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An improved Abbott ARCHITECT® assay for the detection of hepatitis B virus surface antigen (HBsAg)

Sheng C. Lou*, Sandra K. Pearce, Teresa X. Lukaszewska, Russell E. Taylor, Gregg T. Williams, Thomas P. Leary

Research Assay Prototyping, Diagnostics Research, Abbott Laboratories, 100 Abbott Park Road, Abbott Park, IL 60064, USA

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ABSTRACT

Background: The sensitive and accurate detection of hepatitis B virus surface antigen (HBsAg) is critical to the identification of infection and the prevention of transfusion transmitted disease. Improvement in HBsAg assay sensitivity is essential to reduce the window to detect an acute HBV infection. Additionally, the sensitive detection of HBsAg mutants that continue to evolve due to vaccine escape, immune selection and an error prone reverse transcriptase is a necessity.

Objectives and study design: A fully automated HBsAg prototype assay on the Abbott ARCHITECT® instrument was developed to improve sensitivity and mutant detection. This magnetic microparticle-based assay utilizes anti-HBsAg monoclonal antibodies to capture antigen present in serum or plasma. Captured antigen is then detected using anti-HBsAg antibody conjugated with the chemiluminescent compound, acridinium.

Results: The sensitivity of the ARCHITECT® HBsAg prototype assay was improved as compared to the current ARCHITECT®, PRISM®, and competitor HBsAg assays. The enhancement in assay sensitivity was demonstrated by the use of commercially available HBV seroconversion panels. The prototype assay detected more panel members (185 of 383) vs. the current ARCHITECT® (171), PRISM (181), or competitor HBsAg assays (73/140 vs. 62/140, respectively). The ARCHITECT® prototype assay also efficiently detected all mutants evaluated. Finally, the sensitivity improvement did not compromise the specificity of the assay (99.94%).

Conclusions: An improved Abbott ARCHITECT® HBsAg prototype assay with enhanced detection of HBsAg and HBsAg mutants, as well as equivalent specificity was developed for the detection, diagnosis, and management of HBV infection.

1. Background

Hepatitis B virus (HBV) is the most prevalent viral infection worldwide, resulting in over one million deaths per year. Among the approximately 2 billion people that have been infected globally, about 350 million (5% of the world's population) are chronic carriers of the virus.[1–4] Hepatitis B virus surface antigen (HBsAg) is the most important serological marker of acute and chronic HBV infection.[5] HBsAg can be detected in the serum several weeks before the onset of disease and is present during both the acute and chronic stages of infection. The presence of HBsAg indicates that the individual is probably infectious and antigen titers correlate with the relative level of infection and the severity of disease.[1,2,6]

Based on sequence divergence within the genome, HBV has been classified into eight genotypic groups, designated A–H.[7–9] Studies have demonstrated that the various HBV genotypes have distinct geographical distributions.[10] The genetic variability of HBV presents a challenge for HBsAg immunoassays, as all eight genotypes must be detected.[10] Furthermore, mutants of HBsAg continually evolve as a result of vaccine escape, immune selection and an error prone reverse transcriptase, introducing an additional challenge to the detection of HBsAg.[11,12] The most prevalent mutations in the HBsAg gene are amino acid substitutions at positions 145, 141, and 131 within the "a" determinant, although amino acid insertions between amino acids 122 and 123 have been described that pose particular challenges to HBsAg detection.[10,12–14]

To reduce the risk of false negative results, HBsAg immunoassays must be continuously improved to achieve better sensitivity and to detect the most commonly found mutants. The sensitive

* Corresponding author. Present address: Dept. 09PX, Bldg. AP20, Abbott Laboratories, 100 Abbott Park Road, Abbott Park, IL 60064, USA. Tel.: +1 847 937 4564; fax: +1 847 937 1401.

E-mail addresses: sheng.lou@abbott.com (S.C. Lou), sandra.pearce@abbott.com (S.K. Pearce), teresa.lukaszewska@abbott.com (T.X. Lukaszewska), russell.taylor@abbott.com (R.E. Taylor), gregg.williams@abbott.com (G.T. Williams), thomas.leary@abbott.com (T.P. Leary).

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and accurate detection of HBsAg is critical to the clinical diagnosis of HBV infection and the prevention of HBV transmitted disease. In that regard, the current study reports the development of a highly sensitive assay for the detection of HBsAg in human serum and plasma.

