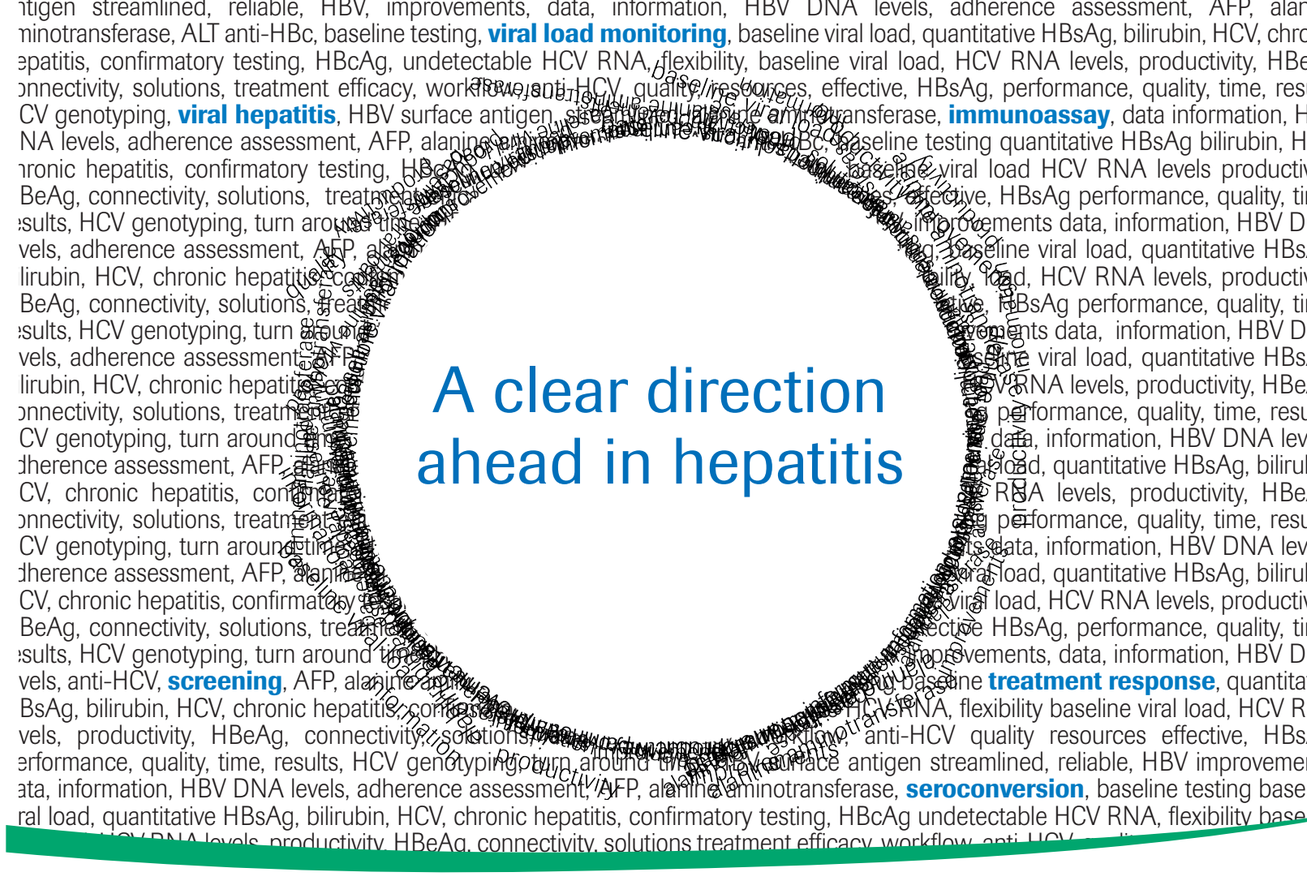

Committed to improving hepatitis disease management

A comprehensive approach to optimized diagnosis and treatment monitoring for hepatitis B and C infection

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cobas®
Life needs answers

Optimized diagnosis and treatment management of patients infected with HCV

Patient management relies on accurate diagnosis

Diagnosis and management of HCV require a combination of tests

Hepatitis C virus (HCV) infection and its clinical stages are diagnosed using a combination of tests for markers of HCV.

