TREATING HCV INFECTION IN 2019: It doesn’t get much better than this

Susanna Naggie, MD, MHS
Associate Professor of Medicine
Duke University School of Medicine
Disclosures

- Dr. Naggie has received research support from AbbVie, Gilead Sciences, Inc, Tacere; serves as scientific advisor for Vir and BioMarin; serves on event adjudication committee for BMS. (Updated 03/01/2019)

- Discussion of off label use
HCV Introduction
Testing
Staging
HCV Drug Targets and Treatments
Pre-treatment assessments
Management post-SVR

www.hcvguidelines.org
Hepatitis C Virus Epidemiology (an update)
Prevalence of Chronic Hepatitis C Infection

Table 4 (with graph). Prevalence of HCV infection (HCV RNA positive) in the general population, by WHO region, with uncertainty intervals, 2015: 71 million persons living with HCV worldwide.
Prevalence of Chronic Hepatitis C Infection

Table 3 (with map). Incidence of HCV infection in the general population, by WHO region, 2015:
1.75 million new infections in 2015

1.75 million – 23.7/100,000
HCV – Leading ID Cause of Death Globally

Fig. 2. Global annual mortality from hepatitis, HIV, tuberculosis and malaria, 2000–2015: unlike HIV, tuberculosis and malaria, the trend in mortality from viral hepatitis is increasing

HCV Screening and Testing
HCV Screening

Risk Based HCV Testing
Risk Behaviors
Risk Exposures
Other Conditions and Circumstances

One Time HCV Testing
For persons born from 1945 to 1965 without prior ascertainment of risk

MMWR August 17 2012
www.hcvguidelines.org
Repeat HCV Testing
People who inject drugs – annually
MSM with HIV and high risk – annually
Other risk – frequency based on risk
HCV Algorithm

- If previously exposed start at HCV RNA
- Anti-HCV can be rapid (POC) or laboratory based
- If at risk of recent exposure repeat testing in 6 months
- 10-15% rate false negative anti-HCV in immunocompromised

www.hcvguidelines.org
Centers for Disease Control and Prevention (CDC), 2013 (CDC, 2013)
Staging Liver Disease – Still Necessary?
Staging of Liver Disease Still Matters

**Recommendations for Pretreatment Assessment**

- Evaluation for advanced fibrosis using liver biopsy, imaging, and/or noninvasive markers is recommended for all persons with HCV infection, to facilitate an appropriate decision regarding HCV treatment strategy and to determine the need for initiating additional measures for the management of cirrhosis (eg, hepatocellular carcinoma screening). (see HCV Testing and Linkage to Care)

Rating: Class I, Level A


Alternatives to Liver Biopsy

- Noninvasive approaches
  - Serum Markers
    - Standard laboratory tests: APRI (<0.3, >2), FIB-4 (>3.25)
    - Commercial assays (FibroSure) (>0.8)
  - Serum Markers
  - Elastography

- Limitations
  - Ability to distinguish F1 versus F2, etc.
    - Better to differentiate advanced versus early fibrosis
  - Serologies impacted by inflammation
  - Indeterminate outcomes common

Radiographic Assessments
Newer Methods

- Ultrasound, CT, MRI
  - Conventional studies are unhelpful in assessment of fibrosis unless patient has decompensated cirrhosis

- Transient elastography
  - Methodology
    - Ultrasonic transducer sends a vibration wave into the liver
    - Elastic shear wave propagates through the liver
    - Velocity of wave correlates with tissue stiffness

- Test characteristics
  - Mean AUROC for the diagnosis of:
    - Severe fibrosis: 0.89 (95% CI, 0.88-0.91)
    - Cirrhosis: 0.94 (95% CI, 0.93-0.95)

