COBAS® AmpliPrep/COBAS® TaqMan® HIV-1 Test, Summary of Safety and Effectiveness

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1. GENERAL INFORMATION

Device Generic Name	In vitro nucleic acid amplification test for the quantitation of HIV-l RNA in human plasma.
Device Trade Name	COBAS® AmpliPrep/COBAS® TaqMan® HIV-1 Test
Applicant's Name and Address	Roche Molecular Systems, Inc. (RMS) 4300 Hacienda Drive Pleasanton, CA 94588
Premarket Approval Application (PMA) Number	BP050069
Date of Notice of Approval	May 11, 2007

2. INDICATIONS FOR USE

The COBAS AmpliPrep/COBAS TaqMan HIV-1 is an *in vitro* nucleic acid amplification test for the quantitation of Human Immunodeficiency Virus (HIV-1) nucleic acid in human plasma, using the COBAS AmpliPrep Instrument for automated sample preparation and the COBAS TaqMan Analyzer or COBAS TaqMan 48 Analyzer for automated amplification and detection. This test is intended for use in conjunction with clinical presentation and other laboratory markers of disease progress for the clinical management of HIV-1 infected patients.

3. DEVICE DESCRIPTION

The COBAS AmpliPrep/COBAS TaqMan HIV-1 Test is based on three major processes:

- Automated specimen preparation to isolate HIV-1 RNA — COBAS AmpliPrep Instrument
- Automated reverse transcription of RNA and Polymerase Chain Reaction (PCR) amplification of the resultant cDNA — COBAS TaqMan Analyzer or COBAS TaqMan 48 Analyzer
- Automated detection of amplified cDNA (amplicon) using cleaved dual fluorescent dye-labeled oligonucleotide detection probes. By including an HIV-1 Quantiation Standard (QS) at a known copy number, it is possible quantitate HIV-1 in real time — COBAS TaqMan Analyzer or COBAS TaqMan 48 Analyzer

The Quantitation of HIV-1 viral RNA is done using the HIV-1 Quantification Standard (QS). It compensates for effects of inhibition and controls the preparation and amplification processes allowing a more accurate quantitation of HIV-1 RNA in each specimen. The HIV-1 QS is a non-infectious Armored RNA construct that contains HIV-1 sequences with identical primer binding sites as the HIV-1 target RNA and a unique probe binding region that allows HIV-1 QS amplicon to be distinguished from HIV-1 target amplicon. The HIV-1 QS is added into each specimen at a known copy number and is carried through the specimen preparation, reverse transcription, PCR amplification and detection steps along with the HIV-1 target. The COBAS TaqMan Analyzer or COBAS TaqMan 48 Analyzer calculates the HIV-1 RNA concentration in the test specimens by comparing the HIV-1 signal to the HIV-1 QS signal for each specimen and control.

4. CONTRAINDICATIONS

There are no known contraindications for the COBAS AmpliPrep/COBAS TaqMan HIV-1 Test. Refer to the Package Insert for a list of warnings and precautions.

5. ALTERNATIVE PRACTICES AND PROCEDURES

There are currently a variety of commercially available direct and indirect methods for the detection and quantitation of human immunodeficiency virus in clinical specimens. These methods provide a means of measuring the progression of disease associated with HIV infection and a patient’s response to antiretroviral therapy.

Some of these are listed below:

- ELISA, EIA and immunoblot procedures for measuring HIV antibody production
- HIV antigen assays including p24 Ag and CD4 and CD8 cell-surface receptors
- Nucleic acid probe technologies for direct detection and quantitation of circulating viral particles

6. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

The possibility of erroneous results exists due to test malfunction or operator error. An erroneously high test results, indicating therapeutic failure and/or a higher likelihood of progression to AIDS or death, may result in unnecessary treatment and/or psychological trauma to a patient. An erroneously low test result may lead to the lack of appropriate treatment and/or a false sense of security by a patient which could lead to a worsening of the patient's condition. The risks of erroneous test results are inherent in all *in vitro* diagnostic products. Based upon the performance of the product in the clinical studies, the probable benefit to the patient from the use of the product greatly outweighs any probable risk of injury or illness to the patient from its use.

