

## Treatment of Hepatitis C, According to Regional Treatment Guidelines

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### ABSTRACT

**Objective:** Was present a general overview of the current treatments for HCV infection in adults.

**Methods:** A review study was conducted, Databases such as PubMed, MEDLINE and Scopus were used as information sources to identify and analyze the current information about the treatment for HCV infection in adults

**Results:** To define a treatment with the best likelihood of success, it is important to identify in each patient, their response predictors such as genotype and viral load as vital determinants. In addition, to age, male gender, prolonged infection, cirrhosis, hepatic fibrosis, elevated plasma ferritin, obesity, insulin resistance, African American and Hispanic ancestry and co-infection with HIV). Recently, it has been approved that the other drugs with direct antiviral activity (DAAs), like the protease inhibitors (Boceprevir and Telaprevir), inhibitors of the polymerase NS5B (deleobuvir and setrobuvir), inhibitors of replication complex NS5A, include daclatasvir, ledipasvir and cyclophilin inhibitors were introduced into clinical practice but this use is subject to the purchasing power of health institutions

**Conclusion:** To define a treatment with the best likelihood of success, it is important to identify in each patient, their response predictors such as genotype and viral load as vital determinants.

**Keywords:** Chronic, hepatitis C, viral transmission

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## **INTRODUCTION**

Hepatitis C Virus (HCV) infection ranks as the leading cause of chronic liver disease worldwide. Approximately 130 to 170 million people are infected chronically with HCV of whom 350,000 die due to complications (1).

The most common forms of viral transmission are related to the use of intravenous drugs, blood transfusion, multiple sexual partners, tattooing, piercings and perinatal origin (2). On the other hand in developing countries such as Mexico the most common cause of HCV transmission are blood transfusion and products (3).

### **Diagnosis**

The first step for HCV infection diagnosis is immunological screening, which is based in the detection of antibodies versus the hepatitis C virus (anti-HCV). The most common test used all over the world is a third-generation anti-HCV ELISA, with sensitivity larger than 99% in immunosuppressed patients. Qualitative tests for the detection of viral RNA are used to confirm active infection with the virus in seropositive patients. It is also useful for diagnosing infection in seronegative cases when infection is clinically suggested (very early infection), in children less than 18 months of age, as well as in immunosuppressed patients (4). Quantitative testing of viral load measurement and detection of genotypes are used to evaluate HCV infection and to establish a prognosis for treatment effectiveness and length (5).

### **Genotype and geographical distribution**

The HCV is an enveloped RNA virus of 30-80 nm in size, from the genus *Hepacivirus* that belongs to the family *Flaviviridae*, which has six genotypes and more than hundred serotypes. Their RNA genome has approximately 9,400 nucleotides, with a long reading frame encoding a polypeptide of 3010-3033 amino acids, which is cleaved by cellular and viral proteases into

structural and nonstructural proteins (6). This broad heterogeneity has important diagnosis and clinical implications, and is associated to the type of response to treatment. Worldwide genotype distribution is different; genotypes 1, 2 and 3 are cosmopolitan, even though genotype 1 is the responsible for 70-75% of all the VHC infections all over Mexico and USA.(figure 1) (7)

It is necessary to determine the viral genotype, before starting any treatment, since it's the most important prognosis factor for antiviral treatment because sustained virological response (SVR) is different among them (8). Furthermore, recent studies have observed different response rates between genetic subtypes also, as in the case of genotypes 1a with poorer response rates genotypes 1b.

Genotype is not used as a prognostic marker of disease progression HCV, since no influence on the risk of chronicity, severity of liver injury or development of extrahepatic disorder. However, it is a strong independent predictor of response to treatment of HCV infection (9).

### **Clinical development**

The clinical consequence of HCV infection is variable, and we have that approximately 55 to 85% of the patients have a chronic progression, while 5 to 25% develop liver cirrhosis within a period of 20-25 years, with an approximate risk of onset of hepatocellular carcinoma of 1 to 4 % per year (10). Some recognized factors influencing the main progression of the disease to cirrhosis are alcohol consumption > 50gr/d, to have African-American ancestry, obesity, insulin resistance, >50 years of age, male gender, elevated levels of Alanine Aminotransferase and Aspartate Aminotransferase values in serum, coinfection with human immune deficiency virus (HIV), hepatitis B virus (HBV), degree of inflammatory activity and general histological state (11).

