

# Treatment of HCV Genotype 3

This is a PDF version of the following document:

Module 5: [Treatment of Chronic Hepatitis C Infection](#)

Lesson 3: [Treatment of HCV Genotype 3](#)

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<https://www.hepatitisC.uw.edu/go/treatment-infection/treatment-genotype-3/core-concept/all>.

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## Introduction

### Background

Among all persons living with hepatitis C virus (HCV) infection in the United States, approximately 10% have HCV genotype 3 infection, with an even higher proportion of HCV genotype 3 among persons who inject drugs.[1,2,3] Individuals with HCV genotype 3, when compared with persons infected with other HCV genotypes, have relatively faster rates of fibrosis progression, higher prevalence of severe (Grade 3) steatosis, and a higher incidence of hepatocellular carcinoma.[4,5,6,7] In the current direct-acting antiviral (DAA) therapy era, HCV genotype 3 infection has been relatively difficult to treat compared with other HCV genotypes, especially in persons with cirrhosis or prior HCV treatment failure. The following discussion regarding initial treatment and retreatment of HCV genotype 3 assumes the person with HCV and their clinician have already made the decision to initiate HCV treatment. This topic review does not address the treatment of HCV genotype 3 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 DAAs 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.[8,9] Adherence with the treatment regimen is of paramount importance. Thus, individuals 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 3 Treatment Regimen

When considering treatment of persons with chronic HCV genotype 3, five major factors influence the choice and duration of therapy: (1) cirrhosis status, (2) prior treatment experience, (3) coexistent renal disease, (4) drug interactions, and (5) medication cost and/or insurance considerations. With certain regimens for treatment-experienced and/or cirrhotic patients, pretreatment NS5A resistance may also influence both the choice of regimen and duration of therapy. The following treatment recommendations are based on the 2013 AASLD/AST Evaluation for Liver Transplantation Guidelines for initial treatment of adults with HCV genotype 3 and for retreatment of adults in whom prior therapy failed, including those with HCV genotype 3.[11]

- [AASLD-IDSA HCV Guidance for Treatment-Naïve Persons with Genotype 3 HCV](#)
- [AASLD-IDSA HCV Guidance for Retreatment of Persons in Whom Prior Therapy Failed](#)

## HCV Genotype 3: Initial Treatment

### Background

Treatment of HCV genotype 3 infection has emerged in the DAA era as the most treatment-refractory of all the HCV genotypes. Sustained virologic response rates at 12 weeks post-treatment (SVR12) with sofosbuvir plus weight-based ribavirin (given for 12 to 16 weeks) are substantially lower in persons with HCV genotype 3 than with HCV genotype 2.[12,13] The relatively lower SVR12 rates with HCV genotype 3 were improved by using a 12-week course of sofosbuvir plus ribavirin plus peginterferon,[14] or extending the all-oral sofosbuvir plus ribavirin regimen to 24 weeks.[15,16] The dual DAA combination of daclatasvir plus sofosbuvir proved more efficacious than sofosbuvir plus ribavirin combination, but required a longer duration (16 or 24 weeks) in patients with HCV genotype 3 infection and cirrhosis; the role of ribavirin remained unclear when duration was extended.[17,18,19,20] Glecaprevir-pibrentasvir and sofosbuvir-velpatasvir have since become the mainstay of DAA therapy for treatment-naïve patients with HCV genotype 3 infection, with both regimens demonstrating high efficacy, including in patients with compensated cirrhosis.[21,22,23,24,25]

### Factors to Consider Prior to Choosing Initial Treatment Regimen

For persons chronically infected with genotype 3 hepatitis C, four factors should be considered when choosing the initial treatment regimen and duration: (1) the presence of baseline NS5A-resistance-associated substitution Y93H (screening required for patients with cirrhosis or prior treatment experience in whom sofosbuvir-velpatasvir or daclatasvir plus sofosbuvir is being considered), (2) presence or absence of cirrhosis, (3) drug interactions, and (4) cost and/or insurance considerations.

### AASLD-IDSA HCV Guidance for Initial Treatment of HCV Genotype 3

The following is a summary of recommendations issued in the AASLD-IDSA HCV Guidance. The recommendations listed below are for persons with hepatitis C genotype 3 infection who are treatment naïve.[26,27] 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 (see [CTP 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 3: Initial Treatment Treatment-Naïve Genotype 3 Patients Without Cirrhosis

Recommended and alternative regimens listed alphabetically

##### Recommended for Treatment-Naïve Genotype 3 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 3 Patients Without 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](#)

Source: AASLD-IDSA. HCV Guidance: Recommendations for testing, management, and treating hepatitis C. Initial treatment of HCV infection: treatment-naive genotype 3 without cirrhosis. [[AASLD-IDSA Hepatitis C Guidance](#)] - Accessed October 11, 2020.

