Journal of Clinical Virology 112 (2019) 45–50

Contents lists available at ScienceDirect

Journal of Clinical Virology

journal homepage: www.elsevier.com/locate/jcv

A multicentre evaluation of the Elecsys® HIV Duo assay

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ARTICLE INFO

Keywords:
HIV
Antigen
Antibody
Sensitivity
Specificity

ABSTRACT

Background: Fourth generation HIV assays, which detect both HIV p24 antigen and HIV antibodies are widely used in HIV screening. The combination of markers enables the fourth generation assays to shorten the window of detection, which is important in real-world testing scenarios. The Elecsys® HIV Duo assay is a fourth generation assay, which provides an overall result based on both the detection of the p24 antigen and HIV antibodies, and lists the sub-results for the antibody and antigen units.

Objectives and study design: The performance of the Elecsys® HIV Duo assay was assessed at five international centres and compared with other available fourth generation assays.

Results: The specificity of the Elecsys® HIV Duo assay in 13,328 blood donor samples was 99.87% (95% confidence interval [CI] 99.80–99.93) and was 100% (95% CI 99.63–100) in 1000 routine diagnostic samples. Sensitivity was assessed in 139 seroconversion panels; the Elecsys® HIV Duo assay detected a greater number of positive samples/number of bleeds compared with other assays investigated. An individual analysis of those seroconversion panels also shows that the Elecsys® HIV Duo assay compared to other fourth generation assays detected HIV up to 2 days earlier than other assays.

The Elecsys® HIV Duo assay also detected 125/130 'early seroconversion' samples assessed, which was greater than the number detected with comparator fourth generation assays.

Conclusion: These results indicate that the Elecsys® HIV Duo assay is appropriate for use in the diagnosis of HIV and for screening of blood donations and is sensitive for the early detection of HIV.

1. Background

HIV continues to be a major public health concern, with more than 36 million people worldwide living with HIV [1]. HIV can be transmitted through certain bodily fluids, for example via sexual intercourse, sharing injection drug equipment, or from mother to child during pregnancy or breastfeeding [2]. It is estimated that only 70% of people living with HIV know their status and, as such, there is a need for patients to have access to effective testing [1]. HIV can also be transmitted via blood transfusion; therefore, sensitive screening assays are vitally important [2].

HIV p24 antigen is one of the earliest markers of HIV infection and typically appears around the first 2 weeks post infection [3,4]. Antibodies to HIV are usually detected later, with IgM and IgG antibodies detected approximately 3 and 6 weeks post infection, respectively [5]. In hospitals and routine laboratories HIV screening is usually performed using antigen/antibody test, unless a person is at high risk of exposure and a nucleic acid test (NAT) might be requested, although this is region specific. In blood donation centres, serological and NAT screening are performed in parallel in most countries [6–8].

Fourth generation HIV assays detect both HIV p24 antigen and antibodies to HIV-1 and HIV-2, decreasing the negative test window to 11–14 days post exposure, compared with assays that detected antibodies alone [3]. Fourth generation tests have been shown to improve the detection rate of HIV in real-world situations and to reduce the turnaround time of results reporting [9–12].

The Elecsys® HIV Duo assay is a new fourth generation assay which provides a result for both the HIV antigen and the HIV antibody

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https://doi.org/10.1016/j.jcv.2018.11.005
Received 19 April 2018; Received in revised form 8 November 2018; Accepted 19 November 2018

modules, in addition to an overall test result. This information can be used to aid in the selection of the confirmation test for reactive samples.

2. Objectives

The objective of this multicentre study was to evaluate the sensitivity and specificity of the Elecsys® HIV Duo assay using blood donor samples, and samples from routine diagnosis, comparing it with other commercially available fourth generation assays.

3. Study design

3.1. Participating laboratories and compliance

Five laboratories from four different countries (Austria [Innsbruck], Germany [Hagen, Augsburg], Spain [Barcelona] and Thailand [Bangkok]) and the Roche Diagnostics laboratory (Penzberg, Germany) participated in the clinical study. An additional two laboratories (Frankfurt and Munich, Germany) participated in the sensitivity analysis. The study was conducted in compliance with all relevant directives of the European Union (EU) parliament and the EU council. Ethical approval was obtained for all blood donation centres. Routine samples were fully anonymised and commercial samples were collected under informed consent.

