

Natural History of Hepatitis C Infection

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Module 2: [Evaluation, Staging, and Monitoring of Chronic Hepatitis C](#)

Lesson 2: [Natural History of Hepatitis C Infection](#)

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Spontaneous Clearance versus Chronic Infection

Background: Most persons who acquire hepatitis C virus (HCV) will develop chronic infection. Following acute infection, HCV is very successful in establishing persistent infection by evading the immune system. Although the mechanism for the high rate of viral persistence is not completely understood, several viral and host factors likely play a significant role. The rate of viral production is high, 10^{10} to 10^{12} virions per day, and the lack of proofreading by the viral polymerase leads to enormous genetic diversity, which in turn creates a major challenge for the host immune response. This broad genetic diversity contributes to the high likelihood of developing chronic infection. Host factors are also involved in the ability to spontaneously clear the virus.

Role of Immune Response in Clearance versus Chronic Infection: Several studies indicate that clearance of HCV is associated with strong and persistent HCV-specific cytotoxic T-lymphocyte and CD4 lymphocyte responses. In addition, persons who clear HCV generally have limited viral diversity, which also points to enhanced immune-mediated response to acute infection.

Rate of Chronicity: The actual rate of chronicity following initial infection with HCV is not well established in prospective studies. Indeed, there has not been a prospective study of unselected patients to answer this question. The chronicity rate has been estimated from cross sectional population-based studies, such as the National Health and Nutrition Examination Survey (NHANES), and numerous retrospective studies. The best estimate is that 75% to 85% of persons infected with HCV will develop chronic infection.

Host Factors Associated with Viral Clearance: The reason HCV infection persists in most patients but resolves spontaneously in others is not well understood. The following characteristics have been associated with a lower rate of chronicity.

- **Younger Age.** The chronicity rate of HCV is lower in younger patients. In the NHANES study, the chronicity rate was 30% in subjects below the age of 20 and 76% in those older than 20 years. In one study of 67 children infected with HCV through contaminated blood transfusions, only 55% developed chronic infection.
- **Female Gender.** In 2 large retrospective analyses involving more than 1600 women who received contaminated Rh immune globulin, the chronicity rate was only 55%, a rate significantly lower than the 75 to 85% typically reported. In contrast, cross sectional studies have not reported gender differences.
- **Nonblack Race.** The chronicity rate in African Americans in the NHANES study was 86% overall and 98% for African American men. In a prospective cohort study involving 1667 injection-drug users, African Americans were more likely to develop chronic infection than other races (91% versus 64%).
- **Symptomatic Acute Infection.** In small studies of acute infection and larger follow-up studies of the women infected with hepatitis C virus through contaminated Rh immune

globulin, only 45 to 50% of people who developed jaundice become chronically infected. It is believed that severe acute infection reflects a more vigorous immune response that results in higher clearance of HCV and thus a lower rate of chronicity.

- **Normal Immune Status.** In a prospective study of injection drug users, HIV-infected individuals were more likely to develop chronic infection than those who did not have HIV (Odds ratio 2.19). In another study of acute infection, HCV persisted in 95% of those coinfecting with HIV. In these patients, HIV coinfection was associated with a lack of critical CD4 T cell responses.
- **IL28B CC Genotype.** The single nucleotide polymorphism (SNP) rs12979860 is located upstream from the IL28B gene and this gene encodes for interleukin 28 (which is also referred to as interferon lambda). Variations in the rs12979860 SNP have been associated with probability of clearance of hepatitis C. Individuals with the CC allele of IL28B genotype are more likely to spontaneously clear HCV than those with CT or TT. In one report involving 1,008 individuals, those with CC genotype cleared the virus 53% of the time compared with a clearance rate of 23% for those with the TT genotype ([Figure 1](#)).

Variable Outcomes of Chronic Infection

Studies Related to Natural History: The natural history of chronic HCV infection has not been fully delineated, primarily because most persons are not identified at the time that they have acute HCV infection and most remain relatively asymptomatic for at least 15 years after becoming infected. Further, it has been difficult to design studies that convincingly define the natural history of chronic HCV infection for multiple reasons, including the difficulty of accurately establishing the time of initial acquisition of infection (which sets the timeline for determining duration of infection) and the necessity to follow patients for decades to see clinical sequelae.

Estimates of Natural History and Outcomes: Once chronicity is established, available data suggest the process runs a clinically indolent course for the first two decades after infection. Serious consequences of chronic hepatitis C infection, such as cirrhosis, end stage liver disease (ESLD), and hepatocellular cancer (HCC), are likely to emerge in the third and fourth decades after initial infection ([Figure 2](#)). Among those with chronic HCV, an estimated 20 to 30% will develop cirrhosis, and cirrhotic patients with HCV have an approximately 1 to 4% annual risk of developing HCC and a similar risk of developing end-stage liver disease ([Figure 3](#)). Overall, approximately half of those who develop cirrhosis will die from their liver disease.

Fibrosis and Cirrhosis: Progression to cirrhosis is usually clinically silent and a wide range of fibrosis rates occur. Annual rates of progression to cirrhosis increase with older age at the time of infection and longer duration of infection but the relationship is not linear. It is estimated that approximately 20 to 30% of those infected with HCV will develop cirrhosis during the 20 to 30 year-period after becoming chronically infected. This progression, however, is variable and it is impossible to predict the expected outcome for an individual early in the course of their disease. There are no predictive models that can accurately estimate the risk of disease progression.

