Rx Only

cobas® HIV-1

Quantitative nucleic acid test for use on the cobas® 5800/6800/8800 Systems

For in vitro diagnostic use

cobas® HIV-1	P/N: 09040803190
For use on the cobas® 5800 System:	
cobas® HBV/HCV/HIV-1 Control Kit	P/N: 09040773190
cobas® NHP Negative Control Kit	P/N: 09051554190
For use on the cobas® 6800/8800 Systems:	
cobas® HBV/HCV/HIV-1 Control Kit	P/N: 06998887190 or P/N: 09040773190
cobas® NHP Negative Control Kit	P/N: 07002220190 or P/N: 09051554190

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Intended use

cobas® HIV-1 is an in vitro nucleic acid amplification test for the quantitation of human immunodeficiency virus type 1 (HIV-1) in EDTA plasma of HIV-1-infected individuals using the automated **cobas**® 5800/6800/8800 Systems for specimen processing, amplification and detection. The test can quantitate HIV-1 RNA over the range of 20-10,000,000 cp/mL (33 to 1.67 x 10^7 International Units/mL).

This test is intended for use in conjunction with clinical presentation and other laboratory markers for the clinical management of HIV-1 infected patients. The test can be used to assess patient prognosis by measuring the baseline HIV-1 level or to monitor the effects of antiretroviral therapy by measuring changes in HIV-1 RNA levels during the course of antiretroviral treatment.

cobas® HIV-1 is not intended for use as a screening test for the presence of HIV-1 in donated blood or plasma or as a diagnostic test to confirm the presence of HIV-1 infection.

Summary and explanation of the test

Background

Human immunodeficiency virus (HIV) is the etiologic agent of acquired immunodeficiency syndrome (AIDS). After seroconversion, infected individuals typically enter a clinically stable, relatively asymptomatic phase that can last for years. The asymptomatic period is characterized by persistent plasma viremia at set points determined by host genetics and a gradual depletion of CD4+ T lymphocytes. Although virus levels in the peripheral blood are relatively low during the asymptomatic phase of the infection, virus replication and clearance appear to be dynamic processes in which high rates of virus production and infection of CD4+ cells are balanced by high rates of virus clearance, death of infected cells and replenishment of CD4+ cells, resulting in relatively stable levels of both plasma viremia and CD4+ cells for approximately 8 years in the average person living with HIV.

Quantitative measurements of HIV viremia in the plasma have shown that higher virus levels are correlated with more rapid clinical progression of HIV disease.[1,2] Furthermore, nearly two decades of clinical research have established that reductions in plasma virus levels with the use of antiretroviral therapy (ART) significantly decrease the risk of clinical progression, including death, development of AIDS, opportunistic infections, and HIV-associated morbidity.[3] HIV viral load is also predictive of the risk of transmission of HIV, and randomized controlled clinical trials have established that early initiation of ART with suppression of the viral load reduces HIV transmission by 96%.[4]

Explanation of the test

cobas® HIV-1 is a quantitative test performed on the **cobas**® 5800 System, **cobas**® 6800 System and **cobas**® 8800 System. **cobas**® HIV-1 enables the detection and quantitation of HIV-1 RNA in EDTA plasma of infected patients. Two probes are used to detect and quantify, but not discriminate group M, N and O subtypes. The viral load is quantified against a non-HIV-1 armored RNA quantitation standard (RNA-QS), which is introduced into each specimen during sample processing. The RNA-QS functions as an internal control to monitor the entire sample preparation and PCR amplification process. In addition, the test utilizes three external controls: a high titer positive, a low titer positive, and a negative control.

Principles of the procedure

cobas® HIV-1 is based on fully automated sample preparation (nucleic acid extraction and purification) followed by PCR amplification and detection. The **cobas**® 5800 System is designed as one integrated instrument. The **cobas**® 6800/8800 Systems consist of the sample supply module, the transfer module, the processing module, and the analytic module. Automated data management is performed by the **cobas**® 5800 or **cobas**® 6800/8800 Systems software which assigns test results for all tests as target not detected, < LLoQ (lower limit of quantitation), > ULoQ (upper limit of quantitation) or HIV-1 RNA detected, a value in the linear range LLoQ ≤ x ≤ ULoQ. Results can be reviewed directly on the system screen, exported, or printed as a report.

Nucleic acid from patient samples, external controls and added armored RNA (RNA-QS) molecules is simultaneously extracted. In summary, viral nucleic acid is released by addition of proteinase and lysis reagent to the sample. The released nucleic acid binds to the silica surface of the added magnetic glass particles. Unbound substances and impurities, such as denatured protein, cellular debris and potential PCR inhibitors are removed with subsequent wash reagent steps and purified nucleic acid is eluted from the magnetic glass particles with elution buffer at elevated temperature.

Selective amplification of target nucleic acid from the sample is achieved by the use of target virus-specific forward and reverse primers which are selected from highly conserved regions of the HIV-1 genome. The HIV-1 gag gene and the HIV-1 LTR region (dual target) are amplified by **cobas**® HIV-1. Selective amplification of RNA-QS is achieved by the use of sequence-specific forward and reverse primers which are selected to have no homology with the HIV-1 genome. A thermostable DNA polymerase enzyme is used for both reverse-transcription and PCR amplification. The target and RNA-QS sequences are amplified simultaneously utilizing a PCR amplification profile with predefined temperature steps and number of cycles. The master mix includes deoxyuridine triphosphate (dUTP), instead of deoxythymidine triphosphate (dTTP), which is incorporated into the newly synthesized DNA (amplicon).[5-7] Any contaminating amplicons from previous PCR runs are eliminated by the AmpErase enzyme, which is included in the PCR master mix, during the first thermal cycling step. However, newly formed amplicons are not eliminated since the AmpErase enzyme is inactivated once exposed to temperatures above 55°C.

The **cobas**® HIV-1 master mix contains two detection probes specific for the HIV-1 target sequences and one for the RNA-QS. The probes are labeled with target specific fluorescent reporter dyes allowing simultaneous detection of HIV-1 target and RNA-QS in two different target channels.[8,9] When not bound to the target sequence, the fluorescent signal of the intact probes is suppressed by a quencher dye. During the PCR amplification step, hybridization of the probes to the specific single-stranded DNA template results in cleavage of the probe by the 5' to 3' exonuclease activity of the DNA polymerase resulting in separation of the reporter and quencher dyes and the generation of a fluorescent signal. With each PCR cycle, increasing amounts of cleaved probes are generated and the cumulative signal of the reporter dye increases concomitantly. Real-time detection and discrimination of PCR products is accomplished by measuring the fluorescence of the released reporter dyes for the viral targets and RNA-QS, respectively.

Reagents and materials

cobas® HIV-1 reagents and controls

The materials provided for **cobas®** HIV-1 can be found in Table 1. Materials required, but not provided can be found in Table 2 through Table 4, Table 9 and Table 10.

Refer to the **Reagents and materials** section and **Precautions and handling requirements** section for the hazard information for the product.

Table 1 cobas® HIV-1

(HIV-1)

Store at 2-8°C
192 test cassette (P/N 09040803190)

Kit components	Reagent ingredients	Quantity per kit 192 tests
Proteinase Solution (PASE)	Tris buffer, < 0.05% EDTA, calcium chloride, calcium acetate, 8% (w/v) proteinase, glycerol EUH210: Safety data sheet available on request. EUH208: Contains Subtilisin. May produce an allergic reaction.	22.3 mL
RNA Quantitation Standard (RNA-QS)	Tris buffer, < 0.05% EDTA, < 0.001% non-HIV related armored RNA construct containing primer and probe specific sequence regions (non-infectious RNA in MS2 bacteriophage), < 0.1% sodium azide	21.2 mL
Elution Buffer (EB)	Tris buffer, 0.2% methyl-4 hydroxybenzoate	21.2 mL
Master Mix Reagent 1 (MMX-R1)	Manganese acetate, potassium hydroxide, < 0.1% sodium azide	7.5 mL
HIV-1 Master Mix Reagent 2 (HIV-1 MMX-R2)	Tricine buffer, potassium acetate, 18% dimethyl sulfoxide, glycerol, < 0.1% Tween 20, EDTA, < 0.12% dATP, dCTP, dGTP, dUTPs, < 0.01% upstream and downstream HIV primers, < 0.01% Quantitation Standard forward and reverse primers, < 0.01% fluorescent-labeled oligonucleotide probes specific for HIV and the HIV Quantitation Standard, < 0.01% oligonucleotide aptamer, < 0.1% Z05D DNA polymerase, < 0.10% AmpErase (uracil-N-glycosylase) enzyme (microbial), < 0.1% sodium azide	9.7 mL

Table 2 cobas® HBV/HCV/HIV-1 Control Kit

(HBV/HCV/HIV-1 CTL)

Store at 2–8°C
For use on the **cobas**® 5800 System (P/N 09040773190)

For use on the **cobas**® 6800/8800 Systems (P/N 06998887190 or P/N 09040773190)

Kit components	Reagent ingredients	Quantity per kit	Safety symbol and warning*
HBV/HCV/HIV-1 Low Positive Control (HBV/HCV/HIV-1 L(+)C) Titer assignment for each analyte is lot specific with the following target concentrations: HBV Target: ~2.3 Log_{10} IU/mL HCV Target: ~2.3 Log_{10} IU/mL HIV-1 Target: ~2.6 Log_{10} cp/mL	< 0.001% armored HIV-1 Group M RNA (non-infectious RNA in MS2 bacteriophage), < 0.001% synthetic (plasmid) HBV DNA encapsulated in Lambda bacteriophage coat protein, < 0.001% synthetic (armored) HCV RNA encapsulated in MS2 bacteriophage coat protein, normal human plasma, non-reactive by licensed tests for antibody to HCV, antibody to HIV-1/2, HBsAg, antibody to HBc; HIV-1 RNA, HIV-2 RNA, HCV RNA, and HBV DNA not detectable by PCR methods. 0.1% ProClin® 300 preservative**	5.2 mL (8 x 0.65 mL)	 **WARNING** H317: May cause an allergic skin reaction. H412: Harmful to aquatic life with long lasting effects. P261: Avoid breathing dust/fume/gas/mist/ vapours/spray. P273: Avoid release to the environment. P280: Wear protective gloves. P333 + P313: If skin irritation or rash occurs: Get medical advice/attention. P362 + P364: Take off contaminated clothing and wash it before reuse. P501: Dispose of contents/container to an approved waste disposal plant. 55965-84-9 Reaction mass of: 5-chloro-2- methyl-4-isothiazolin-3-one [EC no. 247-500-7] and 2-methyl-2H - isothiazol-3- one [EC no. 220-239- 6] (3:1)
HBV/HCV/HIV-1 High Positive Control (HBV/HCV/HIV-1 H(+)C) Titer assignment for each analyte is lot specific with the following target concentrations: HBV Target: ~6.3 Log_{10} IU/mL HCV Target: ~6.3 Log_{10} IU/mL HIV-1 Target: ~5.3 Log_{10} cp/mL	< 0.001% armored HIV-1 Group M RNA (non-infectious RNA in MS2 bacteriophage), < 0.001% synthetic (plasmid) HBV DNA encapsulated in Lambda bacteriophage coat protein, < 0.001% synthetic (armored) HCV RNA encapsulated in MS2 bacteriophage coat protein, normal human plasma, non-reactive by licensed tests for antibody to HCV, antibody to HIV-1/2, HBsAg, antibody to HBc; HIV-1 RNA, HIV-2 RNA, HCV RNA, and HBV DNA not detectable by PCR methods. 0.1% ProClin® 300 preservative**	5.2 mL (8 x 0.65 mL)	 **WARNING** H317: May cause an allergic skin reaction. P261: Avoid breathing dust/fume/gas/mist/ vapours/spray. P272: Contaminated work clothing should not be allowed out of the workplace. P280: Wear protective gloves. P333 + P313: If skin irritation or rash occurs: Get medical advice/attention. P362 + P364: Take off contaminated clothing and wash it before reuse. P501: Dispose of contents/container to an approved waste disposal plant. 55965-84-9 Reaction mass of: 5-chloro-2- methyl-4-isothiazolin-3-one [EC no. 247-500-7] and 2-methyl-2H - isothiazol-3- one [EC no. 220-239- 6] (3:1)

