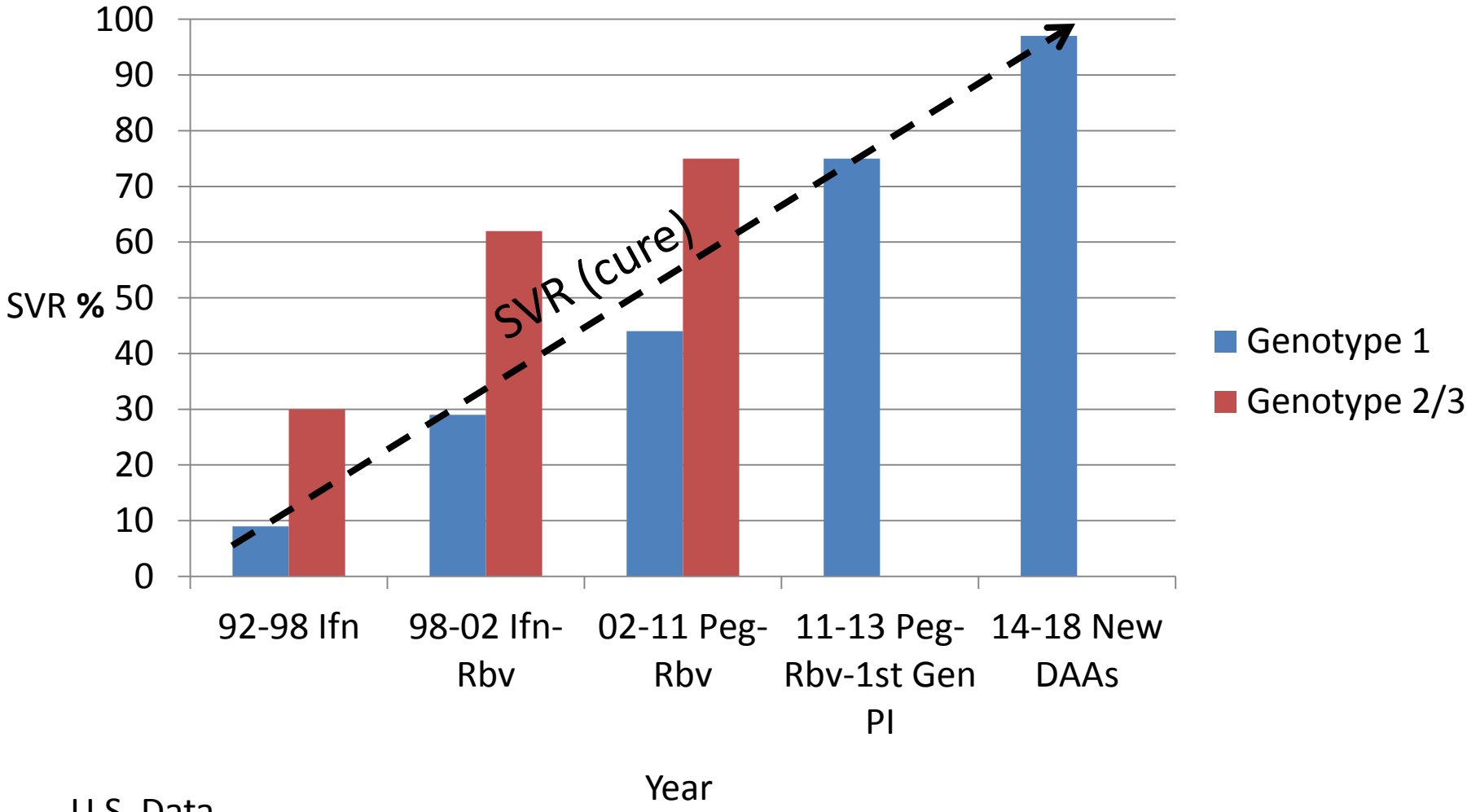
Medications for the Treatment of Chronic Hepatitis C

Conflict of Interest Disclosure Statement

None.

I will only discuss licensed medications and on-label use during this talk.

