REF 30318

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IVD

VIDAS® Anti-HBs Total II (AHBS)

VIDAS Anti-HBs Total II is an automated quantitative test for use on the VIDAS family of instruments, for the immunoenzymatic detection of antibodies to hepatitis B surface antigen (Anti-HBs) in human serum or plasma using the ELFA technique (Enzyme Linked Fluorescent Assay).

SUMMARY AND EXPLANATION

The hepatitis B virus (HBV) is responsible for acute and chronic hepatitis infections, possibly evolving to cirrhosis or primary liver cancer. Chronicity occurs in 5 to 10% of cases in adults, but up to 90% of cases in infants following perinatal transmission. Currently, more than 360 million people worldwide are chronic carriers of the virus (1). The hepatitis B virus can be transmitted by parenteral and perinatal pathways or through sexual contact. People most at risk are health workers, drug addicts, those with multiple sexual partners, multiple transfusion or hemodialysis patients, as well as close friends and family of an infected subject, and newborns of an infected mother (2).

HBs antigen (HBsAg) appears several days to several weeks after contact with the virus and can persist for several months: in this case, the infection is considered to be “chronic”. Disappearance of the HBs antigen is normally followed by the appearance of Anti-HBs, which is a sign of recovery. In this case, the presence of Anti-HBs is associated with that of Anti-HBc.

The detection of Anti-HBs is thus performed to monitor infected patients, but also to check the efficacy of immunization against the hepatitis B virus (vaccination by HBsAg).

Strategies of vaccination against HBV depend on the epidemiological situation. It is strongly recommended for subjects at risk. In vaccinated individuals, only the Anti-HBs are positive. The persistence of Anti-HBs is related to the initial titer obtained after the complete vaccination series has been administered.

The “European Consensus Group” recommends performing Anti-HBs determination 1 to 3 months following vaccination (3). It is only possible to affirm that the immunological memory will confer long-term protection to immunocompetent adults if titers are greater than 100 mIU/mL (3, 4).

Nevertheless, numerous countries have adopted 10 mIU/mL as the lowest titer indicating protective immunity against HBV infection (4).

For the detection of Anti-HBs, there is no reference measurement method that can guarantee immunity to HBV, particularly for low titers. The nature of the Ag used in the vaccine and in Anti-HBs detection tests, may cause the results obtained to vary (5).

USE

- monitoring of patients infected with the hepatitis B virus, treated patients, and patients on the road to recovery,
- monitoring of pre- and/or post-vaccine immunity status of patients.

PRINCIPLE

The assay principle combines an enzyme immunoassay sandwich method with a final fluorescent detection (ELFA).

The Solid Phase Receptacle (SPR®), serves as the solid phase as well as the pipetting device for the assay. Reagents for the assay are ready-to-use and are pre-dispensed in the sealed reagent strips.

The five reaction steps are performed automatically by the instrument. The reaction medium is cycled in and out of the SPR several times. Each step is followed by a wash cycle which eliminates unbound components:

- Specific binding of antibody in the sample to the ad and ay HBs surface antigen coated on the interior of the SPR.
- Formation of an antibody/antigen complex bound to the SPR with the biotinylated antigens in the diluent (HBs sub-types ad and ay).
- Wash cycle.
- Binding of the biotin to the anti-biotin-alkaline phosphatase conjugate.
- Wash cycle.
- Detection: alkaline phosphatase catalyzes the hydrolysis of the substrate (4-Methyl-umbelliferyl phosphate) into a fluorescent product (4-Methyl-umbelliferone) the fluorescence of which is measured at 450 nm.

The intensity of the fluorescence is proportional to the quantity of Anti-HBs in the sample. At the end of the assay, results are automatically calculated by the instrument in relation to the calibration curve stored in memory, and then printed out.

CONTENT OF THE KIT (60 TESTS):

60 AHBS Strips	STR	Ready-to-use.
60 AHBS SPRs 2 x 30	SPR	Ready-to-use. Interior of SPRs coated with recombinant hepatitis B surface antigen, subtypes ad and ay.
AHBS Positive control 1 x 2.4 mL (liquid)	C1	Ready-to-use. Human serum* containing Anti-HBs +preservatives. MLE data indicate the confidence interval in mIU/mL ("Control C1 (+) Dose Value Range").
AHBS Negative control 1 x 5.8 mL (liquid)	C2	Ready-to-use. Human serum* without Anti-HBs + preservatives. MLE data indicate the confidence interval in mIU/mL ("Control C2 (-) Dose Value Range").
Calibrator 2 x 2.4 mL (liquid)	S1	Human serum* containing Anti-HBs + preservatives.
Specifications for the factory master data required to calibrate the test: • MLE data (Master Lot Entry) provided in the kit, or • MLE bar code printed on the box label.		
1 Package insert provided in the kit or downloadable from www.biomerieux.com/techlib.		