* Product safety labeling primarily follows EU GHS guidance
**Hazardous substance

Table 3 cobas® NHP Negative Control Kit

(NHP-NC)

Store at 2-8°C
For use on the **cobas**® 5800 System (P/N 09051554190)

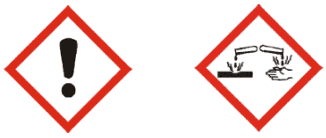
For use on the **cobas**® 6800/8800 Systems (P/N 07002220190 or P/N 09051554190)

Kit components	Reagent ingredients	Quantity per kit	Safety symbol and warning*
Normal Human Plasma Negative Control (NHP-NC)	Normal human plasma, non-reactive by licensed tests for antibody to HCV, antibody to HIV-1/2, HBsAg, antibody to HBc; HIV-1 RNA, HIV-2 RNA, HCV RNA, and HBV DNA not detectable by PCR methods. < 0.1% ProClin® 300 preservative**	16 mL (16 x 1 mL)	 **WARNING** H317: May cause an allergic skin reaction. P261: Avoid breathing dust/fume/gas/mist/ vapours/spray. P272: Contaminated work clothing should not be allowed out of the workplace. P280: Wear protective gloves. P333 + P313: If skin irritation or rash occurs: Get medical advice/attention. P362 + P364: Take off contaminated clothing before reuse. P501: Dispose of contents/ container to an approved waste disposal plant. 55965-84-9 Mixture of: 5-chloro-2-methyl-4-isothiazolin-3-one [EC no. 247-500-7] and 2-methyl-2H-isothiazol-3-one [EC no. 220-239-6] (3:1)

* Product safety labeling primarily follows EU GHS guidance
** Hazardous substance

cobas omni reagents for sample preparation

Table 4 cobas omni reagents for sample preparation

Reagents	Reagent ingredients	Quantity per kit	Safety symbol and warning*
cobas omni MGP Reagent (MGP) Store at 2–8°C (P/N 06997546190)	Magnetic glass particles, Tris buffer, 0.1% methyl-4 hydroxybenzoate, < 0.1% sodium azide	480 tests	Not applicable
cobas omni Specimen Diluent (SPEC DIL) Store at 2–8°C (P/N 06997511190)	Tris buffer, 0.1% methyl-4 hydroxybenzoate, < 0.1% sodium azide	4 x 875 mL	Not applicable
cobas omni Lysis Reagent (LYS) Store at 2–8°C (P/N 06997538190)	43% (w/w) guanidine thiocyanate**, 5% (w/v) polydocanol**, 2% (w/v) dithiothreitol**, dihydro sodium citrate	4 x 875 mL	 **DANGER** H302 + H332: Harmful if swallowed or if inhaled. H314: Causes severe skin burns and serious eye damage. H412: Harmful to aquatic life with long lasting effects. EUH032: Contact with acids liberates very toxic gas. P261: Avoid breathing dust/fume/gas/ mist/vapours/spray. P273: Avoid release to the environment. P280: Wear protective gloves/protective clothing/eye protection/face protection. P303 + P361 + P353: IF ON SKIN (or hair): Take off immediately all contaminated clothing. Rinse skin with water. P304 + P340 + P310: IF INHALED: Remove person to fresh air and keep comfortable for breathing. Immediately call a POISON CENTER/doctor. P305 + P351 + P338 + P310: IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing. Immediately call a POISON CENTER/doctor. 593-84-0 Guanidinium thiocyanate 9002-92-0 Polidocanol 3483-12-3 (R*,R*)-1,4-dimercaptobutane-2,3-diol
cobas omni Wash Reagent (WASH) Store at 15–30°C (P/N 06997503190)	Sodium citrate dihydrate, 0.1% methyl-4 hydroxybenzoate	4.2 L	Not applicable

* Product safety labeling primarily follows EU GHS guidance

** Hazardous substance

Reagent storage and handling requirements

Do not freeze reagents or controls.

Reagents must be stored and handled as specified in Table 5 and Table 7.

When reagents are not loaded on the **cobas**® 5800 or **cobas**® 6800/8800 Systems, store them at the corresponding temperature specified in Table 5.

Table 5 Reagent storage (when reagent is not on the system)

Reagent	Storage temperature
cobas® HIV-1	2–8°C
cobas® HBV/HCV/HIV-1 Control Kit	2–8°C
cobas® NHP Negative Control Kit	2–8°C
cobas omni Lysis Reagent	2–8°C
cobas omni MGP Reagent	2–8°C
cobas omni Specimen Diluent	2–8°C
cobas omni Wash Reagent	15–30°C

Reagent handling requirements for cobas® 5800 System

Reagents loaded onto the **cobas**® 5800 System are stored at appropriate temperatures and their expiration is monitored by the system. The system allows reagents to be used only if all of the conditions shown in Table 6 are met. The system automatically prevents use of expired reagents. Table 6 allows the user to understand the reagent handling conditions enforced by the **cobas**® 5800 System.

Table 6 Reagent expiry conditions enforced by the **cobas**® 5800 System

Reagent	Kit expiration date	Open-kit stability	Number of runs for which this kit can be used	On-board stability (cumulative time on board outside refrigerator)
cobas® HIV-1	Date not passed	90 days from first usage	Max 40 runs	Max 36 days[b]
cobas® HBV/HCV/HIV-1 Control Kit	Date not passed	Not applicable[a]	Not applicable	Max 36 days[b]
cobas® NHP Negative Control Kit	Date not passed	Not applicable[a]	Not applicable	Max 36 days[b]
cobas omni Lysis Reagent	Date not passed	30 days from loading[b]	Not applicable	Not applicable
cobas omni MGP Reagent	Date not passed	30 days from loading[b]	Not applicable	Not applicable
cobas omni Specimen Diluent	Date not passed	30 days from loading[b]	Not applicable	Not applicable
cobas omni Wash Reagent	Date not passed	30 days from loading[b]	Not applicable	Not applicable

[a] Single use reagents

[b] Time is measured from the first time that reagent is loaded onto the **cobas**® 5800 System.

Reagent handling requirements for cobas® 6800/8800 Systems

Reagents loaded onto the **cobas**® 6800/8800 Systems are stored at appropriate temperatures and their expiration is monitored by the system. The **cobas**® 6800/8800 Systems allow reagents to be used only if all of the conditions shown in Table 7 are met. The system automatically prevents use of expired reagents. Table 7 allows the user to understand the reagent handling conditions enforced by the **cobas**® 6800/8800 Systems.

Table 7 Reagent expiry conditions enforced by the **cobas**® 6800/8800 Systems

Reagent	Kit expiration date	Open-kit stability	Number of runs for which this kit can be used	On-board stability (cumulative time on board outside refrigerator)
cobas® HIV-1	Date not passed[a]	90 days from first usage	Max 40 runs	Max 40 hours
cobas® HBV/HCV/HIV-1 Control Kit	Date not passed[a]	Not applicable[b]	Not applicable	Max 8 hours
cobas® NHP Negative Control Kit	Date not passed[a]	Not applicable[b]	Not applicable	Max 10 hours
cobas omni Lysis Reagent	Date not passed[a]	30 days from loading[c]	Not applicable	Not applicable
cobas omni MGP Reagent	Date not passed[a]	30 days from loading[c]	Not applicable	Not applicable
cobas omni Specimen Diluent	Date not passed[a]	30 days from loading[c]	Not applicable	Not applicable
cobas omni Wash Reagent	Date not passed[a]	30 days from loading[c]	Not applicable	Not applicable

[a] Reagents are not expired

[b] Single use reagents

[c] Time is measured from the first time that reagent is loaded onto the **cobas**® 6800/8800 Systems.

Additional materials required for cobas® 5800 System

Table 8 Material and consumables for use on the **cobas**® 5800 System

Material	P/N
cobas omni Processing Plate	08413975001
cobas omni Amplification Plate	08499853001
cobas omni Liquid Waste Plate 24	08413983001
Tip CORE TIPS with Filter, 1mL	04639642001
Tip CORE TIPS with Filter, 300uL	07345607001
cobas omni Liquid Waste Container	07094388001
cobas omni Lysis Reagent	06997538190
cobas omni MGP Reagent	06997546190
cobas omni Specimen Diluent	06997511190
cobas omni Wash Reagent	06997503190
Solid Waste Bag or Solid Waste Bag With Insert	07435967001 or 08030073001

Additional materials required for cobas® 6800/8800 Systems

Table 9 Materials and consumables for use on **cobas**® 6800/8800 Systems

Material	P/N
cobas omni Processing Plate	05534917001
cobas omni Amplification Plate	05534941001
cobas omni Pipette Tips	05534925001
cobas omni Liquid Waste Container	07094388001
cobas omni Lysis Reagent	06997538190
cobas omni MGP Reagent	06997546190
cobas omni Specimen Diluent	06997511190
cobas omni Wash Reagent	06997503190
Solid Waste Bag and Solid Waste Container or Solid Waste Bag With Insert and Kit Drawer	07435967001 and 07094361001 or 08030073001 and 08387281001

Instrumentation and software required

The **cobas**® 5800 software and **cobas**® HIV-1 analysis package for the **cobas**® 5800 System shall be installed on the **cobas**® 5800 instrument. The Data Manager software and PC for the **cobas**® 5800 System will be provided with the system.

The **cobas**® 6800/8800 software and **cobas**® HIV-1 analysis package shall be installed on the instrument(s). The Instrument Gateway (IG) server will be provided with the system.

Table 10 Instrumentation

Equipment	P/N
cobas® 5800 System	08707464001
cobas® 6800 System (Moveable Platform)	05524245001 and 06379672001
cobas® 6800 System (Fix Platform)	05524245001 and 06379664001
cobas® 8800 System	05412722001
Sample Supply Module (**cobas**® 6800/8800 Systems only)	06301037001

Refer to the **cobas**® 5800 System or **cobas**® 6800/8800 Systems – User Assistance and/or User Guides for additional information.
Note: Contact your local Roche representative for a detailed order list for sample racks, racks for clotted tips and rack trays accepted on the instruments.

Precautions and handling requirements

Warnings and precautions

As with any test procedure, good laboratory practice is essential to the proper performance of this assay. Due to the high sensitivity of this test, care should be taken to keep reagents and amplification mixtures free of contamination (Refer to CLSI guideline, MM19-A[10]).