3.2. Assays

The Elecsys® HIV Duo assay (Roche Diagnostics GmbH, Mannheim, Germany) is an electrochemiluminescence assay for use on the cobas **e** analysers. The assay is comprised of an HIV-antigen and an HIV-antibody module, results are reported for each module and in a calculated summarized HIV Duo result. More detailed information about the proteins used and the detection methods can be found in the HIV DUO method sheet (Elecsys HIV DUO [method sheet 2018-10,V 2.0]. Roche Diagnostics GmbH, Sandhofer Strasse 116, D-68305 Mannheim).

Each of the study sites used at least one comparative assay and platform of the following: Elecsys® HIV combi PT (Roche Diagnostics, Rotkreuz, Switzerland), ABBOTT ARCHITECT® and ABBOTT PRISM® HIV Ag/Ab Combo (Abbott Laboratories, Illinois, USA), Enzygnost® HIV Integral 4 (Siemens Healthcare GmbH, Erlangen, Germany), ABBOTT PRISM® HIV O Plus (Abbott Laboratories, Illinois, USA), LIAISON® XL murex HIV Ab/Ag (DiaSorin, Saluggia, Italy), ADVIA Centaur® HIV Ag/Ab Combo (Siemens Healthcare GmbH, Erlangen, Germany; Table 1).

3.3. Samples used for specificity analysis

Specificity analysis was performed using both fresh and frozen serum samples. Assay specificity was tested in: 13,330 blood donor samples, 1000 routine diagnostic samples, 1090 samples from pregnant women and 280 dialysis patients (Table 1). Confirmatory methods used were NAT and an immunoblot test, or an HIV-antigen test was used when NAT was not available (Table 1). In addition, 196 potentially cross-reacting samples were tested.

3.4. Samples used for sensitivity analysis

A total of 139 commercial seroconversion panels were assessed with the Elecsys® HIV Duo and Elecsys® HIV combi PT assays and compared with results from different assays provided by the panel vendor. Those seroconversion panels were individually analysed with the Elecsys® HIV Duo, ABBOTT ARCHITECT® and PRISM® HIV Ag/Ab Combo and LIAISON® XL murex HIV Ab/Ag assays at three centres (Table 1), calculating the average number of days a bleeding tested positive after being NAT positive. Panels with no available data from the panel provider, or panels being positive or negative in all bleeds were excluded from calculation. One hundred and thirty commercially available 'early seroconversion' samples were tested with the Elecsys® HIV Duo and Elecsys® HIV combi PT assays and compared with results from different assays provided by the panel vendor.

In total 1447 commercially obtained samples from various countries were used for the sensitivity analysis, including samples positive for HIV-1 group O and HIV-2 subtypes and HIV-1 p24 antigen samples. These samples were tested as part of the MCE-Study HIV Duo versus HIVcPT in house in Penzberg. The positive samples included different HIV-1, group M subtypes, CRFs, and group O (1447 samples); HIV-2 positives (202 samples); HIV antigen positives (50 samples); and virus lysates (A–J, O, HIV-2) (55 samples). Additionally, 40 viral lysates (A–G, CRF01-AE, HIV2, GrpO) were tested in three dilutions to assess the HIV antigen dilution-reactivity.

To assess and compare the cut-off sensitivity of the HIV antigen module, serial dilutions of the World Health Organization (WHO) HIV-1 p24 Antigen Standard (NIBSC code: 90/636) in human serum were assessed with the Elecsys® HIV Duo assay.

3.5. Reference standard and analyses

Determinations were carried out in single measurements. Initially reactive (IR) specimens were repeated in duplicate determinations, except with characterised positive samples. All repeatedly reactive (RR) results were confirmed with HIV NAT and immunoblot testing. In the routine diagnostic laboratory at Augsburg, plasma was not available and discrepant samples were confirmed with Elecsys® HIV Ag/Elecsys® HIV Ag Confirmatory Test.

4. Results

4.1. Specificity

The specificity of the Elecsys® HIV Duo assay in 13,328 blood donor samples was 99.87% (95% confidence interval [CI] 99.80–99.93) and was similar to the specificities of the comparator assays, and slightly better than that of Elecsys HIV combi PT (Table 2).

