BIOMÉRIEUX

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VIDAS® HAV IgM (HAVM)

IVD

INTENDED USE

VIDAS® HAV IgM is an automated qualitative test for use on the VIDAS® family instruments for the detection of IgM directed against the hepatitis A virus (HAV) after immunocapture, in human serum or plasma (heparin or EDTA), using the ELFA technique (Enzyme Linked Fluorescent Assay).

The detection of IgM antibodies directed against the hepatitis A virus (HAV) with VIDAS® HAV IgM test is an aid in diagnosis of acute hepatitis A infection in patients with symptoms and/or clinical signs of hepatitis A.

SUMMARY AND EXPLANATION

Hepatitis A is a frequent vaccine-preventable acute inflammatory disease of the liver caused by hepatitis A virus (HAV).[1] Hepatitis A can lead to acute liver failure (fulminant hepatitis) but not to chronic infection.

Laboratory diagnosis of hepatitis A is made by detection of anti-HAV IgM in a single acute-phase serum sample, which is the recommended test in routine diagnosis of HAV infection.[1,2] IgM can be detected as soon as the first symptoms appear, and generally persist for 2 to 4 months.

PRINCIPLE

The assay principle combines a two-step enzyme immunoassay after immunocapture, with a final fluorescent detection (ELFA).

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

All of the assay steps are performed automatically by the instrument. The reaction medium is cycled in and out of the SPR device several times.

After diluting the sample, the serum IgM bind with the anti µ chain polyclonal antibodies coating the interior of the SPR device.

Unbound components are eliminated during washing steps.

The anti-HAV IgM are specifically detected by an immune complex, formed of inactivated viral antigen and an alkaline phosphatase-labeled anti-HAV monoclonal antibody.

The unbound immune complex is removed during washing steps.

During the final detection step, the substrate (4-Methylumbelliferyl phosphate) is cycled in and out of the SPR device. The conjugate enzyme catalyzes the hydrolysis of this substrate 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 concentration of antigen in the sample.

At the end of the assay, the results are automatically calculated by the instrument according to the calibration curve stored in memory. The results can then be printed out.

CONTENT OF THE KIT (30 TESTS) - RECONSTITUTION OF REAGENTS

30 HAVM Strips[(a)]	STR	Ready-to-use.
30 HAVM Solid Phase Receptacles 1 x 30	SPR	Ready-to-use. Interior of SPR devices coated with anti-human µ chain polyclonal antibodies (goat).
HAVM Standard 1 x 1.2 mL (liquid)	S1	Ready-to-use. Human* serum with anti-HAV IgM + protein stabilizer + 1 g/L sodium azide.
HAVM Positive Control 1 x 1 mL (liquid)	C1	Ready-to-use. Human* serum with anti-HAV IgM + protein stabilizer + 1 g/L sodium azide. MLE data indicate the index: confidence interval ("Control C1 (+) Test Value Range).
Negative control[(b)] 1 x 1.9 mL (liquid)	C2	Ready-to-use. Phosphate buffer + protein stabilizer of animal origin+ preservatives.

Specifications for the factory master data required to calibrate the assay: MLE (Master Lot Entry) barcode printed on the box label.
1 package insert downloadable from www.biomerieux.com/techlib

* This product has been tested and shown to be negative for HBs antigen, 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.

(a) **DANGER** H318 / P280 / P305 + P351 + P338

(b) **WARNING** EUH208 / H317 / P261 / P280 / P302 + P352

Hazard statements

- H317: May cause an allergic skin reaction.
- EUH208: Contains 2-methyl-2H-isothiazolin-3-one. May produce an allergic reaction.
- H318: Causes serious eye damage.

Precautionary statements

- 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.
- P261: Avoid breathing dust/fume/gas/mist/vapours/spray.
- P302 + P352: IF ON SKIN: Wash with plenty of soap and water.

For further information, consult the Safety Data Sheet.

The SPR device

The SPR device is coated during production with anti-human µ chain polyclonal antibody purified by affinity chromatography. Each SPR device is identified by the HAVM code.

Only remove the required number of SPR devices from the pouch and carefully reseal the pouch after opening.

The Reagent Strip

The strip consists of 10 wells covered with a labeled foil seal. The label comprises a barcode 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 HAVM strip

The strip contains diethanolamine and sodium azide. Refer to the hazard statements “H” and precautionary statements “P” indicated above.(a)

Well	Reagents
1	Sample well.
2	Sample diluent: TRIS buffer (0.05 mol/L) pH 7.4 + Tween + protein and chemical stabilizers + 1 g/L sodium azide (400 µL).
3 - 4 - 5 - 8 - 9	Washing buffer: TRIS buffer (0.05 mol/L) pH 7.4 + protein and chemical stabilizers + 1 g/L sodium azide (600 µL).
6	Inactivated hepatitis A antigen + protein and chemical stabilizers + 1 g/L sodium azide (300 µL).
7	Anti-hepatitis A monoclonal antibody (mouse) conjugated with alkaline phosphatase + 1 g/L sodium azide (300 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).