Hepatitis C Virus Drug Targets and Treatments
Hepatitis C Virus

HCV Genome

5' UTR region

9.6 kb RNA

3' UTR region

IRES-mediated translation

Polyprotein

C E1 E2 NS2 NS3 A NS4B A NS5 B

Polyprotein Processing

Core Envelope glycoproteins

C E1 E2 p7

Serine Protease

Serine Protease Cofactor

NS3-4A Protease

Inhibitors:
Grazoprevir*
Paritaprevir*
Simeprevir
Glecaprevir*
Voxilaprevir*

NS5A

Inhibitors:
Daclatasvir
Elbasvir*
Ledipasvir*
Ombitasvir*
Velpatasvir*
Pibrentasvir*

NS5B Polymerase

Inhibitors:
Dasabuvir (non-nuc)
Sofosbuvir (nuc)

RNA dependent RNA polymerase

Adapted from Naggie et al. J Antimicrob Chemother 2010
HCV Therapeutic Timeline

- Interferon 48W
- Interferon + RBV
- Telaprevir & Boceprevir
- Sofosbuvir & Simeprevir
- Ledipasvir*, Paritaprevir/ Ombitasvir/ Dasabuvir/ Daclatasvir
- Telaprevir & Boceprevir
- Ledipasvir*, Paritaprevir/ Ombitasvir/ Dasabuvir/ Daclatasvir
- First all oral GT 1
- First in ESRD/CKD
- First Pan-genotypic
- Approval in children
- First DAA salvage
- DAA failure salvage
- Elbasvir/ Grazoprevir/ Velpatasvir*
- First in liver transplant
- First all oral GT 2 & 3
- First in liver transplant
- DAA failure salvage
Closing the Gap in HIV
Welcome to the New HCVGuidelines.org
The AASLD and IDSA in partnership with the panel have created an updated web experience to facilitate easier and faster access to this important resource. Please select a patient profile from the menu above, click on a Guidance section below, or use the search box to begin.
**Goal of Treatment**

- The goal of treatment of HCV-infected persons is to reduce all-cause mortality and liver-related health adverse consequences, including end-stage liver disease and hepatocellular carcinoma, by the achievement of virologic cure as evidenced by a sustained virologic response.

  Rating: Class I, Level A

**Recommendations for When and in Whom to Initiate Treatment**

- Treatment is recommended for all patients with chronic HCV infection, except those with short life expectancies that cannot be remediated by treating HCV, by transplantation, or by other directed therapy. Patients with short life expectancies owing to liver disease should be managed in consultation with an expert.

  Rating: Class I, Level A
Recommended regimens for treatment-naïve patients with HCV genotype 1 or 4 without cirrhosis

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<tr>
<th>Regimen</th>
<th>Weeks</th>
<th>Rating</th>
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<td>Glecaprevir/pibrentasvir</td>
<td>8</td>
<td>I, A</td>
</tr>
<tr>
<td>Ledipasvir/sofosbuvir</td>
<td>8*-12</td>
<td>I, A/B</td>
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<tr>
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<td>I, A</td>
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* Shortening to 8 weeks is allowable if Genotype 1 and baseline VL<6 million in persons without HIV or of African descent

www.hcvguidelines.org
Recommended regimens for treatment-naïve patients with HCV genotype 1 or 4 with compensated cirrhosis

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<td>I, A</td>
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www.hcvguidelines.org.
Recommended regimens for treatment-naïve patients with HCV genotype 2 or 3 without/with cirrhosis

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<td>8/12</td>
<td>I, A</td>
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<tr>
<td>Sofosbuvir/velpatasvir*</td>
<td>12</td>
<td>I, A</td>
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*for genotype 3 infection with cirrhosis, baseline NS5A RAS testing is recommended
When starting therapy:

1. Genotype/subtype
2. Cirrhosis – yes/no?
3. Prior treatment experience? To DAA?
4. Is resistance testing required?

5. Other –
   1. Renal function?
   2. Liver function? → Calculate Child Pugh for ALL cirrhotics
   3. Drug interactions?
Approach to retreatment for DAA experienced patients

