Diagnosis of Acute HCV Infection

This is a PDF version of the following document:

Module 1:	Screening and Diagnosis of Hepatitis C Infection
Lesson 5:	Diagnosis of Acute HCV Infection

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Definition of Acute HCV

Definitions of Acute HCV Infection

Acute hepatitis C virus (HCV) infection is defined as the 6-month period following the acquisition of hepatitis C virus.[1,2,3] This definition does not take into account whether the patient has clinical signs or symptoms of acute hepatitis.[2] The rationale for choosing 6 months as the time period to define acute infection is based on evidence that most individuals who spontaneously clear HCV will do so by 6 months.[4,5,6]

Terminology Related to Acute HCV Infection

Various terms have been used to refer to acute hepatitis C infection, including acute infection, acute phase infection, very early infection, recent infection, and newly acquired infection. Very early infection typically refers to patients with a positive HCV RNA and documented HCV antibody seroconversion, with this scenario being the most definitive for diagnosing acute HCV infection. Some experts have suggested limiting the terminology for acute HCV infection to *acute* infection and *recent* infection:[2]

- **Acute Infection**: estimated duration of infection less than 6 months
- **Recent Infection**: estimated duration of infection longer than 6 months, but shorter than 2 years.

Clinical Features of Acute HCV

Clinical Manifestations

Among individuals with acute HCV infection, only 15 to 25% develop a clearly distinguishable symptomatic illness.[7,8,9] In addition, most chronically infected patients cannot recall a time when they were acutely symptomatic. When patients develop symptomatic acute HCV infection, the clinical manifestations typically resemble those that occur with other types of viral hepatitis—fatigue, myalgias, low-grade fever, jaundice, dark urine, nausea, vomiting, right upper quadrant pain.[8,10] Symptoms may consist of malaise only, without jaundice or gastrointestinal symptoms (Figure 1). If symptoms from acute infection develop, they usually do so within 4 to 12 weeks (mean 7 to 8 weeks) after infection has occurred, and they typically persist for 2 to 12 weeks.[7,8,11] Fulminant hepatic failure due to acute HCV infection very rarely occurs, but preexisting chronic hepatitis B infection or steatotic liver disease can increase this risk.[12,13,14]

Relationship of Symptoms and Spontaneous Clearance

Overall, the estimated rate of spontaneous clearance of HCV infection varies widely in the literature from 15 to 60%.[15,16,17,18] The rates of spontaneous clearance are significantly lower (in the range of only 10 to 20%) in Black person and in those individuals who have HIV coinfection.[19,20] In contrast, rates of spontaneous clearance are higher in females and in persons who acquired HCV in childhood.[21,22] It has also been demonstrated that patients who present with symptomatic acute HCV infection and jaundice have higher rates of spontaneous clearance of HCV, in the range of 35 to 50%.[8,16,23] The presence of jaundice is believed to reflect hepatic inflammation caused by a more robust initial immune response against HCV.[6,16]

Clinical Scenarios that Suggest Acute HCV Infection

Symptomatic Presentation

Individuals with acute HCV infection can develop significant symptoms and may present with the new onset of jaundice, fatigue, nausea, abdominal pain, and malaise. More often, however, these individuals have no obvious symptoms or have limited symptoms, such as slight malaise.

History of a Recent HCV Exposure but Without Symptoms

Since acute HCV is usually asymptomatic, clinicians should test a person for HCV if there is a history of potential HCV exposure, regardless of clinical symptoms. The most common exposures include recent injection drug use that involved sharing needles or other injection works, a needlestick injury, and sexual contact with a partner who has known HCV infection. For persons with acute or recent HCV acquisition, HCV testing soon after the exposure can make the diagnosis of a new infection and distinguish acute from chronic infection. Recent injection drug use with shared needles or equipment would be considered the highest risk exposure, especially if the needle-sharing partner is known to have HCV. Although the exact risk of acquiring HCV through sexual contact is controversial, sexual transmission appears to be highest among men who have sex with men (MSM), particularly among MSM with HIV and MSM who have engaged in physically traumatic or rough sex.[24]

Laboratory Studies Used for the Evaluation of Initial HCV Infection

The key laboratory studies utilized in the evaluation of possible acute hepatitis C are HCV RNA, anti-HCV, and alanine aminotransferase (ALT). Patients who become infected with HCV will typically develop abnormal laboratory findings in the following order: detectable HCV RNA, followed by elevation in ALT, and then anti-HCV (Figure 2).[8,25] Patients who develop a clinical illness with acute HCV infection usually have onset of symptoms well after the onset of viremia, but soon after, or concomitant with, increases in ALT levels.

HCV RNA (HCV Nucleic Acid Testing)

In most patients, HCV RNA can be detected in blood within 1 to 2 weeks after infection.[26] The HCV RNA test is often referred to as an HCV nucleic acid test (NAT) or nucleic acid amplification test (NAAT). This period from infection until HCV RNA is detectable in plasma by a commercially available assay is referred to as the previremic (or eclipse) phase.[26,27] During the eclipse phase, HCV has likely established infection in susceptible hepatocytes, and, in some patients, the use of qualitative HCV RNA assays with very high sensitivity will reveal HCV RNA in blood.[26] The eclipse phase is followed by an 8- to 10-day “ramp-up” phase in which HCV replication increases exponentially and readily becomes detectable in plasma; the HCV RNA levels typically peak 6 to 10 weeks after infection (“plateau phase”) and remain near these peak levels for about 40 to 60 days (Figure 3).[26] Detection of HCV RNA during acute infection is not entirely reliable as HCV RNA levels may fluctuate significantly during this period—in some instances, HCV RNA levels fall below detectable levels.[7,26,28] At the onset of symptoms, however, detectable HCV RNA levels are uniformly present.

