

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>.

Introduction

Background

Approximately 10% of all hepatitis C virus infections in the United States result from genotype 3 infection, with an even higher proportion among persons who inject drugs.[1,2,3] Individuals with genotype 3 HCV, when compared with persons infected with HCV genotypes other than 3, 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, genotype 3 infection has been relatively difficult to treat compared with other genotypes, especially in persons with cirrhosis or prior HCV treatment failure. The following discussion regarding initial treatment and retreatment of patients with genotype 3 chronic hepatitis C assumes the patient and their clinician have already made the decision to initiate hepatitis C therapy.

Medications used to Treat Hepatitis C

The [HCV Medications](#) section on this web site provides detailed information for each of the FDA-approved medications listed in the treatment recommendations, including links to the full prescribing information and to patient assistance programs. The direct-acting antiviral agents exert their action at specific steps in the HCV life cycle. There are three major classes of direct-acting antiviral medications: nonstructural proteins 3/4A (NS3/4A) protease inhibitors, NS5A inhibitors, and 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, 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 3 Treatment Regimen

When considering treatment of patients chronically infected with genotype 3 HCV, two key factors influence the choice and duration of therapy: cirrhosis status and prior treatment experience. With certain regimens for treatment-experienced and/or cirrhotic patients, pre-treatment NS5A resistance may also influence both the choice of regimen, duration or inclusion of ribavirin. In addition, the cost of the regimen, insurance coverage, and provider preference can play a major role in the regimen choice. For initial treatment of patients with genotype 3 HCV infection, the estimated wholesale acquisition cost for regimens in the recommended category in the American Association for the Study of Liver Diseases and Infectious Diseases Society of America (AASLD-IDSA) HCV Guidance ranges from approximately \$26,400 to \$74,760 for those without cirrhosis and from \$39,600 to \$74,760 for those with compensated cirrhosis ([Figure 2](#)). The following treatment recommendations are based on the AASLD-IDSA HCV Guidance for patients with genotype 3 HCV.[10,11]

- [AASLD-IDS A HCV Guidance for Treatment-Naïve Patients with Genotype 3 HCV](#)
- [AASLD-IDS A HCV Guidance for Treatment-Experienced Patients with Genotype 3 HCV](#)

HCV Genotype 3: Initial Treatment

Background

Genotype 3 infection has emerged in the DAA era as the most treatment-refractory of all the genotypes. The efficacy of sofosbuvir plus weight-based ribavirin given for 12 to 16 weeks was notably lower, with substantially lower SVR rates (30 to 60%) in patients with genotype 3 than with genotype 2 infection.[12,13] The relatively lower SVR rates with 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] Sofosbuvir-velpatasvir, FDA approved in June 2016, has become the mainstay of DAA therapy for treatment-naïve patients with genotype 3 infection including those with compensated cirrhosis.[21,22,23] The introduction of glecaprevir-pibrentasvir provides another important option in treatment-naïve persons with genotype 3 HCV infection.[24,25]

Factors to Consider Prior to Choosing Initial Treatment Regimen

For persons chronically infected with genotype 3 hepatitis C, three factors should be considered when choosing the initial treatment regimen and duration: (1) baseline NS5A resistant variant 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 and (3) cost or insurance considerations. The management of HCV genotype 3 infection in persons with decompensated cirrhosis, renal impairment, HIV coinfection, acute hepatitis C infection, or post-liver transplantation is not addressed in this lesson.

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. 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](#)

Alternative for Treatment-Naïve Genotype 3 Patients Without Cirrhosis

Daclatasvir

**(60 mg) one tablet once daily for 12 weeks*

+

Sofosbuvir

(400 mg) one tablet once daily for 12 weeks

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

Note: *The dose of daclatasvir may need to be increased or decreased when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. See the daclatasvir prescribing information for details.

Source: AASLD-IDSA. 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 November 22, 2017.

Table 2. AASLD-IDSA HCV Guidance for Genotype 3: Initial Treatment Treatment-Naïve Genotype 3 Patients With Compensated Cirrhosis[^]

Recommended and alternative regimens listed by evidence level and alphabetically

Recommended for Treatment-Naïve Genotype 3 Patients With Compensated Cirrhosis[^]

Glecaprevir-Pibrentasvir

**Fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) once daily for 12 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 With Compensated Cirrhosis[^]

Sofosbuvir-Velpatasvir

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

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

Alternative for Treatment-Naïve Genotype 3 Patients With 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

This regimen is appropriate to consider for patients with cirrhosis and Y93H.

