - CrCl <30ml/min

SOF/LDV[2-4]

- Eligible pts must be
  - Noncirrhotic
  - Treatment naive with GT1
  - HCV RNA < 6 million IU/mL
  - Nonblack
  - No HIV coinfection
  - EASL: caution if F3

1. GLE/PIB [package insert]. 2. SOF/LDV [package insert]. 3. AASLD/IDSA. HCV guidelines. September 2017. 4. EASL. HCV guidelines. September 2016

Case 5



Initiative for CHC

Site Name: [redacted]

Age: 79 Race: AA Gender: M Insurance: [redacted] Wt:

Concomitant Medical Diagnosis	Current Medications
HTN, CAD HEP C, HYPOTHYROID	AMLODIPINE 10mg QD FAMOTIDINE 20m QAM LISINOPRIL 10m QD TOPROL XL 25m QD SYNTHROID 50 MCG QAM ASA 81mg QAM
Treatment Naïve: ☑ YES ○ NO	Smoking: ○ YES ☑ NO
Treatment Experienced/ Specify regimen:	
Requested Regimen: HARVONI FOR 8 WEEKS. STOP FAMOTIDINE	

Health Maintenance

Use of Alcohol? ○ YES ☑ NO	Amount: Stopped in Jan 2017
Substance use? ○ YES ☑ NO	Amount:
Contraception? ○ YES ○ NO	Type:

Case 5

Laboratory Tests and Date Tested- Pre-treatment

TEST	DATE	TEST	DATE	TEST	DATE
HCV Genotype	1a 12/19/2017	ALT 94	11/13/17	Creatinine 1.5	65 12/4/17
HCV RNA Quant	1183285 12/4/17	AST 63	11/13/17	Platelets	14.1 5/23/17
HIV antibody	Neg 12/19/2017	Total Bilirubin 0.9	11/13/17	Hemoglobin	Negative 12/7/2017
Hep B Total Core Antibody	Neg 12/4/17	Hep B Surface Antigen	Neg 12/4/17	Hep B Surface Antibody	
[redacted]	25.7 12/19/17	GFR	54.66 5/23/17		

Staging of Liver Disease

Test	Date	Findings/Results
Liver Biopsy/ Transient Elastography		
Ultrasound	12/15/17	Normal Liver
HCV Fibrosure Assay	12/19/2017	F4 - A2 Score 0.89

Case 5 Summary

- 79 year old African American Male
- GT1a, Treatment naïve, F4
  - Ultrasound- "normal"
  - Compensated cirrhosis
  - Creatinine Clearance- 40 ml/min
- **DAAs in Chronic Kidney Disease**

DAAs with Renal Impairment

Creatinine clearance	Mavyret	Harvoni	Epclusa	Zepatier	Viekira pak	Ribavirin
50 ml/min CKD-1 & 2	No dose adjustment	No dose adjustment	No dose adjustment	No dose adjustment	No dose adjustment	No dose adjustment
30-50 ml/min (CKD-3)	**No dose adjustment**	**No dose adjustment**	**No dose adjustment**	**No dose adjustment**	**No dose adjustment**	**Decrease dose**
< 30 or ESRD	No dose adjustment	Limited data	Limited data	No dose adjustment	Limited data	200 mg/day

AETC Southeast

Treatment-Naive Genotype 1a With Compensated Cirrhosis

Recommended and alternative regimens listed by evidence level and alphabetically for:

Treatment-Naive Genotype 1a Patients With Compensated Cirrhosis[a]

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) for patients without baseline NS5A RASs[b] for elbasvir	12 weeks	I, A
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[a] For decompensated cirrhosis, please refer to the appropriate section.
[b] Includes genotype 1a resistance-associated substitutions at amino acid positions 28, 30, 31, or 93 known to confer antiviral resistance.
[c] This is a 3-tablet coformulation. Please refer to the prescribing information.

AETC Southeast

HCV Recommendations for Renal Impairment

Recommended regimens listed by evidence level and alphabetically for:

Patients With CKD Stage[a] 4 or 5 (eGFR <30 mL/min or End-Stage Renal Disease)

RECOMMENDED	GENOTYPE	DURATION	RATING
Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg)	1a, 1b, 4	12 weeks	I, B
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)[b]	1, 2, 3, 4, 5, 6	8 to 16 weeks[c]	I, B[c]

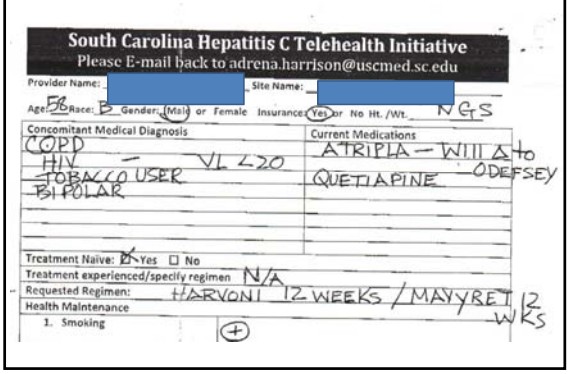
[a] Chronic kidney disease (CKD) stages: 1 = normal (eGFR >90 mL/min); 2 = mild CKD (eGFR 60-89 mL/min); 3 = moderate CKD (eGFR 30-59 mL/min); 4 = severe CKD (eGFR 15-29 mL/min); 5 = end-stage CKD (eGFR ≤15 mL/min)
[b] This is a 3-tablet coformulation. Please refer to the prescribing information.
[c] Patients in this group should be treated as would patients without CKD. Duration of glecaprevir/pibrentasvir should be based on presence of cirrhosis and prior treatment experience (please refer to appropriate section). As such, strength of rating may be lower for certain subgroups.

