Introduction

Background

In the United States, hepatitis C virus (HCV) genotype 4 infections account for only 1 to 2% of all HCV infections.\[^1\] Globally, approximately 8 to 20% of all HCV infections are caused by HCV genotype 4.\[^2,3\] In addition, HCV genotype 4 is the dominant HCV genotype in Central and North Africa, and in some areas of the Middle East.\[^3,4\] In Egypt, approximately 15% of the population has HCV infection and genotype 4 infection accounts for more than 90% of the HCV infections; most of these cases of HCV were acquired via parenteral exposure to contaminated medical equipment in the anti-schistosomiasis program, or with contaminated blood transfusion.\[^5\] More recently, the prevalence of HCV genotype 4 infection has increased significantly in Southern Europe, particularly in France, Italy, Greece, and Spain.\[^6,7\] The following discussion regarding initial treatment and retreatment of persons with chronic HCV genotype 4 assumes patients and their clinicians have already made the decision to initiate hepatitis C therapy. This topic review does not address the treatment of HCV genotype 4 in persons with decompensated cirrhosis, severe renal impairment (or end-stage renal disease), or post-liver transplantation.

Medications used to Treat Hepatitis C

The HCV Medications section on this website provides detailed information for each of the Food and Drug Administration (FDA)-approved medications listed in the treatment recommendations, including links to the full prescribing information and to patient assistance programs. The direct-acting antiviral (DAA) agents exert their action at specific steps in the HCV life cycle. There are three major classes of direct-acting antiviral 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 extremely important. Thus, patients should receive detailed counseling regarding the importance of adherence prior to starting therapy, as well as intensive monitoring and follow-up during therapy.

Approach to Choosing HCV Genotype 4 Regimen

For persons chronically infected with HCV genotype 4, two key factors influence the choice and duration of therapy: cirrhosis status and prior treatment experience. In addition, the cost of the regimen, insurance coverage, and provider or patient preference can play a major role in the regimen choice. The following treatment recommendations are based on the American Association for the Study of Liver Diseases and the Infectious Diseases Society of America (AASLD-IDSA) HCV Guidance for initial treatment of adults with HCV genotype 4 and for retreatment of adults in whom prior therapy failed, including those with HCV genotype
4. [10, 11]

- AASLD-IDSA HCV Guidance for Treatment-Naïve & Patients with Genotype 4 HCV
- AASLD-IDSA HCV Guidance for Retreatment of Persons in Whom Prior Therapy Failed
HCV Genotype 4: Initial Treatment

Background

In the era prior to DAAs, available data suggest treatment-naïve adults with HCV genotype 4 who were treated with a 48-week course of peginterferon plus ribavirin had sustained virologic response rates at 12 weeks (SVR12) post-treatment that ranged from 43 to 70%, with even lower SVR12 rates (25 to 30%) among those with cirrhosis.[12,13,14,15] Subsequently, several studies showed marked improvement in SVR12 rates with initial treatment of individuals with HCV genotype 4 using sofosbuvir plus ribavirin,[16,17] simeprevir plus sofosbuvir,[18,19,20] simeprevir plus peginterferon plus ribavirin,[20] and daclatasvir plus peginterferon plus ribavirin[21]. More recent studies have shown SVR12 rates greater than 95% can be achieved in HCV treatment-naïve adults with genotype 4 HCV with several all-oral DAA regimens, including glecaprevir-pibrentasvir,[22,23,24] sofosbuvir-velpatasvir,[25] elbasvir-grazoprevir,[26,27] and ledipasvir-sofosbuvir.[28,29] Despite the success of DAA therapy for the treatment of genotype 4, emerging data also suggest that individuals with unusual HCV genotype 4 subtypes, such as genotype 4r, may experience high rates of treatment failure, although how this data impacts clinical practice is not yet clear.[30,31] Currently, there are no recommendations to routinely perform HCV genotype 4 subtyping prior to treatment with DAAs.

