

Original Article

## NeuMoDx random access molecular diagnostic system for detection and quantification of hepatitis B virus in clinical samples

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### Abstract

**Introduction:** Currently, several molecular assays are available to detect and quantify HBV DNA in clinical samples. We aimed to characterize and compare the clinical performance of newly designed NeuMoDx PCR to the existing *artus* PCR.

**Methodology:** The plasma HBV DNA levels of 96 clinical and 5 external quality control samples were measured by NeuMoDx and *artus* assays simultaneously in Kocaeli University, Turkey. The linearity, agreement and the correlation between two assays were determined by Deming regression analysis, Bland-Altman plotting, the chi-square and the relative absolute error statistical analyzes. For all statistical analyzes, the XLSTAT statistical program was used.

**Results:** The mean (standard deviation; SD) age was  $45.07 \pm 12.29$ . HBsAg S/Co median (range) was  $4,273.4 \pm 1,138.1$  and ALT U/L median (range) was  $27 \pm 16$ . The mean (SD) of HBV DNA was  $1.46+E6 \pm 1.0+E4$  for NeuMoDx and  $1.54+E5 \pm 4.7 + E4$  for *artus* assays. The Deming regression indicates a linear correlation (95% confidence). The chi-square test indicates strong correlation ( $p < 0.001$ ). Bland-Altman analysis confirms that the measurement difference is acceptable. The relative absolute error analysis for *artus* showed relatively less and more consistent error rate. With 5 external quality check samples, the statistical significance was low ( $p = 0.566$ ).

**Conclusions:** The NeuMoDx HBV assay showed an excellent analytical performance by providing a rapid, high throughput technology in a random-access testing system in clinical samples and may be a new solution for viral load quantification in the management of HBV infections.

**Key words:** Chronic hepatitis B; hepatitis B virus; viral load; polymerase chain reaction; regression analysis; Chi-Square test.

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### Introduction

Hepatitis B is a potentially life-threatening infection of liver which is caused by hepatitis B virus (HBV) belonging to *Hepadnaviridae* family. The infection may progress as clearance of HBV, acute infection or chronic hepatitis B infection resulting organ failure and consequently hepatocellular carcinoma (HCC). Although no cure exists for HBV infection, the best way for prevention is vaccination [1]. HBV is transmitted through unprotected sexual intercourse, sharing infected needles or other injecting equipment and infected mother to baby during pregnancy, birth or breastfeeding [2]. According to the World Health Organization (WHO), an estimated 257 million people were living with chronic hepatitis B (CHB) infection globally and approximately 1.34 million deaths, mostly associated with cirrhosis and HCC was reported. [3]. Turkey with overall 4% hepatitis B surface antigen

(HBsAg) positivity, is located in the intermediate areas (2% - 7%) and at least one third of the population in Turkey has been exposed to HBV infection [4,5]. Although, there is no evidence that anti-viral treatment is effective for acute hepatitis B infection, adequate treatment can reduce the morbidity and mortality rate in chronic HBV infections [1]. Thus, early detection enables an opportunity to identify those at risk of progression, reduce complications of liver cirrhosis and liver cancer, and reduce the risk of transmission of the virus to others.

A laboratory diagnosis of hepatitis B infections can be done by serological tests and nucleic acid tests (NATs). On the other hand, for assessing the level of liver fibrosis, stage of HBV disease and eliminating other causes of liver diseases, liver biopsy is used and still accepted as a gold standard [6]. However, biopsy is an invasive, painful and costly procedure, and there is a

risk of complications and should be done in patients requiring biopsy [7]. Laboratory diagnosis of hepatitis B infection initiates with antigen-antibody-based immunoassay techniques including HBsAg, hepatitis B surface antibody (HBsAb), total hepatitis B core antibody (antiHBc), hepatitis B core antigen (immunoglobulin M (HBcIgM), hepatitis B e antigen (HBeAg), and hepatitis B e antibody (HBeAb / anti-HBe) that can be performed on either serum or plasma. These screening tests based on the measurement of HBV specific antigen and antibodies found in specimens, are performed to determine acute or chronic and current or past infections [8]. However, drug resistance mutations, occult infections as well as low level of HBsAg and viral load values during window period of HBV infections may be undetectable by using one or combination of these serological tests [9-12]. To validate HBV infection and follow up the chronic patients, nucleic acid-based detection assays that quantify viral HBV DNA, determine drug resistance mutations, occult and window period HBV infections in clinical samples, have been widely employed [11,12].

