# The Hepatitis C Crisis

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An estimated 170 million persons (3% of the world's population) are infected with the hepatitis C virus (HCV), and 3 to 4 million persons are newly infected each year. Of those infected, 70%–85% develop chronic viremia with the potential for devastating long-term sequelae, including chronic liver disease, cirrhosis, hepatic failure, and hepatocellular carcinoma. The passivity in the public health sector and in the medical community at large with respect to hepatitis C portends a myriad of societal, fiscal, and personal costs for the United States within the next two decades unless immediate actions are taken to intervene in the natural history of this emerging public health crisis. (*Ethn Dis*. 2005;15[suppl 2]:S2-52–S2-57)

**Key Words:** Antibodies, Chronic Hepatitis C, Hepatitis C, Hepatocellular Carcinoma, Liver Cirrhosis, Liver Transplantation

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## Introduction

The World Health Organization (WHO) estimates 170 million persons, or 3% of the world's population, are currently infected with the hepatitis C virus (HCV), and 3 to 4 million persons are newly infected each year.[1] The global distribution of HCV is shown in Figure 1.

The HCV is a small, enveloped, single-stranded RNA virus of the Flaviviridae family. The HCV virion consists of a nucleocapsid core and two envelope proteins. At least six non-structural proteins are involved in transcription, replication, and protein processing.

The HCV replication rate is $>10^{12}$ virions/day. An HCV viral particle can replicate roughly 600–900 generations each year. By comparison, an estimated 300 generations of humans have existed since *Homo sapiens* evolved. This exceptional replication rate, coupled with the fact that the HCV RNA-dependent RNA polymerase lacks proofreading capabilities, leads to a high rate of spontaneous mutations.

## HCV Transmission and Risk Factors

The HCV is a blood-borne virus. The route of transmission among those currently infected has been reported as follows: 60% injection drug use, 15% sexual contact, 10% blood products, 4% occupational exposure, and 10% unknown.[2]

Although HCV and HIV have shared routes of transmission, the relative efficiency of these routes is distinctly different between the two viruses. The HCV is approximately 10 times more transmissible by percutaneous small volumes of blood than is HIV. The estimated transmission risk from an accidental needle stick is 1.5%–3.0% for HCV, compared to 0.3% for HIV.[3] In contrast, HIV is transmitted far more efficiently via a sexual route than is HCV. The estimated transmission risk of HIV through a single heterosexual or homosexual intercourse is 1%–5%, compared to a risk of 0.1–0.3% for HCV.[4–9]

Many people infected with HCV are not current injection drug users. Many used drugs only once or twice; others were short-term drug users. But given the highly efficient percutaneous transmission of HCV via an IV, a single exposure may result in infection. Up to 90% of the population of injection drug users are HCV RNA-positive. Appropriate harm reduction measures are essential to change future outcomes for the population of injection drug users.

## HCV in the United States

Hepatitis C was first identified in 1992. Before 1992, most non-A, non-B hepatitis cases diagnosed were probably due to hepatitis C. Although reported figures vary, an estimated 70%–85% of people exposed to HCV become chronically infected.

NHANES III, the periodic population-based survey conducted by the Centers for Disease Control and Prevention (CDC), documented the US seroprevalence of anti-HCV at 1.8% (95% confidence interval [CI]: 1.5%–2.3%).[10] The prevalence of HCV RNA among anti-HCV-positive persons was 73.9% (95% CI: 65.8%–83.0%), which indicates that approximately 3.9 million Americans have been infected with HCV, and at least 2.7 million have persistent infection. The HCV was found to be more prevalent among males than females. Persons age 30–39 years had the highest prevalence and accounted

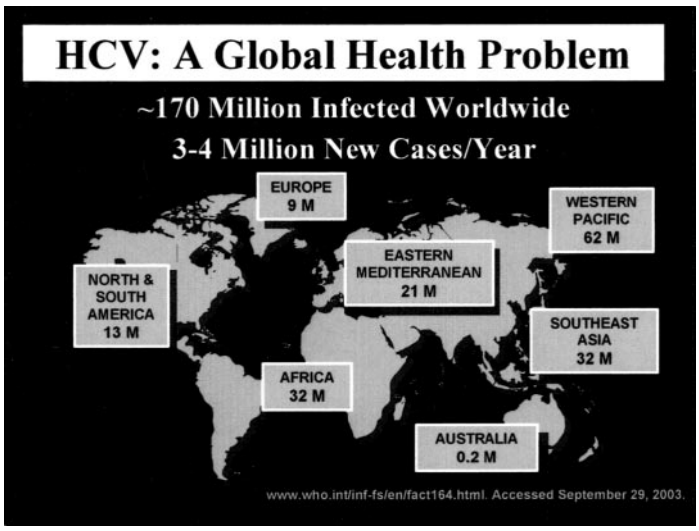


**Fig 1. The global distribution of Hepatitis C**

for 65% of all persons with detectable anti-HCV. Seroprevalence by ethnicity is shown in Table 1.

