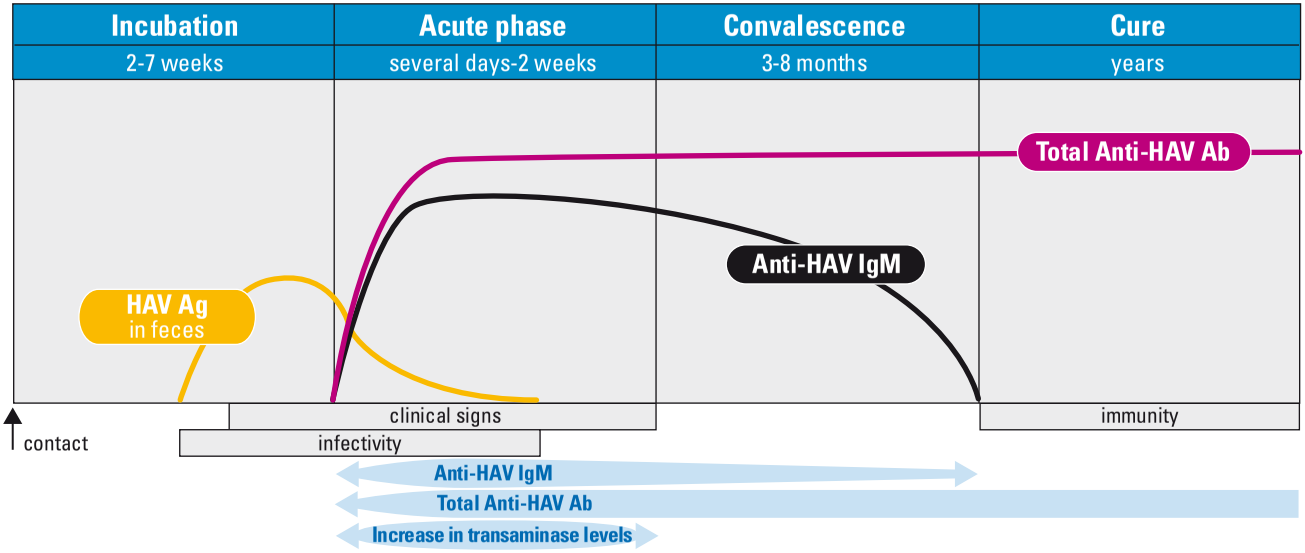
EMPOWERING CLINICAL DECISIONS™

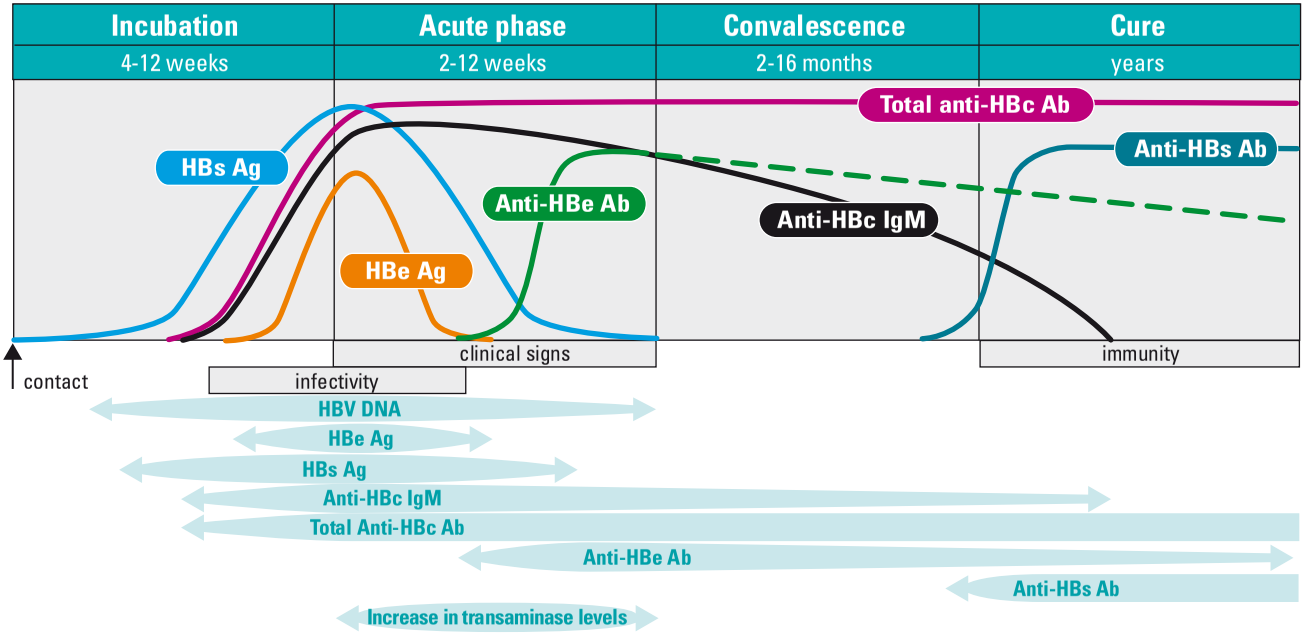
DIAGNOSIS AND MONITORING OF Viral Hepatitis

