Natural History of HCV Infection

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Module 2: Evaluation, Staging, and Monitoring of Chronic Hepatitis C
Lesson 2: Natural History of HCV Infection

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Spontaneous Clearance versus Chronic Infection

Most persons who acquire hepatitis C virus (HCV) will develop chronic infection.[1] 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 play a significant role.[2,3] The actual rate of chronicity following initial infection with HCV is not well established in prospective studies, primarily because of the high percentage of persons who have asymptomatic or unrecognized early infection.[4] The chronicity rate has been estimated from cross-sectional population-based studies, such as the National Health and Nutrition Examination Survey (NHANES), as well as numerous retrospective studies.[5] Overall, it is estimated that 55 to 85% of persons who acquire HCV will develop chronic HCV infection.[6]

Role of Immune Response in Outcome of Early Infection

The rate of HCV 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 viral genetic diversity contributes to the high likelihood of developing chronic infection, whereas certain host factors play an important role in whether an individual will go on to spontaneously clear HCV.[7,8,9] Human and animal studies indicate that clearance of HCV is associated with strong and persistent HCV-specific cytotoxic T-lymphocyte and CD4 lymphocyte responses.[10,11] In addition, persons who clear HCV generally have limited viral diversity, which also points to enhanced immune-mediated response to acute infection.[12]

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 rate of developing chronic HCV infection may be lower in younger persons, including those who acquire HCV during childhood.[13] In one study of 67 children infected with HCV through contaminated blood transfusions, only 55% developed chronic infection.[14] Similarly, in a prospective cohort that assessed viral clearance among 919 persons aged 17 years or older, there was a marginal association between age younger than 45 years and HCV viral clearance.[6]
- **Female Sex**: In a large retrospective analysis of more than 704 women who acquired HCV after receiving contaminated Rh immune globulin, 55% of the 704 women developed chronic HCV infection, a rate on the lower end of that typically reported.[15] In addition, several multicenter prospective studies of patients with acute HCV have reported women were more likely than men to experience

spontaneous clearance of HCV.[8,16]

- **Race**: In the NHANES study, the rate of developing chronic HCV infection was determined by the prevalence of HCV RNA positivity among persons who had a positive HCV antibody test.[5] Overall, HCV viremia was present in 74% of persons with a positive HCV antibody test; however, the rate was 98% for African American men.[5] In a prospective cohort study involving 1,667 persons who inject drugs, African Americans were more likely to develop chronic infection than other races (91% versus 64%).[6] This racial difference in spontaneous clearance may be accounted for, at least in part, by differences in the IL28B gene (presence of CT and TT alleles) and other variations in alleles, which have been associated with a lower rate of spontaneous clearance and may be more prevalent among persons of African descent.[17,18,19]
- **Symptomatic Acute HCV Infection**: In a variety of studies, individuals who presented with clinical symptoms of acute HCV infection, particularly those who developed jaundice, were less likely to develop chronic infection.[3,4] 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.
- **Absence of HIV Coinfection**: In a prospective study of persons who inject drugs (PWID) who acquired HCV, those with HIV were more likely to develop chronic infection than those who did not have HIV.[20] In a subsequent study that enrolled persons with early HCV infection, HCV persisted in 95% of those with HCV and HIV coinfection and persistence was associated with relatively weak HCV-specific T cell responses.[21] Other studies have similarly shown relatively lower clearance of HCV in persons with HIV coinfection and one prospective study of viral clearance among 9,191 persons age 17 years and older found an association between lower CD4 count and decreased odds of HCV clearance.[22,23]
- **IL28B CC Genotype**: The single nucleotide polymorphism (SNP) rs12979860 is located upstream from the IL28B gene that encodes for interleukin 28 (also referred to as interferon lambda). Variations in the rs12979860 SNP have been associated with the probability of clearance of HCV.[17,24,25] Individuals with the CC allele of IL28B genotype are more likely to spontaneously clear HCV than those with CT or TT genotypes. 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).[17]

Variable Outcomes of Chronic Infection

Studies Related to Natural History

The natural history of chronic HCV infection has not been fully delineated. It is 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 HCV infection, which sets the timeline for determining duration of infection, and the necessity of following persons with HCV for decades to see clinical complications.[13,26]

Timing of Development of Liver Complications

Once chronicity is established, available data suggest the process runs an indolent course for the first two decades after infection. If serious liver disease related to chronic HCV infection (e.g., cirrhosis, end-stage liver disease [ESLD], and/or hepatocellular carcinoma [HCC]) develop, such complications are more likely to emerge in the third and fourth decades after initial infection (Figure 2).

Estimates of Frequency of Liver Complications

Among those with chronic HCV, an estimated 20 to 30% will develop cirrhosis, and among those with HCV-related cirrhosis, there is an approximately 1 to 4% annual risk of developing HCC and a 2 to 5% annual risk of progressing to ESLD (Figure 3).[2,27,28]

Fibrosis and Cirrhosis

Annual rates of progression to cirrhosis increase with older age at the time of HCV acquisition and longer duration of infection, but the relationship is not linear.[29] It is estimated that approximately 20 to 30% of those infected with HCV will develop cirrhosis during the 20- to 30-year period after HCV acquisition.[27,30] This progression 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, which is mediated by host, viral, and environmental factors.[31]

Host Factors that Impact Rate of Fibrosis Progression

Multiple factors can influence the natural history, rate of fibrosis progression, and survival of persons with chronic HCV infection, including host factors.[27,32]

Age

The progression of liver fibrosis in persons infected with chronic HCV appears to accelerate at a faster rate in persons older than 40 years of age, when compared to younger individuals. The reason for this age-related difference in fibrosis progression is not known, but may relate to reduced regenerative capacity of the liver or decreased hepatic blood flow in older persons.[27,32] In addition, older age at acquisition of HCV is associated with a more rapid rate of fibrosis progression (Figure 4).[33,34,35] In one study, development of cirrhosis within 20 years of HCV infection occurred in only 2% of participants who acquired HCV before the age of 20, but it developed in 63% of the individuals who acquired HCV after the age of 50.[36]

Rate of Progression by Sex

Multiple studies in persons with chronic HCV have shown that males experience a more rapid fibrosis progression than females.[33,37,38] Even when controlling for alcohol consumption, duration of infection, and age, men still have a fibrosis progression rate approximately twice that of women.[33] The explanation for the more rapid progression in men is not clear, but may relate to differences in sex hormones.[27] Several studies have shown an association between increased serum testosterone levels and advanced hepatic inflammatory activity in men.[39] More recently, investigators have reported that certain variants in genes involved in androgen and estrogen biosynthesis correlate with increased risk of accelerated hepatic fibrosis and inflammation in males.[40]

Metabolic Factors (Obesity, Insulin Resistance, and Hepatic Steatosis)

The relationship between body weight, insulin resistance, and hepatic steatosis is complex. Hepatic steatosis has been strongly associated with fibrosis progression and risk of HCC (Figure 5).[41,42,43] In addition, insulin resistance and diabetes mellitus are independently associated with increased fibrosis progression.[44,45] Given that persons with chronic HCV are more likely than healthy controls to have insulin resistance and diabetes mellitus, it is difficult to tease out the relative importance of obesity on the progression of fibrosis independent of hepatic steatosis and insulin resistance.

