GeneXpert®
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Xpert® HIV-1 Qual

REF **GXHIV-QA-CE-10**

Instructions For Use

CE 2797 **IVD**

Cepheid®

In Vitro Diagnostic Medical Device

301-3048, Rev. L
October 2023

Trademark, Patents, and Copyright Statements

See Section 24 Revision History for a description of changes.

Xpert® HIV-1 Qual

For *In Vitro* Diagnostic Use.

1 Proprietary Name

Xpert® HIV-1 Qual

2 Common or Usual Name

HIV-1 Qual

3 Intended Use

The HIV-1 Qual assay, performed on the GeneXpert Instrument Systems, is a qualitative *in vitro* diagnostic test designed to detect Human Immunodeficiency Virus Type 1 (HIV-1) total nucleic acids on the automated GeneXpert® Systems using human whole blood (WB) and dried blood spot (DBS) specimens from individuals suspected of HIV-1 infection and is validated for specimens across Group M (subtypes A, B, C, D, F, G, H, J, K, CRF01_AE, CRF02_AG, and CRF03_AB), Group N, and Group O.

The HIV-1 Qual assay is intended to aid in the diagnosis of HIV-1 infection in conjunction with clinical presentation and other laboratory markers. The assay is intended to be used by laboratory professionals or specifically-trained healthcare workers. The assay is not intended to be used as a blood donor screening test for HIV-1.

4 Summary and Explanation

Human Immunodeficiency Virus (HIV) is the etiologic agent of Acquired Immunodeficiency Syndrome (AIDS).[1,2,3] It can be transmitted through sexual contact, exposure to infected blood or blood products, prenatal infection of a fetus, or perinatal or postnatal infection of a newborn.[4,5,6] Infected individuals generally develop an acute infection characterized by flu-like symptoms in a period of days to weeks after initial exposure.[7] Acute HIV infections typically last less than 14 days[8] and are associated with high levels of viremia prior to a detectable immune response.[9,10] Therefore, HIV-1 nucleic acid testing can be more sensitive than standard serologic testing in detection of acute infection.[7]

At the end of 2013, there were 35 million (33.2 million–37.2 million) people living with HIV.[11] Of those infected, 2.1 million represent new infections and an estimated 240,000 are children.[11] One-third of all people living with HIV reside in nine countries in southern Africa, which only account for 2% of the global population.[12] Without timely HIV testing and therapy initiation, one-third of HIV-infected infants will die before their first birthday and more than 50% will die before reaching two years old.[11] In contrast, the risk of mortality in children infected with HIV in the U.S. and Europe is only 10–20%.[13] Early diagnosis of HIV infection in infants is a necessity; however, many patients are lost to follow-up while waiting for an early test, usually DNA-PCR, sensitive in the first 18 months of life (which has very limited accessibility) or a rapid test, which is only accurate beginning in the 15 to 18 month age range.[14,15] As a result, HIV-1 nucleic acid testing has been recommended for detecting infection in pediatric patients 18 months of age or younger.[16,17,18,19]

The HIV-1 Qual assay uses reverse transcription polymerase chain reaction (RT-PCR) technology to achieve high sensitivity for the qualitative detection of HIV-1 total nucleic acids in WB or DBS specimen types.

5 Principle of the Procedure

The GeneXpert (GX) Instrument Systems automate and integrate sample preparation, nucleic acid extraction and amplification, and detection of the target sequence in simple or complex samples using real time reverse transcription PCR (RT-PCR). The systems consist of an instrument, personal computer, and preloaded software for performing tests and viewing the results. The systems require the use of single-use disposable GeneXpert cartridges that hold the RT-PCR reagents and host the RT-PCR processes. Because the cartridges are self-contained, cross-contamination between samples is minimized. For a full description of the system, see the *GeneXpert Dx System Operator Manual* or *GeneXpert Infinity System Operator Manual*.

The HIV-1 Qual assay includes reagents for the detection of HIV-1 total nucleic acids in specimens as well as an internal control to ensure adequate processing of the target and to monitor the presence of inhibitor(s) in the RT and PCR reactions. The Probe Check Control (PCC) verifies reagent rehydration, PCR tube filling in the cartridge, probe integrity, and dye stability.

6 Materials Provided

The HIV-1 Qual assay kit contains sufficient reagents to process 10 specimens or quality control samples. The kit contains the following:

HIV-1 Qual assay Cartridges with Integrated Reaction Tubes	**10**
● Bead 1, Bead 2, and Bead 3 (freeze-dried)	1 of each per cartridge
● Lysis Reagent (Guanidinium Thiocyanate)	1.4 mL per cartridge
● Rinse Reagent	0.5 mL per cartridge
● Elution Reagent	2.5 mL per cartridge
● Binding Reagent	2.4 mL per cartridge
● Proteinase K Reagent	0.48 mL per cartridge
HIV-1 Qual assay Sample Reagent Set (Sample Reagent)	**10**
● Lysis Reagent (Guanidinium Thiocyanate)	1.0 mL per vial
Disposable 1 mL Transfer Pipettes	**1 bag of 10 per kit**
Disposable 100 µL Transfer Micropipettes	**1 bag of 10 per kit**
CD	**1 per kit**
● Assay Definition Files (ADF) ● Instructions to import ADF into GeneXpert software ● Instructions for Use (Package Insert)	

Note Safety Data Sheets (SDS) are available at www.cepheid.com or www.cepheidinternational.com under the **SUPPORT** tab.

Note The bovine serum albumin (BSA) in the beads within this product was produced and manufactured exclusively from bovine plasma sourced in the United States. No ruminant protein or other animal protein was fed to the animals; the animals passed ante- and post-mortem testing. During processing, there was no mixing of the material with other animal materials.

7 Storage and Handling

- Store the HIV-1 Qual assay cartridges and reagents at 2–28 °C.
- Do not use any reagents that have become cloudy or discolored.
- Do not use a cartridge that has leaked.

8 Materials Required but Not Provided

- GeneXpert Dx System or GeneXpert Infinity Systems (catalog number varies by configuration): GeneXpert Instrument, computer with proprietary GeneXpert Dx Software Version 4.7b or higher (GeneXpert Dx systems) or Xpertise 6.4b or higher (Infinity-80/Infinity-48s), barcode scanner, and operator manual.
- Printer: If a printer is needed, contact Cepheid Technical Support to arrange for the purchase of a recommended printer.
- If using DBS:
  - DBS Collection Kit (Filter paper cards, e.g., Whatman 903, Munktell or equivalent, lancets, desiccants, plastic sealable bags, and swabs)
  - Scissors, sterile (recommended for excising DBS from filter paper if not using a perforated DBS card)
  - Forceps
  - Serviette/Wipe
  - Bleach
  - Eppendorf ThermoMixer® C (Eppendorf order number 5382 000.015) (for DBS application only)
  - Eppendorf SmartBlock™ (Eppendorf order number 5309 000.007) (for DBS application only)

9 Warnings and Precautions

- Treat all biological specimens, including used cartridges, as if capable of transmitting infectious agents. Because it is often impossible to know which might be infectious, all biological specimens should be treated with standard precautions. Guidelines for specimen handling are available from the U.S. Centers for Disease Control and Prevention[20] and the Clinical and Laboratory Standards Institute.[21]
- Wear protective disposable gloves, laboratory coats, and eye protection when handling specimens and reagents. Wash hands thoroughly after handling specimens and test reagents.
- Follow your institution's safety procedures for working with chemicals and handling biological samples.
- When processing more than one sample at a time, open only one cartridge; add sample and close the cartridge before processing the next sample. Change gloves between samples.
- Good laboratory practices, including changing gloves between handling patient specimens, are recommended to avoid contamination of specimens or reagents.
- Do not substitute HIV-1 Qual assay reagents with other reagents.
- Do not open the HIV-1 Qual assay cartridge lid except when adding the Sample Reagent and WB or the Sample Reagent- treated DBS sample.
- Do not use a cartridge if it appears wet or if the lid seal appears to have been broken.
- Do not use a cartridge that has been dropped after removing it from the packaging.
- Do not shake the cartridge. Shaking or dropping the cartridge after opening the cartridge lid may yield invalid results.
- Do not use a cartridge that has a damaged reaction tube.
- Each single-use HIV-1 Qual assay cartridge is used to process one specimen. Do not reuse spent cartridges.