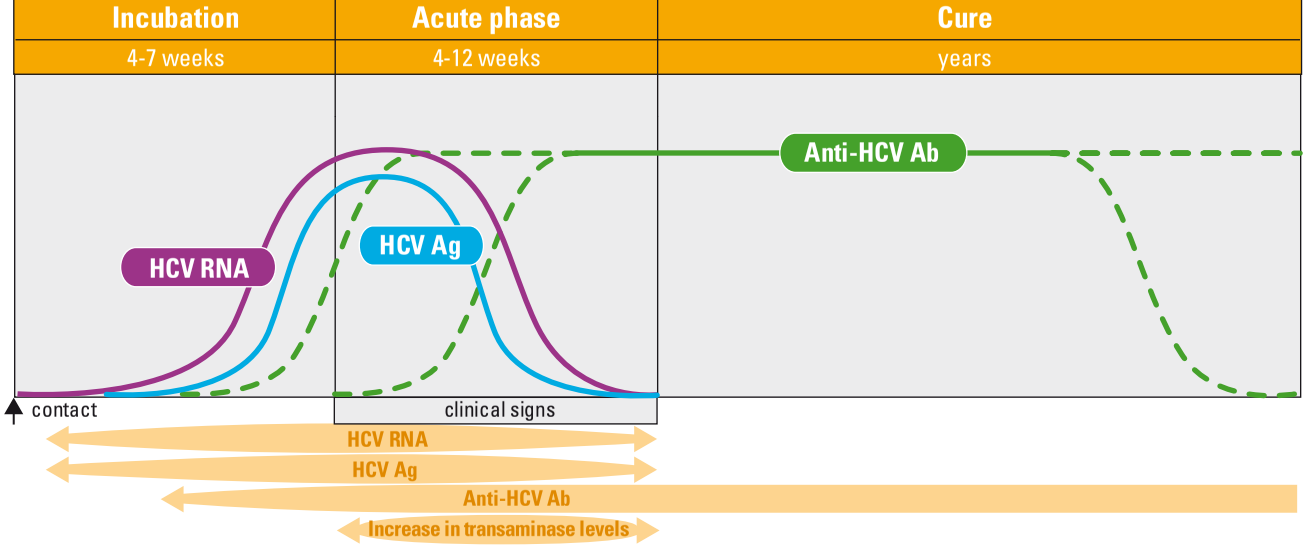
BIOMÉRIEUX

CONTENTS

This paper was prepared with the kind co-operation of Doctor L Castéra (Hepato-gastro-enterology department, CHU, Bordeaux - France), and Professor JM Pawlotsky (Bacterio-virology department, Hôpital Henri Mondor, Créteil - France).


Incubation
2-7 weeks
Acute phase
several days-2 weeks
Convalescence
3-8 months
Cure
years
Total Anti-HAV Ab
Anti-HAV IgM
HAV Ag
in feces
clinical signs
immunity
contact
infectivity
Anti-HAV IgM
Total Anti-HAV Ab
Increase in transaminase levels


Incubation
4-12 weeks
Acute phase
2-12 weeks
Convalescence
2-16 months
Cure
years
Total anti-HBc Ab
Anti-HBs Ab
HBs Ag
Anti-HBe Ab
Anti-HBc IgM
HBe Ag
clinical signs
immunity
contact
infectivity
HBV DNA
HBe Ag
HBs Ag
Anti-HBc IgM
Total Anti-HBc Ab
Anti-HBe Ab
Anti-HBs Ab
Increase in transaminase levels



spontaneously resolvent

Hepatitis A

- **Transmission :** enteral (contaminated food and drink)
- **Clinical signs :** asymptomatic in 90% of cases
- **Cure :** 100% of cases
- **Complications :** fulminant forms (rare)
- **Development of chronic form :** NO
- **Prevention :** vaccination+++ ; hygiene ; specific Ig
- **Main markers :** anti-HAV IgM, total anti-HAV Ab