Currently, the most widely used molecular techniques for quantification of HBV DNA are polymerase chain reaction (PCR), digital droplet PCR, ultraviolet spectrophotometry, isothermal amplification methods, and biosensors [13]. Because of the cost and time limitations of these tests, alternative innovative methods that are time and cost-effective, easy-to-use, analytical sensitive to detect even very low levels of HBV DNA are required to determine, evaluate, and monitor the treatment of HBV infections in chronic carriers.

NeuMoDx HBV Quant molecular diagnostic system has been recently designed and developed for revolutionary diagnostic solutions for fully integrated HBV PCR systems. This new system is easy to use and has random access enabling to mix specimens and tests as well as allowing loading/unloading reagents and specimens at any time. The stability of the reagents at room temperature, allows long in use shelf life for clinical laboratories. NeuMoDx HBV Quant assay offers ‘sample to result’ testing system with turnaround times as low as 40 minutes, compared to more than three hours for other systems, enabling faster treatment decisions for clinicians and better patient outcomes [14-16].

With the development of different measurement assays for the detection of infectious diseases, analytical comparison of the existing methods is required to assess the reliability and accuracy of the new technique. Bland Altman plot is a method of data

plotting in analyzing the correlation and agreement between two different assays for setting up a new laboratory test [17]. Deming regression analysis also called in variables regression, unlike linear regression, is used to compare two measurement methods when both variables are assumed to be measured with error [18].

In this study, the clinical performance of next generation fully integrated NeuMoDx HBV Quant PCR system was characterized and compared by using Deming regression and Bland-Altman plot analyzes to the existing *artus* PCR system for the detection and quantification of HBV in clinical samples as an alternative choice for medical laboratories and clinicians.

## Methodology

A total of 96 daily/routen accepted plasma samples of the patients admitted for screening, diagnosis and treatment control to Kocaeli University, PCR Unit in Turkey, and five external quality control samples (HBV EQQ, Motakk, Ankara, Turkey) were enrolled in this study. In patients with chronic hepatitis B, HBsAg and alanine aminotransferase (ALT) levels were analyzed before performing HBV DNA measurements. The quantitative results of HBsAg were determined by Abbott Architect quantitative screening assay (Abbott, Abbott Diagnostics, Abbott Park, IL, USA). Architect HBsAg test results were evaluated on Sample / Cutt Off (S / CO). HBV DNA levels of laboratory samples and five external quality controls (EQCs) were measured by running both commercially available NeuMoDx (Qiagen, NeuMoDx HBV Quant PCR, Ann Arbor, USA) and *artus* HBV PCR kit (Qiagen, *artus* HBV QS-RGQ, Hilden, Germany) molecular systems in the same day, simultaneously under the same laboratory conditions. The obtained viral loads in IU/mL were converted into log IU/mL values to be used in the correlation analysis between NeuMoDx and *artus* HBV assays. To predict the stage of liver fibrosis and the presence of cirrhosis in CHB patients, Ishak Modified Knodell Score was used [19].

The ethical approval of the study was taken by the Clinical Research Ethics Committee of Kocaeli University with the decision number KKAEK 2011/104.

## Statistical Analysis

The linearity between the two measurements was carried out by Deming regression analysis. For Deming regression analysis, negatives were anchored to the half of the detection limit (LoD) for the particular test,

instead of assuming as zero. The calculations were done via an in-house python script.

In the study, the correlation and the agreement between two assays of the sample measurements of NeuMoDx and *artus* in log IU/mL were interpreted by Bland-Altman plot analysis. The Bland-Altman plot was obtained through plotting the differences and the averages of the measurements using different test methods for each sample. The calculations were done via an in-house python script.

A significance level of 95% was used for calculation of chi-square test between NeuMoDx and *artus* measurements. The p-value was calculated using Microsoft Excel.

Relative absolute errors were calculated as the absolute difference between the logs of measured and true values of the external quality check samples. The significance test was performed using two tailed t-test. The relative absolute error of samples obtained through NeuMoDx and *artus* in comparison to declare true concentrations of external quality control check samples.

For all statistical analyzes and figure, the XLSTAT statistical software program (Addinsoft Inc., New York, USA) was used.