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

Alternative for Treatment-Naïve Genotype 3 Patients With Compensated Cirrhosis[^]

Daclatasvir	+	Sofosbuvir	±	Ribavirin
<i>*(60 mg) one tablet once daily for 24 weeks</i>		<i>(400 mg) one tablet once daily for 24 weeks</i>		<i>1000 mg if <75 kg or 1200 mg if ≥75 kg for 24 weeks (the daily dose is given in two divided doses)</i>

Resistance-associated substitution (RAS) testing for Y93H is recommended for cirrhotic patients. If present, ribavirin should be included in the regimen or sofosbuvir-velpatasvir-voxilaprevir should be considered.

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

Note: *the dose of daclatasvir may need to be increased or decreased when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. See the daclatasvir prescribing information for details

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

Source: AASLD-IDSA. 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](#)] - Accessed November 22, 2017.

Key Studies for 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.

Daclatasvir plus Sofosbuvir

- [ALLY-3](#): The phase 3 ALLY-3 trial enrolled 152 adults with genotype 3 infection (101 treatment-naïve and 51 treatment-experienced).^[17] All patients received a 12-week course of the oral regimen of daclatasvir (60 mg once daily) plus sofosbuvir (400 mg once daily). Patients with compensated cirrhosis were allowed in the trial. Overall, SVR12 was achieved in 89% (84 of 94) of the treatment-naïve patients (97% in those without cirrhosis and 58% in those with cirrhosis).

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 non-cirrhotic treatment-naïve adults with genotype 3 hepatitis C infection; 348 patients were randomized in 2:1 ratio to 12 weeks of either glecaprevir-pibrentasvir or sofosbuvir plus daclatasvir while 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.

- [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.[\[28\]](#) Enrollment included 40 treatment-naïve adults with cirrhosis who received or 12 weeks of glecaprevir-pibrentasvir. For the treatment-naïve participants 98% (39 of 40) achieved a sustained virologic response at 12 weeks post treatment (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 genotype 3 HCV 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

Background

Genotype 3 infection can be particularly challenging to treat in persons with prior treatment failure, especially those with cirrhosis. Sofosbuvir-velpatasvir is currently the main recommended option for peginterferon plus ribavirin-experienced persons without cirrhosis based on the latest AASLD-IDSA HCV Guidance. In peginterferon plus ribavirin-experienced persons with compensated cirrhosis, the AASLD-IDSA HCV Guidance recommends using triple-class DAA therapy that includes an NS5A, NS3/4 protease inhibitor and NS5B inhibitor, in the form of elbasvir-grazoprevir plus sofosbuvir or sofosbuvir-velpatasvir-voxilaprevir.

Factors to Consider Prior to Choosing Retreatment Regimen

For retreatment of adults with genotype 3 hepatitis C, several factors influence the regimen choice, including (1) the prior regimen (categorized as prior peginterferon plus ribavirin or DAA experience), (2) presence of NS5A resistance-associated substitution Y93H if sofosbuvir-velpatasvir or daclatasvir plus sofosbuvir is being considered, (3) presence or absence of cirrhosis, and (4) medication cost or insurance considerations. The retreatment of individuals with HCV genotype 3 and decompensated cirrhosis, renal impairment, acute hepatitis C infection, or post-liver transplantation is not addressed in this lesson.

AASLD-IDSA HCV Guidance for Retreatment of HCV Genotype 3

The following is a summary of AASLD-IDSA HCV Guidance for adults with hepatitis C genotype 3 infection who are treatment-experienced and failed prior therapy with either (1) peginterferon plus ribavirin or (2) DAA (including NS5A inhibitors sofosbuvir).^[29,30,31] 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 3. AASLD-IDSA HCV Guidance for Genotype 3: Retreatment Peginterferon plus Ribavirin-Experienced, Genotype 3 Patients Without Cirrhosis

Recommended and alternative regimens listed by evidence level and alphabetically,

Recommended for Peginterferon plus Ribavirin-Experienced, Genotype 3 Patients Without Cirrhosis

Sofosbuvir-Velpatasvir

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

Baseline resistance-associated substitution (RAS) testing for Y93H is recommended. If the Y93H substitution is identified, a different regimen should be used, or weight-based ribavirin should be added as an alternative option.

