Bio QControl

# P0327
# ViraQ HIV-1 Quant 1000

REF P0327

The kit insert contains a detailed protocol and should be read carefully before testing the run control to ensure optimal performance

## Table of contents

## Intended Use

P0327 ViraQ HIV-1 Quant 1000 is intended to be used as external run control for quantitative human immunodeficiency virus type 1 (HIV-1) RNA amplification assays in combination with the test kits on the platforms defined in table 1. The run control is also suitable for other viral load assays with similar performance characteristics as the methods listed in table 1. The run control helps laboratories to ensure accurate quantification and consistent performance of quantitative HIV-1 nucleic acid amplification technology (NAT) methods with a lower limit of quantification (LOQ) sufficiently below the run control concentration of 1000 copies/mL (~ 1724 International Units (IU)/mL). The run control can also be used to compare copy numbers reported by different HIV-1 viral load assays. The run control is intended for performance evaluation only.

**Table 1**. Test kits and platforms covered by P0327 ViraQ HIV-1 Check 1000 run control

| Manufacturer Platform | Test kits | Test environment |
|---|---|---|
| Abbott m2000 | RealTime HIV-1 assay | Viral load monitoring |
| Roche cobas Ampliprep/TaqMan | CAP/CTM assay | |
| Hologic Panther | Aptima HIV-1 Quant Dx | |
| Cepheid GeneXpert systems | Xpert HIV-1 Viral Load | |
| BioMérieux NucliSens EasyQ | NucliSens EasyQ HIV-1 2.0 | |

The run control should not be used to replace the internal controls or calibrators in the test kits.

## Key to Symbols Used


Manufacturer

Lot number

Catalogue number

Store below -30°C


For performance evaluation only

Biological substance category B


Date of manufacturing

Contents


Caution


Read instructions for use

## Summary and explanation

In the late 1990s the liquid frozen S0012 VQC-Sanquin HIV-1 subtype B standard was among the first reference materials for evaluation of NAT methods[1,2] and used as candidate material in WHO collaborative studies to establish the 1st and 2nd International HIV-1 standards[3]. The bDNA 3.0 assay was used as reference method[4] for calibration in copies/mL and the data from this method in the WHO collaborative study showed a drift in the amount of HIV-RNA per International Unit (IU) from 0.39 (0.34-0.44) to 0.58 (0.51-0.66) copies/IU when the 1st WHO HIV-1 97/656 standard was replaced by the 2nd WHO HIV-1 97/650 standard[5]. Later the 3rd and 4th WHO HIV-1 subtype B standards have been introduced and recent calibration studies against the S0012 VQC-Sanquin standard indicate that currently the conversion factor is 25 (15-41) copies/IU when the Abbott RealTime assay was used[6]. Thorough stability studies have demonstrated that (dilutions

of) the S0012 VQC-Sanquin HIV-1 subtype B standard is completely stable for more than two decades when stored below -65°C[7]. In the period between 1998 and 2004 the quantitative methods reported similar copy numbers on the VQC-Sanquin standard as in 2018 (table 2 and 3)[6]. Hence the liquid frozen primary S0012 HIV-1 subtype B standard calibrated in copies/mL can function as a second anchor for HIV-1 RNA quantification in addition to the WHO standards calibrated in IU/mL. The S0012 VQC-Sanquin HIV-1 RNA subtype B standard was used for preparation of the P0327 ViraQ Quant control containing 1000 copies/mL. The dilutions were made in human citrate plasma to which EDTA was added in order to mimic the matrix of real patient samples. Since the S0012 HIV-1 subtype B standard has been extensively calibrated in both copies and IUs[5] P0327 ViraQ HIV-1 Quant can be used as an independent control for testing the accuracy and precision of quantitative HIV-1 NAT methods. The run control has been set at 1000 copies/mL since the World Health Organization (WHO) recommends this level as a threshold value above which measured viral loads are indicative of lack of virological control in patients receiving anti-retroviral therapy (ART)[8].

