Adult/Geriatric Drug Therapy 2020

Hepatitis C: A New Era of Treatment in the Geriatric Population

Paula Cox-North, PhD, ARNP

Objectives for Learning Outcomes:

1. By the end of session learner will be able to identify first line antiviral therapies for patients with hepatitis C previously untreated with/without cirrhosis
2. By end of session learner will be able to identify treatment options for those with hepatitis C that have previously failed treatment with and without cirrhosis
3. By end of session learner will have the basic understanding of hepatitis C treatment regimens for unique populations

Hepatitis C: A New Era of Treatment in the Geriatric Population

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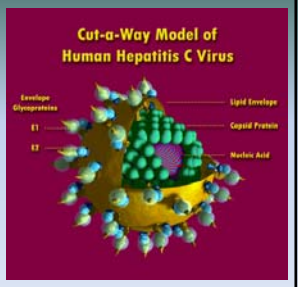
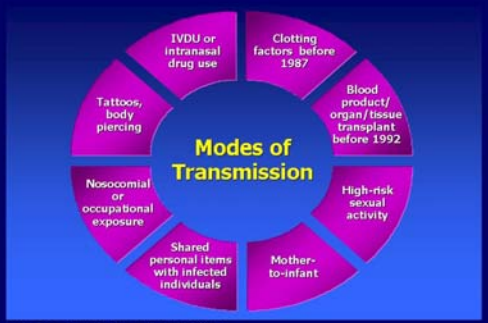
Biology

- ss RNA virus
- RNA-dependent RNA polymerase, lacks proofreading function
- Flaviviridae
- 6 genotypes, type 1 accounts for 70% of infections in US, types 2,3 account for rest
- No easy culture system!

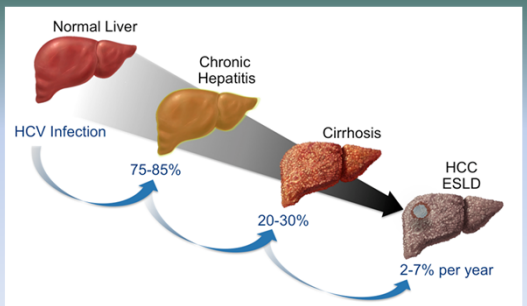


Transmission of HCV

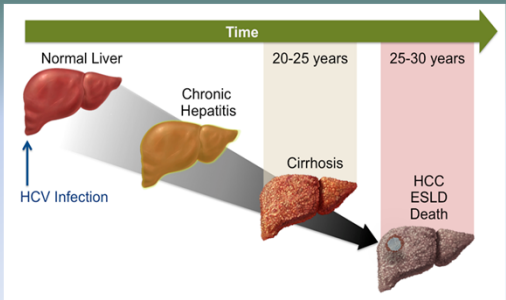


NIH. *NIH Consens State Sci Statements.* 2002;19(3):1-46.

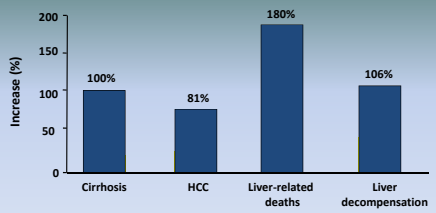
Natural History of Infection



Natural History Over Time



Future Disease Burden: Estimated Increase From 2000 to 2020



HCC=hepatocellular carcinoma.
Davis GL, et al. *Liver Transpl.* 2003;9:331-338.

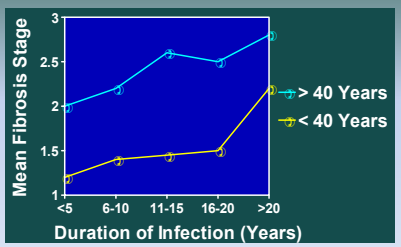
Factors affecting progression

- Age at infection (>40 years old)
  - particularly if contracted via blood transfusion
- Male Gender
- Alcohol abuse
- Obesity
- Co-infection with HIV or HBV
- Iron in the liver, as detected via liver biopsy

Note: HCV progression has *NOT* been demonstrated to be influenced by viral load, serum ALT, or mode of transmission.

