



## Diagnostic Testing in the Management of Viral Hepatitis B and Hepatitis C

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# Diagnostic Testing in the Management of Viral Hepatitis B and C

The clinical consequences of hepatitis B (HBV) and hepatitis C (HCV) infection can be serious and include cirrhosis and liver cancer. In addition, the diagnosis, staging and monitoring of hepatitis is complicated, making diagnostic testing an important element in the management of hepatitis patients.

Diagnostic tests are essential in:

- Identifying patients with HBV or HCV infection, because many infected individuals are asymptomatic
- Determining whether an individual has an acute or chronic infection
- Establishing the viral genotype to help determine therapy
- Monitoring a patient's viral load to assess their disease status and their response to therapy
- Measuring fibrosis and its degree

## Laboratory testing: a key to diagnosis, staging and monitoring

From diagnosis through active disease and chronic progression, laboratory testing plays an important role in the identification, treatment decisions and monitoring of hepatitis patients.

- Blood tests of "liver function" may indicate liver damage
- Testing with immunoassays help diagnose viral hepatitis and whether the infection is acute or chronic
- Nucleic acid testing (NAT) helps confirm diagnosis, guide treatment and indicate prognosis
- Biomarkers, imaging and biopsy, help stage the degree of fibrosis and liver injury
- Viral load testing is used to monitor therapy and indicate response

To help clarify the role of these tests and aid patient management, Siemens Healthcare Diagnostics has developed this pocket guide. It contains an overview of each of these important testing categories with recommendations on their application for patients at various disease stages.

# Hepatitis B and C Infection Worldwide

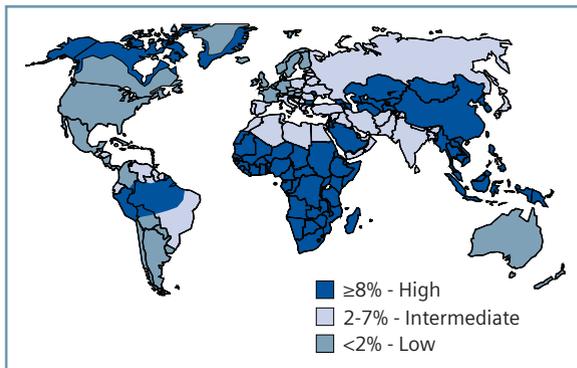
**Viral hepatitis is a global health problem that affects hundreds of millions of people**

## Hepatitis B, a serious global public health problem

According to the World Health Organization<sup>1</sup>:

- 2 billion people have been infected with HBV and more than 360 million have a chronic HBV infection
- Vaccination is 95% effective in preventing chronic HBV infection from developing, although it will not cure current cases of chronic HBV
- In sub-Saharan Africa, most of Asia and the Pacific, 8 - 10% of the general population will develop chronic hepatitis B

## Worldwide HBV prevalence<sup>1</sup>



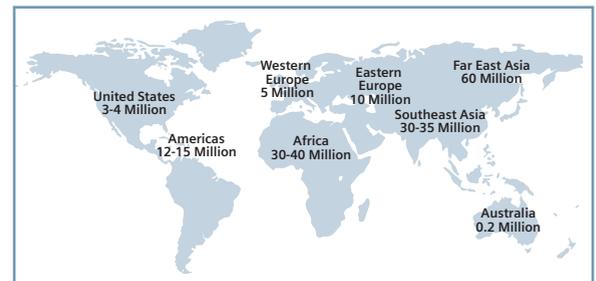
## Hepatitis B is transmitted by contact with an infected person's blood or body fluids

Main routes of HBV transmission are perinatal, child-to-child, unsafe injections and transfusions, and sexual contact

## Hepatitis C, a major cause of acute hepatitis and chronic liver disease, including cirrhosis and liver cancer<sup>2</sup>

- 170 million people have chronic HCV (3% of the world's population) and 3 - 4 million new infections occur every year
- About 80% of newly infected patients develop chronic HCV and are at risk of developing liver cirrhosis and/or liver cancer
- Main causes of HCV infection worldwide are unscreened blood transfusions and re-use of needles and syringes that have not been adequately sterilized

