

Xpert[®] HIV-1 Qual XC

REF GXHIV-QA-XC-CE-10

Instructions For Use

CE 2797 **IVD**

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See Section 27 Revision History for a description of changes.

Xpert[®] HIV-1 Qual XC

For *In Vitro* Diagnostic Use Only.

1 Proprietary Name

Xpert[®] HIV-1 Qual XC

2 Common or Usual Name

Xpert HIV-1 Qual XC

3 Intended Use

Xpert[®] HIV-1 Qual XC (Extended Coverage) is an *in vitro* nucleic acid amplification test for the qualitative detection of human immunodeficiency virus type 1 (HIV-1) total nucleic acids, on the automated GeneXpert[®] System. The test is used to detect HIV-1 in human dried blood spots (DBS) and EDTA capillary or venous whole blood (WB) specimens from individuals suspected of HIV-1 infection.

Xpert[®] HIV-1 Qual XC is intended to aid in the diagnosis of HIV-1 infection in conjunction with clinical presentation and other laboratory markers in infant, adolescent and adult populations.

Xpert[®] HIV-1 Qual XC is intended to be used by laboratory professionals, trained health care professionals or other health care workers receiving appropriate training on the use of the device. This test may be used in laboratory or near-patient testing environments.

The test is not intended to be used as a blood, organ or tissue 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} HIV can be transmitted through sexual contact, exposure to infected blood, body fluids, or blood products, prenatal infection of a fetus, or perinatal or postnatal infection of a newborn.^{4,5,6} Untreated HIV-1 infection is characterized by high-level viral production and CD4 T-cell destruction, despite an often lengthy clinical latency, to significant net loss of CD4 T cells and AIDS.

Globally approximately 38 million people living with HIV. Of those infected, 1.7 million represent new infections and an estimated 150,000 are children. Two-thirds of all people living with HIV reside in sub-Saharan Africa.⁷ Without timely HIV testing and therapy initiation, approximately half of all children with HIV will die before reaching two years of age.⁸ Early diagnosis of HIV infection in infants is a necessity and HIV-1 nucleic acid testing is the mainstay for detecting infection in pediatric patients 18 months of age or younger.⁹

Others with HIV infection generally develop an acute infection characterized by flu-like symptoms in a period of days to weeks after initial exposure.¹⁰ Acute HIV infections typically last less than 14 days¹¹ and are associated with high levels of viremia prior to a detectable immune response.^{12,13} Therefore, HIV-1 nucleic acid testing can be more sensitive than standard serologic testing in detection of acute infection.¹⁰

The Xpert HIV-1 Qual XC test 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 and a personal computer with 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*, the *GeneXpert Infinity System Operator Manual* or the *GeneXpert Edge System User's Guide*.

The Xpert HIV-1 Qual XC test 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 inhibitors in the RT and PCR reactions. Amplification and detection of HIV-1 total nucleic acid is achieved by primers and probes targeted to the highly conserved long terminal repeat (LTR) region and the polymerase (Pol) gene (dual target) of the HIV-1 genome. The Xpert HIV-1 Qual XC test also controls the validity of the sample by detection of the human Hydroxymethylbilane Synthase (HMBS) gene. The Probe Check Control (PCC) verifies reagent rehydration, PCR tube filling in the cartridge, probe integrity, and dye stability.

The Xpert HIV-1 Qual XC test is standardized against the 4th World Health Organization (WHO) International Standard for HIV-1 (NIBSC code: 16/194).¹⁴

6 Materials Provided

The Xpert HIV-1 Qual XC kit contains sufficient reagents to process 10 samples. The kit contains the following:

| | |
|--|----------------------------|
| Xpert HIV-1 Qual XC Cartridges with Integrated Reaction Tubes | 10 |
| Bead 1, Bead 2, and Bead 3 (freeze-dried) | 1 of each per cartridge |
| Lysis Reagent (Guanidinium Hydrochloride) | 1.2 mL per cartridge |
| Rinse Reagent | 0.5 mL per cartridge |
| Elution Reagent | 1.5 mL per cartridge |
| Wash Reagent (Guanidinium Hydrochloride) | 3.2 mL per cartridge |
| Proteinase K Reagent | 0.48 mL per cartridge |
| Disposable 100 µL Transfer Pipettes | 1 bag of 10 per kit |
| CD | 1 per kit |
| <ul style="list-style-type: none"> • Assay Definition File (ADF) • Instructions to import ADF into 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 Xpert HIV-1 Qual XC test cartridges at 2–28 °C.
- Prior to use, bring the Xpert HIV-1 Qual XC test cartridges to 15–30 °C if they have been stored cold.
- Do not open the cartridge lid until you are ready to perform the test.
- Use cartridge within 4 hours after opening the cartridge lid and adding sample.
- Do not use a cartridge that has leaked.

- Do not use cartridges that previously have been frozen.
- Do not use a cartridge past the expiration date.
- Store cartridges in the kit boxes until time for use and avoid exposure of direct sunlight.

8 Materials Required but Not Provided

- GeneXpert Dx System, GeneXpert Infinity System or GeneXpert Edge System (catalog number varies by configuration): GeneXpert instrument, computer with proprietary GeneXpert Software Version 4.7b (GeneXpert Dx System), Xpertise™ 6.4b or higher (Infinity System), GeneXpert Edge Software Version 1.0 (GeneXpert Edge System), barcode scanner, and operator manual
- Printer: If a printer is needed, contact Cepheid Technical Support to arrange for the purchase of a recommended printer.
- Newly prepared 10% bleach / sodium hypochlorite.
- Ethanol or denatured ethanol.
- If using DBS:
 - DBS filter paper cards for 12 mm spots, e.g., Whatman™ 903, Munktell or equivalent
 - Lancets, desiccants, plastic sealable bags
 - Tweezers/forceps (straight, metal, blunt-tipped; see Figure 1), kept sterile with bleach/sodium hypochlorite
 - Scissors, sterile (Only needed if not using a perforated DBS card, to excise DBS from filter paper)
 - Serviette/Wipe
 - Antiseptic
- If using capillary blood:
 - Lancets, Serviette/Wipe
 - Antiseptic



Figure 1. Straight Metal Blunt-tipped Tweezers

9 Warning and Precautions

- For *In Vitro* Diagnostic Use Only.
- 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 Prevention¹⁵ and the Clinical and Laboratory Standards Institute.¹⁶
- Wear protective disposable gloves, laboratory coats and eye protection when handling specimens and reagents. Wash hands thoroughly after handling specimens and test reagents.
- Appropriate safety measures should be taken in the event of a splash that may occur using bleach and facilities for adequate eye washing or skin rinsing are advised to care for such events.
- 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.
- Good laboratory practices, including changing gloves between handling patient specimens, are recommended to avoid contamination of specimens or reagents.
- Do not substitute Xpert HIV-1 Qual XC test reagents with other reagents.
- Do not open the Xpert HIV-1 Qual XC test cartridge lid except when adding the WB or DBS sample.
- Always keep the Xpert HIV-1 Qual XC test cartridge in an upright position to avoid leakage.

- 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.
- Do not place the sample ID label on the cartridge lid or on the barcode label.
- Each single-use Xpert HIV-1 Qual XC test 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 disposal. If country 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.¹⁷
- In the event of contamination of the work area or equipment with samples, thoroughly clean the contaminated area with a freshly prepared solution of 0.5% sodium hypochlorite (or a 1:10 dilution of household chlorine bleach). Follow by wiping the surface with 70% ethanol. Let the work surfaces dry completely before proceeding.
- For Instrument System cleaning and disinfecting instructions, refer to the appropriate *GeneXpert Dx System Operator Manual*, *GeneXpert Infinity System Operator Manual* or *GeneXpert Edge System User's Guide*.

10 Chemical Hazards^{18,19}

- UN GHS Hazard Pictogram:
- Signal Word: DANGER
- **UN GHS Hazard Statements**
 - May be harmful if swallowed.
 - Causes skin irritation.
 - Causes eye irritation.
 - May cause allergy or asthma symptoms or breathing difficulties if inhaled.
- **UN GHS Precautionary Statements**
 - Prevention
 - Wash thoroughly after handling.
 - Wear protective gloves/protective clothing/eye protection/face protection.
 - Avoid breathing dust/fume/gas/mist/vapors/spray.
 - Response
 - IF ON SKIN: Wash with plenty of soap and water.
 - Specific treatment, see supplemental first aid information in Safety Data Sheets (SDS), available at www.cephheid.com or www.cephheidinternational.com under the **SUPPORT** tab.
 - Take off contaminated clothing and wash before reuse.
 - If skin irritation occurs: Get medical advice/attention.
 - IF IN EYE: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing.
 - If eye irritation persists: Get medical advice/attention.
 - IF INHALED: Remove victim to fresh air and keep at rest position comfortable for breathing.
 - If experiencing respiratory symptoms: Call a POISON CENTER or doctor/physician.

11 Sample Collection, Transport, and Storage

11.1 Venous Whole Blood Collection

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

Sample, Transport and Storage

K2 EDTA-anticoagulated venous WB may be stored at 2–8 °C for up to 96 hours or at 2–35 °C for up to 24 hours, prior to preparing and testing the sample.

11.2 Capillary Whole Blood Collection

For collection of capillary WB, use a designated K2 EDTA-coated collection tube for small volumes as per the manufacturer's instructions for use. Collect more than 100 µL (e.g., 150 µL) to compensate volume loss on tube surfaces. If possible, collect enough WB volume for retests, either in the same collection tube or in a separate tube, depending on tube volume.

Sample, Transport and Storage

K2 EDTA-anticoagulated capillary WB may be stored at 2–35 °C for up to 60 minutes, prior to preparing and testing the sample.

11.2.1 Heel-Stick Sample Collection

Important The site used for pediatric sample collection is dependent on the age and weight of the child. Heel stick sampling may not be appropriate in children who are already able to walk and fingerstick collection may be more appropriate.

1. It is suggested that the child is comfortable and if possible, calm, and in a secure position so the heel can be stabilized.
2. Use a new pair of gloves for each patient.
3. Locate the site of the heel for the skin prick and clean the site using a sterilizing wipe. The site should be dry before puncture. The sides of the bottom of the heel may provide the best sites for collection.
4. Using a sterile lancet appropriate for infants, puncture the skin and allow for adequate blood flow. Do not squeeze or repeatedly press the site but gentle pressure of the heel may help the blood to flow more freely.
5. The first drops of blood may be small and of inadequate volume, so these can be wiped off until larger blood drops are seen.
6. Allow blood to flow freely from the site directly into the K2 EDTA coated collection tube. Do not allow the blood to clot or coagulate as this may interfere with testing.
7. Cover the heel site with a bandage after the blood has been collected.

