Treatment of HCV Genotype 5 or 6

Introduction

Background

In the United States, fewer than 2% of hepatitis C virus (HCV) infections involve genotype 5 or 6 infection.[1] In contrast, infection with HCV genotype 5 is endemic in South Africa, where up to 40% of individuals with chronic HCV have genotype 5 infection.[2,3,4] Scattered pockets of HCV genotype 5 have also been isolated from regions in Europe and North and Eastern sub-Saharan Africa.[4,5,6] There is only one subtype of HCV genotype 5 (subtype 5a).[3] Little is known about the natural history of individuals with genotype 5 HCV. Infection with HCV genotype 6 has primarily occurred in China, Hong Kong, Korea, Taiwan, and Southeast Asia, including Thailand, Vietnam, Singapore, and Malaysia.[7,8,9] Almost all cases of HCV genotype 6 in the United States have involved immigrants from Asia and Southeast Asia.[10] Available data suggest that adults with HCV genotype 6 infection have a similar natural history as those with genotype 1.[11] Because of the low prevalence of HCV genotype 5 or 6 in clinical trials, less is known about the optimal treatment of HCV genotype 5 or 6 infection compared with the more common genotypes. The following discussion regarding initial treatment and retreatment of adults with genotype 5 or 6 chronic HCV assumes the person and their clinician have already made the decision to initiate HCV therapy. This topic review does not address the treatment of HCV genotype 5 or 6 in persons with decompensated cirrhosis, severe renal impairment (or end-stage renal disease), or post-liver transplantation.

Medications used to Treat Hepatitis C

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 direct-acting antiviral (DAA) agents exert their action at specific steps in the HCV life cycle. There are three major classes of DAA medications: (1) nonstructural proteins 3/4A (NS3/4A) protease inhibitors, (2) NS5A inhibitors, and (3) NS5B polymerase inhibitors (Figure 1); the NS5B polymerase inhibitors include the nucleoside analogs and nonnucleoside analogs.[12,13] Adherence with the treatment regimen is extremely important. Thus, patients 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 5 or 6 Treatment Regimens

For adults with HCV genotype 5 or 6 chronic infection, two key factors influence the choice and duration of therapy: cirrhosis status and prior treatment experience. In addition, the cost of the regimen, insurance coverage, and patient or 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 genotypes 5 or 6 and for retreatment of adults in whom prior therapy failed, including those with HCV genotypes 5 or 6.\[14,15\]

- AASLD-IDSA HCV Guidance for Treatment-Naïve Patients with Genotype 5 or 6 HCV
- AASLD-IDSA HCV Guidance for Retreatment of Persons in Whom Prior Therapy Failed
HCV Genotype 5 or 6: Initial Treatment

Background

There are relatively few studies dedicated to the treatment of persons with HCV genotype 5 or 6 chronic infection, particularly for DAA therapy. Older studies in treatment-naïve patients with genotype 5 infection that have examined the combination of interferon (or peginterferon) with ribavirin for 48 weeks have reported sustained virologic response rates at 12 weeks (SVR12) post-treatment of approximately 55 to 70%.\[5,16,17,18,19\] Most of the older studies of initial treatment of persons with HCV genotype 6 were observational (with small sample sizes) and have reported SVR12 rates of 70 to 80% with peginterferon plus ribavirin when given for 48 weeks (and only slightly lower when given for 24 weeks).\[20,21,22,23\] Available data suggest SVR12 rates can exceed 95% with glecaprevir-pibrentasvir, sofosbuvir-velpatasvir, or ledipasvir-sofosbuvir for the initial therapy of HCV genotype 5 or 6 infection.\[24,25,26,27,28\]

Factors to Consider Prior to Choosing Treatment Regimen

For individuals with HCV genotype 5 or 6 chronic infection, little is known regarding baseline factors that may predict response to therapy, but as with other genotypes, cirrhosis and treatment experience probably play a role.