## Table 2. AASLD-IDSA HCV Guidance for Genotype 3: Initial Treatment Treatment-Naïve Genotype 3 Patients With Compensated Cirrhosis<sup>^</sup>

Recommended and alternative regimens listed by evidence level and alphabetically

### Recommended for Treatment-Naïve Genotype 3 Patients With Compensated Cirrhosis<sup>^</sup>

#### Glecaprevir-Pibrentasvir

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

For HIV/HCV-coinfected patients, 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).

### Recommended for Treatment-Naïve Genotype 3 Patients With Compensated Cirrhosis<sup>^</sup>

#### Sofosbuvir-Velpatasvir

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

For patients without baseline NS5A resistance-associated substitution (RAS) Y93H for velpatasvir.

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

### Alternative for Treatment-Naïve Genotype 3 Patients With Compensated Cirrhosis<sup>^</sup>

#### Sofosbuvir-Velpatasvir

*Fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (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 baseline NS5A resistance-associated substitution (RAS) Y93H for velpatasvir.

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

### Alternative for Treatment-Naïve Genotype 3 Patients With Compensated Cirrhosis<sup>^</sup>

#### Sofosbuvir-Velpatasvir-Voxilaprevir

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

For patients with baseline NS5A resistance-associated substitution (RAS) Y93H for velpatasvir.

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

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

Source: AASLD-IDSA. HCV Guidance: Recommendations for testing, management, and treating hepatitis C. Initial treatment of HCV infection: treatment-naive genotype 3 with compensated cirrhosis [[AASLD-IDSA Hepatitis C Guidance](#)] - Accessed October 11, 2020.

## Studies of Initial Treatment of Adults with HCV Genotype 3

The following key studies support the recommendations for initial treatment of patients with chronic hepatitis C and genotype 3 infection. The medications are listed in alphabetical order.

### Glecaprevir-Pibrentasvir

- [ENDURANCE-3](#): In this phase 3, randomized study, investigators compared the efficacy and safety of 8 or 12 weeks of glecaprevir-pibrentasvir versus 12 weeks of sofosbuvir and daclatasvir in noncirrhotic treatment-naïve adults with HCV genotype 3 infection; 348 individuals were randomized in 2:1 ratio to receive 12 weeks of either glecaprevir-pibrentasvir or sofosbuvir plus daclatasvir whereas 157 were assigned to 8 weeks of glecaprevir-pibrentasvir.[25] For individuals in the 8-week arm, 95% (149 of 157) achieved an SVR12. Similar results were observed in the 12-week arm—95% (222 of 233) achieved an SVR12.
- [EXPEDITION-8](#): This was a phase 3b, single-arm trial to evaluate the efficacy of an 8-week course of glecaprevir-pibrentasvir in treatment-naïve individuals with HCV genotype 1, 2, 3, 4, 5, or 6 and compensated cirrhosis.[28] Among those enrolled, 67% (231 of 343) of these participants had HCV genotype 1 infection.[28] Among the 63 individuals with HCV genotype 3 and cirrhosis, 95% (60 of 63) achieved an SVR12 by intent-to-treat analysis (95% confidence interval for this estimate was 87%-98%).[28]
- [SURVEYOR-II \(Part 3\)](#): In this partially randomized, open-label, multicenter, phase 3 trial, the safety and efficacy of glecaprevir-pibrentasvir was evaluated in treatment-naïve and treatment-experienced adults with HCV genotype 3.[29] Enrollment included 40 treatment-naïve adults with compensated cirrhosis who received 12 weeks of glecaprevir-pibrentasvir. For the treatment-naïve participants 98% (39 of 40) achieved an SVR12.

### Sofosbuvir-Velpatasvir

- [ASTRAL-3](#): The ASTRAL-3 trial was a randomized, open-label, phase 3 study that compared sofosbuvir-velpatasvir for 12 weeks with sofosbuvir plus ribavirin for 24 weeks in adults with HCV genotype 3 infection.[22] Of the 552 persons enrolled in the study, 30% had compensated cirrhosis and 26% were treatment experienced. For the treatment-naïve participants who received sofosbuvir-velpatasvir, 97% (200 of 206) achieved an SVR12, which was significantly better than the 87% (174 of 201) SVR12 rate in treatment-naïve participants who received sofosbuvir plus ribavirin (P

## HCV Genotype 3: Retreating Persons who Failed Prior Therapy

### Factors to Consider Prior to Choosing Retreatment Regimen

For retreatment of adults with HCV genotype 3 infection, several factors influence the regimen choice, including (1) the prior regimen used when treatment failure occurred, (2) the presence or absence of cirrhosis, and (3) cost or insurance considerations. It is also worth noting that the clinical data for treatment-experienced individuals with HCV genotype 3 is more limited for the newest DAAs, such as glecaprevir-pibrentasvir, since these individuals have been encountered less frequently in recent years due to the efficacy of earlier DAA regimens. Therefore, the optimal duration of therapy for retreatment of persons with HCV genotype 3 with glecaprevir-pibrentasvir is not well established. The retreatment of individuals with HCV genotype 3 who have decompensated cirrhosis, renal impairment, acute HCV, 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 genotype 3 infection.

