# The dawn of a new era: Transforming our domestic response to hepatitis B & C

## Activity 2: Understanding the natural history of chronic HBV and HCV infections


**MODERATOR**

**David L. Thomas, MD, MPH**
Professor of Medicine
Director of Infectious Diseases
Johns Hopkins University School of Medicine
Baltimore, Maryland

**PRESENTERS**

**Adrian M. Di Bisceglie, MD, FACP**
Chairman, Department of Internal Medicine
Chief of Hepatology
Saint Louis University School of Medicine
St Louis, Missouri

**Harvey J. Alter, MD, MACP**
Associate Director of Research
Chief, Infectious Diseases Clinical Studies Section
Department of Transfusion Medicine
National Institutes of Health
Bethesda, Maryland

**Norah A. Terrault, MD, MPH**
Associate Professor of Medicine
Director of Viral Hepatitis Research in Liver Transplantation
University of California School of Medicine
San Francisco, California



**DISCLOSURES**

**Dr Thomas** has no real or apparent conflicts of interest to report.

**Dr Di Bisceglie** reports the following: Consultant: Abbott, Anadys, Bristol-Myers Squibb, GlobeImmune, Inc, Idenix, Novartis, Pharmasset, Roche Pharmaceuticals, Schering-Plough, Vertex Pharmaceuticals. Grant/Research Support: Bristol-Myers Squibb, Gilead Sciences Inc., GlobeImmune, Inc, Idenix, Pharmasset, Roche Pharmaceuticals, Vertex Pharmaceuticals. Speakers Bureau: Novartis

**Dr Alter** has no real or apparent conflicts of interest to report.

**Dr Terrault** reports the following: Consultant: Bristol-Myers Squibb, Roche Pharmaceuticals, Schering-Plough, Siemens Diagnostics. Grant/Research Support: Eisai, Human Genome Sciences, Roche Pharmaceuticals, Vertex Pharmaceuticals


The natural history of hepatitis viral infection refers to the clinical outcomes for individuals with persistent infection who do not receive antiviral treatment. Some individuals infected with hepatitis B virus (HBV) or hepatitis C virus (HCV) will spontaneously control the initial infection, typically in the first year. Those who continue to have evidence of viral replication in the form of detectable levels of hepatitis B surface antigen (HBsAg) or HCV RNA for 6 or more months are considered to have chronic infection and are at risk for cirrhosis and liver cancer. Knowing whether a patient is at risk for these clinical outcomes determines the urgency of treatment.

### Natural history of chronic HBV infection

HBV is transmitted by percutaneous or permucosal exposure to infectious blood or body fluids. HBV is approximately 100 times more infectious than human immunodeficiency virus (HIV) and 10 times more infectious than HCV.[1,2] Acute HBV infection develops in approximately 30% to 50% of adults at the time of initial infection and is characterized by anorexia, nausea, vomiting, and jaundice. The risk of progression varies with age, with the highest rate occurring among infants and young children (25%-90%) and lowest rate occurring among adolescents and adults (<5%). The majority of individuals with chronic HBV infection are asymptomatic, and one-third have no evidence of liver disease. The remainder have chronic hepatitis that can lead to cirrhosis and hepatocellular carcinoma (HCC). Rates of progression to cirrhosis and/or HCC vary according to a number of host, viral, and environmental factors.

The clinical course of chronic HBV infection has several phases that are defined by patterns of HBV DNA levels, biomarkers, and liver enzyme concentrations. The 3 main phases of chronic HBV infection are: immune tolerant, immune active, and inactive.[3] Some experts also include a resolution and a reactivation phase (**TABLE 1**).[4] All of the phases are marked by the continued presence of HBsAg, except for the resolution phase.[3,4]

The natural history of chronic HBV infection depends on when infection first occurred (**FIGURE 1**). Individuals infected as infants (typically from maternal-fetal transmission) nearly always develop chronic infection. The immune tolerant phase is usually clinically silent for years or even decades. Viral replication is active in this phase because HBsAg and high levels of HBV DNA are detectable in the blood. However, liver enzymes such as alanine aminotransferase (ALT) and aspartate aminotransferase are often

