

## II. Natural History of Hepatitis C

### Summary

The ultimate outcome of infection with hepatitis C can vary dramatically. While some people will clear the virus at the outset, others will develop a chronic infection that, over years and decades, may remain benign, progress in severity, or turn deadly. In chronically infected persons, the disease usually advances very slowly but in rare cases can prove fatal within a few years. One individual may sustain only mild-to-moderate liver scarring after twenty years, while another during that time will develop serious liver damage, such as cirrhosis (severely scarred liver tissue), hepatocellular carcinoma (HCC; liver cancer), or hepatic decompensation (liver failure).

Most people are asymptomatic during acute HCV infection. When symptoms develop, they appear approximately six weeks after exposure to HCV and can be described as flu-like, with the exception of jaundice (Koretz 1993). These symptoms resolve a few weeks after their onset. In very rare instances, acute HCV infection has caused fulminant hepatitis (sudden and severe; often liver failure is involved) (Chu 1999; Farci 1996).

Not everyone with acute hepatitis C infection develops chronic HCV infection. Studies show that a wide range—15% to 45%—of acutely infected people develop antibodies to hepatitis C, but do not progress to chronic HCV infection (Alberti 1999; M. J. Alter 1992; M. J. Alter 2002; Gerlach 2003; Kenny-Walsh 1999; Seeff 2000). Viral clearance is the spontaneous elimination of hepatitis C virus from the bloodstream, although evidence of previous infection—antibodies to hepatitis C—usually remains. Viral clearance may be partially attributed to a combination of viral factors and host factors such as age, sex, race, history of a prior cleared hepatitis C infection, and HIV status.

For the 55% to 85% of individuals who do not achieve spontaneous viral clearance, hepatitis C infection is diagnosed as chronic when HCV-antibody testing is positive and HCV RNA (viral load) is detectable on at least two occasions over a six month period. Most people with chronic HCV infections remain asymptomatic for years, although some individuals will experience fatigue, depression, and other extrahepatic manifestations of hepatitis C infection. Not all chronically infected people will develop liver damage; if liver damage does develop, it may take from 10 to 50 years to do so. No clinical, serologic, or virologic feature—such as the HCV viral load, liver enzyme level, or HCV genotype (the particular strain of the hepatitis C virus)—can reliably forecast the outcome of untreated HCV infection, although some prognostic factors have been identified.

The clinical complications of hepatitis C may include fibrosis (mild scarring of liver tissue), cirrhosis and hepatocellular carcinoma. Fibrosis may be accelerated by several factors, including older age (>40 years) at infection, moderate-to-heavy alcohol consumption, male sex, concomitant hepatitis B infection, and coinfection with HIV. Fibrosis progression may be more rapid in individuals who were infected with hepatitis C from transfusions (S. C. Gordon 1998).

Some individuals who have been diagnosed with compensated cirrhosis (severe liver scarring without clinical complications; the liver is still functioning) will remain stable for years. Others develop hepatic decompensation or hepatocellular carcinoma. An estimated 1–4% of cirrhotics per year will develop hepatocellular carcinoma.

Liver transplantation is the only intervention for hepatic decompensation. Hepatitis C-related liver damage is the leading indication for liver transplantation in the United States (CDC 1998). Between 10,000 and 12,000 deaths each year are attributed to hepatitis C-related hepatocellular carcinoma and end-stage liver disease.

Many studies have tracked the natural history of hepatitis C infection. Although much has been learned about what can take place during the first 20 years of infection with hepatitis C virus—prognostic factors have been identified and disease progression models developed—outcomes after the second decade of infection remain largely uncharted. To date, only one small (n=17) study has evaluated outcomes 45 years postinfection (Seeff 2000). Yet, despite the lack of longer-term data, observations from several existing natural history studies can illuminate the risk and rate of disease progression.

### **Acute HCV Infection**

The acute stage of hepatitis C infection remains clinically silent for most infected people, with only 15% to 20% of individuals developing symptoms (Koretz 1993). When they occur, symptoms such as low-grade fever, fatigue, appetite loss, abdominal pain, nausea, and vomiting usually appear during the sixth or seventh week after infection and resolve within a few weeks (CDC 1998; Koretz 1993). Jaundice, a classic sign of hepatitis, appears in only 15% to 20% of acutely infected individuals (Marcellin 1999; Villano 1999); yet, in rare instances, fulminant hepatitis may develop during acute HCV infection, leading to liver failure and death (Farci 1996). The risk of developing fulminant hepatic failure during acute HCV infection may be increased in those with concomitant chronic hepatitis B infection (Chu 1999).

Study of the course of acute HCV infection has proven to be extremely difficult for several reasons. To begin with, identification of people with acute hepatitis C is challenging, since many individuals do not have symptoms or, when they do, they are easily mistaken for those of other common viral infections. Moreover, there is no specific test that will distinguish acute stage hepatitis C from chronic hepatitis C infection (see Chapter V, Diagnostics).

Hepatitis C infection is often not suspected in the clinic. One study reported that health care providers recognized none of 32 acute HCV infections during routine visits among a group of injection drug users (Villano 1999). Prospective studies have been performed in relatively homogenous populations. Although these studies have provided important insights, their relevance may be limited.

It is well established that not all acutely infected people will develop chronic HCV infection, although it is far from clear how many are spared. Published studies suggest that the likelihood of spontaneously clearing hepatitis C ranges broadly, from 15% to 45% (Alberti 1999; M. J. Alter 1992; M. J. Alter 2002; Gerlach 2003; Kenny-Walsh 1999; Seeff 2000). Viral clearance or resolved hepatitis C infection is usually recognized by the presence in the blood of antibodies to HCV and the absence, at least twice, of HCV genetic material (RNA).

The determinants of HCV clearance are multifactorial. There is evidence that the younger a

person is at the time of HCV infection, the less likely they are to become chronically infected. Seventeen years after a cohort of 67 children had been infected with hepatitis C from blood transfusions during cardiac surgery, Vogt and colleagues found that only 37 of them (55%) had detectable HCV RNA. In another study of viral clearance of nosocomially acquired (an infection originating in the hospital) acute HCV, Larghi and colleagues followed 14 people, aged 21 to 45. Seven spontaneously recovered within 13 months of infection, and at month 24, an eighth person cleared HCV infection, reflecting a clearance rate of 57% (Larghi 2002).

Symptomatic individuals appear to be far more likely to achieve spontaneous viral clearance of hepatitis C than asymptomatic persons (Gerlach 2003; Ross 2004; Villano 1999). Gerlach and colleagues identified 60 individuals with acute hepatitis C between January 1993 and August 2000. They reported that all 24 (52%) who achieved spontaneous viral clearance were symptomatic, while none of nine asymptomatic persons cleared their HCV infections ( $P=0.007$  for symptoms vs. no symptoms). With the exception of sex (women were more likely to clear HCV than men;  $P=0.034$ ), there were no significant differences in age, mode of acquisition, HCV genotype or viral load between those who achieved spontaneous viral clearance and those who developed chronic HCV.

Young women may have a high likelihood of clearing hepatitis C infection (Kenny-Walsh 1999; Koretz 1992; Wiese 2000). Seventeen years after a cohort of 704 young Irish women were exposed to hepatitis C from contaminated anti-D immunoglobulin, only 390 (55%) had detectable HCV RNA (Kenny-Walsh 1999). The remaining 45% were HCV-antibody-positive, but had no detectable viremia. Wiese and colleagues observed similar rates of viral clearance among young women in another cohort ( $n=917$ ) exposed to contaminated anti-D immunoglobulin. Of the 85% (779/917) with antibodies to hepatitis C, only 55% (428/779) had detectable HCV RNA (Wiese 2000).

Two studies have reported a decreased likelihood of spontaneous viral clearance among African Americans. Villano and colleagues recruited 142 HIV-negative members from the AIDS Linked to the Intravenous Experience (ALIVE) cohort in Baltimore (a group of 2,921 current and former injection drug users, enrolled between 1988 and 1989) and subsequently characterized 43 cases of acute HCV infection, 28 (65%) among African Americans. Participants were tested repeatedly for HCV RNA over a median follow-up period of 72 months. Spontaneous viral clearance occurred in 6 of 43 (14%) individuals, 4 of whom (67%) were white. Those who cleared their HCV infection were more likely to be white ( $P=0.004$ ), to have experienced jaundice ( $P=0.03$ ), and to have a lower peak viral load ( $P=0.003$ ) (Villano 1999). Thomas and colleagues also observed less frequent viral clearance among African Americans during observation of a cohort of 919 HCV-antibody-positive injection drug users, 729 of whom were African-American. At least five serum samples were collected from each participant over a period of 61 to 92 months, and HCV RNA testing was performed repeatedly to identify individuals who had cleared HCV. Viremia was persistent in 812 individuals, while 90 individuals achieved spontaneous clearance of HCV. Only 9% (10/90) of the individuals who achieved spontaneous viral clearance were African-American (Thomas 2000a).

The risk for developing chronic hepatitis C infection is dependent on the size of the viral inoculum at the time of exposure. Transfusion recipients appear to have a greater risk for developing chronic hepatitis C than individuals with other sources of infection (Alberti 2002).