7. MARKETING HISTORY

COBAS AmpliPrep/COBAS TaqMan HIV-1 Test has not been withdrawn from the following markets for reasons related to safety or effectiveness. Both tests currently are available in the following countries:

Argentina	Iceland	Pakistan
Australia	India	Paraguay
Austria	Indonesia	Philippines
Belarus	Ireland	Poland
Belgium	Israel	Qatar
Canada	Japan	Russia
Chile	Korea	Saudi Arabia
Cyprus	Kuwait	Slovenia
Czech Republic	Lebanon	South Africa
Denmark	Luxembourg	Spain
Ecuador	Malaysia	Sweden
Egypt	Malta	Switzerland
Finland	Mexico	Syria
France	Netherlands	Turkey
Germany	New Zealand	United Arab Emirates
Greece	Norway	United Kingdom
Hong Kong	Oman	Venezuela
Hungary		

8. SUMMARY OF NON-CLINICAL PERFORMANCE

8.1. Limit of Detection

The limit of detection of the COBAS AmpliPrep/COBAS TaqMan HIV-1 Test was determined by analysis of three independent dilution series of a HIV-1 Secondary Standard (prepared from the HIV-1B strain 8E5 LAV in HIV-1-negative human EDTA plasma). The concentration of the HIV-1 Secondary Standard is traceable to the WHO 1st International Standard for HIV-1 RNA for Nucleic Acid-Based Techniques (NAT) (NIBSC 97/656). A total of 108 replicates per concentration level were tested.

The concentration of HIV-1 RNA in EDTA plasma that can be detected with a positivity rate of greater than 95% as determined by Probit Analysis is 48 cp/mL. The study was performed for three lots of COBAS AmpliPrep/COBAS TaqMan HIV-1 Test reagents and the combined results are shown in Table 1.

Table 1: Limit of Detection of the COBAS AmpliPrep/COBAS TaqMan HIV-1 Test Determined with HIV-1B Secondary Standard in EDTA Plasma

Level No.	HIV-1B Input Conc. (copies/mL)	Total Number of Replicates Tested	Number of Positives	Hit Rate
1	100	108	108	100%
2	75	108	108	100%
3	50	108	107	99%
4	40	108	99	92%
5	30	108	98	91%
6	20	108	81	75%
7	10	108	55	51%

8.2. Precision

Precision and linearity of the COBAS AmpliPrep/COBAS TaqMan HIV-1 Test were determined by analysis of serial dilutions prepared from a highly concentrated cell culture stock of the HIV-1B in HIV-1-negative human EDTA plasma. The concentration assignment of the HIV-1B linearity panel was performed by a method that ensures traceability to the WHO 1st International Standard for HIV-1 RNA for Nucleic Acid-Based Techniques (NAT) (NIBSC 97/656).

Within-Run, Run-to-Run and Total Precision were evaluated in accordance with the methods defined in the CLIS Guideline EP5-A, "Evaluation of Precision Performance of Clinical Chemistry Devices." A run, consisting of 5 dilution levels and 7 replicates at each level, was performed daily for 15 days. Each sample was carried through the entire COBAS AmpliPrep/COBAS TaqMan HIV-1 Test procedure, including specimen preparation, amplification and detection using different systems operated by multiple users. Therefore, the precision reported here represents all aspects of the test procedure. The study was performed for three lots of COBAS AmpliPrep/COBAS TaqMan HIV-1 Test reagents, and the results are shown in Table 2.

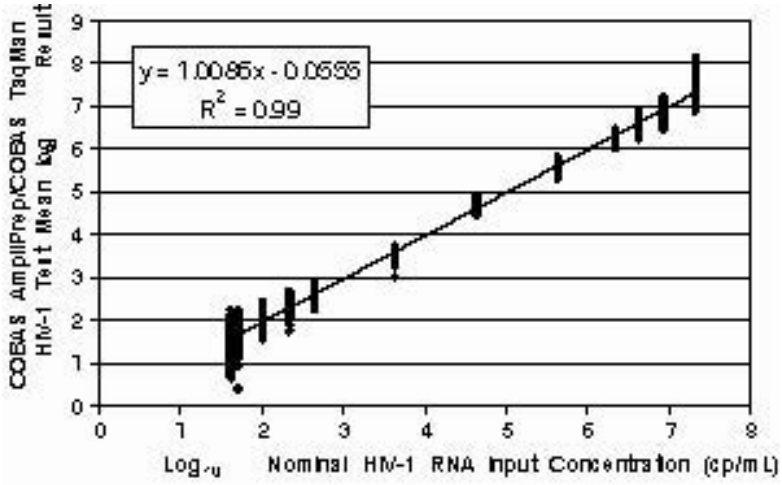
Table 2: Total Precision for Three Lots of the COBAS AmpliPrep/ COBAS TaqMan HIV-1 Test

