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Clinical performance of two new, fully integrated molecular platforms used for HIV-1, HBV and HCV viral load analysis, the NeuMoDx 288 and the Alinity m.

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ABSTRACT

Background: Viral load (VL) determination in patients with human immunodeficiency virus type 1 (HIV-1), hepatitis B virus (HBV) and hepatitis C virus (HCV) is essential for proper patient management and follow-up. New molecular platforms have been developed to fully automate these diagnostic assays.
Objective: Evaluation of the clinical performance of HIV-1, HBV and HCV VL assays on the Alinity m (Abbott) and NeuMoDx (Qiagen) molecular platforms.
Method: Test panels of the three viruses have been compiled of 100 plasma and/or serum samples per target containing non-detectable, non-quantifiable and quantifiable VLs. All samples were retrospectively tested on the Alinity m and NeuMoDx platforms according to manufacturers' instructions.
Results: A total of 74, 86 and 66 samples with valid results for both platforms were included in the HIV-1, HBV and HCV analysis respectively. Overall qualitative agreement of the assays on both platforms was 78% for HIV-1, 93% for HBV and 100% for HCV. Quantitative agreement (less than 0.5 log difference) was shown to be 68% for HIV-1, 68% for HBV and 94% for HCV.
Conclusion: The Alinity m and NeuMoDx HCV assay have a comparable performance. Quantification differences in the HIV-1 assay were mostly apparent in the lower VLs and under-quantification of the NeuMoDx HBV assay was observed.

1. Introduction

The global burden of infections with human immunodeficiency virus (HIV), hepatitis B virus (HBV) and hepatitis C virus (HCV) is substantial with 38 million people living with HIV, 257 million with HBV and 71 million with HCV. Altogether, these viral infections result in around 2 million deaths per year [1,2]. Viral load (VL) determination of these viruses in plasma samples has shown to be essential in managing patients infected with these viruses. VL testing has been reliably performed for over 20 years by (semi)-automated molecular workflow platforms as for example Cobas Ampliprep/Cobas Taqman (Roche Diagnostics) (CAP/CTM) and m2000 SP/RT (Abbott molecular). Analysis of VLs has been used not only to detect active infections, but also to monitor the effect of antiviral treatment or to detect potential development of antiviral resistance of these viruses [3–5].

Some years ago more advanced platforms such as the Cobas6800/8800 (Roche Diagnostics) and Panther (Hologic) have been introduced for VL testing of HIV-1, HCV and HBV infections and for screening of blood products. Recently, two additional platforms became available, the Abbott Alinity m to replace their m2000 system and the NeuMoDx 96/288 systems (Qiagen, Hilden, Germany). These new molecular platforms are highly efficient, flexible and fully-automated, provide a sample-in-result-out format, enable random access and can be bidirectionally linked to laboratory information systems. Importantly, these platforms have been designed to not only run assays for viral detection in plasma but an increasing portfolio of diagnostic tests for other pathogens has been launched or are under development. Based on the medium-size sample throughput of the medical microbiology department of the Leiden University Medical Center (LUMC), the Alinity m and NeuMoDx 288 were considered interesting candidates to further automate the molecular diagnostic workflow. In addition, the accompanying CE-IVD marked assays enable compliance to the European Union (EU) In Vitro Diagnostic Regulations [6]. The throughput of the NeuMoDx 288 platform is 288 samples per 8 h shift, with a time to result of the first

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samples of 60 min for DNA targets and 80 min for RNA targets [7]. The throughput of the Alinity m platform is approximately 300 samples every 8 h with a time to first result of 115 min for both DNA and RNA targets [8].

Despite the availability of international standards, comparative studies between different diagnostic platforms have shown variation in the determined VL in the same samples [9–11]. The aim of the current study is comparative analysis of the clinical performance of the new real-time PCR assays for VL testing of HIV, HBV and HCV on the Alinity m and the NeuMoDx 288 platforms.

