Evaluation of the Hepatitis C Virus–Infected Patient: The Initial Encounter

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Deaths from hepatitis C virus (HCV)–related disease are increasing, now exceeding those from human immunodeficiency virus. Up to 7 million Americans (2.3%) may be infected with HCV, and more than half are undiagnosed. Proposed expansion of hepatitis C screening to include all persons born between 1945 and 1965 will lead to many new diagnoses, and infectious diseases physicians have a unique opportunity to be part of managing these patients. Apart from a liver-focused history and examination, the initial evaluation includes determination of the liver function via serum tests and assessment of liver fibrosis and necroinflammation through biopsy or noninvasive means. Patients with cirrhosis require screening for esophageal varices and for liver cancer. Nonimmune patients need vaccinations against hepatitis A and B, and alcohol abstinence is critical. Initial counseling on therapy emphasizes viral cure rates of currently 70%–80% as well as expected side effects.

New treatments with fewer side effects and potentially higher cure rates are currently in development.

\textbf{Keywords.} chronic hepatitis C; screening; clinical assessment; counseling.

Chronic hepatitis C is the most common etiology of chronic liver disease in the Western world. In the third National Health and Nutrition Examination Survey (NHANES III), conducted by the Centers for Disease Control and Prevention (CDC) in sentinel counties, the prevalence of chronic hepatitis C virus (HCV) infection in the United States has been estimated at 1.33% or about 4 million persons \cite{1}. A subsequent study that adjusted for the omission of institutionalized persons in NHANES III estimated the HCV prevalence in the United States at 1.7%–2.3%, or 5.2–7.0 million persons \cite{2}. Many HCV-infected patients are undiagnosed, and in one study 50% of HCV-infected patients were unaware of their diagnosis \cite{3} Progression to cirrhosis occurs in about 25% of HCV-infected patients, but this process is slow and on average takes 20–30 years. Once cirrhosis has developed, 29% of patients develop liver failure over 10 years and 14% develop hepatocellular carcinoma (HCC). The 5-year survival rate for compensated cirrhosis is still fair at 91%, but after the onset of liver decompensation begins, the 5-year survival rate declines to 50% \cite{4}.

In the United States and other Western countries, a sharp rise in deaths from HCV-related disease has been observed over the last decade (Figure 1) \cite{5}, and since 2007, deaths related to HCV infection have even exceeded deaths from human immunodeficiency virus (HIV) disease \cite{6}. This is the consequence of a large cohort of patients who were infected in the 1960s and 1970s, mainly through injection drug use, that now, 3–4 decades later, reaches the time point when HCV infection has progressed to liver failure and HCC. Most of these patients were born between 1945 and 1965 and are now the target of the CDC’s universal HCV screening recommendation as described below.

Infectious diseases physicians with their long experience of managing the complexities of HIV disease are in a unique position of taking on a growing role in the care of patients with chronic hepatitis C.

\textbf{DIAGNOSIS}

Chronic hepatitis C is largely asymptomatic, with perhaps chronic fatigue as one nonspecific complaint.
States, 1999–2007 (CDC data [5]).

Figure 1. Increase in annual hepatitis C virus–related deaths, United States, 1999–2007 (CDC data [5]).

affecting some patients [7]. However, timely intervention with antiviral therapy and lifestyle counseling even in the absence of symptoms is critical to prevent advanced and fatal liver disease. Therefore, an active screening program is necessary to identify patients with HCV infection. Until recently, the CDC has recommended testing all persons who have 1 or more risk factors for HCV. However, it has been recognized that this approach still leaves a large number of HCV-infected individuals undiagnosed. On 17 August 2012, the CDC published a new recommendation to expand HCV testing from risk groups to a birth cohort, namely, to test all persons born between 1945 and 1965 regardless of risk factors (Table 1) [8]. In the United States, 75% of cases of chronic hepatitis C fall within this cohort, so universal testing in this group is likely to yield a significant number of new diagnoses. In a prior study, this approach has been found to be cost-effective [9]. This change in screening method is similar to the previous implementation of universal screening for HIV infection in 2006 [10].

