



Full length article

Multicenter comparison of the new Cobas 6800 system with Cobas Ampliprep/Cobas TaqMan and Abbott RealTime for the quantification of HIV, HBV and HCV viral load



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ABSTRACT

Background: The new Roche Cobas 6800 platform (C6800) has been recently introduced for viral load (VL) measurement.

Objectives: Comparing C6800 to Cobas Ampliprep/Cobas TaqMan v2.0 (CAP/CTM) for the quantification of HIV, HBV and HCV viremia, and to the Abbott RealTime assay (ABB) for HCV quantification.

Study design: We analysed 121 samples for HBV, and 139 for HIV-1 including 2 group O and 137 group M viruses (36.5% subtype B, 27.0% CRF02_AG, 22.6% from other clades, and 14% subtype not available). For the 100 HCV samples compared with CAP/CTM, 42% were genotype 1 and 17% were genotype 4. For the 68 HCV samples compared with ABB, 52.9% were genotype 1 and 22.1% were genotype 4.

Results: C6800 results correlated well with those of CAP/CTM for all three viruses (R^2 : 0.97–0.99). However, C6800 can yield different viraemia results: higher for HIV (mean difference: $+0.11 \log_{10}$ copies/mL, $p < 0.0001$), and lower for HBV (mean difference: $-0.11 \log_{10}$ IU/mL, $p < 0.0001$). Differences exceeded $0.5 \log_{10}$ for 6.5% of HIV-1 samples and 7.4% of HBV samples. For HCV quantification, C6800 gave mostly lower values than the other assays towards the bottom of the range, and higher values in the upper part of the range, especially in comparisons with ABB, for which 28% of differences exceeded $0.5 \log_{10}$ IU/mL. No particular HCV genotype was identified as responsible for these differences.

Conclusion: Overall, the comparison tests between C6800 and CAP/CTM systems are satisfactory for the three viruses. Frequent discrepancies were observed between C6800 and ABB for HCV.

1. Background

Viral load (VL) quantification is an essential element for the monitoring of patients infected with viruses, such as the human immunodeficiency virus (HIV), hepatitis B (HBV) and C viruses (HCV). Various commercial VL assays based on different technologies are available. New integrated fully automated molecular testing platforms have recently been developed, making it possible to determine VL for different viruses simultaneously, with a higher throughput than for previous devices [1–5]. This is the case for the new Cobas 6800/8800

system (C6800; Roche Diagnostics, Mannheim, Germany) available since 2014 as an alternative to the Cobas AmpliPrep/Cobas TaqMan version 2.0 assay (CAP/CTM). The manufacturers had to modify the various steps of the process used with the CAP/CTM assay to achieve these goals. Previous studies have shown that the wide diversity of HIV-1 and HCV could lead to major discrepancies in quantification between assays [6–10]. The risk of underquantification for HIV-1 and HCV genotype 4 has virtually disappeared in version 2.0 of CAP/CTM, but, with the exception of one publication for HCV test, no data are currently available for C6800/8800 system [2,11–13]. Because the use of a

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threshold HCV VL has been proposed for the adaptation of treatment duration, discrepancies between the different assays may have a clinical impact [14,15]. Finally, HBV DNA VL, particularly 2000 IU/mL threshold, is taken into account to define a patient as inactive HBV carrier, and can also impact the treatment initiation [16,17].

2. Objectives

It is important to assess the possible impact of a switch to C6800 on the VL values obtained and their clinical interpretation. In this study, we compared the results obtained with the C6800 assay with those of the CAP/CTM v2.0 assay for the quantification of HIV-1, HBV and HCV, and with those of the Abbott RealTime assay (ABB, Abbott Molecular, Rungis, France) for HCV quantification.

3. Study design

3.1. Clinical samples

We used leftover EDTA plasma from samples sent to three Parisian laboratories (at the Pitie-Salpetriere, Bichat Claude-Bernard, and Saint-Louis Hospitals) for testing during the year 2016. No additional blood samples were collected for this study. The EDTA samples were centrifuged and tested with CAP/CTM or ABB for viral quantification within 24 h. Then, samples were selected for C6800 assay, in a second step, so as to cover as much of the linear range of the assays as possible. Therefore, the vast majority was performed on the frozen leftover plasma stored at -80°C and thawed once. The C6800 assay was performed at the same time as the initial assay in rare cases only. For the inclusion of a sample in the study, there had to be a sufficiently large volume of plasma to perform the C6800 assay without prior dilution.

