SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

1. GENERAL INFORMATION

Device Generic Name:	In vitro reverse transcription polymerase chain reaction (PCR)-based assay for detection of HIV-1 RNA.
Device Trade Name:	Alinity m HIV-1 Alinity m System
Device Product Code:	MZF, QST OOI
Applicant Name and Address:	Abbott Molecular Inc. 1300 E. Touhy Ave Abbott Molecular Inc.
Establishment Registration Number:	3005248192
Premarket Approval Application (PMA) Number:	BP200455-7
Date of Panel Recommendation:	Not Applicable
Date of FDA Notice of Approval:	July 08, 2022

Material Reviewed/Consulted: The PMA, amendments to the PMA, and other specific documentation used in developing the Summary of Safety and Effectiveness Data (SSED).

Review memos from the following reviewers were used in developing the SSED:

Discipline Reviewed	Reviewer Names
Product Design	Viswanath Ragupathy
Preclinical and Clinical Studies	Viswanath Ragupathy Jiangqin Zhao
Instrumentation and Software	Rana Nagarkatti Nick Anderson
Statistician	Linye Song Zhen Jiang Chunrong Cheng
Bioresearch Monitoring Inspection (BIMO)	Kanaeko Ravenell Dennis Cato
Product and Promotional Labeling (OCBQ/DCM/APLB)	Jun lee Viswanath Ragupathy
Scientific and programmatic aspects	Pradip Akolkar Nick Anderson Julia Lathrop Indira Hewlett
Policy	Julia Lathrop J. Peyton Hobson Hira Nakhasi

2. INDICATIONS FOR USE

The Alinity m HIV-1 assay is an in vitro reverse transcription-polymerase chain reaction (RT-PCR) assay for the detection and quantification of Human Immunodeficiency Virus type 1 (HIV-1) RNA on the automated Alinity m System for confirmation of HIV-1 infection or for monitoring HIV-1 infected individuals. The Alinity m HIV-1 assay is intended for use in the clinical management of HIV-1 infected individuals in conjunction with clinical presentation and other laboratory markers.

The Alinity m HIV-1 assay is intended for use to monitor disease prognosis by measuring baseline plasma HIV-1 RNA level and to assess response to antiretroviral treatment by measuring changes in plasma HIV-1 RNA levels. Performance for quantitative monitoring is not established with serum specimens.

The Alinity m HIV-1 assay is also intended for use as a supplemental test to confirm HIV-1 infection in individuals who have reactive results with HIV immunoassays. Performance for supplemental use is established with both plasma and serum specimens.

The results from the Alinity m HIV-1 assay must be interpreted within the context of all relevant clinical and laboratory findings.

This device is not intended for use as a first line diagnostic test or for screening donors of blood, blood products, or human cells or tissues, or cellular and tissue-based products (HCT/Ps).

3. DEVICE DESCRIPTION

The Alinity m HIV-1 assay utilizes real-time reverse transcription polymerase chain reaction (RT-PCR) to amplify and detect HIV-1 RNA genomic sequences that have been extracted from human plasma or serum specimens. The Alinity m HIV-1 assay is designed to detect two highly conserved regions within the HIV-1 genome: the Integrase (INT) region of the pol gene and the Long Terminal Repeat (LTR) region. Alinity m HIV-1 is intended for use with the Alinity m System, a fully automated, self-contained system. The steps of the Alinity m HIV-1 assay consist of sample preparation, amplification/detection, result calculation and reporting. All steps of the Alinity m HIV-1 assay procedure are executed automatically by the Alinity m System. Manual dilutions may be performed for low-volume specimens to meet the minimum volume requirement, and for high-titer specimens above the upper limit of quantitation (ULoQ).

The Alinity m System is designed to be a random-access analyzer that can perform the Alinity m HIV-1 assay in parallel with other Alinity m assays on the same instrument.

HIV-1 RNA from human plasma or serum is extracted using the Alinity m Sample Prep Kit 2, Alinity m Lysis Solution, and Alinity m Diluent Solution. The Alinity m System employs magnetic microparticle technology to facilitate nucleic acid capture, wash, and elution. The resulting purified RNA is then combined with Alinity m HIV-1 activation reagent and Alinity m HIV-1 amplification/detection reagents and transferred into a reaction vessel. Alinity m Vapor Barrier Solution is then added to the reaction vessel which is then transferred to an amplification/detection unit for reverse transcription, PCR amplification, and real-time fluorescence detection of HIV-1.

At the beginning of the Alinity m HIV-1 sample preparation process, a lyophilized unit-dose Internal Control (IC) on the AMP Tray is rehydrated by the Alinity m System and delivered into each sample preparation reaction. IC is unrelated to HIV-1 target sequence and is derived from the hydroxypyruvate reductase gene from the pumpkin plant, *Cucurbita pepo*. The IC is then processed through the entire sample preparation and RT-PCR procedure along with the specimens, calibrators and controls to demonstrate proper sample processing and validity.

The Alinity m HIV-1 amplification/detection reagents consist of enzymes, primers, probes and activation reagents that enable reverse transcription, polymerization, and detection. The Alinity m HIV-1 amplification/detection reagent also contains Uracil-DNA Glycosylase (UDG) as a contamination control for amplicons containing uracil, which may be present in molecular laboratories.

An HIV-1 calibration curve is required for determination of HIV-1 RNA concentration. Two levels of calibrators are processed through sample preparation and RT-PCR to generate the calibration curve. The concentration of HIV-1 RNA in controls and concentration/detection of HIV-1 RNA in specimen is then determined from the stored calibration curve.

Assay controls are tested at or above an established minimum frequency to help ensure that instrument and reagent performance remains satisfactory. During each control event, a negative control, a low-positive control, and a high-positive control are processed through sample preparation and RT-PCR procedures that are identical to those used for specimens.

4. COMPONENTS OF THE ALINITY m HIV-1 ASSAY

4.1 Alinity m HIV AMP Kit

The Alinity m HIV AMP Kit consists of 2 types of multi-well trays:

- Alinity m HIV AMP TRAY 1 (4 trays x 48 tests): The Alinity m HIV AMP TRAY 1 contains separate wells of lyophilized, unit-dose RT-PCR amplification/detection reagents and lyophilized, unit-dose internal control.

- Alinity m HIV ACT TRAY 2 (4 trays x 48 tests): Alinity m HIV ACT TRAY 2 contains liquid activation reagent.

Each Alinity m HIV AMP TRAY 1 and Alinity m HIV ACT TRAY 2 is provided in a sealed foil pouch (4 pouches of each tray type per Alinity m HIV AMP Kit for up to 192 samples [patient specimens and/or assay controls or calibrators]). Both trays contain 48 unit-dose reagent wells (with reagents as listed above) of which one well of each reagent is used per test (48 tests per tray). The intended storage condition for the Alinity m HIV-1 AMP Kit is 2°C to 8°C.

Additional materials required but purchased separately

4.2 Alinity m HIV CAL Kit

The Alinity m HIV-1 calibrators are for calibration of the Alinity m HIV-1 assay on the automated Alinity m System when used for the quantitative determination of HIV-1 RNA. The Alinity m HIV CAL Kit is composed of the following reagents:

- Alinity m HIV CAL A (4 tubes x 1.95mL)
- Alinity m HIV CAL B (4 tubes x 1.95mL)

The Alinity m HIV CAL A and Alinity m HIV CAL B tubes are intended for single use only. The Alinity m System will process 3 replicates from each calibrator tube. The calibrators are assigned lot specific HIV RNA concentrations based on the results of testing against the Primary Calibrators. The intended storage condition for the Alinity m HIV-1 CAL Kit is –25°C to –15°C.

4.3 Alinity m HIV CTRL Kit

The Alinity m HIV-1 controls are for validity determination of the Alinity m HIV-1 assay used on the automated Alinity m System. The Alinity m HIV-1 CTRL Kit is composed of the following reagents:

- Alinity m HIV-1 Negative CTRL (12 tubes x 1.15mL)
- Alinity m HIV-1 Low Positive CTRL (12 tubes x 1.15mL)
- Alinity m HIV-1 High Positive CTRL (12 tubes x 1.15mL)

The Alinity m HIV-1 control reagents are intended for single-use only. Controls are recommended to be tested at or above the minimum frequency of once every 24 hours. The intended storage condition for the Alinity m HIV-1 CTRL Kit is –25°C to –15°C.

4.4 Alinity m Sample Prep Kit 2

The Alinity m Sample Prep Kit 2 is provided in a liquid, multi-dose format and is shared with other Alinity m assays. It consists of 2 reagents:

- Alinity m Elution Buffer 2 (4 bottles x 22mL)
- Alinity m Microparticles 2 (4 bottles x 24mL)

The Alinity m Sample Prep Kit 2 is used in conjunction with Alinity m System Solutions as part of the sample preparation protocol to extract and concentrate target nucleic acids from biological samples for subsequent Polymerase Chain Reaction (PCR) amplification, and to remove potential inhibitors from the resulting extract.

The sample preparation procedure consists of lysis/binding, washes, and elution. The sample preparation is performed within a disposable multi-well integrated reaction unit that is loaded onto an Assay Processing Unit on the Alinity m System. The intended storage condition for the Alinity m Sample Prep Kit 2 is 2°C to 8°C.

4.5 Alinity m Specimen Dilution Kit I

The Alinity m Specimen Dilution Kit I is intended to allow dilution of specimens for testing on the automated Alinity m System for measurement of nucleic acid. It consists of Alinity m specimen diluent tubes with a pierceable cap (24 tubes x 2.45mL). Each Specimen Dilution Kit I support dilution of up to 24 samples (patient specimens); each tube is for single use and must not be reused. The Alinity m specimen diluent tubes contain Abbott Molecular transport buffer which contains guanidine thiocyanate (GITC) in Tris Buffer. The intended storage condition for the Alinity m Specimen Dilution Kit I is 15°C to 30°C.

4.6 Alinity m System Solutions

The Alinity m System Solutions are used as part of the sample preparation protocol to extract and concentrate target viral nucleic acid from biological samples for subsequent PCR amplification and to remove potential inhibitors from the resulting extract. The Alinity m system solutions are as follows.

- The Alinity m Lysis Solution: 1 bottle × 975mL.
- The Alinity m Diluent Solution: 4 bottles × 975mL.
- The Alinity m Vapor Barrier Solution: 1 bottle × 975 mL.

The intended storage condition for the Alinity m System solutions is 15°C to 30°C.

4.7 Alinity m Tubes and Caps

- The Alinity m LRV Tube consists of Low Residual Volume (LRV) Tubes closed with caps (12 capped tubes per kit).

- Alinity m Transport Tube Pierceable Capped consist of transport tubes closed with pierceable caps (1500 capped tubes per case, 10 boxes of 150 capped tubes).
- Alinity m Transport Tube consist of 1600 tubes per kit.
- Alinity m Pierceable Cap consist of 2000 caps per kit.
- Alinity m Aliquot Tube consist of 1600 tubes per kit.