It is possible to become re-infected with hepatitis C, or to have a mixed infection (identified by the presence of two or more genotypes of HCV). Cases of re-infection with HCV and HCV superinfection have been documented among hemophiliacs, injection drug users, and HCV-infected individuals with documented, nosocomially acquired re-infection (Accapezzato 2002; Jarvis 1994; Proust 2000). This indicates that neither having a prior, resolved infection nor possessing antibodies to HCV confers full protection against a subsequent HCV infection; however, some evidence suggests that having had a prior resolved infection may increase the chances of clearing a new HCV infection.

Mehta and colleagues studied a cohort of 1,344 injection drug users, identifying two sub-groups. One group of 98 individuals had evidence of previous, resolved HCV infection (antibody-positive, but undetectable HCV RNA on two occasions). The other group of 164 had no evidence of exposure to HCV. After a median follow-up of more than two years, 12% (12/98) of previously infected participants were newly infected with HCV. Among the group with no evidence of prior exposure, 21% (35/164) became infected with HCV, although this difference was not statistically significant. In a multivariate analysis, people with a previous, cleared HCV infection were 12 times less likely to develop chronic HCV infection (OR, 0.08; 95% CI, 0.01–0.46; P=0.02) (Mehta 2002).

Aitken and colleagues reported on evidence suggestive of immunity to hepatitis C in a cohort of 198 Australian injection drug users. Each IDU in the study referred up to ten others that they had injected with to investigators. All study participants were interviewed about their drug use, and provided a blood sample for HCV testing. Antibodies to HCV were detected in 86.9% (172/198), and HCV infection was confirmed by testing for HCV-RNA; 69.7% (138/198) had detectable HCV RNA.

Despite the probability of multiple exposures to HCV, 10.6% (21/198) had no evidence of HCV infection (antibodies or HCV-RNA). Five of them had been injecting drugs for at least nine years; their median duration of injection drug use was eleven years. During the preceding six months, all five reported sharing injection equipment (including spoons, water, filters and drug solutions) with another study participant who had HCV. Two of the five had injected with a needle previously used by a person with HCV infection (Aitken 2004). The authors speculate that these injectors possessed an inherent or acquired immunity to HCV infection.

## **Chronic Hepatitis C Virus Infection**

### **Symptoms of Hepatitis C**

While some people with chronic hepatitis C infection are asymptomatic, others may suffer from a constellation of symptoms. Fatigue, arthralgia (joint pain), myalgia (muscle pain), and depression are the most commonly reported symptoms of chronic hepatitis C; however, the relationship between the presence of symptoms and the severity of HCV disease is unclear (Barkhuizen 1999; Goh 1999; Kenny-Walsh 1999).

Fatigue and musculoskeletal pain are characteristic symptoms of liver disease, especially chronic hepatitis C. Barkhuizen and colleagues reviewed the charts of 239 hepatology outpatients,

comparing the incidence of fatigue and musculoskeletal pain among individuals with HCV infection, individuals with HBV infection and individuals with alcoholic liver disease. Significant associations between HCV infection and musculoskeletal pain ( $P=0.0001$ ) and fatigue ( $P=0.001$ ) were identified, with 81% of the HCV-infected participants reporting musculoskeletal pain as compared to 56% of those with other liver diseases. Fatigue was reported by 66% of HCV-infected individuals, 30% of those with alcoholic liver disease, and 29% of individuals with hepatitis B infection. No associations were identified between musculoskeletal pain and the extent of liver disease, aminotransferase levels, or mode of acquisition.

There is some evidence that hepatitis C-related fatigue may be linked with psychological factors. During psychiatric interviews with 50 people with chronic HCV, Dwight and colleagues found fatigue to be more closely related to the degree of depression than to the severity of liver disease (Dwight 2000). An Australian study of 115 HCV-infected liver clinic patients also found a strong correlation between fatigue and the psychological realms of depression, anxiety, somatization, interpersonal sensitivity, and hostility (McDonald 2002). In another study, the fatigue reported by 53% of 1,614 HCV-infected individuals was independently associated with depression (Poynard 2002a). Obhrai and colleagues evaluated fatigue and psychological disturbances in the following five patient groups: chronic HCV infection, chronic HCV infection with chronic alcohol abuse, alcoholic liver disease, chronic nonliver diseases, and healthy controls. This study identified HCV-related fatigue as more severe and intractable than fatigue related to the other conditions. In addition, those with chronic HCV were more depressed and experience more feelings of anger and hostility than those with other, nonliver-related chronic diseases (Obhrai 2001).

The interpretation of rates of depression among people with chronic hepatitis C, however, is typically complicated by a lack of comparison with similar populations. For example, injection drug users experience high rates of preexisting depression and mental illness; HIV infection has also been independently associated with high rates of depression (Brienza 2000; J. G. Johnson 1999). Psychiatric disorders including depression, post-traumatic stress disorder, and anxiety are common in veterans with hepatitis C (el-Serag 2002; Lehman 2002; Muir 2002; Yovtcheva 2001). Therefore, injection drug use history, military service, and HIV coinfection present potentially confounding variables in examining the contribution of HCV infection to depression.

### **Extrahepatic Manifestations of Hepatitis C**

There are several extrahepatic manifestations of chronic hepatitis C infection, the majority of which take the form of immunologic disorders.

**Table 1. Some Extrahepatic Manifestations of Chronic Hepatitis C Infection**

Name of condition	Symptoms
Keratoconjunctivitis sicca	Dryness of the mucous membrane lining the eyelids and outer eye surface due to insufficient secretion of tears.
Lichen planus	Flat, itchy patches of skin, usually found on the wrists, shins, lower back, genitalia and sometimes, the scalp, where it can lead to hair loss.
Glomerulonephritis	Inflammation of the kidney's tiny blood vessels used for filtering waste.
Essential mixed cryoglobulinemia	Abnormal proteins in the blood that can cause blood to thicken and blood vessels to become inflamed; essential mixed cryoglobulinemia involves a mixture of different antibodies that can cause joint pain and swelling, spleen enlargement, and nerve, kidney and heart disease.
Sjögren's syndrome	Keratoconjunctivitis combined with inflammation of the joints and mouth dryness.
Porphyria cutanea tarda	Photosensitivity resulting in blisters and ulcerations of the skin in areas commonly exposed to sunlight, such as the face, ears and the backs of the hands. The skin in these areas may become fragile, with excessive pigmentation and excess hair.

Extrahepatic manifestations include keratoconjunctivitis sicca, lichen planus, glomerulonephritis, and essential mixed cryoglobulinemia. Between 42% and 70% of cryoglobulemic individuals are infected with hepatitis C (R. J. Johnson 1993). Kayali and colleagues did a meta-analysis of data on cryoglobulinemia and liver disease; their analysis suggests that the presence of cryoglobulins may be a prognostic indicator for increased risk of cirrhosis, although referral bias may have been a factor in their findings. Cryoglobulinemia can be treated with drugs that decrease inflammation and suppress the immune system or, in extreme cases, by plasmapheresis (removal of antibody-containing fluids from the blood). Successful HCV treatment (when virus is undetectable six months after completion of treatment) may decrease or eliminate symptoms of cryoglobulinemia. Some HCV-infected persons with long-term cryoglobulinemia appear to be at risk for developing B-cell non-Hodgkin lymphoma (Di Bisceglie 1998); however, hepatitis C infection has also been associated with the development of non-Hodgkin's B-cell lymphoma in the absence of cryoglobulin production (Silvestri 1997). The mechanism involved in HCV-associated lymphoma is unknown (Zuckerman 2002).

Keratoconjunctivitis combined with inflammation of the joints and mouth dryness is called Sjögren's syndrome. An association between chronic HCV and Sjögren's syndrome has been reported (Haddad 1992; Pawlotsky 1994). Sjögren's syndrome, an immunologic disorder, involves the progressive destruction of sweat, saliva, and tear glands (exocrine glands).

Porphyria cutanea tarda (PCT) is another complication of HCV infection. It is not clear if hepatitis C itself causes PCT, or if the damage HCV does to the liver results in PCT (Di Bisceglie 1998). PCT can be treated by the periodic removal of blood to reduce the iron level; medication; or successful treatment of the underlying HCV infection.

Autoimmune thyroid dysfunction, a cluster of conditions in which the immune system can either attack or stimulate thyroid tissue, has been associated with HCV infection (Hadziyannis 1997; Rocco 2001; Tran 1993). The prevalence of thyroid autoantibodies in persons with HCV infection ranges from 4.6% to 15% (Broussolle 1999). Among people infected with HCV, as in the general population, thyroid autoimmune dysfunction is more common among females (Broussolle 1999; Ganne-Carrie 2000; Huang 1999; Rocco 2001).

Hepatitis C infection may be a factor in the development of diabetes. An analysis of the data from the Third National Health and Nutrition Examination Study (NHANES III) found anti-HCV-positive people 40 years of age or older were over three times more likely to have type 2 diabetes than those without HCV infection (Mehta 2000). In a retrospective analysis of 1,117 individuals with chronic viral hepatitis (including hepatitis B infection), Mason and colleagues diagnosed diabetes in 21% of those with HCV as compared to 12% of those with hepatitis B ( $P=0.0004$ ). A multivariate analysis found that hepatitis C infection ( $P=0.02$ ) and age ( $P=0.01$ ) were independent predictors of diabetes.