2. Materials and methods

2.1. Samples

Remnant EDTA plasma and serum samples have been used in this study that were submitted to the LUMC between January 2017 and May 2019 for HIV-1, HCV and or HBV VL determination. Aliquots of these samples had been stored at −80° and were used in a reanalysis using the Alinity m and NeuMoDx platforms. A set of clinical samples was selected to cover a range of VLs and genotypes that were previously determined by CAP/CTM for HIV-1 and HCV, and a laboratory developed test (LDT) for HBV.

The HIV-1 panel consisted of 100 EDTA plasma samples, comprising 50 quantifiable VLs, i.e. VL within the limits of quantification (Table 1), 25 non-quantifiable VLs (NQ), i.e. VL detected but below the lower limit of quantification (LLOQ) and 25 negative samples (ND). The HIV-1 subtype distribution in the quantifiable samples is presented in figure S1. The HBV panel consisted of 92 EDTA plasma and 8 serum samples and comprised 50 quantifiable VLs, 25 NQ VLs, and 25 ND. The HCV panel consisted of 94 EDTA plasma and 6 serum samples and comprised 75 quantifiable VL samples and 25 ND samples. The genotypes distribution is presented in figure S2. Genotypes have been determined by Sanger nucleotide sequence analysis of the polymerase gene for HIV-1 and the NS5B gene for HCV.

After thawing, the samples had been tested within 24 h and residual sample was stored at 4 °C to enable retesting if required. If the volume was not sufficient for both new platforms and the initial VL was over 3.0 log, samples were diluted with negative plasma. In all but one case the maximum dilution was a factor 4. Only in one sample with a log 5 HCV VL, the dilution factor was 20. Testing has been performed according to manufacturer's instructions. Calibrators were tested when needed and controls had been run every 24 h. Additionally, for HBV two reference panels, Qnostics ($n = 13$) and NeuMoDx ($n = 27$) and a small prospective panel of 25 samples have been tested.

2.2. Assays

The LLOQ and upper limit of quantification (ULOQ) of the assays used in this study are summarized in Table 1. Viral loads of HBV and HCV are reported in IU/ml on the Alinity m and the VL of HIV-1 in C/ml.

Table 1
Limits of quantification.

	HIV-1 LLOQ (log)[a]	ULOQ (log)[a]	HCV LLOQ (log)[a]	ULOQ (log)[a]	HBV LLOQ (log)[a]	ULOQ (log)[a]
CAP/CTM	< 1.3	> 7.0	< 1.1	> 8.0	–	–
LDT	–	–	–	–	< 2.0	>7.0
Alinity	< 1.5	> 7.2	< 1.08	> 8.0	< 1.0	> 9.0
NeuMoDx	< 1.5	> 7.7	< 0.9	> 8.2	< 0.9	> 9.02

Abbreviations: LLOQ, lower limit of quantification; ULOQ, upper limit of quantification; LDT, laboratory developed test; CAP/CTM, Cobas Ampliprep/Cobas Taqman (Roche Diagnostics); HIV-1, Human immunodeficiency virus type 1; HBV, hepatitis B virus; HCV, hepatitis C virus.
[a] IU/ml.

For comparison of the HIV assays the Alinity m HIV-1 results have been converted to IU/ml since the NeuMoDx assay was a research use only kit which could only report in IU/ml. For this, the manufacturer's instructions were followed by using a conversion factor of 1.63 IU/C.

2.3. Analysis

Both qualitative and quantitative data have been analysed to investigate the performance of the Alinity m and NeuMoDx assays. The IU/ml have all been converted to logarithmic scale. A quantification difference of more than 0.5 log was considered significant, since this cut-off is generally used in molecular diagnostics and was calculated in samples in which both platforms reported a quantifiable VL or if one had a quantifiable VL and the other reported ND [11–13]. A Deming regression, Bland-Altman analysis and Pearson correlation were performed to analyze the agreement of each assay in samples in which both platforms measured a quantifiable VL. Additional discrepant testing was performed by retesting the samples, if required also by a third method (CAP_CTM or LDT). Statistics were performed using R statistical software, version 4.1.1 (R Core Team, 2021).

