AASLD/IDSA HCV treatment guidelines

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Disclosure Statement for Arthur Kim

Grant/research support to institution, last 12 months:
  Gilead Sciences (grant completed)
Consultant/Scientific Advisory Board: None
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I will discuss the following off-label use in this presentation:
Unapproved direct-acting agents (velpatasvir/sofosbuvir)
Treatment of acute HCV infection

Funding: National Institutes of Health
(National Institute of Allergy and Infectious Diseases,
National Institute of Drug Abuse)
Learning Objectives

• Describe the main treatment options for HCV infection
• List host and viral factors that influence the duration and/or type of antiviral treatment
What’s New and Updates/Changes:

This version of the Guidance has been updated to reflect several important developments, including the recent approval of elbasvir/grazoprevir, together with new information regarding the use of testing for HCV resistance associated variants. Click here for list of all updated sections.

Background of the Hepatitis C Guidance

New direct-acting oral agents capable of curing hepatitis C virus (HCV) infection have been approved for use in the United States. The initial direct-acting agents were approved in 2011, and many more oral drugs are expected to be approved in the next few years. As new information is presented at scientific conferences and published in peer-reviewed journals, health care practitioners have expressed a need for a credible source of unbiased guidance on how best to treat their patients with HCV infection. To provide healthcare professionals with timely guidance, the American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America (IDSA) have developed a web-based process for the rapid formulation and dissemination of evidence-based, expert-developed recommendations for hepatitis C management.

New sections will be added, and the recommendations will be updated on a regular basis as new information becomes available. An ongoing summary of “recent changes” will also be available for readers who want to be directed to updates and changes.

About Hepatitis C

An estimated 3 million to 4 million persons in the United States are chronically infected with HCV, and approximately half are unaware of their status. These individuals may ultimately progress to advanced liver disease and/or hepatocellular cancer. However, those outcomes can be prevented by treatment, which is rapidly improving and offers the potential of a cure to more patients than has been previously possible.

http://hcvguidelines.org
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.

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.
Only just the beginning of the end of hepatitis C

...heralding an era where all patients can be cured, even debating whether eradication is possible.

The main drawback ... is the huge price tag, which will make treatment out of reach for people in the developed and developing world...
The continuum of care in HCV infection in the U.S.
At least 3 million persons infected

Adapted from Holmberg et al. NEJM 2013
### Recommendations for One-time HCV testing

One-time HCV testing is recommended for persons born between 1945 and 1965,* without prior ascertainment of risk.

Other persons should be screened for risk factors for HCV infection, and one-time testing should be performed for all persons with behaviors, exposures, and conditions associated with an increased risk of HCV infection.

**Risk behaviors**
- Injection-drug use (current or ever, including those who injected once)
- Intranasal illicit drug use

**Risk exposures**
- Long-term hemodialysis (ever)
- Getting a tattoo in an unregulated setting
- Healthcare, emergency medical, and public safety workers after needlesticks, sharps, or mucosal exposures to HCV-infected blood
- Children born to HCV-infected women
- Prior recipients of transfusions or organ transplants, including persons who:
  - Were notified that they received blood from a donor who later tested positive for HCV infection
  - Received a transfusion of blood or blood components, or underwent an organ transplant before July 1992
  - Received clotting factor concentrates produced before 1987
  - Persons who were ever incarcerated

**Other**
- HIV infection
- Unexplained chronic liver disease and/or chronic hepatitis including elevated alanine aminotransferase levels
- Solid organ donors (deceased and living)

*Adapted from [http://hcvguidelines.org](http://hcvguidelines.org)*
Recommendation for HCV Testing those with Ongoing Risk Factors

Annual HCV testing is recommended for persons who inject drugs and for HIV-seropositive men who have unprotected sex with men. Periodic testing should be offered to other persons with ongoing risk factors for exposure to HCV.