“Brain fog” (confusion and impaired memory) has been reported by many people with HCV. One study compared 27 individuals with detectable HCV RNA and no biopsy-proven evidence of serious liver damage with 16 individuals who had cleared HCV by administering a computer-based assessment instrument to measure cognitive function. Those with chronic HCV demonstrated greater cognitive impairment than those who had cleared HCV, even after controlling for depression, fatigue, injection drug use history, and severity of symptoms. In an attempt to identify a potential biological basis for cognitive impairment in chronic HCV infection, the researchers also looked at choline/creatine ratios using proton magnetic-resonance spectroscopy (MRS) in a subgroup of 17 persons infected with HCV. The choline/creatine ratio was higher in individuals assessed with cognitive impairment than in unimpaired participants, which suggests an underlying mechanism for the cognitive abnormalities reported in people with HCV (Forton 2002). In another study examining choline/creatine ratios, 30 HCV-infected persons with mild liver inflammation as confirmed by liver biopsy, 29 HCV-negative controls, and 12 people with chronic hepatitis B infection, underwent MRS. Significantly higher ratios of choline/creatine were found in the white matter ( $P=0.001$ ) and basal ganglia ( $P=0.01$ ) of the HCV-infected group as compared to the negative controls or the hepatitis B group ( $P=0.009$  and  $P=0.02$ ) (Forton 2001).

HCV was found in the cerebrospinal fluid of 8 of 13 individuals with chronic HCV infection (Laskus 2002a). As further support for the direct effect of HCV on the brain, the same group reported evidence of HCV replication in autopsied brain tissue from samples of 3 out of 6 individuals (Laskus 2002b). More research is needed to illuminate potential mechanisms of “brain fog” and identify possible interventions.

### **Liver Damage: Fibrosis and Cirrhosis**

The liver is involved with processing nutrients, hormones, and medications, filtering waste and toxins, producing bile, proteins, and other substances and controlling the amount of sugar, fat, and protein that enter the bloodstream. The damage that HCV does to the liver results in scarred liver tissue. Mild liver scarring, known as fibrosis, often develops without any notable symptoms. There are different grades of fibrosis (see Chapter IV, Diagnostics), reflecting mild to severe liver

damage. Serious liver scarring, or cirrhosis, can obstruct the flow of blood through the liver and damage the actual structure of the liver itself. As liver tissue becomes scarred, liver functioning slows down.

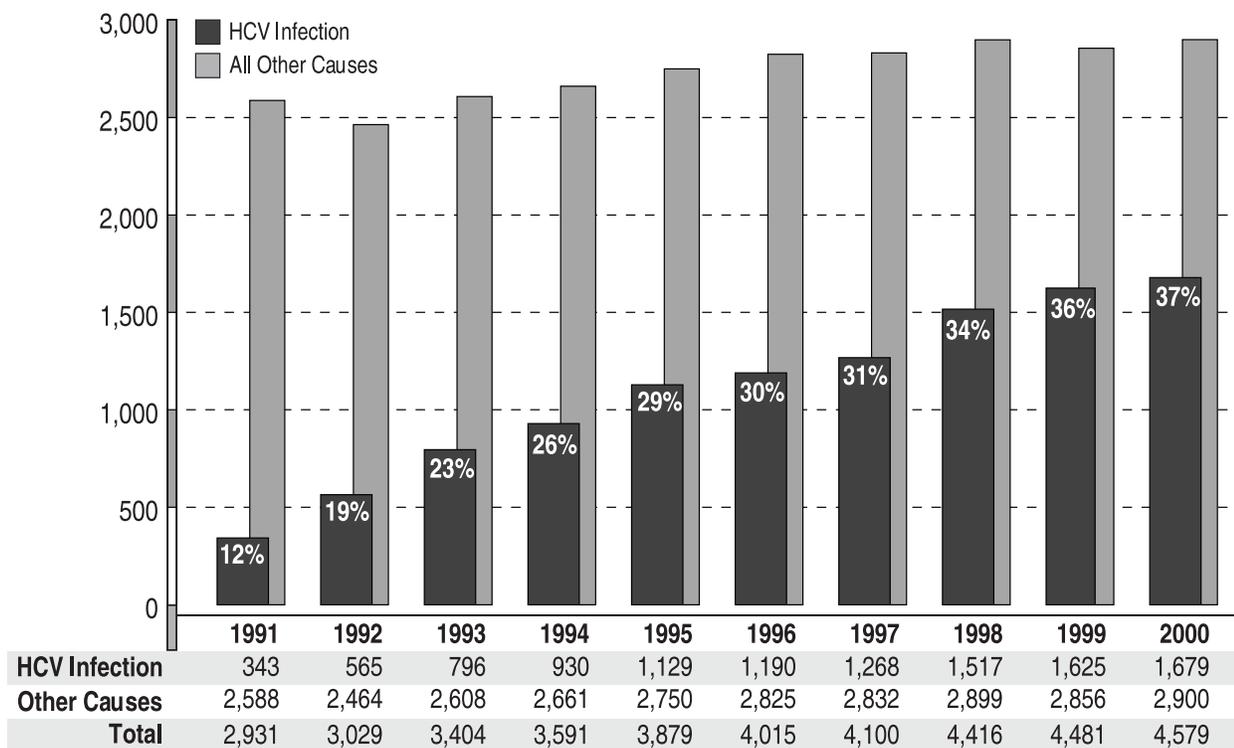
Some experts believe that fibrosis will steadily and inevitably progress to cirrhosis over time; others think that the degree of liver inflammation plays a crucial role in determining the risk of progressive liver injury. Individuals with more advanced fibrosis were found to have a more rapid progression to cirrhosis by Yano and colleagues. Initial biopsy samples from 70 Japanese HCV-infected individuals grouped as stage A (little or no portal fibrosis; less than or equal to liver damage staged as 1.9; and liver disease activity graded as less than or equal to 3.4), stage B (portal/periportal fibrosis with or without portal-bridging fibrosis; liver damage staged as 2.0–2.9; liver disease activity graded as 3.5–4.9), and stage C (septal fibrosis with regions of incomplete nodular regeneration; liver damage staged as 3.0–3.45; liver disease activity graded as greater than or equal to 5.0).

Every individual with stage C liver disease became cirrhotic within five to ten years of their initial biopsy. After 17 years of follow-up, 96% of participants with stage B liver disease developed cirrhosis. Of the stage A group, only 30% progressed to cirrhosis within 13 years of initial biopsy. It is worth noting that much higher rates of HCV-related cirrhosis and hepatocellular carcinoma have been seen in Japan than in the United States (Di Bisceglie 1997; Ikeda 1993; Ikeda 1998; Seeff 1997; Takahashi 1993; Yano 1996).

Cirrhosis can be asymptomatic at first, but symptoms often occur as liver damage increases. Early symptoms of cirrhosis can include fatigue, muscle weakness, loss of appetite, nausea, and weight loss. Some individuals experience loss of sexual desire, amenorrhea (menstrual irregularities), impotence, and breast enlargement (in men). A damaged liver is not able to process medications quickly, so drug levels may accumulate to higher-than-needed levels in the bloodstream, increasing side effects and toxicities. As liver function decreases, more symptoms may occur: edema (fluid retention in the ankles and legs) and ascites (fluid buildup in the abdomen), spontaneous bacterial peritonitis (infected ascites), more frequent bruising and bleeding, visible spider-like blood vessels, jaundice, dark urine, gallstones, and itching.

