New Era in the Management of Hepatitis C

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First diagnosed in 1989, hepatitis C virus is a major public health problem affecting 180 million people worldwide. The percentage of people who are seropositive for anti-HCV antibodies worldwide is estimated to have increased from 2.3% to 2.8% between 1990 to 2005. Most patients (80-85%) who become acutely infected cannot clear the virus and progress to chronic infection. The effects of chronic infection include cirrhosis, portal hypertension, hepatic decompensation with encephalopathy and hepatocellular carcinoma. The landscape of treatment has evolved substantially since the introduction of highly active DAAs in 2011.
Natural History


- **Exposure (Acute phase)**
  - Resolved: 15%-45%
  - Stable: 75%-95%

- **Chronic**
  - 55%-85%

- **Cirrhosis**
  - 5%-25%
  - Over 20-30 Years

- **Liver Decompensation (5%/year)**
  - HCC (2%-8%/year)
Goals of Hepatitis C Treatment

- Viral Eradication
- Delay fibrosis progression
- Alleviate symptoms
- Prevent complications
  - Cirrhosis
  - Liver decompensation
  - HCC
  - Death
- Improve tolerability of medications
- Maximize quality-of-life
Evolution of Hepatitis C Management

Screening and Baseline work up

* One-time HCV testing is recommended for persons born between 1945 and 1965*, without prior ascertainment of risk. **Rating:** Class I, Level B

* Other persons should be screened based on risk factors

  * IVDU or Intranasal illicit drug use
  * Long-term hemodialysis (ever)
  * Tattoo, Needle sticks, sharps, or mucosal exposures to HCV-infected blood
  * Children born to HCV-infected women
  * Prior recipients of transfusions or organ transplants before July 1992 or clotting 1987
  * Incarcerated
  * HIV infection
  * Unexplained chronic liver disease Solid organ donors

**Rating:** Class I, Level B
## Commercially Available Anti-HCV Screening Assays

<table>
<thead>
<tr>
<th>Assay</th>
<th>Manufacturer</th>
<th>Format</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abbott HCV EIA 2.0</td>
<td>Abbott</td>
<td>EIA (Manual)</td>
</tr>
<tr>
<td>Advia Centaur HCV</td>
<td>Siemens</td>
<td>CIA (Automated)</td>
</tr>
<tr>
<td>ARCHITECT Anti-HCV</td>
<td>Abbott</td>
<td>CMIA (Automated)</td>
</tr>
<tr>
<td>AxSYM Anti-HCV</td>
<td>Abbott</td>
<td>MEIA (Automated)</td>
</tr>
<tr>
<td>OraQuick HCV Rapid Antibody Test</td>
<td>OraSure</td>
<td>Immunochromatographic (Manual)</td>
</tr>
<tr>
<td>Ortho HCV Version 3.0 EIA</td>
<td>Ortho</td>
<td>EIA (Manual)</td>
</tr>
<tr>
<td>VITROS Anti-HCV</td>
<td>Ortho</td>
<td>CIA (Automated)</td>
</tr>
</tbody>
</table>

Anti-HCV = HCV antibody; EIA = enzyme immunoassay; CIA = chemiluminescent immunoassay; MEIA = microparticle enzyme immunoassay; CMIA = chemiluminescent microparticle immunoassay
An anti-HCV test is recommended and if positive, HCV RNA test should follow. 
Rating: Class I, Level A

When should a HCV RNA test be done upfront?
- exposure within the past 6 months
- immunocompromised
- Suspicion for reinfection
  Rating: Class I, Level C
Abstinence from alcohol  Rating: Class IIa, Level B
Evaluation for HBV and HIV  Rating: Class IIb, Level B
Evaluation for advanced fibrosis (liver biopsy, imaging, or noninvasive markers)
HCV treatment strategy
Screening for HCC  Rating: Class I, Level B
Hep A and B vaccines  Rating: Class IIa, Level C
Avoiding HCV transmission  Rating: Class I, Level C
Women of childbearing age should be educated to not become pregnant on RBV-containing antiviral regimens, and for up to 6 months after stopping.  Rating: Class I, Level C
Referral to a practitioner who is prepared to provide comprehensive management including consideration of antiviral therapy  Rating: Class IIa, Level C
Strategies to prevent transmission