3. Results

A total of 226 of the 300 samples generated a valid result on both the Alinity m and NeuMoDx platforms. Hence, 74 HIV-1 samples, 86 HBV samples and 66 HCV samples are included for quantitative and qualitative analysis. A sample was excluded for analysis if the Alinity m or the NeuMoDx 288 platform failed to generate a valid result. In total, the Alinity m and NeuMoDx have performed 340 and 338 tests respectively including retesting of samples with invalid results for which sufficient remnant samples was available. The Alinity m had in total 78 invalid results of which 58 were caused by an error of the platform and 20 due to failed test criteria. The NeuMoDx had 48 invalid results of which 38 were caused by a platform error, four due to failed test criteria and six samples were on board of the platform for too long resulting in an expiration error. Six-teen samples were re-tested, due to invalid results, in a different dilution on the NeuMoDx so were therefore excluded, as well as three samples that have not been tested on one or both of the platforms.

3.1. HIV

Seventy-four clinical EDTA plasma samples were available for comparison: 22 ND VLs, 20 NQ VLs and 32 quantifiable VLs based on historical CAP-CTM results. Table 2 presents the distribution of the ND, NQ and >LLOQ results between all platforms. The overall qualitative agreement between the Alinity m and NeuMoDx is 78% (58/74) (Table 2).

The quantitative agreement of the Alinity m and NeuMoDx HIV-1 assays is 68% (27/40) (Fig. 1). In samples with quantifiable VLs determined by both the Alinity m and NeuMoDx, the quantitative agreement is 87% (27/31). One sample had a VL in both platforms which is above the upper limit of quantification. In five samples the NeuMoDx result was ND, but the Alinity m platform measured VLs between 1.5–2.1 log IU/ml and the CAP/CTM between ND and 2.4 log IU/ml. Alternatively, if the Alinity m result was ND, the NeuMoDx platform measured VLs between 2.0–2.4 log IU/ml, and the CAP/CTM between ND and <1.5 log IU/ml. In 4 samples with a significant difference between quantifiable VLs, the CAP/CTM platform measured a VL between the VLs of the Alinity m and NeuMoDx in 3/4 samples, and a higher VL compared to both platforms in one sample. Significant VL differences could not be attributed to specific genotypes (figure S3), although the only included genotype D has a quantifiable VL of 1.9 log IU/ml using the Alinity m assay and tested negative using the NeuMoDx assay, though the historical CAP/CTM result was NQ.

A good correlation between the two assays was found ($r = 0.93$, [95% confidence interval (CI) 0.86 to 0.97]; Deming regression

Table 2
Comparison of HIV-1 viral loads (in IU/ml) Alinity m, NeuMoDx and CAP/CTM ($N = 74$).

		NeuMoDx			CAP/CTM[b]		
		ND[a]	<1.5log	≥1.5log	ND[a]	<1.5log	≥1.5log
Alinity M	**ND[a]**	21	0	4	17	8	0
	<1.5log	7	2	1	3	7	0
	≥1.5log	5	2	32	2	5	32
CAP/CTM[b]	**ND[a]**	19	2	1	–	–	–
	<1.5log	13	2	5	–	–	–
	≥1.5log	1	0	31	–	–	–

[a] ND; non-detectable viral load.
[b] Historical results on fresh samples.

