Elecsys HIV combi PT

HIV-1 antigen and total antibodies to HIV-1 and HIV-2

REF	Σ	SYSTEM
05390095 160	100	**cobas e** 602

For use in the USA only

System information

For **cobas e** 602 analyzers: Application Code Number 111

Intended use

Elecsys HIV combi PT is an immunoassay for the in vitro qualitative determination of HIV-1 p24 antigen and antibodies to HIV-1 (HIV-1 groups M and O) and HIV-2 in human serum and plasma. Elecsys HIV combi PT is intended to be used as an aid in the diagnosis of HIV-1 and/or HIV-2 infection, including acute or primary HIV-1 infection. The assay may also be used as an aid in the diagnosis of HIV-1/HIV-2 infection in subjects greater than 2 years of age and in pregnant women.

The Elecsys HIV combi PT assay is not intended for the screening of blood or plasma donors.

The **e**lectro**c**hemi**l**uminescence **i**mmuno**a**ssay "ECLIA" is intended for use on the **cobas e** 602 immunoassay analyzer.

A reactive result using the Elecsys HIV combi PT assay does not distinguish HIV-1 p24 antigen, HIV-1 antibody, HIV-2 antibody, and HIV-1 group O antibody. The PreciControl HIV Gen II and the PreciControl HIV; HIV-2 + Grp O are intended to be used for quality control of the Elecsys HIV combi PT immunoassay on the **cobas e** 602 immunoassay analyzer.

Summary

The human immunodeficiency virus (HIV), the causative agent of Acquired Immunodeficiency Syndrome (AIDS), belongs to the family of retroviruses. HIV can be transmitted through contaminated blood and blood products, through sexual contact or from a HIV infected mother to her child before, during and after birth.

Two types of human deficiency viruses, called HIV-1 and HIV-2, have been identified to date.[1,2,3,4] Various subtypes of the known human immunodeficiency viruses have been described, each of which has a different geographical distribution. HIV-1 can be divided into 3 distantly related groups: group M (for main), group N (for non-M, non-O) and group O (for outlier).[5,6] Based on their genetic relationship, at least 9 different subtypes (A to D, F to H, J, K) have been identified within HIV-1 group M.[7] Recombinant HIV-1 viruses consisting of sequences of two or even more different subtypes exist and are spreading epidemically.

Antibodies to HIV proteins, indicating the presence of an HIV infection, can be found in the serum usually 6-12 weeks after infection.[8,9] Due to differences in the sequence of immunodominant epitopes, especially in the envelope proteins HIV-1 group M, HIV-1 group O and HIV-2, specific antigens are necessary to avoid failure in the detection of an HIV infection by immunoassays.[9,10] By detecting the HIV-1 p24 antigen in blood specimens of recently infected patients with a high viral load, HIV infection can be detected about 6 days earlier than with traditional antibody assays.[11,12] Anti-HIV antibodies and the HIV-1 p24 antigen can be detected simultaneously using a 4th generation HIV assay. This leads to improved sensitivity and therefore, a shorter diagnostic window as compared to anti-HIV assays.[13,14]

With the Elecsys HIV combi PT assay the HIV-1 p24 antigen and antibodies to HIV-1 and HIV-2 can be detected simultanously within one determination. The assay uses recombinant antigens derived from the *env*- and *pol*-region of HIV-1 (including group O) and HIV-2 to determine HIV-specific antibodies. For the detection of HIV-1 p24, antigen specific monoclonal antibodies are used. Repeatedly reactive samples must be confirmed according to recommended CDC confirmatory algorithms. [15]

Elecsys HIV combi PT

HIV-1 antigen and total antibodies to HIV-1 and HIV-2
Test principle and procedure

For optimum performance of the assay follow the directions given in this document. Refer to the appropriate operator's manual for analyzer specific assay instructions.

Sandwich principle. Total duration of assay: 27 minutes.

- 1st incubation: Pretreatment of 39 µL of sample with detergent agent.
- 2nd incubation: Biotinylated monoclonal anti-p24 antibodies/HIV-specific recombinant antigens/HIV-specific peptides, and monoclonal anti-p24 antibodies/HIV-specific recombinant antigens/HIV-specific peptides labeled with a ruthenium complex[a)] react to form a sandwich complex.
- 3rd incubation: After addition of streptavidin-coated microparticles, the complex becomes bound to the solid phase via interaction of biotin and streptavidin.
- The reaction mixture is aspirated into the measuring cell where the microparticles are magnetically captured onto the surface of the electrode. Unbound substances are then removed with ProCell M. Application of a voltage to the electrode then induces chemiluminescent emission which is measured by a photomultiplier.

  Ensure the samples, calibrators and controls are at 20-25 °C prior to measurement.

  For optimum performance of the assay follow the directions given in this document. Refer to the appropriate operator's manual for analyzer-specific assay instructions.

  Resuspension of the microparticles takes place automatically prior to use.

  PreClean M solution is necessary.

  Bring the cooled reagents to approximately 20 °C and place on the reagent disk (20 °C) of the analyzer. Avoid foam formation. The system automatically regulates the temperature of the reagents and the opening/closing of the bottles.

  Place the reconstituted calibrators in the sample zone.

  All the information necessary for calibrating the assay is automatically read into the analyzer.

  Use calibrators only once for calibration.

a) Tris(2,2'-bipyridyl)ruthenium(II)-complex ($Ru(bpy)_3^{2+}$)

Reagents - working solutions

The reagent rackpack (M, R0, R1, R2) is labeled as HIVCOMPT.

M	Streptavidin-coated microparticles (transparent cap), 1 bottle, 6.5 mL: Streptavidin-coated microparticles 0.72 mg/mL; preservative.
R0	MES buffer 50 mmol/L, pH 5.5; 1.5 % Nonidet P40; preservative (white cap), 1 bottle, 4 mL.
R1	Anti-p24~, HIV-1/-2-specific recombinant antigens (E. coli)~, HIV-1/-2-specific peptides~biotin (gray cap), 1 bottle, 7 mL: Biotinylated monoclonal anti-p24 antibodies (mouse), biotinylated HIV-1/-2-specific recombinant antigens (E. coli), biotinylated HIV-1/-2 specific peptides > 1.3 mg/L; TRIS buffer 50 mmol/L, pH 7.5; preservative.
R2	Anti-p24~, HIV-1/-2-specific recombinant antigens (E. coli)~, HIV-1/-2-specific peptides~$Ru(bpy)_3^{2+}$ (black cap), 1 bottle, 7 mL: Monoclonal anti-p24 antibodies (mouse), HIV-1/-2 specific recombinant antigens, HIV-1/-2 specific peptides labeled with ruthenium complex > 1.5 mg/L; TRIS buffer 50 mmol/L, pH 7.5; preservative.