AASLD-IDSA HCV Guidance for Initial Treatment of HCV Genotype 5 and 6

The following is a summary of the AASLD-IDSA HCV Guidance for initial treatment of adults with HCV genotype 5 or 6 infection, including those with compensated cirrhosis.\[29\] 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 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 5 or 6: Initial Treatment Treatment-Naïve Genotype 5 or 6 Patients With and Without Compensated Cirrhosis^  
Recommended regimens listed by evidence level and alphabetically

<table>
<thead>
<tr>
<th>Recommended for Treatment-Naïve Genotype 5 or 6 Patients With and Without Compensated Cirrhosis^</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Glecaprevir-Pibrentasvir</strong></td>
</tr>
<tr>
<td>Fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) once daily for 8 weeks</td>
</tr>
<tr>
<td>For patients with compensated cirrhosis the rating is I,B. For HIV/HCV-coinfected patients, a treatment duration of 12 weeks is recommended.</td>
</tr>
<tr>
<td>Rating: <strong>Class I, Level A</strong></td>
</tr>
<tr>
<td>Note: *This is taken as 3 tablets once daily with each fixed-dose tablet containing glecaprevir (100 mg)/pibrentasvir (40 mg).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Recommended for Treatment-Naïve Genotype 5 or 6 Patients With and Without Compensated Cirrhosis^</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sofosbuvir-Velpatasvir</strong></td>
</tr>
<tr>
<td>Fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) one tablet once daily for 12 weeks</td>
</tr>
<tr>
<td>For patients with and without compensated cirrhosis</td>
</tr>
</tbody>
</table>
**Recommended for Treatment-Naïve Genotype 5 or 6 Patients With and Without Compensated Cirrhosis**

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

For patients with and without compensated cirrhosis. Not recommended for genotype 6e if subtype is known.

Rating: **Class Ila, Level B**

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

Studies of Initial Treatment of Adults with HCV Genotype 5 or 6

The following key studies support the recommendations for treatment of patients with chronic hepatitis C and genotype 5 or 6 infection who are treatment naïve.

Glecaprevir-Pibrentasvir

- **ENDURANCE-4**: In this single-arm, phase 3 trial, 121 adults with HCV genotype 4, 5, or 6 infection (without cirrhosis) were enrolled to receive treatment with a 12-week course of glecaprevir-pibrentasvir.[25] Among those who were enrolled 32% were treatment experienced (all of whom had previously received either interferon plus ribavirin or peginterferon plus ribavirin).[25] Of the 121 participants included in the trial, 21% (26 of 121) had genotype 5 and 16% (19 of 126) had genotype 6. All participants with genotype 5 or 6 achieved an SVR12.[25]

- **ENDURANCE-5,6**: This phase 3b, open-label trial examined the safety and efficacy of glecaprevir-pibrentasvir in treatment-naïve and treatment-experienced adults with HCV genotype 5 or 6.[30] The duration of treatment was 8 weeks in participants without cirrhosis (n = 75) and 12 weeks in those with compensated cirrhosis (n = 9). Overall, 97.6% (82 of 84) of individuals who received treatment achieved an SVR12; treatment success occurred in 96% (22 of 23) of participants with HCV genotype 5 and in 98% (60 of 61) of those with HCV genotype 6. High efficacy was noted across 14 different HCV genotype 6 subtypes.[30]

- **EXPEDITION-1**: This phase 3, single-arm, open-label trial evaluated the safety and efficacy of 12 weeks of glecaprevir-pibrentasvir in treatment-naïve and treatment-experienced adults with compensated cirrhosis and HCV genotype 1, 2, 4, 5, or 6 infection.[26] All (100%) of participants with genotype 5 (n = 2) or genotype 6 (n = 7) achieved an SVR12.[26]

- **EXPEDITION-8**: This single-arm, phase 3b study evaluated the efficacy of glecaprevir-pibrentasvir for 8 weeks in treatment-naïve adults with compensated cirrhosis and HCV genotypes 1, 2, 3, 4, 5, or 6.[31] Among all participants enrolled, only 1 had HCV genotype 5 and 9 had HCV genotype 6; all participants with HCV genotype 5 or 6 achieved an SVR12.[31]