- 1st gen PI + P/R
- Non-NS5A, SOF-containing
- NS5A Inhibitor Experienced

www.hcvguidelines.org.
Glecaprevir (NS3)/pibrentasvir (NS5A)

- Co-formulated – 3 pills once daily
- Pangentotypic
- Next generation
  - Active vs NS3 RAS at 80, 155, 168 and NS5A RAS at 28, 30, 31, 93
- Negligible renal excretion
- Contains a protease inhibitor
- Has ? interaction with acid suppressing medications
Glecaprevir (NS3)/pibrentasvir (NS5A)

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- Registration program
- 8 weeks in treatment naïve and PEG/RBV failures without cirrhosis
- 12 weeks in cirrhosis
- Renal impairment
- HIV co-infection
- Post-transplant
- Limited in DAA salvage (not in EU)
- Contraindicated in decompensated liver disease
Glecaprevir/pibrentasvir: HIV

- GT 1-6
- Primarily an 8 week study
- 12 weeks in 16 patients with cirrhosis
- TN or TE (19%) with IFN, P/R or SOF+P/R
- VBT on treatment – GT3 with cirrhosis

Rocksroh et al. EASL 2017
Sofosbuvir/velpatasvir/voxilaprevir (NS3)

- Single fixed dose combination daily pill
- Pangenotypic
- Next generation?
  - Active vs NS3 RAS at 80, 155, 168
  - and NS5A RAS at 28, Q30, 31
- Contains a protease inhibitor
- Sofosbuvir still with limited renal data
- Velpatasvir still with acid suppressing issue
Sofosbuvir/velpatasvir/voxilaprevir (NS3)

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- Registration program
- 8 weeks in treatment naïve and PEG/RBV failures
- DAA salvage
  - Non-NS5A
  - NS5A
- No data in HIV, transplant, renal disease
- Contraindicated in decompensated liver disease
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<th>Drug interactions of DAA and ARV</th>
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<td>Boosted ATZ</td>
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<tr>
<td>Boosted DRV</td>
</tr>
<tr>
<td>Efavirenz</td>
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<tr>
<td>Rilpivirine</td>
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<tr>
<td>Etravirine</td>
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<tr>
<td>Raltegravir</td>
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<tr>
<td>Elvitegravir/c</td>
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<tr>
<td>Dolutegravir</td>
</tr>
<tr>
<td>Bictegravir</td>
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<tr>
<td>TDF</td>
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<tr>
<td>TAF</td>
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Other Pretreatment Assessments
HCV Pretreatment Assessment

• Active Substance Use
  • Not a contraindication; only if interferes with adherence
  • NO difference in treatment outcomes
  • Is re-infection a concern?
  • Alcohol use: educate patients on impact on HCV
  • Opportunity for medication assisted treatment (MAT) for opioid use disorder (OUD) or alcohol use disorder (AUD)
HCV Pretreatment Assessment

Barriers to adherence – assess readiness

- The purpose of the adherence assessment is to optimize support, not to deny access to treatment.
- Though HCV treatment regimens are relatively short in duration, assessing a patient’s readiness for treatment and ability to adhere to a medication regimen and medical care appointments before initiating DAA therapy is essential.
- After the pre-treatment assessment and before treatment initiation, a plan can be developed with the patient to address potential barriers and/or to put support resources in place.
- Recommend discussing the cost of the HCV regimen with the patient, as this can reinforce the importance of adherence and value of treatment.
HCV Pretreatment Assessment

- Pregnancy Status/Contraception
  - Perform pregnancy test before starting HCV treatment
  - Before ribavirin: confirm negative pregnancy test, advise patients to use 2 BCM during and for 6 months after treatment, provide BCM counseling
  - **Contraindication**: no RBV for F/M planning conception within 6 months of last dose; including M patients with pregnant partners
  - **Contraindication**: G/P and SOF/VEL/VOX and contraceptives containing ethinyl estradio
HCV Pretreatment Assessment

