Elecsys HTLV-I/II

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REF		Σ	SYSTEM
			cobas e 411
09015175190	09015175500	100	**cobas e** 601
			cobas e 602

English

System information

For **cobas e** 411 analyzer: test number 2440
For **cobas e** 601 and **cobas e** 602 analyzers: Application Code Number 812

Intended use

Immunoassay for the in vitro qualitative determination of antibodies to HTLV-I/II in human serum and plasma.

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

Regulatory approval

This assay has been CE marked according to Directive 98/79/EC. Test performance has been established and certified by a Notified Body according to the Common Technical Specifications (CTS) for diagnostic use and for screening of blood donations and, according to Paul-Ehrlich-Institut (PEI) recommendation,[1] for use of cadaveric blood specimens (specimens collected post-mortem, non-heart-beating).

Summary

Human T-lymphotropic virus (HTLV) type I and II are two closely related retroviruses with 70 % nucleotide sequence homology.[2] HTLV-I comprises the different subtypes A-F. The geographic areas of the highest prevalence are Japan, Africa, the Caribbean islands and South America. Additional endemic regions include the Middle East and the Melanesian islands including Papua New Guinea.[3,4] HTLV-II comprises two main subtypes, A and B.[5] Both are present in intravenous drug users in North America, Europe, and Asia and have been found sporadically in Africa. HTLV-II A is present in certain American Indian tribes of North, Central, and South America, including the Navajo and Pueblo in New Mexico and the Kayapo, Krahô, and Kaxuyana in Brazil.[6,7]

HTLV is transmitted from mother-to-child, between intravenous drug users by needle sharing, by hetero- or homosexual intercourse and contaminated blood products.[2]

With a frequency of 15-30 %, mother-to-child transmission has a similar frequency as that of an untreated HIV-1 infection, and occurs predominantly in the postnatal period through breastfeeding.[8]

Transmission by blood products is strictly cell-associated; the virus is not transmitted by plasma or plasma-derived products.[9] Recipients of contaminated blood seroconvert with a 40-60 % probability and an estimated seroconversion time of 51 days.[4] The majority of HTLV-I infected individuals remain lifelong asymptomatic carriers. Only 2-3 % of the HTLV-I infected individuals develop adult T-cell leukemia (ATL) and 0.25-4 % develop HTLV-I-associated myelopathy/tropical spastic paraparesis (HAM/TSP).[10] Although less than 10 % of HTLV-I carriers progress to ATL or HAM/TSP, the diseases are generally severe and progressively incapacitating. The disease type correlates with the route of infection; breastfeeding has been associated with ATL, and HAM/TSP with blood transfusion.[2] There have been some reports describing a correlation between HTLV-II infection and different diseases[11,12] nevertheless the evidence is not nearly as clear as that for HTLV-I.

The Elecsys HTLV-I/II assay is used for screening of blood donors to ensure the safety of blood products and for diagnosis of HTLV infection.

Test principle

Double antigen sandwich principle. Total duration of assay: 18 minutes.

- 1st incubation: 30 µL of sample, biotinylated HTLV-specific recombinant antigens (HTLV-I gp21 and HTLV-II p24) and HTLV-specific recombinant antigens (HTLV-I gp21 and HTLV-II p24) labeled with a ruthenium complex[a)] react to form a sandwich complex.
- 2nd 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/ProCell M. Application of a voltage to the electrode then induces chemiluminescent emission which is measured by a photomultiplier.
- Results are determined automatically by the software by comparing the electrochemiluminescence signal obtained from the reaction product of the sample with the signal of the cutoff value previously obtained by calibration.

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

Reagents - working solutions

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

M	Streptavidin-coated microparticles (transparent cap), 1 bottle, 6.5 mL: Streptavidin-coated microparticles 0.72 mg/mL; preservative.
R1	HTLV-specific recombinant antigens (E. coli)~biotin (gray cap), 1 bottle, 8 mL: Biotinylated HTLV-specific recombinant antigens (E. coli) > 0.3 mg/L; MES[b)] buffer 50 mmol/L, pH 6.2; preservative.
R2	HTLV-specific recombinant antigens (E. coli)~$Ru(bpy)_3^{2+}$ (black cap), 1 bottle, 8 mL: HTLV-specific recombinant antigens (E. coli) labeled with ruthenium complex > 0.3 mg/L; MES buffer 50 mmol/L, pH 6.2; preservative.

b) MES = 2-morpholino-ethane sulfonic acid

HTLV Cal1	Negative calibrator (white cap), 2 bottles (lyophilized) for 1.0 mL each: Human serum, non reactive for anti-HTLV antibodies.
HTLV Cal2	Positive calibrator (black cap), 2 bottles (lyophilized) for 1.0 mL each: Human serum, reactive for anti-HTLV antibodies.