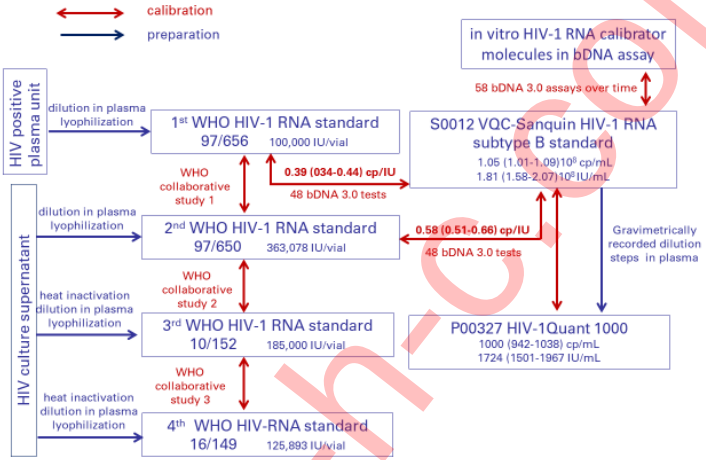
## Principle of method

P0327 ViraQ HIV-1 Check 1000 control has been formulated to mimic natural plasma specimens with a specified HIV-1-RNA viral load of 1000 copies/mL[4,6] or 500 virions/mL (equivalent to 1724 IU/mL[3,5]). The run control has been designed to ensure sufficient accuracy and precision of viral load results by quantitative HIV-1 NAT methods. After thawing the run control tubes are ready for use and can be placed between patient samples at random positions in the work list. The HIV-1-RNA concentration in the run control has been set at 1000 copies/mL, equivalent to a clinical decision level in therapy monitoring[8]. The WHO defines virological failure when the viral load values in a patient persistently exceed 1000 copies/mL in two consecutive viral load measurements within a three-month interval, after at least six months of using ART)[8]. The run control enables laboratories to be alerted in case of a significant change in quantitative results over time. The run control is prepared by gravimetrically recorded dilution steps of the S0012 HIV-1-RNA subtype B standard. which is composed of tissue culture derived virus spiked in plasma[1]. The plasma matrix in which the run control is diluted is manufactured from plasma units that tested negative for all relevant markers of blood borne viruses. The S0012 HIV-1 standard has been historically calibrated in both copies/mL and IU/mL against the 1st and 2nd WHO International Standards (figure 1)[3,5]. The quantitative values obtained by different assays on P0327 HIV-1 Quant 1000 control are representative for a native HIV-1 subtype B virus but not for heat-inactivated HIV-1 subtype B preparations or HIV-1 standards of subtypes A-K and circulating recombinant forms (CRFs). For comparison of quantitative HIV results of different assays on non-subtype B standards the P0140 HIV 1000 copies/mL subtype reference panel can better be used. A quantifiable result within the expected range between 500 and 2000 copies/mL on the run control indicates that the NAT method has been performed with sufficient accuracy and precision. A result outside the expected range is indicative of reduced accuracy and precision and should trigger investigation of the technical performance or recalibration of the assay. The run control generates Ct values or viral loads (expressed in copies/mL) in real time PCR and TMA assays. Statistical analysis of the assay response values generated over a certain period of time allows for comparison of NAT reagent batches and laboratory instruments. The BQC manufacturing and quality control procedures guarantee consistent virus concentrations in consecutive ViraQ HIV-1 Quant 1000 batches[9]. The BQC HIV-1 subtype B standard is available in sufficient supply to ensure batch to batch consistency of ViraQ run controls for a prolonged period of time.

## Traceability to HIV-1 RNA copies and International Units

Figure 1 shows the traceability chain between the P0327 HIV-1 Quant 1000 control, the primary S0012 VQC-Sanquin subtype B standard and the 1st HIV-1 97/656 standard and 2nd WHO HIV-1 97/650 International Standards.

