

# Viral hepatitis C

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**More than 170 million people worldwide are chronically infected with the hepatitis C virus (HCV), which is responsible for more than 100 000 cases of liver cancer per year, with similar numbers of digestive haemorrhage and ascites episodes. Major breakthroughs have been made in diagnosis and treatment, and advances in molecular biology mean that the replicative state of the virus can now be assessed. Genotype and serum viral load are useful predictors of response to treatment. The combination of pegylated interferon and ribavirin can eradicate the virus in more than 50% of patients. These antiviral treatments reduce liver fibrosis progression and can reverse cirrhosis. Unfortunately, even in developed countries, death due to hepatitis C is increasing because of inadequate detection and treatment.**

## Introduction

More than 170 million people worldwide are chronically infected by the hepatitis C virus (HCV).<sup>1</sup> According to the WHO Report of 2002,<sup>2</sup> in 2001, chronic liver diseases were responsible for 1·4 million deaths, including 796 000 due to cirrhosis and 616 000 due to primary liver cancer (see also seminar on hepatitis B<sup>3</sup>). At least 20% of these deaths are probably attributable to HCV infection—more than 280 000 deaths.<sup>2,4</sup>

## Epidemiology

Chronic hepatitis C virus infection is a major cause of chronic liver disease and death throughout the world.<sup>1,2,4-9</sup> Very effective treatment is now available, which eradicates the virus in 60% of cases and reduces progression to cirrhosis in the remaining cases. Unfortunately, even in developed countries, death due to hepatitis C is increasing because of inadequate detection and treatment.<sup>6,8,9</sup>

By comparison with other hepatitis viruses (table), HCV is transmitted mainly through contact with blood and blood products—with blood transfusions, and sharing of non-sterilised needles and syringes being the main causes of its spread. With the advent of routine blood screening for HCV antibodies (in 1991 in most countries), transfusion-related hepatitis C has almost disappeared. At present, intravenous drug use is the most common risk factor. However, many other patients acquire HCV without any known exposure to blood or intravenous drug use. Patients with high-risk sexual behaviour are at higher risk, perhaps because of an association with herpes simplex type-2 infection.<sup>9</sup>

## Natural history

Hepatitis C can cause cirrhosis, digestive tract haemorrhage, liver failure, and liver cancer, and is the major cause of liver transplantation in Europe and the USA. Cumulative evidence strongly suggests that the increase in the number of deaths from hepatocellular carcinoma in most countries is because of hepatitis C infection.<sup>4-8</sup>

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Cirrhosis is the end-stage consequence of fibrosis progression. The median time from infection to cirrhosis is 30 years, with much variability between individuals, which is now better understood.<sup>10-12</sup> Several factors are clearly associated with fibrosis progression rate (panel): duration of infection, age, male sex, alcohol consumption, HIV coinfection, and low CD4 count.<sup>11-20</sup> Metabolic disorders such as overweight and diabetes are emerging as independent cofactors of fibrogenesis.<sup>21,22</sup>

Patients usually complain more about extrahepatic manifestations that impair quality of life (ie, fatigue or myalgia) than about hepatic manifestations, which occur later in the decompensated cirrhotic stage. The extrahepatic clinical manifestations are especially common,<sup>23-26</sup> with 74% of patients presenting with at least one symptom. There is a preponderance of rheumatic (ie, arthralgia, myalgia, paraesthesia) and cutaneous (pruritus, sicca syndrome, Raynaud's phenomenon) symptoms. Six manifestations have a prevalence of more than 10%; these are (in decreasing order): fatigue, arthralgia, paraesthesia, myalgia, pruritus, and sicca syndrome. These non-specific symptoms might or might not be related to HCV in individuals. Systemic vasculitis, which is the severe symptomatic manifestation of cryoglobulinaemia, although rare (1%), is the most frequent systemic inflammatory disease. Psychiatric disorders, especially depression and anxiety, are more frequent in patients with HCV than in male controls who have not been infected.<sup>26</sup>

