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Comparison of four commercial screening assays for the diagnosis of human T-cell Lymphotropic virus types 1 and 2

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Abstract

Serological assays for human T-cell lymphotropic virus types 1 and 2 (HTLV-1/2) are widely used in routine screening of blood donors. The aim of this study was to compare the performance of four commercial screening assays for HTLV-1/2 infection frequently used in South America.

A total of 142 HTLV-1 and HTLV-2 seropositive and 336 seronegative samples were analyzed by using four commercial tests (BioKit, Vironostika, Murex and Fujirebio). These tests are commonly used for HTLV-1/2 detection in blood banks in Argentina. A nested-PCR was used as the reference standard.

The most sensitive tests for HTLV-1/2 were Fujirebio and Biokit (98.6%) followed by Murex (97.2%) and Vironostika (96.5%). The most specific test was Murex (99.7%), followed by Biokit (97.0%), Fujirebio (95.8%), and Vironostika (92.9%). The kappa index of agreement was higher for Murex ($\kappa = 0.97$), followed by BioKit ($\kappa = 0.94$), Fujirebio ($\kappa = 0.92$), and Vironostika ($\kappa = 0.86$).

The highest index of agreement was shown by Murex test while Vironostika had the lowest performance. Of the four tests evaluated, only the Vironostika assay is approved by the Food and Drug Administration. These results should be considered for choosing the most accurate serological screening assays in order to obtain an optimal efficiency of the current algorithm for HTLV-1/2 diagnosis.

Keywords: Comparison; Assays; HTLV-1/2; Sensitivity; Specificity

1. Introduction

The human T-Lymphotropic virus types 1 and 2 (HTLV-1/2) were the first retroviruses to be identified in humans (Poiesz et al., 1980; Kalyanaraman et al., 1982). Both viruses share approximately 60% homology at genetic level (Shimotohno et al., 1985). HTLV-1/2 transmission occurs through sexual contact, from mother-to-child, and through exposure to contaminated blood (Proietti et al., 2005). HTLV-1/2 are present in different high-risk populations and spread globally, with high endemic loci for HTLV-1 in Southern Japan, the Caribbean basin, intertropical Africa, Latin America, and in some restricted areas of the Middle East and Melanesia. HTLV-2 infection is endemic among some native Americans and some Central African tribes (Proietti et al., 2005). In Argentina, HTLV-1 is endemic among natives of the highest altitude area of the northwest (Puna Jujeña), while HTLV-2 is endemic among aboriginal groups in northern areas. In non-endemic areas such as Buenos Aires city, HTLV-1/2 infection has been reported among high-risk populations such as injecting drug users, HIV-positive individuals, female sex workers, and men who have sex with men (Gastaldello et al., 2004).

For the diagnosis of HTLV-1/2 infection, the first immunoassays used HTLV-1 whole-viral lysate as the only antigen. Then, assays were based on recombinant and/or synthetic peptide antigens only or in combination with viral lysates (Thorstensson

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Table 1
Characteristics of the four screening assays according to the manufacturer

Manufacturer	Serodia, Fujirebio	Biokit, Biokit	Vironostika, Biomerieux	Murex, Abbott
Antibody detected	Total	IgG	Total	IgG, IgM IgA
Antigen	Purified and disrupted HTLV-1 with detergent	Recombinant antigenic segments HTLV-1 and 2	Inactivated HTLV-1 and 2 and a recombinant (P21E) of HTLV-1	Synthetic peptides from envelope proteins of HTLV-1 and 2 and recombinant transmembrane of HTLV-2
Total incubation time (min)	120	105	150	90
Cut-off point	–	$0.450 + NC_x$	$0.330 + NC_x$	$0.200 + NC_x$
Wavelength (nm)	–	490–492	450	450
Type of specimen	Serum/plasma	Serum/plasma	Serum/plasma	Serum/plasma
Strategy	Gelatin particles coated with antigen	MSP	MSP	MSP
Type of assay	Passive	Indirect	Indirect	Sandwich
Substrate	–	OPD	TMB	TMB
Sensitivity (%)	–	>99.70	100	100
Specificity (%)	–	>99.00	99.92–99.96	99.75