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.

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

Warning

H317	May cause an allergic skin reaction.
H412	Harmful to aquatic life with long lasting effects.

Prevention:

P261	Avoid breathing dust/fume/gas/mist/vapours/spray.
P273	Avoid release to the environment.
P280	Wear protective gloves.

Response:

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P333 + P313 If skin irritation or rash occurs: Get medical advice/attention.

P362 + P364 Take off contaminated clothing and wash it before reuse.

Disposal:

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

Product safety labeling follows EU GHS guidance.

Contact phone: all countries: +49-621-7590

All human material should be considered potentially infectious.

Both calibrators (HTLV Cal1 and HTLV Cal2) have 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.

However, as no 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.[13,14]

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

Reagent handling

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

HTLV Cal1 and HTLV 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.

cobas e 411 analyzer: The reconstituted calibrators should only be left on the analyzers during calibration at 20-25 °C. After use, close the bottles as soon as possible and store upright at 2-8 °C.

Due to possible evaporation effects, not more than 5 calibration procedures per calibrator bottle set should be performed.

cobas e 601 and **cobas e** 602 analyzers: Unless the entire volume is necessary for calibration on the analyzers, 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.

Please note for **cobas e** 602 analyzer: Both the vial labels, and the additional labels (if available) contain 2 different barcodes. Please turn the vial cap 180° into the correct position so that the barcode between the yellow markers can be read by the system. Place the vial on the analyzer as usual.

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	8 weeks
on the analyzers	4 weeks

Stability of the calibrators	
lyophilized	up to the stated expiration date
reconstituted at 2-8 °C	4 weeks
on **cobas e** 411 at 20-25 °C	up to 5 hours
on **cobas e** 601 and **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

Specimen collected from living patients, blood donors, or individual organ, tissue or cell donors may be used, including donor samples obtained while the donor's heart is still beating.
Performance for the use of cadaveric blood specimens (specimens collected post-mortem, non-heart-beating) was established according to Paul-Ehrlich-Institut recommendation[1] with samples obtained within 24 hours after death.[15] Qualitative differences of neat (non-reactive) or spiked (reactive) specimens from cadaveric compared to living donors were not observed.

Criterion: Mean value of cadaveric specimens compared to specimens from living donors within a recovery of 75-125 %.

Only the specimens listed below were tested and found acceptable.

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

Li-heparin, Na-heparin, K_2-EDTA, K_3-EDTA, ACD, CPD, CP2D, CPDA and Na-citrate plasma as well as K_2-EDTA plasma tubes containing separating gel.

Sampling devices containing liquid anticoagulants have a dilution effect resulting in lower cutoff-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: mean recovery of positive samples within ± 20 % of serum value. Absolute deviation of samples with COI values from 0.00-1.0 within ± 0.2 COI.

Stability:
For living patients and donor specimens obtained while the donor's heart is still beating: Stable for 7 days at 20-25 °C, 14 days at 2-8 °C, 3 months at -20 °C (± 5 °C). The samples may be frozen 5 times.
For cadaveric specimens: Stable for 3 days at 20-25 °C, 7 days at 2-8 °C. The samples may be frozen 3 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/collection system manufacturer.

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

Do not use heat-inactivated samples.

Do not use samples and controls stabilized with azide.

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

Due to possible evaporation effects, samples, calibrators and controls on the analyzers should be analyzed/measured within 2 hours.

The performance of the Elecsys HTLV-I/II assay has not been established with body fluids other than serum and plasma.

Materials provided

See "Reagents – working solutions" section for reagents.

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

Materials required (but not provided)

- REF 07108133190, PreciControl HTLV, for 6 x 1.0 mL
- REF 11776576322, CalSet Vials, 2 x 56 empty snap-cap bottles
- General laboratory equipment
- Distilled or deionized water
- **cobas e** analyzer

Additional materials for the **cobas e** 411 analyzer:

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- REF 11662988122, ProCell, 6 x 380 mL system buffer
- REF 11662970122, CleanCell, 6 x 380 mL measuring cell cleaning solution
- REF 11930346122, Elecsys SysWash, 1 x 500 mL washwater additive
- REF 11933159001, Adapter for SysClean
- REF 11706802001, AssayCup, 60 x 60 reaction cups
- REF 11706799001, AssayTip, 30 x 120 pipette tips
- REF 11800507001, Clean-Liner

Additional materials for **cobas e** 601 and **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

Additional materials for all analyzers:

- REF 11298500316, ISE Cleaning Solution/Elecsys SysClean, 5 x 100 mL system cleaning solution

Assay

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

Resuspension of the microparticles takes place automatically prior to use. Read in the test-specific parameters via the reagent barcode. If in exceptional cases the barcode cannot be read, enter the 15-digit sequence of numbers.

cobas e 601 and **cobas e** 602 analyzers: 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.