Hepatitis B

- **Transmission :** sexual, parenteral, perinatal, direct contact between individuals
- **Clinical signs :** asymptomatic in 90% of cases
- **Cure :** 95% of cases (adults)
- **Complications :** cirrhosis and hepatocellular carcinoma
- **Development of chronic form :** YES (5 % of adult cases)
- **Prevention :** vaccination +++ ; specific IgG
- **Main markers :** HBs Ag, anti-HBc IgM, total anti-HBc A anti-HBs Ab, HBe Ag, anti-HBe Ab, HBV DNA

Hepatitis C

- **Transmission :** parenteral, nosocomial
- **Clinical signs :** asymptomatic in 90% of cases
- **Complications :** cirrhosis and hepatocellular carcinoma
- **Development of chronic form :** YES (80% of cases)
- **Prevention :** hygiene, no vaccination
- **Main markers :** anti-HCV Ab, HCV RNA, HCV Ag, genotyp

Clinical signs

Determination of date of infection to orient diagnosis

- **Non-specific or absent symptoms** (90% of cases) :
  - pain in right hypochondrium
  - fever
  - nausea and vomiting
  - arthralgia
  - urticaria
- **Icterus** (≤ 10% of cases) [1]

First-line approach

Biological profile

- **AST (or SGOT) and ALT (or SGPT) transaminase serum activity assay.**
- **Detection of A, B and C viruses (the most common causes).** [1-5]
  - Anti-HAV IgM
  - HBs Ag
  - Anti-HBc IgM
  - Anti-HCV Ab

Interpretation [2,3,4]

	Acute Hepatitis A	Acute Hepatitis B	Acute Hepatitis C
Transaminases	10 (sometimes 100 to 1000) times the normal level degree of elevation not correlated with the severity of acute hepatitis		
Anti-HAV IgM	+		
HBs Ag		+	
Anti-HBc IgM		+	
Anti-HCV Ab			–/+ *

* In the initial phase of acute hepatitis C, anti-HCV Ab detection may be negative (serological window of 4 to 6 weeks) :
repeat the test for this marker in the weeks following acute infection to confirm seroconversion [1,5].

Early diagnosis during serological window : HCV RNA detection using amplification techniques (eg. Polymerase Chain Reaction) by specialized laboratories [5].

HEPATITIS (1)

- **Severe form : fulminant hepatitis**
  - clinical signs : hepatic encephalopathy
  - biological signs : ↱ prothrombin level (< 50%) ; transaminase level not correlated with the severity of fulminant hepatitis

  Urgent hospitalization in a specialized ward [1]

Prognosis and follow-up

Development of chronic forms

- **No risk for hepatitis A and E viruses** [2].
- **Possible progression to chronic hepatitis for B, C and Δ viruses : risk of cirrhosis and hepatocellular carcinoma** [3,4].

Follow-up

	Hepatitis A	Hepatitis B	Hepatitis C
Risk of chronic form	NO	YES	YES
Probability of cure	100%	90-95% (adults) 50% (children) 5% (newborns)	20%
Indicator of cure	disappearance of anti-HAV IgM	disappearance of HBs Ag + appearance of anti-HBs Ab	negative HCV viral RNA
Protective immunity	YES (Total anti-HAV Ab)	YES (anti-HBs Ab)	NO *

* The presence of anti-HCV antibodies does not ensure protective immunity.

Specific cases :

- **Delta superinfection** in chronic HBs Ag carriers (drug abusers) [3] anti-Δ IgM and IgG detection.
- **Hepatitis E** (subject returning from a stay in an endemic zone, Africa, Asia, South America) [2] : **anti-HEV Ab detection.**

Other causes of acute hepatitis

Epstein-Barr virus, Cytomegalovirus, Herpes virus, etc. [1]

Clinical signs

Generally asymptomatic, no specific clinical signs [1]

- Detected in a routine blood test (chronic rise in transaminase level) or when donating blood.

First-line approach

Biological profile

1 • **Test for signs of chronic hepatitis :**
Transaminase assay (at least 3 assays over a period of at least 6 months)[1].