- **cobas**® HIV-1 is only intended for quantitation of HIV-1 viral load and is not intended for initial clinical diagnosis of HIV-1 infection.
- **cobas**® HIV-1 is not intended for use as a screening test for the presence of HIV-1 in donated blood or plasma or as a diagnostic test to confirm the presence of HIV-1 infection.
- For in vitro diagnostic use only.
- All patient samples should be handled as if infectious, using good laboratory procedures as outlined in Biosafety in Microbiological and Biomedical Laboratories and in the CLSI Document M29-A4.[11,12] Only personnel proficient in handling infectious materials and the use of **cobas**® HIV-1 and **cobas**® 5800/6800/8800 Systems should perform this procedure.
- All human-sourced materials should be considered potentially infectious and should be handled with universal precautions. If spillage occurs, immediately disinfect with a freshly prepared solution of 0.5% sodium hypochlorite in distilled or deionized water (dilute household bleach 1:10) or follow appropriate site procedures.
- **cobas**® HBV/HCV/HIV-1 Control Kit and **cobas**® NHP Negative Control Kit contain plasma derived from human blood. The source material has been tested by licensed antibody tests and found non-reactive for the presence of antibody to HCV, antibody to HIV-1/2, HBsAg, and antibody to HBc. Testing of normal human plasma by PCR methods also showed no detectable HIV-1 (Groups M and O) RNA, HIV-2 RNA, HCV RNA, and HBV DNA. No known test method can offer complete assurance that products derived from human blood will not transmit infectious agents.
- **Do not freeze whole blood or any samples stored in primary tubes.**
- Use only supplied or specified required consumables to ensure optimal test performance.
- Safety Data Sheets (SDS) are available on request from your local Roche representative.
- Closely follow procedures and guidelines provided to ensure that the test is performed correctly. Any deviation from the procedures and guidelines may affect optimal test performance.
- False positive results may occur if carryover of samples is not adequately controlled during sample handling and processing.

Reagent handling

- Handle all reagents, controls, and samples according to good laboratory practice in order to prevent carryover of samples or controls.
- Before use, visually inspect each reagent cassette, diluent, lysis reagent, and wash reagent to ensure that there are no signs of leakage. If there is any evidence of leakage, do not use that material for testing.
- **cobas omni** Lysis Reagent contains guanidine thiocyanate, a potentially hazardous chemical. Avoid contact of reagents with the skin, eyes, or mucous membranes. If contact does occur, immediately wash with generous amounts of water; otherwise, burns can occur.

- **cobas**® HIV-1 kits, **cobas omni** MGP Reagent, and **cobas omni** Specimen Diluent contain sodium azide as a preservative. Avoid contact of reagents with the skin, eyes, or mucous membranes. If contact does occur, immediately wash with generous amounts of water; otherwise, burns can occur. If these reagents are spilled, dilute with water before wiping dry.
- Do not allow **cobas omni** Lysis Reagent, which contains guanidine thiocyanate, to contact sodium hypochlorite (bleach) solution. This mixture can produce a highly toxic gas.
- Dispose of all materials that have come in contact with samples and reagents in accordance with country, state, and local regulations.

Good laboratory practice

- Do not pipette by mouth.
- Do not eat, drink, or smoke in designated work areas.
- Wear laboratory gloves, laboratory coats, and eye protection when handling samples and reagents. Gloves must be changed between handling samples and **cobas**® HIV-1 kits and **cobas omni** reagents to prevent contamination. Avoid contaminating gloves when handling samples and controls.
- Wash hands thoroughly after handling samples and kit reagents, and after removing the gloves.
- Thoroughly clean and disinfect all laboratory work surfaces with a freshly prepared solution of 0.5% sodium hypochlorite in distilled or deionized water (dilute household bleach 1:10). Follow by wiping the surface with 70% ethanol.
- If spills occur on the **cobas**® 5800 instrument, follow the instructions in the **cobas**® 5800 System User Assistance and/or User Guide to properly clean and decontaminate the surface of instrument.
- If spills occur on the **cobas**® 6800/8800 instrument, follow the instructions in the **cobas**® 6800/8800 Systems User Assistance and/or User Guide to properly clean and decontaminate the surface of instrument(s).

Sample collection, transport, and storage

Note: Handle all samples and controls as if they are capable of transmitting infectious agents.

Store all samples at specified temperatures.

Sample stability is affected by elevated temperatures.

If using frozen samples in secondary tubes, place the samples at room temperature (15-30ºC) until completely thawed and then briefly mix (e.g., vortex for 3-5 seconds) and centrifuge to collect all sample volume at the bottom of the tube.

This test has been validated for use with only human plasma collected in EDTA anticoagulant. Testing of specimen collected with other anticoagulants may result in inaccurate results.

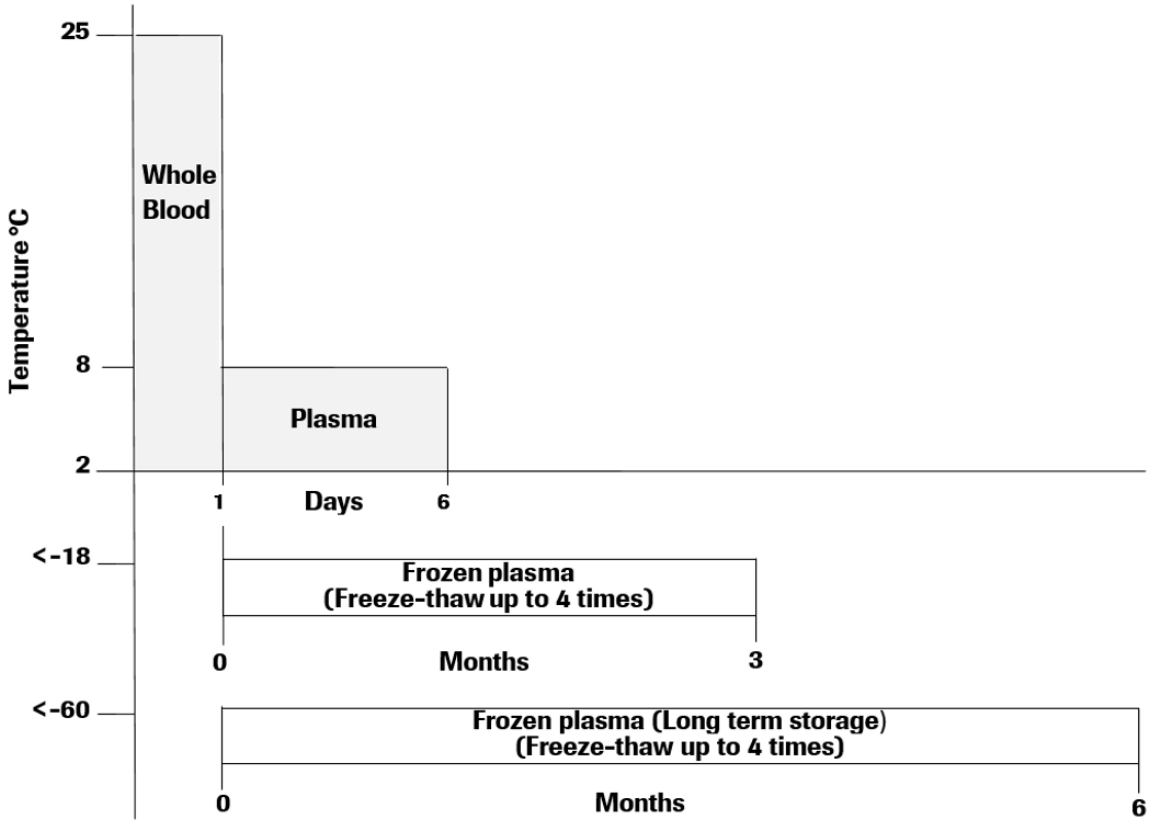
Note: After centrifugation, if there is potential that cells have re-suspended into the plasma, consider re-centrifugation before processing on the instrument.

Samples

- Whole blood should be collected in BD Vacutainer® PPT™ Plasma Preparation Tubes for Molecular Diagnostic Test Methods or in sterile tubes using EDTA as the anticoagulant. Follow the sample collection tube manufacturer instructions. Refer to Figure 1.
- Whole blood collected in EDTA tubes may be stored and/or transported for up to 24 hours at 2°C to 25°C prior to plasma preparation. Centrifugation should be performed according to collection tube manufacturer instructions.
- Upon separation EDTA plasma samples may be stored in secondary tubes for up to 6 days at 2°C to 8°C or up to 12 weeks at ≤ -18°C. For long-term storage up to 6 months, temperatures at ≤ -60°C are recommended.
- Plasma samples are stable for up to four freeze/thaw cycles when stored frozen at ≤ -18°C.

- Ensure sufficient whole blood collection to allow usage of the processing volume for EDTA plasma of 500 µL (for a total minimum sample requirement of 650 µL) or 200 µL (for a total minimum sample requirement of 350 µL).
- If samples are to be shipped, they should be packaged and labeled in compliance with applicable country and/or international regulations covering the transport of samples and etiologic agents.

Figure 1 Sample storage conditions



Instructions for use

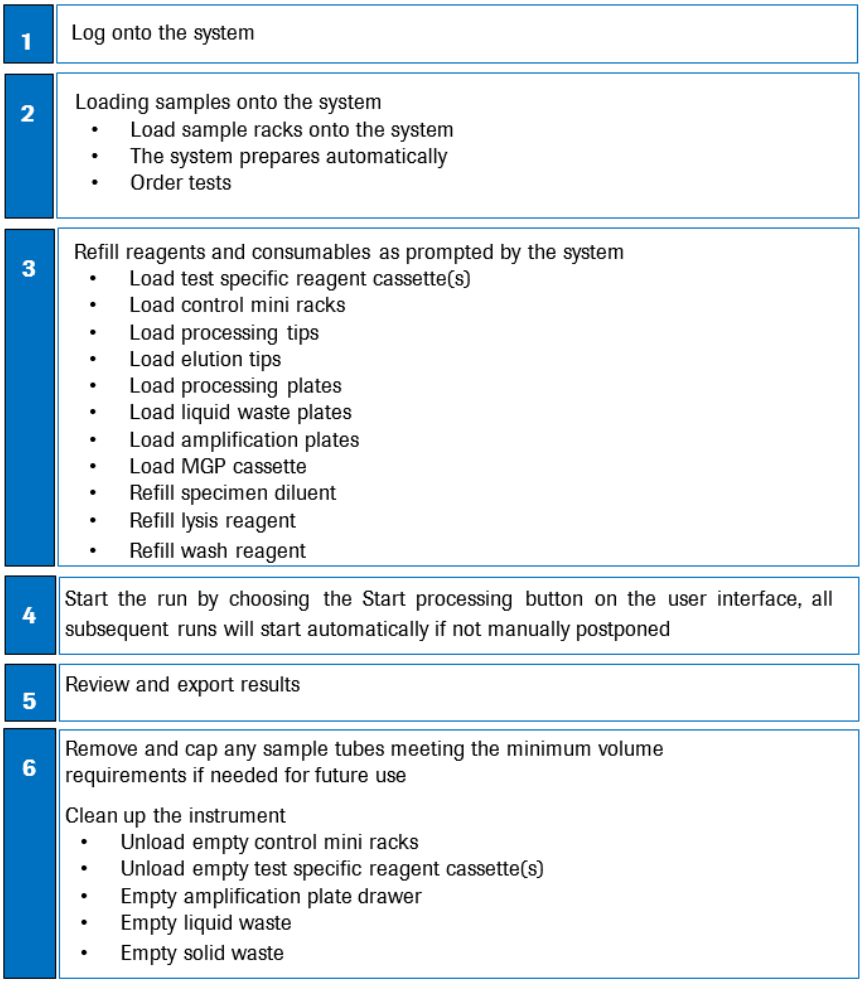
Procedural notes

- Do not use **cobas**® HIV-1 reagents, **cobas**® HBV/HCV/HIV-1 Control Kit, **cobas**® NHP Negative Control Kit, or **cobas omni** reagents after their expiry dates.
- Do not reuse consumables. They are for one-time use only.
- Refer to the **cobas**® 5800 System or **cobas**® 6800/8800 Systems User Assistance and/or User Guides for proper maintenance of instruments.