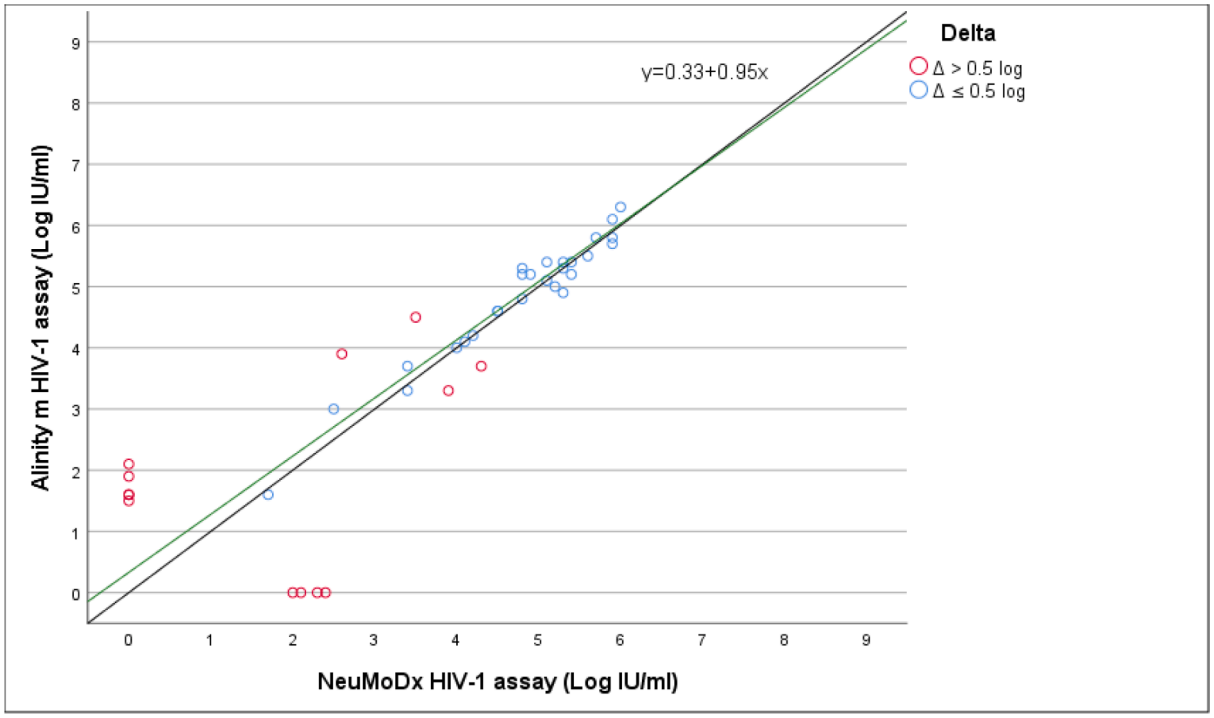

Fig. 1. Quantitative comparison of HIV-1 viral loads Alinity m versus NeuMoDx.
Scatter-plot presenting HIV-1 viral loads detected with Alinity m and NeuMoDx around the expected line (Alinity m log IU/ml = NeuMoDx log IU/ml) and best fit Deming regression line (green).
NB: there are 2 overlapping, indiscriminative dots in which the Alinity m measured a VL of 4.6 log IU/ml and NeuMoDx 4.5 log IU/ml.

equation, $y = 0.33\ [-0.51 - 1.31] + 0.95\ [0.77 - 1.11] * x$; Fig. 1). Bland Altman analysis showed that the Alinity VLs were on average 0.11 log higher than the NeuMoDx VLs (Bias: −0.11, +/- 0.40 log IU/mL).

3.2. HBV

Eighty-six samples were available for analysis, 81 EDTA plasma and 5 serum samples. They include 20 ND, 19 NQ and 47 quantifiable samples as measured in the LDT. Table 3 presents the distribution of the ND, NQ and >LLOQ results between all platforms. The overall qualitative agreement between the Alinity m and NeuMoDx is 93% (80/86). In samples in which the NeuMoDx result was ND, the Alinity m VLs are ≤1.9 log IU/ml.

The quantitative agreement of the Alinity m and NeuMoDx is 68% (36/54) and is displayed in Fig. 2. In samples with quantifiable VLs determined by both the Alinity m and NeuMoDx, the quantitative agreement was 72% (36/50), the VL in one sample was above the limit of quantification on both platforms so no quantitative agreement could be determined. The Alinity m quantified higher in all of the samples with a significant VL difference. The NeuMoDx measured a ND VL in three samples in which the Alinity m result was between log 1.3 (19) and log 1.9 (81) IU/ml and the historical results of the LDT are between ND and

Table 3
Comparison HBV viral loads (IU/ml) Alinity m NeuMoDx and LDT ($N = 86$).

