Retreatment of Patients with Prior HCV Treatment Experience

Introduction

Viral relapse with hepatitis C virus (HCV) treatment can occur in a small percentage of individuals treated with direct-acting antivirals (DAAs) due to a variety of factors that include suboptimal adherence, advanced fibrosis, HCV genotype, and variable pharmacokinetic and/or host immune properties. Although there are options for retreatment in individuals in whom prior DAA therapy failed, the choices, and clinical experience with these combinations are more limited than for treatment-naïve individuals. This lesson will review the recommended and alternative regimens for persons who are HCV treatment-experienced, as outlined by the American Association for the Study of Liver Diseases (AASLD) and Infectious Diseases Society of America (IDSA) HCV Guidance.[1]

The AASLD-IDSA HCV Guidance has organized these pretreatment recommendations according to the following three prior treatment regimen groups associated with the treatment failure: (1) sofosbuvir-containing DAA or elbasvir-grazoprevir, (2) glecaprevir-pibrentasvir, and (3) multiple DAA failures including the salvage regimens of sofosbuvir-velpatasir-voxilaprevir or sofosbuvir plus glecaprevir-pibrentasvir.[2,3,4] Recommended regimens are preferred options due to their proven efficacy and more robust evidence base, as well as their favorable side effect profile and pill burden.[1] Alternative regimens are also effective and may be the best choice for a specific patient, but they are considered secondary options due to higher dosing complexity, greater pill burden, or less clinical data.[1]

Special Considerations with Retreatment

In contrast with persons receiving initial HCV DAA treatment, there are several potential special considerations, as outlined below, that may arise or need to be addressed with retreatment.

Indications for Ordering HCV Genotype

Historically, this topic was addressed by dividing patients into HCV genotype and/or prior interferon-based therapy. However, currently available pangenotypic DAAs are highly efficacious with comparable rates of sustained virologic response (SVR) among treatment-naïve as well as interferon-experienced patients, so interferon experience has much less relevance in today's treatment era. Genotyping is recommended in treatment-experienced patients who previously failed a sofosbuvir-containing DAA regimen or elbasvir-grazoprevir because the presence of genotype 3 can have implications on retreatment in this population. Otherwise, genotype has little relevance for regimen selection when retreating HCV infection. This is also true of resistance testing since the presence of resistance-associated variants has not been shown to influence treatment outcomes significantly. For further discussion about HCV resistance, see the AASLD/IDSA HCV Resistance Primer.[5]

Determination of Prior Treatment Failure or Reinfection

For persons with prior HCV treatment who have a current detectable HCV RNA level, there are three main possible scenarios:

1. They had treatment failure with the prior regimen and never achieved an SVR12;
2. They achieved an SVR12 but had virologic relapse; or
3. They achieved a virologic cure but have become reinfected with HCV.

Accordingly, the approach to retreatment of persons with HCV infection is different for individuals who experienced treatment failure versus those with reinfection. Virologic relapse after obtaining an SVR12 is very rare and this scenario is unlikely to occur in clinical practice. For persons with HCV reinfection, we recommend taking the same treatment approach as for treatment-naïve individuals, since there is no reason to expect they would be more difficult to treat than a person who has never received HCV treatment. For persons with true prior virologic failure (i.e., did not achieve an SRV12), the approach to retreatment should be based on the prior treatment regimen, as outlined in this lesson. In addition, efforts should be made to identify any factors that may have contributed to the treatment failure, such as unrecognized cirrhosis or difficulty with medication adherence. In the rare case of virologic relapse after obtaining an SVR12, retreatment must be based on the prior treatment regimen.

Potential Use of Ribavirin and Safety Concerns

In the simplified treatment approach, ribavirin is not included in any of the recommended regimens. For persons undergoing retreatment, ribavirin is a component of some of the regimens. Accordingly, clinicians should be aware of the main hematologic and teratogenicity safety issues that can arise with the use of ribavirin.[6,7]

- **Hematologic Toxicity**: Ribavirin can cause severe hemolytic anemia, especially at higher doses. For persons taking ribavirin, regular monitoring of hemoglobin is recommended. Ribavirin can also cause leukopenia.
- **Teratogenicity**: Ribavirin is a teratogenic drug in rodents and may cause birth defects and fetal harm when administered to women who are pregnant. It is therefore contraindicated in pregnant women and in men whose female partners are pregnant. In addition, extreme care must be taken to prevent pregnancy in females taking ribavirin and in female partners of male patients taking ribavirin. Women who may become pregnant should have a confirmed negative pregnancy test immediately

prior to planned initiation of ribavirin, and they should be instructed to use at least two forms of effective contraception during treatment with ribavirin and for 6 months after treatment has been stopped.

