Treat HCV Genotype 1

This is a PDF version of the following document:
Module 5: Treatment of Chronic Hepatitis C Infection
Lesson 1: Treatment of HCV Genotype 1

You can always find the most up-to-date version of this document at https://www.hepatitisC.uw.edu/go/treatment-infection/treatment-genotype-1/core-concept/all.

Introduction

Background

In the United States, genotype 1 hepatitis C virus (HCV) accounts for approximately 70 to 75% of all HCV infections.[1] Accordingly, treatment of genotype 1 has the most extensive data and highest clinical relevance for hepatitis C treatment issues in the United States. In recent years, multiple studies using direct-acting antiviral (DAA) agents have shown sustained virologic response rates at 12 weeks post-treatment (SVR12) of greater than 95% in treatment-naive and treatment-experienced genotype 1 patients, including those with compensated cirrhosis. The high cost of these very effective regimens has limited the widespread implementation of hepatitis treatment in the United States, but recently, lower-priced options have become available and negotiated discounting has occurred. The following discussion regarding initial treatment and retreatment of patients with genotype 1 chronic HCV assumes the patient and their clinician have already made the decision to initiate hepatitis C therapy. This topic review does not address the treatment of HCV genotype 1 in persons with decompensated cirrhosis, severe renal impairment (or end-stage renal disease), or post-liver transplantation.

Medications used to Treat HCV Genotype 1

The HCV Medications section on this website provides detailed information for each of the Food and Drug Administration (FDA)-approved medications listed in the treatment recommendations, including links to the full prescribing information and to patient assistance programs. The DAAs exert their action at specific steps in the HCV life cycle. There are three major classes of direct-acting antiviral medications: (1) nonstructural proteins 3/4A (NS3/4A) protease inhibitors, (2) NS5A inhibitors, and (3) NS5B polymerase inhibitors; the NS5B polymerase inhibitors include the nucleoside analogs and nonnucleoside analogs (Figure 1).[2,3] Adherence with the treatment regimen is of paramount importance. Persons receiving treatment for HCV should receive detailed counseling regarding the importance of adherence prior to starting therapy as well as intensive monitoring and follow-up during therapy.

Approach to Choosing HCV genotype 1 Treatment Regimen

For individuals with chronic HCV genotype 1 infection, the main factors that influence the choice and duration of therapy are cirrhosis status and prior treatment experience. With the use of certain regimens for persons with HCV genotype 1a, namely elbasvir-grazoprevir, the genotype 1 subtype (1a or 1b) also impacts the choice of therapy, as elbasvir-grazoprevir is only recommended for persons with HCV genotype 1a who do not have baseline NS5A resistance-associated substitutions (RASs). In addition, the HCV RNA level and the patient’s HIV status can impact the duration of ledipasvir-sofosbuvir, but does not affect the duration of other
regimens. Finally, the cost of the regimen, insurance coverage, and provider preference can play a major role in the regimen choice. The following treatment recommendations are based on the AASLD-IDSA HCV Guidance for initial treatment of adults with HCV genotype 1 and for retreatment of adults in whom prior therapy failed, including those with HCV genotype 1.[4,5]

- AASLD-IDSA HCV Guidance for Treatment-Naïve Patients with Genotype 1 HCV
- AASLD-IDSA HCV Guidance for Retreatment of Persons in Whom Prior Therapy Failed
HCV Genotype 1: Initial Treatment

Background

The treatment landscape for treatment-naïve adults with chronic hepatitis C virus (HCV) genotype 1 infection has rapidly changed in the past decade. Historically, HCV genotype 1 was considered the most difficult HCV genotype to treat. From 1998-2013, therapy evolved from interferon monotherapy, to peginterferon monotherapy, to peginterferon plus ribavirin, to triple therapy with peginterferon plus ribavirin plus an NS3/4A protease inhibitor (boceprevir or telaprevir).[6,7,8,9] Since 2014, the standard of care for HCV genotype 1 has consisted of all-oral therapy with a combination of DAAs. As of 2017, there have been multiple safe, convenient, and highly effective all-oral regimens recommended for the treatment of HCV genotype 1, most of which do not require ribavirin.

Factors to Consider Prior to Choosing Initial Treatment Regimen

For treatment-naïve adults with chronic HCV genotype 1 infection, the main factors that influence the choice and duration of therapy are (1) presence or absence of cirrhosis, and (2) medication cost or insurance considerations. In the case of elbasvir-grazoprevir use, the HCV genotype 1 subtype (1a or 1b) is also important, as the presence of specific baseline NS5A RASs significantly reduces SVR12 rates in persons with HCV genotype 1a.[10,11,12] In cases where the genotype 1 subtype is not known, the individual should be treated as HCV genotype 1a. The baseline HCV RNA level generally does not influence the treatment choice or duration, except in treatment-naïve noncirrhotic patients in whom 8 or 12 weeks of ledipasvir-sofosbuvir is being considered.[13] Additional data from the HCV-TARGET registry and the Veterans Affairs National Healthcare System demonstrated comparable SVR rates of 94 to 98% for adults without cirrhosis treated with either 8 or 12 weeks of ledipasvir-sofosbuvir if the baseline HCV RNA levels were less than 6 million IU/mL.[14,15,16] In addition to the factors noted above, drug interactions may also influence the choice of therapy, particularly for individuals with HIV coinfection who are taking antiretroviral medications. Of note, individuals with HCV and HIV coinfection, depending on their specific antiretroviral therapy, are eligible for most of the same regimens for initial treatment of genotype 1 as for persons with HCV monoinfection, except that persons with HIV should not receive (1) any 8-week option of ledipasvir-sofosbuvir, or (2) the 8-week option of glecaprevir-pibrentasvir if cirrhosis is present.[11,12,17,18]

Baseline Resistance Testing

In treatment-naïve individuals, baseline genotypic drug resistance testing is not recommended for most first-line DAA regimens, except for elbasvir-grazoprevir. Pretreatment NS5A genotypic drug resistance testing is not recommended for all persons, but is recommended specifically for patients with HCV genotype 1a in whom elbasvir-grazoprevir is being considered, notably to detect the presence of NS5A resistance-associated substitutions at the amino acid positions 28, 30, 31, or 93, which are associated with inferior treatment response.[10] The presence of one or more of these resistance-associated substitutions (present in up to 10% of treatment-naïve adults) requires the addition of ribavirin to the treatment regimen and extended duration of elbasvir-grazoprevir from 12 to 16 weeks.[10] In clinical practice, however, this 16-week regimen is rarely used for treatment of genotype 1 given the availability of several other well-tolerated, highly effective 8- or 12-week regimens. Genotypic drug resistance testing is commercially available through several laboratories and typically costs less than $1,000.

AASLD-IDSA HCV Guidance for Initial Treatment of HCV Genotype 1

The following is a summary of the AASLD-IDSA HCV Guidance recommendations for the initial treatment of adults with HCV genotype 1a or 1b; these recommendations include separate tables for adults without cirrhosis and for those with compensated cirrhosis.[11,12,17,18] For individuals with cirrhosis, the AASLD-IDSA HCV Guidance defines compensated cirrhosis as Child-Turcotte-Pugh class A and decompensated cirrhosis as Child-Turcotte-Pugh class B or C (see Child-Turcotte-Pugh Calculator). The recommended
regimens are listed by evidence level; when the evidence level is considered equivalent, the regimens are listed alphabetically.