History of Hepatitis C Treatment Response

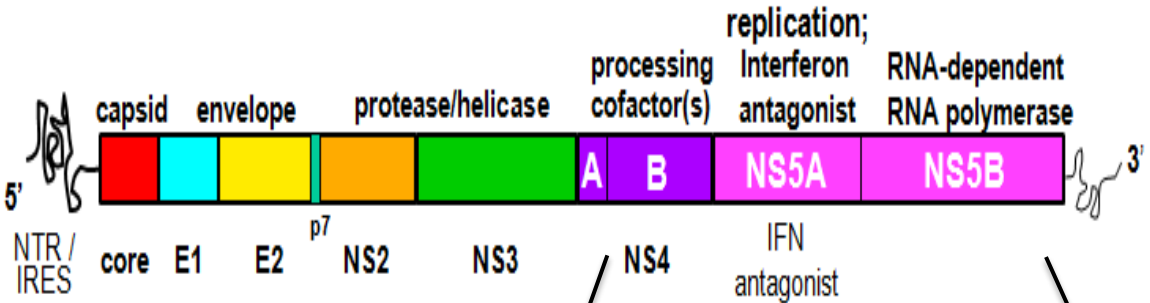


U.S. Data

Hepatitis C Revolution

- Short Treatments
- Once daily dosing
- Few Side effects
- Minimal monitoring on treatment
- >95% cure for most

Where Direct Acting Anti-Virals (DAAs) Target the Hepatitis C Virus



NS3/4 Protease Inhibitors
(…previr)
Simeprevir
Paritaprevir
Grazoprevir
Glecaprevir
Voxilaprevir

NS5A Inhibitors
(…asvir)
Daclatasvir
Ledipasvir
Ombitasvir
Velpatasvir
Elbasvir
Pibrentasvir

NS5B Inhibitors
(…buvir)
Sofosbuvir
Dasabuvir

Virus schematic: University of Washington

Treatment Regimens Available Now to Treat Hepatitis C

sofosbuvir/velpatasvir

Glecaprevir/pibrentasvir

Daclatasvir/sofosbuvir

Ledipasvir/sofosbuvir

Simeprevir/sofosbuvir

Sofosbuvir/vlepatasvir/voxilaprevir

Elbasvir/grazoprevir

Ombitasvir, paritaprevir, ritonavir

Dasabuvir, ombitasvir, paritaprevir, ritonavir

It’s as easy as these 4

Elbasvir/grazoprevir

Glecaprevir/pibrentasvir

Ledipasvir/sofosbuvir

Sofosbuvir/velpatasvir

AASLD/IDSA Recommendations for First-line HCV Treatment

HCV GT	Regimen	Duration, Wks	
		No Cirrhosis	Compensated Cirrhosis
1	GLE/PIB	8	12
	EBR/GZR*	12	12
	SOF/LDV	8 or 12†	12
	SOF/VEL	12	12
2 or 3	GLE/PIB	8	12
	SOF/VEL	12	12‡
4	GLE/PIB	8	12
	SOF/VEL	12	12
	EBR/GZR	12	12
	SOF/LDV	12	12
5 or 6	GLE/PIB	8	12
	SOF/LDV	12	12
	SOF/VEL	12	12

*If GT1a, use only if no baseline NS5A elbasvir RASs detected.

†If nonblack, no HIV, and HCV RNA < 6 million IU/mL, 8-wk duration recommended.

‡For GT3, if Y93H RAS detected, add RBV or consider SOF/VEL/ VOX.

AASLD/IDSA. HCV guidelines. September 2017.

Slide credit: clinicaloptions.com

Elbasvir/Grazoprevir

- Oral once daily HCV regimen for GT 1 & 4
  - Combination NS5A inhibitor and protease inhibitor
  - Requires ribavirin if GT1a with Resistance Associated Substitutions (test for RAS pre-treatment)
- Treatment course 12 weeks
- Side Effects
  - Fatigue (11%)
  - Headache (11%)
  - Nausea (11%)
- Safe use renal disease and hemodialysis, do not use in decomp cirrhosis
- No interactions with antacids – can be used with high dose PPI
- Monitor ALT every 4 weeks on treatment

Glecaprevir/Pibrentasvir

- Glecaprevir 100mg
  - NS3/4A protease inhibitor
- Pibrentasvir 40mg
  - NS5A inhibitor
- Total daily dose 300mg/120mg
- Pangenotypic

(Treats all genotypes 1, 2, 3, 4, 5, & 6)