Initial testing for HCV is performed by HCV antibody testing via enzyme-linked immunosorbent assay, which in its current generation has a sensitivity of close to 100% to detect chronic HCV infection. Chronic HCV infection is confirmed by plasma HCV RNA testing, which also gives quantitation of HCV viral load in international units per milliliter (IU/mL) [11]. Many laboratories already perform reflex HCV RNA testing in the same blood sample that tests anti-HCV positive. This gives the clinician instant information on chronicity of HCV infection and avoids having to recall the patient for a second blood test.

HISTORY AND PHYSICAL EXAMINATION

When evaluating a patient with a new diagnosis of chronic hepatitis C, the detailed history will focus on any events that may be related to advanced liver disease such as upper gastrointestinal bleeding, ascites, hepatic encephalopathy, and other clinical signs of liver failure. Special focus should be given to the psychiatric history with emphasis on alcohol and drug abuse. A detailed history of past and present alcohol consumption will help assess the risk for accelerated progression of hepatic fibrosis in the setting of HCV infection. The use of screening tests for alcohol use disorders such as the Alcohol Use Disorders Identification Test Consumption questionnaire (AUDIT-C) [12] can detect problem drinking when patients do not initially acknowledge it. Likewise, adding a urine drug screen to the panel of initial laboratory tests will uncover active substance abuse that can be referred for treatment with addiction specialists. Untreated and unstable psychiatric illnesses including ongoing substance abuse are major obstacles to successful antiviral therapy and are the most common cause of deferral of HCV therapy [13, 14]. Interferon therapy can cause new neuropsychiatric symptoms or make existing ones worse [15]. But even in the absence of interferon-related neurotoxicity, uncontrolled mental illness is likely to impair full adherence to an antiviral regimen that must be continued without interruption and to scheduled office visits that monitor antiviral efficacy and side effects. The history of medication also needs to include a list of all over-the-counter remedies that the patient is currently taking or is considering taking in the near future. Hepatotoxicity has been documented for many prescription medications, but increasingly the liver toxicity of certain herbal concoctions is being recognized.

The physical examination will naturally focus on stigmata of chronic liver disease such as palmar erythema, spider naevi, or gynecomastia, or clinical signs of liver failure such as jaundice or ascites. The neurological examination will look for signs of hepatic encephalopathy through a detailed mental

Table 1. Centers for Disease Control and Prevention Hepatitis C Virus Testing Recommendations, August 2012

<table>
<thead>
<tr>
<th>New CDC Recommendation:</th>
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<tbody>
<tr>
<td>• Anyone born from 1945 through 1965</td>
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<table>
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<tr>
<th>Existing, Risk-Based Guidelines:</th>
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<tbody>
<tr>
<td>• Anyone who has ever injected illicit drugs</td>
</tr>
<tr>
<td>• Recipients of blood transfusions or solid organ transplants before July 1992, or clotting factor concentrates before 1987</td>
</tr>
<tr>
<td>• Patients who have ever received long-term hemodialysis treatment</td>
</tr>
<tr>
<td>• Persons with known exposure to hepatitis C, such as</td>
</tr>
<tr>
<td>o Healthcare workers after needle sticks, sharps, or mucosal exposure to HCV-positive blood</td>
</tr>
<tr>
<td>o Recipients of blood or organs from a donor who later tested positive for hepatitis C</td>
</tr>
<tr>
<td>• Persons infected with HIV</td>
</tr>
<tr>
<td>• Children born to HCV-positive mothers</td>
</tr>
<tr>
<td>• Persons with persistently elevated levels of alanine aminotransferase</td>
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</table>

Abbreviations: CDC, Centers for Disease Control and Prevention; HCV, hepatitis C virus; HIV, human immunodeficiency virus.
status assessment and testing for flapping tremors when the patient holds the hands upright.