11.2.2 Finger-Stick Sample Collection

1. Use a new pair of gloves for every patient.
2. Locate an appropriate site for the puncture. The sides of the third or fourth fingers with adequate soft tissue often work well. Avoid the very tip of the fingers and the center of the finger pad.
3. Warming of the hands and fingers and holding the downwards may assist with proper blood flow.
4. Clean the site using a sterilizing wipe and ensure that it is dry before attempting the puncture.
5. Using a sterile lancet, puncture the finger slightly to the side of the center of the finger pad. It is advised to use a lancet that will provide free blood flow. Do not squeeze or repeatedly press the site but gentle pressure to the tip of the finger may help the blood to flow more freely.
6. The first drops of blood may be small and of inadequate volume, so these can be wiped off until larger blood drops are seen.
7. Allow blood to flow freely from the site directly into the K2 EDTA coated collection tube. Cover the site with a plaster or adhesive dressing after the blood has been collected.

11.3 Dried Blood Spots Collection

Collect DBS specimens using appropriate clinical procedures.

1. Prepare using Whatman 903 or Munktell filter paper cards or equivalent from capillary blood obtained directly from a heel-, finger- or toe-stick or collected in a K2 EDTA-tube as per the manufacturer's instructions for use. You can also prepare DBS from venous whole blood collected in sterile tubes using K2 EDTA (lavender top) as the anticoagulant.
2. Spot blood inside each delineated 12-millimeter circle of the filter paper card.

3. Ensure that the entire circle is covered with blood (approximately 60–70 µL).
4. Make a minimum of two circles from each specimen to allow for retesting.
5. If WB (venous or capillary) was collected in an EDTA-tube, mix by inverting the tube at least 7 times before applying WB onto the filter.
6. Air-dry the card at room temperature for a minimum of four hours.
7. Package each card in individual resealable bags with a desiccant sachet in each bag.

Sample, 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 frozen at -15 °C or colder for up to 16 weeks. Cards may also be stored at 2–35 °C for up to 8 weeks.

12 Procedure

12.1 Preparing the Cartridge

Important Start the test within 4 hours of adding the sample to the cartridge.

1. Wear protective disposable gloves.
2. Allow Xpert HIV-1 Qual XC test cartridges and sample to equilibrate to 15–30 °C prior to adding sample into the cartridge.
 - Do not add sample into a cartridge that is cold (below 15°C).
3. Inspect the test cartridge for damage. If damaged, do not use it.
4. Label the cartridge with sample identification.
5. Open the lid of the test cartridge.
6. Add the sample to the test cartridge:
 - For *whole blood* sample (venous or capillary), see Section 12.2.
 - For *dried blood spot* sample, see Section 12.3.

12.2 Whole Blood Sample (Venous or Capillary)

1. Invert the WB sample [EDTA (lavender-top) or EDTA capillary collection tube] at least seven times to mix the blood.
2. Immediately transfer 100 µL WB using the micropipette provided (Figure 2) by squeezing the upper bulb and then gently releasing to aspirate the blood into the micropipette. Excess blood will overflow into the lower bulb.

Important Make sure NOT to aspirate air into the pipette after the pipette has been lifted from the blood surface in the EDTA collection vessel, as this can lead to insufficient blood volume (See Figure 2.) Do NOT pour the specimen into the chamber! Discard the pipette after use.

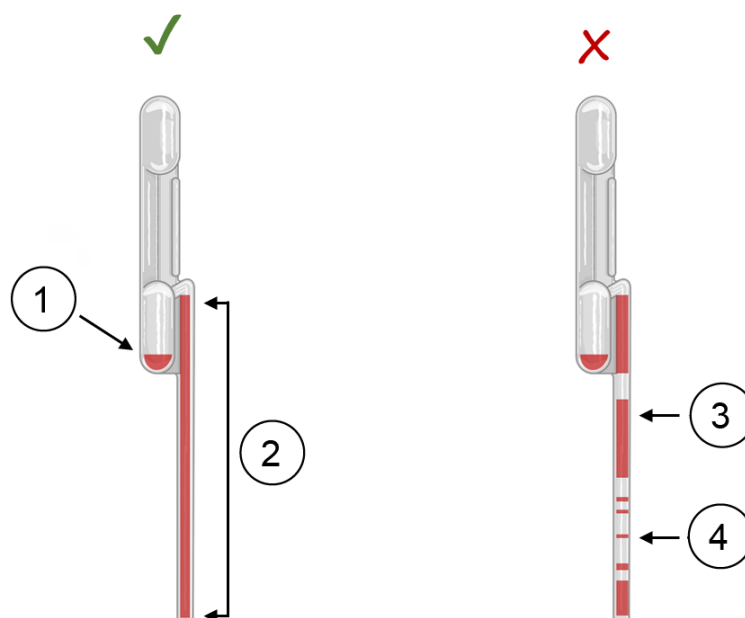


Figure 2. Xpert HIV-1 Qual XC Test 100 µL Transfer Micropipette (Correct and Incorrect Use)

| Number | Description |
|--------|--|
| 1 | Excess sample (avoid pipetting into cartridge!) |
| 2 | 100 µL blood (sample) |
| 3 | Brisk pipetting might result in volume inaccuracies! |
| 4 | Air pocket |

3. Squeeze again to dispense the blood into the sample chamber of the cartridge (Figure 3). Visually inspect that the blood has been dispensed.

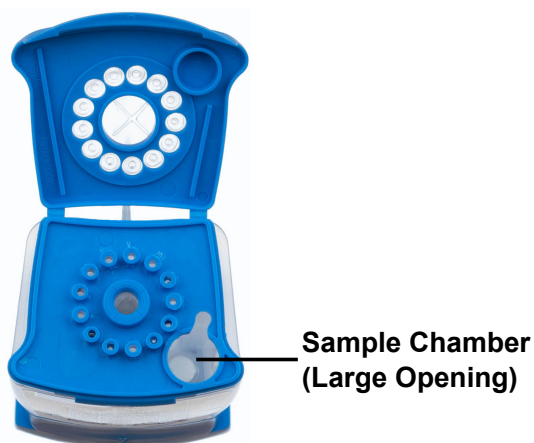


Figure 3. Xpert HIV-1 Qual XC Cartridge (Top View)

4. Close the cartridge lid.

12.3 Dried Blood Spot Sample

Important

To prevent cross contamination, clean and wipe off tweezers and scissors (scissors used only if DBS card is not perforated) with a serviette between specimens using 10% bleach. Make sure DBS gripping surfaces are exposed to the bleach. Dry the tweezers and scissors after each decontamination with a dry serviette or let them air dry. Follow this procedure to prepare the tweezers for use and after every sample.

1. Follow the delineated lines when excising the DBS. Use sterilized tweezers to detach and handle the DBS (Figure 4). When using non-perforated DBS, use sterilized scissors to excise one entire DBS from the filter paper card for each specimen.



Figure 4. Excision of the DBS

2. Hold the DBS with tweezers and insert it into the sample chamber of the cartridge, aligned with the slit extending from the opening of the sample chamber (Figure 3 and Figure 5 marked with an arrow). Keep holding it firmly while gently pushing it down the chamber. There will be some resistance as the DBS first comes in contact with the chamber walls.



Figure 5. Insertion of DBS into Sample Chamber

3. The pressure against the chamber walls will fold the DBS so that it fits. Keep pushing it down to the bottom of the chamber where it reaches a definitive stop (Figure 6). Let go of the DBS before retracting the tweezers, as to not accidentally pull it back up.



Figure 6. DBS Folded at Bottom of the Sample Chamber

Important Visually inspect the cartridge and make sure that the DBS is now at the bottom of the sample chamber.

4. Close the cartridge lid.

13 GeneXpert Dx System

13.1 Importing the Assay Definition File

Before starting the test, make sure the appropriate Assay Definition File (ADF) is imported into the software:

- For *Whole Blood* sample type: **Xpert HIV-1 Qual XC WB.**
- For *Dried Blood Spots* sample type: **Xpert HIV-1 Qual XC DBS.**

If only one of the two Xpert HIV-1 Qual XC ADFs is downloaded to the computer, the **Select Assay** field will also be automatically filled after step 6 in Section 13.2 below. If both the DBS ADF and the WB ADF are available, select the ADF corresponding to the used sample type in the **Select Assay** drop down menu, as shown in Figure 7.

| Name | Version |
|-------------------------|---------|
| Xpert HIV-1 Qual XC WB | 1 |
| Xpert HIV-1 Qual XC DBS | 1 |

Figure 7. Select ADF corresponding to the used sample type

13.2 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.

13.3 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.

14 GeneXpert Edge System

(May not be available in all countries)

14.1 Importing the Assay Definition File

Before starting the test, make sure the appropriate Assay Definition File (ADF) is imported into the software:

- Note**
- For *Whole Blood* sample type: **Xpert HIV-1 Qual XC WB**.
 - For *Dried Blood Spots* sample type: **Xpert HIV-1 Qual XC DBS**.

If only one of the two ADFs is downloaded to the computer, the **Select Assay** field will also be automatically filled after step 8a in Section 14.2 below. Touch **YES** if the displayed information is correct. If both the DBS ADF and the WB ADF are available, the ADF corresponding to the used sample type will have to be selected in the **Select Assay** drop down menu, as shown in Figure 8.

Note

If the barcode on the cartridge does not scan or scanning the barcode results in an error message, 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 will appear indicating the assay definition file is not loaded on the system. If this screen appears, contact Cepheid Technical Support.

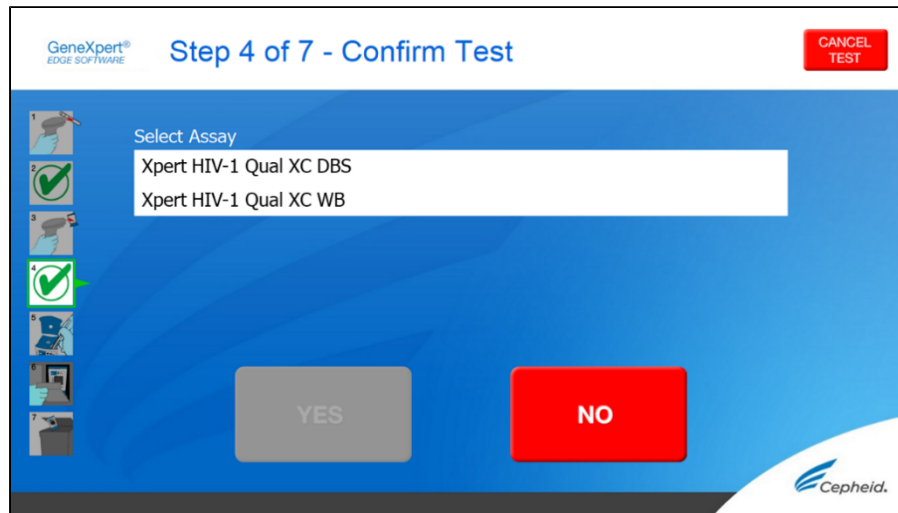


Figure 8. Select ADF corresponding to the used sample type

This section lists the basic steps for running the test. For detailed instructions, see the *GeneXpert Edge System User's Guide*.

