Introduction

Background

In the United States, hepatitis C virus (HCV) genotype 4 infections accounts for only 1-2% of all HCV infections.[1] Globally, approximately 20% of all HCV infections are caused by genotype 4.[2] In addition, genotype 4 is the dominant HCV genotype in Egypt, North Africa, and the Middle East.[3] 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 contaminated needles in the anti-schistosomiasis program, or with contaminated blood transfusion.[4] More recently, the prevalence of HCV genotype 4 infection has increased significantly in Southern Europe, particularly in France, Italy, Greece, and Spain.[5,6] The following discussion regarding initial treatment and retreatment of patients 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, renal impairment, acute HCV infection, or post-liver transplantation.

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 (DAA) 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.[7,8] 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 AASLD-IDSA HCV Guidance for adults with HCV genotype 4 infection.[9,10]

- AASLD-IDSA HCV Guidance for Treatment-Naïve & Patients with Genotype 4 HCV
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 SVR12 rates that ranged from 43-70%, with even lower SVR12 rates (25-30%) among those with cirrhosis.[11,12,13,14] Subsequently, several studies showed improved SVR12 response rates with initial treatment of individuals with HCV genotype 4 using sofosbuvir plus ribavirin,[15,16] simeprevir plus sofosbuvir,[17,18,19] simeprevir plus peginterferon plus ribavirin,[19] and daclatasvir plus peginterferon plus ribavirin.[20]. More recent studies have shown SVR12 rates greater than 95% in HCV treatment-naïve adults with several all-oral DAA regimens, including glecaprevir-pibrentasvir,[21,22,23] sofosbuvir-velpatasvir,[24] elbasvir-grazoprevir,[25,26] ledipasvir-sofosbuvir,[27,28] and ombitasvir-paritaprevir-ritonavir[29,30].

Factors to Consider Prior to Choosing Initial Treatment Regimen

For treatment-naïve adults with chronic HCV genotype 4 infection, the recommended treatment regimens are usually the same in persons without cirrhosis and those with compensated cirrhosis; one important exception is that glecaprevir-pibrentasvir is used for 8 weeks in persons without cirrhosis and for 12 weeks in those with compensated cirrhosis.

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.[31,32] 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 four recommended options: glecaprevir-pibrentasvir, sofosbuvir-velpatasvir, elbasvir-grazoprevir, and ledipasvir-sofosbuvir. 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 4: Initial Treatment Treatment-Naive Genotype 4 Patients Without Cirrhosis

Recommended and alternative regimens listed by evidence level and alphabetically
Elbasvir-Grazoprevir  
Fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) one tablet once daily for 12 weeks  
Rating: **Class IIa, Level B**

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  
Rating: **Class IIa, Level B**

Alternative for Treatment-Naïve Genotype 4 Patients Without Cirrhosis  
Ombitasvir-Paritaprevir-Ritonavir  
*Fixed-dose combination of ombitasvir (25 mg)/paritaprevir (150 mg)/ritonavir (100 mg) one 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 A**  
Note: *This is taken as 2 tablets once daily with each fixed-dose tablet containing ombitasvir (12.5 mg)/paritaprevir (75 mg)/ritonavir (50 mg)*


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  
Recommended for Treatment-Naïve Genotype 4 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**

Recommended for Treatment-Naïve Genotype 4 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 B**
**Recommended for Treatment-Naïve Genotype 4 Patients With Compensated Cirrhosis**

**Elbasvir-Grazoprevir**
*Fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) one tablet once daily for 12 weeks*

Rating: Class IIa, Level B

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

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

Rating: Class IIa, Level B

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

**Ombitasvir-Paritaprevir-Ritonavir**
*Fixed-dose combination of ombitasvir (25 mg)/paritaprevir (150 mg)/ritonavir (100 mg) 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)

See statement on FDA warning regarding the use of paritaprevir/ritonavir/ombitasvir ± dasabuvir in patients with cirrhosis.