Nominal HIV-1 Conc. Levels [cp/mL]	Log_{10} of Nominal Conc.	Lot 1		Lot 2		Lot 3	
		Total CV [%]	Total precision as SD [log_{10}]	Total CV [%]	Total precision as SD [log_{10}]	Total CV [%]	Total precision as SD [log_{10}]
100	2.000	39.5	0.18	41.4	0.18	41.8	0.18
4,310	3.634	24.5	0.11	29.3	0.13	23.1	0.10
43,100	4.634	20.0	0.09	20.6	0.09	16.9	0.08
431,000	5.634	22.4	0.10	20.0	0.09	22.8	0.10
2,150,000	6.333	24.0	0.10	23.5	0.10	24.7	0.10

8.3. Linear Range

As shown in Figure 1, the COBAS AmpliPrep/COBAS TaqMan HIV-1 Test was found to give a linear response from 48 HIV-1 RNA cp/mL to 10,000,000 HIV-1 RNA cp/mL applying the accuracy acceptance criterion of $\pm$ 0.3 log_{10} from the nominal input concentration. The study was performed using one lot of COBAS AmpliPrep/COBAS TaqMan HIV-1 Test reagents, with 103 – 105 replicates per level.

Figure 1: Linear Range of the COBAS AmpliPrep/COBAS TaqMan HIV-1 Test



8.4. Inclusivity

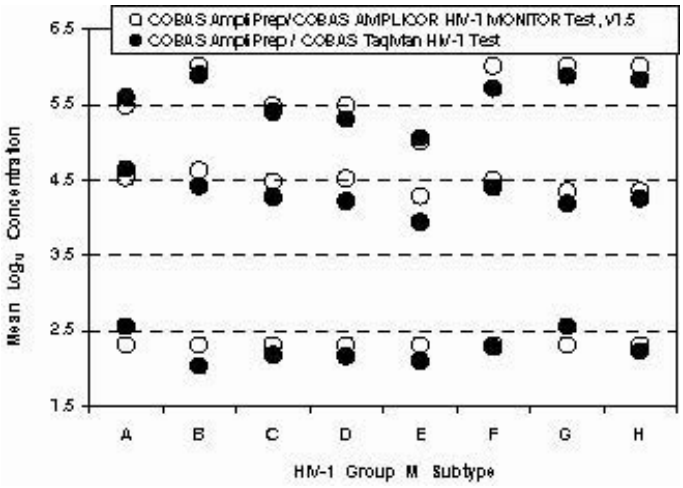
Eight subtype categories have been proposed for HIV-1 group M based on nucleotide divergence. These subtypes are designated with capital alphabetical letters from A through H.

8.4.1. Similar Subtype Quantitation

The performance of the COBAS AmpliPrep/COBAS TaqMan HIV-1 Test on HIV-1 subtypes was evaluated by analysis of cell culture stock material of representatives of each HIV-1 group M subtype A through H. The assignment of nominal concentrations of the cell culture stock solutions was performed by the COBAS AmpliPrep/COBAS AMPLICOR HIV-1 assay method (*see* Figure 2). Based on the determined stock concentrations, the HIV-1 target concentrations of 2.0E+02, 1.9 - 3.3E+04 and 1.0E+05 - 1.0E+06 cp/mL were prepared for each HIV-1 subtype by exact dilution of the cell culture stock solution in EDTA plasma. Afterwards the concentrations were determined by the COBAS AmpliPrep/COBAS TaqMan HIV-1 Test in n=7 replicates per level of each subtype using one reagent lot. Results were compared to the input concentrations as determined by the reference method.

The COBAS AmpliPrep/COBAS TaqMan HIV-1 Test gave equivalent results for all tested representatives of the HIV-1 group M subtypes (*see* Figure 2). Mean observed log_{10} concentration results were within B1 0.3 log_{10} of the respective reference method input concentration.

Figure 2: Performance of the COBAS AmpliPrep/COBAS TaqMan HIV-1 Test on HIV-1 Group M Subtypes A through H Compared Against the Reference Method COBAS AmpliPrep/COBAS AMPLICOR HIV-1 MONITOR Test



8.4.2. Subtype Limit of Detection

Parent solutions containing HIV-1 cell culture material representing HIV-1 subtypes A to H have been obtained as frozen stocks from German National Reference Centre for Retrovirology at University Erlangen-NFCrnberg, Germany. The certified parent input concentration as determined by the VERSANT® HIV-1 RNA 3.0 Assay (bDNA) reference method was used to prepare the Subtype LOD-panels. Two independent dilution series of the different HIV-1 subtypes were evaluated on two days with one lot of the COBAS AmpliPrep/COBAS TaqMan HIV-1 Test in a total of 24 replicates per concentration level for each subtype representative. The results of the probit analyses at 95% hit rate demonstrate that the COBAS AmpliPrep/ COBAS TaqMan HIV-1 Test has a sensitivity of ≦ 50 cp/mL across all subtypes ranging from < 15 to 46 cp/mL of HIV-1 group M as shown in Table 3.