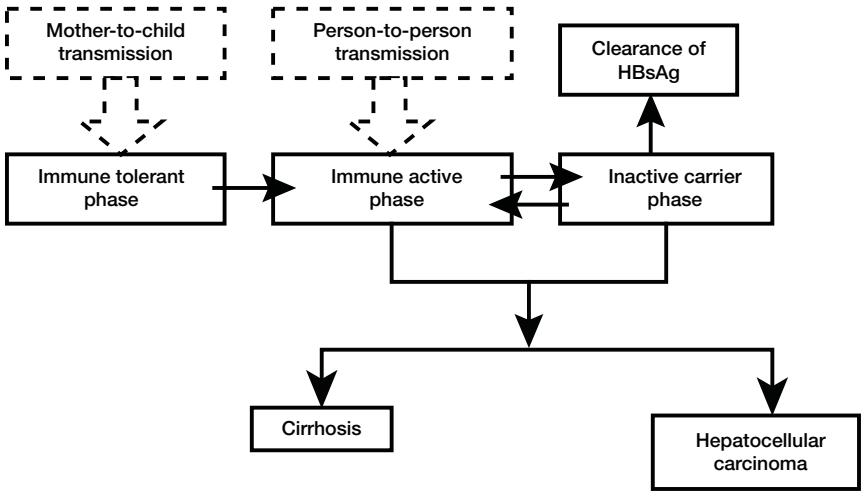
**TABLE 1** Phases of chronic HBV infection

| Phase | ALT levels | Liver histology | HBV DNA/HBeAg levels |
|---|---|---|---|
| Immune tolerant phase[a] | Normal or minimally elevated | Active or inactive minimal inflammation or fibrosis | • >20,000 IU/mL, HBeAg+ |
| Immune active phase[a] | Elevated | Active: Liver biopsy shows chronic hepatitis | • >20,000 IU/mL while HBeAg+<br>• >2000 IU/mL after loss of HBeAg and development of antibody to HBeAg |
| Inactive phase[a] | Persistently normal | Inactive: Liver biopsy shows variable, usually minimal fibrosis | • <2000 IU/mL, HBeAg– |
| Resolution[b] | Normal | Inactive: Scant fibrosis | • No detectable serum HBV DNA (low levels might be detectable in the liver)<br>• HBeAg– and HBsAg– |
| Reactivation phase[b] | Elevated, often fluctuating levels | Active: Liver biopsy showing variable amounts of fibrosis | • Moderate, often fluctuating levels >2000 IU/mL |

ALT, alanine aminotransferase; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus.

[a]McMahon BJ, et al. Hepatology. 2009;49(5 suppl):S45-S55.
[b]Keeffe EB, et al. Clin Gastroenterol Hepatol. 2008;6:1315-1341.