HIVCOMPT Cal1	Negative calibrator (white cap), 2 bottles (lyophilized) for 1.0 mL each: Human serum, negative for anti-HIV-1 and anti-HIV-2.
HIVCOMPT Cal2	Positive calibrator (black cap), 2 bottles (lyophilized) for 1.0 mL each: Anti-HIV-1 positive human serum (inactivated) in human serum negative for anti-HIV-1 and anti-HIV-2.

Elecsys HIV combi PT

HIV-1 antigen and total antibodies to HIV-1 and HIV-2

Precautions and warnings

For in vitro diagnostic use. Exercise the normal precautions required for handling all laboratory reagents. Disposal of all waste material should be in accordance with local guidelines. Safety data sheet available for professional user on request.

For USA: Caution: Federal law restricts this device to sale by or on the order of a physician.

This kit contains components classified as follows in accordance with the Regulation (EC) No. 1272/2008:

2-methyl-2H-isothiazol-3-one hydrochloride

EUH 208 May produce an allergic reaction.

Warning

H319 Causes serious eye irritation.

H412 Harmful to aquatic life with long lasting effects.

Prevention:

P264 Wash skin thoroughly after handling.

P273 Avoid release to the environment.

P280 Wear eye protection/ face protection.

Response:

P305 + P351 + P338 IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing.

P337 + P313 If eye irritation persists: Get medical advice/attention.

Disposal:

P501 Dispose of contents/container to an approved waste disposal plant.

Product safety labeling follows EU GHS guidance.

Contact phone: 1-800-428-2336

All human material should be considered potentially infectious.

The negative calibrator (HIVCOMPT Cal1) has been prepared exclusively from the blood of donors tested individually and shown to be free from HBsAg and antibodies to HCV and HIV.

The testing methods used assays approved by the FDA or cleared in compliance with the European Directive 98/79/EC, Annex II, List A.

The serum containing anti-HIV-1 (HIVCOMPT Cal2) was inactivated using β-propiolactone and UV-radiation.

However, as no inactivation or testing method can rule out the potential risk of infection with absolute certainty, the material should be handled with the same level of care as a patient specimen. In the event of exposure, the directives of the responsible health authorities should be followed.[16,17]

Elecsys HIV combi PT

HIV-1 antigen and total antibodies to HIV-1 and HIV-2

Bring the cooled reagents to approximately 20 °C and place on the reagent disk (20 °C) of the analyzer. Avoid foam formation. Place the reconstituted calibrators in the sample zone. All the information necessary for calibrating the assay is automatically read into the analyzer. Use calibrators only once for calibration.

Avoid foam formation in all reagents and sample types (specimens, calibrators and controls).

The system automatically regulates the temperature of the reagents and the opening/closing of the bottles. Ensure the samples, calibrators and controls are at 20-25 °C prior to measurement.

Reagent handling

The reagents in the kit are ready for use (except for HIVCOMPT Cal1 and HIVCOMPT Cal2) and are supplied in bottles compatible with the system.

HIVCOMPT Cal1 and HIVCOMPT Cal2: Carefully dissolve the contents of one bottle by adding exactly 1.0 mL of distilled or deionized water and allow to stand closed for 15 minutes to reconstitute. Mix carefully, avoiding foam formation.

Transfer the reconstituted calibrators into the supplied empty labeled snap-cap bottles.

Unless the entire volume is necessary for calibration on the analyzer, transfer aliquots of the reconstituted calibrators into empty snap-cap bottles (CalSet Vials). Attach the supplied labels to these additional bottles. Store the aliquots at 2-8 °C for later use.

Perform **only one** calibration procedure per aliquot.

All information required for correct operation is read in from the respective reagent barcodes.

Storage and stability

Store at 2-8 °C.

Do not freeze.

Store the Elecsys reagent kit **upright** in order to ensure complete availability of the microparticles during automatic mixing prior to use.

Stability of the reagent rackpack	
unopened at 2-8 °C	up to the stated expiration date
after opening at 2-8 °C	12 weeks
on **cobas e** 602	28 days

Stability of the calibrators	
lyophilized	up to the stated expiration date
reconstituted at 2-8 °C	12 weeks
on **cobas e** 602 at 20-25 °C	use only once

Store calibrators **upright** in order to prevent the calibrator solution from adhering to the snap-cap.

Specimen collection and preparation

Only the specimens listed below were tested and found acceptable.

Serum collected using standard sampling tubes or tubes containing separating gel.

Li-heparin, Na-citrate, Na-heparin, K_2-EDTA and K_3-EDTA plasma, as well as Li-heparin plasma from tubes containing separating gel. Sampling devices containing liquid anticoagulants have a dilution effect resulting in lower cuttoff index (COI) values for individual patient specimens. In order to minimize dilution effects, it is essential that respective sampling devices are filled completely according to manufacturer's instructions.

Criterion: Correct assignment of negative and positive samples.

Elecsys HIV combi PT

HIV-1 antigen and total antibodies to HIV-1 and HIV-2

Stable for 4 weeks at 2-8 °C, 7 days at 20-25 °C, 3 months at -20 °C (± 5 °C). The samples may be frozen and thawed not more than 5 times.

The sample types listed were tested with a selection of sample collection tubes or systems that were commercially available at the time of testing, i.e. not all available tubes of all manufacturers were tested. Sample collection systems from various manufacturers may contain differing materials which could affect the test results in some cases. When processing samples in primary tubes (sample collection systems), follow the instructions of the tube manufacturer.

Centrifuge samples containing precipitates and frozen samples before performing the assay.

Materials provided

See “Reagents – working solutions” section for reagents.

