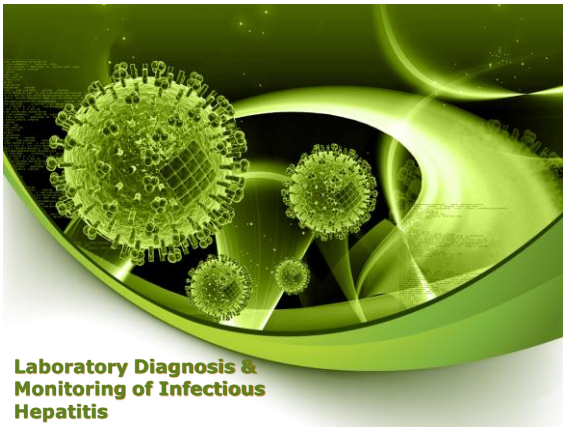
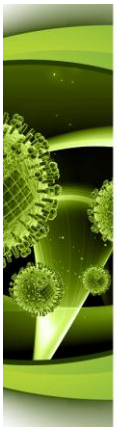


Laboratory Diagnosis & Monitoring of Infectious Hepatitis

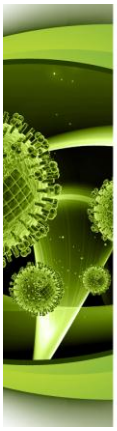
Objectives

- Compare and contrast the major types of hepatitis viruses and explain the disease transmission and progression processes in viral hepatitis cases
- Describe how the clinical laboratory may be used to diagnose and monitor the course of infectious hepatitis
- Compare and contrast the current methods for the treatment and prevention of infectious hepatitis



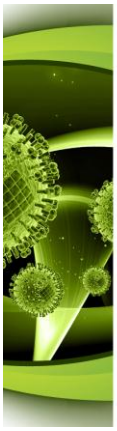
Hepatitis

- General term for inflammation of the liver
- Can be due to non-infectious causes such as:
  - Autoimmune disorders
  - Alcohol abuse
  - Chemical agents
  - Obstruction



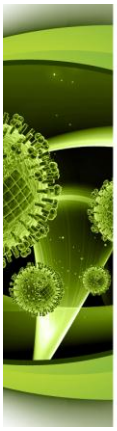
Viral Hepatitis

- Can be caused by a number of viruses
  - Referred to as **Infectious Hepatitis**
  - **Primary hepatitis viruses** – are those whose main clinical effects are on the liver
  - **Secondary hepatitis viruses** – are those that produce liver inflammation secondary to other disease processes



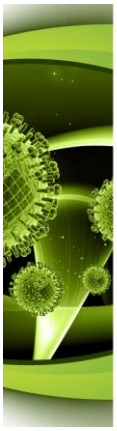
Primary Hepatitis Viruses

- Hepatitis A Virus (HAV)
- Hepatitis B Virus (HBV)
- Hepatitis C Virus (HCV)
- Hepatitis D Virus (HDV)
- Hepatitis E Virus (HEV)



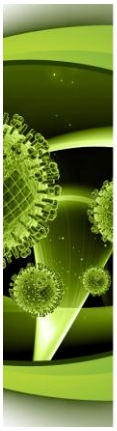
Primary Hepatitis Viruses

- Two main routes of transmission:
  - **Fecal-oral route** – contaminated food or water
    - Hepatitis A virus
    - Hepatitis E virus
  - **Parenteral route** – contact with blood or body fluids
    - Hepatitis B virus
    - Hepatitis C virus
    - Hepatitis D virus



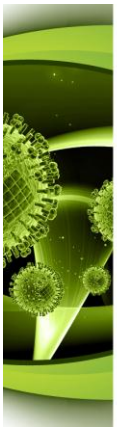
Clinical Forms of Hepatitis

- Acute hepatitis
  - The typical form
  - Includes associated jaundice
  - Includes 4 phases of illness:
    - **Incubation phase** – liver enzymes rise
    - **Preicteric phase** – symptoms occur
    - **Icteric phase** – jaundice occurs
    - **Convalescence** - recovery



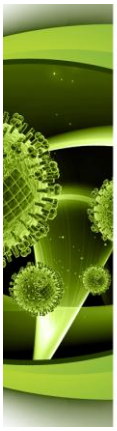
Clinical Forms of Hepatitis

- Fulminant hepatitis
  - Rare form associated with hepatic failure
- Subclinical hepatitis
  - Light or no symptoms
- Chronic hepatitis
  - Hepatic inflammation and necrosis that lasts for at least 6 months