Factors to Consider Prior to Choosing Initial Treatment Regimen

For treatment-naïve adults with chronic HCV genotype 4 infection, the recommended treatment regimens differ slightly between persons without cirrhosis and those with compensated cirrhosis; these differences are outlined in the tables.

AASLD-IDSA HCV Guidance for Initial Treatment of HCV Genotype 4

The following is a summary of the AASLD-IDSA HCV Guidance for the initial treatment of adults with HCV genotype 4 infection, including those without cirrhosis or with compensated cirrhosis.[32,33] 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 treatment-naïve adults with HCV genotype 4 has multiple recommended options; these 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 4: Initial Treatment Treatment-Naïve Genotype 4 Patients Without Cirrhosis

Recommended and alternative regimens listed by evidence level and alphabetically

| Recommended for Treatment-Naïve Genotype 4 Patients Without Cirrhosis |
| Elbasvir-Grazoprevir |
| *Fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) one tablet once daily for 12 weeks |
| Rating: **Class I, Level A** |

| Recommended for Treatment-Naïve Genotype 4 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 4 Patients Without Cirrhosis**

**Ledipasvir-Sofosbuvir**

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

An 8-week regimen can be considered in patients with favorable baseline characteristics (e.g., no cirrhosis, HCV RNA
Studies of Initial Treatment of Adults with HCV Genotype 4

The following key studies were used to support the AASLD-IDSA HCV Guidance for initial treatment of adults with chronic HCV genotype 4 infection.[32,33]

Elbasvir-Grazoprevir

- **C-EDGE Treatment-Naïve**: The C-EDGE Treatment-Naïve trial was a randomized, phase 3 study that evaluated elbasvir-grazoprevir (50/100 mg) once daily in treatment-naïve adults with HCV genotype 1, 4, or 6, including subjects without cirrhosis and those with compensated cirrhosis.[34] Among participants with HCV genotype 4 infection, 100% (18 of 18) achieved an SVR12.[34]

- **Pooled Analysis with HCV GT4**: In this pooled analysis of phase 2 and 3 clinical trials that included treatment-naïve and treatment-experienced adults with HCV genotype 4, investigators analyzed treatment responses to 12 or 16 weeks of elbasvir-grazoprevir, with or without ribavirin in persons with chronic HCV genotype 4 infection.[27] The participants included persons with compensated cirrhosis and with HIV. The SVR12 rates were 96.4% (107/111) in the treatment-naïve participants. Among the treatment-naïve participants who received 12 weeks of elbasvir-grazoprevir without ribavirin, 96.0% (97/101) obtained an SVR12.[27]

Glecaprevir-Pibrentasvir

- **ENDURANCE-4**: In this single-arm trial, 121 noncirrhotic adults with HCV genotype 4, 5, or 6 were assigned to 12 weeks of treatment with glecaprevir-pibrentasvir.[22] Most (68%) of these participants were treatment-naïve. Among the 32% that were treatment-experienced, all had previously received (1) sofosbuvir plus ribavirin, with or without peginterferon, or (2) peginterferon (or interferon) with or without ribavirin.[22] There were 76 participants with HCV genotype 4 infection.[22] All but one of these individuals (99%) achieved an SVR12; the one participant who did not have an SVR12 discontinued treatment early (day 12) due to an adverse event (transient ischemic attack).[22]

- **EXPEDITION-1**: This was an open-label, single-arm, phase 3 trial evaluating the safety and efficacy of glecaprevir-pibrentasvir for 12 weeks in treatment-naïve or treatment-experienced adults with compensated cirrhosis and genotype 1, 2, 4, 5 or 6.[23] Prior treatment included (1) peginterferon with or without ribavirin or (2) sofosbuvir plus peginterferon plus ribavirin. Of the participants with HCV genotype 4 patients enrolled in the study, 100% (16 of 16) achieved an SVR12.[23]