Rating: Class I, Level A

Note: *This is taken as 2 tablets once daily with each fixed-dose tablet containing ombitasvir (12.5 mg)/paritaprevir (75 mg)/ritonavir (50 mg)

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

Studies of Initial Treatment of Adults with HCV Genotype 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.[31,32]

**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.[33] Among participants with HCV genotype 4 infection, 100% (18 of 18) achieved an SVR12.
- **Pooled Analysis of HCV Genotype 4**: 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 12-16 weeks of elbasvir-grazoprevir, with or without ribavirin in persons with chronic HCV GT4 infection.[26] 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.

**Glecaprevir-Pibrentasvir**

- **ENDURANCE-4**: In this single-arm trial, 121 non-cirrhotic adults with genotype 4, 5, or 6 infection were assigned to 12 weeks of treatment with glecaprevir-pibrentasvir.[21] Most (68%) of these participants were treatment-naïve; among the 32% that were treatment-experienced, all had previously received interferon plus ribavirin or peginterferon plus ribavirin.[21] There were 76 patients with genotype 4 infection. All but one of these patients (99%) achieved a sustained virologic response at 12 weeks post-treatment; the one patient discontinued treatment early (day 12) due to an adverse event (transient ischemic attack).[21]
- **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.[23] 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. 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.
- **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 adults with HCV genotype 2, 4, 5, or 6 infection without cirrhosis, of whom 46 had genotype 4 infection (most were treatment-naïve).[21] 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.[21]

**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.[28] 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 non-adherence with therapy.[28]
- **Egyptian Multicenter Study**: This open-label multicenter study evaluated the efficacy of ledipasvir-sofosbuvir, with or without ribavirin, for 8 or 12 weeks in 256 Egyptian adults with HCV genotype 4 infection; 170 were treatment naïve and 85 were treatment experienced.[34] For the treatment-naïve participants without cirrhosis who received 8 weeks of therapy, 97% (35 of 36) of those receiving
ledipasvir-sofosbuvir achieved an SVR12, compared with the 91% (32 of 35) who received ledipasvir-sofosbuvir plus ribavirin.[34] With 12 weeks of therapy in treatment-naïve participants without cirrhosis, the SVR12 rates were 100% (34 of 34) in the ledipasvir-sofosbuvir arm and 97% (33 of 34) with ledipasvir-sofosbuvir plus ribavirin.[34] 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.[34]

**Ombitasvir-Paritaprevir-Ritonavir**

- **AGATE-II**: This phase 3, open-label, partly randomized trial enrolled treatment-naïve or treatment-experienced adults with HCV genotype 4 infection, including 100 participants with cirrhosis and 60 without cirrhosis.[30] The study was conducted at five academic and hepatology centers in Egypt. Participants without cirrhosis received 12 weeks ombitasvir-paritaprevir-ritonavir plus weight-based ribavirin. The regimen used in this trial did not include dasabuvir, because dasabuvir does not have activity against HCV genotype 4. Individuals with compensated cirrhosis were randomized to receive ombitasvir-paritaprevir-ritonavir for 12 weeks or 24 weeks. Overall, including both treatment-naïve and treatment-experienced participants, more than 90% achieved an SVR 12, including 94% (94 of 100) in those without cirrhosis, 97% (30 of 31) in those with compensated cirrhosis treated with 12 weeks, and 93% (27 of 29) in those with compensated cirrhosis treated with 24 weeks.
- **PEARL-I**: In the phase 2b PEARL-I study, investigators examined the efficacy of a 12-week course of ombitasvir plus paritaprevir plus ritonavir with or without ribavirin in adults with HCV genotype 4 infection; the study enrolled treatment-naïve and treatment-experienced adults, but excluded individuals with cirrhosis.[29] The regimen used in this trial did not include dasabuvir, because dasabuvir does not have activity against HCV genotype 4. For the 86 treatment-naïve recipients of ombitasvir plus paritaprevir plus ritonavir without ribavirin, an SVR12 was achieved in 91% (40 of 44) compared with an SVR12 rate of 100% (42 of 42) in participants treated with ombitasvir plus paritaprevir plus ritonavir with ribavirin.[29]

