IVD

VIDAS® Anti-TPO (ATPO)

The VIDAS Anti-TPO assay is an automated quantitative test for use on the instruments of the VIDAS family for the detection of the IgG class of thyroid peroxidase autoantibodies (anti-TPO) in human serum or plasma using the Enzyme Linked Fluorescent Assay (ELFA) technique. The VIDAS Anti-TPO assay is intended as an aid in the diagnosis of autoimmune thyroid disease.

SUMMARY AND EXPLANATION

Disorders of the thyroid gland are frequently caused by autoimmune reactions, resulting in the production of autoantibodies.

Thyroid peroxidase (TPO) is a membrane-bound glycoprotein enzyme with an approximate mass of 107 kDa, which is comprised of a large extracellular domain, a transmembrane domain and a short intracellular domain. The TPO, located at the apical membrane of the thyroid follicular cell, catalyzes the iodination of tyrosine residues on thyroglobulin, during the biosynthesis of T3 and T4 (1).

Elevated serum concentrations of anti-TPO antibodies are found in subjects with autoimmunity-based thyroiditis. High anti-TPO titers are found in up to 90% of patients with chronic Hashimoto's thyroiditis (2, 3). In Graves' (Basedow's) disease, 70% of the patients have an elevated titer (4, 3).

Although the sensitivity of the method can be increased by simultaneously determining additional thyroid antibodies (anti-Tg: anti-thyroglobulin antibody), a negative test result does not definitively rule out the presence of an autoimmune disease.

The level of the antibody titer does not correlate with the clinical activity of the disease. Initially elevated titers may return to normal after lengthy periods of illness or during remission. If antibodies reappear following remission, then a relapse is probable (1 – 8).

The detection of anti-TPO is an aid in the diagnosis of autoimmune thyroid diseases. It enables the physician to differentiate thyroid autoimmune disorders from non-autoimmune goiter or hypothyroidism.

Anti-TPO antibodies are detectable in most cases of postpartum thyroiditis and it has been found that the presence of autoantibody in early pregnancy was associated with a high risk of asymptomatic postpartum hypothyroidism (9 - 11).

Anti-TPO antibodies are frequently found in patients with other autoimmune diseases such as Rheumatoid Arthritis, Addison's Disease and Type I Diabetes (12 - 13).

They are also detectable at low levels in up to 20% of asymptomatic individuals, particularly the elderly, and more often in women than in men, although the clinical significance of these autoantibodies is not totally explained (14 - 15).

PRINCIPLE

The assay principle combines a two-step 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. Reagents for the assay are ready-to-use and pre-dispensed in the sealed reagent strips.

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

After preliminary wash and sample dilution steps, the anti-TPO antibodies present in the sample will bind to the recombinant protein coating the interior of the SPR®.

Unbound components are eliminated during a washing cycle. Anti-human IgG antibodies conjugated with alkaline phosphatase, will attach to the immune complex coating the interior of the SPR.

A final wash step eliminates the excess conjugate.

During the final detection step, the substrate (4-Methyl-umbelliferyl phosphate) is cycled in and out of the SPR. 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 anti-TPO antibodies present 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 (30 TESTS):

30 ATPO Strips	STR	Ready-to-use.
30 ATPO SPRs 1 x 30	SPR®	Ready-to-use. Interior of SPRs coated with recombinant TPO.
ATPO Positive Control 1 x 2.5 mL	C1	Ready-to-use. Monoclonal anti-TPO IgG in phosphate buffer pH 7.2 + protein stabilizer + preservatives. MLE data indicate the confidence interval in IU/mL ("Control C1 (+) Dose Value Range").
ATPO Calibrator 1 x 2.5 mL	S1	Ready-to-use. Monoclonal anti-TPO IgG in phosphate buffer pH 7.2 + protein stabilizer + preservatives. MLE data indicate the concentration in IU/mL ("Calibrator (S1) Dose Value") and the confidence interval in "Relative Fluorescence Value" ("Calibrator (S1) RFV Range").
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.		