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

Alternative for Peginterferon plus Ribavirin-Experienced, Genotype 3 Patients Without Cirrhosis

<p>Daclatasvir <i>*(60 mg) one tablet once daily for 12 weeks</i></p>	+	<p>Sofosbuvir <i>(400 mg) one tablet once daily for 12 weeks</i></p>
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Baseline RAS testing for Y93H is recommended. If the Y93H substitution is identified, a different regimen should be used, or weight-based ribavirin should be added as an alternative option.

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

Note: *The dose of daclatasvir may need to be increased or decreased when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. See the daclatasvir prescribing information for detailed information.

Alternative for Peginterferon plus Ribavirin-Experienced, Genotype 3 Patients Without Cirrhosis

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

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).

Alternative for Peginterferon plus Ribavirin-Experienced, Genotype 3 Patients Without Cirrhosis

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

This regimen is appropriate to consider for patients with Y93H.

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

Source: AASLD-IDSA. Recommendations for testing, management, and treating hepatitis C. Retreatment of persons in whom prior therapy has failed: peginterferon/ribavirin-experienced, genotype 3 patients without cirrhosis. [[AASLD-IDSA Hepatitis C Guidance](#)] - Accessed November 22, 2017.

Table 4. AASLD-IDSA HCV Guidance for Genotype 3: Retreatment Peginterferon plus Ribavirin-Experienced, Genotype 3 Patients With Compensated Cirrhosis[^]

Recommended and alternative regimens listed by evidence level and alphabetically

Recommended for Peginterferon plus Ribavirin-Experienced, Genotype 3 Patients With Compensated Cirrhosis[^]

<p>Elbasvir-Grazoprevir <i>Fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) one tablet once daily for 12 weeks</i></p>	+	<p>Sofosbuvir <i>(400 mg) one tablet once daily for 12 weeks</i></p>
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Rating: [Class I](#), [Level B](#)

Recommended for Peginterferon plus Ribavirin-Experienced, Genotype 3 Patients With 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

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

Alternative for Peginterferon plus Ribavirin-Experienced, Genotype 3 Patients With Compensated Cirrhosis[^]

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)

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

Alternative for Peginterferon plus Ribavirin-Experienced, Genotype 3 Patients With Compensated Cirrhosis[^]

Glecaprevir-Pibrentasvir

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

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).

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

Source: AASLD-IDSA. Recommendations for testing, management, and treating hepatitis C. Retreatment of persons in whom prior therapy has failed: peginterferon/ribavirin-experienced, genotype 3 patients with compensated cirrhosis. [[AASLD-IDSA Hepatitis C Guidance](#)] - Accessed November 22, 2017.

Table 5. AASLD-IDSA HCV Guidance for Genotype 3: Retreatment DAA-Experienced (Including NS5A Inhibitors), Genotype 3 Patients With or Without Compensated Cirrhosis[^]

Recommended for DAA-Experienced (Including NS5A Inhibitors), Genotype 3 Patients 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

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

Recommended for DAA-Experienced (Including NS5A Inhibitors), Genotype 3 Patients 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 prior NS5A inhibitor failure and cirrhosis, weight-based ribavirin is recommended.

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

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

Source: AASLD-IDSa. Recommendations for testing, management, and treating hepatitis C. Retreatment of persons in whom prior therapy has failed: DAA-experienced (including NS5A inhibitors), genotype 3 patients with or without compensated cirrhosis. [[AASLD-IDSa Hepatitis C Guidance](#)] - Accessed November 22, 2017.

Key Studies for Retreatment of Adults with 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.

Daclatasvir plus Sofosbuvir

- [ALLY-3](#): The phase 3 ALLY-3 trial enrolled 152 adults with genotype 3 infection (101 treatment-naïve and 51 treatment experienced).[17] All participants received a 12-week course of the oral regimen of daclatasvir (60 mg once daily) plus sofosbuvir (400 mg once daily). Participants with compensated cirrhosis were allowed in the trial. Overall, SVR12 was achieved in 86% (44 of 51) of the treatment-experienced patients, including a 94% SVR12 rate in those without cirrhosis and 69% in those with cirrhosis).