**Results**

Out of 96 patients admitted from the external center infectious diseases clinics in Kocaeli province (Derince, Golcuk and Darica) and Kocaeli University Hospital internal diseases, urology, neurosurgery, family medicine, infectious disease and gastroenterology clinics, male (n = 64, 64%) patients were more predominant than female (n = 32, 33%). The age of the patients was ranging from 22 to 79 and the mean (standard deviation; SD) age of the patients was calculated as 45.07 ± 12.29. HBsAg S/Co median (range) was 4,273.4 ± 1,138.1 and ALT U/L median (range) was 27 ± 16. In 20 (20%) of 96 patients, there are comorbidity diseases such as B cell neoplasia, lymphoma, liver-colon-endometrium-breast cancer, diabetes, etc. Likewise, in 2 (6%) of 36 patients treated, HCC developed. The clinical, biochemical, serological, demographic, histopathologic and medical records of the patients were assessed all together and is given on Table 1.

Amongst 96 clinical samples measured, the mean (SD) of HBV DNA was 1.46+E6 ± 1.0+E4 for NeuMoDx assay and 1.54+E5 ± 4.7+E4 for *artus* assay. By NeuMoDx assay, HBV DNA was quantitated in 40 (42%) samples however, viral load was not detected in 56 (58%) samples. By *artus* assay, HBV viral load was

detected in 32 (34%) samples however, no viral load was detected in 64 (66%) samples with the same assay. Additionally, while viral load was detected with NeuMoDx assay in 8 (8%) samples, no viral load was detected with the *artus* assay for these samples. Conversely, viral loads detected by *artus* assay (n = 32, 34%) were also detected by NeuMoDx assay. HBV DNA levels of both plasma and the external quality control samples detected by both assays are presented on Table 2.

**Table 1.** Demographic, laboratory and medical findings of the patients

Characteristics	Patient group
<b>Patients, n</b>	96
<b>Gender, M/F, n (%)</b>	64 (64)/32 (33)
<b>Age, years (mean ± SD)</b>	45 ± 13
<b>Sampling, center: clinic; patient, n</b>	<b>Kocaeli univ. hospital:</b> internal medicine;1, urology;21, brain surgery;1, family medicine;1, infectious diseases; 21, gastroenterology; 18 <b>Outer centers in Kocaeli:</b> Derince; 5, Golcuk; 3, Darica; 25
<b>ALT value, U/L mean ± SD</b>	27 ± 16
<b>HBsAg value, S/Co mean ± SD</b>	4273.4 ± 1138.1
<b>NeuMoDx HBV DNA load mean ± SD</b>	1.46+E6 ± 1.0+E4
<b><i>artus</i> HBV DNA load mean ± SD</b>	1.54+E5 ± 4.7+E4
<b>Biopsy status, n (%)</b>	
<b>Patients with biopsy, n = 14 (15)</b>	HAI score; 4 in 4, 5 in 2, 6 in 3, 7 in 3, 8 in 2 Fibrosis score; 0 in 1, 1 in 1, 2 in 4, 3 in 6, 4 in 2
<b>Patients without biopsy, n = 82 (85)</b>	-
<b>Comorbidity, n (%)</b>	19 (20%)
B cell neoplasia	1 (5%)
Lymphoma	2 (11%)
HCC	2 (11%)
Colon-endometrium-breast Ca	3 (16%)
Type 2 diabetes	1 (5%)
Basal cell skin tumor	1 (5%)
Liken planus	1 (5%)
Chronic/erythematous antral gastritis	2 (11%)
Infertility	1 (5%)
Hypertension	1 (5%)
Hepatosteatosi	2 (11%)
Tubular adenoma	1 (5%)
Surrenal adenoma	1 (5%)

M: male; F: female; univ: university; HCC: hepatocellular carcinoma; Ca: cancer.

