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1 **Comparison of two new HTLV-I/II screening methods, Abbott Alinity I rHTLV-I/II and**
2 **Diasorin LIAISON® XL murex recHTLV-I/II, to Abbott architect rHTLV-I/II assay**

3

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15

16 **ABSTRACT**

17 *Background:* Diagnosis of Human T-cell Lymphotropic Virus (HTLV) types I and II infection
18 requires sequential testing with firstly a screening using an Enzyme immunoassay followed
19 by a confirmatory test.

20 *Objectives:* To compare the performances of the Alinity i rHTLV-I/II (Abbott®) and
21 LIAISON® XL murex recHTLV-I/II serological screening tests to the ARCHITECT
22 rHTLV I/II test followed if positive by HTLV BLOT 2.4, MP Diagnostics as the reference.

23 *Study design:* 119 serum samples from 92 known HTLV-I infected patients and 184 from
24 uninfected patients with HTLV were analyzed in parallel with, Alinity i rHTLV-I/II,
25 LIAISON® XL murex recHTLV-I/II and ARCHITECT rHTLV I/II.

26 *Results:* Alinity i rHTLV-I/II and Liaison XL murex recHTLV-I/II exhibited a total
27 agreement with ARCHITECT rHTLV I/II for both positive and negative samples. Both tests
28 are suitable alternatives for HTLV screening.

29

30 *Keywords:*

31 Human T-cell lymphotropic virus, serological assay, method comparison, ARCHITECT
32 rHTLV I/II, Alinity i rHTLV-I/II, LIAISON® XL murex recHTLV-I/II

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38 Abbreviations:

39 HTLV: Human T-cell Lymphotropic Virus, 95% CI: 95% Confidence interval, ATLL: adult
40 T-cell leukemia/lymphoma, HAM: HTLV-associated myelopathy, CMIA: chemiluminescent
41 microparticle immunoassay, CLIA: chemiluminescent immunoassay, RLU: Relative Light
42 Unit, S/CO: signal/cutoff, CV: coefficient of variation, SD: standard deviations.

43

44 **1. Background**

45 Human T lymphotropic virus type I (HTLV-I) and Human T lymphotropic virus type II
46 (HTLV-II) were the first retroviruses discovered, respectively in 1980 [1] and 1982 [2]. They
47 are responsible for adult T-cell leukemia/lymphoma (ATLL) [3], HTLV-associated
48 myelopathy (HAM) [4] and inflammatory diseases such as uveitis, myositis and dermatitis
49 [4]. HTLV in adult population is unevenly distributed worldwide: highly endemic in Japan,
50 Caribbeans and several African areas while virtually absent in other regions [5,6]. However,
51 in both low and high endemic countries prevalence may exhibit discrepancies. For instance
52 areas in Texas or Nevada has seroprevalence more than ten times higher than other parts of
53 the United States [7]. HTLV transmission occurs in utero, peripartum mostly through
54 breastfeeding [8], during sexual relationship [9], intravenous drug use [10], and solid organ or
55 hematopoietic transplantation [11]. Finally, although blood transfusion has been an historical
56 route of HTLV transmission, leukofiltration has significantly reduced this risk [12].

57 To limit blood and graft-born transmission, 35 countries to date test each donor for HTLV
58 serology, and 15 more implement selective testing according to specific risk factors [13].
59 Since serological screening is both the most sensitive [14] and cost-effective way to screen
60 [15] but lack specificity, guidelines recommend a dual-testing algorithm with firstly a third-
61 generation screening using chemiluminescent immunoassay or enzyme-linked immunosorbent
62 assay. In case of reactive or indeterminate result, a specific confirmatory assay with an
63 Immunoblot, Western blot or line immunoassay [16,17], is performed.

64 **2. Objectives**

65 The objective of this study was to compare two screening immunoassays, Alinity i rHTLV-
66 I/II (Abbott®, Rungis, France), LIAISON® XL murex recHTLV-I/II (DiaSorin, Antony,
67 France), with ARCHITECT rHTLV-I/II (Abbott, Rungis, France) followed for positive

68 samples by HTLV BLOT 2.4 (MP Diagnostics™, Illkirch-Graffenstaden, France) as the
69 reference.