  The single-use disposable pipette is used to transfer one specimen. Do not reuse spent disposable pipettes.
- Biological specimens, transfer devices, and used cartridges should be considered capable of transmitting infectious agents requiring standard precautions. Follow your institution’s environmental waste procedures for proper disposal of used cartridges and unused reagents. These materials may exhibit characteristics of chemical hazardous waste requiring specific national or regional disposal procedures. If national or regional regulations do not provide clear direction on proper disposal, biological specimens and used cartridges should be disposed per WHO [World Health Organization] medical waste handling and disposal guidelines.

10 Chemical Hazards[23,24]

- Signal Word: Warning
- **UN GHS Hazard Statements**
  - Harmful if swallowed
  - Causes mild skin irritation
  - Causes eye irritation
- **UN GHS Precautionary Statements**
  - Prevention

- Wash thoroughly after handling.
- Response
  - If skin irritation occurs: Get medical advice/attention.
  - IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing.
  - Call a POISON CENTER or doctor/physician, if you feel unwell.

11 Specimen Collection, Transport and Storage

11.1 Whole Blood Collection

Collect WB in sterile tubes using K2 EDTA (lavender top) as the anticoagulant as per the manufacturer's instructions for use. A minimum of 100 µL of WB is required for the HIV-1 Qual assay.

Specimen Transport and Storage

K2 EDTA-anticoagulated WB may be stored at 31–35 °C for up to 8 hours, 15–30 °C for up to 24 hours or at 2–8 °C for up to 72 hours, prior to preparing and testing the specimen.

11.2 Dried Blood Spots Collection

Collect DBS specimens using appropriate clinical procedures. DBS should be prepared using Whatman 903 or Munktell filter paper cards or equivalent from blood obtained from a heel-, finger- or toe-stick or collected in a K2 EDTA-tube. DBS are made by spotting blood inside each delineated 12-millimeter circle of the filter paper card. Ensure that the entire circle is covered with blood (approximately 60–70 µL). A minimum of two circles should be made from each specimen to allow for retesting.

If WB was collected in a K2 EDTA-tube, mix the specimen by inverting it 8–10 times before applying it onto the filter. Air-dry the card at room temperature for a minimum of four hours. Package each card in individual resealable bags with a desiccant sachet in each bag. Freshly drawn specimens in K2 EDTA-tubes may be held at 31–35 °C for up to 8 hours, 15–30 °C for up to 24 hours or at 2–8 °C for up to 72 hours, prior to making the DBS.

Specimen Transport and Storage

Ship filter paper cards containing DBS to the testing laboratories for further processing in individual resealable bags with a desiccant sachet in each bag. The cards may be stored at 2–25 °C or –15 °C or colder for up to 12 weeks. Cards may also be stored at 31–35 °C for up to 8 weeks.

12 Procedure

Before starting, remove the vial containing the Sample Reagent from the kit and, if it was refrigerated, allow to adjust to room temperature. See Figure 1. If the vial has not been stored in an upright position, make sure the buffer is settled in the bottom by giving the vial a firm shake.

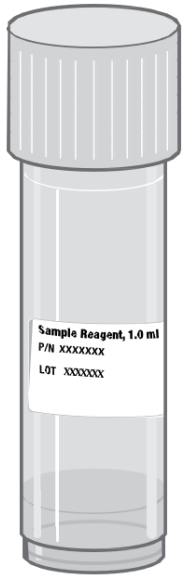

Figure 1. HIV-1 Qual Assay Sample Reagent

12.1 Preparing the Cartridge

Note Do not remove the thin plastic film that covers the inner ring of 13 ports of the test cartridge.

Important **Start the test within 30 minutes of adding the sample to the cartridge.**

Whole Blood

1. Wear protective disposable gloves.
2. Label the Sample Reagent vial with the specimen identification.
3. Inspect the test cartridge for damage. If damaged, do not use.
4. Open the cartridge lid.
5. Use the 1 mL transfer pipette provided (Figure 2) or an automatic pipette to transfer 750 µL of the sample reagent into the sample chamber of the cartridge (Figure 4).

Note Allow the Sample Reagent to adjust to room temperature and mix the bottle by inverting before transferring to the cartridge. Transfer exactly 750 µL into the sample chamber of the cartridge.

6. Mix the WB sample by inverting the vial (EDTA-microtainer or K2 EDTA (lavender-top) tube) at least seven times. Immediately transfer 100 µL using the micropipette provided (see Figure 3) by squeezing the upper bulb and then releasing to aspirate the blood. Squeeze again to dispense the blood into the sample chamber of the cartridge where it will mix with the Sample Reagent already in the sample chamber (Figure 4). Alternatively, use an automatic pipette to dispense the blood into the sample chamber of the cartridge (see Figure 4). Do **NOT** pour the specimen into the chamber!

Note Ensure the 100 µL of blood is added to Sample Reagent already in the sample chamber.

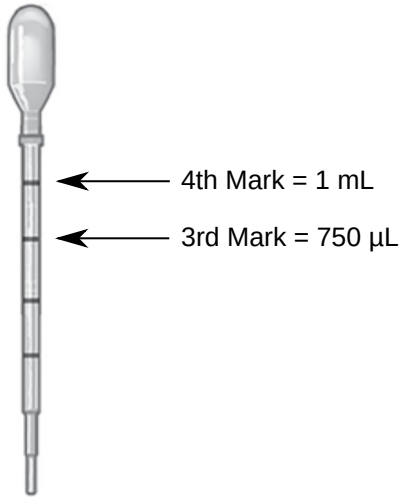

Figure 2. HIV-1 Qual Assay 1 mL Transfer Pipette

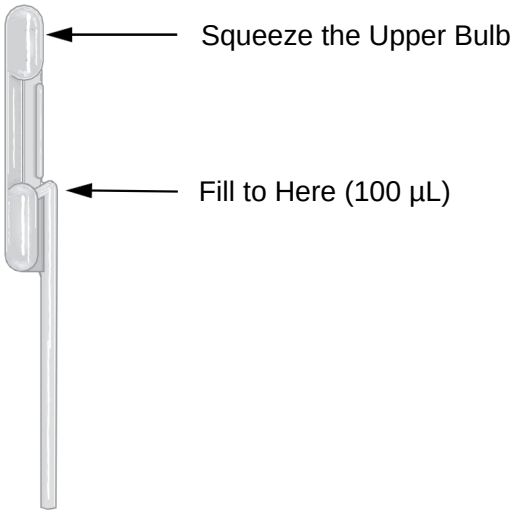

Figure 3. HIV-1 Qual Assay 100 µL Transfer Micropipette

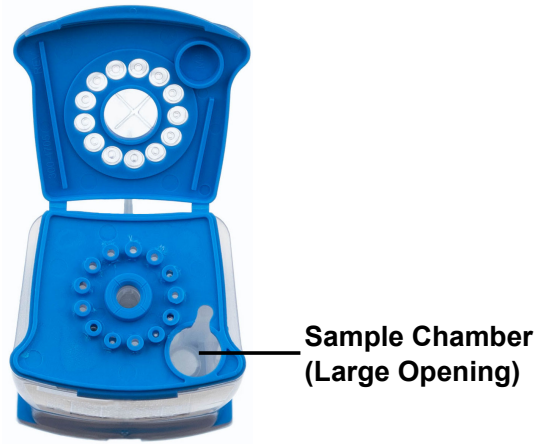

Figure 4. HIV-1 Qual Assay Cartridge (Top View)

Dried Blood Spots

Note To prevent cross contamination, clean and wipe off forceps and scissors (if DBS card is not perforated) with a serviette between specimens using 10% bleach in water. Dry the forceps and scissors after each decontamination.