- **HCV antibodies (anti-HCV)** as first line test to screen for and diagnose infection with HCV
- **HCV RNA** to confirm active infection with HCV and to monitor HCV viral load before, during and after anti-viral therapy
- **HCV genotyping** to determine the HCV genotype and subtype to select an appropriate treatment regimen[1]

The measure of Alanine aminotransferase (ALT) is a supportive aid in the diagnosis of hepatic diseases and for screening of liver damage[1,2]

Roche offers the **cobas**® system family of diagnostic platforms to run the key tests for the diagnosis of HCV infection and management of chronic hepatitis C.

Hepatitis C virus diagnostic pathway

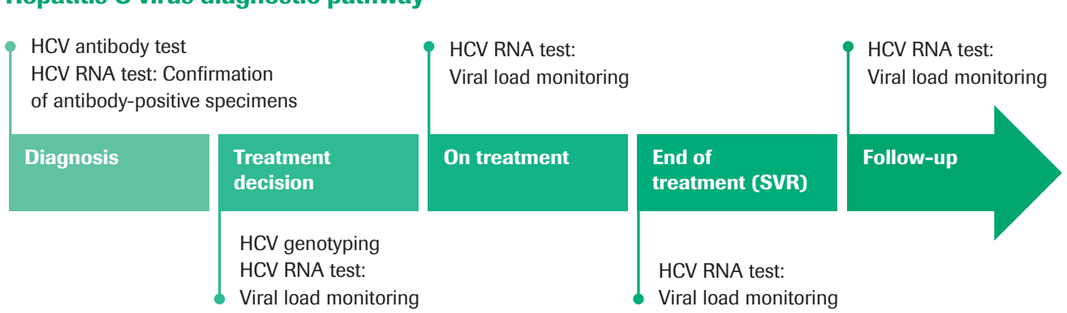


Figure 1: Key steps in the diagnosis and management of HCV infection

Elecsys® Anti-HCV II assay for accurate diagnosis of HCV

Reliable and consistent results for patient-oriented decision making

HCV infection can be detected by measuring the amount of HCV RNA using Polymerase Chain Reaction (PCR), alanine aminotransferase (ALT) and HCV-specific immunoglobulins (anti-HCV) in patient serum samples. This can also indicate if the infection is acute or chronic[1].

Figure 2: Course of markers during acute HCV infection[1]

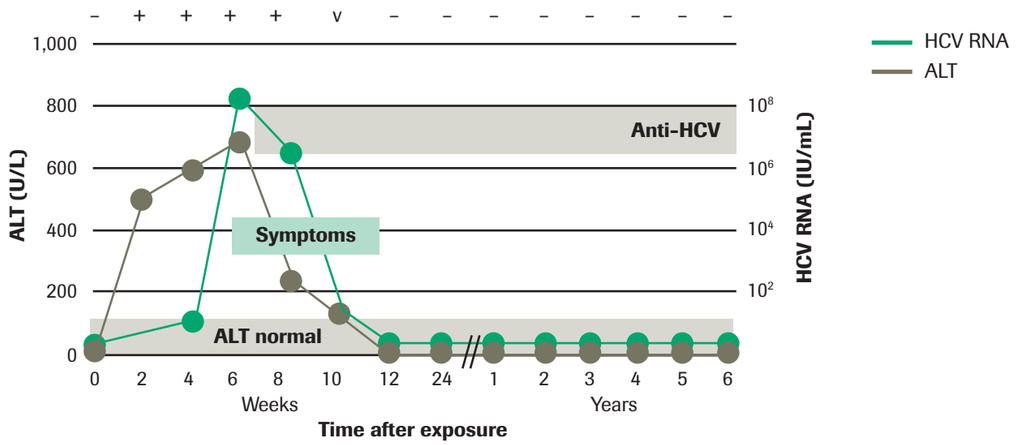
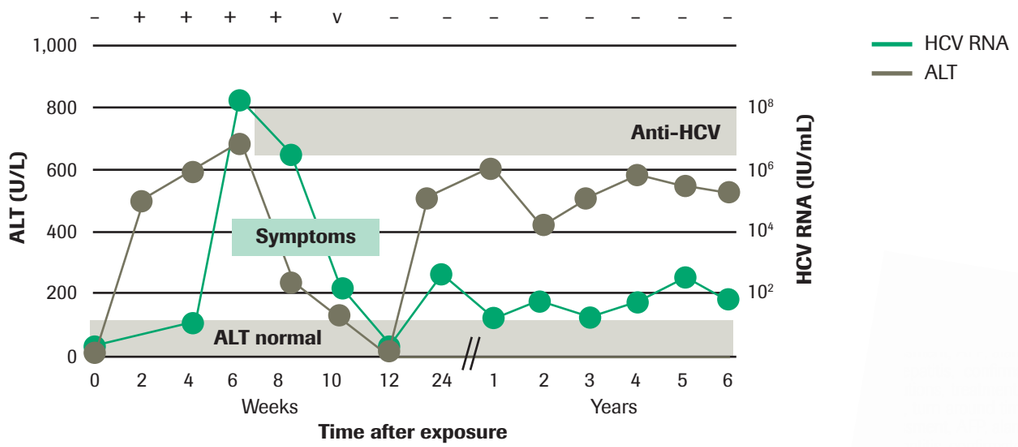