The SPR

The interior of the SPR® is coated during production by adsorption of recombinant TPO. Each SPR is identified by the "ATPO" code. Only remove the required number of SPRs 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 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 ATPO strips

Wells	Reagents
1	Sample Well.
2	Sample diluent: Phosphate buffer + NaCl pH 7.2 + protein stablizer + preservative (600 µL).
3 - 4 - 5	Wash buffer: TRIS buffer + NaCl + Tween pH 7.8 + preservative (600 µL).
6	Conjugate: phosphate buffer + NaCl pH 6.1 + neutralizers + protein and chemical stabilizers + preservative + anti-human IgG antibodies conjugated with alkaline phosphatase (400 µL).
7 - 8	Wash buffer: TRIS buffer + NaCl + Tween pH 7.8 + preservative (600 µL).
9	Empty well.
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 100 µL.
- Powderless, disposable gloves.
- For other specific materials and disposables, please refer to the Instrument User's Manual.
- VIDAS family instrument.

WARNINGS AND PRECAUTIONS

- **For *in vitro* diagnostic use only.**
- **For professional use only.**
- 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 SPRs 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.
- 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.
- The reading cuvette with substrate (well 10) contains an irritant agent (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's 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's Manual).

STORAGE CONDITIONS

- Store the VIDAS Anti-TPO 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.

SPECIMENS

Specimen type and collection:

Human serum or plasma

Types of tubes validated:
– Plain tube,
– Tube with lithium heparin,
– Tube with lithium heparin and separation gel,
– Plastic tube with clot activator,
– Plastic tube with clot activator and separation gel,
– EDTA tube.

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.

Specimen preparation

Plain tubes: wait for samples to coagulate and **centrifuge** according to the tube manufacturer's recommendations to eliminate fibrin.

Other tubes: follow the tube manufacturer's recommendations for use.

Frozen-stored samples: after thawing, all these samples must be homogenized before testing. Mix using a vortex-type mixer. Clarify the samples before by centrifugation, if necessary.

Specimen-related interferences

Interferences were studied according to the recommendations of CLSI® EP7-A2.

None of the following factors have been found to significantly influence this assay:
- hemolysis (after spiking samples with hemoglobin, up to 300 µmol/L (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),
- human albumin: (after spiking samples with human albumin up to 60 g/L).

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

Specimen stability

Sera and plasma samples can be stored at 18-25°C in stoppered tubes for up to 8 hours or at 2-8°C for up to 7 days maximum; if longer storage is required, freeze the sera or plasma at –25 ± 6°C.
Do not freeze the sera more than 3 times.
A study performed on samples frozen for 6 months, showed that the quality of results is not affected.

INSTRUCTION FOR USE

For complete instructions, see the User's 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's 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. Calibration should then be performed 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** (see User's Manual). The calibrator value must be within the set RFV ("Relative Fluorescence Value"). If this is not the case, recalibrate using S1.
The calibrator is referenced against international standard NIBSC 66/387.

Procedure

1. **Only remove the required reagents from the refrigerator. They can be used immediately.**
2. Use one "ATPO" strip and one "ATPO" 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 "ATPO" code on the instrument. The calibrator must be identified by "S1", and tested in **duplicate**. If the positive control is to be tested, it should be identified by "C1".
4. Clarify the samples by centrifugation, if necessary.
5. Mix the calibrator, controls and samples using a vortex-type mixer (for serum or plasma separated from the pellet).

6. **For this test, the calibrator, control, and sample test portion is 100 µL.**
7. Insert the "ATPO" SPRs and "ATPO" strips into the instrument. Check to make sure the color labels with the assay code on the SPRs and the Reagent Strips match.
8. Initiate the assay as directed in the VIDAS User's Manual. All the assay steps are performed automatically by the instrument.
9. Restopper the vials and return them to 2–8°C after pipetting.
10. The assay will be completed **within approximately 25 minutes**. After the assay is completed, remove the SPRs and strips from the instrument.
11. 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 IU/mL (IU = International Units).
Samples with anti-TPO antibodies titers exceeding 1000.0 IU/mL may be reassayed after a 1/10 dilution in negative human serum (1 volume of sample + 9 volumes of human serum negative for anti-TPO antibodies).
Linear dilution may not be possible for some samples due to the diversity of the physicochemical properties of the antibodies.
If the dilution factor has not been entered when the Work List was created (see User's Manual), multiply the result by the dilution factor to obtain the sample concentration.