1. Wear protective disposable gloves.
2. Turn on ThermoMixer to heat to 56 °C.
3. Label the Sample Reagent vial with the specimen identification.
4. Using sterilized scissors, excise one entire DBS from the filter paper card for each specimen. Follow the delineated lines when excising the DBS. If perforated circles are used, use forceps to detach the DBS.
5. Unscrew the lid on the vial containing the Sample Reagent and place one DBS in the vial. If DBS does not settle to the bottom, use the backside of the forceps to gently push it down. Ensure that the DBS is fully submerged in the Sample Reagent buffer.
6. Place the vial with the DBS in a ThermoMixer and incubate for 15 minutes at 56 °C while rotating at 500 rpm.
7. Inspect the test cartridge for damage. If damaged, do not use.
8. Open the cartridge lid.
9. Use the 1 mL transfer pipette provided (see Figure 2) or an automatic pipette to transfer all the liquid from the lysed DBS specimen into the sample chamber of the cartridge (see Figure 4). Ensure the pipette is filled above the third mark on the transfer pipette. Avoid suction of the DBS with the pipette. Do **NOT** pour the specimen into the chamber!
10. Close the cartridge lid.

13 Running the Test

- For the GeneXpert Dx System, see Section 13.1.
- For the GeneXpert Infinity System, see Section 13.2.

13.1 GeneXpert Dx System

13.1.1 Starting the Test

Before you start the test, make sure that:

Important
- The system is running the correct GeneXpert Dx software version shown in section - Materials Required but Not Provided.
- The correct assay definition file is imported into the software.

This section lists the basic steps for running the test. For detailed instructions, see the *GeneXpert Dx System Operator Manual*.

Note The steps you follow can be different if the system administrator changed the default workflow of the system.

1. Turn on the GeneXpert Dx System, then turn on the computer and log on. The GeneXpert software will launch automatically. If it does not, double-click the GeneXpert Dx software shortcut icon on the Windows® desktop.
2. Log on using your username and password.
3. In the **GeneXpert System** window, click **Create Test**.
   The **Create Test** window displays. The **Scan Patient ID barcode** dialog box displays.
4. Scan or type in the Patient ID. If typing the Patient ID, make sure the Patient ID is typed correctly.
   The Patient ID is associated with the test results and displays in the **View Results** window and all the reports. The **Scan Sample ID barcode** dialog box displays.
5. Scan or type in the Sample ID. If typing the Sample ID, make sure the Sample ID is typed correctly.
   The Sample ID is associated with the test results and displays in the **View Results** window and all the reports. The **Scan Cartridge Barcode** dialog box displays.
6. Scan the barcode on the cartridge. Using the barcode information, the software automatically fills the boxes for the following fields: Select Assay, Reagent Lot ID, Cartridge SN, and Expiration Date.

Note If the barcode on the cartridge does not scan, then repeat the test with a new cartridge. If you have scanned the cartridge barcode in the software and the assay definition file is not available, a screen displays indicating the assay definition file is not loaded on the system. If this screen displays, contact Cepheid Technical Support.

7. Click **Start Test**. In the dialog box that displays, type your password, if required.
8. Open the instrument module door with the blinking green light and load the cartridge.
9. Close the door. The test starts and the green light stops blinking.

   When the test is finished, the light turns off.
10. Wait until the system releases the door lock before opening the module door, then remove the cartridge.
11. Dispose of the used cartridges in the appropriate specimen waste containers according to your institution's standard practices.

13.1.2 Viewing and Printing Results

This section lists the basic steps for viewing and printing results. For more detailed instructions on how to view and print the results, see the *GeneXpert Dx System Operator Manual*.

1. Click the **View Results** icon to view results.
2. Upon completion of the test, click the **Report** button of the **View Results** window to view and/or generate a PDF report file.

13.2 GeneXpert Infinity System

13.2.1 Starting the Test

Important

Before you start the test, make sure that:

- The system is running the correct Xpertise software version shown in section - Materials Required but Not Provided.
- The correct assay definition file is imported into the software.

This section lists the basic steps for running the test. For detailed instructions, see the *GeneXpert Infinity System Operator Manual*.

Note The steps you follow can be different if the system administrator changed the default workflow of the system.

1. Power up the instrument. The Xpertise software will launch automatically. If it does not, double-click the Xpertise software shortcut icon on the Windows® desktop.
2. Log on to the computer, then log on to the GeneXpert Xpertise software using your user name and password.
3. In the **Xpertise Software Home** workspace, click **Orders** and in the **Orders** workspace, click **Order Test**.
   The **Order Test - Patient ID** workspace displays.
4. Scan or type in the Patient ID. If typing the Patient ID, make sure the Patient ID is typed correctly.
   The Patient ID is associated with the test results and displays in the **View Results** window and all the reports.
5. Enter any additional information required by your institution, and click the **CONTINUE** button.
   The **Order Test - Sample ID** workspace displays.
6. Scan or type in the Sample ID. If typing the Sample ID, make sure the Sample ID is typed correctly.
   The Sample ID is associated with the test results and displays in the **View Results** window and all the reports.
7. Click the **CONTINUE** button.
   The **Order Test - Assay** workspace displays.
8. Scan the barcode on the cartridge. Using the barcode information, the software automatically fills the boxes for the following fields: Select Assay, Reagent Lot ID, Cartridge SN, and Expiration Date.

Note If the barcode on the cartridge does not scan, then repeat the test with a new cartridge. If you have scanned the cartridge barcode in the software and the assay definition file is not available, a screen displays indicating the assay definition file is not loaded on the system. If this screen displays, contact Cepheid Technical Support.

   After the cartridge is scanned, the **Order Test - Test Information** workspace displays.
9. Verify that the information is correct, and click **Submit**. In the dialog box that displays, type your password, if required.
10. Place the cartridge on the conveyor belt.
    The cartridge automatically loads, the test runs, and the used cartridge are placed into the waste container.

13.2.2 Viewing and Printing Results

This section lists the basic steps for viewing and printing results. For more detailed instructions on how to view and print the results, see the *GeneXpert Infinity System Operator Manual*.

1. In the **Xpertise Software Home** workspace, click the **RESULTS** icon. The Results menu displays.
2. In the Results menu, select the **VIEW RESULTS** button. The **View Results** workspace displays showing the test results.
3. Click the **REPORT** button to view and/or generate a PDF report file.