Treatment Failure with Sofosbuvir-Containing DAA or Elbasvir-Grazoprevir

In nearly all patients with or without compensated cirrhosis who have experienced treatment failure with a sofosbuvir-containing regimen, such as ledipasvir-sofosbuvir or sofosbuvir-velpatasvir, the AASLD-IDSA HCV Guidance recommends retreatment with the triple-class combination of sofosbuvir-velpatasvir-voxilaprevir for 12 weeks.[4] The only exception to this is in patients with cirrhosis and genotype 3; for these individuals, if they do not have a contraindication, the AASLD-IDSA HCV Guidance recommends treatment with sofosbuvir-velpatasvir-voxilaprevir with the addition of ribavirin.[4] The alternative option for patients who have experienced prior failure with sofosbuvir-containing DAAs is 16 weeks of glecaprevir-pibrentasvir.[4] This regimen may be indicated, for example, in patients who require higher-dose or twice-daily proton-pump inhibitor therapy for esophageal disease and therefore cannot take sofosbuvir-velpatasvir-voxilaprevir due to the drug interaction with velpatasvir.

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

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

Ribavirin: 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 failure with a NS3/4 protease inhibitor-containing combination regimens, or (2) persons with genotype 3 infection with sofosbuvir and NS5A inhibitor experience.

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).

^For patients with decompensated cirrhosis, refer to a liver specialist and 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 failed: Sofosbuvir-Based and Elbasvir/Grazoprevir Treatment Failures. [AASLD-IDSA Hepatitis C Guidance] - Accessed September 18, 2023.

For patients who have experienced treatment failure with elbasvir-grazoprevir, the AASLD-IDSA HCV Guidance recommends treatment with sofosbuvir-velpatasvir-voxilaprevir for 12 weeks.[4] Due to limited data and overlapping resistance pathways, the 16-week regimen of glecaprevir-pibrentasvir, which is an alternative regimen for prior failure with a sofosbuvir-containing regimen, is not recommended for prior treatment failure with elbasvir=grazoprevir.[4]

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

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*
Ribavirin: For persons with genotype 3 and cirrhosis, add weight-based ribavirin if there are no contraindications to ribavirin. Rating: Class I, Level A

^For patients with decompensated cirrhosis, refer to a liver specialist and 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 failed: Sofosbuvir-Based and Elbasvir/Grazoprevir Treatment Failures. [AASLD-IDSA Hepatitis C Guidance] - Accessed September 18, 2023.

The following is a summary of the evidence base for these retreatment regimens, including the main trials that evaluated treatment-experienced individuals with the following salvage regimens.

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.[8] 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).[8] Individuals with HCV genotypes 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 at baseline.[8]
- POLARIS-4: In this phase 3, active-comparator, open-label trial, 314 adults with chronic HCV genotypes 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.[8] 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.[8] 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).[8]

Glecaprevir-Pibrentasvir

- MAGELLAN-1 (Part 1): This was an open-label, phase 2 study evaluating the safety and efficacy of glecaprevir-pibrentasvir, with or without ribavirin, for 12 weeks in noncirrhotic individuals with HCV genotype 1, and who previously failed DAA therapy.[9] Fifty participants were enrolled, 6 of whom received low-dose glecaprevir 200 mg plus pibrentasvir 80 mg (arm A), 22 of whom received standard dose glecaprevir-pibrentasvir plus ribavirin 800 mg (arm B), and 22 of whom received standard dose glecaprevir-pibrentasvir without ribavirin (arm C).[9] Fifty percent of persons in the study were NS5A naïve but protease inhibitor experienced, 16% were NS5A treatment-experienced but protease inhibitor naïve, and 34% were NS5A experienced and protease inhibitor experienced.[9] In an intention-to-treat analysis, 100% of participants in arm A, 95% in arm B, and 86% in arm C achieved an SVR12.[9]
- 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.[10] 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.[10] Among those individuals with prior protease inhibitor treatment experience, SVR12 was achieved in 100% in both the 12-week and 16-week arms.[10] 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. [10] 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.[10]
- SURVEYOR-II (Part 3): In this partially randomized, open-label, phase 3 trial, the safety and efficacy of glecaprevir-pibrentasvir was evaluated in treatment-naïve and treatment-experienced adults with HCV genotype 3. Enrollment included 44 treatment-experienced adults with HCV genotype 3 infection without cirrhosis who were randomized 1:1 to receive either 12 or 16 weeks of glecaprevir-pibrentasvir; patients with compensated cirrhosis were treated with 12 weeks if they were treatment naïve (n=40) or 16 weeks if treatment experienced (n = 47). Sustained virologic response (SVR12) was achieved in 98% of treatment-naïve persons with cirrhosis and 96% of treatment-experienced persons with cirrhosis who were treated with 12 and 16 weeks of glecaprevir-pibrentasvir respectively. In the group without cirrhosis, 91% of treatment-experienced participants achieved SVR12 with 12 weeks of glecaprevir-pibrentasvir compared with 95% for those in the 16-week arm.
- HCV-TARGET: In this phase 3b, open-label pragmatic trial, the safety and efficacy of 12 or 16 weeks of glecaprevir-pibrentasvir was evaluated in treatment-experienced adults with HCV genotype 1 infection who experienced viral relapse after previous treatment with sofosbuvir plus an NS5A inhibitor (ledipasvir, velpatasvir or daclatasvir).[11] The study enrolled a total of 177 participants and was stratified as 50 with compensated cirrhosis and 127 without cirrhosis.[11] Within each group, they were randomized to receive either 12 or 16 weeks of glecaprevir-pibrentasvir. Overall, an SVR12 was achieved in 91.5% (162 of 177) of participants.[11] The SVR12 rates were numerically higher in the 16-week arms of both groups: 94% (46 of 49) of noncirrhotic participants and 97% (28 of 29) of cirrhotic participants compared with 90% (70 of 78) and 86% (18 of 21) respectively in the 12-week arm.[11]