Throughout its prolonged evolution to chronic hepatitis, the HCV infection presents with few clinical manifestations, although transaminases remain elevated for long time, and some patients have fluctuating values and even show periods of normality, it is possible to detect the presence of specific serum HCV-RNA as an expression of continuous replication in the liver, although neither genotype nor the concentration of serum HCV-RNA is related to the severity of liver disease (10).

### **Treatment**

The SVR is the end point for treatment, defined by undetectable HCV-RNA in the serum at week 24 after completion of treatment, and is considered the cure of the infection. The rate of response to treatment is the likelihood of achieving an SVR at week 12 of treatment, if the concentration of HCV RNA has not dropped at least 2 log<sup>10</sup> values compared to the baseline, the possibility of achieving SVR after prolonged treatment is virtually null. In contrast, early negative of the viremia at week 4 (rapid virological response) is associated with highly curable scenario (12).

Due to newly developed drugs, the treatment for chronic hepatitis C has seen numerous improvements, mostly by the development of guidelines by various medical societies in different countries, whose aim is to provide to health professionals the best information to take critical decisions for the patient. As part of this aim, international guidelines have been prepared by the European Association for the Study of the Liver (EASL); the American Association for the Study of Liver Diseases (AASLD); the Asia Pacific Association for the Study of the Liver (APASL); the American Association for the Study of the Liver (ALEH); the World Gastroenterology Organization (WGO), and the Clinical Practice Guide of Mexico and the Canadian association for the study of the liver (table 1)(13,14,15).

However, even though these recommendations are based in the best clinical evidence for its use; the high costs for implementation make them inaccessible in developing countries. The concept of "cascades" to make the guidelines applicable to different environments that have very different resources, offering a series of options for diagnosis and treatment, arranged hierarchically in terms of conditions and available resources (16).

### **Initial patient evaluation: the importance of response predictors**

To define a treatment with the best likelihood of success, it is important to identify in each patient, their response predictors, such as genotype and viral load as vital determinants. In addition, to age, male gender, prolonged infection, cirrhosis, hepatic fibrosis, elevated plasma ferritin, obesity, insulin resistance, African American and Hispanic ancestry and co-infection with HIV) (17).

### **Evaluation of liver damage**

The stage of liver fibrosis influences in SVR rate, which determines the likelihood of treatment response, duration and prognosis. Liver biopsy remains the Gold Standard to assess the degree of inflammation and fibrosis stage. However, it is an invasive test not without risks (18).

It's low patient acceptability involves us in a significant number of cases at therapeutic while repetition is difficult to justify when necessary delays. Moreover, several studies have shown its diagnostic variability to achieve the identification of the real stage of fibrosis in a patient. These limitations and the need for periodic evaluations of patients with chronic liver disease have led to the search for non-invasive alternatives to assess the degree of liver fibrosis, such as elastography, based on measuring the stiffness or elasticity tissue and uses a mechanical vibration pulse and an ultrasonic wave. The propagation velocity of the elastic wave is proportional to the stiffness of tissue 5-8 (the harder the faster the wave propagated tissue) (19).

Extrapolating their results to the classification of METAVIR (scale for determining the degree of fibrosis according to biopsy), which considers the F0 stadium for normal liver; F1 when localized fibrosis in portal tracts; F2 when it exceeds these; F3 when bridging fibrosis passing a liver lobule another are formed, and F4 when the above is added the loss of hepatic architecture and is equivalent to cirrhosis assumes values  $\geq 9$  kPa (kilopascals) correspond F2-F3 a stadium with a negative positive predictive value (PPV) of 87% and predictive value (NPV) of 74%; for F4, values  $\geq 14.6$  kPa have a PPV of 86% and NPV of 94%, its limitations are not accurately discriminate between intermediate stages, not provide information on the degree of inflammatory activity and cannot rule out eliminate other injuries (20)

### **Viral load**

SVR rate is inversely related to viral load, measured by quantifying HCV-RNA on serum, which determines the treatment duration according to the schemes guided by virological response. Viral kinetics in week 4 allows identify subjects with low sensitivity to INF, which are those that reduce the CV less than  $2\log^{10}$  and quickly develop resistance to protease inhibitors (21).

### **Polymorphisms**

Determining polymorphisms IL28B is a useful tool to identify the likelihood of response to therapy and clinical decision making for patients with genotypes 1 or 4.