- Treatment duration 8 or 12 weeks for most

Glecaprevir/Pibrentasvir

- Treatment naïve or retreatment
- Safe to use in severe renal disease (eGFR<30)
- Not safe in decompensated cirrhosis
- Side effects – headache (18%), fatigue (15%), nausea (12%) and comparable in patients with or without cirrhosis
- Do not co-administer with rifampin, atazanavir
- Not recommended with ethinyl estradiol, atorvastatin, lovastatin, simvastatin

Ledipasvir/Sofosbuvir

First combination Direct Acting Antiviral (DAA)

NS5A inhibitor and NS5B polymerase inhibitor

Genotypes 1, 4, 5, and 6

Side effects:

fatigue (16%)

headache (14%)

1 pill/day

Treatment duration 8-12 weeks

Safe in mild /moderate renal impairment (GFR ≥ 30)

Safe in severe liver disease (decompensated)

Interactions with acid-suppressing medications:

- Omeprazole 20mg/day ok – Take at same time
- Famotidine 40mg BID ok – Take at same time +/or 12 hrs apart
- Separate aluminum, magnesium containing antacids 4 hrs apart from LED/SOF

Sofosbuvir/Velpatasvir

1 pill/day

- First pangenotypic Direct Acting Antiviral (DAA)
  - Combination NS5B polymerase inhibitor and NS5A inhibitor
- Treatment duration 12 weeks
- Side effects
  - Headache (~22%)
  - Fatigue (~16%)
  - Nausea (~9%)
- Safe in mild to moderate renal impairment (GFR ≥ 30)
- Safe in severe liver disease (decompensated)

Interactions with acid-suppressing medications:

- Omeprazole 20mg/day ok – Take 4 hrs after SOF/VEL
- Famotidine 40mg BID – Take at same time +/or 12 hrs apart
- Separate aluminum, magnesium containing antacids 4 hours apart from SOF/VEL

http://www.gilead.com/~/media/Files/pdfs/medicines/liver-disease/epclusa/epclusa_pi.pdf

Case #1

A 59 year old female patient of yours agreed to Baby Boomer HCV screening with her annual labs earlier this year. The HCV antibody was reactive and HCV RNA was 68,000 iu/mL. She returns to clinic today to review the results. What else is needed to complete the evaluation prior to prescribing treatment?

Initial Evaluation

- Previous Treatment
- Fibrosis Status – If Decompensated refer
- PreTreatment Labs
- Consider Ultrasound (older patient, longer duration of infection)
- Immunizations
  - Hepatitis A and B – check vaccinations, if no record -
    - Check immunity and if not immune vaccinate
  - Hepatitis A total antibody IgG, Hepatitis B surface antigen, surface antibody and core antibody.
- Hepatitis B Co-infection (plan to treat in consultation w/GI/hepatologist or ID)

Initial Labs

- HCV RNA and Genotype
  - To determine active infection and treatment regimen
    - Actual viral load confirms active infection
    - Does not indicate stage of disease
- CBC
  - Platelets
    - < 150: suspect cirrhosis
    - Almost always decrease before INR increases

Initial Labs

- LFT
  - Normal ALT Men ≤30, Women ≤ 20 (most labs < 40)
  - ALT and AST may be normal in HCV and cirrhosis
  - AST:ALT ratio > 1 implies at least moderate fibrosis
    - ratio > 2 suggests EtOH disease
  - Bilirubin – elevations late sign of cirrhosis; also consider Gilbert's
  - Low albumin – consider advanced disease, assess for proteinuria/CKD
- eGFR (≥ 30 if considering treatment w/sofosbuvir)
- PT/INR
- HIV – Coinfection accelerates liver fibrosis
- HBsAg/HBcAb/HBsAb/HAV total ab (IGG)

Your Patient's Lab Results

HCV RNA (viral count): 8,987,654 iu/mL. (confirms active infection)

Genotype: 1a

CBC: Hgb 13.2, plt 256

APRI: 0.234, FIB-4: 0.89 (none or minimal fibrosis)

CMP: ALT 39, AST 24, bili, alk phos and albumin normal, Creat 0.6, eGFR >60

PT/INR: 13/0.9

HIV screen: negative

HBsAg: negative HBcAb: negative HBsAb: negative

HAV Total antibody: negative

APRI

- AST to Platelet Ratio Index
- AST /AST (ULN) /Platelet x 100
- www.hepatitis.uw.edu/page/clinical-calculators/apri
  - <0.5 = no fibrosis
  - 0.5-1.4= indeterminate
  - > 1.5 = advanced fibrosis
  - >2.0 = cirrhosis

https://www.hepatitisc.uw.edu/page/clinical-calculators/apri

Fib-4

- Fibrosis-4 score
- Age (years) x AST /Platelet Count x √ALT
- www.hepatitis.uw.edu/page/clinical-calculators/fib-4