Antibodies to HCV

Antibodies to HCV typically become detectable about 50 to 60 days after infection (range 20 to 150 days); the detection of HCV-specific antibodies significantly lags behind detectable HCV RNA levels.[7,8,26] After 12 weeks, more than 90% of patients will have a positive HCV antibody test. The period from initial infection until seroconversion is often referred to as the “serologic window period” (Figure 4).[29,30] The use of an HCV antibody test as the sole means to diagnose acute HCV is not reliable, since only approximately 50 to 70% of patients have detectable HCV antibodies at the onset of symptoms. In addition, a positive HCV antibody test, which measures both IgM and IgG, does not differentiate acute from chronic HCV infection. Further, IgM antibody is not a reliable indicator of recent infection since it can persist for months in persons with chronic hepatitis C infection.

Hepatitis C Core Antigen

The HCV capsid proteins, which are also referred to as HCV core, make up a spherical capsid (core) structure that surrounds and protects HCV RNA (Figure 5).[31,32] Several studies have shown testing for HCV core antigen can enhance the diagnostic yield of persons with acute HCV when compared with HCV antibody testing alone.[30,33,34] The HCV antigen assays that have been developed for diagnostic purposes include HCV core antigen assays and a combination HCV antibody-HCV core antigen assay.[35,36,37] Although some experts have proposed using HCV core antigen testing as a less expensive option than HCV RNA testing for detecting acute HCV with similar sensitivity, there are no HCV antigen assays (or HCV antigen-antibody combination assays) that are FDA-approved for use in the United States.[38,39]

Alanine Aminotransferase (ALT)

Within 4 to 12 weeks after HCV infection, most patients will have some degree of liver cell injury, as manifested by an elevation in serum ALT levels. Typically, the increases in ALT follow the presence of detectable HCV RNA levels by about 1 to 2 weeks but generally precede the development of HCV antibodies. The mean ALT level after acute infection can reach the 800 IU/L range. The Centers for Disease Control and Prevention uses an increase in ALT to a peak level greater than 200 IU/L during the period of acute illness as

part of the diagnostic criteria.

Diagnosis of Acute HCV Infection

Establishing a Diagnosis of Acute HCV

In the United States, the gold standard for the laboratory diagnosis of acute HCV is an HCV antibody seroconversion (documented negative HCV antibody test followed by a positive antibody test), combined with a positive HCV RNA test and elevated ALT. In clinical practice, many patients do not present with these paired antibody results and often, not in a timely fashion to diagnose acute infection. Thus, a probable diagnosis of acute HCV is made when an individual has a positive HCV RNA and evidence of a negative HCV antibody in the prior 6 months. It can be challenging to differentiate acute infection from chronic infection in patients who have not previously undergone HCV antibody testing.

Potential Missed Diagnosis of Acute HCV Infection

In many laboratories in the United States, HCV testing protocols are in place whereby a positive HCV antibody test triggers automatic (reflex) testing of the sample for HCV RNA, whereas a negative initial HCV antibody test does not trigger further testing. This reflex protocol is ideal for detecting persons with chronic HCV infection and determining whether these individuals have resolved or chronic (active) infection. This protocol, however, can be problematic in the setting of acute HCV since HCV antibody seroconversion may not yet have taken place, and the HCV RNA test will not be run, thereby resulting in a false-negative HCV test. If a patient has suspected acute HCV infections, clinicians should inquire whether the laboratory performing the HCV testing uses a reflex testing protocol; if an HCV reflex testing protocol is in place, the clinician should intentionally place separate orders for the HCV antibody and the HCV RNA so that both tests will be run, regardless of the HCV antibody result. This approach, in the setting of suspected acute HCV infection, will allow for detection of HCV if the individual has not been infected with HCV long enough to have generated HCV antibodies.

Laboratory Testing Following Known Exposure to HCV

In situations where patients have encountered high-risk exposures, serial laboratory testing is the key to promptly establishing the diagnosis of acute HCV infection. The following briefly outlines the recommended sequence of laboratory testing following a known exposure to hepatitis C virus (Figure 6):

- **At Initial Presentation**: HCV antibody, HCV RNA, and ALT
- **At 4 Weeks from Time of Suspected Exposure**: HCV RNA and ALT
- **At 12 Weeks from Time of Suspected Exposure**: HCV antibody, HCV RNA, and ALT
- **At 24 Weeks from Time of Suspected Exposure**: HCV antibody and HCV RNA

CDC Case Definition for Acute Hepatitis C

The Centers for Disease Control and Prevention (CDC) has established criteria for the 2020 case definition of acute Hepatitis C.[40] This definition utilizes clinical criteria, laboratory criteria for diagnosis, criteria to distinguish a new case from an existing case, and a case classification (probable or confirmed).[40]

Summary Points

- Acute HCV infection is usually defined as an estimated duration of infection of less than 6 months.
- Most patients with acute HCV infection do not have a symptomatic illness or have very mild nonspecific symptoms that may include malaise, anorexia, and abdominal pain.
- In the less common situation when patients do develop symptomatic acute HCV infection, they most often present with jaundice, dark urine, nausea, abdominal pain, and malaise.
- The key laboratory studies utilized in the evaluation of possible acute hepatitis C are HCV RNA, HCV antibody, and ALT; the HCV antibody and the HCV RNA tests should be ordered simultaneously and as separate orders, not as an HCV antibody/HCV RNA reflex test, which can miss acute HCV infection.
- With acute HCV, patients usually first have detectable HCV RNA, followed by elevation in ALT, and then followed by development of HCV antibody.
- The gold standard for diagnosis is HCV antibody seroconversion combined with a positive HCV RNA test and elevated ALT.
- Acute HCV infection can rarely cause a life-threatening illness.
- The CDC 2020 case definition for acute hepatitis C includes clinical criteria, laboratory criteria, case classification as probable or confirmed, and criteria to distinguish a new case from an existing case.