- 2 x 4 bottle labels
- 4 empty labeled snap-cap bottles

Materials required (but not provided)

- REF 06924107160, PreciControl HIV Gen II, for 6 x 2 mL
- REF 06924115160, PreciControl HIV; HIV-2 + GrpO, for 4 x 2 mL
- REF 11776576322, CalSet Vials, 2 x 56 empty snap-cap bottles
- **cobas e** 602 analyzer
- Distilled or deionized water

Accessories for **cobas e** 602 analyzers:

- REF 04880340190, ProCell M, 2 x 2 L system buffer
- REF 04880293190, CleanCell M, 2 x 2 L measuring cell cleaning solution
- REF 03023141001, PC/CC-Cups, 12 cups to prewarm ProCell M and CleanCell M before use
- REF 03005712190, ProbeWash M, 12 x 70 mL cleaning solution for run finalization and rinsing during reagent change
- REF 03004899190, PreClean M, 5 x 600 mL detection cleaning solution
- REF 12102137001, AssayTip/AssayCup, 48 magazines x 84 reaction cups or pipette tips, waste bags
- REF 03023150001, WasteLiner, waste bags
- REF 03027651001, SysClean Adapter M
- REF 11298500316, ISE Cleaning Solution/Elecsys SysClean, 5 x 100 mL system cleaning solution

Calibration

Traceability: This method has been standardized against the Human Immunodeficiency Virus Type 1 (HIV-1 p24 Antigen) - 1st International Reference Reagent 1992, code 90/636 - available from NIBSC (National Institute for Biological Standards and Control).

Calibration frequency: Calibration must be performed once per reagent lot using HIVCOMPT Cal1, HIVCOMPT Cal2 and fresh reagent (i.e. not more than 24 hours since the reagent kit was registered on the analyzer).

Renewed calibration is recommended as follows:

- after 1 month (28 days) when using the same reagent lot
- after 7 days (when using the same reagent kit on the analyzer)
- as required: e.g. quality control findings outside the defined limits

Range for the electrochemiluminescence signals (counts) for the calibrators:

Negative calibrator (HIVCOMPT Cal1): 550-2200

Positive calibrator (HIVCOMPT Cal2): 14000-70000

Elecsys HIV combi PT

HIV-1 antigen and total antibodies to HIV-1 and HIV-2

Quality control

For quality control, use PreciControl HIV Gen II and PreciControl HIV; HIV-2 + GrpO.

Controls for the various concentration ranges should be run individually at least once every 24 hours when the test is in use, once per reagent kit, and following each calibration.

The control intervals and limits should be adapted to each laboratory's individual requirements. Values obtained should fall within the defined limits. Each laboratory should establish corrective measures to be taken if values fall outside the defined limits.

If necessary, repeat the measurement of the samples concerned.

Follow the applicable government regulations and local guidelines for quality control.

Calculation

The analyzer automatically calculates the cutoff based on the measurement of HIVCOMPT Cal1 and HIVCOMPT Cal2.

The result of a sample is given either as reactive or non-reactive as well as in the form of a cutoff index (signal sample/cutoff).

Interpretation of the results

Samples with a cutoff index < 1.0 are non-reactive in the Elecsys HIV combi PT assay. These samples are considered negative for HIV-1 Ag and HIV-1/ 2 specific antibodies and do not need further testing. Samples with a cutoff index ≥ 1.0 are considered reactive in the Elecsys HIV combi PT assay. All initially reactive samples should be redetermined in duplicate with the Elecsys HIV combi PT assay. If cutoff index values are ≥ 1.0 in either of the redeterminations, the samples are considered repeatedly reactive and must be confirmed according to recommended CDC confirmatory algorithms.[15]

Limitations of the test

- The Elecsys HIV combi PT assay is for in vitro diagnostic use only.
- This assay is not for screening blood or plasma donors.
- The Elecsys HIV combi PT assay is limited to the detection of p24 antigen and/or antibodies to HIV-1 (HIV-1 groups M and O) and/or HIV-2 in human serum and plasma.
- Heat-inactivated specimens and specimens stabilized with azide should not be used. Specimens should be at 20-25 °C prior to use with the assay.
- Due to possible evaporation effects, specimens placed on the analyzers should be analyzed or measured within 2 hours.
- The calculated values for anti-HIV and/or p24 antigen in a given specimen as determined by assays from different manufacturers can vary due to differences in assay methods and reagent specificity. The results reported by the laboratory to the physician must include the identity of the assay used. Values obtained with different assay methods cannot be used interchangeably. The reported antibody level and/or p24 antigen cannot be correlated to an endpoint titer.
- Heterophilic and Human Antibodies to Mouse antigens (HAMA) in human specimens can react with reagent antibodies, interfering with in vitro immunoassays. Patients routinely exposed to animals or animal serum products for diagnosis or therapies can be prone to this interference and anomalous values may be observed. Specimens from patients who have received mouse monoclonal antibodies for diagnosis or therapy may contain human anti-mouse antibodies and may interfere in assays that employ mouse monoclonal antibodies. Additional information may be required for diagnosis.
- The performance of the Elecsys HIV combi PT assay has not been established with cord blood, neonatal specimens, cadaver specimens, heat-inactivated specimens, or body fluids other than serum and plasma such as saliva, urine, and amniotic or pleural fluids.
- The Elecsys HIV combi PT assay may not detect all infected individuals. A negative test result does not exclude the possibility of exposure to or infection with HIV. HIV antibodies and/or p24 antigen may be undetectable in some stages of the infection and in some clinical conditions.

Elecsys HIV combi PT

HIV-1 antigen and total antibodies to HIV-1 and HIV-2

- A person who has antigen or antibodies to HIV is presumed to be infected with the virus. However, a person who has participated in an HIV vaccine study may develop antibodies to the vaccine and may or may not be infected with HIV.
- The claims, including those pertaining to sample stability made in the labeling of the cleared/approved reagents of Roche Diagnostics are part of the clearance of the overall IVD test system (assay). Sample stability was tested only for the temperatures/time frame as claimed by the manufacturer under the conditions claimed in the method sheet. It is the responsibility of the individual laboratory to use all available references and/or its own studies to determine specific stability criteria for its laboratory.

Effects of Potentially interfereing Substances

The assay is unaffected by icterus (bilirubin < 1026 µmol/L or < 60 mg/dL), hemolysis (Hb < 0.310 mmol/L or < 500 mg/dL), lipemia (Intralipid < 1500 mg/dL), human serum albumin < 10 g/dL and biotin (< 201 nmol/L or < 49 ng/mL).

Samples should not be taken from patients receiving therapy with high biotin doses (i.e. > 5 mg/day) until at least 8 hours following the last biotin administration.

No interference was observed from rheumatoid factors up to a concentration of 1500 IU/mL.

In rare cases, interference due to extremely high titers of antibodies to analyte-specific antibodies, streptavidin or ruthenium can occur. These effects are minimized by suitable test design.

No false negative result due to high-dose hook effect was found with the Elecsys HIV combi PT assay.