Factors Impacting Rate of Progression of Fibrosis

Age: Older persons appear to have more severe disease than younger persons with the same duration of hepatitis C infection. In addition, acquisition of HCV after age 40 is associated with a more rapid fibrosis progression rate ([Figure 4](#)). In one study, progression to cirrhosis over a 20-year period occurred in only 2% of subjects infected before the age of 20 and in 63% of subjects infected after the age of 50 ([Figure 5](#)).

Gender: Male sex has been independently associated with a faster fibrosis progression rate. Even when controlling for alcohol consumption, duration of infection, and age, men still have a fibrosis progression rate two times that of women.

Coinfection with HIV: Coinfection with HIV accelerates the course of HCV-related liver damage to cirrhosis ([Figure 6](#)), ESLD, and death. A meta-analysis of studies examining the impact of HIV on the course of HCV infection (using cirrhosis and decompensated liver disease as their end points) yielded an adjusted relative risk of 2.92 for HIV coinfecting patients compared with HCV monoinfected patients. Studies that only examined decompensated liver disease showed an even higher relative risk of 6.14 with coinfection. In HIV-infected patients, CD4 count less than 200 cells/mm³, alcohol consumption, and older age at the time of HCV acquisition are independently associated with accelerated fibrosis progression.

Coinfection with Hepatitis B: Most studies, although they are small and mostly retrospective, suggest that coinfection with HBV and HCV accelerates liver disease progression. Coinfection with these two viruses has been strongly associated with an increased risk of developing HCC.

Metabolic Factors (Obesity, Insulin Resistance, and Steatosis): The relationship between body weight, insulin resistance, and steatosis is complex. Steatosis has been strongly associated with fibrosis progression ([Figure 7](#)), HCC, and decreased response to therapy for hepatitis C infection. A close relationship between insulin resistance and chronic HCV has been identified. Persons with chronic HCV infection are more likely than healthy controls to have insulin resistance and diabetes mellitus. In addition, insulin resistance and diabetes mellitus are independently associated with increased fibrosis progression. It is difficult to tease out the relative importance of obesity independent of steatosis and insulin resistance.

Use of Alcohol: Use of alcohol in the setting of HCV has consistently been associated with an increased risk of progression to cirrhosis. Most studies that have examined the impact of alcohol on fibrosis progression quantify alcohol intake based on the number of grams of alcohol ingested on a daily basis. As a rough guide, in the United States, "a standard drink of alcohol" is defined as approximately 14 grams of alcohol, with the following considered one standard drink equivalent: a 12-ounce bottle of beer, an 8- to 9-ounce bottle of malt liquor, a 5-ounce glass of table wine, or a 1.5-ounce glass of hard liquor. In a study of more than 2000 HCV-infected patients in France, daily consumption of over 50 grams of alcohol was associated with a 38% increase in fibrosis progression. Another study involving HCV-infected patients found accelerated fibrosis progression in persons with excessive alcohol intake (greater than 40 grams per day for women and greater than 60 grams per day for men) ([Figure 8](#)). In addition, use of alcohol has also been associated with development of HCC and mortality. In a study using population-based mortality data, heavy alcohol use in the setting of HCV infection was strongly associated with premature death.

Use of Marijuana: In several studies, daily use of marijuana has been associated with accelerated fibrosis progression ([Figure 9](#)). In one study a strong independent association was found between heavy use of marijuana and steatosis and the authors postulated a possible steatogenic role of marijuana on the endogenous cannabinoid system.

Use of Coffee: In a prospective study of HCV patients with bridging fibrosis or cirrhosis, regular coffee consumption was associated with slower fibrosis progression. The number of poor clinical

outcomes decreased linearly in relation to number of cups of coffee consumed daily ([Figure 10](#)). Those who drank 3 or more cups per day had a relative risk of 0.46 for developing a poor outcome compared with those who drank no coffee. In addition, several studies, including two meta-analyses, have found an inverse relationship with coffee consumption and the risk of developing HCC among patients with cirrhosis. Taken together, available data suggest that higher levels of coffee ingestion are associated with lower hepatic necroinflammatory injury, slower rate of fibrosis progression, and decreased risk for developing HCC. The mechanism whereby coffee provides hepatoprotective properties remains unknown.

Viral Factors: Despite their importance in the response to hepatitis C treatment, the HCV genotype and HCV RNA level do not appear to influence progression of disease. In some studies, however, genotype 3A has been associated with a higher prevalence of steatosis on liver biopsy and steatosis has been associated with fibrosis progression.

Summary Points

- Approximately 75 to 85%, of persons infected with HCV will develop chronic infection.
- Factors associated with spontaneous clearance of HCV include younger age at infection, female sex, race other than African American, IL-28B CC genotype, and symptomatic acute infection.
- The natural history of HCV infection has not been clearly defined because of the lack of prospective studies. Our understanding of the natural history of hepatitis C is primarily based on retrospective studies.
- Among those who develop chronic HCV infection, approximately 20 to 25% will develop cirrhosis 20 to 30 years after acquiring HCV infection.
- It is impossible to predict the rate of fibrosis progression in an individual early on in their infection.
- Factors associated with an increased rate of fibrosis progression include acquisition of HCV at an older age, increased age independent of duration of infection, male sex, heavy alcohol use, heavy marijuana use, coinfection with HIV or HBV, steatosis and insulin resistance.
- Individuals who develop hepatitis C-related cirrhosis have approximately 1 to 4% risk per year of developing HCC.