14.2 Starting the Test

Important Before you start the test, make sure that the correct assay definition file (ADF) is imported into the software.

This section lists the basic steps for running the test. For detailed instructions, see the *GeneXpert Edge System User's Guide*.

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

1. Put on a clean pair of gloves.
2. Turn on the GeneXpert Edge instrument. The power switch is on the back of the instrument.
3. Turn on the tablet computer and log on.
 - *Windows 7*: The **Windows 7 account** screen displays. Touch the **Cepheid-Admin** icon to continue.
 - *Windows 10*: The **Windows Lock** screen displays. **Swipe up** to continue. The **Windows Password** screen displays.
4. Touch **Password** to display the keyboard, then type your password.
5. Touch the **arrow** button at the right of the password entry area. The GeneXpert Edge software loads automatically, and the **Welcome** screen displays shortly thereafter.
6. Touch the **TOUCH HERE TO BEGIN** button. The **VIEW PREVIOUS TESTS** button initially displays. The **NEW TEST** button displays on the **Home** screen within 3 minutes when the instrument is ready to run.
7. Touch the **RUN NEW TEST** button on the **Home** screen.
8. Follow the on-screen instructions:
 - a) **Scan patient/sample ID** using the barcode scanner, or manually enter the patient/sample ID.
 - b) **Confirm the patient/sample ID.**
 - c) **Scan the cartridge barcode.** The **Select Assay** field automatically fills. Touch **YES** if the displayed information is correct.

Note

If the barcode on the cartridge does not scan or scanning the barcode results in an error message, 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.

- d) **Confirm test** Once the ADF has been selected, confirm the assay.
 - e) **Cartridge preparation** The cartridge preparation is also described in the Preparing the Specimen section. Follow the video or instructions on how to prepare the specimen.
 - f) **Load cartridge** Open the module door with the blinking green light. Load the cartridge with the barcode facing the operator. Close the door.
The green light stops blinking, and the test starts. **Test in Progress** displays on the screen.
 - g) **Remove cartridge**
When the test is done (green light goes out), the door automatically unlocks. Follow the displayed instructions on how to remove the cartridge. Dispose of the used cartridge and gloves in an appropriate specimen waste container according to your institution's standard practices.
9. Touch **CONTINUE** to view the result of the test that has just completed. Touch **CONTINUE** again to go back to **Home** screen.
This completes the procedure for running a test.

14.3 Starting a New Test

An additional test may be started after the first is in progress.

1. Touch the **HOME** button.
The **Home** screen will display the module in use as slightly grey and with the notation that data collection is in progress.
2. Touch **RUN NEW TEST** button and proceed with the new test following the steps in Starting a Test.
3. After the second test is in progress, touch the **HOME** button. The status of both tests is displayed.
When a test is complete, the icon text will change to **Data collection complete** and will show a check mark on the icon.
4. Touch the **Data collection complete** icon to show the **Remove Cartridge** screen. Follow the instructions on the screen to remove the cartridge.

14.4 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 Edge System User's Guide*.

Note

If reporting results using a LIS, confirm that LIS results match system results for the patient ID field; if results conflict, report the system results only.

1. Touch the **VIEW PREVIOUS TESTS** button on the **Home** screen.
2. On the **Select Test** screen, select the test by either touching the test name or using the arrows to select the test.

15 GeneXpert Infinity System

15.1 Importing the Assay Definition File

Before starting the test, make sure the appropriate Assay Definition File (ADF) is imported into the software:

- For *Whole Blood* sample type: **Xpert HIV-1 Qual XC WB**.
- For *Dried Blood Spots* sample type: **Xpert HIV-1 Qual XC DBS**.

If only one of the two Xpert HIV-1 Qual XC ADFs is downloaded to the computer, the **Select Assay** field will also be automatically filled after step 8 in Section 15.2 below. If both the DBS ADF and the WB ADF are available, select the ADF corresponding to the used sample type in the **Select Assay** drop down menu, as shown in Figure 9.

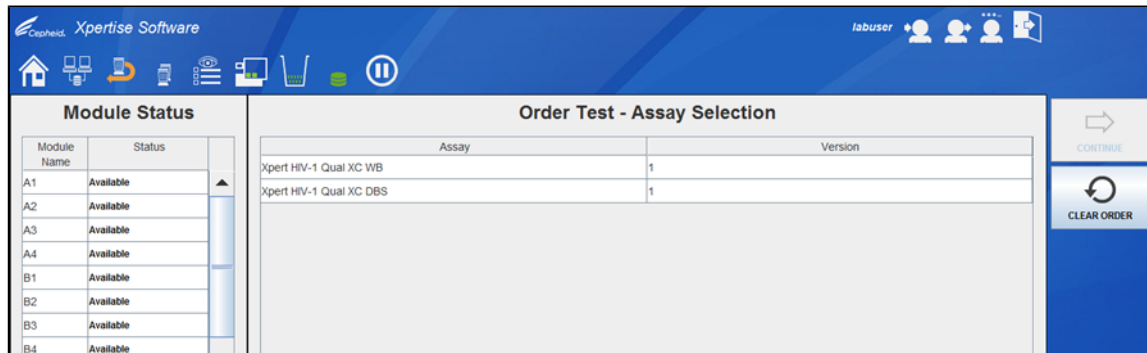


Figure 9. Select ADF corresponding to the used sample type

15.2 Starting the Test

Before you start the test, make sure that:

- Important**
- 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.

15.3 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.

16 Quality Control

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

- **Sample Adequacy Control (SAC):** Ensures that the sample added is a human sample. If a sample has been added that is not a human sample, an insufficient volume or if an empty DBS has been inserted into the cartridge, an **INVALID** result will be displayed after the run. The SAC should be positive in a negative sample and can be negative or positive in a positive sample. If the SAC doesn't meet the validated acceptance criteria, the test result will show **INVALID**.
- **Sample Processing Control (SPC):** Ensures that the sample was correctly processed. The SPC is an Armored RNA® control unrelated to HIV that is included in each cartridge and goes through the whole test process. The SPC verifies that the sample processing is adequate. Additionally, this control detects sample-associated inhibition of the RT-PCR reaction. The SPC shall meet the validated acceptance criteria in a HIV-1 negative sample. If the SPC doesn't meet the validated acceptance criteria, the test result will show **INVALID**. If HIV-1 is detected in a sample the SPC is not required to meet 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 the fluorescence signals meet the validated acceptance criteria.
- **External Controls:** External controls should be used in accordance with local, state, and federal accrediting organizations' requirements as applicable.

17 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 (Figure 10 to Figure 14). Possible results are shown in Table 1.

Table 1. Test Results and Interpretation

| Result | Interpretation |
|--|---|
| HIV-1 DETECTED See Figure 10. | The HIV-1 target nucleic acids are detected. <ul style="list-style-type: none"> • 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. • SAC: NA (not applicable); SAC is ignored because the HIV-1 target amplification occurred. • Probe Check: PASS; all probe check results pass. |
| HIV-1 NOT DETECTED See Figure 11. | The HIV-1 target nucleic acids are not detected. <ul style="list-style-type: none"> • SPC: PASS; SPC has a Ct within the valid range. • SAC: PASS; human sample detected. • Probe Check: PASS; all probe check results pass. |
| INVALID^a See Figure 12. | Presence or absence of the HIV-1 target nucleic acids cannot be determined. <ul style="list-style-type: none"> • SPC: FAIL; SPC Ct is not within valid range. • SAC: FAIL; SAC Ct is not within valid range. • Probe Check: PASS; all probe check results pass. |
| ERROR^a See Figure 13. | Presence or absence of HIV-1 target nucleic acids cannot be determined. <ul style="list-style-type: none"> • HIV-1: NO RESULT • SPC: NO RESULT • Probe Check^b: FAIL; all or one of the probe check results fail. |
| NO RESULT^a NO RESULT - REPEAT TEST^c See Figure 14. | Presence or absence of HIV-1 target nucleic acids cannot be determined. A NO RESULT indicates that insufficient data were collected. For example, the operator stopped a test that was in progress. <ul style="list-style-type: none"> • HIV-1: NO RESULT • SPC: NO RESULT • Probe Check: NA (not applicable). |

^a In case of an **INVALID**, **ERROR** or **NO RESULT**, repeat the test according to instructions in Section 18.2.

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

^c For GeneXpert Edge only

Note Assay screenshots are for example only. Test name and version number may vary from the screenshots shown in this instructions for use.

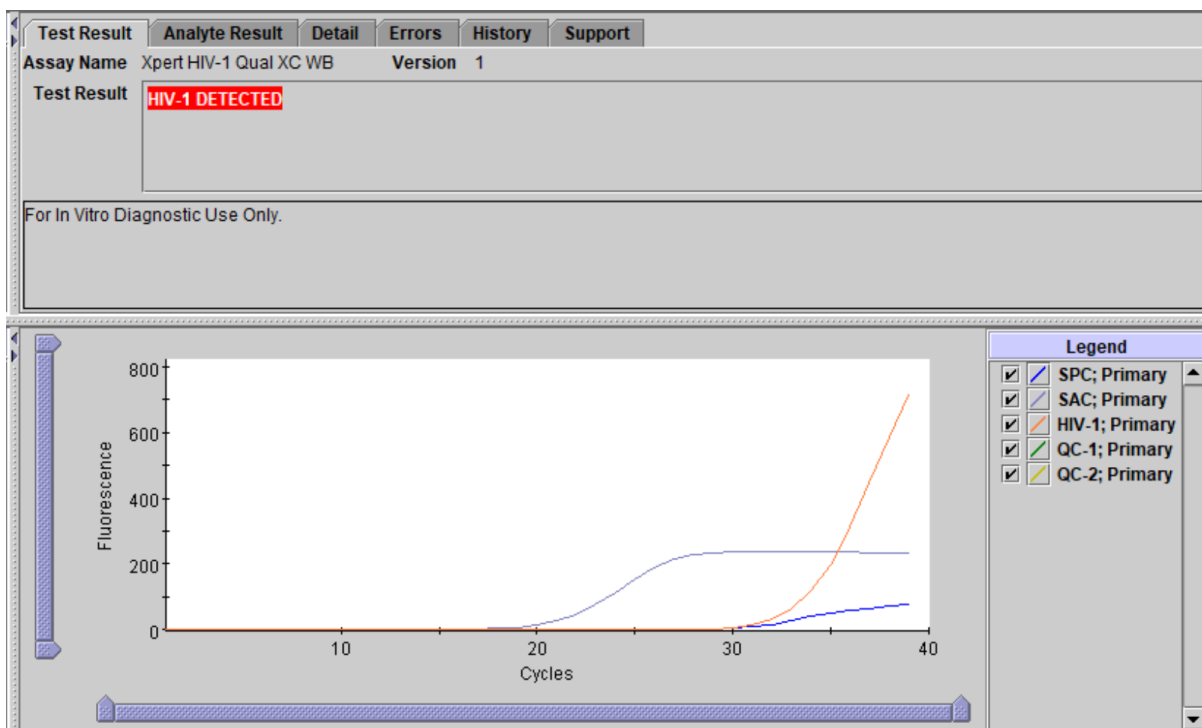


Figure 10. HIV-1 Detected as displayed on GeneXpert Dx System and GeneXpert Infinity System