**Table 1. AASLD-IDSA HCV Guidance for Genotype 1a: Initial Treatment**

<table>
<thead>
<tr>
<th>Treatment-Naïve Genotype 1a Patients Without Cirrhosis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Recommended for Treatment-Naïve Genotype 1a Patients Without Cirrhosis</strong></td>
</tr>
<tr>
<td><strong>Elbasvir-Grazoprevir</strong></td>
</tr>
<tr>
<td>Fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) one tablet once daily for 12 weeks</td>
</tr>
<tr>
<td>For patients without baseline NS5A resistance-associated substitutions (RASs) for elbasvir; these NS5A RASs include genotype 1a RASs at amino acid positions 28, 30, 31, or 93 known to confer antiviral resistance.</td>
</tr>
<tr>
<td>Rating: <strong>Class I, Level A</strong></td>
</tr>
</tbody>
</table>

| **Recommended for Treatment-Naïve Genotype 1a Patients Without Cirrhosis** |
| **Glecaprevir-Pibrentasvir** |
| *Fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) once daily for 8 weeks* |
| Rating: **Class I, Level A** |
| Note: *This is taken as 3 tablets once daily with each fixed-dose tablet containing glecaprevir (100 mg)/pibrentasvir (40 mg).* |

| **Recommended for Treatment-Naïve Genotype 1a Patients Without Cirrhosis** |
| **Ledipasvir-Sofosbuvir** |
| Fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) one tablet once daily for 12 weeks |
| Rating: **Class I, Level A** |

| **Recommended for Treatment-Naïve Genotype 1a Patients Without Cirrhosis** |
| **Ledipasvir-Sofosbuvir** |
| Fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) one tablet once daily for 8 weeks |
| For patients who are HIV-uninfected and whose HCV RNA level is
Studies of Initial Treatment of Adults with HCV Genotype 1

The following summarizes key studies that support the recommendations in the AASLD-IDSA HCV Guidance for initial treatment of patients with chronic hepatitis C and genotype 1 infection, including those without cirrhosis and those with compensated cirrhosis; the medication regimens are listed in alphabetical order.

**Elbasvir-Grazoprevir**

- **C-EDGE Treatment-Naïve:** In this phase 3 trial, investigators enrolled treatment-naïve adults with HCV genotype 1, 4, or 6 to receive a 12-week course of fixed-dose elbasvir-grazoprevir.[19] The study enrollment included 288 patients with genotype 1 infection. The SVR12 rates were 92% (144 of 157) in those with genotype 1a and 99% (129 of 131) with genotype 1b. Participants with genotype 1a who had baseline NS5A resistance-associated substitutions had a significantly lower SVR12 response rate (58%) than those without any baseline NS5A resistance-associated substitution (99%); the baseline resistance-associated substitutions did not significantly impact the SVR12 rates in patients with genotype 1b.

- **C-WORTHY:** This open-label, phase 2 trial enrolled adults with HCV genotype 1, including treatment-naïve adults with compensated cirrhosis (cohort 1, n=123) and treatment-experienced adults with a prior null response to peginterferon plus ribavirin (cohort 2, n=130).[20] Participants were randomized to receive elbasvir plus grazoprevir, with or without ribavirin, for 12 or 18 weeks. In the HCV treatment-naïve cirrhotic cohort, 90-97% achieved an SVR12. A subgroup analysis did not show a significant benefit of adding ribavirin to elbasvir plus grazoprevir.

**Glecaprevir-Pibrentasvir**

- **ENDURANCE-1:** In this phase 3 open-label trial, 703 noncirrhotic adults with HCV genotype 1 were randomized to receive either 8 or 12 weeks of glecaprevir-pibrentasvir; 62% were treatment naïve, with the other 38% having failed a prior interferon-based regimen.[21] Among those enrolled, 33 were coinfected with HIV. The SVR12 rate was 99.1% (333 of 336) for the 8-week arm and 99.7% (333 of 334) for the 12-week arm; the SVR rate remained high in participants with HIV coinfection, prior treatment experience, and baseline resistance-associated substitutions.

- **EXPEDITION-1:** This phase 3, single-arm, open-label trial evaluated the safety and efficacy of 12 weeks of glecaprevir-pibrentasvir in 146 adults with compensated cirrhosis and HCV genotype 1, 2, 4, 5, or 6.[22] Among all participants enrolled, 60% had HCV genotype 1 infection and 75% were treatment naïve, with the other 25% having failed an interferon-based regimen with or without sofosbuvir. For the participants with HCV genotype 1 infection, 99% (89 of 90) achieved an SVR12. One person with genotype 1a experienced a viral relapse at week 8 post-treatment; this individual had a Y93N resistance-associated substitution detected at baseline and at the time of virologic failure.

- **EXPEDITION-2:** This phase 3, open-label, dual-arm trial included 137 noncirrhotic adults with HIV coinfecation and HCV genotype 1, 2, 3, 4, 5 or 6; the 137 participants without cirrhosis received 8 weeks of glecaprevir-pibrentasvir and the 16 participants with compensated cirrhosis received 12 weeks of glecaprevir-pibrentasvir.[23] All (100%) of the 94 participants with HCV genotype 1 achieved an SVR12. Most of the study participants were taking either raltegravir, dolutegravir, or rilpivirine as the anchor drug for HIV antiretroviral therapy.

- **EXPEDITION-8:** This single-arm, multicenter phase 3b trial evaluated the efficacy of the fixed-dose combination of glecaprevir-pibrentasvir for 8 weeks in 343 treatment-naïve participants with compensated cirrhosis and HCV genotypes 1, 2, 3, 4, 5, or 6.[24] For the enrolled individuals 67% (231 of 343) had HCV genotype 1.[24] By intent-to-treat (ITT) analysis, the SVR12 response rates were 98% (325 of 343) overall and 98% (226 of 231) in participants with HCV genotype 1[24].

**Ledipasvir-Sofosbuvir**
• **ION-1**: This phase 3 trial examined the fixed-dose combination of ledipasvir-sofosbuvir, given with or without ribavirin, in treatment-naïve adults with HCV genotype 1, including those with compensated cirrhosis.[25] All treatment arms had SVR12 rates greater than 95%; no differences were observed with respect to receipt of ribavirin, or whether patients received 12 or 24 weeks of treatment.

• **ION-3**: In this phase 3 trial, treatment-naïve adults with HCV genotype 1 received the fixed-dose combination of ledipasvir-sofosbuvir, with or without ribavirin, for 8 or 12 weeks.[13] Persons with cirrhosis were excluded. The SVR12 rates were greater than 90% in all treatment arms. In a post hoc analysis of participants without cirrhosis and without receipt of ribavirin, subjects with a baseline HCV RNA level less than 6 million IU/mL had similar SVR rates and relapse rates with 8 weeks versus 12 weeks of therapy.

**Sofosbuvir-Velpatasvir**

• **ASTRAL-1**: In the phase 3 ASTRAL-1 trial, investigators enrolled treatment-naïve and treatment-experienced adults with chronic HCV genotype 1, 2, 4, 5, or 6 infection and randomized them in a 5:1 ratio to receive a 12-week course of either sofosbuvir-velpatasvir or placebo.[26] For those participants assigned to sofosbuvir-velpatasvir (n=624), 34% had genotype 1a, 19% had genotype 1b, 19% had compensated cirrhosis, and 28% were HCV treatment-experienced.[26] Among the 624 individuals who received sofosbuvir-velpatasvir, the overall SVR12 rate was 99%, including 98% (206 of 210) with genotype 1a and 99% (117 of 118) with genotype 1b. For the HCV treatment-naïve participants, 99% (418 of 423) achieved an SVR12. Among the 121 participants with cirrhosis, 99% (120 of 121) achieved an SVR12.[26] Baseline NS5A RASs, which were present in 42% of evaluated participants, did not appear to influence SVR12. There was no significant difference in the rate of adverse events between the treatment and placebo arms.