**Figure 1**. Traceability chain between P0327 HIV-1 Quant 1000 control, the S0012 VQC-Sanquin HIV-1 subtype B standard and the WHO International Standards




### Calibration of S0012 VQC-Sanquin HIV-1 subtype B standard in copies/mL

The viral concentration in the S0012 VQC-Sanquin HIV-1 RNA subtype B standard was established by laboratories testing dilutions of these standards in the VQC proficiency program organized between 1996 and 2004. Table 2 compares the geometric mean values in copies/mL as reported by different quantitative NAT methods when adjusted to 1000 copies/mL values[5,6]. It was decided to use the Siemens bDNA 3.0 assay as the reference method[4] for quantification and assign the value of 1.05 (1.01-1.09).$10^8$ copies/mL to the undiluted S0012 VQC-Sanquin standard[5].

More recently in 2018 a dilution of 1000 copies/mL of this VQC Sanquin subtype B standard (P0327 ViraQ HIV-1 Quant 1000 run control) was tested in 4 runs of 6 replicate viral load (VL) measurements by 5 laboratories using different quantitative methods[6]. When comparing the quantitative results obtained two decades later (table 3) with those in the early days of NAT (table 2) the results were comparable as was predicted by our stability studies of the liquid frozen S0012 HIV-1 subtype B standard stored at -80°C[7]. However there were still significant differences in the copy numbers reported by the currrent VL assays with geometric mean values varying between 1084 to 2505 copies/mL (table 3).

**Table 2**: Quantification of S0012 VQC-Sanquin HIV-1 RNA subtype B standard in proficiency studies performed between 1996 and 2004. The quantification in the Siemens bDNA 3.0 assay was chosen as the reference method for calibration in copies/mL

| Assay | n | geomean cp/mL | (95% CI) cp/mL |
|---|---|---|---|
| Abbott LCx | 18 | 1819 | (1752-1895) |
| Chiron bDNA 1.0 | 13 | 449 | (188-1067) |
| Bayer bDNA 2.0 | 57 | 1038 | (1000-1086) |
| **Siemens bDNA 3.0** | **58** | **1000** | **(962-1038)** |
| Organon Teknika NucliSens | 119 | 2295 | (2171-2419) |
| Organon Teknika QT-NASBA | 366 | 3162 | (3057-3267) |
| Roche Amplicor Monitor V1.0 | 437 | 2143 | (2095-2181) |
| Roche Amplicor. Monitor mixed primers | 63 | 1457 | (1390-1514) |
| Roche Amplicor Monitor V1.5 | 316 | 1295 | (1238-1352) |
| Roche Amplicor Monitor Ultra | 142 | 1181 | (1124-1229) |

**Table 3.** Quantification of 1000 copies/mL samples of S0012 VQC-Sanquin HIV-1 RNA subtype B standard (P0327 ViraQ HIV-1 Quant 1000) by different laboratories (Viral load assays performed in 2018)[6].

| Assay | n | geomean cp/mL | (95% CI) cp/mL |
|---|---|---|---|
| Abbott m2000 RealTime Assay m2000 | 24 | 1084 | (784-1572) |
| Hologic Aprima | 24 | 1616 | (1324-1973) |
| Roche CAP/CTM | 24 | 1277 | (892-1828) |
| Cepheid Xpert | 24 | 2502 | (1333-3465) |
| BioMerieux NucliSens EasyQ | 24 | 1110 | (690-1900) |

**Calibration of S0012 VQC-Sanquin HIV-1 subtype B standard in IU/mL**

Dr. H. Holmes (NIBSC, Potterbar, UK) kindly shared the raw data of the laboratories that participated in the first WHO collaborative study[3] in which the 1st and 2nd WHO standard were compared with a dilution of the S0012 VQC-Sanquin subtype B standard. The data in table 4 show that the calibration results are dependent on the quantitative NAT method. When using the bDNA 3.0 assay as reference method there was a shift in the conversion factor from 0.39 (0.34-0.44) copies/IU to 0.58 (0.51-0.66) copies/IU when the 1st WHO 97/656 standard was replaced by the 2nd WHO 97/650 standard, which may be due to under-detection of the 2nd WHO standard by the Organon Teknika NucliSens method used at that time[3,5].