Specificity assessed in 1000 routine diagnostic samples was 100% (95% CI 99.63–100) and was comparable to the specificity of comparator assays (Table 3). The specificity of the Elecsys® HIV Duo assay in 1090 samples from pregnant women was 99.82% (95% CI 99.34–99.98) and in 280 samples from dialysis patients was 100% (95% CI 99.68–100; Table 4).

In investigation of potentially cross-reactive factors, the Elecsys® HIV Duo assay had no false positive reaction with any of the 196 potentially cross-reactive samples assessed (Supplementary Table 1).

4.2. Sensitivity

The sensitivity of the Elecsys® HIV Duo assay was assessed in 139 seroconversion panels. Compared with other assays, the Elecsys® HIV Duo assay detected the highest number of positive bleedings vs. panels assessed (number of panels/number of positive bleedings) (Table 5). 52 seroconversion panels were equally represented by Elecsys® HIV Duo, ABBOTT ARCHITECT® and PRISM® HIV Ag/Ab Combo (Table 5). The respective ratio of positive to total bleedings was calculated for all these 52 panels and was highest for Elecsys® HIV Duo (0.363) followed by ABBOTT ARCHITECT® HIV Ag/Ab Combo (0.352), then the ABBOTT PRISM® HIV Ag/Ab Combo (0.336).

An individual analysis of seroconversion panels was used to compare seroconversion sensitivity in a broader number of assays (Fig. 1).

Table 1
Samples assessed and the methods for each centre.

Study site	Reference systems	Confirmatory methods	Samples contributed
Blood donation centres			
Zentralinstitut f. Bluttransfusion und Immunolog. Abt. der tirolkliniken Landeskrankenhaus Innsbruck, Innsbruck, Austria	Elecsys® HIV combi PT on E170 ABBOTT ARCHITECT® HIV Ag/Ab combo Enzygnost® HIV Integral 4	INNO-LIA™ HIV I/II Score, Fujirebio GFE Virus Screening PCR Kit	2029 blood donor samples
DRK Blutspendedienst West, Zentrallabor, Hagen, Germany	Elecsys® HIV combi PT on e602 ABBOTT PRISM® HIV Ag/Ab combo	INNO-LIA™ HIV I/II Score, Fujirebio GFE Virus Screening PCR Kit	4141 blood donor samples
Banc de Sang i Teixits, Transfusion Safety Lab, Barcelona, Spain	ABBOTT PRISM® HIV O Plus ABBOTT ARCHITECT® HIV Ag/Ab combo	INNO-LIA™ HIV I/II Score, Fujirebio Procleix® Ultrio®, Grifols	4160 blood donor samples
Dept. of Transfusion Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand	ABBOTT ARCHITECT® HIV Ag/Ab combo	INNO-LIA™ HIV I/II Score, Fujirebio cobas® MPX Test	3000 blood donor samples
Routine laboratory			
Labor Schottdorf MVZ GmbH, Abt. RIA Augsburg, Germany	Elecsys® HIV combi PT on E170 ABBOTT ARCHITECT® HIV Ag/Ab combo LIAISON® XL Murex HIV Ab/Ag ADVIA Centaur® HIV Ag/Ab Combo	INNO-LIA™ HIV I/II Score, Fujirebio Elecsys® HIV Ag, Elecsys® HIV Ag Confirmatory Test	1000 routine diagnostic samples 1000 samples from pregnant women
Research laboratory			
Roche Diagnostics, Penzberg, Germany	Elecsys® HIV combi PT	INNO-LIA™ HIV I/II Score, Fujirebio	90 samples from pregnant women 280 samples from patients receiving dialysis 196 samples from patients with potentially cross-reacting factors 130 'early' seroconversion panels 139 seroconversion panels 20 seroconversion panels with NAT positivity 1447 samples from different HIV-1 sub-groups WHO p24 standard dilutions
Laboratories involved in sensitivity testing			
Synlab Labor München Zentrum Medinzinisches Versorgungszentrum Gbr, Munich, Germany	ABBOTT ARCHITECT® HIV Ag/Ab Combo ADVIA Centaur® HIV Ag/Ab Combo LIAISON® XL murex HIV Ag/Ab		20 seroconversion panels with NAT positivity
DRK Blutspendedienst Baden-Württemberg-Hessen GmbH Frankfurt, Germany	ABBOTT PRISM® HIV Ag/Ab Combo		20 seroconversion panels with NAT positivity

NAT, nucleic acid test; WHO, World Health Organization.