The probability of obtaining an SVR with PEG-IFN / RBN differs depending on the nucleotide sequence near the IL28B gene on chromosome 19, there have been identified three polymorphisms are CC, CT and TT. CC genotype carriers in genotype 1 patients treated with PEG-INF / RBV have more than 80% SVR and to a lesser extent in genotypes 2 and 3. In Caucasian patients treated with protease inhibitors SVR is 80-90%, 71% and 59-73%, in patients with CC, CT and TT, respectively genotypes.

However, its low negative predictive value should not be used to defer the treatment of unfavorable genotype carriers, as more than half of Caucasians with genotype TT could get SVR (22, 23).

Another polymorphism influences the choice of drug is Q80K polymorphism. The Simeprevir was approved by the FDA with the mandatory condition that patients carrying a polymorphic variant of genotype 1a Q80K should be excluded from treatment (24).

### **Dual therapy with PEG-IFN and ribavirin:**

All patients with chronic hepatitis C are potential candidates for treatment with PR in the absence of contraindications. The combination of PR was considered standard treatment regimens between 24 and 48 weeks, resulted in a SVR of 39 to 85% of infected patients; 65 to 90% of infected patients with genotypes 2 and 3, and 40 to 52% in genotype 1-infected patients.

It was considered that the use of IFN- $\alpha$ 2a were or IFN- $\alpha$ 2b getting similar results, However, current evidence Suggests That PEG-IFN- $\alpha$  and ribavirin is the 2nd with a higher SVR Associated than PEG-IFN- $\alpha$  2b and ribavirin in patients with mono-infected hepatitis C genotypes 1 and particularly for genotypes 4 (25).

### **Adverse effects of dual therapy**

The PR treatment causes many undesirable side effects, so it's not well tolerated in all patients. The most common effects are: flu-like syndrome, neuropsychiatric symptoms, gastrointestinal symptoms and, especially, blood disorders (neutropenia, anemia, thrombocytopenia and lymphopenia) (26).

## **Treatment of genotype 1**

### *a) Infection with HCV without treatment, without cirrhosis*

The naïve patients, non-cirrhotic, with low baseline viral load (<800,000 IU/ml), IL28B CC genotype, low fibrosis index without other risk factors failure to treatment should be treated with dual therapy, because you have mock likely to have very high rates of SVR. In patients with HCV-RNA undetectable after 4 weeks of treatment RVR (rapid viral response) with a baseline viral load <600,000 IU/ml, it has been observed that a shortened treatment was equally effective (12 to 16 weeks for genotype 2 and 3 and 24 weeks for genotype 1 and 4). Treatment should be stopped at week 12 if HCV RNA decrease is less than 2 log<sub>10</sub> IU/ml early virological response (27).

## **Genotypes 2 and 3**

The treatment of choice is the combination of PR. The SVR rate is 74% and 68% for genotypes 2 and 3 respectively, although cases of high viremia, the SVR was achieved in 75 and 58% respectively, and when it is low, the SVR rate ranges from 84-86% (28).

## **Genotypes 4 and 5**

For patients infected with genotypes 4-6, the optimized treatment is the PR for 48 weeks. SVR rates in patients with genotype 4 are ranging from 43% to 70% with the treatment regimen for 48 weeks (29).

In patients with genotype 2 or 3 who presents advance fibrosis, cirrhosis or factors that affect the treatment, I shouldn't be considered a short-cut of 16 weeks, it should be evaluated a longer treatment (48 weeks for genotypes 2 and 3, 72 weeks for genotype 4), even more on patients with a TVRa on the first cycle of treatment (30).



## **New treatment options for Hepatitis C: direct antiviral drugs (DAAs)**

The combination of PEG-IFN/RBV was the approved treatment for chronic HCV infection until in 2011 when it authorized the use of telaprevir (TVR) and boceprevir (BOC), as the first two antiviral drugs of direct action (DAAs) in combination with PEG-IFN/RBV for infection by HCV genotype 1 (31).

These patterns of triple therapy have proved effective in patients who have not received previous treatment (naïve) and in patients who have been treated, including patients without any previous reply to the double therapy of PEG-IFN/RBV (26).