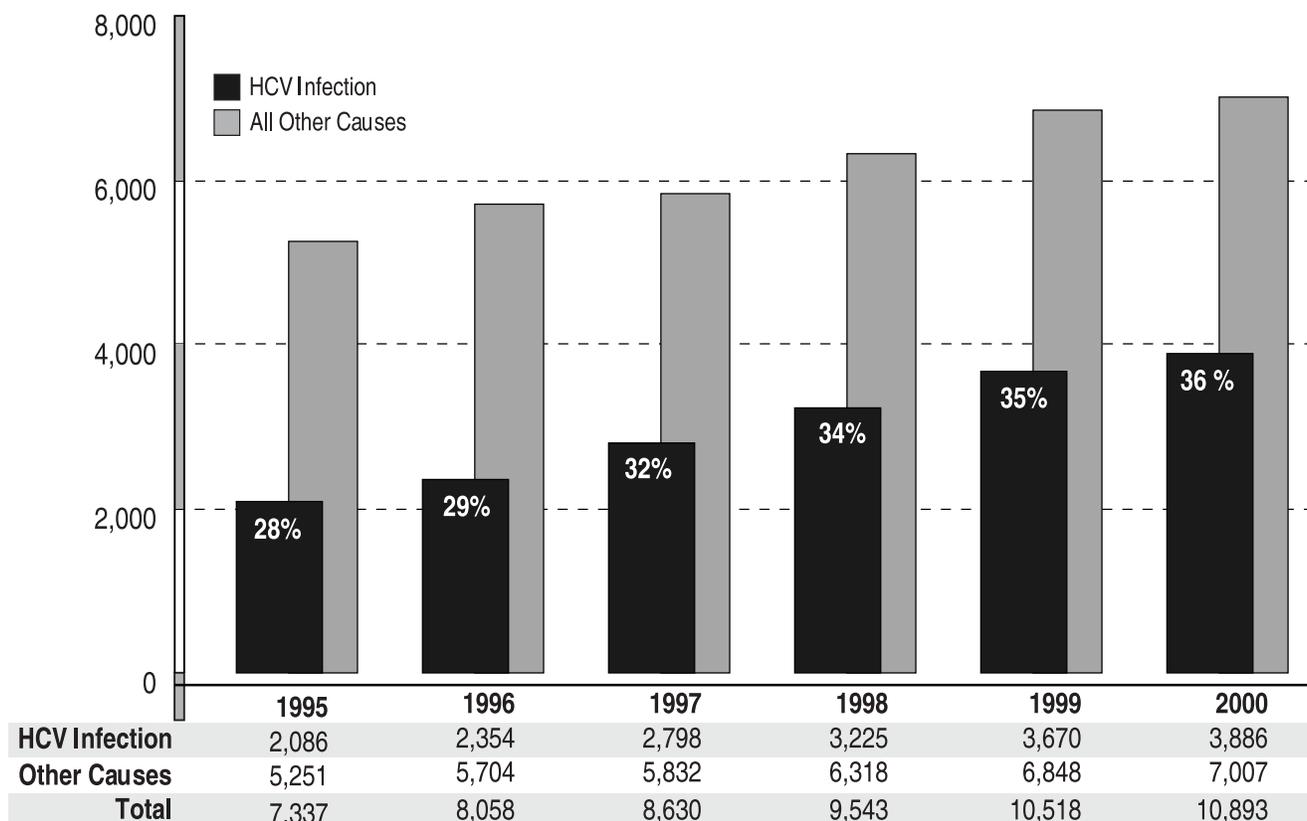
The most serious complications of cirrhosis are varices (development of abnormal veins, which can rupture and cause life-threatening internal bleeding if untreated) and hepatic encephalopathy (toxic build-up in the blood that can enter the brain and result in mental confusion and coma). People with advanced cirrhosis are at risk of hepatic decompensation (liver failure). The only intervention for hepatic decompensation is liver transplantation.

**Figure 1. Number of Liver Transplants in the United State**



Kim 2002b

**Figure 2. Number of Individuals Registered to Liver Transplant Waiting List**



Kim 2002b

## **Hepatocellular Carcinoma (HCC)**

The United States incidence of hepatocellular carcinoma (HCC) in the general population has increased from 1.4 cases per 100,000 between 1976 and 1980, to 2.4 cases per 100,000 during the period between 1991 and 1995 (El-Serag 1999). Since HCC is a known complication of hepatitis C, this rise may be attributable in part to the increased incidence of hepatitis C infection that began decades earlier. Given what we know about the slow progressive liver damage associated with HCV infection, significant numbers of persons infected with HCV during the 1960s and 1970s may have developed hepatocellular carcinoma by the 1980s and 1990s.

The incidence of HCC in the United States reflects the demographics of U.S. hepatitis C infections, where incidence of hepatitis C is higher among African Americans than Whites (3.2% of African Americans as compared with 1.5% of Whites) (M. J. Alter 1999). From 1991 until 1995, the incidence of HCC among African-American males was 6.1 per 100,000; HCC incidence among white males was 2.8 per 100,000. Currently, annual incidence of HCC in hepatitis-C-infected cirrhotics ranges from 1% to 4% (Di Bisceglie 1997; Lauer 2001). Mortality from hepatocellular carcinoma is extremely high, with five-year survival rates of less than 5% (El-Serag 1999).

Although chronic hepatitis C infection causes inflammation, cell injury, and increased turnover of hepatocytes (liver cells)—processes that have also been associated with the pathogenesis of HCC—the specific mechanism by which HCV promotes hepatocellular carcinoma is unknown. Several prognostic factors have been identified, including the presence of cirrhosis, older age, and hepatitis B coinfection. In hepatitis C infection, HCC is almost always preceded by cirrhosis; therefore, cirrhotics are at an increased risk of hepatocellular carcinoma (Colombo 1991; Di Bisceglie 1997; Macías Rodriguez 2000; Tong 2001; Tsukuma 1993). Because alcohol consumption can accelerate HCV disease progression and increase the risk of cirrhosis, alcohol consumption may also indirectly increase the risk of HCC (Schiff 1997).

Aging has been associated with increased risk for HCC, although it is not clear whether this is a function of age itself, duration of infection, or a combination of the two (Aizawa 1999; Ikeda 1993). Two studies of HCV disease progression—one tracking hemophiliacs, the other transfusion recipients—found that an older age at time of infection increased the likelihood of developing HCC (Murakami 1999; Tradati 1998); another study of HCV-infected cirrhotics identified age as the main risk factor for development of HCC, with the relative risk of HCC increasing by 8% per year (Macías Rodriguez 2000). Chiaramonte and colleagues found a 4.5-fold increase in HCC risk among cirrhotic persons over 50 years of age (Chiaramonte 1999). In a longitudinal observational study of 967 cirrhotics, age was the only risk factor for HCC identified by a multivariate analysis (del Olmo 1998).

The risk of HCC is higher in people who are infected with both hepatitis C and hepatitis B (Alberti 1995; Benvegnù 1994; Chiaramonte 1999). Tsai and colleagues reported the annual incidence of HCC during a follow-up of 1185 person-years in four groups of cirrhotics distinguished by type of infection (total n=400). They found annual HCC incidences of 2.0% in those with no viral infection, 6.6% in persons with HBV alone, 7.0% among individuals with HCV alone, and a startling 13.3% in HCV/HBV-coinfected persons (Tsai 1997).

Male sex may be associated with the risk of developing HCC, but some controversy remains about this. Although some research has found an increased risk for HCC in hepatitis C-infected cirrhotic males, other research has found no statistically significant differences according to sex (Chiaromonte 1999; del Olmo 1998; Miyakawa 1996; Tsukuma 1993). In the United States, the incidence of HCC (from all causes) among males is three times higher than among females (El-Serag 1999). This discrepancy may simply reflect higher rates of HCV infection among males (2.5% as compared with 1.2% for females) (M. J. Alter 1999).

## **Factors That May Accelerate Hepatitis C Disease Progression**

### **HIV Coinfection**

See Chapter III, Natural History of HIV/HCV Coinfection.

### **Superinfection with Hepatitis A and/or Hepatitis B**

Individuals who are infected with hepatitis C are at risk for severe, potentially fatal disease if they become superinfected with hepatitis A (Koff 2001; Pramoolsinsap 1999; Vento 1998; Vento 2000). Superinfection with hepatitis B may accelerate progression of an existing hepatitis C infection or cause liver failure and death (Koff 2001; Liaw 2000); therefore, the Centers for Disease Control recommends that all individuals who are infected with, or at risk for, HCV infection be vaccinated to protect against infection with HAV and HBV if they are susceptible to these infections.

There is evidence of decreased immunogenicity of HBV vaccination in individuals with chronic HCV. Researchers have observed significantly reduced responses to HBV vaccination in individuals with chronic HCV. One study identified the main predictor of response to HBV vaccination as the absence of antibodies to HCV (OR, 7.65;  $P < 0.0001$ ) (Leroy 2002). Wiedman and colleagues observed non-response to HBV vaccination among 31% (18/59) of those with HCV, vs. 9% (5/58) of uninfected controls ( $P < 0.005$ ). Response rates increased after a high-dose booster (40  $\mu\text{g}$ ) of recombinant hepatitis B vaccine, with 12 of 15 previous non-responders achieving seroconversion (development of antibodies) (Wiedman 2000). Another strategy for enhancing HBV vaccine immunogenicity is short-course, high-dose vaccination with 40  $\mu\text{g}$  per month for three months—with an 80  $\mu\text{g}$  booster at month four for non-responders. This elicited response rates from 72% (109/152) of those with chronic hepatitis C vs. 92% (24/26) of HCV-negative controls (Idilman 2002).

Although persons with chronic hepatitis C seroconvert after HAV vaccination, their response to HAV vaccination may be less durable than those reported in HCV-negative persons. Keefe and colleagues reported that seroconversion after HAV vaccination occurred at a similar rate among controls and individuals with chronic hepatitis C (98.2% in controls vs. 94.3% in persons with chronic hepatitis C). Another measure of vaccine-induced immunogenicity (the geometric mean concentration of antibodies to HAV) was significantly lower in persons with chronic HCV than in negative controls (467 vs. 1315 among controls;  $P = 0.0001$ ) (Keefe 1998). Anti-HAV antibody

levels of at least 20 MIU/mL confer protection against infection with HAV (Bovier 2002). The higher the anti-HAV level after vaccination, the more durable the response to vaccination will be (Totos 1997). In a group of 120 HCV-negative individuals, the geometric mean concentration level of anti-HAV at 5<sup>1</sup>/<sub>2</sub> years after HAV vaccination was 522, and the average decrease in anti-HAV was 15–20% (Van Herck 2001).