- **SURVEYOR-I and SURVEYOR-II**: The SURVEYOR-I (HCV genotype 1, 4, 5, or 6) and SURVEYOR-II (HCV genotypes 2 or 3) were phase 2, open-label trials of treatment-naïve and treatment-experienced adults without cirrhosis.[32] In the SURVEYOR-I trial, participants with HCV genotype 4, 5, or 6 received 12 weeks of glecaprevir-pibrentasvir. Among those enrolled and treated, one had HCV genotype 5 and 11 had HCV genotype 6.[32] For the participants with HCV genotype 5 or 6, 100% (12 of 12) achieved an SVR12 (data not provided for number of treatment-naïve versus treatment-experienced patients with HCV genotype 5 or 6).[32]

- **SURVEYOR-II (Part 4)**: This phase 2, open-label, single-arm trial evaluated the efficacy of 8 weeks of glecaprevir-pibrentasvir in treatment-naïve and treatment-experienced adults without cirrhosis who had HCV genotype 2, 4, 5, or 6.[25] Treatment-experienced participants had previously received (1) peginterferon (or interferon), with or without ribavirin, or (2) sofosbuvir plus ribavirin, with or without peginterferon.[25] Of the 2 individuals with HCV genotype 5 who were enrolled, both achieved an SVR-12; 90% (9 of 10) of participants with HCV genotype 6 achieved an SVR12, and one was lost to follow up.[25]

Ledipasvir-Sofosbuvir

- **Ledipasvir-Sofosbuvir for HCV Genotype 5**: In a phase 2, open-label study conducted in France, investigators enrolled 21 treatment-naïve and 20 treatment-experienced adults with HCV genotype 5 infection to receive a 12-week course of ledipasvir-sofosbuvir.[28] For the treatment-naïve individuals with HCV genotype 5 infection, 95% (20 of 21) achieved an SVR12. For individuals with cirrhosis, 89% (8 of 9) achieved an SVR12 compared with 97% (31 of 32) without cirrhosis who achieved an SVR12.[28]

- **New Zealand Genotype 3 and 6 Trial**: In this open-label, phase 2 study performed at two centers in New Zealand, investigators enrolled treatment-naïve and treatment-experienced adults with HCV
genotype 3 or 6 infection. [24] One arm of this study enrolled 25 participants with HCV genotype 6 to receive a 12-week course of ledipasvir-sofosbuvir. Overall, 96% (24 of 25) of individuals with HCV genotype 6 achieved an SVR12; the one person in this cohort who did not achieve an SVR12 withdrew from the study at week 8. [24] Only two of the treatment-naïve individuals with HCV genotype 6 had cirrhosis. [24]

• **Systematic Review of HCV Genotype 6 Treatment:** In a 2019 systematic review of response to DAA therapy among persons with genotype 6 HCV, there was significant variability in SVR rates observed following ledipasvir-sofosbuvir therapy. [33] In this review, authors found HCV treatment SVR12 rates varied from a low of 64.1% in a Myanmar study to 100% in a study out of Vietnam. [33] Although factors influencing these discrepant results are felt to be multiple, a variable distribution of genotype 6 subtypes, with a higher prevalence of genotype 6e (a subtype without in vitro activity against ledipasvir-sofosbuvir) in Myanmar, may have contributed to these findings. [33, 34] Pending further data, the AASLD/IDSA guidance recommends against the use of ledipasvir-sofosbuvir in persons with known genotype 6e.