### AASLD-IDSA HCV Guidance for Retreatment of HCV Genotype 3

The following is a summary of AASLD-IDSA HCV Guidance for adults with HCV genotype 3 infection who are treatment experienced and failed prior DAA therapy.<sup>[11,30,31,32]</sup> 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-naïve persons. The recommended regimens are based on prior regimen failure and listed by evidence level; when the evidence level is considered equivalent, the regimens are listed alphabetically.

### Table 3. 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).

Source: 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](#)] - Accessed February 14, 2021.

**Table 4. 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](#)

Source: 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](#)] - Accessed February 14, 2021.

**Table 5. AASLD-IDSA HCV Guidance for All Genotypes: Retreatment Glecaprevir-Pibrentasvir Treatment Failures (All Genotypes), With or Without Compensated Cirrhosis^**

**Recommended for Glecaprevir-Pibrentasvir Treatment Failures (All Genotypes), With or Without**

**Compensated Cirrhosis<sup>^</sup>**

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

**Sofosbuvir-Velpatasvir-Voxilaprevir**  
*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 IIa](#), [Level B](#)

**Recommended for Glecaprevir-Pibrentasvir Treatment Failures (All Genotypes), With or Without Compensated Cirrhosis<sup>^</sup>**

<b>Sofosbuvir-Velpatasvir-Voxilaprevir</b> <i>Fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg) one tablet once daily for 12 weeks</i>	+	<b>Ribavirin</b> <i>1000 mg if &lt;75 kg or 1200 mg if ≥75 kg for 12 weeks (the daily dose is given in two divided doses)</i>
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For patients with compensated cirrhosis

Rating: [Class IIa](#), [Level C](#)

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

Source: AASLD-IDSA. HCV Guidance: Recommendations for testing, management, and treating hepatitis C. Retreatment of persons in whom prior therapy has failed: glecaprevir/pibrentasvir treatment failure (all genotypes). [[AASLD-IDSA](#)] - Accessed February 11, 2021.

**Table 6. AASLD-IDSA HCV Guidance for All Genotypes: Retreatment Multiple DAA Treatment Failures (All Genotypes), Including Sofosbuvir-Velpatasvir-Voxilaprevir or Sofosbuvir Plus Glecaprevir-Pibrentasvir<sup>^</sup>**

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

<b>Glecaprevir-Pibrentasvir</b>	+	<b>Sofosbuvir</b> <i>(400 mg) one tablet once</i>	+	<b>Ribavirin</b> <i>1000 mg if &lt;75 kg or</i>
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*\*Fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) once daily for 16 weeks#*      *daily for 16 weeks#*      *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<sup>^</sup>**

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

<sup>^</sup>For treatment of patients with decompensated cirrhosis, see the AASLD-IDSa Guidance: Unique Populations—Patients with Decompensated Cirrhosis

Source: AASLD-IDSa. HCV Guidance: Recommendations for testing, management, and treating hepatitis C. Retreatment of persons in whom prior therapy has failed: sofosbuvir/velpatasvir/voxilaprevir treatment failure (all genotypes) [[AASLD-IDSa](#)] - Accessed February 11, 2021.

**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).<sup>[11]</sup> 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.<sup>[11]</sup> 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 3 without cirrhosis who are treatment-experienced with peginterferon and ribavirin (with or without an early DAA), there are no published data to support the use of 8 weeks of glecaprevir-pibrentasvir, which is what would be the recommended duration for treatment-naïve

individuals. There are limited data for the use of 16 weeks of glecaprevir-pibrentasvir but given the length of therapy and quality of the data, this should be considered an alternative option.

- In persons with HCV genotype 3 and compensated cirrhosis who are treatment-experienced with peginterferon and ribavirin (with or without an early DAA), 16 weeks of glecaprevir-pibrentasvir would be considered among the recommended options and would not require pre-treatment resistance testing.
- In persons with HCV genotype 3 with or without cirrhosis who are treatment-experienced with peginterferon and ribavirin (with or without an early DAA) in whom sofosbuvir-velpatasvir is being considered, baseline resistance testing to assess for the presence of Y93H substitution is recommended. The presence of this variant would entail the use of sofosbuvir-velpatasvir plus ribavirin or sofosbuvir-velpatasvir-voxilaprevir instead of sofosbuvir-velpatasvir alone.

## Studies of Retreatment of Adults with HCV Genotype 3

The following key studies support the recommendations for treatment of persons with chronic hepatitis C and genotype 3 infection who are treatment-experienced. The medications are listed in alphabetical order.