5. INSTRUMENTATION AND SOFTWARE

The Alinity m System is a fully integrated and automated molecular diagnostics analyzer which utilizes real-time PCR technology in clinical laboratories. It provides sample-to-result uninterrupted processing workflow. The Alinity m System enables continuous and random-access sample processing by using multiple sample processors and PCR thermal cycler/reader modules in parallel. Each individual sample occupies either one sample process lane or PCR Amplification and Detection (amp-detect) lane. Parallel lanes are provided to enable 300 tests in approximately 8 hours.

Each Alinity m System utilizes four (4) independent Assay Processing Units (APUs) to achieve the throughput and random-access requirements. Each APU consists of one extraction unit and one Amp-Detect unit, which automate the steps for nucleic acid purification/extraction and real-time PCR, respectively. This results in the ability to process up to twenty-four (24) different assay types simultaneously (i.e., up to 12 different assay types for purification/extraction and up to 12 different assay types for amplification and detection).

The Alinity m System software is the set of computer instructions that interprets system and assay information, calculates results, and provides the interface for controlling the system hardware.

The Alinity m System software interprets the assay information provided in the specific Application Specification File, along with system information, to control the system hardware and identify the appropriate algorithms for data reduction. Using application specifications, customers create orders for calibrators, controls, and specimens. Customers load racks of calibrators, controls, and specimens in the sample input to begin processing. Once the samples are processed, results are reviewed and released through the software user interface.

6. TEST PROCEDURE

Specimen Collection, Preparation and Storage

Plasma and serum specimens can only be used with this assay on the Alinity m System in the appropriate mode. Human plasma specimens can only be tested for both viral load quantification and for supplemental confirmatory testing. Human serum specimens can only be tested for supplemental confirmatory testing.

- The Alinity m HIV-1 assay can only be performed using plasma collected in dipotassium or tripotassium ethylenediamine tetra acetic acid (K2 or K3 EDTA) or Acid Citrate Dextrose (ACD) anticoagulants and plasma preparation tubes (PPT) with or without gel.
- For supplemental confirmatory testing the Alinity m HIV-1 assay may also be performed using serum collected in Serum Separator Tubes (SST) with or without gel.
- Alinity m HIV-1 assay performance with other specimen types or collection tubes has not been evaluated.
- For blood collection and centrifugation, follow the specimen collection tube manufacturer's instructions.
- Whole blood may be stored in plasma tubes at 2°C to 8°C for up to 2 days or at 15°C to 30°C for up to 24 hours prior to centrifugation and testing with the Alinity m HIV-1 assay.
- Whole blood may be stored in serum tubes at 2°C to 8°C for up to 2 days or at 15°C to 30°C for up to 12 hours prior to centrifugation and testing with the Alinity m HIV-1 assay. Plasma and serum can be tested on the Alinity m system in the primary tube or transferred to the secondary tube for storage.
- After centrifugation, the EDTA, PPT and ACD plasma samples may be stored in primary collection tubes at 15°C to 30°C for up to 24 hours or at 2°C to 8°C for up to 3 days. If transferred to the secondary tube, plasma may be stored at 2°C to 8°C for up to 3 days or stored frozen for up to 60 days at -20°C and 6 months at -70°C. Specimens in EDTA or ACD primary collection tubes should not be frozen.
- After centrifugation, the PPT serum samples (gel or non-gel) may be stored in primary collection tubes at 15°C to 30°C for up to 12 hours or at 2°C to 8°C for up to 2 days. If transferred to the secondary tube, serum may be stored at 2°C to 8°C for up to 3 days or stored frozen for up to 30 days at -20°C and 6 months at -70°C. Serum from primary collection tubes (non-gel) must be transferred to secondary tubes prior to storage. Plasma/Serum samples are stable for up to two freeze-thaw cycles.
- Specimens may be diluted manually for testing on the Alinity m System using the Alinity m Specimen Dilution Kit I.
- Low volume plasma or serum specimens with a minimum of 260µl volume available for Alinity m HIV-1 testing can be diluted 1:2.5. Plasma or serum specimens with 50 to 260µl volume available for Alinity m HIV-1 testing can be diluted 1:50. High-titer plasma specimens above the upper limit of quantitation (> ULOQ) can also be diluted 1:50 before testing.
- Specimens must be tested within 2 hours after dilution and should not be frozen.

6.1 Running the Alinity m HIV assay

The minimum sample volume required for running the Alinity m HIV-1 assay is 750µL. Prior to testing specimens, the calibration and control status should be checked. If recalibration or control testing is required, refer to the Quality Control Procedures section. Calibrators and/or controls may be tested separately or with specimens. Procedural steps are summarized as follows:

- Prior to loading the specimen tubes on the Alinity m System ensure individual specimen tubes are labeled correctly with specimen ID barcodes.
- Specimens should be free of bubbles and foam. If found, bubbles and foam should be removed with a new sterile pipette tip for each tube to prevent cross-contamination.
- Load the ACT TRAY 2 onto the plate adapter (Eppendorf Catalog No. 022638955).
- Load the plate adapter (with the ACT TRAY 2) on a swing plate centrifuge capable of accommodating the plate adapter. Spin at 100 to 800g for 1 to 5 minutes to remove potential bubbles.
- Immediately following centrifugation, carefully transfer the ACT TRAY 2 to the Alinity m Assay Tray Carriers. Take care to minimize disturbance to the ACT TRAY 2. Load the tray carriers per the Alinity m System Operations Manual, Section 5.
- If disturbance occurs during transfer that could potentially introduce bubbles (dropping, bumping, inversion of the ACT TRAY 2), re-centrifuge the ACT TRAY 2.
- Proceed with the reagent and sample inventory management procedure as indicated in the Alinity m System Operations Manual.
- From the Specimen tab on the create order screen, enter the specimen ID (SID), select the assay (HIV-1) and then select the appropriate specimen type (plasma or serum) and dilution (if applicable) being tested. Failure to assign the correct specimen type will invalidate the sample, which should then be re-tested.
- For a detailed description of how to run an assay, refer to the Alinity m System Operations Manual.

The Alinity m System will track the onboard storage time of amplification reagents, calibrators, controls, and specimens while on the instrument. The Alinity m System will not allow the use of amplification reagents, calibrators, controls, or process specimens that have exceeded the allowable onboard storage time.

Specimen tubes need to meet the requirements for minimum sample volume and the use of caps when loaded on the Alinity m System. Blood collection tubes with separated plasma or serum and specimen aliquot tubes may be placed on the Alinity m Universal Sample Rack (sample rack) onboard the Alinity system for up to 4 hours prior to processing.

6.2 Procedural Notes

- Ensure the Alinity m HIV-1 AMP TRAY 1 is tapped prior to loading on the Alinity m System.
- Ensure the Alinity m HIV-1 ACT TRAY 2 is centrifuged prior to loading on the Alinity m System.
- The Alinity m HIV-1 calibrator and control reagents are contained in single-use tubes with pierceable caps. Avoid contamination or damage to the caps after removal from their original packaging. Discard tubes after use.

7. RESULTS

7.1 Calculation

The Alinity m System automatically calculates the concentration of HIV-1 RNA for specimens and controls by comparing the results to a calibration curve. Quantitative viral load results reported for plasma are within the assay's quantitation range. The Alinity m System reports the results in Copies/mL, Log [Copies/mL], IU/mL or Log [IU/mL]. One copy of HIV-1 RNA is equal to 1.63 IU. The conversion factor for copies to International Unit (IU) traceable to the WHO 3rd International Standard for HIV-1 RNA (10/152) is stored in the instrument. For plasma specimens tested using the dilution procedure (1:2.5 or 1:50), software will automatically report the neat result (prior to dilution) by using the dilution factor selected by the user.

Qualitative results are reported for serum specimens as "Positive" or "Negative." No quantitative results are reported for tests performed with serum specimens. For diluted serum specimens (1:2.5 or 1:50), the Alinity m System reports a result with a 'DIL flag' indicating that the serum specimen has been diluted.

7.2 QUALITY CONTROL PROCEDURES

The Alinity m HIV-1 assay contains three quality control procedures.

Assay Calibration

- Lot-specific concentration values can be automatically imported to the Alinity m System via Abbott Mail upon scanning the calibrators (HIV-1 CAL A and HIV-1 CAL B) or controls (HIV-1 NEG CTRL, HIV-1 LOW POS CTRL, and HIV-1 HIGH POS CTRL) tube barcodes.
- Lot specific concentration values can also be obtained from the Abbott Molecular customer portal or provided by local Abbott Representative and imported via a USB drive.

A calibration curve is required to quantitate the HIV-1 RNA concentration. The Alinity m System will process 3 replicates from each calibrator tube. The output data of the 2 calibrators will be used to generate a calibration curve (lot specific HIV-1 concentration versus the threshold cycle [C_t] at which a reactive level of fluorescent signal is detected). The calibration curve slope and intercept are calculated and stored on the instrument. If three replicates of each calibrator are not available, at the minimum one CAL A and one CAL B tube is required for performing an assay calibration.

Once an assay calibration is valid and stored, all subsequent samples may be tested without further calibration unless any of the following situations occur:

- An Alinity m HIV-1 AMP Kit with a new lot number is used.
- An Alinity m Sample Prep Kit 2 or Alinity m Lysis Solution with a new lot number is used.
- The assay calibration has expired.
- A new version of the Alinity m HIV-1 Application Specification File is installed.
- This assay may require recalibration after maintenance to critical parts or subsystems or after service procedures have been performed.

Detection of Inhibition

An IC C_t assay validity parameter is established during a calibration run. A defined, consistent quantity of IC is introduced into each specimen, calibrator, and control at the beginning of sample preparation and measured on the Alinity m System to demonstrate proper specimen processing and assay validity. The median IC C_t value from calibrator samples establishes an IC C_t validity range for subsequently processed specimens and controls.

A message code is assigned to a specimen or control when its IC C_t value is outside of the IC C_t validity range. When the IC C_t value exceeds the upper limit of the IC C_t validity range, abnormal assay conditions, such as inhibition, are indicated. User is trained for corrective actions for message codes and additionally information is available in operator manual section 10.

Negative and Positive Controls

Alinity m HIV-1 Negative CTRL, Low Positive CTRL, and High Positive CTRL are recommended to be tested, at or above the minimum frequency of once every 24 hours, to monitor the performance of the assay and Alinity m System. Valid results for all control levels must be obtained before specimen results are reported. The assay controls are also tested following calibrators and valid results for controls are required to establish a new calibration curve. A flag is

displayed for specimens when a control result is invalid. All of the specimens processed following an invalid assay control must be retested.