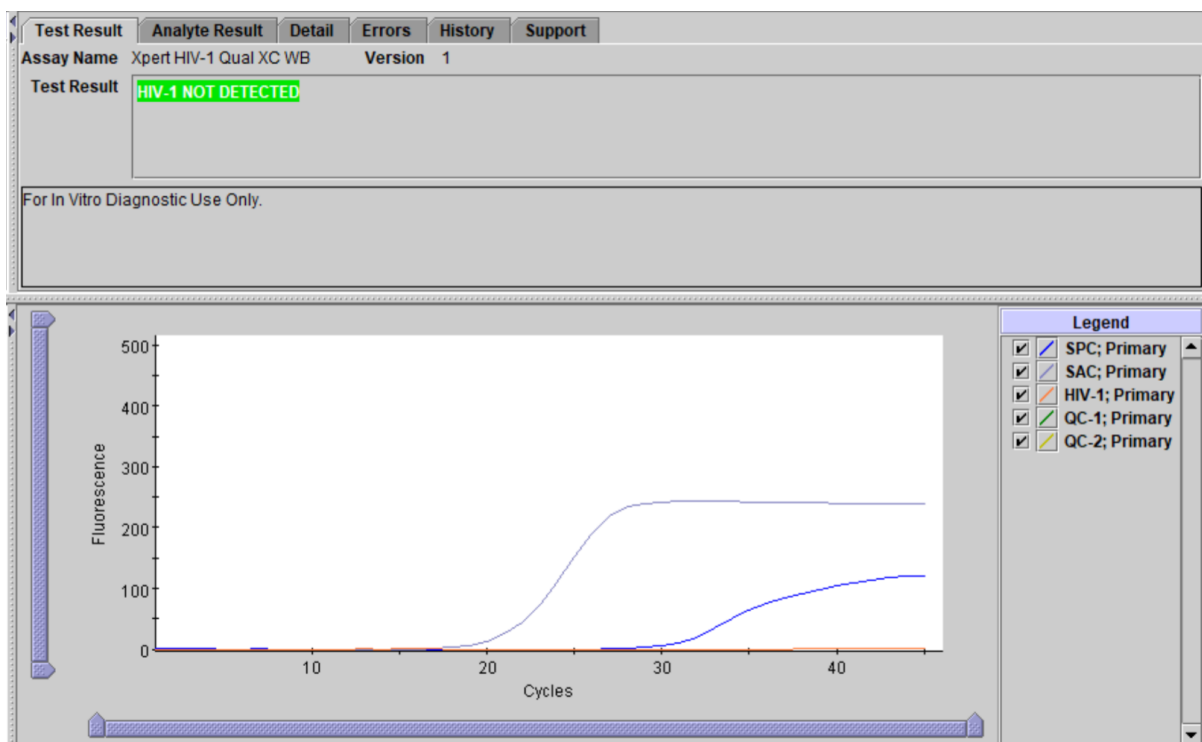


Figure 11. HIV-1 Not Detected as displayed on GeneXpert Dx System and GeneXpert Infinity System

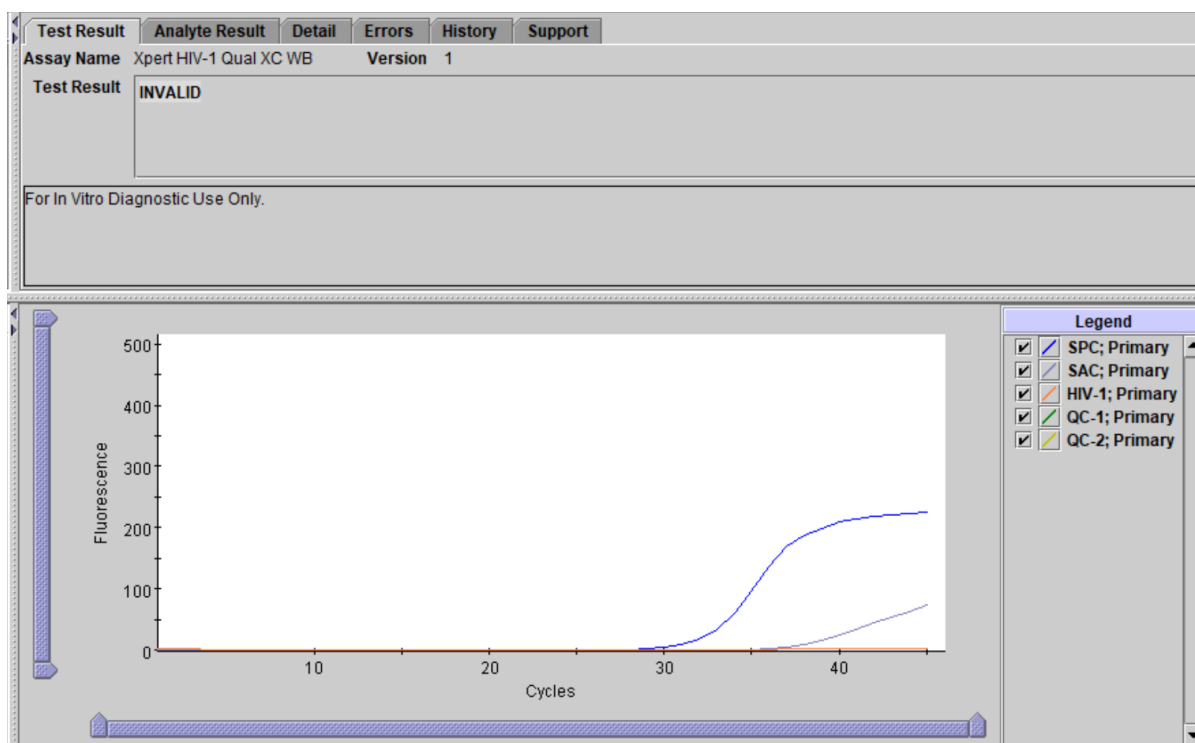


Figure 12. Invalid Result as displayed on GeneXpert Dx System and GeneXpert Infinity System

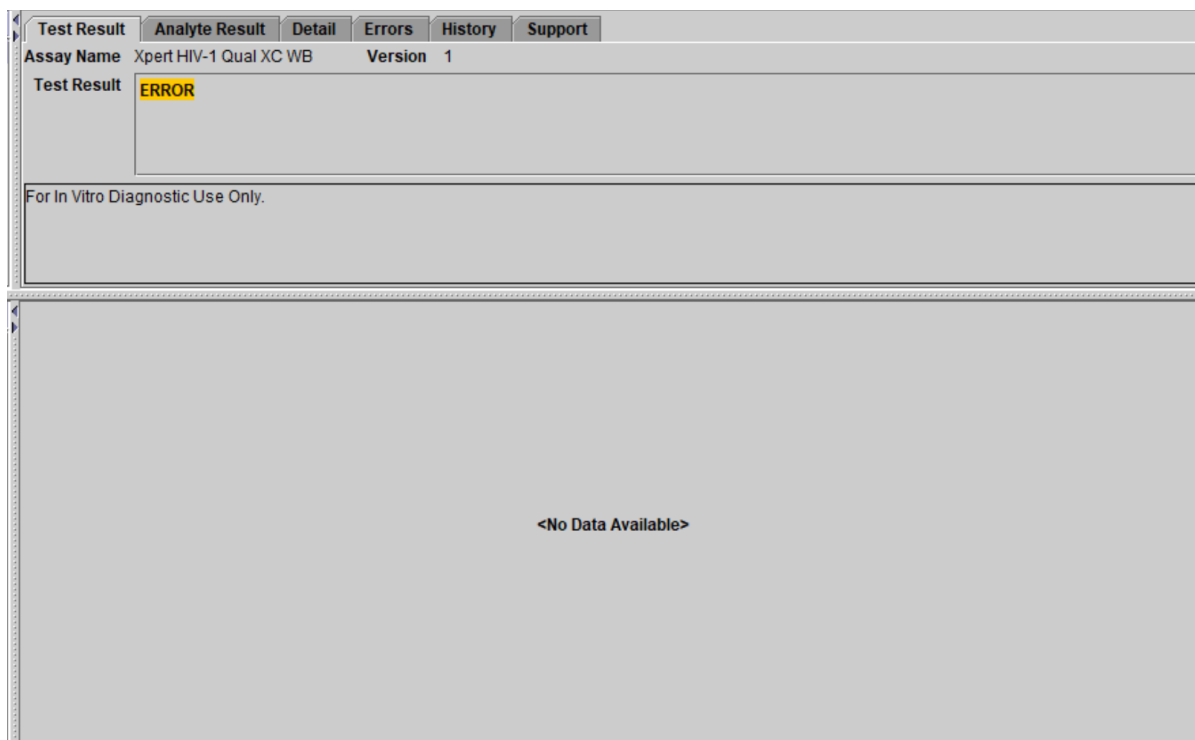


Figure 13. Error as displayed on GeneXpert Dx System and GeneXpert Infinity System