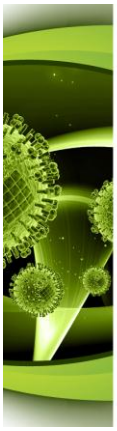
Acute Hepatitis

- All primary hepatitis viruses produce similar clinical syndromes
  - Symptomology
    - Flu-like symptoms
    - Loss of appetite
    - Nausea & vomiting
    - Right upper quadrant pain



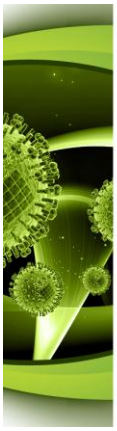
Acute Hepatitis

- Progression of disease
  - Hepatomegaly
  - Jaundice
  - Dark urine
  - Light stools



Acute Hepatitis

- Laboratory results:
  - ALT & AST rise quickly due to necrosis of liver cells
    - These are the most useful tests for detecting hepatic cell damage
    - ALT is most specific since highest levels are in the liver
    - ALT levels may increase to 100 times normal
  - Bilirubin levels rise as disease progresses



Hepatitis A Virus

- HAV is an RNA virus
- Transmitted by fecal-oral route
  - And possibly by close person-to-person contact
- Incubation period of 28 days
- Most infected adults develop **acute hepatitis**
- Most infections in children remain **subclinical**

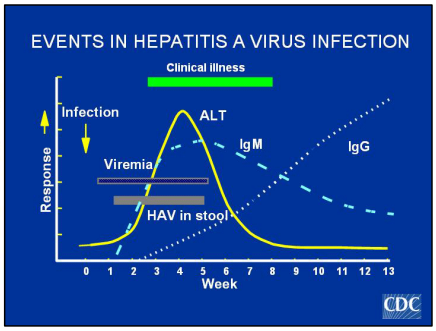
Acute Hepatitis A

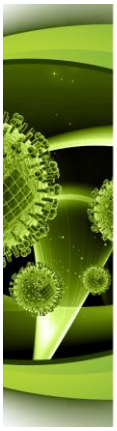
- Symptoms have an abrupt onset and last 1 to 8 weeks
- Infections **do not** progress to a chronic state
- Liver enzymes usually return to normal within 6 months

Hepatitis A – Lab Diagnosis

- Presence of IgM antibodies to HAV indicate **active disease**
  - IgM antibodies peak during the first month of infection, and become undetectable within 6 to 12 months
- Presence of IgG antibodies indicates **immunity** to HAV
  - IgG antibodies are produced either due to an infection or due to immunization

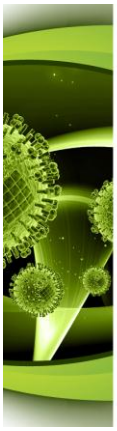
Course of HAV Infection





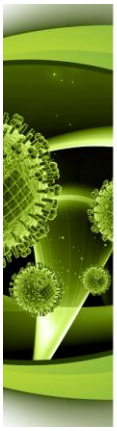
Hepatitis A Treatment & Prevention

- No specific treatment other than supportive therapy
- Preventive measures include:
  - Immunization
  - Food safety
  - Proper sanitation
  - Proper handwashing and hygiene



Hepatitis E

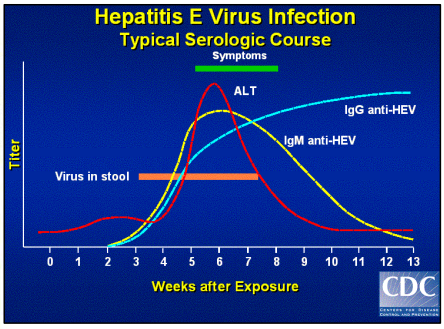
- HEV is an RNA virus
- Transmitted by fecal oral route
  - Usually from contaminated drinking water in developing nations
  - Infection in U.S. is usually associated with travel to endemic regions
- Presents as acute hepatitis and **does not** progress to a chronic state



Hepatitis E – Lab Diagnosis

- IgM antibodies are present during **acute infection** but decline rapidly
- IgG antibodies persist long-term and provide some immunity