The average number of days when bleedings tested serologically positive after being NAT positive was calculated for each assay. For 98 panels, Elecsys® HIV Duo was positive 5.9 days after NAT, HIV combi PT 7.3 days (n = 97), ABBOTT ARCHITECT® HIV Ag/Ab Combo 7.4 days (n = 49), LIAISON Murex XL HIV Ag/Ab Combo 8.1 days (n = 40), ABBOTT PRISM® HIV Ag/Ab Combo 8.19 days after NAT (n = 48) (Fig. 1a). A head to head comparison of a subset of the same seroconversion panels (n = 48) again shows HIV Duo detecting HIV

Table 2
Specificity results in blood donor serum samples.

	Elecsys® HIV Duo	Elecsys® HIV Combi PT	ABBOTT ARCHITECT® HIV Ag/Ab combo	ABBOTT PRISM® HIV Ag/Ab combo	Enzygnost® HIV Integral 4	ABBOTT PRISM® HIV O Plus
N total	13330	6170	9189	4141	2029	4160
Confirmed indeterminate/NR	2/13313	0/6159	2/9178	0/4140	0/2029	2/4154
Negative	13328	6170	9187	4141	2029	4159
IR	17	12	14	3	2	6
RR	17	11	11	1	0	0
RRfpos	17	11	9	1	0	6
RR confirmed positive	0/17	0/11	0/11	0/1	0/0	0/6
RR confirmed indeterminate	0/17	0/11	2/11	0/1	0/0	0/6
RR confirmed negative	17/17	11/11	9/11	1/1	0/0	6/6
Specificity %RR	99.87	99.82	99.90	99.98	100	99.86
CI	99.80–99.93	99.68–99.91	99.81–99.96	99.87–100	99.82–100	99.69–99.95

NR, not reactive; IR, initially reactive; RR, repeatedly reactive; RRfpos, repeatedly reactive false positive; CI, confidence interval.

Table 3
Specificity results in routine diagnostic serum samples.

	Elecsys® HIV Duo	Elecsys® HIV Combi PT	ABBOTT ARCHITECT® HIV Ag/Ab Combo	LIAISON® XL murex HIV Ab/Ag	ADVIA Centaur® CHIV
N total	1000	1000	1000	999*	999
Confirmed indeterminate/NR	1/1000	1/1000	0/998	1/993	1/997
N negative	999	999	999	998*	999
IR	0	1	2	6	2
RR	0	1	2	5	2
RRfpos	0	1	1	5	2
RR confirmed positive	0/0	0/1	0/2	0/5	0/2
RR confirmed indeterminate	0/0	0/1	1/2	0/5	0/2
RR confirmed negative	0/0	1/1	1/2	5/5	2/2
Specificity %RR	100.00	99.90	99.90	99.50	99.80
95% CI	99.63–100	99.44–100	99.44–100	99.83–99.84	99.28–99.98

NR, not reactive; IR, initially reactive; RR, repeatedly reactive; RRfpos, repeatedly reactive false positive; CI, confidence interval.
* One sample excluded as the volume was not sufficient.

earlier than ABBOTT ARCHITECT® HIV Ag/Ab Combo and ABBOTT PRISM® HIV Ag/Ab Combo (Fig. 1b).

In total, 130 early seroconversion bleedings were tested. The assays assessed were positive in 125/130 bleedings for Elecsys® HIV Duo, 114/130 for Elecsys® HIV combi PT, 120/130 for ABBOTT ARCHITECT® and 113/130 for ABBOTT PRISM®.

The 1447 positively characterised samples including HIV-1 subtype O, HIV-2 positives and HIV-1 antigen positives were all correctly identified by the Elecsys® HIV Duo assay (Supplementary Table 2).

Using the WHO HIV p24 antigen standard to confirm the cut-off sensitivity of the Elecsys® HIV Duo assay found that with three independent kit lots the HIV p24 antigen cut-off sensitivity was 0.3 IU/mL. Therefore, the Elecsys® HIV Duo can always ensure a p24 sensitivity of < 1.0 IU/mL.