• **United States-Based HCV Genotype 6 Study:** This open-label, prospective study enrolled noncirrhotic individuals with HCV genotype 6 at 4 United States health centers to receive treatment with ledipasvir-sofosbuvir. [35] The noncirrhotic participants received an 8-week treatment course and those with cirrhosis (or prior treatment experience) received a 12-week course. [35] In the 8-week arm, 95% (19/20) achieved an SVR12. Similarly, in the 12-week arm 90% (38/40) achieved an SVR12. [35]

**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 12-week course of either sofosbuvir-velpatasvir or placebo. [27] The study enrollment included 34 individuals with HCV genotype 5 infection and 41 with HCV genotype 6. [27] Among the treatment-naïve participants treated with sofosbuvir-velpatasvir, 96% (23 of 24) with HCV genotype 5 infection achieved an SVR12 and 100% (38 of 38) with HCV genotype 6 achieved an SVR12. [27]

• **POLARIS-2:** This open-label, phase 3 trial compared 12 weeks of sofosbuvir-velpatasvir versus 8 weeks of sofosbuvir-velpatasvir-voxilaprevir in DAA-naïve persons with HCV genotype 1, 2, 3, 4, 5, or 6. [36] There were no participants with HCV genotype 5 who received sofosbuvir-velpatasvir, but, 94% (17 of 18) with HCV genotype 5 who received 8 weeks of sofosbuvir-velpatasvir-voxilaprevir achieved an SVR12. [36] All participants with HCV genotype 6 achieved an SVR12, including 9 in the sofosbuvir-velpatasvir arm and 30 in the sofosbuvir-velpatasvir-voxilaprevir arm. [36]
HCV Genotype 5 or 6: Retreating Persons who Failed Prior Therapy

Background

Given the very low prevalence of genotypes 5 and 6 in settings where HCV therapy is accessible, limited data and experience exist with retreatment of patients with genotype 5 or 6. Recommendations are primarily based on available data in small numbers of treatment-experienced individuals with genotype 5 or 6 from clinical studies, and by extrapolating from experience with other HCV genotypes.

Factors to Consider Prior to Choosing Treatment Regimen

For patients chronically infected with genotype 5 or 6 hepatitis C, insufficient data exist regarding the impact of cirrhosis on the optimal retreatment regimen or duration of therapy given the small numbers of patients in these trials. The retreatment of genotype 5 or 6 patients with decompensated cirrhosis, severe renal impairment (or end-stage renal disease), or post-liver transplantation is not addressed in this lesson.

Baseline Resistance Testing

Baseline resistance testing is not routinely recommended for treatment-experienced patients with HCV genotype 5 or 6 infection.

AASLD-IDSA HCV Guidance for Retreatment of HCV Genotype 5 or 6

The following is a summary of the AASLD-IDSA HCV Guidance for retreatment of adults with hepatitis C genotype 5 or 6 infection, including those without cirrhosis and those with compensated cirrhosis.[14, 37, 38, 39] For individuals with cirrhosis, compensated cirrhosis is defined 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 major exception is that retreatment of persons with HCV genotype 5 or 6 with compensated cirrhosis with glecaprevir-pibrentasvir should be given for 12 weeks as opposed to only 8 weeks in treatment-naive persons with compensated cirrhosis. In the following tables, the recommended regimens are based on prior regimen failure and are listed by evidence level; when the evidence level is considered equivalent, the regimens are listed alphabetically.

Table 2. AASLD-IDSA HCV Guidance: Retreatment

<table>
<thead>
<tr>
<th>Sofosbuvir-Based Treatment Failures, With or Without Compensated Cirrhosis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Recommended and alternative regimens listed by evidence level and alphabetically</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Recommended for Sofosbuvir-Based Treatment Failures, 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 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 3. 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

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## Table 4. 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>
<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 (400 mg) one tablet once daily for 16 weeks</strong></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 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 Glecaprevir-Pibrentasvir Treatment Failures (All Genotypes), With or Without Compensated Cirrhosis

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

For patients without cirrhosis

Rating: **Class IIa, Level B**

### Recommended for Glecaprevir-Pibrentasvir Treatment Failures (All Genotypes), With or Without Compensated Cirrhosis

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

For patients with compensated cirrhosis

Rating: **Class IIa, Level C**

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


## Table 5. 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**

**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)

#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)

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

**Sofosbuvir-Velpatasvir-Voxilaprevir**
Fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg) one tablet once daily for 24 weeks

**Ribavirin**
1000 mg if <75 kg or 1200 mg if ≥75 kg for 24 weeks (the daily dose is given in two divided doses)

Rating: Class IIa, Level B

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

Studies of Retreatment of Adults with HCV Genotype 5 or 6

There are limited data from studies that adequately address the retreatment of adults with HCV genotype 5 or 6 infection who failed prior therapy.