**Sofosbuvir-Velpatasvir-Voxilaprevir**

• **POLARIS-2**: In this phase 3, open-labeled trial, individuals with chronic HCV genotype 1, 2, 3, or 4 infection who were naïve to DAA therapy (prior peginterferon and ribavirin allowed) were randomized to receive either 8 weeks of sofosbuvir-velpatasvir-voxilaprevir or 12 weeks of sofosbuvir-velpatasvir.[27] Among the 941 participants, 18% had compensated cirrhosis and 49% had HCV genotype 1 infection. Sustained virologic response (SVR) occurred in 95% and 98% in sofosbuvir-velpatasvir-voxilaprevir and sofosbuvir-velpatasvir arms, respectively. Notably, SVR occurred in 90% of persons with cirrhosis in the 8-week arm compared with 99% in the 12-week sofosbuvir-velpatasvir arm.[27] The investigators concluded that this study did not establish sofosbuvir-velpatasvir-voxilaprevir for 8 weeks was noninferior to sofosbuvir-velpatasvir for 12 weeks.[27]
HCV Genotype 1: Retreatment of Persons who Failed Prior Therapy

Background

Direct-acting antiviral combinations have markedly improved treatment outcomes for persons with HCV genotype 1 who failed prior therapy, with SVR12 rates exceeding 95%. Prior failure with a regimen that included an NS3/4A protease inhibitor (boceprevir, simeprevir, or telaprevir) does not impact the success of subsequent therapy with the NS5A inhibitors (elbasvir, ledipasvir, pibrentasvir, or velpatasvir), or NS5B inhibitors (sofosbuvir). In addition, the newer HCV protease inhibitors grazoprevir (coformulated as elbasvir-grazoprevir), glecaprevir (coformulated as glecaprevir-pibrentasvir), and voxilaprevir (coformulated as sofosbuvir-velpatasvir-voxilaprevir) appear to have activity against the typical NS3/4A resistance-associated substitutions encountered in telaprevir- or boceprevir-experienced individuals and can be used effectively in such persons. In a very small subset of treatment-experienced individuals, retreatment must now also consider options for DAA-experienced persons who have previously failed therapy with a regimen that included an NS5A inhibitor and or a newer NS3/4A protease inhibitor.

Factors to Consider Prior to Choosing Retreatment Regimen

For persons with chronic HCV genotype 1 infection who have treatment experience, the key factors that influence the choice of the retreatment regimen are (1) the prior regimen used when treatment failure occurred, (2) the presence or absence of cirrhosis, and (3) cost or insurance considerations.[5] The retreatment of persons with HCV genotype 1 who have decompensated cirrhosis, severe renal impairment (or end-stage renal disease), or post-liver transplantation is not addressed here. For individuals with HCV-HIV coinfection, the approach to retreatment is the same as with HCV monoinfection, with the exception that additional drug interactions between DAAs and antiretroviral medications need to be taken into consideration and treatment duration differs in some circumstances.

Baseline Resistance Testing

Baseline resistance testing is not routinely recommended for treatment-experienced patients with genotype 1 infection.

AASLD-IDSA HCV Guidance for Retreatment of HCV Genotype 1

The following is a summary of the AASLD-IDSA HCV Guidance for adults with HCV genotype 1 infection who are treatment experienced and failed prior DAA therapy, including those without cirrhosis and those with compensated cirrhosis.[5,28,29,30] For individuals with cirrhosis, the AASLD-IDSA HCV Guidance defines compensated cirrhosis as Child-Turcotte-Pugh class A and decompensated cirrhosis as Child-Turcotte-Pugh class B or class C. The AASLD-IDSA HCV Guidance for retreatment is no longer genotype specific, but instead emphasizes a pangenotypic approach to retreatment based on the prior treatment regimen. In addition, the AASLD-IDSA HCV Guidance no longer includes recommendations for the retreatment of persons who experienced prior treatment failure with interferon-based therapy, including interferon plus first-generation protease inhibitors (telaprevir, boceprevir); these individuals have robust cure rates with modern DAA regimens similar to that observed with treatment-naive persons. The recommended regimens in the tables below are based on prior regimen failure and listed by evidence level; when the evidence level is considered equivalent, the regimens are listed alphabetically.

Table 5. AASLD-IDSA HCV Guidance: Retreatment Sofosbuvir-Based Treatment Failures, With or Without Compensated Cirrhosis

Recommended and alternative regimens listed by evidence level and alphabetically
**Recommended for Sofosbuvir-Based Treatment Failures, With or Without Compensated Cirrhosis**

**Sofosbuvir-Velpatasvir-Voxilaprevir**  
*Fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg) one tablet once daily for 12 weeks*

For persons with genotype 3 and cirrhosis, add weight-based ribavirin if there are no contraindications to ribavirin.

Rating: **Class I, Level A**

**Alternative for Sofosbuvir-Based Treatment Failures, With or Without Compensated Cirrhosis**

**Glecaprevir-Pibrentasvir**  
*Fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) once daily for 16 weeks*

This regimen is not recommended for persons with (1) prior exposure to an NS5A inhibitor plus NS3/4 protease inhibitor regimens (eg. elbasvir-grazoprevir or glecaprevir-pibrentasvir), or (2) persons with genotype 3 infection with sofosbuvir and NS5A inhibitor experience (e.g. ledipasvir-sofosbuvir or sofosbuvir-velpatasvir)

Rating: **Class IIa, Level A**  
Note: *This is taken as 3 tablets once daily with each fixed-dose tablet containing glecaprevir (100 mg)/pibrentasvir (40 mg).*

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**Table 6. AASLD-IDSA HCV Guidance: Retreatment Elbasvir-Grazoprevir Treatment Failures, With or Without Compensated Cirrhosis**

Recommended and alternative regimens listed by evidence level and alphabetically

**Recommended for Elbasvir-Grazoprevir Treatment Failures, With or Without Compensated Cirrhosis**

**Sofosbuvir-Velpatasvir-Voxilaprevir**  
*Fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg) one tablet once daily for 12 weeks*

For persons with genotype 3 and cirrhosis, add weight-based ribavirin if there are no contraindications to ribavirin.

Rating: **Class I, Level A**
Table 7. AASLD-IDSA HCV Guidance for All Genotypes: Retreatment Glecaprevir-Pibrentasvir Treatment Failures (All Genotypes), With or Without Compensated Cirrhosis

<table>
<thead>
<tr>
<th>Recommended for Glecaprevir-Pibrentasvir Treatment Failures (All Genotypes), With or Without Compensated Cirrhosis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Glecaprevir-Pibrentasvir</strong></td>
</tr>
<tr>
<td><em>Fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) once daily for 16 weeks</em></td>
</tr>
<tr>
<td><strong>Sofosbuvir</strong> (400 mg) one tablet once daily for 16 weeks</td>
</tr>
<tr>
<td><strong>Ribavirin</strong> 1000 mg if &lt;75 kg or 1200 mg if ≥75 kg for 16 weeks (the daily dose is given in two divided doses)</td>
</tr>
</tbody>
</table>

For patients with or without compensated cirrhosis

Rating: **Class Ila, Level B**

Note: *This is taken as 3 tablets once daily with each fixed-dose tablet containing glecaprevir (100 mg)/pibrentasvir (40 mg)

<table>
<thead>
<tr>
<th>Recommended for Glecaprevir-Pibrentasvir Treatment Failures (All Genotypes), With or Without Compensated Cirrhosis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sofosbuvir-Velpatasvir-Voxilaprevir</strong></td>
</tr>
<tr>
<td><em>Fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg) one tablet once daily for 12 weeks</em></td>
</tr>
</tbody>
</table>

For patients without cirrhosis

Rating: **Class Ila, Level B**

<table>
<thead>
<tr>
<th>Recommended for Glecaprevir-Pibrentasvir Treatment Failures (All Genotypes), With or Without Compensated Cirrhosis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sofosbuvir-Velpatasvir-Voxilaprevir</strong></td>
</tr>
<tr>
<td><em>Fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg) one tablet once daily for 12 weeks</em></td>
</tr>
<tr>
<td><strong>Ribavirin</strong> 1000 mg if &lt;75 kg or 1200 mg if ≥75 kg for 12 weeks (the daily dose is given in two divided doses)</td>
</tr>
</tbody>
</table>

For patients with compensated cirrhosis

Rating: **Class Ila, Level C**

^For treatment of patients with decompensated cirrhosis, see the AASLD-IDSA Guidance: Unique Populations—Patients with Decompensated Cirrhosis
Table 8. AASLD-IDSA HCV Guidance for All Genotypes: Retreatment Multiple DAA Treatment Failures (All Genotypes), Including Sofosbuvir-Velpatasvir-Voxilaprevir or Sofosbuvir Plus Glecaprevir-Pibrentasvir^  

<table>
<thead>
<tr>
<th>Glecaprevir-Pibrentasvir</th>
<th>Sofosbuvir (400 mg) one tablet once daily for 16 weeks#</th>
<th>Ribavirin 1000 mg if &lt;75 kg or 1200 mg if ≥75 kg for 16 weeks# (the daily dose is given in two divided doses)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) once daily for 16 weeks#</em></td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

#Extension of treatment to 24 weeks should be considered in extremely difficult cases (eg, genotype 3 with cirrhosis) or failure following sofosbuvir plus glecaprevir-pibrentasvir.