14 Quality Control

Each test includes a Sample Volume Adequacy (SVA), a Sample Processing Control (SPC) and Probe Check Control (PCC).

- **Sample Volume Adequacy (SVA):** Ensures that the sample was correctly added to the cartridge. The SVA verifies that the correct volume of sample has been added in the sample chamber. The SVA passes if it meets the validated acceptance criteria. If the SVA does not pass, an ERROR 2096 will display if there is no sample or an ERROR 2097 if there is not enough sample. The system will prevent the user from resuming the test.
- **Sample Processing Control (SPC):** Ensures that the sample was correctly processed. The SPC is an Armored RNA® in the form of a dry bead that is included in each cartridge to verify adequate processing of the sample virus. The SPC verifies that lysis of HIV-1 has occurred if the organism is present and verifies that the specimen processing is adequate. Additionally this control detects specimen-associated inhibition of the RT-PCR reaction. The SPC should be positive in a negative sample and can be negative or positive in a positive sample. The SPC passes if it meets the validated acceptance criteria.
- **Probe Check Control (PCC):** Before the start of the PCR reaction, the GeneXpert Instrument System measures the fluorescence signal from the probes to monitor bead rehydration, reaction tube filling, probe integrity, and dye stability. The PCC passes if it meets the validated acceptance criteria.
- **External Controls:** External controls should be used in accordance with local, state, and federal accrediting organizations' requirements as applicable.

15 Interpretation of Results

The results are interpreted automatically by the GeneXpert Instrument System from measured fluorescent signals and embedded calculation algorithms and are clearly shown in the **View Results** window (see Figure 5 and Figure 6). Possible results are shown in Table 1.

Table 1. HIV-1 Qual assay Results and Interpretation

Result	Interpretation
HIV-1 DETECTED See Figure 5.	The HIV-1 target nucleic acids are detected. ● The HIV-1 target nucleic acids have a Ct within the valid range. ● SPC: NA (not applicable); SPC is ignored because the HIV-1 target amplification occurred. ● Probe Check: PASS; all probe check results pass.
HIV-1 NOT DETECTED See Figure 6.	The HIV-1 target nucleic acids are not detected. SPC meets acceptance criteria. ● SPC: PASS; SPC has a Ct within the valid range. ● Probe Check: PASS; all probe check results pass.
INVALID	Presence or absence of the HIV-1 target nucleic acids cannot be determined. Repeat test according to the instructions in Section 16.2. ● SPC: FAIL; SPC Ct is not within valid range. ● Probe Check: PASS; all probe check results pass.
ERROR	Presence or absence of HIV-1 target nucleic acids cannot be determined. Repeat test according to the instructions in Section 16.2. ● HIV-1: NO RESULT ● SPC: NO RESULT ● Probe Check[a]: FAIL; all or one of the probe check results fail.
NO RESULT	Presence or absence of HIV-1 target nucleic acids cannot be determined. Repeat test according to the instructions in Section 16.2. A **NO RESULT** indicates that insufficient data were collected. For example, the operator stopped a test that was in progress. ● HIV-1: NO RESULT ● SPC: NO RESULT ● Probe Check: NA (not applicable).

[a] If the probe check passed, the error is caused by the maximum pressure limit exceeding the acceptable range or by a system component failure.

Note Assay screenshots are for example only. Assay name and version number may vary from the screenshots shown in these instructions for use. QC1 and QC2 in legends of Figure 5 and Figure 6 control for presence of probes (see Probe Check Control in Section 14, Quality Control); amplification curves are not generated.