Figure 3: Course of markers during chronic HCV infection[1]



Anti-HCV assays are used to demonstrate the presence of antibodies against HCV. The antibody-negative but HCV RNA positive window period in HCV infections can be as much as 40-60 days (compared to e.g. around 22 days for HIV)[1]. Anti-HCV assays are able to detect infection on average 6-8 weeks after infection[2].

*Not approved in the US

Confirmatory HCV RNA testing

Sensitive detection of active infection for effective patient management

HCV RNA detection is vital for optimal patient management

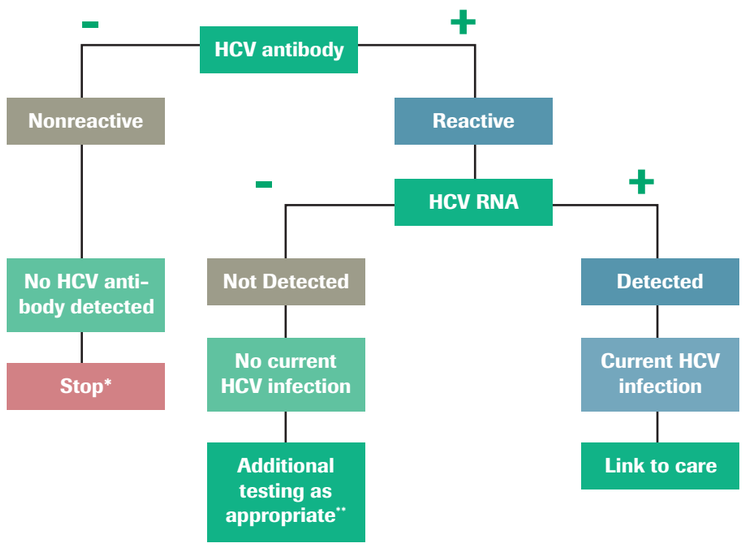
HCV antibody screening can yield positive results in patients who were infected with HCV but who subsequently cleared infection. Therefore, specific testing for HCV RNA is required in order to determine HCV infection status and to confirm the infection[3]. The measure of HCV RNA can also be used in the window period between exposure and seroconversion.

Table 1: Interpretation of assay results for HCV

HCV infection status	Anti-HCV	HCV RNA
No HCV infection	–	–
Resolved HCV infection	+	–
Active HCV infection	+	+
Acute HCV infection or chronic infection in conditions which may suppress antibody	–	+

Detection of HCV RNA by PCR offers a highly sensitive and specific means of detecting active viremia which is associated with chronic HCV infection. The combination of HCV antibody and HCV RNA testing can be used to accurately classify HCV disease status.

Figure 4: CDC recommended testing sequence to identify current infection[4]



*** For persons who might have been exposed to HCV within the past 6 months, testing for HCV RNA or follow-up testing for HCV antibody is recommended. For persons who are immunocompromised, testing for HCV RNA can be considered.*

[1] To differentiate past, resolved HCV infection from biologic false positivity for HCV antibody, testing with another HCV antibody assay can be considered. Repeat HCV RNA testing if the person tested is suspected to have had HCV exposure within the past 6 months or has clinical evidence of HCV disease, or if there is concern regarding the handling or storage of the test specimen.