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Figures

Figure 1 IL-28B and Spontaneous Clearance of HCV

This graphic shows the percentage of persons with spontaneous clearance of HCV after initial infection in relation to the individual's IL28B genotype. Clearance rates are highest among persons with the CC genotype.

Source: Thomas DL, Thio CL, Martin MP, et al. Genetic variation in IL28B and spontaneous clearance of hepatitis C virus. *Nature*. 2009;461:798-801.

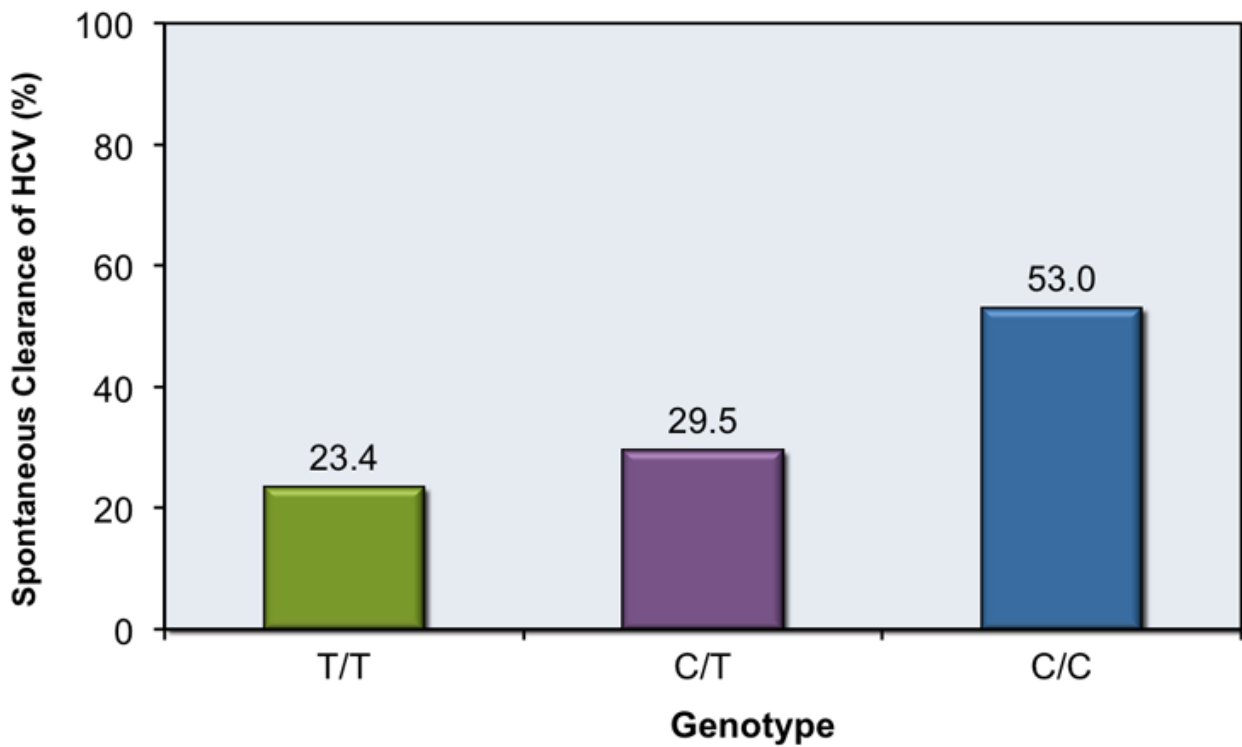


Figure 2 Time Course of Progression with Chronic Hepatitis C Infection

This graphic shows the time course for the natural history of chronic hepatitis C infection. Following initial HCV infection, there is typically a lag of 20 to 25 years before cirrhosis develops.

