



Technical Brief

Hemoglobin Variants and Derivatives on A1C Measurement

Abnormal hemoglobin (Hb) variants (i.e. HbS, HbC, and HbE) and chemically modified derivatives (i.e. carbamyl-Hb) can cause interference and dramatically affect the results of A1C measurement. Such problems should be suspected whenever A1C results are out of keeping with results of self-monitoring of blood glucose.

Prevalence of Hemoglobin Variants and Diabetes in populations of various racial and ethnic backgrounds

The following table summarizes the affected populations and prevalence of common hemoglobinopathies. These hemoglobinopathies may either falsely raise or lower A1C results, depending on the variant and the assay method.^{1,2}

Group	Prevalence of Diabetes	Prevalence of Hemoglobin Variants			
		HbS	HbC	HbE	HbF
African Americans	18.7%	About 8.3%	About 2.3%	-	-
Hispanic Americans	11.8%	About 1%	-	-	-
Asian Americans	8.4%	-	-	About 30% of Southeast Asians	-
Patients with hereditary persistence of fetal hemoglobin, sickle cell anemia, severe anemias, and leukemia	-	-	-	-	1.5% will have HbF concentrations ranging from 2% - 12%

Laboratories use many different assay methods for measuring A1C, but some of these methods can give inaccurate results (falsely high or low) when the patient has a hemoglobin variant such as sickle cell trait or if there is an elevated level of HbF. Health care providers or patients interested in getting information about the accuracy of a particular A1C method for patients with hemoglobin variants should first find out which method their laboratory is using.

Affects of Hemoglobin Variants on A1c Testing Methods

Immunoassays and Ion-exchange methods have been shown to have significant interference from hemoglobin variants where as boronate affinity methods have shown to have no interferences for the following reasons.

- **Ion-exchange** separates hemoglobin species based on charge differences and elution time. The presence of a hemoglobin variant causes an alteration in retention time and can cause a substantial increase in the A1C result depending on the method used.
- **Immunoassays** recognize the glycated amino acid. The antibodies will not recognize this if it is modified from a variant and cause a decreased A1C.
- **Boronate affinity** binds to the cis-diol configuration that forms when the glucose binds to hemoglobin and thus measures all of the glycated components. This specific binding does not allow for interferences from hemoglobin variants.
 - The Afinion™ AS100 Analyzer System has virtually no interference from hemoglobin variants because the method uses boronate affinity chromatography to separate the glycated hemoglobin fraction from the non-glycated fraction.

Because different laboratories use different methods, practitioners should familiarize themselves with the methodology of their local laboratory. Preferably a single laboratory should be used for all measurements for patients of a given physician to lessen confusion.

The table below references some of the more common methods and the Hb variants that will cause interference with the measurements.³

Method	Interference from HbC	Interference from HbS	Interference from HbE	Interference from HbD	Interference from elevated HbF
Abbott Architect/Aeroset	Yes	Yes	†	†	★
Arkray ADAMS A1c HA-8180V (Menarini)	No	No	HbA1c not quantified	HbA1c not quantified	No
Axis-Shield Afinion™	No	No	No	No	★
Bayer A1cNOW®	Yes	Yes	No	No	★
Beckman AU® system	Yes	Yes	No	No	★
Beckman Synchron® System	No	No	No	No	★
Bio-Rad D-10 (A1c program)	No	No	No	No	Yes >10% HbF
Bio-Rad in2it™	Yes	No	Yes	No	★
Bio-Rad Variant II NU	-	-	No	No	Yes >10% HbF
Bio-Rad Variant II Turbo	No	No	Yes	Yes	Yes >5% HbF
Bio-Rad Variant II Turbo 2.0	No	No	No/Yes (conflicting reports)	No	Yes >25% HbF
Ortho-Clinical Vitros®	No	No	No	No	★
Roche Cobas Integra® Gen.2	No	No	No	No	★
Roche/Hitachi (Tina-Quant®)	No	No	No	No	★
Sebia Capillars 2 Flex Piercing	No	No	No	No	No
Siemens Advia A1c (new version)	No	No	†	†	★
Siemens DCA 2000®	No	No	No	No	Yes >10%
Siemens Dimension®	No	No	No	No	★
Tosoh G7	Yes	No	Yes	No	No
Tosoh G8	No	No	Yes	No	No
Trinity (Primus) HPLC (affinity)	No	No	No	No	Yes >15% HbF

Permission granted by National Glycohemoglobin Standardization Program³

† *In the absence of specific method data, it can generally be assumed that immunoassay methods do not have clinically significant interference from HbE and HbD because the E and D substitution are distant from the N-terminus of the hemoglobin beta chain.*¹

★ *In the absence of specific method data, it can generally be assumed that both immunoassay and boronate affinity methods show interference from HbF levels above ~10-15%.*^{2,3}

- *Not yet evaluated.*



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References:

1. Bry L, Chen PC, Sacks DB. Effects of hemoglobin variants and chemically modified derivatives on assays for glycated hemoglobin. *Clin. Chem.* 2001;47:153-63.
2. Centers for Disease Control and Prevention. National Diabetes Fact Sheet: national estimates and general information on diabetes and prediabetes in the United States, 2011. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, 2011.
3. National Glycohemoglobin Standardization Program. Factors that Interfere with HbA1c Test Results (<http://www.ngsp.org/factors.aspx#table1>), data referenced based on content displayed as of July 2013.