About 20% of asymptomatic specimens may have anti-TPO autoantibodies, reflecting the prevalence in apparently healthy populations. Prevalence of anti-TPO may also depend on age, gender, and geographic region of the selected population.
As part of thyroid disease diagnosis, the interpretation of test results should be made taking into consideration the patient's history and the results of any other tests performed.

QUALITY CONTROL

One positive control is included in each VIDAS Anti-TPO kit.
This control 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 this control. The instrument will only be able to check the control value if it is identified by C1.
Results cannot be validated if the control value deviates from the expected value.

Note

It is the responsibility of the user to perform Quality Control in accordance with any local applicable 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 history, and the results of any other tests performed.

EXPECTED VALUES

Following NACB Guideline 33 "Reference Intervals for Thyroid Antibody Tests" (16) serum samples from 145 apparently healthy males were processed using VIDAS Anti-TPO assay.
97.9% (142/145) of subjects had anti-TPO values **less than 8.0 IU/mL.**

n	< 2.0 IU/mL	2.0 - 3.9 IU/mL	4.0 – 7.9 IU/mL	8.0 - 12.0 IU/mL
145	132	8	2	3
%	91.0	5.5	1.4	2.1

These results are given as a guide. It is recommended that each laboratory establish its own reference values from a rigorously selected population, giving due consideration to age, gender, geographical location and their clinical practices (17).

PERFORMANCE

The VIDAS anti-TPO assay performance studies gave the following results:

Measurement range

The measurement range of the VIDAS Anti-TPO assay is: 0.8 – 1000.0 IU/mL.

Precision

A study was performed following CLSI® EP5-A2. Six human serum samples were assayed in duplicate, at two separate times per day over 20 days, using two reagent lots, on three instruments, at two sites (N=240).

Each reagent lot used two calibration curves throughout the study. Data from this study are summarized in the following table.

Sample	N	Mean Concentration (IU/mL)	Repeatability		Within-lot within-instrument reproducibility	
			Standard Deviation (IU/mL)	CV (%)	Standard Deviation (IU/mL)	CV (%)
Sample 1	240	4.7	0.1	3.0	0.2	4.3
Sample 2	240	10.2	0.2	2.3	0.4	3.6
Sample 3	240	22.4	0.5	2.4	0.9	4.0
Sample 4	240	64.3	1.9	2.9	2.8	4.4
Sample 5	240	387.9	11.2	2.9	23.8	6.1
Sample 6	240	605.6	23.9	3.9	45.2	7.5

The VIDAS Anti-TPO assay is designed to have an assay reproducibility ≤12% (total CV) for samples at the cut-off.

Functional detection limit

Functional detection limit is defined as the concentration of anti-TPO that can be measured with an inter-assay CV of 20%. In an internal study, the functional detection limit was determined to be 1.9 IU/mL.

Detection and quantitation limits

The Limit of Detection (LoD) is the concentration of anti-TPO antibodies in a sample that can be distinguished from the blank sample with a probability of 95%. LoD was determined to be 0.6 IU/mL.
The Limit of Quantitation (LoQ) is the lowest concentration of anti-TPO antibodies that can be quantified with a level of acceptable accuracy and precision. LoQ was determined to be 0.8 IU/mL.
The study was performed as recommended by CLSI EP17-A.

Linearity

The VIDAS Anti-TPO assay is linear over the studied range (**2.4 to 1000.0 IU/mL**), based on a study performed following CLSI EP6-A.

Hook effect

No hook effect was found up to anti-TPO antibody concentrations of **27 000 IU/mL.**

Interferences

Drug interferences

Following the recommendations in CLSI® EP7-A2, the potential interferences with commonly used drugs were studied at two anti-TPO concentrations (approximately 10 IU/mL and 100 IU/mL).

