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

Most commonly, acute hepatitis C infection is defined as the 6-month time period following acquisition of hepatitis C virus. The definition of acute hepatitis C is irrespective to whether the patient has clinical signs or symptoms of acute hepatitis. The rationale for choosing 6 months as the time period to define acute infection is based on evidence that most individuals who clear HCV will do so by 6 months.

Terminology Related to Acute HCV Infection

Clinical reviews and research studies have used numerous terms to refer to acute hepatitis C infection, including acute infection, acute phase infection, very early infection, recent infection, and newly acquired infection. Overall, consensus does not exists regarding the terminology and criteria for defining acute HCV infection. Very early infection typically refers to patients with a positive HCV RNA and documented HCV antibody seroconversion and this scenario is the most definitive for diagnosing acute HCV infection. Some experts have suggested limiting the multiple possible terms to acute infection and recent infection:

- 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

Symptomatic or Asymptomatic Presentation

Most patients with acute HCV infection do not have a distinct symptomatic illness and most are not aware of their recent exposure to hepatitis C. When patients develop symptomatic acute HCV infection, the clinical manifestations typically resemble those that occur with other types of viral hepatitis—jaundice, influenza-like symptoms, dark urine, nausea, abdominal pain, and malaise. 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 6 to 7 weeks) after infection has occurred and persist for 2 to 12 weeks. Only 15 to 20% of symptomatic acute liver disease in the United States is thought to result from acute HCV. Fulminant hepatic failure due to acute HCV infection very rarely occurs, but preexisting chronic hepatitis B infection increases this risk.

Frequency of Clinical Illness

For patients with acute HCV infection in the United States, an estimated 60 to 70% will have no obvious symptoms, 20 to 30% will have jaundice, and 10 to 20% will have non-specific symptoms. More recent data suggest that only 17% of patients with acute hepatitis C infection present with a symptomatic illness. In addition, most chronically infected patients cannot recall a time when they were acutely symptomatic.

Relationship of Clinical Symptoms and Spontaneous Clearance

Several studies have shown that patients who present with acute HCV infection and jaundice have higher rates of spontaneous clearance of HCV than asymptomatic persons with acute HCV infection. The presence of jaundice is believed to reflect hepatic inflammation caused by a more robust initial immune response against HCV.

Clinical Scenarios that Suggest Acute HCV infection

- **Symptomatic Presentation:** Symptomatic individuals could present with the new onset of jaundice, fatigue, nausea, abdominal pain, and malaise. Acutely infected persons may have more limited symptoms, such as slight malaise and fatigue without jaundice.
- **History of a Recent HCV Exposure but without Symptoms:** Since acute HCV is usually asymptomatic, clinicians need to test patients as soon as possible following a new incident in which infection could have taken place. Since most cases of acute hepatitis C are asymptomatic, clinicians should not rely on patients to appear clinically ill in order to decide to test patients for acute HCV infection. Providers should suspect the disease in patients exposed to potentially infectious sources (Figure 2) and understand that prompt testing can be critical to making the diagnosis of a new infection and distinguishing acute from chronic infection. Recent injection-drug use with shared needles or equipment would be the most common recent exposure to HCV. Although the risk of HCV transmission through sexual contact is controversial, recent sexual exposure should be considered as a possible risk. The risk of sexual transmission appears to be highest with male-male exposures, particularly if this involves HIV-infected persons engaging in physically traumatic or rough sex.

Laboratory Diagnosis of Acute HCV

Laboratory Studies for Evaluation of Initial 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 hepatitis C virus typically develop abnormal laboratory findings in the following order: detectable HCV RNA, elevation in ALT, and anti-HCV (Figure 3). 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

In most patients, HCV RNA can be detected in blood within 1 to 2 weeks after infection. This period from infection until HCV RNA is detectable in plasma by a commercially available assay is referred to as the “eclipse phase” (Figure 4), or “previremic phase”. During the eclipse phase, HCV has likely established infection in susceptible hepatocytes, and, in some patients, use of qualitative HCV RNA assays with very high sensitivity will reveal blips of HCV RNA (at levels less than 10 copies/mL) in blood. 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 5). 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. At the onset of symptoms, however, detectable HCV RNA levels are uniformly present.