Drug Interferences

In vitro tests were performed on 18 commonly used pharmaceuticals to determine the interference by therapeutic drugs with Elecsys HIV combi PT according to CLSI EP07-A2. Eighteen common therapeutic drugs were tested for potential interference (see table below for the drugs tested and the concentration tested). Each drug was spiked into a negative, anti-HIV antibody positive (s/co 2-4) and a HIV-Ag positive sample (s/co 2-4). The spiked samples were evaluated at a concentration C1 (3-10 times the maximum daily dosage). Each drug was found to be non-interfering at the claimed concentrations.

Elecsys HIV combi PT

HIV-1 antigen and total antibodies to HIV-1 and HIV-2

Compound	Concentration mg/dL
Acetylcysteine	1660
Ampicillin-Na	1000
Ascorbic acid	300
Cyclosporine	5
Cefoxitin	2500
Heparin	5000 U/L
Levodopa	20
Methyldopa + 1.5	20
Metronidazole	200
Phenylbutazone	400
Doxycycline	50
Acetylsalicylic acid	1000
Rifampicin	60
Acetaminophen	200
Ibuprofen	500
Theophylline	100
Tretacycline	50
Ca-Dobesilate	200

For diagnostic purposes, the results should always be assessed in conjunction with the patient's medical history, clinical examination and other findings.

A negative test result does not completely rule out the possibility of an infection with HIV. Serum or plasma samples from the very early (pre-seroconversion) phase or the late phase of HIV infection can occasionally yield negative findings. The presence of HIV antigen or antibodies to HIV is not a diagnosis of AIDS.

Effects of Potentially Medically Interfering Conditions

283 subjects with other infectious agents or medical conditions were tested with the Elecsys HIV combi PT assay comprising specimens:

- containing antibodies against HAV (acute, recovered or chronic), HBV, HCV, HTLV, CMV, EBV, HSV, VSV and Rubella virus
- containing autoantibodies and elevated titers of rheumatoid factor
- containing antibodies against Candida, E. coli, Plasmodium falciparum/vivax, Chlamydia, Treponema pallidum and Mycobacterium tuberculosis
- after vaccination against HAV, HBV, Smallpox and influenza
- from pregnant women in 1st, 2nd and 3rd trimesters and multipara pregnant women

Testing was conducted with neat and aliquots of individually spiked with HIV-1 Ab, HIV-2 Ab and HIV p24 Ag. Results showed no interference from the above agents.

Effect of Potentially Interfering Medical Conditions on sensitivity of Elecsys HIV combi PT

Elecsys HIV combi PT

HIV-1 antigen and total antibodies to HIV-1 and HIV-2

Clinical category	Number tested	Reactivity in Elecsys HIV combi PT
CMV	9	0/9
EBV	10	0/10
HSV	10	0/10
HAV	10	0/10
Rubella	5	0/5
HBV	9	0/9
HCV	9	0/9
ANA	11	0/11
Rheumatoid factor	33	0/33
Malaria	11	0/11
E. coli	11	0/11
Tuberculosis	10	0/10
HTLV	11	0/11
Candida	10	0/10
Influenza Pre Vaccination	8	0/8
Influenza Post Vaccination	8	0/8
HAV/HBV Pre Vaccination	14	0/14
HAV/HBV Post Vaccination	14	0/14
Pregnant 1st Trimester	30	0/30
Pregnant 2nd Trimester	30	0/30
Pregnant 3rd Trimester	30	0/30

Precision and Reproducibility

Precision was determined using Elecsys reagents, eight human serum samples and five levels of controls in a protocol (EP05-A3) of the CLSI (Clinical and Laboratory Standards Institute): 2 runs per day in duplication each for 21 days (n = 84).

A reproducibility study was conducted following CLSI EP05-A3 at 3 external sites on the **cobas e** 602 analyzer using three lots of reagent and one lot each of PreciControl HIV Gen II and PreciControl HIV; HIV-2 + GrpO. Pools for the precision testing included eight spiked human serum pools and control pools. The analysis of the data was based on guidance from CLSI documents EP05-A3. The precision and reproducibility data are summarized in the following tables:

Elecsys HIV combi PT

HIV-1 antigen and total antibodies to HIV-1 and HIV-2

		Repeatability		Inter-Run		Inter-Day	
Specimen type	Mean	SD	CV (%)	SD	CV (%)	SD	CV (%)
HSP06[b)]	2.03	0.087	4.30	0.018	0.88	0.045	2.22
HSP07	51.2	2.01	3.93	0.000	0.00	0.489	0.95
HSP08	1.43	0.049	3.46	0.000	0.00	0.022	1.56
HSP09	38.2	1.30	3.42	0.000	0.00	0.368	0.96
HSP10	2.25	0.157	6.97	0.000	0.00	0.029	1.29
HSP11	58.7	1.97	3.35	0.000	0.00	0.227	0.39
HSP12	4.39	0.181	4.13	0.000	0.00	0.000	0.00
HSP13	0.082	0.014	17.59	0.011	12.95	0.007	8.90
PC[c)]HIV1	0.209	0.018	8.79	0.008	3.81	0.008	4.03
PCHIV2	4.83	0.168	3.48	0.000	0.00	0.035	0.72
PCHIV3	3.92	0.117	2.99	0.032	0.83	0.050	1.27
PCHIV4	5.01	0.127	2.54	0.000	0.00	0.050	1.00
PCHIV5	5.17	0.169	3.28	0.000	0.00	0.061	1.19

b) HSP = Human serum pool

c) PC = PreciControl

Elecsys HIV combi PT

HIV-1 antigen and total antibodies to HIV-1 and HIV-2

		Inter-Site*Lot		Inter-Site	
Specimen type	Mean	SD	CV (%)	SD	CV (%)
HSP06	2.03	0.022	1.08	0.024	1.18
HSP07	51.2	0.666	1.30	0.639	1.25
HSP08	1.43	0.020	1.37	0.011	0.77
HSP09	38.2	0.378	0.99	0.563	1.47
HSP10	2.25	0.033	1.46	0.027	1.19
HSP11	58.7	0.756	1.29	0.656	1.12
HSP12	4.39	0.046	1.05	0.067	1.52
HSP13	0.082	0.009	10.94	0.000	0.00
PCHIV1	0.209	0.011	5.47	0.000	0.00
PCHIV2	4.83	0.048	0.99	0.035	0.73
PCHIV3	3.92	0.050	1.26	0.000	0.00
PCHIV4	5.01	0.054	1.07	0.042	0.84
PCHIV5	5.17	0.065	1.26	0.073	1.42

