HbA1c Direct

En

REF 08V4220
REF 08V4225
REF 08V4230

Alinity c

Diagnostic reagent for the determination of HbA1c concentration.
Liquid. Dual reagent (Ratio: R1/R2: 3/1). Store at +2/+8°C. For In Vitro Diagnostic use. **Do not freeze.**
The products with 08V4220/08V4225/08V4230 reference numbers provided are compatible for use with Abbott Alinity biochemistry autoanalyzer series.

Changes made in the instructions for use are marked as gray.

The instructions must be followed carefully. The reliability of the test results cannot be guaranteed unless these instructions are followed.

NAME
HbA1c Reagent Kit

INTENDED USE
The HbA1c assay is used for the quantitative determination of HbA1c concentration in human whole blood on Alinity c analyzer.

SUMMARY AND EXPLANATION OF THE TEST
HbA1c forms irreversibly by glycosylation through enzymatic or non-enzymatic condensation of one or both of the N-terminal valines in the β-chains of the tetrameric hemoglobin A molecule. This can sometimes also occur by glycosylation of lysine residues in hemoglobin.[1]

The first form is the unstable schiff base (aldimine, pre-HbA1c) structure. The schiff base can dissociate or undergo Amadori rearrangement to form the HbA1c molecule, a stable ketoamine.[2]

The HbA1c test provides an index of average blood glucose levels over the last 2 to 4 months. Although red blood cells have a lifespan of about 120 days, HbA1c levels represent a "weighted" glucose level, with the youngest red blood cells contributing more than older ones. For glycemic control, it is recommended to measure and evaluate HbA1c levels every 3 to 6 months.[1]

The HbA1c test is used in both the diagnosis and follow-up of patients with Diabetes Mellitus (DM). In the follow-up of DM patients, an absolute difference in HbA1c test results between consecutive patient samples of % 0.5 according to the National Glycohemoglobin Standardization Program (NGSP) or 5 mmol/mol according to the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) is a clinically important change in glycemic control.[3]

The Diabetes Control and Complications Trial (DCCT) presented that lowering glucose levels in patients with type 1 diabetes slows and prevents the development of DM-related microvascular complications such as retinopathy, neuropathy and nephropathy.

In the DCCT trials, a 50% to 75% reduction in complications was observed in the intensively treated group of patients whose HbA1c levels were reduced to %7.2 compared to those reduced to %9.0 in the conventionally treated group.7Similarly, a reduction in microvascular complications in type 2 DM patients has been reported in the United Kingdom Prospective Diabetes Study (UKPDS) and some other studies.[1,8]

According to the UKPDS study, reducing HbA1c from %7.9 (63 mmol/mol) to %7.0 (53 mmol/mol) in intensively treated patients decreases microvascular complications by 25% on average. In addition, in the UKPDS follow-up study, it was reported that major complications of DM also decreased due to this treatment approach.1,2 For example, for every %1 reduction in HbA1c (e.g. from 8.0% to %7.0 [64 to 53 mmol/mol]), a 14% risk reduction in the incidence of myocardial infarction has been reported.[9] On the other hand, HbA1c levels in patients without DM are directly associated with cardiovascular disease. In the European Prospective Investigation on Cancer and Nutrition (EPIC-Norfolk) study, a % 1increase in HbA1c was associated with a 28% increased risk of death.[10]

There is no consensus on the frequency of optimal testing for both type 1 and type 2 DM patients. The ADA recommends routine monitoring of HbA1c at least every 6 months in patients who meet treatment goals (and have stable glycemic control).[11] In a study conducted on more than 79,000 patient were reported that the optimum test frequency should be every 3 months to maximize decrease in HbA1c and less frequent testing has resulted in deterioration of control.[12]

HbA1c does not have sufficient specificity and sensitivity in the diagnosis of gestational diabetes mellitus (GDM).2,13 Women with GDM should be screened for diabetes between 4-12 weeks after delivering by use OGTT criteria of non-pregnant. HbA1c is not recommended for antepartum treatment for hyperglycemia. If glucose values are normal, it is recommended that reassessment of glycemia should be done by use glucose or HbA1c testing at least every 3 years.[2]

PRINCIPLES OF THE PROCEDURE
The test has immunoturbidimetric measurement method. More than 250 methods are used in the determination of glycehemoglobin (Ghb). Most methods separate GHb from unglycated hemoglobin using techniques based on charge differences (ion exchange chromatography, HPLC, electrophoresis, and isoelectric focusing) or structural differences (affinity chromatography and immunoassay).[14] Some chemical analyzes (enzymatic, photometry, and spectrophotometry) and, more recently, capillary electrophoresis and enzymatic methods specifically measuring HbA1c have also become commercially available.[2]

Regardless of the method used, HbA1c results are expressed as a fraction of total hemoglobin. In this sense, the Archem HbA1c test states the percentage rate between total hemoglobin concentration (THb) and HbA1c concentration.