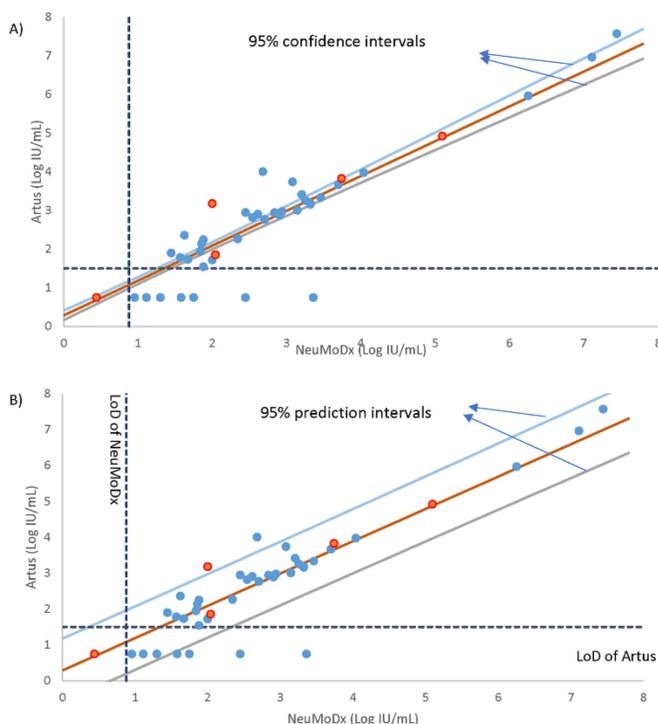
It is thought that the existence of the particular biomarker may not necessarily be zero and equal distribution of real values may be possible below the LoD. Assuming an equal distribution reflects as a mean of the negatives to be at the half of lower LoD. Thus, negatives were replaced in Deming regression with LoD/2 for each particular test as is a common practice. Of the results, Deming regression analysis indicates that there is a linear correlation between the NeuMoDx and *artus* measurements. It is apparent that the higher sensitivity of NeuMoDx result in sample measurements with highest divergence from the regression line. Additionally, the regression line proximity to the origin was small as expected for tests measuring same biomarkers. Deming regression of the log measurements obtained through NeuMoDx and *artus* with the confidence intervals (Figure.1A) and the prediction intervals (Figure. 1B) indicate that the area where any Deming regression between NeuMoDx and *artus* would be expected with 95% confidence and the area where any new sample point is expected to be inside with 95% confidence, respectively. The chi-square test indicates strong correlation between measurement reads of NeuMoDx and *artus* ( $p < 0.001$ ) in accordance with Deming regression analysis (Table 3).

According to the Bland-Altman analysis, the measurement difference between the tests for any sample has rarely surpassed a log of 1 indicating that, it is reasonable to expect that the difference between tests would rarely surpass 10 times of each other. On Bland-Altman plot comparing the NeuMoDx and *artus* measurements, the center line indicates the mean of differences and the upper and lower horizontal lines indicate the 1.96 times the standard deviations (95% of the data) (Figure 2). Deming regression analysis and

Bland-Altman plot analysis of samples measured by both NeuMoDx and *artus* assays, are shown in Figure 1 and Figure 2, respectively.

Based on the relative absolute error analysis, *artus* showed relatively less and more consistent error rate than NeuMoDx assay. However, with only 4 external

**Figure 1.** Deming regression of the log measurements obtained through NeuMoDx and *artus* with confidence intervals (A) or prediction intervals (B). The confidence interval indicates the area where any Deming regression between NeuMoDx and *artus* would be expected with 95% confidence. The prediction interval indicates the area where any new sample point is expected to be inside with 95% confidence.



**Table 2.** NeuMoDx, *artus* and external quality control HBV DNA measurements in clinical samples.

Patient sampling, IU/mL	Results, IU/mL n (%)	
	NeuMoDx	<i>artus</i>
Negative	56 (58%)	64 (66%)
< 10 <sup>1</sup>	1 (1%)	-
> 10 <sup>1</sup>	14 (15%)	18 (19%)
> 10 <sup>2</sup>	21 (22%)	12 (13%)
> 10 <sup>3</sup>	1 (1%)	-
> 10 <sup>5</sup>	1 (1%)	1 (1%)
> 10 <sup>6</sup>	2 (2%)	1 (1%)
<b>EQC sampling</b>		
Negative	1 (20%)	1 (20%)
< 10 <sup>1</sup>	-	1 (20%)
> 10 <sup>1</sup>	2 (40%)	-
> 10 <sup>2</sup>	1 (20%)	2 (40%)
> 10 <sup>4</sup>	1 (20%)	1 (20%)

EQC: external quality control.