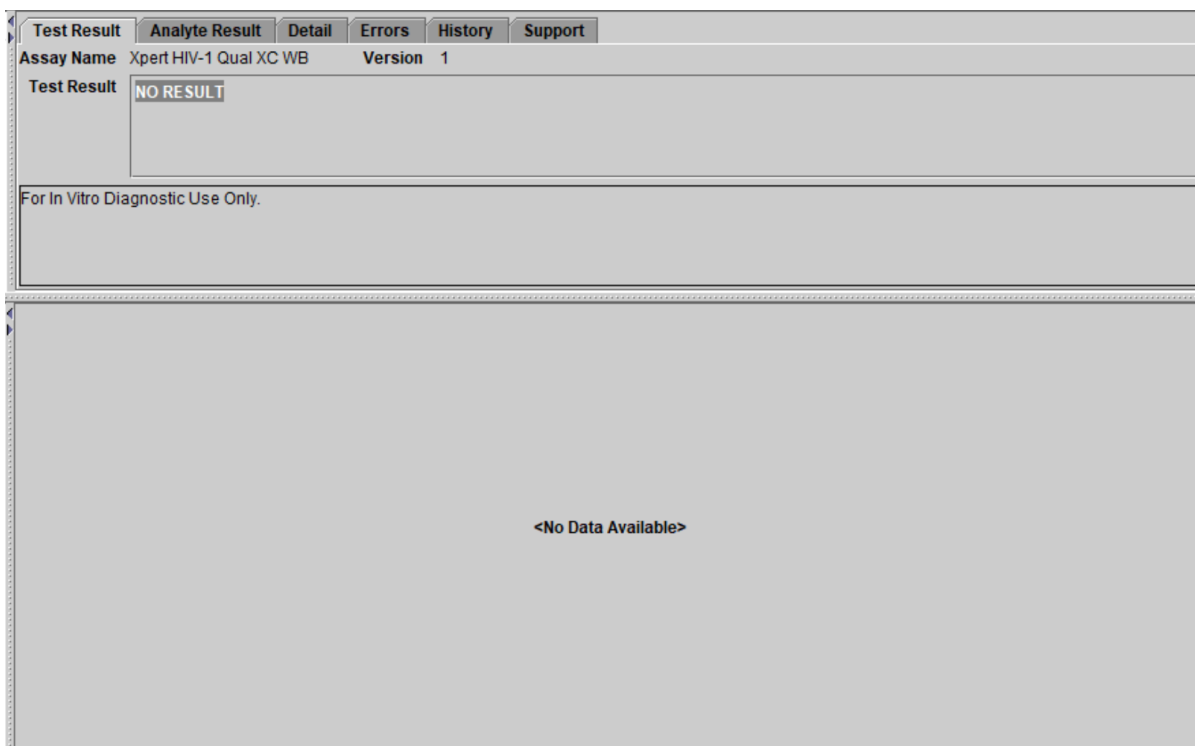


Figure 14. No Result as displayed on GeneXpert Dx System and GeneXpert Infinity System

18 Retesting

18.1 Reasons to Repeat the Test

If any of the test results mentioned below occur, repeat the test according to instructions in Section 18.2.

- An **INVALID** result indicates one or more of the following:
 - The control SPC failed. The sample was not properly processed, or the PCR was inhibited. The cartridge might have been stored longer than its shelf life, or at elevated temperatures.
 - The control SAC failed. An incorrect or no sample was added, or the wrong ADF may have been used for DBS.
- An **ERROR** result indicates that the test was aborted. Possible causes include: 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.

18.2 Retest Procedure

If the result of a test is **INVALID**, **ERROR**, or **NO RESULT**, use a new cartridge to retest the affected sample (do not re-use the cartridge).

1. Remove a new cartridge from the kit.
2. Start another test:
 - For the GeneXpert Dx System, see Section 13.
 - For the GeneXpert Edge System, see Section 14.
 - For the GeneXpert Infinity System, see Section 15.

19 Limitations

- Good laboratory practice and changing gloves between handling samples are recommended to avoid contamination of samples or reagents.
- The performance of the Xpert HIV-1 Qual XC was validated using the procedures provided in this package insert only. Modifications to these procedures may alter the performance of the test.
- Rare mutations, deletions or insertions within the target region of the Xpert HIV-1 Qual XC test may affect primer and/or probe binding resulting in failure to detect the virus.
- The Xpert HIV-1 Qual XC test has been validated only for use with capillary and venous whole blood and with DBS specimens. Testing of other specimen types with this test may lead to inaccurate results.
- The Xpert HIV-1 Qual XC test has been validated only for use with K2 EDTA tubes. Usage of other tubes than K2 EDTA tubes may lead to inaccurate results.
- Proper performance of this test requires appropriate specimen collection, storage, handling, and transport to the test site.
- A negative test result with the Xpert HIV-1 Qual XC test does not preclude HIV-1 infection. Results from the Xpert HIV-1 Qual XC test should be interpreted in conjunction with clinical presentation and other laboratory markers.
- The Xpert HIV-1 Qual XC test is not intended for the screening of blood, plasma, serum, or tissue donations for HIV-1.
- False negative results may occur if virus is present at levels below the analytical limit of detection.
- The effect of interfering substances has only been evaluated for those listed within the labeling. Interference by substances other than those described can lead to erroneous results.
- Detection of HIV-1 is dependent on the number of virus particles present in a sample and may be affected by sample collection methods, patient factors (i.e., age, presence of symptoms), and/or stage of infection.
- A sample that yields an INVALID result twice may contain an inhibitor; retesting is not recommended.
- Whole blood that has clotted or coagulated may lead to errors or invalid results.
- The Xpert HIV-1 Qual XC test has not been evaluated in those receiving pre-exposure prophylaxis (PrEP).
- HIV may be undetectable by the Xpert HIV-1 Qual XC test in those receiving ART.
- The Xpert HIV-1 Qual XC test is intended to aid in the diagnosis of HIV-1 infection and should not be used in isolation but in conjunction with clinical presentation and other laboratory markers.
- 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.

20 Performance Characteristics

20.1 Clinical Performance

Performance characteristics of the Xpert HIV-1 Qual XC test were evaluated at six laboratories or near patient test sites in the Republic of South Africa, Lesotho, Italy, and the United States. Study participants included newborns (28.1%; 0 to 28 days), infants (28.4%; >28 days to 18 months), children (0.7%; >18 months to 9 years), adolescents (1.3%; 10 years to <18 years) and adults (41.4%; ≥18 years), for whom there was clinical suspicion of HIV-1 infection, who were considered at a high risk for HIV-1 infection, and/or for whom a clinician ordered an HIV-1 test. Specimen types included archived or freshly collected dried blood spots (DBS) leftover from standard of care testing, prospectively collected EDTA venous and capillary whole blood (WB), and DBS from fresh prospectively collected EDTA venous and capillary WB (fingerstick or heel stick).

The Xpert HIV-1 Qual XC test performance was compared to a CE-marked nucleic acid amplification test (NAAT).

A total of 675 DBS specimens, 286 venous WB specimens, and 259 capillary WB specimens were tested with the Xpert HIV-1 Qual XC test and the comparator test. The Xpert HIV-1 Qual XC test demonstrated positive percent agreement (PPA) of 97.8% (95%CI: 93.7-99.2), 100.0% (95%CI: 74.1-100.0), and 100.0% (95%CI: 70.1-100.0) for DBS, venous WB, and capillary WB specimens, respectively. The Xpert HIV-1 Qual XC test demonstrated negative percent agreement (NPA) of 99.4% (95%CI: 98.4-99.8), 98.9% (95%CI: 96.8-99.6), and 99.2% (97.1-99.8) for DBS, venous WB, and capillary WB specimens, respectively. Results are shown Table 2.

Table 2. Xpert HIV-1 Qual XC Test vs. Comparator NAAT

| Xpert HIV-1 Qual XC vs. Comparator NAAT | N | TP | FN | TN | FP | PPA (95%CI) | NPA (95%CI) |
|---|-----|-----|----------------|-----|----------------|------------------------|----------------------|
| DBS | 675 | 133 | 3 ^a | 536 | 3 ^b | 97.8% (93.7-99.2) | 99.4% (98.4-99.8) |
| Venous Whole Blood | 286 | 11 | 0 | 272 | 3 ^c | 100.0% (74.1-100.0) | 98.9% (96.8-99.6) |
| Capillary Whole Blood | 259 | 9 | 0 | 248 | 2 ^d | 100.0% (70.1-100.0) | 99.2% (97.1-99.8) |

^a 3/3 insufficient volume available to perform repeat testing by the comparator NAAT; 1/3 result from Xpert HIV-1 Qual XC repeat test positive.

^b 2/3 insufficient volume available to perform repeat testing by the comparator NAAT; 1/3 result from comparator NAAT repeat test negative.

^c 3/3 results from comparator NAAT repeat testing were negative.

^d 2/2 results from comparator NAAT repeat testing were negative.

20.2 Specificity in Seronegative Adult Blood Donors

A total of 500 paired DBS and venous WB specimens from an adult seronegative blood donor population were tested for HIV-1 by the Xpert HIV-1 Qual XC test and the results were compared to the standard of care HIV screening tests which included anti-HIV antibody and antigen testing as well as a NAAT. The Xpert HIV-1 Qual XC test yielded **HIV-1 NOT DETECTED** results for all of the 500 DBS specimens and all of the 500 venous WB specimens. The specificity for each specimen type was 100.0% (95%CI: 99.2-100.0).

20.3 Non-determinate Rate

A total of 1242 specimens were tested by the Xpert HIV-1 Qual XC test (680 DBS, 288 venous WB, and 274 capillary WB) of which 1183 were valid upon initial testing (95.2%) and 59 (4.8%) were non-determinate. Of the 59 specimens with non-determinate results, 58 yielded valid results upon repeat test. The final non-determinate rate of the Xpert HIV-1 Qual XC test was 0.1% (1/1242).

21 Analytical Performance

21.1 Limit of Detection

The limit of detection (LoD) of the Xpert HIV-1 Qual XC test was determined by probit analysis for group M subtype B for both sample types (Whole Blood and DBS) by testing two serial dilution panels prepared from the 4th WHO International Standard for HIV-1 (NIBSC code: 16/194) in HIV-1 negative K2 EDTA whole blood. Each serial dilution panel consisted of in total eight different concentration levels of the WHO International Standard and one negative. Each concentration level of each serial dilution panel was tested across three days for a total of 24 replicates using one kit lot of the Xpert HIV-1 Qual XC test. Different kit lots was used for each of the two serial dilution panels. The LoD results for HIV-1 group M subtype B are shown in Table 3 and Table 4.

The conversion factor for 4th WHO HIV-1 International Standard (NIBSC code 16/194)¹⁴ in the Xpert HIV-1 Qual XC test is 1 copy = 2.06 International Units (IU).

