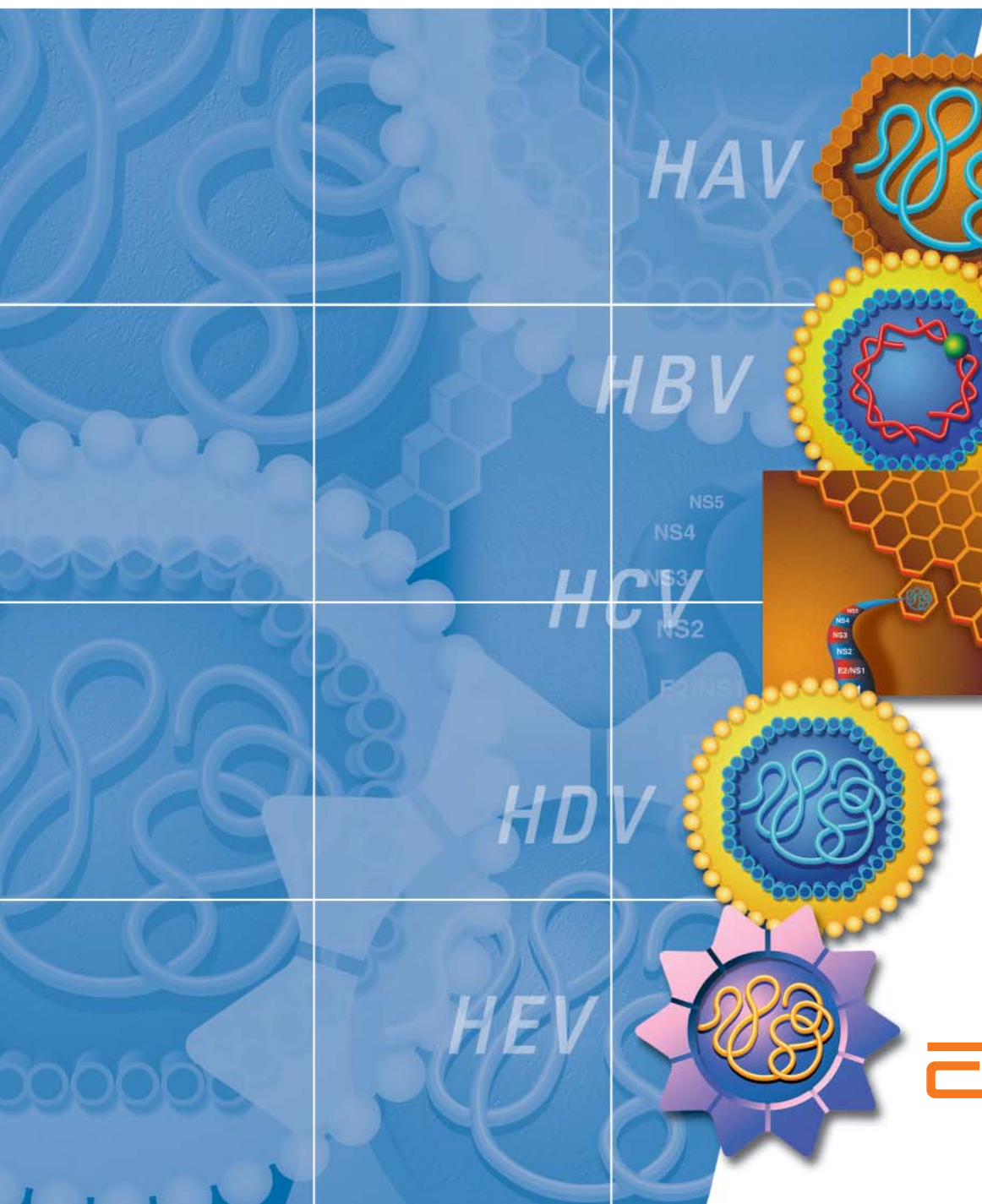




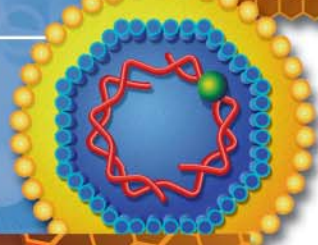
# Hepatitis Learning Guide



HAV

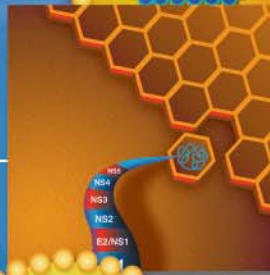


HBV



HCV

NS5  
NS4  
NS3  
NS2  
E2/NS1



HDV



HEV



**ABBOTT**  
DIAGNOSTICS

## About This Learning Guide

**This Learning Guide** presents a discussion of each type of viral hepatitis and an explanation of how serological assessments of the patient can aid in differential diagnosis.

The overview of each type of viral hepatitis has been developed in a case study format to better demonstrate the practicality of the materials. As you progress through the sections, review the learning objectives and complete the quizzes on major points covered in the text.

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# Introduction



NS5  
NS4  
NS3  
NS2  
E2/NS1  
E1  
C

# Introduction

Viral hepatitis continues to be a disease of major significance, in terms of both morbidity and mortality. Between the years 1984 to 1994, the Centers for Disease Control and Prevention (CDC) estimate the breakdown of annual U.S. cases of hepatitis infection as follows: 125,000 – 200,000 HAV infections, 140,000 – 320,000 HBV infections, 35,000 – 180,000 HCV infections, and 6,000 – 13,000 HDV infections. HEV is rare in the U.S.<sup>3, slide 5</sup>

Hepatitis is largely a nondiscriminatory disease. Although each type may target a specific population, the disease is not limited to a small geographical, social, or socioeconomic group. Therefore, the control and diagnosis of viral hepatitis demands that physicians, clinicians, and other healthcare providers be aware of the:

- ***Known and potential risks for acquiring the different types***
- ***Risk behavior histories of their patients***
- ***Appropriate diagnostic tests for each type of hepatitis***
- ***Appropriate preventive and therapeutic measures***

Diagnosing the specific agent responsible for viral hepatitis is difficult because the signs and symptoms of each type are similar. Furthermore, many individuals who contract the disease have few or no symptoms. Hepatitis, then, presents a challenge to physicians who must try to integrate epidemiological, clinical, and serological data before making patient management decisions.

# The Pathology of Viral Hepatitis

## Section 1

*Learning Objectives • Brief History of Viral Hepatitis • The Liver • Effects on the Liver  
Signs and Symptoms • Tests of Liver Functions • Viral Hepatitis Testing  
Serological Markers • Viral Hepatitis Panels • Quiz Questions*



# Learning Objectives

After completing this section, you should be able to:

1. **Name the viruses that cause viral hepatitis**
2. **Describe the symptoms of viral hepatitis**
3. **Indicate the use of liver function tests in the diagnosis of viral hepatitis**
4. **Identify the viral hepatitis panels**

Hepatitis can be caused by viruses, bacteria, drugs, toxins, or excess alcohol intake. Only within recent years have physicians been able to differentiate the five major types of viral hepatitis. In large part, the ability to distinguish the viruses that cause hepatitis is the result of the development of serological tests for specific markers.

The five distinct viruses currently known to cause hepatitis, which will be discussed in this text, are referred to as hepatitis A, B, C, D, and E. Other viruses are presumed to be associated with, or to cause, hepatitis but have not yet been linked to a disease. Cytomegalovirus (CMV) and Epstein-Barr virus (EBV) may also cause hepatitis.

## Brief History of Viral Hepatitis

Outbreaks of epidemic jaundice were known in both Greek and Roman times, but viral hepatitis was first recognized as a distinct clinical entity in the United States and Europe during the late 18th and early 19th centuries. Scattered outbreaks of “infectious hepatitis,” “epidemic hepatitis,” or “catarrhal jaundice” were reported in the medical literature of the times.

During World War II, two types of viral hepatitis—subsequently designated **hepatitis A** and **hepatitis B**—were distinguished. Later studies demonstrated that other viruses could cause hepatitis. One agent, the delta virus, was identified in 1977 and later became known as **hepatitis D** virus (HDV).

With the development of serological assays for HAV and HBV and their use as aids in the diagnosis of hepatitis and with the implementation of HBV screening of blood donors, it became clear that there were additional viruses involved. Hepatitis due to viruses other than the hepatitis A, hepatitis B, or hepatitis D viruses were simply called **non-A, non-B (NANB) hepatitis**. In the late 1980s, this NANB population was further differentiated with the identification of two viruses: **hepatitis C** virus (HCV) and **hepatitis E** virus (HEV).

## HAV, HBV, HCV, HDV, and HEV

*There are five distinct viruses currently known to cause hepatitis; hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), hepatitis D virus (HDV), and hepatitis E virus (HEV).*

# The Liver

To understand the effects of hepatitis on the liver, it is essential to know some of the functions of the liver:

- ***Storage of substances such as glycogen, iron, and vitamins***
- ***Disposal of metabolic wastes such as urea and bile***
- ***Metabolism of sugar, protein, and fat***
- ***Production of proteins that circulate in the blood, such as factors that regulate blood clotting and plasma proteins that influence blood pressure and blood viscosity***
- ***Filtration of toxic substances that could damage the body if allowed to accumulate***

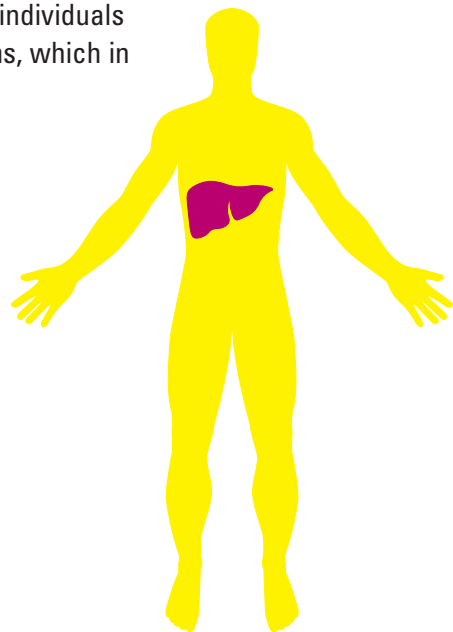
## Effects on the Liver

Regardless of the cause, all types of viral hepatitis affect liver cells. This accounts for the fact that many signs and symptoms for the various types are similar.

## Signs and Symptoms

Because the liver is involved with so many metabolic functions, individuals infected with a hepatitis virus tend to have generalized symptoms, which in the early stages are similar to the flu.

- ***Fatigue***
- ***Joint and muscle pain (myalgia)***
- ***Loss of appetite***
- ***Nausea***
- ***Diarrhea***
- ***Constipation***
- ***Fever***
- ***Jaundice***



As the disease progresses, the liver may become enlarged and tender. At this stage, other symptoms may occur.

- **Chills**
- **Weight loss**
- **Distaste for cigarettes and food**
- **Darker urine and lighter feces**

**Jaundice (icterus).** When the liver's ability to dispose of metabolic waste is impaired, bilirubin accumulates in the blood. Bilirubin is derived from the breakdown of red blood cells and contains a yellow pigment. When high levels of bilirubin accumulate in the blood, the skin and the whites of the eyes turn yellow.

**The variability of symptoms.** The symptoms of hepatitis vary considerably from one individual to another, even when the same causative agent is involved. **Because symptoms are not specific to the causative agent, it is impossible to distinguish among the various causative agents of hepatitis based on clinical symptoms alone; serological testing is required.**

## Tests of Liver Functions

The numerous biochemical tests that detect abnormal liver function can help to confirm the presence of liver disease, but do not define the cause. Three commonly used blood tests that assess liver function include bilirubin, and specific enzymes: alanine aminotransferase (ALT) and aspartate aminotransferase (AST).

Blood levels of all three substances are roughly elevated in proportion to the degree of liver damage. ALT and AST are contained within the liver cells. Inflammation of the liver causes these enzymes to be released in abnormally high amounts into the blood. An elevated test result for one or all of these substances is often the first indication that the patient has an inflamed liver, and is usually the first step in diagnosing hepatitis.

**Bilirubin**

**ALT**

**AST**

*An elevated test result for one or all of these substances is often the first indication that the patient has an inflamed liver, and is usually the first step in diagnosing hepatitis.*

Elevated test results may also be caused by alcoholic hepatitis, acetaminophen, cirrhosis of the liver, biliary tract disease, or viral hepatitis. Until the development of serological assays for specific viral hepatitis markers, physicians determined the diagnosis by integrating liver function tests with patient history, physical examination, and the physician's knowledge of liver diseases.

## Viral Hepatitis Testing

A definitive diagnosis of viral hepatitis is only achievable by the use of viral-specific hepatitis tests.

## Serological Markers

Serology pertains to antigen/antibody reactions *in vitro*. Viral hepatitis assays detect the presence of specific viral antigens and/or antibodies in serum. A physician uses these results to identify, differentiate, and monitor a hepatitis infection.

## Viral Hepatitis Panels

Panels, or groups of assays, to detect serological markers of viral hepatitis are used by physicians for the following purposes:

### Diagnose

- **To differentiate between HAV, HBV, and HCV**
- **To diagnose acute hepatitis A (anti-HAV IgM) or acute hepatitis B (anti-HBc IgM)**

## Screen

- **To screen blood or blood products to prevent the spread of viral hepatitis**
- **To test exposed persons for immunity to HBV using anti-HBc and anti-HBs (in particular, dialysis patients, healthcare workers, recipients of frequent transfusions, and injecting drug users)**
- **To identify HCV infected individuals**
- **To identify HBsAg positive pregnant women who may transmit hepatitis B virus to their newborn infants. Infants who become infected with HBV by perinatal transmission have a 90% risk of developing chronic hepatitis B.**
- **To identify HBV infected individuals**
- **To test sex partners of individuals with acute or chronic HBV in order to minimize the spread of infection by the initiation of prophylaxis**
- **To determine if an individual is currently infected or has antibodies to HBV**

## Monitor

- **To evaluate for late seroconversion and/or disease resolution in a known HBV carrier**
- **To monitor the success of immunoprophylaxis in cases of potential perinatal transmission of HBV (9 – 15 months after birth)**
- **To ensure immunity has been achieved after vaccination for HBV**

The Acute Viral Hepatitis Panel\* is the first laboratory tool for identifying the specific virus responsible for a patient's hepatitis. The Acute Viral Hepatitis Panel tests for four serological markers: anti-HAV IgM (IgM antibody directed against HAV), HBsAg (hepatitis B surface antigen), anti-HBc IgM (IgM antibody directed against the hepatitis B core antigen), and anti-HCV (antibody to HCV).