More recently the VQC-Sanquin standard was recalibrated against the 3rd and 4th WHO heat-inactivated standards in three dilutions varying between 1000 and 10.000 copies/mL (6 replicate Abbott RealTime VL tests per dilution) and the results from the parallel line analysis indicate that the conversion factor nowadays is 0.25 copies/IU (table 5)[6]. With the replacement of the 2nd and 3rd WHO standard there seems to have been a drift to a 40% lower amount of virus per IU. When analysing quantitative data in the WHO collaborative study report of the 4th WHO HIV-1 standard also lower copy numbers (63-89%) were reported on the 4th than on the 3rd WHO standard by the quantitative NAT methods used in the participating laboratories (table 6)[10].

**Table 4**. Calibration of VQC-Sanquin HIV-RNA subtype B standard on the first (97/656) and second (97/650) WHO HIV-1 RNA subtype B standards (containing 100,000 and 363,078 IU per ampoule respectively) as calculated from individual quantitative assays on standard dilutions with five methods as reported by the laboratories participating in the first WHO collaborative study[3]

| | n assays | | | copies/IU on 1st WHO (97/656) standard | | copies/IU on 2nd WHO (97/650) standard | |
|---|---|---|---|---|---|---|---|
| | 1st WHO | 2nd WHO | VQC-Sanquin | mean | (95%CI) | mean | (95%CI) |
| Abbott LCx | 14 | 15 | 14 | 0.76 | (0.60-0.96) | 0.69 | (0.56-0.86) |
| Roche Amplicor Monitor | 125 | 134 | 112 | 0.70 | (0.60-0.81) | 0.93 | (0.80-1.08) |
| Siemens bDNA 3.0 | 64 | 69 | 48 | 0.39 | (0.34-0.44) | 0.58 | (0.51-0.66) |
| Organon Teknika NucliSens | 46 | 51 | 36 | 0.80 | (0.69-0.92) | 0.43 | (0.36-0.50) |
| Roche Amplicor Monitor Ultra | 16 | 15 | 11 | 0.51 | (0.27-0.95) | 0.86 | (0.49-1.51) |

**Table 5**. Recalibration of VQC-Sanquin standard against 3rd and 4th WHO standard in Abbott realTime assay.

| HIV-1 Standard | Nominal value | n | copies/mL | copies/IU (95% CI) |
|---|---|---|---|---|
| VQC-Sanquin | 1000 copies/mL | 18 | 944 (698-1276) | |
| 2nd WHO 97/650 | 1000 IU/mL | 6 | 392 (266-577) | 0.41 (0.27-0.63) |
| 3rd WHO 10/152 | 1000 IU/mL | 18 | 291 (220-577) | 0.31 (0.21-0.45) |
| 4th WHO 16/149 | 1000 IU/mL | 18 | 236 (156-356) | 0.25 (0.15-0.41) |

**Table 6**. copy/IU conversion factor deduced from table 4, 6 and 10 of WHO collaborative study report WHO/BS/2017.2314[10].

| Lab | Quantitative NAT method | copy/IU (95% CI) | | drift copy/IU |
|---|---|---|---|---|
| | | 3rd WHO IS 10/152 | 4th WHO IS 16/194 | |
| 15 | Abbott RealTime HIV-1 assay | 0.47 (..)# | 0.40 (0.34-0.46) | 85% |
| 14 | Biomerieux NucliSENS HIV-1 v2.0 | 0.59 (..) | 0.52 (0.33-0.83) | 88% |
| 4 | Hologic Aptima HIV-1 Quant Dx | 0.85 (..) | 0.76 (0.50-1.14) | 89% |
| 9 | Hologic Aptima HIV-1 Quant Dx | 0.89 (..) | 0.62 (0.56-0.68) | 70% |
| 10 | Roche cobas HIV-1 6800 system | 0.89 (..) | 0.56 (0.41-0.77) | 63% |
| 7 | Roche CAP/CTM HIV-1 V2.0 | 1.05 (..) | 0.81 (0.73-0.90) | 77% |