Citations

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

2. Hajarizadeh B, Grebely J, Dore GJ. Case definitions for acute hepatitis C virus infection: A systematic review. J Hepatol. 2012;57:1349-60.
   [PubMed Abstract] -

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

4. Hofer H, Watkins-Riedel T, Janata O, et al. Spontaneous viral clearance in patients with acute hepatitis C can be predicted by repeated measurements of serum viral load. Hepatology. 2003;37:60-4.
   [PubMed Abstract] -

5. 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] -

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

7. Busch MP, Shafer KA. Acute-phase hepatitis C virus infection: implications for research, diagnosis, and treatment. Clin Infect Dis. 2005;40:959-61.
   [PubMed Abstract] -

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

9. Grebely J, Matthews GV, Dore GJ. Treatment of acute HCV infection. Nat Rev Gastroenterol Hepatol. 2011;8:265-74.
   [PubMed Abstract] -

10. Orland JR, Wright TL, Cooper S. Acute hepatitis C. Hepatology. 2001;33:321-7.
    [PubMed Abstract] -

11. Marcellin P. Hepatitis C: the clinical spectrum of the disease. J Hepatol. 1999;31 Suppl 1:9-16.
    [PubMed Abstract] -

12. Hoofnagle JH, Carithers RL Jr, Shapiro C, Ascher N. Fulminant hepatic failure: summary of a workshop. Hepatology. 1995;21:240-52.
    [PubMed Abstract] -

13. Chu CM, Yeh CT, Liaw YF. Fulminant hepatic failure in acute hepatitis C: increased risk in chronic carriers of hepatitis B virus. Gut. 1999;45:613-7.
    [PubMed Abstract] -

14. Rao A, Rule JA, Cerro-Chiang G, et al. Role of Hepatitis C Infection in Acute Liver Injury/Acute Liver Failure in North America. Dig Dis Sci. 2023;68:304-11.
    [PubMed Abstract] -

15. 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] -

16. Chung RT. Acute hepatitis C virus infection. Clin Infect Dis. 2005;41 Suppl 1:S14-7.
[PubMed Abstract] -

17. 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] -

18. Seo S, Silverberg MJ, Hurley LB, et al. Prevalence of Spontaneous Clearance of Hepatitis C Virus Infection Doubled From 1998 to 2017. Clin Gastroenterol Hepatol. 2020;18:511-3.
[PubMed Abstract] -

19. 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] -

20. 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] -

21. Bulteel N, Partha Sarathy P, Forrest E, et al. Factors associated with spontaneous clearance of chronic hepatitis C virus infection. J Hepatol. 2016;65:266-72.
[PubMed Abstract] -

22. Kimble MM, Javanbakht M, Chew KW, et al. Sociodemographic and clinical characteristics of persons who experienced spontaneous hepatitis C viral clearance. BMC Infect Dis. 2019;19:626.
[PubMed Abstract] -

23. Gerlach JT, Diepolder HM, Zachoval R, et al. Acute hepatitis C: high rate of both spontaneous and treatment-induced viral clearance. Gastroenterology. 2003;125:80-8.
[PubMed Abstract] -

24. Jin F, Matthews GV, Grulich AE. Sexual transmission of hepatitis C virus among gay and bisexual men: a systematic review. Sex Health. 2017;14:28-41.
[PubMed Abstract] -

25. Cox AL, Netski DM, Mosbruger T, et al. Prospective evaluation of community-acquired acute-phase hepatitis C virus infection. Clin Infect Dis. 2005;40:951-8.
[PubMed Abstract] -

26. Glynn SA, Wright DJ, Kleinman SH, et al. Dynamics of viremia in early hepatitis C virus infection. Transfusion. 2005;45:994-1002.
[PubMed Abstract] -

27. Busch MP, Murthy KK, Kleinman SH, et al. Infectivity in chimpanzees (Pan troglodytes) of plasma collected before HCV RNA detectability by FDA-licensed assays: implications for transfusion safety and HCV infection outcomes. Blood. 2012;119:6326-34.
[PubMed Abstract] -

28. Nübling CM, Unger G, Chudy M, Raia S, Löwer J. Sensitivity of HCV core antigen and HCV RNA detection in the early infection phase. Transfusion. 2002;42:1037-45.
[PubMed Abstract] -

29. Stramer SL, Glynn SA, Kleinman SH, et al. Detection of HIV-1 and HCV infections among antibody-negative blood donors by nucleic acid-amplification testing. N Engl J Med. 2004;351:760-8.
[PubMed Abstract] -

30. Laperche S, Nübling CM, Stramer SL, et al. Sensitivity of hepatitis C virus core antigen and antibody combination assays in a global panel of window period samples. Transfusion. 2015;55:2489-98.
[PubMed Abstract] -

31. Gawlik K, Gallay PA. HCV core protein and virus assembly: what we know without structures. Immunol Res. 2014;60:1-10.
[PubMed Abstract] -