MATERIALS AND DISPOSABLES REQUIRED BUT NOT PROVIDED

- Pipette with disposable tip to dispense 100 µL.
- Powderless disposable gloves.
- For other specific materials and disposables, please refer to the Instrument User Manual.
- Instruments of the VIDAS® family.

WARNINGS AND PRECAUTIONS

- **For *in vitro* diagnostic use only.**
- **For professional use only, by qualified laboratory personnel in clinical laboratories.**
- **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; do not inhale).
- Do not use the SPR devices if the pouch is pierced or if the dot sealing a SPR device has come unstuck.
- Do not use visibly deteriorated strips (damaged foil or plastic).
- Do not use reagents after the expiration date indicated on the box 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.
- Kit reagents contain sodium azide which can react with lead or copper plumbing to form explosive metal azides. If any liquid containing sodium azide is disposed of in the plumbing system, drains should be flushed with water to avoid build-up.
- Refer to the hazard statements “H” and precautionary statements “P” indicated 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 (refer to the User Manual for user and preventive maintenance operations).

STORAGE CONDITIONS

- Store the kit at +2°C/+8°C.
- **Do not freeze reagents.**
- **Store all unused reagents at +2°C/+8°C.**
- After opening the kit, check that the SPR pouch is correctly sealed and undamaged. If not, do not use the SPR devices.
- **After use, carefully reseal the pouch with the desiccant inside to maintain stability of the SPR devices, and return the complete kit to +2°C/+8°C.**
- If stored according to the recommended conditions, all components are stable until the expiration date indicated on the box label.

SAMPLES

Specimen type and collection

Serum or plasma (lithium heparinate or EDTA).

It is recommended that each laboratory checks the compatibility of collection tubes used.

None of the following factors have been found to significantly influence this assay:

- hemolysis (after spiking samples with hemoglobin: 0 to 270 µmol/L (monomer)),
- lipemia (after spiking samples with lipids: 0 to 2 mg/mL equivalent in trigycerides),
- bilirubinemia (after spiking samples (naturally icteric plasma) with bilirubin: 0 to 500 µmol/L).

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.

Sample stability

Samples can be stored at +2°C/+8°C in stoppered tubes for up to 7 days. If longer storage is required, freeze the serum or plasma at -31°C/-19°C.

Freeze once only.

A study performed on samples frozen for 12 months, showed that the quality of results is not affected.

INSTRUCTIONS FOR USE

For complete instructions, see the Instrument User Manual.

Reading MLE data

When opening a new lot of reagents

With the external instrument barcode reader, scan the MLE data on the box label before performing the test.

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 standard provided in the kit, must be performed each time a new lot of reagents is opened, after the MLE data have been entered, and then every 14 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 standard, identified by S1, must be tested in duplicate.

The standard value must be within the set RFV (Relative Fluorescence Value) range indicated in the MLE data. If this is not the case, recalibrate.

Procedure

1. **Only remove the required reagents from the refrigerator and allow them to come to room temperature for at least 30 minutes.**
2. Use one "HAVM" strip and one "HAVM" SPR device for each sample, control or standard to be tested. **Make sure the SPR pouch has been carefully resealed after the required SPR devices have been removed.**
3. The test is identified by the "HAVM" code on the instrument. The standard, identified by S1, must be tested in duplicate. If the positive control is to be tested, it should be identified by "C1". If the negative control needs to be tested, it should be identified by "C2".
4. If necessary, clarify samples by centrifugation.
5. Mix the standard, controls and samples using a vortex-type mixer (for serum or plasma separated from the pellet).
6. **For this test, the standard, control and sample test portion is 100 µL.**
7. Insert the "HAVM" SPR devices and "HAVM" strips into the instrument. Check to make sure the color labels with the assay code on the SPR devices and the Reagent Strips match.
8. Initiate the assay as directed in the User Manual. All the assay steps are performed automatically by the instrument.
9. Close the vials and return them to +2°C/+8°C after pipetting.
10. The assay will be completed within **approximately 60 minutes**. After the assay is completed, remove the SPR devices and strips from the instrument.
11. Dispose of the used SPR devices 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 device is introduced into the substrate.

The second reading is taken after incubating the substrate with the enzyme bound to the interior of the SPR device.

The RFV (Relative Fluorescence Value) is calculated by subtracting the background reading from the final result. This calculation appears on the result sheet.

The patient RFV is interpreted by the VIDAS® system as follows:

i = Test value = patient RFV / standard RFV

The test value and interpretation are also indicated on the result sheet.