Tested compound	No significant interference observed up to the concentration of:
Acetaminophen	1324 µmol/L
Acetylsalicylic acid	3.44 mmol/L
Ibuprofen	2425 µmol/L
Heparin	3000 IU
Methimazole	129 µmol/L
Levothyroxyn (L-thyroxin)	1.29 µmol/L

Interferences linked to other auto-immune diseases and to high titer IgG

Following the recommendations in CLSI EP7-A2, potential interferences of other autoimmune diseases and patient samples with high titers of IgG were studied by spiking a high concentration of anti-TPO (approximately 100 IU/mL) in samples characterized for these pathologies.

Clinical Condition	Number of tested samples	Significant Interference observed
Anti-Nuclear Antibody	12	No
Crohn's Disease	12	No
Multiple Sclerosis	5	No
Systemic Lupus Erythematosus	13	No
Rheumatoid Arthritis	14	No
Anti-CCP Antibody	14	No
Hyperglobulinemia (High IgG)	9	No
Insulin Dependent Diabetes Mellitus (type 1)	10	Yes (-8.7%)

Potential interference of ulcerative colitis or specific presence of anti-MPO and anti-DNA antibodies has not been tested.

Interferences linked to other potential interferents

Following the recommendations in CLSI EP7-A2, potential interferences of HAMA and rheumatoid factor (RF) were studied by spiking a high concentration of anti-TPO (>100 IU/mL) in HAMA and RF positive samples.

Other Potential Interferents	Number of tested samples	No significant interference observed up to the concentration of:
HAMA	6	163.3 ng/mL
Rheumatoid Factor	12	908 IU/mL

Cross-reactivity with anti-Tg antibodies

Following the recommendations in CLSI EP7-A2, the cross reactivity was studied at two anti-TPO concentrations (approximately 10 IU/mL and 100 IU/mL) by spiking samples with a solution of anti-Tg antibodies of 10 000 IU/mL. No significant effect of anti-Tg antibodies on the VIDAS Anti-TPO assay was observed.

Comparison with another test

The VIDAS anti-TPO assay performance data were compared to those of another commercially available immunoassay. During this study, 449 samples from a population of patients with thyroid disease and for whom an antithyroid antibody assay had been prescribed, were tested. Among this population, 255 patients presented an autoimmune thyroid disease (Graves' disease (Basedow's disease) or Hashimoto's thyroiditis).
Data from this study are summarized in the following table and agreement is calculated with a 95% confidence interval:

		Other anti-TPO assay		Total
		Positive	Negative	
VIDAS Anti-TPO	Positive (≥ 8.0 IU/mL)	310	3	313
	Negative (< 8.0 IU/mL)	15	121	136
	Total	325	124	449

	%	[95% CI]
Positive agreement	95.4% (310/325)	[92.5% – 97.4%]
Negative agreement	97.6% (121/124)	[93.1% – 99.5%]
Overall agreement	96.0% (431/449)	[93.7% – 97.6%]

Among the 18 discrepancies, 16.7% were samples from Hashimoto's thyroiditis patients, 33.3% were samples from Graves' disease (Basedow's disease) patients and 50.0% were samples from laboratory routine activity.

Clinical sensitivity

The clinical sensitivity of the VIDAS Anti-TPO assay was evaluated. During this study, 134 samples from patients suffering from Hashimoto's thyroiditis and 130 samples from patients suffering from Graves' disease (Basedow's disease) were tested. Data from this study are summarized in the following table:

	N	Number of positive samples	% Positive	[95% CI]
Hashimoto's thyroiditis	134	129	96.3%	[91.5% – 98.8%]
Graves' disease (Basedow's disease)	130	114	87.7%	[80.8% – 92.8%]

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	9300916E	Administrative	INDEX OF SYMBOLS REVISION HISTORY
		Technical	CONTENT OF THE KIT (30 TESTS) WARNINGS AND PRECAUTIONS
2015/06	9300916F	Technical	CONTENT OF THE KIT (30 TESTS) INSTRUCTIONS FOR USE

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