- Do not share toothbrushes, razors or other shaving equipment
- Cover any bleeding wound
- Stop using illicit drugs.
- Not to donate blood and to discuss HCV serostatus prior to donation of body organs, other tissue, or semen.
- Use barrier precautions
- Proper cleaning of blood spills
Work-up prior to starting Therapy

- **Quantitative HCV RNA Rating**: Class I, Level A
- **HCV genotype Rating**: Class I, Level A
- **Drug-drug interactions**
- **CBC**
- **INR**
- **LFT (albumin, total and direct bilirubin, ALT, AST)**
- **TSH if IFN is used**
- **GFR**
- **ANA**

**Rating for all statements above**: Class I, Level C
Fibrotic Progression in Viral Hepatitis

- Liver: Mild, Moderate, Severe
- Cirrhosis: (mild), (severe)
- Hepatocellular carcinoma

There are at least 3 methods to stage

**Accepted staging methods**
- 1. Liver Biopsy
- 2. Blood markers
- 3. Elastography
- 4. Combination of 1-3

**Not for staging**
- 1. Viral load
- 2. HCV Genotype
- 3. Ultrasound
- 4. CT scan or MRI

**Liver Biopsy** is an imperfect Method to Stage as you are sampling 1/50,000 of the entire liver mass, the biopsies are usually too small, there is potential for C/C and they are more Expensive ($1500-2000 USD)

**Serum Markers** can predict liver Fibrosis
- **Fibrotest**: alpha2-macroglobulin, apolipoprotein A1, GGT, haptoglobin, total Bili
- **Fib-4**: AST, ALT, Platelet count, Age
- **APRI**: AST, platelet counts
Progression of Fibrosis in Viral Hepatitis on Biopsy (Metavir)

No Fibrosis

Stage 1
Fibrous expansion of some portal areas

Stage 2
Fibrous expansion of most portal areas with occasional portal to portal bridging

Stage 3
Fibrous expansion of portal areas with marked bridging (portal-to-portal and portal-to-central)

Stage 4
Cirrhosis

Cirrhotic Liver

**Current Indications for Treatment**

* **Highest Priority for Treatment**
  - Metavir F3/F4
  - Organ Transplant
  - Cryoglobulinemia / vasculitis
  - MPGN/ Nephrotic syndrome

* **High Priority for Treatment Owing to High Risk for Complications**
  - Metavir F2
  - Coinfection with HIV or HepB
  - Coexisting Liver disease
  - Diabetes
  - Fatigue
  - PCT (Porphyria Cutanea Tarda)

* **Elevated Risk of HCV Transmission**
  - MSM with high-risk sexual practices
  - Active IVDU
  - Incarcerated
  - Hemodialysis
  - Women of child-bearing potential wishing to get pregnant
  - HCV-infected health care workers who perform exposure-prone procedures
HCV Life cycle

- SS RNA virus that enters the hepatocyte via endocytosis mediated by at least 4 co-receptor molecules.

- Following internalization in the cytoplasm its + stranded RNA is uncoated → translation into ten mature peptides.

- These are cleaved by both host proteases and both virally encoded proteases known as NS3-4a.

- These mature peptides go on to reside on the ER forming a replication complex and contains the NS5 RNA dependent RNA polymerase.

- It catalyzes the RNA + strand into its - strand intermediate which in turn serves as the template for new + strand synthesis.

- These are then packaged with core and envelop glycoprotein into mature virions which then exit the cell via exocytosis.

Targets for Direct Acting Antivirals

### Classes of Direct Acting Agents

<table>
<thead>
<tr>
<th>Protease Inhibitors</th>
<th>NS5A inhibitors</th>
<th>Polymerase Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simeprevir</td>
<td>Ledipasvir</td>
<td>Sofosbuvir</td>
</tr>
<tr>
<td>Paritaprevir</td>
<td>Ombitasvir</td>
<td>Dasabuvir</td>
</tr>
<tr>
<td>Telaprevir</td>
<td>Daclatasvir</td>
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<tr>
<td>Boceprevir</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Protease Inhibitor Simeprevir/Paritaprevir</th>
<th>NS 5A inhibitor Ledipasvir Daclatasvir Ombitasvir</th>
<th>Polymerase Inhibitor Sofosbuvir Dasabuvir</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotypic activity</td>
<td>GT 1,2,4,5,6</td>
<td>Pangenotypic</td>
<td>Pangenotypic</td>
</tr>
<tr>
<td>Dosing</td>
<td>daily (with food)</td>
<td>daily</td>
<td>Daily</td>
</tr>
<tr>
<td>Interactions</td>
<td>CYP3A4</td>
<td>Low potential</td>
<td>Low potential</td>
</tr>
<tr>
<td>Pregnancy Category</td>
<td>C</td>
<td>?</td>
<td>B</td>
</tr>
<tr>
<td>Safety</td>
<td>Well tolerated</td>
<td>Well tolerated</td>
<td>Well tolerated</td>
</tr>
</tbody>
</table>
### DAAs in Late-Stage Clinical Development for Chronic HCV Infection