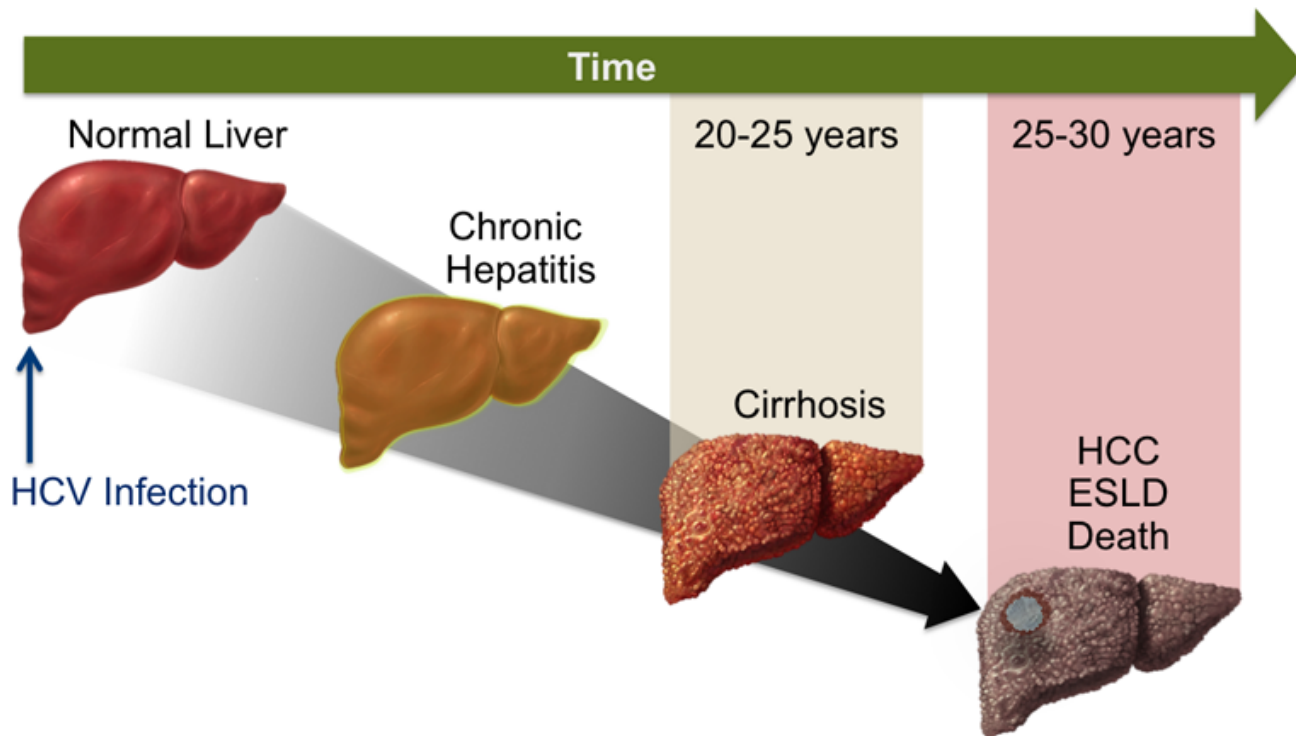


Figure 3 Natural History Following Initial Infection with HCV

Following initial infection with HCV, approximately 75 to 85% of persons develop chronic infection. Among those with chronic infection, approximately 20 to 30% will eventually develop cirrhosis. Patients