Course of HEV Infection

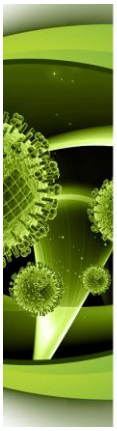


Hepatitis E Treatment & Prevention

- No specific treatment other than supportive therapy
- Preventive measures include:
  - Food & water safety
  - Proper sanitation
  - Proper handwashing and hygiene

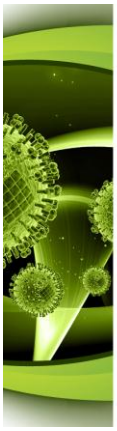
Hepatitis B

- HBV is a DNA virus
- Transmitted by the parenteral route
  - Transmission has been associated with:
    - Sexual contact, blood transfusions, sharing of needles, tattooing, & occupational needle-stick injury
    - May also be transmitted from mother to infant during delivery or from breast feeding



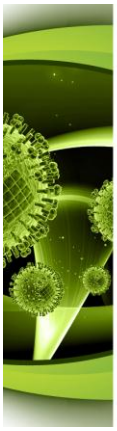
Hepatitis B Infection

- Incubation period of 60 to 90 days
- Clinical course is highly variable
  - Many remain subclinical & asymptomatic
  - 30 to 50% develop symptoms of **acute hepatitis** which last 1 to 4 weeks



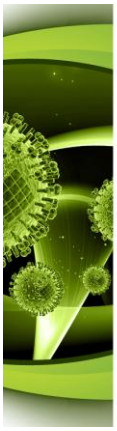
Hepatitis B Infection

- Most HBV-infected adults recover within 6 months and develop immunity
- 1 to 2% develop **fulminant disease** - High fatality rate
- Chronic HBV infection develops in 5 to 10% of infected adults
  - These have an increased risk of developing cirrhosis or hepatocellular carcinoma



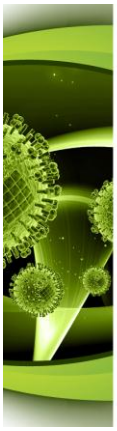
Hepatitis B Epidemiology

- About 300 million people, worldwide, are thought to be chronic carriers of the virus
- It is estimated that HBV causes about 1,000,000 deaths per year, worldwide



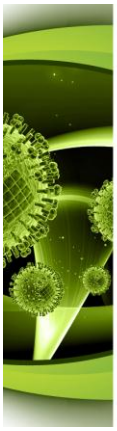
HBV Structure

- Nucleocapsid core surrounded by an outer envelope of lipoprotein
- Viral core contains:
  - Circular, double-stranded DNA
  - DNA polymerase
  - Hepatitis B core antigen (HBcAg)
  - Hepatitis Be antigen (HBeAg)

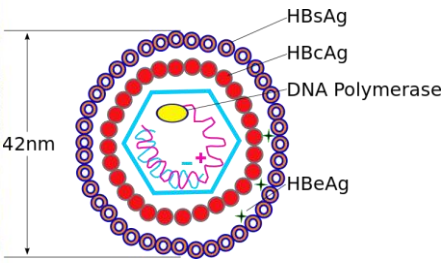


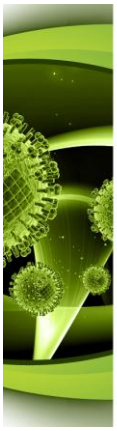
HBV Structure

- **Hepatitis B surface antigen** (HBsAg) is a protein found in the outer envelope of the virus
- **HBsAg** is also found in particles that float freely in the blood of infected individuals



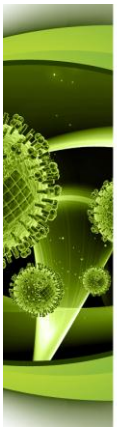
HBV Structure





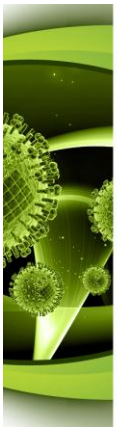
HBV – Serologic Markers

- Viral proteins, or the antibodies directed against them, are used to:
  - Diagnose HBV infection
  - Monitor the course of infection
  - Assess immunity to the virus
  - Screen blood products



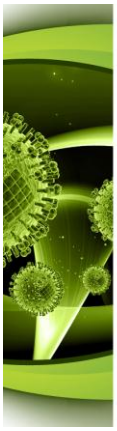
Hepatitis B Surface Antigen (HBsAg)

- The **first marker to appear** in HBV infection
- Becomes detectable 2 to 12 weeks after exposure
- Levels peak during acute stage of infection, then decline as the patient develops antibodies to the antigen