Identifying HCV genotype

Making the right choice of therapy

HCV genotyping is essential for chronic hepatitis C treatment decisions

HCV genotype has been one of the strongest baseline predictors for achieving sustained virological response (SVR), with the old Standard of Care, pegylated-interferon α (pIFN) in combination with ribavirin (RBV). For the new therapies based on direct acting antivirals (DAAs), antiviral efficacy is genotype or genotype 1 subtype (a/b) selective, and the genotype in combination with other factors, like treatment experience and liver status, guides the physician to determine the right combination of antiviral drugs and treatment duration.[5]

Determination of HCV genotype, on which the regimen, dosing, and duration of therapy as well as likelihood of response depends, is thus essential to making decisions about treatment.

Table 2: Treatment duration (in weeks) for non-cirrhotic patients according to EASL guidelines 2015[5]

genotype	SOF/P/R	SMV/P/R	SOF/R	SOF/LPV	PTVr/ OBV/DBV	PTVr/OBV	SOF/SMV	SOF/DCV
1a	12	12-24	12	8-12	12+R	12+R	12	12
1b					12			
2								
3								
4		12-24		12		12+R	12	
5, 6				12				

Table 3: Treatment duration (in weeks) for cirrhotic patients according to EASL guidelines 2015[5]

genotype	SOF/P/R	SMV/P/R	SOF/R	SOF/LPV	PTVr/ OBV/DBV	PTVr/OBV	SOF/SMV	SOF/DCV
1a	12	12-24		12+R or 24	24+R		12+R or 24	12+R or 24
1b					12 +R			12
2			16-20					24
3								12+R or 24
4		12-24		12+R or 24		24+R	12+R or 24	12+R or 24
5, 6								

P: pegylated interferon; R: ribavirin; SOF: sofosbuvir; LPD: ledipasvir; PTVr: ritonavir-boosted paritaprevir; OBV: ombitasvir; DBV: dasabuvir; SMV: simeprevir; DCV: daclatasvir

*__cobas__® HCV GT for use on the __cobas__® 4800 System is not approved or available in the United States and Canada.

The value of HCV RNA testing
A critical assessment tool in the age of direct-acting antivirals

Effectively manage HCV treatment with quantitative HCV RNA testing

To achieve an optimal treatment outcome, regular HCV viral load assessment should be utilized to guide therapy decisions. A quantitative HCV RNA test allows to:

- Assess viral suppression in response to therapy
- Identify adherence or non-compliance
- Detect treatment non-responders
- Differentiate viral breakthrough from relapse at end of treatment
- Determine treatment futility (simeprevir triple therapy only)
- Determine treatment duration based on the HCV RNA baseline level (sofosbuvir/ledipasvir combination therapy)

Monitoring of treatment efficacy is based on repeated measurements of HCV RNA levels using a sensitive (limit of detection ≤15 IU/mL), accurate assay with a broad dynamic range of quantification. Using such an assay, the endpoint of therapy (sustained virologic response, SVR) is defined as undetectable HCV RNA 12 or 24 weeks after end of treatment[5,6].

Table 4: Recommended viral load testing points according to EASL guidelines 2015[5]

	Baseline	Week 2	Week 4	Week 12	EOT	SVR
sofosbuvir + IFN + RBV	◉		◉		◉	◉
simeprevir + IFN + RBV	◉		◉	◉	◉	◉
IFN-free regimens	◉	◉	◉		◉	◉

IFN: pegylated interferon; RBV: ribavirin; EOT: end of treatment; SVR: sustained virologic response

Table 5: Treatment discontinuation in patients with inadequate on-treatment virologic response[4]

	Week 4	Week 12	Week 24
simeprevir + IFN + RBV	≥ 25 IU/mL	≥ 25 IU/mL	≥ 25 IU/mL

Table 6: Treatment duration with interferon-free combination of sofosbuvir and ledipasvir in treatment-naïve patients without cirrhosis[5]

	12 weeks	8 weeks
baseline viral load	≥ 6.8 $\log_{10}$ IU/mL	< 6.8 $\log_{10}$ IU/mL

Optimized diagnosis and treatment management of HBV infected patients
Patient management relies on accurate diagnosis

Hepatitis B serologic testing involves measurement of several hepatitis B virus (HBV)-specific antigens and antibodies. Different serologic "markers" or combinations of markers are used to identify different phases of HBV infection[8,9]