3.2. Quantification assays

The initial quantification assay for HIV-1 and HBV was CAP/CTM v2.0 at the three laboratories. HCV viral load was quantified with either CAP/CTM v2.0 or the ABB assay, depending on the laboratory. All tests were performed according to the manufacturer's instructions, provided in the packaging. VL is expressed in \log_{10} copies/mL for HIV-1, and in \log_{10} IU/mL for HBV and HCV. The lower limit of quantification (LLOQ) and sample input volume for the CAP/CTM v2.0 assay were 1.30 \log_{10} and 1 mL, respectively for HIV. The LLOQ was 1.30 \log_{10} for HBV and 1.18 \log_{10} for HCV, with a sample input volume of 500 μL for both hepatitis viruses. The same parameters were used with the C6800 system, except for the input volume for HIV, which was decreased to 500 μL , and the LLOQ for HBV, which decreased to 1.00 \log_{10} . In the ABB assay for HCV RNA quantification, the LLOQ was 1.08 \log_{10} and the input volume was 500 μL of plasma.

Both the CAP/CTM and C6800 assays can amplify HIV-1 group M and O, and HCV genotypes (GT) 1–6, which are also amplified by the ABB assay.

3.3. Determination of HCV genotype and HIV subtype

HCV genotype was determined either by the sequence analysis of the NS5b region as previously described, or by the Line Probe Assay INNO-LiPA 2.0 Assay (Innogenetics, Ghent, Belgium) depending on the laboratory [18]. HIV-1 subtype was determined by analyzing the protease and reverse transcriptase gene sequences with the Los Alamos HIV subtyping tool (www.hiv.lanl.gov).

3.4. Data analysis

Bland-Altman analysis was used to determine the strength of agreement between the C6800 system and the other two assays based on the mean difference and standard deviation (SD). The VL values

obtained in two different assays were compared in Wilcoxon tests. Deming regression line and coefficient of determination (R^2) were calculated for each comparison test. For these analyses, we excluded all samples with a VL below the LLOQ in each assay. If the VL was unquantifiable in only one of the two assays, it was set at the corresponding LLOQ for the analysis.

4. Results

4.1. CAP/CTM v2.0 versus the C6800 system for HIV-1 RNA quantification

We analysed 139 plasma of HIV-1-infected patients, after the exclusion of 12 samples unquantifiable in both assays. The VL was below the LLOQ in only one of the two assays for six samples, and values of 1.30 \log_{10} copies/mL were therefore assigned to these specimens for the assays concerned. 137 samples contained HIV-1 group M with 50 subtypes B (36.5%), 37 CRF02_AG (27.0%), 19 subtypes not available (13.9%) and 31 other clades (22.6%) including subtype A, C, D, F, G, H, CRF_01, 06, 07, 13, 22, 36, 57, and non_typable recombinants. Two samples contained HIV-1 group O.

The determination coefficient (R^2) of 0.98 and the Deming regression line revealed a good correlation between the results obtained in the two assays, with a slope of 0.942 and an intercept of 0.109 (Fig. 1a). The C6800 results were slightly higher than the CAP/CTM values ($p < 0.0001$), and Bland-Altman analysis showed that the mean difference (C6800 minus CAP/CTM) was +0.11 \log_{10} , with a SD of 0.24 \log_{10} (Fig. 1b). On the Bland Altman plot, C6800 values tended to be more often higher for a mean VL above 4.5 \log_{10} copies/mL. Nine differences (6.5%) exceeded 0.5 \log_{10} copies/mL. For one of these differences, the value obtained with CAP/CTM (for an undetermined