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  - What if diagnosis made during pregnancy?
### Safety in Pregnancy

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<th>DAA</th>
<th>Animal Toxicology Pregnancy</th>
<th>Animal Toxicology Breast Feeding/Lactation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sofosbuvir/Velpatasvir ± Voxilaprevir</td>
<td>No observed AE Sof with increased exposures during gestation</td>
<td>All DAA detected in breast milk and/or pups</td>
</tr>
<tr>
<td>Ledipasvir/sofosbuvir</td>
<td>No observed AE</td>
<td>Ledipasvir detected in pups</td>
</tr>
<tr>
<td>Elbasvir/Grazoprevir</td>
<td>No observed AE, cross placenta</td>
<td>Both DAA detected in breast milk</td>
</tr>
<tr>
<td>Glecaprevir/pibrentasvir</td>
<td>Gle: No data for rabbits due to low (7%) exposures; Pib no observed AE</td>
<td>Both DAA detected in breast mild and/or pups</td>
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Rising HCV Epidemic Among Pregnant Women Delivering at Magee-Womens Hospital in Pittsburgh, Pennsylvania

HCV prevalence (%)

HIV/HCV Co-infection: An AETC National Curriculum

Boneva L, et al. CID. 2014

Slide courtesy of Catherine Chappell
Study Design

- **Enrollment**: 23-24 weeks’ gestation
- **PK-visit 1**: 25-26 weeks’ gestation
- **PK-visit 2**: 29-30 weeks’ gestation
- **PK-visit 3**: 33-34 weeks’ gestation
- **Delivery**

**12 week treatment course LDV/SOF**

**HCV viral load and adverse events**

- **Delivery**
- **Visit 1 (8w)**
- **Visit 2 (6m)**
- **Visit 3 (12m)**

**HCV viral load, adverse events, physical exam, growth and neurodevelopmental assessment**

**Sustained viral response (SVR)12 visit (post-partum)**

Follow-up is ongoing

HIV/HCV Co-infection: An AETC National Curriculum

Slide courtesy of Catherine Chappell, CROI 2019 Abstract #87
Recruitment: October 2016 to October 2018

170 HCV+ pregnant women

29 patients screened

9 enrolled

9 completed study medication and delivered

9 infants enrolled

Screen Fails (n=20)
- 5 genotype 2
- 5 genotype 3
- 4 ongoing drug use
- 3 declined to participate
- 2 not delivering at Magee
- 1 APRI score >1

8 completed SVR assessment, 1 still in follow-up

5 have completed 1 year follow-up, 4 still in follow-up

100% SVR

Slide courtesy of Catherine Chappell, CROI 2019 Abstract #87
Take home:

- Screening for HCV in pregnant women is important for early identification and to guide testing in infant
- Emerging data of safety and efficacy, PK data pending
- Difficult conversation, larger studies are needed
What else?
HBV Reactivation

Definition:

• Loss of HBV immune control in a patient with inactive or “resolved” HBV infection

Clinically:

• Ranges from subclinical to fatal hepatitis
• Rise in HBV DNA
• ALT increase (mild to very dramatic)
• May progress to liver failure/death despite antiviral therapy

Agents Reported to Cause HBV Reactivation

Risk Stratification

Host-

- HBsAg+
- Isolated HBcAb+
- HBsAb and cAb+

Drug-

- Rituximab
- Cytotoxic chemotherapy
- DAA

Immunomodulatory Therapy

- Anti-TNF (infliximab, adalimumab, etanercept)
- Anti-TNF (infliximab, adalimumab, etanercept)
- Other (rituximab, cyclosporine)
- Anti-TNF (infliximab, adalimumab, etanercept)
- Antimetabolite (methotrexate)

- Purine Analogues (azathioprine/6mp)
- Steroids (prednisone, budesonide)