Alanine Aminotransferase (ALT)

Within 4 to 12 weeks after HCV infection, most patients will have 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 anti-HCV. The mean ALT after acute infection reaches 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.

Antibodies to HCV

Anti-HCV usually become detectable between 8 and 12 weeks after infection and thus significantly lags behind detectable HCV RNA levels. After 12 weeks, more than 90% of patients will have positive anti-HCV. The time period from initial infection until seroconversion is often referred to as the “serologic window period” (Figure 6). Use of anti-HCV to diagnose acute HCV is not reliable since only approximately 50 to 70% of patients have detectable anti-HCV at the onset of symptoms. Further, positive anti-HCV does not differentiate acute from chronic HCV infection.

Gold Standard for Diagnosis

The gold standard for the laboratory diagnosis of acute HCV is anti-HCV seroconversion (negative anti-HCV before suspected exposure and positive anti-HCV following potential exposure), combined with a positive HCV RNA test and elevated ALT. In clinical practice, many patients do not present early enough after a potential exposure and so it is not always possible to demonstrate an initial negative antibody followed by a positive antibody.

- An example of an ideal documented sequence of testing:
  1 week after potential infection: anti-HCV negative, HCV RNA negative, ALT normal

4 weeks after potential infection: anti-HCV negative, HCV RNA positive, ALT elevated
8 weeks after potential infection: anti-HCV positive, HCV RNA positive, ALT elevated

Distinguishing Acute HCV from Chronic HCV

Outside of the gold standard scenario, it can be challenging to differentiate an acute infection from chronic infection in patients who have not previously undergone anti-HCV testing. Most often, the diagnosis of acute HCV is made based on the first time detection of HCV RNA and newly elevated ALT when no previous testing for HCV antibody or HCV RNA has been done.

Laboratory Testing Following Known Exposure

In situations where patients have encountered high-risk exposures, follow-up with serial laboratory testing is the key to establishing the diagnosis. The following outlines the recommended laboratory testing following a known exposure to hepatitis C virus:

- At initial presentation: anti-HCV, HCV RNA, and ALT
- At 4 weeks from time of suspected exposure: anti-HCV, HCV RNA, and ALT
- At 12 weeks from time of suspected exposure: anti-HCV, HCV RNA, and ALT

2016 CDC Case Definition for Acute HCV

The Centers for Disease Control and Prevention (CDC) has established criteria for the 2016 case definition of acute Hepatitis C; this definition utilized clinical criteria, laboratory criteria for diagnosis, criteria to distinguish a new case from an existing case, and a case classification (probable or confirmed).

Clinical Criteria

An illness with discrete onset of any sign or symptom consistent with acute viral hepatitis (e.g., fever, headache, malaise, anorexia, nausea, vomiting, diarrhea, and abdominal pain),
AND
(a) jaundice, **OR**
(b) a peak elevated serum alanine aminotransferase (ALT) level >200 IU/L during the period of acute illness.

Laboratory Criteria for Diagnosis

A positive test for antibodies to hepatitis C virus (anti-HCV)
Hepatitis C virus detection test:

- Nucleic acid test (NAT) for HCV RNA positive (including qualitative, quantitative or genotype testing)
- A positive test indicating presence of hepatitis C viral antigen(s) (HCV antigen)*.

*When and if a test for HCV antigen(s) is approved by FDA and available.

Criteria to Distinguish a New Case from an Existing Case

A new acute case is an incident acute hepatitis C case that meets the case criteria for acute hepatitis C and has not previously been reported. A new probable acute case may be re-classified as confirmed acute case if a positive NAT for HCV RNA or a positive HCV antigen(s) test is reported within the same year. A confirmed acute case may be classified as a confirmed chronic case if a positive NAT for HCV RNA or a positive HCV antigen is reported one year or longer after acute case onset. A confirmed acute case may not be reported as a probable chronic case (i.e., HCV antibody positive, but with an unknown HCV RNA NAT or antigen status). States and territories may choose to track resolved hepatitis C cases in which spontaneous clearance of infection or sustained viral response to treatment are suspected to have occurred before national notification or are known to have occurred after national notification as a confirmed or probable case to CDC.

Case Classification

Probable

- A case that meets clinical criteria and has a positive anti-HCV antibody test, but has no reports of a positive HCV NAT or positive HCV antigen tests,
  AND
- Does not have test conversion within 12 months or has no report of test conversion.