Glecaprevir-Pibrentasvir

- [SURVEYOR-II \(Part 3\)](#): In this partially randomized, open-label phase 3 trial, 44 treatment-experienced adults with genotype 3 infection without cirrhosis were randomized 1:1 to receive either 12 or 16 weeks of glecaprevir-pibrentasvir.[28] In addition, 47 treatment-experienced genotype 3 participants with 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. An SVR12 was achieved in 96% (45 of 47) of treatment-experienced cirrhotics with 16 weeks of glecaprevir-pibrentasvir. In the non-cirrhotic, treatment-experienced group, 91% (20 of 22) of treatment-experienced patients achieved an SVR12 with 12 weeks of glecaprevir-pibrentasvir compared with 95% (21 of 22) in the 16-week arm.

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 genotype 3 HCV infection.[\[22\]](#) Of the 552 participants enrolled in the study, 26% were treatment-experienced with a prior interferon-containing regimen. For the treatment-experienced recipients of velpatasvir-sofosbuvir 90% (64 of 71) achieved an SVR 12, which was significantly better than the 64% (44 of 69) in the treatment-experienced participants who received sofosbuvir plus ribavirin. For the treatment-experienced persons who received velpatasvir-sofosbuvir, the SVR rates were similar without cirrhosis (91%) and with compensated cirrhosis (89%).

Sofosbuvir-Velpatasvir-Voxilaprevir

- [POLARIS-3](#): In this phase 3, open-labeled trial, adults with genotype 3 HCV 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.
- [POLARIS-4](#): In this phase 3, active-comparator, open-labeled trial, 314 adults with chronic hepatitis C genotype 1-3 with prior DAA therapy without an NS5A inhibitor were randomized to receive 12-weeks of therapy with either sofosbuvir-velpatasvir-voxilaprevir or sofosbuvir-velpatasvir. Compensated cirrhosis was present in 46% and prior sofosbuvir exposure in 80% of participants. A total of 104 of enrollees had HCV genotype 3. For 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.

HCV Genotype 3: Treatment Regimens under Study

Regimens under Study for Persons with HCV Genotype 3

Note: the regimen listed below is investigational and currently not recommended in the AASLD-IDSA HCV guidance.

- **Grazoprevir-Ruzasvir-Uprifosbuvir (MK-3682)**. A new 3-class DAA combination that includes grazoprevir (NS3/4 protease inhibitor) coformulated with ruzasvir, a novel NS5A inhibitor and uprifosbuvir, a novel NS5B inhibitor is currently being studied, with or without ribavirin, in the C-CREST trials in treatment-naïve and experienced adults with genotype 3 infection.[[32](#),[33](#),[34](#)] The 12-week option without ribavirin was shown to be highly effective (96-98%) in phase 2 trials for individuals with genotype 3 HCV infection, including those with cirrhosis and prior peginterferon and ribavirin experience.

Summary Points

- In the new direct-acting antiviral treatment era, genotype 3 has emerged as the most difficult genotype to treat.
- For treatment-naïve patients 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 patients with compensated cirrhosis, two regimens are recommended: (1) glecaprevir-pibrentasvir for 12 weeks or (2) sofosbuvir-velpatasvir for 12 weeks. Baseline NS5A genotype 3 resistance testing should be performed, and ribavirin should be added to sofosbuvir-velpatasvir if the Y93H mutation is detected.
- For treatment-experienced patients without cirrhosis, the main recommended regimen with evidence rating of IA is: sofosbuvir-velpatasvir for 12 weeks. Baseline NS5A genotype 3 resistance testing should be performed, and ribavirin should be added to sofosbuvir-velpatasvir if the Y93H mutation is detected.
- For treatment-experienced patients with compensated cirrhosis and prior peginterferon plus ribavirin experience, two regimens are recommended: (1) elbasvir-grazoprevir plus sofosbuvir for 12 weeks or (2) sofosbuvir-velpatasvir-voxilaprevir for 12 weeks.
- The recommended regimen for genotype 3 treatment-experienced patients who have failed prior treatment with DAA (including NS5A inhibitors) consists of sofosbuvir-velpatasvir-voxilaprevir for 12 weeks. Weight-based ribavirin is recommended in addition to this for patients with cirrhosis and prior NS5A failure.
- For treatment-naïve patients with compensated cirrhosis and treatment-experienced non-cirrhotic patients, baseline NS5A genotype 3 resistance testing should be performed for those in whom sofosbuvir-velpatasvir or sofosbuvir plus daclatasvir is being considered. Ribavirin should be added to sofosbuvir-velpatasvir or sofosbuvir plus daclatasvir if the Y93H mutation is detected.