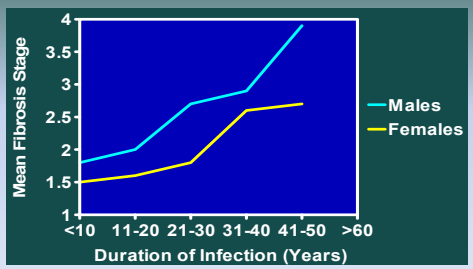
Freeman, et al *Hepatology* 2001; 34:809

AGE AT INFECTION



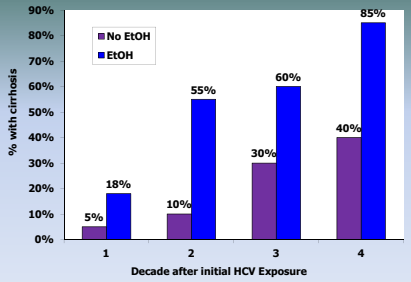
Lancet 1997;349:825-832

GENDER AND PROGRESSION

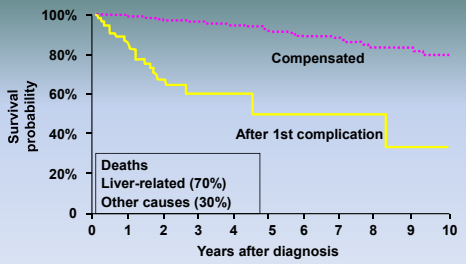


Lancet 1997;349:825-832

Alcohol Use And Progression



Natural History of HCV Cirrhosis



Adapted from Fattovich G, et al. Gastroenterology. 1997; 112: 466-467

Screening and Counseling for Hepatitis C

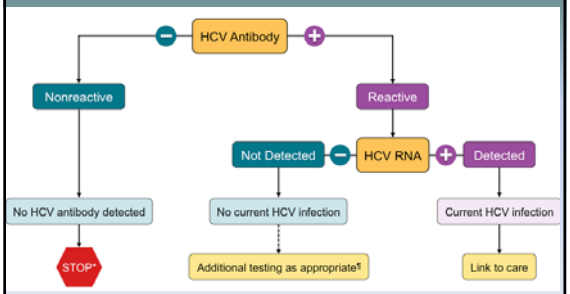
Who Should be Screened- CDC

- **Universal hepatitis C screening**:
  - Hepatitis C screening at least once in a lifetime for **all adults** aged 18 years and older, except in settings where the prevalence of HCV infection (HCV RNA-positivity) is less than 0.1%*
  - Hepatitis C screening for **all pregnant women during each pregnancy**, except in settings where the prevalence of HCV infection (HCV RNA-positivity) is less than 0.1%*

Who Should You Screen-USPSTF

- Screening for hepatitis C virus (HCV) infection in adults aged 18 to 79 years.

Testing Sequence for HCV



CDC 2013

Interpreting Results

Interpretation of Test Results for HCV Infection and Further Actions

Test Outcome	Interpretation	Further Action
HCV antibody nonreactive	No HCV antibody detected	• Sample can be reported as nonreactive for HCV antibody. No further action required. • If recent HCV exposure in person tested is suspected, test for HCV RNA.*
HCV antibody reactive	Presumptive HCV infection	• A repeatedly reactive result is consistent with current HCV infection, or past HCV infection that has resolved, or biologic false positivity for HCV antibody. Test for HCV RNA to identify current infection.
HCV antibody reactive, HCV RNA detected	Current HCV infection	• Provide person tested with appropriate counseling and link person tested to medical care and treatment.†
HCV antibody reactive, HCV RNA not detected	No current HCV infection	• No further action required in most cases. • If distinction between true positivity and biologic false positivity for HCV antibody is desired, and if sample is repeatedly reactive in the initial test, test with another HCV antibody assay. • In certain situations§ follow up with HCV RNA testing and appropriate counseling.

* If HCV RNA testing is not feasible and person tested is not immunocompromised, do follow-up testing for HCV antibody to demonstrate seroconversion. If the person tested is immunocompromised, consider testing for HCV RNA.