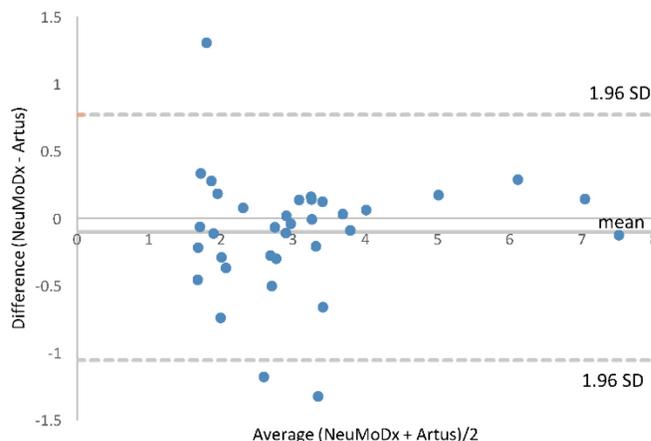
quality control samples, the statistical significance of the two distributions were low ( $p = 0.566$ ) and it is not possible to reject the two distributions are of separate. The relative absolute error of samples obtained through NeuMoDx and artus in comparison to declare true concentrations of the external quality control samples ( $p = 0.566$ ) is shown on Figure 3.

**Discussion**

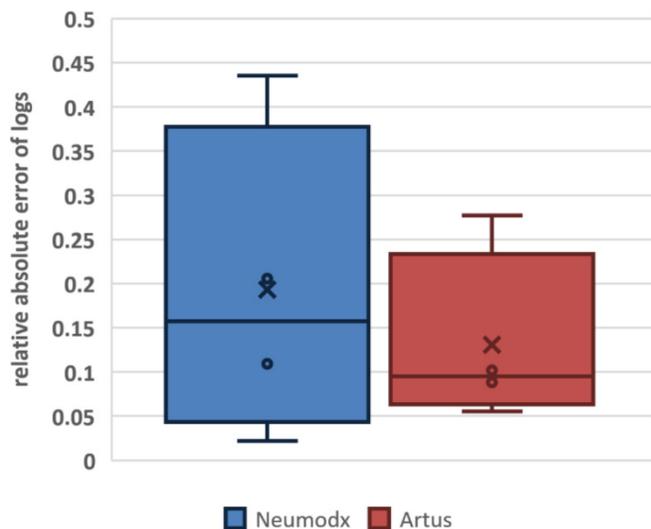
Viral load measurement is a crucial tool in determination, diagnosis and the proper treatment of patients with HBV infection. As, antiviral treated HBV patients need to be constantly monitored to measure the effectiveness of antiviral agents, HBV DNA levels in blood should be measured by using NAT assays [20]. Until now, viral load can be determined by several commercially available nucleic acid testing platforms [21]. The most widely used artus HBV PCR provides excellent analytical performance with high sensitivity, specificity and with broad range of linear quantification. However, newly designed fully automated PCR based molecular diagnostic system NeuMoDx HBV assay provides faster time to result for NAT producing initial results within an hour with continuous random-access processing and prove 100% analytical specific quantitative viral load levels [14-16].

In the present study, we investigated the performance of the new NeuMoDx Quant HBV PCR assay for the diagnosis and monitoring of HBV infection because, apart from few abstracts, there has not been enough research in the literature regarding performance characteristics of this new system in clinical samples [14-16,22]. The clinical performance characteristics of NeuMoDx assay was evaluated by comparing with commonly used artus assay and the measurements received by both assays were analyzed and the relationship between them were determined by Deming regression analysis, Bland-Altman plotting, the chi-square and the relative absolute error statistical

**Figure 2.** Bland-Altman plot comparing the NeuMoDx and artus measurements. The center line indicates the mean of differences and the upper and lower horizontal lines indicate the 1.96 times the standard deviations (95% of the data).



**Figure 3.** The relative absolute error of samples obtained through NeuMoDx and artus in comparison to declared true concentrations of external quality control check samples ( $p=0.566$ ).



**Table 3.** Contingency table comparing the distributions of sample measurements of NeuMoDx and artus in UI/mL.

NeuMoDx	artus								Total
	< 10 IU/mL	b/w 10 - 10 <sup>2</sup>	b/w 10 <sup>2</sup> - 10 <sup>3</sup>	b/w 10 <sup>3</sup> - 10 <sup>4</sup>	b/w 10 <sup>4</sup> - 10 <sup>5</sup>	b/w 10 <sup>5</sup> - 10 <sup>6</sup>	b/w 10 <sup>6</sup> - 10 <sup>7</sup>	> 10 <sup>7</sup>	
< 10 IU/mL	57	0	0	0	0	0	0	0	57
b/w 10 - 10 <sup>2</sup>	6	5	3	0	0	0	0	0	14
b/w 10 <sup>2</sup> - 10 <sup>3</sup>	0	3	8	1	1	0	0	0	13
b/w 10 <sup>3</sup> - 10 <sup>4</sup>	1	0	0	11	0	0	0	0	12
b/w 10 <sup>4</sup> - 10 <sup>5</sup>	0	0	0	1	0	0	0	0	1
b/w 10 <sup>5</sup> - 10 <sup>6</sup>	0	0	0	0	1	0	0	0	1
b/w 10 <sup>6</sup> - 10 <sup>7</sup>	0	0	0	0	0	1	0	0	1
> 10 <sup>7</sup>	0	0	0	0	0	0	1	1	2
<b>Total</b>	<b>64</b>	<b>8</b>	<b>11</b>	<b>13</b>	<b>2</b>	<b>1</b>	<b>1</b>	<b>1</b>	<b>101</b>