The HCV prevalence documented by NHANES III may underestimate the actual rate because several high-risk populations are not represented, including incarcerated and homeless persons. HCV seroprevalence rates of up to 15% have been seen among prison inmates[11] and up to 22% among homeless persons.[12] Taking into account populations that were either excluded or under-represented in NHANES III, some experts estimate 5 million Americans have persistent HCV viremia. Demographic characteristics of various population groups and associated seroprevalence rates are shown in Table 2.

According to NHANES III, nearly a quarter (24%) of those who have been exposed to HCV are living below poverty level, and nearly three quarters (73.5%) have a high school education or less. The differences in seroprevalence rates across various population groups demonstrate a risk differential based at least in part on socioeconomic status.

At least 30% of HIV-positive people in the United States are coinfected with HCV. Since the introduction of highly active antiretroviral therapy (HAART), HIV-related mortality has dropped precipitously. However, HIV-positive patients now have another virus to be concerned about, hepatitus C. Not only does HIV coinfection accelerate HCV disease progression, but today, more coinfected people die from HCV-related liver disease than from AIDS.[13]

## NATURAL HISTORY OF HEPATITIS C

The first 6–9 months after HCV infection is the acute phase. Liver enzymes (especially the transaminases) typically spike 7–8 weeks after exposure. Anti-HCV antibodies are usually detectable 3–12 weeks after infection. Acute hepatitis C is often asymptomatic, with only 25%–35% of infected people experiencing a mild illness with vague, nonspecific symptoms. Of persons acutely infected with HCV, 15%–45% spontaneously clear the virus. The mechanisms of spontaneous clearance are an active arena of HCV research. The remaining 55%–85% of people exposed to HCV are chronically viremic.[14,15]

Approximately 25% of those with chronic hepatitis C (CHC) have a clinically quiescent course, and many have persistently or intermittently normal liver enzyme levels. Nonetheless, evidence suggests that HCV may be progressive despite clinical and biochemical quiescence. Over a 20-year period, approximately 20%–30% of people with CHC develop cirrhosis. Ten percent of those with cirrhosis eventually progress to end-stage liver disease and/or develop hepatocellular carcinoma (HCC). Coinfection with HIV and/or hepatitis B virus (HBV), and ongoing alcohol consumption accelerate HCV-related disease progression.[16–18]

The pathophysiology of CHC is slowly progressive fibrosis leading to cirrhosis. Chronic inflammation appears to drive the fibrotic process, although some experts suggest that direct actions of the virus also contribute to progressive structural and functional liver deterioration. From a population-based perspective, several factors influence the course of CHC. The most significant of these factors are shown in Table 3.

While the overall natural history of progressive CHC is relatively well-understood, the clinical course of CHC within a given individual is largely unpredictable.[29]

**Table 1. HCV seroprevalence in the United States, 1988–1994**

| Group | Percent Anti-HCV Positive | Est. Infections in Millions (95% CI) | Percent of Infections |
|---|---|---|---|
| White | 1.5 | 2.4 (1.8–3.1) | 61 |
| African-American | 3.2 | 0.8 (0.6–1.0) | 20 |
| Mexican-American | 2.1 | 0.3 (0.2–0.3) | 7 |
| Other | 2.9 | 0.5 (0.3–1.0) | 13 |
| Total | 1.8 | 3.9 (3.1–4.8) | 100 |

**Table 2. HCV demographics and seroprevalence, NHANES III**

| Characteristic | Number Tested | HCV Seroprevalence % (95% CI) | Estimated Nationwide |
|---|---|---|---|
| Below poverty level | 5,345 | 3.2 (2.4–4.3) | 937,000 |
| At or above poverty | 13,974 | 1.6 (1.2–2.0) | 2,625,000 |
| ≤12 years education | 11,971 | 2.8 (2.1–3.6) | 2,866,000 |
| >12 years education | 4,528 | 1.3 (0.8–2.0) | 899,000 |
| Men | 10,076 | 2.5 (2.0–3.2) | 2,586,000 |
| Women | 11,165 | 1.2 (0.9–1.6) | 1,289,000 |