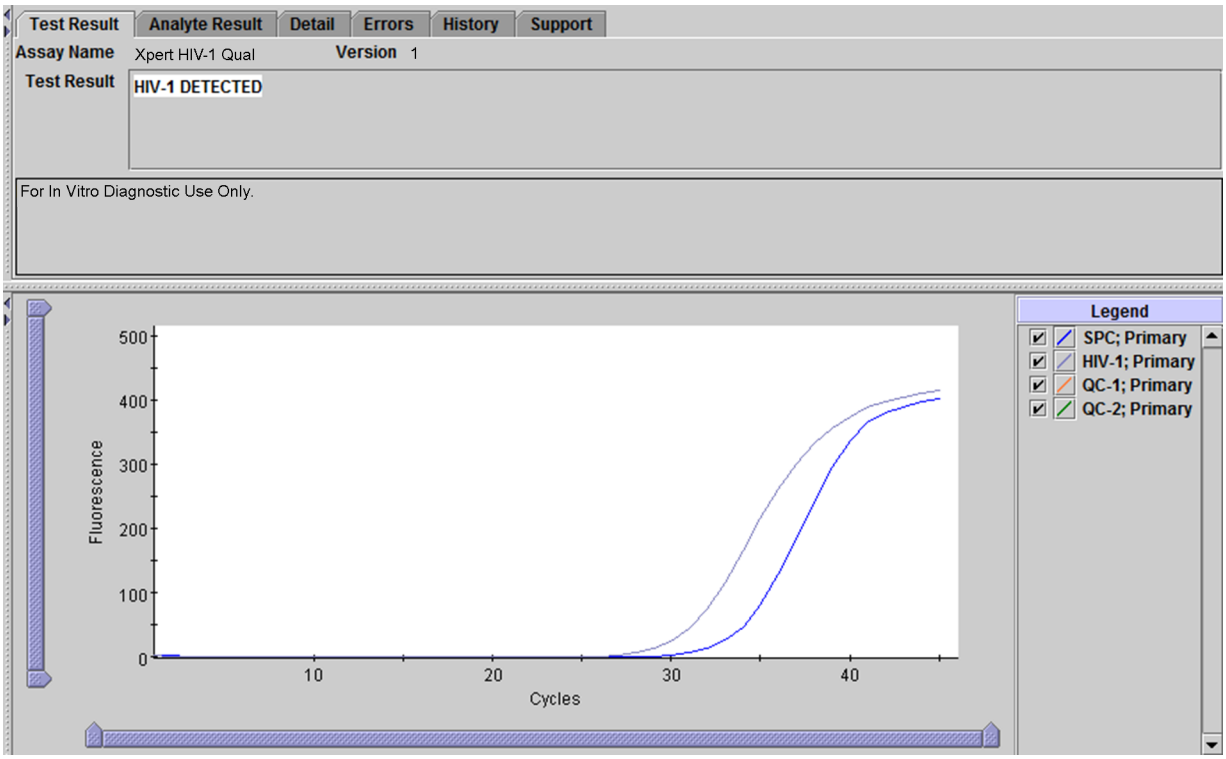

Figure 5. HIV-1 Detected

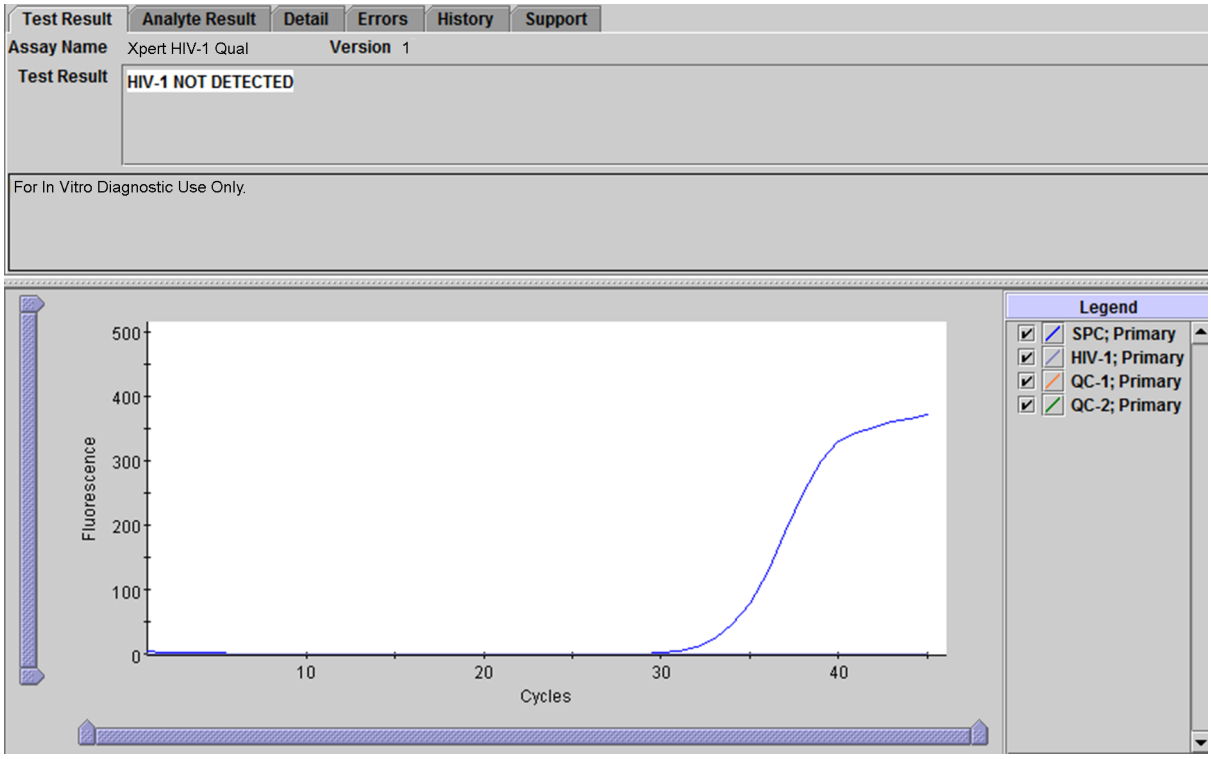

Figure 6. HIV-1 Not Detected

16 Retesting

16.1 Reasons to Repeat the Test

If any of the test results mentioned below occur, repeat the test according to instructions in Section 16.2.

- An **INVALID** result indicates one or more of the following:
  - The control SPC failed.
  - The sample was not properly processed or PCR was inhibited.
- An **ERROR** result indicates that the assay was aborted. Possible causes include: insufficient volume of sample was added, the reaction tube was filled improperly, a reagent probe integrity problem was detected, or the maximum pressure limit was exceeded.
- A **NO RESULT** indicates that insufficient data were collected. For example, the operator stopped a test that was in progress, or a power failure occurred.

16.2 Retest Procedure

For retest of a **INVALID**, **ERROR**, or **NO RESULT**, (do not re-use the cartridge) and new reagents.

1. Remove a new cartridge from the kit.
2. See Section 12, including Section 12.1 and one of the following:
   - For the GeneXpert Dx System, see Section 13.1.
   - For the GeneXpert Infinity System, see Section 13.2.

17 Limitations

- Good laboratory practices and changing gloves between handling specimens are recommended to avoid contamination of reagents.
- Rare mutations within the target region of the HIV-1 Qual assay may affect primer and/or probe binding resulting in failure to detect the virus.
- A negative test result does not preclude HIV-1 infection. Results from the HIV-1 Qual assay should be interpreted in conjunction with clinical presentation and other laboratory markers.
- The Xpert HIV-1 Qual test has been validated only for use with K2 EDTA. Using this test to analyze other types of samples may give inaccurate results.
- Patients who have received CAR-T therapies may display positive results with Xpert (HIV-1 Qual XC, HIV-1 VL, etc.) as the result of the presence of the LTR target within certain chimeric antigen receptor T-cell (CAR-T) products. Additional confirmatory testing should be performed to determine the patient's HIV status in people who have received CAR-T treatment.

18 Performance Characteristics

18.1 Limit of Detection

The limit of detection (LOD) of the HIV-1 Qual assay was determined for both WB and DBS procedures by testing two different HIV-1 subtype B reference standards including the Viral Quality Assurance Laboratory (VQA) reference material of the AIDS Clinical Trials Group and the WHO 3rd International Standard NIBSC code 10/152 diluted in HIV-1 negative EDTA WB. Testing was performed with three dilution series, each analyzed with a unique reagent lot across two operators and three days. In total 72 replicates per level were tested. The evaluation was performed according to CLSI guideline E17-A2.22 The HIV-1 RNA concentration that can be detected with a positivity rate greater than 95% was determined by Probit regression analysis. The combined results for all three lots tested with both specimens in WB and DBS are shown in Table 2 and Table 3.

Table 2. Limit of Detection in Whole Blood for the HIV-1 Qual Assay using Probit Regression[a]

	Nominal Concentration (copies/mL)	No. Replicates	No. Positives	Positivity Rate (%)	LOD with 95% Probability Estimated by Probit (95% Confidence Interval)
VQA	200	72	66	92	203 copies/mL (95% CI: 181-225 copies/mL)
	150	72	55	76	
	100	71	45	63	
	75	72	35	49	
	50	72	34	47	
	25	72	12	17	
	0	72	0	0	
WHO	420	72	72	100	278 copies/mL (95% CI: 253-304 copies/mL)
	300	72	66	92	
	240	72	62	86	
	180	72	57	79	
	120	71	47	66	
	60	72	18	25	
	30	72	13	18	
	0	72	0	0	

[a] Conversion factor 1 copy = 1.72 IU used

Table 3. Limit of Detection in Dried Blood Spots for the HIV-1 Qual Assay using Probit Regression[a]

	Nominal Concentration (copies/mL)	No. Replicates	No. Positives	Positivity Rate (%)	LOD with 95% Probability Estimated by Probit (95% Confidence Interval)
VQA	800	72	72	100	531 copies/mL (95% CI: 474-587 copies/mL)
	600	71	64	90	
	400	72	64	89	
	200	72	43	60	
	100	72	23	32	
	50	72	4	6	
	0	72	0	0	
WHO	1000	72	71	99	668 copies/mL (95% CI: 593-742 copies/mL)
	750	72	69	96	
	500	72	60	83	
	250	72	43	60	
	125	72	22	31	
	75	72	12	17	

	Nominal Concentration (copies/mL)	No. Replicates	No. Positives	Positivity Rate (%)	LOD with 95% Probability Estimated by Probit (95% Confidence Interval)
	0	72	0	0	

[a] Conversion factor 1 copy = 1.72 IU used

18.2 Precision

The precision of the HIV-1 Qual assay was determined for both WB and DBS specimens using four serial dilution panels prepared each with two different HIV-1 subtype B reference standards: the Viral Quality Assurance Laboratory (VQA) reference material of the AIDS Clinical Trials Group and the WHO 3rd International Standard NIBSC code 10/152. Each panel was prepared by spiking the reference standard into HIV-1 negative EDTA WB. Each panel contained an HIV-1 negative WB or DBS panel member. The dried blood spots were prepared by spotting the spiked WB on the filter paper cards with 65 µL and dried prior to testing. The WB and DBS panels were tested per the HIV-1 Qual assay procedure. Each panel member was tested in replicates of four by two operators over nine days. Three different kit lots were used.