* This product has been tested and shown to be negative for HBs surface antigen and antibodies to HIV1, HIV2 and HCV. However, since no existing test method can totally guarantee their absence, this product must be treated as potentially infectious. Therefore, usual safety procedures should be observed when handling.

The SPR®

The interior of the SPR is coated during production with recombinant hepatitis B surface antigen subtypes ad and ay (6). Each SPR is identified by the code "AHBS". Only remove the required number of SPRs from the pouch and **carefully reseal the pouch after opening**.

The strip

The strip consists of 10 wells covered with a labeled, foil seal. The label comprises a bar code which mainly indicates the assay code, kit lot number and expiration date. The foil of the first well is perforated to facilitate the introduction of the sample. The last well of each strip is a cuvette in which the fluorometric reading is performed. The wells in the center section of the strip contain the various reagents required for the assay.

Description of the AHBS strip:

Wells	Reagents.
1	Sample well.
2	Sample diluent: calf serum + Tetraborate (pH 7.8) + biotin-labeled ad and ay surface antigen + fetal calf serum + preservatives (300 µL).
3 - 4 - 6 - 7 - 8 - 9	Wash solution: buffer pH 7.8 + Tween 20 + preservatives (600 µL).
5	Detection conjugate: Tris buffer + alkaline phosphatase-labeled anti-biotin antibody + preservatives (400 µL).
10	Reading cuvette with substrate: 4-Methyl-umbelliferyl phosphate (0.6 mmol/L) + diethanolamine (DEA*) (0.62 mol/L or 6.6%, pH 9.2) + 1 g/L sodium azide (300 µL).

* Signal Word: **DANGER**

Hazard statement

H318: Causes serious eye damage.

Precautionary statement

P280: Wear protective gloves/protective clothing/eye protection/face protection.
P305 + P351 + P338: IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing.

For further information, refer to the Material Safety Data Sheet.

MATERIALS AND DISPOSABLES REQUIRED BUT NOT PROVIDED

- Pipette with disposable tip to dispense **200 µL**.
- Powderless, disposable gloves.
- For other specific materials and disposables, please refer to the Instrument User Manual.
- Instrument of the VIDAS family.

WARNINGS AND PRECAUTIONS

- **For *in vitro* diagnostic use only.**
- **For professional use only.**
- **This kit contains products of human origin. No known analysis method can totally guarantee the absence of transmissible pathogenic agents. It is therefore recommended that these products be treated as potentially infectious and handled observing the usual safety precautions (see Laboratory Biosafety Manual - WHO - Geneva - latest edition).**
- This kit contains products of animal origin. Certified knowledge of the origin and/or sanitary state of the animals does not totally guarantee the absence of transmissible pathogenic agents. It is therefore recommended that these products be treated as potentially infectious and handled observing the usual safety precautions (do not ingest or inhale).
- Do not use the SPR®s if the pouch is pierced.
- Do not use visibly deteriorated STRs (damaged foil or plastic).
- Do not use reagents after the expiration date indicated on the label.
- Do not mix reagents (or disposables) from different lots.
- Use **powderless** gloves, as powder has been reported to cause false results for certain enzyme immunoassay tests.
- The substrate in well 10 contains an irritant agent (6.6% diethanolamine). Refer to the hazard statements "H" and the precautionary statements "P" above.
- Spills should be wiped up thoroughly after treatment with liquid detergent or a solution of household bleach containing at least 0.5% sodium hypochlorite. See the User Manual for cleaning spills on or in the instrument. Do not autoclave solutions containing bleach.
- The instrument should be regularly cleaned and decontaminated (see the User Manual).

STORAGE CONDITIONS

- Store the VIDAS Anti-HBs Total II kit at 2-8°C.
- **Do not freeze reagents.**
- **Store all unused reagents at 2-8°C.**
- After opening the kit, check that the SPR pouch is correctly sealed and undamaged. If not, do not use the SPRs.
- **Carefully reseal the pouch with the desiccant inside after use to maintain stability of the SPRs and return the complete kit to 2-8°C.**
- If stored according to the recommended conditions, all components are stable until the expiration date indicated on the label. Refer to the kit composition table for special storage conditions.