### Elbasvir-Grazoprevir plus Sofosbuvir

- [C-ISLE](#): In this randomized, open-label, phase 2 trial, the safety and efficacy of elbasvir-grazoprevir plus sofosbuvir with or without ribavirin was evaluated in treatment-naïve and peginterferon/ribavirin-experienced adults with HCV genotype 3 and compensated cirrhosis.[\[33\]](#) Among the treatment-naïve participants, 23 received 8 weeks of elbasvir-grazoprevir plus sofosbuvir plus ribavirin and 24 received 12 weeks of elbasvir-grazoprevir plus sofosbuvir. The 53 treatment-experienced participants were randomized 1:1:1 to receive (1) elbasvir-grazoprevir plus sofosbuvir for 12 weeks, (2) elbasvir-grazoprevir plus sofosbuvir plus ribavirin for 12 weeks, or (3) elbasvir-grazoprevir plus sofosbuvir for 16 weeks.[\[33\]](#) In an intent-to-treat analysis, the SVR12 rates ranged from 94 to 100% among the treatment arms, with only 2 viral relapses occurring and both were in the 8-week arm. Among the treatment-experienced participants, the SVR12 rates ranged from 94 to 100%, with the only study failures involving 1 person who withdrew consent and 1 who discontinued due to an adverse event.[\[33\]](#)

### Glecaprevir-Pibrentasvir

- [SURVEYOR-II \(Part 3\)](#): In this partially randomized, open-label, phase 3 trial, 44 treatment-experienced adults with HCV genotype 3 infection (without cirrhosis) were randomized 1:1 to receive either 12 or 16 weeks of glecaprevir-pibrentasvir.[\[29\]](#) In addition, 47 treatment-experienced adults with HCV genotype 3 who had compensated cirrhosis received 16 weeks of glecaprevir-pibrentasvir. Prior treatment experience was with (1) peginterferon (or interferon), with or without ribavirin, or (2) sofosbuvir plus ribavirin, with or without peginterferon.[\[29\]](#) An SVR12 was achieved in 96% (45 of 47) of the treatment-experienced participants with compensated cirrhosis who were treated with 16 weeks of glecaprevir-pibrentasvir.[\[29\]](#) In the noncirrhotic, treatment-experienced group, 91% (20 of 22) of treatment-experienced participants achieved an SVR12 with 12 weeks of glecaprevir-pibrentasvir, compared with 95% (21 of 22) in the 16-week arm.[\[29\]](#)

### Sofosbuvir-Velpatasvir

- [ASTRAL-3](#): The ASTRAL-3 trial was a randomized, open-label, phase 3 study that compared sofosbuvir-velpatasvir for 12 weeks with sofosbuvir plus ribavirin for 24 weeks in adults with HCV genotype 3 infection.[\[22\]](#) Of the 552 participants enrolled in the study, 26% were treatment experienced with a prior interferon-containing regimen.[\[22\]](#) A total of 90% (64 of 71) of treatment-experienced recipients in the velpatasvir-sofosbuvir group achieved an SVR 12, which was significantly better than the 64% (44 of 69) of the treatment-experienced participants who received sofosbuvir plus ribavirin.[\[22\]](#) The SVR12 rates for treatment-experienced persons who received velpatasvir-sofosbuvir were similar in participants with or without cirrhosis (SVR12 rates of 89% and 91%, respectively).[\[22\]](#)

### Sofosbuvir-Velpatasvir-Voxilaprevir

- [POLARIS-3](#): In this phase 3, open-label trial, adults with HCV genotype 3 infection and compensated cirrhosis who were DAA naïve (prior peginterferon and ribavirin experience permitted) were randomized to receive 8 weeks of sofosbuvir-velpatasvir-voxilaprevir or 12 weeks of sofosbuvir-velpatasvir.[\[23\]](#) Thirty-one percent were treatment experienced. For the treatment-experienced participants, the SVR12 rate was 97% (34 of 35) for the sofosbuvir-velpatasvir-voxilaprevir arm and 91% (29 of 32) for the sofosbuvir-velpatasvir arm. All persons with baseline NS5A resistance-associated substitutions achieved an SVR12.[\[23\]](#)

- [POLARIS-4](#): In this phase 3, active-comparator, open-label trial, 314 adults with chronic HCV genotype 1, 2, or 3 with prior DAA therapy (but without an NS5A inhibitor) were randomized to receive 12 weeks of therapy with either sofosbuvir-velpatasvir-voxilaprevir or sofosbuvir-velpatasvir.[\[34\]](#) Compensated cirrhosis was present in 46% and prior sofosbuvir exposure in 80% of participants.[\[34\]](#) A total of 104 enrollees had HCV genotype 3. For these individuals with HCV genotype 3, the SVR12 rates were 94% (51 of 54) for the sofosbuvir-velpatasvir-voxilaprevir group and 85% (44 of 52) for the sofosbuvir-velpatasvir group. Virologic relapse was confirmed at week 4 for 8 individuals with HCV genotype 3 who received sofosbuvir-velpatasvir.[\[34\]](#) Eight of the 16 virologic failures had genotype 3; all 8 had detectable Y93H mutation at the time of treatment failure and were in the sofosbuvir-velpatasvir arm.[\[34\]](#)

