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Performance of the Alere Determine™ HIV-1/2 Ag/Ab Combo Rapid Test with specimens from HIV-1 seroconverters from the US and HIV-2 infected individuals from Ivory Coast

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ABSTRACT

Background: FDA-approved HIV Antigen/Antibody combo (4th generation) immunoassays (IAs) can identify HIV-1 infections before the Western blot (WB) becomes positive. In the US, increased detection of acute HIV infections has been facilitated by using 4th generation IAs, but there is no FDA-approved 4th generation rapid test (RT). The Alere Determine™ HIV-1/2 Ag/Ab Combo (Determine Combo) RT detects and distinguishes HIV p24 Antigen (Ag) from Antibody (Ab) to HIV-1 + HIV-2 and thus has the potential to improve diagnosis of acute HIV infection.
Objective: To evaluate the ability of Determine Combo RT to detect acute/early HIV-1 infections and HIV-2 antibody in well-characterized plasma specimens.
Study design: In HIV-1 seroconverters from the US, Determine Combo reactivity was evaluated by performing the 50% cumulative frequency analysis and by comparing with 3rd and 4th generation IAs' reactivity. HIV-2 plasma specimens from Ivory Coast were tested with Determine Combo.
Results: The 50% cumulative frequency analysis in 17 seroconverters placed Determine Combo (Ag+/Ab−, Ag+Ab+, Ag−/Ab+) and Ab-component reactivity at 15.5 and 7 days before WB positivity, respectively. In 26 seroconverters, Determine Combo was reactive in 99.0% and 92.5% of 3rd and 4th generation IAs-reactive specimens, respectively. All HIV-2 plasma specimens were Ab-reactive/Ag-non-reactive by Determine Combo.
Conclusions: Based on previous results with the same seroconversion panels, combined Ag/Ab reactivity of the Determine Combo appears between FDA-approved 4th and 3rd generation laboratory IAs. These data indicate that this RT could detect HIV-1 infection earlier than other RTs and it performs well in HIV-2 specimens.

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1. Background

Simultaneous detection of HIV antigen (Ag) and antibodies (Ab) by 4th generation combo immunoassays (IAs) narrows the HIV diagnostic window period, improving identification of acute/early infections while maintaining accurate detection of established infections. [1–4] Previous data from a relative sensitivity analysis of specimens from HIV seroconverters indicate the laboratory-based 4th generation IAs available in the United States (US) detect HIV-1 infection approximately 18–20 days before the Western blot (WB) becomes positive. [4] However, the Food and Drug Administration (FDA)-approved 4th generation IAs do not distinguish Ag from Ab reactivity, a disadvantage for distinguishing acute infections from infections in which seroconversion has occurred. In addition, current FDA-approved HIV rapid tests (RT) fail to detect some early HIV infections, even when antibodies are documented to be present. [5]

An Ag/Ab combo lateral flow RT has been used outside the US since 2009. The Alere Determine™ HIV-1/2 Ag/Ab Combo test (Determine Combo) allows the differentiation of Ag (HIV-1 p24) from HIV-1/2 Ab reactivity. Therefore a specimen can be identified as Ag positive, Ab positive, Ag and Ab positive, or Ag and Ab negative. [6] The test can be performed with serum, plasma or whole blood and results are read in 20 min. Increasing early HIV diagnosis and referral to care is one strategy to reduce HIV transmission from individuals with higher viremia. [7] Therefore, a test such as Determine Combo with the potential for detection of acute/early infection in a rapid format, when individuals have a greater chance

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for transmission, may have the public health benefit of improving linkage to care. [8]

Since the introduction of the Determine Combo, several studies from field and laboratory evaluations have shown that the assay reliably detects the presence of Abs to HIV, but detection of Ag lacked sensitivity and did not significantly improve detection of acute HIV infections. [9–16] A study from 2010 reported that the sensitivity and specificity for Ab were 100%, whereas the sensitivity for Ag was 86.6% and the limit of detection of p24 was approximately 3 IU/ml. [11] In addition, results suggest that genetic diversity (e.g. subtypes) might be responsible for decreased Ag detection in HIV infections. [11,14] The assay also does not detect p27 Ag, the HIV-2 counterpart to HIV-1 p24, so detection of acute HIV-2 infection is unlikely. [11] After early reports of poor performance of Detemine Combo, the manufacturer introduced modifications in the RT to overcome the reported limitations. The modified version used in this study became available outside of the US in 2011.