- **EXPEDITION-8**: This single-arm, phase 3b study evaluated the efficacy of glecaprevir-pibrentasvir for 8 weeks in treatment-naïve adults with compensated cirrhosis and HCV genotypes 1, 2, 3, 4, 5, or 6.[35] Among the genotype 4 participants enrolled in the trial, 100% (13 of 13) achieved an SVR12.[35]

- **SURVEYOR-I and SURVEYOR-II**: The SURVEYOR-I (for HCV genotype 1, 4, 5, or 6) was a phase 2, open-label trial of non-cirrhotic adults, including treatment-naïve and peginterferon plus ribavirin-experienced participants.[24] Part 1 of this study evaluated the efficacy of various doses of glecaprevir-pibrentasvir for 12 weeks and Part 2 examined the optimized dose of 300/120 mg for 8 versus 12 weeks.[24] Of the 22 participants with genotype 4 infection who received 12 weeks of glecaprevir-pibrentasvir 300/120 mg daily, 100% (22 of 22) achieved an SVR12.[24]

- **SURVEYOR-II (Part 4)**: The SURVEYOR-II (Part 4) was a phase 3, single-arm, open-label trial to evaluate the safety and efficacy of 8 weeks of glecaprevir-pibrentasvir in 203 noncirrhotic adults with HCV genotype 2, 4, 5, or 6, of whom 46 had genotype 4 infection (most were treatment-naïve).[22] Using intent-to-treat analysis, 93% (43 of 46) of the participants with HCV genotype 4 achieved an SVR12; the 3 who did not achieve an SVR12 were lost to follow-up and their response to treatment was unknown.[22]

Ledipasvir-Sofosbuvir

- **NIAID SYNERGY (Genotype 4)**: This single-center, open-label, phase 2a trial evaluated the safety and efficacy of a 12-week course of ledipasvir-sofosbuvir in 21 adults with HCV genotype 4 infection;
among those enrolled, 62% (13 of 21) were treatment naïve and 33% (7 of 21) had compensated cirrhosis.\[29\] An SVR12 was achieved in 100% (20 of 20) of the participants. In the intent-to-treat analysis, there was one treatment failure; this individual was treatment naïve and withdrew at week 7 of the study due to nonadherence with therapy.\[29\]

- **Egyptian GT4 Multicenter Study:** This open-label, multicenter study evaluated the efficacy of ledipasvir-sofosbuvir, with or without ribavirin, for 8 or 12 weeks in 255 Egyptian adults with HCV genotype 4 infection; 170 were treatment naïve and 85 were treatment experienced.\[36\] For the treatment-naïve participants without cirrhosis who received 8 weeks of therapy, 97% (35 of 36) who received ledipasvir-sofosbuvir achieved an SVR12, compared with the 91% (32 of 35) who received ledipasvir-sofosbuvir plus ribavirin.\[36\] In treatment-naïve participants without cirrhosis who received 12 weeks of therapy, the SVR12 rates were 100% (34 of 34) in the ledipasvir-sofosbuvir arm and 97% (33 of 34) in the ledipasvir-sofosbuvir plus ribavirin arm.\[36\] For treatment-naïve individuals with compensated cirrhosis, the SVR12 rates were 100% (8 of 8) with 12 weeks of ledipasvir-sofosbuvir plus ribavirin; all other regimens had SVR12 rates less than 90%, but the number of persons with cirrhosis in the treatment-naïve group was small.\[36\]

- **HEPNED-001:** This single-arm, prospective, open-label study from the Netherlands and Belgium evaluated the effectiveness of 8 weeks of ledipasvir-sofosbuvir for noncirrhotic adults with an HCV RNA level less than 10 million IU/mL, including individuals with HCV monoinfection and HCV-HIV coinfection.\[37\] Following 8 weeks of treatment, 93% (28/30) of the participants with HCV-HIV coinfection and 100% (10/10) of the participants with HCV monoinfection achieved an SVR12.\[37\]