Table 3: Inclusivity as Limit of Detection of the COBAS AmpliPrep/ COBAS TaqMan HIV-1 Test as Determined with Cell-Cultured Viral Stocks of the Different HIV-1 Subtypes Diluted in EDTA Plasma

Subtype	Isolate Designation	95% hit rate conc. by Probit model [cp/mL]	95% Confidence Interval [cp/mL]		Lowest Level with ≥ 95% Hit Rate [cp/mL]
			Lower	Upper	
A	92UG029	20			**30**
A	92UG037	52			**50**
A	4237A/98	< 15			**15**
A combined	92UG029/92UG037/4237A/98	**23**	12	34	**40**
B	HIV-1 Secondary Standard (8E5 LAV)	38			**40**
B	WHO 1st Int. Std. for HIV-1 RNA (97/656)	46			**50**
B	MVP-899-87	35			**50**
B combined	HIV-1 Secondary Standard (8E5 LAV)/ WHO 1st Int. Std. for HIV-1 RNA (97/656)/ MVP-899-87	**40**	33	50	**50**
C	92BR025	16			**30**
C	98TZ017	50			**50**
C	3777A/97	16			**15**
C combined	92BR025/98TZ017/3777A/97	**31**	25	41	**40**
D	92UG021	35			**40**
D	92UG035	< 15			**15**
D	92UG024	17			**30**
D combined	92UG021/92UG035/92UG024	**26**	22	34	**40**
E	92TH022	< 15			**15**
E	92TH009	44			**50**
E	92TH001	34			**50**
E combined	92TH022/92TH009/92TH001	**33**	27	44	**50**
F	93BR020	**46**	34	82	**40**
G	ARP173/RU570	**< 15**	NA	NA	**15**
H	ARP175/HIV V1557	**< 15**	NA	NA	**15**

NA, not applicable (no analysis possible since the statistical software does not allow calculating a confidence interval based on the observed hit rate profile)

8.5. Specificity

The clinical specificity of the COBAS AmpliPrep/COBAS TaqMan HIV-1 Test was determined by analysis of HIV-1-negative EDTA plasma specimens from blood donors. A total of 513 individual EDTA plasma specimens were tested. All specimens were negative for HIV-1 RNA. Based on these results, the clinical specificity of the COBAS AmpliPrep/COBAS TaqMan HIV-1 Test is 100% with the confidence interval ranging from 99.3 to 100%.

8.6. Analytical Specificity

The analytical specificity of the COBAS AmpliPrep/COBAS TaqMan HIV-1 Test was evaluated by adding cultured organisms (viruses, bacteria, yeast) or DNA (HTLV-2) at 50,000 particles/mL input concentration into HIV-1-negative human EDTA plasma and into HIV-1-positive human EDTA plasma at 10,000 cp/mL HIV-1 (*see* Table 4). The cultured organisms added to specimens have been shown not to interfere with the quantitation of HIV-1 RNA or impact the specificity of COBAS AmpliPrep/COBAS TaqMan HIV-1 Test.

Table 4: Analytical Specificity Organisms

Virus	**Bacteria**
Adenovirus type *Cytomegalovirus* *Epstein-Barr Virus* *Human Herpes Virus type 6* *Herpes simplex virus type 1* *Herpes simplex virus type 2* *Human T-Cell Lymphotropic viruss type 1* *Human T-Cell Lymphotropic viruss type 2* *Influenza A* *Hepatitis A virus* *Hepatitis B virus* *Hepatitis C virus*	*Staphylococcus aureus* *Propionibacterium acnes* **Yeast** *Candida albicans*

8.7. Method Correlation

The performance of the COBAS AmpliPrep/COBAS TaqMan HIV-1 Test was compared to the COBAS AmpliPrep/COBAS AMPLICOR HIV-1 Test to the COBAS AMPLICOR HIV-1 MONITOR Test, v1.5 and to the VERSANT HIV-1 RNA 3.0 Assay (bDNA) by analysis of n=71 undiluted clinically characterized plasma specimens from HIV-1 infected patients.