2. Objectives

This study used well characterized plasma specimens from HIV-1 seroconverters that have been previously used to evaluate FDA-approved assays [4] and specimens from HIV-2 groups A and B infected individuals from Ivory Coast to evaluate the ability of the modified Determine Combo to detect acute/early HIV-1 infections and HIV-2 antibodies.

3. Study design

3.1. HIV assays

The Alere Determine™ HIV-1/2 Ag/Ab Combo, manufactured by Orgenics, Ltd. (Yavne, Israel), was kindly provided by Alere Medical Co., Ltd. The assay was performed as indicated in the package insert [6] for frozen plasma specimens. All specimens were tested in singlet and repeated only if invalid results were obtained as previously reported. [4,17]

The Genetic Systems™ HIV-1/2 plus O (GS + O) and HIV-1/2 Combo Ag/Ab IAs (GS Combo) (Bio-Rad Laboratories, Redmond, WA) were used as comparator assays for Ab (3rd generation IA) and Ag/Ab (4th generation IA) detection, respectively. All plasma specimens from seroconverters were also tested with COBAS Ampliprep/COBAS TaqMan HIV-1 test v2.0 (Roche Diagnostics, Indianapolis, IN) to allow for comparisons between viral load values and p24 detection by Determine Combo. Estimation of p24 concentrations from viral load copies was performed using previously published data (11–18 pg/ml equivalent to approximately 30,000–50,000 copies/ml). [18]

3.2. HIV-1 specimens

Serial plasma specimens ($n = 230$) from 26 well-characterized HIV-1 seroconversion panels from the US (presumably subtype B) were obtained from Zeptometrix, Inc. (Buffalo, NY) and BBI-SeraCare Diagnostics (West Bridgewater, MA). Each panel had at least one specimen that was WB indeterminate (9 seroconverters with 64 total specimens) or WB positive (17 seroconverters with 166 total specimens) and all panels had at least one specimen that was NAAT-positive. [4] Previously determined p24 antigen reactivity results (Coulter or Abbott p24 assays) were available for 24 of 26 of the seroconversion panels and were supplied by the specimen vendors.

No ethical approval was sought because all specimens used in this study were from commercially available sources and contained no personal identifiers.

3.3. Analysis of assay performance in acute/early HIV-1 infection

The relative sensitivity of the Determine Combo (Ag+/Ab−, Ag+/Ab+, Ag−/Ab+) and Ab-only component reactivity during acute/early infection was calculated from a plot of the cumulative frequency of positive test results versus the days before the WB became positive in 17 seroconverters (166 specimens). [4,17] The sequence of reactivity was compared with other tests by ranking the tests in the order in which the cumulative frequency of positive results for each test was 50%.

The difference in reactivity during early infections between tests was analyzed statistically using McNemar's test with one degree of freedom and continuity correction (95% confidence interval).

3.4. HIV-2 specimens

Eighty-six plasma specimens from HIV-2 infected individuals identified in Ivory Coast during 2009, were obtained from BocaBiolistic, Inc. (Coconut Creek, FL). The specimens were classified as HIV-2 antibody positive by Multispot HIV-1/HIV-2 rapid test (Bio-Rad Laboratories, Redmond, WA) in the field and further characterized with HIV-2 WB (MP Diagnostics, The Cavendish, Singapore) at CDC. The genotype of the integrase region (390 bp) was available from a subset of 30 of the HIV-2 plasma specimens: 7 group A and 23 group B.

4. Results

4.1. Relative sensitivity of Determine Combo in early HIV-1 infections

4.1.1. Cumulative frequency analysis

The relative sensitivity of the overall Determine Combo assay and the Determine Ab-only component in plasma specimens was estimated by calculating the 50% cumulative frequency as described above and compared to previous estimates for FDA-approved assays from the same specimen set. [4] The sequence of test reactivity expressed as the number of days before the first positive WB is shown in Fig. 1. The Determine Combo reactivity was estimated to be 15.5 days before the first positive WB and places Determine Combo between 4th and 3rd generation IAs. The reactivity of the Determine Combo Ab-only component was 7 days before the first positive WB (Fig. 1) comparable to FDA-approved flow-thru RTs.

