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## Comparison of two new HTLV-I/II screening methods, Abbott Alinity i rHTLV-I/II and Diasorin LIAISON® XL murex recHTLV-I/II, to Abbott Architect rHTLVI/II assay

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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 4<sup>th</sup> 2022 to March 1<sup>st</sup> 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  $\geq 1$  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 ( $\delta$ )  
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  $\delta$  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  $\delta$  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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208 **Declaration of Competing Interests**

209 The authors declare that they have no competing financial interests or personal relationships  
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211

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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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310 **Table 1**

311 Distribution of S/CO values<sup>1</sup> for positive and negative samples with Architect, Alinity and Liaison  
 312 assays.

<b>Type of samples</b>		<b>Architect</b>	<b>Alinity</b>	<b>Liaison</b>
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 <sup>1</sup>S/CO, signal/cut off.

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317 **Supplemental Table 1**

318 Values of S/CO<sup>1</sup> 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	<b><u>8.35</u></b>	<b><u>7.40</u></b>
1:100	7.51	7.99	18	<b><u>1.01</u></b>	0.95	0.99
1:200	3.89	4.16	10	0.56	0.52	0.62
1:500	<b><u>1.76</u></b>	<b><u>1.76</u></b>	4.5	0.32	0.25	0.36
1:1000	0.96	0.98	<b><u>2.4</u></b>	0.22	0.18	0.30
1:10000	0.2	0.16	0.45	0.15	0.08	0.26

320 <sup>1</sup> S/CO, signal/cut off. S/CO ≥ 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.

<b>Results for positive and negative controls with</b>			
	<b>Architect</b>	<b>Alinity</b>	<b>Liaison</b>
<b>Positive controls</b>			
Reproducibility	6.9 (5.6-9.4) <sup>1</sup>	4.7 (3.7-6.4) <sup>1</sup>	9.6 (7.7-13.1) <sup>1</sup>
(min-max)			
Repeatability	3.7 (3-5.1)	1.3 (1-1.7)	2.3 (1.9-3.2)
(min-max)			
<b>Negative controls</b>			
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 <sup>1</sup> Results are expressed as Coefficient of variation (%) (95% CI). 95% CI, 95% confidence interval.

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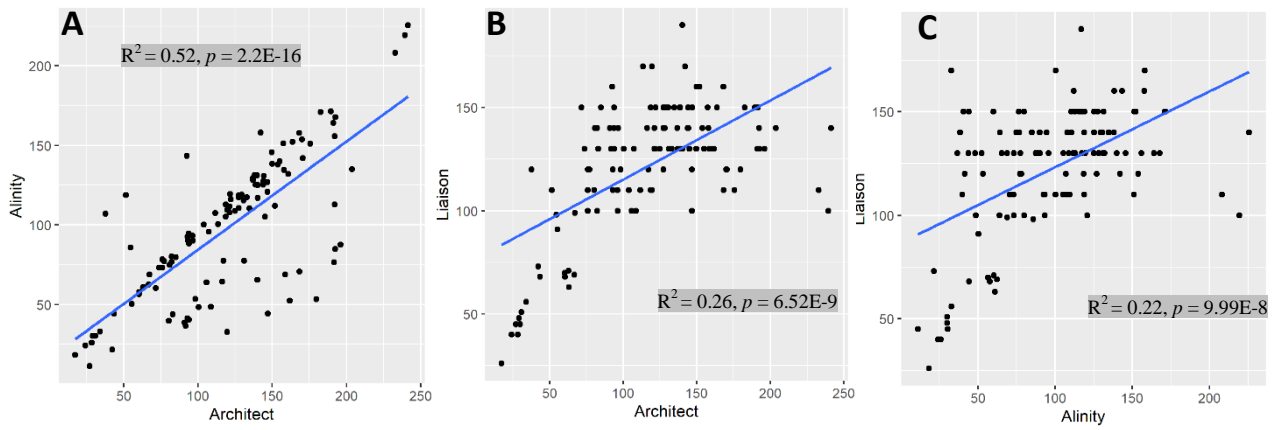


Figure 1: S/CO and correlation for reactive samples for Architect and Alinity (A), Architect and Liaison (B) and Alinity and Liaison (C).

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