Four extrahepatic biological abnormalities have a prevalence of more than 5%: cryoglobulin, antinuclear antibodies, antibodies against smooth muscle, and a low

## Search strategy and selection criteria

We searched MEDLINE (2000–03) using the search terms HCV, HBV, hepatitis C virus, or hepatitis B virus, and epidemiology, clinical manifestation, biological manifestation, virological test, biopsy, or treatment. We selected publications mostly from the past 5 years, but did not exclude commonly referenced and highly regarded older publications. We also searched the reference list of articles identified by the search strategy and selected those that were relevant. Selected review articles and meta-analyses or book chapters were included because they provide comprehensive overviews that would be beyond the scope of this seminar. The reference list was subsequently modified during the peer review process on the basis of comments from the reviewers and editors. Because one of the authors (TP) has a financial interest in the success of a non-invasive diagnostic marker of fibrosis, mention of this marker has been excluded.

	Genome	Transmission	Chronic hepatitis	Fulminant hepatitis	Treatment	Vaccine
<b>Virus</b>						
Hepatitis A	RNA	Oral	No	Yes	No	Yes
Hepatitis B	DNA	Mother to infant, blood, sexual	10%	Yes	Interferon, lamivudine, adefovir	Yes
Hepatitis C	RNA	Blood, rarely mother to infant, very rarely sexual	70%	Very rare	Interferon, ribavirin	No
Hepatitis D	DNA	Blood, sexual	50%	Yes	Interferon	Yes
Hepatitis E	RNA	Oral	No	Yes	No	No
Hepatitis G	RNA	Blood	No	No	No	No

#### Summary of main viral hepatitis characteristics

thyroxine concentration. At least one biological abnormality is present in 50% of patients.<sup>23,24</sup> Mixed cryoglobulinaemia is the main extrahepatic biological manifestation and is present in about 40% of patients with chronic hepatitis C. However, despite the high frequency of cryoglobulin in patients with HCV, severe symptomatic mixed cryoglobulinaemia with vasculitis is rare—noted in 2–3% of patients who are cryoglobulin positive. No association has been recorded between biological and clinical symptoms and a positive autoantibody state. 10% of patients have low thyroxine concentrations, but only 1% have high concentrations of thyroid stimulating hormone. The number of patients who have antibodies against thyroid is the same as in the general population of comparable age and sex.<sup>23,24</sup>

#### Genotype and serotype

Hepatitis C consists of six genotypes. Knowledge of the genotype or serotype (genotype-specific antibodies) is helpful for prediction of sustained virological response and the choice of treatment duration.<sup>27–36</sup> Response rates to treatment by pegylated interferon and ribavirin combination are about 88% for genotypes 2 and 3, and about 48% for genotypes 1, 4, 5, and 6. Genotypes do not change during the course of infection and do not need to be tested for again. Although serotyping could be cost effective, subtype determination (ie, 1a versus 1b) is not clinically helpful. The severity of the disease (fibrosis stage) has no relation to the genotype.<sup>15</sup>

#### Factors associated with fibrosis progression in patients infected with HCV

##### Definitely associated

Fibrosis stage  
Age at infection  
Duration of infection  
Age at biopsy  
Consumption of alcohol >50 g per day  
HIV coinfection  
CD4 count <200/mL  
Male sex  
Necrosis  
Body-mass index, diabetes, steatosis

##### Possibly associated

Inflammation  
Haemochromatosis heterozygote  
Cigarette consumption  
Moderate alcohol consumption  
Genotype 3  
Schistosomiasis