## CASE FINDING AND DIAGNOSIS

Although HCV is primarily a hepatotrophic virus, CHC is a systemic disease. Symptoms are often constitutional and non-specific and include fatigue, impaired cognitive function, low-grade fever, abdominal discomfort, appetite disturbance, digestive disturbance, migratory arthralgia or myalgia, depression, and anxiety. Case finding is one of the many challenges we face in battling HCV-related disease. As a consequence of the lack of symptoms associated with hepatitis C viremia and the lack of specific symptoms, two out of three HCV-positive Americans are unaware they are infected with the virus. Many new cases are diagnosed because of an incidental finding, such as elevated liver enzymes on a routine chemistry screen. Many symptoms associated with hepatitis C are common complaints and have a myriad of possible causes. Inclusion of HCV risk factors in the patient interview can help distinguish whether CHC should be included in the differential diagnosis for such patients. Topics to be explored include history of receiving blood or blood products, organ transplantation prior to 1992, any use of injection or intranasal street drugs, history of occupational exposure, body piercing and tattoos, sexual activity involving blood contact, and sharing personal care items. A compassionate exploration of a patient's medical and personal risk factors may tip the scales in favor of early diagnosis and treatment versus making the diagnosis when liver decompensation has already ensued.

A number of asymptomatic hepatitis C patients have normal liver enzyme levels. In one study, as many as 44% of HCV RNA-positive patients had normal enzyme levels on initial evaluation.[30] Further, liver enzyme levels often fluctuate with CHC. Therefore, a single set of normal liver enzymes does not rule out CHC. Conversely, the common clinical silence of HCV justifies a high index of suspicion whenever liver enzyme abnormalities are noted in an otherwise asymptomatic patient.

The 2002 *Management of Hepatitis C* consensus conference statement issued by the National Institutes of Health (NIH) recommends anti-HCV antibody enzyme immunoassay (EIA) testing for screening at-risk populations. The testing is also recommended for screening patients with clinical liver disease. In cases of a normal alanine aminotransferase but a positive anti-HCV enzyme immunosorbent assay (EIA), a confirmatory HCV RNA test is used to determine the presence of the virus.

Antibody screening tests detect the presence of anti-HCV antibodies, not HCV RNA. Therefore, screening detects HCV exposure, not current infection. Further, some patients with chronic HCV are serosilent; ie, they do not have detectable anti-HCV. Serosilence is most often found in HIV-coinfected patients but can occur outside of this setting. Therefore, in the face of a high index of suspicion and elevated liver enzymes, an HCV RNA test may be appropriate despite a negative EIA screening test. Figures 2 and 3 show HCV diagnostic algorithms.

Three methods are currently used for qualitative and quantitative HCV nucleic acid testing: polymerase chain reaction (PCR), transcription-mediated amplification (TMA), and branched DNA (bDNA). HCV viral loads fluctuate widely, a well-known phenomenon in untreated CHC, although viral loads are not reflective of hepatic status or disease progression.

To date, six HCV genotypes (numbered 1 through 6) and more than 90 subtypes have been identified. In a study of >6,000 patients with CHC in the United States, the genotype distribution was 73% genotype 1, 14% genotype 2, 8% genotype 3, 4% mixed genotype, and <1% for genotypes 4, 5, and 6.[31] HCV genotype testing is used to predict potential response to treatment and the required duration of curative intent therapy. The differential response to interferon-based therapy associated with the different HCV genotypes is an area of active research. Currently, subtypes

**Table 3. Factors influencing HCV disease progression**

| Characteristic | Effect |
|---|---|
| Age | People infected after age 35 appear to have more rapid disease progression compared to those infected at younger ages.[19–21] |
| Sex | Overall, women (especially those under age 50) have a significantly better prognosis than their male counterparts.[22,31] Women also appear to spontaneously clear the virus more frequently than men do.[23–25] |
| Alcohol consumption | Alcohol appears to exacerbate the damage caused by HCV and accelerate disease progression.[26] |
| Coinfection | Coinfection with HBV and/or HIV accelerates disease progression.[27] |
| Steatosis | Steatosis is associated with higher degrees of hepatic fibrosis.[28] |