Note: Human T-lymphotropic virus type 1 (HTLV-1) and type 2 (HTLV-2); NC_x: mean absorbances of negative controls; MSP: micro ELISA strip plate; OPD: *o*-phenylenediamine; TMB: tetramethylbenzidine. The sensitivity and specificity of the PA test are not reported by the manufacturer.

et al., 2002). Furthermore, HTLV-2 specific antigens were included, which improved the sensitivity for detection of HTLV-2 antibodies (Thorstensson et al., 2002). At present, the initial diagnosis of HTLV-1/2 infection is based mainly on screening for antibodies by enzyme-linked immunosorbent assays (ELISA) and particle agglutination (PA). Even the lack of Food and Drug Administration (FDA) licensure for HTLV-1/2 Western blot (WB) assay, it is generally applied to all repeatedly reactive samples for further confirmation of HTLV-1/2 infection (CDC, 1988). In some cases, however, it is necessary to perform a complementary assay such as a nested-polymerase chain reaction (nested-PCR) in order to confirm true HTLV-1/2 infection and to obtain a conclusive diagnosis (Vandamme et al., 1997).

When WB is used for confirmation, a significant proportion of the samples reports indeterminate results, ranging from 0.02% in non-endemic areas (Lu and Chen, 2003) to 50% in endemic ones (Cesaire et al., 1999), although it has been observed that indeterminate samples could result in true HTLV-1/2 infection, even in non-endemic areas (Rouet et al., 2001; Mangano et al., 2004; Berini et al., 2007). Several studies have shown that most low-risk HTLV-seroindeterminate and asymptomatic individuals are negative for HTLV-1/2 infection after testing with a highly sensitive nested-PCR (Mangano et al., 2004; Berini et al., 2007).

It is known that the use of highly efficient screening assays may reduce significantly false reactive results, diminishing the amount of samples further submitted to WB and/or nested-PCR analysis for confirmation. One of the strategies proposed to reduce the number of samples requiring confirmatory testing is the use of a dual ELISA algorithm (Thorstensson et al., 2002; Stramer et al., 2006).

The aim of the present study was to undertake an update on the performance of four commercial screening tests (three ELISAs and one PA test) available currently for initial diagnosis of HTLV-1/2 infection in some countries of South America, tested on well-characterized serum panels in order to improve the current HTLV-1/2 diagnosis algorithms and cost–benefits of the health care system.

2. Materials and methods

2.1. Study population

The study included a panel of 478 samples (86 HTLV-1, 56 HTLV-2 seropositive and 336 seronegative) collected at the National Reference Center for AIDS and Fernandez Hospital between 1997 and 2005 from different populations and laboratories throughout the country. Most of the HTLV-1/2 positive samples were referred because they had been repeatedly reactive in an initial screening.

A WB (HTLV blot 2.4, Genelabs Diagnostics, Science Park, Singapore) was used as the "gold standard" for selecting positive specimens. Seropositivity was interpreted according to the stringent criteria issued by the HTLV European Research Network (The HTLV European Research Network, 1996). All samples were subjected to a complementary "in-house" nested-PCR (Tuke et al., 1992). Nested PCR was performed in duplicate on each sample and if both replicates were positive, the sample was considered positive for HTLV-1 or HTLV-2, respectively. Samples with no clinical history of HTLV-related diseases were included.

The HTLV-1 positive serum panel included 64 blood donors and 22 samples from previous epidemiological studies (11 HIV positive patients, four injecting drug users, four patients with sexually transmitted infections and three patients with tuberculosis, all of them from Buenos Aires).

The HTLV-2 positive serum panel included 24 blood donors and 32 samples from previous epidemiological studies (seven HIV positive patients, 17 injecting drug users from Buenos Aires, eight pregnant women—seven from the Formosa Province and one from the Mendoza Province).