**FURTHER WORKUP**

The recommended initial series of tests is summarized in Table 2. Although the liver-specific enzyme alanine aminotransferase (ALT) is considered to reflect liver inflammation, the correlation between ALT level and necroinflammation on histology is loose at best, and higher grades of necroinflammation can be seen even with normal ALT levels [16]. The correlation between ALT level and liver fibrosis is even less pronounced, and a normal ALT level can exist in the presence of advanced bridging fibrosis or even cirrhosis [17]. Thrombocytopenia (platelet count <150 000/μL) is often a sign of portal hypertension and liver cirrhosis, but this finding by itself has limited sensitivity (68%) and specificity (76%) for a diagnosis of cirrhosis [18]. An aspartate aminotransferase (AST)/ALT ratio >1 is another laboratory marker suggestive of cirrhosis, but an AST/ALT ratio >1 can also be seen in the setting of alcohol abuse without cirrhosis. Combinations of commonly used laboratory tests have been found to correlate better with the degree of liver fibrosis, such as the AST-to-platelet ratio index (APRI) [19], the Forns index [20], or, in HIV/HCV-coinfected patients, the FIB-4 index [21], and they may be used to estimate the likelihood of cirrhosis in the absence of a liver biopsy.

A liver biopsy is still the most accurate way to assess necroinflammation and fibrosis. Figure 2 shows 4 different stages of HCV-related liver fibrosis according to the Ishak staging system [22]. A biopsy also provides other information on liver pathology such as the presence of steatosis and of hepatic iron. Steatosis and nonalcoholic fatty liver disease are on the rise as the prevalence of obesity and the metabolic syndrome are increasing. In HCV-infected patients with cirrhosis, steatosis has been linked to an increased risk of HCC [23]. However, liver biopsies face the problem of sampling error, especially if the length is <15 mm, since advanced fibrosis may be missed in such samples [24]. As an invasive procedure, liver biopsies have a small but real risk of complications with a rate of serious adverse events of 1.1% and risk of bleeding of 0.6% with an increased risk of bleeding with a platelet count <60 000/μL and an international normalized ratio ≥1.3 [25]. Because of this risk, a liver biopsy is not universally accepted by patients and clinicians.

Noninvasive tests of hepatic fibrosis avoid the complications of liver biopsies, but they do not give information on steatosis and other concurrent liver disease. Tests using serum markers include the above-mentioned common laboratory tests and commercial tests using specialized serum markers like the fibrotest (Fibrosure, LabCorp) [26] and the Enhanced Liver Fibrosis test (ELF, Siemens Diagnostics) [27]. Noninvasive fibrosis tests using imaging techniques include transient elastography (Fibroscan, Echosense) to measure liver stiffness through a combination of vibration and ultrasound waves in a sample volume of about 4 cm³ [28]. It has been shown to be more accurate in predicting liver cirrhosis than serum tests [29]. As noninvasive measures of liver fibrosis become more accurate, the need to perform liver biopsies will decrease. The issue of

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**Table 2. Initial Tests to Assess Chronically Hepatitis C Virus–Infected Patients**

<table>
<thead>
<tr>
<th>Test</th>
<th>Purpose</th>
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<tbody>
<tr>
<td><strong>All patients</strong></td>
<td></td>
</tr>
<tr>
<td>Comprehensive metabolic panel</td>
<td>Liver function, including synthetic function</td>
</tr>
<tr>
<td>Complete blood count</td>
<td>Assess for possible cirrhosis (thrombocytopenia)</td>
</tr>
<tr>
<td>Prothrombin time / International normalized ratio</td>
<td>Synthetic function</td>
</tr>
<tr>
<td>Anti-HAV, HBsAg, anti-HBc, anti-HBs</td>
<td>Immunity against Hepatitis A and B and need for vaccination Screen for HBV coinfection</td>
</tr>
<tr>
<td>HIV</td>
<td>Screen for HIV coinfection</td>
</tr>
<tr>
<td>Anti-nuclear antibody</td>
<td>Screen for concurrent autoimmune hepatitis</td>
</tr>
<tr>
<td>25-hydroxy-vitamin D3 level</td>
<td>Screen for vitamin D deficiency</td>
</tr>
<tr>
<td>Drug screen</td>
<td>Screen for substance abuse</td>
</tr>
<tr>
<td>AUDIT-C</td>
<td>Screen for unhealthy alcohol consumption</td>
</tr>
<tr>
<td>Abdominal ultrasound</td>
<td>Screen for hepatic tumors, ascites</td>
</tr>
<tr>
<td>Liver biopsy</td>
<td>Assess necroinflammation, fibrosis stage, concurrent steatosis and iron overload</td>
</tr>
<tr>
<td>Alternatives to liver biopsy</td>
<td>Assess liver fibrosis</td>
</tr>
<tr>
<td>Transient elastography (Fibroscan®)</td>
<td>*</td>
</tr>
<tr>
<td>Specialized serum tests (fibrotest or enhanced liver fibrosis test)</td>
<td></td>
</tr>
<tr>
<td><strong>In patients with cirrhosis</strong></td>
<td></td>
</tr>
<tr>
<td>Calculate CTP score every 3–6 months</td>
<td>Severity of liver disease and prognosis of survival</td>
</tr>
<tr>
<td>Calculate MELD score every 3–6 months</td>
<td>Prognosis of overall survival, perioperative mortality, priority for liver transplantation</td>
</tr>
<tr>
<td>Esophagogastroduodenoscopy</td>
<td>Screen for esophageal varices</td>
</tr>
<tr>
<td>Semiannual abdominal ultrasound</td>
<td>Surveillance program to screen for HCC</td>
</tr>
<tr>
<td>Referral to liver transplant center</td>
<td>Assessment for transplant if MELD score ≥12 listing</td>
</tr>
</tbody>
</table>

