At Siemens Healthineers, our purpose is to enable healthcare providers to increase value by empowering them on their journey toward expanding precision medicine, transforming care delivery, and improving patient experience, all made possible by digitalizing healthcare.

An estimated 5 million patients globally benefit every day from our innovative technologies and services in the areas of diagnostic and therapeutic imaging, laboratory diagnostics, and molecular medicine, as well as digital health and enterprise services.

We are a leading medical technology company with over 120 years of experience and 18,000 patents globally. Through the dedication of more than 50,000 colleagues in 75 countries, we will continue to innovate and shape the future of healthcare.

Product availability may vary from country to country and is subject to varying regulatory requirements. Please contact your local representative for availability.

References:

1. Lee K, et al. Ann Lab Med. 2013;33:420-5.
2. Vallefuoco L, et al. Expert Rev Mol Diagn. 2016;16:723-32.
3. Krajden M, et al. J Clin Virol. 2014;61:132-7.
4. Kim S, et al. Clin Vaccine Immunol. 2010;17:1642-4.
5. Akl P, et al. Lab Med. 2014;45:259-63.
6. Garcia T, et al. J Med Microbiol. 2009;58:1529-30.
7. Vallefuoco L, et al. Intervirology. 2014;57:106-11.
8. Chavez P, et al. J Clin Virol. 2011;52 Suppl 1:S51-5.
9. Wilson KM, et al. AIDS. 2004;18:2253-9.
10. Branson BM, et al. Laboratory testing for the diagnosis of HIV infection: update recommendations. Atlanta, GA: Centers for Disease Control and Prevention and Association of Public Health Laboratories; 2014 Jun 24 [cited 2018 Jan 31]. Available from: http://stacks.cdc.gov/view/cdc/23447.
11. Niederhauser C, et al. J Clin Virol. 2009;45:367-9.
12. Busch MP, et al. Am J Med. 1997;102:117-24; discussion 25-6.
13. CDC: Centers for Disease Control and Prevention [Internet]. Atlanta (GA): CDC; 2018 Jan 26. HIV testing; 2018 Jan 9 [cited 2018 Jan 31]. Available from: https://www.cdc.gov/hiv/testing/index.html.
14. Goudsmit J, et al. J Virol Methods. 1987;17:19-34.
15. Gokengin D, et al. Int J STD AIDS. 2014;25:695-704.
16. Pumarola T, et al. J Virol Methods. 2010;170:16-20.
17. Mitchell EO, et al. J Clin Virol. 2013;58(Suppl 1): e79-84.
18. Taegtmeyer M, et al. PLoS One. 2011;6:e28019.
19. Patibandla S, et al. Performance characteristics of the ADVIA Centaur HIV Ag/Ab Combo (CHIV) assay for the simultaneous qualitative detection of HIV p24 antigen and antibodies to HIV-1 (groups M and O) and HIV-2 in human serum or plasma [oral presentation]. 2012 National Summit on HIV and Viral Hepatitis Diagnosis, Prevention and Access to Care. 2012 Nov 27; Washington DC.
20. Delaney K, et al. Evaluation of newly approved HIV antigen-antibody tests individually and when used in the CDC/APHL HIV diagnostic algorithm [oral presentation C2]. HIV Diagnostics Conference; 2016 Mar 21-24; Atlanta, GA, U.S. Conference presented by the Centers for Disease Control and Prevention (CDC), the Association of Public Health Laboratories (APHL), the American Sexual Health Association (ASHA), and the American Sexually Transmitted Diseases Association (ASTDA).
21. Peele S. Performance of the Abbott Architect HIV Ag/Ab Combo assay in the US Army HIV diagnostic algorithm. HIV Diagnostics Conference; 2016 Mar 21-24; Atlanta, GA.
22. Liu P, et al. AIDS Res Ther. 2016;13:1.
23. Lavoie S, et al. J Clin Virol. 2018;104:23-8.