who have HCV-related cirrhosis have a 2 to 7% per year risk of developing either end-stage liver disease or hepatocellular carcinoma. Abbreviations: ESLD = end stage liver disease HCC = hepatocellular carcinoma

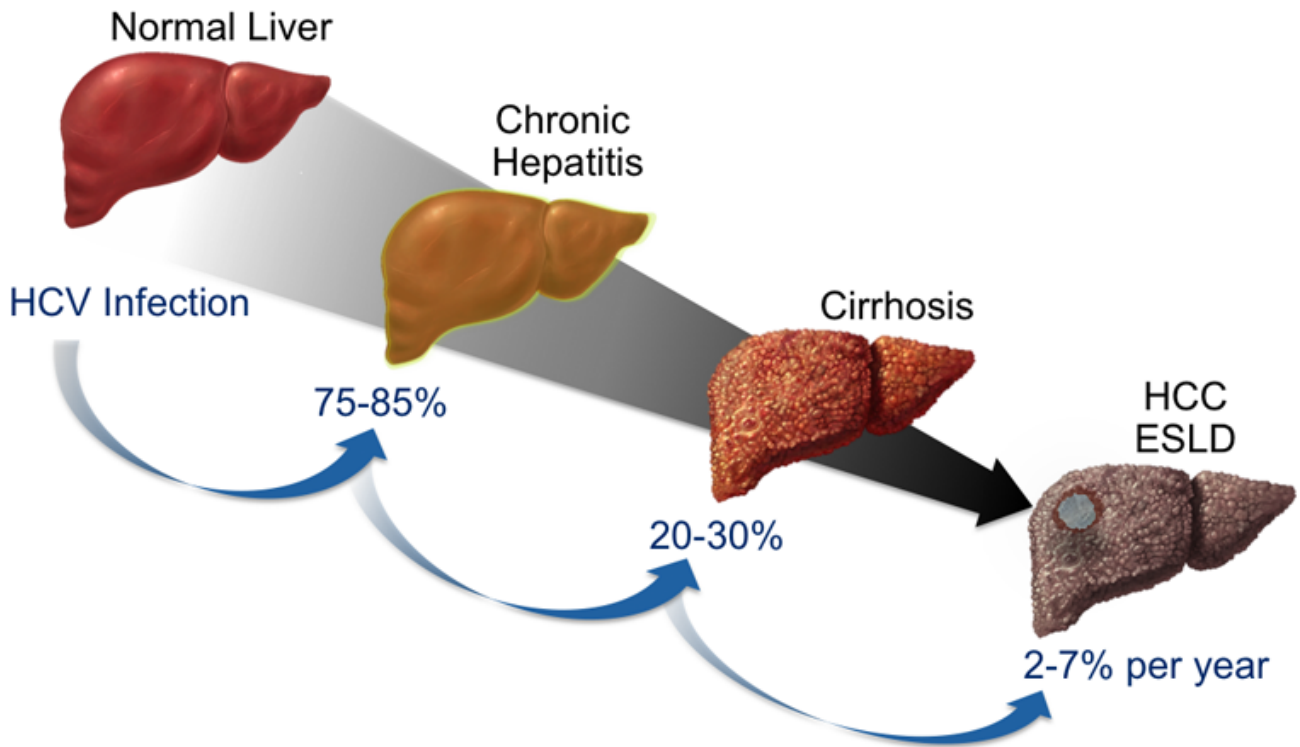
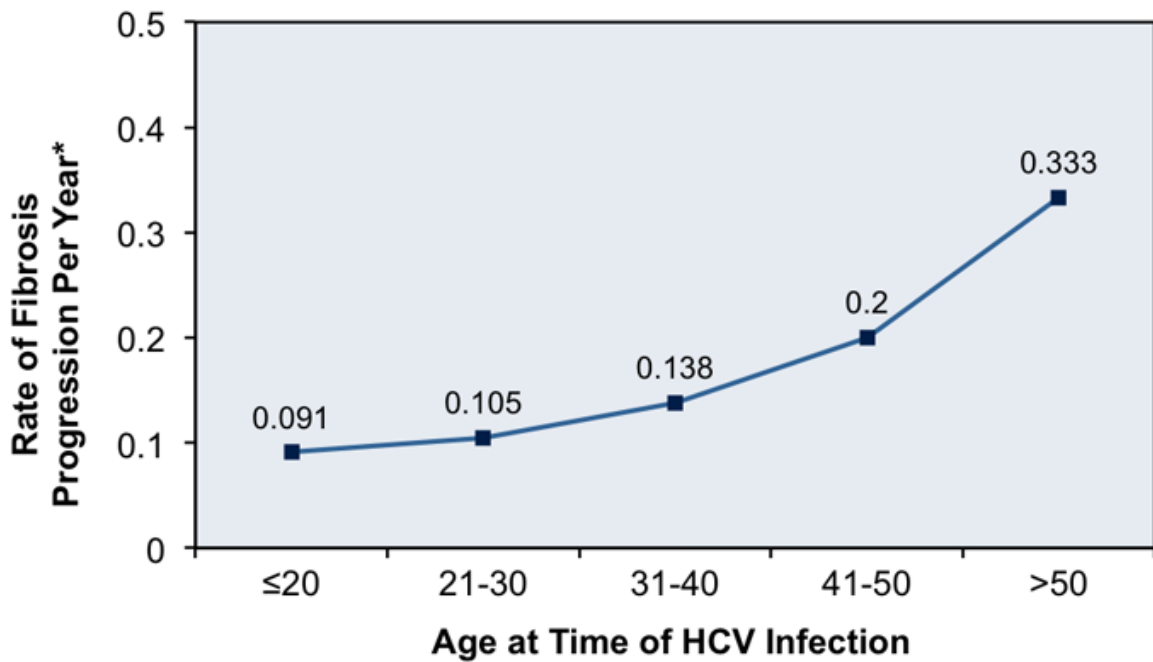