**Sofosbuvir-Velpatasvir**

- **ASTRAL-1**: In the phase 3 ASTRAL-1 trial, investigators randomized treatment-naïve and treatment-experienced adults with chronic HCV genotype 1, 2, 4, 5, or 6 infection in a 5:1 ratio to receive a 12-week course of either sofosbuvir-velpatasvir or placebo.[24] The study included 116 adults with HCV genotype 4. Among the treatment-naïve participants with genotype 4 infection who received sofosbuvir-velpatasvir, 100% (64 of 64) achieved an SVR12.[24]
- **POLARIS-2**: In this phase 3, open-labeled trial, adults 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.[35] Compensated cirrhosis was present in 18%. For the participants with genotype 4 infection treated with sofosbuvir-velpatasvir, 98% (56 of 57) achieved an SVR12.
HCV Genotype 4: Retreating Persons who Failed Prior Therapy

Background

The data regarding the retreatment of adult with HCV genotype 4 who have failed prior therapy are limited but they suggest high efficacy of currently available 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 than latter group.

Factors to Consider Prior to Choosing Retreatment Regimen

For retreatment of adults with HCV genotype 4 in whom prior therapy with peginterferon and ribavirin failed, the recommended treatment regimens are very similar for individuals without cirrhosis or those with compensated cirrhosis; the only difference is that ribavirin is added to the ledipasvir-sofosbuvir regimen in persons with compensated cirrhosis, thus making this an alternative regimen rather than a recommended regimen for this subset.

AASLD-IDSA HCV Guidance for Retreatment of HCV Genotype 4

The following is a summary of the AASLD-IDSA HCV Guidance for retreatment of adults with HCV genotype 4; the retreatment guidance includes (1) adults in whom prior therapy with peginterferon and ribavirin failed, and (2) adults in whom a DAA-based regimen failed, including failures with NS5A inhibitors.[32, 36] 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 4: Retreatment Peginterferon plus Ribavirin-Experienced, Genotype 4 Patients Without Cirrhosis

Recommended and alternative regimens listed by evidence level and alphabetically
*Fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) one tablet once daily for 12 weeks

For patients who experienced virologic relapse after prior peginterferon plus ribavirin therapy.

Rating: Class IIa, Level B

Recommended for Peginterferon plus Ribavirin-Experienced, Genotype 4 Patients Without Cirrhosis

**Ledipasvir-Sofosbuvir**

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

Rating: Class IIa, Level B

**Ombitasvir-Paritaprevir-Ritonavir**

*Fixed-dose combination of ombitasvir (25 mg)/paritaprevir (150 mg)/ritonavir (100 mg) once daily for 12 weeks

+ Ribavirin

1000 mg/day if <75 kg or 1200 mg/day if ≥75 kg for 12 weeks (the daily dose is given in two divided doses)

Rating: Class I, Level A

Note: *This is taken as 2 tablets once daily with each fixed-dose tablet containing ombitasvir (12.5 mg)/paritaprevir (75 mg)/ritonavir (50 mg)

**Elbasvir-Grazoprevir**

*Fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) one tablet once daily for 16 weeks

+ Ribavirin

1000 mg/day if <75 kg or 1200 mg/day if ≥75 kg for 16 weeks (the daily dose is given in two divided doses)

*For patients with prior on-treatment virologic failure (failure to suppress or breakthrough) while on peginterferon plus ribavirin.

Rating: Class IIa, Level B


**Table 4. AASLD-IDSA HCV Guidance for Genotype 4: Retreatment**

AASLD-IDSA HCV Guidance for Peginterferon plus Ribavirin-Experienced, Genotype 4 Patients With Compensated Cirrhosis^
Recommended for AASLD-IDSA HCV Guidance for Peginterferon plus Ribavirin-Experienced, Genotype 4 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**

**Elbasvir-Grazoprevir**

*Fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) one tablet once daily for 12 weeks*

For patients who experienced virologic relapse after prior peginterferon plus ribavirin therapy.

Rating: **Class IIa, Level B**

**Glecaprevir-Pibrentasvir**

*Fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) once daily for 12 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 AASLD-IDSA HCV Guidance for Peginterferon plus Ribavirin-Experienced, Genotype 4 Patients With Compensated Cirrhosis

**Ombitasvir-Paritaprevir-Ritonavir**

*Fixed-dose combination of ombitasvir (25 mg)/paritaprevir (150 mg)/ritonavir (100 mg) once daily for 12 weeks* + **Ribavirin**

1000 mg/day if <75 kg or 1200 mg/day if ≥75 kg for 12 weeks (the daily dose is given in two divided doses)

#Please see statement on FDA warning regarding the use of ombitasvir-paritaprevir-ritonavir ± dasabuvir in patients with cirrhosis.