The antibody used in the Archem HbA1c test does not cross-react with labile HbA1c, making it specific for the ketoamine form of HbA1c. Stable HbA1c does not rise and fall in response to rapid changes in physiologic factors and therefore allows individuals to measure average blood glucose levels over several months.

This method uses the interaction of antigen and antibody to directly detect the HbA1c level in whole blood. THb and HbA1c molecules have a non-specific absorption rate against latex particles. When mouse anti-human HbA1c monoclonal antibody (R2) is added to the reaction medium, it forms a complex with latex-bound HbA1c. When goat anti-mouse IgG polyclonal antibody is added to the medium, agglutination occurs. The amount of agglutination is proportional to the HbA1c absorbed onto the surface of the latex particles. The turbidity caused by agglutination is measured by absorbance reading at a wavelength of 660 nm (800 nm wavelength is used for dual wavelength preferences).

REAGENTS

Kit Contents

R1 Latex particles (< 0.15 %). Buffer. Stabilizers.

R2 Mouse anti-human HbA1c monoclonal antibody (< 0.06 mg/mL). Goat anti-mouse IgG polyclonal antibody (< 0.09 mg/dL). Buffer. Stabilizers.

Lyse Reagent: Stabilizers. Buffer. Lysing agent. Water.

Warnings and Precautions
IVD: For in Vitro Diagnostic use only.
Do not use expired reagents.
Reagents with two different lot numbers should not be interchanged.
For professional use.

Follow Good Laboratory Practice (GLP) guidelines.

CAUTION: Human source samples are processed with this product. All human source samples must be treated as potentially infectious materials and must be handled in accordance with OSHA standards.

Danger
EUH032 :Releases a very toxic gas if contacts with acid.
H317 :May cause allergic skin reaction.

Precaution
P280 :Use protective gloves / clothes / glasses / mask.
P264 :Wash your hands properly after using.
P272 :Contaminated work clothes should not be allowed to be used outside of the workplace.

Intervention
P302+P352 :Wash with plenty of water and soap if it contacts with skin.
P333+P313 :Seek medical help if it irritates your skin or develops rash.
P362+P364 :Remove contaminated clothes and wash properly before using.

Disposal
P501 :Dispose the vials and contents according to the local regulations.

Reagent Handling

- Reagent cartridges should be kept in an upright position for at least 8 hours after receipt and before use to eliminate any air bubbles that may have formed inside.
- If the cartridge is dropped, it should be kept upright for 8 hours before use to allow the air bubbles to dissipate.
- Foam and air bubbles may form in the reagents; this may prevent accurate detection of the reagent level inside the cartridge, leading to insufficient reagent aspiration and potentially affecting the analysis results.

Reagent Storage [15]

	Storage Temperature	Maximum Storage Time	Additional Storage Instructions
Unopened	+2/+8°C	Until expiration date	Store in upright position.
Onboard	System Temperature	30 days	

Do not freeze.

Indications of Reagent Deterioration

When a calibration error occurs or the control value falls outside the accepted range, the reagents may be considered to have deteriorated. In this case, the test results are not valid and the samples should be reanalyzed. Recalibration may be required.

Alternative Result Units

Use the unit conversion table provided below for alternative result units. The IFCC method reports HbA1c as mmol/mol (HbA1c/total Hb)[16] and is automatically calculated by the system using the following formula:[17]

Default Unit	Conversion Factor	Result Unit
(HbA1c/THb)	1000	mmol/mol

Conventional Units (NGSP):

HbA1c according to the NGSP method is reported as a percentage of total hemoglobin in the NGSP system. These values, which are equivalent to those reported by DCCT and UKPDS, represent the most widely used reporting system in patient care and in the published literature.

The comparison between the IFCC and NGSP networks has resulted in a master equation that allows conversion between the two reference systems.[18] For example, an HbA1c result of 7.0% (in NGSP/DCCT/UKPDS units) is equivalent to 53 mmol/mol (in IFCC units).

Calculators for unit conversion are freely available on various websites, such as http://www.ngsp.org/convert1.asp.[2] The unit conversion calculation is performed according to the formula provided below.