2 • **Test for signs of complications**[1] **:**
- prothrombin level,
- Serum protein electrophoresis (globulins)
- Liver scan

3 • **Test for the viral cause**[1] **:**
- HBV : HBs Ag, total anti-HBc Ab, anti-HBs Ab
- HCV : anti-HCV Ab

4 • **Test for other possible causes**
(in event of negative viral serologies)[1] **:**
Alcoholism, administration of therapeutic drugs, steatosis, hemochromatosis, auto-immune hepatitis, etc.

Interpretation[3]

Hepatitis B

Transaminases	HBs Ag	Total anti-HBc Ab	Anti-HBs Ab
Elevated to 1 to 10 times the normal level	+ on 2 samples over more than 6 months	+	–

* Perform at least 3 assays over a period of at least 6 months.

Hepatitis C [4]

Confirm the presence of anti-HCV Ab on a 2nd sample :

- Present in 100% of immunocompetent subjects with chronic hepatitis C.
- May be undetectable in hemodialysis patients or immunocompromised subjects : a negative result for anti-HCV Ab does not eliminate a possible diagnosis.

- Detected at the compensated or complicated cirrhosis stage (ascites, icterus, digestive hemorrhage).

Second-line approach [3-5]

Biological profile

Test for

- HBV and HVΔ: HBe Ag, Anti-HBe Ab, HBV DNA, anti-Δ IgM and total anti-Δ Ab
- HCV : HCV RNA

Interpretation [1,3]

Hepatitis B

	HBe Ag	Anti-HBe Ab	Viral replication (HBV DNA)
«Wild» B virus	+	–	+
«Pre-core mutant» B virus (up to 50% of cases in some countries)	–	+	+
Non-replicating B virus carriers (1/3 of chronic HBs Ag carriers)	–	+	–

Specific case for hepatitis B + Δ :
- Total anti-Δ Ab (+) and anti-Δ IgM (+ or -) ; RNA of Δ virus detectable.

Hepatitis C [4-6]

Test for HCV RNA

- **If presence of anti-HCV Ab :** active viral replication is confirmed by the presence of HCV RNA.
- **If absence of anti-HCV Ab :**
(hemodialysis patients or immunocompromised subjects) : the presence of viral RNA confirms the diagnosis of chronic hepatitis C.

Liver biopsy

- **Diagnosis of certainty of chronic hepatitis.**
- **To be envisaged systematically for any patient with a chronic rise in transaminase levels (over 6 months), irrespective of the extent of the rise.**

Aim : to determine the severity of hepatic lesions on 3 criteria to decide on the administration of an antiviral treatment [3,4] :
- Extent of necrosis and inflammation
- Degree of fibrosis
- Any associated lesions

Acute hepatitis

- No specific treatment of acute viral hepatitis.
- Symptomatic treatment : rest and elimination of alcoholic beverages until transminase levels return to normal.

Hepatitis B

Interferon-α : 5 to 6 million units 3 times/week subcutaneously for 4 to 6 months. Disappearance of HBV DNA from serum, and of HBe Ag, with appearance of anti-HBe Ab (HBe seroconversion in approximately 20% of cases).

Current Nucleoside

Nucleoside analogue	Dose	Reduction in serum HBV DNA
Lamivudine (3TC)	100 mg qd	4-6 $\log_{10}$
Famciclovir	500 mg tds	1-2 $\log_{10}$
Adefovir dipivoxil (bis-POM-PMEA)	5-30 mg qd	4-8 $\log_{10}$
Entecavir (BMS-200475)	0.5-2.5 mg qd	2-3 $\log_{10}$
Emtricitabine [5 fluorothiacytidine (FTC)]	200 mg (capsules) qd or 240 mg (24 mL) oral solution qd	2-4 $\log_{10}$
Tenofovir	300 mg qd	4-6 $\log_{10}$

Hepatitis C (7)

Pegylated Interferon-α (subcutaneous route), associated with ribavirin (per os), for 6 to 12 months :

Management of the main

	Type of side effect	Specific treatment
Treatment with pegylated Interferon- α	**Influenza-like syndrome (70 % of cases) :** within hours of injection; predominant at start of treatment (1st and 2nd months).	**Paracetamol :** (1g before each injection followed by 1 to 3g over the next 24 hours)
	Leukoneutropenia and thrombopenia (30% of cases) : monitoring of CBC and platelet count	**None**
Treatment with ribavirin	**Hemolytic anemia:** monitoring hemoglobin level	**None**

CBC: complete blood count ;

Chronic hepatitis [1,3,4,6]

Aims of treatment : prevention of viral replication and / or definitive elimination of virus from the body ;
prevention of progression to complications (cirrhosis, hepatocellular carcinoma).