4.1.2. Comparison with laboratory 3rd and 4th generation IAs

Reactivity of the Determine Combo was analyzed and compared to FDA-approved 3rd and 4th generation IAs in 26 seroconverters (Table 1). The Determine Combo detected 124 (92.5%) of the 134 specimens detected by the GS Combo: 34 showed reactivity to the Ag line, 15 to both the Ag and Ab lines and 75 to the Ab line only. Two other specimens were reactive by Determine Combo, but negative in the 4th generation IA. Overall, the performance of Determine Combo compared to the 4th generation IAs (GS Combo) in early HIV-1 infections was significantly lower when analyzed using the McNemar's test ($p = 0.0433$) (Table 1). In a comparison of reactivity for 230 specimens, between the Determine Combo and the 3rd generation Ab IA, 23 more specimens were detected by Determine Combo ($p < 0.0001$) (Table 1). Of 102 3rd generation Ab IA-reactive specimens, 101 (99.0%) were reactive by Determine Combo. The Ab component of the Determine Combo detected significantly fewer (90 of 102) specimens than the 3rd generation Ab IA ($p = 0.0015$).

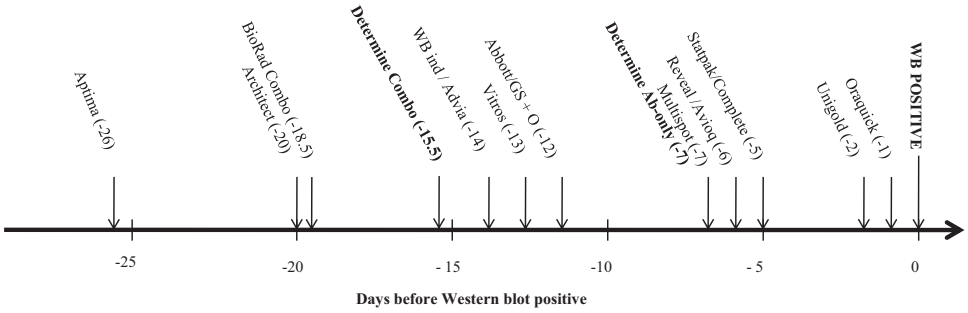

Fig. 1. Sensitivity of assays reactivity during early HIV-1 infections relative to number of days before first positive WB. The names, abbreviations, and sources, of the HIV assays are as follows [4]: APTIMA HIV-1 Quantitative assay (Aptima, Gen-Probe, Inc., San Diego, CA); ARCHITECT® HIV Ag/Ab Combo assay (Architect; Abbott Diagnostics, Wiesbaden Germany; CE marked version was used as the US version was not available when testing was conducted); GS HIV-1/2 Combo Ag/Ab (BioRad Combo; Bio-Rad Laboratories, Redmond, WA); GS HIV-1/HIV-2 Plus O EIA (GS + O; Bio-Rad Laboratories, Redmond, WA); VITROS anti-HIV 1+2 assay (Vitros; Ortho-Clinical Diagnostics, Buckinghamshire, UK); ADVIA Centaur HIV 1/O/2 enhanced assay (Advia; Bayer, Tarrytown, NY); Abbott HIVAB HIV-1/HIV-2 (rDNA) EIA (Abbott; Abbott Laboratories, Abbott Park, IL); Avioq HIV-1 Microelisa system (Avioq; Avioq, Inc, Rockville, MD); Multispot HIV-1/HIV-2 rapid test (Multispot; Bio-Rad Laboratories); Clearview HIV-1/2 STAT-PAK (Statpak; Inverness Medical, Princeton, NJ); Clearview COMPLETE HIV-1/2 (Complete; Inverness Medical); Reveal G2 and G3 Rapid HIV-1 antibody tests (Reveal G2 or G3; MedMira Laboratories, Inc.; Halifax, Nova Scotia, Canada); OraQuick ADVANCE Rapid HIV-1/2 antibody test (Oraquick; OraSure Technologies, Inc.; Bethlehem, PA); Uni-Gold Recombigen HIV (Unigold; Trinity Biotech USA, St. Louis, MO). These assays have manufacturer reported point estimates for sensitivity ranging from 99.60% to 100.00% and point estimates for specificity ranging from 98.60% to 99.90%. The Genetic Systems HIV-1 Western blot (WB; Bio-Rad Laboratories) and Cambridge Biotech HIV-1 Western blot (WB; Maxim Biomedical Inc., Rockville, MD) have been shown to give concordant interpretations in studies conducted to qualify use in our clinical laboratory and were used interchangeably. ind: indeterminate.

However, 11 of the 12 Ab-non-reactive specimens by Determine showed reactivity to Ag (Table 1).