		NeuMoDx			LDT[b]		
		ND[a]	<0.9 log	≥0.9 log	ND[a]	<2.0 log	≥2.0 log
Alinity m	**ND[a]**	24	0	0	16	8	0
	<1.0 log	2	0	2	0	3	1
	≥1.0 log	4	3	51	4	8	46
LDT[b]	**ND[a]**	17	0	3	–	–	–
	<2.0 log	11	1	7	–	–	–
	≥2.0 log	2	2	43	–	–	–

[a] ND; non-detectable viral load.
[b] Historical results on fresh samples.

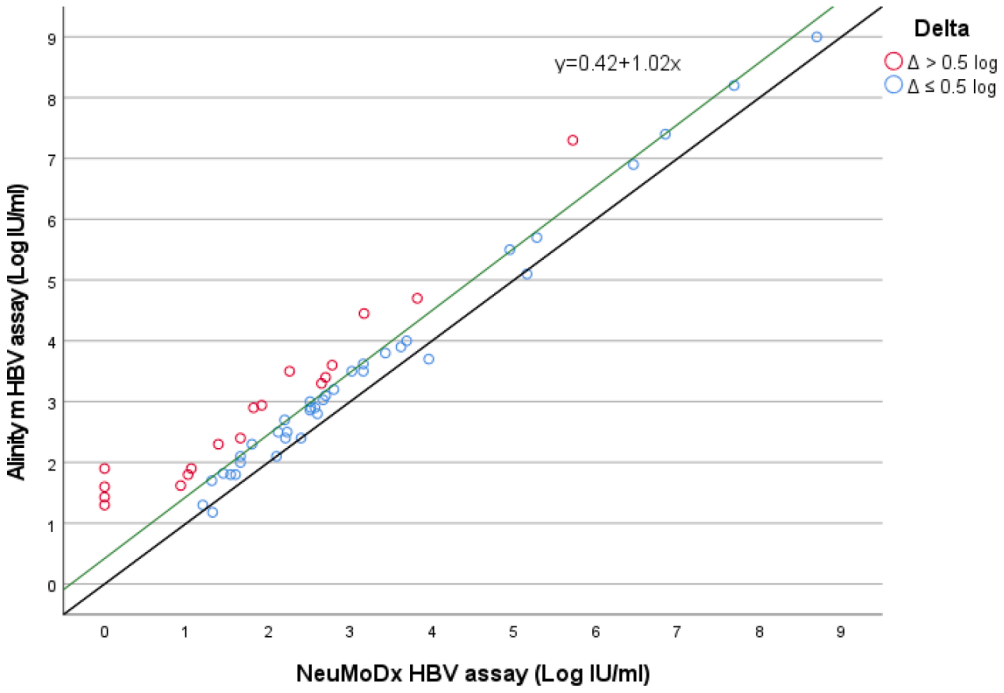

Fig. 2. Quantitative comparison HBV viral loads Alinity m versus NeuMoDx.
Scatter-plot presenting HBV viral loads detected with Alinity m and NeuMoDx around the expected line (Alinity m log IU/ml = NeuMoDx log IU/ml) and best fit Deming regression line (green).

log 2.6 (383) IU/ml.

A good correlation between the two assays was found ($r = 0.98$ [CI 0.96 to 0.99]; Deming regression equation, $y = 0.42$ [0.18 – 0.60] + 1.02 [0.97 – 1.11] * x; Fig. 2), and the Bland Altman analysis showed that the Alinity VLs were on average 0.48 log higher (bias: 0.48 ± 0.36 log IU/mL).

3.2.1. *Re-tested samples historical cohort and reference panel*

Since the results imply a possible under-quantification of the VL by the NeuMoDx assay for HBV as compared to the Alinity m assay, retesting 25 samples confirmed the under-quantification of the NeuMoDx (table S1). However, testing two reference panels, one obtained from NeuMoDx and one from Qnostics showed comparable results (table S2, S3 and Figure S4 and S5).