  <1.45 = no/minimal fibrosis

  1.45-3.25= indeterminate

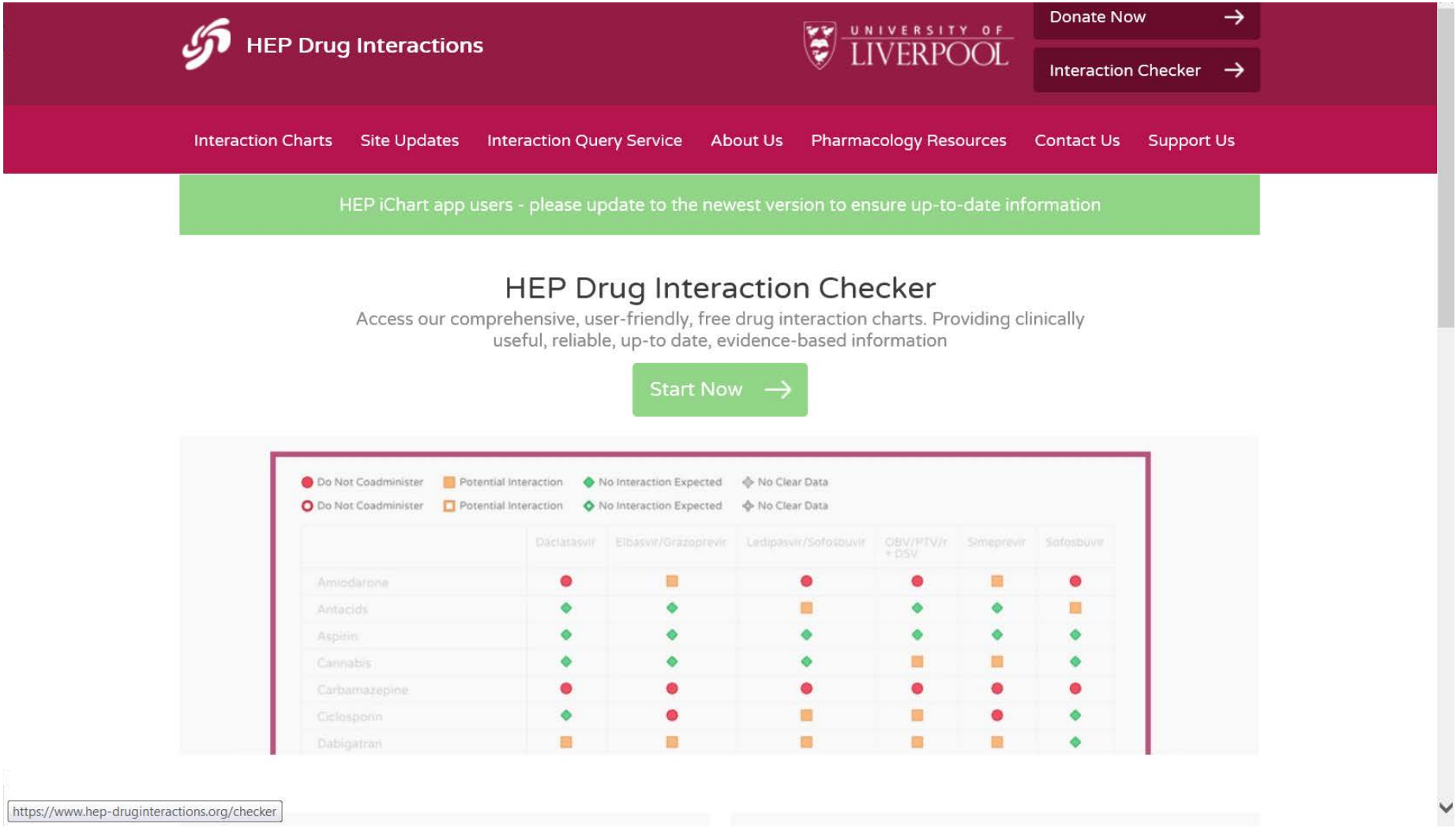
  > 3.25 = advanced fibrosis

https://www.hepatitisc.uw.edu/page/clinical-calculators/fib-4

Your patient returns to discuss lab results and treatment options. You start Hep A and B vaccines. You review her current medications with her and she tells you she is taking –