Confirmed

- A case that meets clinical criteria and has a positive hepatitis C virus detection test (HCV NAT or HCV antigen),
  OR
- A documented negative HCV antibody, HCV antigen or NAT laboratory test result followed within 12 months by a positive result of any of these tests (test conversion).

Summary Points

- Acute HCV infection is usually defined as an estimated duration of infection less than 6 months.
- Most patients with acute HCV infection do not have a symptomatic illness or have very mild non-specific symptoms that may include malaise, anorexia, and abdominal pain.
- When patients 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, anti-HCV, and alanine aminotransferase (ALT).
- With acute HCV, patients usually first have detectable HCV RNA, followed by elevation in ALT, and followed last by development of anti-HCV.
- The gold standard for diagnosis is anti-HCV seroconversion combined with a positive HCV RNA test and elevated ALT.
- Acute HCV infection can rarely cause a life-threatening illness.
- The CDC 2016 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.

References

- 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] -

- 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] -

- Centers for Disease Control and Prevention (CDC). National Notifiable Diseases Surveillance System (NNDSS). Hepatitis C, acute: 2012 case definition.
[CDC and NNDSS] -

- 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] -

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

- 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] -

- 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] -

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

- 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] -

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

- McGovern BH, Birch CE, Bowen MJ, Reyor LL, Nagami EH, Chung RT, Kim AY. Improving the diagnosis of acute hepatitis C virus infection with expanded viral load criteria. Clin Infect Dis. 2009;49:1051-60.
[PubMed Abstract] -

- Mondelli MU, Cerino A, Cividini A. Acute hepatitis C: diagnosis and management. J Hepatol. 2005;42 Suppl(1):S108-14.
[PubMed Abstract] -

- Recommendations for prevention and control of hepatitis C virus (HCV) infection and HCV-related chronic disease. Centers for Disease Control and Prevention. MMWR Recomm Rep.

1998;47(RR-19):1-39.
[CDC and MMWR] -

Figures

Figure 1 Symptoms with Acute Hepatitis C Infection.

This graph shows the clinical features among 51 patients with acute hepatitis C 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.