Table 3. Limit of Detection in whole blood for the Xpert HIV-1 Qual XC test using the 4th WHO International Standard for HIV-1

| Group/Subtype | Nominal HIV-1 Concentration (copies/mL) | Number of Valid Replicates | Number of Positive Replicates | Positivity Rate (%) | LoD with 95% Probability Estimated by Probit (95% Confidence Interval) |
|---|---|----------------------------|-------------------------------|---------------------|--|
| Group M/ Subtype B (Panel 1) | 300 | 24 | 24 | 100.0 | 135.7 copies/mL (110.2-161.1) |
| | 200 | 24 | 23 | 95.8 | |
| | 135 | 24 | 23 | 95.8 | |
| | 90 | 24 | 19 | 79.2 | |
| | 60 | 24 | 18 | 75.0 | |
| | 40 | 24 | 10 | 41.7 | |
| | 25 | 24 | 6 | 25.0 | |
| | 15 | 24 | 6 | 25.0 | |
| Group M/ Subtype B (Panel 2) | 300 | 24 | 24 | 100.0 | 161.6 copies/mL (135.0-188.2) |
| | 200 | 24 | 22 | 91.7 | |
| | 135 | 24 | 22 | 91.7 | |
| | 90 | 24 | 17 | 70.8 | |
| | 60 | 24 | 14 | 58.3 | |
| | 40 | 24 | 6 | 25.0 | |
| | 25 | 24 | 2 | 8.3 | |
| | 15 | 24 | 2 | 8.3 | |

Table 4. Limit of Detection in Dried Blood Spots for the Xpert HIV-1 Qual XC test using the 4th WHO International Standard for HIV-1

| Group/Subtype | Nominal HIV-1 Concentration (copies/mL) | Number of Valid Replicates | Number of Positive Replicates | Positivity Rate (%) | LoD with 95% Probability Estimated by Probit (95% Confidence Interval) |
|---|---|----------------------------|-------------------------------|---------------------|--|
| Group M/ Subtype B (Panel 1) | 1000 | 24 | 24 | 100.0 | 450.4 copies/mL (354.2-546.6) |
| | 650 | 24 | 24 | 100.0 | |
| | 400 | 24 | 21 | 87.5 | |
| | 250 | 24 | 15 | 62.5 | |
| | 150 | 24 | 10 | 41.7 | |
| | 100 | 24 | 14 | 58.3 | |
| | 60 | 24 | 6 | 25.0 | |
| | 40 | 24 | 4 | 16.7 | |
| Group M/ Subtype B (Panel 2) | 1000 | 24 | 23 | 95.8 | 706.4 copies/mL (571.8-841.1) |
| | 650 | 24 | 23 | 95.8 | |
| | 400 | 24 | 16 | 66.7 | |
| | 250 | 24 | 12 | 50.0 | |
| | 150 | 24 | 11 | 45.8 | |
| | 100 | 24 | 6 | 25.0 | |
| | 60 | 24 | 4 | 16.7 | |
| | 40 | 24 | 1 | 4.2 | |

The limit of detection in whole blood for the HIV-1 group M subtypes A, C, D, F, G, H, J, K, CRF-A/B, CRF-A/E, CRF-A/G, CRF-B/C, group N, group O and group P was determined by testing serial dilutions of cell culture stocks or clinical specimens representing each HIV-1 group and subtype in HIV-1 negative K2 EDTA whole blood. In total 5 to 9 concentration levels of each HIV-1 group and subtype was tested with one kit lot across three days for a total of 24 replicates per concentration level.

The assignment of the nominal concentration of the cell culture stocks and clinical specimens was determined using CE-marked HIV-1 viral load tests.

The HIV-1 RNA concentration that can be detected with a positivity rate of 95% was determined by PROBIT regression. The results for each HIV-1 group M subtypes A, C, D, F, G, H, J, K, CRF-A/B, CRF-A/E, CRF-A/G, CRF-B/C, group N, group O and group P are shown in Table 5.

Table 5. Limit of Detection in whole blood for the Xpert HIV-1 Qual XC test using cell culture stocks and clinical specimens

| Group | Subtype | LoD by PROBIT (copies/mL) | 95% Confidence Interval (copies/mL) |
|----------------|------------|---------------------------|-------------------------------------|
| Group M | A | 98.1 | 84.4-111.7 |
| | C | 70.1 | 55.4-84.9 |
| | D | 69.1 | 54.4-83.9 |
| | F | 96.8 | 74.2-119.4 |
| | G | 90.7 | 72.5-108.8 |
| | H | 150.9 | 114.6-187.3 |
| | J | 124.6 | 91.7-157.6 |
| | K | 151.7 | 114.3-189.1 |
| | CRF A/B | 147.8 | 115.1-180.6 |
| | CRF A/E | 128.2 | 94.8-161.6 |
| | CRF A/G | 108.4 | 81.1-135.7 |
| | CRF B/C | 141.8 | 133.1-170.5 |
| Group N | N/A | 121.2 | 93.3-149.1 |
| Group O | N/A | 191.5 | 150.2-232.9 |
| Group P | N/A | 101.7 | 80.6-122.7 |

21.2 Verification of the Limit of Detection

The limit of detection for both sample types (whole blood and DBS) was verified for HIV-1 Group M, subtypes A, B, C, D, F, G, H, J, K, Circulating Recombinant Forms ,CRF-A/B, CRF-A/E, CRF-A/G, CRF-B/C, HIV-1 group N, HIV-1 group O and HIV-1 group P by testing dilutions of up to 13 cell culture stocks or clinical specimens representing each HIV-1 group and subtype in HIV-1 negative K2 EDTA whole blood. Each cell culture stock or clinical specimen was tested with at least 10 replicates using one kit lot of the Xpert HIV-1 Qual XC test.

The assignment of the nominal concentration of the cell culture stocks and clinical specimens was determined using CE marked HIV-1 viral load tests.

The limit of detection for the Xpert HIV-1 Qual XC test was verified at a concentration of 200 copies/mL or lower for whole blood and 900 copies/ml or lower for DBS, depending on HIV-1 group and subtype. The results are shown in Table 6 and Table 7.

The Xpert HIV-1 Qual XC limit of detection was determined to 200 copies/ml for whole blood and 900 copies/ml for DBS.

Table 6. LoD Verification in Whole Blood

| HIV-1 Subtype / Group | No of cellculture stocks/ clinical specimens | No of valid replicates | No of Reactive replicates | Conc. (cp/ml) | Reactive % | Acceptance criteria based on CLSI EP17-A2 |
|-----------------------|--|------------------------|---------------------------|---------------|------------|---|
| B | 13 | 140 | 132 | 200 | 94.3 | 92 |
| C | 13 | 130 | 121 | 200 | 93.1 | 92 |
| A | 4 | 40 | 37 | 200 | 90.0 | 88 |
| D | 4 | 40 | 38 | 160 | 95.0 | 88 |
| F | 4 | 40 | 36 | 200 | 90.0 | 88 |
| G | 4 | 40 | 37 | 160 | 92.5 | 88 |
| H | 4 | 40 | 39 | 155 | 97.5 | 88 |
| J ^a | 3 | 40 | 39 | 200 | 97.5 | 88 |
| K | 4 | 40 | 36 | 152 | 90.0 | 88 |
| AB ^a | 0 | NA | NA | 148 | NA | 85 ^b |
| AE | 4 | 40 | 37 | 200 | 92.5 | 88 |
| AG | 4 | 40 | 38 | 173 | 95.0 | 88 |
| BC | 4 | 40 | 37 | 142 | 92.5 | 88 |
| N ^a | 1 | 10 | 10 | 200 | 100.0 | 85 ^b |
| O | 4 | 40 | 40 | 192 | 100.0 | 88 |
| P ^a | 1 | 10 | 10 | 102 | 100.0 | 85 ^b |

^a LoD have been verified using fewer than 5 specimens. For recombinant A/B no additional specimen was available for verification.

^b In the case of 20 or fewer measurements, a criterium of 85 % hit rate was used.

Table 7. LoD Verification in Dried Blood Spots

| HIV-1 Subtype / Group | No of cellculture stocks/ clinical specimens | No of valid replicates | No of Reactive replicates | Conc. (cp/ml) | Reactive % | Acceptance criteria based on CLSI EP17-A2 |
|-----------------------|--|------------------------|---------------------------|---------------|------------|---|
| B | 13 | 140 | 139 | 900 | 99.3 | 92 |
| C | 14 | 140 | 131 | 900 | 93.6 | 92 |
| A | 5 | 50 | 45 | 900 | 90.0 | 88 |
| D | 5 | 50 | 46 | 900 | 92.0 | 88 |
| F | 5 | 50 | 45 | 900 | 90.0 | 88 |
| G | 5 | 50 | 46 | 699 | 92.0 | 88 |
| H | 5 | 50 | 49 | 678 | 98.0 | 88 |
| J ^a | 3 | 40 | 39 | 900 | 97.5 | 88 |
| K | 5 | 50 | 48 | 900 | 96.0 | 88 |
| AB ^a | 1 | 10 | 9 | 646 | 90.0 | 85 ^b |
| AE | 5 | 50 | 45 | 560 | 90.0 | 88 |
| AG | 5 | 50 | 45 | 758 | 90.0 | 88 |
| BC | 5 | 50 | 45 | 621 | 90.0 | 88 |
| N ^a | 2 | 20 | 17 | 900 | 85.0 | 85 ^b |
| O | 5 | 50 | 49 | 837 | 98.0 | 88 |
| P ^a | 1 | 20 | 19 | 445 | 95.0 | 85 ^b |

^a LoD have been verified using fewer than 5 specimens.

^b In the case of 20 or fewer measurements, a criterium of 85 % hit rate was used.

21.3 Analytical Reactivity (Inclusivity)

In addition to verification of the limit of detection, the ability of the Xpert HIV-1 Qual XC test to detect HIV-1 groups and subtypes was demonstrated by testing additional unique cell culture stocks and clinical specimens representing HIV-1 group M, Subtypes A, D, F, G, H, K, Circulating Recombinant Forms, CRF-A/E, CRF-A/G, CRF-B/C, CRF-06 and HIV-1 Group O.

Each cell culture stock and clinical specimen was diluted to a concentration of 600 copies/mL (3xLoD) in K2 EDTA whole blood and one replicate was tested with one kit lot of the Xpert HIV-1 Qual XC test. The results are shown in Table 8.

Table 8. Analytical Reactivity (Inclusivity)

| Subtype / Group | Number of cell culture stocks / clinical specimens | Number of valid replicates | Number of reactive replicates |
|-----------------|--|----------------------------|-------------------------------|
| A | 5 | 5 | 5 |
| D | 5 | 5 | 5 |
| F | 5 | 5 | 5 |
| G | 5 | 5 | 5 |
| H | 5 | 5 | 5 |
| K | 3 | 3 | 3 |
| CRF-A/E | 5 | 5 | 5 |
| CRF-A/G | 5 | 5 | 5 |
| CFR-B/C | 1 | 1 | 1 |
| CRF-06 | 1 | 1 | 1 |
| O | 5 | 5 | 5 |

21.4 Measuring Range

The measuring range of the Xpert HIV-1 Qual XC test was determined by analysis of a five-member panel each for both sample types whole blood and DBS ranging from 600 to 1×10^7 copies/mL and from 2700 to 1×10^7 copies/mL respectively.