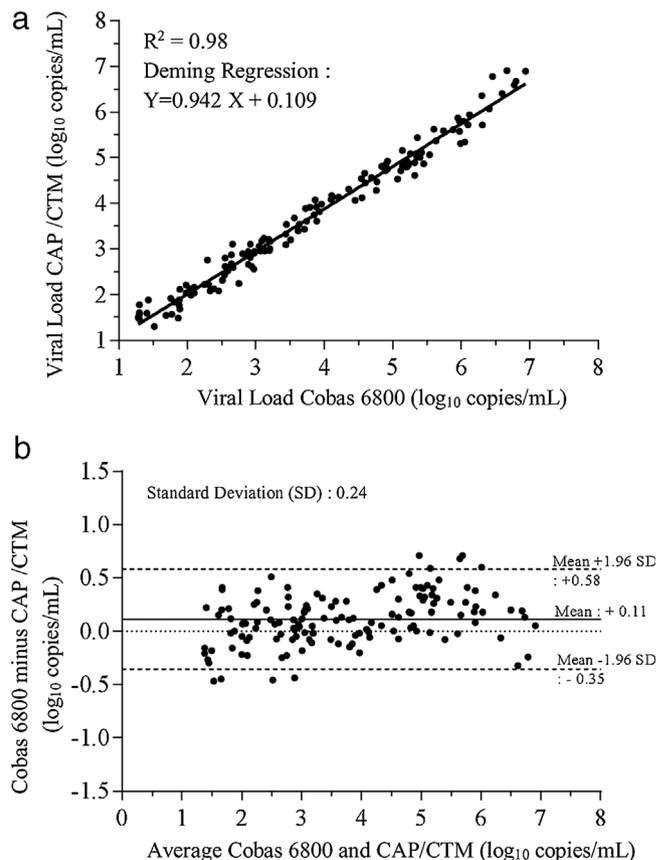


Fig. 1. (a) Correlation Curve for Cobas 6800 HIV-1 versus CobasAmpliprep/Cobas TaqMan (CAP/CTM) (n = 139). (b) Bland-Altman plot for Cobas 6800 HIV-1 versus Cobas Ampliprep/Cobas TaqMan (CAP/CTM) (n = 139).

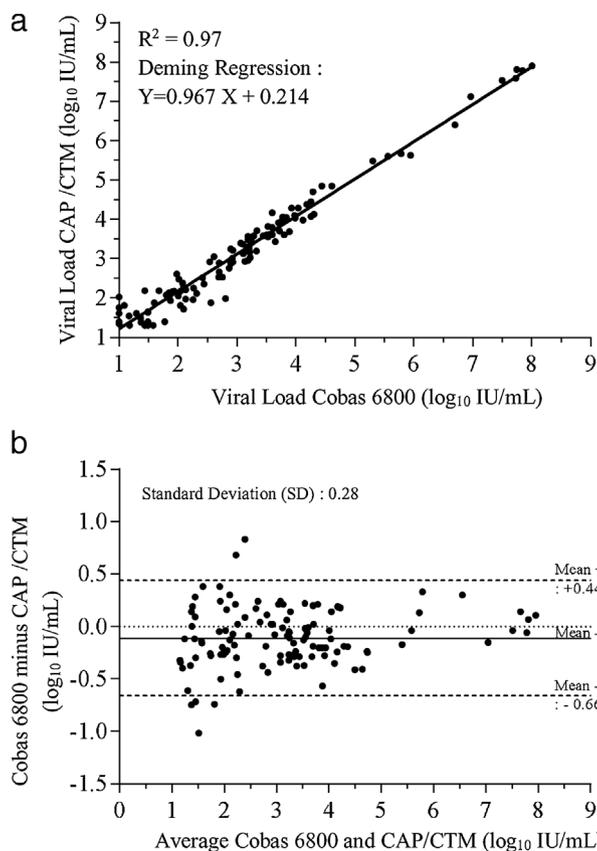


Fig. 2. (a) Correlation Curve for Cobas 6800 HBV versus Cobas Ampliprep/Cobas TaqMan (CAP/CTM) (n = 121). Bland-Altman plot for Cobas 6800 HBV versus Cobas Ampliprep/Cobas TaqMan (CAP/CTM) (n = 121).

subtype) was higher ($-0.53 \log_{10}$), whereas, for the other eight of these differences, the higher value was obtained with C6800, with differences ranging from 0.51 to 0.71 \log_{10} (2 subtype B viruses, 4 subtype CRF02_AG viruses, 1 BF recombinant, and 1 HIV-1 group O virus). Thus, no particular HIV subtype seemed to be responsible for these discrepancies.