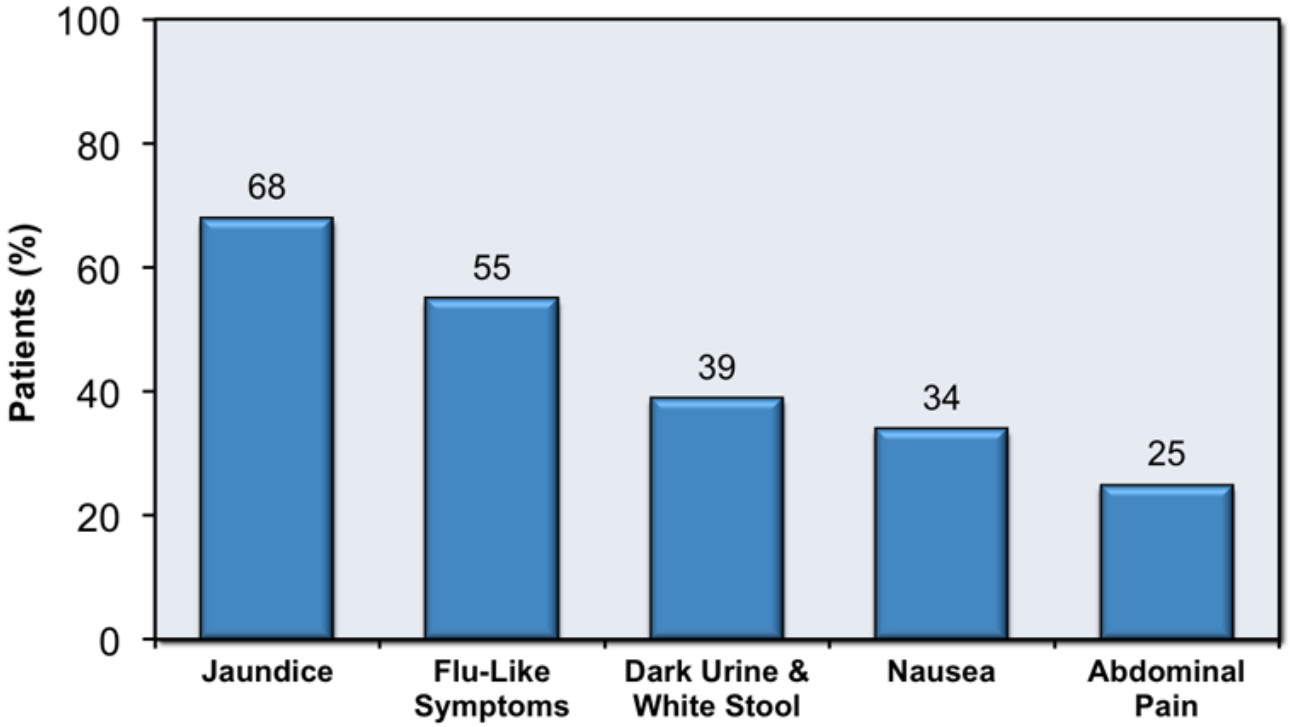

Figure 2 Potential Hepatitis C Exposures.

Potential Source of Exposure to Hepatitis C Virus
Recent injection drug use
Needle stick injury
Procedures involving potentially reused needles: tattooing, body-piercing, acupuncture
Exposure to re-used sharp objects or re-used vials of injectable materials
Nosocomial exposure to contaminated equipment, or potential direct exposure to blood
High risk sexual practices: fisting, bleeding during sex, use of sharp objects during sex
Sexual contact with a known HCV-infected partner
Sexual contact with known HIV positive partner
Sexual contact with known sexually transmitted infections in patient or their partner
Blood transfusion or unsafe therapeutic procedures during travel in a developing country

Figure 3 Laboratory Markers with Acute Hepatitis C 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 anti-HCV.