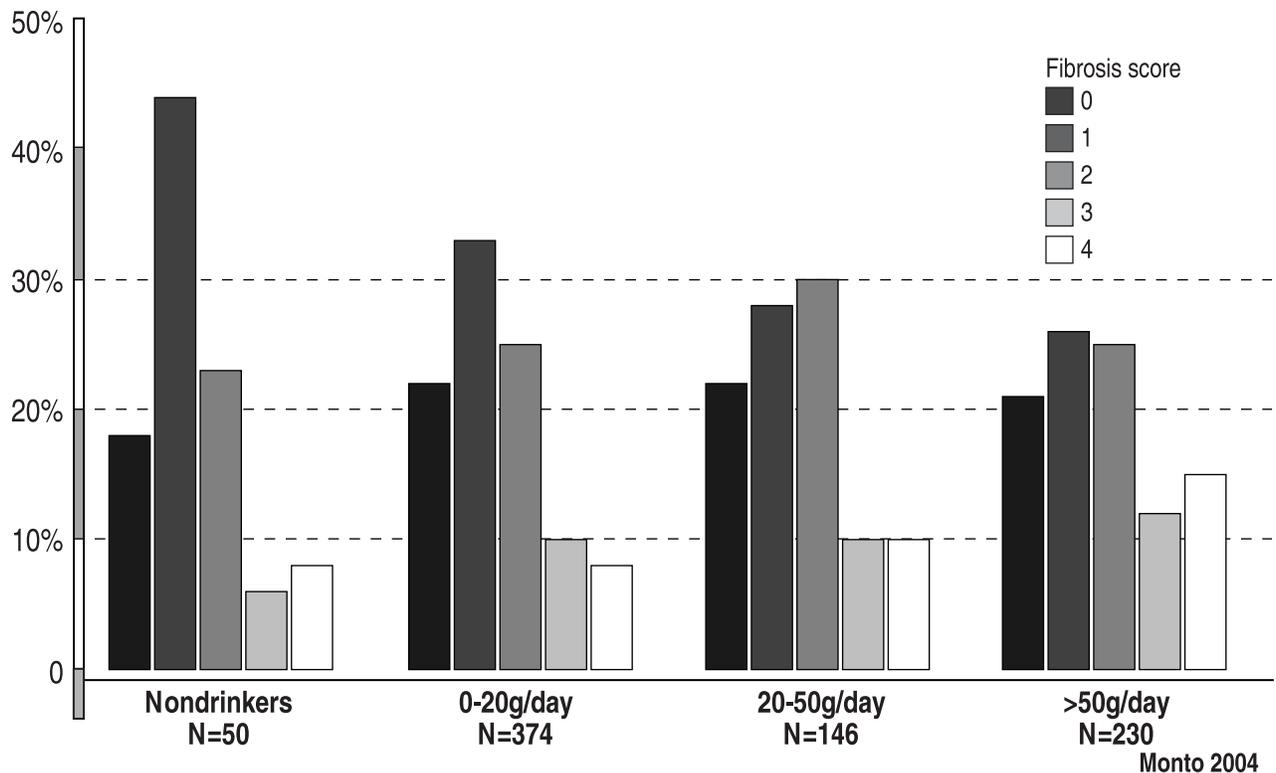
### **Alcohol Consumption**

A large body of data has confirmed that alcohol consumption of more than 50 grams per day (the equivalent of four or five glasses of wine) accelerates the progression of HCV-related liver disease (Harris 2002; Poynard 1997; Thomas 2000a). Thomas and colleagues followed a cohort of 1,667 HCV-infected individuals for a median interval of 8.8 years. The relative risk of ESLD among individuals with alcohol consumption of more than 260 grams per week was 3.60 (95% CI, 1.73–7.52). In a cohort of 176 HCV-infected individuals, alcohol intake of over 60 grams per day in males and over 40 grams per day in females for a period of at least five years resulted in a 2- to 3-fold greater risk of cirrhosis and ESLD (Wiley 1998).

Monto and colleagues performed a cross-sectional study of the effect of alcohol intake on fibrosis progression among 800 individuals with chronic hepatitis C. The duration, frequency and quantity of individual alcohol intake were assessed by a detailed questionnaire, and each participant had a liver biopsy. Lifetime alcohol consumption (in grams per day) was determined by multiplying the number of drinks by the alcohol content of each drink, which was estimated at 10 grams per drink. The result was divided by the length of time since drinking was initiated. Fibrosis progression was estimated by dividing the fibrosis score by the duration of infection.

Alcohol intake was not correlated with fibrosis progression, although it was associated with the presence of fibrosis in a multivariate analysis. The odds of fibrosis increased among those with alcohol consumption  $\geq$  80 grams/day vs. non-drinkers (OR, 1.76; 95% CI, 0.99–3.12;  $P=0.05$ ). Yet after controlling for other factors, only age, histological inflammation and alanine aminotransferase level were independent predictors of fibrosis ( $P<0.0001$ ,  $P<0.003$  and  $P<0.0001$ , respectively). Although alcohol intake was not an independent predictor of fibrosis, varying degrees of fibrosis and cirrhosis were present in non-drinkers, and at every threshold of alcohol consumption (Monto 2004).

**Figure 3. Fibrosis Score by Daily Alcohol Intake**



Although one might leap to the conclusion that light to moderate alcohol intake does no harm to the liver, the relationship between alcohol intake and fibrosis progression is more complex. Westin and colleagues reported that fibrosis progressed among individuals who drank more than a median of 5.7 grams/day; those with median alcohol consumption of >2.6 grams/day did not have fibrosis progression on sequential biopsies (Westin 2002).

Alcohol consumption may be more deleterious for some individuals than others. HCV-infected women with light to moderate alcohol intake may be at a greater risk for fibrosis than men with a similar alcohol intake, but there is little data—and some controversy—regarding the relationship of alcohol intake to fibrosis progression in women with hepatitis C. Monto and colleagues did not observe a difference in fibrosis among 187 women with chronic hepatitis C by alcohol intake, although only 23 of them drank more than 50 grams of alcohol per day. Even the women who drank heavily (>50 grams/day) did not have more fibrosis than those who did not drink at all, or who drank less (Monto 2004). Hezode and colleagues reported that fibrosis and cirrhosis were more prevalent among people with chronic hepatitis C who drank 31–50 grams/day. They suggested that moderate alcohol intake (21–50 grams/day) might worsen fibrosis among women with hepatitis C (Hezode 2003b).

More research on the effects of light or moderate alcohol consumption on HCV disease progression—especially that which considers sex and/or genetic and ethnic factors—is needed.

## **Smoking**

The role of smoking as a potential cofactor for developing HCC is controversial. In a large study of people with chronic liver disease, many of whom were HCV-antibody-positive (433/731), Tsukuma and colleagues found an increased risk of HCC among cirrhotic smokers (adjusted rate ratio of 7.96 for current smokers and 3.44 for former smokers) than cirrhotic nonsmokers (Tsukuma 1993). Interestingly, non-cirrhotic smokers were not at higher risk of developing HCC. While additional research has reported a correlation between smoking and HCC, smoking has not been identified as a promoter of hepatitis C-related hepatocellular carcinoma in particular; however, one study has linked smoking with severity of HCV-related liver damage. In a multivariate analysis, Pessione and colleagues linked smoking with increased fibrosis scores ( $P=0.03$ ) and increased histologic activity scores ( $P=0.04$ ). Since smoking often accompanies alcohol use, and in this study smokers were more likely to drink alcohol than nonsmokers ( $P=0.001$ ), it is not possible to isolate the contribution of smoking to the development of HCC.

## **Genotype**

There are at least six different genotypes (viral strains) of hepatitis C. The prevalence of HCV genotypes varies among countries and regions. Genotypes 1, 2, and 3 are globally distributed; in the United States, HCV genotypes 1a and 1b are the most prevalent, accounting for at least 75% of HCV infections (Blatt 2000; Zein 1996a). In the United States, infection with HCV genotype 1 is more prevalent among African Americans ( $P<0.001$ ) and individuals in the northeastern, southeastern, and midwestern regions (Blatt 2000). Before 1955, genotype 1b was predominant in the United States (Zein 2000). Genotype 1a arrived in the late 1950s and quickly became the most prevalent. Genotypes 1a and 1b were joined by genotype 2 in the 1960s and genotype 3 in the 1970s (Zein 2000). In Japan, as many as 73% of HCV infections are genotype 1b (Takada 1993). Genotype 2a and 2b are fairly prevalent in North America, Europe, and Japan (Zein 2000). Subtype 2c has been observed most often in Northern Italy, and genotype 3a is prevalent in injection drug users in Europe and the United States (Pawlotsky 1995). HCV genotype 4 infections occur most frequently in the Middle East and North Africa; genotype 5a is predominant in South Africa (Abdulkarim 1998; Chamberlain 1997a; Chamberlain 1997b; Nousbaum 1998). Genotype 6 infections are prevalent in Southeast Asia (Adams 1997). Researchers have not yet agreed whether or not five different viruses, three found only in Vietnamese individuals, the remaining two seen in Indonesians, are actually subtypes of genotype 6 or ought to be designated as genotypes 7 through 11.