**FIGURE 1** Natural history of chronic HBV infection



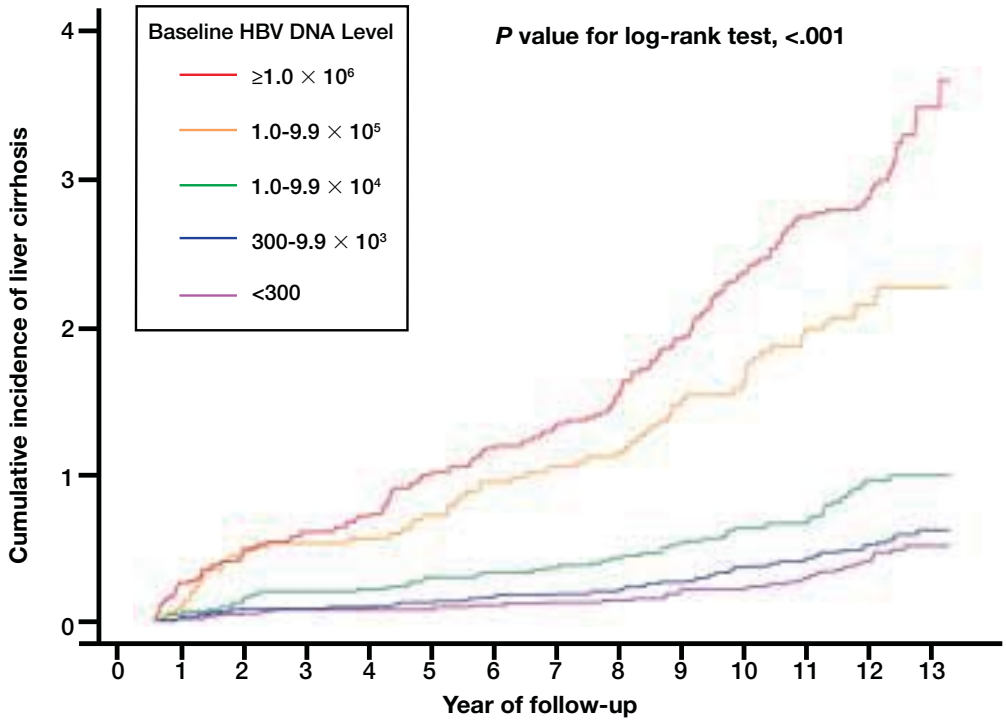

HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus.

Sorrell MF, et al. Ann Intern Med. 2009;150:104-110. © 2009 by American College of Physicians—Journals. Reproduced with permission.

not elevated, most likely because there is little cellular immunity attempting to clear the infection. This immune tolerant phase eventually progresses to an immune active phase, heralded by evidence of liver inflammation and elevations in liver enzymes.[5]

HBV infection takes a substantially different course in individuals infected for the first time as adults. Most individuals who acquire HBV infection as adults sponta-

**FIGURE 2** Cumulative incidence of liver cirrhosis




HBV, hepatitis B virus.



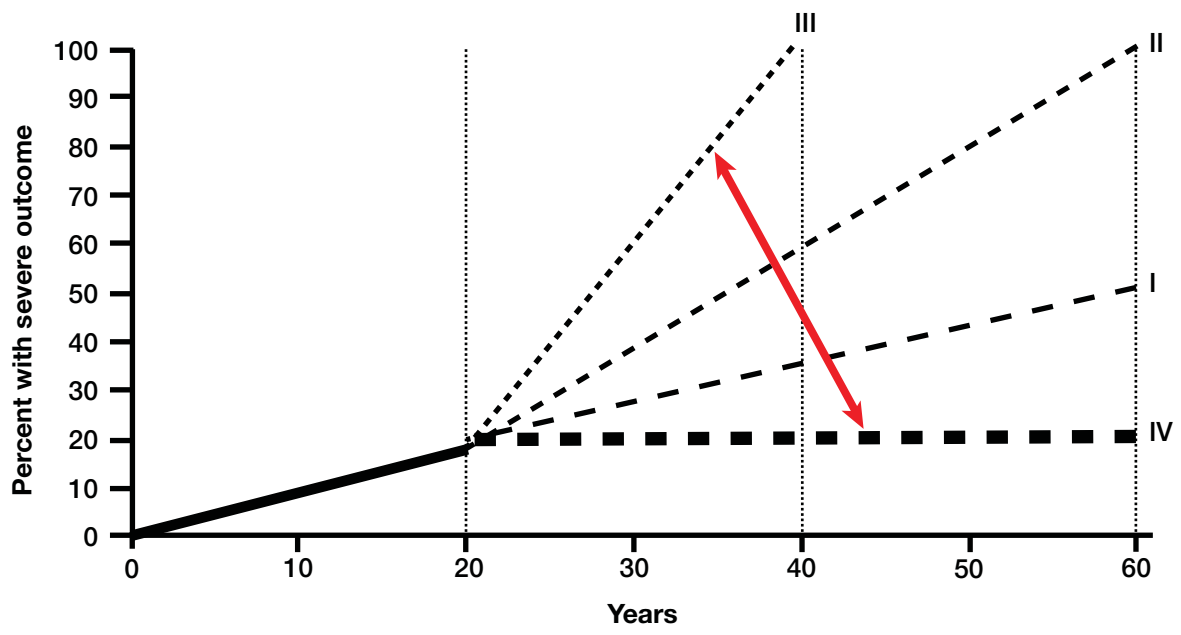
neously clear it.[5,6] In those who progress to chronic HBV infection, the initial phase is typically immune active; the liver is injured by inflammation (necroinflammation) and develops scarring that can progress to cirrhosis.