##### No association

Last serum viral load  
Genotypes non-3  
Mode of infection  
Liver viral load

#### Pathophysiology

Chronic hepatitis C is not the consequence of the direct destruction of hepatic cells by the virus. Rather, it results from an intermediate immune response that is large enough to induce hepatic cell destruction and fibrosis but not enough to eradicate the virus from its reservoirs.<sup>37</sup> Quantitatively, hepatitis C virus specific CD4 and CD8 T-cell responses are weaker in the chronic phase than in the acute phase of infection.<sup>38</sup> Patients with poor responses in the acute phase are often asymptomatic (no jaundice) and are more likely to become chronic carriers than are those with good responses. Qualitatively, HCV specific CD8 T cells have impaired effector function (both in secretion of antiviral cytokines and lytic activity). The effectiveness of the interferon and ribavirin combination is probably explained by its antiviral activity and restoration of a specific immune response.

#### Diagnostic tests

Diagnostic tests for HCV infection are divided into serological assays for antibodies and molecular tests for viral particles. Diagnosis is based on large-scale screening with detection for serum antibodies against HCV. Screening assays based on antibody detection have greatly reduced the risk of transfusion-related infection. Once seroconversion occurs these tests usually remain positive. However, the concentration of HCV antibodies decreases gradually over time in the few patients in whom infection spontaneously resolves.<sup>39</sup> Therefore, the spontaneous rate is sometimes underestimated.

Antibodies against HCV are detected by enzyme immunoassays that are very sensitive and very specific. The third-generation enzyme immunoassays used at present contain the core protein and non-structural proteins, and can detect antibodies within 4–10 weeks of infection. Immunosuppressed patients can have false-negative results, including those with HIV-1 infection, renal failure, and HCV-associated essential mixed cryoglobulinaemia. Antibodies against HCV are still detectable during and after treatment, whatever the response, and need not be tested for again.<sup>27,40</sup>

Assays based on molecular detection of HCV RNA have also been introduced. Qualitative HCV RNA tests are based on the PCR technique and have a lower limit of detection of fewer than 100 copies of HCV RNA per mL of serum (50 IU/mL). Testing for HCV RNA is a reliable way of showing HCV infection and is the most specific test of infection.<sup>27,40</sup> A qualitative PCR assay is especially useful when transaminase concentrations are normal, when other causes of liver disease are present (ie, alcohol consumption), in immunosuppressed patients (ie, graft recipients, HIV coinfecting patients), and in acute hepatitis C before antibodies have developed. An ELISA test has also been developed to quantify HCV core antigen, which could offer a practical, less expensive alternative to quantitative or qualitative PCR.<sup>27,40</sup>

Occult infection with HCV has been suspected in patients with abnormal transaminases and negative HCV

PCR in the serum, but positive HCV PCR in the liver, or positive in-situ hybridisation, or positive detectable HCV RNA in peripheral blood mononuclear cells.<sup>41</sup> This finding, if confirmed, will extend the prevalence and the risk of HCV infection.

### Measurement of HCV RNA in serum

Methods measuring the viral load have used quantitative PCR and a branched DNA test. An effort has been made to clinically define relevant HCV RNA loads in standardised international units for use in routine clinical and research applications. This definition was based on standardised quantitative assays, which had been validated with appropriate calibrated panels.<sup>27,40</sup>

Knowledge of the viral load is helpful for prediction of treatment response and relapse. Patients with high initial viral loads have higher relapse rates and benefit more from a 48-week treatment regimen than do patients with low viral loads. Patients with less than a two-log decrease from the baseline viral load after 12 weeks of treatment have a very low sustained response rate.<sup>27</sup> Therefore, treatment could be stopped in these patients if there is no extensive fibrosis, which would justify a longer treatment to reduce fibrosis progression. By contrast with HIV infection, the viral load does not correlate with the severity of hepatitis (fibrosis progression).<sup>15,27,40</sup>

### Liver biopsy

Biopsy is generally recommended for initial assessment of patients with chronic HCV infection.<sup>42</sup> It is useful for staging the severity of disease (fibrosis stage) and for grading the amount of necrosis and inflammation.<sup>43</sup> Biopsy can also be helpful in ruling out other causes of liver disease such as alcoholic features, non-alcoholic steatohepatitis, autoimmune hepatitis, drug-induced liver disease, or iron overload.