FDA Drug Safety Communication: FDA warns about the risk of hepatitis B reactivating in some patients treated with direct-acting antivirals for hepatitis C

Safety Announcement

[10-04-2016] The U.S. Food and Drug Administration (FDA) is warning about the risk of hepatitis B virus (HBV) becoming an active infection again in any patient who has a current or previous infection with HBV and is treated with certain direct-acting antiviral (DAA) medicines for hepatitis C virus. In a few cases, HBV reactivation in patients treated with DAA medicines resulted in serious liver problems or death.
Between November 22, 2013 and July 18, 2016, 24 unique cases with confirmed HBV reactivation were identified, 5 more later added.

Case definition:
- Temporal association with HCV DAA initiation AND
- Evidence of increase in HBV DNA level or HBsAg seroconversion from negative to positive

HBV reactivation usually occurred within 4-8 weeks (average-52 days) of DAA initiation.

Fatal and life-threatening events in 3 patients (deaths-2, liver transplant-1).

A delay in identification and treatment of HBV reactivation associated with DAA therapy was noted.
What do the guidelines say?

- All patients initiating HCV DAA therapy should be assessed for HBV coinfection with HBsAg, anti-HBs, and anti-HBc. Rating: Class IIa, Level B
- For HBsAg+ patients who are not already on HBV suppressive therapy:
  - Start on NA therapy if criteria met per GL
  - Monitoring of HBV DNA levels during and immediately after DAA therapy for HCV is recommended and antiviral treatment for HBV should be given if HBV DNA changes >10 fold from BL or >10,000 if previously <LLOQ. Rating: Class IIa, Level B
  - Start on NA therapy for prophylaxis for those with low level DNA <1000 or <LLOQ, continue for 12 weeks
Take home:

- HBVr does occur in setting of DAA therapy, although unclear it is more common
- HBVr is rare in isolated HBcAb and further testing not recommended unless ALT increase
- Prophylaxis is recommended by EASL while AASLD/IDSA provides as option vs monitoring ( риск of withdrawal of prophylaxis? )

HIV/HCV Co-infection: An AETC National Curriculum
Management Post-SVR

- When do you stop testing for HCV RNA?
- Do liver enzymes (AST, ALT) normalize? (what is normal?)
- Did patient have steatosis on imaging?
- Does patient drink ETOH?
- Did patient have severe fibrosis on pre-treatment assessment?
- HCC screening, CP and MELD monitoring, ?EGD
- Is patient at risk of re-exposure?
Extras
HCV Reinfection: High in HIV-infected persons

Proportion free from reinfection vs. Time (years)

Number at risk:
- People: 552, 471, 373, 272, 198, 131

95% CI Survivor function

Ingiliz et al, J Hep 2016
Carollo et al. CROI 2019 Abstract #86
HCV Reinfection: High in HIV-infected persons

Proportion free from reinfection

Number at risk: 552

Person/years: 4.4/100

Ingiliz et al, J Hep 2016
Carollo et al. CROI 2019 Abstract #86
Take Home on Re-infection

- Re-infection rate in NYC (4.4/100) similar to areas of Europe
- In era of TasP, inadequate level of HCV treatment among MSM in NYC
- Gap in US in incident HCV infection rates and re-infection rates – target populations with higher prevalence and transmission risks for elimination efforts
- Need to treat early
- Prevention is essential....

Poster 596- HPTN 078- high rates of HCV exposure in MSM without HIV (~20%), not associated with HIV Infection
Poster 598- MSM cohort recently acquired HCV, 40% without HIV infection, 67% sexual transmission
Treat early or treat as chronic?