NGSP%= [0,09148 x (IFCC)] + 2,152

Many journals now require HbA1c results to be reported in both NGSP/DCCT and SI units.[16]

In a prospective study involving multiple countries, the relationship between HbA1c concentrations and long-term glucose levels was evaluated. The study demonstrated a linear correlation that allows the calculation of estimated average glucose (eAG) from HbA1c measurements.[19]

The regression equations are as follows:

eAG mg/dL= 28,7 × HbA1c – 46,7 and
eAG mmol/L= 1,59 × HbA1c – 2,59

Some clinicians and many diabetes educators believe that eAG facilitates communication with patients.[20] The ADA and AACC recommend that laboratories report both HbA1c and eAG. For example, an HbA1c value of 7.0% (53 mmol/mol) corresponds to an eAG of 140 mg/dL. However, the concept of expressing HbA1c in terms of average glucose is not universally accepted.[21,22]

SAMPLE COLLECTION AND PREPARATION FOR ANALYSIS

Sample Types

The recommended sample types for this test are listed below.

Sample Type	Collection Tube
Anticoagulated venous whole blood	Tubes containing dipotassium ethylenediaminetetraacetate (K2-EDTA) or tripotassium EDTA (K3-EDTA)

Follow the instructions provided with your sample collection tubes for use and handling.

Sample Conditions

- Fresh samples should be used.
- To obtain reliable results, serum should be free of fibrin, blood cells, or foreign particles. In samples obtained from individuals receiving anticoagulant or thrombolytic therapy, fibrin residues may be observed due to incomplete clotting.
- To reduce the risk of contamination between samples, a new pipette or pipette tip should be used for each procedure.
- Whole blood samples collected in anticoagulant vacutainers other than those containing EDTA should not be used.
- High levels of HbF may lead to underestimation of HbA1c.
- Sample tubes should not be overfilled; whole blood levels exceeding 78 mm from the bottom may cause instrument errors and prevent result generation.
- Only whole blood samples collected in plastic tubes using standard venipuncture methods should be used.
- For the analysis of whole blood samples less than 600 µL, 12 × 75 mm polypropylene tubes with a conical bottom should be used. The minimum required volume for sample containers used in the Alinity c system is 150 µL.
- **Samples should not be centrifuged.**

Preparation for Analysis

- Before starting the test, whole blood samples should be gently inverted until homogeneous to resuspend erythrocytes.
- When preparing sample tubes, the manufacturer's instructions should be followed; separation by standing alone is not sufficient.
- Samples should be free of air bubbles. Before analysis, bubbles should be removed using a stick, and a separate stick should be used for each sample.
- If samples contain fibrin, erythrocytes, or other particulate matter, clots and particles should be removed using an applicator stick to ensure reliable results.
- If samples do not appear homogeneous, they should be mixed by low-speed vortexing or by inverting the tube 10 times.

Sample Storage

Sample Type	Temperature	Maximum Storage Time
Whole Blood	+20/+25°C	8 hours
	+2/+8°C	7 days
Hemolysate	+20/+25°C	4 hours
	+2/+8°C	1 days

The information provided applies to whole blood samples. Repeated freeze–thaw cycles of samples should be avoided. Samples that have been converted to hemolysate should not be frozen.

PROCEDURE

Materials Provided
HbA1c Reagent Kit
Materials Required but Not Provided

- HbA1c Calibrator Set – lyophilized
- HbA1c Direct Control Set (Low / High) – lyophilized or commercially available controls

Assay Procedure

- If primary or aliquot tubes are used, ensure that a sufficient amount of sample is available.
- To prevent evaporation of the specimen, make sure that the tube volume is adequate before each test.
- Minimum Sample Volume Requirements:
  - Sample volume for a single test: 3,2 µL

Sample Dilution Procedures

This method demonstrates measurement linearity up to 15.5%. For concentrations above this value, manual dilution may be performed.

Manuel Dilution Procedures

The recommended dilution is 1:2.
Add 250 µL of whole blood from the HbA1c sample to be measured to 250 µL of a low HbA1c sample with a known value (i.e., < 6.0% HbA1c), and mix thoroughly before testing. Before applying the dilution calculation, the result should be higher than 4.0% HbA1c. Calculate the sample value using the following equation:

Sample value (%): (Observed concentration × 2) − Low sample concentration

The manual dilution procedure can only be applied if the Hb concentrations of both the patient sample and the low HbA1c sample are within the range of 7 to 20 g/dL.

Calibration

The use of a Lyophilized HbA1c Calibrator Set is required for this test.