Name	Short name	Utility
Surface Antigen	HBsAg	HBV envelope protein. First line test to diagnose HBV infection and marker of viral replication. Its presence over 6 months refers to chronic infection.
HBV DNA viral load	HBV DNA	Correlates with levels of circulating viral particles. Determine baseline viral load prior to treatment, monitor antiviral response during treatment and survey virological breakthrough.
Antibodies to core (capsid) Antigen	Anti-HBc	Indicates a prior exposure to HBV. Infection may be resolved (HBsAg-negative) or ongoing (HBsAg-positive).
IgM Antibodies to core Antigen	Anti-HBc IgM	Indicates presence of acute infection
Antigen e	HBeAg	Determines active replication and risk of transmission
Antibodies to Antigen e	Anti-HBe	Usually associated with lower levels of HBV DNA (<2,000 IU/mL), indicates partial immune control of the infection
Quantitative Surface Antigen	HBsAg quant	Monitoring patients on therapy and risk of disease progression, identifying inactive carriers.
Antibodies to Surface Antigen	Anti-HBs	Develops in response to HBV vaccination and during recovery from acute hepatitis B, denoting past infection and immunity

Hepatitis B virus diagnostic pathway

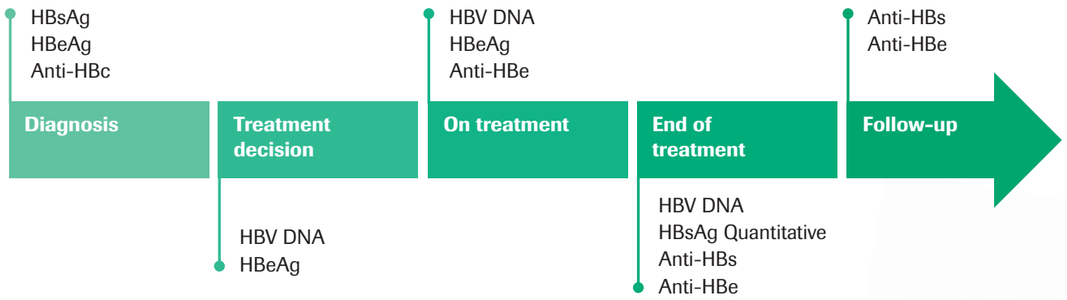


Figure 5: Key steps in the diagnosis and management of HBV

Elecsys® serological assays for accurate diagnosis of HBV

Reliable and consistent results for patient-oriented decision making

The natural history of hepatitis B virus (HBV) infection is complex and variable and is greatly influenced by the age at infection, the level of HBV replication, and host immune status[10]. Diagnosis of the presence and stage of HBV infection is achieved by measuring the serum markers discussed above.

Figure 6: Typical course of acute hepatitis B infection with recovery[11]

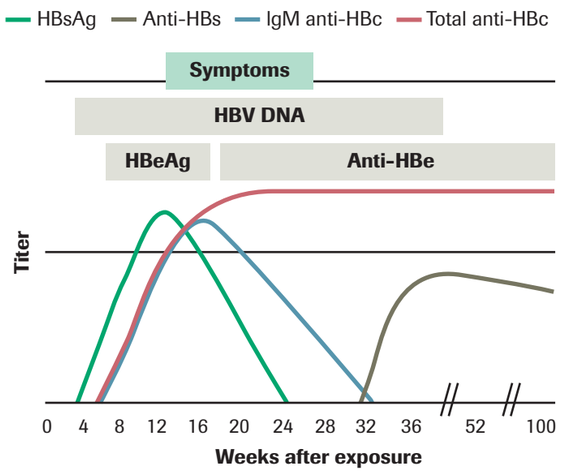
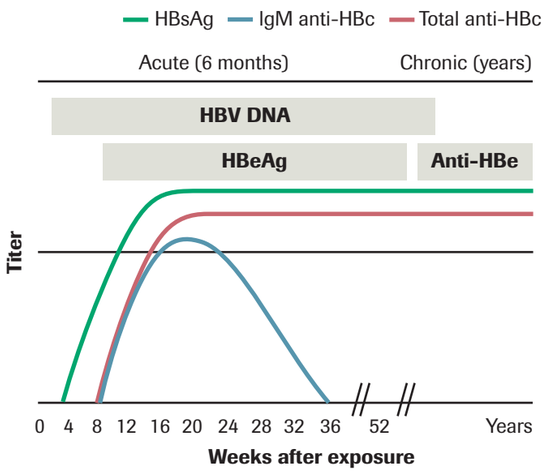