32. Klein KC, Polyak SJ, Lingappa JR. Unique features of hepatitis C virus capsid formation revealed by de novo cell-free assembly. J Virol. 2004;78:9257-69.
[PubMed Abstract] -

33. Tuke PW, Grant PR, Waite J, Kitchen AD, Eglin RP, Tedder RS. Hepatitis C virus window-phase infections: closing the window on hepatitis C virus. Transfusion. 2008;48:594-600.
[PubMed Abstract] -

34. Hullegie SJ, GeurtsvanKessel CH, van der Eijk AA, Ramakers C, Rijnders BJA. HCV antigen instead of RNA testing to diagnose acute HCV in patients treated in the Dutch Acute HCV in HIV Study. J Int AIDS Soc. 2017;20:21621.
[PubMed Abstract] -

35. Ottiger C, Gygli N, Huber AR. Detection limit of architect hepatitis C core antigen assay in correlation with HCV RNA, and renewed confirmation algorithm for reactive anti-HCV samples. J Clin Virol. 2013;58:535-40.
[PubMed Abstract] -

36. Ross RS, Viazov S, Salloum S, Hilgard P, Gerken G, Roggendorf M. Analytical performance characteristics and clinical utility of a novel assay for total hepatitis C virus core antigen quantification. J Clin Microbiol. 2010;48:1161-8.
[PubMed Abstract] -

37. Laperche S, Le Marrec N, Girault A, et al. Simultaneous detection of hepatitis C virus (HCV) core antigen and anti-HCV antibodies improves the early detection of HCV infection. J Clin Microbiol. 2005;43:3877-83.
[PubMed Abstract] -

38. Freiman JM, Tran TM, Schumacher SG, et al. Hepatitis C Core Antigen Testing for Diagnosis of Hepatitis C Virus Infection: A Systematic Review and Meta-analysis. Ann Intern Med. 2016;165:345-55.
[PubMed Abstract] -

39. Khan H, Hill A, Main J, Brown A, Cooke G. Can Hepatitis C Virus Antigen Testing Replace Ribonucleic Acid Polymearse Chain Reaction Analysis for Detecting Hepatitis C Virus? A Systematic Review. Open Forum Infect Dis. 2017;4:ofw252.
[PubMed Abstract] -

40. Centers for Disease Control and Prevention (CDC). National Notifiable Diseases Surveillance System (NNDSS). Hepatitis C, Acute: 2020 Case Definition.
[CDC and NNDSS] -

References

- Aisyah DN, Shallcross L, Hully AJ, O'Brien A, Hayward A. Assessing hepatitis C spontaneous clearance and understanding associated factors-A systematic review and meta-analysis. J Viral Hepat. 2018;25:680-698.
[PubMed Abstract] -

- Araujo AC, Astrakhantseva IV, Fields HA, Kamili S. Distinguishing acute from chronic hepatitis C virus (HCV) infection based on antibody reactivities to specific HCV structural and nonstructural proteins. J Clin Microbiol. 2011;49:54-7.
[PubMed Abstract] -

- Centers for Disease Control and Prevention (CDC). National Notifiable Diseases Surveillance System (NNDSS). Hepatitis C, Perinatal Infection 2018 Case Definition
[CDC] -

- Dustin LB, Rice CM. Flying under the radar: the immunobiology of hepatitis C. Annu Rev Immunol. 2007;25:71-99.
[PubMed Abstract] -

- Dustin LB. Too low to measure, infectious nonetheless. Blood. 2012;119:6181-2.
[PubMed Abstract] -

- Hullegie SJ, Arends JE, Rijnders BJ, et al. Current knowledge and future perspectives on acute hepatitis C infection. Clin Microbiol Infect. 2015;21:797.e9-797.e17.
[PubMed Abstract] -

- Lamoury FMJ, Soker A, Martinez D, et al. Hepatitis C virus core antigen: A simplified treatment monitoring tool, including for post-treatment relapse. J Clin Virol. 2017;92:32-38.
[PubMed Abstract] -

- Wietzke-Braun P, Manhardt LB, Rosenberger A, Uy A, Ramadori G, Mihm S. Spontaneous elimination of hepatitis C virus infection: a retrospective study on demographic, clinical, and serological correlates. World J Gastroenterol. 2007;13:4224-9.
[PubMed Abstract] -

- Zibbell JE, Asher AK, Patel RC, et al. Increases in Acute Hepatitis C Virus Infection Related to a Growing Opioid Epidemic and Associated Injection Drug Use, United States, 2004 to 2014. Am J Public Health. 2018;108:175-181.
[PubMed Abstract] -

- Zibbell JE, Iqbal K, Patel RC, et al. Increases in hepatitis C virus infection related to injection drug use among persons aged ≤30 years - Kentucky, Tennessee, Virginia, and West Virginia, 2006-2012. MMWR Morb Mortal Wkly Rep. 2015;64:453-8.
[PubMed Abstract] -

Figures

Figure 1 Symptoms of Acute HCV Infection

This graph shows the clinical features of 51 patients with symptomatic acute HCV infection.

Source: Gerlach JT, Diepolder HM, Zachoval R, et al. Acute hepatitis C: high rate of both spontaneous and treatment-induced viral clearance. Gastroenterology. 2003;125:80-8.