Additional controls may be tested in accordance with local, state, and/ or federal regulations or accreditation requirements and user laboratory's quality control policy.

The presence of HIV-1 must not be detected in the negative control. HIV-1 detection in the negative control is indicative of contamination by other samples or by amplified product. To avoid contamination, the Alinity m System should be cleaned for repeat sample processing of controls and specimens following the procedural precautions in this package insert. If negative controls are persistently reactive, an Abbott Representative may be contacted for resolution.

When a set of assay controls are being processed, the lot-specific concentration values of the Alinity m HIV-1 Low Positive CTRL and Alinity m High Positive CTRL can be automatically imported to the Alinity m System via Abbott Mail upon scanning the barcode labels on control tubes (HIV-1 LOW POS CTRL and HIV-1 HIGH POS CTRL) or obtained through customer portal or from Abbott local representative.

8. INTERPRETATION OF RESULTS

Undiluted Plasma Specimens (Viral Load Testing)

The Alinity m System will report a result and an interpretation for each plasma specimen (Table 1). If applicable, message codes or flags will also be displayed.

Diluted Plasma Specimens (Viral Load Testing)

For plasma specimens diluted 1:2.5 or 1:50, the Alinity m System reports a viral load result, a viral load interpretation (if applicable), and a DIL flag indicating that the plasma specimen has been diluted. The quantitative results represent the HIV-1 RNA concentration in the plasma specimen prior to dilution.

For diluted specimens from which the HIV-1 signal is not detected, no result is reported, and a message code (9827) is displayed. These specimens cannot be interpreted as "Target not detected" and should be retested with undiluted specimens or from a newly prepared dilution. For diluted specimens with a result of < LLoQ (Lower Limit of Quantitation), it is recommended to collect and test another neat specimen.

Table 1. HIV-1 Viral Load Result Interpretation: Plasma

Alinity m System Reported	
Result	**Interpretation**
Not Detected	Target not detected
< LLoQ	Detected < LLoQ
20 Copies/mL to ≤ ULoQ (1.30 Log Copies/mL to ≤ ULoQ)	Detected and quantified
> ULoQ	> ULoQ[a]

[a] Specimens tested neat or with 1:2.5 dilution procedure that have >ULoQ (Upper Limit of Quantitation) interpretation may be retested using the 1:50 dilution procedure to determine a result within the quantitation range.

Supplemental Assay: Undiluted and Diluted Plasma Interpretation

The supplemental confirmatory interpretation is not reported by the Alinity m System. A confirmatory interpretation is performed by the user, based on the viral load result/interpretation of detected/not detected (Table 2). The user interprets a "Target Not Detected" interpretation as "Negative" and a "Detected < LLOQ", "Detected and quantified", or > ULOQ" as "Positive".

Table 2. HIV-1 Qualitative Result Interpretation: Plasma

Alinity m System Reported		User Interpretation
Result [a]	**Alinity m Interpretation**	**Confirmatory Interpretation**
Not Detected [b]	Target not detected [b]	Negative [b]
< LLOQ	Detected < LLOQ	Positive
20 Copies/mL to ≤ ULOQ (1.30 Log Copies/mL to ≤ ULOQ)	Detected and quantified	Positive
> ULOQ	> ULOQ	Positive

[a] Specimens tested with a dilution will have an LLOQ and ULOQ as described in the Diluted Plasma Specimens (Viral Load Testing) section above.

[b] For diluted specimens from which the HIV-1 signal is not detected, no result is reported, and a message code (9827) is displayed. These specimens cannot be interpreted as "Target not detected" or "Negative" and should be retested with undiluted specimens or from a newly prepared dilution.

Supplemental Assay: Undiluted Serum Interpretation

Quantitative viral load results are not reported for serum specimens. As shown in the Table 3 below, for each serum specimen the Alinity m System will report a qualitative result and interpretation. If applicable, message codes or flags will also be displayed. The supplemental confirmatory interpretation is directly reported by the Alinity m System for serum specimens.

Table 3. HIV-1 Qualitative Result Interpretation: Serum

Alinity m System Reported	
Result	**Interpretation**
HIV-1 RNA Not Detected	Negative
HIV-1 RNA Detected	Positive

Supplemental Assay: Diluted Serum Interpretation

For serum specimens diluted 1:2.5 or 1:50, the Alinity m System reports a result (Table 4), an interpretation (if applicable), and a DIL flag indicating that the serum specimen has been diluted.

For diluted serum specimens from which the HIV-1 signal is not detected, a message code (9827) is displayed, and no result is reported. These specimens cannot be interpreted as “Negative” and should be retested with a new undiluted specimen or from a newly prepared dilution.

Table 4. Serum Specimens Tested Using 1:2.5 or 1:50 Dilution

Alinity m System Reported	
Result	**Interpretation**
HIV-1 RNA Detected	Positive
No Result Reported [a]	No Interpretation Reported (Re-test undiluted or newly prepared dilution) [a]

[a] Refer to Message Code 9827.

Flags, Results Codes, and Message Codes

Some results may contain information in the flags and codes fields. For a description of the flags and result codes that may appear in these fields, user must refer to the Alinity m System operations manual sections 5 and 10.

9. WARNINGS AND PRECAUTIONS

- For In Vitro Diagnostic Use
- Wear gloves when handling specimens or reagents.
- Do not pipette by mouth.
- Do not eat, drink, smoke, apply cosmetics, or handle contact lenses in areas where these materials are handled.
- Clean and disinfect spills of specimens by including the use of a tuberculocidal disinfectant such as 1.0% sodium hypochlorite or other suitable disinfectant.
- Decontaminate and dispose of all potentially infectious materials in accordance with local, state, and federal regulations.
- To reduce the risk of invalid results, carefully read the entire package insert and the Alinity m System Operator's Manual prior to performing this assay.
- Use only supplied or specified required consumables to ensure optimal test performance.

10. PROCEDURAL LIMITATIONS

- Optimal performance of this test requires appropriate specimen collection and handling (refer to the Specimen Collection and Preparation for Analysis section of this package insert.)
- Only Human serum (including SST) and plasma (ACD, K2 EDTA, K3 EDTA, and PPT) specimens can be used with the Alinity m HIV-1 assay. The use of other anticoagulants has not been evaluated.
- Debris within plasma and serum specimens (e.g., clots, fibrin strands) may interfere with sample processing.
- Performance of the supplemental test to confirm HIV-1 infection in individuals who have reactive results with HIV immunoassays was established for HIV-1 viral load at ≥100 copies/mL.
- Diluted specimens must be tested within 2 hours after dilution and should not be frozen.
- If the HIV-1 results are inconsistent with clinical evidence, additional testing is suggested to confirm the result.
- HIV-1 RNA concentration (i.e., number of virus particles present in the samples) may be affected by patient factors (age, presence of symptoms), and/or stage of infection.
- Though rare, mutations within the highly conserved regions of a viral genome detected by Alinity m HIV may affect primers and/or probe binding resulting in the under-quantitation of virus or failure to detect the presence of virus. To ensure assay robustness, the Alinity m HIV-1 assay is designed to target two highly conserved sequences within the HIV-1 genome.

- Due to inherent differences between technologies, it is recommended that, prior to switching from one technology to the next, users perform method correlation studies in their laboratory to evaluate technology differences. Users should follow their own specific policies/procedures.
- The instruments and assay procedures reduce the risk of contamination by amplification product. However, nucleic acid contamination from the calibrators, positive controls, or specimens must be controlled by good laboratory practice and careful adherence to the procedures specified in this package insert.
- Assay linearity for HIV-1 Group M subtype BF, subtype H and Group N quantification was tested up to 10,000 Copies/mL for subtype BF, 300,000 Copies/mL for subtype H and 1,000,000 Copies/mL for Group N, respectively.

11. CONTRAINDICATIONS

There are no known contraindications for use for this test.

12. ALTERNATIVE PRACTICES AND PROCEDURES

There are currently several FDA approved Class III in vitro diagnostic tests for the quantitation of HIV-1 RNA. Once the diagnosis of HIV has been established, $CD4^+$ cell count and HIV-1 viral load are the two most commonly utilized surrogate markers of HIV disease progression.

13. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

When used according to the instructions in the package insert, there are no known direct adverse effects of this device on the health of the user. No specific adverse effects occurred during conduct of the clinical studies.

An error with the quantification of viral load may occur with the Alinity m HIV-1 assay which may lead a clinician to believe that the current therapy is effective when it is not. Consequently, the clinician could fail to implement a more appropriate therapy. A high viral load result may lead a clinician to believe that the current therapy is not effective. Consequently, the clinician could implement an inappropriate change in therapy. There were no specific adverse events that occurred in the clinical studies.

14. MARKETING HISTORY

The Alinity m HIV-1 assay (with quantitative and qualitative indications) was CE-marked in 2019. The assay with indication for HIV-1 RNA quantification was approved by FDA for the US market in 2020. The Alinity m HIV-1 AMP Kit, Alinity m HIV-1 CTRL Kit, Alinity m HIV-1 CAL Kit, Alinity m Sample Prep Kit 2, Alinity m Specimen Dilution Kit I, Alinity m Tubes and Caps and Alinity m System

Solutions are identical in formulation to the US kits, except for kit labeling, and were introduced to multiple foreign markets outside of the United States.

The Alinity m System was self-certified for commercialization in the European Union, and the European Free Trade Association (EFTA) since December 2017.

The Alinity m HIV-1 kits and Alinity m System have not been withdrawn from the market for reasons related to safety or effectiveness.

15. SUMMARY OF NONCLINICAL STUDIES

15.1 Limit of Detection

The limit of detection (LOD) was determined by testing dilutions of the World Health Organization (WHO) 3rd International Standard for HIV-1 RNA (NIBSC code: 10/152) prepared in HIV-1 negative human plasma to create a 7-dilution panel. Eight replicates of each panel members were run on four Alinity m systems using four reagent lots over three days for a total of 96 replicates for each dilution. The International Unit (IU) and copies/ml conversion used in this assay is traceable to WHO 3rd International Standard for HIV-1 RNA where one copy of HIV-1 RNA is equivalent to 1.63 IU. The results of the analytical sensitivity performance of Alinity m HIV-1, are summarized in Table 5.