Additional panels will be discussed in the upcoming sections.

\*As defined in CPT code #80074

## Acute Viral Hepatitis Panel

*The Acute Viral Hepatitis Panel tests for four serological markers: anti-HAV IgM (IgM antibody directed against HAV), HBsAg (hepatitis B surface antigen), anti-HBc IgM (IgM antibody directed against HBcAg), and anti-HCV (antibody to HCV).*

## Quiz Questions – Pathology of Viral Hepatitis

1. *Name the five major viruses currently known to cause viral hepatitis:*
  
2. *List four general symptoms associated with viral hepatitis:*
  
3. *True or false? Physicians are able to differentially diagnose cases of viral hepatitis based on symptoms alone.*
  
4. *How are liver function tests used in the diagnosis of viral hepatitis?  
(Choose one or more of the following)*
  - a. *To indicate the status of liver function*
  - b. *To indicate roughly the amount of liver damage*
  - c. *To indicate the viral agent involved*
  
5. *Viral hepatitis panels are used to:*
  - a. *Diagnose*
  - b. *Monitor*
  - c. *Screen*
  - d. *All of the above*



# Hepatitis A

## Section 2

*Learning Objectives • Case Study #1 • Hepatitis A Virus • Routes of Transmission  
Individuals at Risk • Incidence/Prevalence • Clinical Course • Prevention/Prophylaxis  
Therapy • Viral Hepatitis Overview • Quiz Questions*

HAV



# Learning Objectives

After completing this section, you should be able to:

1. *Indicate how the hepatitis A virus (HAV) is transmitted*
2. *Identify individuals at risk for infection by the hepatitis A virus*
3. *Recognize the incidence and prevalence of hepatitis A*
4. *Describe the symptoms and clinical course of the disease*

## Case Study #1

Janet, a 26-year-old daycare teacher felt fatigued, had diarrhea, and was running a fever. Assuming it was just the flu, she rested for a couple of days. When symptoms continued for more than a week, she went to her physician. Janet informed her physician of her symptoms, including the fact that her stools had changed color. Upon further examination, the physician observed that both her skin and the whites of her eyes were slightly yellow.

This last observation, in particular, prompted the physician to check Janet's bilirubin and liver enzymes. Laboratory tests showed that Janet's bilirubin and ALT levels were abnormally elevated. At this point, the physician ordered the Acute Viral Hepatitis Panel. Below are the results of the Acute Panel:



**Janet**

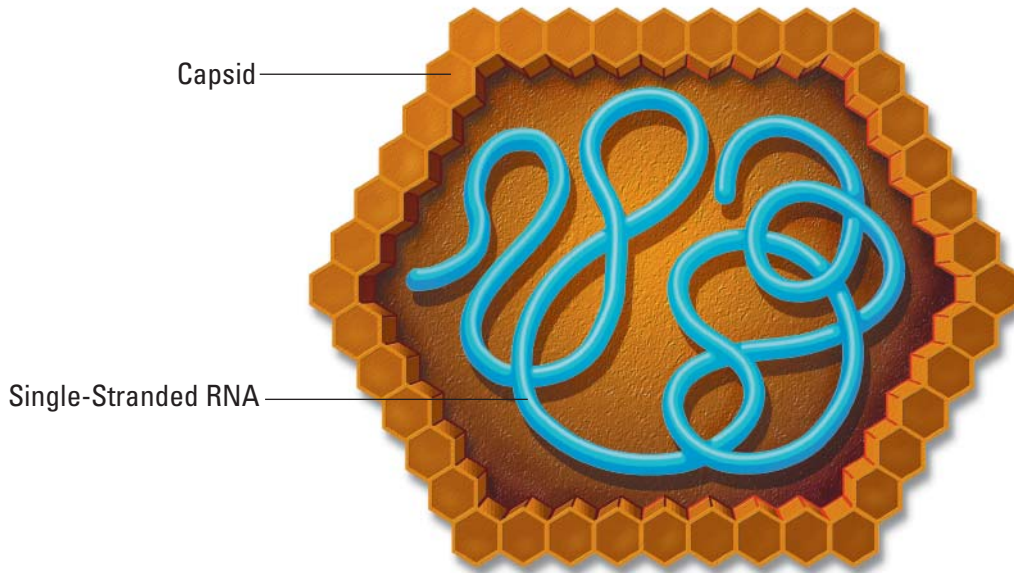
*Daycare Teacher.*

### Acute Viral Hepatitis Panel

ASSAY	HBsAg	Anti-HAV IgM	Anti-HBc IgM	Anti-HCV
RESULTS	–	+	–	–

*In this case, the panel definitively diagnosed an acute infection with HAV. While the hepatitis A virus is rarely detectable in serum, the IgM antibody to HAV (anti-HAV IgM) is detectable in serum and indicated that Janet had acute hepatitis A.*

# Hepatitis A Virus



- ***Small, single-stranded RNA virus***
- ***A member of the Picornaviridae family***
- ***Infects the liver***

## Routes of Transmission

Transmission usually occurs enterically (fecal-oral) through:

- ***Close person-to-person contact***
- ***Ingestion of contaminated food or water***

These routes could be facilitated by poor personal hygiene and poor sanitation.

*Evaluation of the risk factors associated with HAV infection relative to Janet's history suggested that she was probably exposed to HAV by one of the daycare attendees. Most likely a diapered child was infected and transmission may have occurred by Janet not washing her hands well after diapering.*

## Individuals at Risk

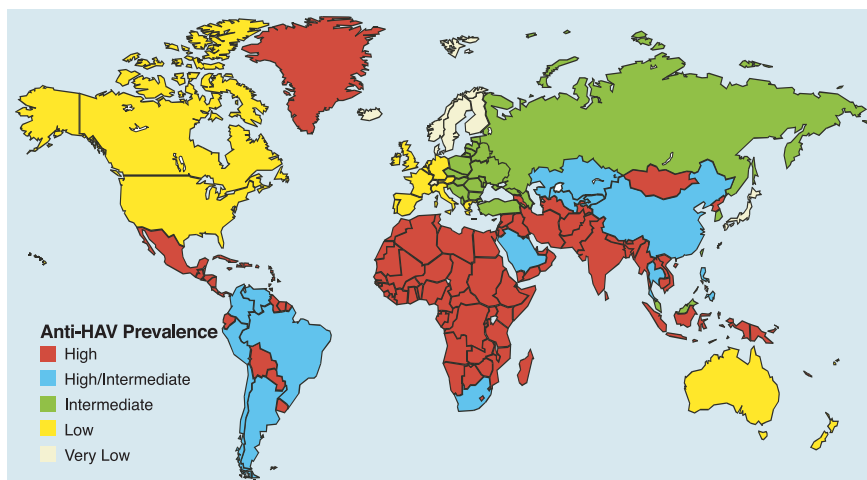
- **Those in close contact with an infected individual**
- **Men having sex with men**
- **Injecting and noninjecting drug users where high risk behavior or environmental conditions occur that contribute to acquiring the infection (i.e., fecal-oral)<sup>1, p12</sup>**
- **Children in daycare centers where hepatitis A outbreaks occur and their families**
- **Travelers and military personnel in areas with widespread disease and where clean water and proper sewage disposal are unavailable (i.e., most developing countries)**
- **Patients and staff in custodial institutions**

As a young adult working in a daycare center where hepatitis A is occurring, Janet was in a typical at-risk situation.

## Incidence/Prevalence

- **In the U.S. there are an estimated 125,000 to 200,000<sup>3, slide 5</sup> total infections per year. About one third of the U.S. population has serologic evidence of ever having had HAV infection<sup>3A, slide 13</sup>**
- **In terms of morbidity, approximately 100 deaths per year are associated with fulminant hepatitis A<sup>3, slide 5</sup>**
- **Almost one-third of reported HAV cases are in children younger than the age of 15<sup>3A, slide 14</sup>**
- **The map below represents prevalence patterns of HAV infections worldwide**
- **Large, nationwide outbreaks tend to occur every 10 – 15 years; the last outbreak was in 1995<sup>3A, slide 12</sup>**

### Geographic Distribution of HAV Infection<sup>3A, slide 9</sup>

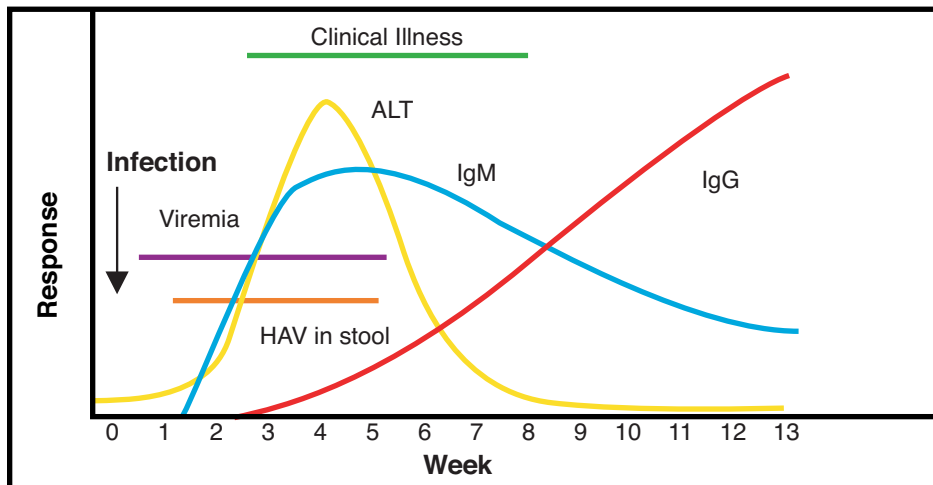


Note: This map has been generalized from available data.

## Clinical Course

- Onset of symptoms is usually abrupt with symptoms lasting approximately 1 – 8 weeks
- Jaundice develops in 70 – 80 percent of adults and in less than 10 percent of children under the age of 6<sup>3A, slide 5</sup>
- Among children under age 6, 70 percent of infections are asymptomatic<sup>1, p2</sup>
- HAV replicates in the liver and is shed in the stool<sup>1, p2</sup>
- Peak infectivity occurs during the 2-week period before onset of jaundice or elevation of liver enzymes when the concentration of virus in stool is highest<sup>1, p2</sup>
- The concentration of virus in stool declines after jaundice appears<sup>1, p2</sup>
- Children and infants can shed HAV up to several months after onset of clinical illness<sup>1, p3</sup>
- A true indication of immunity to HAV is the presence of total anti-HAV and absence of IgM anti-HAV in serum

## Hepatitis A Virus Infection<sup>3A, slide 6</sup>



Within three weeks Janet's symptoms had disappeared. She can now be considered immune to the hepatitis A virus. There is no chronic carrier state for hepatitis A.

## Prevention/Prophylaxis

- **Good sanitary habits help with the prevention of HAV infection**
- **Prevention of clinical illness using immune globulin, providing short-term protection, has proven to be advantageous<sup>2</sup>**
- **When given before exposure or early in the incubation period, immune globulin is greater than 80 – 90 percent effective at preventing illness with HAV<sup>3A, slide 31</sup>**
- **Pre-exposure prophylaxis with immune globulin can be given to travelers who:**
  - **Will be visiting developing countries and**
  - **Plan to live in or visit areas where sanitation is poor and water and food are potentially contaminated**
- **HAV vaccination has been shown to reduce community HAV infection during community-wide outbreaks<sup>1, p20</sup>**
- **Hepatitis A vaccinations, providing long-term protection, are available for individuals older than two years of age and are recommended for all persons at risk of exposure, and those who seek immunity<sup>2</sup>**
- **1999 ACIP (Advisory Committee on Immunization Practices) recommendations indicate that children older than two should be vaccinated based on the hepatitis rate in their geographical area<sup>3A, slide 3</sup>**
- **Two vaccines are commercially available in the U.S.: Havrix<sup>®</sup> (GlaxoSmithKline) and Vaqta<sup>™</sup> (Merck & Co., Inc.)<sup>3A, slide 21</sup>**

## Therapy

There is no specific therapy available.



## Vaccination

*Hepatitis A vaccinations, providing long-term protection, are available for individuals older than two years of age.*

## Viral Hepatitis Overview

	Hepatitis A Virus				
<b>VIRUS FAMILY</b>	<i>Picornaviridae</i>				
<b>ROUTE OF TRANSMISSION</b>	Fecal-oral route				
<b>ONSET</b>	Usually abrupt				
<b>INCUBATION</b>	15 – 50 days				
<b>CHRONICITY</b>	None				
<b>MORTALITY</b>	≤ 39 years: ≤ 0.3% ≥ 40 years: 2.1%				

## Quiz Questions – Hepatitis A

1. *Cite two routes of HAV transmission:*

---

2. *Individuals most at risk for contracting HAV include:*

- a. *Food-handlers*
- b. *Children in day-care centers as well as their families*
- c. *Individuals in close contact with an infected individual*
- d. *Law enforcement personnel*

3. *Which of the following describe the incidence of hepatitis A?*

- a. *Approximately 100 deaths from fulminant HAV are reported each year in the U.S.*
- b. *Recently HAV incidence in the U.S. has been estimated at 125,000 – 200,000 cases per year*
- c. *Almost one-third of reported HAV cases are in children younger than 15 years of age*
- d. *All of the above*

4. *Which of the following describe the most common symptoms and clinical course associated with HAV? (Choose one or more of the following)*

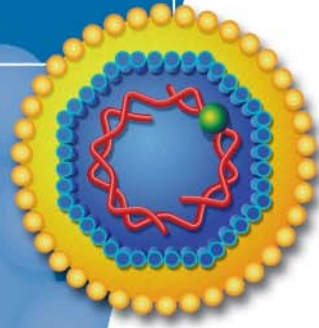
- a. *Jaundice always occurs*
- b. *Onset is usually abrupt*
- c. *Most cases involving children under age 6 are asymptomatic (70 percent)*
- d. *Patients are potentially infectious for up to several weeks before onset of symptoms*

# Hepatitis B

## Section 3

*Learning Objectives • Case Study #2 • Hepatitis B Virus • Routes of Transmission • Individuals at Risk  
Incidence/Prevalence • Clinical Course • Hepatitis B Panels • Chronic HBV Infection  
Prevention/Prophylaxis • Therapy • Viral Hepatitis Overview • Quiz Questions*