		Inter-Lot		Reproducibility	
Specimen type	Mean	SD	CV (%)	SD	CV (%)
HSP06	2.03	0.058	2.87	0.120	5.91
HSP07	51.2	1.27	2.48	2.59	5.07
HSP08	1.43	0.058	4.07	0.083	5.78
HSP09	38.2	0.89	2.34	1.76	4.61
HSP10	2.25	0.066	2.94	0.177	7.90
HSP11	58.7	2.31	3.94	3.21	5.46
HSP12	4.39	0.216	4.93	0.294	6.69
HSP13	0.082	0.021	25.94	0.030	36.73
PCHIV1	0.209	0.035	16.56	0.042	20.31
PCHIV2	4.83	0.165	3.41	0.245	5.08
PCHIV3	3.92	0.093	2.37	0.168	4.30
PCHIV4	5.01	0.286	5.71	0.324	6.47
PCHIV5	5.17	0.233	4.50	0.310	6.00

Specimen type: PCHIV1 - Negative for HIV (antigen and antibody), PCHIV2 - Positive for anti-HIV-1 antibodies, PCHIV3- Positive for HIV p24 antigen, PCHIV4 - Positive for HIV-2 antibodies, PCHIV5 - Positive

Elecsys HIV combi PT

HIV-1 antigen and total antibodies to HIV-1 and HIV-2

for HIV-1 (Group O) Antibodies, HSP06 - HIV-1 antibody group M low positive sera, HSP07 - HIV-1 antibody group M high positive sera, HSP08 - HIV Ag low positive sera, HSP09 - Ag high positive sera, HSP10 - HIV-2 Ab low positive sera, HSP11 - HIV-2 Ab high positive sera, HSP12 - HIV-1 O Ab positive sera, HSP13 - HIV Ab and Ag negative sera

Results: The precision and reproducibility of the Elecsys HIV combi PT and PreciControls demonstrated only minor variability from run to run, day to day or reagent lot to reagent lot. The total CV for the panel members ranged below the acceptance criterion of 10 %.

The results show that the precision and repeatability of Elecsys HIV combi PT demonstrated only minor variations

Analytical sensitivity

The Elecsys HIV combi PT assay was designed to have an analytical sensitivity of ≤ 2 IU/mL using the 1st International Standard HIV-1 p24 Antigen, NIBSC code 90/636. In an internal study, the standard was diluted with HIV negative serum. Using three lots of reagent, six dilution steps for each standard were prepared and measured in duplicate, recovering an average of 0.84 ± 0.11 IU/mL.

Seroconversion Panel

Seroconversion sensitivity of the Elecsys HIV combi PT assay was shown by testing 20 commercially available seroconversion panels with a total of 140 samples and comparing Elecsys HIV combi PT results to the reference assay. Seroconversion testing resulted in positive detection with the Elecsys HIV combi PT one bleed later than with the FDA approved assay in two panels. Equivalent performance was observed in 138 of the 140 total bleeds tested.

Elecsys HIV combi PT Assay Reactivity in Seroconversion Panels

Elecsys HIV combi PT

HIV-1 antigen and total antibodies to HIV-1 and HIV-2

	FDA approved HIV Ag/Ab combo assay		Elecsys HIV combi PT assay		Difference in Panel Number to the Elecsys HIV combi PT Reactivity
Panel ID	**NR[d)]**	**RX[e)]**	**NR**	**RX**	
PRB933	0	21	0	21	0
PRB942	9	14	9	14	0
PRB943	5	7	5	7	0
PRB946	4	7	4	7	0
PRB948	20	23	20	23	0
PRB951	2	8	2	8	0
PRB955	0	3	3	7	-4 (difference of 1 bleed)
PRB956	42	47	42	47	0
PRB958	2	7	2	7	0
PRB960	21	28	21	28	0
6243	20	25	25	27	-2 (difference of 1 bleed)
6244	26	28	26	28	0
6247	21	23	21	23	0
9011	28	36	28	36	0
9012	14	16	14	16	0
6248	14	18	14	18	0
9019	3	38	3	38	0
9013	23	25	23	25	0
9015	21	30	21	30	0
9016	27	30	27	30	0

d) NR represents the last draw with a non-reactive result in days since the first draw

e) RX represents the first draw with a reactive result in days since the first draw

Summary of Clinical studies

Clinical sensitivity

Reactivity in individuals known to be positive for Antibodies to HIV-1

A multi-site clinical study was performed to assess the sensitivity of Elecsys HIV combi PT in 1460 individuals who were known to be HIV-1 antibody positive, including confirmed positive adults (symptomatic or asymptomatic), positive adults from outside the US, pediatric subjects, pregnant women positive for HIV, HIV-1 group M subtypes and HIV-1 p24 antigen/antibody positive subjects. All 1460 specimens were repeatedly reactive using Elecsys HIV combi PT.

Elecsys HIV combi PT

HIV-1 antigen and total antibodies to HIV-1 and HIV-2

		Elecsys HIV combi PT assay			FDA Approved HIV assay		
Population	**Number tested**	**NR[f)]**	**IR[g)]**	**RR[h)]**	**NR**	**IR**	**RR**
Adults - asymptomatic	820	0	820	820	0	820	820
Adults - symptomatic	205	0	205	205	0	205	205
Adults - non-US	200	0	200	200	0	200	200
Pediatrics	50	0	50	50	0	50	50
Pregnant	60	0	60	60	0	60	60
HIV-1 Grp M subtypes	75	0	75	75	0	75	75
Antibody +	50	0	50	50	0	50	50
Total	1460	0	1460	1460	0	1460	1460

f) Non-reactive

g) Initially reactive

h) Repeatedly reactive

Results: The overall sensitivity of Elecsys HIV combi PT in the HIV-1 antibody positive cohort was 100.00 % with exact 95 % confidence interval of 99.75 % to 100.00 %. The sensitivity of Elecsys HIV combi PT in HIV-1 antibody positive adult cohorts (excluding pregnant and pediatric populations) was 100.00 % (1350/1350) with exact 95 % confidence interval of 99.73 % to 100.00 %.

Reactivity with samples from High Risk Individuals

A total of 758 samples from high risk adult, pediatric and pregnant subjects were tested with Elecsys HIV combi PT in a multi-site study. The pediatric samples were collected from subjects ranging in age from 2 to 21 years.