70 **3. Study design**

71 *3.1 Samples*

72 The study included a retrospective part of clinical and analytical sensitivity, and an
73 exploratory prospective part of specificity. All serum samples had been tested following the
74 routine algorithm of the Service of Virology at the Pitié Salpêtrière Hospital (Paris, France).
75 Architect rHTLV-I/II was used as the screening method with HTLV BLOT 2.4 as the
76 confirmatory assay for reactive results. Only samples confirmed HTLV positive were
77 included in the retrospective study. For clinical sensitivity, 119 serum samples from 92
78 HTLV-I subjects were included. Serum samples were stored at -20°C before use. Analytical
79 sensitivity was done using dilutions of positive serum samples from two HTLV-I infected
80 patients. For the exploratory specificity prospective study, 184 fresh non-reactive serum
81 samples using Architect rHTLV-I/II were included from January 4th 2022 to March 1st 2023.
82 They were stored at +4°C before use. Reproducibility and repeatability were assessed with
83 positive and negative controls of the kits.

84 *3.2 Methods and analysis*

85 For clinical sensitivity, all samples were tested the same day according to the manufacturer's
86 instructions with the three methods: Architect rHTLV-I/II, Alinity i rHTLV-I/II and
87 LIAISON® XL murex recHTLV-I/II. Architect rHTLV-I/II and Alinity i rHTLV-I/II are
88 based on chemiluminescent microparticle immunoassay (CMIA) and LIAISON® XL murex
89 recHTLV-I/II is based on chemiluminescent immunoassay (CLIA). All methods use HTLV-
90 I/II gp46 synthetic peptides and HTLV-I p21 recombinant protein. In addition, LIAISON®
91 XL murex recHTLV-I/II contains HTLV-II p21 recombinant protein. Results for all three

92 methods were expressed as the ratio of the Relative Light Unit (RLU) of the sample (signal)
93 to the RLU of the cutoff (S/CO). A reactive result was defined as a ratio ≥ 1 and a non-
94 reactive result was defined as a ratio < 1 . Of note, none of the three assays allocated
95 undetermined results.

96 To evaluate repeatability, positive and negative controls were tested 23 times in the same run
97 following previous guidelines [18]. Reproducibility was assessed by testing positive and
98 negative controls of the kit once a run for 30 consecutive days. Repeatability and
99 reproducibility were evaluated by analyzing coefficients of variation (CV), defined as the
100 ratio of standard deviation of the S/CO value to the mean S/CO value.

101 Dilution for analytical sensitivity analyses were: 1:10, 1:100, 1:200, 1:500, 1:1000, 1:10000.

102 The three methods were performed in parallel.

103 For the prospective exploratory specificity study, 184 non-reactive samples using Architect
104 rHTLV-I/II were tested with LIAISON® XL murex recHTLV-I/II and Alinity i rHTLV-I/II in
105 parallel the same day.

106

107 *3.3 Statistical analysis*

108 Statistical analyses were conducted using R version 4.2.1 [19]. S/CO values were
109 compared using Spearman correlation coefficient (r) and Wilcoxon's test for paired data. All
110 reported P values are two-sided, with $p < 0.05$ considered statistically significant. Delta (δ)
111 value was used to estimate the methods' abilities to separate reactive and non-reactive
112 populations from the cut off [20–22]. Delta value was defined for both reactive and non-
113 reactive population as the distance between the population mean and the CO, expressed in
114 standard deviation (SD) units of the log transformed population distribution according to the
115 following formula:

116 $Delta (\delta) = \frac{Population\ mean\ (log(S/CO))}{SD\ (log(S/CO))}$

117 **4. Results**

118 With ARCHITECT rHTLV-I/II followed for reactive sera by HTLV BLOT 2.4, MP
119 Diagnostics as the reference assay, Alinity i rHTLV-I/II and LIAISON® XL murex recHTLV-
120 I/II identified correctly all 119 positive samples leading to a sensitivity of 100% with a 95%
121 CI [97%-100%]. All S/CO ranges were similar for the three methods, but Alinity i rHTLV-I/II
122 had a mean S/CO value lower in comparison with Architect ($p = 7.5E-16$) and Liaison ($p =$
123 $1.2E-11$) (Table 1). Mean S/CO value for reactive samples was higher for Liaison murex
124 recHTLV-I/II than Architect rHTLV-I/II ($p = 0.045$). For 92 serum samples, S/CO values
125 were lower using Alinity i rHTLV-I/II in comparison with the other two methods. Reactive
126 S/CO values were well correlated between ARCHITECT rHTLV-I/II and Alinity i rHTLV-
127 I/II ($R^2 = 0.53$, $p < 2.2E-16$), but less correlated between ARCHITECT rHTLV-I/II and
128 Liaison XL ($R^2 = 0.26$, $p = 6.5E-9$) or Alinity i rHTLV-I/II and LIAISON® XL murex
129 recHTLV-I/II ($R^2 = 0.22$, $p = 9.9E-8$) (Fig. 1). A phenomenon of saturation was observed for
130 LIAISON® XL murex recHTLV-I/II for S/CO values above 130 when Architect rHTLV-I/II
131 positivity was over 75 IU (Fig. 1).

132 Results of sensitivity for endpoint dilutions were similar for the three methods, with a
133 negatvation around 1:10000 for patient 1, and around 1:200 for patient 2 (reported in
134 Supplemental Table 1).

135 Results of reproducibility were similar for all three methods, with CV for positive control
136 ranging from 4.7% (95% CI [3.7%-6.4%]) for Alinity i rHTLV-I/II to 9.6% (95% CI [7.7%-
137 13.1%]) for LIAISON® XL murex recHTLV-I/II Assays, and for negative control ranging
138 from 5.7% (95% CI [4.7-7.7]) to 20.1% (95% CI [16.0-27.2]) (reported in Supplemental
139 Table 2). Results of repeatability were also similar for all three methods, with CV for positive

140 control ranging from 1.3% (95% CI [1.0-1.7]) for Alinity i rHTLV-I/II to 3.7% (95% CI [3.0-
141 5.1]) for ARCHITECT rHTLV-I/II. For negative controls, CV ranged from 5.7% (95% CI
142 [4.5-7.7]) for LIAISON® XL murex recHTLV-I/II to 10.7% (95% CI [8.3-15.1]) for Alinity i
143 rHTLV-I/II. None of the positive and negative controls tested was misclassified.

144 Of note, for the exploratory study of specificity, with ARCHITECT rHTLV-I/II as the
145 reference assay, Alinity i rHTLV-I/II and LIAISON® XL murex recHTLV-I/II identified
146 correctly the 184 negative serum samples.

147 The ability for each test to allow a high discrimination between reactive and non-reactive
148 populations was assessed by the δ coefficient with the higher absolute value the better
149 discrimination. Interestingly, compared with ARCHITECT rHTLV-I/II (-4.8 for non-reactive
150 and 8.8 for reactive), Alinity i rHTLV-I/II seemed to be less discriminant assay (-9.1 for non-
151 reactive and 7.9 for reactive) for reactive samples, while LIAISON® XL murex recHTLV-I/II
152 might be the most discriminant (-9.5 for non-reactive and +13.9 for reactive) (Fig. 2).

153

154 **5. Discussion**

155 All 119 samples from HTLV-I-infected patients were tested positive with the two studied
156 methods, although S/CO values were moderately correlated. A phenomenon of saturation of
157 the signal was observed with LIAISON® XL murex recHTLV-I/II above 130 S/CO, and
158 positive ratios were lower using Alinity i rHTLV-I/II. Of note, all 184 uninfected patients
159 were non-reactive with the two methods. Positive and negative results were highly
160 discriminated, especially for LIAISON® XL murex recHTLV-I/II with a δ coefficient at -9.5
161 for non-reactive and +13.9 for reactive samples.