## Hepatitis C: 170 million to 200 million carriers worldwide<sup>2,3</sup>



# Evaluating Liver Function Using Routine Laboratory Tests

## Routine liver function tests often serve as initial screening tests for hepatitis B and C

- Elevated liver function tests (LFTs) may be the first indication of risk of liver injury
- LFTs are used to assess liver function but do not specifically diagnose hepatitis
- LFTs are commonly used to assess liver function during routine physical examinations but often are not abnormal until liver injury

## Many routine liver function tests indicate liver injury but not the cause

- Transaminases
  - AST – aspartate aminotransferase or (SGOT)
  - ALT – alanine aminotransferase or (SGPT)
- Cholestatic liver enzymes
  - GGTP – gamma-glutamyl transpeptidase
  - AP – alkaline phosphatase
- Other LFTs
  - Bilirubin
  - Albumin
  - Total protein

# HBV and HCV Histology Testing Determines Degree of Fibrosis and Cirrhosis

## Today, liver biopsy is the standard test performed to assess histology and degree of fibrosis, but it has limitations<sup>4</sup>

- A liver biopsy provides information on possible contributions of iron, steatosis and alcoholic liver disease to cirrhosis progression
- Although the liver biopsy is the current standard, it should *not* be performed in patients with:
  - Acute hepatitis A
  - Medication-induced liver disease
  - Severe disease making them too ill to undergo a biopsy
- Ultrasound-guided biopsies are the most common type performed today

## Evolving alternatives (non-invasive tests)

- Blood tests detect direct biomarkers of fibrosis and may accurately assess the extent of liver injury
  - Liver fibrosis markers include P111NP, TIMP-1 and hyaluronic acid (HA)
- Image-based testing
  - Ultrasound-based testing is used to detect liver masses
  - CT scans are used to further evaluate a mass found on a sonogram
  - MRIs help detect a fatty liver, iron overload and hemangiomas
  - Ultrasound elastography evaluates liver stiffness, a measure of liver damage

# Hepatitis B Virus (HBV) Testing Identifies Those with Acute or Chronic HBV

## HBV serologic testing involves measurement of several antigens and antibodies

Different combinations of markers are used to identify whether a patient has an acute or chronic infection, is immune to HBV as a result of prior infection or vaccination, or is susceptible to infection.

## Interpreting HBV serologic test results<sup>5</sup>

HBsAg	negative	Susceptible
anti-HBc	negative	
anti-HBs	negative	
HBsAg	negative	Immune due to natural infection
anti-HBc	positive	
anti-HBs	positive	
HBsAg	negative	Immune due to hepatitis B vaccination
anti-HBc	negative	
anti-HBs	positive	
HBsAg	positive	Acutely infected
anti-HBc	positive	
anti-HBc IgM	positive	
anti-HBs	negative	
HBsAg	positive	Chronically infected
anti-HBc	positive	
anti-HBcIgM	negative	
anti-HBs	negative	
HBsAg	negative	Interpretation unclear; four possibilities:
anti-HBc	positive	
anti-HBs	negative	
		1. Resolved infection (most common)
		2. False-positive anti-HBc, thus susceptible
		3. "Low level" chronic infection
		4. Resolving acute infection

# HBV Patient Classification Based on LFTs, Molecular Testing and Histology

## Laboratory tests may be used to monitor and stage individuals with chronic HBV

Patients with chronic HBV have been HBsAg positive for 6 months or more and may be divided into the following categories:

- Inactive carrier
  - HBcAb positive
  - HBeAg negative
  - HBeAb positive
  - AST/ALT normal
  - Viral Load (HBV DNA) none
  - Liver biopsy reveals minimal or no fibrosis
- Active carrier
  - HBeAg positive
  - AST/ALT persistently or intermittently elevated
  - Viral Load elevated
  - Liver biopsy reveals inflammation or fibrosis
- Carrier with precore mutation
  - HBeAg negative
  - AST/ALT persistently or intermittently elevated
  - Viral Load elevated
  - Liver biopsy reveals inflammation or fibrosis
- Resolved infection
  - HBsAg negative
  - HBeAg negative
  - HBeAb positive, occasionally negative
  - HBsAb positive
  - AST/ALT normal
  - Viral Load minimal or none