The data were analyzed by calculating the percent hit rate for each panel member for each kit lot by specimen type. The HIV-1 Qual assay demonstrates consistent performance at and above the LOD for both WB and DBS specimens as demonstrated by the p-values at >0.05 using the Chi-square statistic. See Table 4 and Table 5.

Table 4. Precision of HIV-1 Qual Assay in DBS Specimens

DBS – VQA Reference Standard				
Nominal Concentration HIV-1 RNA copies/mL	**Hit Rate (%) (No. pos/No. replicates)**			***p*-value**
	Lot 1	**Lot 2**	**Lot 3**	
800	100 (24/24)	100 (24/24)	100 (24/24)	1.00
600	92 (22/24)	96 (22/23)	83 (20/24)	0.35
400	92 (22/24)	83 (20/24)	92 (22/24)	0.57
DBS – WHO Reference Standard				
Nominal Concentration HIV-1 RNA copies/mL	**Hit Rate (%) (No. pos/No. replicates)**			***p*-value**
	Lot 1	**Lot 2**	**Lot 3**	
1000	100 (24/24)	96 (23/24)	100 (24/24)	0.36
750	92 (22/24)	96 (23/24)	100 (24/24)	0.35
500	88 (21/24)	71 (17/24)	92 (22/24)	0.12

Table 5. Precision of HIV-1 Qual Assay in WB Specimens

WB – VQA Reference Standard				
Nominal Concentration HIV-1 RNA copies/mL	**Hit Rate (%) (No. pos/No. replicates)**			***p*-value**
	Lot 1	**Lot 2**	**Lot 3**	
200	88 (21/24)	96 (23/24)	92 (22/24)	0.58
150	88 (21/24)	79 (19/24)	63 (15/24)	0.12
WB – WHO Reference Standard				
WB – VQA Reference Standard				
Nominal Concentration HIV-1 RNA copies/mL	**Hit Rate (%) (No. pos/No. replicates)**			***p*-value**
	Lot 1	**Lot 2**	**Lot 3**	
Nominal Concentration HIV-1 RNA copies/mL	**Hit Rate (%) (No. pos/No. replicates)**			***p*-value**
	Lot 1	**Lot 2**	**Lot 3**	
420	100 (24/24)	100 (24/24)	100 (24/24)	1.00
300	92 (22/24)	100 (24/24)	83 (20/24)	0.11
240	79 (19/24)	83 (20/24)	96 (23/24)	0.22

18.3 Linear Range

The linearity of the HIV-1 Qual assay was determined for both the WB and DBS procedures by analysis of a five member panel prepared with serial dilutions of HIV-1 subtype B RNA in HIV-1 negative WB. HIV-1 concentrations ranged from 1 x 10^3 to 1 x 10^7 copies/mL for WB and from 2.5 x 10^3 to 2.5 x 10^7 copies/mL for DBS and each panel member was analyzed in replicates of six using one reagent lot. The reference material used was Acrometrix HIV-1 control. Results for WB and DBS are shown in Figure 7 and Figure 8, respectively, and demonstrate that the assay is linear within a range of 1 x 10^3 to 1 x 10^7 copies/mL with an R^2 value (which is the product of a standard curve) of 0.9931 for WB and within a range 2.5 x 10^3 to 2.5 x 10^7 copies/mL with an R^2 value of 0.9955 for DBS.