4.2. CAP/CTM v2.0 versus C6800 system for HBV DNA quantification

We analysed 121 plasma samples of HBV-infected patients, after the exclusion of 17 samples unquantifiable in both assays. Four plasma samples had VL between 1.18 and 1.58 \log_{10} IU/ml with C6800, with detectable but not quantifiable viremia with CAP/CTM, for which the value of the LLOQ (1.30 \log_{10} IU/mL) was assigned. Conversely, 6 other samples had values between 1.32 and 1.62 \log_{10} IU/ml with CAP/CTM, with a VL that was detectable but not quantifiable with C6800, for which the LLOQ value of 1.00 \log_{10} IU/mL was assigned. The determination coefficient R^2 of 0.97 and the Deming regression line revealed a good correlation, with a slope of 0.967 and an intercept of 0.214. (Fig. 2a). Bland-Altman analysis showed agreement between the two assays, with a homogeneous distribution of differences, at least below 5.0 \log_{10} IU/mL, the area containing the vast majority of points (Fig. 2b). However, significantly different ($p < 0.0001$) and slightly lower results were obtained with the C6800 system, with a mean difference (C6800 minus CAP/CTM) of $-0.11 \log_{10}$ IU/mL and a SD of 0.28. Differences exceeded 0.5 \log_{10} for nine samples (7.4%), with higher values with C6800 in two cases and with CAP/CTM in seven cases. One difference (0.8%) exceeded 1.0 \log_{10} ($-1.02 \log_{10}$ IU/mL).

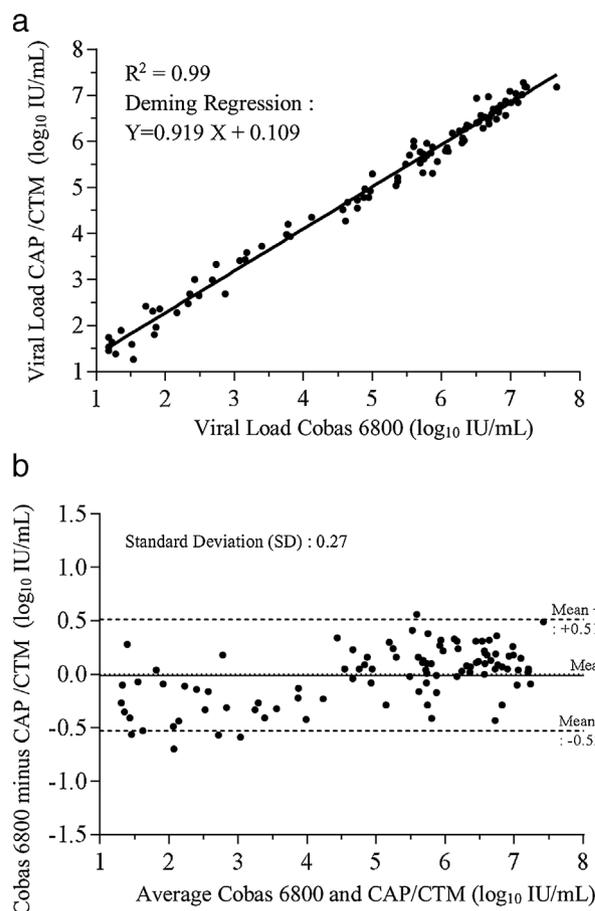


Fig. 3. Correlation Curve for Cobas 6800 HCV versus Cobas Ampliprep/Cobas TaqMan (CAP/CTM) (n = 100). (b) Bland-Altman plot for Cobas 6800 HCV versus Cobas Ampliprep/Cobas TaqMan (CAP/CTM) (n = 100).

4.3. CAP/CTM v2.0 versus C6800 system for HCV RNA quantification

In the comparison between CAP/CTM and C6800 for the quantification of HCV RNA, five plasma had values below the LLOQ in both assays. The HCV genotype (GT) of the 100 remaining samples were as follows: 24 GT1a, 14 GT1b, 2 GT1e, 1 GT1h, 1 GT1a/1c (recombinant), 5 GT2, 19 GT3a, 17 GT4, 2 GT6, and 15 GT not available. Three samples had a VL between 1.45 and 1.74 \log_{10} IU/mL with CAP/CTM and were detectable but not quantifiable with C6800; the corresponding LLOQ (1.18 \log_{10}) was therefore assigned to these samples. The correlation analysis showed good result with a R^2 value of 0.99, and a Deming line with a slope of 0.919 and an intercept of 0.109 (Fig. 3a). Bland-Altman analysis revealed a small mean difference (C6800 minus CAP/CTM) of $-0.01 \log_{10}$ IU/mL and a SD of 0.27 (Fig. 3b). This difference between the results of the two assays was not statistically significant ($p = 0.78$). However, the Bland Altman plot demonstrated that viral loads were mostly higher with CAP/CTM for samples with a mean viremia below 4.5 \log_{10} IU/mL, and often higher with C6800 above that threshold. For six samples, the difference exceeded 0.5 \log_{10} . Five of them (1 GT 1a, 2 GT 3, 1 GT 4 and 1 GT not available) had higher values with CAP/CTM, while their mean VL with both assays was below 3.5 \log_{10} IU/mL. The sixth sample (GT1e) had higher value with C6800 with a mean value of 5.59 \log_{10} IU/mL. None of the differences exceeded 1.0 \log_{10} .