Viral Factors that Impact Rate of Fibrosis Progression

Several viral factors may significantly impact the rate of fibrosis progression.

HCV Factors

In general, the HCV RNA level and HCV genotypes do not appear to influence the progression of liver disease.[6] One exception is the impact of chronic infection with HCV genotype 3. Multiple studies have shown that persons infected with genotype 3 have a higher prevalence of hepatic steatosis on liver biopsy, which has been associated with a greater likelihood of progression to cirrhosis and HCC.[46,47,48,49,50]

Coinfection with HIV

Coinfection with HIV accelerates the course of HCV-related liver damage and progression to cirrhosis (Figure 6), ESLD, HCC, and death.[51,52,53] A meta-analysis of studies examining the impact of HIV on the course of HCV infection (using cirrhosis and decompensated liver disease as their endpoints) yielded an adjusted relative risk of 2.92 for persons with HCV and HIV coinfection compared with persons who have HCV monoinfection.[54] In this same review, studies that only examined decompensated liver disease showed an even higher relative risk of 6.14 with coinfection.[54] In persons with HIV infection, CD4 count less than 200 cells/mm^3, alcohol consumption, and older age at the time of HCV acquisition are independently associated with accelerated fibrosis progression.[52] The mechanism whereby HIV causes accelerated hepatic fibrosis in persons with HCV remains unclear, but may result from an alteration in the host cytokine milieu that favors fibrosis, possibly related to HIV-related depletion in gut-associated lymphoid tissue and enhanced microbial translocation.[53] Unfortunately, it appears that fully suppressive therapy for HIV only partially neutralizes the negative impact of HIV on HCV-related progression of liver disease.[53,55]

Coinfection with Hepatitis B

Approximately 2 to 10% of persons with chronic HCV infection have coinfection with hepatitis B.[27] Most studies, although small and mostly retrospective, suggest that coinfection with HBV and HCV accelerates liver disease progression, increases the risk of cirrhosis, HCC, and death.[56,57] The adverse impact of HBV coinfection only occurs in patients with ongoing HBV replication (viremia).[57]

Environmental Factors that Impact Rate of Fibrosis Progression

Several environmental factors have been shown to impact the rate of fibrosis progression in persons with chronic HCV infection.

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, the National Institute on Alcohol Abuse and Alcoholism defines “a standard drink of alcohol” as approximately 14 grams of alcohol, with the following considered one standard drink equivalent: 12 ounces of regular beer, 8 to 9 ounces of malt liquor, 5 ounces of table wine, or 1.5 ounces of hard liquor. In a study of more than 2,000 persons living with HCV infection in France, daily consumption of over 50 grams of alcohol was associated with a 38% increase in fibrosis progression.[36] Another study involving persons with HCV infection 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 7).[58] In addition, alcohol use has also been associated with development of HCC and mortality.[59,60] In a study using population-based mortality data, heavy alcohol use in the setting of HCV infection was strongly associated with premature death.[61]

Cannabis

Data on cannabis intake and its impact on the natural history of HCV are conflicting.[62,63,64,65] In several studies, daily use of cannabis (marijuana) has been associated with accelerated fibrosis progression.[63,64,66] In one study, a strong independent association was found between heavy use of marijuana and hepatic steatosis, and the authors postulated a possible steatogenic role of marijuana on the endogenous cannabinoid system.[64] Other studies, however, have shown that regular use of cannabis in persons with chronic HCV reduces insulin resistance and the risk of hepatic steatosis.[62,65] Ultimately, the evidence base is mixed and not supportive of an overt association between cannabis use and fibrosis.

Coffee

In a prospective study of HCV patients with bridging fibrosis or cirrhosis, regular coffee consumption was associated with slower fibrosis progression (Figure 8).[67] In a separate study, investigators showed that persons with chronic HCV infection who drank 3 or more cups per day had relatively reduced liver histologic activity.[68] In addition, several studies, including two meta-analyses, have found an inverse relationship between coffee consumption and the risk of developing HCC among patients with cirrhosis.[69,70] Taken together, available data suggest that higher levels of coffee consumption 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.

Summary Points

- Approximately 55 to 85% of persons who acquire HCV will develop chronic HCV infection.
- Factors associated with spontaneous clearance of HCV include younger age at infection, female sex, race other than African American, IL28B CC genotype, and symptomatic acute HCV 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, an estimated 20 to 30% will develop cirrhosis.
- It is impossible to predict the rate of fibrosis progression in an individual early on in their infection, but there are several host, viral, and environmental factors that have been shown to influence disease progression.
- 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, coinfection with HIV or HBV, hepatic steatosis, and insulin resistance.
- Individuals who develop HCV-related cirrhosis have an approximately 1 to 4% risk per year of developing HCC.

Citations

1. Hoofnagle JH. Course and outcome of hepatitis C. Hepatology. 2002;36:S21-9.
[PubMed Abstract] -

2. Liang TJ, Rehermann B, Seeff LB, Hoofnagle JH. Pathogenesis, natural history, treatment, and prevention of hepatitis C. Ann Intern Med. 2000;132:296-305.
[PubMed Abstract] -

3. Maheshwari A, Ray S, Thuluvath PJ. Acute hepatitis C. Lancet. 2008;372(9635):321-32.
[PubMed Abstract] -

4. Micallef JM, Kaldor JM, Dore GJ. Spontaneous viral clearance following acute hepatitis C infection: a systematic review of longitudinal studies. J Viral Hepat. 2006;13:34-41.
[PubMed Abstract] -

5. Alter MJ, Kruszon-Moran D, Nainan OV, et al. The prevalence of hepatitis C virus infection in the United States, 1988 through 1994. N Engl J Med. 1999;341:556-62.
[PubMed Abstract] -

6. Thomas DL, Astemborski J, Rai RM, et al. The natural history of hepatitis C virus infection: host, viral, and environmental factors. JAMA 2000;284:450-6.
[PubMed Abstract] -

7. Kamal SM. Acute hepatitis C: a systematic review. Am J Gastroenterol. 2008;103:1283-97.
[PubMed Abstract] -

8. Grebely J, Page K, Sacks-Davis R, et al. The effects of female sex, viral genotype, and IL28B genotype on spontaneous clearance of acute hepatitis C virus infection. Hepatology. 2014;59:109-20.
[PubMed Abstract] -