Recommendations for Follow-up of Initial Testing

An anti-HCV test is recommended for HCV testing, and if the result is positive, current infection should be confirmed by a sensitive HCV RNA test.

Among persons with a negative anti-HCV test who are suspected of having liver disease, testing for HCV RNA or follow-up testing for HCV antibody is recommended if exposure to HCV occurred within the past six months; testing for HCV RNA can also be considered in persons who are immunocompromised.

Among persons at risk of reinfection after previous spontaneous or treatment-related viral clearance, initial HCV-RNA testing is recommended because an anti-HCV test is expected to be positive.

Quantitative HCV-RNA testing is recommended prior to the initiation of antiviral therapy to document the baseline level of viremia (ie, baseline viral load).

Testing for HCV genotype is recommended to guide selection of the most appropriate antiviral regimen.

If found to have positive results for anti-HCV test and negative results for HCV RNA by polymerase chain reaction (PCR), persons should be informed that they do not have evidence of current (active) HCV infection.

Adapted from http://hcvguidelines.org
Key issues to determine prior to initiation of treatment

**Goals of treatment**
Life expectancy
Extrahepatic conditions

**Factors that affect natural history:**
Alcohol use
HIV / Hepatitis B
Prior immunizations HAV / HBV / pneumococcus

**Factors that affect regimen choice/duration:**
Genotype
High viral load (for certain regimens)
Interferon/DAA experience (for some regimens)
Current medications
Cirrhosis (for many regimens)
  - If cirrhotic, compensated or decompensated?

**History / tests / interventions**
Hx, MELD
Hx, PE, cryoglobulins, urine protein

Alcohol screen
HIV / HBsAg
Immunizations HAV / HBV / PCV-13

HCV genotype / subtype
Quantitative HCV RNA
History / Chart review
Medication reconciliation
Determination of fibrosis / cirrhosis
  - Child-Turcotte-Pugh A/B/C

**Recommendations for Counseling those with Current (Active) HCV Infection and 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).
Key issues to determine prior to initiation of treatment

Factors that may affect access / adherence:
- Current psychosocial status
- Current drug use / alcohol
- Housing status
- Insurance status

Factors that affect regimen monitoring / safety:
- Advanced fibrosis / cirrhosis
- Renal function, baseline anemia (for RBV)
- Drug-drug interactions

Factors that may affect infection risk:
- Needle exposures, needle/sex partner status
- Pregnancy planning for young women
- Reinfection risks: Injection drug use, high risk sex

History / tests / interventions
- Hx, Social work consult
- Substance use disorder consult

- Counseling (household, sex)
- beta-HCG, OCPs
- Repeat HCV RNA yearly

Determine fibrosis/cirrhosis
- BUN/creatinine, Hgb/Hct
- Univ. of Liverpool website
Potential Therapeutic Targets in the HCV Replication Cycle

- Translation of HCV RNA
- Polyprotein processing
- NS2
- NS3
- NS4B
- NS5A
- NS5B
- RNA replication
- Fusion and uncoating
- Viral assembly
- Transport and release
- NS3/4A protease inhibitors - previr
- NS5B polymerase inhibitors - buvir
- NS5A inhibitors - asvir
- NSSA inhibitors

Adapted from slide courtesy Ray Chung
Possible combinations of HCV treatments then are applied to different viral genotypes.
Antiviral HCV treatments
(FDA-approved as of February 12, 2016)