Glecaprevir-Pibrentasvir

- **Combination Analysis**: This combined analysis of phase 2 and 3 studies evaluating 8 weeks or 12 weeks of glecaprevir-pibrentasvir included 30 individuals with HCV genotype 5 and 44 with HCV genotype 6.[40] No participants had cirrhosis and 22% had prior interferon-based treatment failure. Among individuals with HCV genotype 5, 2 received 8 weeks of glecaprevir-pibrentasvir and 28 received 12 weeks; all participants with HCV genotype 5 achieved an SVR12.[40] Among participants with HCV genotype 6, 92% (12/13) of those receiving 8 weeks and 100% (31/31) of those receiving 12 weeks of glecaprevir-pibrentasvir achieved an SVR12. In addition, the single treatment failure in the 8-week group was a nonvirologic failure.[40]

  - **ENDURANCE-5,6**: This phase 3b, open-label trial examined the safety and efficacy of glecaprevir-pibrentasvir exclusively in treatment-naïve and treatment-experienced adults with HCV genotype 5 or 6.[30] Duration of treatment was 8 weeks in participants without cirrhosis (n = 75) and 12 weeks in those with compensated cirrhosis (n = 9). Overall, 97.6% (82 of 84) of individuals enrolled achieved an SVR12; treatment success occurred in 96% (22 of 23) of participants with HCV genotype 5 and in 98% (60 of 61) of those with HCV genotype 6.[30] High efficacy was noted across 14 different HCV genotype 6 subtypes.[30]

  - **EXPEDITION-1**: This phase 3, single-arm, open-label trial evaluated the safety and efficacy of 12 weeks of glecaprevir-pibrentasvir in treatment-naïve and treatment-experienced adults with HCV genotype 1, 2, 4, 5, or 6 HCV infection.[26] All (100%) of participants with HCV genotype 5 (n=2) or HCV genotype 6 (n=7) achieved an SVR12 (data not provided for number of treatment-naïve versus treatment-experienced individuals with HCV genotype 5 or 6).[26]

  - **SURVEYOR-I and SURVEYOR-II**: The SURVEYOR-I (HCV genotypes 1, 4, 5 and 6) and SURVEYOR-II (HCV genotypes 2 and 3) were phase 2, open-label trials that enrolled treatment-naïve and treatment-experienced adults without cirrhosis.[32] In the SURVEYOR-I trial, participants with HCV genotype 4, 5, or 6 received 12 weeks of glecaprevir-pibrentasvir.[32] Among those enrolled and treated, one had HCV genotype 5 and the other 11 had HCV genotype 6.[32] All (100%) with HCV genotype 5 or 6 achieved an SVR12 (data not provided for number of treatment-naïve versus treatment-experienced patients with HCV genotype 5 or 6).[32]

Ledipasvir-Sofosbuvir

- **Ledipasvir-Sofosbuvir for Genotype 5 Infection**: In a small, open-label study conducted in France, investigators enrolled 21 treatment-naïve adults and 20 treatment experienced adults with HCV genotype 5 to receive a 12-week course of ledipasvir-sofosbuvir.[28] For the treatment-experienced participants with HCV genotype 5 infection, 95% (19 of 20) achieved an SVR12; cirrhosis status did not impact the SVR12 rates.[28] Analysis of treatment response by cirrhosis status showed SVR12 rates of 89% (8 of 9) for participants with cirrhosis compared with 97% (31 of 32) for those without cirrhosis.[28]