Hepatitis B e antigen (HBeAg) status has been used to classify the natural history of infection. HBeAg is detected in the immune active phase and, accordingly, has been used as a correlate of high replication and infectivity. If HBeAg is spontaneously cleared, an antibody to HBeAg (anti-HBe) can be detected. This event corresponds with a lower HBV DNA level and lower risk of HCC and cirrhosis. However, transitions occur between these phases, and while about three-fourths of HBeAg–positive adults will seroconvert (ie, become HBeAg-negative and anti-HBe–positive), a proportion will revert to HBeAg-positive status.[7,8]

In the natural course of HBV infection, transitions occur between phases.[5] Individuals in the immune active phase often clear much of the infection and move to the inactive phase. In the latter phase, liver enzymes are normal and HBV DNA levels are less than 2000 IU/mL, but HBsAg remains detectable. Individuals can then either revert to a clinically (and immunologically) active phase while they remain HBeAg-negative or clear HBsAg from their blood completely. When complete HBsAg clearance occurs, the infection will remain controlled or dormant unless it is reactivated by immunosuppression from other diseases or use of drugs such as rituximab or cancer chemotherapy.[3,5,9]

The majority of liver damage occurs during the immune active phase, and the longer an individual remains in this phase, the greater the risk of developing cirrhosis or HCC. Certain factors appear to influence the risk of developing cirrhosis, including older age, presence of HBeAg, HBV genotype C, excessive alcohol consumption, and coinfection with HIV, HCV, or hepatitis D virus.[5,10] Elevated HBV DNA levels have also been identified as a risk factor for the development of cirrhosis.[3,11]

**FIGURE 3** Projected outcomes in chronic HCV infection[a]




[a]Curve I: Observed outcomes at 20 years will continue on the same trajectory over ensuing decades.

Curves II and III: Assume acceleration of fibrosis; thus, every HCV-infected individual would develop a severe outcome if he or she does not die of another illness in the 40 to 60 years from the onset of infection.

Curve IV: Individuals who have not progressed in 20 years will not suffer deleterious outcomes.

HCV, hepatitis C virus.

Alter HJ, Seeff L. Recovery, persistence and sequelae in HCV infection: a perspective on long-term outcome. Semin Liver Dis. 2000;20:17-35. Reprinted with permission.

Chronic HBV infection can progress to HCC. Risk factors include male gender, older age, family history of HCC, alcohol consumption, HBV genotype C, seropositivity for HBsAg, seropositivity for HBeAg, presence of cirrhosis, and high serum HBV DNA levels.[3,12] In the large, prospective Risk Evaluation Viral Load Elevation and Associated Liver Disease (REVEAL) study, an elevated serum HBV DNA level (≥10,000 copies/mL) was a strong risk predictor of HCC, independent of HBeAg status, ALT level, and liver cirrhosis.[12] Investigators found that for all participants, the adjusted hazard ratio (HR) of developing HCC was 1.1 for those with serum HBV DNA levels of 300 to 9999 copies/mL ($P$=.86) and 6.1 for those with HBV DNA levels ≥1 million copies/mL ($P$<.001). Risk began to increase significantly at HBV DNA levels of 10,000 to 99,999 copies/mL (HR, 2.3; $P$=.02) relative to patients with HBV DNA levels <300 copies/mL.[12] In an analysis of the REVEAL cohort involving 3582 patients, the development of cirrhosis was highly dependent on baseline HBV DNA levels, increasing from 4.5% among patients with HBV DNA levels <300 copies/mL to 36% among those with ≥1 million copies/mL (**FIGURE 2**).[11]

## Natural history of chronic HCV infection

Since Dr Harvey Alter first characterized HCV, its natural history has been controversial owing to the great heterogeneity of this virus and the many cofactors that can influence its course and progression.[13] Our understanding of the natural history of HCV infection is still evolving.

The natural history of HCV infection involves 2 major clinical transitions: spontaneous resolution vs viral persistence and asymptomatic viral persistence vs cirrhosis. Spontaneous resolution is highly variable and occurs in approximately 10% to 60% of individuals, typically in the first 6 to 12 months of infection. This occurs more frequently in women than in men, and more frequently in

whites than in African Americans.[13,14] Chronic infection develops in 75% to 85% of individuals infected as older adults (>45 years) and 50% to 60% of those infected as adolescents or younger adults.[1,15] The majority of individuals with chronic HCV infection are asymptomatic, and approximately 30% have no evidence of liver disease. The risk for progression to cirrhosis also varies by age at infection, from 10% to 20% after 20 years of infection among those infected as older adults to <5% among individuals infected as adolescents or younger adults.[1] In addition, those without HBV infection, HIV infection, other forms of immunosuppression, or excess alcohol consumption are more likely to recover from acute HCV infection than are those who are immunocompromised or those who abuse alcohol. Complete recovery also occurs more often in individuals with particular polymorphisms in human leukocyte antigen genes and genes involved in interferon lambda production.[16,17]