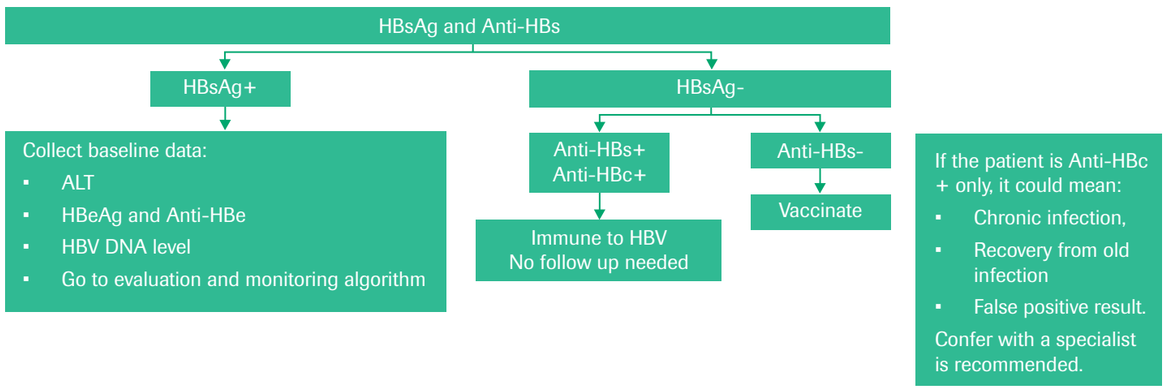
Figure 7: Typical course of a hepatitis B virus infection with progression to chronic hepatitis B[11]



HBsAg and Anti-HBs are the core tests for screening and diagnosis of HBV infection

Screening is recommended in all patients who are at increased risk of contracting HBV, especially those from HBV-endemic regions of the world (HBV prevalence ≥2%). Current guidelines specify the groups that should be routinely screened for HBV infection[12,13].

Figure 8: HBV Screening Algorithm for at risk patients[12,13]



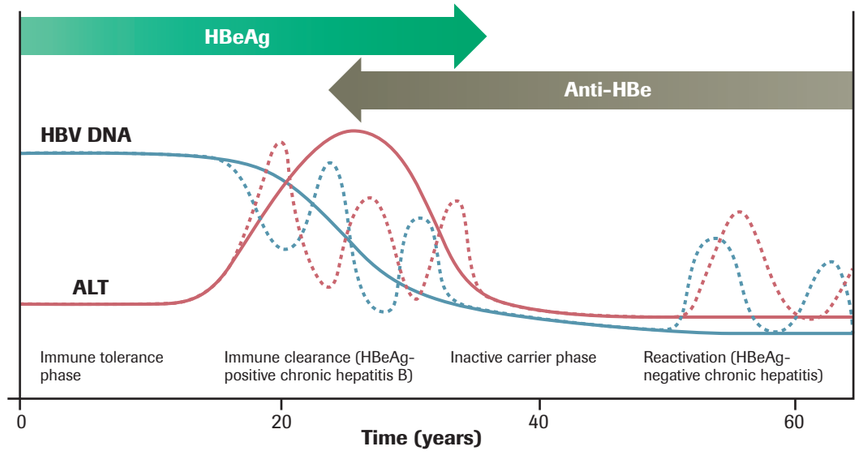
The value of HBV DNA testing

A critical assessment tool for long term patient monitoring

The natural course of chronic HBV infection consists of 4 phases; determined by serum levels of alanine aminotransferase (ALT), Hepatitis B virus (HBV) DNA levels, and the presence or absence of hepatitis B e antigen (HBeAg)[10,11].

Measurement of HBV levels is the standard tool for the clinical management of chronic HBV to establish a baseline prior to treatment, monitor antiviral response during treatment and survey virological breakthrough. Serum HBV DNA level is an important and independent risk factor for disease progression in chronic hepatitis B.