The HTLV-1/2 negative serum panel was composed of 336 samples drawn from the "Juan A. Fernandez" blood bank in Buenos Aires. All negative samples were non-reactive in an initial screening with different tests and confirmed negative by nested-PCR.

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2.2. Screening assays

Four commercial screening assays were evaluated: a PA test (Serodia HTLV-1, Fujirebio, Tokyo, Japan) (Fujirebio, 2005), and three ELISAs, BioELISA (HTLV-1+2, BioKit, Barcelona, Spain) (Biokit, 2005), Vironostika (HTLV-1/2, bioMerieux, Boxtel, The Netherlands) (Biomerieux, 2005), and Murex (HTLV-1+2, Murex Diagnostics, Dartford, England) (Abbott, 2005). Assay procedures and results interpretation were performed in strict compliance with the instructions provided by the manufacturer. The characteristics of the four screening assays are shown in Table 1. The sensitivity and specificity for each test, shown in Table 1, were taken from the package inserts of the respective tests and therefore, they were only considered as additional information and were not taken into consideration when evaluating the relative test performance.

2.3. Western blot assay

All repeatedly reactive samples were confirmed by the WB assay (HTLV blot 2.4, Genelabs Diagnostics, Science Park, Singapore). The WB assay reduces the number of false positive transmembrane results thereby increasing the specificity for serological confirmation of HTLV-1/2 (Medrano et al., 1997). This assay contains viral lysates and recombinant proteins. MTA-1 is a unique HTLV-1 envelope recombinant protein (rgp46-I), K-55 is a unique HTLV-2 envelope recombinant protein (rgp46-II), and GD21 is a common yet specific HTLV-1 and HTLV-2 epitope recombinant envelope protein. An HTLV-1 positive sample was considered when there were bands for the *gag* proteins p19 and p24, and the *env* proteins GD21 and rgp46-I; HTLV-2 positive if p24, GD21, and rgp46-II bands were present; an indeterminate sample when there were specific bands for the virus that did not meet the HTLV-1/2 positivity criteria, and a negative result for those samples that did not exhibit any specific band.

2.4. Nested-PCR assay

All HTLV-1/2 positive samples by nested-PCR were positive for at least two genes (*tax* and *pol*). Nested-PCR for the *pol* region was performed with outer primers SK-110/SK-111 specific for HTLV-1/2 and inner primers pol 1.1/pol 3.1 and pol 1.2/pol 3.2 for HTLV-1, and HTLV-2, respectively. Nested-PCR for the *tax* region was performed with outer primers SK-43/SK-44 specific for HTLV-1/2, and inner primers as described by Tuke et al. (1992). The size of the nested-PCR products were 135 bp and 137 bp for *pol* of HTLV-1 and 2, respectively. The size of the nested-PCR products for the *tax* region was 127 for both HTLV-1 and 2. Restriction enzyme assays for typing were done as described by Tuke et al. Sample preparation and amplification conditions were performed as described previously (Tuke et al., 1992).

Table 2a
Sensitivity of four commercial screening tests against nested-PCR for HTLV-1 and HTLV-2 infection

Tests	Sensitivity	
	HTLV-1% (95% CI)	HTLV-2% (95% CI)
Fujirebio	98.8 (94.4, 99.9)	98.2 (91.5, 99.9)
Biokit	100.0 (96.6, 100.0)	96.4 (88.7, 99.4)
Vironostika	97.7 (92.5, 99.6)	94.6 (86.1, 98.6)
Murex	98.8 (94.4, 99.9)	94.6 (86.1, 98.6)

2.5. Statistical analysis

Nested-PCR results were used as the "reference standards". Sensitivity, specificity and the likelihood ratio of a positive result with 95% confidence interval were calculated for each screening test and for each combination of two tests. A kappa index was calculated to measure test agreement. All statistical analyses were performed using STATA version 8.0 (Stata Corporation, TX, USA).

