

# Treatment of HCV Genotype 4

This is a PDF version of the following document:

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

Lesson 4: [Treatment of HCV Genotype 4](#)

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<http://www.hepatitisc.uw.edu/go/treatment-infection/treatment-genotype-4/core-concept/all>.

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## Introduction

**Background:** In the United States, genotype 4 infection accounts for only 1 to 2% of all hepatitis C infections. Globally, approximately 20% of all hepatitis C infections are caused by genotype 4. In addition, genotype 4 is the dominant HCV genotype in Egypt, North Africa, and sub-Saharan Africa. In Egypt, approximately 15% of the population has hepatitis C infection and genotype 4 infection accounts for more than 90% of the HCV infections in Egypt; most of these cases of hepatitis C were acquired via contaminated needles in the anti-schistosomiasis program or with contaminated blood transfusion. More recently, the prevalence of hepatitis C genotype 4 infection has increased significantly in Southern Europe, particularly in France, Italy, Greece, and Spain. Approximately 70% of patients with genotype 4 HCV have moderate to severe steatosis with or without sinusoidal fibrosis. For treatment-naïve and treatment-experienced patients with genotype 4 infection, the cost of therapy for recommended and alternative regimens in the 2016 American Association for the Study of Liver Diseases (AASLD) and Infectious Diseases Society of America (IDSA) guidance ranges from approximately \$55,000 to \$189,000 ([Figure 1](#)). The following discussion regarding initial treatment and retreatment of patients with genotype 4 chronic hepatitis C assumes patients and their clinicians 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. 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.

## Genotype 4: Initial Treatment

**Background:** Given the low prevalence of genotype 4 infection in the United States, relatively few patients with genotype 4 have been enrolled in clinical trials conducted in the United States. In the era prior to availability of direct-acting antivirals, available data suggest that treatment-naive genotype 4 patients who were treated with a 48-week course of peginterferon plus ribavirin had SVR rates that ranged from 43 to 70%, with even lower SVR rates in genotype 4 patients with cirrhosis (25 to 30%). Available data with newer all-oral regimens in the treatment of genotype 4 infection suggest SVR12 rates in treatment-naive patients are greater than 95%, similar to the excellent SVR rates seen with genotype 1 infection.

**Factors to Consider Prior to Choosing Initial Treatment Regimen:** For patients chronically infected with genotype 4 hepatitis C, the recommended regimens for a treatment-naive patient are the same for patients without cirrhosis or those with compensated cirrhosis. The management of genotype 4 patients with decompensated cirrhosis, renal impairment, HIV coinfection, acute hepatitis C infection, or post-liver transplantation is not addressed in this lesson.

**AASLD/IDSA Guidance (see [Initial Treatment of HCV Infection](#)):** The following is a summary of joint recommendations issued by the American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America (IDSA). The recommendations listed below are for patients with hepatitis C genotype 4 infection who will receive initial treatment, or who are undergoing retreatment and had previously failed a regimen that included peginterferon plus ribavirin. The recommended regimens are listed in alphabetical order and are considered to have similar efficacy. How a provider decides between these recommended regimens depends on assessment of potential drug-drug interactions, cost, and insurance coverage.

## Genotype 4: Initial Treatment

### Table 1. Treatment-Naive Patients

Recommended regimens are listed in groups by level of evidence, then alphabetically.

#### Recommended for Genotype 4 patients without Cirrhosis

**Ombitasvir-Pa +  
ritaprevir-  
Ritonavir**

*Fixed-dose  
combination of  
ombitasvir (12.5  
mg)/paritaprevir (75  
mg)/ritonavir (50  
mg) two tablets  
once daily for 12  
weeks*

## Genotype 4: Retreating Persons who Failed Prior Therapy

**Background:** Given the low prevalence of genotype 4 infection in the United States, relatively few patients with genotype 4 and prior nonresponse to peginterferon and ribavirin have been enrolled in clinical trials conducted in the United States. Limited data using new direct-acting antiviral therapy suggest that genotype 4 patients who failed prior therapy with peginterferon and ribavirin should be able to achieve SVR rates greater than 90% with one of the recommended regimens.