HBV



# Learning Objectives

After completing this section, you should be able to:

1. **Recognize the incidence and prevalence of hepatitis B**
2. **Describe the symptoms and clinical course of the disease**
3. **Indicate the physical features of the virus**
4. **Indicate how the hepatitis B virus (HBV) is transmitted**
5. **Identify individuals at risk for infection by the hepatitis B virus**
6. **Recognize that hepatitis B is a sexually transmitted disease**
7. **Identify the types of hepatitis B panels and describe their purpose**

## Case Study #2

Susan, a college student, had been experiencing the following symptoms for over a week: persistent fatigue, loss of appetite, nausea, vomiting, and abdominal pain. She scheduled an appointment at her campus health clinic. After completing her patient history, this is what the physician learned:

- **About one week ago, Susan had become sexually active with a new boyfriend**
- **Both Susan and her partner had multiple sex partners before they started dating**
- **Susan had not always used condoms with her partners**
- **The symptoms appeared about one week ago, and were still present**

The physician ordered tests for other sexually transmitted diseases, HIV, and pregnancy; all came back negative. Because of Susan's persistent abdominal tenderness, the physician ordered liver function tests. Susan's bilirubin and liver enzyme results were elevated, prompting the physician to order an Acute Viral Hepatitis Panel. Below are the results:

### Acute Viral Hepatitis Panel

ASSAY	HBsAg	Anti-HBc IgM	Anti-HAV IgM	anti-HCV
RESULTS	+	+	-	-

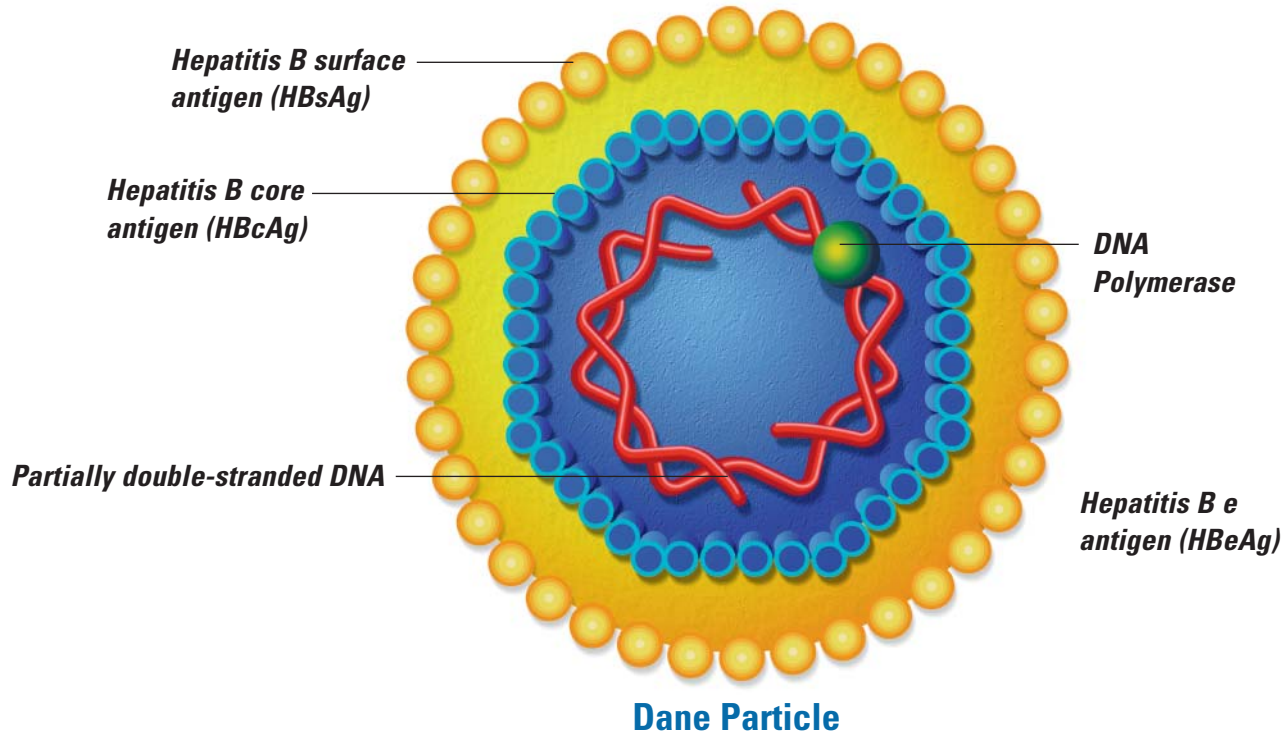
Susan was HBsAg positive, indicating that she was infected with HBV. Susan's test results also showed that anti-HBc IgM was present, indicating an acute HBV infection.



**Susan**

College Student.

# Hepatitis B Virus

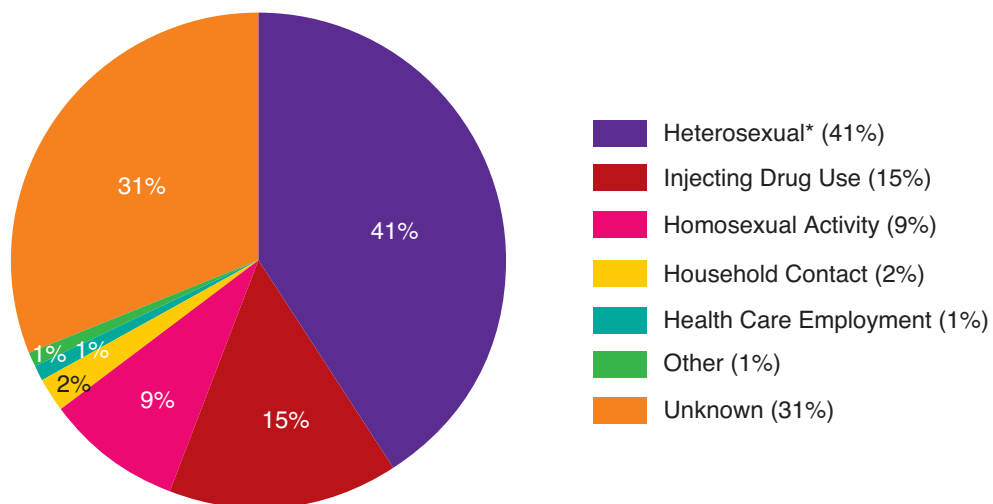


- *Partially double-stranded circular DNA virus*
- *A member of the Hepadnaviridae family*
- *Virus consists of a central core nucleocapsid containing viral DNA and a surrounding envelope containing the surface protein or surface antigen*

# Routes of Transmission

- **Percutaneous**
  - **Contaminated needle stick (injecting drug use and occupational exposure)**
  - **Hemodialysis**
  - **Human bite**
  - **Transplant or transfusion of unscreened blood or blood products**
  - **Acupuncture, tattooing, and body-piercing with unsterilized needles**
  - **Sharing razors**
- **Per mucosal**
  - **Sexual intercourse**
  - **Perinatal – infant born to an HBV infected mother**
  - **Contact with infected household objects (i.e., toothbrush or razor that may have blood on it)**

## Risk Factors for Acute Hepatitis B in the U.S., 1992 – 93. <sup>3B, slide 12</sup>



Source: Centers for Disease Control and Prevention Sentinel Counties Study of Viral Hepatitis

\*Includes sexual contact with acute cases, carriers, and multiple partners.

*Most likely, due to the long incubation period characteristic of an HBV infection, which averages 60 to 90 days, Susan had probably contracted the virus from a previous partner. Her current partner was not experiencing any symptoms, but because many individuals infected with HBV are asymptomatic, her previous and current partners should also be tested and counseled.*

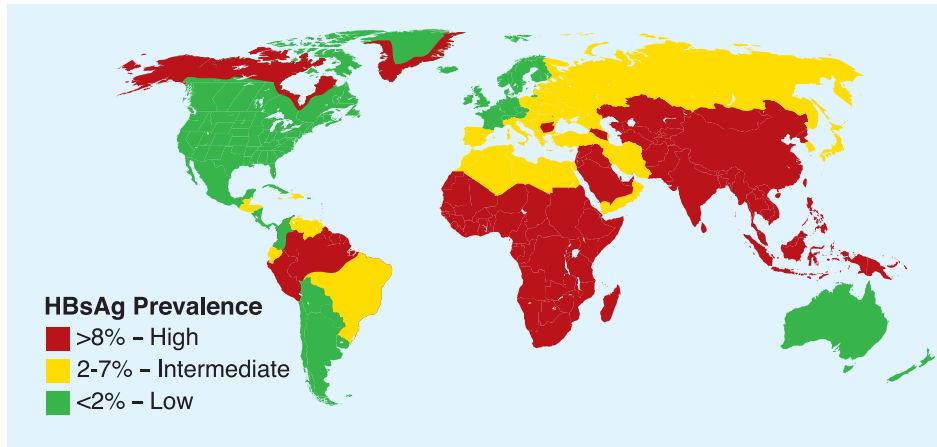
## **Individuals at Risk**

- ***Sexual contacts of an acute or chronically infected person***
- ***Injecting drug users***
- ***Persons with multiple sex partners or a history of sexually transmitted diseases***
- ***Infants born to HBV infected mothers***
- ***Individuals who have occupational contact with blood:***
  - ***Medical and dental workers***
  - ***Laboratory and support personnel***
  - ***Public service employees (i.e., paramedics, EMTs)***
- ***Recipients of unscreened blood or blood-derived products that have not undergone a viral inactivation process***
- ***Hemodialysis patients (due to poor equipment sterilization, not blood)***
- ***Household contacts of HBV infected individuals***
- ***Institutionalized populations (i.e., individuals in prisons and facilities for the developmentally disabled)***
- ***Persons born in HBV endemic areas (i.e., Africa, Asia, Eastern Europe, and South America)***

*Susan had unprotected sex with multiple partners which placed her at risk for HBV infection.*

# Incidence/Prevalence

## Geographic Distribution of Chronic HBV Infection\*



Source: <sup>3B</sup>, slide 9

\*Note: The map of HBsAg prevalence generalizes available data, patterns may vary within countries.

- **Worldwide, it is estimated that there are 350 million HBV carriers**<sup>13, p6</sup>
- **One in 20 Americans will contract HBV during their lives**<sup>6, p1</sup>
- **In the U.S., 1.0 – 1.25 million people are chronically infected with HBV. The number of acute HBV infections in the U.S. is estimated to be approximately 140,000 – 320,000 per year**<sup>3, slide 5</sup>
- **Most new cases occur among people aged 15 – 39; however, since 1985, the incidence among this age group has been declining steadily**<sup>4, p1</sup>
- **Approximately 30 – 50 percent of patients greater than 5 years old with HBV infection develop clinical illness (jaundice)**<sup>3B, slide 2</sup>, most lasting from 4 – 8 weeks.<sup>13, p22</sup> **Less than 10 percent of children less than 5 years of age have clinical illness (jaundice) associated with acute infection**<sup>3B, slide 2</sup>
- **Approximately 5,000 individuals in the U.S. die each year due to chronic liver disease associated with HBV**<sup>3, slide 5</sup>

Susan's age placed her in the population with the largest percentage of new cases that occur each year.



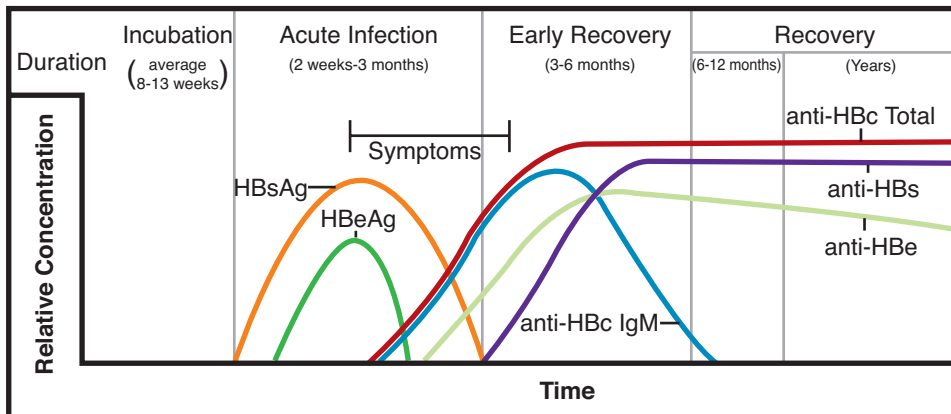
## 350 Million

Worldwide, it is estimated that there are 350 million HBV carriers.

# Clinical Course

- **Incubation period averages 60 – 90 days with the range being 45 – 180 days.**<sup>3B, slide 2</sup> Length of incubation depends on the amount of virus to which the person is exposed, the mode of transmission and host factors<sup>13, p22</sup>
- **Onset is often insidious**<sup>3B, slide 2</sup>
- **HBV causes clinical illness (jaundice) in 30 – 50 percent of all individuals age five and older, but less than 10 percent of those aged under five years**<sup>3B, slide 2</sup>
- **Symptoms include anorexia, fatigue, nausea, vomiting, abdominal pains, muscle or joint aches, mild fever, dark urine, skin rashes, and jaundice**<sup>4, p1</sup>
- **Most HBV infected adults will recover within six months and develop immunity**
- **Of those infected with HBV, 30 – 90 percent of children less than five years of age and 2 – 10 percent of the population over five years of age will progress to chronic infection**<sup>3B, slide 2</sup>
- **Among all age groups, 15 – 25 percent of those who become chronically infected with HBV die prematurely as a result of chronic liver disease**<sup>3B, slide 2</sup>

## Acute Hepatitis B Diagnostic Profile



Since Susan's symptoms were so persistent, the physician followed up the initial Acute Viral Hepatitis Panel with the Hepatitis B Monitoring Panel. It was important for the physician to understand the stage of Susan's infection.