Rating: Class Ila, Level B  
Note: *This is taken as 3 tablets once daily with each fixed-dose tablet containing glecaprevir (100 mg)/pibrentasvir (40 mg)

<table>
<thead>
<tr>
<th>Sofosbuvir-Velpatasvir-Voxilaprevir</th>
<th>Ribavirin 1000 mg if &lt;75 kg or 1200 mg if ≥75 kg for 24 weeks (the daily dose is given in two divided doses)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg) one tablet once daily for 24 weeks</td>
<td>+</td>
</tr>
</tbody>
</table>

Rating: Class Ila, Level B

^For treatment of patients with decompensated cirrhosis, see the AASLD-IDSA Guidance: Unique Populations—Patients with Decompensated Cirrhosis


Retreatment of Persons with Prior PegInterferon and Ribavirin Failure

The latest version of the AASLD-IDSA HCV Guidance (changes effective January 21, 2021) no longer provides specific recommendations for retreatment of persons with a history of peginterferon plus ribavirin therapy, with or without an earlier generation direct-acting antiviral agent (telaprevir, boceprevir, sofosbuvir or simeprevir).[5] The AASLD-IDSA HCV Guidance notes that these individuals respond to retreatment similar to treatment-naïve persons, thus implying the treatment approach should be the same as with treatment-naïve individuals.[5] Although the pool of persons with a history of failure with a peginterferon-based regimen who need retreatment is small and diminishing, there are some individuals with this treatment history who need retreatment and may require special consideration that differs from that of treatment-naïve individuals. The
following outlines a few of these key considerations based on available data and previous guidance that should be noted when retreating an individual with a history of prior treatment failure with peginterferon plus ribavirin, with or without an earlier generation DAA (boceprevir, simeprevir, sofosbuvir, or telaprevir). Note that except for the 8-week option of glecaprevir-pibrentasvir (for which there is little data in treatment-experienced patients), when retreating these individuals with first-line DAA combinations that have pangenotypic activity (glecaprevir-pibrentasvir or sofosbuvir-velpatasvir), the treatment will be the same as their treatment-naïve counterparts.

- Persons with HCV genotype 1 and compensated cirrhosis who are treatment-experienced with peginterferon and ribavirin (with or without an early DAA) are not eligible for the 8-week glecaprevir-pibrentasvir retreatment option; the 8-week treatment course can be used in treatment-naïve persons with genotype 1 and compensated cirrhosis if they do not have HIV infection.
- Persons with HCV genotype 1 without cirrhosis who are treatment-experienced with peginterferon and ribavirin (with or without an early DAA) are not eligible for the shorter 8-week option of ledipasvir-sofosbuvir which may be considered for those who are treatment-naïve, HIV-uninfected, and have an HCV RNA level is less than 6 million IU/mL.
- Persons with HCV genotype 1a with compensated cirrhosis who have prior peginterferon and ribavirin experience, the treatment regimen ledipasvir-sofosbuvir for 12 weeks without ribavirin should not be considered a recommended regimen. These treatment-experienced individuals should have ribavirin added to the ledipasvir-sofosbuvir regimen, which contrasts with the recommended use of ledipasvir-sofosbuvir alone in treatment-naïve persons with genotype 1a and compensated cirrhosis. The addition of ribavirin, due to its additional complexity and toxicity, would make this regimen an alternative option for this subset of individuals.
- For persons with HCV genotype 1 without cirrhosis who are treatment-experienced with peginterferon and ribavirin plus one of the earlier NS3 protease inhibitors (boceprevir, or simeprevir, or telaprevir), the use of elbasvir-grazoprevir would require the addition of ribavirin and therefore would be considered an alternative regimen. For treatment-naïve persons with genotype 1 without cirrhosis, the use of elbasvir-grazoprevir does not include ribavirin.
- For persons with HCV genotype 1 and compensated cirrhosis who are treatment-experienced with peginterferon and ribavirin plus one of the earlier NS3 protease inhibitors (boceprevir, simeprevir, or telaprevir), the regimens of ledipasvir-sofosbuvir or elbasvir-grazoprevir would require the use of ribavirin, thus making these both alternative (rather than recommended) options. For treatment-naïve persons with genotype 1 and compensated cirrhosis, treatment with ledipasvir-sofosbuvir or elbasvir-grazoprevir would not require the addition of ribavirin.
Studies of Retreatment of Adults with HCV Genotype 1

The following key studies support the recommendations in the AASLD-IDSA HCV Guidance for retreatment of adults with chronic HCV genotype 1 infection who previously failed therapy.

Elbasvir-Grazoprevir

- **C-EDGE Treatment-Experienced**: This phase 3 trial enrolled 420 treatment-experienced adults with HCV genotype 1, 4, or 6 to receive the fixed-dose elbasvir-grazoprevir, with or without ribavirin, for 12 or 16 weeks.[31] Overall, 89% of participants enrolled had HCV genotype 1 (54% with genotype 1a and 35% with genotype 1b). For participants with HCV genotype 1 who received 12 weeks of treatment, SVR12 was achieved in 94.7% (89 of 94) in the elbasvir-grazoprevir arm and 94.4% (84 of 89) in the elbasvir-grazoprevir plus ribavirin arm. For those with HCV genotype 1 who received 16 weeks of treatment, SVR12 was obtained in 95.8% (91 of 95) in the elbasvir-grazoprevir arm and in 100% (92 of 92) in the elbasvir-grazoprevir plus ribavirin arm. For individuals with HCV genotype 1 who had baseline NS3 resistance-associated substitutions detected, the SVR12 responses were clearly improved by the addition of ribavirin and the best responses were seen with the addition of ribavirin and extension of treatment to 16 weeks.

- **Pooled NS5A Resistance Study of Elbasvir-Grazoprevir**: This publication summarized a pooled multi-study analysis of baseline NS5A resistance data from the phase 2/3 trials of elbasvir-grazoprevir.[32, 33] Among those enrolled with HCV genotype 1a, approximately 5% of the treatment-naïve and 10% of the prior peginterferon plus ribavirin nonresponders were found to have at least one NS5A resistance-associated substitution at baseline.[32, 33] The resistance-associated substitutions at positions 30, 31, and 93 (detected by population-based sequencing or next-generation sequencing at a sensitivity threshold of 10%) were found to have the greatest impact on treatment efficacy. In comparison, participants with HCV genotype 1b were minimally impacted by the presence of baseline NS5A resistance-associated substitutions.