Running cobas® HIV-1 on cobas® 5800 System

cobas® HIV-1 can be run with required sample volumes of 350 µL for the 200 µL sample workflow or 650 µL for the 500µL sample workflow. The test procedure is described in detail in the **cobas**® 5800 System User Assistance and/or User Guide. Figure 2 below summarizes the procedure.

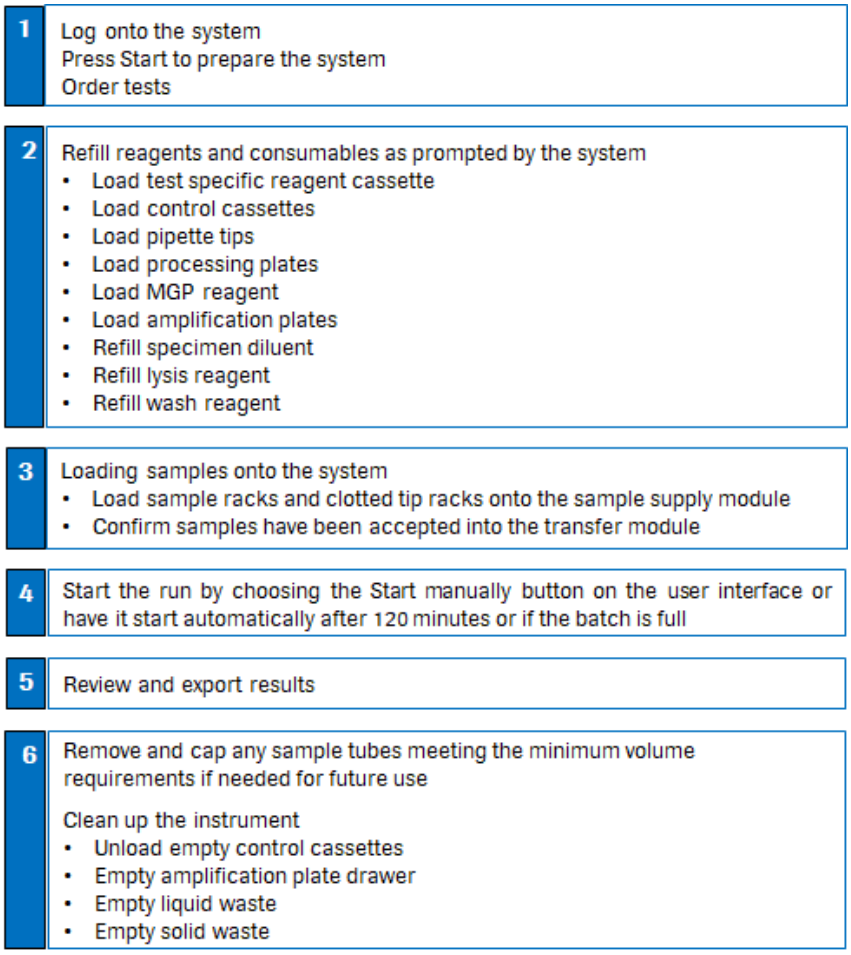
Figure 2 cobas® HIV-1 test procedure on **cobas**® 5800 System



Running cobas® HIV-1 on cobas® 6800/8800 Systems

cobas® HIV-1 can be run with a minimum required sample volume of 650 µL for the 500 µL sample workflow or 350 µL for the 200 µL sample workflow. The test procedure is described in detail in the **cobas**® 6800/8800 Systems User Assistance and/or User Guide. Figure 3 below summarizes the procedure.

Figure 3 cobas® HIV-1 test procedure on **cobas**® 6800/8800 Systems



Results

The **cobas**® 5800 System and **cobas**® 6800/8800 Systems automatically determine the HIV-1 RNA concentration for the samples and controls. The HIV-1 RNA concentration is expressed in copies per milliliter (cp/mL) or International Units per milliliter (IU/mL). The conversion factor for **cobas**® HIV-1 is 0.6 cp/IU.

Quality control and validity of results on the cobas® 5800 System

- One Normal Human Plasma Negative Control [(–) C], a low positive control [HIV-1 L(+)C] and a high positive control [HIV-1 H(+)C] are processed at least every 72 hours or with every new kit lot. Positive and/or negative controls can be scheduled more frequently based on laboratory procedures and/or local regulations.
- In the **cobas**® 5800 software and/or report, check for flags and their associated results to ensure the result validity.

Invalidation of results is performed automatically by the **cobas**® 5800 software based on negative or positive control failures.

NOTE: The **cobas**® 5800 System will be delivered with the standard setting of running a set of controls (positive and negative) with every run, but can be configured to a less frequent scheduling up to every 72 hours based on laboratory procedures and/or local regulations. Please contact your Roche service engineer and/or Roche customer technical support for more information.

Control results on cobas® 5800 System

The results of the controls are shown in the **cobas**® 5800 software in the "Controls" app.

- Controls are marked with "Valid" in the column "Control result" if all Targets of the control are reported valid. Controls are marked with 'Invalid' in the column "Control result" if all or one Target of the control are reported invalid.
- Controls marked with 'Invalid' show a flag in the "Flags" column. More information on why the control is reported invalid including flag information is shown in the detail view.
- If one of the positive controls is invalid, repeat testing of the all positive controls and all associated samples.
- If the negative control is invalid, repeat testing of all controls and all associated samples.

Quality control and validity of results on the cobas® 6800/8800 Systems

- One Normal Human Plasma negative control [(–) C] and two positive controls, a low positive control [HIV-1 L(+)C] and a high positive control [HIV-1 H(+)C], are processed with each batch.
- In the **cobas**® 6800/8800 software and/or report, check for flags and their associated results to ensure the batch validity.
- The batch is valid if no flags appear for all three controls, which include one negative control and two positive controls: HIV-1 L(+)C, HIV-1 H(+)C. The negative control result is displayed as (–) C and the low and high positive controls are displayed as HxV L(+)C and HxV H(+)C.

Validation of results is performed automatically by the **cobas**® 6800/8800 software based on negative and positive control results.

Control flags on the cobas® 6800/8800 Systems

Table 11 Control flags for negative and positive controls

Negative Control	**Flag**	**Result**	**Interpretation**
(–) C	Q02 (Control batch failed)	Invalid	An invalid result or the calculated titer result for the negative control is not negative.
Positive Control	**Flag**	**Result**	**Interpretation**
HxV L(+)C	Q02 (Control batch failed)	Invalid	An invalid result or the calculated titer result for the low positive control is not within the assigned range.
HxV H(+)C	Q02 (Control batch failed)	Invalid	An invalid result or the calculated titer result for the high positive control is not within the assigned range.

If the batch is invalid, repeat testing of the entire batch including samples and controls.

HxV L(+)C stands for **cobas**® HBV/HCV/HIV-1 low positive control and HxV H(+)C stands for **cobas**® HBV/HCV/HIV-1 high positive control in the **cobas**® 6800/8800 software.

Interpretation of results

For a valid batch, check each individual sample for flags in the **cobas**® 5800 and **cobas**® 6800/8800 Systems software and/or report. The result interpretation should be as follows:

- A valid batch may include both valid and invalid sample results.

Table 12 Target results for individual target result interpretation

Results	Interpretation
Target Not Detected	HIV-1 RNA not detected. Report results as "HIV-1 not detected."
< Titer Min	Calculated titer is below the Lower Limit of Quantitation (LLoQ) of the assay. Report results as "HIV-1 detected, less than (Titer Min)." Titer min = 20 cp/mL and 33 IU/mL (500 µL sample processing volume) Titer min = 50 cp/mL and 83 IU/mL (200 µL sample processing volume)
Titer	Calculated titer is within the Linear Range of the assay – greater than or equal to Titer Min and less than or equal to Titer Max. Report results as "(Titer) of HIV-1 detected".
> Titer Max[a]	Calculated titer is above the Upper Limit of Quantitation (ULoQ) of the assay. Report results as "HIV-1 detected, greater than (Titer Max)." Titer max = 1.00E+07 cp/mL and 1.67E+07 IU/mL (for the 500 µL and 200 µL sample processing volumes)

[a] Sample result > Titer Max refers to HIV-1 positive samples detected with titers above the upper limit of quantitation (ULoQ). If a quantitative result is desired, the original sample should be diluted with HIV-1 negative EDTA plasma, depending on the type of the original sample, and the test should be repeated. Multiply the reported result by the dilution factor.

Interpretation of results on the cobas® 5800 System

The results of the samples are shown in the **cobas**® 5800 software in the "Results" app.
For a valid control batch, check each individual sample for flags in the **cobas**® 5800 software and/or report. The result interpretation should be as follows:

- Samples associated with a valid control batch are shown as 'Valid' in the "Control result" column if all Control Target Results reported valid. Samples associated with a failed control batch are shown as 'Invalid' in the "Control result" column if all Control Target Results reported invalid.
- If the associated controls of a sample result are invalid, a specific flag will be added to the sample result as follows:
  - Q05D : Result validation failure because of an invalid positive control
  - Q06D :Result validation failure because of an invalid negative control
- The values in "Results" column for individual sample target result should be interpreted as show in Table 12 above.
- If one or more sample targets are marked with "Invalid" the **cobas**® 5800 software shows a flag in the "Flags" column. More information on why the sample target(s) is reported invalid including flag information is shown in the detail view.

Interpretation of results on the cobas® 6800/8800 Systems

For a valid batch, check each individual sample for flags in the **cobas®** 6800/8800 Systems software and/or report. The result interpretation should be as follows:

- Samples are marked with "Yes" in the column 'Valid' if all requested Target Results reported valid results. Samples marked with "No" in the column 'Valid' may require additional interpretation and action.
- The values for individual sample target result should be interpreted as show in Table 12 above.

Procedural limitations

- **cobas®** HIV-1 has been evaluated only for use in combination with the **cobas®** HBV/HCV/HIV-1 Control Kit, **cobas®** NHP Negative Control Kit, **cobas omni** MGP Reagent, **cobas omni** Lysis Reagent, **cobas omni** Specimen Diluent, and **cobas omni** Wash Reagent for use on the **cobas®** 5800/6800/8800 Systems.
- Reliable results depend on proper sample collection, storage and handling procedures.
- Quantitation of HIV-1 RNA is dependent on the number of virus particles present in the samples and may be affected by sample collection methods.
- Though rare, mutations within the highly conserved regions of a viral genome covered by **cobas®** HIV-1 may affect primers and/or probe binding resulting in the under-quantitation of virus or failure to detect the presence of virus.
- The detection rate of HIV-1 group O at 20 cp/mL (claimed LLoQ for the **cobas®** HIV-1 with the 500 µL sample processing volume) was observed to be 90.5%. Similarly, the detection rate of HIV-1 CRF01_AE, HIV-1 Group O at 50 cp/mL (claimed LLoQ for the **cobas®** HIV-1 with the 200 µL sample processing volume) was observed to be 90.5% and 88.9% respectively. Both detection rates are lower than what was observed for all other genotypes for both sample processing volumes.
- Due to inherent differences between technologies, it is recommended that, prior to switching from one technology to the next, users perform method correlation studies in their laboratory to qualify technology differences. Users should follow their own specific policies/procedures.
- **cobas®** HIV-1 is not intended for use as a screening test for the presence of HIV-1 in donated blood or plasma , or as a diagnostic test to confirm the presence of HIV-1 infection.
- Samples from subjects under 19 years of age were not evaluated.

Non-clinical performance evaluation

Key performance characteristics

Limit of Detection (LoD)

WHO International Standard

The limit of detection of **cobas**® HIV-1 was determined by analysis of serial dilutions of the WHO International Standard for HIV-1 RNA for Nucleic Acid Amplification Technology Assays (2nd WHO International Standard) group M subtype B obtained from NIBSC, in HIV-negative human EDTA plasma using sample processing volumes of 500 µL and 200 µL. Panels of five concentration levels plus a negative were tested over three lots of **cobas**® HIV-1 test reagents, multiple runs, days, operators, and instruments.