In the life cycle of HCV there are no intermediaries of integration into the genome of the host, which makes it possible, in the presence of effective treatments, its elimination and therefore the healing of the patient. The development of the DAAs has meant a great advance in the treatment of chronic hepatitis, have significantly improved the SVR rate and has allowed shorten the time of treatment in many patients with chronic HCV genotype 1(32). The DAAs drugs that are currently in various stages of clinical development and are classified into four groups according to their site of action:

1. protease inhibitors (IP) NS3/4 of HCV, that end in "-previr". Structurally are classified in linear (telaprevir, boceprevir, BI-201355) and macrocyclics (danoprevir, simeprevir, asunaprevir, ABT-450, GS-9451 and MK-5172, among others) protease inhibitors telaprevir and boceprevir were the first 2 DAAs authorized, block the activity of the serine-protease of virus C, show a great antiviral activity against the genotype 1, but its low genetic barrier to resistance makes these drugs cannot be used in monotherapy. There are authorized for the treatment of genotype1 infection in combination with PEG-IFN/RVN, to lessen the appearance of resistance. Its main

influence has been in the treatment of patients with HCV genotype 1 not dealt with earlier and in the treatment of patients who experience relapse after pre-treatment with PEG-IFN/RBV (33).

2. inhibitors of the polymerase NS5B of HCV, that end in "buvir". The viral polymerase NS5B is a RNA polymerase dependent on RNA that is responsible for the viral replication. Are subdivided in 2 groups: nucleoside analogues, which are drugs with a structure similar to the natural substrates of the enzyme and which act as terminators in the chain of polymerization of RNA, are potentially active against all genotypes of HCV (pangenotípica activity), have a high genetic barrier and low cross-resistance of class after monotherapy during 3-14 days, these drugs get a reduction of between 0.7 to 2.7 log viral load, and include the sofosbuvir, mericitabine and ALS-2200 (VX-135); and non-nucleoside analogues, which are allosteric inhibitors of RNA polymerase, and induce conformational changes in the enzyme inactivating the complex of replication as the deleobuvir, setrobuvir, ABT-072, ABT-333, BMS-791325 and VX-222 (34).

3. Inhibitors of replication complex NS5A, that end in "asvir", its mechanism of action is likely to reside in the inhibition of the interrelationship between the NS5A protein and the places of intracellular replication of HCV21 include daclatasvir, ledipasvir and ABT-267 (35).

4. cyclophilin inhibitors. The cyclophilin are proteins that participate in the replication cycle of HCV as functional regulators of the activity of the RNA polymerase (NS5B). Include the alisporivir and SCY-635. The alispovir has demonstrated antiviral activity against to the genotypes 1-4 of HCV, with a good antiviral activity, achieving decreases up to 4.5 log in the CV after 4 weeks of treatment, in combination with PEG-RBV. Present high genetic barrier to the resistance and cross-resistance of class is low (36).

c) Triple therapy

PEG- IFN + RBV + protease inhibitor

In patients infected with genotype 1, use of triple therapy increases approximately 25- 30% in the rates of SVR with respect to dual therapy, offering opportunity to cure patients with lower rate of SVR with dual therapy; also has an extended RVR, allows shortening of treatment. In the Phase III of BOC and TVR in naïve patients, triple therapy patterns achieved SVR rates superior to dual therapy (63-66% versus 38%). In patients with a response to IFN- $\alpha$ , the advantage of adding a PI is to shorten the overall duration to 24 weeks treatment with the pattern including TVR and 28 weeks treatment with the pattern including BOC (37).

The combination of DAAs with PR partially protects against the onset of mutations associated with resistance and when it is used in mono-therapy cause rapid emergence of resistant variants, which are currently approved for use in combination with PR (38).

A difference between both PI is that while the BOC was administered throughout the time of treatment, in the case of TVR only administered during the first 12 weeks. In phase III studies, the treatment was associated with a TVR along with PEG-IFN- $\alpha$ 2a addition while treatment with BOC was studied with both PEG-IFN. In a randomized study, TVR treatment reached equivalent SVR rates when used in combination with PEG-IFN (39).

### **Adverse effects on triple therapy**

Adding a PI can promote some adverse effects of treatment with PR, especially hematologic and also use of TVR produces pruritus, rash, nausea, diarrhea and anemia, with BOC, most frequent adverse effects include anemia, direct bone marrow toxicity and dysgeusia (40).