The two five-member panels (whole blood and DBS) were prepared by parallel dilutions of HIV-1 reference material (HIV-1 subtype B) in HIV-1 negative K2 EDTA whole blood. The reference material used was calibrated to the WHO 4th International standard for HIV-1 (NIBSC code: 16/194). Each of the two five-member panels (whole blood and DBS) was tested using one kit lot of the HIV-1 Qual XC test with 6 replicates per panel member.

The results from the whole blood and DBS panel are presented in Figure 15 and Figure 16. The Xpert HIV-1 Qual XC test is linear within a range from 600 copies/mL to 1×10^7 copies/mL with an R^2 0.998 for WB and within a range from 2700 copies/mL to 1×10^7 copies/mL with an R^2 0.967 for DBS.

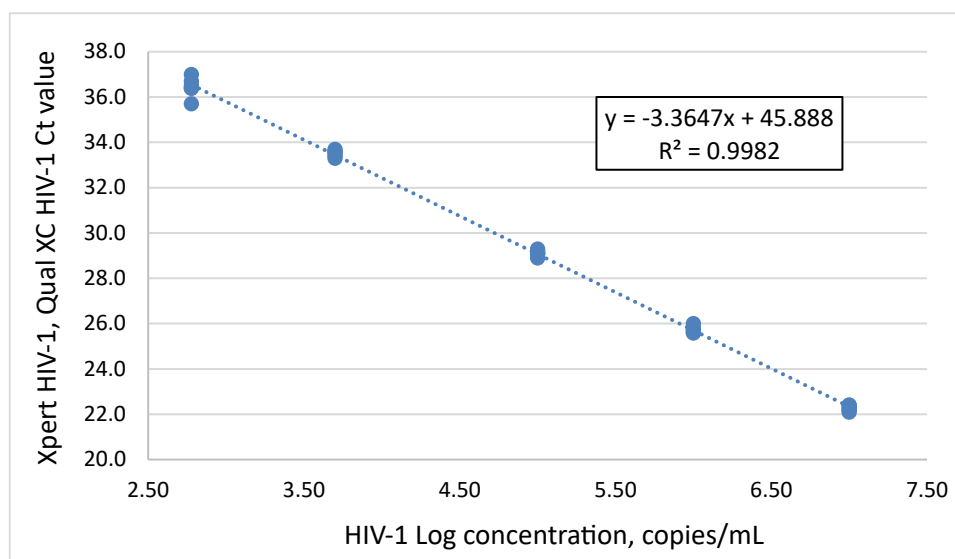


Figure 15. Linearity In Whole Blood for the Xpert HIV-1 Qual XC test

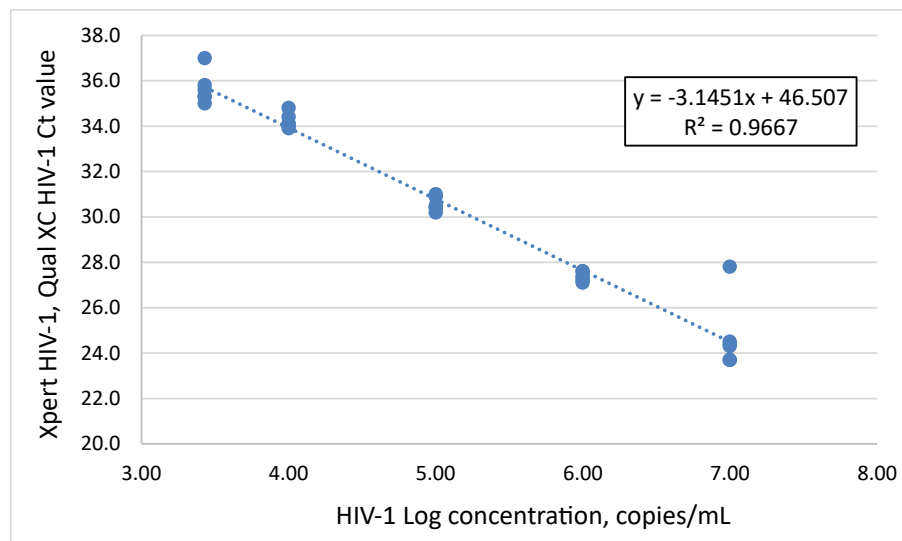


Figure 16. Linearity In Dried Blood Spots for the Xpert HIV-1 Qual XC test

21.5 Analytical Specificity (Exclusivity)

The analytical specificity of the Xpert HIV-1 Qual XC test was evaluated by adding potentially cross-reactive or interfering organisms at a concentration of 1×10^5 CFU/mL for microorganisms, or $\geq 1 \times 10^5$ copies/mL or TCID₅₀/mL for viruses into HIV-1 negative K2 EDTA whole blood and K2 EDTA whole blood containing HIV-1 reference material at a concentration of 600 copies/mL (3xLoD). The HIV-1 reference material used was calibrated to the 4th WHO International standard for HIV-1 (NIBSC code: 16/194). Tested organisms are shown in Table 9. None of the tested organisms showed cross-reactivity or interfered with the detection of HIV-1.

Table 9. Analytical Specificity Organisms

| Virus | Bacteria | Fungi/Yeast | Parasites |
|--------------------------------|------------------------------------|-------------------------------|-----------------------|
| Chikungunya virus | <i>Mycobacterium tuberculosis</i> | <i>Candida Albicans</i> | Leishmania Major |
| Cytomegalovirus | <i>Propionibacterium acnes</i> | <i>Candida Glabrata</i> | Plasmodium Falciparum |
| Epstein-Barr virus | <i>Staphylococcus aureus</i> | <i>Candida Tropicalis</i> | Trypanosoma brucei |
| Hepatitis A virus | <i>Staphylococcus epidermidis</i> | <i>Pneumocystis jirovecii</i> | Trypanosoma cruzi |
| Hepatitis B virus | <i>Staphylococcus haemolyticus</i> | | |
| Hepatitis C virus | | | |
| Herpes simplex virus 1 | | | |
| Herpes simplex virus 2 | | | |
| Human Herpesvirus 6 | | | |
| Human Immunodeficiency virus 2 | | | |
| Human Papillomavirus | | | |

| Virus | Bacteria | Fungi/Yeast | Parasites |
|--|----------|-------------|-----------|
| Human T-cell lymphotropic virus type 1 | | | |
| Human T-cell lymphotropic virus type 2 | | | |
| Influenza virus A | | | |

21.6 Potentially Interfering Substances

The susceptibility of the Xpert HIV-1 Qual XC test to interference by elevated levels of endogenous substances, by drugs prescribed to HIV-1 infected patients or for those who may have co-infections or other co-morbidity, and autoimmune disease markers was evaluated. The inhibitory effects were evaluated in presence and absence of HIV-1 reference material at a concentration of approximately 3xLoD. The HIV-1 reference material used was calibrated to the WHO 4th International standard for HIV-1 (NIBSC code: 16/194).

Elevated levels of the endogenous substances shown in Table 10 were shown to not interfere with the detection of HIV-1 or impact the specificity of the Xpert HIV-1 Qual XC test when tested in presence and absence of HIV-1.

Table 10. Endogenous Substances and Concentration Tested

| Substance | Tested Concentration |
|--------------------------|----------------------|
| Albumin | 9.6 g/dL |
| Bilirubin | 62 mg/dL |
| Hemoglobin | 20 g/L |
| Human DNA | 0.4 mg/dL |
| Triglycerides | 3200 mg/dL |
| White blood Cells (WBCs) | 1.70E+09 cells/dL |

The drug components as shown in Table 11 were shown to not interfere with the detection of HIV-1 or impact the specificity of the Xpert HIV-1 Qual XC test when tested at three times peak level concentration (C_{max}) in the presence and absence of HIV-1.

Table 11. Drug Pools Tested

| Pool | Drugs |
|------|--|
| 1 | Atazanavir , Abacavir sulfate, Bictegravir, Cidofovir |
| 2 | Darunavir, Dolutegravir, Doravirine, Efavirenz |
| 3 | Emtricitabine, Lamivudine. 3TC, Lopinavir, Maraviroc |
| 4 | Nevirapine , Raltegravir, Tenofovir disoproxil fumarate, Zidovudine |
| 5 | Daclatasvir, Dasabuvir. ABT-333, Grazoprevir, Pibrentasvir, Sofosbuvir |
| 6 | Ombitasvir, Paritaprevir, Ribavirin, Simeprevir, Velpatasvir |
| 7 | Interferon alfa-2b, Peginterferon 2a, Adefovir dipivoxil, Entecavir, Telbivudine |
| 8 | Acyclovir, Foscarnet, Ganciclovir, Valganciclovir HCl |
| 9 | Azithromycin, Ciprofloxacin, Clarithromycin |
| 10 | Acetaminophen, Acetylsalicylic acid, Atorvastatin, Loratadine |
| 11 | Nadolol, Ascorbic acid, Phenylephrine, Ibuprofen |
| 12 | Artemether, Desethylamodiaquine, Mefloquine, Quinine |

| Pool | Drugs |
|------|---|
| 13 | Primaquine, Chloroquine, Doxycycline |
| 14 | Rifampin, INH, Ethambutol, Pyrazinamide |
| 15 | Moxifloxacin, Levofloxacin, Amikacin, Bedaquiline ^a |
| 16 | Trimethoprim / Sulfamethoxazole, Gentamicin, Metronidazole, Ceftriaxone |

^a Tested separately

Testing of whole blood specimens from individuals positive for each of the autoimmune disease markers; systemic lupus erythematosus (SLE), anti-nuclear antibodies (ANA) or rheumatoid factor (RF) were shown to not interfere with the detection of HIV-1 or impact the specificity of the Xpert HIV-1 Qual XC test when tested in presence and absence of HIV-1.

21.7 Seroconversion Sensitivity

The sensitivity of the Xpert HIV-1 Qual XC test was evaluated by testing sequential plasma specimens from twelve seroconversion panels. The Xpert HIV-1 Qual XC test detected HIV-1 RNA in 44 out of 61 specimens compared to 11 out of 61 that were detected by at least one HIV-1 antibody test (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 HIV 1/O/2 Enhanced ADVIA Centaur). A HIV-1 positive test result was generated earlier with the Xpert HIV-1 Qual XC test in all twelve panels as compared to the HIV-1 antibody screening test. The seroconversion sensitivity is shown in Table 12.