The best way to determine if an individual has chronic vs resolved HCV infection is to test for both HCV-specific antibodies and for HCV RNA.[18] Individuals with spontaneous resolution of HCV infection have only HCV antibodies in their blood, while those with chronic HCV have both HCV antibodies and viral RNA. Repeated detection of HCV RNA at 6-month intervals provides strong evidence of chronic HCV infection.

Individuals who do not achieve spontaneous recovery develop chronic infection. During the first few decades after becoming infected, the majority of individuals lack clinical manifestations of HCV infection. However, some will undergo the transition to liver failure or HCC. In a recent Markov simulation of chronic HCV infection, progression from cirrhosis to HCC occurred in approximately 18% of patients after 20 years of exposure.[19] An earlier study found a slightly lower risk, with 7% of patients progressing to HCC in 5 years and 18% experiencing decompensation (ie, liver failure).[20]

Progression is neither linear nor inevitable; in the initial 2 to 3 decades postexposure, 80% of HCV-infected patients will be asymptomatic and suffer no complications. Various projected long-term outcomes are shown in **FIGURE 3**. In the absence of treatment, the natural history of HCV infection may lie between curves I and IV. In other words, about 30% of patients will experience a severe outcome after 60 years of infection.[15]

## Complications of chronic HCV infection

Laboratory clues that cirrhosis is advancing (rather than compensated) are a low serum albumin concentration, low blood platelet count, high serum creatinine level, and high total bilirubin level. These laboratory and clinical findings are used in various systems (such as the Model for End-Stage Liver Disease and Child-Pugh score) to stage cirrhosis and anticipate the need for liver transplantation.

In addition to laboratory findings, there are confounding factors that influence the rate at which chronic HCV infection progresses to cirrhosis and liver failure. The course of chronic HCV infection has been shown to be influenced by age at infection, gender, and coinfection. Rapid progression of liver fibrosis has occurred in individuals who are coinfected with HBV or HIV.[21] In one study of people with chronic HCV infection, cirrhosis developed in 37% of HIV-positive individuals after 20 years and in 69% after 25 years, compared with 10% in HIV-negative individuals at either time point.[22] Excessive alcohol intake (>60 g/d for men and >40 g/d for women) has been associated with a 2- to 3-fold greater risk of cirrhosis and decompensated liver disease and more rapid development of cirrhosis, with 58% of excessive drinkers becoming cirrhotic by the second decade vs 10% of nondrinkers.[23] Evidence suggests that nonalcoholic steatohepatitis (NASH), a severe form of fatty liver disease, may impact the disease course as well. Fibrosis was seen at a median duration of infection of 23 years in 54% of HCV-positive patients with NASH, in 32% with steatosis (fat only, with no associated inflammation), and in 16% with chronic HCV alone.[24] Males also appear to be at increased risk for fibrosis.

In individuals with chronic HCV infection, HCC rarely occurs unless there is significant liver fibrosis, defined as either cirrhosis or bridging fibrosis. The factors associated with the development of HCC in this population are essentially the same as those associated with the development of cirrhosis. Unlike chronic HBV infection, there does not appear to be a strong association between the HCV RNA level and the development of cirrhosis or HCC. ■


References

1. Weinbaum C, Lyerla R, Margolis HS; Centers for Disease Control and Prevention. Prevention and control of infections with hepatitis viruses in correctional settings. Centers for Disease Control and Prevention. MMWR Recomm Rep. 2003;52(RR-1):1-36; quiz CE31-34.
2. Weinbaum, CM, Williams I, Mast EE, et al; Centers for Disease Control and Prevention. Recommendations for identification and public health management