**Factors to Consider Prior to Choosing Retreatment Regimen:** For retreatment of patients with genotype 4 hepatitis C in whom prior therapy with peginterferon and ribavirin failed, the recommended treatment regimen are very similar for patients without cirrhosis or those with compensated cirrhosis; the only difference is that ribavirin is added to the ledipasvir-sofosbuvir regimen in patients with compensated cirrhosis. The management of genotype 4 patients with decompensated cirrhosis, renal impairment, HIV coinfection, acute hepatitis C infection, or post-liver transplantation is not addressed in this lesson.

**AASLD/IDSA Guidance (see [Retreatment of Persons in Whom Prior Therapy has Failed](#)):** The following is a summary of joint recommendations issued by the American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America (IDSA). The recommendations listed below are for retreatment of patients with hepatitis C genotype 4 in whom prior therapy with peginterferon and ribavirin failed. The four recommended regimens are listed in alphabetical order and are considered to have similar efficacy. The data to support the regimen of sofosbuvir plus ribavirin plus peginterferon are from the NEUTRINO trial, which enrolled only treatment-naive patients. How a provider decides between these three regimens depends on assessment of potential drug-drug interactions, cost, and insurance coverage. Note that acid suppressing medications may significantly decrease the absorption of ledipasvir-sofosbuvir, thereby potentially causing lower drug levels.

### Genotype 4: Retreatment

#### Table 2. Peginterferon plus Ribavirin Treatment-Experienced Patients

Recommended regimens are listed in groups by level of evidence, then alphabetically.

#### Recommended for Retreatment of Genotype 4 patients without Cirrhosis

**Ombitasvir-Pa +  
ritaprevir-  
Ritonavir**

*Fixed-dose  
combination of  
ombitasvir (12.5  
mg)/paritaprevir (75  
mg)/ritonavir (50  
mg) two tablets  
once daily for 12  
weeks*

## Genotype 4: Future Treatment Options

**Future Direct-Acting Antiviral Agents:** In vitro data have shown that a number of investigational direct-acting antiviral agents have activity against genotype 4 HCV. Since most phase 2 and 3 clinical trials for investigational direct-acting antiviral agents are performed in the United States, which has a low HCV genotype 4 prevalence, relatively limited data exist regarding future treatment options for patients with genotype 4 infection. The following list below summarizes ongoing or planned phase 2 and 3 trials for patients with genotype 4 infection. Phase 3 clinical trials will need to be completed to establish the efficacy and safety of new direct-acting antiviral agents for the treatment of patients with genotype 4 infection.

- **Ravidasvir:** The investigational NS5a inhibitor ravidasvir has been used in combination with sofosbuvir, with or without ribavirin in Egyptian patients with HCV genotype 4 infection, with excellent SVR rates.
- **Mericitabine:** In the PROPEL and JUMP studies, patients with HCV genotypes 1 and 4 infection were treated with the nonnucleoside polymerase inhibitor mericitabine combined with peginterferon and ribavirin. The SVR12 rates were markedly lower than SVR12 rates observed with other new and future therapies. In addition, these regimens required 24 to 48 weeks of peginterferon and ribavirin. Thus, it is unlikely this combination will have any impact on the future treatment of genotype 4 infection.
- **Nitazoxanide:** Preliminary data suggest that nitazoxanide may have activity against hepatitis C virus or augment treatment responses. A phase 2, randomized, placebo-controlled trial examined the impact of nitazoxanide 500 mg twice daily in the treatment of 50 patients with chronic hepatitis C genotype 4. The investigators compared three arms: (a) peginterferon alfa-2a plus ribavirin for 48 weeks, (b) nitazoxanide monotherapy for 12 weeks, followed by peginterferon alfa-2a for 36 weeks, or (c) nitazoxanide monotherapy for 12 weeks, followed by peginterferon alfa-2a plus ribavirin for 36 weeks. Patients that had nitazoxanide added to the regimen had better SVR rates than patients who received peginterferon alfa-2a plus ribavirin alone. A follow-up, open-label study that used a 4-week lead-in with nitazoxanide also suggested a benefit when added to peginterferon and ribavirin, but results were compared with historical controls. In a more recent study, a larger and randomized trial found no benefit using a 4-week lead-in with nitazoxanide. There are no published data that support a role of nitazoxanide as an adjunct to interferon-free direct-acting antiviral therapy.