<table>
<thead>
<tr>
<th>NS3/4A Protease Inhibitors</th>
<th>Nucleotide NS5B Polymerase Inhibitors</th>
<th>Non-Nucleoside NS5B Polymerase Inhibitors</th>
<th>NS5A Replication Complex Inhibitors</th>
<th>Cyclophilin Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Approved</strong></td>
<td>Simeprevir</td>
<td>Sofosbuvir</td>
<td>Dasabuvir</td>
<td>Ledipasvir Ombitasvir Daclatasvir</td>
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<tr>
<td></td>
<td>Boceprevir</td>
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<tr>
<td></td>
<td>Telaprevir</td>
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<tr>
<td></td>
<td>Paritaprevir/r</td>
<td></td>
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<tr>
<td><strong>Phase 3</strong></td>
<td></td>
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<tr>
<td></td>
<td>Asunaprevir*</td>
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<tr>
<td></td>
<td>Grazoprevir</td>
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<tr>
<td></td>
<td>Beclabuvir</td>
<td></td>
<td></td>
<td>Elbasvir GS-5816</td>
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<tr>
<td><strong>Phase 2</strong></td>
<td>GS-9256</td>
<td>ACH-3422</td>
<td>ABT-072</td>
<td>ABT-530 SCY-635</td>
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<td></td>
<td>GS-9451</td>
<td>MK-3682</td>
<td>GS-9669</td>
<td>GSK2336805</td>
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<td></td>
<td>ABT-493</td>
<td></td>
<td>TMC647055</td>
<td>MK-8408</td>
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<tr>
<td></td>
<td>Sovaprevir</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>GS-9857</td>
<td></td>
<td></td>
<td>PPI-668</td>
</tr>
</tbody>
</table>

Not all inclusive.
Hepatitis C Genotypes

- Worldwide distribution of HCV genotypes 1 to 6.
- Source: Clinical Gastroenterol Hepatol 3: 597.
Pipeline for Hepatitis C
Mix and Match Agents

Polymerase Inhibitor

NS5A Inhibitor

Protease Inhibitor

RBV
Genotype 1a/b

OMB+PAR+RTV+DAS+RBV  LDV+SOF  DAC+SOF +_RBV

SAPPHIRE-1  PEARL-4  TURQUOISE-II  ION-1  ION-2  ION-3  ALLY-2  ALLY-1

GT1a/b  GT1a-/RBV  12 vs. 24 wk  100% cirrhosis
GT1a/b  16% cirrhosis
GT1a/b  +/− RBV  8 vs. 12 wk  No cirrhosis
12 vs. 24 wk  Non-cirrhotics
12 vs. 24 wk  Cirrhotics

96  97  89  99  96  94  100  97

Genotype 1 - Three options

- Ledipasvir/sofosbuvir:
  - Genotype 1a and 1b (no cirrhosis and compensated cirrhosis): I-A.
- Sofosbuvir + simeprevir:
  - Genotype 1a and 1b (no cirrhosis and compensated cirrhosis): I-A.
- Ombitasvir/paritaprevir/r + dasabuvir + RBV:
  - Genotype 1a and 1b (no cirrhosis and compensated cirrhosis): I-A.
- Daclatasvir + sofosbuvir + RBV:
  - Genotype 1a and 1b (no cirrhosis: I-B; compensated cirrhosis: IIa-B).