162 This study is in agreement with the study of Malm et al. where 38 positive samples were
163 tested with ARCHITECT rHTLV-I/II and Murex recHTLV-I/II EIA method in a microplate
164 formate used as the reference method [23]. Similar results were obtained by Qiu et al. on 498

165 samples from patients infected by HTLV-I/II that were tested in parallel with ARCHITECT
166 rHTLV-I/II and murex recHTLV-I/II in microplate [21]. Our results differed from those
167 obtained by Gantner et al. who reported, on a panel of 66 samples, a sensitivity of LIAISON®
168 XL murex recHTLV-I/II at 78% when comparing with the results obtained with
169 ARCHITECT rHTLV-I/II [24]. However this study included positive samples based on low
170 Architect S/CO values as a reference without confirmatory assay and so may have introduced
171 a classification bias due to the high proportion of false-positive for low Architect S/CO
172 positive values [25]. Surprisingly, to date no other study have compared sensitivities of the
173 Alinity assay to another platform.

174 On a limited number of samples, our study found a specificity of 100% for the three methods.
175 These values are within the range of previous published studies, which found a specificity at
176 99.98% with 95%CI [99.92%-100%] for ARCHITECT rHTLV-I/II [21], at 99.4% with
177 95%CI [98.3%-99.8%] for ARCHITECT rHTLV-I/II [23], at 99.5% with 95%CI [98.0-99.9]
178 for LIAISON® XL murex recHTLV-I/II [25] and 99.92% for the Alinity assay [26].

179 The main limitation of our study was the use of the Architect assay as the screening reference.
180 As a consequence, when testing pure serum samples, we were not able to determine if any of
181 the other tests were more sensitive than the Architect. This point was slightly evaluated with
182 end-point dilutions although results were roughly identical for the three techniques. Moreover,
183 as we had a limited number of negative samples tested, we may have lacked power to rank the
184 assays according to their specificities and had to use the delta coefficient as a surrogate
185 marker. Finally, as we defined positive sample as both ARCHITECT rHTLV-I/II and HTLV
186 BLOT 2.4 positivity we may have missed patients with low reactivity, and as we managed to
187 include only HTLV-I positive samples our results should be taken with caution depending on
188 local epidemiology.

189

190 **6. Conclusion**

191 On a serum panel of 119 infected and 184 uninfected patients with HTLV-I/II, Alinity i
192 rHTLV-I/II and LIAISON® XL murex recHTLV-I/II exhibited a total agreement compared
193 with Architect rHTLV-I/II as the referent assay. These two tests are therefore suitable for the
194 screening of HTLV-I/II infection in donors, subject at risk and patients with ATLL or HAM.

195

196

197 **Author contributions**

198 Vincent Guiraud data analyzes, writing- original draft preparation, submission of the final
199 manuscript. Florian Crémoux supervision, acquisition and analyzes of data, validation.
200 Isabelle Leroy visualization, samples testing. Julien Cohier samples testing. Pierre Hernandez
201 samples testing. Safietou Mansaly samples testing and Agnès Gautheret-Dejean
202 conceptualization, methodology, writing- reviewing and editing.

203

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207

208 **Declaration of Competing Interests**

209 The authors declare that they have no competing financial interests or personal relationships
210 that could have influenced the work reported in this paper.

211

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216 interpretation, manuscript writing nor submission to publication. The authors thank Mostafa
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218

219 **Ethics**

220 This study complies with Good Clinical Practices and ethical principles of the Helsinki
221 declaration. All data were anonymized before analysis. Patients were systematically notified
222 of any supplementary biological analyses on frozen samples, initially collected as part of
223 routine clinical practice.

224

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308

309

310 **Table 1**

311 Distribution of S/CO values¹ for positive and negative samples with Architect, Alinity and Liaison
 312 assays.

Type of samples		Architect	Alinity	Liaison
Positive samples (n=119)	S/CO \geq 1	119	119	119
	Minimum	17.4	11.2	26
	Mean	118.4	100.3	130
	Standard deviation	49.1	44.0	31.3
	Maximum	241.4	225.7	190
Negative samples (n=184)	S/CO<1	184	184	184
	Minimum	0.07	0.05	0.21
	Mean	0.19	0.10	0.28
	Standard deviation	0.066	0.030	0.045
	Maximum	0.47	0.28	0.67

313 ¹S/CO, signal/cut off.