The results for EDTA plasma from both sample processing volumes are shown in Table 13 and Table 14. The study demonstrates that **cobas**® HIV-1 detected HIV-1 RNA with a detection rate of 95%, as determined by PROBIT, at a concentration of 13.2 cp/mL (22.0 IU/mL) for the 500 µL sample processing volume and at a concentration of 35.5 cp/mL (59.2 IU/mL) for the 200 µL sample processing volume.

Table 13 HIV-1 RNA WHO International Standard limit of detection in EDTA plasma (500 µL)

Input titer concentration (HIV-1 RNA cp/mL)	Input titer concentration (HIV-1 RNA IU/mL)	Number of valid replicates (N)	Number of positives (n)	Detection rate in % (n/N)
40.0	66.7	189	189	100.0%
20.0	33.3	189	186	98.4%
10.0	16.7	189	171	90.5%
5.0	8.3	189	125	66.1%
2.5	4.2	189	67	35.4%
0.0	0.0	189	0	0.0%

LoD by PROBIT at 95% detection rate: 13.2 cp/mL, 95% confidence range: 11.4 – 15.9 cp/mL
LoD by PROBIT at 95% detection rate: 22.0 IU/mL, 95% confidence range: 19.0 – 26.5 IU/mL

Table 14 HIV-1 RNA WHO International Standard limit of detection in EDTA plasma (200 µL)

Input titer concentration (HIV-1 RNA cp/mL)	Input titer concentration (HIV-1 RNA IU/mL)	Number of valid replicates (N)	Number of positives (n)	Hit rate (n/N)
200.0	333.3	189	189	100.0%
100.0	166.7	188	188	100.0%
50.0	83.3	189	186	98.4%
25.0	41.7	189	164	86.8%
12.5	20.8	189	112	59.3%
0.0	0.0	188	0	0.0%

LoD by PROBIT at 95% hit rate: 35.5 cp/mL, 95% confidence range: 30.8 – 43.2 cp/mL
LoD by PROBIT at 95% hit rate: 59.2 IU/mL, 95% confidence range: 51.3 – 72.0 IU/mL

Linear range

The linearity of **cobas**® HIV-1 was evaluated using dilution series consisting of 12 panel members for the 500 µL sample processing volume and 11 panel members for the 200 µL sample processing volume, spanning the linear range of the assay for the predominant HIV-1 group M subtype B. Panel members were prepared from a high titer HIV-1 RNA positive cell culture supernatant specimen. The evaluation was performed according to CLSI Guideline EP06-A.[13] Three reagent lots were analyzed on three **cobas**® 6800/8800 Systems, three operators for a total of 16 replicates per panel member and lot across four testing days (total of 12 testing days; four replicates per kit lot and day).

With the 500 µL sample processing volume, **cobas**® HIV-1 was demonstrated to be linear from 20 cp/mL to 1.00E+07 cp/mL (33.3 IU/mL to 1.67E+07 IU/mL) (Figure 4).

With the 200 µL sample processing volume, **cobas**® HIV-1 was demonstrated to be linear from 50 cp/mL to 1.00E+07 cp/mL (83.3 IU/mL to 1.67E+07 IU/mL) (Figure 5).

Figure 4 Linear range determination in EDTA plasma (500 µL)

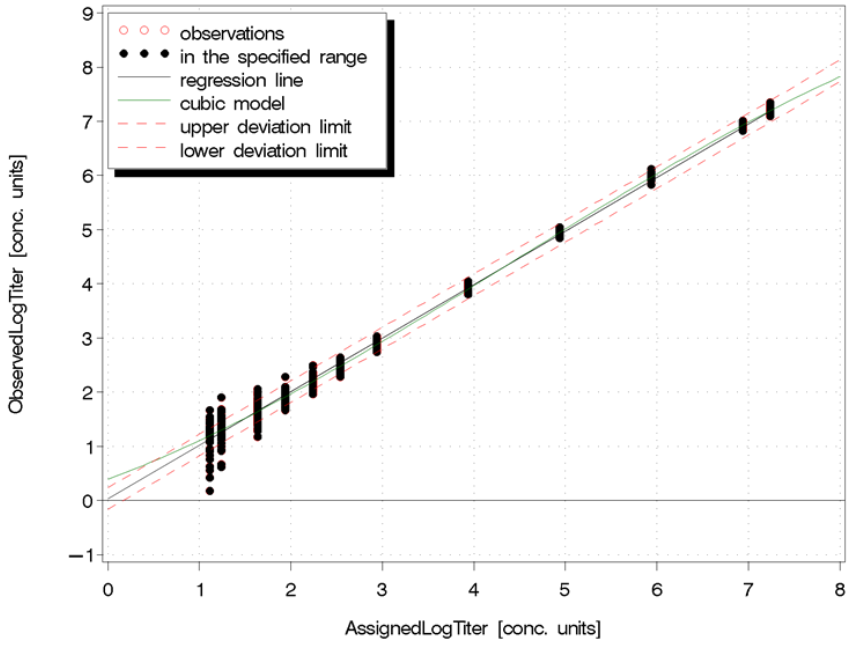
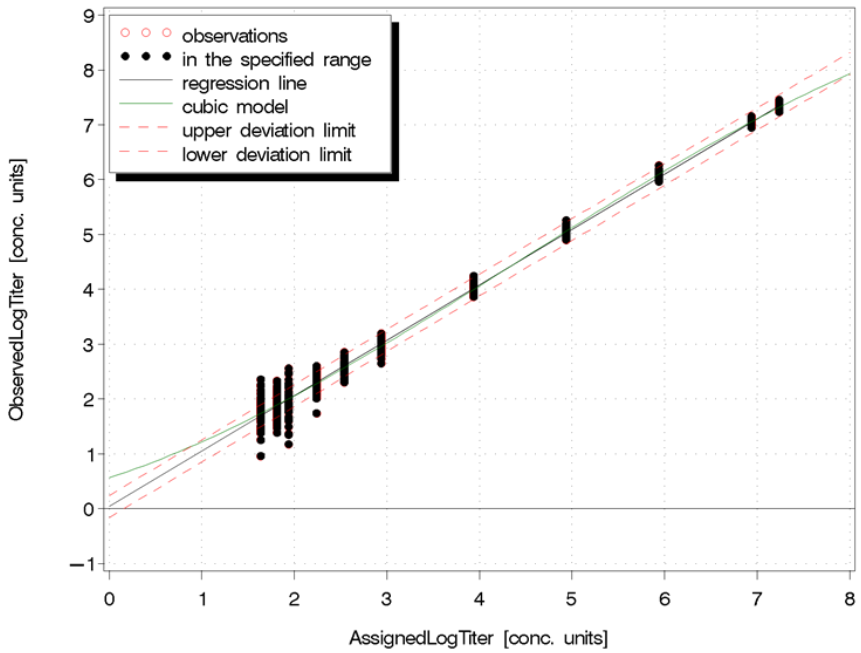


Figure 5 Linear range determination in EDTA plasma (200 µL)



Precision – within laboratory

Precision of **cobas**® HIV-1 was determined by analysis of serial dilutions of an HIV-1 high positive sample (Group M Subtype B; cultured virus) in HIV negative EDTA plasma. Eight dilution levels (500 µL sample processing volume) and seven dilution levels (200 µL sample processing volume) were tested in 48 replicates for each level across three lots of **cobas**® HIV-1 test reagents using three **cobas**® 6800/8800 Systems and three operators over 12 days. The results are shown in Table 15 and Table 16.

cobas® HIV-1 showed excellent precision for three lots of reagents tested across a concentration range of 1.00E+02 cp/mL to 1.00E+07 cp/mL with the 500 µL sample processing volume and 2.00E+02 cp/mL to 1.00E+07 cp/mL with the 200 µL sample processing volume.

Table 15 Within laboratory precision of **cobas**® HIV-1 (EDTA plasma samples – sample processing volume of 500 µL)*

Nominal concentration (cp/mL)	Assigned concentration (cp/mL)	Source material	Lot 1 SD	Lot 2 SD	Lot 3 SD	All Lots Pooled SD
1.00E+07	8.67E+06	Cultured Virus	0.04	0.06	0.03	0.05
1.00E+06	8.67E+05	Cultured Virus	0.06	0.05	0.04	0.05
1.00E+05	8.67E+04	Cultured Virus	0.05	0.07	0.04	0.05
1.00E+04	8.67E+03	Cultured Virus	0.06	0.06	0.04	0.05
1.00E+03	8.67E+02	Cultured Virus	0.07	0.06	0.07	0.07
4.00E+02	3.47E+02	Cultured Virus	0.09	0.10	0.09	0.09
2.00E+02	1.73E+02	Cultured Virus	0.11	0.08	0.14	0.11
1.00E+02	8.67E+01	Cultured Virus	0.15	0.11	0.10	0.12

* Titer data are considered to be log-normally distributed and are analyzed following $\log_{10}$ transformation. Standard deviations (SD) columns refer to the log-transformed titers obtained with each of the three reagent lots and with all lots combined.

Table 16 Within laboratory precision of **cobas**® HIV-1 (EDTA plasma samples – sample processing volume of 200 µL)*

Nominal concentration (cp/mL)	Assigned concentration (cp/mL)	Source material	Lot 1 SD	Lot 2 SD	Lot 3 SD	All Lots Pooled SD
1.00E+07	8.67E+06	Cultured Virus	0.04	0.05	0.04	0.04
1.00E+06	8.67E+05	Cultured Virus	0.07	0.05	0.05	0.06
1.00E+05	8.67E+04	Cultured Virus	0.07	0.07	0.06	0.07
1.00E+04	8.67E+03	Cultured Virus	0.08	0.08	0.06	0.08
1.00E+03	8.67E+02	Cultured Virus	0.12	0.12	0.08	0.11
4.00E+02	3.47E+02	Cultured Virus	0.11	0.13	0.09	0.11
2.00E+02	1.73E+02	Cultured Virus	0.20	0.12	0.15	0.16

* Titer data are considered to be log-normally distributed and are analyzed following $\log_{10}$ transformation. Standard deviation (SD) columns refer to the log-transformed titer for each of the three reagent lots and with all lots combined.

Subtype verification

The performance of **cobas**® HIV-1 on HIV-1 group M subtypes, group O and group N was evaluated by:

- Verification of the limit of detection for group M subtypes, group O and group N
- Verification of the linearity for group M subtypes, group O and group N
- Titer assignment was performed using **cobas**® HIV-1

Verification of limit of detection for group M subtypes, group O and group N

Cultured HIV-1 samples for HIV-1M (A, C, D, F, G, H, CRF01_AE, CRF02_AG), HIV-1O, HIV-1N were diluted to three different concentration levels in EDTA plasma. The detection rate determination was performed with 63 replicates for each level. Testing was conducted with one lot of **cobas**® HIV-1 reagents. The results from EDTA plasma using 500 µL are shown in Table 17. These results verify that **cobas**® HIV-1 detected HIV RNA of HIV-1M (A, C, D, F, G, H, CRF01_AE, CRF02_AG), and HIV-1N at 20 cp/mL or below with a rate of ≥ 95%. HIV-1O was detected at 20 cp/mL with a rate of 90.5%.