- **SHARED Trial:** This was a single-arm, open-label trial evaluating the safety and efficacy of ledipasvir-sofosbuvir among 300 adults with HCV genotype 4 in Rwanda.\[31\] On viral subtyping, the majority of individuals had HCV genotype 4K (n = 134), 4r (n = 48), 4q (n = 42), or 4v (n = 24). The overall SVR12 rate was 87%, but the SVR12 rate for genotype 4r was only 56% in comparison to 93% for other subtypes.\[31\]

**Sofosbuvir-Velpatasvir**

- **ASTRAL-1:** In the phase 3 ASTRAL-1 trial, investigators randomized treatment-naïve and treatment-experienced adults with HCV genotype 1, 2, 4, 5, or 6 infection in a 5:1 ratio to receive a 12-week course of either sofosbuvir-velpatasvir or placebo.\[25\] The study included 116 participants with HCV genotype 4, including individuals without cirrhosis and with compensated cirrhosis.\[25\] Among the treatment-naïve participants who received sofosbuvir-velpatasvir, 100% (64 of 64) achieved an SVR12.\[25\]

- **POLARIS-2:** In this phase 3, open-labeled trial, patients with chronic hepatitis C genotype 1-4 infection who were naïve to direct-acting antiviral therapy (prior peginterferon and ribavirin allowed) were randomized to either 8 weeks of sofosbuvir-velpatasvir-voxilaprevir or 12 weeks of sofosbuvir-velpatasvir.\[38\] Among the 57 patients with genotype 4 in the 12-week arm, 98% (56 of 57) achieved an SVR12.\[38\]
HCV Genotype 4: Retreating Persons who Failed Prior Therapy

Background

The data regarding the retreatment of adults with HCV genotype 4 who have failed prior therapy are limited, but they suggest high efficacy of DAA therapy. For treatment-experienced persons with HCV genotype 4, more choices exist when prior treatment involved peginterferon plus ribavirin as opposed to a DAA-based regimen, largely because more retreatment data exist for the former group.

Factors to Consider Prior to Choosing Retreatment Regimen

For retreatment of adults with HCV genotype 4, the key factors that influence the choice of the retreatment regimen are (1) the prior regimen used when treatment failure occurred, (2) the presence or absence of cirrhosis, and (3) cost or insurance considerations.

Baseline Resistance Testing

Baseline resistance testing is not routinely recommended for treatment-experienced patients with HCV genotype 4 infection.

AASLD-IDSA HCV Guidance for Retreatment of HCV Genotype 4

The following is a summary of the AASLD-IDSA HCV Guidance for adults with HCV genotype 4 who are treatment experienced and failed prior DAA therapy, including those without cirrhosis and those with compensated cirrhosis.[11, 39, 40, 41] 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. 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 are 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 Ila**, **Level A**

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


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**Table 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

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

**Sofosbuvir-Velpatasvir-Voxilaprevir**

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

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

Rating: **Class I**, **Level A**

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**Table 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

**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)

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


### 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

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

**Glecaprevir-Pibrentasvir**  
(400 mg) one tablet 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)
*Fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) once 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^:

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

Rating: Class Iia, Level B

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


Retreatment of Persons with Prior PegInterferon and Ribavirin Failure

The latest version of the AASLD-IDSA HCV Guidance (changes effective January 21, 2021) no longer provides specific recommendations for retreatment of persons with a history of peginterferon plus ribavirin therapy, with or without an earlier generation direct-acting antiviral agent (telaprevir, boceprevir, sofosbuvir or simeprevir).[11] 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.[11] 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.

- Available data suggest that persons with HCV genotype 4 infection and prior treatment experience with peginterferon and ribavirin have good treatment responses with 12 weeks of elbasvir-grazoprevir (without ribavirin). It is important to note the sample size of persons with genotype 4 and treatment
experience is much smaller than those for genotype 1 and the estimates of SVR12 are only in the range of 86 to 88% for this subset of persons treated with 12 weeks of elbasvir-grazoprevir.\cite{27,42} For these reasons, 12 weeks of treatment with elbasvir-grazoprevir in this setting is a potentially less appealing option when compared with several other DAA combination regimens.