Reference
<table>
<thead>
<tr>
<th>Duration of Therapy (weeks)</th>
<th>Genotype 1a</th>
<th>Genotype 1b</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No Cirrhosis</td>
<td>With Cirrhosis*</td>
</tr>
<tr>
<td>Ledipasvir/sofosbuvir (90/400 mg qd)</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>Sofosbuvir (400 mg qd) + simeprevir (150 mg qd) + RBV†</td>
<td>12 (no RBV)</td>
<td>24 (without Q80K)</td>
</tr>
<tr>
<td>Ombitasvir/paritaprevir/r (25/150/100 mg qd) + dasabuvir (250 mg bid) + RBV</td>
<td>12 (with RBV)</td>
<td>24† (with RBV)</td>
</tr>
<tr>
<td>Daclatasvir (80 mg qd)† + sofosbuvir (400 mg qd) + RBV</td>
<td>12 (no RBV)</td>
<td>24</td>
</tr>
</tbody>
</table>

Weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]).
*Compensated cirrhosis.
†Role of RBV is unclear, awaiting results from larger phase 3 studies for clarification.
*12 weeks may be considered for some patients based on prior treatment history.
†Dose may need to increase or decrease when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively.

GT2 infection

AASLD and IDSA: Regimens for HCV Genotype 2

**Treatment-Naïve Patients**

- **Sofosbuvir (400 mg qd) + RBV for 12 weeks**
  - (16 weeks is recommended for cirrhotics*)
- **Daclatasvir (60 mg qd)† + sofosbuvir (400 mg qd) for 12 weeks**
  - (unable to tolerate RBV)

**Failure of Prior PR Treatment**

- **Sofosbuvir (400 mg qd) + RBV for 16 or 24 weeks**
  - *Alternative*: sofosbuvir (400 mg qd) + PR for 12 weeks (IFN eligible)

**Failure of Prior Sofosbuvir + RBV or PR Failure**

- **Sofosbuvir (400 mg qd) + PR for 12 weeks (IFN eligible)**
- **Daclatasvir (60 mg qd)† + sofosbuvir (400 mg qd) + RBV for 24 weeks**
  - (IFN-ineligible)

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Weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]).
PR: pegIFN + RBV.
*Compensated cirrhosis.
†Dose may need to increase or decrease when used concomitantly with cytochrome P450 3A4 inducers and inhibitors, respectively.
Sofosbuvir +RBV for GT3 infection, naïve patients

- Naïve, no cirrhosis
  - 12 week: 65
  - 24 week: 94
- Naïve with cirrhosis
  - 12 week: 37
  - 24 week: 92

Peg-IFN + Sofosbuvir +RBV x 12 wks for GT3

LONESTAR 2 included high rate of cirrhotics (55%) and non responders (85%)

2/4 nonresponders in GT3
LONESTAR2 group were lost to f/u

ALLY-3 Study: Treatment Outcomes
Daclatasvir + Sofosbuvir in HCV Genotype 3

- Overall SVR12 rates were 90% and 86% among treatment-naïve and treatment-experienced patients, respectively. However, SVR12 rates were substantially lower among patients with cirrhosis (58% and 69%, respectively).\(^1\)
- No virologic breakthroughs
- Virologic relapse (n=16)
  * Cirrhosis (n=11)
  * Y93H at relapse (n=9)
- Generally safe and well tolerated
  * No discontinuations due adverse events
- Further options for optimizing SVR rates with daclatasvir + sofosbuvir in genotype 3 patients with cirrhosis are being evaluated

SVR12 Rates

AASLD and IDSA: Regimens for HCV Genotype 3 Patients

**Treatment-Naïve Patients**
- Sofosbuvir (400 mg qd) + PR for 12 weeks
- Daclatasvir (60 mg qd)† + sofosbuvir (400 mg qd) for 12 weeks (no cirrhosis)
- Daclatasvir (60 mg qd)† + sofosbuvir (400 mg qd) + RBV for 24 weeks (cirrhotics*)
  
  *Alternative*: sofosbuvir (400 mg qd) + RBV for 24 weeks (IFN ineligible)

**Failure of Prior PR Treatment**
- Sofosbuvir (400 mg qd) + PR for 12 weeks (IFN eligible)
- Daclatasvir (60 mg qd)† + sofosbuvir (400 mg qd) for 12 weeks (no cirrhosis)
- Daclatasvir (60 mg qd)† + sofosbuvir (400 mg qd) + RBV for 24 weeks (cirrhotics*)
  
  *Alternative*: none

**Failure of Prior Sofosbuvir + RBV or PR Failure**
- Sofosbuvir (400 mg qd) + PR for 12 weeks (IFN eligible)
- Daclatasvir (60 mg qd)† + sofosbuvir (400 mg qd) + RBV for 24 weeks

Weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]).
PR: pegIFN + RBV.
*Compensated cirrhosis.
†Dose may need to increase or decrease when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors.