5. Discussion

The results of the Elecsys® HIV Duo assay in more than 13,300 blood donation samples, assessed at four different test sites, demonstrates a comparable specificity (99.87%) to the routine assays used at each centre. There is a potential for selection bias when comparing a new assay to an established, in-house assay at a blood donation centre; the routine assay tends to be positively biased as reactive donations are rejected, ruling out potentially false positive donors over the time.

The specificity of the Elecsys® HIV Duo assay in 1000 routine diagnostic samples was 100% and slightly better than the specificity of the Elecsys® HIV combi PT, ABBOTT ARCHITECT® HIV Ag/Ab Combo, LIAISON® XL murex HIV Ab/Ag and ADVIA Centaur® CHIV assays; however, the difference was not significant.

The combination of HIV antigen and antibody testing with the fourth generation immunoassays shortens the window period for HIV by detecting HIV antigen, which appears in the blood before seroconversion [3,5,11,12]. Analysis of the seroconversion panels indicated the Elecsys® HIV Duo assay has a good seroconversion sensitivity compared with other fourth generation assays. In 52 panels that were tested with Elecsys® HIV Duo, ABBOTT ARCHITECT® and PRISM® HIV Ag/Ab Combo in parallel, the Elecsys® HIV Duo assay detected more positive samples/total number of bleeds than the comparators. Also in an additional analysis of the same seroconversion panels, calculating the average number of days when bleedings were reactive after being NAT positive the Elecsys® HIV Duo detected positive bleedings more than half a day earlier than the comparator assays, further establishing excellent seroconversion sensitivity compared with other fourth generation HIV assays.

The assessment of the cut-off sensitivity for the Elecsys® HIV Duo assay may help to explain the high sensitivity of the assay. The cut-off sensitivity calculated in this study was 0.3 IU/mL. Cut-off sensitivities reported for other fourth generation assays range from 0.19 to 1.77 IU/mL indicating that cut-off sensitivity for the Elecsys® HIV Duo is within the lower range accepted for fourth generation assays [13].

Cases have been reported of HIV antigen/antibody assays having some cross-reactivity with Epstein-Barr Virus and metastatic cancer [14]. The Elecsys® HIV Duo assay showed no cross-reactivity with any of the 19 potentially cross-reacting factors assessed, including

Table 4
Specificity results in serum samples from pregnant women and dialysis patients.

	Samples from pregnant women					Samples from dialysis patients	
	Elecsys® HIV Duo	Elecsys® HIV Combi PT	ABBOTT ARCHITECT® HIV Ag/Ab Combo	LIAISON® XL murex HIV Ab/Ag	ADVIA Centaur® CHIV	Elecsys® HIV Duo	Elecsys® HIV Combi PT
N total	1090	1090	1000	1000	999*	280	280
Confirmed indeterminate/NR	3/1087	3/1087	3/998	3/996	3/996	2/279	2/278
N negative	1087	1087	997	997	996*	278	278
IR	3	4	2	6	4	1	2
RR	3	4	2	6	3	1	2
RRfpos	2	3	1	4	1	0	1
RR confirmed positive	1/3	1/4	1/2	1/6	1/3	0/1	0/2
RR confirmed indeterminate	0/3	0/4	0/2	1/6	1/3	1/1	1/2
RR confirmed negative	2/3	3/4	1/2	4/6	1/3	0/1	1/2
Specificity %RR	99.82	99.72	99.90	99.60	99.90	100.00	99.64
95% CI	99.34–99.98	99.20–99.94	99.44–100	98.98–99.89	99.44–100	98.68–100	98.01–99.99

NR, not reactive; IR, initially reactive; RR, repeatedly reactive; RRfpos, repeatedly reactive false positive; CI, confidence interval.
* A sample was excluded for ADVIA Centaur® CHIV due to insufficient sample volume.

Table 5
The assessment of seroconversion panels.