2. Objectives

The present study was conducted to demonstrate that the new ARCHITECT® HBsAg prototype assay has improved sensitivity and mutant detection with equivalent assay specificity.

3. Study design

3.1. Assay configuration

The Abbott PRISM® HBsAg assay (Abbott List 06D19) is a 2-step chemiluminescent immunoassay that utilizes a single monoclonal antibody on the solid phase to capture HBsAg from 100 μl of sample volume, and a goat polyclonal conjugate to detect captured antigen. The ARCHITECT® HBsAg Qualitative assay (Abbott List 01P97) is a 1-step chemiluminescent immunoassay in which HBsAg present in 75 μl of sample forms a sandwich between dual monoclonal antibody coated solid phases and a goat polyclonal conjugate. The ARCHITECT® HBsAg prototype assay consists of dual monoclonal antibody coated solid phases and a combination of monoclonal and goat polyclonal antibody conjugates for detection. In each of the assays, a ratio of signal/cutoff (S/CO) greater than or equal to 1.00 is a reactive result.

3.2. Analytical sensitivity

Lyophilized HBsAg (33 IU) of the 2nd International WHO Standard (00/588 for HBsAg Subtype adw2, Genotype A) was re-hydrated with distilled water as per the manufacturer's instructions, then diluted with normal human plasma to make a 1 IU/ml stock solution. Subsequently, a 10 member panel was prepared in normal human plasma by dilution of the 1 IU/ml stock to achieve concentrations of HBsAg ranging from 0 to 0.500 IU/ml. This 10 member panel was utilized to assess the analytical sensitivities of the immunoassays in this study. Each panel member was tested in triplicate with the respective assays. The mean S/CO values for each panel member and the corresponding concentrations of HBsAg were utilized to perform linear regression analyses. The analytical sensitivity of each assay was determined based on the concentration of HBsAg (IU/ml) which corresponds to an S/CO of 1.00.

3.3. Seroconversion sensitivity

Seroconversion sensitivity was assessed by comparing the number of reactive bleeds (S/CO ≥ 1.00) from 32 commercially available seroconversion panels tested in singlet with PRISM® HBsAg, ARCHITECT® HBsAg Qualitative and the ARCHITECT® HBsAg prototype assay. Seroconversion sensitivity between the ARCHITECT® HBsAg assays and the competitor assay was assessed by comparing the number of reactive bleeds (S/CO ≥ 1.00) from 14 selected HBV panels.

3.4. Mutant detection

An eleven member panel, including wild type, negative control, and nine recombinant HBsAg mutants of the "a" determinant was utilized to evaluate mutant detection by the immunoassays used in this study. The panel members were tested in triplicate and the mean S/CO value determined for each. S/CO values equal to or greater than 1.00 indicate a positive test result for the mutant.

3.5. Assay specificity

A total of 6482 blood donor specimens (serum or plasma) and 496 routine hospital specimens from the United States and Germany were tested with the ARCHITECT® HBsAg Qualitative assay and the ARCHITECT® HBsAg prototype assay. All specimens were assayed in singlet with each assay. Specimens with an initial test result ≥1.0 S/CO were retested in duplicate. Upon retest, samples with at least 1 repeat reactive result were subjected to HBsAg Confirmatory testing.

3.6. Endogenous sample interference

Two hundred and six potentially interfering specimens were used to assess the performance of the ARCHITECT® HBsAg prototype assay. Assay specificity was evaluated using samples from a number of clinical conditions unrelated to HBV. Specimens with an initial reactive result were retested in duplicate, followed by evaluation in a prototype ARCHITECT® HBsAg Confirmatory assay to confirm the presence of HBsAg. In an antigen recovery study, anti-HBsAg negative samples were spiked with HBsAg to obtain a 2 S/CO target value. All samples spiked with HBsAg were confirmed with the Confirmatory assay.

4. Results

4.1. Analytical sensitivity

The analytical sensitivity of PRISM® HBsAg, ARCHITECT® HBsAg Qualitative and the ARCHITECT® HBsAg prototype assay was determined by testing dilutions of the 2nd International WHO HBsAg Standard at concentrations ranging from 0 to 0.500 IU/ml. The analytical sensitivity of both the PRISM® HBsAg and the ARCHITECT® HBsAg prototype assays was 0.016 IU/ml while the analytical sensitivity of the ARCHITECT® HBsAg Qualitative assay was 0.027 IU/ml (Table 1). Based on this study, the ARCHITECT® HBsAg prototype assay is equivalent to the PRISM® HBsAg assay in terms of assay sensitivity and represents an approximate 40% assay sensitivity improvement over the ARCHITECT® HBsAg Qualitative assay.