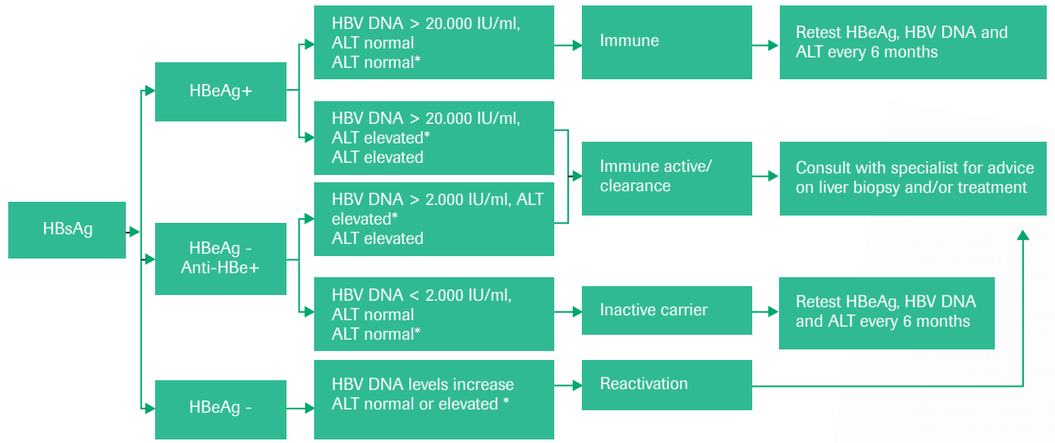
Figure 9: The four stages of chronic Hepatitis B



The four stages of chronic Hepatitis B

HBV DNA levels can fluctuate markedly during the course of chronic HBV infection. The natural course of the disease is highly dynamic and not every patient requires therapy[17].

Figure 10: HBV Evaluation and Monitoring Algorithm[14,15,16]



*Elevated ALT ≥ 19 IU/ml for women and ≥ 30 IU/ml for men

The value of HBsAg quantification

An additional marker to assist in patient management

Combination of HBsAg levels with serum HBV DNA levels is valuable in the following scenarios[18].

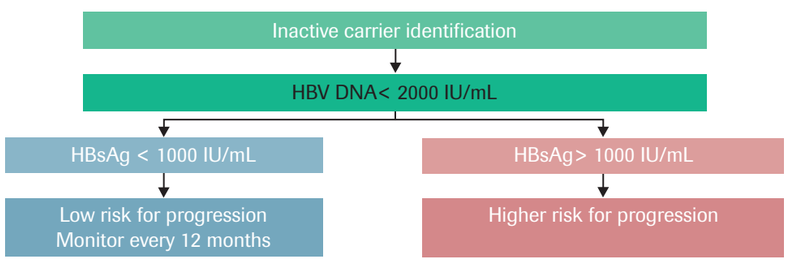
- **Identifying inactive carriers and assessing risk for disease progression for Hepatocellular carcinoma (HCC):**

  A number of independent studies and the current recommendations for the American and European guidelines have shown that the combination of **HBV DNA < 2000 IU/mL and HBsAg < 1000 IU/mL** can reliably identify inactive carriers[20,21,22].

  They are at low risk of disease progression and with appropriate management have an excellent chance of achieving hepatitis B surface antigen (HBsAg) clearance, closest outcome to a clinical cure.

  The HBsAg level ≥ 1000 IU/mL identified as a new independent risk factor in patients with HBV DNA < 2000 IU/mL[19].

Figure 11: Inactive carrier identification



Under current clinical practive guidelines, these patients would not be considered for therapy.

- **Response-guided therapy in peg-interferon alfa-2a monitoring: Help to identify if patients are responding to therapy and if they are on track to achieving sustained immune control.**

Figure 12: Practical application of response-guided therapy during PEG-IFN-a treatment using HBsAg levels[23]
*Response in HBeAg positive patients defined as HBeAg seroconversion 6 months post-treatment.
Response in HBeAg negative patients defined as HBV DNA ≤10,000 copies/mL 1 year post-treatment.

Response-guided therapy in peg-interferon alfa-2a monitoring

	Identify responders* (PPV)	Identify non-responders (NPV)
HBeAg-positive	Week 12 or 24: HBsAg<1,500 IU/mL[7]	Week 24: Both HBsAg and HBV DNA levels >20,000 IU/mL[8]
HBeAg-negtive	Week 12 or 24: >10% decline in HBsAg from baseline[9]	Week 12 or 24: <10% decline in HBsAg from baseline[9]
	▪ Motivates patients to continue with therapy ▪ Track success	▪ Identify early non-response ▪ Allows alterations to treatment regimen

*Response in HBeAg positive patients defined as HBeAg seroconversion 6 months post-treatment. Response in HBeAg negative patients defined as HBV DNA ≤10,000 copies/mL 1 year post-treatment.