- Omeprazole 20mg bid
- Lisinopril 10 mg daily
- Atorvastatin 20 mg daily

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



Drug Drug Interactions

- Antacids/PPIs
  - Ledipasvir/sofosbuvir, sofosbuvir/velpatasvir, glecaprevir/pibrentasvir
    - Antacid/PPI affect absorption and decrease cure if not dosed correctly.
    - Give patient dosing instructions
    - Decrease omeprazole to 20mg
    - Consider elbasvir/grazoprevir if unable to decrease dose

Correctly dosing acid suppressing drugs w/LED/SOF or SOF/LED

Acid reducing agents decrease absorption (of NS5A) negatively affecting cure if not dosed correctly.

- Antacids – [Al(OH)3 and Mg(OH)3] separate dosing from LED/SOF or SOF/VEL by 4 hours
- H_2-receptor antagonists (famotidine) admin simultaneously with or 12 hours apart. Dose not to exceed equivalent to famotidine 40mg bid
- PPI's (equivalent to omeprazole 20mg)
  - Not rec w/SOF/VEL If necessary admin. 4 hours after SOF/VEL and take SOF/VEL w/food
  - Admin simultaneously with LED/SOF

What about Statins?

- Watch interaction w/some DAA's due to increased concentration of the statin.
  - Do not give GLE/PIB w/ atorvastatin. Switch to rosuvastatin 5 mg.
  - Monitor closely if atorvastatin given with EBR/GZR, LED/SOF or SOF/VEL and consider lowering dose.

https://hep-druginteractions.org/checker

Treatment options for genotype 1, treatment naïve, noncirrhotic?

- Need diagram here or navigate participants through our website
- https://anthc.org/what-we-do/clinical-and-research-services/hep/hep-c-treatment-information/

Monitoring on treatment

Your patient starts treatment and comes to see you 4 weeks later.

What will you review at today's visit?

- 1. Adherence
- 2. Side effects
- 3. Any new medications
- 4. Labs – CBC, Creat, GFR, LFT and HCV RNA
  - Repeat LFT q 4 wk w/ EBR/GZR

https://www.hcvguidelines.org/evaluate/monitoring

Monitoring HCV RNA on treatment

- If detected at week 4
- Repeat in 2 weeks
  - If > 10 fold --- discontinue treatment (I've never seen this on new DAA's)
  - If lower continue treatment
  - Not much guidance…if any questions consult

https://www.hcvguidelines.org/evaluate/monitoring

Monitoring ALT on Treatment

- 10 fold increase – discontinue treatment
- < 10 fold increase with weakness, nausea, vomiting, jaundice; or bilirubin, alkaline phosphatase or INR increase – discontinue treatment
- Asymptomatic increase < 10 fold retest at 2 week intervals and consider discontinuing treatment if it remains elevated

https://www.hcvguidelines.org/evaluate/monitoring

End of Treatment

Your patient has finished all of her medication. She returns for an end of treatment appointment.

1. Document last day of medication
2. Consider obtaining an HCV RNA to show suppression of virus (determine relapse or not)
3. Check for sustained virologic response (SVR) in 12 weeks.

https://www.hcvguidelines.org/evaluate/monitoring

SVR

- No HCV RNA 12 weeks or later after the end of treatment
- Some patients will achieve this even if they do not complete treatment
- Benefit
  - 70% reduction in risk of HCC
  - 90% reduction in liver related mortality and transplant

Van Der Meer, et al. JAMA 2012: 308:2584-2593

AFTER SVR

- For those without advanced liver disease
  - Follow up same as though they were never infected with hepatitis C
  - Assess for recurrence only if risk factors are present or unexplained elevation of ALT
  - HCV RNA preferred test as HCV antibody will remain positive
- Cirrhotic and advanced fibrosis patients

  Continue HCC surveillance RUQ US every 6 months (consider AFP)

https://www.hcvguidelines.org/evaluate/monitoring

Case #2

- Katy is a 22 year old female, diagnosed at age 18 with HCV, GT 2a. She has a history of IVDU. She just returned from treatment (sober from drugs and alcohol for 4 months), working in landscaping and is living with an older sibling. She has no health care coverage. She made today's appointment to discuss hepatitis C treatment.