Figure 4 Impact of Age at the Time of Initial HCV Infection and Rate of Fibrosis

This graphic clearly shows higher rates of progression of hepatic fibrosis in patients who were older at the time of initial HCV infection.

Source: Poynard T, Bedossa P, Opolon P. Lancet. Natural history of liver fibrosis progression in patients with chronic hepatitis C. The OBSVIRC, METAVIR, CLINIVIR, and DOSVIRC groups. Lancet. 1997;349:825-32.



*Fibrosis progression per year = ratio between fibrosis stage in Metavir units and the duration of infection

Figure 5 Impact of Age at the Time of Initial HCV Infection and Risk of Cirrhosis

This graphic clearly shows the risk of developing cirrhosis increases with older age at the time of initial HCV infection.

Source: Poynard T, Ratziu V, Charlotte F, Goodman Z, McHutchison J, Albrecht J. Rates and risk factors of liver fibrosis progression in patients with chronic hepatitis C. *J Hepatol.* 2001;34:730-9.

Development of Cirrhosis within 20 Years after HCV Infection

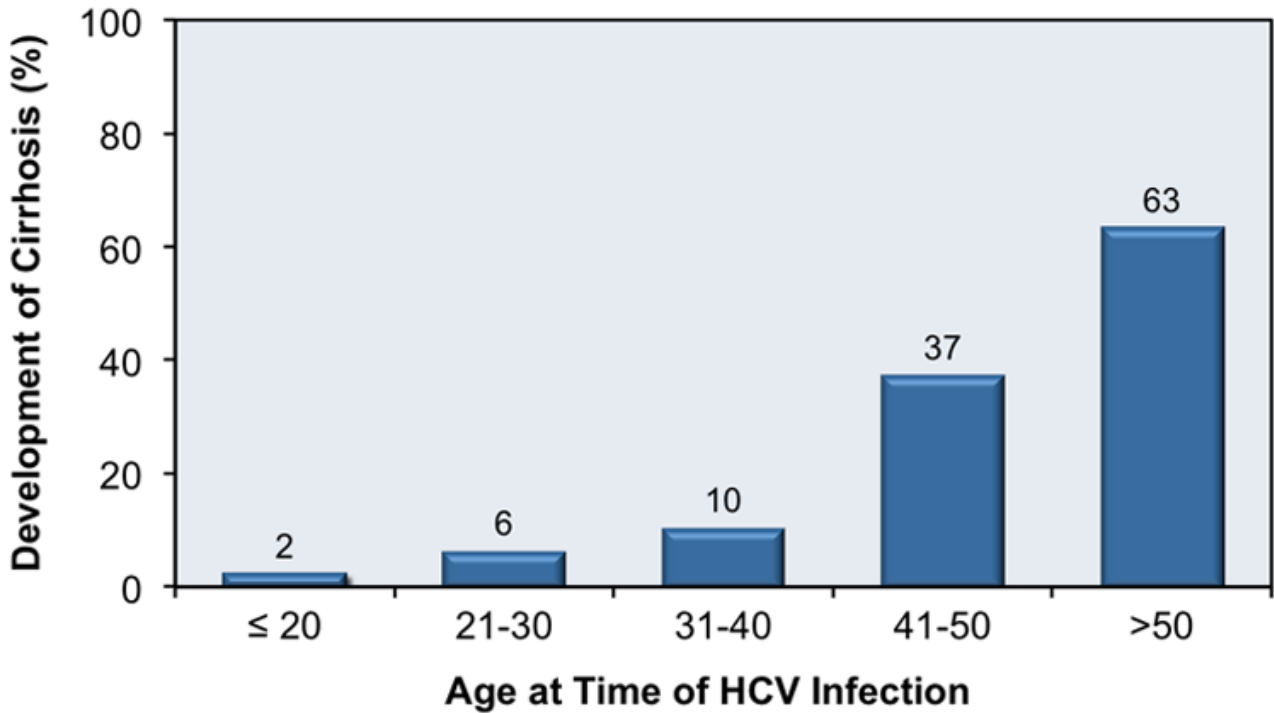


Figure 6 Impact of Coinfection with HIV and Progression of Hepatic Fibrosis

This graphic compares the progression of hepatic fibrosis over a 25-year period in HCV monoinfected individuals compared with those coinfecting with HCV and HIV. Coinfection with HIV accelerates the progression of hepatic fibrosis.

Source: 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;34:1193-9.

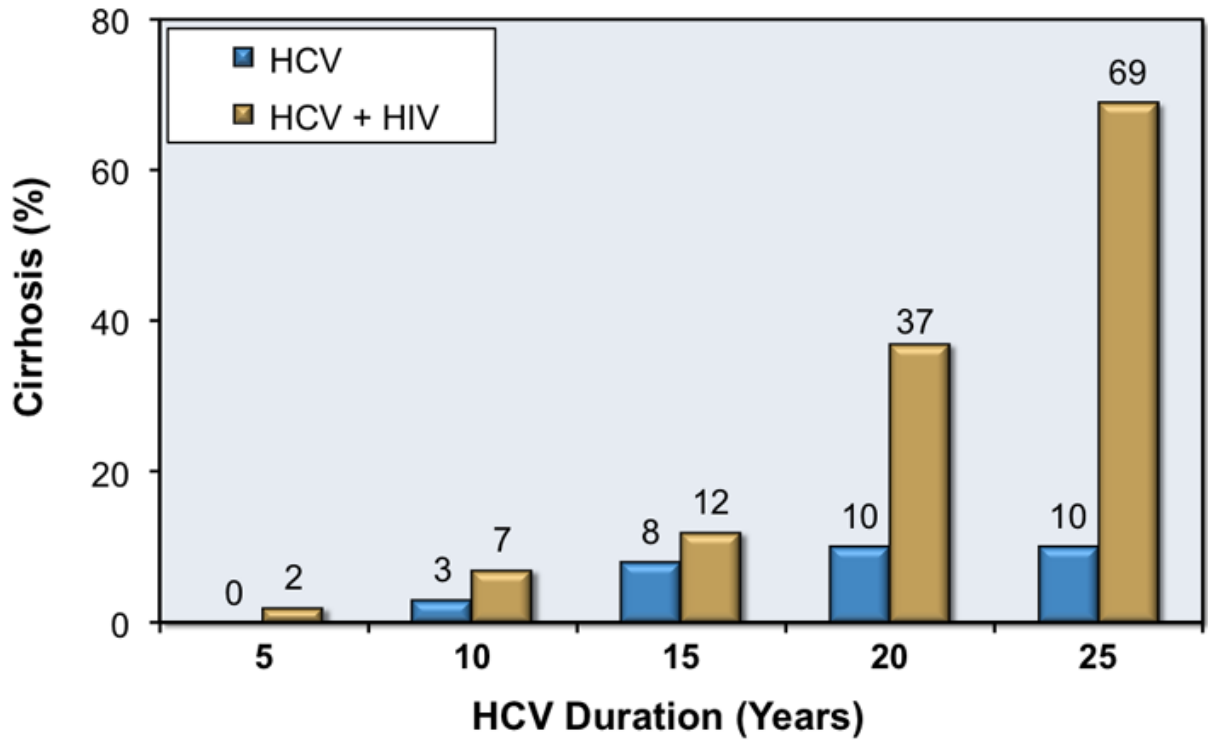


Figure 7 Impact of Steatosis on Progression of Hepatic Fibrosis

This graphic shows a correlation of degree of steatosis at initial biopsy with cumulative risk of hepatic fibrosis. The trends are clearly seen on both the year 4 (blue bars) and year 6 (orange bars) follow-up period.

Source: Fartoux L, Chazouillères O, Wendum D, Poupon R, Serfaty L. Impact of steatosis on progression of fibrosis in patients with mild hepatitis C. *Hepatology*. 2005;41:82-7.