Treatment Failure with Glecaprevir-Pibrentasvir

For patients who have experienced treatment failure with glecaprevir-pibrentasvir, the AASLD-IDSA HCV Guidance recommends using either 16 weeks of glecaprevir-pibrentasvir with sofosbuvir and ribavirin (weight-based) or 12 weeks of sofosbuvir-velpatasvir-voxilaprevir.[2] The addition of weight-based ribavirin to the 12-week sofosbuvir-velpatasvir-voxilaprevir regimen is recommended for those patients with compensated cirrhosis, regardless of genotype.[2]

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^

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 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^

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^

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 IIa, Level C

^For patients with decompensated cirrhosis, refer to a liver specialist and 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 September 18, 2023.

The following provides a summary of the evidence base for these retreatment regimens, including the main trials that evaluated treatment-experienced individuals.

Glecaprevir-pibrentasvir plus Sofosbuvir and Ribavirin

- MAGELLAN-3: This was an open-label, single-arm phase 3 study that evaluated the safety and efficacy of 16 weeks of glecaprevir-pibrentasvir plus sofosbuvir with weight-based ribavirin for participants who experienced virologic failure with a standard 12-week course of glecaprevir-pibrentasvir in a parent trial.[12] Twenty-three enrolled in the study; 14/23 (61%) had genotype 3 HCV, 7/23 (30%) had genotype 1 HCV, and 2/23 (9%) had genotype 2 HCV infection. Seven (30%) had compensated cirrhosis, and most (21/23, 91%) had baseline resistance-associated substitutions in NS5A. Overall, 22/23 (96%) achieved a sustained virologic response SVR. The retreatment regimen was well tolerated in this group, and there were no treatment discontinuations.[12]

Sofosbuvir-Velpatasvir-Voxilaprevir

- SOF-VEL-VOX in G/P Failure: This was a single-arm prospective study that enrolled 31 adults from three clinical centers with a history of treatment failure with glecaprevir-pibrentasvir to undergo 12 weeks of sofosbuvir-velpatasvir-voxilaprevir at standard dose.[13] For 28 (90%) of the participants, glecaprevir-pibrentasvir was their first HCV treatment regimen. A majority of these participants had cirrhosis (58%) and/or genotype 3 infection (58%). Most (90%) had baseline resistance-associated substitutions (RAS) to NS5A +/- NS3. Overall, SVR12 was achieved in 94% (29/31) of participants. Those with baseline RAS had an SVR12 rate of 93% while those without had 100%. The SVR12 rates were 94% and 92% for genotypes 3 and 1a, respectively. Treatment was well tolerated, with no early discontinuations. Of note, the addition of ribavirin was not evaluated in this study; however, the addition of ribavirin to sofosbuvir-velpatasvir-voxilaprevir is recommended for patients with compensated cirrhosis based on other treatment studies in patients who experienced DAA failure.[13]

Treatment Failure with Multiple DAA Regimens

There are very limited data to guide the retreatment of patients who experienced treatment failure with multiple DAA regimens, including treatment failure with the regimen of sofosbuvir-velpatasvir-voxilaprevir.[3] For prior treatment failure with sofosbuvir-velpatasvir-voxilaprevir, the AASLD-IDSA HCV Guidance recommends using a longer duration of treatment and incorporating ribavirin into the treatment regimen.[3]

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)

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

^For patients with decompensated cirrhosis, refer to a liver specialist and 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 September 18, 2023.