† It is recommended before initiating antiviral therapy to retest for HCV RNA in a subsequent blood sample to confirm HCV RNA positivity.

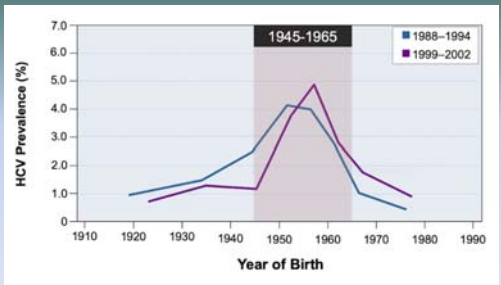
§ If the person tested is suspected of having HCV exposure within the past 6 months, or has clinical evidence of HCV disease, or if there is concern regarding the handling or storage of the test specimen.

Patient Counseling

- Low household transmission <5%
- Avoid sharing razors, shaving equipment, toothbrushes, dental equipment, nail clippers, or other personal care items.
- Cover cuts or sores on the skin to keep from spreading infectious blood
- Hepatitis C virus can survive outside the body for at least 16 hours so any blood spill (including dried blood) should be cleaned up using a dilution of one part household bleach to 10 parts water by a person wearing gloves during the entire clean up
- HCV is not spread through food, water, eating utensils, or casual contact (such as sneezing, coughing, touching, hugging).

HCV in the Geriatric Population

Prevalence of HCV Ab by Year of Birth



Source: Armstrong GL, Wasley A, Simard EP, McQuillan GM, Kuhnert WL, Alter MJ. The prevalence of hepatitis C virus infection in the United States, 1999 through 2002. Ann Intern Med. 2006;144:705-14.

Liver Blood Flow, Volume & Function with Aging

- Liver volume decreases by 20-40%
- Neural fat and cholesterol volumes in the liver expand
- Metabolism of LDL cholesterol decreases by 35%
- More vulnerable to acute liver failure
- Increased fibrogenic response

Kim, I.H, Kisseleva, T., Brenner, D.A. (2015) Current Opinion Gastroenterology; 31, 184-191

Cost Effectiveness based on these Factors

- Level of liver fibrosis (F1-F4)
- Age (65, 70, 75, 80)
- Frailty (robust, pre-frail, frail)

Ciaccio, A., 2017; Liver International;37; 982-994

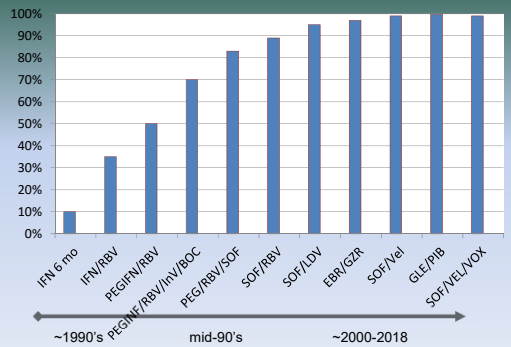
Treatment Effectiveness

- Treatment less cost effective in those with mild fibrosis (F1 or F2) vs. those with more advanced fibrosis (F3 or F4).
- Effectiveness of treatment declines with decreasing fibrosis and increasing age and frailty.
- Marked improvement in the reduction of hepatocellular carcinoma in those with cirrhosis that were treated.

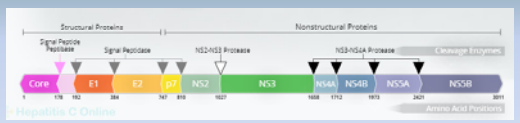
Ciaccio, A., 2017; Liver International;37; 982-994

Treatment Options

Evolution of HCV Therapy



HCV Genome



Direct Acting Antivirals

- **NS5B Inhibitors** (RNA polymerase Inhibitors)
  - Sofosbuvir
- **NS3/4B** (Protease Inhibitors)
  - Grazo**previr**
  - Voxila**previr**
  - Gleca**previr**
- **NS5A Inhibitors** (Phosphoproteins)
  - Ledip**asvir**
  - Elb**asvir**
  - Velpat**asvir**
  - Pibrent**asvir**