## Summary Points

- In the DAA era, HCV genotype 3 has emerged as the most difficult HCV genotype to treat.
- For treatment-naïve adults without cirrhosis, two regimens are recommended with equal evidence rating: (1) glecaprevir-pibrentasvir for 8 weeks, or (2) sofosbuvir-velpatasvir for 12 weeks.
- For treatment-naïve adults with compensated cirrhosis, two regimens are recommended: (1) glecaprevir-pibrentasvir for 8 weeks (in persons without HIV infection), or (2) sofosbuvir-velpatasvir for 12 weeks. If considering use of sofosbuvir-velpatasvir, baseline NS5A genotype 3 resistance testing should be performed, and ribavirin should be added to sofosbuvir-velpatasvir if the Y93H resistance-associated substitution (RAS) is detected.
- Retreatment of persons with HCV genotype 3 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 3.
- The retreatment of DAA-experienced adults with HCV genotype 3 infection depends on the prior DAA regimen that was taken.

## Citations

1. Robaeys G, Bielen R, Azar DG, Razavi H, Nevens F. Global genotype distribution of hepatitis C viral infection among people who inject drugs. *J Hepatol.* 2016;65:1094-1103.  
[\[PubMed Abstract\]](#) -
2. Gordon SC, Trudeau S, Li J, et al. Race, Age, and Geography Impact Hepatitis C Genotype Distribution in the United States. *J Clin Gastroenterol.* 2019;53:40-50.  
[\[PubMed Abstract\]](#) -
3. Germer JJ, Mandrekar JN, Bendel JL, Mitchell PS, Yao JD. Hepatitis C virus genotypes in clinical specimens tested at a national reference testing laboratory in the United States. *J Clin Microbiol.* 2011;49:3040-3.  
[\[PubMed Abstract\]](#) -
4. McMahon BJ, Bruden D, Townshend-Bulson L, et al. Infection With Hepatitis C Virus Genotype 3 Is an Independent Risk Factor for End-Stage Liver Disease, Hepatocellular Carcinoma, and Liver-Related Death. *Clin Gastroenterol Hepatol.* 2017;15:431-437.e2.  
[\[PubMed Abstract\]](#) -
5. Kanwal F, Kramer JR, Ilyas J, Duan Z, El-Serag HB. HCV genotype 3 is associated with an increased risk of cirrhosis and hepatocellular cancer in a national sample of U.S. Veterans with HCV. *Hepatology.* 2014;60:98-105.  
[\[PubMed Abstract\]](#) -
6. Bochud PY, Cai T, Overbeck K, et al. Genotype 3 is associated with accelerated fibrosis progression in chronic hepatitis C. *J Hepatol.* 2009;51:655-66.  
[\[PubMed Abstract\]](#) -
7. Nkontchou G, Ziol M, Aout M, et al. HCV genotype 3 is associated with a higher hepatocellular carcinoma incidence in patients with ongoing viral C cirrhosis. *J Viral Hepat.* 2011;18:e516-22.  
[\[PubMed Abstract\]](#) -
8. Scheel TK, Rice CM. Understanding the hepatitis C virus life cycle paves the way for highly effective therapies. *Nat Med.* 2013;19:837-49.  
[\[PubMed Abstract\]](#) -
9. Manns MP, Buti M, Gane E, et al. Hepatitis C virus infection. *Nat Rev Dis Primers.* 2017;3:17006.  
[\[PubMed Abstract\]](#) -
10. 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. Lawitz E, Mangia A, Wyles D, et al. Sofosbuvir for previously untreated chronic hepatitis C infection. *N Engl J Med.* 2013;368:1878-87.  
[\[PubMed Abstract\]](#) -
12. Jacobson IM, Gordon SC, Kowdley KV, et al. Sofosbuvir for hepatitis C genotype 2 or 3 in patients without treatment options. *N Engl J Med.* 2013;368:1867-77.  
[\[PubMed Abstract\]](#) -
13. Gane EJ, Stedman CA, Hyland RH, et al. Nucleotide polymerase inhibitor sofosbuvir plus ribavirin for

hepatitis C. N Engl J Med. 2013;368:34-44.