Table 17 LoD verification of HIV-1 group M subtypes, group O, and group N in 500 µL EDTA plasma

Group (Subtype)	10 cp/mL Number of valid replicates	10 cp/mL Number of positives	10 cp/mL Detection rate in % (95% CI*)	20 cp/mL Number of valid replicates	20 cp/mL Number of positives	20 cp/mL Detection rate in % (95% CI*)	40 cp/mL Number of valid replicates	40 cp/mL Number of positives	40 cp/mL Detection rate in % (95% CI*)
M (A)	63	59	93.7% (97.8%)	63	63	100% (100%)	63	63	100% (100%)
M (C)	63	51	81.0% (88.6%)	63	61	96.8% (99.4%)	63	63	100% (100%)
M (D)	63	48	76.2% (84.7%)	62	60	96.8% (99.4%)	63	63	100% (100%)
M (F)	63	59	93.7% (97.8%)	63	63	100% (100%)	63	63	100% (100%)
M (G)	63	54	85.7% (92.3%)	63	63	100% (100%)	63	63	100% (100%)
M (H)	63	52	82.5% (89.9%)	63	63	100% (100%)	63	63	100% (100%)
M (CRF01_AE)	63	52	82.5% (89.9%)	63	62	98.4% (99.9%)	63	63	100% (100%)
M (CRF02_AG)	63	56	88.9% (94.7%)	63	62	98.4% (99.9%)	63	63	100% (100%)
O	63	49	77.8% (86.0%)	63	57	90.5% (95.8%)	63	63	100% (100%)
N	63	57	90.5% (95.8%)	63	63	100% (100%)	63	63	100% (100%)

* Upper one-sided 95% confidence interval

Similarly, the limit of detection was verified for the 10 subtypes tested with the 200 µL sample processing volume. The data are summarized in Table 18. These results verify that **cobas**® HIV-1 detected HIV RNA of HIV-1M (A, C, D, F, G, H, CRF02_AG), and HIV-1N at 50 cp/mL or below with a rate of ≥ 95%. HIV-1 CRF01_AE and HIV-1O were detected at 50 cp/mL with a rate of 90.5 and 88.9% respectively.

Table 18 LoD verification of HIV-1 group M subtypes, group O and group N in 200 µL EDTA plasma

Group (Subtype)	25 cp/mL Number of valid replicates	25 cp/mL Number of positives	25 cp/mL Hit rate in % (95% CI*)	50 cp/mL Number of valid replicates	50 cp/mL Number of positives	50 cp/mL Hit rate in % (95% CI*)	100 cp/mL Number of valid replicates	100 cp/mL Number of positives	100 cp/mL Hit rate in % (95% CI*)
M (A)	63	54	85.7% (92.3%)	63	60	95.2% (98.7%)	63	63	100% (100%)
M (C)	63	50	79.4% (87.3%)	63	62	98.4% (99.9%)	63	63	100% (100%)
M (D)	63	51	81.0% (88.6%)	63	63	100% (100%)	63	63	100% (100%)
M (F)	63	56	88.9% (94.7%)	63	62	98.4% (99.9%)	63	63	100% (100%)
M (G)	63	52	82.5% (89.9%)	63	62	98.4% (99.9%)	63	63	100% (100%)
M (H)	63	61	96.8% (99.4%)	63	63	100% (100%)	63	63	100% (100%)
M (CRF01_AE)	63	53	84.1% (91.1%)	63	57	90.5% (95.8%)	63	63	100% (100%)
M (CRF02_AG)	63	49	77.8% (86.0%)	63	63	100% (100%)	63	63	100% (100%)
O	63	44	69.8% (79.3%)	63	56	88.9% (94.7%)	63	63	100% (100%)
N	63	55	87.3% (93.5%)	63	63	100% (100%)	63	63	100% (100%)

* Upper one-sided 95% confidence interval

Verification of linear range for group M subtypes, group O and group N

The dilution series used in the verification of subtypes linearity study of **cobas**® HIV-1 consists of seven panel members spanning the linear range for the 500 µL sample processing volume and six panel members for the 200 µL sample processing volume. Panel members were prepared from high titer HIV-1 RNA positive cell culture supernatant specimens of the respective subtype. Testing was conducted with two lots of **cobas**® HIV-1 reagent; 14 replicates per level were tested in EDTA plasma.

The linear range of **cobas**® HIV-1 was verified for group M subtypes, group O and group N. The maximum deviation between the linear regression and the better fitting non-linear regression was equal to or less than 0.2 $\log_{10}$.

Performance with HIV-1 negative specimens

The performance of **cobas**® HIV-1 was determined by analyzing 600 EDTA plasma samples from healthy HIV negative individuals. Each of these samples was tested with two lots of **cobas**® HIV-1 reagents. All samples tested negative for HIV-1 RNA. In the test panel, the results of all specimens tested with **cobas**® HIV-1 was 100% "Target Not Detected" (95% confidence interval: 99.5, 100%).

Potentially interfering microbial contaminants

The analytical specificity of **cobas**® HIV-1 was evaluated by testing a panel of microorganisms prepared in HIV RNA negative EDTA plasma (Table 19). Potential interference was evaluated by testing the same organisms in EDTA plasma

containing low levels of HIV-1 RNA. None of the non-HIV pathogens interfered with test performance. Negative results were obtained with **cobas®** HIV-1 for all microorganism samples without HIV-1 target and positive results were obtained on all of the microorganism samples with HIV-1 target. The mean $\log_{10}$ titer of each of the positive HIV-1 samples containing potentially cross-reacting organisms was within ± 0.3 $\log_{10}$ of the mean $\log_{10}$ titer of the respective positive spike control.

Table 19 Microorganisms tested for cross-reactivity

Viruses	Bacteria	Yeast
Adenovirus type 5	*Propionibacterium acnes*	*Candida albicans*
Cytomegalovirus	*Staphylococcus aureus*	-
Epstein-Barr Virus	-	-
Hepatitis A Virus	-	-
Hepatitis B Virus	-	-
Hepatitis C Virus	-	-
Hepatitis D Virus	-	-
Human T-Cell Lymphotropic Virus types 1 and 2	-	-
Human Herpes Virus Type-6	-	-
Herpes Simplex Virus Type 1 and 2	-	-
Varicella-Zoster Virus	-	-
West Nile Virus	-	-
St. Louis encephalitis Virus	-	-
Murray Valley encephalitis Virus	-	-
Dengue virus types 1, 2, 3, and 4	-	-
TBE Virus (strain HYPR)	-	-
Influenza Virus A	-	-
Zika Virus	-	-
Human Papillomavirus	-	-
Yellow Fever Virus	-	-

Potentially interfering endogenous and exogenous substances

Elevated levels of triglycerides (up to 34.5 g/L), conjugated bilirubin (0.252 g/L), unconjugated bilirubin (0.253 g/L), albumin (58.7 g/L), hemoglobin (up to 2.85 g/L) and human DNA (2 mg/L) in samples as well as the presence of autoimmune diseases such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and antinuclear antibody (ANA) have been tested in presence and absence of HIV-1 RNA.

In addition, drug compounds listed in Table 20 were tested at three times the C_{max} in presence and absence of HIV-1 RNA.

All potentially interfering substances show no interference with the test performance. Negative results were obtained with **cobas®** HIV-1 for all samples without HIV target and positive results were obtained on all of the samples with HIV-1 target. The mean $\log_{10}$ titer of each of the positive HIV-1 samples containing potentially interfering substances was within ± 0.3 $\log_{10}$ of the mean $\log_{10}$ titer of the respective positive spike control.

Table 20 Drug compounds tested for interference with the quantitation of HIV RNA by **cobas®** HIV-1

Class of drug	Generic drug name
Immune Modulators	Peginterferon α-2a
Immune Modulators	Peginterferon α-2b
Immune Modulators	Ribavirin
HIV Entry Inhibitor	Maraviroc
HIV Integrase Inhibitors	Elvitegravir/Cobicistat
HIV Integrase Inhibitors	Raltegravir
Non-nucleoside HIV Reverse Transcriptase Inhibitors	Efavirenz
Non-nucleoside HIV Reverse Transcriptase Inhibitors	Etravirine
Non-nucleoside HIV Reverse Transcriptase Inhibitors	Nevirapine
Non-nucleoside HIV Reverse Transcriptase Inhibitors	Rilpivirine
HIV Protease inhibitors	Atazanavir
HIV Protease inhibitors	Tipranavir
HIV Protease inhibitors	Darunavir
HIV Protease inhibitors	Fosamprenavir
HIV Protease inhibitors	Lopinavir
HIV Protease inhibitors	Nelfinavir
HIV Protease inhibitors	Ritonavir
HIV Protease inhibitors	Saquinavir
HCV Protease Inhibitors	Boceprevir
HCV Protease Inhibitors	Simeprevir
HCV Protease Inhibitors	Telaprevir
Reverse Transcriptase or DNA Polymerase Inhibitors	Abacavir
Reverse Transcriptase or DNA Polymerase Inhibitors	Emtricitabine
Reverse Transcriptase or DNA Polymerase Inhibitors	Entecavir
Reverse Transcriptase or DNA Polymerase Inhibitors	Foscarnet
Reverse Transcriptase or DNA Polymerase Inhibitors	Cidofovir
Reverse Transcriptase or DNA Polymerase Inhibitors	Lamivudine
Reverse Transcriptase or DNA Polymerase Inhibitors	Ganciclovir
Reverse Transcriptase or DNA Polymerase Inhibitors	Tenofovir
Reverse Transcriptase or DNA Polymerase Inhibitors	Adefovir dipivoxil
Reverse Transcriptase or DNA Polymerase Inhibitors	Telbivudine
Reverse Transcriptase or DNA Polymerase Inhibitors	Zidovudine
Reverse Transcriptase or DNA Polymerase Inhibitors	Acyclovir
Reverse Transcriptase or DNA Polymerase Inhibitors	Valganciclovir
Reverse Transcriptase or DNA Polymerase Inhibitors	Sofosbuvir
Compounds for Treatment of Opportunistic Infections	Azithromycin
Compounds for Treatment of Opportunistic Infections	Clarithromycin
Compounds for Treatment of Opportunistic Infections	Ethambutol
Compounds for Treatment of Opportunistic Infections	Fluconazole
Compounds for Treatment of Opportunistic Infections	Isoniazid
Compounds for Treatment of Opportunistic Infections	Pyrazinamide
Compounds for Treatment of Opportunistic Infections	Rifabutin
Compounds for Treatment of Opportunistic Infections	Rifampicin
Compounds for Treatment of Opportunistic Infections	Sulfamethoxazole
Compounds for Treatment of Opportunistic Infections	Trimethoprim

Cross contamination

The cross-contamination rate for **cobas**® HIV-1 was determined by testing 240 replicates of HIV negative human EDTA-plasma sample and 225 replicates of a high titer HIV-1 sample at 4.00E+06 cp/mL. The study was performed using the **cobas**® 6800 System. In total, five runs were performed with positive and negative samples in a checkerboard configuration.

All 240 replicates of the negative sample were negative, resulting in a cross-contamination rate of 0%. The two-sided 95% exact confidence interval was 0% for the lower bound and 1.5% for the upper bound [0%: 1.5%].

Clinical performance evaluation

Reproducibility

Reproducibility of **cobas®** HIV-1 was evaluated in EDTA plasma using the 500 µL sample processing volume on the **cobas®** 6800 System. The study was performed using panels constructed from well characterized HIV-1 group M, subtype B cultured virus stock and from EDTA plasma that was negative for HIV-1 RNA and HIV-1/2 antibodies. The 8-member panel included one negative panel member and 7 positive panel members covering the linear range of **cobas®** HIV-1 as well as key medical decision points for the intended use, supported by the Department of Health and Human Services Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents.[3] Testing was done with three reagent lots, three sites, two operators per site, two runs per day, 6 days of testing per reagent lot, and three replicate per run. Reproducibility was evaluated using a random effects model including lot, site, operator, day, run, and within-run. Table 21 shows the total variance, total precision SDs, and lognormal CVs for **cobas®** HIV-1 as determined by analysis of variance. The within-run component contributed the most variability for the majority of the panel members.