Specimens were obtained from Teragenix (Fort Lauderdale, FL, USA). Correlation was determined using the specimens for which quantitative results were obtained with each method under comparison. Specimens with a concentration result above the measuring range of the COBAS AmpliPrep/COBAS AMPLICOR HIV-1 Test using the ultrasensitive procedure (PHS) were prediluted to fall into the measuring range of the PHS. Bivariate linear regression analysis was performed on those specimens that yielded results within the linear range as shown in Figure 3, Figure 4, and Figure 5. The results obtained with the three methods under comparison showed high correlation.

Figure 3: Correlation of the COBAS AmpliPrep/COBAS TaqMan HIV-1 Test and the COBAS AmpliPrep/COBAS AMPLICOR HIV-1 MONITOR Test, v1.5

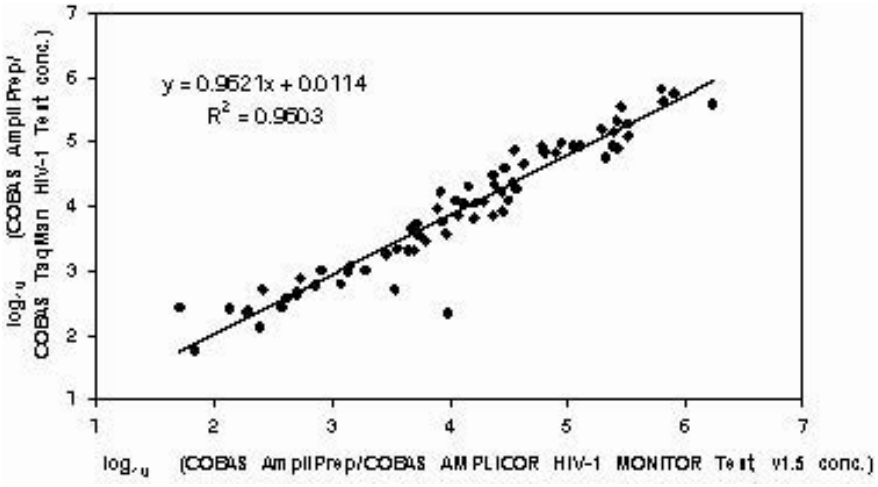


Figure 4: Correlation of the COBAS AmpliPrep/COBAS TaqMan HIV-1 Test and the COBAS AMPLICOR HIV-1 MONITOR Test, v1.5

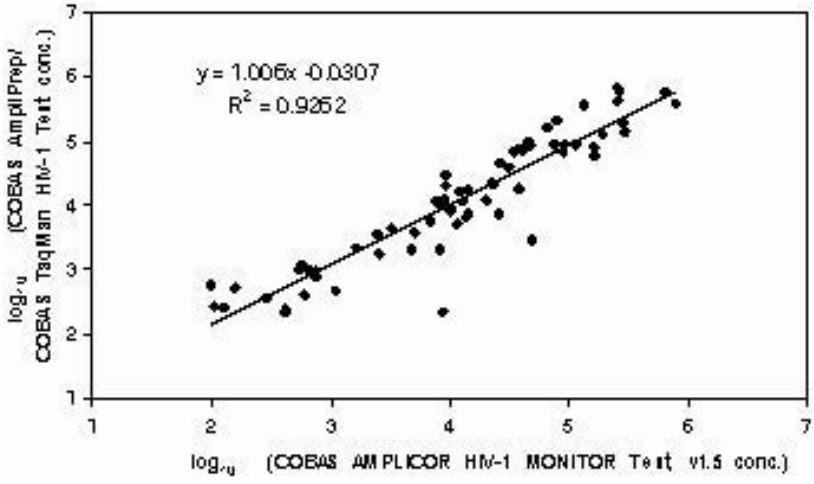
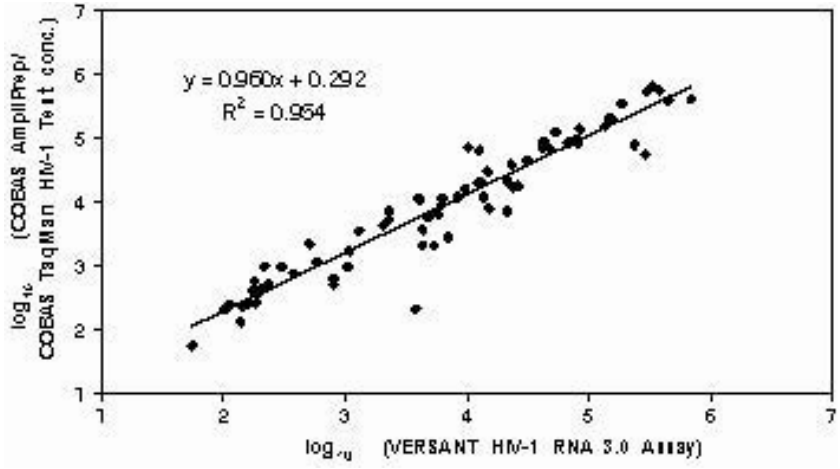