Elbasvir-Grazoprevir (*Zepatier*)

- **Indications and Usage**
  - Indicated for the treatment of chronic HCV genotypes 1 or 4 in adults.
- **Class & Mechanism:** HCV NS5A inhibitor/NS3/4A protease inhibitor
- **Adverse Effects (AE)**:
  - Fatigue, headache, and nausea
  - Increase in ALT > 5x normal in 1% of subjects
- **Drug Interactions:** contraindicated with concomitant use of organic ion transporter polypeptide 1B (OATP1B) inhibitors, strong inducers of cytochrome P450 3A (CYP3A), and efavirenz
- **Clinical Trials:** 187 subjects aged 65 years and over. Higher elbasvir and grazoprevir plasma concentrations were observed in subjects aged 65 years and over. A higher rate of late ALT elevations was observed in subjects aged 65 years and over in clinical trials. No dosage adjustment of ZEPATIER is recommended in geriatric patients

Elbasvir/grazoprevir (Zepatier™)

Drug Interactions

- **Anticonvulsants**
  - **Contraindication:** carbamazepine, phenytoin
- **Antibiotics/Antimycobacterials**
  - **Contraindication:** rifampin
  - Nafcillin (co-administration not recommended)
- **Anticoagulants**
  - Warfarin – frequent monitoring of INR
- **HIV-Antiretrovirals**
  - **Contraindication:** efavirenz, atazanavir, darunavir, lopinavir, saquinavir, tipranavir
  - Etravirine, elvitegravir/cobicistat/ emtricitabine/ tenofovir DF or AF (co-administration not recommended)
- **Immunosuppressant**
  - **Contraindication:** cyclosporine
  - Tacrolimus (frequent monitoring of levels)
- **Herbal Products**
  - **Contraindication:** St. John's Wort (*Hypericum perforatum*)
- **HMG-CoA Reductase Inhibitors**
  - Rosuvastatin (max dose 10mg), atorvastatin (max dose 20mg), fluvastatin, lovastatin, simvastatin
- **Antifungals**
  - Ketoconazole (co-administration not recommended)
- **Miscellaneous**
  - Bosentan (co-administration not recommended)
  - Modafinil (co-administration not recommended)

Ledipasvir-Sofosbuvir (Harvoni)

- **Indication & Usage:** GT 1 HCV, single pill combination given for 8 to 12 weeks depending on prior treatment and fibrosis
- **Class & Mechanism:** NS5a inhibitor/NS5B polymerase inhibitor
- **Adverse Effects** : Fatigue, headache
- **Drug Interactions**: Not recommended with anticonvulsants/ antimycobacterials/Herbal Supplements, Tipranavir/ritonavir
- **Clinical Trials**: 225 subjects aged 65 and over,no overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. No dosage adjustment of HARVONI is warranted in geriatric patients

Ledipasvir/sofosbuvir (Harvoni®)

Drug Interactions

- **Acid Reducing Agents**
  - Antacids – administer 4 hours apart from Harvoni ®
  - H2RA – administer at the same time or 12 hours apart from Harvoni® – NTE 40mg of famotidine twice daily or comparable dose
  - PPI – administer at same time as Harvoni® – NTE 20mg of omeprazole or comparable dose
- **Antiarrhythmics**
  - Amiodarone – may result in serious symptomatic bradycardia
  - Digoxin – may increase levels of digoxin
- **Anticoagulants**
  - Warfarin – frequent monitoring of INR
- **Antidiabetics**
  - Changes in hepatic function can result in alerted blood glucose control – monitor for hypoglycemia
- **Anticonvulsants**
  - Carbamazepine, phenytoin, phenobarbital, oxcarbazepine – DECREASES ledipasvir and sofosbuvir levels; coadministration not recommended
- **Antimycobacterials**
  - Rifampin, rifabutin, rifapentine – coadministration not recommended
- **HIV-Antiretrovirals**
  - Tenofovir (TDF)
    - Monitor for tenofovir-associated adverse reactions, especially with a boosted PI regimen or cobicistat
  - Not recommended to administer with Stribil® (elvitegravir, cobicistat, emtricitabine and tenofovir DF) or tipranavir/ritonavir
- **HCV Products**
  - Simeprevir – coadministration not recommended
- **Herbal Products**
  - St. John's wort (*Hypericum perforatum*) – DECREASES levels of ledipasvir and sofosbuvir
- **HMG-CoA Reductase Inhibitors**
  - Rosuvastatin – levels of statin can increase – coadministration not recommended
  - Atorvastatin – levels of statin can increase – monitor closely for adverse effects
- **P-gp Inducers**
  - P-gp inducers – DECREASE levels of ledipasvir and sofosbuvir and concomitant use is not recommended