- In persons with HCV genotype 4 (with or without cirrhosis) who are treatment-experienced with peginterferon and ribavirin (with or without an early DAA), there are limited data to support the use of 8 weeks of glecaprevir-pibrentasvir.
- In persons with HCV genotype 4 (with or without cirrhosis) who are treatment-experienced with peginterferon and ribavirin (with or without an early DAA), there are limited data to support the use of 8 weeks of ledipasvir-sofosbuvir.
Studies of Retreatment of Adults with HCV Genotype 4

The following key studies were used to support the recommendations for treatment of adults with HCV genotype 4 infection who have previously received treatment. Unless noted otherwise, treatment experience in these studies refers to a history of virologic relapse or nonresponse with a regimen that included peginterferon and ribavirin.

Elbasvir-Grazoprevir

- **C-EDGE Treatment-Experienced**: In the phase 3 C-EDGE Treatment-Experienced trial, investigators enrolled 420 previously treated adults with HCV genotypes 1, 4, or 6 to receive 12 or 16 weeks of elbasvir-grazoprevir, with or without ribavirin.[24] All participants had previously failed peginterferon and ribavirin. For the individuals with HCV genotype 4 who received treatment, 86% (32 of 37) achieved an SVR12.[24]

- **Integrated Pooled Analysis of Elbasvir-Grazoprevir**: In this study, investigators conducted a pooled analysis of 155 adults with HCV genotype 4 infection who were enrolled in a phase 2/3 elbasvir-grazoprevir trial.[27] Of these participants, 44 were treatment experienced (with prior peginterferon plus ribavirin therapy) and 41% had cirrhosis. For the treatment-experienced participants, the SVR12 rate was 88.6% (39 of 44) overall for all combinations of 12 or 16 weeks of elbasvir-grazoprevir (with or without ribavirin) and 87.5% (14 of 16) among those participants who received 12 weeks of elbasvir-grazoprevir without ribavirin.[27] No treatment failures were seen in participants who relapsed after prior peginterferon plus ribavirin therapy; however, response rates were lower in those with prior on-treatment virologic failure in the non-ribavirin containing arm (12 weeks, 78%; 16 weeks, 60%) versus the ribavirin-containing arm (12 weeks, 91%; 16 weeks, 100%).

Glecaprevir-Pibrentasvir

- **ENDURANCE-4**: In this single-arm, phase 3 trial, 121 adults with HCV genotype 4, 5, or 6 infection (without cirrhosis) were enrolled to receive treatment with a 12-week course of glecaprevir-pibrentasvir.[22] Among those who were enrolled 32% were treatment-experienced (all of whom had previously received either interferon plus ribavirin or peginterferon plus ribavirin). There were 76 participants with HCV genotype 4, but details regarding how many of these individuals with HCV genotype 4 were treatment experienced were not given.[22] Among the participants with HCV genotype 4 infection, 99% (75 of 76) achieved an SVR12; the one individual who did not achieve an SVR12 had discontinued therapy after only 12 days. Findings from ENDURANCE-4 were published in conjunction with ENDURANCE-2 and SURVEYOR-II, Part 4.[22]

- **EXPEDITION-1**: This was an open-label, single-arm, phase 3 trial evaluating the safety and efficacy of glecaprevir-pibrentasvir for 12 weeks in adults with compensated cirrhosis and genotype 1, 2, 4, 5, or 6 who were either treatment naïve or treatment experienced.[23] Prior treatment experience included (1) peginterferon with or without ribavirin, or (2) peginterferon plus ribavirin plus sofosbuvir.[23] Of the participants with HCV genotype 4 (unknown number with prior treatment experience), 100% (16 of 16) achieved an SVR12.[23]