b/w: between.

analyses. According to WHO guidelines on hepatitis B and C testing, HBV DNA is measured in international units (IU/mL) as the recognized international standard [23]. However, a logarithmic transformation of original data is commonly preferred in method comparison studies to obtain a better distribution of the differences [24-27]. Thus, HBV DNA measurements in IU/mL were transformed to log values in the current study to assess the agreement and the correlation of data.

The study pointed out that NeuMoDx HBV assay has a strong correlation and agreement over the complete linear range (95% limits of agreement) with 95% confidence. Similarly, Couture *et al.* reported an excellent linear correlation ( $R^2 > 0.99$ ) between NeuMoDx and Beckman –VERIS systems in clinical samples [22]. Apart from analytical sensitivity in linearity, lower limit of quantification (LLoQ) and upper limit of quantification (ULoQ) values were also established and the manufacturer provides LLoQ and ULoQ of NeuMoDx HBV assay as 0.88 Log<sub>10</sub> IU/mL (7.6 IU/mL) and 9.02 Log<sub>10</sub> IU/ml respectively for all HBV genotypes. For *artus* assay, the analytical detection limit (95%) by the manufacturer is given as 3.8 IU/mL ( $p = 0.005$ ) and the *artus* HBV assay covers a linear range from 1.1 IU/mL to at least  $4 \times 10^9$  IU/mL. Based on the results, the manufacturer provides the analytical sensitivity and the specificity of the NeuMoDx HBV assay as 100% (CI 96.4% - 100%) and 95.6% (CI 91.9% - 97.7%), respectively. In the current study, we clearly stated that NeuMoDx results in sample measurements with highest divergence from the regression line by Deming regression analysis (95% confidence) (Figure 1). However, the most divergent measurements lay beyond the lower LoD of *artus* assay, thus the biggest difference may be attributed to the higher sensitivity of NeuMoDx as its LoDs is lower. Also, for tests measuring the same biomarkers, the proximity of the regression line to the origin was found to be small (the regression line intersects at 0.29 Log IU/mL) (Figure 1). According to the Bland -Altman plot analysis, some of the samples tested were considered to exceed 1 log but, the rarely measured difference between the tests is acceptable (Figure 3).

The observed difference between the viral loads obtained by both assays is that the results of the NeuMoDx assay are slightly higher than those from the *artus* assay (Table 2). Another difference was that *artus* showed relatively less and constant error rate than NeuMoDx assay. However, the relative absolute error analysis confirmed that the absolute difference between the logs of measured and true values of the external quality control samples were low ( $p = 0.566$ ) which

indicates no significant difference between methods in regards to error may be detected with the current set of samples (Figure 3). As compatibility with Deming regression analysis, the chi-square test also indicated strong correlation between measurements received by NeuMoDx and *artus* with a significance level of 95% ( $p < 0.001$ ) (Table 3).

Although NeuMoDx HBV assay showed an excellent clinical performance, the assay has a significant limitation. The clinical performance of the kit has been assessed only for plasma specimens prepared from whole blood collected with ethylene diamine tetra acetic acid (EDTA)/anticoagulant citrate dextrose (ACD) as anti-coagulant. Whereas, serum samples have been used in *artus* assay although, manufacturers also recommend the use of plasma samples [21]. As, different types of of clinical samples including serum, have not been performed for NeuMoDx yet, the analytical performance of the test in different sample types is not yet known.

## Conclusion

Briefly, our findings have shown that the NeuMoDx HBV assay provides excellent analytical performance in clinical samples, providing a fast and high throughput technology in a random- access test system. However, testing with a larger sample set is advised to improve statistical significance of our assessments. These features could make the NeuMoDx HBV test a new solution for viral load measurement for effective patient management in laboratories and clinics.

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