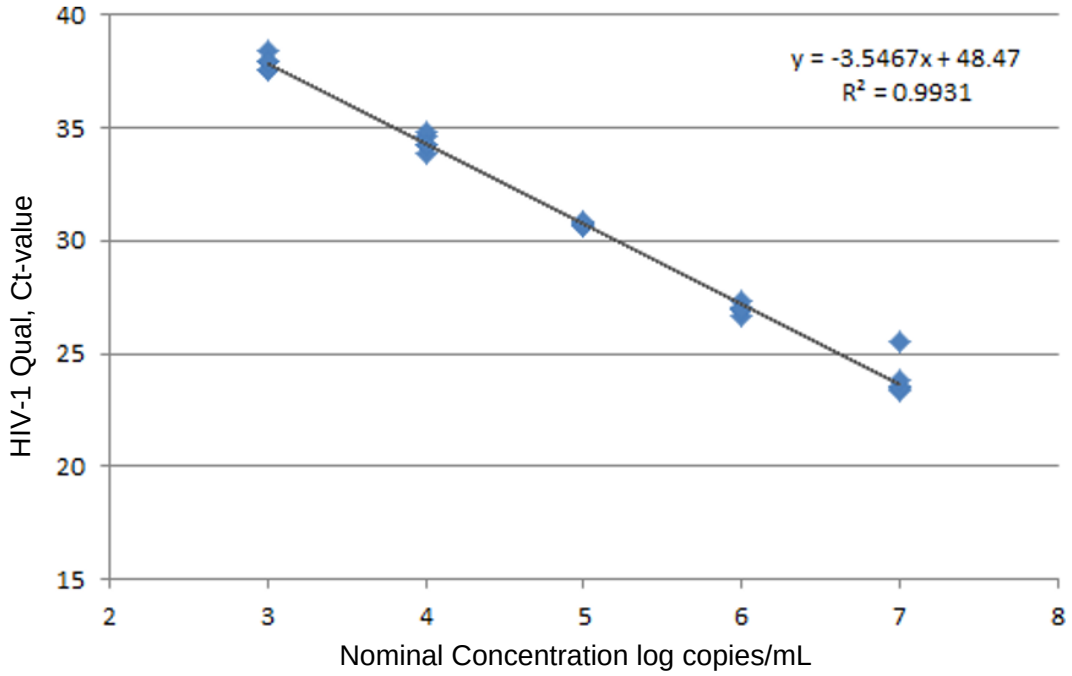

Figure 7. Linearity in Whole Blood for the HIV-1 Qual Assay

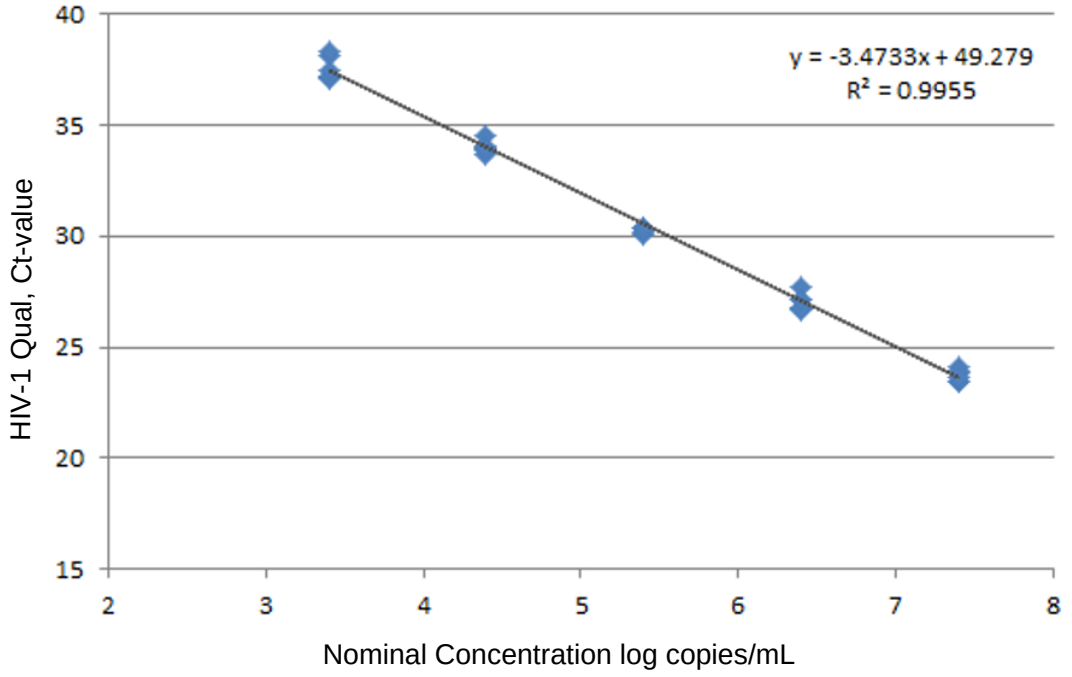

Figure 8. Linearity in Dried Blood Spots for the HIV-1 Qual Assay

18.4 Analytical Reactivity (Inclusivity)

The analytical reactivity of the HIV-1 Qual assay was evaluated by testing thirteen isolates representing the HIV-1 Group M subtypes A, C, D, F, G, H, CRF AG/GH, A/E and A/B, Group N, and Group O. The assignment of the nominal stock concentration was performed by Abbott HIV-1 RealTime RT-PCR assay (a polymerase chain reaction). Dilution series consisting of at least six levels cell culture supernatants in HIV-1 negative EDTA WB were made and the limit of detection (LOD) was determined. Each level was tested in replicates of twenty using two reagent lots and the WB procedure. The

HIV-1 RNA concentration that can be detected with a positivity rate greater than 95% was determined by Probit regression analysis for each isolate. The determined LOD was verified with the same isolate in replicates of twenty on a third unique reagent lot and with a second isolate of the same group/subtype in replicates of twenty on one reagent lot. Additionally verification was done with one isolate in replicates of 10-20 with one reagent lot using the DBS procedure and the estimated DBS LOD level. The results for LOD and verifications with WB and DBS procedure are summarized in Table 6 and show that the HIV-1 Qual assay detects HIV-1 RNA for thirteen different group/subtypes at concentrations of 680 copies/mL (or lower) for WB and 1400 copies/mL (or lower) for DBS with 95% positivity rate.

Table 6. Analytical Reactivity (Inclusivity) for the HIV-1 Qual Assay

	LOD in Whole Blood, 2 Reagent Lots			Verification of LOD in Whole Blood, 3rd Unique Reagent Lot (680 copies/mL)	Verification of LOD with 2nd Isolate in Whole Blood, 1 Reagent Lot (680 copies/mL)		Verification of Recognition with DBS, 1 Reagent Lot (1400 copies/mL)	
Group/ Subtype	**Isolate Designation**	**LOD (copies/ mL)**	**95% CI**	**Positivity Rate (%) (n=20)**	**Isolate Designation**	**Positivity Rate (%) (n=20)**	**Isolate Designation**	**Positivity Rate (%) (n=10-20)**
GroupM/ Subtype A	92UG029	553	427-678	100	UG275	100	92UG029	100
Group M/ Subtype C	98TZ017	159	117-201	100	92BR025	100	92BR025	100
Group M/ Subtype D	94UG114	379	286-471	100	92UG035	100	92UG035	100
Group M/ Subtype F	93BR020	262	204-320	100	BZ126	100	93BR020	100
Group M/ Subtype G	RU570	345	267-423	100	BCF-DIOUM	100	RU570	100
Group M/ Subtype H	VI557	171	139-237	100	BCF-KITA	100	V1557	100
Group M/ Subtype J	Clinical Specimen	438	348-527	100	Clinical Specimen	100	Clinical Specimen	100
Group M/ Subtype K	WWRB305-16	550	433-667	100	NA	ND	WWRB305- 16	94.4
Group M/ Subtype CRF A/B	WWRB305-11	208	153-263	100	WWRB305-12	100	WWRB305- 11	100
Group M/ Subtype CRF A/E	92TH001	228	172-285	100	92TH022	95.0	92TH022	100
Group M/ Subtype CRF AG/ GH	V1525	501	399-603	100	01CM.0008 BBY (A-G)	100	01CM.0008 BBY	100
Group N	YBF30	232	187-277	100	N1FR2011	100	YBF30	100
Group O	MVP5180	189	145-234	100	CA-9	100	MVP5180	100

18.5 Analytical Specificity (Exclusivity)

The analytical specificity of the HIV-1 Qual assay was evaluated by adding cultured organisms at 5 x 10^3 particles or copies/mL into HIV-1 negative EDTA WB and into HIV-1 positive EDTA WB at 900 copies/mL HIV-1 reference material (subtype B). Organisms were tested using the WB procedure. Tested organisms are listed in Table 7. None of the organisms tested showed cross reactivity or interference with the HIV-1 detection.

Table 7. Analytical Specificity Organisms

Candida albicans
Cytomegalovirus
Epstein-Barrvirus
Hepatitis A virus
Hepatitis B virus
Hepatitis C virus
Herpes simplex virus 1
Herpes simplex virus 2
Human herpesvirus 6
Human Immunodeficiency virus 2
Human T-cell lymphotropic virus type 1
Human T-cell lymphotropic virus type 2
Influenza A
Staphylococcus aureus

18.6 Potentially Interfering Substances

The susceptibility of the HIV-1 Qual assay to interference by elevated levels of endogenous substances and autoimmune disease markers was evaluated. For endogenous substances HIV-1 negative EDTA WB and HIV-1 positive EDTA WB at 2000 copies/mL HIV-1 reference material (subtype B) spiked with the substances were tested.

HIV-1 positive and negative samples with endogenous substances were prepared as DBS and further tested. Elevated levels of the endogenous substances listed in Table 8 were shown to not impact the assay specificity or interfere with the HIV-1 detection.

Table 8. Endogenous Substances and Concentration Tested

Substance	Tested Concentration
Albumin (BSA)	90 mg/mL
Bilirubin	0.2 mg/mL
Hemoglobin	5 mg/mL
Human DNA	4 µg/mL
Triglycerides	30 mg/mL

Testing of plasma specimens from five individuals per autoimmune disease marker with and without spiked HIV-1 reference material (subtype B) at 900 copies/mL was done using the WB procedure. No interference with the autoimmune disease markers systemic lupus erythematous (SLE), anti-nuclear antibodies (ANA) or rheumatoid factor (RF) using the HIV-1 Qual assay were shown.

18.7 Seroconversion Sensitivity

The diagnostic sensitivity of the HIV-1 Qual assay was evaluated by testing sequential plasma specimens from fifteen seroconversion panels using the WB procedure. Equivalence of WB and plasma as sample matrix has been proven (see Section 18.8). The HIV-1 Qual assay detected HIV-1 in 52 out of 79 total number of samples compared with 10 out of 79 that were detected by an HIV-1 antibody test (Abbott HIV 1/2 EIA, Abbott PRISM HIV-1/2, Abbott DiaSorin Murex HIV 1.2.O HIV, Bio-Rad GS HIV-1/HIV-2 Plus O EIA, or Siemens HIV 1/O/2 Enhanced ADVIA Centaur). A positive HIV-1

test result in HIV-1 Qual assay was generated earlier in all fifteen panels as compared to the HIV-1 antibody screening. In addition, the first HIV-1 positive response occurred earlier in twelve of the fifteen panels with the HIV-1 Qual assay as compared to the p24 antigen tests (Abbott, Coulter HIV-1 p24 Antigen, Innogenetics RL29, or Perkin Elmer Alliance HIV-1 p24 ELISA). The seroconversion sensitivity is presented in Table 9.