Genotyping of HCV is clinically significant because genotype is the single most important predictor of response to HCV treatment. Individuals with genotypes 1a, 1b, 4, and 5 have poorer responses to interferon (Fried 2002; Germer 2001; Mondelli 1999; A. U. Neumann 2000; Nousbaum 1998; Poynard 1998; Rosenberg 2001; Zein 1996b). Forty-eight weeks of HCV treatment is recommended for individuals with genotype 1; for individuals with genotypes 2 and 3, the recommended duration of treatment is only 24 weeks (McHutchinson 2002; Poynard 2000; Soriano 2002). Infection with genotype 1 has also been associated with high HCV RNA levels (Kobayashi 1996; Pageaux 1997). In their analysis of 6,807 HCV-infected individuals, Blatt and colleagues discovered significantly higher HCV RNA levels among individuals with genotype 1 as compared with genotypes 2 and 3 ( $P<0.001$ ) (Blatt 2000).

Infection with hepatitis C genotype 3 and subtype 3a has been associated with hepatic steatosis (fat in liver cells), which contributes to HCV disease progression (Hofer 2002; Kumar 2002; Serfaty 2001). The amount of hepatocellular steatosis has been linked to the extent of fibrosis in the liver tissue (Adinolfi 2001; Hourigan 1999; Monto 2002a; Monto 2002b). Among 55 HCV-infected individuals with hepatic steatosis, Hwang and colleagues found higher fibrosis scores in those with steatosis ( $1.9 \pm 1.2$  vs.  $1.3 \pm 1.0$  without steatosis;  $P=0.016$ ) (Hwang 2001); however, when HCV treatment is successful in genotype-3- and genotype-3a-infected individuals, reductions in steatosis are often seen. Kumar and colleagues observed significantly reduced hepatic steatosis ( $P<0.001$ ) in individuals with HCV genotype 3a and sustained virologic responses (SVR; no detectable HCV RNA six months after completion of HCV treatment). No improvements in hepatic steatosis were observed in non-responders to interferon (Kumar 2002).

Infection with genotype 1b may increase the likelihood of chronic infection, although more information from larger studies is needed. Among 42 individuals with acute HCV infection, Amoroso and colleagues found a higher rate of chronic infection among those with genotype 1b. A majority of the participants were infected with a subtype of genotype 1. Thirty-eight percent (16/42) of the participants were infected with subtype 1a, and 33.9% (14/42) with subtype 1b. The overall chronicity rate after more than a year of follow-up was 59.5% (25/42). Ninety-two percent (23/42) of the individuals who developed chronic infection had genotype 1b. No significant association between mode of transmission—which included injection drug use, transfusion, nosocomial, and unknown factors—and chronic infection was identified (Amoroso 1998).

HCV genotype 1b has been associated with more aggressive and serious liver disease, but this association remains controversial. In Japan, where genotype 1b is very common, research has found a more frequent and a more rapid development of HCC in individuals with hepatitis C (Takahashi 1993; Yano 1993); however, when the HCV genotypes of 72 Japanese with HCC and 131 without HCC were examined, there was no significant difference in the prevalence of HCC by genotype (Yotsuyanagi 1995). The controversy about the association of genotype 1b with HCV disease severity has carried over into the United States, where Zein and colleagues saw an HCC prevalence of 28% among those with HCV genotype 1b vs. a 3% HCC prevalence among those with all other genotypes (Zein 1996c). However, when Reid and colleagues looked at 28 HCV-infected individuals with HCC and 38 HCV-infected cirrhotics, they did not find a significant association between HCV genotype and the development of HCC (Reid 1999).

Factors influencing the prevalence of genotype 1b among individuals with advanced liver disease might include the duration of infection, age at time of infection, or mode of transmission. In the United States and France, many individuals with genotype 1b are older than those with other genotypes, and many genotype 1b infections resulted from blood transfusions (Pol 1995; Rosen 1999). Both older age at infection and infection via transfusion are poor prognostic factors. It is therefore possible that genotype 1b may be an indirect marker of more severe disease—due to mode of transmission or age at infection—rather than a cause of it.

Some research suggests that recurrent HCV infection among transplant recipients is more aggressive in individuals with genotype 1, especially genotype 1b (Feraÿ 1995; Gane 1996; F. D. Gordon 1997; Pageaux 1997; Shuhart 1997). During a median follow-up interval of 40.4 months, Shuhart and colleagues found that individuals with genotypes 1a and 1b had a risk of recurrence

or death 3.47 times greater than that of individuals with genotypes 2 and 3 combined (95% CI, 1.15–10.56;  $P=0.02$ ). Only those with genotypes 1a and 1b developed post-transplant fibrosis or cirrhosis. More people in this study had genotypes 1a and 1b (46.9% genotype 1a; 28.6% genotype 1b; 20.4% genotype 2b; and 4.1% genotype 3a). Gane and colleagues followed transplant recipients for a median of 36 months. Twenty of 43 individuals with genotype 1b (46%) developed chronic hepatitis C or cirrhosis compared with 13 of 53 (24%) with other genotypes ( $P=0.02$ ). Genotype 1b infection was associated with a greater frequency of damage to the transplanted organ than infection with other genotypes (odds ratio, 3.4; 95% CI, 1.4–8.5;  $P=0.01$ ) (Gane 1996).

Other research, however, does not support a correlation between genotype 1/1b infections and more aggressive post-transplant HCV disease (Boker 1997; Charlton 1998; Crespo 1997b; Zhou 1996). Zhou and colleagues found no significant association between HCV genotypes 1 and 1b and disease severity or graft survival among 124 transplant recipients, despite a significantly longer median follow-up of individuals with genotype 1b (31.1 months vs. 24.5 months;  $P=0.02$ ). Charlton and colleagues found a significant association between HCV RNA levels before transplant and length of post-transplant survival (cumulative survival at five years was 57% in individuals with pre-transplant HCV RNA  $\geq 1 \times 10^6$  vEq/mL, increasing to 84% in those with HCV RNA  $<1 \times 10^6$  vEq/mL), but they did not find an association between the genotype of HCV and post-transplantation patient or graft survival. Crespo and colleagues did not find a relationship between genotype and of post-transplant HCV RNA level or disease severity (Crespo 1997b). It is difficult to reach a conclusion about the role of genotype in post-transplant disease; in addition to conflicting results, a lack of consistent data collection, differing methodology across studies, and uneven duration of follow-up are confounding, as with most other HCV studies conducted to date.

Cases of re-infection and coinfection with more than one genotype of hepatitis C have been documented, although the prognostic impact of mixed infection is unclear (Accapezzato 2002; De Socio 1996; García-Samaniego 1997; Jarvis 1994; Tuveri 1997). Although Benvegnù and colleagues did not find a correlation with a particular genotype and the course of HCV-related cirrhosis, they observed that individuals with mixed infections had more rapid worsening of cirrhosis, and increased mortality ( $P<0.05$ ). However, only six of the 109 individuals (5.5%) in this study had mixed infections (Benvegnù 1997).

The effect of mixed genotype infection on HCV viral load merits investigation, because a high hepatitis C virus load ( $\geq 2$  million copies/mL or  $\geq 800,000$  IU) decreases the likelihood of response to HCV treatment. Schijman and colleagues examined HCV viral loads in 257 people with hepatitis C; twelve were infected with two different genotypes. Their median HCV viral loads did not differ significantly from those infected with a single genotype (356,000 IU/ml for mixed-genotype infections vs. 344,000 IU/ml for single-genotype infections) (Schijman 2004).

HCV genotyping also provides valuable epidemiological information. It has been used for tracing the source outbreaks of infection and to establish evidence of transmission from one individual to another. HCV genotyping can identify transmission networks and provide guidance for targeted prevention, education, and treatment initiatives.

## **Hepatic Steatosis**

Hepatitis steatosis, a condition in which the deterioration of liver tissue is accompanied by deposits of fat in liver cells, is a common feature of chronic hepatitis C. The presence of steatosis has been associated with increased fibrosis progression and advanced liver damage (Adinolfi 2001; Hu 2003; Lonardo 2004; Vadan 2003; Walsh 2004) and decreased response to treatment for hepatitis C (Poynard 2003; Ratziu 2004).

Hepatic steatosis is especially prevalent in genotype 3, which may have a direct cytopathic effect (Castéra 2004; Cholet 2004; Hezode 2003a; Kumar 2002; Rubbia-Brandt 2004; Sharma 2004; Westin 2002). Genotype 3-associated steatosis has been associated with higher HCV RNA levels and impaired response to hepatitis C treatment (Hezode 2003a; Patton 2003; Zeuzem 2003).

Steatosis may originate from metabolic abnormalities as well; in hepatitis C genotype 1, there is a strong correlation between steatosis, body mass index and metabolic abnormalities such as visceral adiposity, and insulin resistance, which is a predictor of diabetes (Conjeevaram 2003; Hezode 2003a; A. Gordon 2003; Qadri 2004). Insulin resistance and high levels of serum glucose have been associated with an accelerated fibrosis progression rate in persons with HCV (Hui 2003; Lecube 2004; Ratziu 2003).