Chart review shows she's fully vaccinated against Hepatitis A and B. Hep B surface antigen and core antibody are negative.

Medications: ethinyl estradiol/norethindrone OCP, St. John's Wort

PE: Without stigmata of liver disease

You get pretreatment labs…

Pre treatment Lab Review

HCV RNA - 1,003,458 iu/ml,

CBC- WNL, Plt 340

ALT - 49, AST 34, Alk 69, Alb 4.6, t. bili 0.4,

eGFR - 112

PT/INR - 13/1.0

HIV – negative

HBsAg and HBcAb - negative

APRI: 0.250; FIB-4: 0.31 (no or mild fibrosis)

What are her treatment options ?

DDI's

Ethinyl Estradiol-containing products w/ GLE/PIB

- May increase risk of ALT elevations
- Co-administration not recommended

St John's Wort

- Decreases absorption of all DAA's
- Do not co-administer

Genotype 2 Treatment Naïve, Noncirrhotic Options

- https://anthc.org/what-we-do/clinical-and-research-services/hep/hep-c-treatment-information/

Genotype 3

- 58 yo male with a history of htn, hld, type 2 DM and CKD. Known HCV infection since 1996. Never wanted to take interferon. Asks if you will treat his Hepatitis C with “that new pill I see on TV”.
- You review his immunization status. He is fully vaccinated against hepatitis A and B.
- Hepatitis screen shows an isolated hepatitis B core antibody, indicating past exposure.

Risk of Reactivating HBV w/DAA Therapy

- Assess and Refer if co-infected HBV/HCV

- Isolated anti-HBc+ ?

  Check HBV DNA

  Pretreatment

  12 weeks post treatment

  Refer to GI/hepatology if HBV DNA (+)

https://www.hcvguidelines.org/evaluate/monitoring
https://anthc.org/wp-content/uploads/2017/11/Treatment-Checklists-Outside-ASU.pdf

Pretreatment labs

Genotype 3, HCV RNA is 9,634,568 iu/ml,

CBC- WNL, Plt 240

ALT 109, AST 58, Alk 120, Alb 4.0, t. bili 0.5,

eGFR 38, Cr 1.3

PT/INR 13/1.0

HIV – negative

HBV DNA is not detected

Fibrosis Staging

- Calculated APRI= 0.604 (indeterminant)
- FIB-4= 1.34 (no/minimal fibrosis)
- Fibrotest-Actitest (Quest)= 0.43 (F2/moderate)
- Other options –
  - Transient Elastography
  - Ultrasound – Nodular liver=cirrhosis. Normal liver on US does not r/o cirrhosis
  - P.E. – look for stigmata of liver disease

Kidney Function and HCV Treatment Medications

	Ledipasvir/ Sofosbuvir	Sofosbuvir/ Velpatasvir	Elbasvir/ Grazoprevir	Glecaprevir/ Pibrentasvir
eGFR	<30*	<30*	No dose adjustment required	No dose adjustment required

*LED/SOF and SOF/VEL– For severe renal impairment, no dosage recommendation can be given. Consult nephrologist and Liver Disease provider before beginning treatment.

Genotype 3 treatment options algorithm

- https://anthc.org/what-we-do/clinical-and-research-services/hep/hep-c-treatment-information/

Compensated Cirrhosis

- Bill is 57 yo, he was diagnosed with hepatitis C in 2012 at a routine physical. He was screened per CDC recommendations that all baby boomers have a one time screening for hepatitis C. Upon questioning he doesn't recall a history of risk behavior or exposure.

Pretreatment labs

HCV RNA 1,003,458 iu/ml, Genotype 1b

CBC- Plt 140

ALT 49, AST 60, Alk 69, Alb 3.6, t. bili 1.0,

eGFR 65

PT/INR 13/1.2

HIV – negative

HBsAg and HBcAb - negative

APRI score: 3.49 (cirrhosis), FIB-4 3.49 (advanced fibrosis)

Cirrhosis - Compensated or Decompensated?