Sofosbuvir-Velpatasvir (Epclusa)

- **Indication & Usage:** Single-pill combination regimen that is pangenotypic given for 12 weeks.
- **Class & Mechanism**: NS5B polymerase inhibitor /NS5A inhibitor.
- **Adverse Effects**: Headache and Fatigue
- **Drug Interactions:** Topotecan ,proton-pump inhibitors, oxcarbazepine, phenobarbital, phenytoin, rifabutin, rifapentine, efavirenz, and tipranavir
- **Clinical Trials:** 156 subjects aged 65 and over, no overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. No dosage adjustment of EPCLUSA is warranted in geriatric patients

Epclusa (Gilead) - package insert

Sofosbuvir/Velpatasvir (Epclusa®)

Drug Interactions

- **Acid Reducing Agents**
  - Antacids – administer 4 hours apart from Epclusa®
  - H2RA – administer at the same time or 12 hours apart from Epclusa® – NTE 40mg of famotidine twice daily or comparable dose
  - PPI (VEL solubility more sensitive to increases in pH compared to LDV)
    - Coadministration not recommended!
    - If medically necessary to coadminister, Epclusa® should be taken with food 4 hours before omeprazole 20mg
    - Use with other PPIs has not been studied
- **Antiarrhythmics**
  - Amiodarone – may result in serious symptomatic bradycardia
  - Digoxin – may increase levels of digoxin
- **Anticancers**
  - Topotecan – may increase levels of topotecan, coadministration not recommended
- **Anticoagulants**
  - Warfarin – frequent monitoring of INR
- **Antimycobacterial**
  - Rifampin, rifabutin, rifapentine – coadministration not recommended
- **Anticonvulsants**
  - Carbamazepine, phenytoin, phenobarbital, oxcarbazepine – DECREASE velpatasvir and sofosbuvir levels – coadministration not recommended
- **HIV-Antiretrovirals**
  - Tenofovir (TDF)
    - Monitor for tenofovir-associated adverse reactions, especially with a boosted PI regimen
  - Not recommended to administer with efavirenz-containing regimen or tipranavir/ritonavir
- **Herbal Products**
  - St. John's wort (*Hypericum perforatum*) – DECREASES levels of velpatasvir and sofosbuvir
- **HMG-CoA Reductase Inhibitors**
  - Rosuvastatin – levels of statin can increase – coadministration of a dose that does not exceed 10 mg is recommended
  - Atorvastatin – monitor for increased side effects from atorvastatin (myopathy and rhabdomyolysis)
- **Antidiabetics**
  - Changes in hepatic function can result in alerted blood glucose control – monitor for hypoglycemia
- **Inducers of P-gp, CYP2B6, CYP2C8, CYP3A4** – coadministration not recommended

Epclusa® (velpatasvir/sofosbuvir) [package insert]. Foster City, CA: Gilead Sciences, Inc; November 2018.

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Glecaprevir-Pibrentasvir (*Mavyret*)

- **Indications and Usage** Treatment of patients without/with cirrhosis (Child-Pugh A) or previously treated patients with a regimen containing an HCV NS5A inhibitor or an NS3/4A protease inhibitor, but not both
- **Class & Mechanism:** HCV NS3/4A protease inhibitor/ NS5A inhibitor
- **Adverse Effects (AE)**: Headache and fatigue
- **Drug Interactions: D**rugs that inhibit or induce hepatic P-gp, BCRP, or OATP1B1/3 may increase/decrease the plasma concentrations of glecaprevir and/or pibrentasvir.
- **Clinical Trials:** 328 subjects were age 65 years and over and 47 subjects were age 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger subjects. No dosage adjustment of MAVYRET is warranted in geriatric patients

Source: *Mavyret* Prescribing Information. AbbVie., Inc.