9. Kim AY, Kuntzen T, Timm J, et al. Spontaneous control of HCV is associated with expression of HLA-B 57 and preservation of targeted epitopes. Gastroenterology. 2011;140:686-696.e1.
[PubMed Abstract] -

10. Blackard JT, Shata MT, Shire NJ, Sherman KE. Acute hepatitis C virus infection: a chronic problem. Hepatology. 2008;47:321-31.
[PubMed Abstract] -

11. Gerlach JT, Diepolder HM, Jung MC, et al. Recurrence of hepatitis C virus after loss of virus-specific CD4(+) T-cell response in acute hepatitis C. Gastroenterology. 1999;117:933-41.
[PubMed Abstract] -

12. Rosen HR. Emerging concepts in immunity to hepatitis C virus infection. J Clin Invest. 2013;123:4121-30.
[PubMed Abstract] -

13. Thomas DL, Seeff LB. Natural history of hepatitis C. Clin Liver Dis. 2005;9:383-98.
[PubMed Abstract] -

14. Vogt M, Lang T, Frösner G, et al. Prevalence and clinical outcome of hepatitis C infection in children who underwent cardiac surgery before the implementation of blood-donor screening. N Engl J Med. 1999;341:866-70.

[PubMed Abstract] -

15. Kenny-Walsh E. Clinical outcomes after hepatitis C infection from contaminated anti-D immune globulin. Irish Hepatology Research Group. N Engl J Med. 1999;340:1228-33.
[PubMed Abstract] -

16. Wang CC, Krantz E, Klarquist J, et al. Acute hepatitis C in a contemporary US cohort: modes of acquisition and factors influencing viral clearance. J Infect Dis. 2007;196:1474-82.
[PubMed Abstract] -

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

18. Valencia A, Vergara C, Thio CL, et al. Trans-ancestral fine-mapping of MHC reveals key amino acids associated with spontaneous clearance of hepatitis C in HLA-DQβ1. Am J Hum Genet. 2022;109:299-310.
[PubMed Abstract] -

19. Wojcik GL, Thio CL, Kao WH, et al. Admixture analysis of spontaneous hepatitis C virus clearance in individuals of African descent. Genes Immun. 2014;15:241-6.
[PubMed Abstract] -

20. Mehta SH, Cox A, Hoover DR, et al. Protection against persistence of hepatitis C. Lancet. 2002;359:1478-83.
[PubMed Abstract] -

21. Danta M, Semmo N, Fabris P, et al. Impact of HIV on host-virus interactions during early hepatitis C virus infection. J Infect Dis. 2008;197:1558-66.
[PubMed Abstract] -

22. Newsum AM, Schinkel J, van de Laar TJW, van der Meer JTM, Prins M. Spontaneous Clearance of Hepatitis C Virus Infection Among Human Immunodeficiency Virus-Infected Men Who Have Sex With Men. Open Forum Infect Dis. 2017;4:ofx090.
[PubMed Abstract] -

23. Smith DJ, Jordan AE, Frank M, Hagan H. Spontaneous viral clearance of hepatitis C virus (HCV) infection among people who inject drugs (PWID) and HIV-positive men who have sex with men (HIV+ MSM): a systematic review and meta-analysis. BMC Infect Dis. 2016;16:471.
[PubMed Abstract] -

24. Grebely J, Petoumenos K, Hellard M, et al. Potential role for interleukin-28B genotype in treatment decision-making in recent hepatitis C virus infection. Hepatology. 2010;52:1216-24.
[PubMed Abstract] -

25. Tillmann HL, Thompson AJ, Patel K, et al. A polymorphism near IL28B is associated with spontaneous clearance of acute hepatitis C virus and jaundice. Gastroenterology. 2010;139:1586-92.
[PubMed Abstract] -

26. Seeff LB. Natural history of hepatitis C. Hepatology. 1997;26(3 Suppl 1):21S-28S.
[PubMed Abstract] -

27. Lingala S, Ghany MG. Natural History of Hepatitis C. Gastroenterol Clin North Am. 2015;44:717-34.
[PubMed Abstract] -

28. Hajarizadeh B, Grebely J, Dore GJ. Epidemiology and natural history of HCV infection. Nat Rev Gastroenterol Hepatol. 2013;10:553-62.
[PubMed Abstract] -

29. Ryder SD, Irving WL, Jones DA, Neal KR, Underwood JC; Trent Hepatitis C Study Group. Progression of hepatic fibrosis in patients with hepatitis C: a prospective repeat liver biopsy study. Gut. 2004;53:451-5.
[PubMed Abstract] -

30. Freeman AJ, Dore GJ, Law MG, et al. Estimating progression to cirrhosis in chronic hepatitis C virus infection. Hepatology. 2001;34:809-16.
[PubMed Abstract] -

31. Missiha SB, Ostrowski M, Heathcote EJ. Disease progression in chronic hepatitis C: modifiable and nonmodifiable factors. Gastroenterology. 2008;134;1699-714.
[PubMed Abstract] -

32. Maasoumy B, Wedemeyer H. Natural history of acute and chronic hepatitis C. Best Pract Res Clin Gastroenterol. 2012;26:401-12.
[PubMed Abstract] -

33. 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.
[PubMed Abstract] -

34. Minola E, Prati D, Suter F, et al. Age at infection affects the long-term outcome of transfusion-associated chronic hepatitis C. Blood. 2002;99:4588-91.
[PubMed Abstract] -

35. Pradat P, Voirin N, Tillmann HL, Chevallier M, Trépo C. Progression to cirrhosis in hepatitis C patients: an age-dependent process. Liver Int. 2007;27:335-9.
[PubMed Abstract] -

36. 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.
[PubMed Abstract] -

37. Freeman AJ, Law MG, Kaldor JM, Dore GJ. Predicting progression to cirrhosis in chronic hepatitis C virus infection. J Viral Hepat. 2003;10:285-93.
[PubMed Abstract] -

38. Harris HE, Ramsay ME, Andrews N, Eldridge KP. Clinical course of hepatitis C virus during the first decade of infection: cohort study. BMJ. 2002;324:450-3.
[PubMed Abstract] -

39. White DL, Tavakoli-Tabasi S, Kuzniarek J, Pascua R, Ramsey DJ, El-Serag HB. Higher serum testosterone is associated with increased risk of advanced hepatitis C-related liver disease in males. Hepatology. 2012;55:759-68.
[PubMed Abstract] -

40. White DL, Liu Y, Garcia J, et al. Sex hormone pathway gene polymorphisms are associated with risk of advanced hepatitis C-related liver disease in males. Int J Mol Epidemiol Genet. 2014;5:164-76.
[PubMed Abstract] -

41. Charlton MR, Pockros PJ, Harrison SA. Impact of obesity on treatment of chronic hepatitis C. Hepatology. 2006;43:1177-86.
[PubMed Abstract] -