Comments

The «pre-core mutant» B virus is generally more severe and more resistant to treatment.

Carriers of the non-replicating B virus do not require treatment.

Analogues (approved or in clinical trials)

Proposed mechanism of action	Stage
Competitive inhibition with dCTP	Approved
Competitive inhibition with dGTP	Approved
Competitive inhibition with dATP	Approved
Competitive inhibition with dGTP	Approved
Competitive inhibition with dCTP	Approved
Competitive inhibition with dATP	Approved (Europe) Pending (US)

qd: once daily / tds: three times daily.

Prevention of viral replication (> 50% of cases) ; definitive cure in the majority of cases responding to the treatment.

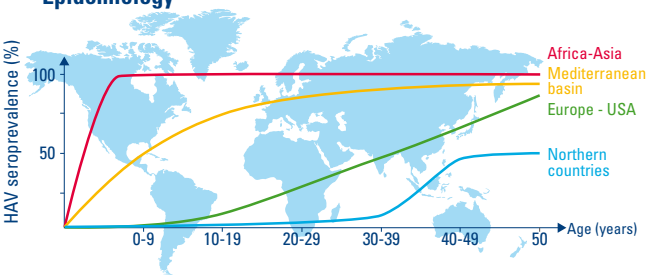
treatment-related side effects

Dosage adaptation	Discontinuation of treatment
NO : improvement if IFN is injected in evening before going to bed	**NO**
IFN dosage reduction	**Discontinuation** (< 10% of cases) if PN< 500/mm^3 or pl< 50,000/mm^3
Very frequent dosage reduction	**Rare**

IFN: interferon ; PN: polynuclear neutrophils ; pl: platelets.

Hepatitis A

Epidemiology [10]

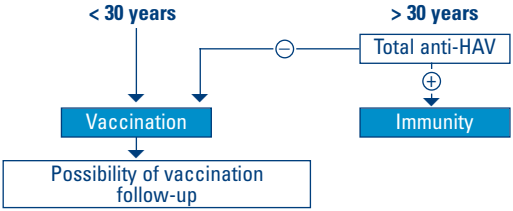


Transmission : Enteral (contaminated food and drink) [2].

At risk subjects [2]**:**

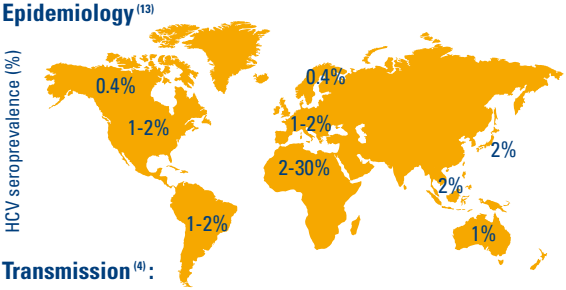
- travelers or army personnel in endemic zones
- healthcare and childcare personnel
- close family and friends of an infected subject
- children in institutional care
- catering personnel

Vaccination [1,2]**:** recommended for at-risk group



Hepatitis C [4]

Epidemiology [13]



Transmission [4]**:**

- parenteral ++++
- nosocomial

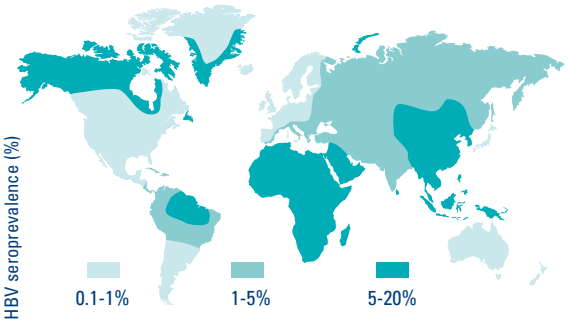
At risk subjects :

- Drug abusers
- Subjects exposed to nosocomial infection
- Healthcare personnel

Vaccination : None

Hepatitis B [1,3]

Epidemiology [10]



Transmission :

- Parenteral +++ and percutaneous +
- Sexual +++ and perinatal +++
- Direct contact between individuals

At risk subjects [2] :

- Drug abusers
- Hemodialysis patients
- Close family and friends of an infected subject
- Healthcare personnel
- Subjects with multiple partners
- Children born to mothers carrying HBV

Vaccination / at risk population :

	Vaccination strategy	Pre-vaccination serological profile *	Post-vaccination immunity test
Newborns and children	Recommended by the WHO (universal vaccination program) [12]	HBs Ag Anti-HBs Ab Total anti-HBc Ab	Not essential
Adults	Compulsory for certain at risk groups in some countries		YES for at risk subjects Anti-HBs Ab protective titer > 10 mIU/ml, 2 to 3 months after vaccination.**

* If HBs Ag (+) and/or total anti-HBc Ab (+), continue the profile.
If total anti-HBc Ab (+) and anti-HBs Ab (+), vaccination not necessary.