Rating: **Class I, Level A**

Note: #*This is taken as 2 tablets once daily with each fixed-dose tablet containing ombitasvir (12.5 mg)/paritaprevir (75 mg)/ritonavir (50 mg)

**Elbasvir-Grazoprevir**

*Fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) one tablet once daily for 16 weeks* + **Ribavirin**

1000 mg/day if <75 kg or 1200 mg/day if ≥75 kg for 16 weeks (the daily dose is given in two divided doses)

For patients with prior on-treatment virologic failure (failure to suppress or breakthrough) while on peginterferon plus ribavirin
Alternative for AASLD-IDSA HCV Guidance for Peginterferon plus Ribavirin-Experienced, Genotype 4 Patients With Compensated Cirrhosis^  

**Ledipasvir-Sofosbuvir**  
Fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) one tablet once daily for 12 weeks  
Rating: **Class IIa, Level B**

**Ribavirin**  
1000 mg/day if <75 kg or 1200 mg/day if ≥75 kg for 12 weeks (the daily dose is given in two divided doses)

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


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**Table 5. AASLD-IDSA HCV Guidance for Genotype 4: Retreatment DAA-Experienced (Including NS5A Inhibitors), Genotype 4 Patients With or Without Compensated Cirrhosis^**

Recommended and alternative regimens listed by evidence level and alphabetically

**Recommended for DAA-Experienced (Including NS5A Inhibitors), Genotype 4 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**

^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 4 patients with or without compensated cirrhosis. [AASLD-IDSA Hepatitis C Guidance] - Accessed April 28, 2019.
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.[23] 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.[23]

- **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.[26] 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.[26]

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.[21] 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 infection were treatment-experienced were not given.[21] Among the participants with HCV genotype 4, 99% (75 of 76) achieved an SVR12; the only 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.[21]

Ledipasvir-Sofosbuvir

- **Egyptian Multicenter Study**: This open-label multicenter study evaluated the efficacy of ledipasvir-sofosbuvir, with or without ribavirin for 8 or 12 weeks in 256 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).[34] The interferon-experienced participants were randomized to receive a 12-week treatment course with either ledipasvir-sofosbuvir or ledipasvir-sofosbuvir plus ribavirin.[34] 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.[34]
- **NIAID SYNERGY (Genotype 4)**: In this phase 2a, open-label cohort, investigators enrolled 21 adults with HCV genotype 4 infection to receive a 12-week course of ledipasvir and sofosbuvir.[28] Twenty participants completed the 12-week treatment course and 12 received the fixed-dose combination of ledipasvir-sofosbuvir.[28] For those enrolled, 38% (8 of 21) had failed prior treatment. Among the treatment-experienced participants, 100% (8 of 8) achieved an SVR12.[28]
Ombitasvir-Paritaprevir-Ritonavir

- **PEARL-I**: In the phase 2b PEARL-I study, investigators examined the efficacy of a 12-week course of ombitasvir plus paritaprevir plus ritonavir, with or without ribavirin in treatment-naïve and treatment-experienced adults with HCV genotype 4 infection; the treatment-experienced participants all received a regimen that included ribavirin.[29] Individuals with cirrhosis were excluded from the study. Among the treatment-experienced participants, 100% (49 of 49) achieved an SVR12 with ombitasvir plus paritaprevir plus ritonavir and ribavirin. Note the regimen used in this trial did not include dasabuvir since dasabuvir does not have activity against HCV genotype 4.[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 either sofosbuvir-velpatasvir or placebo.[24] The study included 116 participants with HCV genotype 4. Among the treatment-experienced participants who received sofosbuvir-velpatasvir, 100% (52 of 52) achieved an SVR 12.[24]