Glecaprevir/pibrentasvir (Mavyret™)

Drug Interactions

- **Antiarrhythmics**
  - G/P → ↑ digoxin levels → reduce digoxin concentrations by decreasing the dose by approximately 50% or by modifying the dosing frequency and continue monitoring
- **Anticoagulants**
  - G/P → ↑ dabigatran → refer to prescribing information for dabigatran dose modifications with P-gp inhibitors in the setting of renal impairment
  - G/P → warfarin → may cause fluctuation in INR, monitor closely
- **Anticonvulsants**
  - Carbamazepine, phenytoin → ↓ G/P → Coadministration may lead to reduced therapeutic effect of G/P and is not recommended
- **Antimycobacterials**
  - Rifampin → ↓ G/P → Coadministration is contraindicated because of potential loss of therapeutic effect of G/P
- **Antidiabetics**
  - Changes in hepatic function can result in alerted blood glucose control – monitor for hypoglycemia
- **Ethinyl Estradiol-Containing Products**
  - G/P + EE → may increase the risk of ALT elevations and is not recommended
- **Herbal Products**
  - St. John's Wort → ↓ G/P → Coadministration may lead to reduced therapeutic effect of G/P and is not recommended
- **HIV-Antiviral Agents**
  - Atazanavir → ↑ G/P → may increase the risk of ALT elevations and coadministration is contraindicated
  - Darunavir, lopinavir, ritonavir → ↑ G/P →Coadministration is not recommended
  - Efavirenz ↓ G/P → Coadministration may lead to reduced therapeutic effect of G/P and is not recommended

Glecaprevir/pibrentasvir (Mavyret™)

Drug Interactions

- **HMG-CoA Reductase Inhibitors**
  - Atorvastatin, lovastatin, simvastatin → ↑ statin level → coadministration with these statins is not recommended
  - Pravastatin→ ↑ statin level → reduce pravastatin dose by 50%
  - Rosuvastatin → ↑ statin level→ reduce rosuvastatin to 10 mg
  - Fluvastatin, pitavastatin → ↑ statin level → use the lowest approved dose; if higher doses are needed, use the lowest necessary statin dose based on a risk/benefit assessment
- **Immunosuppressants**
  - Cyclosporine ↑ G/P → not recommended for use in patients requiring stable cyclosporine doses > 100 mg/day
- **PPIs**
  - Omeprazole ↓ glecaprevir
  - **US Package Insert:** no dosage adjustment required
  - Phase 2 and 3 data for G/P: among 2,369 patients evaluated → 263 patients (11%) were receiving PPIs
  - 25% were on omeprazole 40 mg or equivalent PPI dose
  - 75% were on omeprazole 20 mg or equivalent PPI dose
  - **SVR12 was not impacted by concomitant PPI use** (SVR12: 97% with concomitant PPI use versus 97% without concomitant PPI use)

Sofosbuvir-Velpatasvir-Voxilaprevir (Vosevi)

- **Indication and Usage:** Pangenotypic regimen for patients who have experienced treatment failure with DAA therapy
- **Adverse effects:** Headache, Fatigue, Diarrhea, Nausea
- **Class & Mechanism:** NS5B polymerase inhibitor/NS5A replication complex inhibitor/ NS3/4A protease inhibitor.
- **Drug Interactions**: Drugs that are inducers of P-gp and/or moderate to strong inducers of CYP2B6, CYP2C8, or CYP3A4 may significantly decrease plasma concentrations of sofosbuvir, velpatasvir, and/or voxilaprevir leading to reduced therapeutic effect of VOSEVI.
- **Clinical trials:** 74 subjects aged 65 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. No dosage adjustment of VOSEVI is warranted in geriatric patients

Vosevi Package Insert- Gilead Sciences

Sofosbuvir/velpatasvir/voxilaprevir (Vosevi™)