<table>
<thead>
<tr>
<th>Monotherapies</th>
<th>Combination Therapies</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFN-2a</td>
<td>Daclatasvir + Sofosbuvir (GT1,3)*§</td>
</tr>
<tr>
<td>IFN-2b</td>
<td>Elbasvir + Grazoprevir (GT1,4)*</td>
</tr>
<tr>
<td>PEG-IFN 2a</td>
<td>Ledipasvir + Sofosbuvir (FDC, GT1,4,5,6)*§</td>
</tr>
<tr>
<td>PEG-IFN 2b</td>
<td>Paritaprevir / ritonavir / ombitasvir (FDC) + dasabuvir (GT1)</td>
</tr>
<tr>
<td></td>
<td>Paritaprevir / ritonavir / ombitasvir (FDC) (GT4)</td>
</tr>
<tr>
<td></td>
<td>Simeprevir + Sofosbuvir (GT1)</td>
</tr>
<tr>
<td>IFN-2a + Ribavirin</td>
<td></td>
</tr>
<tr>
<td>IFN-2b + Ribavirin</td>
<td></td>
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<tr>
<td>PEG-IFN 2a + Ribavirin*</td>
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<tr>
<td>PEG-IFN 2b + Ribavirin</td>
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<tr>
<td>PEG-IFN + ribavirin plus either:</td>
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<tr>
<td>Boceprevir (GT1)</td>
<td></td>
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<tr>
<td>Telaprevir (GT1)</td>
<td></td>
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<tr>
<td>Simeprevir (GT1)</td>
<td></td>
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<tr>
<td>In combination with other agents:</td>
<td></td>
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<tr>
<td>Sofosbuvir</td>
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</tbody>
</table>

*approved for HIV/HCV coinfection
§approved for GT1 - decompensated and post-liver
Predictors of relapse to sofosbuvir-based regimens

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

Results: Predictors of Relapse
Multivariate Regression Analysis (combined dataset)

<table>
<thead>
<tr>
<th>Factor</th>
<th>Odds Ratio</th>
<th>p-Value</th>
</tr>
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<tbody>
<tr>
<td>Treatment experienced</td>
<td>2.3</td>
<td>0.001</td>
</tr>
<tr>
<td>Male</td>
<td>2.3</td>
<td>0.01</td>
</tr>
<tr>
<td>Weight ≥75 kg</td>
<td>2.5</td>
<td>0.01</td>
</tr>
<tr>
<td>IL28B non-CC</td>
<td>3.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>4.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HCV RNA ≥800,000 IU/mL</td>
<td>4.7</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Foster et al. EASL 2014 Abstract 66
Predictors of relapse to sofosbuvir-based regimens

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

Six factors associated with relapse:
- Treatment-experienced
- IL28B non-CC
- Male sex
- Weight > 75 kg
- Cirrhosis
- High viral load >800,000 IU/mL

Foster et al. EASL 2014 Abstract 66
Genotype 1a Treatment-naïve Patients without Cirrhosis - Recommended

Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) for 12 weeks is a Recommended regimen for treatment-naïve patients with HCV genotype 1a infection who do not have cirrhosis and in whom no baseline high fold-change NS5A RAVs§ for elbasvir are detected.

Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for 12 weeks is a Recommended regimen for treatment-naïve patients with HCV genotype 1a infection who do not have cirrhosis.

Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) plus twice-daily dosed dasabuvir (250 mg) with weight-based RBV for 12 weeks is a Recommended regimen for treatment-naïve patients with HCV genotype 1a infection who do not have cirrhosis.

Daily simeprevir (150 mg) plus sofosbuvir (400 mg) for 12 weeks is a Recommended regimen for treatment-naïve patients with HCV genotype 1a infection who do not have cirrhosis.

Daily daclatasvir (60 mg*) plus sofosbuvir (400 mg) for 12 weeks is a Recommended regimen for treatment-naïve patients with HCV genotype 1a infection who do not have cirrhosis.