# Hepatitis B Panels

## Hepatitis B Monitoring Panel

When a patient tested with the Acute Viral Hepatitis Panel has positive results for surface antigen (HBsAg) and IgM antibody to the core antigen (anti-HBc IgM), the diagnosis of acute hepatitis B is established. To follow the patient's progress, serial testing with the monitoring panel is indicated. This panel consists of four hepatitis B markers: HBsAg, HBeAg, anti-HBe, and anti-HBs.\* With the hepatitis B monitoring panel, a physician can:

- **Determine the patient's potential for developing chronic HBV infection due to the persistence of the surface antigen (HBsAg)**
- **Determine relative infectivity (HBeAg)**
- **Monitor seroconversion from HBeAg to anti-HBe, which usually indicates progression toward a resolution of the disease**
- **Monitor seroconversion from HBsAg to anti-HBs positivity, which indicates resolution of the disease and establishment of immunity**

*In Susan's case, the results of the monitoring panel would help identify her degree of infectivity.*

## Hepatitis B Monitoring Panel

ASSAY	HBsAg	HBeAg	Anti-HBe	Anti-HBs
RESULTS	+	+	-	-

*The results show that Susan was highly infectious. At this point the physician informed Susan of the following:*

- **Need to advise sex partners and household contacts of her infectious state**
- **Clinical course of the hepatitis B virus infection and possible outcomes**
- **Importance of NOT DONATING BLOOD**

*The physician also informed her that she was going to be monitored every month until resolution of the disease. Six months later, the results were negative for HBsAg and HBeAg and positive for anti-HBe and anti-HBs. This indicated that Susan had resolved the infection.*

*If Susan's HBsAg had persisted for more than six months, she would have been considered chronically infected with HBV.*

\*Example of a Hepatitis B monitoring panel used by a large reference laboratory.

# Chronic HBV Infection

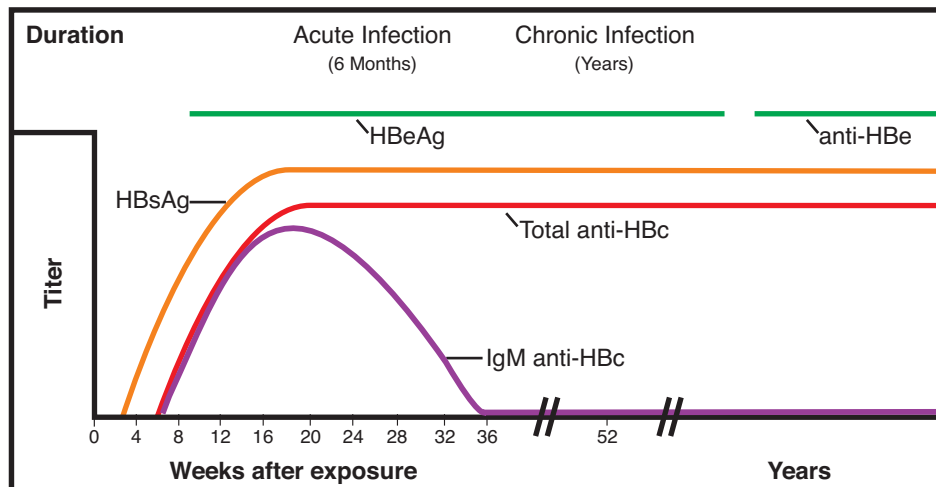
An individual is considered chronically infected if HBsAg is present for more than six months.

Three markers are used to determine the stage of chronic infection: HBsAg, HBeAg, and anti-HBc total. HBsAg and anti-HBc total will almost always be present; HBeAg may or may not be present, depending on the stage of disease progression.

Chronically infected individuals with HBeAg typically have higher viral loads than those with anti-HBe. Both patient groups should be considered infectious.

## Progression to Chronic HBV Infection

### Typical Serologic Course<sup>3B, slide 4</sup>



## Testing to Determine Immunity: Anti-HBs

Anti-HBs (antibody to the surface antigen) is the only marker for determining immunity to a HBV infection. Anti-HBs appears early in recovery and the titer may eventually decline. Other indicators of recovery are normal liver enzyme levels and negative tests for HBsAg.

The first hepatitis vaccine available in the United States was produced from the plasma of persons chronically infected with HBV. The hepatitis B vaccines currently available are produced by recombinant DNA technology.

Because immunity to hepatitis B is dependent on a highly individual response to the vaccine, it is recommended that following the vaccine series, an anti-HBs test be done for certain groups.

Anti-HBs testing is recommended for:

- **Healthcare workers**
- **Babies born to HBV infected mothers**
- **Sex partners of persons with chronic HBV infection**
- **Immunocompromised individuals**

Internationally, some countries recommend quantitating levels of anti-HBs in order to:

- **Screen individuals to determine the need for initial vaccination**
- **Establish an individual's initial level of anti-HBs after the vaccination series**
- **Determine whether revaccination is needed due to an inadequate response to the initial vaccine series**
- **Assess recovery from HBV infection**

Quantitation of anti-HBs is possible using a panel of anti-HBs standards that determine antibody levels. Standards are run to generate a standard curve. Results are calculated as anti-HBs concentration in mIU/mL by comparing the sample result to the curve.

## Pre-Vaccination Testing

Anti-HBc total, total antibody (i.e., IgM and IgG) to the hepatitis B core antigen, is an indicator of a current or previous HBV infection. It is also used with anti-HBs and HBsAg for screening at-risk populations for hepatitis B to determine their immune status. Individuals found to be positive for both anti-HBc and anti-HBs are presumed to be immune by prior natural infection. Those found to be negative are at risk for HBV infection and should be recommended for vaccination. The CDC recommends a prevention strategy that includes prenatal testing for HBsAg to identify pregnant women whose newborns require prophylaxis and whose household members require vaccination.<sup>5, p6</sup>

## Post-Vaccination Testing

The level of circulating anti-HBs is used to determine the effectiveness of vaccination. The hepatitis B vaccine is designed to induce only anti-HBs (the protective antibody) and will not induce an anti-HBc response. In the U.S., an antibody level of 10 mIU/mL or higher indicates immunity.<sup>5, p8</sup> Outside the U.S., other levels of antibody may be used to determine immunity. These levels may vary from country to country.

## Prevention/Prophylaxis

Measures to prevent HBV infection include:<sup>13</sup>

- **Worldwide screening of blood and blood products**
- **Destruction of disposable needles, and adequate sterilization of reusable materials such as surgical or dental instruments**
- **Effective use of universal precautions and barrier techniques (such as use of sterile equipment, the wearing of gloves, and wearing of eye/face protection)**

Due to the lack of a fully effective therapy, prophylaxis against HBV infection is essential. Prophylaxis is effective using either Hepatitis B Immune Globulin (HBIG) to provide temporary, passive protection, or the hepatitis B vaccine to provide active, prolonged immunity.

**Hepatitis B vaccine.** The conventional regimen is a series of three intramuscular doses of the vaccine given over a six-month period: initial vaccination, again at 30 days, and the third dose at 6 months. This regimen induces an adequate antibody response in over 90 percent of healthy young adults and in more than 95 percent of infants, children, and adolescents (up to age 19).<sup>5, p8</sup>

- **Immunization is one of the most medically efficient and cost-effective means of controlling viral hepatitis**<sup>5, p3</sup>
- **Countries with universal vaccination programs are seeing declines in chronic HBV infections**<sup>13, p45</sup>
- **Achieving universal immunity requires an increase in public awareness of the severity of health problems caused by HBV**<sup>13, p52</sup>

While the hepatitis B vaccine is 80 – 95 percent effective in many segments of the population, response to the vaccine is highly individual; not all vaccinated individuals become immune. An individual's health at the time of the vaccination affects his/her response to the vaccine and influences the occurrence and duration of immunity. Factors that negatively influence an individual's ability to become immune to hepatitis B as a result of vaccination include:

- **Increased age**
- **Obesity/body size**
- **Cigarette smoking**
- **Immunosuppression**

In the United States, the CDC recommends that hepatitis B vaccinations be a part of childhood immunization programs, and the CDC has expanded their recommendations for HBV vaccinations to include all unvaccinated children at age 11 – 12 as well as all “high-risk” children and adolescents of all ages.<sup>3B, slide 14</sup>

**Hepatitis B Immune Globulin (HBIG)** is administered for temporary passive protection from hepatitis B. Post-exposure prophylaxis with both hepatitis B immune globulin and hepatitis B vaccine should be offered to infants born to HBV infected mothers, infants less than 12 months of age whose mothers or primary care givers have acute hepatitis B, and sex partners of individuals with acute hepatitis B. Unvaccinated healthcare workers who sustain a needlestick injury from a patient infected with HBV should also receive HBIG and should start the hepatitis B vaccine series.<sup>5</sup>

## Prenatal Screening

Infants born to mothers who are chronically infected with hepatitis B have a high probability of contracting the infection, of becoming chronically infected, and of developing chronic liver disease later in life. Therefore, HBsAg testing is recommended in the U.S. for prenatal screening of all pregnant women.<sup>5, p3</sup>

Women should be tested early in their pregnancy. If the mother's HBsAg status is unknown at the time of admission for delivery, HBsAg testing should be performed as soon as possible. If test results are not available, the infant should receive the hepatitis B vaccine. If the mother is identified as HBsAg positive, the infant should also be given hepatitis B immune globulin (HBIG) within 12 hours of birth, and the vaccine series should be completed as scheduled.<sup>5, p4</sup>

Routine vaccination of all infants is now recommended.<sup>3B, Slide 14</sup>



## HBV and Infants

*Infants born to mothers who are chronically infected with hepatitis B have a high probability of contracting the infection, of becoming chronically infected, and of developing chronic liver disease later in life.*

## Developments in HBV Testing<sup>14, p657</sup>

Researchers have developed assays that detect and accurately measure HBV DNA. These assays detect the viral genome and measure the level of circulating virus in an infected individual. The level of HBV DNA in the blood is often referred to as “viral load.”

Investigational applications for hepatitis B virus DNA assays include:

- ***Directly assess circulating virus in an infected individual***
- ***Predict response to antiviral therapy based on pretreatment viral load***
- ***Monitor the effectiveness of antiviral therapy (HBV DNA falls rapidly in patients who respond to treatment)***
- ***Provides additional information to help confirm a diagnosis in cases with ambiguous serology***

If a physician can determine viral load, then he or she can better gauge whether or not to initiate therapy, as well as more accurately monitor its effect.

# Therapy

Individuals with chronic HBV infection should be evaluated for evidence of chronic liver disease and potential need for treatment. Drugs currently licensed for treatment of chronic hepatitis B include adefovir dipivoxil, alpha interferon, and lamivudine. Other antiviral drugs are being studied experimentally.

## Viral Hepatitis Overview

	Hepatitis A Virus	Hepatitis B Virus			
<b>VIRUS FAMILY</b>	<i>Picornaviridae</i>	<i>Hepadnaviridae</i>			
<b>ROUTE OF TRANSMISSION</b>	Fecal-oral route	Percutaneous, permucosal			
<b>ONSET</b>	Usually abrupt	Usually insidious			
<b>INCUBATION</b>	15 – 50 days	Average 60 – 90 days, range 45 – 180 days			
<b>CHRONICITY</b>	None	2 – 10% of everyone (5+ years of age) 30 – 90% of children (0 – 5 years of age)			
<b>MORTALITY</b>	≤ 39 years: ≤ 0.3% ≥ 40 years: 2.1%	0.5 – 1.0%			

## Quiz Questions – Hepatitis B

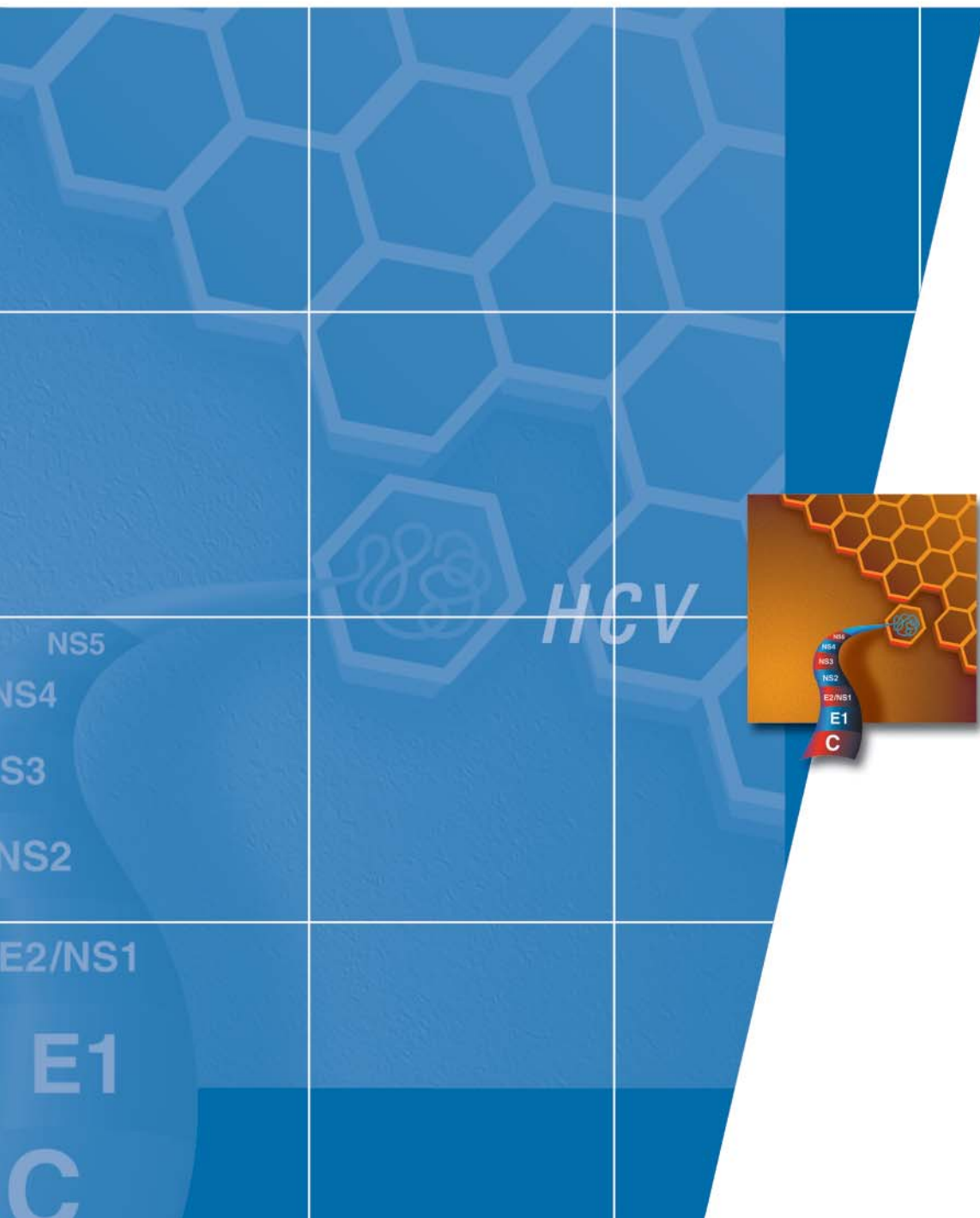
- 1. Which of the following is not a route of transmission for HBV?**
  - a. Needlestick**
  - b. Sexual contact**
  - c. Tattoo**
  - d. Contaminated water**
- 2. Name the six serological markers for hepatitis B:**
- 3. Chronic HBV infection worldwide is approximately:**
  - a. 2 million**
  - b. 150 million**
  - c. 350 million**
  - d. 1 billion**
- 4. True or false? In the U.S. there are 1.0 – 1.25 million people chronically infected with hepatitis B.**
- 5. True or false? 20 percent of new hepatitis B cases occur among people aged 15 – 39.**
- 6. List five symptoms that may be associated with an acute HBV infection:**
- 7. The average incubation period of hepatitis B is:**
  - a. 20 – 30 days**
  - b. 60 – 90 days**
  - c. 90 – 120 days**
- 8. Of those infected with HBV, \_\_\_\_\_ percent of children less than 5 years of age progress to a chronic HBV infection.**
  - a. 2 – 10%**
  - b. 15 – 20%**
  - c. 30 – 90%**
  - d. 100%**