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Figures

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

NS3/4A Protease Inhibitors	NS5A Inhibitors	NS5B Polymerase Inhibitors
Boceprevir	Daclatasvir	Dasabuvir
Glecaprevir	Elbasvir	Sofosbuvir
Grazoprevir	Ledipasvir	
Paritaprevir	Ombitasvir	
Simeprevir	Pibrentasvir	
Telaprevir	Velpatasvir	
Voxilaprevir		

Figure 2 Cost of Medication Regimens used for Initial Treatment Genotype 3 Chronic HCV

This figure shows the approximate cost of a treatment course with AASLD-IDSA recommended regimens for treatment-naïve adults with genotype 3 HCV, including those without cirrhosis and those with compensated cirrhosis. The cost listed is based on available wholesale acquisition price data.

Estimated Cost of Recommended Regimens for Initial Treatment HCV GT3	
Regimens and Duration of Therapy	Cost of Regimen*
Genotype 3 HCV Without Cirrhosis	
Glecaprevir-Pibrentasvir for 8 weeks	\$26,400
Sofosbuvir-Velpatasvir for 12 weeks	\$74,760
Genotype 3 HCV With Compensated Cirrhosis	
Glecaprevir-Pibrentasvir for 12 weeks	\$39,600
Sofosbuvir-Velpatasvir for 12 weeks	\$74,760
*Cost estimates based on Wholesale Acquisition Cost (WAC)	

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](#)

Alternative for Treatment-Naïve Genotype 3 Patients Without Cirrhosis

Daclatasvir

**(60 mg) one tablet once daily for 12 weeks*

+

Sofosbuvir

(400 mg) one tablet once daily for 12 weeks

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

Note: *The dose of daclatasvir may need to be increased or decreased when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. See the daclatasvir prescribing information for details.

Source: AASLD-IDSA. 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 November 22, 2017.

Table 2. AASLD-IDSA HCV Guidance for Genotype 3: Initial Treatment Treatment-Naïve Genotype 3 Patients With Compensated Cirrhosis[^]

Recommended and alternative regimens listed by evidence level and alphabetically

Recommended for Treatment-Naïve Genotype 3 Patients With Compensated Cirrhosis[^]

Glecaprevir-Pibrentasvir

**Fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) once daily for 12 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 With Compensated Cirrhosis[^]

Sofosbuvir-Velpatasvir

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

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

Alternative for Treatment-Naïve Genotype 3 Patients With 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

This regimen is appropriate to consider for patients with cirrhosis and Y93H.

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

Alternative for Treatment-Naïve Genotype 3 Patients With Compensated Cirrhosis[^]

Daclatasvir

**(60 mg) one tablet once daily for 24 weeks*

+

Sofosbuvir

(400 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)

Resistance-associated substitution (RAS) testing for Y93H is recommended for cirrhotic patients. If present, ribavirin should be included in the regimen or sofosbuvir-velpatasvir-voxilaprevir should be considered.

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

Note: *the dose of daclatasvir may need to be increased or decreased when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. See the daclatasvir prescribing information for details

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

Source: AASLD-IDSA. 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 November 22, 2017.

Table 3. AASLD-IDSA HCV Guidance for Genotype 3: Retreatment Peginterferon plus Ribavirin-Experienced, Genotype 3 Patients Without Cirrhosis

Recommended and alternative regimens listed by evidence level and alphabetically,

Recommended for Peginterferon plus Ribavirin-Experienced, Genotype 3 Patients Without Cirrhosis

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

Baseline resistance-associated substitution (RAS) testing for Y93H is recommended. If the Y93H substitution is identified, a different regimen should be used, or weight-based ribavirin should be added as an alternative option.