HbA1c Direct Calibrator Set (4 Levels)
Ref. No: 01R97-01

Calibration stability is 30 days. Unopened calibrator vials are stable at +2/+8°C until their expiration date. The HbA1c Direct Calibrator Set is provided in lyophilized form. The lyophilized content should be reconstituted with the amount of deionized water specified on the label, according to the instructions, and allowed to stand for 30 minutes before use. Reconstituted calibrators are recommended to be stored at +2/+8°C in sample containers compatible with the autoanalyzer, tightly closed. Calibrators stored in this way at +2/+8°C are stable for 30 days. Changes in the reagent lot number require recalibration. Calibration is necessary if quality control results are not within acceptable limits.

Quality Control Procedures

Commercially available control materials with values assigned by this method may be used. Recommended:

HbA1c Direct Control Set (Low / High)
Ref. No: 01R96-01

Unopened control vials are stable at +2/+8°C until their expiration date. The HbA1c Control Set is provided in lyophilized form. The lyophilized content should be reconstituted with the amount of deionized water specified on the label, according to the instructions, and allowed to stand for 30 minutes before use. Reconstituted controls are recommended to be stored at +2/+8°C in tightly closed, autoanalyzer-compatible sample containers. Controls stored in this way at +2/+8°C are stable for 30 days.

At least two levels of control should be run every 24 hours. Each laboratory should establish its own quality control procedures. If more stringent control monitoring is required, refer to the quality control procedures established for your laboratory.

LIMITATIONS OF THE PROCEDURE

- The linearity of the measurement method is up to 15.5% HbA1c. Dilution and/or repeat testing should not be performed for samples with values below 15.5%.
- In patients with diabetes mellitus (DM) and poor glycemic control, values may rise to two times or more above the upper limit of the reference range; however, they rarely exceed 15.0% HbA1c. Values greater than 15.0% (140 mmol/mol) or lower than 4.0% (20 mmol/mol) require further investigation to determine the possible presence of variant hemoglobin.[27] In such cases, HbA1c should be reanalyzed, if possible, using a method based on a different analytical principle than the initial test.[2]
- The interpretation of HbA1c depends on red blood cells with a normal lifespan. Significant decreases in HbA1c test results may be observed in patients with hemolytic disease or other conditions that shorten red blood cell lifespan.[27]
- Individuals with recent significant blood loss may have falsely low values due to a higher proportion of young erythrocytes.[2]
- Race affects HbA1c concentration. Published evidence indicates that HbA1c concentrations are higher in Black, Asian, and Latin American populations compared to White individuals.

EXPECTED VALUES

Each laboratory should investigate the transferability of expected values for its own patient population and, if necessary, establish its own reference range.

Reference Range [10,11]

HbA1c values are expressed as a percentage of total blood hemoglobin. In the past, one of three main HbA1c forms—HbA1, HbA1c, or total GHb—was measured. Today, many countries, including the United States, Canada, Australia, New Zealand, and the United Kingdom, report all results as HbA1c.

Currently, HbA1c values are widely used, along with blood glucose concentrations, for the diagnosis of DM and for identifying individuals at high risk of DM. The target values for DM and high DM risk based on HbA1c, as defined by the ADA, are as follows:[6]

Recommended Diagnosis	HbA1c (%)*	HbA1c (mmol/mol)*
Diabetic	≥ 6.5	≥ 48
Prediabetes	5.7–6.4	39–47
Normal	< 5.7	< 39

*: The % values are given according to NGSP, and the values in mol are given according to IFCC units.

In 2009, the International Expert Committee (IEC) recommended adopting an HbA1c clinical decision point of 6.5% (48 mmol/mol) for the diagnosis of type 2 DM,[4,5] which has been endorsed by leading organizations such as the American Diabetes Association (ADA),[6] the World Health Organization (WHO), and the European Association for the Study of Diabetes (EASD), and has been widely used as a diagnostic criterion for type 2 DM.[2,4]

For evaluating metabolic control in patients with DM, target values established by DCCT and UKPDS and recommended by ADA and other organizations are used rather than reference values.

There is no specific HbA1c value that completely eliminates the risk of developing DM complications. While the ADA generally recommends that the treatment goal should be to maintain HbA1c below 7.0% (53 mmol/mol), some other organizations recommend a target HbA1c below 6.5% (48 mmol/mol).[2,11]

In pregnant women with pre-existing DM, HbA1c should be targeted below 6.5% to protect the fetus from congenital malformations and to reduce complications in both the mother and the infant (these target values are valid only if the test method is certified by NGSP according to the DCCT reference).[2]

The effects of age on the reference range are controversial.[23] While some studies report an age-related increase (approximately 0.1% per decade after the age of 30), others show no increase in non-diabetic individuals.[24,25]

Each laboratory should investigate the transferability of expected values for its own patient population and, if necessary, establish its own reference range.