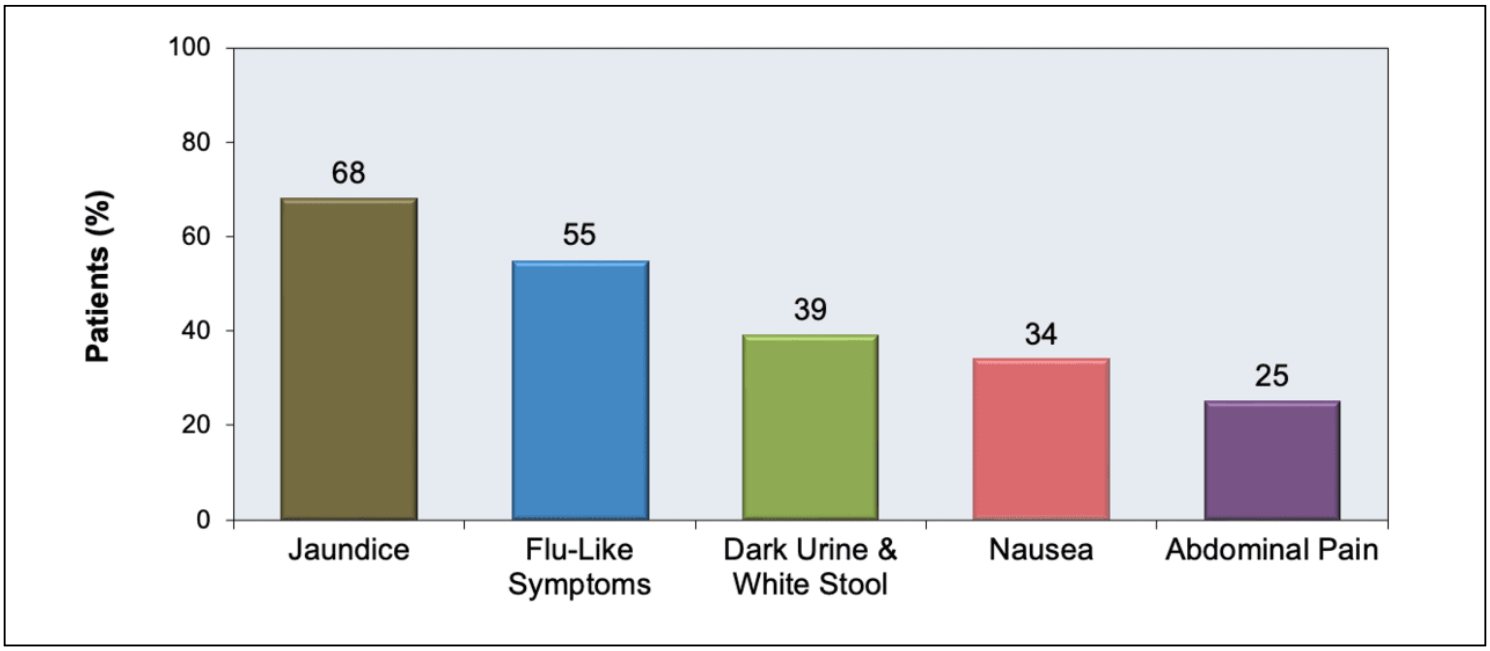


Figure 2 Laboratory Markers with Acute HCV Infection

Note the temporal appearance of laboratory markers typically observed with acute hepatitis C infection: HCV RNA levels first become detectable, followed by increases in ALT levels, and then detectable HCV antibodies.

Source: Centers for Disease Control and Prevention (CDC).