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317 **Supplemental Table 1**

318 Values of S/CO¹ according to sera dilutions for two HTLV-I-infected patients. Last detectable
 319 dilutions (end-point dilutions) are in bold underlined.

Serum dilution	Results for patient 1 with			Results for patient 2 with		
	Architect	Alinity	Liaison	Architect	Alinity	Liaison
1:1	82.32	76.74	140	62.84	60.37	71
1:10	40.7	39.7	73	8.45	<u>8.35</u>	<u>7.40</u>
1:100	7.51	7.99	18	<u>1.01</u>	0.95	0.99
1:200	3.89	4.16	10	0.56	0.52	0.62
1:500	<u>1.76</u>	<u>1.76</u>	4.5	0.32	0.25	0.36
1:1000	0.96	0.98	<u>2.4</u>	0.22	0.18	0.30
1:10000	0.2	0.16	0.45	0.15	0.08	0.26

320 ¹ S/CO, signal/cut off. S/CO \geq 1 are positive. Values in bold underlined
 321 correspond to the last positive value for each method. Due to low sample
 322 volume we were unable to do replicates.

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325 **Supplemental table 2**

326 Reproducibility and repeatability for positive controls with Architect, Alinity and Liaison assays.

Results for positive and negative controls with			
	Architect	Alinity	Liaison
Positive controls			
Reproducibility	6.9 (5.6-9.4) ¹	4.7 (3.7-6.4) ¹	9.6 (7.7-13.1) ¹
(min-max)			
Repeatability	3.7 (3-5.1)	1.3 (1-1.7)	2.3 (1.9-3.2)
(min-max)			
Negative controls			
Reproducibility	6.9 (5.6-9.4)	6.9 (5.6-9.4)	6.9 (5.6-9.4)
(min-max)			
Repeatability	6.9 (5.6-9.4)	6.9 (5.6-9.4)	6.9 (5.6-9.4)
(min-max)			

327 ¹ Results are expressed as Coefficient of variation (%) (95% CI). 95% CI, 95% confidence interval.

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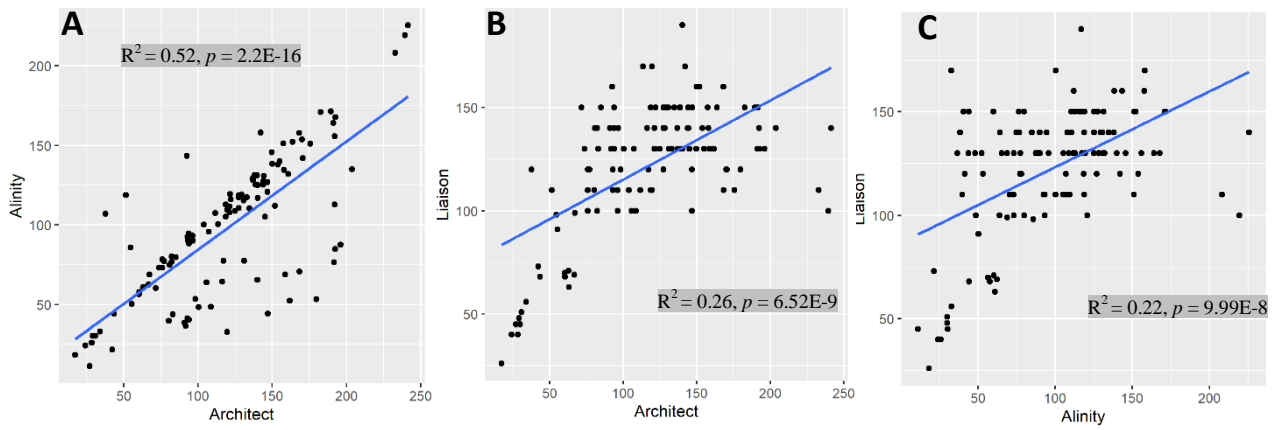


Figure 1: S/CO and correlation for reactive samples for Architect and Alinity (A), Architect and Liaison (B) and Alinity and Liaison (C).

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