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.[37] 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.[37]
- **POLARIS-4**: In this phase 3, active-comparator, open-labeled 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.[37] 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.[37]
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 infection without cirrhosis, four regimens are recommended in the AASLD-IDSA HCV Guidance: (a) glecaprevir-pibrentasvir for 8 weeks, (b) sofosbuvir-velpatasvir for 12 weeks, (c) elbasvir-grazoprevir for 12 weeks, or (d) ledipasvir-sofosbuvir for 12 weeks.
- For initial therapy of adults with HCV genotype 4 and compensated cirrhosis, the recommended regimens and rating of evidence are the same as for persons without cirrhosis, with the exception of glecaprevir-pibrentasvir should be given for 12 weeks in individuals with compensated cirrhosis (versus 8 weeks in persons without cirrhosis).
- For retreatment of adults with HCV genotype 4 without cirrhosis who previously failed therapy with peginterferon and ribavirin, the recommended regimens are similar to those noted above for treatment-naïve individuals: (a) glecaprevir-pibrentasvir for 8 weeks, (b) sofosbuvir-velpatasvir for 12 weeks, (c) elbasvir-grazoprevir for 12 weeks (in those patients who had a viral relapse with peginterferon plus ribavirin), or (d) ledipasvir-sofosbuvir for 12 weeks.
- For the retreatment of adults with HCV genotype 4 and compensated cirrhosis (with prior peginterferon/ribavirin experience), three 12-week regimens are recommended: (a) sofosbuvir-velpatasvir, (b) elbasvir-grazoprevir (same conditions as noted above), or (c) glecaprevir-pibrentasvir.
- For the retreatment of adults with HCV genotype 4 (with or without cirrhosis) who are DAA-experienced (with or without prior NS5A inhibitor treatment), the only recommended regimen is sofosbuvir-velpatasvir-voxilaprevir.
Citations


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

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


31. 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]

32. 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]


36. AASLD-IDSA. Recommendations for testing, management, and treating hepatitis C. Retreatment of persons in whom prior therapy has failed: peginterferon plus ribavirin-experienced, genotype 4 patients without cirrhosis. [AASLD-IDSA Hepatitis C Guidance]

References

- AASLD-IDSA. Recommendations for testing, management, and treating hepatitis C. Retreatment of persons in whom prior therapy has failed: peginterferon/ribavirin-experienced, genotype 4 patients with compensated cirrhosis. [AASLD-IDSA Hepatitis C Guidance] -


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**Figures**

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

<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>Regimen</th>
<th>Dose Details</th>
<th>Rating</th>
<th>Note</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Recommended for Treatment-Naïve Genotype 4 Patients Without Cirrhosis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glecaprevir-Pibrentasvir</td>
<td>*Fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) once daily for 8 weeks</td>
<td>Class I, Level A</td>
<td>*This is taken as 3 tablets once daily with each fixed-dose tablet containing glecaprevir (100 mg)/pibrentasvir (40 mg).</td>
</tr>
<tr>
<td>Sofosbuvir-Velpatasvir</td>
<td>Fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) one tablet once daily for 12 weeks</td>
<td>Class I, Level A</td>
<td></td>
</tr>
<tr>
<td>Elbasvir-Grazoprevir</td>
<td>Fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) one tablet once daily for 12 weeks</td>
<td>Class IIa, Level B</td>
<td></td>
</tr>
<tr>
<td>Ledipasvir-Sofosbuvir</td>
<td>Fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) one tablet once daily for 12 weeks</td>
<td>Class IIa, Level B</td>
<td></td>
</tr>
<tr>
<td><strong>Alternative for Treatment-Naïve Genotype 4 Patients Without Cirrhosis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ombitasvir-Paritaprevir-Ritonavir</td>
<td>*Fixed-dose combination of ombitasvir (25 mg)/paritaprevir (150 mg)/ritonavir (100 mg) once daily for 12 weeks</td>
<td>Class I, Level A</td>
<td>*This is taken as 2 tablets once daily with each fixed-dose tablet containing ombitasvir (12.5 mg)/paritaprevir (75 mg)/ritonavir (50 mg)</td>
</tr>
<tr>
<td>Ribavirin</td>
<td>1000 mg if &lt;75 kg or 1200 mg if ≥75 kg for 12 weeks (the daily dose is given in two divided doses)</td>
<td></td>
<td></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>Regimen</th>
<th>Description</th>
<th>Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sofosbuvir-Velpatasvir</td>
<td>Fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) one tablet once daily for 12 weeks</td>
<td>Class I, Level A</td>
</tr>
<tr>
<td>Glecaprevir-Pibrentasvir</td>
<td>*Fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) once daily for 12 weeks</td>
<td>Class I, Level B</td>
</tr>
<tr>
<td></td>
<td>Note: *This is taken as 3 tablets once daily with each fixed-dose tablet containing glecaprevir (100 mg)/pibrentasvir (40 mg).</td>
<td></td>
</tr>
<tr>
<td>Elbasvir-Grazoprevir</td>
<td>Fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) one tablet once daily for 12 weeks</td>
<td>Class Ia, Level B</td>
</tr>
<tr>
<td>Ledipasvir-Sofosbuvir</td>
<td>Fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) one tablet once daily for 12 weeks</td>
<td>Class Ia, Level B</td>
</tr>
</tbody>
</table>