  - **New Zealand Genotype 3 and 6 Trial**: In this open-label, phase 2 study performed at two centers in New Zealand, investigators enrolled treatment-naïve and treatment-experienced adults with HCV genotype 3 or 6 infection.[24] One arm of this study enrolled 25 participants with HCV genotype 6 to receive a 12-week course of ledipasvir-sofosbuvir.[24] Overall, 96% (24 of 25) of the individuals with HCV genotype 6 achieved an SVR12; the one person in this cohort who did not achieve an SVR12 withdrew from the study at week 8. Only two of the treatment-naïve individuals with HCV genotype 6 had cirrhosis.[24]

Sofosbuvir-Velpatasvir
**ASTRAL-1**: In the phase 3 ASTRAL-1 trial, investigators randomized treatment-naïve and treatment-experienced adults with HCV genotype 1, 2, 4, 5, or 6 infection in a 5:1 ratio to receive a 12-week course of either sofosbuvir-velpatasvir or placebo.\[27\] The study included 34 individuals with HCV genotype 5 and 41 with HCV genotype 6. The SVR12 rates for the treatment-experienced participants treated with sofosbuvir-velpatasvir were 100% (11 of 11) in those with HCV genotype 5 and 100% (3 of 3) with HCV genotype 6.\[27\]

**Sofosbuvir-Velpatasvir-Voxilaprevir**

- **POLARIS-1**: In this phase 3, placebo-controlled trial, investigators enrolled adults with HCV genotype 1, 2, 3, 4, 5, or 6 who had previously received treatment that included an NS5A inhibitor to receive sofosbuvir-velpatasvir-voxilaprevir for 12 weeks.\[41\] Individuals with HCV genotype 2, 3, 4, 5, or 6 were all 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 individuals in the active arm.\[41\] For the participants with HCV genotype 5 (n = 1) or HCV genotype 6 infection (n = 6), all (100%) achieved an SRV12.\[41\]
Summary Points

- Infection with HCV genotype 5 is uncommon in the United States, but endemic in South Africa.
- Infection with HCV genotype 6 is also uncommon in the United States and is primarily found in China, Korea, Taiwan, and Southeast Asia.
- Recommendations for initial treatment or retreatment of individuals with HCV genotype 5 or 6 are based on in vitro data, limited data from clinical trials, and observational studies.
- The recommended regimens for initial treatment of adults with HCV genotype 5 or 6, with or without compensated cirrhosis, are: glecaprevir-pibrentasvir for 8 weeks (extend to 12 weeks in persons with HIV infection), sofosbuvir-velpatasvir for 12 weeks, or ledipasvir-sofosbuvir for 12 weeks.
- The recommended regimens for retreatment of peginterferon plus ribavirin-experienced adults with HCV genotype 5 or 6 infection, with or without cirrhosis, are the same as for initial treatment, except that glecaprevir-pibrentasvir should be given for 12 weeks in persons with compensated cirrhosis as opposed to 8 weeks with treatment-naive persons with compensated cirrhosis.
- The recommended regimen for retreatment of DAA-experienced adults with HCV genotype 5 or 6 depends on the prior regimen that was taken.
Citations


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

15. AASLD-IDSA. Recommendations for testing, management, and treating hepatitis C. Treatment-Naive Genotype 5 or 6. [AASLD-IDSA Hepatitis C Guidance] -


29. AASLD-IDSA. Recommendations for testing, management, and treating hepatitis C. Initial treatment of HCV infection: treatment-naive genotype 5 or 6. [AASLD-IDSA Hepatitis C Guidance] -


37. AASLD-IDSA. 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] -
38. AASLD-IDSA. 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] -

39. AASLD-IDSA. 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] -


References

- European Association for the Study of the Liver. EASL recommendations on treatment of hepatitis C: Final update of the series”. J Hepatol. 2020:S0168-8278(20)30548-1. [EASL] -


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>
<td></td>
</tr>
<tr>
<td>Paritaprevir</td>
<td>Ombitasvir</td>
<td></td>
</tr>
<tr>
<td>Simeprevir</td>
<td>Pibrentasvir</td>
<td></td>
</tr>
<tr>
<td>Telaprevir</td>
<td>Velpatasvir</td>
<td></td>
</tr>
<tr>
<td>Voxilaprevir</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Table 1. AASLD-IDSA HCV Guidance for Genotype 5 or 6: Initial Treatment
Treatment-Naïve Genotype 5 or 6 Patients With and Without Compensated Cirrhosis