Figure 5: Correlation of the COBAS AmpliPrep/COBAS TaqMan HIV-1 Test and the VERSANT HIV-1 RNA 3.0 Assay (bDNA)



9. SUMMARY OF CLINICAL PERFORMANCE STUDIES

9.1. Reproducibility

This study was conducted to evaluate the reproducibility of the COBAS AmpliPrep/COBAS AMPLICOR HIV-1 Test in EDTA plasma. Well characterized HIV-1 group M, subtype B virus stock cultures and EDTA that was negative for HIV-1 RNA and HIV 1/2 antibodies were used to construct a 10-member panel. The study was designed to measure inter-run, intra-run, lot to lot, day to day, site to site, and operator to operator variability. Each panel was tested by multiple operators at each of three sites; one internal Roche Molecular Systems, Inc. (RMS) site, and two sites external to RMS. Each operator performed 5 days of testing on each of 3 lots of reagents with each panel. Each operator was to complete 1 run per day. Each run comprised a single panel with each panel member tested in duplicate.

Precision was evaluated using a random effects model with terms for lot, site/instrument, operator within site, between day/run and within-run components.

Table 5 shows the total precision variance and total precision standard deviation as determined by analysis of variance. Analysis of variance provides an estimate of the total precision of the test that properly weights the between-lot, between-site/instrument, between-operator, between-day/run (day-to-day) and within-run components. The total precision reported as lognormal variance was less more than 35% for all panel members except the panel member with lowest concentration (100 copies/mL). The within-run component contributed the most variability (56% to 98%), followed by lot-to-lot variability. The site/instrument, operator and day/run components contributed less to variability.

Table 6 summarizes the results for the HIV-1 Negative Panel Member. The negative panel member was used to estimate the analytical specificity of COBAS AmpliPrep/ COBAS TaqMan HIV-1 Test. One false positive result was observed out of 179 valid test results giving a specificity of 99% [95% Confidence Interval (CI) = (0.97, 1.00)].

Table 5: Precision Results Summary

HIV-1 RNA Concentration (log10 cp/mL)			Contribution to Total Variance (%)					Total Precision
Expected	Observed (Average)	N	Lot	Site / Instrument	Operator	Day / Run	Within Run	Standard Deviation (Lognormal %CV)
2.000	2.020	147	0%	0%	0%	0%	**100%**	0.19 (46%)
2.699	2.743	173	2%	6%	4%	20%	**68%**	0.14 (34%)
3.000	2.995	178	0%	8%	0%	8%	**84%**	0.14 (32%)
3.699	3.743	178	16%	5%	3%	18%	**57%**	0.14 (34%)
4.301	4.410	179	14%	6%	2%	5%	**74%**	0.14 (32%)
4.699	4.836	178	21%	1%	0%	2%	**76%**	0.12 (29%)
5.398	5.501	178	32%	0%	0%	6%	**62%**	0.13 (31%)
5.699	5.837	178	28%	0%	0%	3%	**68%**	0.14 (34%)
6.699	6.871	108	32%	4%	0%	9%	**56%**	0.13 (30%)

Note: Within assay range results are from 4.80E+1 cp/mL to 1.00E+7 cp/mL inclusive.