*Alternative for Treatment-Naïve Genotype 4 Patients With Compensated Cirrhosis^*

| Ombitasvir-Paritaprevir-Ritonavir    | + Ribavir 1000 mg if <75 kg or 1200 mg if ≥75 kg for 12 weeks (the daily dose is given in two divided doses) | Class I, Level A |
|                                      | See statement on FDA warning regarding the use of paritaprevir/ritonavir/ombitasvir ± dasabuvir in patients with cirrhosis. |
| Note:                               | *This is taken as 2 tablets once daily with each fixed-dose tablet containing ombitasvir (12.5 mg)/paritaprevir (75 mg)/ritonavir (50 mg) |                |
For treatment of patients with decompensated cirrhosis, see the AASLD-IDSA Guidance: Unique Populations—Patients with Decompensated Cirrhosis.

### Table 3. AASLD-IDSA HCV Guidance for Genotype 4: Retreatment Peginterferon plus Ribavirin-Experienced, Genotype 4 Patients Without Cirrhosis

Recommended and alternative regimens listed by evidence level and alphabetically

<table>
<thead>
<tr>
<th>Recommended for Peginterferon plus Ribavirin-Experienced, Genotype 4 Patients Without Cirrhosis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sofosbuvir-Velpatasvir</strong>&lt;br&gt;Fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) one tablet once daily for 12 weeks&lt;br&gt;Rating: <strong>Class I, Level A</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Recommended for Peginterferon plus Ribavirin-Experienced, Genotype 4 Patients Without Cirrhosis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Glecaprevir-Pibrentasvir</strong>&lt;br&gt;*Fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) once daily for 8 weeks&lt;br&gt;Note: *This is taken as 3 tablets once daily with each fixed-dose tablet containing glecaprevir (100 mg)/pibrentasvir (40 mg).&lt;br&gt;Rating: <strong>Class I, Level B</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Recommended for Peginterferon plus Ribavirin-Experienced, Genotype 4 Patients Without Cirrhosis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Elbasvir-Grazoprevir</strong>&lt;br&gt;*Fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) one tablet once daily for 12 weeks&lt;br&gt;For patients who experienced virologic relapse after prior peginterferon plus ribavirin therapy.&lt;br&gt;Rating: <strong>Class IIa, Level B</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Recommended for Peginterferon plus Ribavirin-Experienced, Genotype 4 Patients Without Cirrhosis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ledipasvir-Sofosbuvir</strong>&lt;br&gt;Fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) one tablet once daily for 12 weeks&lt;br&gt;Rating: <strong>Class IIa, Level B</strong></td>
</tr>
</tbody>
</table>

### Alternative for Peginterferon plus Ribavirin-Experienced, Genotype 4 Patients Without Cirrhosis

<table>
<thead>
<tr>
<th>Ombitasvir-Paritaprevir-Ritonavir</th>
<th>Ribavirin</th>
</tr>
</thead>
<tbody>
<tr>
<td>*Fixed-dose combination of ombitasvir (25 mg)/paritaprevir (150 mg)/ritonavir (100 mg) once daily for 12 weeks&lt;br&gt;<strong>Ombitasvir-Paritaprevir-Ritonavir</strong></td>
<td>1000 mg/day if &lt;75 kg or 1200 mg/day if ≥75 kg for 12 weeks (the daily dose is given in two divided doses)&lt;br&gt;Ribavirin</td>
</tr>
</tbody>
</table>