[\[PubMed Abstract\]](#) -

14. Zeuzem S, Dusheiko GM, Salupere R, et al. Sofosbuvir and ribavirin in HCV genotypes 2 and 3. N Engl J Med. 2014;370:1993-2001.  
[\[PubMed Abstract\]](#) -
15. Foster GR, Pianko S, Brown A, et al. Efficacy of sofosbuvir plus ribavirin with or without peginterferon-alfa in patients with hepatitis C virus genotype 3 infection and treatment-experienced patients with cirrhosis and hepatitis C virus genotype 2 infection. Gastroenterology. 2015;149:1462-70.  
[\[PubMed Abstract\]](#) -
16. Nelson DR, Cooper JN, Lalezari JP, et al. All-oral 12-week treatment with daclatasvir plus sofosbuvir in patients with hepatitis C virus genotype 3 infection: ALLY-3 phase III study. Hepatology. 2015;61:1127-35.  
[\[PubMed Abstract\]](#) -
17. Kowdley KV, Nelson DR, Lalezari JP, et al. On-treatment HCV RNA as a predictor of sustained virological response in HCV genotype 3-infected patients treated with daclatasvir and sofosbuvir. Liver Int. 2016;36:1611-1618.  
[\[PubMed Abstract\]](#) -
18. Hézode C, Lebray P, De Ledinghen V, et al. Daclatasvir plus sofosbuvir, with or without ribavirin, for hepatitis C virus genotype 3 in a French early access programme. Liver Int. 2017;37:1314-24.  
[\[PubMed Abstract\]](#) -
19. Sundaram V, Kowdley KV. Dual daclatasvir and sofosbuvir for treatment of genotype 3 chronic hepatitis C virus infection. Expert Rev Gastroenterol Hepatol. 2016;10:13-20.  
[\[PubMed Abstract\]](#) -
20. Everson GT, Towner WJ, Davis MN, et al. Sofosbuvir With Velpatasvir in Treatment-Naive Noncirrhotic Patients With Genotype 1 to 6 Hepatitis C Virus Infection: A Randomized Trial. Ann Intern Med. 2015;163:818-26.  
[\[PubMed Abstract\]](#) -
21. Foster GR, Afdhal N, Roberts SK, et al. Sofosbuvir and velpatasvir for HCV genotype 2 and 3 infection. N Engl J Med. 2015;373:2608-17.  
[\[PubMed Abstract\]](#) -
22. Jacobson IM, Lawitz E, Gane EJ, et al. Efficacy of 8 Weeks of Sofosbuvir, Velpatasvir, and Voxilaprevir in Patients With Chronic HCV Infection: 2 Phase 3 Randomized Trials. Gastroenterology. 2017;153:113-22.  
[\[PubMed Abstract\]](#) -
23. Kwo PY, Poordad F, Asatryan A, et al. Glecaprevir and pibrentasvir yield high response rates in patients with HCV genotype 1-6 without cirrhosis. J Hepatol. 2017;67:263-271.  
[\[PubMed Abstract\]](#) -
24. Zeuzem S, Foster GR, Wang S, et al. Glecaprevir-Pibrentasvir for 8 or 12 Weeks in HCV Genotype 1 or 3 Infection. N Engl J Med. 2018;378:354-69.  
[\[PubMed Abstract\]](#) -
25. AASLD-IDSA. HCV Guidance: Recommendations for testing, management, and treating hepatitis C. Initial treatment of HCV infection: treatment-naive genotype 3 without cirrhosis.

[\[AASLD-IDSA Hepatitis C Guidance\]](#) -

26. AASLD-IDSA. HCV Guidance: Recommendations for testing, management, and treating hepatitis C. Initial treatment of HCV infection: treatment-naïve genotype 3 with compensated cirrhosis [\[AASLD-IDSA Hepatitis C Guidance\]](#) -
27. Brown RS Jr, Buti M, Rodrigues L, et al. Glecaprevir/pibrentasvir for 8 weeks in treatment-naïve patients with chronic HCV genotypes 1-6 and compensated cirrhosis: The EXPEDITION-8 trial. *J Hepatol.* 2020;72:441-9. [\[PubMed Abstract\]](#) -
28. Wyles D, Poordad F, Wang S, et al. Glecaprevir/pibrentasvir for hepatitis C virus genotype 3 patients with cirrhosis and/or prior treatment experience: A partially randomized phase 3 clinical trial. *Hepatology.* 2018;67:514-23. [\[PubMed Abstract\]](#) -
29. AASLD-IDSA. HCV Guidance: Recommendations for testing, management, and treating hepatitis C. Retreatment of persons in whom prior therapy failed: Glecaprevir/Pibrentasvir Treatment Failures. [\[AASLD-IDSA Hepatitis C Guidance\]](#) -
30. 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. [\[AASLD-IDSA Hepatitis C Guidance\]](#) -
31. 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. [\[AASLD-IDSA Hepatitis C Guidance\]](#) -
32. Foster GR, Agarwal K, Cramp ME, et al. Elbasvir/grazoprevir and sofosbuvir for hepatitis C virus genotype 3 infection with compensated cirrhosis: A randomized trial. *Hepatology.* 2018;67:2113-2126. [\[PubMed Abstract\]](#) -
33. Bourlière M, Gordon SC, Flamm SL, et al. Sofosbuvir, Velpatasvir, and Voxilaprevir for Previously Treated HCV Infection. *N Engl J Med.* 2017;376:2134-46. [\[PubMed Abstract\]](#) -