42. 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.
[PubMed Abstract] -

43. Marrero JA, Fontana RJ, Fu S, Conjeevaram HS, Su GL, Lok AS. Alcohol, tobacco and obesity are synergistic risk factors for hepatocellular carcinoma. J Hepatol 2005; 42:218-24.
[PubMed Abstract] -

44. Serfaty L. Metabolic Manifestations of Hepatitis C Virus: Diabetes Mellitus, Dyslipidemia. Clin Liver Dis. 2017;21:475-486.
[PubMed Abstract] -

45. Everhart JE, Lok AS, Kim HY, et al. Weight-related effects on disease progression in the hepatitis C antiviral long-term treatment against cirrhosis trial. Gastroenterology. 2009;137:549-57.
[PubMed Abstract] -

46. Nkontchou G, Ziol M, Aout M, et al. HCV genotype 3 is associated with a higher hepatocellular carcinoma incidence in patients with ongoing viral C cirrhosis. J Viral Hepat. 2011;18:e516-22.
[PubMed Abstract] -

47. McMahon BJ, Bruden D, Townshend-Bulson L, et al. Infection With Hepatitis C Virus Genotype 3 Is an Independent Risk Factor for End-Stage Liver Disease, Hepatocellular Carcinoma, and Liver-Related Death. Clin Gastroenterol Hepatol. 2017;15:431-437.e2.
[PubMed Abstract] -

48. Kanwal F, Kramer JR, Ilyas J, Duan Z, El-Serag HB. HCV genotype 3 is associated with an increased risk of cirrhosis and hepatocellular cancer in a national sample of U.S. Veterans with HCV. Hepatology. 2014;60:98-105.
[PubMed Abstract] -

49. Bochud PY, Cai T, Overbeck K, et al. Genotype 3 is associated with accelerated fibrosis progression in chronic hepatitis C. J Hepatol. 2009;51:655-66.
[PubMed Abstract] -

50. Wu N, Rao HY, Yang WB, et al. Impact of hepatitis C virus genotype 3 on liver disease progression in a Chinese national cohort. Chin Med J (Engl). 2020;133:253-61.
[PubMed Abstract] -

51. 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.
[PubMed Abstract] -

52. Benhamou Y, Bochet M, Di Martino V, et al. Liver fibrosis progression in human immunodeficiency virus and hepatitis C virus coinfected patients. The Multivirc Group. Hepatology. 1999;30:1054-8.
[PubMed Abstract] -

53. Ingiliz P, Rockstroh JK. Natural history of liver disease and effect of hepatitis C virus on HIV disease progression. Curr Opin HIV AIDS. 2015;10:303-8.

[PubMed Abstract] -

54. Graham CS, Baden LR, Yu E, Mrus JM, Carnie J, Heeren T, Koziel MJ. Influence of human immunodeficiency virus infection on the course of hepatitis C virus infection: a meta-analysis. Clin Infect Dis. 2001;33:562-9.
[PubMed Abstract] -

55. Thein HH, Yi Q, Dore GJ, Krahn MD. Natural history of hepatitis C virus infection in HIV-infected individuals and the impact of HIV in the era of highly active antiretroviral therapy: a meta-analysis. AIDS. 2008;22:1979-91.
[PubMed Abstract] -

56. Jamma S, Hussain G, Lau DT. Current Concepts of HBV/HCV Coinfection: Coexistence, but Not Necessarily in Harmony. Curr Hepat Rep. 2010;9:260-9.
[PubMed Abstract] -

57. Kruse RL, Kramer JR, Tyson GL, et al. Clinical outcomes of hepatitis B virus coinfection in a United States cohort of hepatitis C virus-infected patients. Hepatology. 2014;60:1871-8.
[PubMed Abstract] -

58. 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.
[PubMed Abstract] -

59. Benvegnu L, Gios M, Boccato S, Alberti A. Natural history of compensated viral cirrhosis: a prospective study on the incidence and hierarchy of major complications. Gut. 2004;53:744-9.
[PubMed Abstract] -

60. Donato F, Tagger A, Gelatti U, et al. Alcohol and hepatocellular carcinoma: the effect of lifetime intake and hepatitis virus infections in men and women. Am J Epidemiol. 2002;155:323-31.
[PubMed Abstract] -

61. Chen CM, Yoon YH, Yi HY, Lucas DL. Alcohol and hepatitis C mortality among males and females in the United States: a life table analysis. Alcohol Clin Exp Res. 2007;31:285-92.
[PubMed Abstract] -

62. Carrieri MP, Serfaty L, Vilotitch A, et al. Cannabis Use and Reduced Risk of Insulin Resistance in HIV-HCV Infected Patients: A Longitudinal Analysis (ANRS CO13 HEPAVIH). Clin Infect Dis. 2015;61:40-8.
[PubMed Abstract] -

63. 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.
[PubMed Abstract] -

64. Hézode C, Zafrani ES, Roudot-Thoraval F, et al. Daily cannabis use: a novel risk factor of steatosis severity in patients with chronic hepatitis C. Gastroenterology. 2008;134(2):432-9.
[PubMed Abstract] -

65. Nordmann S, Vilotitch A, Roux P, et al. Daily cannabis and reduced risk of steatosis in human immunodeficiency virus and hepatitis C virus-co-infected patients (ANRS CO13-HEPAVIH). J Viral Hepat. 2018;25:171-179.
[PubMed Abstract] -

66. Ishida JH, Peters MG, Jin C, Louie K, Tan V, Bacchetti P, Terrault NA. Influence of cannabis use on

severity of hepatitis C disease. Clin Gastroenterol Hepatol. 2008;6:69-75.
[PubMed Abstract] -

67. 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.
[PubMed Abstract] -

68. Costentin CE, Roudot-Thoraval F, Zafrani ES, Medkour F, Pawlotsky JM, Mallat A, Hézode C. Association of caffeine intake and histological features of chronic hepatitis C. J Hepatol. 2011;54:1123-9.
[PubMed Abstract] -

69. Carrieri MP, Protopopescu C, Marcellin F, et al. Protective effect of coffee consumption on all-cause mortality of French HIV-HCV co-infected patients. J Hepatol. 2017;67:1157-1167.
[PubMed Abstract] -

70. Hodge A, Lim S, Goh E, et al. Coffee Intake Is Associated with a Lower Liver Stiffness in Patients with Non-Alcoholic Fatty Liver Disease, Hepatitis C, and Hepatitis B. Nutrients. 2017;9:56.
[PubMed Abstract] -

References

- Abenavoli L, Masarone M, Peta V, et al. Insulin resistance and liver steatosis in chronic hepatitis C infection genotype 3. World J Gastroenterol. 2014;20:15233-40.
[PubMed Abstract] -

- Huang YW, Yang SS, Fu SC, et al. Increased risk of cirrhosis and its decompensation in chronic hepatitis C patients with new-onset diabetes: a nationwide cohort study. Hepatology. 2014;60:807-14.
[PubMed Abstract] -