Elecsys HIV combi PT

HIV-1 antigen and total antibodies to HIV-1 and HIV-2

		Elecsys HIV combi PT assay			FDA Approved HIV assay		
Specimen population	**Number tested**	**NR**	**IR**	**RR**	**NR**	**IR**	**RR**
Adults	499	485	14	14	488	11	11
Pediatrics	134	133	1	1	133	1	1
Pregnant	125	89	36	36	96	29	29
Total	758	707	51	51	717	41	41

NR = Non-reactive, IR = initially reactive, RR = repeatedly reactive

		Repeatedly reactive specimens (Number Reactive/Positive by method)				
Specimen population	**Number tested**	**HIV-1 Western Blot**	**HIV-2 EIA**	**HIV-1 p24 Ag**	**HIV-1 RNA PCR**	**HIV-2 Western Blot**
Adults	499	11	0	0	0	0
Pediatrics	134	1	NA[i)]	NA	NA	NA
Pregnant	125	26	0	0	0	0
Total	758	38	0	0	0	0

i) NA indicated Not Applicable within this clinical study.

	FDA approved HIV assay		
Elecsys HIV combi PTassay	**Repeatedly reactive**	**Non-reactive**	**Total**
Repeatedly reactive	41	10	51
Non-reactive	0	707	707
Total	41	717	758

A total of 51/758 specimens from high risk individuals were repeatedly reactive using the Elecsys HIV combi PT assay, 41 were found to be repeatedly reactive with the FDA approved assay and 38 were confirmed to be positive by western blot.

Reactivity in Individuals Known to be Positive for Antibodies to HIV-2

The sensitivity of Elecsys HIV combi PT was determined in an internal study in subjects who were known to be positive for antibodies to HIV-2. With the Elecsys HIV combi PT 276 confirmed positive subjects were identified, including 211 subjects that tested positive on an HIV-2 Western Blot. All 211 specimens confirmed with an HIV-2 western blot are analyzed in Table below.

		Elecsys HIV combi PT assay			FDA approved HIV assay		
Specimen population	**Number tested**	**NR**	**IR**	**RR**	**NR**	**IR**	**RR**
Known Positives for ab to HIV-2	211	0	211	211	0	211	211
Total	211	0	211	211	0	211	211

NR = Non-reactive, IR = initially reactive, RR = repeatedly reactive

HIV-1 antigen and total antibodies to HIV-1 and HIV-2

The sensitivity of Elecsys HIV combi PT in the HIV-2 antibody positive cohort was 100.00 % (211/211) with a 95 % confidence interval of 98.27 % to 100.00 %.

Reactivity in Individuals from an HIV-2 endemic area

A total 706 samples from high risk subjects was tested with Elecsys HIV combi PT in a multi-site study. These samples provided by a vendor and originated from Ivory Coast, Africa, a known HIV-2 endemic region. With Elecsys HIV combi PT 276 confirmed positive subjects were identified, including 211 subjects that tested positive on an HIV-2 western blot.

		Elecsys HIV combi PT assay			FDA Approved HIV assay		
Specimen population	**Number tested**	**NR**	**IR**	**RR**	**NR**	**IR**	**RR**
HIV-2 Endemic area	706	421	286	285	422	284	284
Total	706	421	286	285	422	284	284

NR = Non-reactive, IR = initially reactive, RR = repeatedly reactive

		Repeatedly reactive specimens (Number Reactive/Positive by method)				
Specimen population	**Number tested**	**HIV-1 Western Blot**	**HIV-2 EIA**	**HIV-1 p24 Ag**	**HIV-1 RNA PCR**	**HIV-2 Western Blot**
HIV-2 Endemic area	706	237	275	1	1	211
Total	706	237	275	1	1	211

A total 706 specimens from high risk subjects was tested using the Elecsys HIV combi PT in a multi-site study. These specimens were provided by a vendor and originated from Ivory Coast, known HIV-2 endemic region from Africa.

One specimen out of 706 had an inconclusive final diagnosis and was non-reactive for the Elecsys HIV combi PT but reactive using the FDA approved assay. It was, therefore, excluded from the calculation, reducing the total number to 705. Of the 705 specimens tested, 285 were found to be repeatedly reactive using the Elecsys HIV combi PT assay, 284 were repeatedly reactive using the FDA approved assay, and 211 were confirmed to be positive with HIV-2 western blot.

	FDA approved HIV assay		
Elecsys HIV combi PT assay	**Repeatedly reactive**	**Non-reactive**	**Total**
Repeatedly reactive	277	8	285
Non-reactive	7	414	421
Total	284	422	706

Results: The overall sensitivity of the Elecsys HIV combi PT assay in the HIV-2 endemic region cohort was 99.64% (276/277) with exact 95% confidence interval of 98.01% to 99.99 %. The sensitivity of the Elecsys HIV combi PT assay in the HIV-2 western blot confirmed subjects from the HIV-2 endemic region cohort was 100 % (211/211) with exact 95 % confidence interval of 98.27 % to 100.00 %..

Reactivity in Pregnant Females

A multi-site clinical study was performed to compare the performance of Elecsys HIV combi PT to an FDA approved HIV assay using specimens from pregnant females. Prospectively and retrospectively collected samples from 440 pregnant women across all three trimesters were tested.

Elecsys HIV combi PT

HIV-1 antigen and total antibodies to HIV-1 and HIV-2

		Elecsys HIV combi PT assay			FDA Approved HIV assay		
Specimen population	**Number tested**	**NR**	**IR**	**RR**	**NR**	**IR**	**RR**
HIV-Positive pregnant females	25	0	25	25	0	25	25
High-risk pregnant females	125	89	36	36	96	29	29
Healthy Pregnant	290	290	0	0	290	0	0
Total	440	379	61	61	386	54	54

NR = Non-reactive, IR = initially reactive, RR = repeatedly reactive

		Repeatedly reactive specimens (Number Reactive/Positive by method)				
Specimen population	**Number tested**	**HIV-1 Western Blot**	**HIV-2 EIA**	**HIV-1 p24 Ag**	**HIV-1 RNA PCR**	**HIV-2 Western Blot**
HIV-positive pregnant females	25	25	NA[j)]	NA	NA	NA
High-risk pregnant females	125	26	0	0	0	0
Healthy Pregnant	290	NA	NA	NA	NA	NA
Total	440	51	0	0	0	0

j) NA indicated Not Applicable within this clinical study.