- **SURVEYOR-II (Part 4)**: This phase 2, open-label, single-arm trial evaluated the efficacy of 8 weeks of glecaprevir-pibrentasvir in treatment-naïve and treatment-experienced adults without cirrhosis who had HCV genotype 2, 4, 5, or 6.[22] Treatment-experienced participants had previously received (1) peginterferon (or interferon), with or without ribavirin, or (2) sofosbuvir plus ribavirin, with or without peginterferon.[22] Among those enrolled, 46 had HCV genotype 4, among whom 27 were treatment experienced.[22] The SVR12 rate for individuals with HCV genotype 4 was 93% (43 of 46); there were 3 study participants who were lost to follow up and they accounted for all of the participants who did not achieve an SVR12.[22] There were no virologic failures among participants with HCV genotype...
Ledipasvir-Sofosbuvir

- **Egyptian GT4 Multicenter Study**: This open-label multicenter study evaluated the efficacy of ledipasvir-sofosbuvir, with or without ribavirin for 8 or 12 weeks in 255 Egyptian adults with HCV genotype 4 infection; among those enrolled, 74 were interferon-experienced and 11 had prior treatment with sofosbuvir (either sofosbuvir plus ribavirin or ledipasvir-sofosbuvir, with or without ribavirin).[36] The interferon-experienced participants were randomized to receive a 12-week treatment course with either ledipasvir-sofosbuvir or ledipasvir-sofosbuvir plus ribavirin.[36] For this group of participants, 94% (34 of 36) achieved an SVR12 with ledipasvir-sofosbuvir and 100% (38 of 38) had an SVR12 with ledipasvir-sofosbuvir plus ribavirin. All sofosbuvir-experienced participants were assigned to the 12-week regimen of ledipasvir-sofosbuvir plus ribavirin and 100% (11 of 11) achieved an SVR12.[36]

- **NIAID SYNERGY (Genotype 4)**: In this phase 2a, open-label cohort, investigators enrolled 21 adults with HCV genotype 4 to receive a 12-week course of ledipasvir and sofosbuvir.[29] Twenty participants completed the 12-week treatment course and 100% achieved an SVR12.[29] For those enrolled, 38% (8 of 21) had failed prior treatment. Among the treatment-experienced participants, 100% (8 of 8) achieved an SVR12.[29]

Sofosbuvir-Velpatasvir

- **ASTRAL-1**: In the phase 3 ASTRAL-1 trial, investigators randomized treatment-naïve and treatment-experienced adults with HCV genotype 1, 2, 4, 5, or 6 infection in a 5:1 ratio to receive a 12-week course of sofosbuvir-velpatasvir or placebo.[25] The study included 116 participants with HCV genotype 4. Among the treatment-experienced participants who received sofosbuvir-velpatasvir, 100% (52 of 52) achieved an SVR12.[25]

Sofosbuvir-Velpatasvir-Voxilaprevir

- **POLARIS-1**: In this phase 3, placebo-controlled trial, investigators enrolled adults with HCV genotype 1, 2, 3, 4, 5, or 6 who had previously received treatment that included an NS5A inhibitor to receive retreatment with a 12-week course of sofosbuvir-velpatasvir-voxilaprevir.[43] Most participants were either ledipasvir- or daclatasvir-experienced (51% and 27% respectively) and compensated cirrhosis was present in 46% of individuals in the active arm. Among participants with HCV genotype 4 infection, 91% (20 of 22) achieved an SVR12 with sofosbuvir-velpatasvir-voxilaprevir treatment. This study was published in tandem with the POLARIS-4 study.[43]

- **POLARIS-4**: In this phase 3, active-comparator, open-label trial, 314 adults with HCV genotype 1, 2, or 3 with prior DAA treatment experience (without an NS5A inhibitor) were randomized to receive a 12-week course with either sofosbuvir-velpatasvir-voxilaprevir or sofosbuvir-velpatasvir.[43] In addition, the study included 19 individuals with HCV genotype 4, all of whom were assigned to the sofosbuvir-velpatasvir-voxilaprevir arm. For these HCV genotype 4 participants, 100% (19 of 19) achieved an SRV12. This study was published in tandem with POLARIS-1.[43]
Summary Points