**Decompensated Cirrhosis**  
*CTPclass B or C*  
Daily fixed-dose combination ledipasvir /sofosbuvir and RBV for 12 weeks. Rating: Class IIb, Level C  
-or-  
24 weeks if cannot tolerate RBV. Rating: Class IIb, Level C

**HIV/HCV Coinfection**  
HIV/HCV-coinfected persons should be treated and retreated the same as persons without HIV infection, with special consideration to drug-drug interactions.

**Renal Impairment**  
-CrCl >30 mL/min- no dosage adjustment is required. Rating: Class I, Level A;  
-CrCl below 30 mL/min, daily fixed-dose combination of paritaprevir/ritonavir/ombitasvir/dasabuvir +/- RBV. Rating: Class IIb, Level C

**Recurrent Hepatitis C post Liver transplant**  
Ldaclatasvir+Sofosbuvir+RBV(low dose) x12 weeks or Ledipasvir/sofosbuvir with RBV for 12 weeks is recommended for patients. Rating: Class I, Level B;  
Alternative: Daily fixed-dose combination of paritaprevir/ritonavir/ombitasvir/ dasabuvir and weight-based RBV for 24 weeks
Recommended Pre-Treatment Assessments in HIV/HCV-Coinfected

- **Liver disease status**
  - HCV RNA, HCV genotype, AFP* and US for HCC, HBV status (HBsAg, anti-HBc), anti-HAV IgG, assessment of fibrosis, MELD calculation

- **HIV disease status**
  - Presence or history of OIs, HIV-associated malignancy, **CD4 cell count, HIV RNA, details of ART**

- **Factors** precluding HCV therapy or **requiring control** prior to initiating HCV therapy
  - TSH; screen for depression or other psychiatric disease†; CBC; **blood sugar**; history of significant cardiac, renal, or pulmonary disease; fundus examination†; **beta HCG (women of childbearing potential)**; **social support**; treatment adherence

*Most hepatologists recommend; not recommended by AASLD.

†In the IFN-free era, some clinicians may question the need for screening for depression (unless if it affects adherence) conducting a fundus examination.

SVR12 rates were >94% overall and regardless of prior HCV treatment status or presence of cirrhosis at baseline.\textsuperscript{1} No impact on SVR12 rate: gender, HCV genotype, baseline HCV RNA, IL28B genotype, cirrhosis, prior HCV treatment, ART regimens, and baseline CD4 count. Lower SVR12 rate observed among black patients (90%). Naggie S, et al. \textit{N Engl J Med.} 2015;373:705-713
The SVR12 rates in the 12- and 24-week arms was 94% and 91%, respectively.\(^1\)

There were a total of 2 virologic failures at the time of this preliminary report. Both were genotype 1a, prior PR null responders, and cirrhotic at baseline.\(^1\)

There were a total of 5 HIV RNA breakthroughs.\(^1\)

There were no treatment-emergent serious adverse events or discontinuations due to adverse events. RBV dose reduction was required in 6 patients, all of whom achieved an SVR.\(^1\)

The most common adverse events included fatigue, insomnia, nausea, and headache. Indirect hyperbilirubinemia was most common laboratory abnormality (17/63 overall; 15 of 17 were receiving atazanavir-based ART).\(^1\)

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ALLY-2 Study: SVR12 Rates for Daclatasvir + Sofosbuvir in HIV/HCV Coinfection

SVR12 rates were highest among patients receiving the 12-week regimen. Patients in the 8-week treatment arm had lower SVR12 rates across all 3 genotypes.12-week regimen: no impact of race, baseline HCV RNA, cirrhosis, baseline NS5A RAVs, or ART regimens on SVR12.

HIV/HCV-coinfected persons should be treated and retreated the same as persons without HIV infection, after recognizing and managing interactions.

Many HIV/HCV-coinfected patients are on ART regimens with drug interactions that absolutely preclude otherwise recommended DAA regimens.