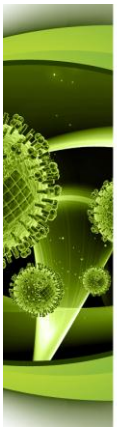
Hepatitis B Surface Antigen (HBsAg)

- **HBsAg is an indicator of an active infection**
- Acute infections
  - Levels become undetectable by 12 to 20 weeks after onset of symptoms
- Chronic infections
  - **Levels remain elevated**



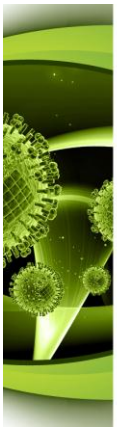
Hepatitis Be Antigen (HBeAg)

- Appears shortly after HBsAg appears
- Disappears shortly before HBsAg disappears
- **Present during periods of active replication**
  - Indicates a high degree of infectivity when present
  - May be elevated during chronic infection



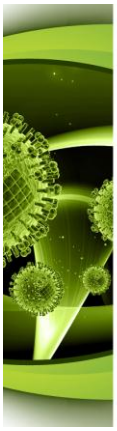
Hepatitis B Core Antibody (Anti-HBc)

- The HBcAg is **not detectable** in serum because the viral envelope masks it
- But as the host develops an immune response, antibodies to HBc appear
- **IgM anti-HBc is the first to appear**
  - IgM anti-HBc is an indicator of a current or recent acute infection



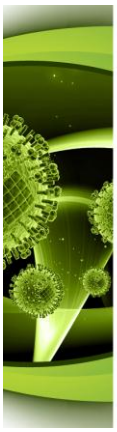
Anti-HBc IgM

- Usually appears 2 weeks after HBsAg in an acute infection
- May be detected for up to 6 months
- **Useful for detecting infection during the "core window"**
  - "Core window" is the period of time between the disappearance of HBsAg and the appearance of anti-HBsAg
  - This makes it useful for screening donor blood



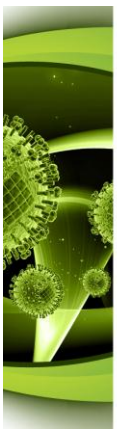
Anti-HBc IgG

- Appears before IgM anti-HBc disappears
- Persists for the lifetime of the individual
- **May be used to detect a past infection**



Hepatitis Be Antibody (Anti-HBe)

- Appears shortly after the disappearance of HBeAg
- **Indicates that the patient is recovering from HBV**



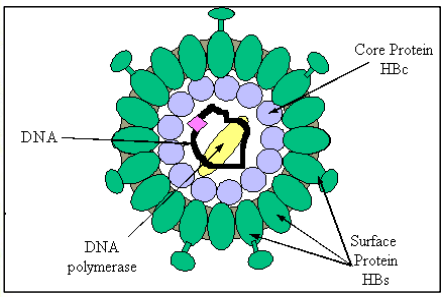
Hepatitis B Surface Antibody (Anti-HBs)

- Appears during the recovery period of acute HBV
- Appears weeks to months after the disappearance of **HBsAg**
- **Provides protective immunity**
- **Not produced during chronic HBV infection – immunity fails**

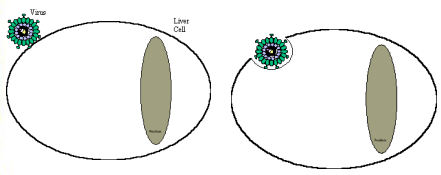
Anti-HBs

- **Produced after immunization with the HBV vaccine**
- The vaccine consists of recombinant HBsAg produced from genetically engineered yeast
- **Used to test for immunity**