Table 9. Seroconversion Sensitivity for the HIV-1 Qual Assay

Old Panel Part Code	Number of Members	Days Spanned	No. of Reactive Panel Members		Days to First Reactive Result		Days between First Reactive Result with HIV-1 Qual and any AB test[a]
			HIV-1 Qual	Antibody (AB) test[a]	HIV-1 Qual	Antibody (AB) test[a]	
PRB946-00-1.0	4	11	3	0	4	11[b]	7
PRB948-00-1.0	4	23	2	0	20	23c	3
PRB950-00-1.0	4	28	3	1	18	28	10
PRB955-1.0	5	14	5	2	0[c]	12	12
PRB956-1.0	5	50	4	1	40	50	10
PRB962-1.0	6	17	4	0	7	17[b]	10
PRB963-1.0	7	21	3	0	14	21[b]	7
PRB964-1.0	6	22	3	0	15	22[b]	7
PRB966-1.0	10	51	5	2	35	48	13
PRB973-1.0	4	11	4	1	0[c]	11	11
PRB974-1.2	4	16	3	1	7	16	9
PRB975-1.0	5	14	3	0	7	14[b]	14
PRB976-1.2	4	9	4	0	0[c]	9[b]	9
PRB977-1.0	4	15	3	2	2	13	11
PRB978-1.0	7	33	3	0	26	33[b]	7
Total	79		52	10			

[a] Antibody tests, based on vendor data: Abbott HIV 1/2 EIA, Abbott PRISM HIV-1/2, Abbott Murex HIV 1.2.O HIV, Bio-Rad GS HIV-1/HIV-2 Plus O EIA, Siemens HIB 1/O/2 Enhanced ADVIA Centaur

[b] All bleeds were non-reactive for HIV-1 Antibodies (based on vendor information). The last bleed day is used as “Days to First Reactive Result”

[c] All bleed results were detected with the HIV Qual assay

18.8 Sample Type Equivalence (Whole Blood and Plasma)

The equivalent performance for the two different sample types EDTA WB and EDTA plasma using the HIV-1 Qual assay was demonstrated with specimens from sixteen HIV-1 negative individuals. Each specimen was split and prepared in one plasma aliquot and one WB aliquot. Both aliquots were spiked with HIV-1 RNA at 700 copies/mL. The aliquots were analyzed side-by- side using the WB protocol. Equivalent performance between the sample types was shown.

19 Clinical Performance

Performance characteristics of the HIV-1 Qual assay were evaluated at two institutions in Africa.

Subjects included individuals whose routine care called for collection of WB or DBS specimens for HIV-1 testing. For eligible subjects, aliquots of leftover specimens were obtained for testing with the HIV-1 Qual assay and comparator testing. Patient management continued at the site per their standard practice independent of the investigational test results.

The HIV-1 Qual assay performance was compared to a CE-marked comparator assay. The comparator assay was validated for DBS and not for WB therefore HIV-1 Qual WB assay results were compared to DBS results of the comparator method. Repeat testing on both the HIV-1 Qual assay and the comparator assay was performed on specimens where the HIV-1 Qual assay and the comparator assay were discrepant, and is provided for informational purposes only.

19.1 Results of WB Specimens

A total of 106 WB specimens were tested for HIV-1 by the HIV-1 Qual assay and the comparator assay. The HIV-1 Qual assay demonstrated positive percent agreement (PPA) of 98.2% (95% CI 90.3-100), and negative percent agreement (NPA) of 98.0% (95% CI 89.6-100), on WB relative to the comparator assay. Results are shown in Table 10.

Table 10. HIV-1 Qual Assay Performance vs. Comparator Assay – WB Specimens

		Comparator HIV-1 Qual Assay – DBS		
		POS	**NEG**	**Total**
HIV-1 Qual WB	POS	54	1[a]	55
	NEG	1[b]	50	51
	Total	55	51	106
		PPA:	98.2% (95% CI: 90.3-100)	
		NPA:	98.0% (95% CI: 89.6-100)	

[a] Upon retesting, specimen was Xpert POS / comparator POS

[b] Upon retesting, specimen was Xpert NEG / comparator POS

19.2 Results of DBS Specimens

A total of 399 DBS specimens were tested for HIV-1 by the HIV-1 Qual assay and the comparator assay. The HIV-1 Qual assay demonstrated a sensitivity with PPA of 95.6% (95% CI 91.8-98.0), and specificity with NPA of 98.5% (95% CI 95.6-99.7), on DBS relative to the comparator assay. Results are shown in Table 11.

19.3 Specificity in HIV Sero-Negative Adult Blood Donors

Table 11. HIV-1 Qual Assay Performance vs. Comparator Assay – DBS Specimens

		Comparator HIV-1 Qual Assay – DBS		
		POS	**NEG**	**Total**
HIV-1 Qual Assay	POS	194	3[a]	197
	NEG	9[b]	193	202
	Total	203	196	399

	Comparator HIV-1 Qual Assay – DBS		
	POS	NEG	Total
PPA:	95.6% (95% CI: 91.8-98)		
NPA:	98.5% (95% CI: 95.6-99.7)		

[a] Upon retesting, 1 of 3 specimens was Xpert NEG / comparator NEG, and 2 of 3 specimens were Xpert POS / comparator POS

[b] Upon retesting, 5 of 9 specimens were Xpert POS / comparator POS, 3 of 9 specimens were Xpert NEG / comparator POS, and 1 of 9 was Xpert NEG / comparator NEG.

WB collected in EDTA was collected from 1017 blood donors at two sites in the United States. The specimens were determined to be HIV-1 negative by standard blood bank FDA-licensed antibody and nucleic acid methods. Of the 1017 specimens 503 were prepared as DBS and 514 were tested as WB by the HIV-1 Qual assay. One DBS and two WB specimens were indeterminate on both initial and retest, and therefore excluded from the specificity calculation. The specificity of the assay was 100% (1014/1014), 95% CI: 99.6-100.0).

19.4 Assay Success Rate

Of the HIV-1 Qual assay runs performed with eligible specimens, 97.0% (1483/1529) of these specimens were successful on the first attempt. The remaining 46 gave indeterminate results on the first attempt. Of the 46 indeterminate cases, 36 yielded valid results upon repeat assay; three were indeterminate upon retest and seven of the indeterminate cases were not repeated due to insufficient remaining volume. The overall rate of assay success was 99.3% (1519/1529).

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22 Technical Assistance

Before Contacting Us

Collect the following information before contacting Cepheid Technical Support:

- Product name
- Lot number
- Serial number of the instrument
- Error messages (if any)
- Software version and, if applicable, Computer Service Tag Number

United States Technical Support

Telephone: + 1 888 838 3222
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23 Table of Symbols

Symbol	Meaning
	Catalog number
	*In vitro* diagnostic medical device
	CE marking – European Conformity
	Do not reuse
	Batch code
	Consult instructions for use
	Manufacturer
	Country of manufacture
	Contains sufficient for *n* tests
	Control
	Expiration date
	Temperature limitation
	Biological risks
	Caution
	Authorized Representative in Switzerland
	Importer

Cepheid AB
Röntgenvägen 5
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CE 2797 IVD

24 Revision History

Description of Changes: 301-3048, Rev. K to Rev. L

Section	Description of Change
11, 12.1, 17	Specified K2 for EDTA collection tubes.
13	Separated procedures for GeneXpert Dx System and GeneXpert Infinity System.
24	Added Revision History section.