**Page 26/31**
Rating: Class I, Level A
Note: *This is taken as 2 tablets once daily with each fixed-dose tablet containing ombitasvir (12.5 mg)/paritaprevir (75 mg)/ritonavir (50 mg)

**Alternative for Peginterferon plus Ribavirin-Experienced, Genotype 4 Patients Without Cirrhosis**

Elbasvir-Grazoprevir + Ribavirin

*Fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) one tablet once daily for 16 weeks

**For patients with prior on-treatment virologic failure (failure to suppress or breakthrough) while on peginterferon plus ribavirin.**

Rating: Class Ila, Level B

## Table 4. AASLD-IDSA HCV Guidance for Genotype 4: Retreatment

AASLD-IDSA HCV Guidance for Peginterferon plus Ribavirin-Experienced, Genotype 4 Patients With Compensated Cirrhosis

Recommended and alternative regimens listed by evidence level and alphabetically

### Recommended for AASLD-IDSA HCV Guidance for Peginterferon plus Ribavirin-Experienced, Genotype 4 Patients With Compensated Cirrhosis

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Description</th>
<th>Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sofosbuvir-Velpatasvir</strong></td>
<td>Fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) one tablet once daily for 12 weeks</td>
<td>Class I, Level A</td>
</tr>
<tr>
<td><strong>Elbasvir-Grazoprevir</strong></td>
<td>Fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) one tablet once daily for 12 weeks</td>
<td>Class IIa, Level B</td>
</tr>
<tr>
<td><strong>Glecaprevir-Pibrentasvir</strong></td>
<td>*Fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) once daily for 12 weeks</td>
<td>Class IIa, Level B</td>
</tr>
</tbody>
</table>

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

### Alternative for AASLD-IDSA HCV Guidance for Peginterferon plus Ribavirin-Experienced, Genotype 4 Patients With Compensated Cirrhosis

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Description</th>
<th>Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ombitasvir-Paritaprevir-Ritonavir</strong></td>
<td>*Fixed-dose combination of ombitasvir (25 mg)/paritaprevir (150 mg)/ritonavir (100 mg) once daily for 12 weeks</td>
<td>Class I, Level A</td>
</tr>
</tbody>
</table>

Note: #*This is taken as 2 tablets once daily with each fixed-dose tablet containing ombitasvir (12.5 mg). Please see statement on FDA warning regarding the use of ombitasvir-paritaprevir-ritonavir ± dasabuvir in patients with cirrhosis.
mg)/paritaprevir (75 mg)/ritonavir (50 mg)

Alternative for AASLD-IDSA HCV Guidance for Peginterferon plus Ribavirin-Experienced, Genotype 4 Patients With Compensated Cirrhosis

Elbasvir-Grazoprevir

Fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) one tablet once daily for 16 weeks

+ Ribavirin

1000 mg/day if <75 kg or 1200 mg/day if ≥75 kg for 16 weeks (the daily dose is given in two divided doses)

For patients with prior on-treatment virologic failure (failure to suppress or breakthrough) while on peginterferon plus ribavirin

Rating: Class Ila, Level B

Ledipasvir-Sofosbuvir

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

+ Ribavirin

1000 mg/day if <75 kg or 1200 mg/day if ≥75 kg for 12 weeks (the daily dose is given in two divided doses)

Rating: Class Ila, Level B

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

Table 5. AASLD-IDSA HCV Guidance for Genotype 4: Retreatment DAA-Experienced (Including NS5A Inhibitors), Genotype 4 Patients With or Without Compensated Cirrhosis

Recommended and alternative regimens listed by evidence level and alphabetically

<table>
<thead>
<tr>
<th>Recommended for DAA-Experienced (Including NS5A Inhibitors), Genotype 4 Patients With or Without Compensated Cirrhosis^</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sofosbuvir-Velpatasvir-Voxilaprevir</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>
<tr>
<td>Rating: <strong>Class I, Level A</strong></td>
</tr>
</tbody>
</table>

^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 4 patients with or without compensated cirrhosis. [AASLD-IDSA Hepatitis C Guidance] - Accessed April 28, 2019.