Siemens Healthineers Headquarters
Siemens Healthcare GmbH
Henkestr. 127
91052 Erlangen, Germany
Phone: +49 9131 84-0
siemens-healthineers.com

Published by
Siemens Healthcare Diagnostics Inc.
Laboratory Diagnostics
511 Benedict Avenue
Tarrytown, NY 10591-5005
USA
Phone: +1 914-631-8000

Published by Siemens Healthcare Diagnostics Inc. · Order No. 30-21-DX-1060-76 · 09-2021 ·

The Siemens Healthineers ADVIA Centaur* and Abbott ARCHITECT HIV Ag/Ab Combo Assays

Clinical Performance of Two Fourth-Generation HIV Assays

siemens-healthineers.com

Clinical Brief

Summary

Early diagnosis of HIV infection is important to reduce transmission and manage therapeutic intervention. The availability of sensitive, automated combination (combo) assays that detect HIV antigen (Ag) and antibody (Ab) can facilitate detection of early acute infection.[1-3] However, combo assays may be associated with more false-positive (FP) results than assays that detect antibody only.[4-6] While published data support good performance for two widely used combo assays—the ADVIA Centaur® HIV Ag/Ab Combo (CHIV) assay* from Siemens Healthineers (hereinafter, the ADVIA Centaur 4th gen assay) and the ARCHITECT HIV Ag/Ab Combo assay from Abbott Laboratories (hereinafter, the Abbott 4th gen assay)—performance differences have been observed.[2,7,8] Comparisons of these assays and relevant clinical implications are reviewed in this brief.

HIV: Infection course and serological markers

A typical HIV seroconversion profile is shown in Figure 1. Viral RNA is first to appear. As viremia increases in acute infection, p24 Ag, the primary protein composing the nucleocapsid, can often be detected. Fourth-generation (4th gen) HIV Ag/Ab combo tests can identify infections about 3 to 5 days earlier than sensitive third-generation (3rd gen) Ab-only assays. This is because Ag is briefly present prior to Ab formation. With seroconversion to p24 Ab, Ag is bound by Ab and typically becomes challenging to detect.[9-14]

Testing guidelines

Guidelines for testing can vary by country and may include both risk-based and routine screening recommendations. Use of a combo assay is either mandated or preferred for initial testing due to the increased sensitivity for acute infection. The window of Ag-only positivity is brief in infected individuals, who during this period are likely to be highly viremic and infectious. To reduce reporting of inaccurate screening results, confirmation testing using alternate immunoassays (including ones able to differentiate HIV-1 from HIV-2) and molecular RNA testing are recommended.[10,15]

False-positive concerns

As laboratories move to more sensitive testing with a combo assay, a corresponding decrease in specificity may occur. Most studies suggest an increase in FP results when moving from a 3rd gen to a 4th gen assay, although observations to the contrary have been reported.[2,3,6,16–18] FP results are associated with increased time to diagnosis and cost, and they may occur more frequently when testing a lower risk population such as pregnant women.[4,5,18] Importantly, while most combo assays are designed for the detection of HIV-1 group M, HIV-1 group O, HIV-2, and p24 Ag, design differences may affect comparative performance. Design characteristics such as analyte anchoring and Ab selection may contribute to observed differences in sensitivity and specificity among assays.

**Not available for sale in the U.S. for use on the ADVIA Centaur CP system.*
The ADVIA Centaur HIV assays are developed, manufactured and sold by Siemens Healthineers for Ortho-Clinical Diagnostics, Inc. and Grifols Diagnostic Solutions Inc.

SIEMENS Healthineers

Comparison of the ADVIA Centaur HIV Ag/Ab Combo (CHIV) assay* from Siemens Healthineers and the Abbott ARCHITECT HIV Ag/Ab Combo assay: Sensitivity and specificity

The ADVIA Centaur and Abbott 4th gen assays are fully automated assays designed to detect Ab and Ag. Studies suggest similar performance for the assays on patient samples and seroconversion panels.[7,16,19] Some reports have noted concerns of potential clinical relevance regarding FP results.