AETC Southeast

Recommendations

- **GLE/PIB x 12 weeks**
- SOF/LDV x 12 weeks
- SOF/VEL X 12 weeks
- GZR/EBR (would need resistance test prior to DAA initiation)

Case 6



South Carolina Hepatitis C Telehealth Initiative
Please E-mail back to adrena.harrison@uscmed.sc.edu

Provider Name: [redacted] Site Name: [redacted]

Age: 56 Race: B Gender: (Male) or Female Insurance: (Yes) or No Ht. /Wt. NGS

Concomitant Medical Diagnosis	Current Medications
COPD	ATRIPLA – WILL Δ to ODEFSEY
HIV – VL 220	
TOBACCO USER	QUETIAPINE
BIPOLAR	

Treatment Naive: ☒ Yes ☐ No

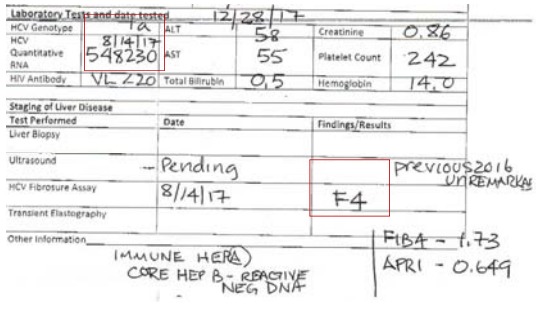
Treatment experienced/specify regimen: N/A

Requested Regimen: HARVONI 12 WEEKS / MAYYRET 12 WKS

Health Maintenance

1. Smoking (+)

Case 6



Laboratory Tests and date tested: 12/28/17

HCV Genotype	1a	ALT	58	Creatinine	0.86
HCV Quantitative RNA	8/4/17 5482300	AST	55	Platelet Count	242
HIV Antibody	VL 220	Total Bilirubin	0.5	Hemoglobin	14.0

Staging of Liver Disease

Test Performed	Date	Findings/Results
Liver Biopsy		
Ultrasound	Pending	previous 2016 UNREMARKABLE
HCV Fibrosure Assay	8/4/17	F4
Transient Elastography		

Other Information: IMMUNE HEP B CORE REACTIVE NEG DNA

FIB4 - 1.73
APRI - 0.649

Case 6 Summary

- 58 year old, AA male, VL- 548000
- GT1a, HIV co-infected, cirrhotic, treatment-naïve, normal creatinine clearance

Excellent SVRs in HCV/HIV Co-Infected Patients

Study	HCV/HIV-Coinfected Pts, N	HCV Treatment Naive/Exp'd, N	HCV Genotypes	Regimen	SVR12, %
ION-4	335	150/185	1, 4	12 wks' LDV/SOF	96
ALLY-2	153	101/52	1, 2, 3, 4	12 wks' DCV + SOF	97
C-EDGE CO-INFECTION	218	218/0	1, 4, 6	12 wks' GZR/EBR	96
ASTRAL-5	106	75/31	1, 2, 3, 4	12 wks' SOF/VEL	95
TURQUOISE-I	31	20/11	1	12 wks' OBV/PTV/RTV + DSV + RBV	94
EXPEDITION-2	137	111/26	1, 2, 3, 4, 6	8 wks' GLE/PIB	99
ENDURANCE-1	15	10/5	1	8 wks' GLE/PIB	100

AASLD-IDSA. HCV guidelines. September 2017.

Medication Recommendations

HCV Regimen	Do NOT Use With:
LDV/SOF (Harvoni®)	**Avoid TDF if CrCl <60ml/min;** TDF toxicity is exacerbated when administered with ritonavir/cobicistat regimens. TAF may be an alternate
EBR/GZR (Zepatier®)	**COBI, EFV,** ETV, NVP, or any **HIV PI**
GLE/PIB (Mavyret®)	**ATV, RTV-containing ART regimens, EFV,** or ETV
SOF/VEL (Epclusa®)	**EFV,** ETV, or NVP
SOF/VEL/VOX (Vosevi®)	**ATV/RTV, EFV**, ETV, or NVP

AASLD-IDSA. HCV guidelines. September 2017

Recommendations

- Do not interrupt HIV therapy
- Switch HIV regimen one month prior to initiating Hepatitis C therapy
- EFV/TDF/FTC (Atripla®) okay to coadminister with LDV/SOF (not GLE/PIB)
- LDV/SOF, GLE/PIB both okay to co-administer with Odefsey®

El-Sadr WM, et al. N Engl J Med. 2006;355:2283-2296

Guideline Recommendation

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- **South East Hepatitis C Telehealth Initiative**
  - CME accredited clinical training and case-based consultations via video conferencing for clinicians and other providers at FQHCs, Ryan White Clinics & AIDS Services Organizations
  - University of South Carolina in collaboration with Vanderbilt and MUSC