- 9. Which of the following individuals are typically at risk for hepatitis B?**
- a. Injecting drug users**
  - b. Travelers to endemic areas (for short periods of time)**
  - c. Sexual contact with HBV infected individuals**
  - d. Household contacts of persons with chronic HBV infections**
- 10. What assays are included in the hepatitis B Monitoring Panel?**
- 11. True or false? Anti-HBc is used primarily to assess infectivity.**
- 12. What test is used in the prenatal screening of pregnant women?**
- a. Anti-HBs**
  - b. HBsAg**
  - c. HBeAg**
  - d. Anti-HBc Total**
- 13. True or false? The hepatitis B vaccine is administered to provide temporary passive protection.**
- 14. HBIG should be given to:**
- a. Infants born to HBV infected mothers**
  - b. Sexual partners of individuals with acute HBV**
  - c. Unvaccinated healthcare workers involved in needlestick incidents where HBV is known**
  - d. All of the above**
- 15. True or false? Anti-HBs is the only test available today to determine immunity to HBV.**

# Hepatitis C

## Section 4

*Learning Objectives • Case Study #3 • Hepatitis C Virus • Routes of Transmission  
Individuals at Risk • Incidence/Prevalence • Clinical Course • Prevention/Prophylaxis  
Therapy • Viral Hepatitis Overview • Quiz Questions*



# Learning Objectives

After reading this section, you should be able to:

1. **Indicate how the hepatitis C virus (HCV) is transmitted**
2. **Identify individuals at risk for infection by HCV**
3. **Recognize the incidence and prevalence of HCV infection**
4. **Describe the symptoms and clinical course of a HCV infection**

## Case Study #3

Donald, a 39-year-old emergency room nurse, accidentally stuck himself with a needle as he removed it from a patient's vein. When he reviewed the patient's chart, he noticed that this individual was anti-HCV positive. He immediately scheduled an appointment with his physician. Even though the needlestick occurred less than 24 hours previously (too soon for an antibody response), the physician still ordered an Acute Viral Hepatitis Panel to check for current infection with HAV, HBV, and/or HCV. An HIV test was also ordered.



**Donald**

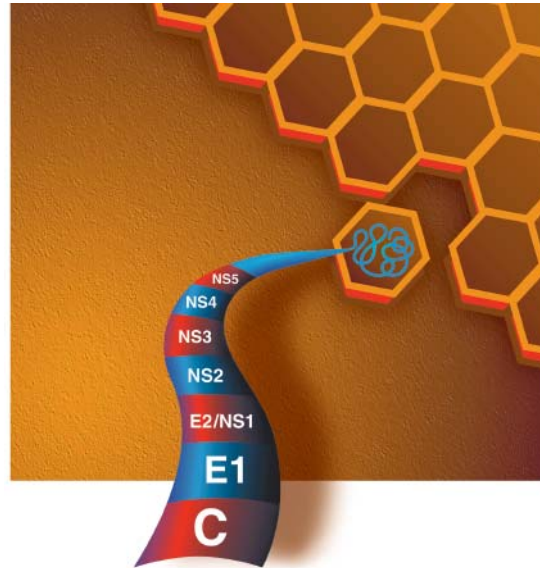
*Emergency Room Nurse.*

### Acute Viral Hepatitis Panel

ASSAY	HBsAg	Anti-HAV IgM	Anti-HBc IgM	Anti-HCV
RESULTS	–	–	–	–

*All tests came back negative, including HIV. Because of the recent exposure to the hepatitis C virus, the physician advised Donald that follow-up testing would be needed in order to rule out an HCV infection.<sup>7</sup>*

# Hepatitis C Virus



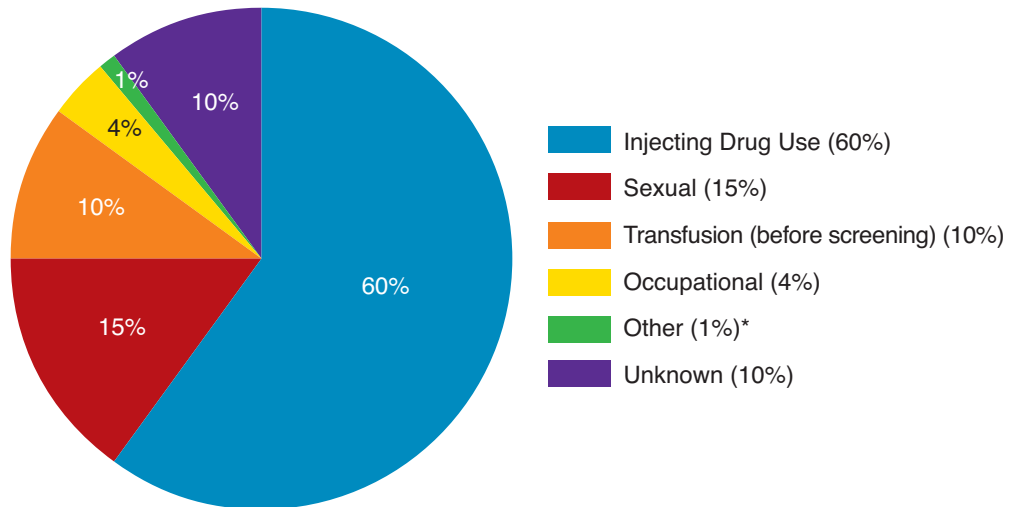
- **Single, positive-stranded RNA virus of approximately 10,000 nucleotides**
- **Small (less than 50 nanometers in diameter); lipid-enveloped virus**
- **Member of the Flaviviridae family**

## Routes of Transmission

HCV is a blood-borne virus. There are no known cases of HCV transmitted enterically (oral-fecal) through breast milk, semen, or saliva. The following routes of transmission are well-documented:

- **Percutaneous**
  - **Contaminated needlestick (injecting drug use and occupational exposure)**
  - **Hemodialysis**
  - **Human bite**
  - **Transplant or transfusion of unscreened blood or blood products**
  - **Acupuncture, tattooing, and body-piercing with unsterilized needles**
- **Per mucosal**
  - **Sexual intercourse**
  - **Perinatal – infant born to HCV infected mother**
  - **Contact with infected household objects (i.e., toothbrush or razor that may have blood on it)**

## Sources of Infection for Persons With Hepatitis C<sup>3C</sup>, Slide 21



\*Nosocomial; iatrogenic; perinatal

Source: Centers for Disease Control and Prevention

## Individuals at Risk

- ***Injecting drug users***
- ***Persons occupationally exposed to blood***
- ***Hemodialysis patients***
- ***Transfusion and transplant recipients (prior to 1992)***

*The route by which Donald was exposed to HCV, as well as his occupation, put him at risk for a HCV infection.*

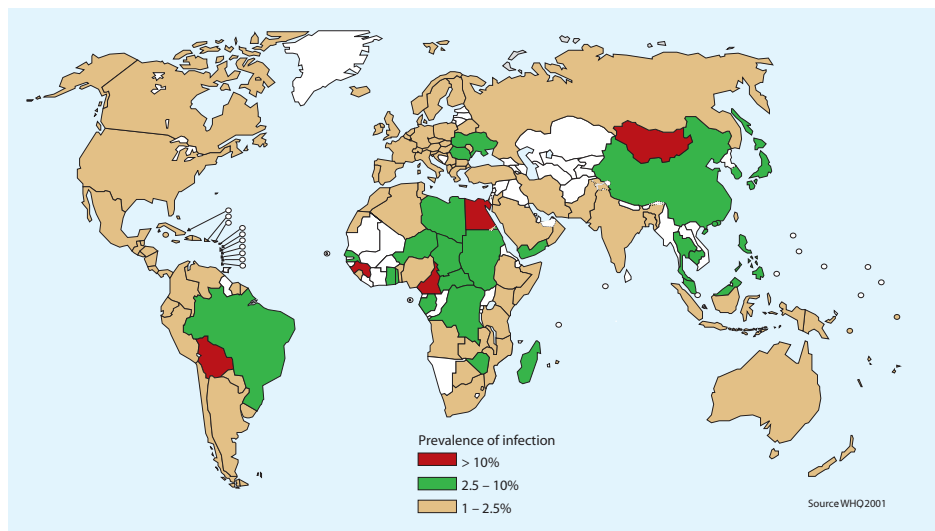
## Incidence/Prevalence

Because acute infection is asymptomatic in most cases, incidence data on a global scale is not well known.

It is important to note that since the availability of multi-antigen testing in 1992, the incidence of post-transfusion HCV has declined significantly. The risk is now less than 1 in 1,000,000 units transfused.<sup>12</sup>

- ***In the U.S., the annual number of newly acquired acute HCV infections has declined from an estimated 240,000 in the mid-1980s to about 25,000 in 2001<sup>12</sup>***
- ***In terms of prevalence, an estimated 3.9 million Americans (1.8 percent) have been infected with the virus (2.7 million chronically infected)<sup>12</sup>***
- ***WHO estimates that up to 3.0 percent of the world's population has been infected with HCV***
- ***Worldwide, there may be more than 170 million chronic carriers of HCV***

### Global Distribution of Hepatitis C, 2001<sup>15, p47</sup>



## Clinical Course

- **The incubation period varies from 2 – 26 weeks; the average is 6 – 7 weeks**<sup>3C, slide 2</sup>
- **Onset is usually insidious**
- **Majority of infected persons, 60 – 70 percent, may be asymptomatic**<sup>8, p12</sup>
- **10 – 20 percent of patients develop nonspecific symptoms (e.g., anorexia, malaise, fatigue, or abdominal pain)**<sup>8, p12</sup>
- **20 – 30 percent of individuals with acute HCV might have jaundice**<sup>8, p12</sup>
- **Patients with acute HCV infection may take an average of eight to nine weeks from exposure for seroconversion to occur; the average time from exposure to the development of symptoms is six to seven weeks**<sup>8, p12</sup>
- **Individuals positive for HCV antibody, even if liver enzyme tests are normal, are considered potentially infectious for the virus**
- **About 60 – 85 percent of HCV infected individuals become chronically infected with the virus**<sup>9, p10</sup>
- **Of persons with chronic hepatitis C, 10 – 20 percent will develop cirrhosis**<sup>8, p13</sup>
- **Hepatocellular carcinoma develops in 1 – 5 percent of individuals with chronic HCV infection over 20 – 30 years**<sup>8, p13</sup>
- **Mortality: In the U.S., between 10,000 and 12,000 individuals die each year from HCV associated chronic liver disease**<sup>9, p11</sup>
- **HCV is now the leading cause for liver transplantation in the U.S.**<sup>9, p6</sup>
- **Various factors, including alcohol use and co-infection with HIV, can affect the clinical course of HCV**<sup>9, p10</sup> (abstinence from alcohol in infected individuals is recommended)<sup>10</sup>

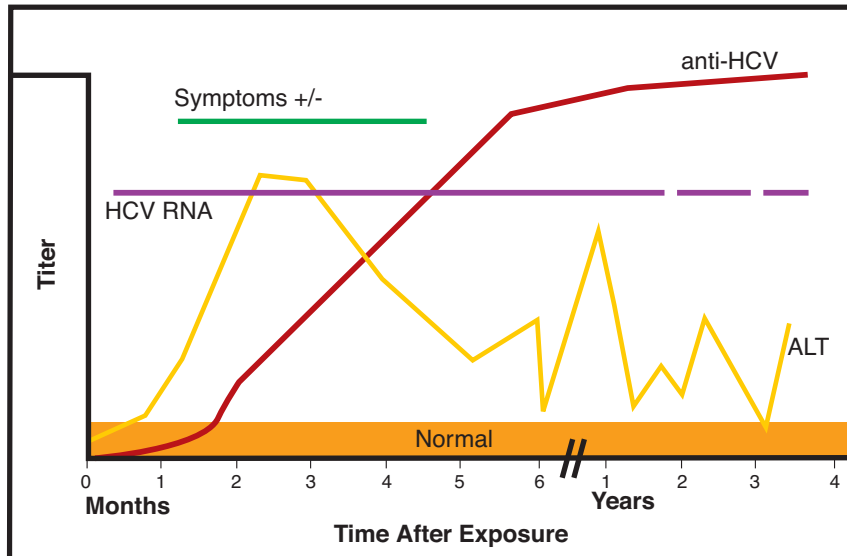
Three months after the needlestick incident, Donald's anti-HCV result was still negative and his liver enzymes were normal. As a precaution, his physician routinely tested Donald for anti-HCV. At the one-year follow-up, he remained negative for anti-HCV, and the physician reassured him that although exposed to HCV, he had not become infected.

## Chronic HCV Infection

About 60 – 85 percent of HCV infected individuals become chronically infected.

Of persons with chronic hepatitis C, 10 – 20 percent will go on to develop cirrhosis.