SPECIMENS

Specimen type and collection:

Human serum or plasma**.**
Frozen-stored samples: after thawing, these samples must be homogenized before analysis. Mix using a vortex-type mixer. If necessary, clarify the samples by centrifugation before analysis.

Types of tubes validated:
- Silicone coated tube
- PET tube with clot activator
- PET tube with separator gel
- Tube with lithium heparin
- Tube with sodium heparin
- Tube with lithium heparin and separator gel

Follow the tube manufacturer's recommendations for use.

Note: Blood sampling tube results may vary from one manufacturer to another depending on the materials and additives used.
It is the responsibility of each laboratory to validate the type of sample tube used and to follow the manufacturer's recommendations for use.

Sample-related interference

None of the following factors have been found to significantly influence this assay:
- albumin up to 60 g/L
- rheumatoid factor up to 800 IU/mL
- hemolysis, after spiking samples with purified hemoglobin up to 300 µmol/L or 500 mg/dL (monomer),
- lipemia (after spiking samples with lipids up to 30 g/L equivalent in triglycerides),
- bilirubinemia (after spiking samples with bilirubin up to 510 µmol/L or 30 mg/dL).

However, it is recommended not to use samples that are clearly hemolyzed or lipemic and, if possible, to collect a new sample.
Do not inactivate samples.

Specimen stability

The stability of samples separated from the clot has been validated using samples in stoppered tubes:
- at 18-25°C for 8 hours
- at 2-8°C for 5 days.

If longer storage is required, freeze the sera at -25 ± 6°C.
Three freeze/thaw cycles have been validated over a period of six months.
These studies did not reveal any impact on the quality of results.

INSTRUCTIONS FOR USE

For complete instructions, see the User Manual.

Reading VIDAS® Protocole Test Change (PTC) protocol data and MLE data

When using the assay for the first time:

With the external instrument barcode reader,

1. Scan the PTC barcode(s) at the end of the package insert. or downloadable from www.biomerieux.com/techlib. This reading allows VIDAS® PTC protocol data to be transferred to the instrument software for its update.
2. Scan the MLE data on the box label.

Note: If the MLE data have been read before the VIDAS® PTC protocol, read the MLE data again.

When opening a new lot of reagents:

Enter the specifications (or factory master data) into the instrument using the master lot entry (MLE) data.

If this operation is not performed before initiating the tests, the instrument will not be able to print results.

Note: the master lot data need only be entered once for each lot.

It is possible to enter MLE data **manually or automatically** depending on the instrument (refer to the User Manual).

Calibration

Calibration, using the calibrator provided in the kit, must be performed each time a new lot of reagents is opened, after the master lot data have been entered, and then every 28 days. This operation provides instrument-specific calibration curves and compensates for possible minor variations in assay signal throughout the shelf-life of the kit.

The calibrator, identified by S1, must be tested in duplicate. The calibration values must be within the set RFV ("Relative Fluorescence Value"). If this is not the case, recalibrate.

Procedure

1. **Remove the required reagents from the refrigerator. They can be used immediately.**
2. Use one "AHBS" strip and one "AHBS" SPR for each sample, control or calibrator to be tested. **Make sure the storage pouch has been carefully resealed after the required SPRs have been removed.**
3. The test is identified by the "AHBS" code on the instrument. The calibrator must be identified by "S1" and tested **in duplicate**.The positive control is identified by “C1” and tested singly. The negative control is identified by “C2” and tested singly.
4. Mix the calibrator, controls, and samples using a vortex-type mixer (for serum or plasma separated from the pellet).
5. **For this test, the calibrator, control, and sample test portion is 200 µL.**
6. Insert the "AHBS" SPRs and "AHBS" strips into the instrument. Check to make sure the color labels with the assay code on the SPRs and the Reagent Strips match.
7. Initiate the assay as directed in the User Manual. All the assay steps are performed automatically by the instrument.
8. Reclose the vials and return them to the recommended temperature after pipetting.
9. The assay will be completed within approximately 60 minutes. After the assay is completed, remove the SPRs and strips from the instrument.
10. Dispose of the used SPRs and strips into an appropriate recipient.

RESULTS AND INTERPRETATION

Once the assay is completed, results are analyzed automatically by the computer. Fluorescence is measured twice in the Reagent Strip’s reading cuvette for each sample tested. The first reading is a background reading of the substrate cuvette before the SPR is introduced into the substrate. The second reading is taken after incubating the substrate with the enzyme remaining on the interior of the SPR. The RFV (Relative Fluorescence Value) is calculated by subtracting the background reading from the final result. This calculation appears on the result sheet.