## **Mapping the Natural History of Hepatitis C**

Because the data available to assess the risk and rate of HCV disease progression come from widely different patient populations with varying lengths of follow-up, estimates of disease progression, morbidity, and mortality can differ dramatically from one study to the next. Comparisons of progression rates across studies are also difficult to perform due to differences in study design. Not all studies can establish the duration of infection, and uninfected control groups are often not identified. In addition, the use and frequency of biopsy to stage liver disease has been inconsistent, with researchers using various endpoints that preclude simple comparisons. Nevertheless, some distinctive trends emerge within clusters of studies.

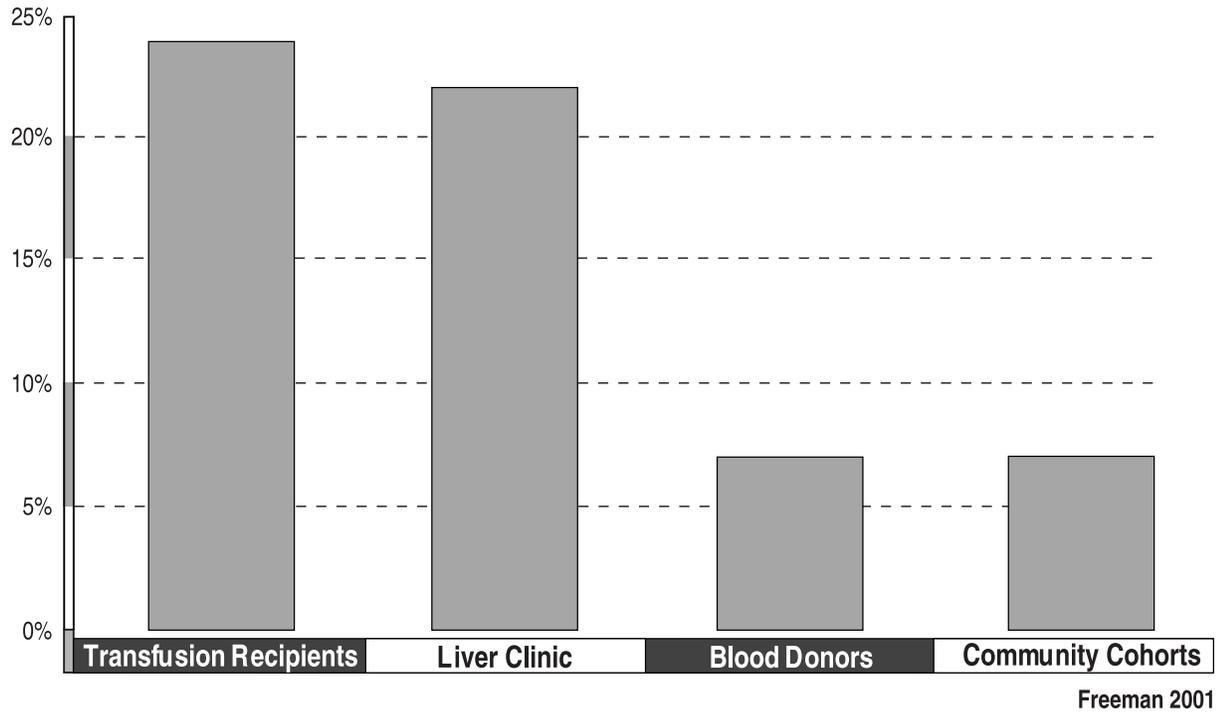
One group of studies has identified individuals with liver disease, often recruited from liver disease clinics, and attempted to correlate disease severity with duration of infection. These studies typically present worst-case scenario data, with high rates of cirrhosis (30–46%) and hepatocellular carcinoma (11–19%) (Seeff 1997).

Another typical group of studies has tracked cases of transfusion-related non-A, non-B hepatitis from the onset of acute infection. These studies support a low rate of morbidity and mortality during the first decade of hepatitis C infection, with cirrhosis appearing in 8% to 24% of individuals. Hepatocellular carcinoma was rare, and death from liver disease occurred in 1.6% to 6% of those observed (Seeff 2000).

Different methods have attempted to create a timeline of the natural history of hepatitis C infection. Freeman and colleagues shed some light with their analysis of 57 studies of HCV disease progression. They grouped the natural history studies used in their evaluation into one of four categories: 1) liver clinic patients; 2) transfusion recipients; 3) blood donors (people whose

infections were detected when they donated blood); and 4) longitudinal community-based cohorts. Twenty years postinfection, estimated progression to cirrhosis among liver clinic patients was 22% (95% CI, 18–26%); progression among transfusion recipients was 24% (95% CI, 11–37%); progression to cirrhosis among blood donors was 7% (95% CI, 1–7%), and progression among community-based cohorts was 7% (95% CI, 4–10%) (Freeman 2001).

**Figure 4. Risk of Developing Cirrhosis in 20 Years**



Dore and colleagues developed a mathematical model to estimate progression to cirrhosis based on data from natural history studies. They concluded that people with hepatitis C infection have on average a 7% risk of progressing to cirrhosis after 20 years of infection, and a 20% risk of cirrhosis after 40 years (Dore 2002).

Salomon and colleagues reviewed data from various sources on HCV prevalence, natural history, and mortality, examining a range of values to estimate a rate of progression to cirrhosis, and compared these models to existing epidemiological statistics. They found that the model that best fit the available data predicts that males infected at age 25 would have a median time to cirrhosis of 46 years, while less than 30% of females infected at the same age would progress to cirrhosis in 50 years (Salomon 2002).

According to the National Institutes of Health’s most recent Consensus Development Conference Statement on Hepatitis C, when individual prognostic factors are controlled for, the actual overall risk of developing cirrhosis within 20 years is estimated to lie between 10% and 15% (NIH 2002). Since these estimates used the total number of people who have ever been infected with HCV—including those who cleared the virus—the risk of developing cirrhosis may be higher among chronically infected individuals.

Fibrosis progression may be linear or, to some extent, exponential (de Torres 2003; Dore 2003; Poynard 2001; Ryder 2004). Poynard and colleagues propose dividing individuals with HCV disease into three groups: rapid fibrosers, intermediate fibrosers, and slow fibrosers. Two thousand two hundred and thirty-five people from the French OBSVIRC, METAVIR, and DOSVIRC groups—chronic hepatitis C patients from different retrospective and prospective studies—were evaluated to determine the effect of nine factors on fibrosis progression: age at time of infection; duration of infection; age at biopsy; gender; alcohol consumption; HCV genotype; HCV viremia; cause of infection; and grade of histological activity. Only three of these factors—older age (above 40) at time of infection, alcohol consumption over 50 grams/day, and male gender—were associated with fibrosis progression. Using this data, projected estimates for median time to cirrhosis were developed. The estimated median time (without treatment) to cirrhosis was 30 years, although 33% had an estimated median projection to cirrhosis of less than 20 years, and 31% were projected to develop cirrhosis after at least 50 years, if ever (Poynard 1997).

### **Forty-five Years Later**

A study that provides documentation of the earliest HCV infection in the United States is also the only study that provides data on individuals who have been infected with hepatitis C for longer than 25 years. Although the number of HCV-positive people in this study is small, it is important for what is suggested about the lifetime consequences of HCV infection.

Seeff and colleagues screened 8,568 frozen blood samples from military recruits who were tested between 1948 and 1954 for group A streptococcal infection and acute rheumatic fever. The stored samples were tested for HCV antibodies and, if repeatedly reactive, for HCV RNA. Seventeen (0.2%) of 8,568 samples were anti-HCV-positive. Twelve of the HCV-positive individuals were African-American (1.8% of 684), four were white (0.07% of 5902), and one was of unknown race/ethnicity. Mean age at the time of the original blood draw was 21.5 in the HCV-positive group and 20.7 in the HCV-negative group.

During the 45 years since the samples were taken, 2 of the 17 HCV-positive persons (11.8%) and 205 of the 8,551 HCV-negative persons (2.4%) had developed liver disease (ethnicity-adjusted relative risk, 3.56; 95% CI, 0.94–13.52). One HCV-positive individual died from liver disease 42 years later; 119 HCV-negative individuals (1.4%) died from liver disease. Death from all causes was more frequent in the HCV-positive group (41%) than in the HCV-negative group (26%), although the difference in age at death between the two groups was not significant (Seeff 2002). The low rates of hepatitis C-related morbidity and mortality seen in this group and in the two women's cohorts suggest that progression to cirrhosis and end-stage liver disease is not inevitable for all persons with HCV infection.

### **HCV Infection Acquired at Birth or During Early Childhood**

HCV infections acquired at birth or in early childhood usually progress slowly (Casiraghi 2004; Guido 1998; Kage 1997), but these infections are not always mild. Badizadegan and colleagues found significant fibrosis in 58% (23/40) and cirrhosis in 8% (3/40) of biopsy samples from children aged 2 to 18.6. The average duration of infection was 6.8 years (Badizadegan 1998).