Interpretation of results according to test value is as follows:

Test Value	Interpretation
i < 0.4	Negative
i ≥ 0.4 and i < 0.5	Equivocal**
i ≥ 0.5	Positive

** It is advisable to control equivocal results by performing a new test using a second sample.

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

QUALITY CONTROL

One positive control and one negative control are included in each 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.

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

LIMITATIONS OF THE METHOD

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 clinical history and the results of any other tests performed.

PERFORMANCE

Studies performed using the VIDAS® HAV IgM assay gave the following results:

Precision

Within-run reproducibility

3 samples were tested 15 times in a same run.

	Number	Mean RFV	CV (%)
Negative	15	74.5	4.05
Weak positive	15	994	1.79
Strong positive	15	2,627	1.8

Between-run reproducibility

3 samples were tested in triplicate in 3 different runs on 3 sites.

	Number	Mean RFV	CV (%)
Negative	27	0.05	7.63
Weak positive	27	1.01	2.07
Strong positive	27	3.45	2.4

Negative Percent Agreement (NPA)

Out of the 544 blood donors who were found to be negative with another EIA technique; 538 were found to be negative and 3 were found to be positive with VIDAS® HAV IgM, giving **a Negative Percent Agreement of 99.45%***.

(95% Confidence Interval [98.39 ; 99.89]%)

* Equivocal results were not included in the specificity calculation.

Study of clinical trials

The Postive Percent Agreement (PPA) was tested on sera corresponding to samples from patients with clinically and biologically documented hepatitis A or from patients at risk with anti-HAV IgM, detectable using another EIA technique.

1. Acute hepatitis A or positive anti-HAV IgM antibody in patients presenting either an increase in transaminase levels or a risk factor (travel, contact with infection):
Of the 205 sera tested:

- 201 were found to be positive with both VIDAS® HAV IgM and the comparative EIA technique
- 4 were found to be equivocal

The PPA is therefore 100.00%* (95% CI: [98.18 ; 100.00]%).

* Equivocal results were not included in PPA calculation.

2. Monitoring of 8 clinically and biologically documented cases of acute hepatitis A:
Of the 55 sera tested:

- 23 were found to be negative with VIDAS® HAV IgM. Discrepancies were found for six sera with the EIA technique which found them positive
- 30 were found to be positive with both VIDAS® HAV IgM and the comparative EIA technique
- 2 were equivocal

The PPA is therefore 83.33%* (95% CI: [68.11 ; 92.13]%).

* Equivocal results were not included in PPA calculation.

The 6 discrepant sera were from two patients who were being monitored for hepatitis A. They probably correspond to residual IgM which were later detected using the comparatvie EIA technique.

CROSS REACTIVITY AND RELEVANT INTERFERENTS

Tested sera	Number of positives/total
Anti-HBc + IgM	0 / 14
Anti-CMV + IgM	0 / 28
Anti-VCA + IgM	1 / 19 *
Automimmune hepatitis +	0 / 10
Cryoglobulinemia +	0 / 22
Rhumatoid factor +	0 / 20
Heterophilic + antibody	0 / 10
Anti-nuclear + antibody	0 / 6
Anti HCV + antibody	0 / 3

* The serum that was found to be positive with VIDAS® HAV IgM was confirmed to be positive with the other EIA technique, used as reference.

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

1. Miller JM, Binnicker MJ, Campbell S, *et al.* A Guide to Utilization of the Microbiology Laboratory for Diagnosis of Infectious Diseases: 2018 Update by the Infectious Diseases Society of America and the American Society for Microbiology. *Clin Infect Dis*. 2018 Aug 31; 67(6): e1-e94.

2. Workowski KA, Bolan GA. Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2015. *MMWR Recomm Rep*. 2015 Jun 5; 64(RR-03):1-137.

INDEX OF SYMBOLS

Symbol	Meaning
REF	Catalogue number
IVD	*In Vitro* Diagnostic Medical Device
	Manufacturer
	Temperature limit
	Use by date

Symbol	Meaning
LOT	Batch code
	Consult Instructions for Use
	Contains sufficient for <n> tests
	Date of manufacture

LIMITED WARRANTY

bioMérieux warrants the performance of the product for its stated intended use provided that all procedures for usage, storage and handling, shelf life (when applicable), and precautions are strictly followed as detailed in the instructions for use (IFU).

Except as expressly set forth above, bioMérieux hereby disclaims all warranties, including any implied warranties of merchantability and fitness for a particular purpose or use, and disclaims all liability, whether direct, indirect or consequential, for any use of the reagent, software, instrument and disposables (the "System") other than as set forth in the IFU.

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
2016/05	07206R	Technical change	Content of the Kit (30 tests) - Reconstitution of reagents
2019-10	054828-01	Administrative	Limited Warranty
		Technical change	Content of the Kit (30 tests) - Reconstitution of reagents Warnings and Precautions
2020-11	054828-02	Administrative	Formatting and wording changes.
		Technical change	Summary and Explanation Warnings and Precautions Literature References

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