Table 5. Alinity m HIV-1 Limit of Detection (LOD)

Matrix	HIV-1 RNA (Copies/mL)	HIV-1 RNA Concentration (IU/mL)	No. of Valid Replicates	No. of Detected Replicates	Detection Rate (%)	LOD by Probit [95% CI]	LOD
Plasma	40.00	65.20	94	94	100.0	13.99 Copies/mL [11.69 to 19.22 Copies/mL]	20 Copies/mL (1.30 Log Copies/mL)
	20.00	32.60	90	87	96.7		
	15.00	24.45	90	87	96.7		
	12.50	20.38	90	85	94.4		
	10.00	16.30	91	80	87.9		
	7.50	12.23	87	69	79.3		
	5.00	8.15	91	63	69.2		
Serum	40.00	65.20	96	96	100.0	15.94 Copies/mL [13.30 to 21.53 Copies/mL]	20 Copies/mL (1.30 Log Copies/mL)
	20.00	32.60	96	95	99.0		
	15.00	24.45	95	90	94.7		
	12.50	20.38	95	87	91.6		
	10.00	16.30	96	80	83.3		
	7.50	12.23	95	75	78.9		
	5.00	8.15	96	68	70.8		

Summary: The LoD study using plasma samples demonstrated that the Alinity m HIV-1 detected HIV-1 RNA at a concentration of 13.99 copies/mL (22.80 IU/mL), with a rate of detection of 95% as estimated by PROBIT analysis (Table 5).

The Lower Limit of Quantitation (LLoQ) and LOD for the Alinity m HIV-1 in plasma is 20 copies/mL (1.30 Log Copies/mL) (32.60 IU/mL) and has been demonstrated to generate positive results with a rate of detection of 96.7% (87/90) (Table 5).

The LoD study using serum samples demonstrated that the Alinity m HIV-1 detected HIV-1 RNA at a concentration of 15.94 copies/mL (25.98 IU/mL), with a rate of detection of 95% as estimated by PROBIT analysis (Table 5).

The LOD for the Alinity m HIV-1 in serum is 20 copies/mL (1.3 Log Copies/mL) (32.60 IU/mL) and has been demonstrated to generate positive results with a rate of detection of 99% (95/96) (Table 5).

15.2 Limit of Detection Across Groups and Subtypes

HIV-1 group M (subtypes A, BF, C, D, CRF01-AE, F, CRF02-AG, G and H), group O and group N panels were prepared by diluting HIV-1 viral stock or HIV-1 positive clinical specimens to three different concentrations (0.5x LoD, 1.0x LoD, and 2.0x LoD) in HIV-1 negative human plasma and serum. Eight replicates of each diluted sample were tested using four Alinity m kit lots over three days for a total of 96 replicates tested for each dilution. For HIV-1 groups/subtypes, an LOD of 20 copies/mL was demonstrated at a detection rate (hit rate) greater than or equal to 95%. The results are shown in Table 6 and Table 7.

Table 6. Alinity m HIV-1 Limit of Detection (LOD) in Plasma Across Groups and Subtypes.

Group/Subtype	HIV-1 RNA (Copies/mL)	No. of Valid Replicates	No. of Detected Replicates	Detection Rate (%)
Group M, subtype A	40	93	93	100.0
	20	95	94	98.9
	10	94	88	93.6
Group M, subtype BF	40	94	94	100.0
	20	95	95	100.0
	10	96	82	85.4
Group M, subtype C	40	95	95	100.0
	20	95	95	100.0
	10	94	92	97.9
Group M, subtype D	40	95	95	100.0
	20	95	94	98.9
	10	96	86	89.6
Group M, CRF01-AE	40	93	93	100.0
	20	96	96	100.0
	10	94	89	94.7

Group M, subtype F	40	94	94	100.0
	20	96	95	99.0
	10	93	88	94.6
Group M, CRF02-AG	40	93	93	100.0
	20	94	94	100.0
	10	94	90	95.7
Group M, subtype G	40	96	96	100.0
	20	93	93	100.0
	10	91	84	92.3
Group M, subtype H	40	92	92	100.0
	20	95	95	100.0
	10	91	89	97.8
Group O	40	90	90	100.0
	20	92	92	100.0
	10	92	91	98.9
Group N	40	96	96	100.0
	20	92	92	100.0
	10	95	95	100.0

Table 7. Alinity m HIV-1 Limit of Detection (LOD) in Serum Across Groups and Subtypes

Group/Subtype	HIV-1 RNA (Copies/mL)	No. of Valid Replicates	No. of Detected Replicates	Detection Rate (%)
Group M, subtype A	40	94	94	100.0
	20	95	95	100.0
	10	96	95	99.0
Group M, subtype BF	40	95	95	100.0
	20	94	93	98.9
	10	95	89	93.7
Group M, subtype C	40	93	93	100.0
	20	96	96	100.0
	10	96	96	100.0
Group M, subtype D	40	94	94	100.0
	20	95	95	100.0
	10	94	89	94.7
Group M, CRF01-AE	40	96	96	100.0
	20	96	96	100.0

	10	96	96	100.0
Group M, subtype F	40	95	95	100.0
	20	96	96	100.0
	10	95	92	96.8
Group M, CRF02-AG	40	96	96	100.0
	20	95	95	100.0
	10	95	93	97.9
Group M, subtype G	40	95	95	100.0
	20	95	95	100.0
	10	96	93	96.9
Group M, subtype H	40	96	96	100.0
	20	96	96	100.0
	10	96	94	97.9
Group O	40	94	94	100.0
	20	95	95	100.0
	10	95	95	100.0
Group N	40	93	93	100.0
	20	96	96	100.0
	10	95	95	100.0

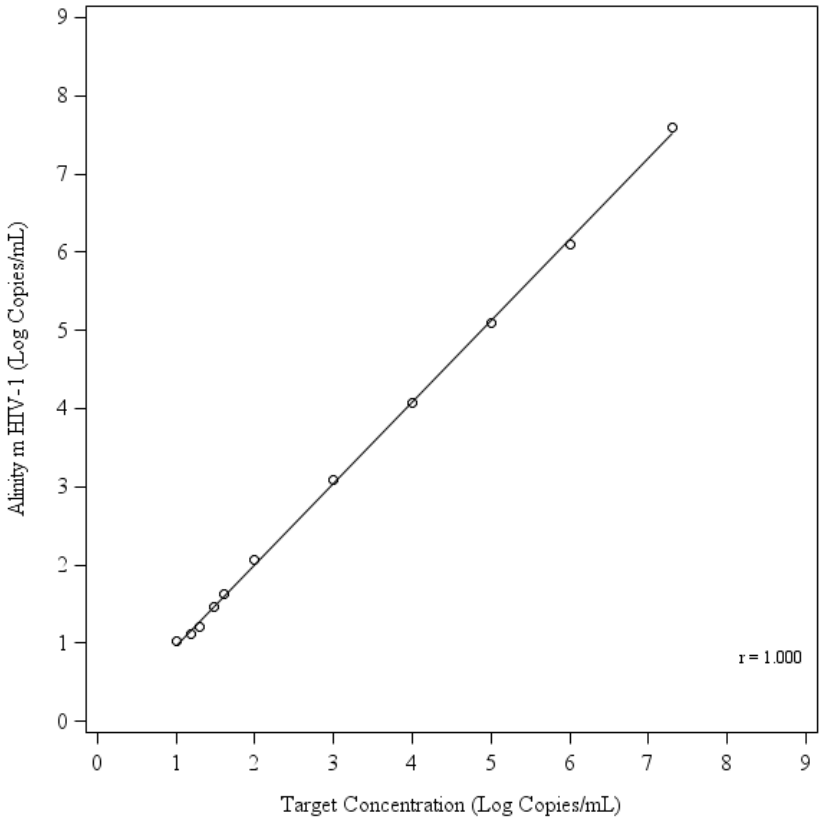
Summary: The results from this study demonstrate that the detection rate at LOD (20 copies/mL) ranged from 98.9% to 100.0% across HIV-1 groups / subtypes, and at 2x LOD (40 copies/mL) was 100.0% for all HIV-1 groups/ subtypes. The results support the LOD of 20 copies/mL for the Alinity m HIV-1 assay in plasma and serum for HIV-1 Group M Subtypes A, BF, C, D, CRF01-AE, F, CRF02-AG, G, H, Group O, and Group N.

15.3 Linear Range

Linearity was evaluated by testing 11 panel members formulated using HIV-1 Group M, subtype B high titer viral stock in HIV-1 negative plasma that spanned the intended dynamic range of the assay (20 copies/mL to 10,000,000 copies/mL), including two members below the expected Lower Limit of Quantification (LLoQ, 20 copies/mL), and a member exceeding the expected Upper Limit of Quantification (ULOQ, 10,000,000 copies/mL). This range covers the medical decision points. All titers were calculated and converted into log titer. The data were analyzed for maximum deviation between the linear regression

and the better fitting non-linear regression. In addition, the LLoQ was determined for the lowest concentration level (20 copies/mL) in the LOD panel with a detection rate ≥ 95 %. To determine LLoQ a statistical approach described in CLSI EP06-A was used. Testing was conducted using one reagent lot.

Figure 1. Linearity



The markers in the plot represent the mean Alinity m HIV-1 concentration (in Log Copies/mL) for each panel member.

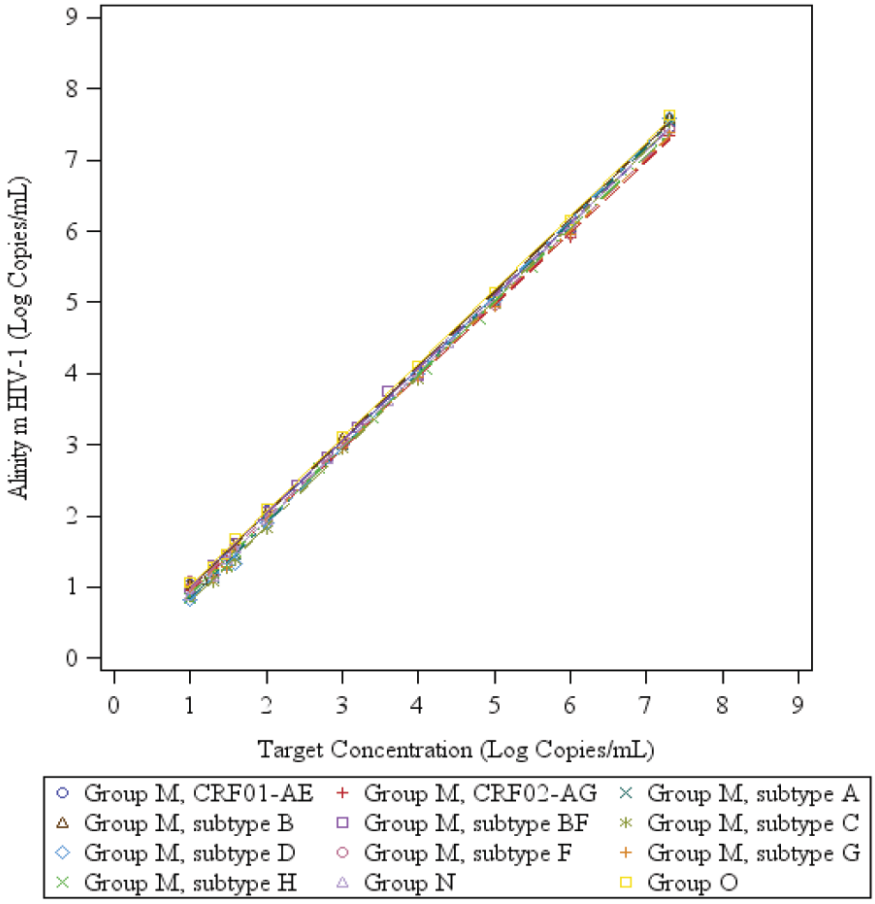
Summary: As shown in Figure 1, the Alinity m HIV-1 assay was linear across the range of HIV-1 RNA concentrations tested ranging from 10 copies/mL to 20,000,000 copies/mL (1.0 log copies/mL to 7.30 log copies/mL) and the LLoQ was determined as 20 copies/mL using the input sample volume 0.6mL. The difference in the predicted concentration between the fitted nonlinear model and the linear model was less than 0.50 Log copies/mL for each panel member tested. The performance of Alinity m HIV-1 assay is acceptable.