The results are automatically calculated using calibration curves which are stored by the instrument (4-parameter logistics model) and are expressed in mIU/mL. The measuring range is 3-500 mIU/mL.

VIDAS Anti-HBs Total II is calibrated against the international standard (WHO Second International Standard 07/164 for anti-hepatitis B surface antigen (Anti-HBs) immunoglobulin).

Interpretation of results is as follows:

TITER (mIU/mL)	INTERPRETATION
Titer < 8	**Negative**
8 ≤ Titer < 12	**Equivocal**
Titer ≥ 12	**Positive**

All equivocal results must be confirmed using a second sample.

Interpretation of test results should be made taking into consideration the patient history, and the results of any other tests performed.

Specimen dilution

Only dilute specimens which, when first tested, gave a positive result > 500 mIU/mL with VIDAS Anti-HBs Total II.

The specimens should be diluted in the C2 negative control. In most cases, a 1:10 dilution (1 volume of sample + 9 volumes of negative control) enables a result to be obtained which is within the measurement range.

If the dilution factor has not been entered when the Work List was created (see User Manual), multiply the result by the dilution factor to obtain the sample concentration.

QUALITY CONTROL

One positive control and one negative control are included in each VIDAS Anti-HBs Total II kit.
These controls must be performed immediately after opening a new kit to ensure that reagent performance has not been altered. Each calibration must also be checked using these controls. The instrument will only be able to check the control values if they are identified by C1 and C2.
Results cannot be validated if the control values deviate from the expected values. All the samples tested since the last valid control will have to be retested.

Note

It is the responsibility of the user to perform Quality Control in accordance with any applicable local regulations.

LIMITATIONS OF THE METHOD

Recent studies have shown that the Anti-HBs measuring range following vaccination depends on both the vaccine and the test kit (5).
In HBV infected patients, the simultaneous presence of HBsAg and Anti-HBs can affect the detection of Anti-HBs.
Interference may be encountered with certain sera containing antibodies directed against reagent components. For this reason, assay results should be interpreted taking into consideration the patient's history and the results of any other tests performed.
In the context of vaccination, samples with concentrations <10 mIU/mL are considered to be non-reactive (negative) and samples with concentrations >10 mIU/mL are considered to be reactive (positive).
Nevertheless, since the VIDAS Anti-HBs Total II assay has an equivocal zone, it is recommended to refer to the results and interpretation section of this package insert.
Given the diversity of antibodies, the results obtained can differ depending on the assay used. If assays from different manufacturers are used with the same sample, the results can vary as much as four-fold (in rare cases as much as ten-fold). If the test system is changed during vaccination follow-up, the Anti-HBs level must be determined in parallel on the two systems during the transitional period (7).

PREVALENCE

The prevalence (8) of Anti-HBs varies depending on the endemic disease and vaccination policies.

Region of the world	Anti-HBs (%)
Northern, eastern, and central Europe, North America, Australia.	4 - 6
Eastern Europe, Mediterranean basin, Russia, Southwest Asia, South America.	20 - 55
Southeast Asia, tropical Africa.	70 - 95

Vaccination produces anamnestic responses in approximately 90% of vaccinated individuals, if they are healthy adults less than 40 years of age. The factors associated with a waning antibody response are age, smoking, obesity, HIV infection or chronic disease (9).

The following table indicates the seroconversion rates which may be observed according to age (10).

Neonates	> 95%
2-19 years	~ 99%
20-29 years	~ 95%
30-39 years	~ 90%
40-49 years	~ 85%
50-59 years	~ 70%
>59 years	~ 50%
Renal failure, HIV infection, other immunosuppression	50-70%
Liver disease	60-70%

PERFORMANCE

Diagnostic Sensitivity and Specificity

The VIDAS Anti-HBs Total II assay performance was established using characterized samples. The status of samples was defined by the agreement of results obtained using three commercially available EIAs (CE marked).
The samples with indeterminate status (discordant results between the three systems) were excluded from the analysis (82 samples or 3.7% of the samples tested).
A total of 2110 samples were tested and analyzed at two laboratories: 641 blood donor samples and 1469 clinical samples. Among these samples, 1041 had a positive status (including 116 samples from naturally infected patients and 925 from patients vaccinated against hepatitis B) and 1069 had a negative status.
The following results were obtained:

VIDAS Anti-HBs Total II results	**Sample Status**		
	Positive	**Negative**	**Total**
Positive	1019	11	1030
Negative	10	1043	1053
Total	1029	1054	2083*

* Equivocal results obtained with VIDAS Anti-HBs Total II excluded from the analysis (34 samples or 1.6% of the samples tested).