3. Results

The sensitivity and specificity of the various assays for the detection of HTLV-1 and 2 are summarized in Table 2. The sensitivity for HTLV-1 ranged from 97.7% to 100%, with Biokit (100%) the most sensitive screening test for HTLV-1 infection, followed by Fujirebio (98.8%), Murex (98.8%), and Vironostika (97.7%). The sensitivity for HTLV-2 ranged from 94.6% to 98.2% (Table 2a). Fujirebio (98.2%) was the most sensitive test for HTLV-2 infection followed by Biokit (96.4%), Murex (94.6%) and Vironostika (94.6%) (Table 2a). The HTLV-1/2 sensitivity (Table 2b) ranged from 96.5% to 98.6%, with the Fujirebio and Biokit tests being the most sensitive (98.6%), followed by Murex (97.2%), and Vironostika (96.5%).

Of the 478 samples evaluated in this study, 142 (30%) samples were HTLV-1/2 positive, 305 (64%) were negative, and 31 (6%) were indeterminate by WB assay (Table 3a). On the other hand, 86 samples were HTLV-1 positive, 56 were HTLV-2 positive, and 336 were HTLV-1/2 negative by nested-PCR (Table 3b).

Table 2b
Performance characteristics of four commercial screening tests against nested-PCR for HLTV-1/2 infection

Tests	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	Likelihood ratio+ (%) (95% CI)	Kappa (%) (95% CI)
Fujirebio	98.6 (95.4, 99.8)	95.8 (93.3, 97.6)	23.7 (14.1, 39.3)	0.92 (0.88, 0.96)
Biokit	98.6 (95.4, 99.8)	97.0 (94.8, 98.5)	33.1 (18.0, 61.0)	0.94 (0.91, 0.97)
Vironostika	96.5 (92.4, 98.7)	92.9 (89.7, 95.3)	13.5 (9.2, 19.9)	0.86 (0.81, 0.91)
Murex	97.2 (93.4, 99.1)	99.7 (98.5, 100)	326.5 (46.1, 2311.9)	0.97 (0.95, 1.00)

Note: HTLV, human T-Lymphotropic virus; CI, confidence interval.

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Table 3a
Cross-tabulation of four commercial screening tests results against Western blot assay for HTLV-1/2 diagnosis

Western blot	Fujirebio		BioKit		Vironostika		Murex	
	Positive no.	Negative no.	Positive no.	Negative no.	Positive no.	Negative no.	Positive no.	Negative no.
Positive ($n=142$)	140	2	140	2	137	5	138	4
HTLV-1 ($n=86$)	85	1	86	0	84	2	85	1
HTLV-2 ($n=56$)	55	1	54	2	53	3	53	3
Negative ($n=305$)	1	304	5	300	2	303	0	305
Indeterminate ($n=31$)	13	18	5	26	22	9	1	30
Total ($n=478$)	154	324	150	328	161	317	139	339

Note: HTLV, human T-lymphotropic virus.

Table 3b
Cross-tabulation of four commercial screening tests results against nested-PCR for HTLV 1/2 diagnosis

Nested-PCR	Fujirebio		BioKit		Vironostika		Murex	
	Positive no.	Negative no.	Positive no.	Negative no.	Positive no.	Negative no.	Positive no.	Negative
Positive ($n=142$)	140	2	140	2	137	5	138	4
HTLV-1 ($n=86$)	85	1	86	0	84	2	85	1
HTLV-2 ($n=56$)	55	1	54	2	53	3	53	3
Negative ($n=336$)	14	322	10	326	24	312	1	335
Total ($n=478$)	154	324	150	328	161	317	139	339

Note: HTLV, human T-lymphotropic virus.

All 31 indeterminate WB results and the 305 negative samples were negative by nested-PCR. Concerning sensitivity for HTLV-1 infection, three screening assays were responsible for four false negative results in two different samples: one sample was not detected neither by Fujirebio, Vironostika nor Murex at the same time; and the other sample was not detected by Vironostika only. On the other hand, in the case of the 56 HTLV-2 positive samples, there were 10 false negative results with 7 different samples: 2 samples were not detected neither by Fujirebio, Vironostika nor Murex at the same time (one HTLV-1 and one HTLV-2); 2 other samples were not detected by Biokit or Murex concomitantly (two HTLV-2); and the last three samples were not detected by Vironostika only (one HTLV-1 and two HTLV-2). Out of the seven samples with false negative results, five were HTLV-2 positive.