Table 21 Attributable percentage of total variance(%TV), total precision standard deviation, and lognormal CV(%) of HIV RNA quantitation by positive panel member on the **cobas®** 6800 System (reproducibility)

Expected HIV RNA Conc. (log_{10} cp/mL)	Observed Mean[a] HIV RNA Conc. (log_{10} cp/mL) (SD)[b]	No. of Tests[c]	Lot %TV (CV%)[d]	Site %TV (CV%)[d]	Operator %TV (CV%)[d]	Day %TV (CV%)[d]	Run %TV (CV%)[d]	Within-Run %TV (CV%)[d]	Total Variance CV(%)[d]
1.70	1.69 (0.191)	323	17% (18.23)	0% (0.00)	0% (0.00)	1% (3.42)	5% (9.66)	78% (40.32)	46.25
2.30	2.22 (0.116)	321	32% (15.15)	0% (0.00)	1% (2.26)	4% (5.60)	0% (0.00)	63% (21.55)	27.27
2.60	2.48 (0.102)	323	34% (13.84)	4% (4.85)	3% (3.75)	0% (0.00)	1% (2.74)	58% (17.99)	23.86
3.00	2.84 (0.092)	324	39% (13.30)	0% (0.00)	1% (2.01)	0% (0.00)	7% (5.67)	52% (15.37)	21.33
4.00	3.86 (0.081)	324	43% (12.33)	1% (1.94)	3% (3.34)	10% (5.82)	6% (4.54)	37% (11.39)	18.85
5.00	4.92 (0.084)	324	43% (12.64)	0% (0.00)	3% (3.56)	6% (4.65)	6% (4.52)	42% (12.60)	19.44
6.70	6.63 (0.087)	324	45% (13.60)	0% (0.00)	2% (3.00)	3% (3.42)	0% (0.00)	50% (14.23)	20.32

Note: This table only includes results with detectable viral load.

[a] Calculated using SAS MIXED procedure based on log_{10} transformed measurements.

[b] Calculated using the total variability from the SAS MIXED procedure based on log_{10} transformed measurements.

[c] Number of valid tests with detectable viral load.

[d] CV% = Lognormal model used for CV(%) = sqrt(10^[SD^2 * ln(10)] - 1) * 100.

HIV = human immunodeficiency virus; RNA = ribonucleic acid; Conc = concentration; SD = standard deviation; No. = number; CV(%) = percent coefficient of variation; sqrt = square root.

In Table 22 below, the negative percent agreement (NPA) for the **cobas®** 6800 System using all valid negative panel member tests was 100%.

Table 22 Negative percent agreement using the negative panel member

Expected HIV RNA Concentration	No. of Tests	Positive Results	Negative Results	Negative Percent Agreement (NPA)[a]	95% CI[b]
Negative	322	0	322	100.00	(98.86, 100.00)

[a] NPA = (number of negative results / total number of valid tests in negative panel member) * 100.

[b] Calculated using the Clopper-Pearson exact binomial confidence interval method.

HIV = human immunodeficiency virus; RNA = ribonucleic acid; No. = number; NPA = negative percent agreement; CI = confidence interval.

Validation of viral load quantitation

The performance of **cobas®** HIV-1 on the **cobas®** 6800 System was compared to that of the FDA-approved COBAS® AmpliPrep/COBAS® TaqMan® HIV-1 Test v2.0 (TaqMan® HIV-1 Test, v2.0) by analysis of paired EDTA plasma specimens from 410 subjects with HIV-1 viral loads spanning the linear range of both tests. Demographic characteristics of the subjects are shown in Table 23.

Table 23 Summary of demographic characteristics

Demographic Characteristics	Groups	Statistics
Number of Subjects	Total (N)	410
Age (years)	Mean (SD)	41.8 (11)
Age (years)	Median	43
Age (years)	Range	19 – 72
Gender, n (%)	Male	321 (78.3%)
Gender, n (%)	Female	89 (21.7%)
Race, n (%)	Asian	5 (1.2%)
Race, n (%)	Black	163 (39.8%)
Race, n (%)	Latino	17 (4.1%)
Race, n (%)	White	94 (22.9%)
Race, n (%)	Other	91 (22.2%)
Race, n (%)	Unknown	40 (9.8%)
Ethnicity, n (%)	Hispanic	101 (24.6%)
Ethnicity, n (%)	Non-Hispanic	231 (56.3%)
Ethnicity, n (%)	Unknown	78 (19.0%)
Antiviral Medication, n (%)	Yes	208 (50.7%)
Antiviral Medication, n (%)	No	137 (33.4%)
Antiviral Medication, n (%)	Unknown	65 (15.9%)
CD4 Cell Count (cells/µL) , n (%)	N	391
CD4 Cell Count (cells/µL) , n (%)	Mean (SD)	438.1 (267.7)
CD4 Cell Count (cells/µL) , n (%)	Median	401
CD4 Cell Count (cells/µL) , n (%)	Range	0 – 1548

SD = standard deviation.

Of 410 paired samples tested, 305 paired samples had viral load measurements within the linear range of both assays. Table 24 shows the mean paired viral load difference between **cobas**® HIV-1 and the TaqMan® HIV-1 Test, v2.0.

Table 24 Mean of paired viral load difference between **cobas**® HIV-1 and the TaqMan® HIV-1 Test, v2.0

Number of Paired Samples	Mean of Paired Difference (log_{10} cp/mL)	Standard Error for Mean of Paired Difference	95% CI[a] for Mean of Paired Difference
305	0.112	0.013	(0.086, 0.137)

[a]CI = confidence interval.

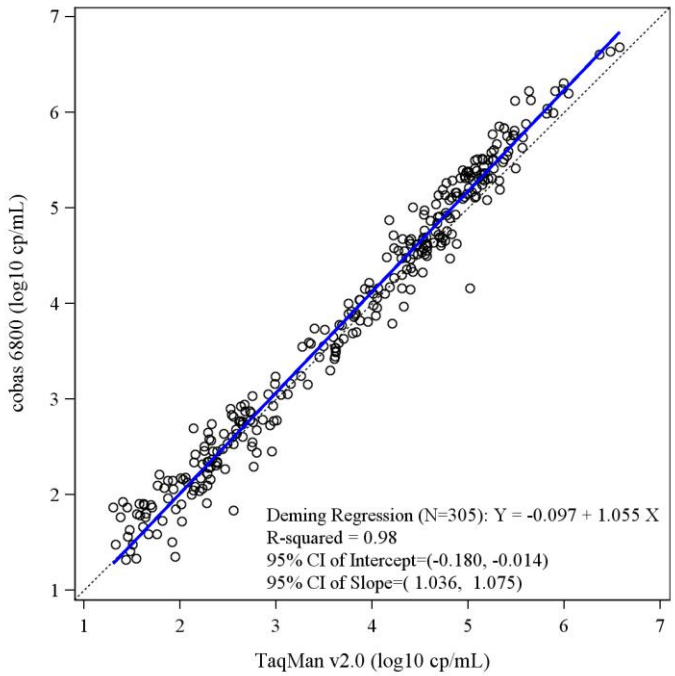
The results of Deming regression analysis between **cobas**® HIV-1 and the TaqMan® HIV-1 Test, v2.0 are tabulated in Table 25 and shown graphically in Figure 6. The dashed line indicates perfect agreement between the two test methods.

Table 25 Parameter estimates of Deming regression analysis between **cobas**® HIV-1 on the **cobas**® 6800 System and the TaqMan® HIV-1 Test, v2.0

Number of Paired Samples	Parameter	Parameter Estimate (log_{10} cp/mL)	Standard Error	95% CI[a]	R^2
305	Intercept	-0.097	0.042	(-0.180, -0.014)	0.98
305	Slope	1.055	0.010	(1.036, 1.075)	0.98

[a]CI = confidence interval; R^2 = R squared = Coefficient of multiple correlation.

Figure 6 Deming regression analysis between **cobas**® HIV-1 on the **cobas**® 6800 System and the TaqMan® HIV-1 Test, v2.0



Subsets of paired samples were also tested to compare **cobas®** HIV-1 results using the 200 µL and 500 µL sample processing volumes on both the **cobas®** 6800 and **cobas®** 8800 Systems. All comparisons showed a mean of paired difference of less than 0.095 $\log_{10}$ cp/mL.

For the comparison across sample volumes, Table 26 shows the mean paired difference between **cobas®** HIV-1 results using the 200 µL and 500 µL sample processing volumes on the **cobas®** 6800 System.

Table 26 Mean of paired viral load difference between the 200 µL and 500 µL sample processing volumes on the **cobas®** 6800 System

Number of Paired Samples	Mean of Paired Difference ($\log_{10}$ cp/mL)	Standard Error for Mean of Paired Difference	95% CI[a] for Mean of Paired Difference
111	0.094	0.014	(0.067, 0.121)

[a]CI = confidence interval.

Table 27 shows the mean paired difference between **cobas®** HIV-1 results using the 200 µL and 500 µL sample processing volumes on the **cobas®** 8800 System.

Table 27 Mean of paired viral load difference between the 200 µL and 500 µL sample processing volumes on the **cobas®** 8800 System

Number of Paired Samples	Mean of Paired Difference ($\log_{10}$ cp/mL)	Standard Error for Mean of Paired Difference	95% CI[a] for Mean of Paired Difference
111	0.080	0.012	(0.056, 0.105)

[a]CI = confidence interval.

For the comparison across systems, Table 28 shows the mean paired difference between **cobas®** HIV-1 results on the **cobas®** 6800 System and the **cobas®** 8800 System using the 200 µL sample processing volume.

Table 28 Mean of paired viral load difference between the **cobas®** 6800 System and **cobas®** 8800 System using the 200 µL sample processing volume

Number of Paired Samples	Mean of Paired Difference ($\log_{10}$ cp/mL)	Standard Error for Mean of Paired Difference	95% CI[a] for Mean of Paired Difference
109	0.011	0.013	(-0.014, 0.036)

[a]CI = confidence interval.

Table 29 shows the mean paired difference between **cobas®** HIV-1 results on the **cobas®** 6800 System and the **cobas®** 8800 System using the 500 µL sample processing volume.

Table 29 Mean of paired viral load difference between the **cobas®** 6800 System and **cobas®** 8800 System using the 500 µL sample processing volume

Number of Paired Samples	Mean of Paired Difference ($\log_{10}$ cp/mL)	Standard Error for Mean of Paired Difference	95% CI[a] for Mean of Paired Difference
123	-0.001	0.012	(-0.024, 0.022)

[a]CI = confidence interval.

A subset of paired samples spanning the linear range of the assay was also tested to compare **cobas®** HIV-1 results from BD Vacutainer® PPT™ Plasma Preparation Tubes for Molecular Diagnostic Test Methods and EDTA plasma tubes without a gel separator. This comparison was done using the **cobas®** 6800 System. The results are shown in Table 30.

Table 30 Mean of paired viral load difference between BD Vacutainer® PPT™ Plasma Preparation Tubes and EDTA plasma tubes

Number of Paired Samples	Mean of Paired Difference (log_{10} cp/mL)	Standard Error for Mean of Paired Difference	95% CI[a] for Mean of Paired Difference
42	0.026	0.027	(-0.029, 0.081)

[a]CI = confidence interval.