The reference range has been verified using the CLSI EP28-A3c protocol.[26]

SPECIFIC PERFORMANCE CHARACTERISTICS

Precision

			Within-Run (Repeatability)[31,32]		Within-Laboratory (Total)*[31,32]	
Sample	n	Mean (%)	SD	%CV	SD	%CV
Level 1	80	5.1	0.06	1.17	0.11	2.15
Level 2	80	10.4	0.16	1.53	0.22	2.11

*: Includes within-run, between-run, and between-day variability.

Lower Measurement Limits

The lower measurement limits refer to the range between the lower limit of quantitation (LLoQ) and the upper limit of quantitation (ULoQ), within which the analyte concentration can be measured with the required medical and laboratory accuracy without dilution, concentration, or any pre-treatment.[28] The LoD and LoQ values have been verified using the CLSI EP17-A2:2012 protocol.[29]

	%
LoD**	2.9
LoQ***	3.9

**** :** The LoD represents the lowest concentration at which the analyte can be detected with 95% probability, based on ≥ 60 replicates of samples with low analyte levels.
*****:** When determining the LoQ value, a coefficient of variation (%CV) of ≤20% is used as the basis.

Measuring Interval

This method shows measurement linearity in the activities between %3.9-15.5. For samples with results above this value, the manual dilution procedure described below should be applied. For additional information, please refer to the instrument's user manual. Linearity studies data have been verified by using CLSI EP06-A:2003 protocol.[30]

Interference

Endogenous interferant and analyte concentrations that have been used in the HbA1c scanning tests has been determined according to "CLSI EP37-ED1:2018" and "CLSI EP07-ED3:2018" manuals.[33,34]

The total acceptable error rate, which is going to be used to detect whether the observed differential value obtained from HbA1c interference scanning test is appropriate, is determined as ±10%.[35]

In HbA1c test results, no significant interaction has been observed in the determined endogenous interferant and analyte concentrations or between interferants and analyte.

Interferant-Concentration	HbA1c Target (%)	N*	Observed Recovery %
Bilirubin 48,0 mg/dL	6.2	3	94
Lipemia 2000 mg/dL	6.1	3	96

*In calculating how many times the control and test samples (containing interferent), prepared as a serum pool, would be run repetitively, the within-run SD values previously determined for the relevant method and the total allowable error rate defined as the interference limit were used. In the calculations, a type 1 error (α error) rate of 5% and a type 2 error (β error) rate of 10% (90% power) were accepted.[19]

It should be noted that, in addition to endogenous interferents, various drugs and metabolites; anticoagulants (e.g., heparin, EDTA, citrate, oxalate) and preservatives (e.g., sodium fluoride, iodoacetate, hydrochloric acid); substances that may come into contact with samples during collection and handling (such as serum separation devices, sample collection containers and their contents, catheters, catheter flushing solutions, skin disinfectants, hand sanitizers and lotions, glassware detergents, powdered gloves, etc.); dietary substances known to affect certain tests (e.g., caffeine, beta-carotene, poppy seeds); or certain substances present in a sample that may cause interference due to foreign proteins (e.g., heterophilic antibodies), autoimmune responses (e.g., autoantibodies), or malignancy (e.g., paraproteins causing interference in phosphate tests and indirect ion-selective electrode methods) may lead to various interferences and erroneous evaluations for many different reasons.[19]

These performance characteristics were obtained using an autoanalyzer. Results may vary when different equipment or manual procedures are used.

Hemoglobin Variants

Since HbF is included in the total hemoglobin measurement, samples with elevated HbF levels (>9.2%) may yield lower HbA1c results than expected.

HbF (%)	HbA1c (%)	% Interference
2.5	5.6	-2.6
5.2	5.4	-3.1
7.2	5.2	-4.3
9.2	5.7	-4.8
13.1	5.0	-11.6

Method Comparison

As a result of the statistical evaluation of method comparison data, the table was constructed according to the Passing–Bablok regression method as follows:

Archem HbA1c – Roche Cobas Integra 400 Plus

	Units	n	Correlation Coefficient	Intercept	Slpoe	Concentration Range
Whole Blood	%	100	0.9953	0.1070	0.9903	4, – 14,4

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CE

SYMBOLS

IVD	In Vitro Diagnostic Medical Device
LOT	Lot Number
R1	Reagent 1
R2	Reagent 2
GTIN	Global Trade Item Number
REF	Reference Number
GLP	Good Laboratory Practices
FOR USE WITH	Identifies Products to Be Used Together
PRODUCT OF TURKEY	Product of Turkey
	Manufacturer
	Expiration Date
	Temperature Limits
	Consult Instructions for Use
	Caution
	Number of Tests