• Adapted from http://hcvguidelines.org
Ledipasvir / sofosbuvir FDC for genotype 1

ION-1 and 2: RBV arms not shown but did not enhance SVR, therefore RBV not necessary for many receiving LDV/SOF

Tx-Exp (ION-2) 24 wks LDV/SOF 108/109 SVR

ION-1 Afdhal et al. NEJM 4/12/2014, ION-2 Afdhal et al. NEJM 2014; 370(16):1483, ION-3 Kowdle et al. NEJM 4/12/2014. ION studies are RBV-sparing arms only
Daclatasvir + Sofosbuvir +/- RBV
Genotype 1 arms only, 12 or 24 weeks

*3 patients missed SVR24 appointment
SVR12 rate 100%/95%

Sulkowski et al. NEJM 2014
ALLY-2: Study Design

**Naive**
- Randomize 2:1
- 101 patients
- DCV 30/60/90 mg + SOF 400 mg QD

**Experienced**
- 50 patients
- DCV 30/60/90 mg + SOF 400 mg QD

*HCV RNA <LLOQ (TD or TND) at posttreatment Week 12, assessed using the Roche HCV COBAS TaqMan Test v2.0 (LLOQ 25 IU/mL).*
Daclatasvir + Sofosbuvir ALLY-2 study for HIV/HCV 8/12 weeks for naïve, 12 for experienced

**GT 1 (N = 168)**
- 12-Week Naive: 96%, 80/83
- 12-Week Experienced: 98%, 43/44
- 8-Week Naive: 76%, 31/41

**All Patients (N = 203)**
- 12-Week Naive: 97%, 98/101
- 12-Week Experienced: 98%, 51/52
- 8-Week Naive: 76%, 38/50

**DCV** 60 mg standard dose, 30 mg with boosted PIs, 90 mg with NNRTIs except rilpivirine

Follow-up Wk 12 data missing (n = 1)
- Detectable at EOT (n = 1)
- Relapse (n = 1)

Relapse (n = 1)
- Follow-up Wk 12 data missing (n = 2)

Wyles et al. NEJM 2015
Multiple regimens that achieve >90% SVR for GT1


SAPPHIRE/TURQUOISE are 12 week arms only. ION studies are RBV-sparing arms only

ION-1 and 2: RBV arms not shown but did not enhance SVR, therefore RBV not necessary for many receiving LDV/SOF

Cirrhotics (TURQUOISE) 24 weeks 95.9% SVR

Tx-Exp (ION-2) 24 wks LDV/SOF 108/109 SVR
For PrOD, demonstrated role of RBV for 1a

Ferenci et al. NEJM 2014
Extension of therapy beyond 12 weeks may be necessary for cirrhotic patients with GT1a

<table>
<thead>
<tr>
<th></th>
<th>12 weeks</th>
<th>24 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naive</td>
<td>92/64</td>
<td>93/56</td>
</tr>
<tr>
<td>100% cirrhosis</td>
<td>93/14/15</td>
<td>100/13/13</td>
</tr>
<tr>
<td>Partial</td>
<td>100/11</td>
<td>100/10</td>
</tr>
<tr>
<td>Null</td>
<td>80/40/50</td>
<td>93/39/42</td>
</tr>
</tbody>
</table>

FDA Warning issued regarding rare cases of decompensation in CTP-A cirrhosis

Poordad et al. TURQUOISE - II, NEJM 2014

http://www.fda.gov/Drugs/DrugSafety/ucm468634.htm
OPTIMIST 1 and OPTIMIST-2: 12 weeks SMV/SOF by HCV subtype and Q80K: Q80K impacts on cirrhotic patients

8 week arm SVR rate for OPTIMIST-1 was 83%

C-EDGE: RBV and nucleoside/nucleotide sparing 12-week regimen for genotype 1/4/6 HCV infection

9 relapers, 1 breakthrough in 1a
Similar SVR for n=218 HIV co-infected individuals on DTG/RAL/RPV

Cirrhosis does not seem to significantly impact SVR rates for 12 weeks of EBR/GZR

AEs are similar between cirrhotic and non cirrhotic patients in these trials

Genotype 1a Treatment-naïve Patients with Compensated Cirrhosis - Recommended

Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) for 12 weeks is a Recommended regimen for treatment-naïve patients with HCV genotype 1a infection who do not have cirrhosis and in whom no baseline high fold-change NS5A RAVs§ for elbasvir are detected.

Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for 12 weeks is a Recommended regimen for treatment-naïve patients with HCV genotype 1a infection who do not have cirrhosis.

Genotype 1a Treatment-naïve Patients with Compensated Cirrhosis - Alternative

Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) plus twice-daily dosed dasabuvir (250 mg) with weight-based RBV for 24 weeks is a Recommended regimen for treatment-naïve patients with HCV genotype 1a infection who do not have cirrhosis.

Daily simeprevir (150 mg) plus sofosbuvir (400 mg) +/- RBV for 24 weeks is a Recommended regimen for treatment-naïve patients with HCV genotype 1a infection who do not have cirrhosis.

Daily daclatasvir (60 mg*) plus sofosbuvir (400 mg) +/- RBV for 24 weeks is a Recommended regimen for treatment-naïve patients with HCV genotype 1a infection who do not have cirrhosis.

• Adapted from http://hcvguidelines.org
EBR/GZR - impact of RAVs

Effect of RAVs at specific baseline positions on likelihood to achieve SVR12 (Tables 7 and 8)

Table 7. GT1a-infected TN/TE patients given EBR/GZR 12 weeks (no RBV)

<table>
<thead>
<tr>
<th>RAV Position</th>
<th>SVR12 patients with RAVs (NGS 1% ST)</th>
<th>SVR12 patients with RAVs (PopSeq)</th>
</tr>
</thead>
<tbody>
<tr>
<td>24</td>
<td>15/18 (83.3%)</td>
<td>4/4 (100.0%)</td>
</tr>
<tr>
<td>28</td>
<td>61/68 (89.7%)</td>
<td>29/33 (87.9%)</td>
</tr>
<tr>
<td>30</td>
<td>14/23 (60.9%)</td>
<td>4/10 (40.0%)</td>
</tr>
<tr>
<td>31</td>
<td>15/23 (65.2%)</td>
<td>5/13 (38.5%)</td>
</tr>
<tr>
<td>32</td>
<td>1/1 (100.0%)</td>
<td>—</td>
</tr>
<tr>
<td>38</td>
<td>9/9 (100.0%)</td>
<td>—</td>
</tr>
<tr>
<td>58</td>
<td>75/77 (97.4%)</td>
<td>48/49 (98.0%)</td>
</tr>
<tr>
<td>92</td>
<td>6/6 (100.0%)</td>
<td>3/3 (100.0%)</td>
</tr>
<tr>
<td>93</td>
<td>9/14 (64.3%)</td>
<td>5/8 (62.5%)</td>
</tr>
</tbody>
</table>

NGS 1% ST supplemented by PopSeq when NGS was not available.
NS5A Class RAV List = any variant from reference strain at NS5A position 24, 28, 30, 31, 32, 38, 58, 92, and 93.

Table 8. GT1b-infected TN/TE patients given EBR/GZR 12 weeks (no RBV)

<table>
<thead>
<tr>
<th>RAV position</th>
<th>SVR12 patients with RAVs (PopSeq)</th>
</tr>
</thead>
<tbody>
<tr>
<td>24</td>
<td>8/8 (100.0%)</td>
</tr>
<tr>
<td>28</td>
<td>4/4 (100.0%)</td>
</tr>
<tr>
<td>30</td>
<td>16/16 (100.0%)</td>
</tr>
<tr>
<td>31</td>
<td>17/19 (89.5%)†</td>
</tr>
<tr>
<td>32</td>
<td>—</td>
</tr>
<tr>
<td>38</td>
<td>—</td>
</tr>
<tr>
<td>58</td>
<td>—</td>
</tr>
<tr>
<td>92</td>
<td>32/32 (100.0%)</td>
</tr>
<tr>
<td>93</td>
<td>18/18 (100.0%)</td>
</tr>
<tr>
<td>93</td>
<td>21/22 (95.5%)‡</td>
</tr>
</tbody>
</table>

*At position 31, SVR was achieved in 14/16 (87.5%) with L31M and 3/3 (100%) with L31I.
†At position 93, SVR was achieved in 20/21 (95.2%) with Y93H and 1/1 (100%) with Y93S.