Table 1
Analytical sensitivity: comparison of ARCHITECT HBsAg prototype, ARCHITECT HBsAg Qual, and PRISM HBsAg.

The 2nd WHO International Standard for HBsAg (IU/ml)	S/CO values		
	ARCHITECT HBsAg prototype	ARCHITECT HBsAg Qual	PRISM HBsAg
0.500	20.89	13.01	16.05
0.250	10.91	6.77	8.54
0.150	7.15	4.42	5.66
0.100	4.35	2.79	3.71
0.050	2.38	1.56	2.08
0.040	2.25	1.48	1.98
0.030	1.51	1.01	1.41
0.025	1.25	0.92	1.10
0.010	0.60	0.49	0.63
0.000	0.16	0.21	0.32
HBsAg concentration (IU/ml) at which the S/CO = 1.00	0.016	0.027	0.016

Table 2
Seroconversion sensitivity: comparison of ARCHITECT® HBsAg prototype, ARCHITECT® HBsAg Qualitative, and PRISM® HBsAg assays with 32 seroconversion panels.

Panel ID	Panel members	ARCHITECT® HBsAg prototype	ARCHITECT® HBsAg Qualitative	PRISM® HBsAg
PHM 925	5	4	3	3
PHM 926	8	6	5	5
PHM 927	6	5	5	5
PHM 928	7	5	4	4
PHM 929	9	5	5	5
PHM 930	5	4	4	4
PHM 933	5	4	4	4
PHM 934	6	6	6	6
PHM 935B	12	9	10	10
6271	5	3	3	3
6272	26	7	7	7
6273	6	3	2	2
6274	7	7	7	7
6275	7	5	3	5
6279	9	2	2	2
11000	9	5	4	6
11001	8	4	4	4
11002	6	4	4	4
11003	8	3	3	3
11005	14	3	3	3
11006	17	6	5	6
11007	14	5	4	5
11008	18	5	4	5
11009	23	6	5	6
11011	14	6	5	6
11012	6	3	3	3
11013	35	8	6	6
11014	12	3	3	3
11016	10	5	5	5
11017	14	6	5	6
43527/3453	27	21	21	21
1807/3463	25	17	17	17
Total panel members detected	383	185	171	181

4.2. Seroconversion sensitivity

An evaluation of HBV seroconversion sensitivity between PRISM® HBsAg and the ARCHITECT® HBsAg assays was conducted using 32 commercially available panels (Table 2). Seroconversion sensitivity is an assessment of the reduction in the early window period during the acute phase of HBV infection. In this study, the ARCHITECT® HBsAg prototype assay detected more panel members (185 of 383) than the ARCHITECT® HBsAg Qualitative assay (171) or the PRISM® HBsAg assay (181). In addition, seroconversion sensitivity of the ARCHITECT® HBsAg prototype assay was evaluated against a competitor HBsAg assay with 14 challenging seroconversion panels (Table 3). In this case, the ARCHITECT® HBsAg prototype assay detected more panel members than a competitor HBsAg assay (73/140 vs. 62/140, respectively). Therefore, the ARCHITECT® HBsAg prototype assay has better detection of acute HBV infection than any of the comparator assays.

4.3. Mutant sensitivity

An eleven member panel, including wild type, negative control, and nine recombinant HBsAg mutants of the "a" determinant was utilized to evaluate mutant detection using the PRISM® and ARCHITECT® HBsAg assays. The recombinant mutants consisted of recombinant HBsAg antigens with five single amino acid substitutions at positions 123, 129,133, 144, 145, and two double amino acid substitutions at positions 142 and 145, and two insertion mutants at amino acid position 122. The recombinant antigens had concentrations ranging from 0.053 to 1.143 ng/ml and were targeted to achieve an S/CO of approximately 2.0 S/CO in the ARCHITECT® HBsAg prototype assay (Table 4). A mean S/CO value equal to or greater than 1.00 is considered reactive in each assay. The PRISM® HBsAg assay detects all first and second loop mutants except for T123A and the 122 insertion mutants. Though both ARCHITECT® HBsAg assays have the ability to detect each of the 10 recombinant antigens tested, the ARCHITECT® HBsAg Qualitative assay does not detect substitutions at positions T123A and D144A of the "a" determinant at the concentrations evaluated. This difference between the two ARCHITECT® HBsAg assays reflects the enhanced sensitivity of the prototype assay. Based on this data, the ARCHITECT® HBsAg prototype assay has broader detection of HBsAg mutants than the PRISM® HBsAg assay and is more sensitive than the ARCHITECT® HBsAg Qualitative assay.