# HBV Molecular DNA Testing Helps Monitor and Stage Chronic HBV

Critical to determine a patient's virus level (load) and degree of fibrosis before deciding on therapy

## HBV DNA (viral load) testing

- HBV DNA is more sensitive than HBeAg for detecting viruses
- Used to monitor antiviral therapy in patients with chronic HBV infections
- Positive test indicates HBV can be spread to others

## HBV genotyping may also be considered

- 8 HBV genotypes (A-H) are known<sup>6</sup>
- Genotypes have a distinct geographic distribution and correlate with liver disease severity<sup>6</sup>

HBV genotype	Possible significance for patients <sup>6</sup>
C	More severe liver disease
B	Lower rate of HBeAg positivity
C & D	Lower response rate to alpha interferon than those infected with A and B
A	Lamivudine resistance more common than in those infected with D

## HBV Resistance Testing may also be considered

- Polymerase (pol) sequencing identifies HBV drug resistant strains

# Hepatitis C Testing

Hepatitis C is a major public health problem and a leading cause of liver disease and liver transplantation. In more than 90% of cases of HCV, a risk factor can be identified

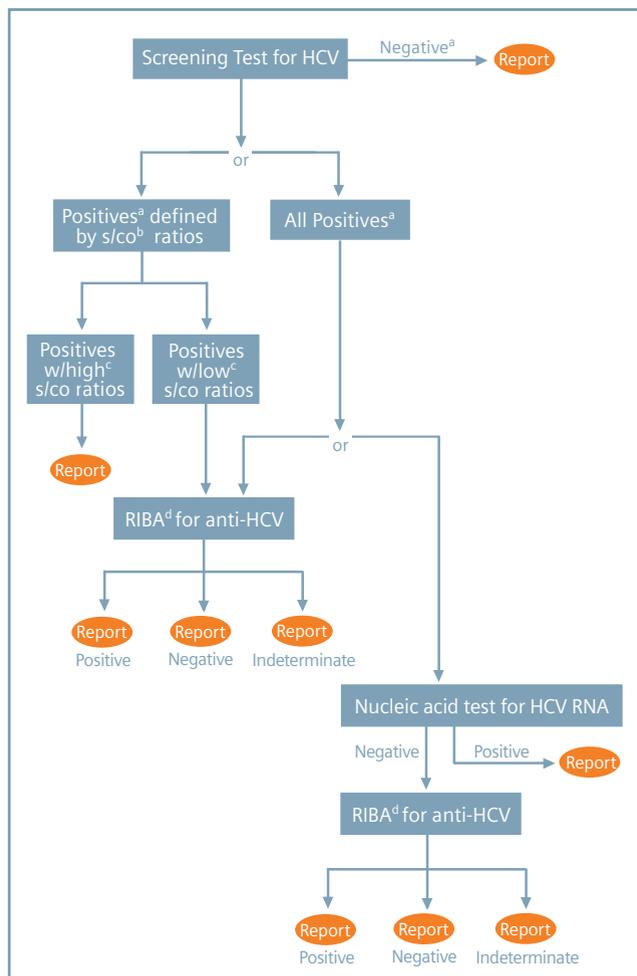
## Anti-HCV is the immuno/serologic test used for screening

- Anti-HCV persists in the blood whether the infection is resolved, acute or chronic
  - About 85% of HCV infections become chronic
- Anti-HCV is an immunoassay test that indicates exposure to HCV but cannot indicate the presence of active infection
  - Results are reported as positive, negative or weakly positive but do not indicate the presence of active infection
- Third generation anti-HCV immunoassay tests are more sensitive than 2nd generation tests and HCV RIBA (recombinant immunoblot assay) tests, typically used for positive confirmation
- Although continually improving, all anti-HCV tests can give false positive results and should be confirmed before reporting

## HCV RIBA antibody test may be used to confirm a positive anti-HCV test

- An HCV RIBA has a greater specificity (fewer false positives) than the anti-HCV immunoassays used for screening
  - Results are reported as positive, negative or indeterminate
- A positive HCV RIBA test confirms exposure to HCV but not active infection
- A single negative or indeterminate test does not exclude active infection and may only reflect a transient decline in viral load below the level of detection and therefore should be reconfirmed with a follow-up test

## CDC recommended algorithm for HCV testing and reporting<sup>7</sup>



Adapted from: Centers for disease Prevention MMWR 2003;52(No.RR-3)<sup>7</sup>

<sup>a</sup>Interpretation based on manufacturers criteria.