Staging of fibrosis is helpful in determining whether or not to treat the patient and the duration of treatment. Lesions should be assessed histologically even in patients with persistently normal serum transaminases since advanced fibrosis has been shown in many of these patients.<sup>44</sup>

Although regarded as the gold standard, liver biopsies have serious limitations. The major limitations are the sampling variability and the number of adverse events. Sampling variability accounts for the high discordance rate (greater than 20%) between stages of fibrosis or grades of activity when biopsy samples are taken from different parts of the liver at the same time.<sup>45-47</sup> The coefficient of variation of the staging of 15-mm biopsy sample, the usual mean length of biopsy samples in routine, is 55%.<sup>47</sup> The incidence of severe adverse events in 98 445 liver biopsy samples compiled from nine studies was 3.1 per 1000 with a mortality rate of 0.3 per 1000.<sup>48</sup> Liver biopsy might become unnecessary in many cases in the next few years as serum markers become validated.<sup>49,50</sup>

### Treatment

There is no vaccine available for hepatitis C, and the infection is best prevented by keeping blood exposure to a minimum. In the past 10 years much progress has been made in management of chronic hepatitis C, both in terms of achieving viral eradication and improving histology. The natural history of hepatitis C suggests three different goals for treatment: prevention of cirrhosis and its complications; reduction of extrahepatic manifestations; and preventing contamination of other people (ie, surgeon or drug user). High alcohol consumption must be avoided,<sup>51</sup> and metabolic disorders (diabetes, overweight, steatosis, steatohepatitis) improved.<sup>52</sup>

### Treatment-naïve patients

Several main treatment regimens have been assessed in large trials, the first of which (standard interferon regimen monotherapy with three injections three times a week) was approved in 1990 and the last (combination of ribavirin and pegylated interferon) in 2002. The specifics of these treatments are: standard interferon alfa (alfa 2a or 2b) 3 MU three times a week for 24 weeks and then 48 weeks;<sup>53</sup> a combination of standard interferon (3 MU three times a week) and ribavirin (1000–1200 mg per day) for 24 weeks or 48 weeks;<sup>28-30</sup> pegylated interferon for 48 weeks (alfa 2a 180 µg, or alfa 2b at three doses: 0.5 µg, 1.0 µg, or 1.5 µg per kg);<sup>31-33</sup> and 48 weeks' combination pegylated interferon and ribavirin (different doses of pegylated interferon and ribavirin).<sup>34-36</sup> Combination therapies have always been more effective than interferon monotherapy, even pegylated interferon monotherapy.

Two pegylated interferons are licensed. The first is a 12 kD pegylated interferon alfa 2b that is dosed according to bodyweight (1.5 µg per kg, once a week) and combined with ribavirin adjusted also by weight (11 mg per kg),<sup>34</sup> which has a dose ranging from 800 to 1400 mg per day. The second is a 40 kD pegylated interferon alfa 2a, which is used at a fixed dose of 180 µg per week and is combined with ribavirin at a dose of 1000 or 1200 mg per day.<sup>35,36</sup> The effectiveness of the regimens has not been compared directly, but results from the published trials suggest that the two compounds have similar response rates and similar adverse events.

Figure 1 summarises treatment progress according to HCV genotype, the main factor associated with viral response. The histological effects of these ten different regimens on fibrosis stage and necroinflammatory grade are shown in figure 2. All regimens significantly reduced fibrosis progression rates by comparison with rates before treatment, and cirrhosis was reversed in 75 (49%) of 153 patients with cirrhosis at baseline.<sup>54</sup>