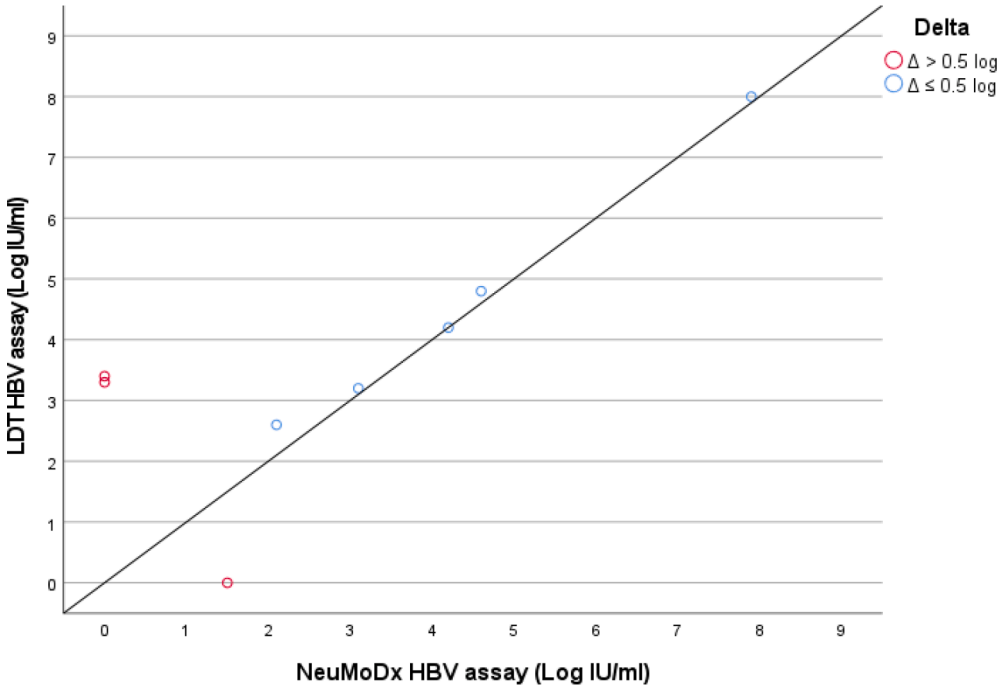

Fig. 3. Prospective quantitative comparison of HBV viral loads in NeuMoDx versus LDT.
Scatter-plot presenting HBV viral loads detected with Alinity m and NeuMoDx around the expected line (Alinity m log IU/ml = NeuMoDx log IU/ml).

This raised the question of the different outcomes could be attributed to differences in using frozen and fresh samples. A small prospective sample group of fresh samples was tested on the NeuMoDx. Twenty-one samples have been tested simultaneously on the NeuMoDx and the diagnostic LDT. Overall qualitative agreement is 76% (16/21). VLs detected by the LDT, which were ND in de NeuMoDx, are ≤3.4 log IU/ml. The quantitative agreement of the viral loads detected with LDT and NeuMoDx is 63% (5/8) as shown in Fig. 3 and are suggestive of an under-quantification in lower VLs by the NeuMoDx.

3.3. HCV

A total of 66 HCV samples were available for analysis, 64 EDTA plasmas and 2 sera, of which 49 had quantifiable loads and 18 were ND samples as measured in CAP/CTM. Table 4 shows the distribution of the ND, NQ and >LLOQ results between all tested platforms. The overall qualitative agreement between the Alinity m and the NeuMoDx is 100% (66/66).

Fig. 4 presents the quantitative agreement of samples in which both platforms measure a quantifiable VL or one platform measures a quantifiable VL and the other platform a ND VL. The quantitative agreement between the Alinity m and NeuMoDx results of these samples is 94% (46/49). Significant VL differences between samples are equally distributed between both assays. One had a genotype 3a and for the other 2 samples the genotype was not determined (figure S6).