## References

- European Association for Study of the Liver. EASL Clinical Practice Guidelines: management of hepatitis C virus infection. *J Hepatol.* 2014;60:392-420. [\[PubMed Abstract\]](#) -
- Gane EJ, Pianko S, Roberts SK, et al. Safety and efficacy of an 8-week regimen of grazoprevir plus ruzasvir plus uprifosbuvir compared with grazoprevir plus elbasvir plus uprifosbuvir in participants without cirrhosis infected with hepatitis C virus genotypes 1, 2, or 3 (C-CREST-1 and C-CREST-2, part A): two randomised, phase 2, open-label trials. *Lancet Gastroenterol Hepatol.* 2017;2:805-13. [\[PubMed Abstract\]](#) -
- Gane EJ, Schwabe C, Hyland RH, et al. Efficacy of the Combination of Sofosbuvir, Velpatasvir, and the NS3/4A Protease Inhibitor GS-9857 in Treatment-Naïve or Previously Treated Patients With Hepatitis C Virus Genotype 1 or 3 Infections. *Gastroenterology.* 2016;151:448-456.e1.

[\[PubMed Abstract\]](#) -

- Hagan LM, Yang Z, Ehteshami M, Schinazi RF. All-oral, interferon-free treatment for chronic hepatitis C: cost-effectiveness analyses. *J Viral Hepat.* 2013;20:847-57.  
[\[PubMed Abstract\]](#) -
- 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, Lalezari JP, Hassanein T, et al. Sofosbuvir in combination with peginterferon alfa-2a and ribavirin for non-cirrhotic, treatment-naive patients with genotypes 1, 2, and 3 hepatitis C infection: a randomised, double-blind, phase 2 trial. *Lancet Infect Dis.* 2013;13:401-8.  
[\[PubMed Abstract\]](#) -
- Lawitz E, Poordad F, Brainard DM, et al. Sofosbuvir with peginterferon-ribavirin for 12 weeks in previously treated patients with hepatitis C genotype 2 or 3 and cirrhosis. *Hepatology.* 2015;61:769-75.  
[\[PubMed Abstract\]](#) -
- Lonardo A, Loria P, Adinolfi LE, Carulli N, Ruggiero G. Hepatitis C and steatosis: a reappraisal. *J Viral Hepat.* 2006;13:73-80.  
[\[PubMed Abstract\]](#) -
- Pianko S, Flamm SL, Shiffman ML, et al. Sofosbuvir Plus Velpatasvir Combination Therapy for Treatment-Experienced Patients With Genotype 1 or 3 Hepatitis C Virus Infection: A Randomized Trial. *Ann Intern Med.* 2015;163:809-17.  
[\[PubMed Abstract\]](#) -
- Poordad F, Landis CS, Asatryan A, et al. High antiviral activity of NS5A inhibitor ABT-530 with paritaprevir/ritonavir and ribavirin against hepatitis C virus genotype 3 infection. *Liver Int.* 2016;36:1125-32.  
[\[PubMed Abstract\]](#) -
- Shiffman ML, Ghany MG, Morgan TR, et al. Impact of reducing peginterferon alfa-2a and ribavirin dose during retreatment in patients with chronic hepatitis C. *Gastroenterology.* 2007;132:103-12.  
[\[PubMed Abstract\]](#) -
- Sulkowski MS, Gardiner DF, Rodriguez-Torres M, et al. Daclatasvir plus sofosbuvir for previously treated or untreated chronic HCV infection. *N Engl J Med.* 2014;370:211-21.  
[\[PubMed Abstract\]](#) -
- Wyles D, Wedemeyer H, Ben-Ari Z, et al. Grazoprevir, ruzasvir, and uprifosbuvir for hepatitis C virus after NS5A treatment failure. *Hepatology.* 2017;66:1794-1804.  
[\[PubMed Abstract\]](#) -
- Zeuzem S, Hultcrantz R, Bourliere M, et al. Peginterferon alfa-2b plus ribavirin for treatment of chronic hepatitis C in previously untreated patients infected with HCV genotypes 2 or 3. *J Hepatol* 2004;40:993-9.  
[\[PubMed Abstract\]](#) -

## 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.

### NS3/4A Protease Inhibitors

### NS5A Inhibitors

### NS5B Polymerase Inhibitors

Boceprevir	Daclatasvir	Dasabuvir
Glecaprevir	Elbasvir	Sofosbuvir
Grazoprevir	Ledipasvir	
Paritaprevir	Ombitasvir	
Simeprevir	Pibrentasvir	
Telaprevir	Velpatasvir	
Voxilaprevir		

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

Recommended and alternative regimens listed alphabetically

### Recommended for Treatment-Naïve Genotype 3 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 3 Patients Without 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](#)

Source: AASLD-IDSA. HCV Guidance: Recommendations for testing, management, and treating hepatitis C. Initial treatment of HCV infection: treatment-naïve genotype 3 without cirrhosis. [[AASLD-IDSA Hepatitis C Guidance](#)] - Accessed October 11, 2020.