- Hui JM, Sud A, Farrell GC, et al. Insulin resistance is associated with chronic hepatitis C virus infection and fibrosis progression. Gastroenterology. 2003;125:1695-704.
[PubMed Abstract] -

- Krahn M, Wong JB, Heathcote J, Scully L, Seeff L. Estimating the prognosis of hepatitis C patients infected by transfusion in Canada between 1986 and 1990. Med Decis Making. 2004;24:20-9.
[PubMed Abstract] -

- Levine RA, Sanderson SO, Ploutz-Snyder R, et al. Assessment of fibrosis progression in untreated Irish women with chronic hepatitis C contracted from immunoglobulin anti-D. Clin Gastroenterol Hepatol. 2006;4:1271-7.
[PubMed Abstract] -

- McCombs J, Matsuda T, Tonnu-Mihara I, et al. The risk of long-term morbidity and mortality in patients with chronic hepatitis C: results from an analysis of data from a Department of Veterans Affairs Clinical Registry. JAMA Intern Med. 2014;174:204-12.
[PubMed Abstract] -

- Morgan RL, Baack B, Smith BD, Yartel A, Pitasi M, Falck-Ytter Y. Eradication of hepatitis C virus infection and the development of hepatocellular carcinoma: a meta-analysis of observational studies. Ann Intern Med. 2013;158:329-37.
[PubMed Abstract] -

- Noureddin M, Wong MM, Todo T, Lu SC, Sanyal AJ, Mena EA. Fatty liver in hepatitis C patients post-

sustained virological response with direct-acting antivirals. World J Gastroenterol. 2018;24:1269-1277. [PubMed Abstract] -

- Ragonnet R, Deuffic-Burban S, Boesecke C, et al. Estimating the Time to Diagnosis and the Chance of Spontaneous Clearance During Acute Hepatitis C in Human Immunodeficiency Virus-Infected Individuals. Open Forum Infect Dis. 2017;4:ofw235. [PubMed Abstract] -

- Westbrook RH, Dusheiko G. Natural history of hepatitis C. J Hepatol. 2014;61:S58-68. [PubMed Abstract] -

- Wirth TC, Manns MP. The impact of the revolution in hepatitis C treatment on hepatocellular carcinoma. Ann Oncol. 2016;27:1467-74. [PubMed Abstract] -

Figures

Figure 1 IL28B 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.