A good correlation between the two assays was found ($r = 0.97$ [CI 0.94 – 0.98]; Deming regression equation, $y = 0.43$ [0.05 – 0.86] + 0.91 [0.84 – 0.97]] * x; Fig. 4) and the Bland Altman analysis showed a weak bias, since the Alinity VLs were on average 0.06 log lower (bias: −0.06 ± 0.34 log IU/mL).

4. Discussion

In this study, the performance of the Alinity m and NeuMoDx HIV-1, HBV and HCV assays have been evaluated in a head-to-head qualitative and quantitative comparison. The HCV assays showed a good correlation, though the HIV-1 assays showed quantitative differences in the lower VL ranges and the HBV assay of the NeuMoDx resulted in lower VLs compared to the Alinity m assay.

Both the Alinity m and the NeuMoDx confirmed the samples with ND VL of HIV-1 in the CAP/CTM and HBV in LDT. Samples with a NQ VL in the CAP/CTM could not always be confirmed by the new platforms. This can be expected when using archived frozen samples, which may have decreased the quality of the samples. Additionally, these differences may have been caused by the stochastic effect of PCR amplification in clinical samples with low viral loads of around the limit of detection (LOD) of the respective assays.

Table 4
Comparison HCV viral loads (IU/ml) Alinity m, NeuMoDx and CAP/CTM ($N = 66$).

		Alinity m			CAP CTM [b]		
		ND[a]	<1.08 log	≥1.08 log	ND[a]	<0.9 log	≥0.9 log
NeuMoDx	**ND[a]**	17	0	0	17	0	0
	<0.9 log	0	0	0	0	0	0
	≥0.9 log	0	0	49	0	0	49
CAP CTM [b]	**ND[a]**	17	0	0	–	–	–
	<1.1 log	0	0	0	–	–	–
	≥1.1 log	0	0	49	–	–	–

[a] ND; non-detectable viral load.
[b] Historical results on fresh samples.

A number of articles have been published recently on the HIV-1, HBV and HCV assays using the Alinity m [14–18] and on the NeuMoDx HBV and HCV assays [19]. These articles evaluated the performance of these assays compared to other commercial assays. In these comparisons, the Alinity m and NeuMoDx corresponded with the other tested assays in the quantifiable range with some minor quantification differences. Differences in detection were apparent in the lower ranges. This can be expected and is in line with our observation, in which most of the differences between HBV assays were observed in the lower quantification ranges.

Differences in quantification by assays could be caused by differences in the LOD and assay variability by the use of different PCR targets on the viral genome. However, most of the analytical differences in VLs in this comparative study, are unlikely to result in differences in clinical decisions. In one potential exception, the NeuMoDx measured a ND in two samples in which the LDT resulted in log 3.3 and log 3.4 in the small prospective HBV cohort.

A possible explanation of the lower HBV and HIV VL by the NeuMoDx assay could be the use of frozen samples. The samples were collected between January 2017 and May 2019, though there was no obvious difference in quantification and the age of the sample. For HBV, two reference panels, one from NeuMoDx and one from Qnostics, were tested and resulted in similar VLs in the NeuMoDx as compared to the LDT. In a small prospective study on 21 samples, in five samples with VL >100 IU/ml no significant difference in VL was observed. In two samples a VL of over 3 log was detected using the LDT, that remained undetected in the NeuMoDx, indicating some level of under-quantification in some clinical diagnostic samples. Due to the small sample size, conclusions should be drawn with caution. Unfortunately, these kind of experiments could not be performed for HIV, as the NeuMoDx machine was no longer available in the laboratory.

As this study has been performed early after the launch of both machines, we encountered several practical issues, such as reagents that expired during maintenance of one of the platforms, the logistics to get both platforms running at the same time, and unexpected invalid results on both platforms. This resulted in a reduction of samples for which a fair comparison could be made. Seventy-eight (23%) of the 340 tests performed on the Alinity m and 48 (14%) of the 338 tests performed on the NeuMoDx resulted in invalid results. Most of these, 58 and 38 respectively on the Alinity m and NeuMoDx, were caused by platform issues which were subsequently addressed by the manufactures. The initial Alinity m platform had various mechanical issues, which were acknowledged by Abbott and resulted in replacement during this study. After the replacement, no more platform issues have been encountered. Qiagen also acknowledged the issues with the NeuMoDx and replaced several components. As a result, part of the samples were lost for inclusion in the comparison, which was partly caused by the limited volume of remnant sample available. If we could have re-tested after the platform issues had been resolved, more valid results would have been generated.