4.2. Characterization of p24 detection by Determine Combo

Determine Combo was reactive for Ag in 22 of 26 seroconverters. For these 22 individuals, the median time between the first Determine Combo Ag-reactive and the first Ab-reactive specimen was 7 days (range: 2, 20 days). Specimens from 11 of these 22 showed dual reactivity to Ag and Ab; the remaining 11 transitioned from Ag-only to Ab-only reactivity (data not shown).

Results from independent p24 Ag tests were available from the vendors for 24 of 26 seroconverters. The analysis of 114 specimens collected before the first Determine Combo Ab-reactive specimen, showed that the laboratory p24 IAs were reactive (ratio OD-specimen/cutoff ≥ 1) for p24 in 36 (31.6%) (Table 2). Determine Combo was reactive for p24 Ag in 29 (25.4%) of the 114 specimens. Of the 29 specimens reactive for Ag by Determine Combo, 26 (89.7%) were also reactive by a laboratory p24 IA and 3 (10.3%) were non-reactive by laboratory p24 IAs (Table 2). These 3 specimens had detectable viral loads between 10^4 and 10^5 RNA copies/ml.

The analysis of 77 specimens (26 seroconverters) with detectable viral load collected prior to Determine Ab reactivity showed that p24 antigen was detected in 35 of the 77 (45.5%) specimens. Two specimens had viral loads less than 8.5×10^3 RNA copies/ml and 33 reactive specimens had viral loads higher than 1×10^4 copies per/ml (Table 3).

Table 1
Detection of early infections by Determine Combo in plasma specimens from HIV-1 seroconverters from the US.

	Determine Combo results			
	Ag−/Ab−	Ag+/Ab−	Ag+/Ab+	Ag−/Ab+
Bio-Rad assays				
HIV-1/2 Combo Ag/Ab				
Positive (n = 134)	10	34	15	75
Negative (n = 96)	94	1	0	1
HIV-1/2 plus O				
Positive (n = 102)	1	11	15	75
Negative (n = 128)	104	24	0	0

Reactivity was analyzed in 230 specimens from 26 seroconverters and compared with 4th generation GS HIV-1 Combo Ag/Ab IA and 3rd generation GS HIV-1/2 plus O IA.

Table 2
Analysis of HIV p24 (Ag) reactivity by Determine Combo and laboratory p24 assays before the first Ab-reactive.

	Determine Combo Ag reactivity	
	Ag+	Ag−
IA p24 reactivity (S/CO)		
≥1(positive)	26	10
<1(negative)	3	75

The analysis was performed in 114 specimens collected before the first Ab-reactive result from 24 seroconverters with p24 available data (Coulter or Abbott). S/CO: ratio of specimen OD/Cutoff; IA: immunoassay.

Table 3
HIV-1 viral load in specimens collected prior to Determine Ab reactivity.

Viral load	Determine Combo	
RNA copies/ml	Ag−	Ag+
$<2 \times 10^1$ (BRD)	2	0
2×10^1–9.99×10^2	17	1
1×10^3–9.99×10^3	10	1
1×10^4–9.99×10^4	7	8
1×10^5–9.99×10^5	6	14
1×10^6–9.99×10^6	0	7
$>1 \times 10^7$	0	4

The COBAS Ampliprep/COBAS TaqMan HIV-1 test v2.0 was performed on plasma specimens collected before Determine Combo Ab-reactivity. BRD: below range of detection.

4.3. HIV-2 detection by Determine Combo

All 86 HIV-2 plasma specimens were Ab-reactive by Determine Combo. Of the 30 specimens with genotype data, Determine Combo was reactive with 7 HIV-2 Group A and 23 Group B. The Determine Combo Ag line was not reactive with any of the HIV-2 specimens.

5. Discussion

Our study is the first to report on the performance of the 2011 version of Alere Determine™ HIV-1/2 Ag/Ab combo RT in plasma specimens collected during early stages of HIV-1 infection. The results from the relative sensitivity analysis (compared with previously published results from 14 FDA-approved HIV tests performed on the same seroconversion panels) [4,18] indicates that the

Determine Combo RT is reactive approximately 15.5 days before a positive WB, between the time of reactivity of 4th generation (approximately 19 days) and 3rd generation (approximately 13 days) laboratory IAs. The Ab component of the Determine Combo RT detects infection approximately 7 days before WB positivity, and sooner than some lateral-flow tests, but similar to flow-thru RTs. [4,18] In addition, our results show that Determine Combo was able to detect HIV-2 Ab in all plasma specimens obtained from individuals with groups A and B HIV-2 infections. Furthermore, we did not observe reactivity to the Ag line with the HIV-2 specimens.