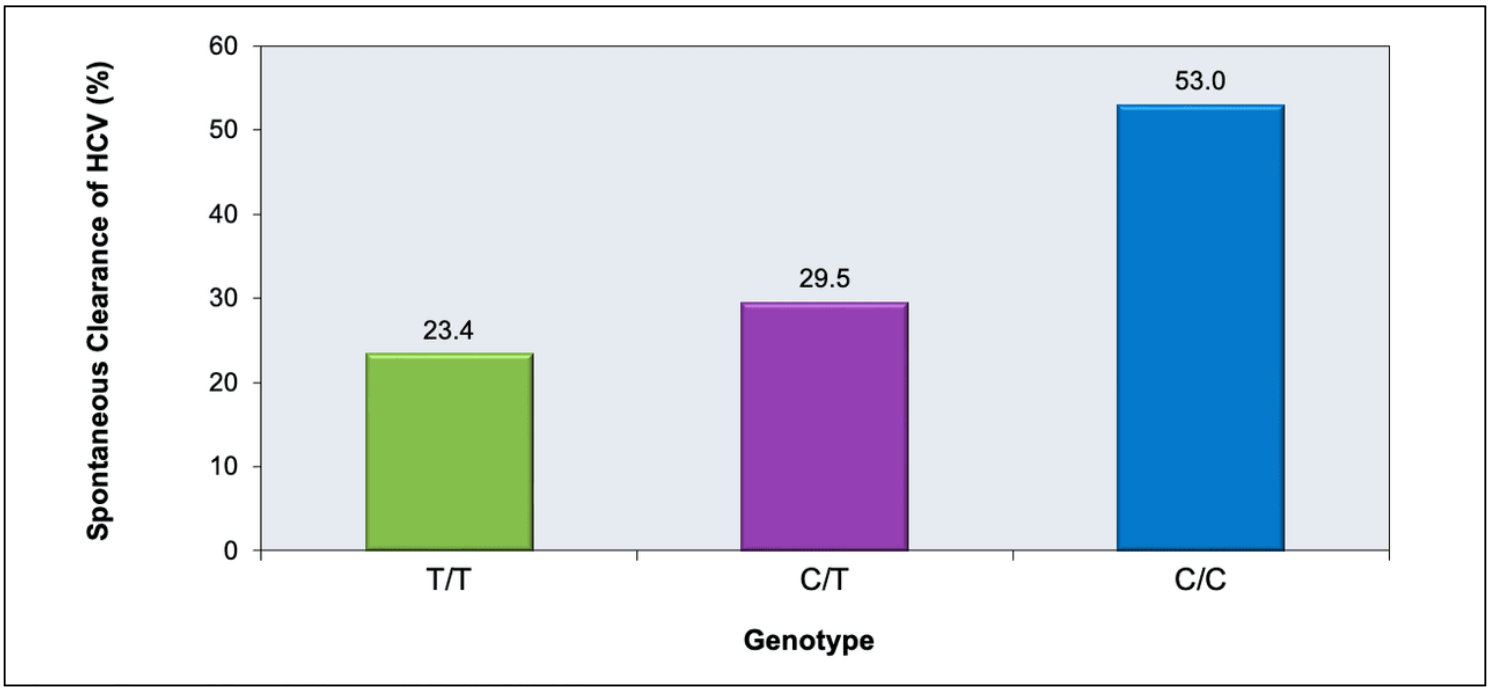

Figure 2 Time Course of Progression with Chronic Hepatitis C Infection

Abbreviations: HCC = hepatocellular cancer; ESLD = end-stage liver disease

Illustration: David H. Spach, MD

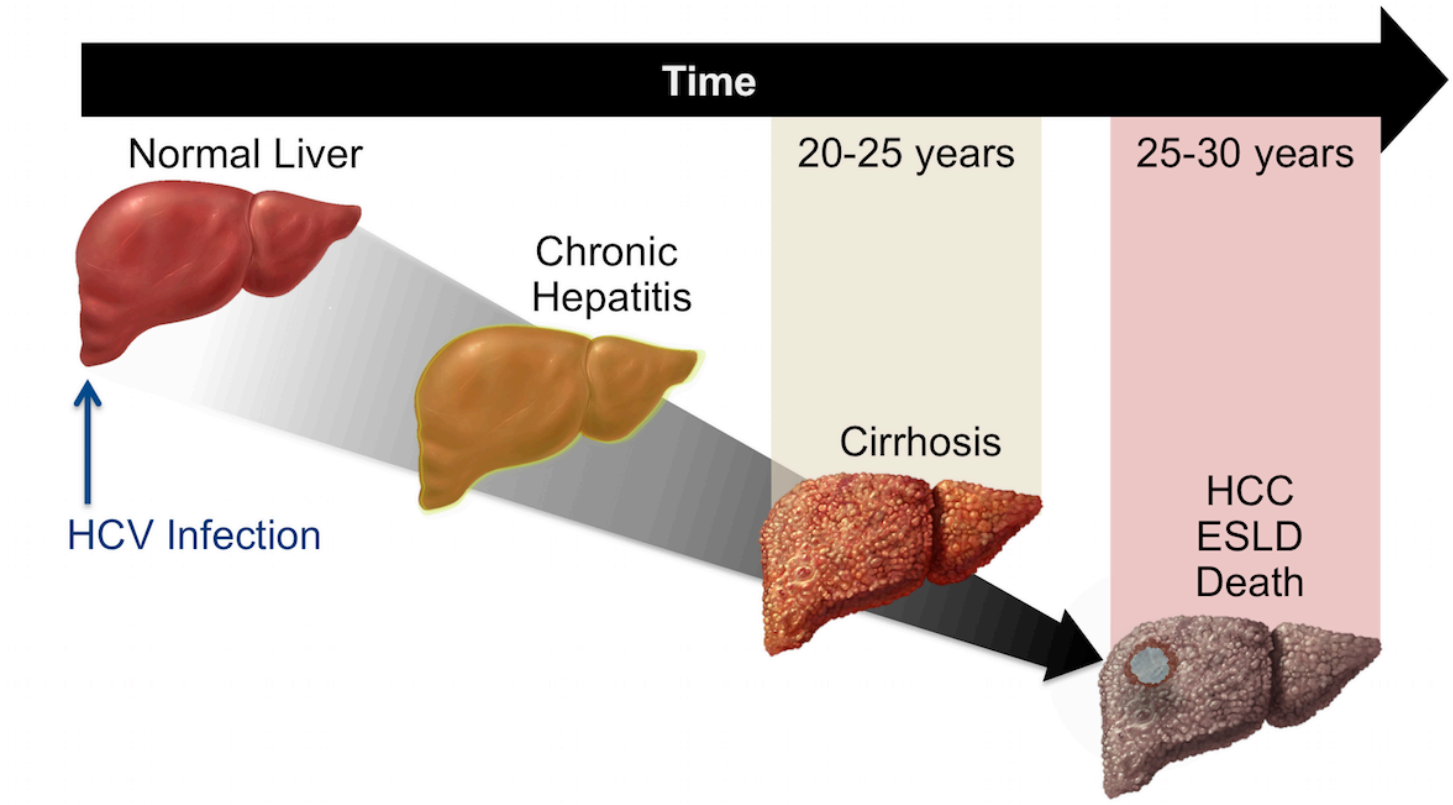

Figure 3 Natural History Following Initial Infection with HCV

Abbreviations: ESLD = end-stage liver disease HCC = hepatocellular carcinoma

Source: Lingala S, Ghany MG. Natural History of Hepatitis C. Gastroenterol Clin North Am. 2015;44:717-34.

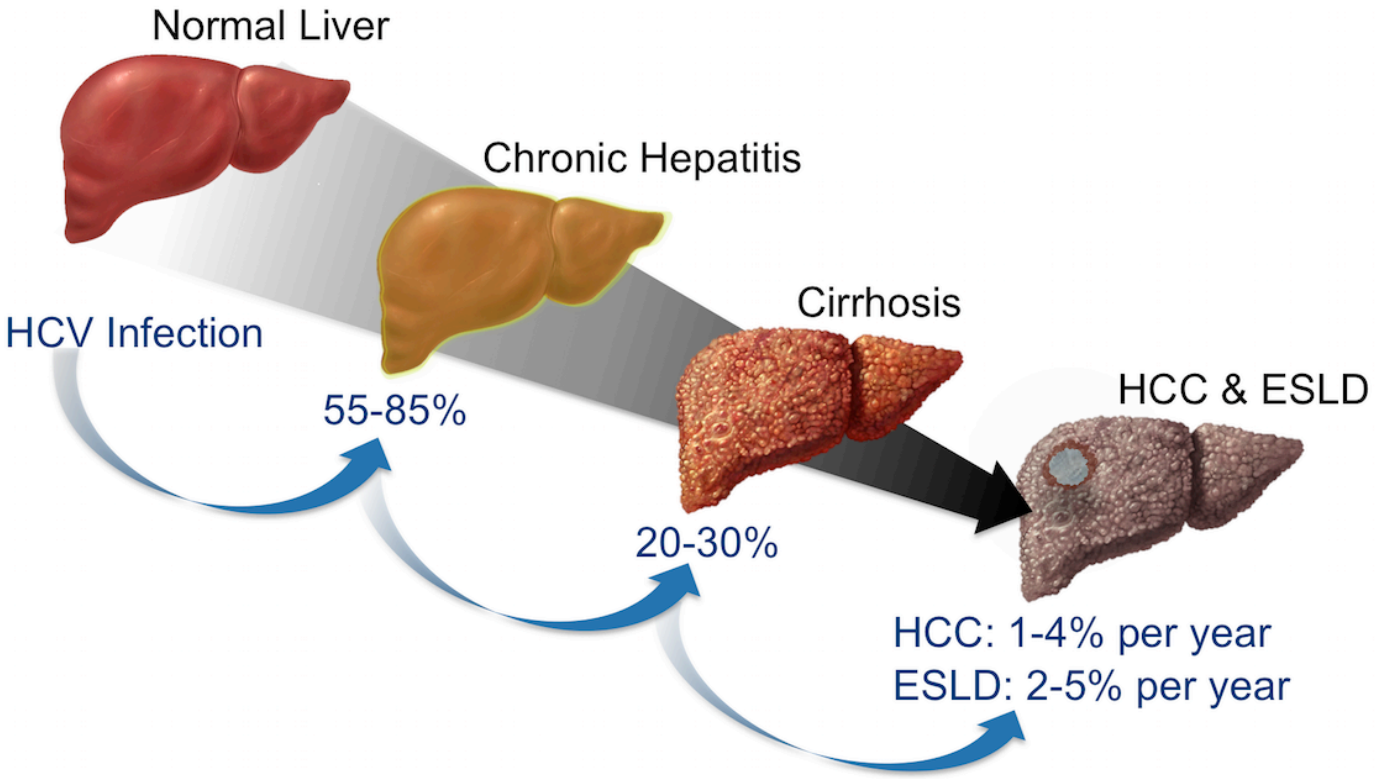

Figure 4 Impact of Age at the Time of Initial HCV Infection and Rate of Fibrosis

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.