4.4. Versus C6800 system for HCV quantification

Five samples had HCV VL values below the LLOQ in CAP/CTM and ABB assays. The genotypes of the other 68 samples were as follows: 20

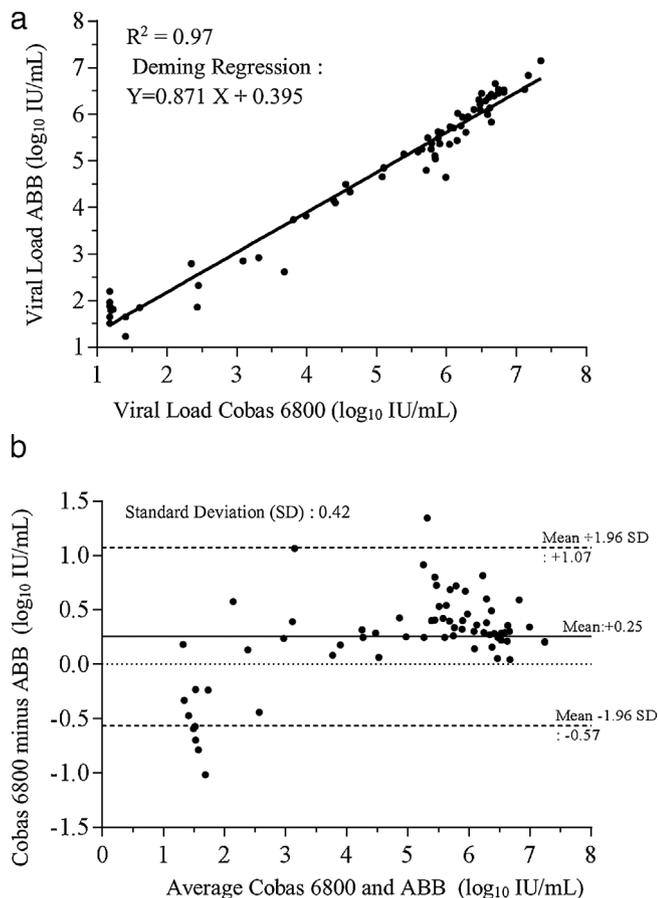


Fig. 4. (a) Correlation Curve for Cobas 6800 HCV versus Abbott RealTime (ABB) ($n = 68$). (b) Bland-Altman plot for Cobas 6800 HCV versus Abbott RealTime (ABB) ($n = 68$).

GT1a (29.4%), 13 GT1b (19.1%), 3 GT1e/h (4.4%), 5 GT2 (7.3%), 3 GT3 (4.4%), 15 GT4 (22.1%), 1 GT5 (1.5%) and 8 (11.8%) GT not available or undetermined. VL was quantifiable with CAP/CTM (1.65–2.20 \log_{10} IU/mL) but not with C6800 for four samples. The LLOQ value of 1.18 IU \log_{10} was therefore assigned to these samples for the C6800 assay. The determination coefficient R^2 was 0.97 and the Deming regression line had a slope of 0.871 and an intercept of 0.395 (Fig. 4a). In Bland-Altman analysis, the mean difference (C6800 minus ABB values) was + 0.25 \log_{10} IU/mL and the SD was 0.42 (Fig. 4b). The values obtained with C6800 were significantly higher than those obtained with the ABB assay ($p < 0.0001$). The Bland-Altman plot showed considerable dispersion of the points. VL was higher with the C6800 system for samples with a mean VL below about 5.0 \log_{10} IU/mL, but lower with the C6800 system for mean VL values above about 2.0 \log_{10} . Nineteen samples (27.9%) had differences exceeding 0.5 \log_{10} (–1.02 to +1.34 \log_{10} IU/mL). These samples had the following genotypes: 4 GT1a (21.0%), 5 GT1b (26.3%), 1 GT2 (5.3%), 1 GT3 (5.3%), 4 GT4 (21.0%), 1 GT5 (5.3%) and 3 GT not available (15.8%). Three of these differences (4%) exceeded 1.0 \log_{10} (2 GT1b higher with C6800, and 1 GT4 higher with ABB).