The evidence base comprises small case series and reports and includes the following salvage regimen options.

Glecaprevir-Pibrentasvir plus Sofosbuvir and Ribavirin

Glecaprevir and pibrentasvir each appear to retain antiviral activity in vitro against the more common amino acid substitutions known to confer resistance to the earlier-generation NS5A inhibitors and NS3/4A protease inhibitors.[14,15] For this reason, it is considered in retreatment regimens even when patients have failed glecaprevir-pibrentasvir.

- In MAGELLAN-3, the open-label, single-arm trial, investigators evaluated the safety and efficacy of glecaprevir-pibrentasvir with sofosbuvir and ribavirin (weight-based) for 16 weeks in patients who had virologic failure with glecaprevir-pibrentasvir.[12] They enrolled 23 such patients, 30% of whom had compensated cirrhosis and 91% who had baseline resistance-associated substitutions for NS5A. All but two (21 of 23) achieved an SVR12.[12]
- In a report from Europe, the same combination (glecaprevir-pibrentasvir with sofosbuvir and weight-based ribavirin) was one of the most commonly used rescue therapies in 40 individuals who experienced viral relapse with sofosbuvir-velpatasvir-voxilaprevir.[16] Most of them had genotype 3 or 1A infection, and 70% had cirrhosis. Of the 15 individuals who received glecaprevir-pibrentasvir with sofosbuvir (with or without ribavirin, n=8 and n=7 respectively) of varying duration (12, 16, or 24 weeks), 11 (73%) achieved an SVR12.[16]

Extended duration of therapy may need to be considered in some individuals who are experienced with multiple DAA regimens. How best to identify these individuals who may benefit from extended therapy is unclear. One case report described a patient with genotype 3 infection and advanced fibrosis who did not achieve an SVR12 with sofosbuvir and daclatasvir (first regimen), sofosbuvir-velpatasvir and ribavirin (second regimen) and finally sofosbuvir-velpatasvir-voxilaprevir.[17] She ultimately achieved SVR12 after a 24-week course of glecaprevir-pibrentasvir with sofosbuvir and ribavirin.[17]

Sofosbuvir-Velpatasvir-Voxilaprevir plus Ribavirin

At this time, there are no published reports of the efficacy of extending the duration to 24 weeks with sofosbuvir-velpatasvir-voxilaprevir and ribavirin in patients who have experienced treatment failure with multiple DAA regimens. The AASLD-IDSA HCV Guidance for using sofosbuvir-velpatasvir-voxilaprevir with ribavirin in this setting is based on data from a multicenter, single-arm study that examined the efficacy of 24 weeks of sofosbuvir-velpatasvir plus weight-based ribavirin in patients who had prior experience with NS5A-NS5B combination therapy with or without an NS3/4 protease inhibitor.[18] In this study, the SVR rate with this treatment combination was 91% (63 of 69), with higher rates observed in persons with HCV genotype 1 (97%) and genotype 2 (93%), compared with genotype 3 (78%).[18]

Summary Points

- Retreatment options exist for patients who experience DAA failure, but these options are more limited than those available for treatment-naïve individuals.
- For most patients who experienced treatment failure with a sofosbuvir-containing regimen such as ledipasvir-sofosbuvir or sofosbuvir-velpatasvir, the recommended option for retreatment is the triple-class combination of sofosbuvir-velpatasvir-voxilaprevir for 12 weeks.
- Patients with cirrhosis and genotype 3 who experience treatment failure with a sofosbuvir-containing regimen should receive sofosbuvir-velpatasvir-voxilaprevir with ribavirin.
- For patients who have experienced treatment failure with glecaprevir-pibrentasvir, the recommended regimens include either 16 weeks of glecaprevir-pibrentasvir with sofosbuvir and ribavirin (weight-based) or 12 weeks of sofosbuvir-velpatasvir-voxilaprevir. The addition of weight-based ribavirin to the 12-week regimen is recommended for those patients with compensated cirrhosis.
- There are very limited data to guide the retreatment of patients who experienced treatment failure with multiple DAA treatment regimens. Recommended options in this setting include triple-class combinations of an NS5A inhibitor plus NS5B inhibitor plus NS3/4A protease inhibitor with ribavirin for an extended duration of 16 or 24 weeks.

Citations

1. 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] -

2. 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] -

3. 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] -

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[AASLD-IDSA Hepatitis C Guidance] -

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[PubMed Abstract] -

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[PubMed Abstract] -

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