Recommended regimens listed by evidence level and alphabetically

<table>
<thead>
<tr>
<th>Recommended for Treatment-Naïve Genotype 5 or 6 Patients With and Without Compensated Cirrhosis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Glecaprevir-Pibrentasvir</strong>&lt;br&gt;<em>Fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) once daily for 8 weeks</em>&lt;br&gt;For patients with compensated cirrhosis the rating is I,B. For HIV/HCV-coinfected patients, a treatment duration of 12 weeks is recommended.</td>
</tr>
<tr>
<td>Rating: <strong>Class I</strong>, <strong>Level A</strong>&lt;br&gt;Note: *This is taken as 3 tablets once daily with each fixed-dose tablet containing glecaprevir (100 mg)/pibrentasvir (40 mg).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Recommended for Treatment-Naïve Genotype 5 or 6 Patients With and Without Compensated Cirrhosis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sofosbuvir-Velpatasvir</strong>&lt;br&gt;<em>Fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) one tablet once daily for 12 weeks</em>&lt;br&gt;For patients with and without compensated cirrhosis</td>
</tr>
<tr>
<td>Rating: <strong>Class I</strong>, <strong>Level B</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Recommended for Treatment-Naïve Genotype 5 or 6 Patients With and Without Compensated Cirrhosis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ledipasvir-Sofosbuvir</strong>&lt;br&gt;<em>Fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) one tablet once daily for 12 weeks</em>&lt;br&gt;For patients with and without compensated cirrhosis. Not recommended for genotype 6e if subtype is known.</td>
</tr>
<tr>
<td>Rating: <strong>Class IIA</strong>, <strong>Level B</strong></td>
</tr>
</tbody>
</table>

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

# Table 2. 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 3. AASLD-IDSA HCV Guidance: Retreatment Elbasvir-Grazoprevir Treatment Failures, With or Without Compensated Cirrhosis

Recommended and alternative regimens listed by evidence level and alphabetically

<table>
<thead>
<tr>
<th>Recommended for Elbasvir-Grazoprevir Treatment Failures, With or Without Compensated Cirrhosis</th>
</tr>
</thead>
</table>
| **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 4. 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>
<tr>
<td>For patients with or without compensated cirrhosis</td>
</tr>
<tr>
<td>Rating: <a href="#">Class IIa, Level B</a></td>
</tr>
<tr>
<td>Note: <em>This is taken as 3 tablets once daily with each fixed-dose tablet containing glecaprevir (100 mg)/pibrentasvir (40 mg)</em></td>
</tr>
</tbody>
</table>

<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>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 patients without cirrhosis</td>
</tr>
<tr>
<td>Rating: <a href="#">Class IIa, Level B</a></td>
</tr>
</tbody>
</table>

<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>Fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg) one tablet once daily for 12 weeks</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>
<tr>
<td>For patients with compensated cirrhosis</td>
</tr>
<tr>
<td>Rating: <a href="#">Class IIa, Level C</a></td>
</tr>
</tbody>
</table>

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

Table 5. 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 |
|---|---|---|
| **Glecaprevir-Pibrentasvir**<br> *Fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) once daily for 16 weeks#* | **Sofosbuvir**<br> (400 mg) one tablet once daily for 16 weeks# | **Ribavirin**<br> 1000 mg if <75 kg or 1200 mg if ≥75 kg for 16 weeks# (the daily dose is given in two divided doses) |

#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

| **Sofosbuvir-Velpatasvir-Voxilaprevir**<br> *Fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg) one tablet once daily for 24 weeks* | **Ribavirin**<br> 1000 mg if <75 kg or 1200 mg if ≥75 kg for 24 weeks (the daily dose is given in two divided doses) |

Rating: **Class IIa, Level B**

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