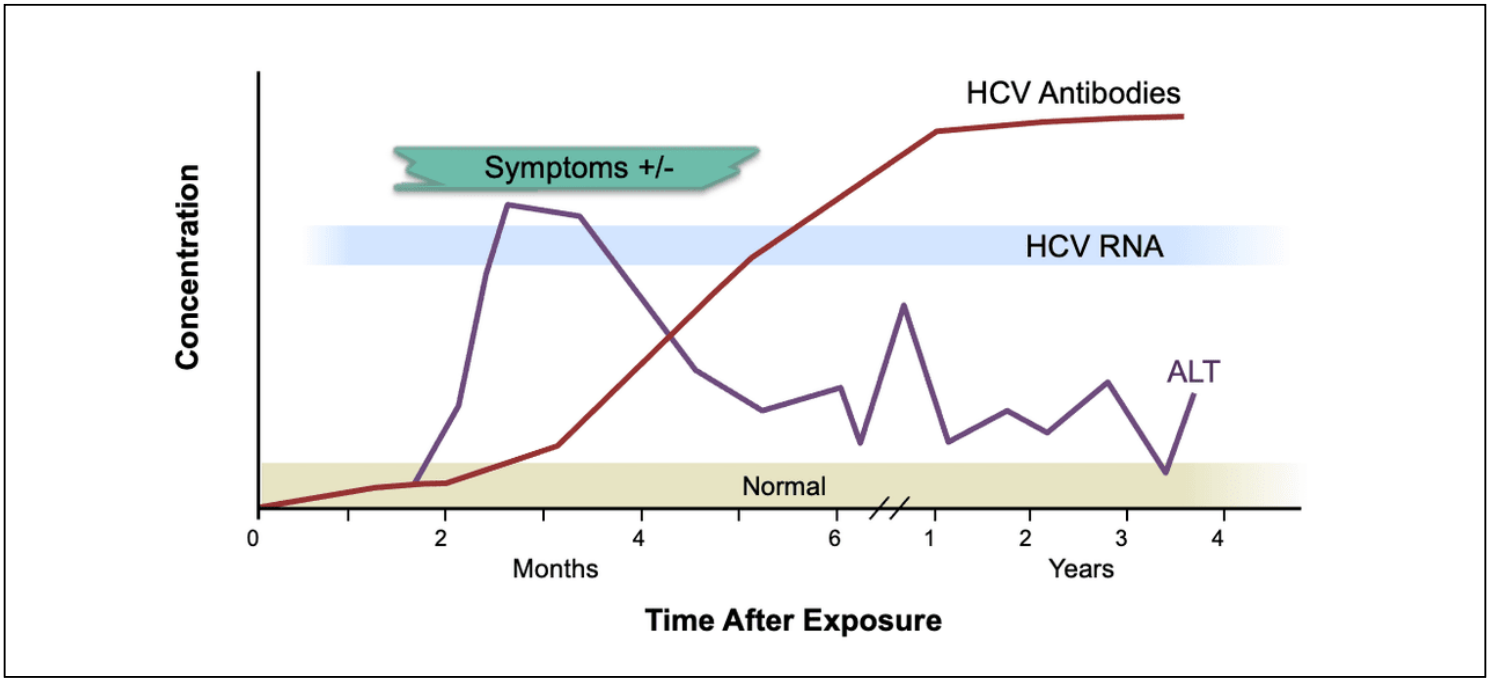


Figure 3 Acute HCV Infection: Viral Dynamics

This graph illustrates the early phases of viral dynamics observed following HCV acquisition: eclipse, ramp up, and plateau.

Source: Glynn SA, Wright DJ, Kleinman SH, et al. Dynamics of viremia in early hepatitis C virus infection. Transfusion. 2005;45:994-1002. Illustration: David H. Spach, MD

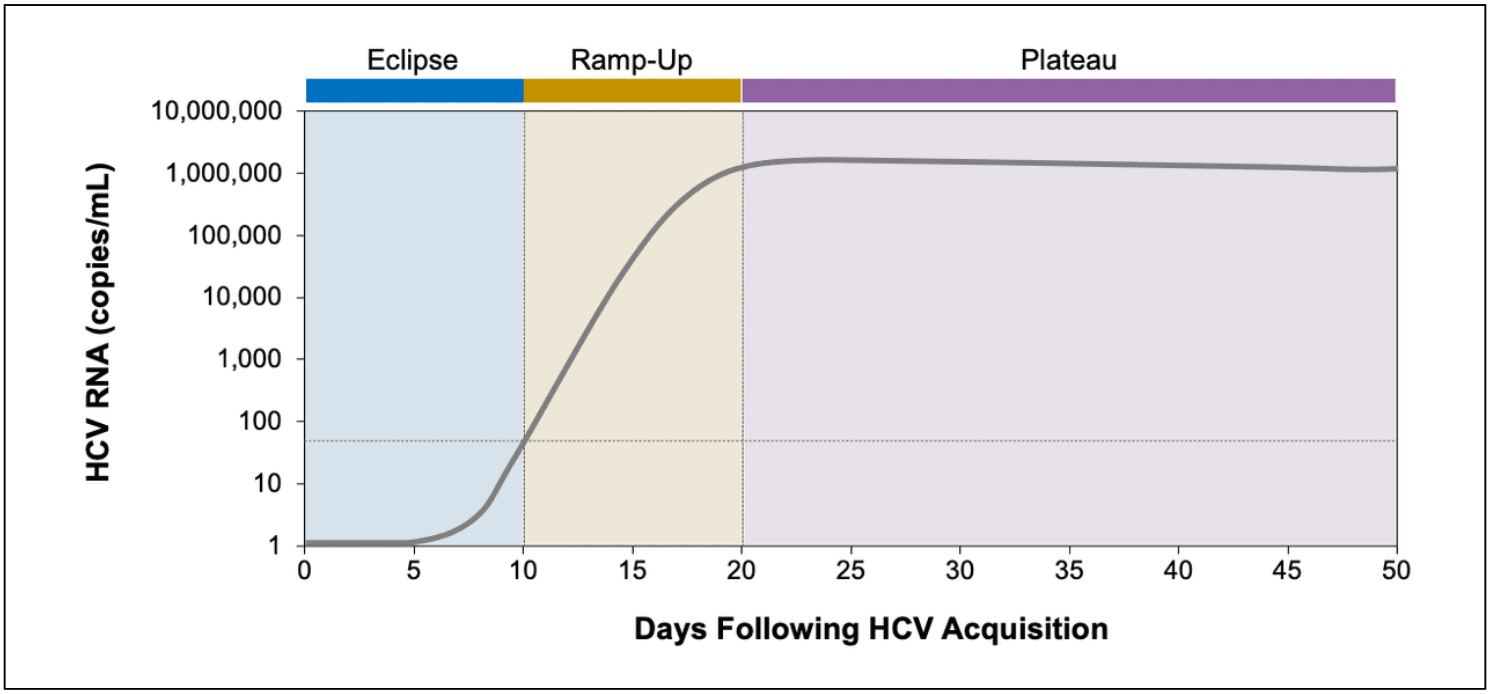


Figure 4 Acute HCV Infection: Serologic Window Period

The serologic window period is the time between HCV infection and clinically detectable HCV antibodies. The window period for HCV infection is typically 50 to 60 days.