15.4 Linearity Across Groups and Subtypes

Linearity of the Alinity m HIV-1 assay for HIV-1 group M (subtypes A, BF, C, D, CRF01-AE, F, CRF02-AG, G and H), group O and group N was confirmed by testing a dilution series consisting of 10 panel members for each group/subtype, prepared using HIV-1 cultured virus or HIV-1 positive clinical specimens diluted

in HIV-1 negative human plasma. Linearity panel members spanned the intended dynamic range of the assay (20 copies/mL to 10,000,000 copies/mL). However, for Group M/subtype BF, H and Group N the targeted concentration for testing ranged from 10 - 10,000 copies/mL, 10 – 300,000 copies/mL and 10 – 1,000,000 copies/mL, respectively. All titers were calculated and converted into log titer.

Figure 2. Linearity Across Groups and Subtypes



Summary: As shown in Figure 2, Alinity m HIV-1 assay was linear between 10 copies/mL to 20,000,000 copies/mL for HIV-1 Group M subtypes A, C, D, CRF01-AE, CRF02-AG, F, G and Group O. For HIV-1 Group M subtypes BF, H and Group N, the assay was linear from 10 copies/mL to the highest concentration tested. For each subtype analyzed the maximum deviation between the linear regression and the better fitting non-linear regression was less than 0.5 Log copies/mL.

15.5 Precision

The precision of the Alinity m HIV-1 assay was determined by analyzing an 8-member plasma panel, prepared by diluting an HIV-1 viral stock into HIV-1 negative human plasma that spanned the dynamic range of the assay (20 copies/mL to 10,000,000 copies/mL). Each panel member was tested in 5 replicates, twice each day for 12 days, on 3 Alinity m Systems with 3 Alinity m HIV-1 AMP Kit lots by 3 operators for a total of 360 replicates per panel member (5 replicates x 2 runs/day x 3 kit lots x 12 days). A statistical approach of total assay variability was determined. The overall precision results shown in Table 8.

Table 8. Precision in Plasma

Panel	N[a]	Mean Conc (Log Copies/mL)	Within-Run Component		Between-Run Component		Between-Day Component		Within-Laboratory[b]		Between-Instrument Component		Total[c]	
			SD	% CV	SD	% CV	SD	% CV	SD	% CV	SD	% CV	SD	% CV
08	349	7.34	0.04	0.5	0.01	0.2	0.00	0.1	0.04	0.6	0.08	1.1	0.09	1.2
07	347	6.02	0.04	0.7	0.00	0.0	0.01	0.2	0.04	0.7	0.05	0.8	0.07	1.1
06	348	5.04	0.04	0.8	0.02	0.3	0.01	0.2	0.04	0.9	0.02	0.5	0.05	1.0
05	353	4.04	0.05	1.3	0.00	0.0	0.01	0.3	0.05	1.3	0.03	0.8	0.06	1.5
04	353	3.11	0.05	1.5	0.01	0.5	0.01	0.2	0.05	1.6	0.04	1.2	0.06	2.0
03	353	2.40	0.09	3.6	0.02	1.0	0.00	0.0	0.09	3.7	0.04	1.5	0.10	4.0
02	352	1.87	0.15	8.2	0.00	0.0	0.03	1.5	0.16	8.4	0.04	1.9	0.16	8.6
01	353	1.34	0.27	19.8	0.02	1.7	0.00	0.0	0.27	19.9	0.05	3.4	0.27	20.2

[a] Number of valid replicates.
[b] Within-Laboratory includes Within-Run, Between-Run and Between-Day Components.
[c] Total includes Within-Run, Between-Run, Between-Day and Between-Instrument Components.

Precision of the Alinity m HIV-1 in serum was determined by testing a 4-member panel prepared by diluting an HIV-1 viral stock into HIV-1 negative human serum that spanned the dynamic range of the assay (20 copies/mL to 10,000,000 copies/mL). Each panel member was tested in five replicates, twice each day for 12 days, on three Alinity m Systems with three Alinity m HIV-1 AMP Kit lots by three operators for a total of 360 replicates per panel member (5 replicates x 2 runs/day x 3 kit lots x 12 days). A statistical approach of total assay variability was determined. The overall precision results shown in Table 9.

The positive agreement rates and the precision results (Cycle threshold, Ct) shown in Table 9.

Table 9. Precision in Serum

Serum Panel Member	Target Conc (Log Copies/mL)	N[a]	n[b]	Agreement (n/N)	Mean	Within-Run Component		Between-Run Component		Between-Day Component		Within-Laboratory[c]		Between-Instrument Component		Total[d]	
					(Ct)	SD	% CV	SD	% CV	SD	% CV	SD	% CV	SD	% CV	SD	% CV
4	7.00	356	356	100.0%	7.49	0.18	2.4	0.07	1.0	0.05	0.7	0.20	2.7	0.11	1.4	0.23	3.0
3	4.00	350	350	100.0%	17.91	0.14	0.8	0.04	0.2	0.06	0.4	0.16	0.9	0.07	0.4	0.17	0.9
2	1.78	354	354	100.0%	25.08	0.41	1.6	0.03	0.1	0.11	0.4	0.43	1.7	0.20	0.8	0.47	1.9
1	1.30	357	354	99.2%	26.39	0.82	3.1	0.18	0.7	0.00	0.0	0.84	3.2	0.11	0.4	0.85	3.2

[a] Number of valid replicates.
[b] Number of replicates with detectable HIV-1; the number of replicates were used in the Mean and SD calculation.
[c] Within-Laboratory includes Within-Run, Between-Run, and Between-Day components.
[d] Total includes Within-Run, Between-Run, Between-Day, and Between-Instrument components.

Summary: The Alinity m HIV-1 assay results demonstrated acceptable precision for plasma and serum across the dynamic range of assay (1.34 to 7.34 log HIV-1 RNA copies/mL) and total variance is less than 0.5 log HIV-1 RNA copies/mL for plasma and less than 0.85 HIV-1 ct for serum when tested with three lots of reagents.

15.6 Performance with HIV-1 negative specimens (Specificity)

The specificity of the Alinity m HIV-1 assay was determined by testing 250 HIV-1 negative plasma specimens and 259 HIV-1 negative serum specimens obtained from HIV-1 negative whole blood donors (as determined using an FDA approved Ag/Ab assay) and demonstrated to be HIV-1 RNA negative using the Abbott RealTime HIV-1 assay. The study was conducted using one lot of Alinity m HIV-1 AMP kit reagents and one Alinity m System.

Summary: All 509 HIV-1 negative specimens reported HIV-1 RNA ‘Not Detected’ interpretation when tested on Alinity m HIV-1 assay. Diagnostic specificity was 100.0% (95% CI: 98.5%, 100.0%) for HIV-1 negative plasma specimens and HIV-1 negative serum specificity was 100% (95% CI: 98.6 to 100.0%). The overall specificity for plasma and serum combined was 100.0% (95% CI: 99.3 to 100.0%). The specificity of the Alinity m HIV-1 assay was determined to be acceptable.

15.7 Seroconversion Sensitivity

The sensitivity of the Alinity m HIV-1 assay with seroconversion samples was evaluated by testing 11 commercially sourced HIV-1 seroconversion panels (Table 10) and comparing the Alinity m HIV results to an FDA approved 4th generation HIV Ag/Ab serology assay reported in the Certificate of Analysis of the samples. A total of 111 specimens were evaluated.

Table 10. Days to First Reactive Result for Alinity m HIV-1 and HIV antigen/antibody Combo.

Panel	Number of Panel Members Tested	Number of Detected/Reactive Panel Members		Days to First Detected/Reactive Result		Difference in Days [a]
		Alinity m HIV-1 Assay	HIV Antigen/Antibody Combo	Alinity m HIV-1 Assay	HIV Antigen/Antibody Combo	
01	11	5	2	23	38	15
02	16	7	3	33	59	26
03	10	5	4	21	25	4
04	10	6	4	14	22	8
05	10	5	3	19	26	7
06	8	4	3	14	16	2
07	7	2	1	12	14	2
08	8	2	1	23	25	2
09	11	4	3	32	34	2
10	10	4	2	33	40	7
11	10	4	3	21	28	7
Total	**111**	**48**	**29**			

[a] The difference in days to first reactive result between the HIV antigen/antibody combo detection and the Alinity m HIV-1 Assay detection.

Summary: The Alinity m HIV-1 assay detected HIV-1 RNA in 48 out of 111 total number of bleeds compared to 29 that were reactive by a 4th generation HIV antigen/antibody combination assay. Among the bleeds reactive by the HIV antigen/antibody combination assay, 100% (29/29) were detected by Alinity m HIV-1. The first detected bleed for Alinity m HIV-1 occurred earlier than the HIV antigen/ antibody combination assay in all 11 panels (median 7.0 days; mean 7.5 days). These results indicate that the Alinity m HIV-1 assay confirmed the presence of HIV on the same or an earlier draw than the reference serology method in all panels (Table 10).

15.8 Carryover

The carryover rate for the Alinity m HIV-1 assay was determined by testing 720 samples (360 HIV-1 negative and 360 HIV-1 positive samples) across 15 runs. Each run consisted of 24 replicates of the HIV-1 high-positive sample (1.00E+07 copies/mL) and 24 replicates of the HIV-1 negative sample. HIV-1 high-positive and HIV-1 negative sample replicates were placed in alternating positions within the sample input rack, so that each negative sample replicate was processed adjacent to a positive sample replicate during sample preparation and RT-PCR processes.

Summary: Of the 720 replicates of HIV-1 negative samples tested, one sample was reported positive for HIV-1. The overall sample carryover rate was 0.1% (95% CI: 0.0% to 0.8%). These results are acceptable for the performance of Alinity mHIV-1.