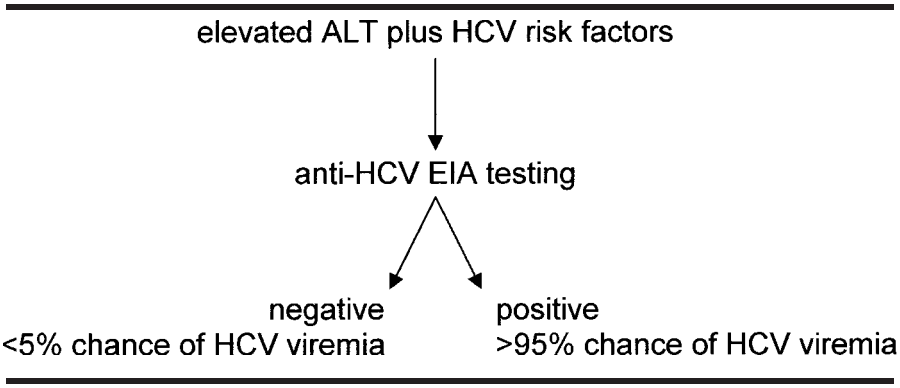


**Fig 2. Diagnosing HCV in a patient with an elevated ALT**

1a and 1b account for 65%–75% of chronic HCV in the United States. People with genotype 1 infection have the lowest response rate to interferon-based therapy. Genotypes 2 and 3, much less common in the United States, have shown higher sustained viral clearance rates with standard therapy using pegylated interferon plus ribavirin.

Alcohol consumption is the single most important factor influencing HCV disease progression. Cromie et al found decreased alcohol consumption among patients resulted in significant decreases in both hepatic disease activity and viral RNA titer.[32] Perhaps the single most important message healthcare providers can convey to patients with CHC is the dangerous, synergistic effect of alcohol on HCV.

Neither liver enzyme levels, HCV viral load, nor HCV genotype provide information about the histologic status of the liver. Liver biopsy is the only way to accurately assess hepatic inflammation and fibrosis. Liver biopsy helps provide a specific diagnosis, ie, HCV versus other causes of chronic hepatitis. In addition, biopsy provides a structured assessment of inflammation and fibrosis/cirrhosis (stage and grade). Finally, it may identify comorbid hepatic conditions (eg, iron overload, steatosis) that may require intervention and/or affect management decisions. Among patients with persistent viremia, liver biopsy every 3–5 years is recommended to monitor disease progression. Saadeh et al found that 20% of HCV cases with biopsy-proven cirrhosis were unsuspected based on clinical and biochemical assessment.[33] These findings reinforce the importance of liver biopsy in monitoring CHC.

## Treatment of Chronic Hepatitis C

As with most medical decisions, whether one pursues treatment for CHC and what treatments are pursued are personal choices. Important considerations include the histologic status of the liver, comorbid conditions, as well as age, lifestyle, and numerous other personal factors.

For some patients, the decision to treat or enter into a course of watchful waiting is clear; for others, it is much less certain. Considerations that often enter into the equation in favor of watchful waiting include the slowly progressive nature of CHC, limited efficacy of current standard therapy (≈50% for people with genotype 1), treatment expense, and treatment side effects.

Interferon-based therapy is the only treatment for CHC that has been proven in clinical trials to lead to sustained viral response (SVR). The primary goal of interferon-based therapy is HCV eradication. Secondary goals include slowing disease progression, improving hepatic function, and decreasing HCC risk.

Advances in interferon-based therapy over the past 10 years have been remarkable. In the early 90s, interferon monotherapy produced SVR in only ≈10% of those treated. Current therapy with pegylated interferon plus ribavirin has demonstrated an overall SVR of close to 60%. Despite therapeutic advances, treatment for chronic HCV remains challenging. A series of recent studies suggests that for every 100 patients evaluated for therapy, only 10%–20% successfully complete treatment.[34–37]

The decision whether to treat CHC from the clinician's perspective is complex and must be evaluated on a case-by-case basis. However, interferon-based therapy should be considered in each of the scenarios shown in Table 4.