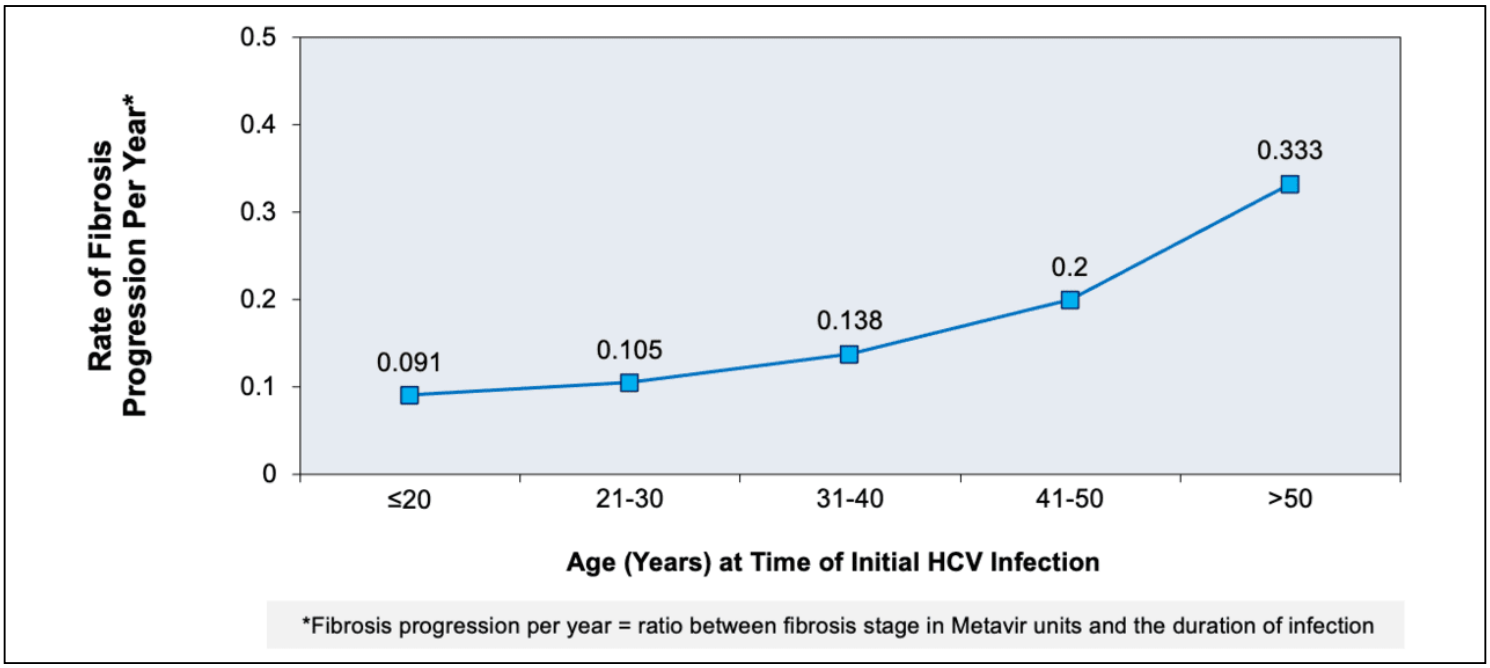

Figure 5 Impact of Steatosis on Progression of Hepatic Fibrosis

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 periods.

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.

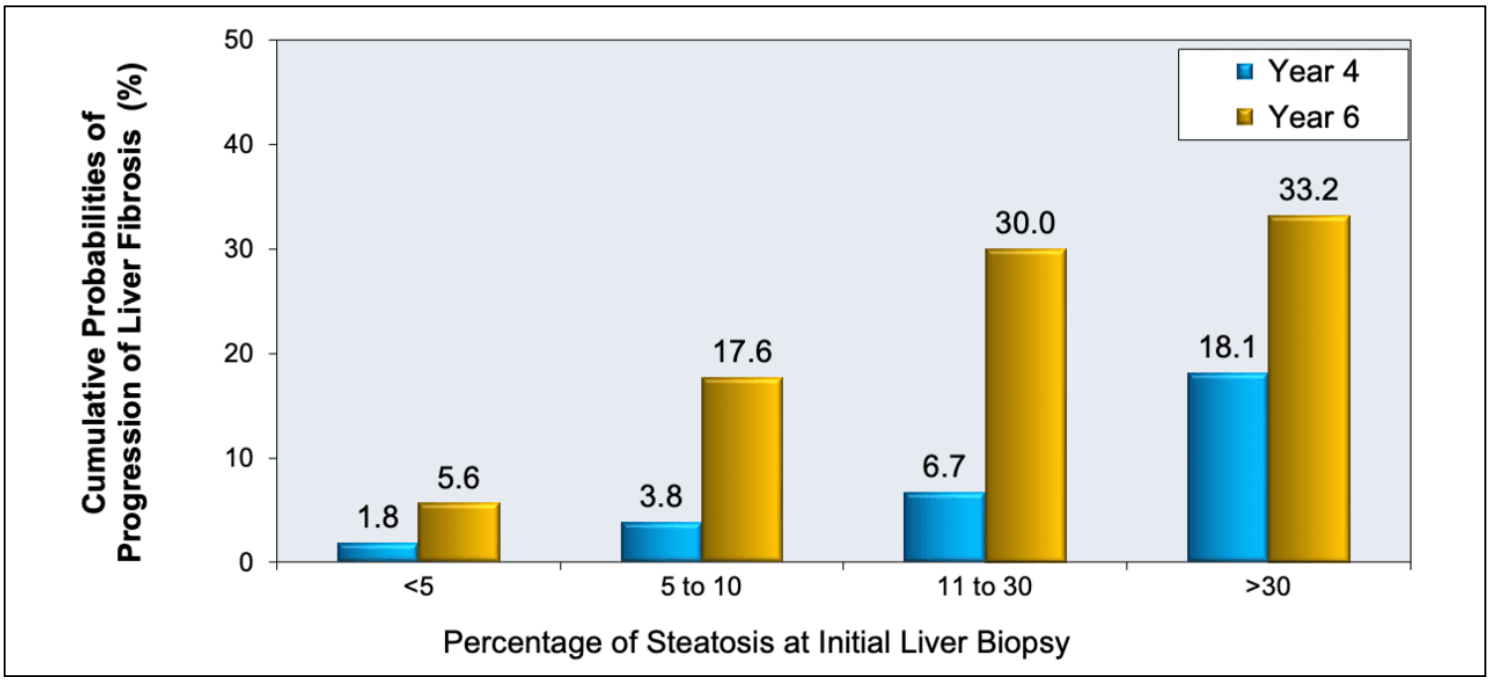

Figure 6 Impact of Coinfection with HIV and Progression of Hepatic Fibrosis

This graphic compares the progression of hepatic fibrosis over a 25-year period among individuals with HCV monoinfection compared with those with HCV and HIV coinfection. As shown, 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.