25/25 specimens from HIV-positive pregnant females were found to be positive using both the Elecsys HIV combi PT assay and the FDA approved reference assay. Of 125 specimens tested from high risk females 36 were found to be repeatedly reactive using the Elecsys HIV combi PT assay and 29 using the FDA approved assay and 26 were confirmed by HIV-1 western blot. None of 290 specimens from healthy pregnant females were found to be reactive using both assays.

Reactivity of Pregnant Females at High Risk for Infection with HIV

A multi-site clinical study was performed to compare the performance of Elecsys HIV combi PT to an FDA approved HIV assay using specimens from pregnant females at high risk for infection with HIV. One hundred twenty five samples were tested to determine the specificity in this cohort.

		Elecsys HIV combi PT assay			FDA approved HIV assay		
Specimen population	**Number tested**	**NR**	**IR**	**RR**	**NR**	**IR**	**RR**
First Trimester	18	11	7	7	11	7	7
Second Trimester	44	30	14	14	33	11	11
Third Trimester	63	48	15	15	52	11	11
Total	125	89	36	36	96	29	29

NR = Non-reactive, IR = initially reactive, RR = repeatedly reactive

Of 125 specimens tested 36 were repeatedly reactive using the Elecsys HIV combi PT assay and 29 were repeatedly reactive using the FDA approved assay.

Elecsys HIV combi PT

HIV-1 antigen and total antibodies to HIV-1 and HIV-2

Reactivity with Pediatric Samples

A multi-site clinical study was performed to compare the performance of Elecsys HIV combi PT to an FDA approved HIV assay using specimens from pediatric subjects. A total of 775 samples, collected prospectively or retrospectively, were tested. The pediatric samples include 591 low risk, 134 high risk and 50 know positive pediatric samples. Samples collected were in the age range 2 to 21 years.

Age range	Number of Samples
≥ 2-5 years	126
6-10 years	65
11-15 years	58
16-21 years	526

		Elecsys HIV combi PT assay			FDA Approved HIV assay		
Specimen population	**Number tested**	**NR**	**IR**	**RR**	**NR**	**IR**	**RR**
Pediatric HIV low risk	591	589	3	2	591	0	0
Pediatric High-risk	134	133	1	1	133	1	1
Pediatric HIV Positive	50	0	50	50	0	50	50
Total	775	772	54	53	724	51	51

NR = Non-reactive, IR = initially reactive, RR = repeatedly reactive

Of 134 specimens from a high risk pediatric population, one was found to be repeatedly reactive using both Elecsys HIV combi PT and FDA approved assays and confirmed as positive by western blot. Of 591 specimens from a low risk pediatric population, 2 were found to be repeatedly reactive using the Elecsys HIV combi PT assay and none using the FDA approved assay but were negative by western blot. None of the specimens were repeatedly reactive using the FDA approved assay.

		Repeatedly reactive specimens (Number Reactive/Positive by method)				
Specimen population	**Number tested**	**HIV-1 Western Blot**	**HIV-2 EIA**	**HIV-1 p24 Ag**	**HIV-1 RNA PCR**	**HIV-2 Western Blot**
Pediatric HIV low risk	591	0	0	0	0	0
Pediatric High-risk	134	1	NA[k)]	NA	NA	NA
Pediatric HIV Positive	50	49	NA	NA	NA	NA
Total	775	50[l)]	0	0	0	0

k) NA indicated Not Applicable within this clinical study.

l) Note: 1 sample with insufficient volume was positive based on vendor Certificate of Analysis

50/50 specimens from HIV positive pediatric patients were found to positive using both Elecsys HIV combi PT assay and the FDA approved assay. For one specimen, confirmatory testing was not performed due to insufficient specimen volume, but was classified as HIV positive based on information provided on the vendor Certificate of Analysis.

Elecsys HIV combi PT

HIV-1 antigen and total antibodies to HIV-1 and HIV-2

High Risk Pediatric Specimens Categorized by Age Range and Gender

A multi-site clinical study was performed to compare the performance of Elecsys HIV combi PT to an FDA approved HIV assay using specimens from high risk pediatric subjects. A total of 134 samples, collected prospectively, were tested. Result categorized by age range and gender are shown below

			Elecsys HIV combi PT assay			FDA Approved HIV assay		
Age	**Sex**	**Number tested**	**NR**	**IR**	**RR**	**NR**	**IR**	**RR**
2 to 5 years	Female	2	2	0	0	2	0	0
2 to 5 years	Male	2	2	0	0	2	0	0
6 to 10 years	Female	4	4	0	0	4	0	0
6 to 10 years	Male	4	4	0	0	4	0	0
11 to 15 years	Female	8	8	0	0	8	0	0
11 to 15 years	Male	6	6	0	0	6	0	0
16 to 21 years	Female	63	63	0	0	63	0	0
16 to 21 years	Male	45	44	1	1	44	1	1
Total		134	133	1	1	133	1	1

NR = Non-reactive, IR = initially reactive, RR = repeatedly reactive

Elecsys HIV combi PT

HIV-1 antigen and total antibodies to HIV-1 and HIV-2

			Repeatedly reactive specimens (Number Reactive/Positive by method)				
Age	**Sex**	**Number tested**	**HIV-1 Western Blot**	**HIV-2 EIA**	**HIV-1 p24 Ag**	**HIV-1 RNA PCR**	**HIV-2 Western Blot**
2 to 5 years	Female	2	NA	NA	NA	NA	NA
2 to 5 years	Male	2	NA	NA	NA	NA	NA
6 to 10 years	Female	4	NA	NA	NA	NA	NA
6 to 10 years	Male	4	NA	NA	NA	NA	NA
11 to 15 years	Female	8	NA	NA	NA	NA	NA
11 to 15 years	Male	6	NA	NA	NA	NA	NA
16 to 21 years	Female	63	NA	NA	NA	NA	NA
16 to 21 years	Male	45	1	NA	NA	NA	NA
Total		134	1	NA	NA	NA	NA

The Elecsys HIV combi PT assay and the FDA approved HIV assay were reactive in 1/134 specimens in the pediatric population in different age groups at high risk for HIV infection.

Clinical Specificity

A multi-site clinical study was performed to determine the specificity of Elecsys HIV combi PT and compare to an FDA approved HIV assay. HIV confirmatory testing was performed using FDA approved HIV-1 Western Blot, HIV-2 EIA and HIV-1 RNA PCR tests and using research use-only HIV-2 Western Blot and HIV-1 p24 Antigen assays. The specificity of Elecsys HIV combi PT was determined in individuals who were at low risk for HIV infection. The low-risk population (6843 specimens) included 6050 specimens from low risk adults, 202 specimens from pregnant females negative for HIV, and 591 low risk pediatric subjects. All samples were prospectively collected. Of the 87 repeatedly reactive specimens, 83 were confirmed positive.