15.9 Potentially Interfering Microbial Contaminants

The impact of potential cross-reactivity and/or interference of pathogens in the Alinity m HIV assay was evaluated. The study was designed according to CLSI: EP7-A2 Interference testing in clinical chemistry. HIV-1 negative or positive test specimens were spiked with microorganisms or purified nucleic acid from microorganisms to achieve a final titer of 10^5 units/mL for viruses and yeast, and 10^6 CFU/mL for bacteria (Table 11). Cross-reactivity was analyzed using an HIV negative sample and microbial interference was analyzed using an HIV positive sample at 60 copies/mL (3x LLoQ) and from the 200 copies/mL sample. Three replicates for each cross reactant were tested.

Table 11. Potential Cross-Reactants

Viruses
Adenovirus type 5
BK polyomavirus
Cytomegalovirus
Dengue Virus 1
Dengue Virus 2
Dengue Virus 3
Dengue Virus 4
Epstein-Barr Virus
GB virus C / Hepatitis G Virus
Hepatitis A Virus
Hepatitis B Virus
Hepatitis C Virus
Herpes Simplex Virus 1
Herpes Simplex Virus 2
Human Herpesvirus 6B
Human Herpesvirus 8
Human Immunodeficiency Virus 2
Human Papilloma Virus 16
Human Papilloma Virus 18
Human T Lymphotropic Virus Type 2
Human T Lymphotropic Virus Type 1
Influenza A
Vaccinia Virus
Varicella-Zoster Virus
Bacteria
Chlamydia trachomatis

Mycobacterium gordonae *Mycobacterium smegmatis* *Neisseria gonorrhoeae* *Propionibacterium acnes* *Staphylococcus aureus* *Staphylococcus epidermidis*
Yeast
Candida albicans

Summary: No cross-reactivity of the Alinity m HIV-1 assay with the potential cross-reactants tested was observed. In addition, there was no impact on the detection or quantitation by the Alinity m HIV-1 assay by the organisms listed.

15.10 Potentially Interfering Substances (Endogenous)

The impact of potentially interfering endogenous substances, the presence of autoimmune disorders, and markers of other diseases on the analytical specificity and detection/quantitation of the Alinity m HIV-1 assay was evaluated by testing spiked samples as well as patient samples with naturally elevated levels of endogenous substances. Ten samples from healthy blood donors (individuals who report no history of HIV or liver disease, such as hepatitis) were tested for each interfering substance with one replicate each. As a control, one replicate of each donor sample was also tested without the addition of any potentially interfering endogenous substance. HIV-1 positive samples were prepared by adding HIV-1 viral stock to HIV-1 negative plasma at a final concentration of 60 copies/mL (3x LLoQ) of assay (detection) and at 200 copies/mL (quantitation).

Summary: No interference was observed in the presence of albumin (60 mg/mL), hemoglobin (2 mg/mL), triglycerides (37 mM), conjugated bilirubin (0.342 mM), unconjugated bilirubin (0.342 mM), or human genomic DNA (2 mg/L) that were introduced in the sample. In addition, no interference was observed in specimens collected from individual donors containing the naturally elevated interfering substances, albumin (>5.1 g/dL), bilirubin (>2 mg/dL), hemoglobin (>2 g/L) or triglycerides (>325 mg/dL).

15.11 Potentially Interfering Substances (Exogenous)

The impact of potentially interfering drugs commonly prescribed for the treatment of HIV-1 and other disease states on the performance of Alinity m HIV-1 assay was evaluated. Ten samples from healthy blood donors were tested for each interfering drug pool or single drug with one replicate each. As a control, one replicate of each donor sample was also tested without the addition of any potentially interfering drug compounds. The HIV-1 positive samples were prepared at two HIV-1 levels by adding HIV viral stock to HIV-1 negative plasma at a final concentration of 60 copies/mL (3x LLoQ) of assay (detection) and at 200 copies/mL (quantitation). The drug compounds listed in Table 12 were tested

at three times the reported maximum concentration (Cmax) evaluated with and without HIV-1 viral targets.

Table 12. Drugs Tested for Interference with the Quantitation of HIV-1 RNA by the Alinity m HIV-1 Assay

Pools Tested	Drug Compounds
1	Abacavir sulfate, Acetaminophen, Acyclovir, Adefovir, Amitriptyline, Amlodipine, Aspirin, Atazanavir, Atenolol, Atorvastatin, Azithromycin, Celecoxib, Cidofovir, Clarithromycin, Clopidogrel
2	Didanosine, Efavirenz, Entecavir, Fluconazole, Fluoxetine, Ibuprofen, Indinavir, Kaletra (Lopinavir and Ritonavir), Lamivudine, Levofloxacin, Maraviroc, Nelfinavir, Nevirapine, Paroxetine
3	Prednisone, Raltegravir, Ribavirin, Rifamate (Rifampin and Isoniazid), Saquinavir, Sertraline, Stavudine, Stribild (Elvitegravir, Cobicistat, Emtricitabine, and Tenofovir), Bactrim (Sulfamethoxazole and Trimethoprim)
4	Darunavir, Ethambutol, Etravirine, Flucytosine, Fluticasone propionate, Furosemide, Hydrochlorothiazide, Levothyroxine, Rifabutin, Rilpivirine, Salmeterol xinafoate, Simeprevir, Sofosbuvir, Telaprevir, Tenofovir alafenamide, Trazodone, Warfarin, Zalcitabine
5	Fosamprenavir, Keflex (Cephalexin), Metformin, Naproxen, Pyrazinamide
6	Tipranavir
7	Ceftriaxone, Ciprofloxacin, Foscarnet, Lisinopril, Peginterferon alfa-2a, Enfuvirtide, Imipramine
8	Cyclosporine, Telbivudine, Valacyclovir, Valganciclovir, Zidovudine, Amphotericin B, Ganciclovir
9	Acetaminophen, Hydrocodone
10	Biotin

Summary: No interference was observed in the presence of drug compounds tested in pools that are listed in Table 6, at a concentration of 3 times the reported Cmax or higher.

15.12 Alinity m HIV-1 Testing Using Dilution Procedure

The Alinity m HIV-1 assay design provides optional manual dilution procedures for low volume or for high viral load specimens (upper limit of quantification). To verify that the Alinity m HIV-1 assay provides accurate quantitation, plasma dilution procedures were evaluated by comparing quantitation of neat specimens and specimens tested using the Alinity m HIV-1 dilution procedure (1:2.5 and 1:50). Plasma specimens were diluted using Alinity m Specimen Dilution Kit I. A Ten-member panel was prepared for assay's linear range (2.18 to 7.3 log copies/mL) and tested both neat as well as diluted (Table 13).

Table 13. Alinity m HIV-1 Results for Plasma Samples Tested Using Dilution Procedure

Dilution	Neat	Dilution Procedure
	Mean Conc. (Log Copies/mL)	Mean Conc. (Log Copies/mL)
1:2.5	2.20	2.11
	3.06	2.98
	3.56	3.50
	3.89	3.84
	4.19	4.15
	5.10	4.97
	5.21	5.16
	5.57	5.46
	5.76	5.60
	5.84	5.74
1:50	3.56	3.30
	3.89	3.66
	4.19	4.02
	5.10	4.89
	5.21	4.97
	5.57	5.32
	5.76	5.43
	5.84	5.58
	6.81	6.63
	7.58	7.17

For serum samples, the 1:2.5 and 1:50 dilution procedures were evaluated by comparing detection of neat samples and samples tested using the Alinity m HIV-1 dilution procedure. A two-member panel (150 copies/mL and 3000 copies/mL of HIV-1 RNA) was prepared and tested as neat and diluted for a minimum of four replicates each. The 150 copies/mL sample was tested neat and using the 1:2.5 dilution procedure. The 3,000 copies/mL sample was tested neat and using the 1:50 dilution procedure.

Summary: This study demonstrated that the mean plasma quantitation differences between the diluted (test) and undiluted specimens (control condition) are within the medical decision threshold level <0.5log copies/mL. HIV-1 RNA from serum was detected in all replicates of each panel member whether tested in neat or diluted. Thus, Alinity m HIV-1 assay provides accurate quantitation of plasma specimens when tested using the dilution procedure. Also, dilution procedure studies support supplemental tests for a qualitative detection of serum or plasma HIV-1 as described in the package insert.

15.13 Precision of Alinity m HIV-1 Using Dilution Procedures

The purpose of this study was to demonstrate the within-laboratory precision of the Alinity m HIV-1 assay for diluted specimens. Precision was evaluated in plasma by testing 3 panel members with HIV-1 target concentrations of 2.8 Log

copies/mL, 4.7 Log copies/mL, and 6.7 Log copies/mL, that were diluted using Alinity m Specimen Dilution Kit I. Panel member 2.8 log copies/mL was diluted for 1:25 and other two panel members are diluted for 1:50. Testing was performed using 3 replicates per panel member using 3 kit lots on 3 Alinity m systems for 12 days and 2 runs per day. A total of 360 replicates tested per panel member (5 replicates x 2 runs/day x 3 kit lots x 12 days). The results are summarized in Table 14.

Table 14. Precision of Alinity m HIV-1 Using Dilution Procedures for Plasma

Panel Member	Dilution Factor	N[a]	Mean Conc. (Log Copies/ mL)	Within-Run Component		Between-Run Component		Between-Day Component		Within-Laboratory[b]		Between-Instrument Component		Total[c]	
				SD	% CV	SD	% CV	SD	% CV	SD	% CV	SD	% CV	SD	% CV
3	1:50	341	4.60	0.06	1.3	0.01	0.3	0.02	0.4	0.06	1.3	0.01	0.2	0.06	1.4
2	1:50	352	6.32	0.05	0.7	0.00	0.0	0.02	0.3	0.05	0.8	0.03	0.5	0.06	0.9
1	1:2.5	340	2.82	0.08	2.9	0.04	1.3	0.00	0.0	0.09	3.2	0.02	0.6	0.09	3.2

[a] Number of valid replicates.
[b] Within-Laboratory includes Within-Run, Between-Run and Between-Day components
[c] Total includes Within-Run, Between-Run, Between-Day and Between-Instrument components.

Summary: The analyses demonstrated that the Alinity m HIV-1 assay has a within-laboratory SD of 0.25 Log copies/mL or less for samples tested using dilution procedures. The performance of Alinity m HIV-1 assay is acceptable because the differences are within the threshold of medical decision point.

15.14 Specimen and collection tube type equivalency

The Alinity m HIV-1 test uses plasma and serum samples collected in either Di-Potassium Ethylenediaminetetraacetic Acid (K2 EDTA) tubes, Tri-Potassium EDTA (K3 EDTA) tubes, Acid Citrate Dextrose (ACD) tubes, Plasma Preparation Tubes (PPT) and Serum Separator Tubes (SST). Both PPT and SST tubes are used with or without gel. For each plasma tube type, matched specimens from 25 unique HIV-1 negative blood donors were collected in each of the 4 tube types. HIV-1 was spiked into each specimen to a target HIV-1 level of approximately 60 copies/mL (3x LLoQ) or 200 copies/mL. The levels used included HIV-1 RNA detection and quantification. In addition, 25 HIV-1 matched negative, un-infected specimens were also analyzed. For serum tubes (non-gel) and SST (gel) tubes equivalency, 12 whole blood (WB) samples were spiked with target HIV-1 level of approximately 3x LOD (60 copies/mL) in primary non-gel and gel SST and tested for detection.