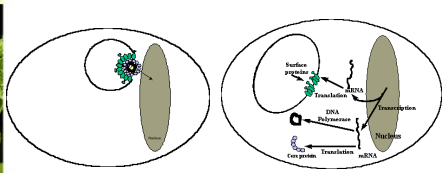
HBV Infection



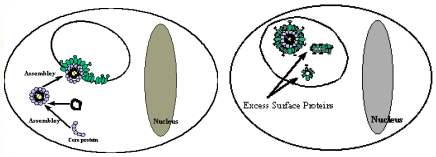
HBV Infection



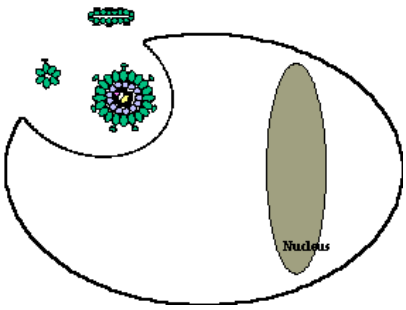
HBV Infection



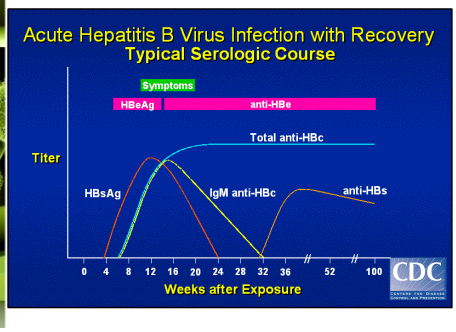
HBV Infection



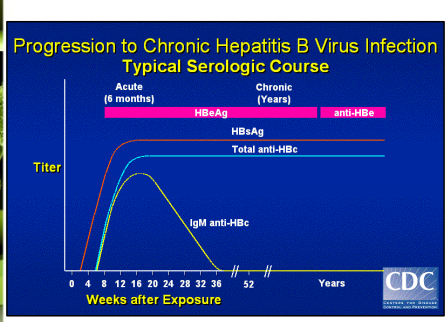
HBV Infection



Acute Hepatitis B

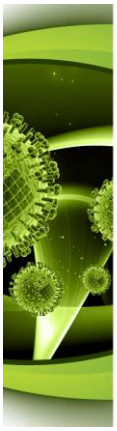


Chronic Hepatitis B



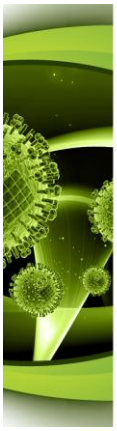
HBV Treatment

- Acute cases are typically self-limiting and only require supportive therapy
- Chronic cases are treated with antiviral therapies such as interferon and other antiviral agents such as Ribavirin
- Molecular methods such as PCR can be used to measure viral DNA to monitor antiviral therapy



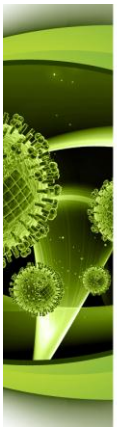
HBV Prevention

- Primary preventive measures:
  - **Vaccination is #1**
  - Hand hygiene
  - Safe handling and disposal of sharps and biological waste
  - Safe cleaning of equipment
  - Testing of donated blood
  - Training of health personal
  - Safe sex practices



Hepatitis D

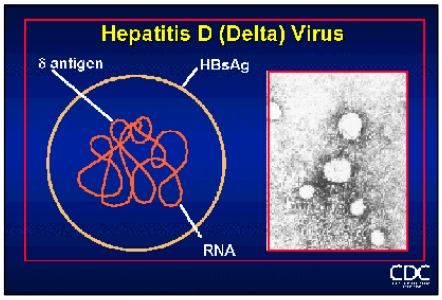
- Transmitted through parenteral route
- **Can only occur in the presence of HBV**
- Because HDV incorporates the HBsAg into its outer protein coat which it requires to replicate & infect host cells



Hepatitis D

- Presence of HDV in people infected with HBV results in a greater risk of fulminant hepatitis or chronic liver disease
- Indicated by the presence of anti-HDV in the patient's serum

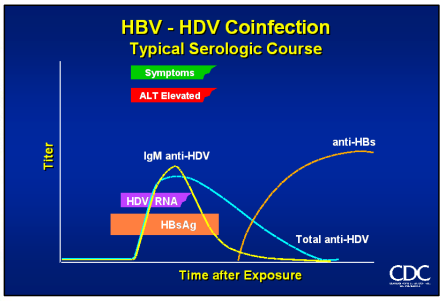
Hepatitis D Virus



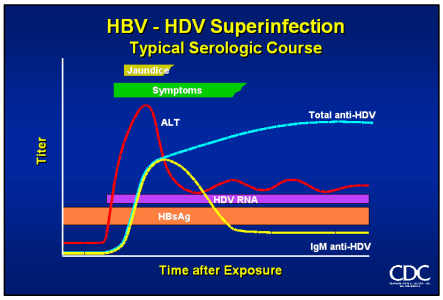
Hepatitis D Antibody (Anti-HDV)