- Switching an optimized ART regimen carries risks
  - Adverse effects
  - HIV RNA breakthrough
- To avoid unnecessary switching of effective ART, daclatasvir and sofosbuvir are recommended
  - Compatible with nearly all ART regimens

PR: pegIFN + RBV.
### AASLD, IDSA, and DHHS: Recommendations Related to HCV Medication Interactions With ART

<table>
<thead>
<tr>
<th>Medication Combination</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ledipasvir/sofosbuvir</td>
<td>Increases tenofovir DF levels. Avoid concomitant use if CrCl &lt;60 mL/min. Avoid ledipasvir/sofosbuvir in patients in on RTV-boosted PI regimens containing tenofovir DF (unless ART can’t be changed and the urgency for treatment is high).</td>
</tr>
<tr>
<td>Ombitasvir/paritaprevir/ritonavir + dasabuvir</td>
<td>No substantial drug interactions with raltegravir (probably dolutegravir), enfuvirtide, tenofovir DF, emtricitabine, lamivudine, atazanavir. The dose of ritonavir used for boosting HIV PIs may need to be adjusted (or held) until HCV therapy is completed. HIV PI should be administered at the same time as the HCV treatment.</td>
</tr>
<tr>
<td>Simeprevir</td>
<td>No substantial interactions with raltegravir (probably dolutegravir), rilpivirine, maraviroc, enfuvirtide, tenofovir DF, emtricitabine, lamivudine, abacavir.</td>
</tr>
<tr>
<td>Daclatasvir</td>
<td>Requires dose adjustment with RTV-boosted atazanavir (decrease to 30 mg/day) and efavirenz or etravirine (increase to 90 mg/day).</td>
</tr>
</tbody>
</table>

**For combinations expected to increase tenofovir levels, baseline and ongoing assessment for tenofovir DF nephrotoxicity is recommended.**

All ART drug switches, if needed, should be done in collaboration with the HIV practitioner. Expert consultation is recommended for ART and HCV direct-acting antiviral agents not addressed in the above table.

Monthly clinic visits (medication adherence, adverse events and drug-drug interactions with newly prescribed medications).

CBC, GFR, LFTs are recommended every 4 weeks. Discontinue if > 10-fold increase in ALT at week 4 or any increase with symptoms of weakness, nausea, vomiting, or jaundice, or accompanied by increased bilirubin, alkaline phosphatase, or international normalized ratio. If however asymptomatic and ALT <10-fold - monitor at week 6 and week 8. Rating: Class I, Level B

TSH is recommended every 12 weeks for patients receiving IFN.

HCV viral load testing after 4 weeks and at end of treatment and at 12 weeks following the completion of therapy is recommended. And can be considered at 24 weeks following completion. Rating: Class I, Level B.

If HCV viral load is detectable at week 4 of treatment, repeat at week 6. If > 10-fold (>1 log_{10} IU/mL) then discontinue. Significance of a lower level at weeks 6 or week 8 is unknown.
Predictors of relapses to sofosbuvir-based regimens

Who will do poorly with currently available SOF-based regimens?

SVR12 rates by Number of negative predictors

<table>
<thead>
<tr>
<th>Predictors</th>
<th>RBV+SOF 12 week</th>
<th>RBV+SOF 24 week</th>
<th>PEG+RBV+SOF 12 week</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment-experienced</td>
<td>IL28B non-CC</td>
<td>Male sex</td>
<td>Weight &gt;75 Kg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cirrhosis</td>
<td>High Viral load &gt;800,000IU/ml</td>
</tr>
</tbody>
</table>

Fontaine et al. EASL 2014 Abst 66.
Assessment for HCV recurrence or reinfection with a **quantitative HCV RNA** is ongoing. Rating: Class I, Level A

Surveillance for hepatocellular carcinoma with **twice-yearly ultrasound** testing is recommended for Metavir stage F3 or F4 who achieve an SVR. Rating: Class I, Level C

**A baseline endoscopy** is recommended to screen for varices if cirrhosis is present. Rating: Class I, Level C

**Monitoring for HCV during chemotherapy and immunosuppression.** Prospective monitoring for HCV recurrence among patients who achieved a SVR and who are receiving immunosuppressive treatment is **NOT routinely recommended.** Rating: Class III, Level C
Primary Care issues /monitoring