The diagnostic specificity of VIDAS Anti-HBs Total II for this population is: **99.0%** (95% confidence interval: [98.1 – 99.5]%).

The diagnostic sensitivity of VIDAS Anti-HBs Total II for this population is: **99.0%** (95% confidence interval: [98.2 – 99.5]%).

Sensitivity for seroconversion panels

During a study, twelve commercial seroconversion panels were detected by the device and the results were comparable to those claimed by the manufacturers. They consisted of 11 follow up panels and 1 seroconversion panel.

Limits of detection and quantitation

The Limit of Detection (LoD), corresponding to the concentration of Anti-HBs in a sample likely to be distinguished from the blank sample with a 95% probability, is equal to 1.03 mIU/mL. The Limit of Quantitation (LoQ), corresponding to the lowest concentration of anti-HBs that can be quantified with an acceptable level of precision and accuracy, is equal to 2.58 mIU/mL. The study was performed as recommended in the CLSI® EP17-A document.

Linearity

The VIDAS Anti-HBs total II assay is linear over the claimed measurement range, according to the study performed following the recommendations of the CLSI® EP6-A document.

Hook effect

No hook effect was observed up to Anti-HBs concentrations of 75000 mIU/mL.

Precision

The repeatability and reproducibility of the VIDAS Anti-HBs Total II assay were evaluated according to the recommendations of the CLSI® EP5-A2 document. Four human samples were tested in duplicate using two lots of reagents (N = 240). Testing was performed twice a day for 10 days on 3 instruments. Two calibrations were used for each lot (5 test days per calibration and per lot). The combined results of this study are summarized in the following table:

Sample	Mean measured value (mIU/mL)	Repeatability		Between-lot; Between-system Reproductiblity	
		Standard deviation	CV (%)	Standard deviation	CV (%)
Sample 1	5.72	0.21	3.7	0.46	8.0
Sample 2	16.82	0.55	3.3	1.37	8.1
Sample 3	241.00	10.03	4.2	16.65	6.9
Sample 4	324.80	12.88	4.0	20.95	6.5

Cross-reactivity

Cross-reactivity is based on the study of samples that are negative with the assay being evaluated and positive for the potentially interfering physiological state. The results of the potentially interfering samples tested are shown in the table below:

	Number of patients	VIDAS Anti-HBsT II positive results % cross-reactivity
Anti-nuclear antibodies	20	0 (0%)
Anti Pichia	11	0 (0%)
CMV IgG	10	0 (0%)
EBV IgG	13	0 (0%)
FR	16	0 (0%)
HAMA	10	0 (0%)
HAV T	12	0 (0%)
HBc T	16	0 (0%)
HCV	21	0 (0%)
HEV	3	0 (0%)
HIV	15	0 (0%)
HSV IgG	15	0 (0%)
Rub IgG	15	0 (0%)
Syphilis IgG	11	0 (0%)
Toxoplasma IgG	12	0 (0%)
Multiparous pregnant women	10	0 (0%)
Non-viral liver disease	3	0 (0%)

WASTE DISPOSAL

Dispose of used or unused reagents as well as any other contaminated disposable materials following procedures for infectious or potentially infectious products.
It is the responsibility of each laboratory to handle waste and effluents produced according to their nature and degree of hazardousness and to treat and dispose of them (or have them treated and disposed of) in accordance with any applicable regulations.

LITERATURE REFERENCES

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INDEX OF SYMBOLS

Symbol	Meaning
REF	Catalog number
IVD	*In Vitro* Diagnostic Medical Device
	Manufacturer
	Temperature limit
	Use by date
LOT	Batch code
	Consult Instructions for Use
	Contains sufficient for <n> tests
	Date of manufacture

WARRANTY

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REVISION HISTORY

Change type categories:

N/A	Not applicable (First publication)
Correction	Correction of documentation anomalies
Technical change	Addition, revision and/or removal of information related to the product
Administrative	Implementation of non-technical changes noticeable to the user

Note: *Minor typographical, grammar, and formatting changes are not included in the revision history.*

Release date	Part Number	Change Type	Change Summary
2015/01	9304018E	Administrative	INDEX OF SYMBOLS REVISION HISTORY
		Technical	CONTENT OF THE KIT (60 TESTS) WARNINGS AND PRECAUTIONS
2015/09	9304018F	Technical	CONTENT OF THE KIT (60 TESTS) INSTRUCTIONS FOR USE
2016/10	9304018G	Technical	PERFORMANCE

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