Table 6: HIV-1 Negative Panel Member Summary

Total Valid Results	Target Not Detected	Target Detected	Analytical Specificity	Exact 95% CI
179	178	1	0.99	(0.97, 1.00)

9.2. Clinical Sensitivity and Specificity

9.2.1. Methodology

This study was designed to evaluate the clinical specificity and sensitivity of the COBAS AmpliPrep/COBAS TaqMan HIV-1 Test by testing fresh and frozen samples collected from normal healthy donors and patients with HIV-1. This study compared Test results obtained with the CAP/CTM to those obtained with an FDA-approved test, ie, the COBAS AMPLICOR HIV-1 MONITOR Test, v1.5 (CA). Clinical specificity of the CAP/CTM was evaluated by testing 399 frozen samples and 120 fresh samples, in EDTA plasma, collected from normal healthy blood donors who were negative for HIV-1 antibodies. Frozen samples were randomly distributed across testing sites. Fresh samples were distributed to testing sites in a non-random manner. Clinical sensitivity of the CAP/CTM was evaluated testing 351 frozen samples with HIV-1 RNA concentrations ≥50 cp/mL and 122 fresh samples in EDTA plasma, collected from

HIV-1-positive blood donors. Frozen samples were randomly distributed across testing sites, stratified by CD4 count category. Fresh samples were distributed to testing sites in a non-random manner. Frozen samples used in this study were previously tested with CA and, therefore, were not retested in this study on that platform. Collection of frozen normal donor (HIV-1-negative) samples occurred at 4 sites: 1 each in Tennessee, Florida, Pennsylvania, and California. Collection of frozen HIV-1-positive samples occurred at 6 sites: 1 each in California, New Jersey, Maryland, and Missouri, and at 2 sites in Florida. Collection of fresh samples occurred at 5 sites, as follows: HIV-1-positive samples were collected at 4 sites: 2 in Florida, 2 in California; samples from normal healthy donors were collected at 1 site in Tennessee. Fresh samples collected for this study were tested prospectively on the CA platform. Testing was performed at 3 sites, with 1 COBAS AmpliPrep/COBAS TaqMan 48 Analyzer (CAP/CTM 48) system per site, with at least 3 reagent lots.

9.2.2. Statistical Methods

Normal subjects were considered evaluable if they contributed both valid CAP/CTM and CA results (where the CA result was Target Not Detected). HIV-1 subjects were considered evaluable if they contributed both valid CAP/CTM and CA results (where the CA result was ≥50 cp/mL).

CAP/CTM clinical specificity was calculated as the percentage (95% exact confidence interval [CI]) of normal subjects with Target Not Detected CA results, who had Target Not Detected CAP/CTM results. CAP/CTM clinical specificity was calculated overall and by sample type (fresh and frozen separately).

CAP/CTM clinical sensitivity was calculated as the percentage (95% exact CI) of HIV-1 subjects with CA results ≥50 cp/mL, who had detectable HIV-1 viral load on the CAP/CTM. CAP/CTM clinical sensitivity was calculated overall and by CD4 count category (<200, 200-500, >500 cells/uL) and sample type (fresh and frozen separately).

9.2.3. Results

Table 7 summarizes the number of fresh and frozen samples from evaluable normal and HIV-1 subjects in this study.

Table 7: Number of Evaluable Normal and HIV-1 Subjects by Sample Type

Sample Type	Normal Subjects	HIV-1 Subjects	Total
Fresh	120 (23.1%)	122 (25.8%)	242
Frozen	399 (76.9%)	351 (74.2%)	750
Total	519	473	992

Table 8 shows the CAP/CTM clinical specificity results from the 519 evaluable normal subjects. The CAP/CTM clinical specificity was 99.4% (516/519; 95% CI = 98.3% to 99.9%). The HIV-1-positive CAP/CTM results were all <40 cp/mL.

Table 8: CAP/CTM Specificity — Evaluable Normal Subjects

CA Result	CAP/CTM Result		Total	CAP/CTM Clinical Specificity (95% Exact CI)
	HIV-1 Positive	HIV-1 Negative		
HIV-1 Negative	3 (0.6%)	516 (99.4%)	519	99.4% (98.3%, 99.9%)

Note: CI = Confidence Interval

Table 9 shows the CAP/CTM clinical sensitivity results from the 473 evaluable HIV-1 subjects. The CAP/CTM clinical sensitivity was 98.3% (465/473; 95% CI = 96.7% to 99.3%).

Table 9: CAP/CTM Sensitivity — Evaluable HIV-1 Subjects

CA Result	CAP/CTM Result		Total	CAP/CTM Clinical Sensitivity (95% Exact CI)
	HIV-1 Positive	HIV-1 Negative		
HIV-1 Positive	465 (98.3%)	8 (1.7%)	473	98.3% (96.7%, 99.3%)

** All 8 samples that were determined to be positive for HIV-1 by the COBAS AMPLICOR HIV-1 MONITOR Test, v1.5 but not by the COBAS AmpliPrep/COBAS TaqMan HIV-1 Test had a low copy number: 6 of the 8 had HIV-1 titers of < 100 cp/mL, 1 had a titer of 253 cp/mL, and the remaining sample had a titer of 479 cp/mL.*

Table 10 shows the CAP/CTM clinical sensitivity by CD4 count category (<200, 200-500, >500 cells/uL).