Illustration: David H. Spach, MD

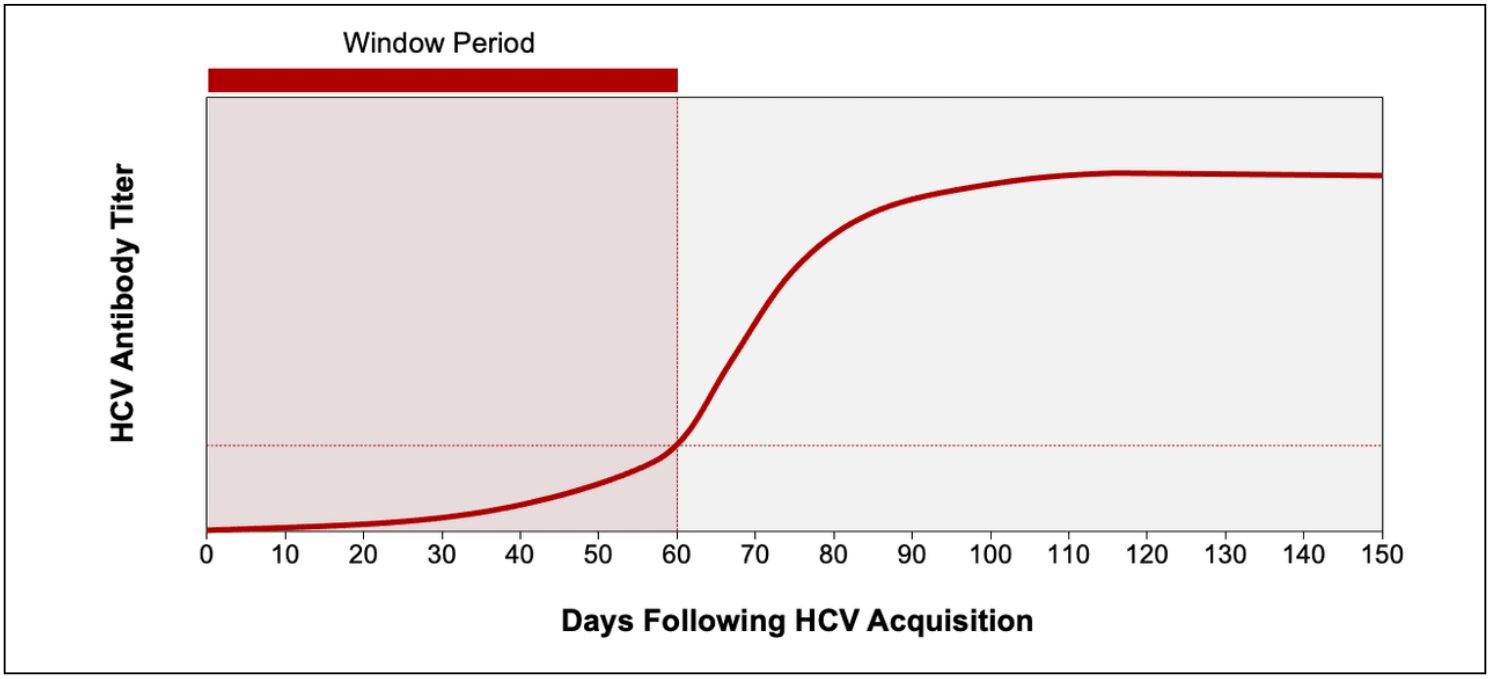


Figure 5 Hepatitis C Capsid

The central element shown in purple is the hepatitis C virus (HCV) capsid, which is also referred to as the HCV core. The HCV capsid is made up entirely by the HCV capsid protein.

Illustration: Cognition Studio, Inc.