Table 12. Seroconversion Sensitivity

| Panel No. | Number of panel members | Days Spanned | Number of Reactive panel members | | | Days to first reactive result | | | Days between first reactive result with Xpert HIV-1 Qual XC and any AB-test |
|-----------|-------------------------|--------------|----------------------------------|----------------------------|-------------------------------|-------------------------------|----------------------------|-------------------------------|---|
| | | | Xpert HIV-1 Qual XC | Antibody test ^a | Antigen p24 test ^b | Xpert HIV-1 Qual XC | Antibody test ^a | Antigen p24 test ^b | |
| PRB945 | 6 | 20 | 4 | 3 | 4 | 7 | 13 | 7 | 6 |
| PRB950 | 4 | 28 | 3 | 1 | 3 | 18 | 28 | 18 | 10 |
| PRB955 | 5 | 14 | 5 | 2 | 4 | 0 ^c | 12 | 3 | 12 |
| PRB956 | 5 | 50 | 4 | 1 | 2 | 40 | 50 | 47 | 10 |
| PRB962 | 6 | 17 | 4 | 0 | 2 | 7 | 17 ^d | 14 | >10 |
| PRB963 | 7 | 21 | 3 | 0 | 2 | 14 | 21 ^d | 17 | >7 |
| PRB973 | 4 | 11 | 4 | 1 | 2 | 0 ^c | 11 | 7 | 11 |
| PRB974 | 4 | 16 | 3 | 1 | 2 | 7 | 16 | 9 | 9 |
| PRB975 | 5 | 14 | 3 | 0 | 1 | 7 | 14 ^d | 14 | >7 |
| PRB976 | 4 | 9 | 4 | 0 | 2 | 0 ^c | 9 ^d | 7 | >9 |
| PRB977 | 4 | 15 | 4 | 2 | 2 | 0 ^c | 13 | 13 | 13 |
| PRB978 | 7 | 33 | 3 | 0 | 1 | 26 | 33 ^d | 33 | >7 |

^a Antibody test 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 HIV 1/O/2 Enhanced ADVIA Centaur

^b Antigen p24 test based on vendor data: Coulter HIV-1 p24 Antigen, Perkin Elmer Alliance HIV-1 p24 ELISA

^c All bleeds were detected with the Xpert HIV-1 Qual XC test.

^d All bleeds were non-reactive for HIV antibodies (based on vendor information). The last bleed day is used to determine “days to first reactive result”.

21.8 Whole System Failure Rate

The whole system failure rate for the Xpert HIV-1 Qual XC test was determined by testing 10 unique HIV-1 subtype B specimen diluted in K2 EDTA whole blood to a target concentration of 600 copies/mL (3xLoD) and tested in replicates of 10 by one user using one kit lot of the Xpert HIV-1 Qual XC test.

The results of this study showed that all 100 replicates were valid and reported HIV-1 positive, resulting in a whole system failure rate of 0%.

21.9 Carry Over Contamination

A high titer HIV-1 positive specimen (1 x 10⁷ copies/mL) was tested, immediately followed by testing a HIV-1 negative specimen in the same GeneXpert instrument module. The procedure was repeated twenty (20) times in two different modules for both whole blood and DBS sample type. The carryover rate for the Xpert HIV-1 Qual XC test was 0%.

22 Reproducibility and Precision

The reproducibility and precision of the Xpert HIV-1 Qual XC test was determined for both DBS and WB specimens using 15 panel members. Testing was performed at 3 sites. The positive panel members were prepared by using HIV-1 material spiked into K2-EDTA HIV-1 negative whole blood to target concentrations of ~1xLoD, ~3xLoD, and ~5-7xLoD. The negative panel members were prepared from HIV-1 negative K2-EDTA whole blood. Each panel member was tested in replicates of 2 twice per day by two operators over 6 days. Six different kit lots were used.

The data were analyzed by calculating the qualitative percent agreement for each panel member. Results of the DBS panel members are shown in Table 13 and the results of the WB panel members are shown in Table 14. Per poolability analyses, there were no significant differences in results across the study sites or kit lots. The percent agreement and lack of statistically significant differences demonstrate acceptable reproducibility and precision performance.

Table 13. Percent Agreement of Qualitative Results for HIV-1 Detection – DBS Panel Members

| Panel Member | Site 1 | | | Site 2 | | | Site 3 | | | Total Agreement by Panel Member (n/ N) and 95% CI |
|---|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|---|
| | Op1 | Op2 | Site | Op1 | Op2 | Site | Op1 | Op2 | Site | |
| DBS Moderate Positive ~5-7xLoD 1 | 100.0% (24/24) | 100.0% (24/24) | 100.0% (48/48) | 100.0% (24/24) | 100.0% (24/24) | 100.0% (48/48) | 100.0% (24/24) | 100.0% (24/24) | 100.0% (48/48) | 100.0% (144/144) 97.4-100.0 |
| DBS Moderate Positive ~5-7xLoD 2 | 100.0% (24/24) | 100.0% (24/24) | 100.0% (48/48) | 100.0% (24/24) | 100.0% (24/24) | 100.0% (48/48) | 100.0% (24/24) | 100.0% (24/24) | 100.0% (48/48) | 100.0% (144/144) 97.4-100.0 |
| DBS Low Positive ~3xLoD 1 | 100.0% (24/24) | 100.0% (24/24) | 100.0% (48/48) | 100.0% (24/24) | 100.0% (24/24) | 100.0% (48/48) | 100.0% (24/24) | 100.0% (24/24) | 100.0% (48/48) | 100.0% (144/144) 97.4-100.0 |
| DBS Low Positive ~3xLoD 2 | 100.0% (24/24) | 100.0% (24/24) | 100.0% (48/48) | 100.0% (24/24) | 100.0% (24/24) | 100.0% (48/48) | 100.0% (24/24) | 100.0% (24/24) | 100.0% (48/48) | 100.0% (144/144) 97.4-100.0 |
| Negative DBS 1 | 100.0% (24/24) | 100.0% (24/24) | 100.0% (48/48) | 100.0% (24/24) | 100.0% (24/24) | 100.0% (48/48) | 100.0% (24/24) | 100.0% (24/24) | 100.0% (48/48) | 100.0% (144/144) 97.4-100.0 |
| DBS Low Positive ~1xLoD 1 | 100.0% (24/24) | 95.8% (23/24) | 97.9% (47/48) | 83.3% (20/24) | 91.7% (22/24) | 87.5% (42/48) | 95.8% (23/24) | 91.7% (22/24) | 93.8% (45/48) | 93.1% (134/144) 87.7-96.2 |

| Panel Member | Site 1 | | | Site 2 | | | Site 3 | | | Total Agreement by Panel Member (n/N) and 95% CI |
|----------------|-------------------|-------------------|-------------------|------------------|-------------------|------------------|-------------------|-------------------|-------------------|--|
| | Op1 | Op2 | Site | Op1 | Op2 | Site | Op1 | Op2 | Site | |
| Negative DBS 2 | 100.0% (24/24) | 100.0% (24/24) | 100.0% (48/48) | 95.8% (23/24) | 100.0% (24/24) | 97.9% (47/48) | 100.0% (24/24) | 100.0% (24/24) | 100.0% (48/48) | 99.3% (143/144) 96.2-99.9 |

Table 14. Percent Agreement of Qualitative Results for HIV-1 Detection – WB Panel Members

| Panel Member | Site 1 | | | Site 2 | | | Site 3 | | | Total Agreement by Panel Member (n/N) and 95% CI |
|---------------------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|--|
| | Op1 | Op2 | Site | Op1 | Op2 | Site | Op1 | Op2 | Site | |
| WB Moderate Positive ~5-7xLoD 1 | 100.0% (24/24) | 100.0% (24/24) | 100.0% (48/48) | 100.0% (24/24) | 100.0% (24/24) | 100.0% (48/48) | 100.0% (24/24) | 100.0% (24/24) | 100.0% (48/48) | 100.0% (144/144) 97.4-100.0 |
| WB Moderate Positive ~5-7xLoD 2 | 100.0% (24/24) | 100.0% (24/24) | 100.0% (48/48) | 100.0% (24/24) | 100.0% (23/23) | 100.0% (47/47) | 100.0% (24/24) | 100.0% (24/24) | 100.0% (48/48) | 100.0% (143/143) 97.4-100.0 |
| WB Low Positive ~3xLoD 1 | 100.0% (24/24) | 100.0% (24/24) | 100.0% (48/48) | 10.00% (24/24) | 100.0% (24/24) | 100.0% (48/48) | 100.0% (24/24) | 100.0% (24/24) | 100.0% (48/48) | 100.0% (144/144) 97.4-100.0 |
| Negative WB 1 | 100.0% (24/24) | 100.0% (24/24) | 100.0% (48/48) | 100.0% (24/24) | 100.0% (24/24) | 100.0% (48/48) | 100.0% (24/24) | 100.0% (24/24) | 100.0% (48/48) | 100.0% (144/144) 97.4-100.0 |
| WB Low Positive ~3xLoD | 100.0% (24/24) | 100.0% (24/24) | 100.0% (48/48) | 100.0% (24/24) | 96.0% (23/24) | 98.0% (47/48) | 100.0% (24/24) | 100.0% (24/24) | 100.0% (48/48) | 99.3% (143/144) 96.2 – 99.9 |
| Negative WB 2 | 100.0% (24/24) | 100.0% (24/24) | 100.0% (48/48) | 100.0% (24/24) | 100.0% (24/24) | 100.0% (48/48) | 100.0% (24/24) | 100.0% (24/24) | 100.0% (48/48) | 100.0% (144/144) 97.4-100.0 |
| WB Low Positive ~1xLoD 3 | 100.0% (24/24) | 95.8% (23/24) | 97.9% (47/48) | 91.7% (22/24) | 83.3% (20/24) | 87.5% (42/48) | 100.0% (24/24) | 95.8% (23/24) | 97.9% (47/48) | 94.4% (136/144) 89.4-97.2 |
| Negative WB 3 | 100.0% (24/24) | 100.0% (24/24) | 100.0% (48/48) | 100.0% (24/24) | 100.0% (24/24) | 100.0% (48/48) | 100.0% (24/24) | 100.0% (24/24) | 100.0% (48/48) | 100.0% (144/144) 97.4-100.0 |

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25 Technical Assistance

Before Contacting Us

Collect the following information before contacting Cepheid Technical Support:

- Product name
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26 Table of Symbols

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



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27 Revision History

Description of Changes: 302-3767, Rev. E to Rev. F

| Section | Description of Change |
|------------|---|
| Throughout | Xpert HIV-1 Qual XC |
| 12.1 | Corrected error in Preparing the Cartridge section. |
| 25 | Corrected error in Technical Assistance section. |