## Summary Points

- Genotype 4 hepatitis C virus infection is not common in the United States, but it is highly prevalent in the Middle East, Africa, and Southern Europe.
- For initial therapy of genotype 4 patients without cirrhosis, four 12-week regimens are recommended regimens in the AASLD/IDSA guidance: (a) ombitasvir-paritaprevir-ritonavir plus ribavirin, (b) sofosbuvir-velpatasvir, (c) elbasvir-grazoprevir, or (d) ledipasvir-sofosbuvir. Among these four regimens, the ombitasvir-paritaprevir-ritonavir plus ribavirin and the sofosbuvir-velpatasvir have the highest rating.
- For initial therapy of genotype 4 patients with compensated cirrhosis, the recommended regimens and rating of evidence are the same as those patients without cirrhosis.
- For retreatment of genotype 4 patients without cirrhosis who previously failed therapy with peginterferon and ribavirin, the AASLD/IDSA recommends three regimens: (a) ombitasvir-paritaprevir-ritonavir plus ribavirin for 12 weeks, (b) sofosbuvir-velpatasvir for 12 weeks, (c) elbasvir-grazoprevir for 12 weeks (with addition of ribavirin and extension to 16 weeks if the patient had prior on-treatment virologic failure), or (d) ledipasvir-sofosbuvir for 12 weeks. Among these four regimens, the ombitasvir-paritaprevir-ritonavir plus ribavirin and the sofosbuvir-velpatasvir have the highest rating.
- The recommended regimens and ratings for the retreatment of genotype 4 patients with compensated cirrhosis are the same as for those for retreatment of genotype 4 patients without cirrhosis, except that ribavirin should be added to the ledipasvir-sofosbuvir regimen.
- The major barrier to treatment of patients with genotype 4 infection is the high cost of a treatment course.

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## Figures

**Figure 1 Cost of Medication Regimens Used to Treat Genotype 4 Chronic HCV**

This figure shows the approximate cost of regimens used for either initial treatment or retreatment of patients with genotype 4 chronic HCV, including recommended and alternative regimens. The cost estimates are based on available wholesale acquisition price data.

Estimated Medication Cost* for Treatment of Genotype 4 Chronic HCV	
Regimen and Duration	Cost of Regimen*
Ombitasvir-Paritaprevir-Ritonavir + Ribavirin x 12 weeks	\$77,000
Sofosbuvir-Velpatasvir x 12 weeks	\$74,760
Elbasvir-Grazoprevir x 12 weeks	\$54,600
Ledipasvir-Sofosbuvir x 12 weeks	\$94,500

^Regimen and Duration of therapy for Initial treatment of patients with Genotype 4 without cirrhosis and with compensated cirrhosis  
 \*Cost of regimen estimated based on Wholesale Acquisition Cost (WAC)

## Genotype 4: Initial Treatment

### Table 1. Treatment-Naive Patients

Recommended regimens are listed in groups by level of evidence, then alphabetically.

#### Recommended for Genotype 4 patients without Cirrhosis

**Ombitasvir-Pa  
ritaprevir-  
Ritonavir** + **Ribavirin**  
*Fixed-dose  
combination of  
ombitasvir (12.5  
mg)/paritaprevir (75  
mg)/ritonavir (50  
mg) two tablets  
once daily for 12  
weeks*  
*1000 mg if <75 kg  
or 1200 mg if ≥75  
kg for 12 weeks*

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

Note: The ribavirin daily dose is given in two divided doses.