Rockstroh et al: N=26, HIV infected, later treatment, asymptomatic

Deterding et al: N=20, not HIV infected, immediate treatment, primarily symptomatic
HCV Infection - Treatment is Prevention

- Declining HCV incidence in Dutch HIV+ MSM after unrestricted access to HCV therapy – Boerekamps et al. Clin Inf Dis, 2018 in press

Cost-saving
Cost-effective (ICER>$0/QALY and <$100,000/QALY)
Not cost-effective (ICER>$100,000/QALY)

Spontaneous clearance rate

SVR rate of treatment of acute HCV

Number of acute HCV infections
Ledipasvir and Tenofovir

AUC\textsubscript{tau} (ng.h/mL)

<table>
<thead>
<tr>
<th>Combination</th>
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<tr>
<td>LDV/SOF + EFV/TDF/FTC</td>
<td>3600 (4400)</td>
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<td>LDV/SOF + RPV/TDF/FTC</td>
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German et al, Clin Pharm 2014; German et al. CROI 2015 Abstract 82; Naggie et al. NEJM 2015
Velpatasvir and Tenofovir (TDF)

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ASTRAL 5
SOF/VEL
Unboosted
N=35

German et al, Clin Pharm 2014; German et al. CROI 2015 Abstract 82; Naggie et al. NEJM 2015; ASTRAL-5 unpublished data
Velpatasvir and Tenofovir (TDF)

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ASTRAL 5

SOF/VEL

Unboosted

N=35

Boosted

N=56

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DDI with Glecaprevir/pibrentasvir

- P-GP, BCRP, OATP inhibitors and weak inhibitors of P450 isoenzymes (CYP3A, 1A2) and UGT1A1
- Substrates of P-GP, BCRP and glecaprevir is substrate of OATP1B1/3
- Not Recommended
  - Carbamazepine
  - St. John’s wort
  - Rifampin
  - Ethinyl Estradiol
  - ARVs: EFV, ATV, DRV, LPV
  - Statin: Atorva, Lova, Simva
  - Cyclosporine

Figure 3. Interaction between ABT-493 and ABT-530 with Rilpirvirine (Central Value Ratios and 90% CIs)

Rockstroh et al. EASL 2017, Kosloski et al. CROI
DDI with Glecaprevir/pibrentasvir

- P-GP, BCRP, OATP inhibitors and weak inhibitors of P450 isoenzymes (CYP3A, 1A2) and UGT1A1
- Substrates of P-GP, BCRP and glecaprevir is substrate of OATP1B1/3
- Not Recommended
  - Carbamazepine
  - St. John’s wort
  - Rifampin
  - Ethinyl Estradiol
  - ARVs: EFV, ATV, DRV, LPV
  - Statin: Atorva, Lova, Simva
  - Cyclosporine

Figure 4. Interaction between ABT-493 and ABT-530 with Raltegravir (Central Value Ratios and 90% CIs)

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Compensated Cirrhosis 2 fold increase

Rockstroh et al. EASL 2017, Kosloski et al. CROI
DDI with SOF/VEL/VOX

- P-GP, BCRP, OATP inhibitors
- Substrates of P-GP, BCRP and voxilaprevir is substrate of OATP1B1/3. VEL and VOX with substrate of multiple CYP isoenzymes
- Not Recommended
  - Amiodarone
  - Carbamazepine (antiepileptic)
  - St. John’s wort
  - Rifampin
  - ARVs: EFV, ATV, TPV
  - Statin: Rosuva, pitava
  - Cyclosporine
- Omeprazole
- elvitegravir/cobicistat, ?DRV/r

Effect of SOF/VEL/VOX on HIV ARV PK
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Garrison et al, Clin Pharm AVT 2017
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Effect of HIV ARV Regimens on VOX PK

HIV/HCV Co-infection: An AETC National Curriculum

Garrison et al, Clin Pharm AVT 2017
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  - Statin: Rosuva, pitava
  - Cyclosporine
- Omeprazole
- elvitegravir/cobicistat, ?DRV/r

Effect of HIV ARV Regimens on VOX PK

Compensated Cirrhosis 2 fold increase