- Infection with HCV genotype 4 is uncommon in the United States, but it is highly prevalent in the Middle East, Africa, and Southern Europe.
- For initial therapy of adults with HCV genotype 4 without cirrhosis, four regimens are recommended: glecaprevir-pibrentasvir for 8 weeks; ledipasvir-sofosbuvir for 12 weeks; sofosbuvir-velpatasvir for 12 weeks; or elbasvir-grazoprevir for 12 weeks.
- For initial therapy of adults with HCV genotype 4 and compensated cirrhosis, the recommended regimens are the same as for persons without cirrhosis, except that glecaprevir-pibrentasvir should be given for 12 weeks in individuals with HIV coinfection.
- For retreatment of adults with HCV genotype 4 who have prior peginterferon and ribavirin experience, with or without a first-generation protease inhibitors (telaprevir, boceprevir), the recommended regimens are usually the same as for treatment-naïve individuals.
- For the retreatment of adults with HCV genotype 4 and compensated cirrhosis (with prior peginterferon/ribavirin experience), three 12-week regimens are recommended: sofosbuvir-velpatasvir; elbasvir-grazoprevir (same conditions as noted above); or glecaprevir-pibrentasvir.
- The retreatment of DAA-experienced adults with HCV genotype 4 infection depends on the prior DAA regimen that was taken.


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

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


25. Feld JJ, Jacobson IM, Hézode C, et al. Sofosbuvir and Velpatasvir for HCV Genotype 1, 2, 4, 5, and 6


32. AASLD-IDSA. Recommendations for testing, management, and treating hepatitis C. Initial treatment of HCV infection: treatment-naive genotype 4 without cirrhosis. [AASLD-IDSA Hepatitis C Guidance]

33. AASLD-IDSA. Recommendations for testing, management, and treating hepatitis C. Initial treatment of HCV infection: treatment-naive genotype 4 with compensated cirrhosis. [AASLD-IDSA Hepatitis C Guidance]


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

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

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


References


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


• Lenz O, Vijgen L, Berke JM, et al. Virologic response and characterisation of HCV genotype 2-6 in


Figures

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

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

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

**Treatment-Naïve Genotype 4 Patients Without Cirrhosis**

Recommended and alternative regimens listed by evidence level and alphabetically

<table>
<thead>
<tr>
<th>Recommended for Treatment-Naïve Genotype 4 Patients Without Cirrhosis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Elbasvir-Grazoprevir</strong></td>
</tr>
<tr>
<td><em>Fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) one tablet once daily for 12 weeks</em></td>
</tr>
<tr>
<td>Rating: <a href="#">Class I, Level A</a></td>
</tr>
<tr>
<td>Note: <em>This is taken as 3 tablets once daily with each fixed-dose tablet containing elbasvir (100 mg)/grazoprevir (100 mg).</em></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Recommended for Treatment-Naïve Genotype 4 Patients Without Cirrhosis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Glecaprevir-Pibrentasvir</strong></td>
</tr>
<tr>
<td><em>Fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) once daily for 8 weeks</em></td>
</tr>
<tr>
<td>Rating: <a href="#">Class I, Level A</a></td>
</tr>
<tr>
<td>Note: <em>This is taken as 3 tablets once daily with each fixed-dose tablet containing glecaprevir (100 mg)/pibrentasvir (40 mg).</em></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Recommended for Treatment-Naïve Genotype 4 Patients Without Cirrhosis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ledipasvir-Sofosbuvir</strong></td>
</tr>
<tr>
<td><em>Fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) one tablet once daily for 12 weeks</em></td>
</tr>
<tr>
<td>Rating: <a href="#">Class I, Level A</a></td>
</tr>
<tr>
<td>An 8-week regimen can be considered in patients with favorable baseline characteristics (e.g., no cirrhosis, HCV RNA &lt;6 million IU/mL, and absence of genotype 4r).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Recommended for Treatment-Naïve Genotype 4 Patients Without Cirrhosis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sofosbuvir-Velpatasvir</strong></td>
</tr>
<tr>
<td><em>Fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) one tablet once daily for 12 weeks</em></td>
</tr>
<tr>
<td>Rating: <a href="#">Class I, Level A</a></td>
</tr>
</tbody>
</table>