Glecaprevir-Pibrentasvir

- **ENDURANCE-1**: In this phase 3 open-label trial, 703 noncirrhotic adults with HCV genotype 1 were randomized to receive either 8 or 12 weeks of glecaprevir-pibrentasvir.[21] Among those enrolled, 38% were treatment experienced (3 were sofosbuvir experienced and the remainder interferon experienced) and 33 had HIV coinfection.[21] The SVR12 rate was 99% for the 8-week arm and 99.7% for the 12-week arm, and the SVR rate remained high in persons with HIV coinfection, prior treatment experience, and baseline resistance-associated substitutions.

- **EXPEDITION-1**: This phase 3, single-arm, open-label trial evaluated the safety and efficacy of 12 weeks of glecaprevir-pibrentasvir in 146 adults with compensated cirrhosis and HCV genotype 1, 2, 4, 5, or 6 infection.[22] Sixty percent had HCV genotype 1 and 75% were treatment naïve. For participants with HCV genotype 1 infection, 99% (89 of 90) achieved an SRV12. One participant with HCV genotype 1a had a viral relapse at week 8 post-treatment; resistance testing detected a Y93N resistance-associated substitution at baseline and at the time of failure.

- **EXPEDITION-2**: This phase 3, open-label, dual-arm trial enrolled adults with HCV genotype 1, 2, 3, 4, 5, or 6 and HIV coinfection; 137 participants without cirrhosis received 8 weeks of glecaprevir-pibrentasvir and 16 participants with compensated cirrhosis received 12 weeks of glecaprevir-pibrentasvir.[23] Among the 94 participants with HCV genotype 1, 100% achieved an SRV12. All but 10 who enrolled in the study were taking either raltegravir, dolutegavir, or rilpivirine as the anchor drug for HIV antiretroviral therapy.

- **MAGELLAN-1 (Part 1)**: This was an open-label phase 2 study evaluating the safety and efficacy of glecaprevir plus pibrentasvir, with or without ribavirin, for 12 weeks in noncirrhotic individuals with HCV genotype 1 who previously failed DAA therapy.[34] Fifty participants were enrolled, 6 of whom received glecaprevir 200 mg plus pibrentasvir 80 mg (arm A), 22 of whom received glecaprevir 300 mg plus pibrentasvir 120 mg plus ribavirin 800 mg (arm B), and 22 of whom received glecaprevir 200
mg plus pibrentasvir 120mg (arm C).[34] Fifty percent of persons in the study were NS5A naïve but protease inhibitor experienced, 16% were NS5A experienced but protease inhibitor naïve, and 34% were NS5A experienced and protease inhibitor experienced.[34] In an intention-to-treat analysis, 100% of participants in arm A, 95% in arm B, and 86% in arm C achieved an SVR12.[34]

**MAGELLAN-1 (Part 2):** This was a randomized, open-label, phase 3 study evaluating the safety and efficacy of fixed dose glecaprevir-pibrentasvir for 12 or 16 weeks in DAA treatment-experienced adults with HCV genotype 1 or 4.[35] Of the 91 participants enrolled, 30% had compensated cirrhosis, 30% were protease inhibitor treatment experienced, 37% were NS5A treatment experienced, and 33% were protease inhibitor and NS5A treatment experienced.[35] Among those individuals with prior protease inhibitor treatment experience, an SVR12 was achieved in 100% in both the 12-week and 16-week arms.[35] Among those with prior NS5A treatment experience, SVR12 was obtained in 88% of those in the 12-week arm and 94% in the 16-week arm.[35] Only 79% and 81% of the NS5A and protease inhibitor treatment-experienced participants achieved an SVR12 in the 12-week and 16-week arms, respectively.[35]

**Ledipasvir-Sofosbuvir**

- **ION-2:** In this phase 3 trial, 440 treatment-experienced adults with HCV genotype 1 infection, with or without cirrhosis, received a 12- or 24-week treatment with fixed-dose combination ledipasvir-sofosbuvir, with or without ribavirin.[36] For participants in the 12-week arm, SVR12 was achieved in 94% (102 of 109) treated with ledipasvir-sofosbuvir and in 96% (107 of 111) treated with ledipasvir-sofosbuvir plus ribavirin; with 24 weeks of therapy the SVR12 rates were 99%, with or without ribavirin. Individuals with cirrhosis who received 12 weeks of therapy had lower SVR rates than those without cirrhosis. In addition, participants with cirrhosis had higher SVR rates with 24 weeks of ledipasvir-sofosbuvir than with 12 weeks (100% versus 86%).

- **NIAID Retreatment of Sofosbuvir Failures (Genotype 1):** In this small single-arm study by the NIAID, adults with HCV genotype 1 infection who had relapsed with prior therapy with 24 weeks of sofosbuvir and ribavirin in the SPARE study were subsequently treated with 12 weeks of ledipasvir-sofosbuvir and 100% (14 of 14) achieved an SVR12.[37]

- **Retreatment of Sofosbuvir Failures from prior Clinical Trials:** This phase 2 trial enrolled adults with genotype 1 chronic HCV who failed a sofosbuvir-containing regimen while participating in a phase 2 or 3 Gilead-sponsored clinical trial.[38] In a 12-week treatment arm, study participants received retreatment with ledipasvir-sofosbuvir plus ribavirin. The study design permitted enrollment of individuals with compensated cirrhosis. Preliminary results from this 12-week group showed an SVR12 rate of 98% (50 of 51).

- **SIRIUS** This phase 2, double-blind trial compared the efficacy of a 12-week course of ledipasvir-sofosbuvir plus ribavirin versus a 24-week course of ledipasvir-sofosbuvir in treatment-experienced adults with HCV genotype 1 and compensated cirrhosis.[39] Investigators enrolled 155 participants in the trial and all had previously sequentially failed dual therapy with peginterferon and ribavirin and triple therapy with peginterferon and ribavirin and an NS3/4A protease inhibitor. Among persons who received a 12-week course of ledipasvir-sofosbuvir plus ribavirin, 96% achieved an SVR12 compared with 97% in the group that received a 24-week course of ledipasvir-sofosbuvir. This study suggests that in genotype 1 treatment-experienced patients with cirrhosis, a 12-week course of ledipasvir-sofosbuvir plus ribavirin provides similar SVR12 rates as a 24-week course of ledipasvir-sofosbuvir and this 12-week regimen provides a more cost-effective option.[39]

**Sofosbuvir-Velpatasvir**

- **ASTRAL-1:** In the phase 3 ASTRAL-1 trial, investigators randomized treatment-naïve and treatment-experienced adults with chronic HCV genotype 1, 2, 4, 5, or 6 infection in a 5:1 ratio to receive a
A 12-week course of either sofosbuvir-velpatasvir or placebo.[26] For those participants assigned to sofosbuvir-velpatasvir (n=624), 34% had genotype 1a, 19% had genotype 1b, 19% had compensated cirrhosis, and 28% were treatment experienced (most of whom had interferon-based therapy; those with prior NS5A or NS5B experience were excluded). Among treatment-experienced participants, the SVR rate was 100% (78/78) in those with genotype 1a infection and 97% (31/32) in those with genotype 1b.[26]

Polaris-2: In this phase 3 open-labeled trial, adults with chronic HCV genotype 1, 2, 3, or 4 who were naïve to DAA therapy (prior peginterferon and ribavirin allowed) were randomized to either 8 weeks of sofosbuvir-velpatasvir-voxilaprevir or 12 weeks of sofosbuvir-velpatasvir.[27] Among the 941 participants, compensated cirrhosis was present in 18% and HCV genotype 1 in 49%. Sustained virologic response occurred in 95% and 98% in sofosbuvir-velpatasvir-voxilaprevir and sofosbuvir-velpatasvir arms, respectively. Only 93% of the HCV genotype 1 participants achieved an SVR12 in the 8-week arm (92% among genotype 1a versus 97% among genotype 1b). Notably, SVR occurred in 90% of participants with cirrhosis in the 8-week arm compared with 99% in the 12-week arm. The investigators concluded this study did not establish sofosbuvir-velpatasvir-voxilaprevir for 8 weeks as noninferior to sofosbuvir-velpatasvir for 12 weeks.