Child-Turcotte Pugh Score

	POINTS*		
	1	2	3
Encephalopathy	None	Grade 1-2 (or precipitant-induced)	Grade 3-4 (or chronic)
Ascites	None	Mild/Moderate (diuretic-responsive)	Severe (diuretic-refractory)
Bilirubin (mg/dL)	<2	2-3	>3
Albumin (g/dL)	>3.5	2.8-3.5	<2.8
INR	<1.7	1.7-2.3	>2.3

Add score for each parameter.
CTP **class**:
A = 5-6 points (compensated)
B = 7-9 points (decompensated)
C = 10-15 points (decompensated)

http://www.hepatitis.va.gov/provider/tools/child-pugh-calculator.asp

Cirrhotic?

Compensated

Child-Pugh score 5-6

Decompensated

Child Pugh score $\geq$ 6

Refer to Specialist for treatment

Recommendations

- HCC* surveillance – US every 6 mo (consider afp)
- Varices screening – EGD (if plts $\leq$ 150 or FibroScan > 20)
- Hep A & B and pneumoccocal vaccinations

*HCC – Hepatocellular Carcinoma

Genotype 1, treatment naïve, compensated cirrhosis

- https://anthc.org/what-we-do/clinical-and-research-services/hep/hep-c-treatment-information/

Person using Drugs

Shelly is a 24 yo client being seen for annual well woman exam. During the interview she shares with you –"I use heroin most days" . You determine that she's been using injecting drugs for over 4 years.

STI screening – HCV ab +; HCV RNA 2,000,000 iu/mL

PWIDs who are HCV +

- Current guidelines recommend treating active drug users
- Refer to syringe exchange, substance use treatment, medication assisted treatment
- My opinion: smoking is safer than injecting
- Stigma…treat as a person w/ a health issue

Pretreatment labs

HCV Genotype 1b, HCV RNA 2,000,000 iu/mL

CBC- Plt 320

ALT 49, AST 40, Alk 69, Alb 3.8, t. bili 1.0

eGFR 65

PT/INR 11/1.0

HIV – negative

HBsAg and HBcAb – negative

Fully vaccinated against hepatitis A and B

APRI score: 0.31, FIB-4: 0.47 = no or minimal fibrosis

*Consider acute HCV if recent IDU; may want to delay treatment start until repeat HCV RNA 4-6 mo still present

HCV GT 1b, HCV Tx Options

- https://anthc.org/what-we-do/clinical-and-research-services/hep/hep-c-treatment-information/

Monitoring On Treatment

Clinic visit or phone call monthly to ensure medication adherence

- Monitor for adverse effects
- Check for DDI's

At week 4

- CBC, CMP (monitor renal and liver functions)
- HCV RNA
  - if detectable at week 4 repeat at week 6 and if increased > 10 fold: discontinue treatment.*

Week 8 (ELB/GRA)

- LFT

End of treatment

- Consider HCV RNA

12 weeks after Treatment completion

- HCV RNA for test of cure

*http://hcvguidelines.org/full-report/monitoring-patients-who-are-starting-hepatitis-c-treatment-are-treatment-or-have

AFTER SVR

- For those without advanced liver disease
  - Follow up same as though they were never infected with hepatitis C
  - Assess for recurrence only if risk factors are present or unexplained elevation of ALT
  - HCV RNA preferred test as HCV antibody will remain positive
- Cirrhotic and advanced fibrosis patients

  Continue HCC surveillance RUQ US every 6 months (consider AFP)

Take-Home Points

- Only 4 regimens now recommended for first-line treatment of HCV
  - GLE/PIB – GZR/EBR
  - SOF/LDV – SOF/VEL
- GLE/PIB indicated and recommended by the AASLD/IDSA for treatment-naive pts with GT1-6 HCV
  - No cirrhosis: 8 wks; cirrhosis: 12 wks
  - Can be used with no dose adjustment for pts with renal impairment

Resources

- Clinical calculators - Calculate APRI, FIB-4, MELD, Child's Pugh Score
  - Hepatitis C Score Calculator – free App for your phone
  - https://www.hepatitisc.uw.edu/page/clinical-calculators/meld
- AASLD/IDSA guidelines
  - https://www.hcvguidelines.org/
- Viral Hepatitis Drug Interactions
  - https://hep-druginteractions.org/checker
- ANTHC Liver Disease and Hepatitis Program

  https://anthc.org/hep/

Thank-You

- Questions?