The dose of BOC or TVR should not be reduced during treatment, since it favors the appearance of resistance to antiviral medication; with both PI treatment should be discontinued altogether, or continue with the same dose whenever a prescribed adjuvant treatment. After

discontinuing administration of BOC or TVR, these drugs shouldn't reintroduced into the same treatment scheme (41).

**Rule for treatment withdrawal**

In patients with triple therapy with TVR or BOC, HCV-RNA should be determined at week 4, 12, 24, end of treatment and at 12 or 24 weeks after the end of. The SVR rate achievement with continued treatment in these patients is less than 2%. The suspension rules for BOC establishment are at week 12 and 24. All drugs should be discontinued if HCV RNA > 100 IU/ml at week 12 of treatment, if HCV RNA is detectable at week 24 of treatment, and in case of viral relapse (42).

When the HCV-RNA becomes undetectable at 8 and 12 weeks of, treatment should be discontinued at week 24. If at week 8 but is detectable in 12th week, treatment with BOC is maintained up to week 36, treatment with PR prolonged up to 48 week. The same duration is established in patients with relapsed and those with partial response.

The European Medicines Agency recommended that patients with HCV-RNA undetectable at week 8, continued to be undetectable at week 24, can suspend the treatment at week 28; In patients with detectable HCV-RNA in between weeks 8 and 24, should be continued with triple therapy until week 36; In case with BOC should be discontinued; and treatment should be continued with PR until week 48.

To TVR, the suspension rules are based on viral load at weeks 4 and 12. Must cease all drugs if HCV RNA > 1,000 IU/ml at week 4 or 12 of treatment, and in case of viral relapse later. The overall duration of treatment with triple therapy containing TVR reducing to 24 weeks in patients with previously untreated with RVR, as it should be continued until 48 week in patients without RVRe (43).

### **HCV infection without previous treatment, with cirrhosis**

It's only recommended starting treatment in patients with compensated cirrhosis, in order to prevent complications because the current triple therapy has no application in patients with decompensated liver disease. SVR in patients with advanced fibrosis is associated with decrease in the clinical decompensating and hepatocellular carcinoma. However, rate with PR and triple therapy are lower in patients with advanced fibrosis or cirrhosis compared to patients with mild to moderate fibrosis (44).

The guided virologic treatment should be avoided in the presence of cirrhosis, treatment with PEG-IFN/RBV should be continued until week 48, regardless of the kinetics of RNA-HCV, since the rate of SVR in cirrhotic with RVR was higher when treatment was maintained through week 48 (92% versus 67%) (45).

Response rates to triple therapy of patients with previous partial or no response to PR is discouraging. In cirrhotic patients protease inhibitors have varied SVR still better on prolonged therapy, in which PR with BOC or TVR recommends treatment regimen for 48 week (46).

### **Retreatment of patients with non-sustained virological response to PR**

There are a substantial number of patients receiving prior treatment with PR not achieving SVR. In this case, it is essential to characterize the response to previous treatment for being a critical determinant of triple therapy to administer. The likelihood of achieving SVR using retreatment with PR to the same dose is low, and the probability does not exceed 10%-15% for prior null responders and 30%-40% in patient responders /relapses. Therefore, it's advisable to retreat by triple therapy with a PI (47).

The addition of BOC to non-responders during the lead-in, lead to SVR rates significantly better if the patient is alone with PR (28% to 38% vs 4%). Therefore, a poor

response to the lead-in shouldn't be used to deny access to IP therapy. The re-treated patients with BOC more PR with HCV RNA > 100 IU at week 12 should be removed from any treatment (Class 1, Level B), and patients re-treated with TVR more PR with HCV RNA > 1,000 IU weeks 4 or 12 should be removed from any treatment (Class 1, Level B) (48).

**Prognosis**

Treatment of hepatitis C is subjected to constant changes in response to the availability of new drugs and the identification of polymorphisms associated with the response to treatment.

Thereby maintaining optimism that in the near future be available antivirals directed at different targets of the HCV cycle that will treat all genotypes with greater efficiency, facility to administer and shorter duration of treatment.