Table 3
Seroconversion sensitivity: comparison of ARCHITECT® HBsAg prototype and a competitor HBsAg assay with 14 seroconversion panels.

Panel ID	Panel members	ARCHITECT® HBsAg prototype	Competitor
PHM 903	6	4	3
PHM 908	8	4	3
PHM 909	7	5	4
PHM 910	6	4	4
PHM 911	25	6	6
PHM 912	9	3	2
PHM 915	12	11	6
PHM 916	11	3	2
PHM 919	9	6	5
PHM 920	6	4	4
PHM 922	12	7	8
6277	11	6	5
6278	11	8	8
6279	7	2	2
Total panel members detected	140	73	62

Table 4
Mutant detection: comparison of ARCHITECT® HBsAg prototype, ARCHITECT® HBsAg Qualitative, and PRISM® HBsAg.

Abbott HBsAg recombinant mutant panel	HBsAg concentration (ng/ml)	ARCHITECT® HBsAg prototype (positive, S/CO ≥ 1)	ARCHITECT® HBsAg Qualitative (positive, S/CO ≥ 1)	PRISM® HBsAg (positive, S/CO ≥ 1)
Wild type	0.123	2.19	1.56	2.24
Q129H	0.107	2.04	1.48	1.86
M133L	0.129	2.06	1.54	2.11
D144A	0.053	1.71	0.75	1.14
G145R	0.200	2.52	2.39	3.57
P142L + G145R	0.214	2.58	2.80	5.17
P142S + G145R	0.217	2.61	2.92	4.80
T123A	0.108	1.89	0.66	Not detected
122NT (insertion)	1.143	3.75	4.48	Not detected
122RA (insertion)	0.500	2.64	2.65	Not detected
Negative control	0	0.21	0.19	0.27

4.4. Assay specificity

To evaluate assay specificity, a total of 6482 blood donor specimens (serum or plasma) and 496 routine hospital samples from the United States and Germany were tested with the ARCHITECT® HBsAg Qualitative assay and the ARCHITECT® HBsAg prototype assay. The results presented in Table 5 demonstrate that total assay specificity of the ARCHITECT® HBsAg prototype is 99.94% whereas the specificity of the ARCHITECT® HBsAg Qualitative assay is 99.96%. Though slight differences exist between blood donors and the diagnostic populations tested, these differences are more reflective of the sample numbers rather than actual differences observed. The data indicate that the sensitivity improvement of the ARCHITECT® HBsAg prototype assay does not compromise assay specificity.

4.5. Assay interference

Two hundred-six potentially interfering specimens from viral or bacterial infections, autoimmune diseases, pregnant or multiparous females, elevated IgG and/or IgM levels, human anti-mouse antibodies (HAMA), hemodialysis, or multiple transfusion recipients were used to assess specificity performance of the ARCHITECT® HBsAg prototype assay. Of the 206 specimens, S/CO values ranging from 0.18 to 0.93 were observed (Table 6). Therefore, no adverse effect on the performance of the ARCHITECT® HBsAg prototype assay was observed for any of the medical conditions evaluated. Further, none of the medical conditions had an effect on antigen recovery as HBsAg spiked at low levels (S/CO approximately 2.0) was detected by the prototype assay (data not shown).

Table 6
Results of ARCHITECT® HBsAg prototype assay tested with interfering specimens.