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

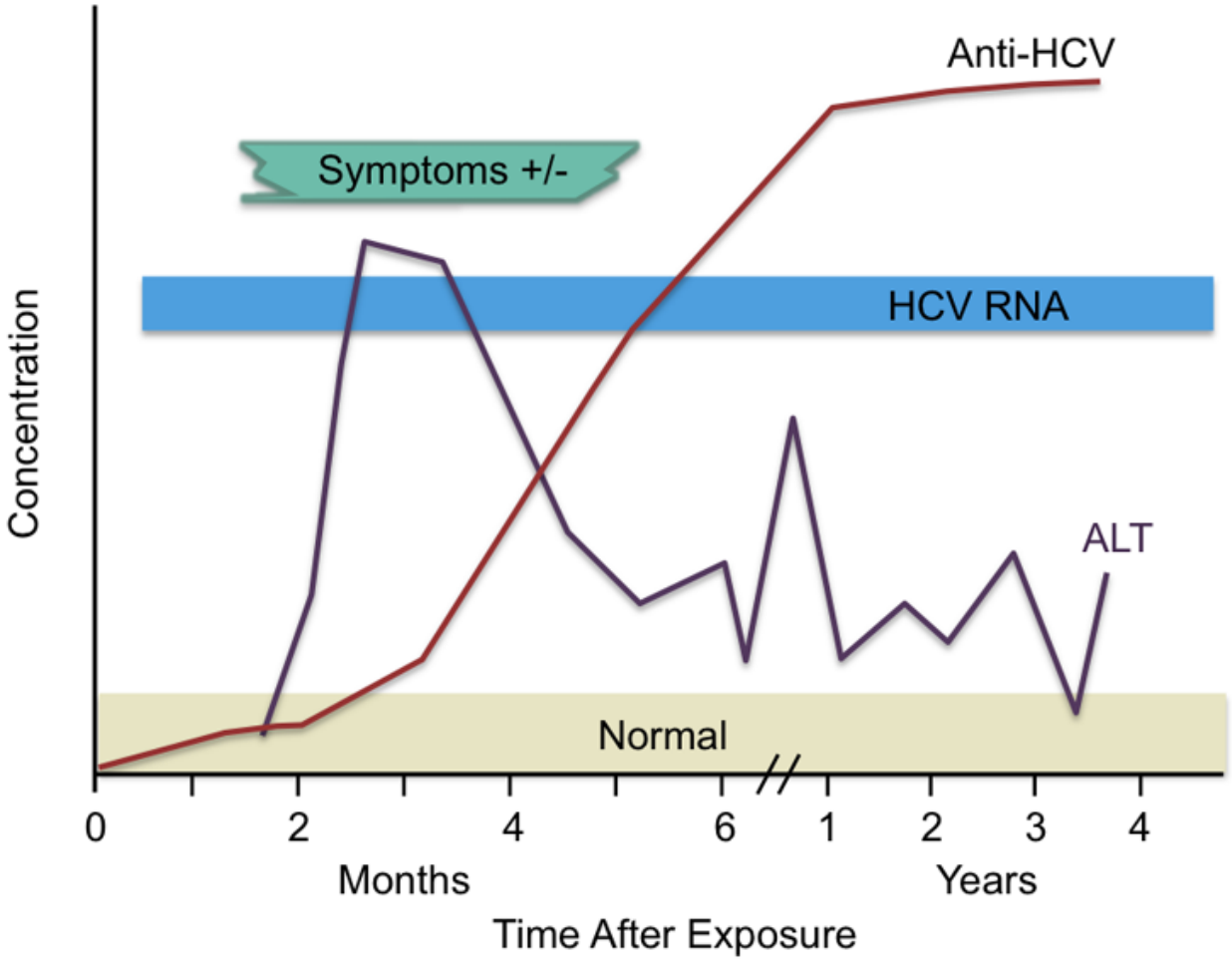

Figure 4 Acute Hepatitis C Infection: Eclipse Phase.

The eclipse phase is the time between HCV infection and the appearance of detectable HCV RNA.