#### Recommended for Genotype 4 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](#)

#### Recommended for 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 IIa](#), [Level B](#)

#### Recommended for 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](#)

## Recommended

### Recommended for Genotype 4 patients with Compensated Cirrhosis

**Ombitasvir-Pa  
ritaprevir-  
Ritonavir** + **Ribavirin**  
*1000 mg if <75 kg  
or 1200 mg if ≥75  
kg for 12 weeks*

*\*Fixed-dose  
combination of  
ombitasvir (12.5  
mg)/paritaprevir (75  
mg)/ritonavir (50  
mg) two tablets  
once daily for 12  
weeks*

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

Note: \*(i) See the warning in the product information regarding risk of serious liver injury when using ombitasvir-paritaprevir-ritonavir in patients with cirrhosis; (ii) the ribavirin daily dose is given in two divided doses.

### Recommended for 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 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 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](#)

Source: AASLD/IDSA. Recommendations for testing, management, and treating hepatitis C. Initial treatment of HCV infection. [[AASLD/IDSA Hepatitis C Guidance](#)] - Accessed March 10, 2017.

## Genotype 4: Retreatment

### Table 2. Peginterferon plus Ribavirin Treatment-Experienced Patients

Recommended regimens are listed in groups by level of evidence, then alphabetically.

#### Recommended for Retreatment of Genotype 4 patients without Cirrhosis

**Ombitasvir-Pa  
ritaprevir-  
Ritonavir** + **Ribavirin**  
*1000 mg/day if <75  
kg or 1200 mg/day if  
≥75 kg for 12 weeks*  
*Fixed-dose  
combination of  
ombitasvir (12.5  
mg)/paritaprevir (75  
mg)/ritonavir (50  
mg) two tablets  
once daily for 12  
weeks*

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

Note: The ribavirin daily dose is given in two divided doses.

#### Recommended for Retreatment of Genotype 4 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](#)

#### Recommended for Retreatment of Genotype 4 patients without Cirrhosis

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

**\*Genotype 4 patients with prior on-treatment virologic failure (failure to suppress or breakthrough) while on peginterferon plus ribavirin should be treated with 16 weeks of elbasvir-grazoprevir and have weight-based ribavirin (1000 mg if <75 kg or 1200 mg if ≥75 kg for 12 weeks) added to the treatment regimen.**

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

Note: If ribavirin is used, the daily dose is given in two divided doses.

#### Recommended for Retreatment of 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](#)

Note: The ribavirin daily dose is given in two divided doses.

## Recommended

### Recommended for Retreatment of Genotype 4 patients with Compensated Cirrhosis

**Ombitasvir-Pa  
ritaprevir-  
Ritonavir** + **Ribavirin**  
1000 mg if <75 kg  
or 1200 mg if ≥75  
kg for 12 weeks

\*Fixed-dose  
combination of  
ombitasvir (12.5  
mg)/paritaprevir (75  
mg)/ritonavir (50  
mg) two tablets  
once daily for 12  
weeks

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

Note: (i) \*See the warning in the product information regarding risk of serious liver injury when using ombitasvir-paritaprevir-ritonavir in patients with cirrhosis; (ii) the ribavirin daily dose is given in two divided doses.

### Recommended for Retreatment of 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 Retreatment of 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

**\*Genotype 4 patients with prior on-treatment virologic failure (failure to suppress or breakthrough) while on peginterferon plus ribavirin should be treated with 16 weeks of elbasvir-grazoprevir and have weight-based ribavirin (1000 mg if <75 kg or 1200 mg if ≥75 kg for 12 weeks) added to the treatment regimen.**

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

### Recommended for Retreatment of Genotype 4 patients with Compensated Cirrhosis

**Ledipasvir-  
Ribavirin**  
+  
1000 mg if <75 kg

**Sofosbuvir**

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

*or 1200 mg if  $\geq 75$   
kg for 12 weeks*

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

**Alternative for Retreatment of Genotype 4 patients with Compensated Cirrhosis**

**Ledipasvir-  
Sofosbuvir**

*Fixed-dose  
combination of  
ledipasvir (90  
mg)/sofosbuvir (400  
mg) one tablet once  
daily for 24 weeks*

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

Source: AASLD/IDSA. Recommendations for testing, management, and treating hepatitis C. Retreatment of persons in whom prior therapy has failed. [[AASLD/IDSA Hepatitis C Guidance](#)] - Accessed March 10, 2017.