Concerning specificity, among all 336 HTLV-1/2 negative samples, there were 49 false positive results (14 by Fujirebio, 10 by Biokit, 24 by Vironostika, and one by Murex).

Among all false positive results, 27 samples were reactive with one of the assays at a time while the other 11 samples showed reactivity with two different assays concomitantly (Fujirebio and Biokit; Fujirebio and Vironostika; and Biokit and Vironostika). Out of the 38 false reactive samples, seven were negative by WB while the other 31 samples were indeterminate. Among all indeterminate WB samples, 23 profiles showed reactivity to p19, p26, p28, p32 and p53, generally called HTLV-1

Table 4
Analysis to determine the optimum-screening algorithm using two different assays in combination

Order combination	Negative samples with false reactive results in the 1st analysis	Positive samples with false negative results in the 1st analysis	Sensitivity	Specificity	LR+
1st-Biokit, 2nd-Murex	10	2 (HTLV-2)	97.18	100.00	∝
1st-Murex, 2nd-Biokit	1	4 (1 HTLV-1; 3 HTLV-2)			
1st-Fujirebio, 2nd-Murex	14	2 (1 HTLV-1; 1 HTLV-2)	97.18	100.00	∝
1st-Murex, 2nd-Fujirebio	1	4 (1 HTLV-1; 3 HTLV-2)			
1st-Fujirebio, 2nd-Biokit	14	2 (1 HTLV-1; 1 HTLV-2)	97.18	100.00	∝
1st-Biokit, 2nd-Fujirebio	10	2 (HTLV-2)			
1st-Fujirebio, 2nd-Vironostika	14	2 (1 HTLV-1; 1 HTLV-2)	96.48	97.92	46.31
1st-Vironostika, 2nd-Fujirebio	24	5 (2 HTLV-1; 3 HTLV-2)			
1st-Vironostika, 2nd-Murex	24	5 (2 HTLV-1; 3 HTLV-2)	95.07	100.00	∝
1st-Murex, 2nd-Vironostika	1	4 (1 HTLV-1; 3 HTLV-2)			
1st-Biokit, 2nd-Vironostika	10	2 (HTLV-2)	95.07	99.40	159.72
1st-Vironostika, 2nd-Biokit	24	5 (2 HTLV-1; 3 HTLV-2)			

Note: HTLV, human T-lymphotropic virus.

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gag indeterminate pattern (HGIP), five showed reactivity to *gag* proteins and only three had reactivity to GD21.

The specificities for HTLV-1/2 infection were 99.7%, 97.0%, 95.8%, and 92.9% for Murex, Biokit, Fujirebio and Vironostika, respectively (Table 2b). In addition, the likelihood ratio (LR+) for a HTLV-1/2 positive test was higher for Murex (LR+ = 326.5) and Biokit (LR+ = 33.1). In addition, the kappa index of agreement was higher for Murex ($\kappa = 0.97$, 95% CI: 0.95–1.00) in comparison with the other tests (Table 2b).

Table 4 shows the analysis performed in order to determine the optimum-screening algorithm using two different assays in combination. Conjunctice positive criterion of combination tests was used, thus samples were labeled as positive only if they were reactive by both assays.

4. Discussion

HTLV-1 and 2 infections are endemic in northern Argentina and are also present in different populations around the country. Among blood donors, HTLV-1/2 prevalence ranges from 0.03% in Buenos Aires to 0.16% in Jujuy (Gastaldello et al., 2004). In at high-risk population prevalence ranges from 0.5 to 16.6% (Gastaldello et al., 2004). In Argentina, as well as in other countries of South America, HTLV-1/2 detection has become mandatory in recent years. Therefore, the accuracy of four different methods (Fujirebio, BioKit, bioMerieux, Murex) largely used for diagnosis of HTLV infection in blood banks and health care centers throughout South America was compared. To date, out of the four screening assays evaluated in this study, Vironostika is the only test approved by the FDA.