HBV and HCV diagnostic and monitoring tests from Roche offer clinically relevant performance

Roche offers different quantitative HCV RNA and HBV DNA tests for its family of diagnostic platforms that fulfills the sensitivity requirements for monitoring and aiding in clinical management. These tests provide robust, clinically relevant assay performance with a broad linear range and high sensitivity and deliver optimal results throughout critical medical decision points and across all genotypes. All tests offer an optimised and fully automated workflow to maximize laboratory efficiency.

Product Description	LOD*	Linear range
COBAS® AmpliPrep/COBAS® TaqMan® HBV Test, v2.0	20 IU/mL	20–1.7x10^8 IU/mL
cobas® HBV for use on the **cobas**® 6800 and 8800 Systems (CE-IVD)	2.7 IU/mL (500 µL#) 15.5 IU/mL (200 µL#)	10-1×10^9 IU/mL 25-1×10^9 IU/mL
cobas® HBV for use on the **cobas**® 6800 and 8800 Systems (US-IVD)	Plasma: 6.6 IU/mL Serum: 3.5 IU/ml	10-1×10^9 IU/mL
cobas® HBV for use on the **cobas**® 4800 System&,1	4.4 IU/mL (400 µL#) 7.6 IU/mL (200 µL#)	10-1×10^9 IU/mL 10-1×10^9 IU/mL
COBAS® AmpliPrep/COBAS® TaqMan® HCV Quantitative Test v2.0	15 IU/mL	15-1×10^8 IU/mL
cobas® HCV for use on the **cobas**® 6800/8800 Systems (CE-IVD)	15 IU/mL (500 µL#) 40 IU/mL (200 µL#)	15-1×10^8 IU/mL 40-1×10^8 IU/mL
obas® HCV for use on the **cobas**® 6800/8800 Systems (US-IVD)	Plasma: 12 IU/mL Serum: 13.7 IU/mL	15-1×10^8 IU/mL
cobas® HCV for use on the **cobas**® 4800 System&	9.2 IU/mL (400 µL#) 15.2 IU/mL (200 µL#)	15-1×10^8 IU/mL 25-1×10^8 IU/mL

*Limit of Detection by PROBIT, #sample processing volume
& **cobas**® HBV and **cobas**® HCV for use on the **cobas**® 4800 System is not approved or available in all markets
1 **cobas**® HBV for use on the **cobas**® 4800 System is pending for CE-IVD approval
$ not approved or available in the United States

Anti-HCV test

The Elecsys® Anti-HCV II test is intended for the qualitative detection of antibodies to HCV in human serum and plasma.
It is ready-to-use and shows excellent early detection of infection as well as state-of-the-art clinical specificity and sensitivity.

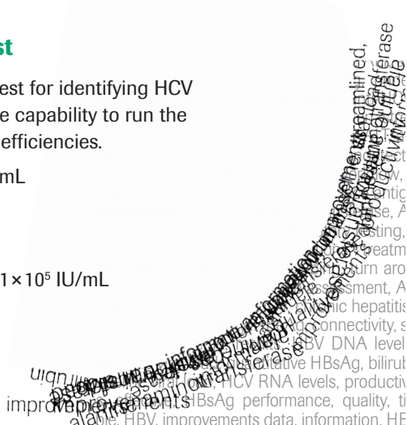
Product Description	Sensitivity	Specificity
Elecsys® Anti-HCV	100 % (n = 765)	99.84 % (n = 6850, blood donors) 99.66 % (n = 3922, hospitalized patients)

cobas® HCV GT* – automated and highly accurate HCV genotyping test

cobas® HCV GT for use on the **cobas**® 4800 System* is an automated, real-time PCR based test for identifying HCV genotypes 1 to 6 and subtypes 1a and 1b. The test provides high genotyping accuracy and the capability to run the test in mixed batches with **cobas**® HCV for viral load testing allowing for increased workflow efficiencies.

- Highly sensitive test using three target regions (5'-UTR, NS5B, Core): LOD = 50-1000 IU/mL
- Excellent genotyping and subtyping accuracy compared to Sanger sequencing:
  - > Genotyping accuracy = 99.4%; subtyping accuracy = 100%
- Capability to detect both genotypes in mixed infections down to a ratio of 1:100 (1×10^3 : 1×10^5 IU/mL

*__cobas__® HCV GT for use on the **cobas**® 4800 System is not approved or available in the United States



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