Cumulative Progression of Fibrosis Based on Steatosis at Initial Biopsy

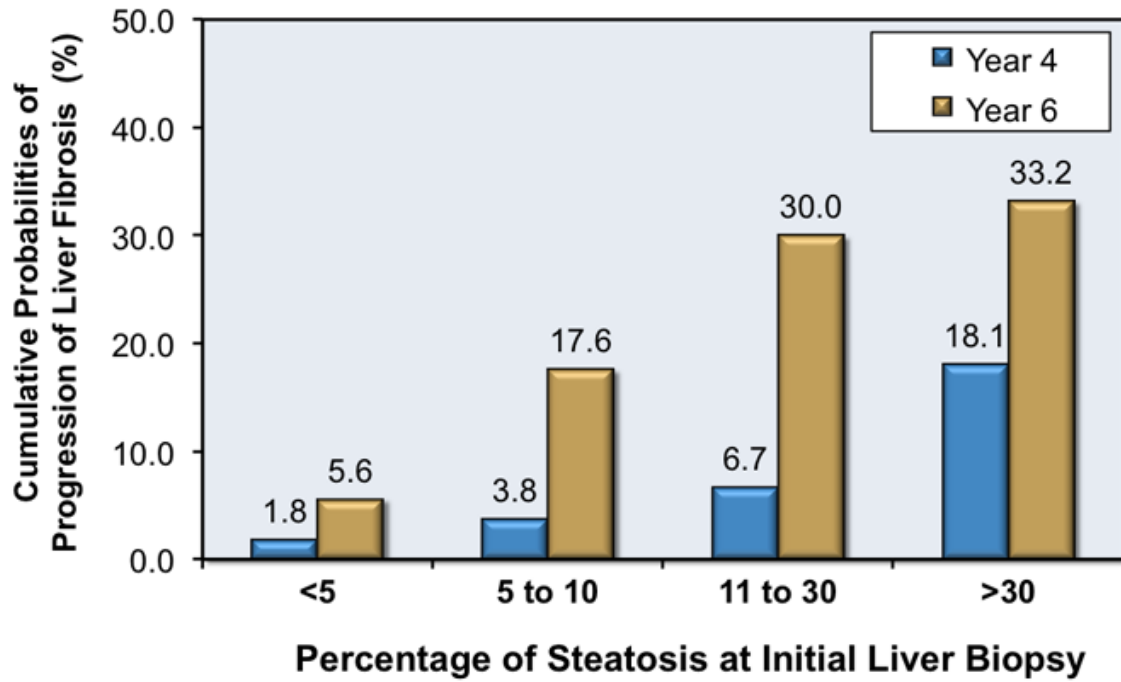
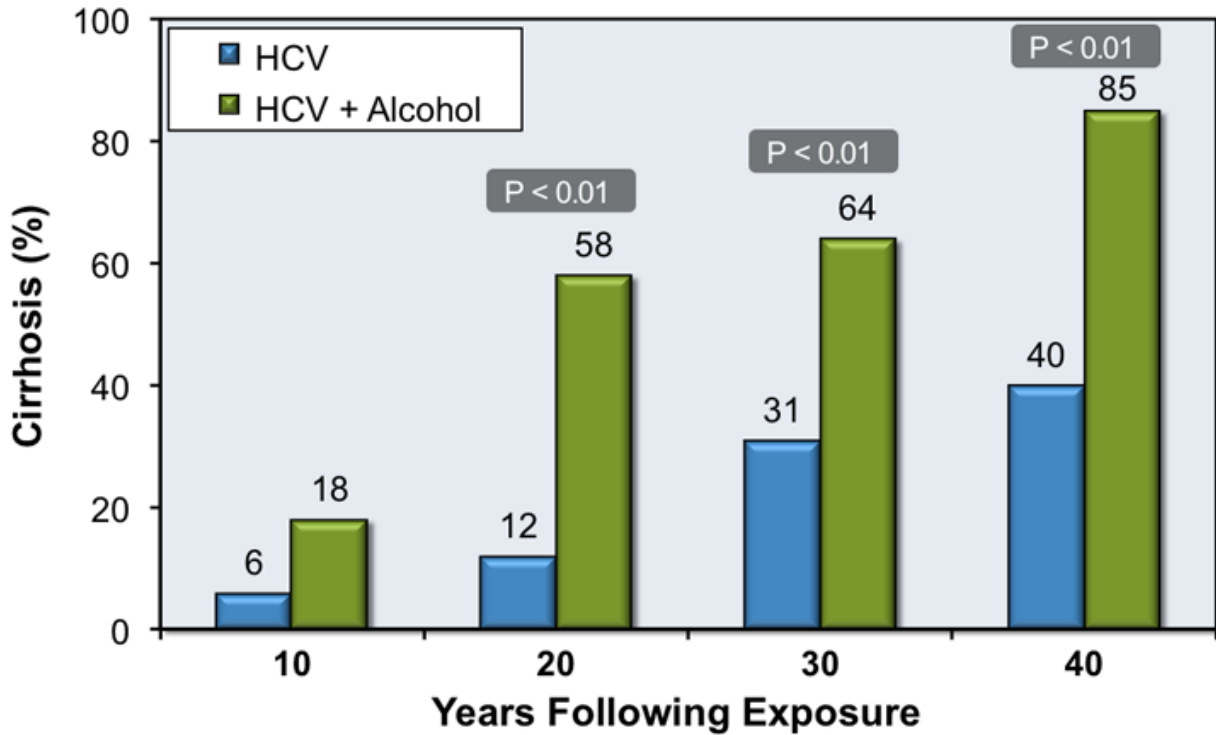


Figure 8 Impact of Alcohol Consumption on Progression of Hepatic Fibrosis

This graphic compares the progression of hepatic fibrosis over a 40-year period in persons without excessive alcohol use compared with those who had excessive alcohol use. Individuals with excessive alcohol use clearly had a greater risk of developing cirrhosis.