Sofosbuvir-Velpatasvir-Voxilaprevir

Polaris-1: In this phase 3 placebo-controlled trial, investigators enrolled adults with chronic HCV genotypes 1, 2, 3, 4, 5, or 6 who had previously received treatment that included an NS5A inhibitor.[40] Participants with HCV genotype 1 were randomized in a 2:1 ratio to either the active arm, a fixed-dose combination of sofosbuvir-velpatasvir-voxilaprevir once daily for 12 weeks, or placebo arm (that received sofosbuvir-velpatasvir-voxilaprevir after follow-up).[40] Individuals with HCV genotype 2, 3, 4, 5, or 6 were assigned to the active arm. Most participants were either ledipasvir or daclatasvir experienced (51% and 27%, respectively) and compensated cirrhosis was present in 46% of those in the active arm. The overall SVR12 rate was 96% by intent-to-treat analysis, with 6 viral relapses among those who failed sofosbuvir-velpatasvir-voxilaprevir. An SVR12 occurred in 99% of those who were not cirrhotic and 93% of cirrhotic patients. The SVR12 rates were not associated with the presence of NS5A or other resistance-associated substitutions.[40]

Polaris-4: In this phase 3, active-comparator, open-labeled trial, 314 adults with chronic HCV genotype 1, 2, or 3 with prior direct-acting antiviral therapy without an NS5A inhibitor were randomized to receive either sofosbuvir-velpatasvir-voxilaprevir or sofosbuvir-velpatasvir for 12 weeks.[40] Compensated cirrhosis was present in 46% of participants and prior sofosbuvir exposure in 80%. For participants with HCV genotype 1a, the SVR12 rates were 98% and 89% for the sofosbuvir-velpatasvir-voxilaprevir and sofosbuvir-velpatasvir arms, respectively. For HCV genotype 1b, the SVR12 rates were 96% for the sofosbuvir-velpatasvir-voxilaprevir arm and 95% for the sofosbuvir-velpatasvir arm.[40] Virologic relapse was confirmed at week 4 for 1 sofosbuvir-velpatasvir-voxilaprevir recipient and in 14 participants who received sofosbuvir-velpatasvir (5 of whom had genotype 1a).[40]
Summary Points

- For initial therapy of HCV genotype 1a infection in adults without cirrhosis, four coformulated regimens with similar efficacy are recommended in the AASLD-IDSA HCV Guidance: elbasvir-grazoprevir (12 weeks, if no key resistance-associated substitutions are detected on pretreatment NS5A testing); glecaprevir-pibrentasvir (8 weeks); ledipasvir-sofosbuvir (8 weeks for persons without HIV infection and HCV RNA less than 6 million IU/mL; otherwise 12 weeks); or sofosbuvir-velpatasvir (12 weeks).
- For initial therapy of HCV genotype 1a infection in adults who have compensated cirrhosis, three 12-week regimens with similar efficacy are recommended: elbasvir-grazoprevir (if no key resistance-associated substitutions are detected on pretreatment NS5A testing); ledipasvir-sofosbuvir; or sofosbuvir-velpatasvir. One 8-week regimen is also recommended: glecaprevir-pibrentasvir.
- For initial therapy of HCV genotype 1b infection in adults with cirrhosis, the recommended regimens are the same as for noncirrhotic adults with HCV genotype 1a, except that baseline NS5A resistance testing is not required for elbasvir-grazoprevir treatment of persons with HCV genotype 1b, since treatment of HCV genotype 1b with elbasvir-grazoprevir is not significantly impacted by baseline NS5A resistance-associated substitutions.
- For initial therapy of HCV genotype 1b infection in adults with compensated cirrhosis, the recommended regimens are the same as for genotype 1a with compensated cirrhosis, except that baseline NS5A resistance testing is not required for genotype 1b adults treated with elbasvir-grazoprevir, since treatment of HCV genotype 1b with elbasvir-grazoprevir is not significantly impacted by baseline NS5A resistance-associated substitutions.
- Retreatment of persons with HCV genotype 1 and prior failure with peginterferon-based therapy, including peginterferon plus first-generation protease inhibitors (telaprevir, boceprevir) is usually the same as for initial treatment of persons with HCV genotype 1.
- The retreatment of DAA-experienced adults with HCV genotype 1 infection depends on the prior DAA regimen that was taken.
**Citations**


4. AASLD-IDSA. HCV Guidance: Recommendations for testing, management, and treating hepatitis C. Treatment-Naive Genotype 1. [AASLD-IDSA Hepatitis C Guidance]

5. AASLD-IDSA. HCV Guidance: Recommendations for testing, management, and treating hepatitis C. Retreatment of persons in whom prior therapy failed. [AASLD-IDSA Hepatitis C Guidance]


11. AASLD-IDSA. HCV Guidance: Recommendations for testing, management, and treating hepatitis C. Initial treatment of HCV infection: treatment-naive genotype 1a without cirrhosis. [AASLD-IDSA Hepatitis C Guidance]

12. AASLD-IDSA. HCV Guidance: Recommendations for testing, management, and treating hepatitis C. Initial treatment of HCV infection: treatment-naive genotype 1a with compensated cirrhosis. [AASLD-IDSA Hepatitis C Guidance]


17. AASLD-IDSA. HCV Guidance: Recommendations for testing, management, and treating hepatitis C. Initial treatment of HCV infection: treatment-naive genotype 1b without cirrhosis.

18. AASLD-IDSA. HCV Guidance: Recommendations for testing, management, and treating hepatitis C. Initial treatment of HCV infection: treatment-naive genotype 1b with compensated cirrhosis.


20. Lawitz E, Gane E, Pearlman B, et al. Efficacy and safety of 12 weeks versus 18 weeks of treatment with grazoprevir (MK-5172) and elbasvir (MK-8742) with or without ribavirin for hepatitis C virus genotype 1 infection in previously untreated patients with cirrhosis and patients with previous null response with or without cirrhosis (C-WORTHY): a randomised, open-label phase 2 trial. Lancet. 2015;385:1075-86.


28. AASLD-IDSA. HCV Guidance: Recommendations for testing, management, and treating hepatitis C. Retreatment of persons in whom prior therapy failed: Glecaprevir/Pibrentasvir Treatment Failures. [AASLD-IDSA Hepatitis C Guidance]

29. AASLD-IDSA. HCV Guidance: Recommendations for testing, management, and treating hepatitis C. Retreatment of persons in whom prior therapy failed: Multiple DAA Treatment Failures (All Genotypes), Including Sofosbuvir/Velpatasvir/Voxilaprevir or Sofosbuvir Plus Glecaprevir/Pibrentasvir. [AASLD-IDSA Hepatitis C Guidance]

30. AASLD-IDSA. HCV Guidance: Recommendations for testing, management, and treating hepatitis C. Retreatment of persons in whom prior therapy failed: Sofosbuvir-Based and Elbasvir/Grazoprevir Treatment Failures. [AASLD-IDSA Hepatitis C Guidance]


References

- AASLD-IDSA. HCV Guidance: Recommendations for testing, management, and treating hepatitis C. [AASLD-IDSA Hepatitis C Guidance]

- AASLD-IDSA. HCV Guidance: Recommendations for testing, management, and treating hepatitis C. Retreatment of persons in whom prior therapy has failed: peginterferon/ribavirin-experienced, genotype 1b patients without cirrhosis. [AASLD-IDSA Hepatitis C Guidance]


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• Lawitz E, Buti M, Vierling JM, et al. Safety and efficacy of a fixed-dose combination regimen of grazoprevir, ruzasvir, and uprifosbuvir with or without ribavirin in participants with and without cirrhosis with chronic hepatitis C virus genotype 1, 2, or 3 infection (C-CREST-1 and C-CREST-2, part B): two randomised, phase 2, open-label trials. Lancet Gastroenterol Hepatol. 2017;2:814-23. [PubMed Abstract] -


• Lawitz E, Matusow G, DeJesus E, et al. Simeprevir plus sofosbuvir in patients with chronic hepatitis C


  [PubMed Abstract]

  [PubMed Abstract]

  [PubMed Abstract]

  [PubMed Abstract]

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Figures

Figure 1 Classes of Direct-Acting Antiviral Agents Used to Treat HCV

Note that all medications in gray boxes have been discontinued and are no longer manufactured in the United States.