#standard deviation d not reported

## Stability of HIV-1 standards and run control

The long term stability of the liquid frozen S0012 HIV-1 subtype B standard dilutions stored at ≤65˚C has been firmly established[7]; hence the stock solutions from which the run control is prepared have shown to be stable for more than two decades in the BQC storage facilities. Stability experiments using quantitative NAT assays showed less than 10% degradation of HIV-1 RNA per year in S0012 HIV-1 standard dilutions when stored at -30˚C[7]. Hence, it can be guaranteed that the run control is still functional and should generate quantitative results within the expected range of 500-2000 copies/mL when stored at -30˚C and used before the expiration date (two years after preparation of the run control batch).

## Kit Contents (materials provided)

The run control contains tissue culture derived HIV-1 virus human plasma without preservatives and is provided in one format as detailed in table 7.

**Table 7. Description of kit formats and contents**

| Cat. Code | Description of contents | Primary packing | Secondary packing |
|---|---|---|---|
| P0327 | 10 x 1.2 mL run control | 2 mL vial | Plastic zip bag |

## Materials required but not supplied

The test kits and liquid handling devices provided by the NAT manufacturer such as those as specified in Table 1.

## Storage instructions

The run controls should be stored at or below -30˚C for a maximum of two years[7]. When stored below -65˚C the run controls can be stored for a maximum of five years. Once thawed the run control samples should be used within 8 hours. During this period, when not in use, store sample at 2-8°C[7]. Do not refreeze the controls after thawing to prevent formation of cryoprecipitates. Any control sample that appears cloudy or contains precipitates after thawing and mixing should be discarded.

## Warning and precautions

The P0327 ViraQ HIV-1 Quant 1000 contains native HIV-1 virus particles in a plasma matrix and should be treated as bio-hazardous. The plasma matrix is prepared from human blood plasma that tested negative for blood borne viruses (HBV-DNA, HCV-RNA, HIV-RNA, HBsAg, anti-HBc, anti-HIV, anti-HCV and anti-Treponema *pallidum*). No test method can offer complete assurance that products derived from human blood cannot transmit (unknown) infectious agents. Observe the universal precautions for prevention of transmission of infectious agents when handling these materials[11,12].

- Do not pipette by mouth.
- Use personal protective equipment, including lab coats, gloves and safety glasses.
- Do not eat, drink or smoke in areas where the run control is handled.
- Disinfect spills using a 0.5% hypochlorite solution (1:10 v/v household bleach) or equivalent disinfectant.
- Dispose unused or spilled materials according to the normal practices for biological waste disposal in your institution.
- If precipitates are visible, mix the run controls for 2 minutes thoroughly.

- Once thawed, do not re-freeze and thaw the run control samples to avoid formation of cryoprecipitates that could alter reactivity or cause pipetting errors in the automated sampling systems.
- Store run controls in an upright position.
- A laboratory protocol for (possible) transmission of HIV-1 must be in place

## Reagent preparation

- Thaw the run control quickly in a water bath at 37°C.
- Mix gently during thawing until contents are just thawed.
- Immediately after thawing remove the run control tube from the water bath.
- Vortex the run control.
- Give a short spin in a centrifuge to remove liquid before releasing screw cap from vial.
- Minimise the time period from thawing until usage of the control samples.
- Use within 8 hours after thawing
- After thawing when not in use: store at 2-8°C

## Test procedure and calculations

The run control should be tested in a manner identical to that of clinical specimens and the result be calculated according to the instructions for use of the NAT procedure.

***Quantitative detection of HIV-1 RNA by viral load assays***

For monitoring the accuracy and precision in viral load assays one can use a Levey-Jennings QC chart for trend analysis.