Abbreviations: Anti-HAV, hepatitis A virus antibody; anti-HBc, hepatitis B core antibody; anti-HBs, hepatitis B surface antibody; AUDIT-C, alcohol use disorder identification test, consumption; CTP, Child-Turcotte-Pugh; HBV, hepatitis B virus; HBsAg, hepatitis B surface antigen; HCC, hepatocellular carcinoma; HIV, human immunodeficiency virus; MELD, model for end-stage liver disease.

* As of 2012, not approved in the United States.
liver biopsies and noninvasive fibrosis markers will be discussed in more detail in a subsequent article in this series.

An abdominal ultrasound is typically performed during the initial evaluation, but its utility is limited to ruling out hepatic masses, hepatosplenomegaly, and ascites. Ultrasound is not sensitive enough to diagnose or rule out cirrhosis, and it also has low accuracy in diagnosing hepatic steatosis [30].

Additional blood tests should include antinuclear antibodies to rule out coexisting autoimmune hepatitis as well as serology for hepatitis A and B viruses to determine immunity and need for vaccination. Patients with a positive hepatitis B surface antigen should be further tested for hepatitis B e antigen and antibody and hepatitis B virus (HBV) DNA level and assessed for HBV antiviral therapy [31]. Because of shared risk factors, all HCV-infected patients should be tested for HIV, if this has not been done already as part of universal HIV testing [10]. HIV/HCV coinfection has been shown to accelerate HCV-induced liver fibrosis, especially with ongoing HIV viremia [32, 33]. A test for the 25-hydroxy-vitamin D3 level will detect vitamin D deficiency, which recently has been found to be independently correlated with reduced antiviral activity of peg-interferon plus ribavirin [34–36].

HCV-infected patients with liver cirrhosis require special follow-up regardless of considerations for antiviral therapy. They should be monitored every 3–6 months with clinical examinations and laboratory tests (comprehensive metabolic panel, coagulation profile, complete blood count) for signs of decompensation. At each visit, the Child-Turcotte-Pugh

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**Table 3. Child-Turcotte-Pugh Classification of Severity of Liver Disease**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Scoring</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilirubin (mg/dL)</td>
<td>≤2</td>
<td>2–3</td>
<td>&gt;3</td>
<td></td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>&gt;3.5</td>
<td>2.8–3.5</td>
<td>&lt;2.8</td>
<td></td>
</tr>
<tr>
<td>INR</td>
<td>&lt;1.8</td>
<td>1.8–2.3</td>
<td>&gt;2.3</td>
<td></td>
</tr>
<tr>
<td>Ascites</td>
<td>none</td>
<td>mild (or controlled with medication)</td>
<td>moderate to severe</td>
<td></td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>none</td>
<td>grade 1–2</td>
<td>grade 3–4</td>
<td></td>
</tr>
</tbody>
</table>