<table>
<thead>
<tr>
<th>NS3/4A Protease Inhibitors</th>
<th>NS5A Inhibitors</th>
<th>NS5B Polymerase Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boceprevir</td>
<td>Daclatasvir</td>
<td>Dasabuvir</td>
</tr>
<tr>
<td>Glecaprevir</td>
<td>Elbasvir</td>
<td>Sofosbuvir</td>
</tr>
<tr>
<td>Grazoprevir</td>
<td>Ledipasvir</td>
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<tr>
<td>Paritaprevir</td>
<td>Ombitasvir</td>
<td></td>
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<tr>
<td>Simeprevir</td>
<td>Pibrentasvir</td>
<td></td>
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<tr>
<td>Telaprevir</td>
<td>Velpatavir</td>
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<tr>
<td>Voxilaprevir</td>
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</table>
# Table 1. AASLD-IDSA HCV Guidance for Genotype 1a: Initial Treatment

Treatmen-Naïve Genotype 1a Patients Without Cirrhosis

Recommended and alternative regimens listed by evidence level and alphabetically

<table>
<thead>
<tr>
<th>Recommended for Treatment-Naïve Genotype 1a Patients Without Cirrhosis</th>
<th>Elbasvir-Grazoprevir</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) one tablet once daily for 12 weeks</em></td>
<td>Rating: <strong>Class I</strong>, <strong>Level A</strong></td>
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<tr>
<td>For patients without baseline NS5A resistance-associated substitutions (RASs) for elbasvir; these NS5A RASs include genotype 1a RASs at amino acid positions 28, 30, 31, or 93 known to confer antiviral resistance.</td>
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</tr>
</tbody>
</table>

<table>
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<tr>
<th>Recommended for Treatment-Naïve Genotype 1a Patients Without Cirrhosis</th>
<th>Glecaprevir-Pibrentasvir</th>
</tr>
</thead>
<tbody>
<tr>
<td>&quot;Fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) once daily for 8 weeks&quot;</td>
<td>Rating: <strong>Class I</strong>, <strong>Level A</strong></td>
</tr>
<tr>
<td>Note: &quot;This is taken as 3 tablets once daily with each fixed-dose tablet containing glecaprevir (100 mg)/pibrentasvir (40 mg).&quot;</td>
<td></td>
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</tbody>
</table>

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<tr>
<th>Recommended for Treatment-Naïve Genotype 1a Patients Without Cirrhosis</th>
<th>Ledipasvir-Sofosbuvir</th>
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<tbody>
<tr>
<td>&quot;Fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) one tablet once daily for 12 weeks&quot;</td>
<td>Rating: <strong>Class I</strong>, <strong>Level A</strong></td>
</tr>
</tbody>
</table>

<table>
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<tr>
<th>Recommended for Treatment-Naïve Genotype 1a Patients Without Cirrhosis</th>
<th>Ledipasvir-Sofosbuvir</th>
</tr>
</thead>
<tbody>
<tr>
<td>&quot;Fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) one tablet once daily for 8 weeks&quot;</td>
<td>Rating: <strong>Class I</strong>, <strong>Level B</strong></td>
</tr>
<tr>
<td>For patients who are HIV-uninfected and whose HCV RNA level is &lt;6 million IU/mL.</td>
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<table>
<thead>
<tr>
<th>Recommended for Treatment-Naïve Genotype 1a Patients Without Cirrhosis</th>
<th>Sofosbuvir-Velpatasvir</th>
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<tr>
<td>&quot;Fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) one tablet once daily for 12 weeks&quot;</td>
<td>Rating: <strong>Class I</strong>, <strong>Level A</strong></td>
</tr>
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</table>

Source: AASLD-IDSA. HCV Guidance: Recommendations for testing, management, and treating hepatitis C. Initial treatment of HCV infection: treatment-naïve genotype 1a without cirrhosis. [AASLD-IDSA Hepatitis C](https://www.hepatitis.com)
Table 2. AASLD-IDSA HCV Guidance for Genotype 1a: Initial Treatment
Treatment-Naïve Genotype 1a Patients With Compensated Cirrhosis^

Recommended and alternative regimens listed by evidence level and alphabetically

| Recommended for Treatment-Naïve Genotype 1a Patients With Compensated Cirrhosis^ |
| Elbasvir-Grazoprevir |
| Fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) one tablet once daily for 12 weeks |
| For patients without baseline NS5A resistance-associated substitutions (RASs) for elbasvir; these NS5A RASs include genotype 1a RASs at amino acid positions 28, 30, 31, or 93 known to confer antiviral resistance. |
| Rating: Class I, Level A |

| Recommended for Treatment-Naïve Genotype 1a Patients With Compensated Cirrhosis^ |
| Ledipasvir-Sofosbuvir |
| Fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) one tablet once daily for 12 weeks |
| Rating: Class I, Level A |

| Recommended for Treatment-Naïve Genotype 1a Patients With Compensated Cirrhosis^ |
| Sofosbuvir-Velpatasvir |
| Fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) one tablet once daily for 12 weeks |
| Rating: Class I, Level A |

| Recommended for Treatment-Naïve Genotype 1a Patients With Compensated Cirrhosis^ |
| Glecaprevir-Pibrentasvir |
| *Fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) once daily for 8 weeks |
| For persons with HIV/HCV coinfection, a treatment duration of 12 weeks is recommended. |
| Rating: Class I, Level B |
| Note: *This is taken as 3 tablets once daily with each fixed-dose tablet containing glecaprevir (100 mg)/pibrentasvir (40 mg). |

^For treatment of patients with decompensated cirrhosis, see the AASLD-IDSA Guidance: Unique Populations—Patients with Decompensated Cirrhosis.

# Table 3. AASLD-IDSA HCV Guidance for Genotype 1b: Initial Treatment
Treatment-Naïve Genotype 1b Patients Without Cirrhosis

Recommended and alternative regimens listed by evidence level and alphabetically.

## Recommended for Treatment-Naïve Genotype 1b Patients Without Cirrhosis

### Elbasvir-Grazoprevir

Fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) one tablet once daily for 12 weeks

An 8-week regimen can be considered in those with genotype 1b infection and mild fibrosis.

Rating: [Class I, Level A](#)

### Glecaprevir-Pibrentasvir

*Fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) once daily for 8 weeks

Note: *This is taken as 3 tablets once daily with each fixed-dose tablet containing glecaprevir (100 mg)/pibrentasvir (40 mg)

Rating: [Class I, Level A](#)

### Ledipasvir-Sofosbuvir

Fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) one tablet once daily for 12 weeks

For patients who are HIV-uninfected, and whose HCV RNA level is <6 million IU/mL. For HIV-HCV coinfected patients, a treatment duration of 12 weeks is recommended.

Rating: [Class I, Level B](#)

### Sofosbuvir-Velpatasvir

Fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) one tablet once daily for 12 weeks

Rating: [Class I, Level A](#)

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Source: AASLD-IDSA. HCV Guidance: Recommendations for testing, management, and treating hepatitis C. Initial treatment of HCV infection: treatment-naïve genotype 1b without cirrhosis. [AASLD-IDSA Hepatitis C](#)
### Table 4. AASLD-IDSA HCV Guidance for Genotype 1b: Initial Treatment

**Treatment-Naïve Genotype 1b Patients With Compensated Cirrhosis**

Recommended and alternative regimens listed by evidence level and alphabetically.