*Levey-Jennings QC chart.*

Test the run control at least 10 times during the reference period, apply log transformation on values expressed in IU/mL or copies/mL, estimate the geometric mean, standard deviation (SD) and its confidence interval (CI) as described below. [If Ct values are used no log transformation is required and confidence intervals can be calculated from the arithmetic mean and SD]. The Levey-Jennings chart is designed to identify individual aberrant values outside the 95% and 99% confidence intervals. With collecting additional data the chart characteristics may be updated.

The quantitative values for [HIV-1 RNA] are 'log normal' distributed.

- Calculate from each measurement the log(concentration) in IU/mL or copies/mL.
- Calculate mean and SD on these log values
- Take anti-log of the mean of log values, i.e. the geometric mean of the measurements in IU/mL or copies/mL.

Use table 8 to obtain Student-t-values belonging to the 95% and 99% CI for different number of observations (n). Calculate the log(95% and 99% CI) as follows:

- Log (99% Lower limit): log (Average) – (99%) Student-t-Value x log(SD)
- Log (95% Lower limit): log (Average) – (95%) Student-t-Value x log(SD)
- Log (95% Upper limit): log (Average) + (95%) Student-t-Value x log(SD)
- Log (99% Upper limit): log (Average) + (99%) Student-t-Value x log(SD)

**Table 8**. Relation of Student t value and numbers of runs (n) to calculate CI's.

| Run (n) | t-value at 95% C.I. | t-value at 99% C.I. |
|---|---|---|
| 10 | 2.306 | 3.355 |
| 20 | 2.101 | 2.878 |
| 30 | 2.048 | 2.763 |
| infinite | 1.960 | 2.576 |

Use the Westgard rules[21] to identify deviations in the Levey Jennings trend analysis.

*Comparison of variation in quantitative values between result sets*

For this analysis result sets could represent e.g. laboratory, reagent batch, instrument, operator, etcetera.

The cumulative Chi-square distribution is used to calculate the probability that the SD of the test population (s) is different from the SD of reference population (σ):

- n is number of measurements over the evaluated period
- Within the set evaluated: calculate SD on the log(concentration): s
- Within the reference set: calculate SD on the log(concentration): σ.
- Calculate $X^2 = (n-1)\frac{s^2}{\sigma^2}$

Use table 9 to determine if the precision of the quantitative NAT method has significantly changed.

**Table 9**. Chi-square ($X^2$) values for p=0.05

| n-1 (df) | $X^2$ | n-1 (df) | $X^2$ | n-1 (df) | $X^2$ |
|---|---|---|---|---|---|
| 11 | 19.69 | 21 | 32.67 | 40 | 55.76 |
| 12 | 21.04 | 22 | 33.92 | 50 | 67.51 |
| 13 | 22.36 | 23 | 35.17 | 60 | 79.08 |
| 14 | 23.69 | 24 | 36.42 | 70 | 90.53 |
| 15 | 25.00 | 25 | 37.65 | 80 | 101.88 |
| 16 | 26.30 | 26 | 38.89 | 90 | 113.15 |
| 17 | 27.59 | 27 | 40.11 | 100 | 124.34 |
| 18 | 28.87 | 28 | 41.34 | | |
| 19 | 30.14 | 29 | 42.56 | | |
| 20 | 31.41 | 30 | 43.77 | | |

Interpretation:

Chi-square: $X^2_{(Calculated)} < X^2_{(P=0.05)}$: precision is not significantly changed.

Chi-square: $X^2_{(Calculated)} \geq X^2_{(P=0.05)}$: precision has changed significantly.

## Interpretation of test results on run control

P0327 ViraQ HIV-1 Quant 1000 should be used in conjunction HIV-1 viral load assays with an LOQ sufficiently below 500 copies/mL. Table 10 gives the expected frequency of different categories of results on the run control in these viral load assays.