- IgM anti-HDV appears 6 to 7 weeks after exposure
- Remains elevated through acute phase of illness, then declines
- IgG anti-HDV is produced during convalescence & declines to undetectable levels if infection resolves
- **<u>Both IgM & IgG remain elevated in chronic infections</u>**

Course of HDV



Course of HDV

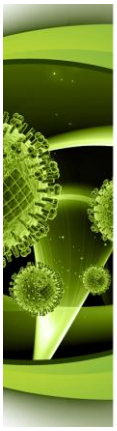


Hepatitis D Treatment & Prevention

- Treatment and prevention is the same as for Hepatitis B due to its dependence on HBV

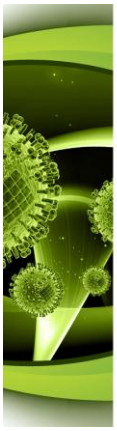
Hepatitis C

- Transmitted through the parenteral route
- Average incubation time of 7 to 8 weeks
- Produces symptoms of acute hepatitis in 20% of individuals
- Majority of infections are subclinical & asymptomatic



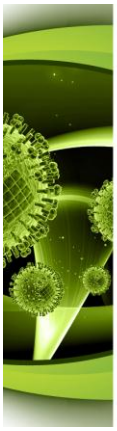
Hepatitis C

- But **85% develop a chronic infection** which may slowly develop into cirrhosis
- HCV accounts for 1/3 of liver transplants
  - Antiviral therapy following liver transplant is essential to prevent or slow the rate of reinfection



Hepatitis C

- HCV is an RNA virus
- 6 different genotypes and 50 subtypes have been discovered
- A high mutation rate allows it to escape the immune response and persist in the patient



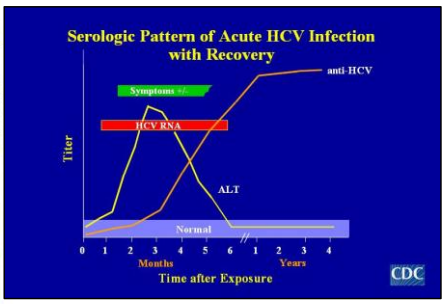
Hepatitis C Testing

- HCV is diagnosed by detecting HCV antibodies
- With current assays, antibodies can usually be detected at the time symptoms appear (7 to 8 weeks after exposure)
- **Current tests do not distinguish between acute or chronic infection**

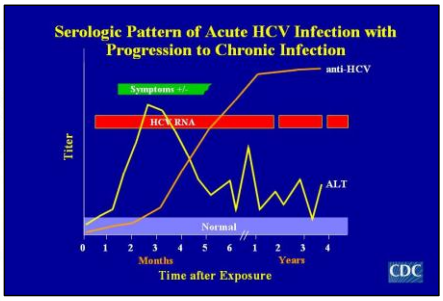
Hepatitis C Testing

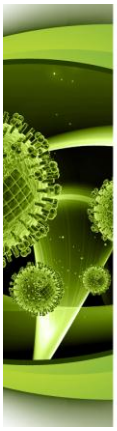
- Molecular testing such as PCR may also be used to confirm positive results
- PCR may be done as a qualitative or quantitative test
- **Quantitative PCR can be used to monitor the viral load**
- HCV RNA appears in serum in as little as 1 week

Acute Hepatitis C



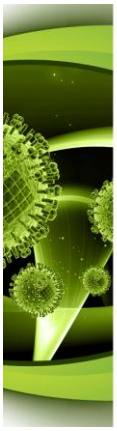
Chronic Hepatitis C





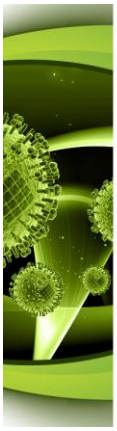
Hepatitis C Treatment

- Currently the standard treatment is combination therapy consisting of:
  - Interferon
  - Ribavirin
- Interferon is poorly tolerated in some patients
  - However, combination therapy can be potentially life-saving
- **There is no vaccine available**



Hepatitis C Prevention

- Primary preventive measures:
  - Hand hygiene
  - Safe handling and disposal of sharps and waste
  - Safe cleaning of equipment
  - Testing of donated blood
  - Training of health personal
  - Safe sex practices



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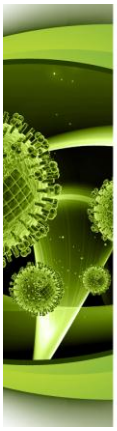

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