Disease progression may accelerate as the duration of infection lengthens. Guido and colleagues reported that fibrosis progression was not linear in 13 children with paired liver biopsies; all were infected with hepatitis C during infancy. Age at biopsy and duration of infection were significantly associated with fibrosis stage ( $P < 0.002$  and  $P < 0.0005$ , respectively). The fibrosis stage differed significantly between individuals who had been infected for less or more than a decade ( $P < 0.0006$ ) (Guido 2003). Aging may accelerate fibrosis progression, as liver damage increases in adolescence and young adulthood (Jara 2003).

Casiraghi and colleagues reported on the long-term outcomes of 31 individuals infected with HCV at birth. In 1968, 43 infants were given mini blood transfusions (21–30 mL) from 29 donors. Years later, when HCV antibody testing became available, 15 of the donors were tested for hepatitis C; one donor was infected with HCV. In 1998, a follow-up study began with 31 of the 43 individuals who received mini transfusion from the infected donor plus 31 controls (mini transfusion recipients from anti-HCV negative donors). Eighteen mini transfusion recipients were anti-HCV positive; 16/18 (88.9%) had chronic HCV, confirmed by HCV-RNA testing. Phylogenetic analysis linked the virus of mini transfusion recipients to that of the infected donor.

Liver biopsy samples were available from 11 participants; a majority had no fibrosis or mild fibrosis (Ishak stage 0–1). Only two had moderate to marked fibrosis (Ishak stage 3–4). Disease activity was minimal to mild (Ishak grade 3–6) in ten of eleven. Five years after the initial biopsy, five individuals had a second biopsy. Only one had any significant change in liver histology, progression from stage 0 to stage 1 (Casiraghi 2004).

### **Transfusion Cohorts**

Transfusion recipients often became infected at older ages than those infected through injection drug use or sexual contact. Age at infection may not be the only factor distinguishing transfusion recipients from those with community-acquired HCV infection. Gordon and colleagues compared disease progression by mode of transmission and found that people with transfusion-associated HCV infection were more likely to develop liver decompensation than those infected in other ways (relative risk: 3.921; 95% CI, 2.205–7.015), even after controlling for duration of infection and age at infection (S. C. Gordon 1998).

Seeff and colleagues looked at long-term mortality from groups of non-A, non-B (NANB) hepatitis-infected transfusion recipients and two matched control groups of uninfected transfusion recipients. The 568 NANB-infected transfusion recipients from five different studies were matched with 526 first controls and 458 second controls. While, over an 18-year period, the overall frequency of liver-disease-related mortality was low, the number of deaths from liver disease among those with non-A, non-B hepatitis was significantly higher than among the uninfected transfusion recipients. Nineteen NANB-infected persons died from liver disease (3.3%) compared to six first controls (1.1%) and nine second controls (2 %) (Seeff 1992).

Tong and colleagues studied the clinical outcomes of 131 people with transfusion-associated hepatitis C who had been referred to liver specialists. The mean age at the time of transfusion was 35, and mean age at follow-up was 57. Fifty-one percent (67/131) had cirrhosis and 5.3% (7/131) had hepatocellular carcinoma. Of the cirrhotics, 10% (7/67) developed HCC over an average

time of 36 months. The estimated time from transfusion to cirrhosis was  $20.6 \pm 10.1$  years. The estimated time from transfusion to HCC was  $28.3 \pm 11.5$  years (Tong 1995).

Kiyosawa and colleagues found similar results in a study of 231 people who were infected with non-A, non-B hepatitis mainly through transfusions. Eighty-six point four percent of the 81 cirrhotics had antibodies to HCV; 94.4% of the 54 who were diagnosed with hepatocellular carcinoma were anti-HCV-positive. The mean interval between transfusion and the development of HCV-related cirrhosis was 21.2 years; the mean interval between transfusion and the development of HCV-related hepatocellular carcinoma was 29 years (Kiyosawa 1990).

### **Female Transfusion Cohorts Infected Through Anti-D Immunoglobulin**

Two different studies have identified cohorts of women infected from a single source and have tracked them over a period of time. These studies delineate a very slow disease progression, with few serious complications developing; in the 17 to 20 years after infection, the rates of cirrhosis in these cohorts were 0.4% and 2% (Kenny-Walsh 1999; Wiese 2000).

Liver biopsies were performed on 182 of the cohort of young German women who had been infected with HCV from anti-D immunoglobulin 20 years earlier. While 94% of the women had mild-to-moderate liver inflammation, only four (0.4%) of the women had cirrhosis. Two women had died, one from fulminant hepatitis B infection and the other from alcoholism and cirrhosis (Wiese 2000). Similar findings were obtained from liver biopsies of 363 women in the Irish cohort who had been infected 17 years earlier. Although 98% had liver inflammation, only 16 (4%) of the women had serious inflammation; 177 (49%) of the women had no fibrosis, and only 7 (2%) had cirrhosis. Two of the cirrhotic women reported heavy drinking (Kenny-Walsh 1999).

Natural history studies and estimates of disease progression can provide information, but they cannot clarify uncertainty about disease progression in individuals. People with hepatitis C and their doctors look to such data in order to assess the risk of liver disease and evaluate the need for treatment. Treatment decisions may be guided in part by estimates of the risk of disease progression, giving particular consideration to prognostic factors such as age at infection and gender. The good news is that chronic infection with hepatitis C does not necessarily predict serious liver damage; the bad news is that some people—Poynard's "rapid fibrosers"—will likely develop cirrhosis sooner rather than later.

## Recommendations

### **Investigate the role of genetic and ethnic factors in susceptibility to HCV infection, disease progression, and response to treatment.**

Hepatitis C infection is twice as prevalent among black Americans as white Americans. The highest observed prevalence of hepatitis C in the United States—a shocking 9.8%—occurs among black males aged 40 to 49 (M. J. Alter 1999). African Americans appear less likely to achieve spontaneous viral clearance of HCV (Thomas 2000; Villano 1999). In addition, race appears to have a substantial impact on the efficacy of interferon. Significantly lower treatment response rates have been observed in Blacks than in Whites, Latinos, or Asian Americans (Jeffers 2002; McHutchison 2000; Reddy 1999). Research is needed to understand the mechanisms that account for these disparities and to identify strategies to improve treatment response. The National Institutes of Health and the Centers for Disease Control must support this research.

### **Investigate the role of sex differences in HCV disease progression.**

High rates of spontaneous viral clearance have been observed in two cohorts of premenopausal women, and some evidence suggests that the course of hepatitis C disease in this population may be less severe (Benhamou 1999; Kenny-Walsh 1999; Poynard 1997; Weise 2000). No research has explored why female sex appears to be a favorable prognostic factor. The role of hormones, and the immunological differences between males and females warrant further investigation from the National Institutes of Health and the Centers for Disease Control.

### **Identify possible causes of, and interventions for, HCV-related “brain fog.”**

Confusion, memory loss, and an inability to concentrate have been reported by many individuals with chronic HCV. HCV is present in the cerebrospinal fluid of some individuals with chronic HCV infection (Laskus 2002a). Evidence to support the direct effect of HCV on the brain was discovered by the same group who detected HCV replication in autopsied brain tissue from samples of three out of six individuals (Laskus 2002b). More research should be supported by the National Institutes of Health to illuminate potential mechanisms of “brain fog” and identify possible interventions.

### **Promote screening and vaccination for hepatitis A and hepatitis B among individuals infected with HCV or coinfecting with HIV/HCV.**

Individuals infected with HCV are at risk for severe, potentially fatal, disease if they become superinfected with hepatitis A (Koff 2001; Pramoolsinsap 1999; Vento 1998; Vento 2000). Coinfection with hepatitis B may accelerate progression of an existing hepatitis C infection or even cause liver failure and death (Koff 2001; Liaw 2000). Because of these risks, CDC recommends vaccination against HAV and HBV for all individuals infected with or at risk for HCV infection; yet many are not receiving vaccinations. A survey of primary care physicians found that only 1.6% of their HCV patients were vaccinated against HAV, and only 3% had been vaccinated against HBV (Nicklin 1999).

Physicians, health educators, and direct service staff need to be educated about the importance of vaccination against HAV and HBV. Screening and vaccination initiatives are needed. Vaccination should be available in correctional facilities and outside of clinic and hospital-based settings, especially in venues such as syringe exchange programs, substance abuse treatment programs, shelters, and methadone maintenance clinics, where high-prevalence and high-risk groups receive services. Screening and vaccination should be provided free of charge. Congress and the administration must provide public health funding for these services.

**Investigate the influence of light-to-moderate alcohol consumption on HCV disease progression.**

A large body of data has confirmed that alcohol consumption of more than 50 grams per day accelerates the progression of HCV-related liver disease (Harris 2002; Poynard 1997; Thomas 2000). Less is known about the effect of light to moderate alcohol consumption on hepatitis C disease progression. Some studies have associated light alcohol intake with fibrosis progression, while others have reported that light to moderate alcohol consumption is not significantly associated with fibrosis (Monto 2004; Westin 2002). The effect of alcohol on HCV progression may vary by sex and/or genetic and ethnic factors. Without more specific information, most clinicians simply recommend abstinence from alcohol. Data to support or modify recommendations of abstinence are needed. The National Institutes of Health should provide funding for this research.