<table>
<thead>
<tr>
<th>Recommended for Treatment-Naïve Genotype 1b Patients With Compensated Cirrhosis</th>
<th>Rating:</th>
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</table>
| **Elbasvir-Grazoprevir**<br>
*Fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) one tablet once daily for 12 weeks* | **Class I, Level A** |
| **Ledipasvir-Sofosbuvir**<br>
*Fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) one tablet once daily for 12 weeks* | **Class I, Level A** |
| **Sofosbuvir-Velpatasvir**<br>
*Fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) one tablet once daily for 12 weeks* | **Class I, Level A** |
| **Glecaprevir-Pibrentasvir**<br>
*Fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) once daily for 8 weeks*<br>
For HIV/HCV-coinfected patients, a treatment duration of 12 weeks is recommended. | **Class I, Level B** |

Note: *This is taken as 3 tablets once daily with each fixed-dose tablet containing glecaprevir (100 mg)/pibrentasvir (40 mg).*

^For treatment of patients with decompensated cirrhosis, see the AASLD-IDSA Guidance: Unique Populations—Patients with Decompensated Cirrhosis.

### Table 5. AASLD-IDSA HCV Guidance: Retreatment
Sofosbuvir-Based Treatment Failures, With or Without Compensated Cirrhosis

Recommended and alternative regimens listed by evidence level and alphabetically

#### Recommended for Sofosbuvir-Based Treatment Failures, With or Without Compensated Cirrhosis

**Sofosbuvir-Velpatasvir-Voxilaprevir**

*Fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg) one tablet once daily for 12 weeks*

For persons with genotype 3 and cirrhosis, add weight-based ribavirin if there are no contraindications to ribavirin.

Rating: **Class I, Level A**

#### Alternative for Sofosbuvir-Based Treatment Failures, With or Without Compensated Cirrhosis

**Glecaprevir-Pibrentasvir**

*Fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) once daily for 16 weeks*

This regimen is not recommended for persons with (1) prior exposure to an NS5A inhibitor plus NS3/4 protease inhibitor regimens (e.g. elbasvir-grazoprevir or glecaprevir-pibrentasvir), or (2) persons with genotype 3 infection with sofosbuvir and NS5A inhibitor experience (e.g. ledipasvir-sofosbuvir or sofosbuvir-velpatasvir)

Rating: **Class IIa, Level A**

Note: *This is taken as 3 tablets once daily with each fixed-dose tablet containing glecaprevir (100 mg)/pibrentasvir (40 mg).*

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Table 6. AASLD-IDSA HCV Guidance: Retreatment Elbasvir-Grazoprevir Treatment Failures, With or Without Compensated Cirrhosis

Recommended and alternative regimens listed by evidence level and alphabetically

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<thead>
<tr>
<th>Recommended for Elbasvir-Grazoprevir Treatment Failures, With or Without Compensated Cirrhosis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sofosbuvir-Velpatasvir-Voxilaprevir</strong></td>
</tr>
<tr>
<td>Fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg) one tablet once daily for 12 weeks</td>
</tr>
<tr>
<td>For persons with genotype 3 and cirrhosis, add weight-based ribavirin if there are no contraindications to ribavirin.</td>
</tr>
<tr>
<td>Rating: Class I, Level A</td>
</tr>
</tbody>
</table>

Table 7. AASLD-IDSA HCV Guidance for All Genotypes: Retreatment Glecaprevir-Pibrentasvir Treatment Failures (All Genotypes), With or Without Compensated Cirrhosis

<table>
<thead>
<tr>
<th>Recommended for Glecaprevir-Pibrentasvir Treatment Failures (All Genotypes), With or Without Compensated Cirrhosis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Glecaprevir-Pibrentasvir</strong> + <strong>Sofosbuvir</strong> + <strong>Ribavirin</strong></td>
</tr>
</tbody>
</table>

- **Glecaprevir-Pibrentasvir**
  - Fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) once daily for 16 weeks
- **Sofosbuvir**
  - (400 mg) one tablet once daily for 16 weeks
- **Ribavirin**
  - 1000 mg if <75 kg or 1200 mg if ≥75 kg for 16 weeks (the daily dose is given in two divided doses)

For patients with or without compensated cirrhosis

Rating: **Class Ila, Level B**

Note: *This is taken as 3 tablets once daily with each fixed-dose tablet containing glecaprevir (100 mg)/pibrentasvir (40 mg)

<table>
<thead>
<tr>
<th>Recommended for Glecaprevir-Pibrentasvir Treatment Failures (All Genotypes), With or Without Compensated Cirrhosis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sofosbuvir-Velpatasvir-Voxilaprevir</strong></td>
</tr>
</tbody>
</table>

- Fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg) one tablet once daily for 12 weeks

For patients without cirrhosis

Rating: **Class Ila, Level B**

<table>
<thead>
<tr>
<th>Recommended for Glecaprevir-Pibrentasvir Treatment Failures (All Genotypes), With or Without Compensated Cirrhosis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sofosbuvir-Velpatasvir-Voxilaprevir</strong> + <strong>Ribavirin</strong></td>
</tr>
</tbody>
</table>

- **Sofosbuvir-Velpatasvir-Voxilaprevir**
  - Fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg) one tablet once daily for 12 weeks
- **Ribavirin**
  - 1000 mg if <75 kg or 1200 mg if ≥75 kg for 12 weeks (the daily dose is given in two divided doses)

For patients with compensated cirrhosis

Rating: **Class Ila, Level C**

^For treatment of patients with decompensated cirrhosis, see the AASLD-IDSA Guidance: Unique Populations—Patients with Decompensated Cirrhosis

Table 8. AASLD-IDSA HCV Guidance for All Genotypes: Retreatment Multiple DAA Treatment Failures (All Genotypes), Including Sofosbuvir-Velpatasvir-Voxilaprevir or Sofosbuvir Plus Glecaprevir-Pibrentasvir

Recommended for Multiple DAA Treatment Failures (All Genotypes), Including Sofosbuvir-Velpatasvir-Voxilaprevir or Sofosbuvir Plus Glecaprevir-Pibrentasvir^  

<table>
<thead>
<tr>
<th>Glecaprevir-Pibrentasvir</th>
<th>Sofosbuvir (400 mg) one tablet once daily for 16 weeks#</th>
<th>Ribavirin</th>
</tr>
</thead>
<tbody>
<tr>
<td>*Fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) once daily for 16 weeks#</td>
<td></td>
<td>1000 mg if &lt;75 kg or 1200 mg if ≥75 kg for 16 weeks# (the daily dose is given in two divided doses)</td>
</tr>
</tbody>
</table>

#Extension of treatment to 24 weeks should be considered in extremely difficult cases (eg, genotype 3 with cirrhosis) or failure following sofosbuvir plus glecaprevir-pibrentasvir.

Rating: **Class IIa, Level B**  
Note: *This is taken as 3 tablets once daily with each fixed-dose tablet containing glecaprevir (100 mg)/pibrentasvir (40 mg)

Recommended for Multiple DAA Treatment Failures (All Genotypes), Including Sofosbuvir-Velpatasvir-Voxilaprevir or Sofosbuvir Plus Glecaprevir-Pibrentasvir^  

<table>
<thead>
<tr>
<th>Sofosbuvir-Velpatasvir-Voxilaprevir</th>
<th>Ribavirin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg) one tablet once daily for 24 weeks</td>
<td>1000 mg if &lt;75 kg or 1200 mg if ≥75 kg for 24 weeks (the daily dose is given in two divided doses)</td>
</tr>
</tbody>
</table>

Rating: **Class IIa, Level B**

^For treatment of patients with decompensated cirrhosis, see the AASLD-IDSA Guidance: Unique Populations—Patients with Decompensated Cirrhosis