## Serologic Pattern of Acute HCV Infection With Progression to Chronic Infection<sup>3C, slide 5</sup>



### Diagnostic Testing for Hepatitis C

HCV is diagnosed serologically by detecting antibodies specific to the hepatitis C virus (anti-HCV), and by ruling out other viruses such as HAV or HBV. There are limitations on using any anti-HCV assay alone to diagnose or monitor a case of hepatitis. Retesting for anti-HCV may be necessary if the initial result is negative, but clinical signs and symptoms suggest a HCV infection. Furthermore, anti-HCV does not distinguish between an acute, chronic or resolved infection. A supplemental test, RIBA (recombinant immunoblot assay), can also be used to confirm a positive anti-HCV result.<sup>10</sup>

Nevertheless, as a screening assay for the blood supply, current anti-HCV assays have been very effective in the U.S. at reducing post-transfusion hepatitis to a very low level.

## Developments in HCV Testing

Researchers have developed assays that detect and accurately measure HCV RNA. These assays detect the viral genome and measure the level of circulating virus in an infected individual. The level of HCV RNA in the blood is often referred to as the “viral load.” Several polymerase chain (PCR) tests for HCV RNA are now available.<sup>9, p13</sup>

Applications for hepatitis C virus RNA assays include:<sup>9, p13</sup>

- **Directly assess circulating virus in an infected individual**
- **Evaluate suspect HCV infection before seroconversion occurs**
- **Assess viral load before antiviral therapy is administered (patients with low, pretreatment viral load are more likely to respond; however, a high HCV RNA should not preclude treatment)<sup>9, p14</sup>**
- **Monitor the effectiveness of antiviral therapy (interferon and ribavirin)**
- **Detect HCV infection in cases with ambiguous serology**

## Prevention/Prophylaxis

There is currently no vaccine for HCV. The difficulty in developing a vaccine is due, in part, to the mutability of the HCV genome. In addition, there is no effective, short-term prevention such as HBIG or immune globulin. In the absence of the above, all precautions to prevent HCV infection must be taken.

WHO recommendations on measures to prevent HCV include:

- **Screening of blood and blood products**
- **Destruction of disposable needles and adequate sterilization of reusable material such as surgical or dental instruments**
- **Effective use of universal precautions and barrier techniques (such as use of sterile equipment, the wearing of gloves, and wearing eye/face protection)**
- **Education about the risks of using unsterilized material and high-risk drug and sexual behaviors**



## Universal Precautions

Effective use of universal precautions and barrier techniques (such as use of sterile equipment and the wearing of gloves) are some of the recommendations to prevent HCV infection.

# Therapy

- **No post-exposure prophylaxis is available for hepatitis C; immune globulin is not recommended**
- **Combination therapy with pegylated interferon and ribavirin is the treatment of choice. Sustained response rates vary from 40 – 80 percent.<sup>10</sup>**

## Viral Hepatitis Overview

	Hepatitis A Virus	Hepatitis B Virus	Hepatitis C Virus		
<b>VIRUS FAMILY</b>	<i>Picornaviridae</i>	<i>Hepadnaviridae</i>	<i>Flaviviridae</i>		
<b>ROUTE OF TRANSMISSION</b>	Fecal-oral route	Percutaneous, permucosal	Percutaneous, permucosal		
<b>ONSET</b>	Usually abrupt	Usually insidious	Insidious		
<b>INCUBATION</b>	15 – 50 days	Average 60 – 90 days, range 45 – 180 days	14 – 182 days		
<b>CHRONICITY</b>	None	2 – 10% of everyone (5+ years of age) 30 – 90% of children (0 – 5 years of age)	60 – 85%		
<b>MORTALITY</b>	≤ 39 years: ≤ 0.3% ≥ 40 years: 2.1%	0.5 – 1.0%	10,000 – 12,000 annually		

## Quiz Questions – Hepatitis C

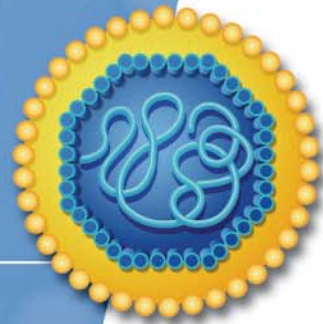
1. *Name two routes of transmission of the hepatitis C virus:*
  
2. *The number of persons with chronic HCV infection worldwide is:*
  - a. *2 million*
  - b. *80 million*
  - c. *170 million*
  - d. *450 million*
  
3. *What percent of individuals infected with the hepatitis C virus go on to become chronic carriers?*
  - a. *10%*
  - b. *30 – 45%*
  - c. *50%*
  - d. *60 – 85%*
  
4. *Approximately what percent of those chronically infected go on to develop cirrhosis?*
  - a. *1 – 5%*
  - b. *10 – 20%*
  - c. *50%*
  - d. *100%*
  
5. *Which of the following is NOT a recommendation by the World Health Organization to prevent the spread of HCV:*
  - a. *Worldwide screening of blood and blood products*
  - b. *Implementation of water purification systems in developing countries*
  - c. *Adequate sterilization of reusable materials such as surgical or dental instruments*
  - d. *Effective use of universal precautions and barrier techniques (i.e., disposable gloves)*
  
6. *True or false? Immune globulin can be used for the short-term prevention of HCV infection; however, no vaccine currently exists.*

# Hepatitis D

## Section 5

*Learning Objectives • Case Study #4 • Hepatitis D Virus • Routes of Transmission  
Individuals at Risk • Incidence/Prevalence • Clinical Course • Prevention/Prophylaxis  
Therapy • Viral Hepatitis Overview • Quiz Questions*

HDV



# Learning Objectives

After completing this section, you should be able to:

1. **Understand the relationship of the hepatitis D virus (HDV) to the hepatitis B virus (HBV)**
2. **Recognize how and when HDV is transmitted**
3. **Identify individuals at risk for HDV infection**
4. **Describe the symptoms and clinical course of the disease**

## Case Study #4

William, a patient with chronic HBV infection and a 20-year history of illegal injection drug use, had been experiencing the following symptoms for about two weeks: nausea, abdominal pain, and diarrhea. Given William’s chronic HBV infection, the physician suspected superinfection with another virus. He ordered the Acute Viral Hepatitis Panel and a HIV test.



### William

*Patient with chronic HBV infection and a 20-year history of illegal injection drug use.*

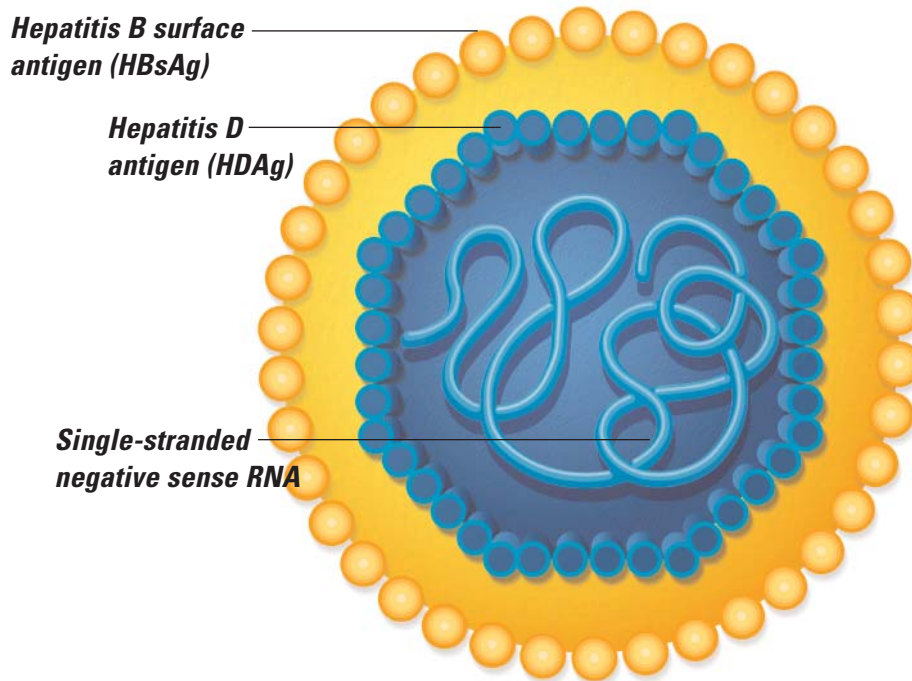
### Acute Viral Hepatitis Panel

ASSAY	HBsAg	Anti-HAV IgM	Anti-HBc IgM	Anti-HCV
RESULTS	+	-	-	-

*The lab results came back negative for HIV, HAV, and HCV. In order to rule out a superinfection with hepatitis D, the physician ordered an anti-HDV test as well.*

*The lab result was positive for anti-HDV, confirming a HDV superinfection of this chronically infected patient. William was counseled on the severity of his situation. A superinfection can often lead to fulminant hepatitis or hepatocellular carcinoma. The mortality rate for HDV infection is 2 – 20 percent.<sup>16, p16</sup> The physician continued to periodically run the chronic hepatitis B panel, anti-HDV, and liver enzymes. This individual was never able to resolve his HBV and HDV infections and died one year later of liver failure.*

# Hepatitis D Virus



- **36 – 43 nanometers in diameter**<sup>16, p10</sup>
- **Single-stranded RNA virus**<sup>3D, slide 1</sup>
- **Hepatitis D virus depends on the synthesis of the hepatitis B surface antigen (HBsAg). Without the HBsAg coating, HDV cannot infect on its own.**

## Routes of Transmission

- **Similar to those for HBV (except perinatal transmission is rare)**<sup>3D, slide 3</sup>
- **Percutaneous**<sup>3D, slide 3</sup>
  - **Contaminated drug use equipment**
  - **Transfusion of infected blood and blood products**<sup>16, p20</sup>
- **Per mucosal**<sup>3D, slide 7</sup>
  - **Sexually transmitted, although less efficient than for HBV**

# Individuals at Risk

- **Individuals with HBV**
- **Anyone at risk for HBV**
- **Injecting drug users**
- **Hemophiliacs/hemodialysis patients**
- **Homosexuals and heterosexuals with multiple sex partners**

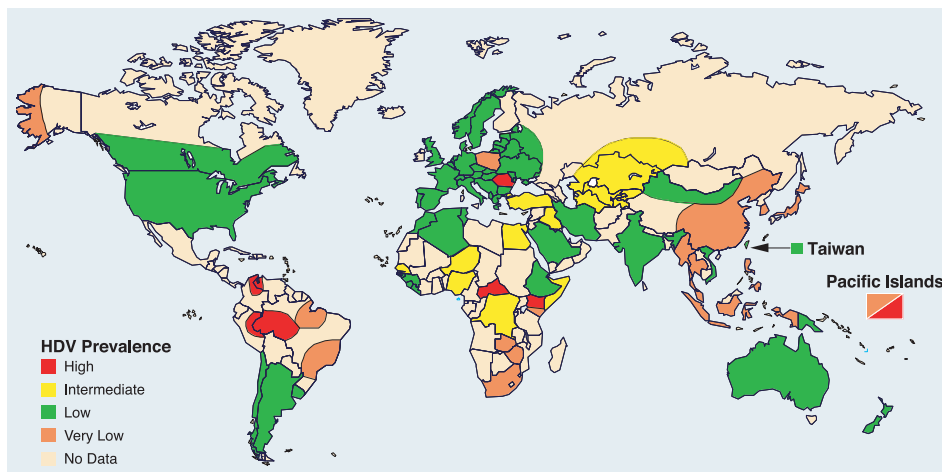
# Incidence/Prevalence

- **Infects on average 4 percent of acute hepatitis B cases in the United States**<sup>3, slide 4</sup>
- **Generally corresponds (proportionally) to the prevalence of chronic HBV infection worldwide; however, distinct features have been documented**<sup>3D, slide 6</sup>
- **For those countries in which the prevalence of chronic HBV is low, distribution of HDV is generally low among both asymptomatic HBV carriers (<10%) and among patients with chronic HBV related liver disease (<25%). In these countries, HDV infection most commonly occurs among injecting drug users and patients with hemophilia**<sup>3D, slide 6</sup>

## HDV & HBV

HDV prevalence corresponds (proportionally) to the prevalence of chronic HBV infection worldwide; however, several distinct features have been documented.<sup>3D, Slide 6</sup>

## Geographic Distribution of HDV Infection<sup>3D, slide 6</sup>

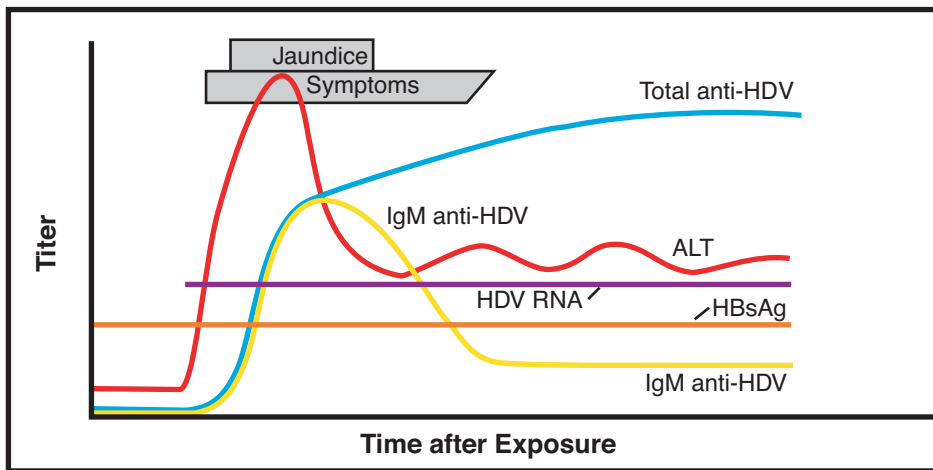


\*Note: The map of anti-HDV prevalence generalizes available data and patterns may vary within countries.