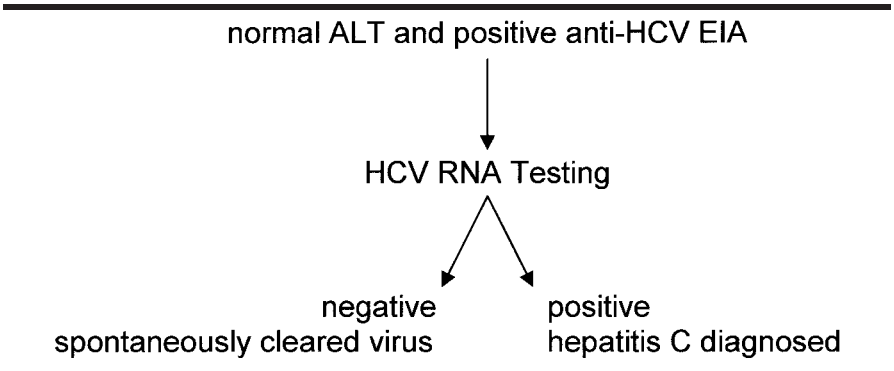


**Fig 3. Diagnosing HCV in a patient with a normal ALT and a positive anti-HCV screen**

**Table 4. Scenarios that necessitate consideration of interferon-based therapy**

| Medical Circumstance | Rationale to Treat |
|---|---|
| Genotype 2 or 3, low viral load | Combination therapy should be considered because the durable response rate is greater than 70%–80% after 24 weeks of therapy with pegylated interferon plus ribavirin. |
| Stage 2–3 fibrosis and/or grade 2–4 necrosis/inflammation | These patients will almost invariably progress to cirrhosis; treatment should be considered sooner rather than later. |
| Stage 4 fibrosis (cirrhosis) with compensated hepatic function | Treatment is a high priority in these patients because without disease stabilization, these patients will progress to decompensation with their only hope of longevity resting with liver transplantation. |
| Severe symptoms related to cirrhosis or extrahepatic symptoms (eg, cryoglobulinemia) | Treatment is the most likely avenue to relief. |
| Desire to be pregnant without risk of vertical transmission | Viral clearance eliminates the possibility of vertical transmission of HCV. |

## A LOOK TO THE FUTURE

Taking into account the fact that many people with CHC remain undiagnosed, along with the knowledge that only one out of 10 patients evaluated for therapy actually completes treatment, a substantial population exists in whom potentially devastating sequelae of CHC such as chronic liver disease, cirrhosis, and HCC may develop.

Total costs for HCV in the United States in 1997 were estimated at just under $5.5 billion.[38] Chronic liver disease ranks among the top 10 causes of death for all Americans age 25–74 years, ranking fourth among those 45–54 years, sixth among those 35–44 years, and seventh for those 55–64 years.[39] The HCV is responsible for approximately 40%–60% of all chronic liver disease in the United States.[2] Furthermore, HCV-related disease is the leading indication for liver transplantation. Approximately 12,000 people die each year of HCV-related liver disease. The CDC projects HCV-related deaths may double or triple by 2010[40] unless immediate, population-based action is taken to intervene. A study by Wong et al[41] predicted an increase in HCV-related morbidity, mortality, and cost as shown in Table 5.

The message of these projections is clear: we must take immediate action to intervene in the hepatitis C crisis or face the dire personal, societal, and fiscal consequences of our inaction in the decades to come.

The population-based response to hepatitis C has been inadequate to date. However, researchers give us reasons to be hopeful about treatment advances as we look toward the future. Basic scientists are examining the molecular mechanisms involved in cell entry and destruction. Vaccine research continues with an eye toward preventing infection and/or limiting hepatic injury in the presence of infection. New modifications to interferon and ribavirin molecules are being tested in an attempt to improve efficacy and decrease treatment side effects. Enzyme-specific inhibitors are also being examined, an approach similar to the breakthrough in HIV disease associated with HAART.

Much work remains to be done. The HCV treatment must be made more readily available to populations with a high prevalence of infection. Educational efforts must be expanded to bolster prevention and treatment efficacy. Adequate funding must be provided to expand current research.

**Table 5. Projected HCV-related morbidity, mortality, and costs in the United States, 2010–2019**

| Parameter | Projection |
|---|---|
| Deaths from HCV-related chronic liver disease | 165,900 |
| Deaths from hepatocellular carcinoma | 27,200 |
| Direct medical costs | $10.3 billion |
| Years of decompensated cirrhosis or HCC among those ≤65 years of age | 720,700 years |
| Cost of lost productivity due to decompensated cirrhosis or HCC | $21.3 billion |
| Years of life lost for those ≤65 years of age | 1.83 million years |

## CONCLUSION

The CHC is not an esoteric, orphan disease. It is the most common bloodborne, chronic viral infection affecting Americans. Moreover, despite its slowly progressive course, CHC is far from a benign disease. As the frontline protectors of both individuals' and the public's health, primary care providers are key figures in turning the tide in the currently evolving hepatitis C crisis. The words of former Surgeon General C. Everett Koop provide the charge for all healthcare professionals.

> "Hepatitis C does not discriminate. It affects people of all ages, gender, and sexual orientations. . .. It affects people from all walks of life, in every state, in every country. . .. All Americans must understand the risk that this disease poses. We must help America become a leader in the fight against this disease, both here at home and around the world."[32]

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