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

SVR %

Year

92-98 Ifn
98-02 Ifn-Rbv
02-11 Peg-Rbv
11-13 Peg-Rbv-1st Gen PI
14-18 New DAAs

Genotype 1
Genotype 2/3

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

Virus schematic: University of Washington

**NS3/4 Protease Inhibitors**
- ...previr
  - Simeprevir
  - Paritaprevir
  - Grazoprevir
  - Glecaprevir
  - Voxilaprevir

**NS5A Inhibitors**
- ...asvir
  - Daclatasvir
  - Ledipasvir
  - Ombitasvir
  - Velpatasvir
  - Elbasvir
  - Pibrentasvir

**NS5B Inhibitors**
- ...buvir
  - Sofosbuvir
  - Dasabuvir
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

<table>
<thead>
<tr>
<th>HCV GT</th>
<th>Regimen</th>
<th>Duration, Wks</th>
<th>Compensated Cirrhosis</th>
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<tr>
<td>1</td>
<td>GLE/PIB</td>
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<td>12</td>
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<td>EBR/GZR*</td>
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<td>SOF/LDV</td>
<td>8 or 12†</td>
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<td>SOF/VEL</td>
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<td>4</td>
<td>GLE/PIB</td>
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<td>SOF/VEL</td>
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<td>SOF/VEL</td>
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</tr>
</tbody>
</table>

*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.
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%) 
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

• **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 +/- 12 hrs apart
  - Separate aluminum, magnesium containing antacids 4 hours apart from SOF/VEL

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/临床计算器/apri
  - <0.5 = no fibrosis
  - 0.5-1.4= indeterminate
  - > 1.5 = advanced fibrosis
  - >2.0 = cirrhosis

https://www.hepatitisc.uw.edu/page/临床计算器/apri
Fib-4

- Fibrosis-4 score
- Age (years) x AST / Platelet Count x \sqrt{ALT}
- [www.hepatitis.uw.edu/page/clinical-calculators/fib-4](https://www.hepatitis.uw.edu/page/clinical-calculators/fib-4)
  
  - <1.45 = no/minimal fibrosis
  - 1.45-3.25 = indeterminate
  - > 3.25 = advanced fibrosis
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
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

• H₂-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 rosvuastatin 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

Ethynyl 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

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
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

<table>
<thead>
<tr>
<th></th>
<th>Ledipasvir/Sofosbuvir</th>
<th>Sofosbuvir/Velpatasvir</th>
<th>Elbasvir/Grazoprevir</th>
<th>Glecaprevir/Pibrentasvir</th>
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<tbody>
<tr>
<td>eGFR &lt;30*</td>
<td>&lt;30*</td>
<td>&lt;30*</td>
<td>No dose adjustment required</td>
<td>No dose adjustment required</td>
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</table>

*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

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

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

Add score for each parameter.

CTP class:
A = 5-6 points (compensated)
B = 7-9 points (decompensated)
C = 10-15 points (decompensated)

Cirrhotic?

Compensated

Child-Pugh score 5-6

 Decompensated

Child Pugh score ≥ 6

Refer to Specialist for treatment

Recommendations

• HCC* surveillance – US every 6 mo (consider afp)
• Varices screening – EGD (if plts ≤ 150 or FibroScan > 20)
• Hep A & B and pneumococcal vaccinations

*HCC – Hepatocellular Carcinoma
Genotype 1, treatment naïve, compensated cirrhosis

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

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](https://www.hepatitisc.uw.edu/page/clinical-calculators/meld)

- AASLD/IDSA guidelines
  - [https://www.hcvguidelines.org/](https://www.hcvguidelines.org/)

- Viral Hepatitis Drug Interactions
  - [https://hep-druginteractions.org/checker](https://hep-druginteractions.org/checker)

- ANTHC Liver Disease and Hepatitis Program
  - [https://anthc.org/hep/](https://anthc.org/hep/)
Thank-You

• Questions?