**Table 10**. Interpretation of a single quantitative NAT test result on P0327 ViraQ HIV-1 Check 1000 control and expected frequency of viral load measurements above the lower limit of quantification (LOQ) of the current commercial real time PCR and TMA assays.

| Result | HIV-cp/mL | Expected frequency | Interpretation |
|---|---|---|---|
| Reactive quantifiable | ≥LOQ | 100% | This is an expected result. |
| Reactive quantifiable | ≥500 ≤2000 | >95% | This is an expected result. |
| Reactive quantifiable | <500 >2000 | <5% | This is an unexpected result but is possible. An investigation of technical performance or calibration of the NAT system is recommended |
| Reactive nonquantifiable or nonreactive | <LOQ | 0% | This is an unexpected result. An investigation of technical performance of the NAT system is required |

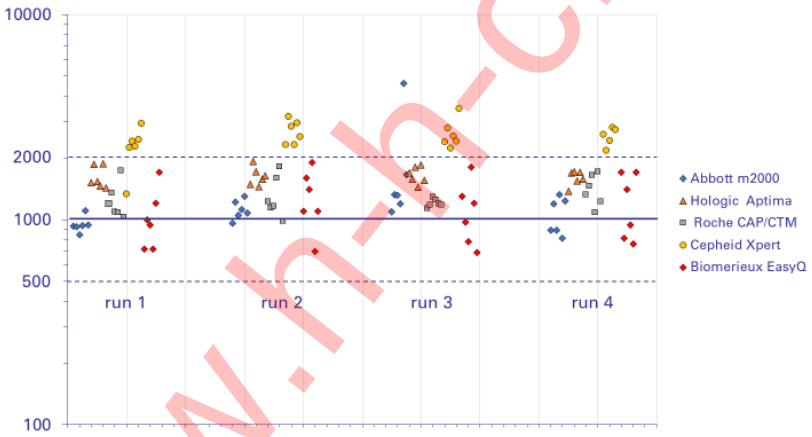
The linear range of the quantitative NAT methods tests starts at enough distance below the run control concentration of 1000 copies/mL to expect quantifiable results (above the LOQ) within a range between 500 and 2000 copies/mL in more than 95% of test runs[5].

One should be careful with comparing the copies/mL and IU/mL levels because different methods and standards have been used for calibration of the run control and (calibrators of) the NAT systems.

## Monitoring performance of quantitative NAT methods on run control

For the identification of aberrant quantitative results log (viral load) values should be recorded in a Levey-Jennings chart to visualise trends over time. The Westgard rules[13] provide guidance on the interpretation of results outside the 95% or 99% confidence intervals. An example of a Levey-Jennings scatter plot is given in figure 2 showing quantitative results obtained in five HIV-1 viral load assays in which P0327 ViraQ HIV-1 Quant 1000 control was tested in four test runs of 6 replicate tests.

**Figure 2**. Reproducibility of five different HIV-1 viral load assays on P0327 ViraQ HIV-1 Check 1000 control presented in a Levey-Jennings chart.




The distance from the solid line at a level of 1000 copies/mL represents the deviation from the expected quantitative result on the run control. The dotted lines represent the range of expected results between 500 and 2000 copies/mL.

One can use the quantitative results on the run control for comparison of different experimental conditions, such as different laboratories, NAT methods, NAT reagent lots or instruments. In the example above four assays found results within the expected range of 500- 2000 copies/mL, but one assay reported higher values (table 3, figure 2).

## Limitations

- P0327 ViraQ HIV-1 Quant 1000 Control must not be substituted for the mandatory controls or calibrators provided with NAT test kits for calculating the cut-off and/or quantitative test results or for setting criteria not to release clinical test results.
- The expected distributions of assay response values on P0327 ViraQ HIV-1 Quant 1000 Control that are presented in this package insert were based on evaluation studies involving a limited number of assays and reagent batches. Therefore it cannot be guaranteed that slightly different results will be found on other assay versions or reagent batches.
- P0327 ViraQ HIV-1 Quant 1000 should not be used for establishing accuracy of quantitative NAT results expressed in IU/mL. For this purpose only a dilution of the current WHO International Standard can be used.

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BioQControl B.V.
Droogmakerij 31h
1851 LX, Heiloo
The Netherlands

Telephone : +31-72-2020730
Telefax : +31-72-2020731
E-mail: info@bioQControl.com
Internet: www.bioQControl.com

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