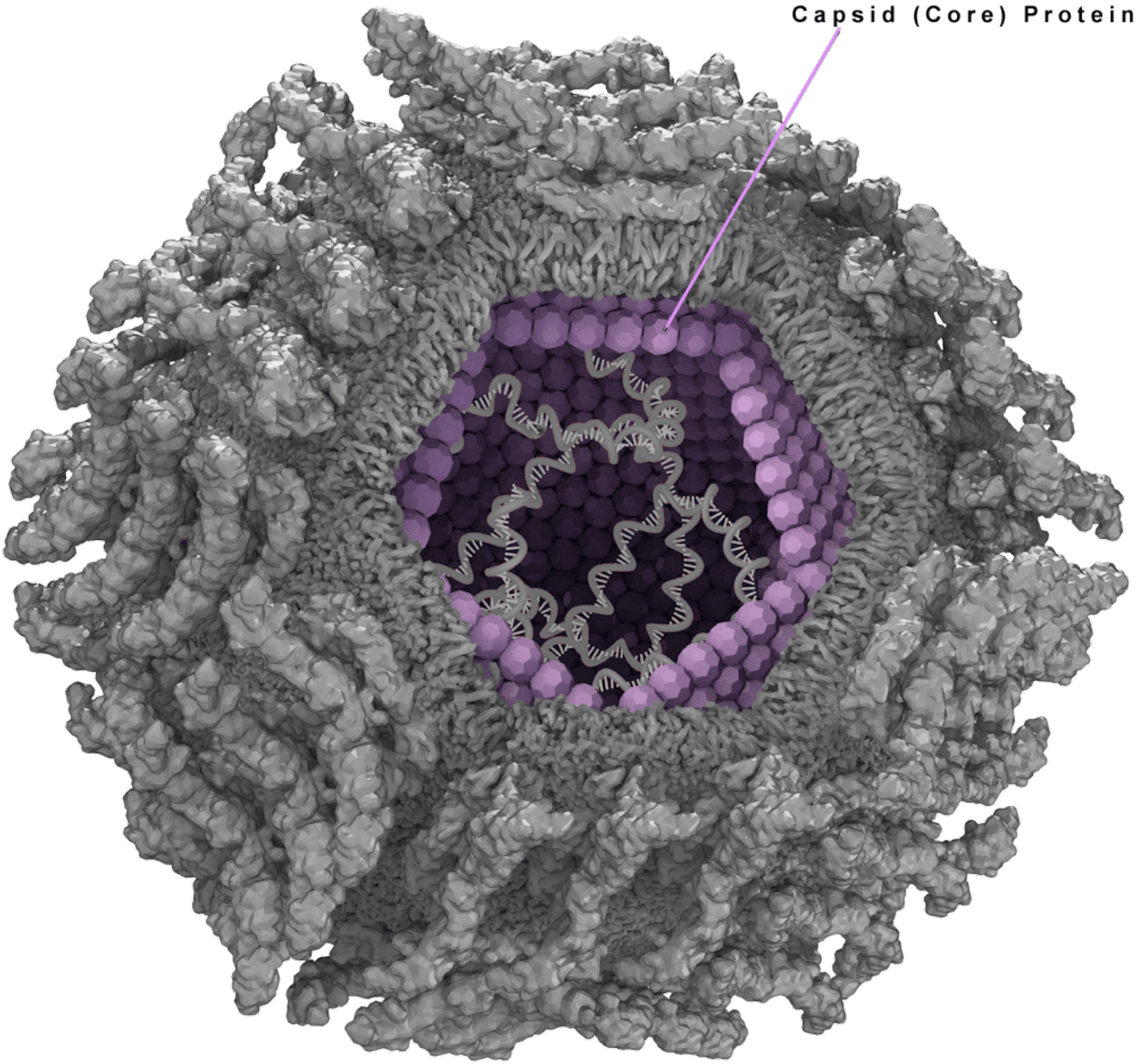
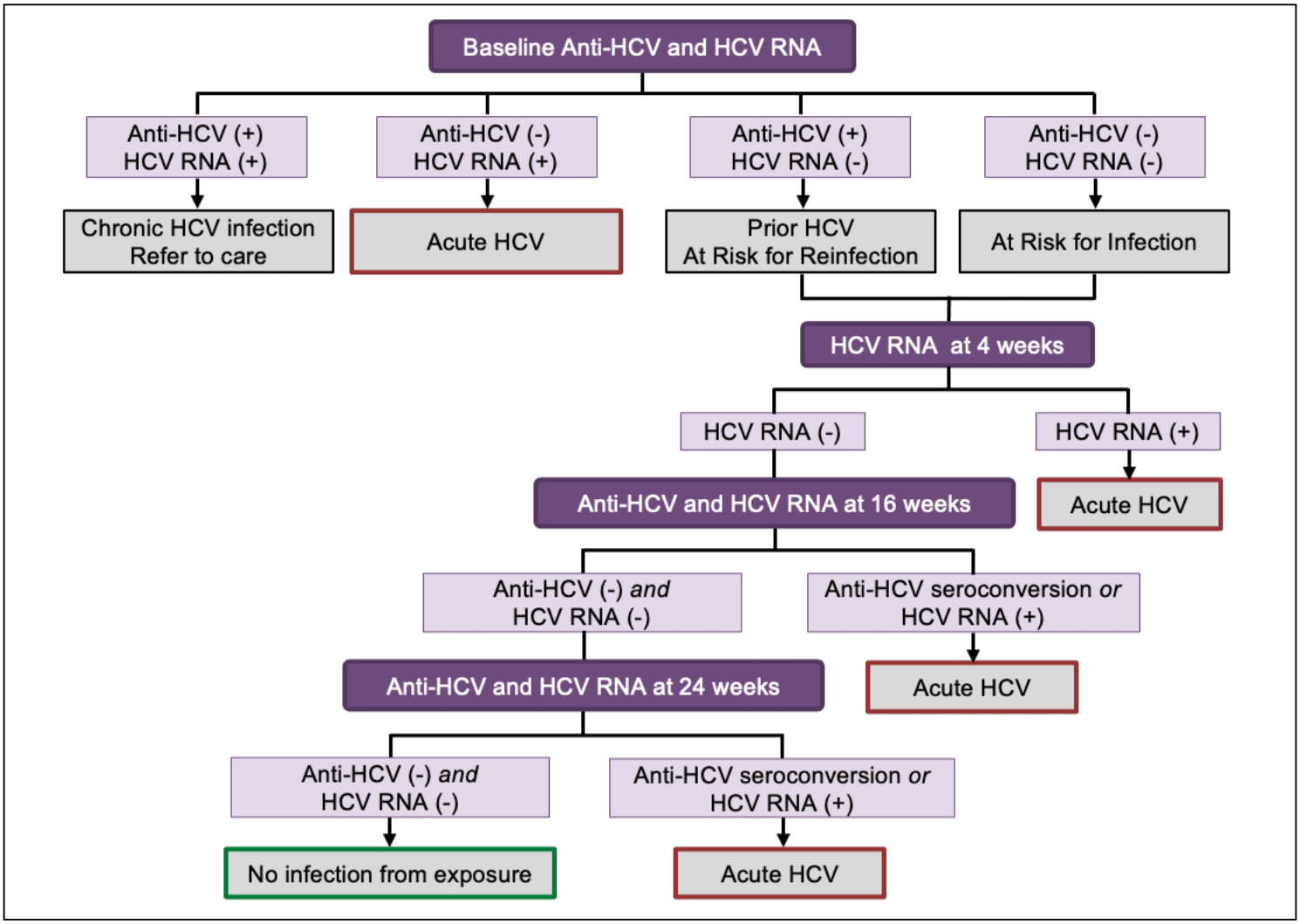


Figure 6 Laboratory Evaluation for Persons Exposed to HCV

Note: for prior infection, this may be due either to spontaneous clearance of HCV or following a sustained virology response after treatment.