This study has several limitations. Due to the lack of sufficient remnant sample volume, it was not possible to retest all samples that showed significant quantification differences between the two platforms. Some samples have been stored at 4 °C for some days if there was a test failure before they were tested. During the inclusion, we added as much different HIV-1 and HCV genotypes. The majority of HIV-1 samples were genotype B and the majority of HCV included genotypes are 1 and 3, if genotyping was performed. This is in line with the European genotype distribution of these two viruses [20,21]. Despite the limitations, the Alinity m and NeuMoDx HCV assay showed a good agreement, but quantification differences were apparent between the HIV and HBV assays, mostly in the lower VLs.

Implementing these fully integrated diagnostic platforms will further automate molecular diagnostics and increase microbiological diagnostic services, not only for blood screening. Once pre-analytical automation

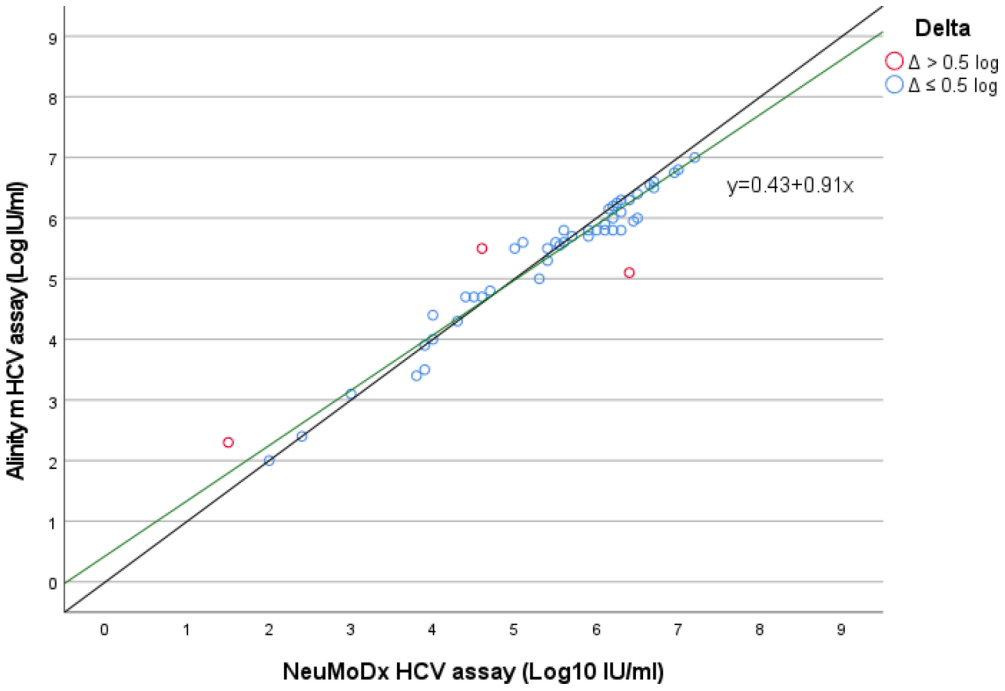

Fig. 4. Quantitative comparison HCV viral loads Alinity m versus NeuMoDx.
Scatter-plot presenting HCV viral loads detected between Alinity m and NeuMoDx around the expected line (Alinity m log IU/ml = NeuMoDx log IU/ml) and best fit Deming regression line (green).

procedures are available as well, integration of all bulk molecular microbiological assays in large diagnostic tracks becomes feasible.

Declaration of Competing Interest

We hereby declare that none of the authors has a conflict of interest to declare for this manuscript.

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Reagents for this study were provided by Abbott and Qiagen whom further had no role in the design and execution of the studies.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jcv.2022.105376.

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