Table 10: CAP/CTM Sensitivity by CD4 Count Category — Evaluable HIV-1 Subjects

CD4 Count Category (cells/uL)	CA Result	CAP/CTM Result		Total	CAP/CTM Clinical Sensitivity (95% Exact CI)
		HIV-1 Positive	HIV-1 Negative		
<200	HIV-1 Positive	141 (99.3%)	1 (0.7%)	142	99.3% (96.1%, 100.0%)
200 – 500	HIV-1 Positive	212 (98.6%)	3 (1.4%)	215	98.6% (96.0%, 99.7%)
>500	HIV-1 Positive	112 (96.6%)	4 (3.4%)	116	96.6% (91.4%, 99.1%)

Note: CI = Confidence Interval

9.2.4. Conclusion

When compared with results from the COBAS AMPLICOR HIV-1 MONITOR Test, v1.5, clinical specificity of the COBAS AmpliPrep/COBAS TaqMan HIV-1 Test was 99.4%, and clinical sensitivity was 98.3%, indicating similar performance of both tests. Furthermore, in both fresh and frozen samples, the COBAS AmpliPrep/COBAS TaqMan HIV-1 Test showed similar specificity (>98%) and sensitivity (>98%), indicating comparable test performance for both sample types.

Selection of the HIV-1 samples included in this study was based on a single test result with the COBAS AMPLICOR HIV-1 MONITOR Test, v1.5. For low titer samples, the results from the COBAS AMPLICOR HIV-1 MONITOR Test, v1.5 are subject to large variability (coefficient of variation = 50% at 100 cp/mL). All 8 samples that were determined to be positive for HIV-1 by the COBAS AMPLICOR HIV-1 MONITOR Test, v1.5 but not by the COBAS AmpliPrep/COBAS TaqMan HIV-1 Test had a low copy number: 6 of the 8 had HIV-1 titers of <100 cp/mL, 1 had a titer of 253 cp/mL, and the remaining sample had a titer of 479 cp/mL. The COBAS AmpliPrep/COBAS TaqMan HIV-1 Test was able to detect 111 out of the 119 samples with titers <480 cp/mL. The observed results are consistent with what is expected with low-titer samples. Furthermore, the COBAS AmpliPrep/COBAS TaqMan HIV-1 Test

and the COBAS AMPLICOR HIV-1 MONITOR Test, v1.5 appeared to show comparable agreement across the linear range.

The COBAS AmpliPrep/COBAS TaqMan HIV-1 Test also showed similar clinical sensitivity among CD4 count categories (>96% overall), suggesting comparable performance in samples from HIV-1 patients with various CD4 counts.

10. CONCLUSIONS DRAWN FROM THE CLINICAL STUDIES

10.1. Risk/Benefit Analysis

The COBAS AmpliPrep/COBAS TaqMan HIV-1 Test is an in vitro nucleic acid amplification test for the quantitation of Human Immunodeficiency Virus Type I (HIV-1) RNA in human plasma. The test is intended for use in conjunction with clinical presentation and other laboratory markers as an indicator of disease prognosis by measuring baseline HIV-1 RNA levels or to monitor the effects of antiretroviral drug therapy on HIV-1 RNA levels. The COBAS AmpliPrep/COBAS TaqMan HIV-1 Test is not intended to be used as a screening test for HIV or as a diagnostic test to confirm the presence of HIV infection.

Quantitative measurements of HIV viremia in the peripheral blood have shown that high levels of viral load correlate with a higher risk of clinical progression to Acquired Immunodeficiency Syndrome (AIDS) or death. Therefore, the measurement of plasma HIV-1 RNA may be an effective tool for early prognosis in HIV infected patients. In addition, changes in viral load have been shown to be an effective measure of response to antiretroviral drug therapy or lack of response to therapy. Accordingly, the measurement of changes in plasma HIV-1 RNA levels due to antiretroviral drug therapy can be used to monitor a patient’s response to the therapy.

10.2. Safety

As a diagnostic test, the COBAS AmpliPrep/COBAS TaqMan HIV-1 Test involves removal of blood from an individual for testing purposes. The test, therefore, presents no more safety hazards to an individual being tested than other tests where blood is drawn.