of persons with chronic hepatitis B virus infection. MMWR Recomm Rep. 2008;57(RR-8):1-20.
3. McMahon BJ. The natural history of chronic hepatitis B virus infection. Hepatology. 2009;49(5 suppl):S45-S55.
4. Keeffe EB, Dieterich DT, Han SH, et al. A treatment algorithm for the management of chronic hepatitis B virus infection in the United States: 2008 update. Clin Gastroenterol Hepatol. 2008;6:1315-1341; quiz 1286.
5. Sorrell MF, Belongia EA, Costa J, et al. National Institutes of Health Consensus Development Conference Statement: management of hepatitis B. Ann Intern Med. 2009;150:104-110.
6. Thio CL, Astemborski J, Bashirova A, et al. Genetic protection against hepatitis B virus conferred by CCR5Delta32: Evidence that CCR5 contributes to viral persistence. J Virol. 2007;81:441-445.
7. McMahon BJ, Holck P, Bulkow L, et al. Serologic and clinical outcomes of 1536 Alaska Natives chronically infected with hepatitis B virus. Ann Intern Med. 2001;135:759-768.
8. Hsu YS, Chien RN, Yeh CT, et al. Long-term outcome after spontaneous HBeAg seroconversion in patients with chronic hepatitis B. Hepatology. 2002;35: 1522-1527.
9. Ostuni P, Botsios C, Punzi L, et al. Hepatitis B reactivation in a chronic hepatitis B surface antigen carrier with rheumatoid arthritis treated with infliximab and low dose methotrexate. Ann Rheum Dis. 2003;62:686-687.
10. Tamura I, Kurimura O, Koda T, et al. Risk of liver cirrhosis and hepatocellular carcinoma in subjects with hepatitis B and delta virus infection: a study from Kure, Japan. J Gastroenterol Hepatol. 1993;8:433-436.
11. Iloeje UH, Yang HI, Su J, et al. Predicting cirrhosis risk based on the level of circulating hepatitis B viral load. Gastroenterology. 2006;130:678-686.
12. Chen CJ, Yang HI, Su J, et al. Risk of hepatocellular carcinoma across a biological gradient of serum hepatitis B virus DNA level. JAMA. 2006;295:65-73.
13. Alberti A, Benvegnú L. Management of hepatitis C. J Hepatol. 2003;38(suppl 1):S104-S118.
14. Thomas DL, Astemborski J, Rai RM, et al. The natural history of hepatitis C virus infection: host, viral, and environmental factors. JAMA. 2000;284:450-456.
15. Alter HJ, Seeff LB. Recovery, persistence, and sequelae in hepatitis C virus infection: a perspective on long-term outcome. Semin Liver Dis. 2000;20:17-35.
16. Khakoo SI, Thio CL, Martin MP, et al. HLA and NK cell inhibitory receptor genes in resolving hepatitis C virus infection. Science. 2004;305:872-874.
17. Thomas DL, Thio CL, Martin MP, et al. Genetic variation in IL28B and spontaneous clearance of hepatitis C virus. Nature. 2009;461:798-801.
18. Ghany MG, Strader DB, Thomas DL, et al; American Association for the Study of Liver Diseases. Diagnosis, management, and treatment of hepatitis C: an update. Hepatology. 2009;49:1335-1374.
19. Thein HH, Yi Q, Dore GJ, et al. Estimation of stage-specific fibrosis progression rates in chronic hepatitis C virus infection: a meta-analysis and meta-regression. Hepatology. 2008;48:418-431.
20. Fattovich G, Giustina G, Degos F, et al. Morbidity and mortality in compensated cirrhosis type C: a retrospective follow-up study of 384 patients. Gastroenterology. 1997;112:463-472.
21. Sulkowski MS, Mehta SH, Torbenson MS, et al. Rapid fibrosis progression among HIV/hepatitis C virus-co-infected adults. AIDS. 2007;21:2209-2216.
22. Di Martino V, Rufat P, Boyer N, et al. The influence of human immunodeficiency virus coinfection on chronic hepatitis C in injection drug users: a long-term retrospective cohort study. Hepatology. 2001;34:1193-1199.
23. Wiley TE, McCarthy M, Breidi L, et al. Impact of alcohol on the histological and clinical progression of hepatitis C infection. Hepatology. 1998;28:805-809.
24. Bedossa P, Moucari R, Chelbi E, et al. Evidence for a role of nonalcoholic steatohepatitis in hepatitis C: a prospective study. Hepatology. 2007;46: 380-387.