After calibration has been performed, store the calibrators at 2-8 °C or discard (**cobas e** 601 and **cobas e** 602 analyzers).

Calibration

Traceability: No internationally accepted standard for HTLV-I/II exists. This method has been standardized against a Roche standard. The units have been selected arbitrarily.

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

Calibration interval may be extended based on acceptable verification of calibration by the laboratory.

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
- more frequently when this is required by pertinent regulations

Range for the electrochemiluminescence signals (counts) for the calibrators:
Negative calibrator (HTLV Cal1): 350-3000 (**cobas e** 411 analyzer), 350-2000 (**cobas e** 601 and **cobas e** 602 analyzers)
Positive calibrator (HTLV Cal2): 20000-100000 (all analyzers)

Quality control

For quality control, use PreciControl HTLV.

All controls 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 HTLV Cal1 and HTLV 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 < 1.00 are non-reactive in the Elecsys HTLV-I/II assay. These samples are considered negative for HTLV-I/II-specific antibodies and do not need further testing.

Samples with a cutoff index ≥ 1.00 are considered reactive in the Elecsys HTLV-I/II assay.

All initially reactive samples should be redetermined in duplicate with the Elecsys HTLV-I/II assay. If cutoff index values < 1.00 are found in both cases, the samples are considered negative for HTLV-specific antibodies. Initially reactive samples giving cutoff index values of ≥ 1.00 in either of the redeterminations are considered repeatedly reactive.

Repeatedly reactive samples must be confirmed according to recommended confirmatory algorithms. Confirmatory tests include Western Blot and HTLV PCR tests.

Limitations - interference

The effect of the following endogenous substances and pharmaceutical compounds on assay performance was tested. Interferences were tested up to the listed concentrations and no impact on results was observed.

Endogenous substances

Compound	Concentration tested
Bilirubin	≤ 1129 µmol/L or ≤ 66 mg/dL
Hemoglobin	≤ 0.6 mmol/L or ≤ 1000 mg/dL
Intralipid	≤ 2000 mg/dL
Biotin	≤ 4912 nmol/L or ≤ 1200 ng/mL
Rheumatoid factors	≤ 1200 IU/mL
IgG	≤ 3.2 g/dL
IgA	≤ 7 g/dL
IgM	≤ 1 g/dL

Criterion: Mean recovery of positive samples within ± 15 %. Absolute deviation of samples with COI values from 0.00-1.0 within ± 0.2 COI.

Studies have been performed to assess the high-dose hook effect. Out of 1149 positive samples no false negative result was found. Occurence of high-dose effect cannot be completely excluded.

Pharmaceutical substances
In vitro tests were performed on 17 commonly used pharmaceuticals. No interference with the assay was found.

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.

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 HTLV-I/II. Serum or plasma samples from the very early (pre-seroconversion) phase or the late phase of HTLV-I/II infection can occasionally yield negative findings.

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Specific performance data

Representative performance data on the analyzers are given below. Results obtained in individual laboratories may differ.

Precision

Precision was determined using Elecsys reagents, samples and controls in a protocol (EP05-A3) of the CLSI (Clinical and Laboratory Standards Institute): 2 runs per day in duplicate each for 21 days (n = 84). The following results were obtained:

cobas e 411 analyzer					
		Repeatability[c]		**Intermediate precision**[d]	
Sample	Mean COI	SD COI	CV %	SD COI	CV %
HS[e] 1	0.163	0.003	1.6	0.010	6.3
HS 2	0.929	0.008	0.8	0.046	4.9
HS 3	0.881	0.007	0.8	0.041	4.6
HS 4	1.05	0.012	1.2	0.050	4.8
HS 5	5.45	0.111	2.0	0.294	5.4
HS 6	24.1	0.269	1.1	1.19	4.9
PC[f] HTLV 0	0.180	0.004	2.1	0.011	6.4
PC HTLV 1	5.18	0.045	0.9	0.233	4.5
PC HTLV 2	2.68	0.025	0.9	0.128	4.8