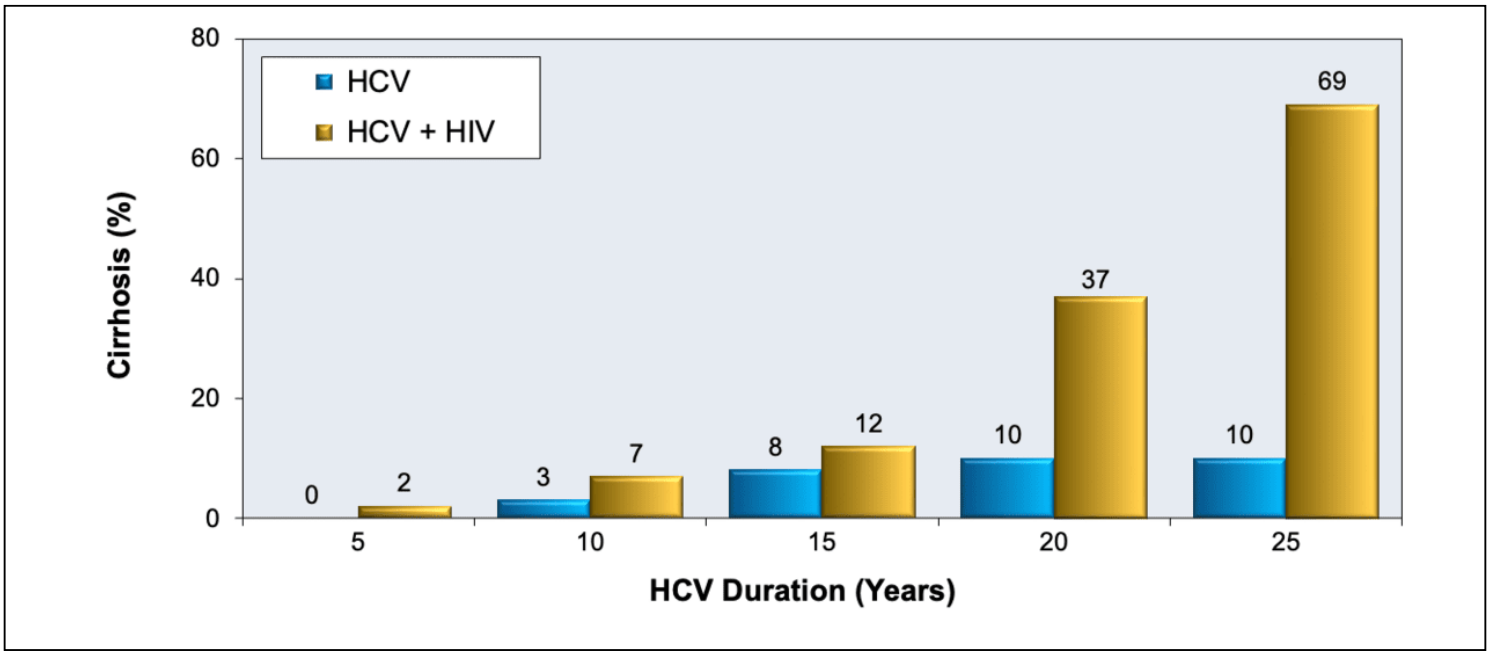

Figure 7 Impact of Alcohol Consumption and Excessive Alcohol Use* on Progression of Hepatic Fibrosis

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.

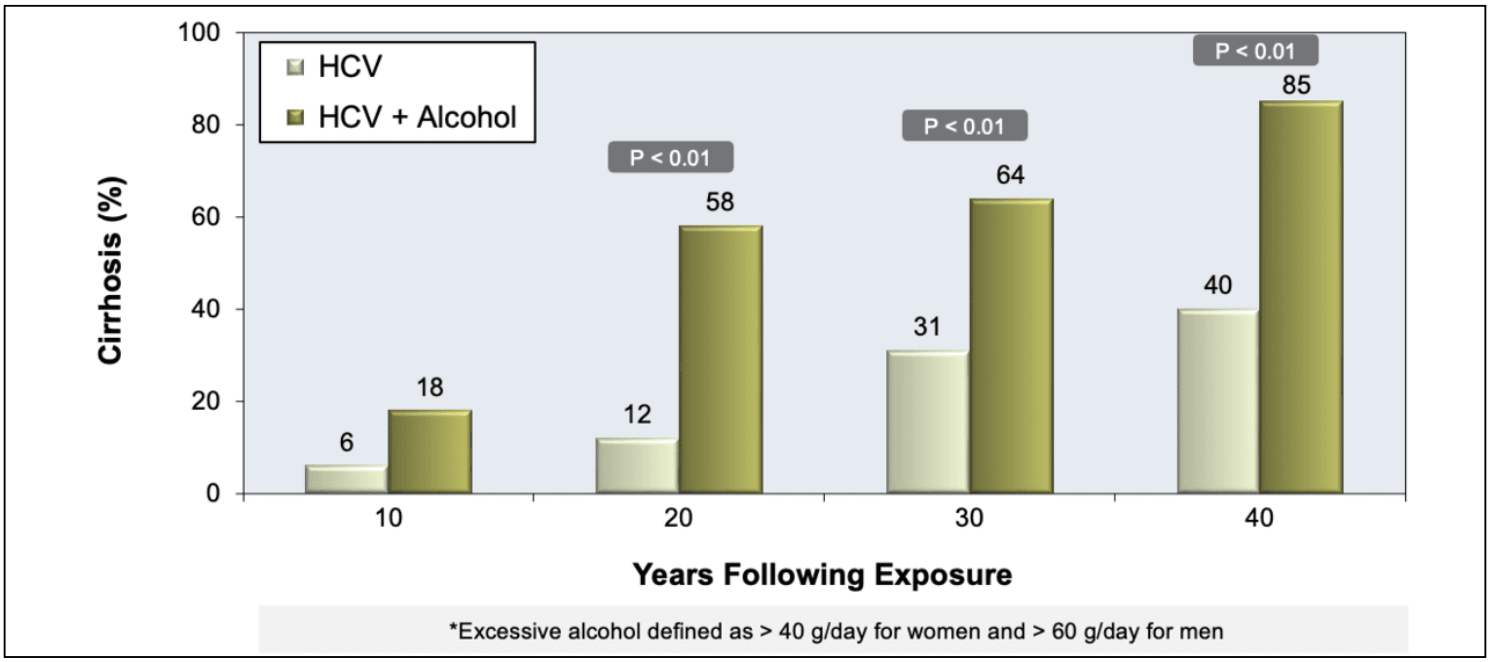

Figure 8 Impact of Coffee Consumption on Liver Disease Progression

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 of more than 1 cup per day was associated with a lower risk of liver disease progression.
RR= relative risk

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.