The choice of 24 or 48 weeks for combination therapy has been clarified for the earlier combination therapy of interferon and ribavirin but is unknown for the current treatment of pegylated interferon and ribavirin.<sup>30</sup> In one study,<sup>36</sup> of pegylated interferon alfa 2a in combination with ribavirin for 24 or 48 weeks, patients with HCV genotype 1, but not genotypes 2 or 3 significantly improved their sustained virological response with longer treatment, independent of pretreatment viral load. Furthermore, patients with HCV genotype 1 responded better to higher doses (1000–1200 mg per day) of ribavirin than did those with genotypes 2 and 3.<sup>36</sup>

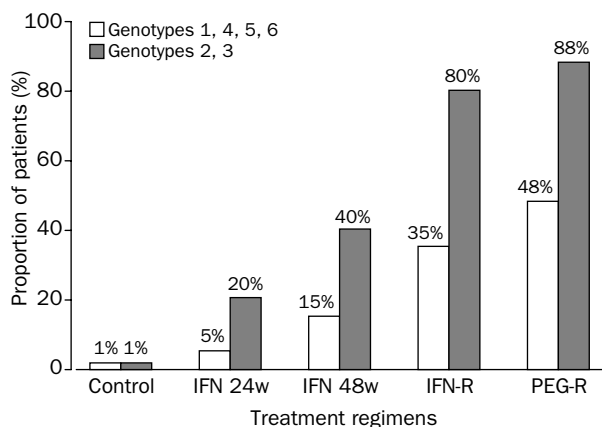


Figure 1: Progress in treatment of chronic hepatitis C

Data are proportions of patients with undetectable HCV RNA at the end of follow-up, according to genotype. IFN=interferon. w=weeks. R=ribavirin. PEG=pegylated interferon.

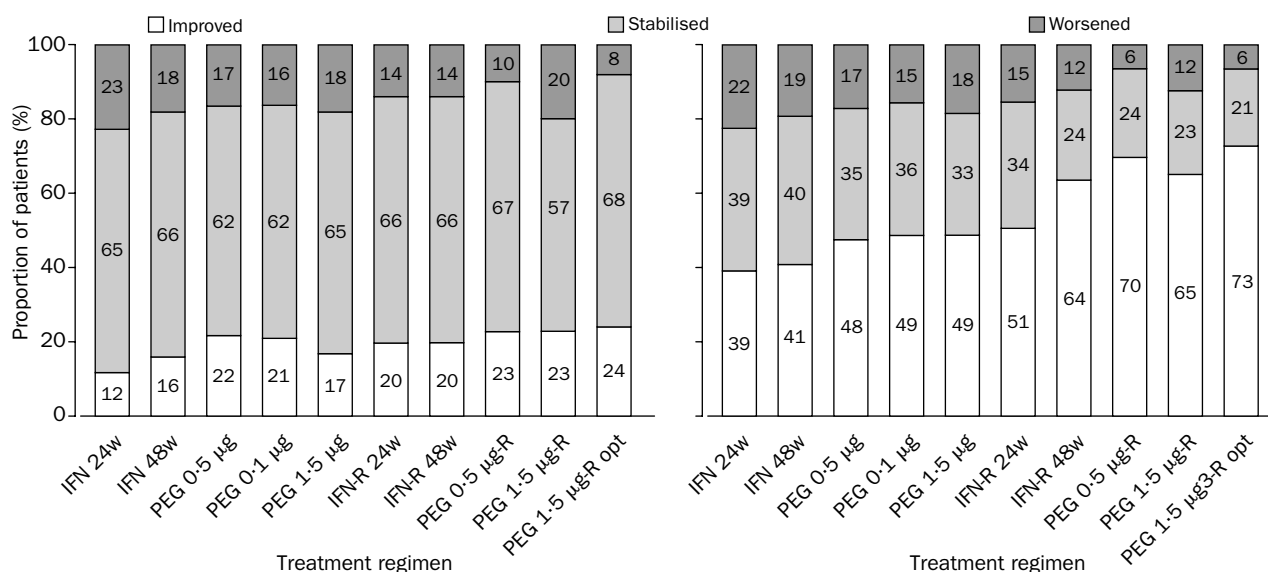


Figure 2: **Effect of regimens on fibrosis stage (left) and necroinflammatory activity grade (right)**

A total of 3010 patients with paired biopsies were analysed by the same pathologist. PEG=pegylated interferon. w=weeks. R=ribavirin. opt=optimised according to weight. IFN=interferon.