Summary: The Alinity m HIV-1 test demonstrated comparable performance (25/25) for matched HIV-1 positive RNA plasma collected in EDTA, ACD and PPT. All 25 matched HIV-1 negative specimens collected from uninfected individuals collected in EDTA, ACD and PPT tested negative. Viral loads were

comparable for HIV-1 positive paired samples collected in EDTA or ACD and PPT. HIV-1 RNA was 100% detected in all (12/12) serum tubes. The tube equivalence study demonstrated acceptable performance between the different plasma or serum tubes.

15.Real-Time Reagent Stability

Realtime stability studies were performed to establish the shelf-life for the Alinity m HIV-1 assay. Three (3) lots of reagent kits were stored at the intended storage temperature indicated in Table 15 and then tested at various time points throughout the study. Performance was assessed against clinically relevant acceptance criteria (within ±0.5 log copies/mL) using controls, calibrators and an internal stability panel consisting of three panel members PM1 (3.00 log copies/mL), PM2 (5.00 log copies/mL), PM3 (2.4 log copies/mL). The Shelf-life study included the assessment of an inverted condition, as well as a condition that simulated fluctuating (hot/cold) temperature extremes during shipping.

The effect of the On-Board Storage (OBS) on reagent performance was also assessed by testing one lot of reagents at the maximum on-board (34 days) temperature/humidity conditions allowed by the Alinity m Instrument System (i.e., 30ºC [±2 ºC], 65% [±10%] relative humidity [RH]) for the intended OBS of the reagents. Results of the OBS conditions were compared to the results when the reagents were stored at their intended storage condition. Real time shelf life and on-board storage conditions are summarized in Table 15.

Table 15. Reagent Shelf Life and On-Board Stability for the Alinity m HIV-1 and Alinity m Accessory Kits

Kit/Reagents	Shelf Life and Intended Storage Condition	On-board Stability
Alinity m HIV-1 AMP Kit	24 months 2°C to 8°C	30 days
Alinity m HIV-1 CTRL Kit	24 months -15°C to -25°C	4 hours
Alinity m HIV-1 CAL Kit	24 months -15°C to -25°C	4 hours
Alinity m Sample Prep Kit 2 (Elution Buffer 2 and Microparticles 2)	24 months 2°C to 8°C	10 days
Alinity m System Solutions (Lysis Solution, Diluent Solution and Vapor Barrier Solution)	24 months 15°C to 30°C	Lysis Solution: 30 days Diluent Solution: 30 days Vapor Barrier Solution: until expiration
Alinity m Specimen Dilution Kit I	24 months 15°C to 30°C	N/A

Summary: Study results demonstrate that reagents are stable at their intended storage condition and continue to meet acceptance criteria 24 months after the date of manufacture, including when shipped upon exposure to fluctuating temperature extremes. In addition, on-board study results demonstrate that reagents are stable on-board the Alinity m Instrument and continue to meet acceptance criteria for the intended on-board storage time.

16. SUMMARY OF PRIMARY CLINICAL STUDIES

To assess clinical performance of Alinity m HIV-1 assay when used as a supplemental test to confirm HIV-1 infection in individuals who have reactive results with HIV immunoassays or to monitor disease prognosis by measuring the baseline plasma HIV-1 RNA level and to assess viral response to antiretroviral treatment by measuring changes in plasma HIV-1 RNA levels, the applicant performed following clinical studies to establish a reasonable assurance of safety and effectiveness:

- Clinical Specificity
- Clinical Sensitivity
- Method Comparison
- Reproducibility.

All clinical studies were performed at three US clinical sites.

16.1 Clinical Specificity

596 Retrospectively collected plasma specimens and 391 serum specimens from HIV-1 negative volunteer whole blood donors were included in the evaluation for Alinity m HIV-1 assay clinical specificity study. The HIV-1 negative whole blood donors were confirmed to be ”Not Detected” with an FDA approved RNA assay prior to testing with the Alinity m HIV-1 assay. All valid HIV-1 negative plasma and serum were tested with Alinity m HIV and an FDA approved HIV-1 RNA assay as a comparator. Testing was performed with two lots at three clinical testing sites for plasma and three lots at three clinical sites for serum. Clinical specificity was calculated as the percentage of HIV-1 negative specimens with the results of “Not Detected”.

Summary: HIV-1 RNA was not detected in any of 987 (plasma and serum) specimens. The clinical specificity in plasma was 100.0% (596/596, 95% CI: 99.4% to 100.0%) and in serum was 100.0% (391/391, 95% CI: 99.1%,100.0%). The specificity study demonstrated acceptable performance as HIV-1 RNA was not detected.

16.2 HIV-1 Clinical Sensitivity

The performance of the Alinity m HIV-1 assay was compared with that of an FDA-approved HIV-1 RNA assay using specimens from subjects known to be

HIV-1 positive. Samples were repeat reactive in an FDA-approved Ab/Ag assay and had viral loads of ≥ 100 copies/mL as determined by an FDA-approved comparator assay. A total of 440 (166 serum and 274 plasma) retrospectively collected specimens were included in the analysis (Table 16). Testing was performed at three clinical testing sites with multiple Alinity m HIV-1 reagent kit lots.

Table 16. HIV-1 Sensitivity of Plasma and Serum Specimens

Population Specimen Type	Total Known Positive Specimens	Number Alinity m HIV-1 RNA Detected	Sensitivity	95% Exact CI
Overall	440	440	100.0%	(99.2%,100.0%)
Serum	166	166	100.0%	(97.8%,100.0%)
Plasma	274	274	100.0%	(98.7%,100.0%)

Summary: The overall HIV-1 sensitivity of Alinity m HIV-1 was 100.0% (440/440, 95% CI: 99.2% to 100.0%). The sensitivity of Alinity m HIV-1 for serum specimens was 100.0% (166/166, 95% CI: 97.8% to 100.0%). The sensitivity of Alinity m HIV-1 for plasma specimens was 100.0% (274/274, 95% CI: 98.7% to 100.0%) (Table 16). The sensitivity study demonstrated acceptable performance for detection of HIV-1 RNA in serum or plasma.

16.3 Agreement Between Alinity m HIV-1 and FDA Approved HIV-1 Nucleic Acid Test (NAT) Comparator Assay for Repeat Reactive Confirmed Negative (RRCN) and Repeat Reactive Confirmed Indeterminate (RRCI) specimens.

Performance in repeatedly reactive/confirmed negative and repeatedly reactive/confirmed indeterminate was established for HIV-1 viral loads above and below 100 cp/mL. These samples were repeatedly reactive with an initial serological diagnostic test; subsequent confirmation testing produced negative or indeterminate results with an FDA approved serological HIV-1 differentiation assay. These specimen types are referred to as repeatedly reactive confirmed negative (RRCN) and repeatedly reactive confirmed indeterminate (RRCI). Of 120 (8 plasma and 112 serum) valid serological discordant samples evaluated, 109 samples were reported as RRCN and 11 samples reported as RRCI. The PPA, and NPA for the Alinity m HIV-1 assay were calculated relative to a NAT comparator result (Table 17).

Table 17. Agreement between Alinity m HIV-1 Assay and FDA Approved NAT HIV-1 Assay for RRCN and RRCI (Combined EDTA Plasma and Serum).

Specimen Type	HIV-1 Differentiation Assay	Sample Matrix	N	NAT Comparator + and Alinity m +	NAT Comparator + and Alinity m -	NAT Comparator - and Alinity m -	NAT Comparator - and Alinity m +	PPA (%)		NPA (%)	
								Estimate (95% CI)	n/N	Estimate (95% CI)	n/N
ALL	Negative and Indeterminate	Serum and EDTA Plasma	120	14	2	101	3	87.5 (61.7, 98.4)	14/16	97.1 (91.8, 99.4)	101/104
RRCN	Negative	Serum	103	9	1	92	1	90.0 (55.5, 99.7)	9/10	98.9 (94.2, 100.0)	92/93
	Negative	EDTA Plasma	6	0	0	6	0	N/A	0/0	100.0 (54.1, 100.0)	6/6
RRCI	Indeterminate	Serum	9	5	0	2	2	100.0 (47.8, 100.0)	5/5	50.0 (6.8, 93.2)	2/4
	Indeterminate	EDTA Plasma	2	0	1	1	0	0.0 (0.0, 97.5)	0/1	100.0 (2.5, 100.0)	1/1

Summary: Results of the Alinity m HIV-1 assay were compared with an FDA approved HIV-1 NAT assay. Agreement analysis results indicate that Negative percent agreement (NPA) was 97.1% (101/104) with 95% CI of (91.8%, 99.4%) and the positive percent agreement (PPA) was 87.5% (14/16) with 95% CI of (61.7%, 98.4%). There are five discordant results (2 positive and 3 negative) between the Alinity m HIV-1 assay and the comparator NAT assay. Samples with discordant results all have HIV-1 Viral loads <100 copies/mL. Since performance of the supplemental confirmatory test has been validated to detect HIV-1 viral load >100 copies/mL, these results with discordant sample results are acceptable.

16.4 Validation of Viral Load Quantitation (Method Comparison Study)

The performance of the Alinity m HIV-1 assay was compared with an FDA-approved viral load assay. The evaluation was performed at three clinical sites using a total of 326 specimens. Of these, 236 (72.4%) specimens were tested using frozen aliquots and 90 (27.6%) were tested fresh. The test specimens were obtained from 231 (70.9%) males, 94 (28.8%) females, and one of unknown

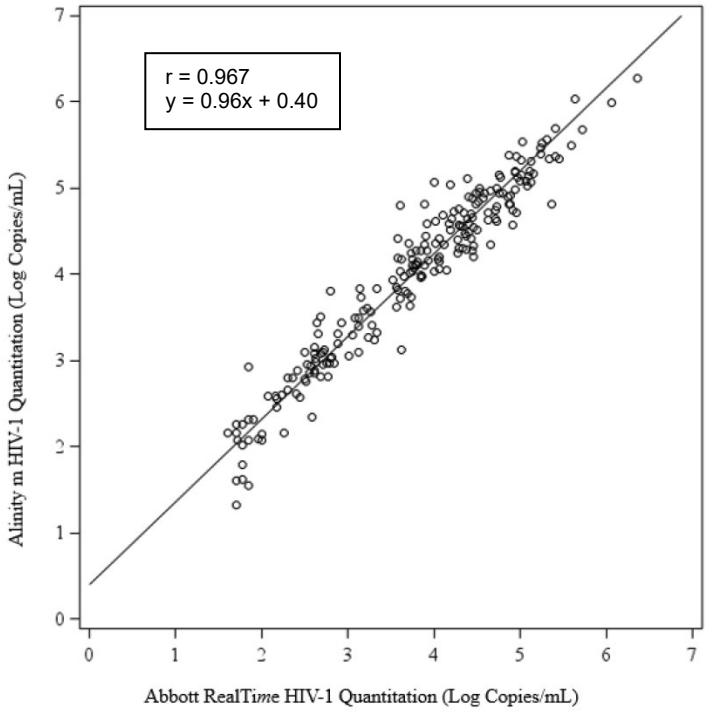
gender (0.3%) with an age range of 5 to 75 years. Sample characteristics were shown in Table 18.