Source: Wiley TE, McCarthy M, Breidi L, McCarthy M, Layden TJ. Impact of alcohol on the histological and clinical progression of hepatitis C infection. *Hepatology*. 1998;28:805-9.



*Excessive alcohol defined as > 40 g/day for women and > 60 g/day for men

Figure 9 Impact of Cannabis Consumption on Progression of Hepatic Fibrosis

In this study, investigators analyzed the impact of cannabis consumption on the progression of hepatic fibrosis in 270 patients with chronic hepatitis C. Cannabis use was categorized as occasional use or daily use. This analysis was further adjusted based on alcohol consumption (less than or equal to 30 g per day or greater than 30 g per day). Patients with daily cannabis use had greater likelihood of having advanced liver fibrosis than those with occasional cannabis use, regardless of alcohol intake.

Source: Hézode C, Roudot-Thoraval F, Nguyen S, et al. Daily cannabis smoking as a risk factor for progression of fibrosis in chronic hepatitis C. *Hepatology*. 2005;42:63-71.

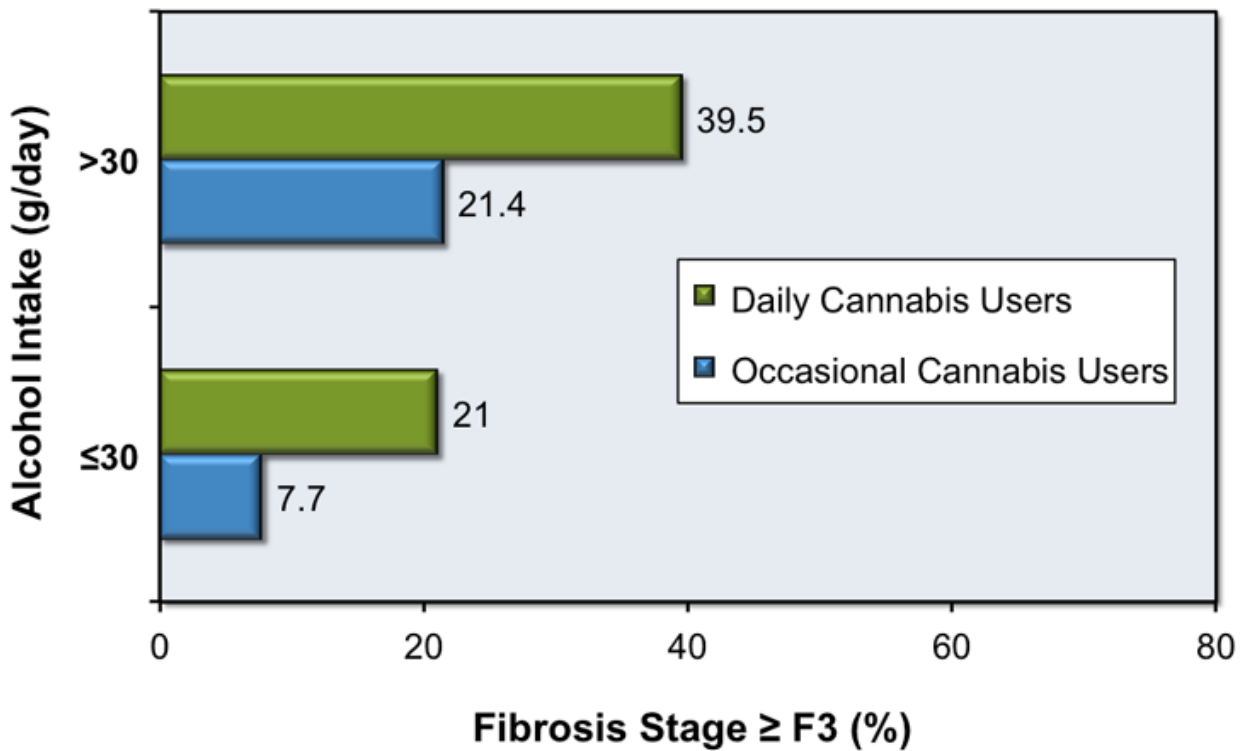


Figure 10 impact of Coffee Consumption

In this study, investigators examined the relationship of coffee intake and progression of liver disease in 766 patients with chronic hepatitis C. They found that regular coffee consumption was associated with a lower rate of progression of hepatic fibrosis.

Source: Freedman ND, Everhart JE, Lindsay KL, et al. Coffee intake is associated with lower rates of liver disease progression in chronic hepatitis C. *Hepatology*. 2009;50:1360-9.

Outcome Rates and Coffee Ingestion in Patients with Advanced Hepatitis C