### Table 2. AASLD-IDSA HCV Guidance for Genotype 4: Initial Treatment

**Treatment-Naïve Genotype 4 Patients With Compensated Cirrhosis**

Recommended and alternative regimens listed by evidence level and alphabetically

<table>
<thead>
<tr>
<th>Recommended for Treatment-Naïve Genotype 4 Patients With Compensated Cirrhosis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sofosbuvir-Velpatasvir</strong></td>
</tr>
<tr>
<td><em>Fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) one tablet once daily for 12 weeks</em></td>
</tr>
<tr>
<td>Rating: <strong>Class I, Level A</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Recommended for Treatment-Naïve Genotype 4 Patients With Compensated Cirrhosis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Glecaprevir-Pibrentasvir</strong></td>
</tr>
<tr>
<td><em>*Fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) one daily for 8 weeks</em></td>
</tr>
<tr>
<td>For HIV/HCV-coinfected patients, a treatment duration of 12 weeks is recommended.</td>
</tr>
<tr>
<td>Rating: <strong>Class I, Level B</strong></td>
</tr>
<tr>
<td>Note: <em>This is taken as 3 tablets once daily with each fixed-dose tablet containing glecaprevir (100 mg)/pibrentasvir (40 mg).</em></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Recommended for Treatment-Naïve Genotype 4 Patients With Compensated Cirrhosis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Elbasvir-Grazoprevir</strong></td>
</tr>
<tr>
<td><em>Fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) one tablet once daily for 12 weeks</em></td>
</tr>
<tr>
<td>Rating: <strong>Class IIa, Level B</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Recommended for Treatment-Naïve Genotype 4 Patients With Compensated Cirrhosis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ledipasvir-Sofosbuvir</strong></td>
</tr>
<tr>
<td><em>Fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) one tablet once daily for 12 weeks</em></td>
</tr>
<tr>
<td>Rating: <strong>Class IIa, Level B</strong></td>
</tr>
</tbody>
</table>

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

### Table 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 (e.g. elbasvir-grazoprevir or glecaprevir-pibrentasvir), or (2) persons with genotype 3 infection with sofosbuvir and NS5A inhibitor experience (e.g. ledipasvir-sofosbuvir or sofosbuvir-velpatasvir)

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

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

---

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

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^ |
|--------------------------------------------------|--------------------------------------------------|--------------------------------------------------|
| **Glecaprevir-Pibrentasvir**                     | **Sofosbuvir**                                   | **Ribavirin**                                    |
| *Fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) once daily for 16 weeks* | *(400 mg) one tablet once daily for 16 weeks*    | 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)

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

For patients without cirrhosis

Rating: **Class IIa, Level B**

| Recommended for Glecaprevir-Pibrentasvir Treatment Failures (All Genotypes), With or Without Compensated Cirrhosis^ |
|--------------------------------------------------|--------------------------------------------------|--------------------------------------------------|
| **Sofosbuvir-Velpatasvir-Voxilaprevir**           | **Ribavirin**                                    |
| *Fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg) one tablet once daily for 12 weeks* | 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 treatment of patients with decompensated cirrhosis, see the AASLD-IDSA Guidance: Unique Populations—Patients with Decompensated Cirrhosis

### 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

<table>
<thead>
<tr>
<th>Glecaprevir-Pibrentasvir</th>
<th>Sofosbuvir (400 mg) one tablet once daily for 16 weeks#</th>
<th>Ribavirin for patients weighing ≤75 kg/1200 mg for patients weighing ≥75 kg for 24 weeks# (the daily dose is given in two divided doses)</th>
</tr>
</thead>
<tbody>
<tr>
<td>*Fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) once daily for 16 weeks#</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

Rating: Class Ila, Level B

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

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

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

Rating: Class Ila, Level B

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