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

Alternative for Peginterferon plus Ribavirin-Experienced, Genotype 3 Patients Without Cirrhosis

Daclatasvir + **Sofosbuvir**
**(60 mg) one tablet once daily for 12 weeks* + *(400 mg) one tablet once daily for 12 weeks*

Baseline RAS testing for Y93H is recommended. If the Y93H substitution is identified, a different regimen should be used, or weight-based ribavirin should be added as an alternative option.

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

Note: *The dose of daclatasvir may need to be increased or decreased when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. See the daclatasvir prescribing information for detailed information.

Alternative for Peginterferon plus Ribavirin-Experienced, Genotype 3 Patients Without Cirrhosis

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

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).

Alternative for Peginterferon plus Ribavirin-Experienced, Genotype 3 Patients Without Cirrhosis

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

This regimen is appropriate to consider for patients with Y93H.

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

Source: AASLD-IDSA. Recommendations for testing, management, and treating hepatitis C. Retreatment of persons in whom prior therapy has failed: peginterferon/ribavirin-experienced, genotype 3 patients without cirrhosis. [[AASLD-IDSA Hepatitis C Guidance](#)] - Accessed November 22, 2017.

Table 4. AASLD-IDSA HCV Guidance for Genotype 3: Retreatment Peginterferon plus Ribavirin-Experienced, Genotype 3 Patients With Compensated Cirrhosis[^]

Recommended and alternative regimens listed by evidence level and alphabetically

Recommended for Peginterferon plus Ribavirin-Experienced, Genotype 3 Patients With Compensated Cirrhosis[^]

<p>Elbasvir-Grazoprevir Fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) one tablet once daily for 12 weeks</p>	+	<p>Sofosbuvir (400 mg) one tablet once daily for 12 weeks</p>
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Rating: [Class I](#), [Level B](#)

Recommended for Peginterferon plus Ribavirin-Experienced, Genotype 3 Patients With 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

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

Alternative for Peginterferon plus Ribavirin-Experienced, Genotype 3 Patients With Compensated Cirrhosis[^]

<p>Sofosbuvir-Velpatasvir Fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) one tablet once daily for 12 weeks</p>	+	<p>Ribavirin 1000 mg if <75 kg or 1200 mg if ≥75 kg for 12 weeks (the daily dose is given in two divided doses)</p>
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Rating: [Class I](#), [Level B](#)

Alternative for Peginterferon plus Ribavirin-Experienced, Genotype 3 Patients With Compensated Cirrhosis[^]

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

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).

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

Source: AASLD-IDSA. Recommendations for testing, management, and treating hepatitis C.

Retreatment of persons in whom prior therapy has failed: peginterferon/ribavirin-experienced, genotype 3 patients with compensated cirrhosis. [[AASLD-IDSA Hepatitis C Guidance](#)] - Accessed November 22, 2017.

Table 5. AASLD-IDSA HCV Guidance for Genotype 3: Retreatment DAA-Experienced (Including NS5A Inhibitors), Genotype 3 Patients With or Without Compensated Cirrhosis[^]

Recommended for DAA-Experienced (Including NS5A Inhibitors), Genotype 3 Patients 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
 Rating: [Class I](#), [Level A](#)

Recommended for DAA-Experienced (Including NS5A Inhibitors), Genotype 3 Patients With or Without Compensated Cirrhosis[^]

<p>Sofosbuvir-Velpatasvir-Voxilaprevir <i>Fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg) one tablet once daily for 12 weeks</i></p>	+	<p>Ribavirin <i>1000 mg if <75 kg or 1200 mg if ≥75 kg for 12 weeks (the daily dose is given in two divided doses)</i></p>
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For patients with prior NS5A inhibitor failure and cirrhosis, weight-based ribavirin is recommended.

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

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

Source: AASLD-IDSA. Recommendations for testing, management, and treating hepatitis C. Retreatment of persons in whom prior therapy has failed: DAA-experienced (including NS5A inhibitors), genotype 3 patients with or without compensated cirrhosis. [[AASLD-IDSA Hepatitis C Guidance](#)] - Accessed November 22, 2017.