Specimen category	*N*	Reactive	S/CO range
Anti-nuclear antigen	3	0	0.21–0.24
Chlamydia trachomatis	5	0	0.27–0.30
Cytomegalovirus	10	0	0.22–0.63
Dialysis patients	25	0	0.19–0.31
Epstein-Barr virus	5	0	0.19–0.29
HAMA	10	0	0.23–0.48
Hepatitis C virus	10	0	0.22–0.28
Herpes simplex	9	0	0.20–0.24
Hemophilia	9	0	0.22–0.28
HIV antigen	10	0	0.21–0.86
HIV 1	9	0	0.22–0.32
HIV 2	10	0	0.22–0.93
HTLV I/II	6	0	0.21–0.27
Influenza immunized	10	0	0.21–0.28
Multiparous females	10	0	0.18–0.25
Multiple myeloma	10	0	0.20–0.26
Neisseria gonorrhoeae	5	0	0.23–0.32
Rheumatoid factor	9	0	0.20–0.34
Toxoplasma gondii	4	0	0.21–0.32
Treponema pallidum	8	0	0.20–0.34
Pregnancy – first trimester	10	0	0.19–0.23
Pregnancy – second trimester	10	0	0.19–0.58
Pregnancy – third trimester	9	0	0.19–0.46
Samples tested	206		
Reactive (S/CO ≥ 1.00)		0	
S/CO range			0.18–0.93

5. Discussion

It has been reported that the Abbott PRISM® HBsAg assay has superior performance for the detection of HBV seroconversion among 17 CE-marked HBsAg immunoassays.[15] In this study, we demonstrate that the sensitivity of the ARCHITECT® HBsAg prototype assay is slightly better than that of PRISM® HBsAg, detecting 185 vs. 181 samples from 32 commercially available HBV seroconversion panels (total of 383 bleeds), and much better than a competitor's HBsAg assay (73 vs. 62 out of 140 total seroconversion bleeds). Additionally, the sensitivity improvement of the ARCHITECT® HBsAg prototype assay was demonstrated in analytical performance, detecting 0.016 IU/ml vs. 0.027 IU/ml for the ARCHITECT® HBsAg Qualitative assay, an approximate 40% sensitivity improvement.

Furthermore, the sensitivity improvement of the ARCHITECT® HBsAg prototype assay also enhanced the detection of HBsAg mutants, including the T123A substitution mutant. It has been reported that the ARCHITECT® HBsAg assay (Abbott list 06C36)

Table 5
Specificity: comparison of ARCHITECT® HBsAg prototype and ARCHITECT® HBsAg Qualitative using blood donors and diagnostic samples.

Country	Samples	ARCHITECT® HBsAg prototype	ARCHITECT® HBsAg Qualitative
USA	Blood donors (*n* = 3992)	99.97% (IR = 4, RR = 1)	99.97% (IR = 3, RR = 1)
USA	Diagnostic (*n* = 99)	100% (IR = 0, RR = 0)	100% (IR = 0, RR = 0)
Germany	Blood donors (*n* = 2490)	99.96% (IR = 3, RR = 1)	99.96% (IR = 1, RR = 1)
Germany	Diagnostic (*n* = 397)	99.50% (IR = 2, RR = 2)	99.75% (IR = 1, RR = 1)
Total	All (*n* = 6978)	99.94% (IR = 9, RR = 4) IRR = 0.129%	99.96% (IR = 5, RR = 3) IRR = 0.072%

IR, initial reactive; RR, repeat reactive; IRR, initial reactive rate.

detected all recombinant HBsAg mutants evaluated, particularly those from amino acid regions (110–150) where other HBsAg assays have impaired reactivity.[16] However, this assay failed to detect a native HBsAg mutant sample (L94S, L97V, L98V, and T123A) from a Thailand donor.[17] We have demonstrated that the current ARCHITECT® HBsAg prototype assay can detect this native mutant with a 1.60 S/CO while the ARCHITECT® HBsAg Qualitative assay fails to detect it with a 0.61 S/CO (data not shown). This result further indicates that by utilizing a combination monoclonal and polyclonal antibody conjugate for detection, the ARCHITECT® HBsAg prototype assay has improved sensitivity for HBsAg mutant detection.

Also of significance, the sensitivity improvement of the ARCHITECT® HBsAg prototype assay did not compromise assay specificity (99.94%, $N = 6978$) and did not result in any adverse effects on assay performance when testing specimens from unrelated medical conditions. Therefore, we conclude that the HBsAg prototype assay offers high sensitivity and broad mutant detection for the detection, diagnosis, and management of HBV infection on the Abbott ARCHITECT® instrument, at the same time providing automation and high sample throughput.

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None.

Conflict of interest

All authors are employees of Abbott Laboratories. There is no conflict of interest to be declared.

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