Clinical evaluation

The use of **cobas®** HIV-1 in monitoring HIV-1-infected subjects on antiretroviral treatment was examined by testing specimens from participants in a phase III clinical trial completed by Boehringer Ingelheim Pharmaceuticals, Inc. (BI) trial number BI 1100.1486 (VERxVE trial) using the 500 µL sample processing volume on the **cobas®** 6800 System. Subjects were included if they had sufficient sample volume up to 144 weeks of follow-up for **cobas®** HIV-1 and had not discontinued the VERxVE trial due to adverse events. Viral load results after 24 and 48 weeks of treatment using a 50 cp/mL threshold and a 200 cp/mL threshold were compared to a virological definition of treatment failure. Virological failure was defined as a viral load of greater than or equal to 50 cp/mL at the subject's last trial visit after at least 48 weeks of treatment.

Table 31 shows the demographic characteristics of the 355 subjects included in the study.

Table 31 Demographics characteristics

Demographic Characteristics	Groups	Statistics
Number of Subjects	Total, N	355
Age (years)	Mean (SD)	38 (9.3)
Age (years)	Median	38
Age (years)	Range	19 – 68
Gender, n (%)	Male	322 (90.7%)
Gender, n (%)	Female	33 (9.3%)
Race/Ethnicity, n (%)	Asian	5 (1.4%)
Race/Ethnicity, n (%)	Black / African-American	45 (12.7%)
Race/Ethnicity, n (%)	White / Caucasian	303 (85.4%)
Race/Ethnicity, n (%)	Other	2 (0.6%)
CD4 Count at Screening (cells/µL), n (%)	50 to < 200	117 (33.0%)
CD4 Count at Screening (cells/µL), n (%)	200 to < 350	209 (58.9%)
CD4 Count at Screening (cells/µL), n (%)	350 to < 400	17 (4.8%)
CD4 Count at Screening (cells/µL), n (%)	≥ 400	9 (2.5%)
CD4 Count at Screening (cells/µL), n (%)	Unknown	3 (0.8%)

SD = standard deviation.

The results of comparisons using the 50 cp/mL and 200 cp/mL thresholds at 24 and 48 weeks of treatment virological failure are shown in Table 32 and Table 33.

The analyses of the 50 cp/mL virological threshold with virological failure (at Week 24 and Week 48) are shown in Table 32. At Week 24, the PPV was 15.6% (10/64, 95% CI: 7.8%, 26.9%), and, at Week 48, the PPV was 25.7% (9/35, 95% CI: 12.5%, 43.3%). At Week 24, the NPV was 90.9% (251/276, 95% CI: 86.9%, 94.1%), and, at Week 48, the NPV was 91.1% (285/313, 95% CI: 87.3%, 94%). At Week 24, the OR was 1.86 (95% CI: 0.75, 4.29), which was not statistically significant (p = 0.191). At Week 48, the OR was 3.51 (95% CI: 1.31, 8.71) which was statistically significant (p = 0.012).

Table 32 Comparison of a 50 cp/mL virological threshold with virological failure

On-Treatment Visit	Virological Threshold	Virological Failure[a] Yes	Virological Failure[a] No	Total
Week 24	≥ 50 cp/mL	10	54	64
Week 24	< 50 cp/mL	25	251	276
Week 24	Total	35	305	340+
Week 48	≥ 50 cp/mL	9	26	35
Week 48	< 50 cp/mL	28	285	313
Week 48	Total	37	311	348+

+ Valid results obtained by **cobas®** HIV-1.

[a] Virological Failure is classified as 'Yes' if the viral load of a specimen was greater than or equal to 50 cp/mL at Week 144 or at the final visit if there was no Week 144 visit. Final visit had to be at Week 48 or later.

When 200 cp/mL thresholds were used to define virological failure as shown in Table 33, at Week 24, the PPV was 22.2% (2/9, 95% CI: 2.8%, 60%), and, at Week 48, the PPV increased to 100% (2/2, 95% CI: 15.8%, 100%). At Week 24, the NPV was 90.0% (298/331, 95% CI: 86.3%, 93%), and, at Week 48, the NPV was 89.9% (311/346, 95% CI: 86.2%, 92.9%). At Week 24, the OR was 2.57 (95% CI: 0.25, 14.27), which was not statistically significant (p = 0.469). At Week 48, the OR was 20.76 (95% CI: 2.46, Not Calculable) which was statistically significant (p = 0.022).

Table 33 Comparison of a 200 cp/mL virological threshold with virological failure

On-Treatment Visit	Virological Threshold	Virological Failure[a] Yes	Virological Failure[a] No	Total
Week 24	≥ 200 cp/mL	2	7	9
Week 24	< 200 cp/mL	33	298	331
Week 24	Total	35	305	340+
Week 48	≥ 200 cp/mL	2	0	2
Week 48	< 200 cp/mL	35	311	346
Week 48	Total	37	311	348+

+ Valid results obtained by **cobas®** HIV-1.

[a] Virological Failure is classified as 'Yes' if the viral load of a specimen was greater than or equal to 50 cp/mL at Week 144 or at the final visit if there was no Week 144 visit. Final visit had to be at Week 48 or later.

All odds ratios were above 1 and increased between 24 to 48 weeks of treatment. Statistically significant odds ratios were seen for both thresholds at Week 48. At both thresholds, the high NPV demonstrates the ability of the test to predict which patients are not failing treatment at each timepoint.

Analysis of odds ratios also demonstrated that viral load measurements of patients on treatment that are greater than the given thresholds have higher likelihood of correlation with subsequent virological failure (positive predictive value, or PPV). However, the small number of treatment failures in the study limited the statistical analysis of PPV for virologic failure.

Conclusion

cobas® HIV-1 can reliably quantitate HIV-1 and monitor response to antiretroviral treatment. The results of these studies support the utility of the test in the clinical management of HIV-1-infected patients.

System equivalency / system comparison

System equivalency of the **cobas**® 5800, **cobas**® 6800 and **cobas**® 8800 Systems was demonstrated via performance studies.

The results presented in the Instructions for Use support equivalent performance for all systems.

Additional information

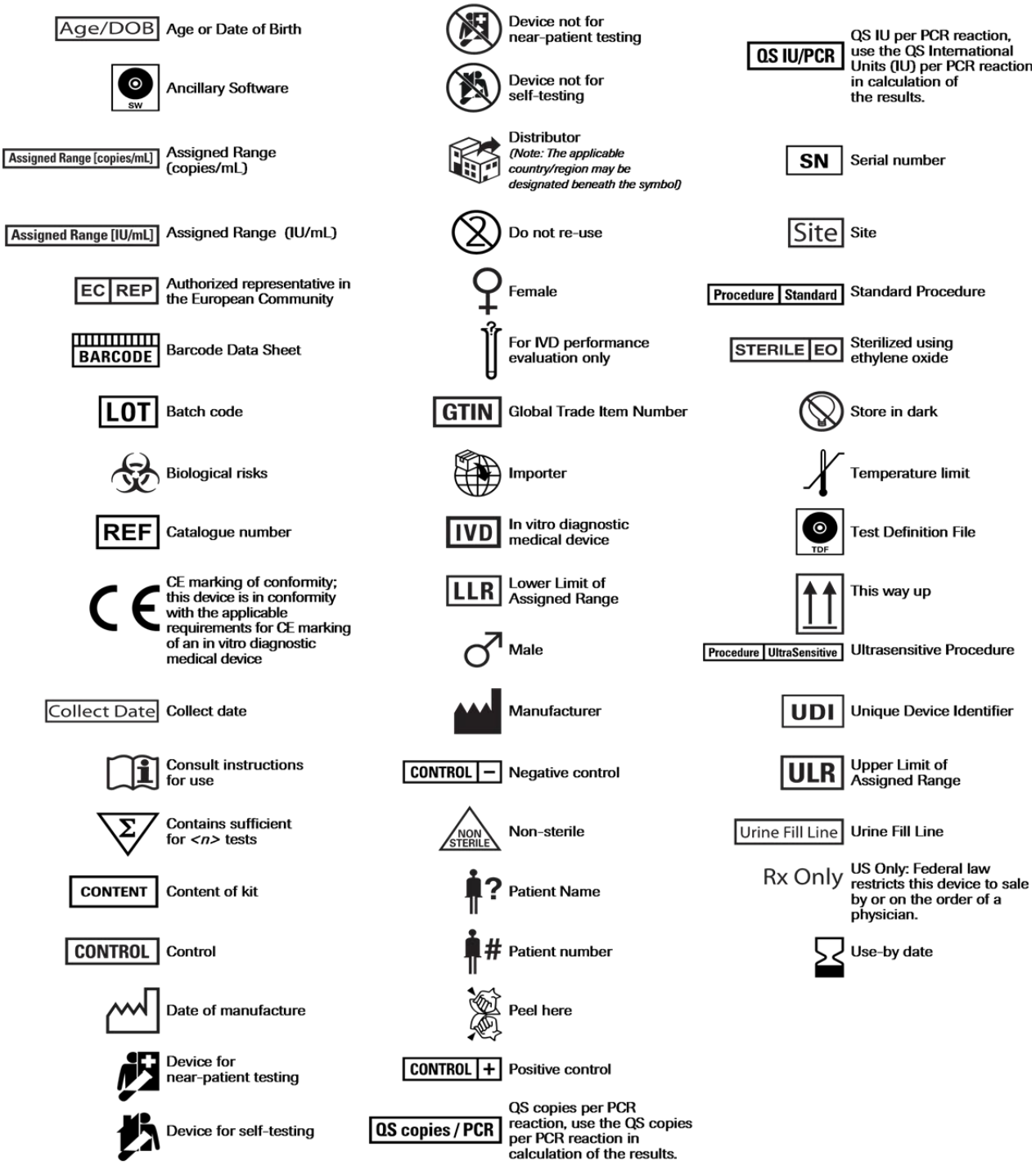
Key test features

Sample type	EDTA plasma
Minimum amount of sample required	650 µL or 350 µL
Sample processing volume	500 µL or 200 µL
Analytical sensitivity	13.2 cp/mL (500 µL)
	35.5 cp/mL (200 µL)
Linear range	20 cp/mL – 1.0E+07 cp/mL (500 µL)
	50 cp/mL – 1.0E+07 cp/mL (200 µL)
Performance with HIV-1 negative specimens	100% (two sided 95% confidence interval: 99.5%, 100%)
Genotypes detected	HIV-1M (A–D, F–H, CRF01_AE, CRF02_AG), HIV-1O, HIV-1N

Symbols

The following symbols are used in labeling for Roche PCR diagnostic products.

Table 34 Symbols used in labeling for Roche PCR diagnostics products



Technical support

For technical support (assistance) please reach out to your local affiliate:
https://www.roche.com/about/business/roche_worldwide.htm

Manufacturer and distributor

Table 35 Manufacturer and distributor

	Manufactured in the United States
	Roche Molecular Systems, Inc. 1080 US Highway 202 South Branchburg, NJ 08876 USA www.roche.com
	Made in USA
Distributed by	Roche Diagnostics 9115 Hague Road Indianapolis, IN 46250-0457 USA (For Technical Assistance call the Roche Response Center toll-free: 1-800-526-1247)

Trademarks and patents

See https://diagnostics.roche.com/us/en/about-us/patents

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Document revision

Document Revision Information	
Doc Rev. 3.0 09/2022	Updated front page with separate information for the Positive and Negative Control Kit use. Updated patent web address. Updated to current economic operators. Updated the harmonized symbol page. Please contact your local Roche Representative if you have any questions.
Doc Rev. 4.0 11/2022	Added **cobas**® 5800 specific information. Increased minimum sample volume. Please contact your local Roche Representative if you have any questions.
11/2022	Change minimum sample volume from 375 and 675 µL to 350 and 650 µL. Please contact your local Roche Representative if you have any questions.