**Interpretation**

<table>
<thead>
<tr>
<th>Points</th>
<th>Class</th>
<th>1-Year Survival</th>
<th>2-Year Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>5–6</td>
<td>A</td>
<td>100%</td>
<td>85%</td>
</tr>
<tr>
<td>7–9</td>
<td>B</td>
<td>81%</td>
<td>57%</td>
</tr>
<tr>
<td>10–15</td>
<td>C</td>
<td>45%</td>
<td>35%</td>
</tr>
</tbody>
</table>

Abbreviation: INR, international normalized ratio.
Table 4. Calculation of Model for End-Stage Liver Disease Score

\[
\text{MELD} = 3.78 \times \ln \text{serum bilirubin (mg/dL)} + 11.2 \times \ln \text{INR} + 9.57 \times \ln \text{serum creatinine (mg/dL)} + 6.43
\]

MELD calculators can be found online, e.g., at http://www.mayoclinic.org/meld/mayomodel6.html

Abbreviations: INR, international normalized ratio; Ln, natural logarithm; MELD, model for end-stage liver disease.

(CTP) score (Table 3) [37] should be updated to assess liver function and prognosis. Calculating the Model for End-Stage Liver Disease (MELD) score [38] (Table 4) will determine the likelihood that a patient with end-stage liver disease is a candidate for liver transplantation. The CTP score is the oldest measure of liver function and was originally developed to assess perioperative mortality risk in patients with cirrhosis. The MELD score eliminates the more subjective clinical assessments of ascites and encephalopathy and is only composed of 3 laboratory values. It has been found to better predict overall survival than the CTP score. Therefore, since February 2002 the MELD score is used to prioritize patients awaiting liver transplants. Recently, the MELD score has also been shown to consistently predict perioperative mortality in patients with cirrhosis [39]. It is further recommended that patients with cirrhosis undergo a screening esophagogastroduodenoscopy to screen for esophageal varices [40]. All patients with HCV-related cirrhosis need to undergo a continuing program of HCC screening, and in its guidelines of 2011, the American Association for the Study of Liver Disease recommends semiannual ultrasonography (not computed tomography or magnetic resonance imaging) [41, 42]. Testing serum alfa-fetoprotein (AFP) levels for HCC screening is no longer recommended in these guidelines because of its low sensitivity and specificity [43]. However, some authors question the omission of AFP from HCC screening [44, 45].

Patients who show biochemical or clinical signs of liver decompensation or have a MELD score of ≥12 should be referred to a hepatologist for further management of decompensation and assessment for liver transplantation. If the abdominal ultrasound shows a mass lesion, a workup to rule out HCC needs to be initiated. If a subsequent 3-phase contrast computed tomography of the abdomen shows a typical contrast enhancement pattern (early arterial enhancement plus early venous washout), a diagnosis of HCC can be made even in the absence of a tumor biopsy.

**INITIAL COUNSELING**

Many patients with chronic hepatitis C come to the initial visit with great concerns about the prognosis of the disease, having heard about the virus being a “silent killer.” Because most patients present initially with compensated liver disease, stating that a patient is compensated and showing laboratory tests to prove it will reassure many patients of their worst fear that they are about to die soon. Explaining the natural history of a long time period between initial infection and end-stage liver disease and how stages of liver disease can be assessed by liver biopsy and other means will further help the patient get a better understanding of the disease. Importantly, the message that the infection can now be cured in more than two-thirds of patients may instill hope in patients, even though therapy is currently complex and frequently has side effects. Potential side effects of HCV therapy, especially of interferon, need to be discussed openly, together with an emphasis on the fact that many side effects such as rash, anemia, or mood swings can be successfully treated to allow patients to continue antiviral therapy. However, before any consideration is given to HCV therapy, the patient should be counseled on abstinence of alcohol, since alcohol consumption accelerates liver disease in HCV-infected patients [46]. It is not known if there is an amount of alcohol consumption that can be considered safe in patients with chronic hepatitis C, and typically complete abstinence is recommended. Patients who are nonimmune to hepatitis A virus and HBV need to be vaccinated accordingly to prevent acute hepatitis A or B, which in HCV-infected patients may be severe or even fatal [47].