	Number of panels tested	HIV positive bleedings/ Number bleedings	Number of panels/ Number of positive bleedings	Assays tested with the same seroconversion panels	Number of panels tested	HIV positive bleedings/ Number bleedings	Number of panels/ Number of positive bleedings
Elecsys® HIV Duo	139	0.549	0.235	Elecsys® HIV Duo*	52	0.363	0.317
Elecsys® HIV combi PT	139	0.524	0.246	ABBOTT ARCHITECT® HIV Ag/Ab Combo	52	0.352	0.327
Dade Behring Enzygnost® Anti-HIV 1/2 Plus	79	0.288	0.451	ABBOTT PRISM® HIV Ag/Ab Combo	52	0.336	0.342
bioMérieux VIDAS® HIV DUO	5	0.239	0.455				
ABBOTT PRISM® Anti-HIV 1/2	42	0.247	0.457				
ABBOTT ARCHITECT® HIV Ag/Ab Combo	52	0.352	0.327				
ABBOTT PRISM® HIV Ag/Ab Combo	52	0.336	0.342				
LIAISON Murex® XL HIV Ag/Ab combo	42	0.338	0.323				
ABBOTT HIV Ag 1 Monoclonal	99	0.341	0.388				
Coulter HIV p24 Ag assay	38	0.279	0.392				

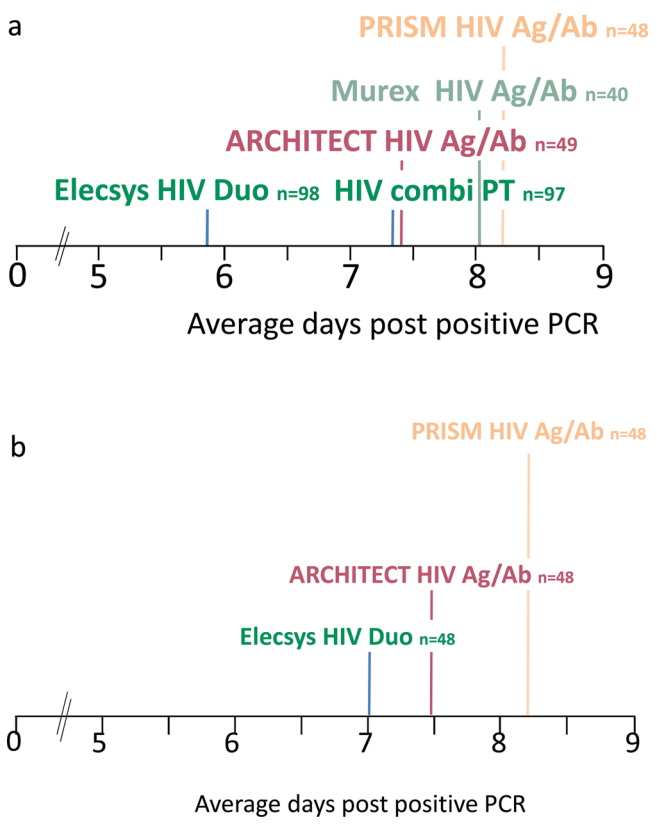

Fig. 1. a. Individual analysis of seroconversion panels. b. Direct comparison with ABBOTT ARCHITECT test.

lymphoma and EBV infection, which is reassuring, as with routine diagnosis patients may have co-infections or medical conditions.

6. Conclusion

This study demonstrates that the Elecsys® HIV Duo assay shows a higher sensitivity than the tested comparator CE marked methods, and a specificity that is comparable to existing CE marked assays. In addition to the overall Elecsys® HIV Duo result, a separate HIV antigen and antibody result is reported, this could be used as an aid during the costly confirmation testing of positive and indeterminate samples. Thus, the Elecsys® HIV Duo assay is suitable for blood donor screening and routine diagnostic use.

Funding

Medical writing assistance was provided by Rose-Marie Falconer (Elements Communications Ltd, Westerham, UK) and was funded by Roche Diagnostics. Study funding was provided by Roche Diagnostics (Rotkreuz, Switzerland).

Ethical approval

Ethical approval was obtained for all blood donation centres; for Augsburg, a full sample anonymization was done and hence no ethical approval was necessary. At Penzberg, only samples from commercial providers were analysed that had been collected under informed consent.

Conflicts of interest

Markus Klinkicht and Mario Gloeck are currently employed by Roche Diagnostics GmbH (Penzberg, Germany). All other authors declare no conflicts of interest.

CRediT authorship contribution statement

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Acknowledgements

The authors would like to thank Harald Schennach (Central Institute for Blood Transfusion and Immunology, University Hospital, Innsbruck, Austria), Volkmar Schottstedt (DRK Blutspendedienst West, Hagen, Germany), Michael Gleich (Labor Schottdorf, Augsburg, Germany) and Yi Hao (Roche Diagnostics, Penzberg, Germany) for their contributions to the study.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.jcv.2018.11.005.

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