Jacobson et al AASLD 2015, San Francisco
EBR/GZR - impact of RAVs may be overcome with extension from 12 to 16 weeks and adding RBV

Figure 4. Efficacy of EBR/GZR 16/18 weeks (+ RBV) in GT1a PR non-responders with baseline NS5A RAVs†

Population Sequencing
EBR RAVs | NS5A Class RAVs
---|---
No RAVS: 51/52 (98%) | No RAVS: 44/52 (85%)

Next-Generation Sequencing at 1% ST‡
EBR RAVs | NS5A Class RAVs
---|---
No RAVS: 48/52 (92%) | No RAVS: 38/52 (73%)

SVR12 (%)

Patients without RAVs | Patients with RAVs
---|---
EBR RAVs | NS5A class RAVs
---|---
100 | 100
51 | 1
44 | 8
8 | 8

†One GT1a patient was missing baseline PopSeq data but had baseline NGS data.
‡NGS 1% ST supplemented by PopSeq when NGS was not available.
EBR/GZR - C-SURFNER established safety and efficacy in patients with CKD stage 4/5

Roth et al. Lancet 2015

Treatment naive and experienced
Mean age 56
~6% cirrhosis

Hypertension or diabetes as primary etiologies
Prior renal transplant n=17

SAE 14.4% in treatment
SAE 16.8% in deferred

Roth et al. Lancet 2015
Benefits include reduction of transmission in a hemodialysis setting

HCV+ / HCV+ renal transplantation is an excellent option - waiting lists are months rather than years

Adapted from http://hcvguidelines.org

Recommended Regimens for Patients with Severe Renal Impairment, Including Severe Renal Impairment (Creatinine Clearance [CrCl] <30 mL/min) or End-Stage Renal Disease (ESRD)

For patients with genotype 1a, or 1b, or 4 infection and CrCl below 30 mL/min for whom the urgency to treat is high and kidney transplant is not an immediate option, daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100mg) for 12 weeks is a Recommended regimen.

For patients with genotype 1b infection and CrCl below 30 mL/min for whom the urgency to treat is high and kidney transplant is not an immediate option, daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) plus twice-daily dosed dasabuvir (250 mg) for 12 weeks is a Recommended regimen.
Daclatasvir (NS5A inhibitor) + Sofosbuvir (polymerase inhibitor) +/- RBV for triple therapy failure