Determine Combo has been previously evaluated and compared to 4th generation laboratory-based IAs in stored plasma [16,19] and fingerstick [15] specimens likely using the previous version of the RT. Results in stored plasma showed that Determine Combo detected fewer HIV-positive specimens compared to 4th generation laboratory-based IAs (59.4% vs.75% [16] and 59% vs. 89% [19]). However, Determine Combo was reactive in fingerstick specimens from 90.5% of the persons with 4th generation IA-reactive plasma specimens [15], similar to our results in which 92.5% of the 4th generation IA-reactive specimens from the 26 seroconversion panels were reactive by Determine Combo. Although the Determine Combo was not as sensitive during early infection as the laboratory-based 4th generation IAs, our results with the modified version indicate an improvement in the performance with plasma specimens over what has been previously published. [16,19]

The Ab component of the Determine Combo detected 88.2% of specimens positive with a 3rd generation Ab IA. However, 99.0% of the specimens were detected when specimens that were also reactive on the p24 line but non-reactive in Ab line in Determine Combo were included in the analysis. An explanation of these results may be the presence of Ag/Ab immune-complexes early in seroconversion that could result in variably reactive Ag and/or Ab results around the detection limits of the assay components and which is dependent on the concentrations of Ag and Ab and their complexes. [20,21] Our data show that the Determine Combo Ab component performs as well or better than antibody only RTs currently in use in the US, with the Ag detection component conferring an advantage prior to seroconversion when p24 Ag could also be detected in plasma specimens (median of 7 days).

Other studies have compared p24 Ag detection by Determine Combo with other p24 Ag assays in frozen plasma specimens. [10,13] Our finding that the Determine Combo detected 72.2% of specimens reactive for p24 Ag in stand-alone p24 assays is higher than the 50% estimated in the UK [10] and much higher than what was reported in African cities [13].

Our seroconversion panels allow monitoring p24 reactivity after infection and before seroconversion because sequential bleeds were collected with a median interval between collection times of 5 days. Our data show a median time of 7 days between the first Ag-reactive and the first Ab-reactive Determine Combo result in 22 seroconverters, similar to the 5–9 days reported by the manufacturer in studies outside the US. [6] These results for Ag reactivity, which contradict published studies [9,12,13,16] in which acute infections were not detected by the Ag component of the Determine Combo, might be due to differences in the test after the manufacturer's modifications.

The sensitivity of any assay for detecting p24 during acute HIV-1 infections must overcome the challenge of the formation of Ag/Ab immune-complexes in early stages of seroconversion. [20,21] Determine Combo is a lateral flow RT, so its p24 sensitivity is not expected to be similar to 4th generation laboratory-based IAs that incorporate steps for disassociation of Ag/Ab immune-complexes. Although the Determine Combo does not involve any dissociation, lysis, or heating step to increase p24 detection, the 35 specimens with p24-positive results by Determine Combo, that were collected prior to Ab reactivity, had a viral loads ranging from 2×10^1 to $>10^7$ RNA copies/ml. If this viral load range is used to estimate p24 levels as has been previously reported [18], the concentrations of p24 detected would range from 0.3 to 3660 pg/ml. These data indicate that detection of p24 by Determine Combo would fall within the range of sensitivities reported for other HIV Ag/Ab combo assays (range: 11.9–33.5 pg of p24/ml-French National standard) [22].

A limitation of our study is that the evaluation of the modified Determine Combo was not performed in whole blood, the specimen type likely to be used in point-of-care settings. Since plasma is a component of whole blood, it is possible that the clinical sensitivity of the test may be lower when testing with this specimen type. Field evaluations with whole blood are needed to assess the real-world performance. Another limitation of our study is that we have not estimated the sensitivity and specificity of the modified test in a prospective or cross-sectional study. However, the findings of this study indicate the performance of the Determine Combo RT is as good as or better than current RTs on the US market for detecting acute or early HIV infection in plasma specimens. If approved by the FDA and is shown to have comparable sensitivity when used with whole blood, the Determine Combo could play a role in the prevention of HIV transmission in the US by facilitating early detection of HIV infection, improving receipt of results and early linkage to care.

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Competing interest

No financial disclosures were reported by the authors of this paper.

Ethical approval

No ethical approval was sought because all specimens used in this study were from commercially available sources and contained no personal identifiers.

Disclaimer

The findings and conclusions in this report are ours and do not necessarily represent the views of the Centers for Disease Control and Prevention. Use of brand names is for identification purposes and does not imply endorsements by the US Department of Health and Human Services.

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