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Table: Treatment guidelines recommended by management in various regions of the world for chronic HCV-genotype 1

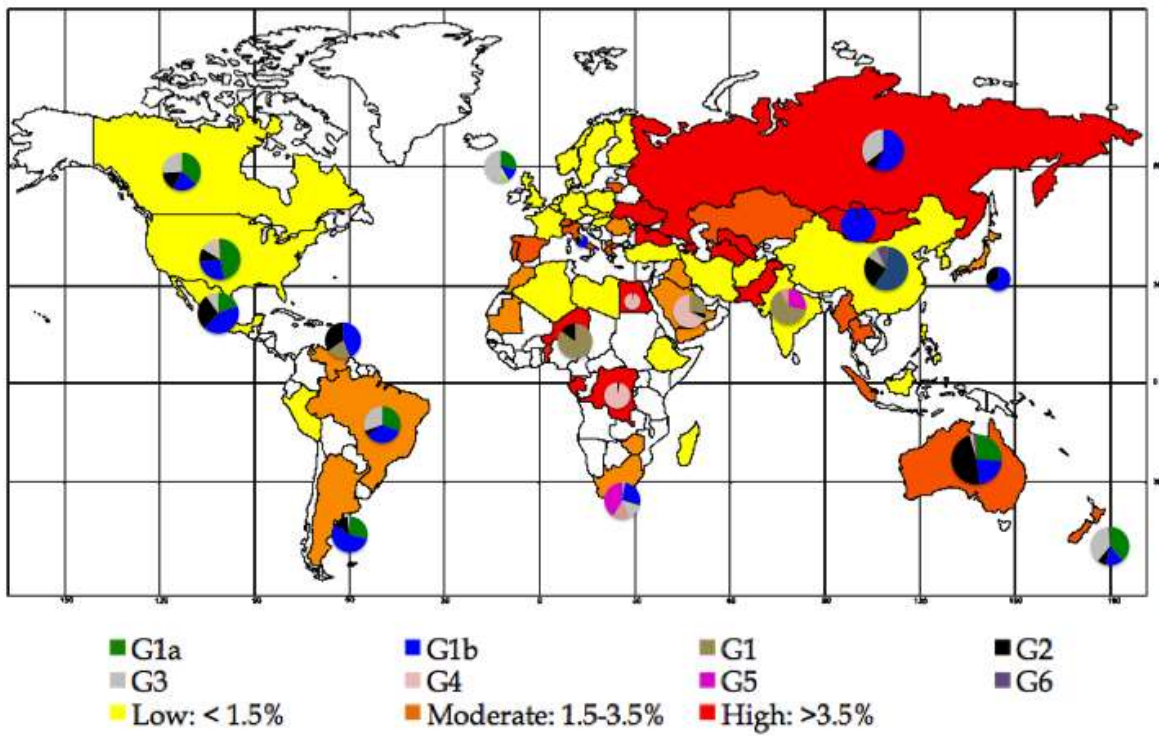
Guide / Publication	Patient Profile	Cirrhosis	Scheme	Response evaluation time/treatment time (weeks)	RVS (%)	Reviews
GPC	Naive		<b>PEG-INF + RBV</b>	12/12 to 24 or 48		
EASL	Naive		<b>peg-INF + RBV</b>			In patients with poor response factors can be assessed add IP
ALEH	Non-responders	Not	PR in the absence of factors of poor response.	4 / 48	40-50	Patients Treated With BOC and PEGINF / RBV With undetectable HCV RNA at weeks 8 and 24 Considered for a shortened duration of treatment of 28 weeks. Patients treated With TVR and undetectable HCV RNA at weeks 4 and 12 Considered for a shortened duration of therapy of 24 weeks. Patients treated with BOC or TVR With PEG-IFN / RBV should receive therapy for 48 weeks
		Yes	<b>peg-INF + RBV + IP</b>			
WGO	NAIVE		pegIFN / RBV	48		IL28B genotype non-CC, F3-F4 fibrosis and / or poor response

RELAPSE	pegIFN / RBV + IP	
NON RESPOND ERS	pegIFN / RBV + IP	BOC: 12, 24 TLV: 4,12 and 24

add IP  
(BOCoTLV)  
If the RVR is not  
obtained add IP

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GPC Clinical Practice; EASL. European Association for the Study of the Liver; AASLD American Association for the Study of Liver Diseases; APASL Asia Pacific Association for the Study of the Liver; ALEH American Association for the Study of the Liver; WGO World Gastroenterology Organization.



**Figure:** Map of estimated adult anti-HCV seroprevalence and genotype distribution by country.