No impact of PI mutations on viral kinetics

### Patients with NS3 polymorphisms, n

<table>
<thead>
<tr>
<th>Polymorphism</th>
<th>n</th>
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<tbody>
<tr>
<td>V36M-R155K</td>
<td>6</td>
</tr>
<tr>
<td>R155K</td>
<td>3</td>
</tr>
<tr>
<td>V36L-R155K</td>
<td>1</td>
</tr>
<tr>
<td>T54S-R155K</td>
<td>1</td>
</tr>
<tr>
<td>T54S-V55I-R155K</td>
<td>1</td>
</tr>
<tr>
<td>V36M</td>
<td>1</td>
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<tr>
<td>V36M-V55I</td>
<td>1</td>
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<tr>
<td>V36M-V55A-R155K</td>
<td>1</td>
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<tr>
<td>V36M-R155K-I170T</td>
<td>1</td>
</tr>
<tr>
<td>V36A</td>
<td>1</td>
</tr>
<tr>
<td>V55A</td>
<td>1</td>
</tr>
<tr>
<td>V170T</td>
<td>1</td>
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<tr>
<td>Genotype 1a PEG-IFN/RBV Treatment-experienced Patients without Cirrhosis</td>
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<tr>
<td>-----------------------------</td>
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<tr>
<td>Genotype 1a PEG-IFN/RBV Treatment-experienced Patients with Compensated Cirrhosis</td>
<td></td>
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<tr>
<td>Genotype 1b PEG-IFN/RBV Treatment-experienced Patients without Cirrhosis</td>
<td></td>
</tr>
<tr>
<td>Genotype 1b PEG-IFN/RBV Treatment-experienced with Compensated Cirrhosis</td>
<td></td>
</tr>
<tr>
<td>Genotype 1 Sofosbuvir plus Ribavirin with or without PEG-IFN Treatment-experienced Patients</td>
<td></td>
</tr>
<tr>
<td>Genotype 1 HCV nonstructural protein 3 (NS3) protease inhibitor (telaprevir, boceprevir, or simeprevir) plus PEG-IFN/RBV Treatment-experienced Patients without Cirrhosis</td>
<td></td>
</tr>
<tr>
<td>Genotype 1 HCV nonstructural protein 3 (NS3) protease inhibitor (telaprevir, boceprevir, or simeprevir) plus PEG-IFN/RBV Treatment-experienced Patients with Compensated Cirrhosis</td>
<td></td>
</tr>
<tr>
<td>Genotype 1 Simeprevir plus Sofosbuvir Treatment-experienced Patients</td>
<td></td>
</tr>
<tr>
<td>Genotype 1 HCV NS5A inhibitor Treatment-experienced Patients</td>
<td></td>
</tr>
</tbody>
</table>

- Adapted from [http://hcvguidelines.org](http://hcvguidelines.org)
## Certain safety issues regarding regimens for HCV genotype 1

<table>
<thead>
<tr>
<th>Renal</th>
<th>Monitoring</th>
<th>C-T-P B/C</th>
</tr>
</thead>
<tbody>
<tr>
<td>GZR EBR</td>
<td>• ALT / AST increases ~ 8 weeks</td>
<td>STOP</td>
</tr>
<tr>
<td>LDV SOF</td>
<td>• Monitor antacid use</td>
<td>Approved</td>
</tr>
<tr>
<td>PTV/r OBV DSV</td>
<td>• Child-Turcotte-Pugh A - scattered reports</td>
<td>STOP</td>
</tr>
<tr>
<td>SMV SOF</td>
<td>• Phototoxicity</td>
<td>STOP</td>
</tr>
<tr>
<td>DCV SOF</td>
<td>• Increased bilirubin, especially in East Asian</td>
<td>Approved</td>
</tr>
</tbody>
</table>

### Renal
- GZR EBR: Not renally metabolized
- LDV SOF: GS-331007
- PTV/r OBV DSV: Not renally metabolized
- SMV SOF: GS-331007
- DCV SOF: GS-331007
# Summary of issues regarding regimens for HCV genotype 1

<table>
<thead>
<tr>
<th>Duration</th>
<th>12-16w</th>
<th>8-24w</th>
<th>12-24w</th>
<th>12-24w</th>
<th>12-24w</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GT1a v. 1b</strong></td>
<td>Add RBV for 1a</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cirrhosis</strong></td>
<td>Add RBV to 12w or extend to 24w for cirrhosis+TE</td>
<td>Extend to 24 weeks for 1a</td>
<td>Extend to 24w for cirrhosis and no Q80K (GT1a)</td>
<td>Extend to 24 weeks for cirrhosis</td>
<td></td>
</tr>
<tr>
<td><strong>HCV RNA levels</strong></td>
<td>Consider 8 wks for &lt;6,000,000 IU/mL, no cirrhosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>CKD stage 4/5</strong></td>
<td>Safety, efficacy n=122</td>
<td>Concern regarding GS-331007</td>
<td>Small pilot trial n=20</td>
<td>Concern regarding GS-331007</td>
<td>Concern regarding GS-331007</td>
</tr>
<tr>
<td><strong>Key drug interactions</strong></td>
<td>multiple</td>
<td>antacids/H2 blockers/PPIs</td>
<td>multiple</td>
<td>multiple</td>
<td>strong CYP3A4 inducers/inhibitors</td>
</tr>
<tr>
<td><strong>Baseline RAVs</strong></td>
<td>NS5A at positions 28, 30, 31, 93 - for 1a extend to 16w and add RBV</td>
<td></td>
<td></td>
<td></td>
<td>? avoid with 1a + NS3 Q80K + cirrhosis</td>
</tr>
</tbody>
</table>
**Sofosbuvir + RBV for GT2 infection**