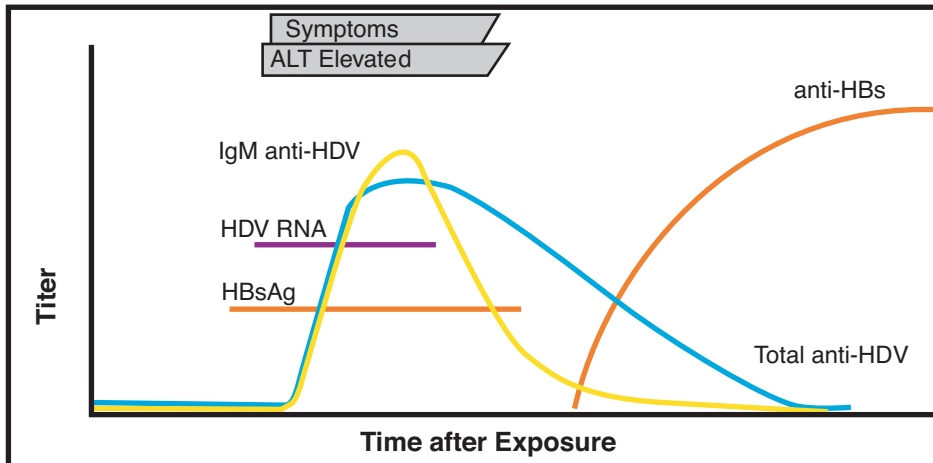
# Clinical Course

- Can be acquired either as a coinfection or as a superinfection in persons already infected with HBV
- Incubation period ranges from 3 – 7 weeks<sup>16, p16</sup>
- Symptoms of a coinfecting HBV-HDV patient are similar to those of HBV alone, but can be more severe<sup>3D, slide 2</sup>
- 70 – 80 percent of chronic HBV carriers with HDV superinfection develop evidence of chronic liver disease with cirrhosis, compared to 15 – 30 percent of patients with chronic HBV infection alone<sup>3D, slide 2</sup>

## Hepatitis D Superinfection of a Chronic HBV Carrier – Typical Serologic Course<sup>3D, slide 5</sup>



## Hepatitis D Coinfection – Typical Serologic Course<sup>3D, slide 4</sup>



## Prevention/Prophylaxis

- **No vaccine specific for HDV exists**
- **Since HDV is dependent on HBV for replication, the most important tool for preventing HBV-HDV coinfection is immunization with a hepatitis B vaccine**
- **Follow pre- and post-exposure prophylaxis recommendations for HBV infection to prevent HBV-HDV coinfection**<sup>3D, slide 7</sup>
- **Education to reduce risk behaviors is the primary tool for the prevention of HBV-HDV superinfection**<sup>3D, slide 7</sup>

## Therapy

- **Individuals with chronic HDV and HBV infection should follow HBV therapy**
- **There is no therapy specifically for chronic hepatitis D**

## Viral Hepatitis Overview

	Hepatitis A Virus	Hepatitis B Virus	Hepatitis C Virus	Hepatitis D Virus	
<b>VIRUS FAMILY</b>	<i>Picornaviridae</i>	<i>Hepadnaviridae</i>	<i>Flaviviridae</i>	<i>Hepadnaviridae</i>	
<b>ROUTE OF TRANSMISSION</b>	Fecal-oral route	Percutaneous, permucosal	Percutaneous, permucosal	Percutaneous, permucosal	
<b>ONSET</b>	Usually abrupt	Usually insidious	Insidious	Usually abrupt	
<b>INCUBATION</b>	15 – 50 days	Average 60 – 90 days, range 45 – 180 days	14 – 182 days	21 – 49 days	
<b>CHRONICITY</b>	None	2 – 10% of everyone (5+ years of age) 30 – 90% of children (0 – 5 years of age)	60 – 85%	<5% of coinfections, ≤ 80% of superinfections	
<b>MORTALITY</b>	≤ 39 years: ≤ 0.3% ≥ 40 years: 2.1%	0.5 – 1.0%	10,000 – 12,000 annually	2 – 20%	

## Quiz Questions – Hepatitis D

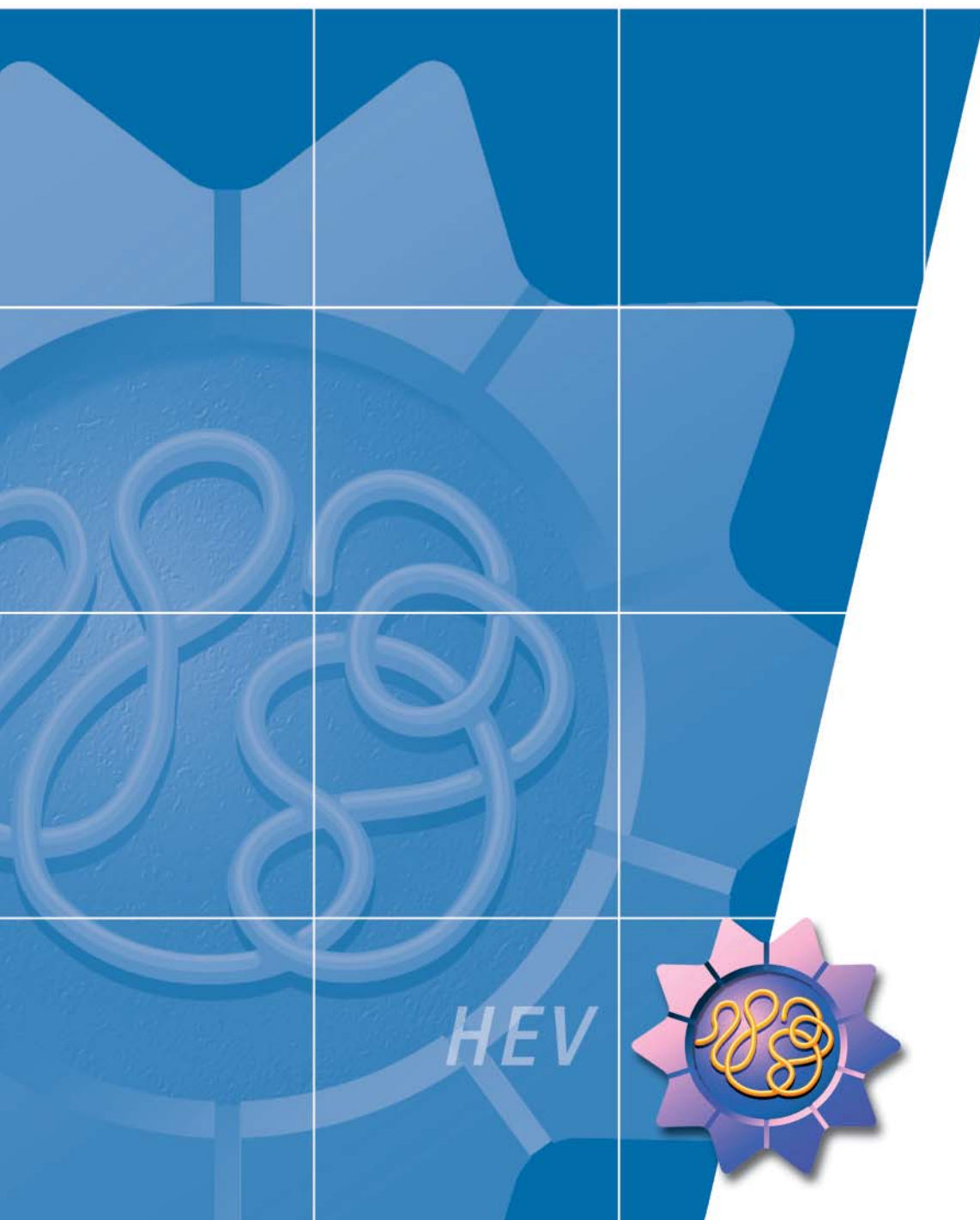
1. *HDV is transmitted via:*
  - a. *Percutaneous routes*
  - b. *Enteric routes*
  - c. *Per mucosal routes*
  - d. *Community contact*
  - e. *a and c*
2. *Who is at risk for a HDV infection?*
  - a. *Anyone at risk for HBV infection*
  - b. *Injecting drug users*
  - c. *Hemophiliacs*
  - d. *Homosexuals and heterosexuals with multiple sex partners*
  - e. *All of the above*
3. *A patient who develops a HDV infection:*
  - a. *Is not coinfecting with any other hepatitis virus*
  - b. *Rarely suffers direct liver damage*
  - c. *Has a mortality rate of 2 – 20 percent*
  - d. *When compared to HBV infection shows less evidence of chronic liver disease with cirrhosis*
  - e. *All of the above*
4. *True or false? Hepatitis D prevalence generally corresponds proportionally to the prevalence of chronic HBV infection worldwide.*
5. *True or false? Immunity to HDV relies solely on vaccination against HDV.*
6. *HDV can be acquired as a \_\_\_\_\_ or \_\_\_\_\_ in persons with HBV infection.*



# Hepatitis E

## Section 6

*Learning Objectives • Case Study #5 • Hepatitis E Virus • Routes of Transmission  
Individuals at Risk • Incidence/Prevalence • Clinical Course • Prevention/Prophylaxis  
Therapy • Viral Hepatitis Overview • Quiz Questions*



# Learning Objectives

In this section, you should be able to:

1. **Indicate how the hepatitis E virus (HEV) is transmitted**
2. **Identify individuals at risk for infection by HEV**
3. **Recognize the incidence and prevalence of HEV infection**
4. **Describe the symptoms and clinical course of HEV infection**

## Case Study #5

Eight weeks after Elizabeth returned from her vacation in Central America, she went in for her annual physical. She joked with her physician about consuming both unbottled beverages and food from local vendors without getting a typical case of “travelers diarrhea.” Elizabeth had recently been experiencing what seemed to be the flu. She explained her symptoms of fatigue and abdominal pain to her physician.

Due to the late onset of Elizabeth’s symptoms in relation to her travel, and comment about drinking unbottled water, the physician wanted to rule out a parasite or viral infection as the cause of her abdominal pain and fatigue. He ordered a liver panel, and the results showed an elevation of bilirubin and ALT, indicating an inflammation of the liver. Next, the physician ordered an Acute Viral Hepatitis Panel.



**Elizabeth**

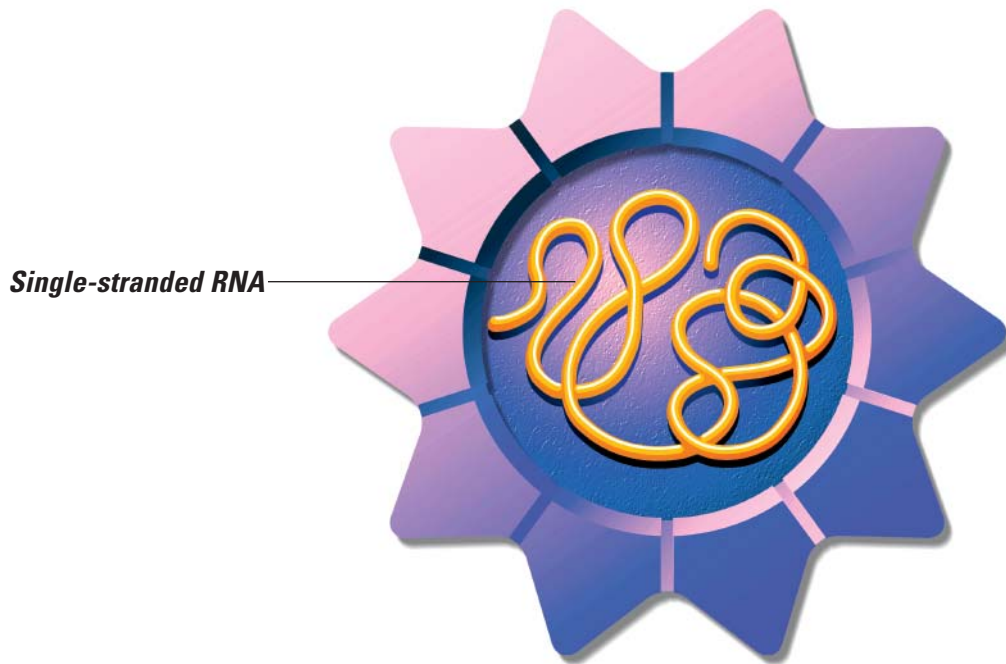
*Vacationed in Central America eight weeks ago.*

### Acute Viral Hepatitis Panel

ASSAY	HBsAg	Anti-HAV IgM	Anti-HBc IgM	Anti-HCV
RESULTS	–	–	–	–

*The results ruled out HAV, HBV, HCV, and HDV, and after ruling out parasites, the physician suspected HEV due to Elizabeth’s recent vacation to an endemic area. Currently, a diagnostic test for anti-HEV is available in Europe, Asia, and Latin America, but not in the U.S.*

# Hepatitis E Virus



- **Single-stranded, positive-sense RNA virus**
- **Belongs to an unassigned genus of HEV-like viruses**
- **Spherical, icosahedral, and nonenveloped virus, approximately 32 – 34 nanometers in diameter**<sup>3E, slide 1</sup>

## Routes of Transmission

Transmission usually occurs enterically (fecal-oral) through:

- **Ingestion of contaminated water supplies or food (most common)**
- **Poor personal hygiene**
- **Person-to-person (uncommon)**

Since Elizabeth had recently visited a region where HEV is endemic, she was at risk for transmission through the ingestion of contaminated water or food purchased at open-air markets.

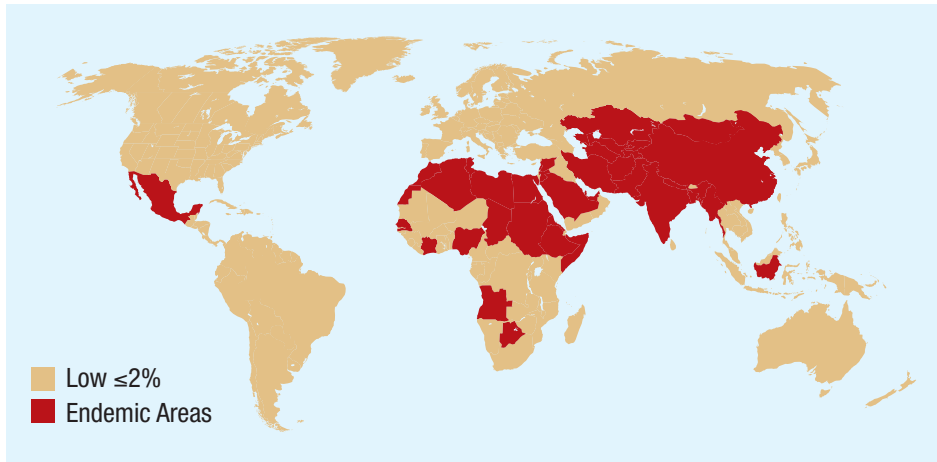
## Individuals at Risk

- **Residents of endemic regions**
- **Travelers to endemic regions**

Elizabeth's exposure probably occurred during her visit to Central America.