- Serious Slowing of Heart rate when antiarrythmic drug **amiodarone** is taken together with Sofosbuvir with another DAA
- Coadministration of **anticonvulsants** can reduce the effect of polymerase inhibitor, protease inhibitor and NS5A inhibitor
- Coadministration with **Rifamycins** can reduce the effect of polymerase inhibitor, HCV protease inhibitor
- Herbal supplements like **St. Johns wort** can reduce the effect of polymerase inhibitor, HCV protease inhibitor
- Use of **Ribavirin** can cause birth defects or death of fetus
- The BPH agent **alfluzosin** is contraindicated with HCV PI like simeprevir and paritaprevir as they inhibit CYP3A4
- Increased QT prolongation if **Gemfibrozil** or **Clopidrogel (PLAVIX)** used with Dasabuvir
- Acute **Ergot toxicity** is administered with ritonavir
- Potential for rhabdomyolysis/myopathy with **statins** and HCV PI
- Potential for priapism with **sildenafil** and HCV PI
- Increased sedation or respiratory depression if **benzodiazepines** co-administered with ritonavir or HCV PI
HCV antibody and HCV RNA testing are recommended when acute HCV infection is suspected due to exposure, clinical presentation or raised LFTs (Class 1, Level C)
Preexposure or postexposure prophylaxis is NOT recommended. 
Rating: Class III, Level C

Monitor ALT until normalizes and Monitor HCV RNA (eg, every 4-8 weeks) for 6 - 12 months to determine spontaneous clearance. 
Rating: Class I, Level B

Counseling to avoid hepatotoxic insults - drugs (eg, acetaminophen) and alcohol and to reduce the risk of HCV transmission to others. 
Rating: Class I, Level C

Referral to an addiction medicine specialist if injection drug use. 
Rating: Class I, Level B
It is acceptable to delay treatment and monitor for spontaneous clearance until a minimum of 6 months.

If a decision has been made to initiate treatment during the acute infection period, monitoring HCV RNA for at least 12 weeks to 16 weeks is recommended to allow for spontaneous clearance before starting treatment. Rating: Class IIa, Level C

When the decision is made to initiate treatment after 6 months, treating as described for chronic hepatitis C is recommended owing to the high efficacy and safety of the current regimens. Rating: Class IIa, Level C

Alternative regimen for patients with acute HCV infection who are eligible to receive IFN.

PEG with or without RBV for 16 weeks (for those with HCV genotype 2 or 3 who have a rapid virologic response) to 24 weeks (for those with HCV genotype 1). Rating: Class II, Level A
What the future holds!
### Sofosbuvir + GS-5816 ± RBV in Treatment-Naïve, Non-Cirrhotic, HCV Patients (Genotypes 1-6)

**Phase 2**  
(Part A: 12 Weeks)

**Open-label**
**Treatment-naïve**
**Non-cirrhotic**
BMI ≥18 kg/m²
HCV RNA: ≥10K IU/mL

<table>
<thead>
<tr>
<th>Genotype 1</th>
<th>Genotype 3</th>
<th>Genotypes 2, 4-6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sofosbuvir + GS-5816 25 mg qd (n=27)</td>
<td>Sofosbuvir + GS-5816 25 mg qd (n=27)</td>
<td>Sofosbuvir + GS-5816 25 mg qd (n=11/7/0/4)</td>
</tr>
<tr>
<td>91%</td>
<td>93%</td>
<td>93%</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Sofosbuvir + GS-5816 100 mg qd (n=28)</td>
<td>Sofosbuvir + GS-5816 100 mg qd (n=27)</td>
<td>Sofosbuvir + GS-5816 100 mg qd (n=10/7/0/5)</td>
</tr>
<tr>
<td>100%</td>
<td>93%</td>
<td>4/6: 86/100</td>
</tr>
<tr>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

**Week 0 8 12 24**

Everson and Tran reported on a 2-part phase 2 trial to evaluate the efficacy and safety of sofosbuvir + GS-5816 ± RBV in patients with HCV. SVR12 rates ranged from 91% to 100% with 3 of 154 patients experiencing relapse.¹

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Sofosbuvir 400 mg qd.
Primary endpoint: SVR12.
Baseline demographics:
Male: 64%.
Age: 50 years.
Black: 8%.
Genotype 1a: 29%.
IL28B non CC: 82%.
HCV RNA (log10 IU/mL): 6.4.
Among treatment-naïve non-cirrhotics, the SVR12 rates were 33% and 87% in the 4- and 6-week arms, respectively. Among cirrhotic patients, SVR12 rates were 80% and 94% in the 6- and 8-week arms, respectively.\(^1\)