- **Naive with cirrhosis:**
  - 96%

- **Naive, no cirrhosis:**
  - 92-98%

- **Tx-Exp, no cirrhosis:**
  - 75%

- **Tx Exp, cirrhosis:**
  - 91-93%
  - 96%
  - 50%
  - 75%
  - 92-98%

- **Tx Exp, cirrhosis (16 wks):**
  - 25/26
  - 60
  - 7/9

*Lawitz et al. NEJM 2013, Jacobson et al. NEJM 2013*
Sofosbuvir + RBV for GT3 infection, naïve patients

- **12 weeks**
  - Naïve, no cirrhosis: 61-68%
  - Naïve with cirrhosis: 37%

- **24 weeks**
  - Naïve, no cirrhosis: 94%
  - Naïve, cirrhosis: 92%

- Lawitz et al. NEJM 2013, Jacobson et al. NEJM 2013, Antiviral Drugs Advisory Committee Meeting, Gilead Review 10/25/13; Zeuzem et al. AASLD 2013
Peg-IFN + sofosbuvir + RBV x 12 wks for GT3 infection

LONESTAR2 included high rate of cirrhotics (55%) & nonresponders (85%)

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

Regimen achieved 96% SVR for GT2

PROTON, & ELECTRON, Lawitz et al. Lancet 2013, LONESTAR2 (Lawitz et al. AASLD 2013)
DCV/SOF x 12 weeks for GT3 infection ALLY-3

12 weeks

Nelson et al. Hepatology 2015; 61(4):1127-35. 9 of 16 relapses developed Y93H in NS5A
### Genotype 2 Treatment-naïve Patients - Recommended

Daily sofosbuvir + weight-based RBV for 12w if no cirrhosis  
   extend to 16-24 with compensated cirrhosis  
Daily daclatasvir + sofosbuvir for 12 weeks  
   extend to 16-24 with compensated cirrhosis

### Genotype 3 Treatment-naïve Patients - Recommended

Daily daclatasvir + sofosbuvir for 12 weeks  
   extend to 24 weeks with compensated cirrhosis, ? add RBV  
Daily sofosbuvir + weight-based RBV + weekly PEG-IFN for 12 weeks

### Genotype 3 Treatment-naïve Patients - Alternative

Daily sofosbuvir + weight-based RBV for 24 weeks

- Adapted from [http://hcvguidelines.org](http://hcvguidelines.org)
Response rates for pangenotypic regimen in development: Genotypes 1-6

12 weeks for GT1,2,4,5,6
19% compensated cirrhosis
32% nonresponders

8 week arms of phase II trial:
lower SVRs at 100 mg VEL
dos (81-88%)

AASLD / IDSA Guidelines: Treatment

• Novel interferon-free and ribavirin-free paradigms
  – Potent combinations can overcome prior barriers
  – 12 week regimens available for many patients
    – Cirrhosis will increase duration for many regimens
    – Resistance-associated variants may reduce efficacy of certain regimens / require increased duration/RBV

• Special populations
  – Regimens for CKD stage 4/5
  – HIV/HCV coinfection
  – Decompensated cirrhosis
  – Acute - treat as chronic

• Improving cascade of care and removing restrictions to access will be critical to maximize the impact of treatment
ACTHIV 2016: A State-of-the-Science Conference for Frontline Health Professionals