5. Discussion

For HIV-1 RNA quantification, the correlation analyses showed comparable results between C6800 and CAP/CTM assays. However, the C6800 assay tended to yield slightly higher results, particularly for the upper part of the range. Current guidelines recommend the initiation of antiretroviral treatment in all HIV-1-infected patients, regardless of CD4 cell count or HIV viraemia [19,20]. The small differences observed

between these two assays in this study would, therefore, have no impact on treatment decisions. However, the goal of antiretroviral treatment is to decrease viral load to below 50 copies/mL or below the LLOQ of the test, depending on the guidelines. Further studies, including a larger number of samples with low viral loads, are therefore required to confirm the slightly higher sensitivity of C6800 towards the bottom of the range, and to determine whether the use of this test would result in the detection of more cases of low-level viraemia, or detectable HIV-1-RNA, than the use of CAP/CTM or another quantification assay.

For HBV DNA quantification, the comparison between the C6800 and CAP/CTM systems revealed a good correlation and homogeneous results. The C6800 system seemed to provide slightly lower results. Although VL is one of the parameters determining the treatment for chronic hepatitis B, other hepatic parameters are taken into account, and the slight difference between these two assays reported here should have no significant clinical consequence [16].

For HCV RNA quantification, we compared the Cobas 6800 system with the CAP/CTM and ABB assays, for various genotypes. The results of the C6800 assay were well correlated with those of the other two tests, but this correlation was weaker for the ABB assay. The HCV VL values obtained with the C6800 and ABB assays were significantly different, with discrepancies exceeding 0.5 \log IU/mL in 28% of cases. No particular HCV genotype seemed to be involved in these differences, although HCV GT4, for which quantification problems have already been reported, accounted for about 20% of the samples included in both comparison studies [9,10]. The VL obtained was lower with C6800 for samples with a mean VL in the lower part of the range, and higher with C6800 for samples with a mean VL in the upper part of the range. This phenomenon was observed with CAP/CTM and was more marked with the ABB assay. Similar findings can be also observed in a recent study comparing the C6800 and CAP/CTM assays for HCV quantification, in which the Bland-Altman plot also showed lower values with C6800 in the lower part of the range, and higher values with C6800 in the upper part of the range [2]. It is therefore difficult to compare mean differences between studies because these differences depend on the VL distribution of the samples between the high and low HCV viraemia included in the analysis. These data are consistent with recent observation of Vermehren et al. who discussed the applicability of a cut-off used to tailor HCV treatment duration [15]. With such a recommendation, patient monitored with the C6800 assay may receive HCV treatment for longer, because their VL is more likely to be above the cut-off. However, in the future, the duration of new treatments may no longer depend on viral load. As for the risk of missing low VL, this does not seem to be a major problem since they do not predict an absence of sustained virological response [21].

The aim of this study was to assess the possible impact of a switch to C6800 on the VL values obtained comparing results of patient samples. Analytical performance, in terms of linear range, quantification and detection limits, and within- and between-run reproducibility, was not assessed. Various HCV genotypes and HIV-1 subtypes, representative of those observed in infected patients in Europe, were included in the study. No particular strain seemed to be responsible for the discrepancies observed in our results. However, specific studies may help to explore the C6800 performances more closely depending on the genetic diversity.

Overall, the results obtained with the C6800 system were well correlated with those of the CAP/CTM assay for HIV-1, HBV and HCV quantification. However, C6800 may yield different VL values from other assays, with slightly lower values for HBV, and higher values for HIV-1. For HCV quantification, C6800 seems to generate lower values towards the bottom of the range, and higher values in the upper part of the range. These observations remind that it is preferable to base the virologic follow-up on results from the same assay. Further studies are required to determine whether these discrepancies, including the slight differences between C6800 and CAP/CTM, may affect the duration of HCV treatment, or may increase the proportion low-level HIV VL and

detectable viremia in HIV-infected patients on treatment. The present study reported that some differences in viral loads can result from the switch to C6800 system. However their consequences are mostly minor, and a priori insufficient to call into question the technical and throughput benefits provided by this platform.

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Competing interests

None declared.

Ethical approval

Not required.

Author contributions

All authors contributed to the following: (1) the conception and design of the study, or acquisition of data, or analysis and interpretation of data, (2) drafting the article or revising it, and (3) final approval of the version to be submitted.

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