Table 18. Sample Characteristics

Antiviral Medication	Statistics, n (%)
	(N=326)
Yes	217 (66.6%)
No	109 (33.4%)
CD4+ Cell Count (cells/µL)	
< 200	78 (23.9%)
200-500	113 (34.7%)
> 500	110 (33.7%)
Unknown	25 (7.7%)

Summary: Of 326 specimens tested, 216 had viral load measurements within the linear range (20 copies/mL to 1.00E+07 copies/mL) for both assays and were used for method comparison analysis. The remaining 110 specimens had viral load levels outside of the quantifiable ranges for both assays and were not used for the validation study. The results demonstrate that the Alinity m HIV-1 assay, and the FDA approved assay are comparable based on the Deming regression analysis (Fig 3) with a correlation coefficient of 0.967 and mean paired viral load difference between the two assays is 0.25 Log Copies/mL with a 95% CI of (0.21, 0.28). These differences are lower than the clinically meaningful difference of 0.5 log10 copies/mL.

Figure 3. Deming regression analysis



Viral Load Discrimination at Clinically Meaningful Thresholds

In the method comparison study, concordance between the Alinity m HIV-1 assay and the FDA approved comparator assay was evaluated at the medical decision points of 50 copies/mL, 200 copies/mL, and 1000 copies/mL. Using the results from the method comparison study, the bias at medical decision points was calculated from the Deming regression line and results are presented in Table 19.

Table 19. Bias Analysis for Alinity m HIV-1 Assay at Medical Decision Points

Medical Decision Point		Bias	SE	95% CI of Bias
Copies/mL	Log Copies/mL			
50	1.70	0.33	0.050	(0.23, 0.43)
200	2.30	0.31	0.044	(0.22, 0.39)
1000	3.00	0.28	0.040	(0.20, 0.36)

Summary: The bias and 95% confidence intervals (CI) are within ± 0.5 Log copies/mL for the 50 copies/mL, 200 copies/mL, and 1000 copies/mL medical decision points. The concordance analysis demonstrates that the Alinity m HIV-1 assay can be used to accurately quantitate HIV-1 RNA in HIV-1 infected patients and define virological outcomes of antiviral therapy.

16.5 Reproducibility

Reproducibility of the Alinity m HIV-1 assay was evaluated by testing a 10-member reproducibility panel. All panel members were prepared using HIV-1 virus diluted in HIV-1 negative human plasma with concentration levels targeted to span the linear quantitation range of the assay. A total of three different Alinity m HIV-1 AMP Kit lots were used. Each of the 3 clinical sites tested two Alinity m HIV-1 AMP Kit lots, on five non-consecutive days for each lot. Five replicates of each panel member were tested on each of 5 days. The design (3 sites x 5 replicates in one panel x 1 run/day x 5 days x 2 lots/site) accounts for a total of 150 replicates per panel member. Results are shown in Table 19.

Table 20. Reproducibility

Panel	N[a]	Mean Concentration	Within-Run Component		Between-Run Component		Within-Laboratory[b]		Between-Lot Component		Between-Site Component		Total[c]	
		(Log Copies /mL)	SD	% CV	SD	% CV	SD	% CV	SD	% CV	SD	% CV	SD	% CV
10	149	7.35	0.06	0.8	0.04	0.5	0.07	1.0	0.05	0.7	0.00	0.0	0.09	1.2
9	150	6.47	0.06	1.0	0.05	0.7	0.08	1.2	0.03	0.5	0.01	0.2	0.09	1.4
8	149	5.81	0.09	1.5	0.05	0.9	0.10	1.8	0.00	0.0	0.02	0.4	0.11	1.8
7	150	5.14	0.07	1.3	0.06	1.2	0.09	1.7	0.00	0.0	0.03	0.6	0.09	1.8
6	150	4.45	0.08	1.8	0.05	1.1	0.09	2.1	0.01	0.2	0.01	0.2	0.09	2.1
5	149	3.78	0.08	2.0	0.04	1.1	0.09	2.3	0.02	0.5	0.00	0.0	0.09	2.4
4	150	3.09	0.08	2.7	0.05	1.7	0.10	3.1	0.03	1.0	0.02	0.6	0.10	3.4
3	149	2.43	0.10	4.1	0.06	2.3	0.11	4.7	0.06	2.4	0.00	0.0	0.13	5.3
2	150	1.85	0.16	8.6	0.07	3.6	0.17	9.3	0.05	2.5	0.04	2.0	0.18	9.8
1	149	1.38	0.31	22.3	0.10	7.1	0.32	23.4	0.05	3.7	0.00	0.0	0.33	23.7

[a] Number of valid replicates.
[b] Within-Laboratory includes Within-Run and Between-Run Components.
[c] Total includes Within-Run, Between-Run, Between-Lot, and Between-Site Components.

Summary: Table 20 shows the reproducibility and precision of Alinity m HIV-1 assay results for each positive panel members within-run, between-run, within-laboratory, between-lot, and between-site variations. The overall analysis of data from all three sites demonstrates a total standard deviation (SD) rate of 0.09 to 0.33 with a total percent coefficient of variation (%CV) range of 1.2% to 23.7% across panel members. When only the clinically relevant viral loads of 2.43 to 7.35 log copies/mL (panel 3-10) are evaluated, total variance is <6% and SD is 0.09-0.13. For viral load 1.38 and 1.85 log copies/mL (~1 to 3x LLoQ) total variance was >20% and SD, 0.18-0.33. The within-laboratory component contributed the most variability for low viral panel members 1 and 2, which was acceptable. The overall estimated detectable viral load differences were well below the medical decision threshold (0.5 log copies/mL), therefore performance of Alinity m HIV-1 assay is acceptable.

17. INSPECTIONS

17.1 Manufacturing Facilities Review/Inspection

Facility information and data provided in the PMA were reviewed by CBER and found to be sufficient and acceptable. The facilities involved, activities performed

in the manufacture of Alinity m HIV-1 Assay and inspectional histories are listed in the table below.

Table 21: Manufacturing Facilities Alinity m HIV-1 Quant Assay and Alinity m System

Facility	Activity	Inspection/ Waiver	Most Recent Inspection
Abbott Molecular Inc. 1300 E Touhy Avenue, Des Plaines, IL 60018 (FEI # 3005248192)	Device Component Manufacturing; Finished Device Manufacturing; Device Packaging / Labeling; QC and Release Testing	Waived	July 2019 ORA Post market Inspection NAI

NAI – No Action Indicated
Based on the Team Biologics recent inspection, DMPQ recommends an inspection waiver for this PMA.

17.2 Bioresearch Monitoring (BIMO) Inspections

CBER Bioresearch Monitoring (BIMO) conducted inspections for three out of four clinical sites. The inspections did not note any violative study conduct at all three testing sites. The fourth clinical testing site that participated for the applicant's current CBER PMA supplement was inspected in 2020 and did not note significant inspectional observations at the testing site. These inspections did not reveal significant problems that impact the data submitted in this PMA supplement. The inspections were classified as No Action Indicated (NAI).

18. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

18.1 Effectiveness Conclusions

The clinical study results in combination with the non-clinical performance evaluations supports the effectiveness of the Alinity m HIV-1 assay for the intended uses in the detection and clinical management of HIV-1 infected individuals by measuring the plasma baseline HIV-1 RNA level or to monitor the effects of antiretroviral therapy by measuring changes in HIV-1 RNA levels during the course of antiretroviral treatment. The data also support the use of the Alinity m HIV-1 assay as a supplemental test using plasma or serum to confirm HIV-1 infection in individuals who have reactive results with HIV immunoassays.

18.2 Safety Conclusions

The risk of the device is based on data collected in the clinical study conducted to support PMA approval as described above. Based on the results of the clinical

studies, the Alinity m HIV-1 assay, when used according to the labeling and in conjunction with other serological and clinical information, is safe to use and poses minimal risk to the patient due to false test results.

19. Benefit-Risk Determination

The benefits outweigh the risks at the level of performance observed in the pivotal clinical studies. Complimentary analytical studies strengthen this conclusion. The primary benefit of a supplemental NAT assay is to confirm results from serologic assays with a different technology. For monitoring viral loads, accurate quantitation of HIV-1 RNA is an essential component of the treatment of HIV-1 infection. In an era of highly active antiretroviral therapy for HIV infection, accurate quantitation of viral load to monitor treatment and assess sustained virological suppression has substantial individual benefit (i.e., reduction of the risk of disease progression). Risk related to inaccurate detection and quantitation was substantially mitigated by device design (i.e., use of controls). Appropriate warnings to address routine risks encountered in the laboratory practice are contained in the labeling and package inserts for the device. Standard good laboratory practices are considered sufficient to mitigate the risks to the end user.

In conclusion, given the available information above, the data support that for the management of HIV-1 patients who are undergoing antiretroviral therapy and for use as a supplemental test to confirm HIV-1 infection in individuals who have reactive results with HIV immunoassays, the probable benefits outweigh the probable risks.

20. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use. The data from the nonclinical studies demonstrated acceptable analytical sensitivity, linearity, precision, and analytical specificity of the Alinity m HIV-1 assay for both serum and plasma when used according to the instructions for use as stated in the labeling, the warnings and precautions, and limitations sections of the labeling. The clinical studies and the statistical analysis of clinical data in this application has shown that the Alinity m HIV-1 assay is informative in supplemental test to confirm HIV-1 infection and assessing viral response to antiretroviral treatment by measuring changes in plasma HIV-1 RNA levels, and that the assay is safe and effective when used according to the directions for use in the labeling.

21. APPROVAL SPECIFICATIONS

- Directions for use: See device labeling.
- Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the device labeling.
- Post-approval Requirements and Restrictions: See approval order.

22. PANEL RECOMMENDATIONS

Not Applicable – This product was not submitted for review by the Blood Products Advisory Committee.

23. FDA/CBER DECISION

The PMA supplement BP200455-7 is recommended for approval.