Much confusion exists among patients on how HCV is transmitted and how it is not. By far the most common mode of HCV transmission is injection drug use. Patient counseling needs to stress that HCV is not transmitted through household contact or through shaking hands, hugging, or kissing. In the absence of HIV or other sexually transmitted infections, HCV is also not transmitted sexually, and the CDC does not recommend barrier protection between HCV-serodiscordant sex partners. Two large prospective studies of serodiscordant married couples over 5–10 years have not demonstrated any sexual transmission of HCV [48, 49]. However, sexual transmission of HCV with subsequent acute hepatitis C has been observed in several studies of HIV-infected men who have sex with men [50, 51].

In addition to counseling by their physician, patients can also educate themselves on chronic hepatitis C through a variety of online sources, such as the CDC [52], the American Liver Foundation [53], or the US Department of Veterans Affairs [54]. A comprehensive list of the latest results of hepatitis C clinical trials presented as abstracts at international meetings can be found at the National AIDS Treatment Advocacy Project (NATAP) website [55], which has expanded its extensive reporting of research findings from HIV to hepatitis C and B.
TREATMENT DECISION

When counseling the patient about treatment for chronic hepatitis C, emphasis should be placed on the fact that a viral cure is possible with a time-limited therapy. A viral cure is defined as a sustained viral response (SVR) to anti-HCV therapy with undetectable plasma HCV RNA 24 weeks after the end of therapy. Once a viral cure is achieved, it is long-lasting with no viral relapse found after several years of follow-up [56]. The rare exceptions are cases of reinfection in patients who relapse to injection drug use [57]. A viral cure leads to resolution of hepatic inflammation. This over time leads to regression of hepatic fibrosis to little or no residual fibrosis, and such regression even occurs in patients with cirrhosis [56, 58]. Patients with advanced fibrosis or cirrhosis who achieve an SVR after therapy have a much reduced risk of developing liver failure or HCC [59, 60]. One recent cohort study of 16,800 HCV-infected patients also showed a decrease in all-cause mortality by 30%–49% in patients with SVR [61]. While the risk of developing HCC is reduced, it is not eliminated. Therefore, patients with HCV-related liver cirrhosis and SVR need to continue HCC screening for life.

HCV therapy for HCV-monoinfected patients in 2012 consists of 24 weeks of peginterferon alfa plus ribavirin for HCV genotypes 2 and 3 and 24–48 weeks of peginterferon alfa plus ribavirin plus a protease inhibitor (boceprevir or telaprevir) for genotype 1. In treatment-naïve patients, these therapies achieve SVR in 70%–80% of patients [62–64]. A detailed analysis of current and future HCV treatment modalities for both HCV-monoinfected and HIV/HCV-coinfected patients will be presented in this journal in subsequent articles of this series.

In preparation for HCV treatment, a number of factors should be discussed with the patient. The most important is timing of therapy. As a general rule, the more advanced the liver fibrosis, the more urgent is initiation of therapy, since the patient may develop liver decompensation within the near future. Once decompensated liver disease has developed, antiviral therapy is no longer recommended outside of defined experimental protocols. Thus, in patients with advanced bridging fibrosis or cirrhosis, most clinicians will advise HCV therapy within less than a year. However, in patients with less advanced fibrosis, watchful waiting is an option, in particular since newer HCV therapies with potentially fewer side effects and higher cure rates than the current 75% are on the horizon. This includes addition of 1 or more direct antiviral agents (DAAs) with better side effect profiles than the current protease inhibitors to peginterferon plus ribavirin as well as interferon-free combinations of DAAs. However, at present it is not clear when such new therapies will be approved, and this may not be until 2014 or 2015. Until then, some patients may wish to be treated with newer investigational HCV agents through a clinical trial, and for them the US government-sponsored website www.ClinicalTrials.gov lists all available hepatitis C trials with location of participating sites.

CONCLUSIONS

At the initial encounter with the HCV-infected patient, much value can be provided by giving the patient an understanding of the disease, discussing lifestyle changes, exploring treatment options, and in general giving hope that the future holds great promise for a cure in most patients. Infectious diseases physicians have been instrumental in such counseling for HIV-infected patients for the last 3 decades and are in a great position to embrace the care of HCV-infected individuals as well.

Notes

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Potential conflicts of interest. Author certifies no conflicts of interest.

The author has submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References