Drug Interactions

- **Acid Reducing Agents**
  - Antacids – administer 4 hours apart from Vosevi ™
  - H2RA – administer at the same time or staggered from Vosevi™ – NTE 40mg of famotidine twice daily or comparable dose
  - PPI
    - Omeprazole 20mg can be administered at any time with Vosevi™
    - Use with other PPIs has not been studied
- **Antiarrhythmics**
  - Amiodarone – may result in serious symptomatic bradycardia
  - Digoxin – may increase levels of digoxin
- **Anticoagulants**
  - Dabigatran – may increase levels of dabigatran
  - Warfarin – frequent monitoring of INR
- **Anticancers**
  - Topotecan – may increase levels of topotecan, coadministration not recommended
- **Anticonvulsants**
  - Carbamazepine, phenytoin, phenobarbital, oxcarbazepine – DECREASE sofosbuvir, velpatasvir, and voxilaprevir levels – coadministration not recommended
- **Antimycobacterial**
  - Rifampin (contraindicated), rifabutin, rifapentine – coadministration not recommended
- **Antidiabetics**
  - Changes in hepatic function can result in alerted blood glucose control – monitor for hypoglycemia
- **HIV-Antiretrovirals**
  - Tenofovir (TDF)
    - Monitor for tenofovir-associated adverse reactions, especially with a boosted PI regimen
  - Not recommended to administer with efavirenz, atazanavir, lopinavir, or tipranavir/ritonavir-containing regimen
- **Herbal Products**
  - St. John's wort (*Hypericum perforatum*) – DECREASES levels of velpatasvir, voxilaprevir, and sofosbuvir– coadministration not recommended
- **HMG-CoA Reductase Inhibitors**
  - Rosuvastatin & pitavastatin – levels of statin can increase; coadministration not recommended
  - Pravastatin – may be administered at dose that does not exceed pravastatin 40mg
  - Atorvastatin, fluvastatin, lovastatin, and simvastatin – monitor for increased side effects from statin (myopathy and rhabdomyolysis)
- **Immunosuppressants**
  - Cyclosporine – coadministration not recommended as voxilaprevir levels are substantially increased

Vosevi™ [sofosbuvir, velpatasvir, and voxilaprevir] [package insert]. Foster City, CA: Gilead Sciences, Inc; November 2019.[97]

General Precautions

- Do not use **protease inhibitors** in those with advanced liver disease (Child's B or C)
- Do not use sofosbuvir containing regimens in those with eGFR <30
- Statin use should be dose adjusted or stopped during treatment.
- **BLACK BOX WARNING:**

WARNING: RISK OF HEPATITIS B VIRUS REACTIVATION IN PATIENTS COINFECTED WITH HCV AND HBV

See full prescribing information for complete boxed warning.

Hepatitis B virus (HBV) reactivation has been reported, in some cases resulting in fulminant hepatitis, hepatic failure, and death. (5.1)

Child-Turcotte-Pugh Classification for Severity of Cirrhosis

Clinical and Lab Criteria	Points*		
	1	2	3
Encephalopathy	None	Grade 1 or 2	Grade 3 or 4
Ascites	None	Mild to moderate (diuretic responsive)	Severe (diuretic refractor
Bilirubin (mg/dL)	< 2	2-3	>3
Albumin (g/dL)	> 3.5	2.8-3.5	<2.8
Prothrombin time Seconds prolonged or International normalized ratio	<4 <1.7	4-6 1.7-2.3	>6 >2.3

*Child-Turcotte-Pugh Class obtained by adding score for each parameter (total points)

Class A = 5 to 6 points
Class B = 7 to 9 points
Class C = 10 to 15 points

Risk of Hepatic Decompensation/Failure in Patients with Evidence of Advanced Liver Disease: Hepatic decompensation/failure, including fatal outcomes, have been reported mostly in patients with cirrhosis and baseline moderate or severe liver impairment (Child-Pugh B or C) **in those on protease inhibitors**. Monitor for clinical and laboratory evidence of hepatic decompensation. Discontinue medications in patients who develop evidence of hepatic decompensation/failure

Thank You for your Attention

Questions??