RUBY-1: Ombitasvir/Paritaprevir/r + Dasabuvir + RBV in Severe Renal Impairment or ESRD

- Non-cirrhotic HCV genotype 1
  - HCV RNA >1000 IU/mL
  - eGFR: <30 mL/min/1.73 m²
  - Hemoglobin ≥10 g/dL
  - Black/Hispanic: 85%
- Ombitasvir/paritaprevir/r + dasabuvir
  - Genotype 1a with RBV, genotype 1b: no RBV
- Primary outcome: SVR12
  - Interim SVR4 analysis (n=11)
- Safety (n=13)
  - No discontinuations due to adverse events
  - Hemoglobin reductions were managed with monitoring and RBV dose interruption (for 8/13 patients) and erythropoietin administration (for 4/13 patients)

C-SURFER: Grazoprevir/Elbasvir in HCV Genotype 1 Patients With Stage 4/5 Chronic Kidney Disease


Grazoprevir/elbasvir 100/50 mg qd.
Primary endpoint: SVR12 (modified ITT).
Chronic kidney disease stage 4 (eGFR 15-29 mL/min/1.73 m²) and 5 (eGFR <15 mL/min/1.73 m² or on dialysis).
Baseline demographics:
  Male: 73%.
  Black: 46%.
  Genotype 1a: 52%.
  Treatment-naïve: 80%.
  Cirrhosis: 6%.
  Diabetes: 34%
  Dialysis: 76%.
  CKD stage 4/5: 19%/81%.

The overall SVR12 (modified full-set analysis) rate was 99% (115/116). Efficacy was consistent across different subpopulations (ie, genotype 1a and 1b, diabetes, HD).¹

¹C-SURFER was an double-blind, placebo-controlled, phase 2/3 study evaluating 12 weeks of grazoprevir/elbasvir in HCV genotype 1 treatment-naïve and -experienced patients with stage 4/5 chronic kidney disease. The primary endpoint was SVR12.¹

Compensated cirrhosis allowed
No HBV or HIV
Take Home Points

* **One-time HCV testing** is recommended for persons born between 1945 and 1965, and others based on risk factors

* An anti-HCV test is recommended, but if immunocompromised host or suspicion for reinfection- **HCV RNA test upfront**

* **Education** regarding abstinence from alcohol, evaluation for HBV and HIV, administering Hep A and B, avoiding HCV transmission, and not become pregnant for up to 6 months after stopping RBV

* **For acute infection period**, monitoring HCV RNA for at least 12 weeks to 16 weeks is recommended to allow for spontaneous clearance before starting treatment.

* Current treatment selection requires the knowledge of **Genotype- but results from phase 3 trials for all-oral agents with pangenotypic activity against HCV are excellent, with well tolerated regimens and high SVR rates**

* **Highest Priority for Treatment** are individuals with Metavir F3/F4, Organ Transplant or ones with extrahepatic manifestations.

* There can be **serious drug-drug interactions** with commonly prescribed primary care medications (amiodarone, anticonvulsants, statins, gemfibrozil and BZD, sildenafil etc)

* **Surveillance for hepatocellular carcinoma** with twice-yearly ultrasound testing is recommended for Metavir stage F3 or F4 who achieve an SVR

* The long awaited highly effective **all oral – Interferon free** regimens are a reality and >90% effective, although currently come with a high price tag
<table>
<thead>
<tr>
<th>Treatment Regimen</th>
<th>Duration</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ledipasvir+Sofosbuvir (HARVONI)</td>
<td>12 week</td>
<td>$96500</td>
</tr>
<tr>
<td>Daclatasvir +Sofosbuvir</td>
<td>12 week</td>
<td>$60000 + $90000 = $150,000</td>
</tr>
<tr>
<td>Ombitasvir+Paritrepervir+Dasabuvir + RBV (VIEKIRA PAK) + RBV</td>
<td>12 week</td>
<td>$83320 + $2500 = $85820</td>
</tr>
<tr>
<td>Sofosbuvir +Simeprevir +RBV</td>
<td>12 week</td>
<td>$150,000</td>
</tr>
</tbody>
</table>

As the zenith in HCV therapeutic development approaches, it may now be possible to imagine the global eradication of Hepatitis C, but challenges remain!

Thank you!