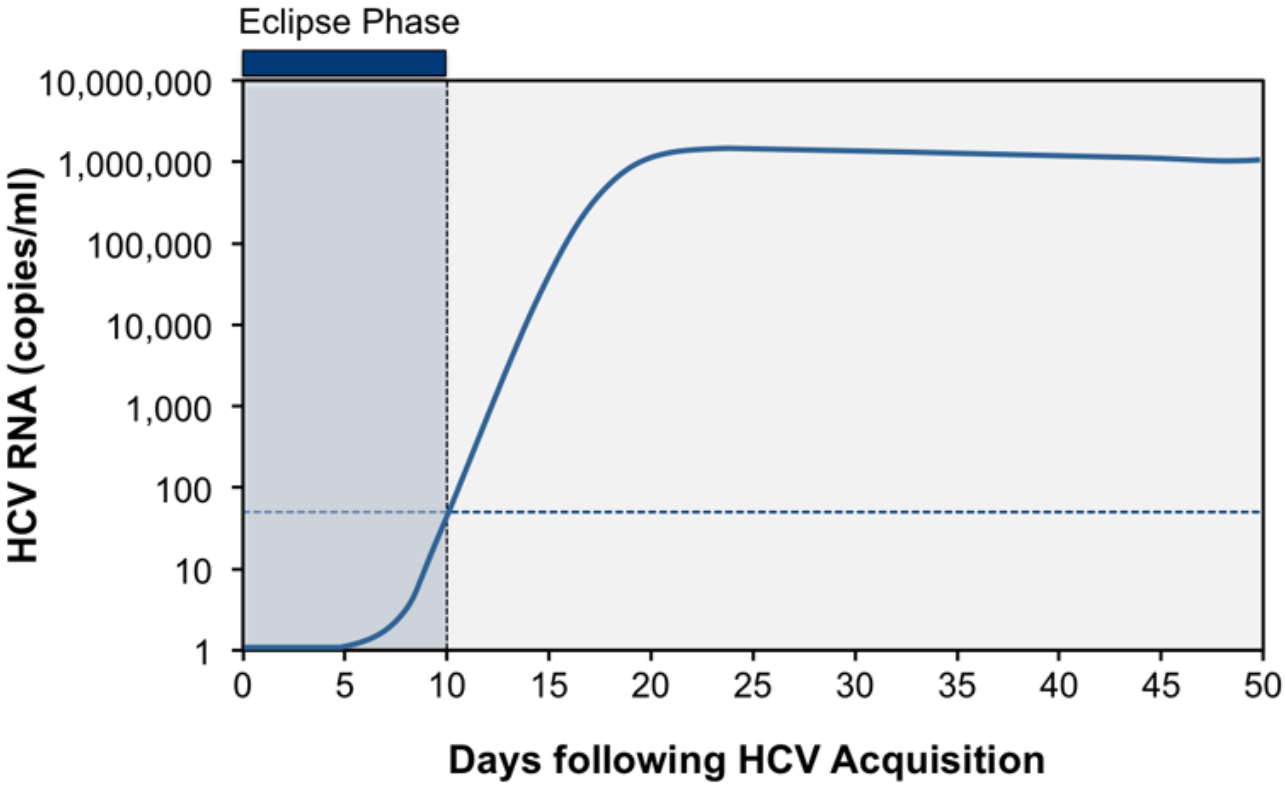

Figure 5 Acute Hepatitis C Infection: Viral Dynamics

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

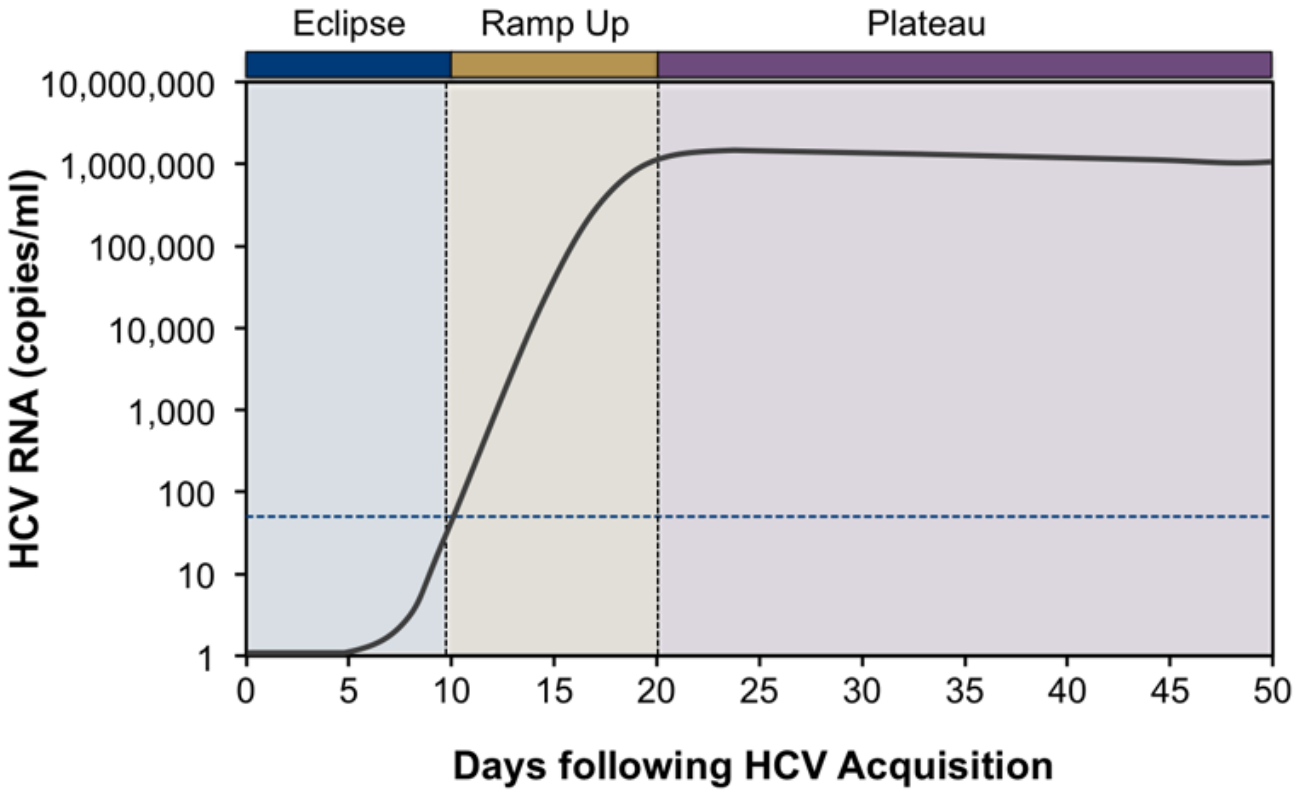

Figure 6 Acute Hepatitis C Infection: Serologic Window Period

The serologic window period is the time between HCV infection and clinically detectable anti-HCV.