On the basis of previous results,<sup>30</sup> it would not be prudent to recommend a strategy based on virological characteristics alone. Besides viral load or viral kinetics, several independent response factors (better response in patients without extensive fibrosis, without steatosis, younger than 40 years, and female sex) have been identified. Taking into account only the viral factors is an oversimplification that could lead to errors in different populations.<sup>30</sup> Therefore, other independent factors of response and tolerance to treatment should be taken into account when deciding the length of treatment. Because of the antifibrotic effect of interferon, a long treatment period could benefit patients with extensive fibrosis or rapid fibrosis progression.<sup>54-57</sup> Because cirrhosis complications cause such an economic burden, treatments for hepatitis C are cost effective.<sup>58</sup>

#### Safety of pegylated interferon and ribavirin combination

Patients should be fully informed of the potential adverse events of pegylated interferon and ribavirin before starting treatment. The main severe adverse events related to interferon are depression, suicidal ideation, suicide, and sustained hypothyroidism. Sometimes patients with pre-existing psychosis or depression can be treated after consultation and under close monitoring by a psychiatrist.

The main severe adverse events related to ribavirin are anaemia and teratogenic effects. The mean haemoglobin concentration drops by 30 g/L in the first 4 weeks of treatment. Blood cell counts must be checked at least 2 and 4 weeks after starting therapy, and every 4 weeks thereafter.

The most frequent adverse events associated with interferon are influenza-like symptoms and alopecia. The most frequent adverse event related to ribavirin is anaemia, and, less frequently, pharyngitis, insomnia, dyspnoea, pruritus, rash, nausea, and anorexia. Absolute contraindications to ribavirin are pregnancy and non-reliable methods of contraception.

#### Management of virological relapsers and non-responders

Virological relapsers are patients who have serum HCV RNA that is undetectable at the end of treatment but detectable afterwards. A virological non-responder is defined as a patient whose serum HCV RNA is still detectable at the end of treatment.

Since there is no viral resistance to the standard interferon and ribavirin combination, the latest approved regimen for naive patients (pegylated interferon and ribavirin combination) should also be prescribed for relapsers or non-responders to standard interferon and ribavirin combination.<sup>34-36</sup> If relapse occurs after combination of pegylated interferon and ribavirin, the best strategy is unknown; longer duration of treatment could be considered, especially in patients with extensive fibrosis. In non-responders to the combination pegylated interferon and ribavirin, the best strategy is unknown. One option is to treat patients with extensive fibrosis by pegylated interferon alone (maintenance therapy) to decrease the progression rate to cirrhosis,<sup>55-57</sup> while waiting for a new generation of drugs.<sup>59,60</sup> Similar changes have been seen in patients given both types of pegylated interferon. The best maintenance therapy (dose and duration) is unknown and trials of pegylated interferons are in progress.

#### Management of patients with cirrhosis

Overviews<sup>54,61,62</sup> of randomised trials clearly show that compensated cirrhosis is an indication of interferon-ribavirin treatment. The combination of pegylated interferon and ribavirin in patients with compensated cirrhosis is logically the first-line treatment, with better results than pegylated interferon alone.<sup>34-36</sup> Interferon toxic effects on platelets and neutrophils must be carefully monitored. Liver transplantation is the primary treatment option for patients with decompensated cirrhosis.