# Incidence/Prevalence

## Geographic Distribution of Hepatitis E<sup>3E, Slide 5</sup>



*Outbreaks or Confirmed Infection in >25% of Sporadic Non-ABC Hepatitis*

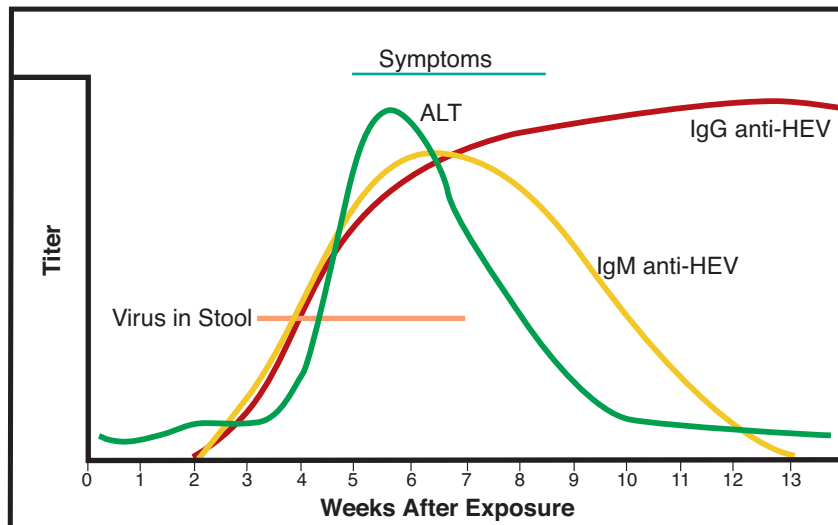
*\*Note: The map of HEV infection generalizes available data, patterns may vary within countries.*

- **Leading cause (>50%) of acute sporadic hepatitis in both children and adults in some high endemic areas**<sup>3E, slide 4</sup>
- **Occurrence in the United States is mostly associated with travel to endemic regions**<sup>3E, slide 4</sup>

## Clinical Course

- **Incubation period is 15 – 60 days, with an average of 40 days**<sup>3E, slide 2</sup>
- **Symptoms are usually abrupt**
- **Symptoms are similar to other types of viral hepatitis infection: malaise, anorexia, nausea/vomiting, abdominal pain, and fever**
- **The highest rates of symptomatic disease (jaundice) have been in young to middle-age adults**<sup>3E, slide 2</sup>
- **Lower disease rates in younger groups may be accredited to anicteric and/or subclinical HEV infection**<sup>3E, slide 2</sup>
- **No chronic cases have been reported**
- **Mortality worldwide is approximately 1 – 3 percent. In pregnant women, mortality reaches 15 – 25 percent**<sup>3E, slide 2</sup>

## Hepatitis E Virus Infection – Typical Serologic Course<sup>3E, slide 3</sup>



## Prevention/Prophylaxis

- ***IgG anti-HEV persists and appears to provide at least short-term protection against disease***<sup>3E, slide 3</sup>
- ***There is currently no vaccine or immune globulin available to prevent the transmission of HEV***
- ***Long-term prevention relies primarily on provision of safe drinking water, prudent hygiene, and avoiding uncooked shellfish, fruits, and vegetables in endemic areas***<sup>3E, slide 6</sup>

## Therapy

There is currently no therapy available.

# Viral Hepatitis Overview

	Hepatitis A Virus	Hepatitis B Virus	Hepatitis C Virus	Hepatitis D Virus	Hepatitis E Virus
<b>VIRUS FAMILY</b>	<i>Picornaviridae</i>	<i>Hepadnaviridae</i>	<i>Flaviviridae</i>	<i>Hepadnaviridae</i>	Not Classified
<b>ROUTE OF TRANSMISSION</b>	Fecal-oral route	Percutaneous, permucosal	Percutaneous, permucosal	Percutaneous, permucosal	Fecal-oral (especially contaminated water)
<b>ONSET</b>	Usually abrupt	Usually insidious	Insidious	Usually abrupt	Usually abrupt
<b>INCUBATION</b>	15 – 50 days	Average 60 – 90 days, range 45 – 180 days	14 – 182 days	21 – 49 days	15 – 60 days, average 40 days
<b>CHRONICITY</b>	None	2 – 10% of everyone (5+ years of age) 30 – 90% of children (0 – 5 years of age)	60 – 85%	<5% of coinfections ≤ 80% of superinfections	None reported
<b>MORTALITY</b>	≤ 39 years: ≤ 0.3% ≥ 40 years: 2.1%	0.5 – 1.0%	10,000 – 12,000 annually	2 – 20%	About 1 – 3%, 15 – 25% in pregnant women

## Quiz Questions – Hepatitis E

- HEV is most commonly transmitted through \_\_\_\_\_.**
- \_\_\_\_\_ are most at risk for contracting HEV.**
  - Healthcare workers**
  - Infants born to infected mothers**
  - Residents of/travelers to endemic areas**
  - Injecting drug users**
- Which of the following statement(s) is/are true regarding HEV?**
  - Most common form of viral hepatitis reported in U.S.**
  - Leading cause of acute sporadic hepatitis in both children and adults in some high endemic areas**
  - Not found in developed countries**
  - Both a and b**
- True or false? No chronic cases of HEV have been reported to date.**
- True or false? Normal HEV incubation period is 5 – 15 days.**

# Glossary, Appendix, and References



# Glossary

**Acute** – Of short and sharp course; not chronic (new infection).

**ALT (alanine aminotransferase)** – An enzyme normally produced by the liver; blood levels may increase in cases of liver damage; formerly known as SGPT.

**Anti-HAV** – Antibody to hepatitis A virus.

**Anti-HAV IgM** – M class immunoglobulin antibody to hepatitis A virus.

**Anti-HBc** – Antibody to hepatitis B core antigen.

**Anti-HBc IgM** – M class immunoglobulin antibody to hepatitis B core antigen.

**Anti-HBe** – Antibody to hepatitis B e antigen.

**Anti-HBs** – Antibody to hepatitis B surface antigen.

**Antibody (Ab)** – A Y-shaped protein molecule (immunoglobulin) in serum or body fluid that either neutralizes an antigen or tags it for attack by other cells or chemicals; acts by uniting with and firmly binding to an antigen. The prefix anti- followed by initials of a virus, refers to a specific antibody against the virus.

**Antigen (Ag)** – A substance capable of causing the body to produce specific antibodies; any substance that stimulates lymphocytes (white blood cells) to initiate an immune response.

**Assay** – A test to determine the presence, absence, or quantity of one or more components of a substance.

**Asymptomatic** – Without overt symptoms.

**Chronic hepatitis** – A condition in which liver inflammation persists for more than six months.

**Chronic infection** – An individual with HBsAg in the serum for periods longer than six months is infectious, and may or may not exhibit symptoms of hepatitis; also applies to a large number of individuals with HCV infection.

**Chronicity** – The quality of being chronic or persisting over a long period of time.

**Cirrhosis** – Irreversible scarring of the liver that may occur with chronic hepatitis.

**Coinfection** – A condition whereby an uninfected individual becomes infected with two or more different infectious agents.

**Core** – The central part of the hepatitis B virus, as well as other viruses.

**Delta agent** – Previously used name to identify a unique RNA virus that causes acute or chronic hepatitis; requires hepatitis B virus for replication and only infects patients who are HBsAg positive; comprised of delta antigen core and hepatitis B surface antigen coat; today referred to as hepatitis D virus (HDV).

**DNA (deoxyribonucleic acid)** – The coded genetic material in the nucleus of most cells that controls heredity; automatically controls the formation of RNA, which spreads throughout the cell and controls the formation of specific proteins. The genome of HBV is DNA.

**DNA polymerase** – An enzyme that catalyzes DNA synthesis; present in the core of hepatitis B virus.

**Endemic** – Present in a community at all times.

**Enteric** – Pertaining to the intestines.

**Enteric route** – The spread of organisms via the fecal-oral cycle of infection.

**Enterovirus** – One of a group of similar viruses infecting the gastrointestinal tract and discharged in the feces.

**Epidemiology** – The study of the incidence, distribution, and control of disease in a population.

**Flavivirus** – A family of small RNA viruses, formerly referred to as the arboviruses. HCV is a member of the *Flavivirus* family.

**Fulminant hepatitis** – The most severe form of hepatitis; may lead to acute liver failure and death.

**Genome** – The complete set of genetic information.

**HAV Ag** – Hepatitis A virus antigen.

**HAV** – Hepatitis A virus.

**HBcAg** – Hepatitis B core antigen.

**HBIG** – Hepatitis B immune globulin (specific to hepatitis B virus, see immune globulin).

**HBsAg** – Hepatitis B surface antigen.

**HBV** – Hepatitis B virus.

**HCV** – Hepatitis C virus.

**HDV** – Hepatitis D virus.

**HEV** – Hepatitis E virus.

**Hemophilia** – A hereditary disorder in which the blood clots very slowly due to a deficiency of one of the coagulation factors.

**Hepadnavirus** – One of a group of DNA viruses; HBV is a member of this group of viruses.

**Hepatitis** – Inflammation of the liver.

**Hepatitis A** – Viral hepatitis caused by the hepatitis A virus; formerly known as infectious hepatitis.

**Hepatitis B** – Viral hepatitis caused by the hepatitis B virus; formerly known as serum hepatitis.

**Hepatitis C** – Viral hepatitis caused by the hepatitis C virus.

**Hepatitis D** – Viral hepatitis caused by the hepatitis D virus.

**Hepatitis E** – Viral hepatitis caused by the hepatitis E virus.

**Hepatocellular carcinoma** – Cancer of the liver cells.

**IgG** – A form of immunoglobulin that occurs late in an infectious process.

**IgM** – A form of immunoglobulin that occurs early in an infectious process.

**Immune** – A state of protection afforded against infection as the result of the presence of antibodies in the body's circulatory system.

**Immune globulin** – A sterile solution of water-soluble proteins that contains those antibodies normally present in adult human blood; used as a passive immunizing agent against various viruses such as HAV. Other names include immune serum globulin (ISG) and gamma globulin.

**Incidence** – The number of new episodes of illness arising in a population over an estimated period.

**Incubation period** – The interval of time between the moment of entrance of the infecting organism into the body and the first appearance of symptoms of the disease.

**Infectious hepatitis** – An old term for hepatitis A.

**Insidious** – Stealthy; denotes a disease that progresses with few or no symptoms to indicate its presence or its gravity.

**Interferon** – A substance that is produced by cells infected with a virus, which has the ability to inhibit viral growth.

**Jaundice** – A syndrome characterized by increased levels and deposits of bile pigment in the skin, giving the individual a yellowish skin color and may include yellowing of whites of the eyes; usually caused by liver changes.

**Malaise** – A general feeling of being unwell; feeling may be accompanied by identifiable physical discomfort and may indicate the presence of disease.

**Marker** – An antigen or antibody used to indicate the status of disease or recovery.

**Mediate** – Act indirectly to affect a result.

**Morbidity** – The state of being diseased.

**Myalgia** – Pain in the muscles.

**NANB (non-A non-B) hepatitis** – Viral hepatitis caused by viruses other than A or B.

**Parenteral** – Used to refer to entering the body subcutaneously (under the skin), intramuscularly (into a muscle), or intravenously (into a blood vessel); may refer to any other means whereby the organism reaches the bloodstream directly.

**Percutaneous** – Through the skin.

**Per mucosal** – Through the mucous membranes.

**Picornavirus** – A virus family consisting of small RNA viruses, HAV belongs to the *Picornavirus* family.

**Prevalence (of a disease)** – The percentage of a population that is affected with a particular disease at a given time.

**Prophylaxis** – The prevention of disease.

**Replication** – Production of a copy or image of itself; encompasses the steps that a virus goes through to reproduce (the term “duplication” is used for cells that split in two to reproduce themselves).

**RNA (ribonucleic acid)** – A substance formed in the cell nucleus, under the control of DNA; transfers genetic code into the cell for the synthesis of proteins.

**Sequela** – An illness or condition that follows as a consequence of another disease (plural form: sequelae).

**Seroconversion** – An immune response that is characterized by a conversion from the absence of a specific antibody to the presence of that specific antibody in a patient or the disappearance of an antigen followed by the appearance of its corresponding antibody.

**Serological** – Pertaining to antigen-antibody reactions *in vitro*.

**Seronegativity** – Blood serum showing a negative result to a specific test.

**Seropositivity** – Blood serum showing a positive result to a specific test.

**Serum hepatitis** – Old term for hepatitis B.

**Superinfection** – A condition whereby an already infected individual becomes infected with a virus different from the original infecting agent.

**Subclinical** – Without clinical manifestations or symptoms.

**Syndrome** – A set or collection of symptoms and signs that occur together.

**Viral load** – The amount or concentration of virus in the circulation.

**Virology** – The study of viruses.

**Virus** – A collection of proteins and nucleic acids capable of infecting other cells; viruses can multiply only within the cells that they are infecting.

# Appendix

## Pathology Quiz Answers

1) A,B,C,D,E; 2) Any four of the following: fatigue, myalgia, loss of appetite, nausea, diarrhea, constipation, fever, jaundice; 3) False; 4) a and b; 5) d

## HAV Quiz Answers

1) Close person-to-person contact, ingestion of contaminated food or water; 2) c; 3) d; 4) b, c, d

## HBV Quiz Answers

1) d; 2) HBsAg, HBeAg, Total anti-HBc, anti-HBc IgM, anti-HBe, anti-HBs, and if listed, HBV DNA could be included in this list as well; 3) c; 4) True; 5) False (70%); 6) Nausea, diarrhea, malaise, dark urine, jaundice; 7) b; 8) c; 9) a, c, d; 10) HBsAg, HBeAg, anti-HBe and anti-HBs; 11) False; 12) b; 13) False (provides prolonged immunization); 14) d; 15) True

## HCV Quiz Answers

1) Any two of the following: injecting drug use, use of inadequately sterilized or completely unsterilized healthcare equipment, transfused blood not screened for HCV, organ or tissue transplants from an HCV infected donor, sexual or household contacts, perinatal exposure, body piercing, tattooing; 2) c. 170 million; 3) d. 60 – 85%; 4) b. 10 – 20%; 5) b.; 6) False. There is currently no vaccine for HCV, and immune globulin is not recommended.

## HDV Quiz Answers

1) e; 2) e; 3) c; 4) True; 5) False; 6) Coinfection, superinfection

## HEV Quiz Answers

1) Ingestion of contaminated water; 2) c; 3) b; 4) True; 5) False (incubation period averages 40 days)

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# Notes



## Notes

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