c) Repeatability = within-run precision

d) Intermediate precision = between-run

e) HS = human serum

f) PC = PreciControl

cobas e 601 and **cobas e** 602 analyzers					
		Repeatability		**Intermediate precision**	
Sample	Mean COI	SD COI	CV %	SD COI	CV %
HS 1	0.088	0.001	1.6	0.002	2.3
HS 2	0.957	0.018	1.9	0.026	2.8
HS 3	0.913	0.018	1.9	0.022	2.5
HS 4	1.11	0.019	1.7	0.027	2.4
HS 5	6.00	0.125	2.1	0.195	3.2
HS 6	26.4	0.533	2.0	0.736	2.8
PC HTLV 0	0.089	0.002	1.8	0.002	2.6
PC HTLV 1	5.56	0.106	1.9	0.159	2.9
PC HTLV 2	2.86	0.053	1.9	0.074	2.6

Analytical specificity

222 samples containing potentially interfering substances were tested with the Elecsys HTLV-I/II assay comprising specimens containing antibodies:

- against HIV, EBV, HSV-1/2, Rubella, HAV, HBV, HCV, E. coli
- from autoimmune diseases (e.g. ANA) and elevated titers of rheumatoid factor

No false reactive results were found with the Elecsys HTLV-I/II assay resulting in a specificity of 100 %. Two samples were found repeatedly reactive with the Elecsys HTLV-I/II assay and were confirmed positive with HTLV immunoblot.

Clinical sensitivity

Of 1149 samples from HTLV-I/II infected patients of different geographical origin in different stages of the disease 1149 were found to be repeatedly reactive with the Elecsys HTLV-I/II assay. The sensitivity of the Elecsys HTLV-I/II assay in this study was 100 %.

Cohorts (by geographical origin)	N	Confirmed positive samples	Sensitivity %
Japan	420	420	100
South America	134	134	100
Carribean	97	97	100
USA	259	259	100
Europe/Middle East	236	236	100
Africa	3	3	100

Cohorts (summarized by virus type)	N	Confirmed positive samples	Sensitivity %
Total HTLV I	926	926	100
Total HTLV II	200	200	100
Total HTLV type unknown	23	23	100
Total	1149	1149	100

Clinical specificity

A total of 13974 samples (diagnostic routine, pregnant women and blood donors) from 6 centers in Europe and Japan were tested with the Elecsys HTLV-I/II assay. The resulting specificity in the study was 99.95 % in blood donors (n = 11575) and 99.83 % in diagnostic routine including pregnant women (n = 2399). The 95 % lower confidence limit was 99.89 % in blood donors and 99.56 % in diagnostic routine including pregnant women.

Cohort	N	Confirmed positive samples	Indeterminate samples	Specificity[g] %
Blood donor serum	9551	1	2	99.94 (99.86-99.98)
Blood donor EDTA plasma	2024	0	1	100 (99.82-100)
Diagnostic routine (including pregnant women)	2399	59	3	99.83 (99.56-99.95)

g) 95 % confidence interval, two sided

References

1 Proposal for the Validation of Anti-HIV-1/2 or HIV Ag/Ab Combination Assays, anti-HCV-Assays, HBsAg and Anti-HBc assays for Use with Cadaveric Samples; PEI 08/05/2014.

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12 Zehender G, Colasante C, Santambrogio S, et al. Increased Risk of Developing Peripheral Neuropathy in Patients Coinfected With HIV-1 and HTLV-2. JAIDS 2002;31:440-447.

13 Occupational Safety and Health Standards: Bloodborne pathogens. (29 CFR Part 1910.1030). Fed. Register.

14 Directive 2000/54/EC of the European Parliament and Council of 18 September 2000 on the protection of workers from risks related to exposure to biological agents at work.

15 Commission Directive 2006/17/EC of 8 February 2006 implementing Directive 2004/23/EC of the European Parliament and of the Council as regards certain technical requirements for the donation, procurement and testing of human tissues and cells.

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

A point (period/stop) is always used in this Method Sheet as the decimal separator to mark the border between the integral and the fractional parts of a decimal numeral. Separators for thousands are not used.

Symbols

Roche Diagnostics uses the following symbols and signs in addition to those listed in the ISO 15223-1 standard (for USA: see dialog.roche.com for definition of symbols used):

CONTENT	Contents of kit
SYSTEM	Analyzers/Instruments on which reagents can be used
REAGENT	Reagent
CALIBRATOR	Calibrator
→	Volume for reconstitution
GTIN	Global Trade Item Number

CE 0123

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