#### Effect of treatment on morbidity and mortality

There is an obvious ethical problem in doing large randomised trials comparing treatment of chronic hepatitis C (which is very effective on virological and histological endpoints) with placebos to prove the reduction of mortality. Studies, which have been mostly retrospective, whether controlled or not, have shown a decrease in morbidity and mortality in patients given interferon, especially in reducing development of hepatocellular carcinoma.<sup>63-66</sup> Mortality is significantly reduced in patients who do not have a sustained virological response, but is higher in those with a sustained virological response and in non-cirrhotic patients.<sup>67,68</sup>

### Management of patients coinfecting with HCV and HIV

In patients infected with HIV, HCV coinfection must be systematically screened for, and treatment of HCV must be discussed when fibrosis is seen at liver biopsy.<sup>69</sup> Anti-HIV treatments are often associated with increases in transaminases (stavudine, didanosine, abacavir, nevirapine, protease inhibitor). The following factors are sometimes involved: alcohol consumption, illicit intravenous drug use, drug toxic effects, coinfection with HBV or Delta virus, opportunistic liver infection, immune restoration, and sclerosing cholangitis. The effect of immune reconstitution on liver fibrosis progression is unknown. Because of the very severe natural history, the most effective treatment of hepatitis C should be given to patients who are coinfecting.<sup>69-72</sup> Results and tolerance are lower than those of patients infected by HCV alone, but the benefit-risk ratio could be higher.<sup>69,70</sup>

### Treatment of acute hepatitis C

Because of the small number of symptomatic patients, randomised trials are not a rapid method to identify new regimens in acute hepatitis C.<sup>73,74</sup> Overviews of randomised or non-randomised trials showed that interferon alone is very effective by comparison with control groups. At the end of 6 months' follow-up, 32% (95% CI 21-46) of patients given interferon showed a virological sustained response compared with only 4% (0-13) of controls ( $p < 0.0001$ ).

A multicentre study<sup>75</sup> included 44 patients who received 5 million U of interferon alfa-2b subcutaneously daily for 4 weeks and then three times per week for another 20 weeks. At the end of treatment and follow-up, 43 patients (98%) had undetectable concentrations of HCV RNA in serum and normal serum alanine aminotransferase concentrations. Therefore, a regimen with high dose of interferon alfa for 24 weeks can be recommended in treatment of acute hepatitis C. The benefit-risk of pegylated interferon alone or in combination with ribavirin is unknown.

Treatment could be started 12 weeks after jaundice if HCV-RNA is still detectable. In patients without jaundice a treatment can be discussed earlier according to the high risk of chronicity and the high effectiveness of interferon.

### Conclusion

Chronic hepatitis C is a leading cause of cirrhosis, hepatocellular carcinoma, digestive haemorrhage, and hepatic insufficiency. Major breakthroughs have been achieved in diagnosis and treatment. Antiviral treatments reduce liver fibrosis progression and can even reverse cirrhosis. Unfortunately, even in developed countries, death due to hepatitis C is increasing due to inadequate detection and treatment.

### Conflict of interest statement

T Poynard is a consultant for and owns 15% of Biopredictive, which markets FibroTest-AdiTest. The patent for this test belongs to Assistance Publique Hopitaux de Paris, a public organisation (reference US Patent Application No 09/68,459). He has taken part in trials of pegylated interferon and ribavirin for Schering and Roche, lamivudine for GlaxoSmithKline, adefovir for Gilead, telbivudine for Idenix, and entecavir for Bristol-Myers Squibb. His department has participated in the trial of BILN2061 for Boehringer. M F Yuen has taken part in trials of lamivudine for GlaxoSmithKline, adefovir for Gilead, L-deoxythymidine for Idenix, and entecavir for Bristol-Myers Squibb. V Ratzu has taken part in trials of telbivudine for Idenix. C L Lai has taken part in trials of lamivudine for GlaxoSmithKline, adefovir for Gilead, L-deoxythymidine for Idenix, and entecavir for Bristol-Myers Squibb. He received a Bristol-Myers Squibb unrestricted Biomedical Research Grant for Infectious disease.

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