<sup>b</sup>Signal-to-cut-off.

<sup>c</sup>S/CO screening-test-positive results classified as “high” if ratios are above a predetermined value that predicts a supplemental-test-positive result  $\geq 95\%$  of the time; results are classified as “low” if their ratios are below this value.

<sup>d</sup>Recombinant immunoblot assay.

## HCV Molecular (RNA) Testing Is Key in Optimizing Therapy

HCV genotype (GT) helps guide length of treatment, predict success<sup>8</sup>

HCV Genotype	SVR	Therapy Duration (weeks)
GT 1 (most common in US)	40 – 50%	48/24 <sup>a</sup>
GT 2	85 – 90%	24/12 <sup>a</sup>
GT 3	80 – 85%	24/12 <sup>a</sup>
GT 4	70 – 80%	48/24 <sup>a</sup>
GT 5	75 – 80%	24
GT 6	75 – 80%	24

<sup>a</sup>If SVR and other measurements are achieved, therapy duration could potentially be reduced.

HCV quantitative (viral load) test helps evaluate clearance rate and outcome

- HCV viral loads provide important information on the likelihood of a successful response to therapy
- Early Viral Response (EVR), as defined by a 2 log drop in viral load, indicates a successful response to therapy

HCV RNA qualitative test assesses clearance and treatment success

- Definite test for clearance (viral eradication)
- Sustained Viral Response (SVR), which correlates to a cure requires a 2nd negative qualitative test 6 months post therapy

# Outlook for the Future

This is an exciting time in the fields of virology and hepatology. New advances in the understanding of viruses and their infections have led to the recent development of several promising pharmaceutical agents for the treatment of HBV and HCV.

While chronic HBV has become a treatable disease, further research is needed to develop individualized treatment protocols and the ability to predict a prolonged, sustained antiviral response. Additional options are also needed for those patients who fail therapy.

For HCV, there are about 80 active pharmaceutical projects aimed at directly targeting the virus, several of which are small molecule agents. Many of these drugs are in late stage clinical trials. Some of the most promising of these are protease inhibitors and polymerase inhibitors.

These drugs could potentially reach the market within the next several years and will surely drive the development of diagnostics. A promising, logical option is resistance testing for these compounds, much like HIV-1 is evaluated and treated today. Such advances hold the potential to help the physician make informed decisions regarding those therapies appropriate for individual hepatitis patients to prolong their lives, while advancing the field of diagnostic therapeutics.

## References:

1. World Health Organization. Weekly Epidemiological Record. 2004;79(28):253-264.
2. World Health Organization. Hepatitis C. Fact Sheet No 164. <http://www.who.int/wer>. Accessed October 6, 2008.
3. Centers for Disease Control Division of Viral Hepatitis. FAQs for Health Professionals. <http://www.cdc.gov/hepatitis/HCV/HCVfaq.htm>. Accessed October 6, 2008.
4. Palmer M. Hepatitis and liver disease. What you need to know. New York, NY:Avery;2004.
5. Centers for Disease Control. MMWR. 2005;54(No. RR-16).
6. Liu W, et al. J Clin Microbiol. 2006;44:4491-4497.
7. Centers for Disease Control. MMWR. 2003;52(No. RR-3).
8. National Institute of Diabetes and Digestive and Kidney Diseases. National Institutes of Health. Chronic Hepatitis C: Current Disease Management. <http://digestive.niddk.nih.gov/ddiseases/pubs/chronichepc>. Accessed October 6, 2008.

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