** At risk subjects : Recommend a booster injection for anti-HBs titers between 10 and 100 mIU/ml. [11]

- **Pregnancy not affected by the existence of chronic**
- **No pejorative progression of chronic hepatitis during**

Hepatitis A

- No specific risk or follow-up for pregnant women.

Hepatitis B

	Status of pregnant woman	Risk of contamination of newborn	Seroprophylaxis and vaccination
Hepatitis B **Test for HBs antigen in pregnant women** **(compulsory in some countries)**	Chronic carriage of HBs antigen	+++ at childbirth	**compulsory at birth :** injection of anti-HBs immunoglobulins associated with the first vaccine injection.

- Mother-child contaminations during childbirth (+++) and the post-natal period
- Mother infected during pregnancy or, most frequently, mother is a chronic HBV carrier
- Vaccination possible during pregnancy

Maternal status	Risk of transmission	Risk of progression of infection to chronic form in newborns
Mother infected during 1st trimester of pregnancy	Almost none	95%
Mother infected during 2nd trimester of pregnancy	6%	
Mother infected during 3rd trimester of pregnancy	67%	
Mother = chronic carrier of -HBV DNA	< 10%	
Mother = chronic carrier of +HBV DNA	90%	

T WOMEN (1-4)

hepatitis.
pregnancy.

Hepatitis C

	Status of pregnant woman	Risk of contamination of newborn	Vaccination
Hepatitis C **Test for anti-HCV antibodies not compulsory but recommended in the event of risk factors (transfusion or drug abuse)**	Presence of hepatitis C	Low (5 to 10% of cases) Increased in the event of HIV co-infection (20%) Breastfeeding recommended*	No vaccine available

* C virus is not passed into breast milk.

Hepatitis E

	Status of pregnant woman	Risk for newborn	Vaccination
Hepatitis E	Fulminant forms of hepatitis E during 3rd trimester	20% maternal-fetal mortality	Vaccine under development Travel to HEV endemic zones not recommended for pregnant women

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Internet sites to consult

http://www.hepfi.org
http://www.hepatitis-central.com/
http://www.cdc.gov/ncidod/diseases/hepatitis/
http://www.who.int/topics/hepatitis/en
http://www.hepnet.com

HEPATITIS Product Range

VIDAS® range

Hepatitis A parameters	Kits	Ref.
VIDAS HAV IgM	30 tests	30 307
VIDAS Anti-HAV Total	30 tests	30 312

Hepatitis B parameters	Kits	Ref.
VIDAS HBs Ag Ultra*	60 tests	30 315
VIDAS HBs Ag Ultra confirmation	30 tests	30 317
VIDAS Anti-HBs total Quick	60 tests	30 238
VIDAS Anti-HBc Total II	60 tests	30 314
VIDAS HBc IgM II	30 tests	30 439
VIDAS HBe/Anti-HBe	30 tests	30 305

VIDIA® range

Hepatitis B parameters	Kits	Ref.
VIDIA HBs Ag	100 tests	38 800
VIDIA HBs Ag confirmation	30 tests	38 802
VIDIA Anti-HBs Total	100 tests	38 801
VIDIA Anti-HBc Total	100 tests	38 803
VIDIA Anti-HBc IgM	50 tests	38 804

Microtiter plate range

Hepatitis B parameters	Kits	Ref.
HEPANOSTIKA® HBsAg Ultra	192 tests	28 4132
HEPANOSTIKA HBsAg Ultra	576 tests	28 4133
HEPANOSTIKA HBsAg Ultra Confirmatory	25 tests	28 0253
HEPANOSTIKA anti-HBc	192 tests	28 4144
HEPANOSTIKA anti-HBc	576 tests	28 4147

Immunochromatographic test range

Hepatitis B parameters	Kits	Ref.
VIKIA® HBs Ag*	25 kits	31 113

**This rapid test is only available in countries not applying IVD CE and FDA regulations.*

Your stamp

The information in this booklet is given as a guideline only and is not intended to be exhaustive. It in no way binds bioMérieux S.A. to the diagnosis established or the treatment prescribed by the physician."

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