		Elecsys HIV combi PT assay			FDA Approved HIV assay		
Specimen population	**Number tested**	**NR**	**IR**	**RR**	**NR**	**IR**	**RR**
Adults	6050	5965	91	85	5960	92	90
Pediatrics	591	589	3	2	591	0	0
Pregnant women negative for HIV	202	202	0	0	202	0	0
Total	6843	6756	94	87	6753	92	90

NR = Non-reactive, IR = initially reactive, RR = repeatedly reactive

Elecsys HIV combi PT

HIV-1 antigen and total antibodies to HIV-1 and HIV-2

		Repeatedly reactive specimens (Number Reactive/Positive by method)				
Specimen population	**Number tested**	**HIV-1 Western Blot**	**HIV-2 EIA**	**HIV-1 p24 Ag**	**HIV-1 RNA PCR**	**HIV-2 Western Blot**
Adults	6050	83	2	0	0	0
Pediatrics	591	0	0	0	0	0
Pregnant women negative for HIV	202	NA	NA[m)]	NA	NA	NA
Total	6843	83	2[n)]	0	0	0

m) Note: NA indicated Not Applicable within this clinical study.

n) Note: Two samples with an inconclusive final diagnosis were counted against Elecsys HIV combi PT and included in the calculation.

The specificity of the Elecsys HIV combi PT assay in the overall low risk population was 99.94 % (6754/6758) with exact 95 % confidence interval of 99.85 % to 99.98 %. The specificity of the Elecsys HIV combi PT assay in the adult low risk population was 99.97 % (5963/5965) with exact 95 % confidence interval of 99.88 % to 100.00 %.

Results: Two samples out of 6843 had an inconclusive final diagnosis and were non-reactive for Elecsys HIV combi PT. Hence, they were regarded as positive for the final diagnosis, so they are not considered for the calculation of the overall specificity; the total number reduces accordingly to 6841. Two samples out of 6050 had an inconclusive final diagnosis and were non-reactive for Elecsys HIV combi PT. Hence, they were regarded as positive for the final diagnosis, so they are not considered for the calculation of the specificity for low risk adults; the total number reduces accordingly to 6048. The specificity of the Elecsys HIV combi PT assay in the overall low risk population was 99.94 % (= (6841 subjects - 87 Elecsys HIV combi PT repeatedly reactive subjects) / (6841 subjects - 83 confirmed positives) = 6754/6758) with exact 95 % confidence interval of 99.85 % to 99.98 %. The specificity of the Elecsys HIV combi PT assay in the adult low risk population (excluding pregnant and pediatric populations) was 99.97 % (= (6048 subjects - 85 Elecsys HIV combi PT repeatedly reactive subjects) / (6048 subjects - 83 confirmed positives) = 5963/5965) with exact 95 % confidence interval of 99.88 % to 100.00 %.

Reactivity with Specimens Reactive for HIV-1 p24 Antigen, Antibody Negative and Western Blot Negative / Indeterminate

The sensitivity of Elecsys HIV combi PT was determined in a multi-site study in a total of 27 antigen positive, antibody negative, western blot negative / indeterminate specimens. The cohort consisted of samples from seroconversion panels and identified as authentic p24 antigen positive based on the certificate of analysis. A total of 26 samples were reactive with Elecsys HIV combi PT and the reference assay .

		Elecsys HIV combi PT assay			FDA Approved HIV assay		
Specimen population	**Number tested**	**NR**	**IR**	**RR**	**NR**	**IR**	**RR**
Authentic p24 Ag+/Ab- specimens	27	1	26	NT[o)]	1	26	NT
Total	27	1	26	NT	1	26	NT

o) Note: NT indicated Not Tested within this clinical study.

NR = Non-reactive, IR = initially reactive, RR = repeatedly reactive

Results: The sensitivity of Elecsys HIV combi PT for HIV p24 antigen only samples was 96.30 % with exact 95 % confidence interval of 81.03 % to 99.91 %.

Reactivity with HIV-1 group M subtypes

The HIV-1 group M cohort was tested with Elecsys HIV combi PT and a FDA approved HIV antigen/antibody reference assay. The HIV-1 group M cohort consisted of a total of 75 samples across 5 different subtypes: A,

Elecsys HIV combi PT

HIV-1 antigen and total antibodies to HIV-1 and HIV-2

B, C, D, and circulating recominant form, CRF01_AE, wich were all tested in the clinical study. In addition, 10 samples of circulating recominant form, CRF02_AG, were tested internally.

Subtype	Number of specimens tested	Elecsys HIV combi PT	Reference assay
A	15	15/15	15/15
B	15	15/15	15/15
C	15	15/15	15/15
D	15	15/15	15/15
CRF01_AE[p)]	15	15/15	15/15
CRF02_AG	10	10/10	10/10

p) CRF = circulating recombinant form

Elecsys HIV combi PT

HIV-1 antigen and total antibodies to HIV-1 and HIV-2

Reactivity in Specimens Positive for Antibodies to HIV-1 group O

The HIV-1 group O cohort from outside the US (Cameroon) was tested with the Elecsys HIV combi PT assay and a FDA approved HIV antigen/antibody reference assay. The HIV-1 group O cohort consisted of 42 prospectively collected native subjects. The sensitivity of Elecsys HIV combi PT was determined in a multi-site study with specimens from individuals known to be positive for HIV-1 Group O based on certificate of analysis and/or from genetic sequencing provided prior to enrollment.

		Elecsys HIV combi PT assay			FDA Approved HIV assay		
Specimen population	**Number tested**	**NR**	**IR**	**RR**	**NR**	**IR**	**RR**
Group O	42	0	42	42	0	42	42
Total	42	0	42	42	0	42	42

NR = Non-reactive, IR = initially reactive, RR = repeatedly reactive

The sensitivity of Elecsys HIV combi PT in the HIV-1 Group O cohort was 100.00 % (42/42) with exact 95 % confidence interval of 91.59 % to 100.00 %.

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Elecsys HIV combi PT

HIV-1 antigen and total antibodies to HIV-1 and HIV-2

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For further information, please refer to the appropriate operator's manual for the analyzer concerned, the respective application sheets, the product information and the Method Sheets of all necessary components (if available in your country).

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