## Table 2. AASLD-IDSA HCV Guidance for Genotype 3: Initial Treatment Treatment-Naïve Genotype 3 Patients With Compensated Cirrhosis<sup>^</sup>

Recommended and alternative regimens listed by evidence level and alphabetically

### Recommended for Treatment-Naïve Genotype 3 Patients With Compensated Cirrhosis<sup>^</sup>

#### Glecaprevir-Pibrentasvir

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

For HIV/HCV-coinfected patients, 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).

### Recommended for Treatment-Naïve Genotype 3 Patients With Compensated Cirrhosis<sup>^</sup>

#### Sofosbuvir-Velpatasvir

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

For patients without baseline NS5A resistance-associated substitution (RAS) Y93H for velpatasvir.

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

### Alternative for Treatment-Naïve Genotype 3 Patients With Compensated Cirrhosis<sup>^</sup>

#### Sofosbuvir-Velpatasvir

*Fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (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 baseline NS5A resistance-associated substitution (RAS) Y93H for velpatasvir.

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

### Alternative for Treatment-Naïve Genotype 3 Patients With Compensated Cirrhosis<sup>^</sup>

#### Sofosbuvir-Velpatasvir-Voxilaprevir

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

For patients with baseline NS5A resistance-associated substitution (RAS) Y93H for velpatasvir.

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

<sup>^</sup>For treatment of patients with decompensated cirrhosis, see the AASLD-IDSA Guidance: Unique

Populations—Patients with Decompensated Cirrhosis.

Source: AASLD-IDSA. HCV Guidance: Recommendations for testing, management, and treating hepatitis C. Initial treatment of HCV infection: treatment-naive genotype 3 with compensated cirrhosis [[AASLD-IDSA Hepatitis C Guidance](#)] - Accessed October 11, 2020.

### Table 3. 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).

Source: 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](#)] - Accessed February 14, 2021.

## Table 4. 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](#)

Source: 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](#)] - Accessed February 14, 2021.

### Table 5. AASLD-IDSA HCV Guidance for All Genotypes: Retreatment Glecaprevir-Pibrentasvir Treatment Failures (All Genotypes), With or Without Compensated Cirrhosis<sup>^</sup>

#### Recommended for Glecaprevir-Pibrentasvir Treatment Failures (All Genotypes), With or Without Compensated Cirrhosis<sup>^</sup>

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

##### **Sofosbuvir-Velpatasvir-Voxilaprevir**

*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 IIa](#), [Level B](#)

#### Recommended for Glecaprevir-Pibrentasvir Treatment Failures (All Genotypes), With or Without Compensated Cirrhosis<sup>^</sup>

<b>Sofosbuvir-Velpatasvir-Voxilaprevir</b> <i>Fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg) one tablet once daily for 12 weeks</i>	+	<b>Ribavirin</b> <i>1000 mg if &lt;75 kg or 1200 mg if ≥75 kg for 12 weeks (the daily dose is given in two divided doses)</i>
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For patients with compensated cirrhosis

Rating: [Class IIa](#), [Level C](#)

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

Source: AASLD-IDSA. HCV Guidance: Recommendations for testing, management, and treating hepatitis C. Retreatment of persons in whom prior therapy has failed: glecaprevir/pibrentasvir treatment failure (all genotypes). [[AASLD-IDSA](#)] - Accessed February 11, 2021.

**Table 6. AASLD-IDSA HCV Guidance for All Genotypes: Retreatment Multiple DAA Treatment Failures (All Genotypes), Including Sofosbuvir-Velpatasvir-Voxilaprevir or Sofosbuvir Plus Glecaprevir-Pibrentasvir<sup>^</sup>**

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

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

<p><b>Sofosbuvir-Velpatasvir-Voxilaprevir</b> Fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg) one tablet once daily for 24 weeks</p>	+	<p><b>Ribavirin</b> 1000 mg if &lt;75 kg or 1200 mg if ≥75 kg for 24 weeks (the daily dose is given in two divided doses)</p>
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Rating: [Class IIa](#), [Level B](#)

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

Source: AASLD-IDSA. HCV Guidance: Recommendations for testing, management, and treating hepatitis C. Retreatment of persons in whom prior therapy has failed: sofosbuvir/velpatasvir/voxilaprevir treatment failure (all genotypes) [[AASLD-IDSA](#)] - Accessed February 11, 2021.