Repeatedly reactive samples in screening assays require further testing for HTLV confirmation. Generally, WB is the assay used most frequently for this purpose especially in blood banks (Vandamme et al., 1997). Previous studies have also reported screening tests with low specificity yield more indeterminate WB results (Cesaire et al., 1999; Rouet et al., 2001). Many samples which do not undergo initial screening tests and are submitted directly for WB analysis, yield indeterminate results (Prince and Gross, 2001). Consequently, the use of highly efficient screening assays may significantly reduce false positive results, and therefore, diminish the number of samples furtherly submitted to WB and/or nested-PCR analysis.

On the other hand, several studies have demonstrated that at low-risk individuals, even from endemic areas for HTLV-1/2 infection, exhibiting HGIP or *gag* (p24) seroindeterminate profiles are unlikely to be infected with HTLV-1/2 and strongly suggest that an HGIP does not reflect HTLV-1/2 infection (Rouet et al., 2001). Nevertheless, the presence of *env* or *gag* profiles may represent seroconvertion as demonstrated previously in at high-risk groups, especially when GD21 is present (Medrano et al., 1997; Berini et al., 2007). In this study, it was observed that the majority of indeterminate WB profiles belonging to false reactive samples exhibited an HGIP profile in agreement with previous data.

In this study, all assays had a high sensitivity for HTLV-1, which is in accordance with previous evaluations (Thorstensson et al., 2002; Stramer et al., 2006). According to these results, the test with the highest index of performance ($\kappa = 0.97$) for detecting HTLV-1/2 antibodies was the Murex ELISA, followed by Biokit, Fujirebio and Vironostika which reported the lowest performance ($\kappa = 0.86$). Even though the PA test is based on disrupted HTLV-1 only, the highest sensibility for HTLV-2 was reported. This is an important fact that should be considered in countries where both viral types are endemic. At present, no gold standard test exists for diagnosis of HTLV-1/2 infection; therefore, the use of a nested-PCR is proposed as a complementary technique to confirm infection, to enable interpretation of indeterminate WB results, and to differenciate between HTLV-1 and 2 in HTLV-positive samples by WB assay.

In Argentina, where HTLV-1/2 detection is compulsory in blood banks and it is becoming more frequent in health care wards, there have been discrepancies in results. The discrepancies may occur since different screening assays differ in performance. Blood banks from different provinces of the country have reported high false positive rates resulting in a loss of blood units and time as well as money-consuming efforts shipping samples across the country to reference centers and getting confirmation tests performed. According to these results, although based on a small sample set, blood banks would benefit from the use of a combination of a PA and ELISA (Biokit or Murex) assays as well as the combination of Biokit and Murex ELISAs together, as shown in Table 4.

In summary, the use of highly efficient screening assays available in the market may represent an important positive cost-benefit in health care, especially in countries where the detection of HTLV-1/2 antibodies is mandatory. Furthermore, all possible strategies to diminish false positive screening should be considered, including the use of a dual ELISA algorithm (Thorstensson et al., 2002; Stramer et al., 2006). In order to get a final diagnosis of HTLV-1/2 infection it has been recommended the use of both serologic and Deoxyribonucleic Acid (DNA) PCR assays to allow determine the real status of these infections and to help health care professionals about counseling. This strategy would reduce considerably time and the costs of the total diagnosis. Moreover, this would not require further sampling or individuals waiting long for final diagnosis results.

Access to the optimal screening algorithm will diminish inconclusive diagnosis and provide appropriate preventive and clinical assistance for HTLV-1/2 infection, since its related diseases should be considered of public health concern in endemic areas of South America. The results of this study help to choose the best systematic screening for these infections improving cost-benefits and for recruiting donors for blood survaillance system.

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