A study by Krajden et al. examined samples from a high-risk patient cohort (STD clinic patients) and compared the performance of the 3rd gen (Ab-only) ADVIA Centaur HIV 1/O/2 Enhanced (EHIV) assay from Siemens Healthineers, the ADVIA Centaur 4th gen assay, and the Abbott 4th gen assay, and pooled RNA testing on 9550 samples from 7442 unique individuals.[3] Uninfected samples as well as preseroconversion and early-seroconversion acute HIV infection samples were included. The results are shown in Table 1. The uninfected population yielded increased FP results for both of the 4th gen assays compared to the 3rd gen assay. However, in the 9435 uninfected samples, the ADVIA Centaur 4th gen assay demonstrated FP results slightly fewer than half those for the Abbott 4th gen assay: 33 vs. 74, respectively.

None of the 74 Abbott-FP samples tested positive with the ADVIA Centaur 4th gen assay, and none of the 33 ADVIA Centaur–FP samples tested positive with the Abbott 4th gen assay, suggesting manufacturer-specific versus sample-specific bias. While both 4th gen assays correctly identified all established infection and early-seroconversion (defined as Western blot–negative) samples, a difference was observed in a small number (n = 6) of preseroconversion samples (defined as RNA positive but 3rd gen negative). Pooled RNA testing identified all 6 samples, whereas the ADVIA Centaur 4th gen assay identified 2 and the Abbott 4th gen assay identified 4 of these samples.

Although this difference could be attributed to slightly better low-end sensitivity for p24 for the Abbott 4th gen assay, other published data suggest involvement of additional factors.[2,20] One study using four commercially available seroconversion panels for HIV found that the ADVIA Centaur 4th gen assay detected seroconversion one bleed earlier in one panel and at the same bleed in the remaining three panels compared to the Abbott 4th gen assay.[7]

A study presented at the 2016 HIV Diagnostics Conference reported that the ADVIA Centaur 4th gen assay detected an acute infection missed by the Abbott 4th gen assay, potentially further indicating that p24 analytic sensitivity alone is likely insufficient for early detection (Table 2).[20]

Also noted were differences in resolved specificity among assays. At the same meeting, another study proposed using a second 4th gen immunoassay (in this case, the Bio-Rad GS HIV Combo Ag/Ab EIA assay) to reduce the rate of FPs observed with the Abbott 4th gen assay.[21] Testing of the reactive samples from the Abbott platform that were first reflexed for testing with the Bio-Rad assay resulted in a significant reduction of samples requiring confirmation (Table 3). Confirmation, which typically involves an HIV 1/2 differentiation assay and/or nucleic acid testing, can both be costly and delay reporting that the patient is HIV negative.

The clinical impact of FP HIV results

Clinical reports underscore the risk of FP results in the clinical setting. One report from 2014 describes a pregnant woman presenting in the emergency department for delivery.[5] According to that report, because no prenatal HIV testing was on record for her, testing was performed, the patient's serum sample was reactive by the Abbott 4th gen assay, and antiretroviral therapy was administered to her newborn. The report noted that subsequent testing revealed that the serum sample was repeatedly positive by the Abbott 4th gen assay, but it tested negative by both the ADVIA Centaur HIV 1/2/O Enhanced (EHIV) assay and a point-of-care rapid test. RNA tested negative, and therapy was discontinued. When a plasma sample was used, the Abbott 4th gen assay result was negative. The authors concluded that plasma may be a more appropriate specimen type for this assay.

The authors of a 2016 case report describe FP results for three patients with the Abbott 4th gen assay.[22] They reported that a FP result was also obtained for one of the samples with the confirmatory assay (Bio-Rad MULTISPOT HIV-1/HIV-2 Rapid Test). According to the authors, this resulted in the initiation of postexposure prophylaxis on the physician with the presumptive infection. Therapy was discontinued when negative results were obtained with both RNA and proviral DNA tests. The authors discuss the spectrum of FP 4th gen HIV test results in the clinical setting, especially when both screening and confirmatory tests are affected.

A recently published study addressing the FP results associated with the Abbott ARCHITECT but not the ADVIA Centaur 4th gen HIV assays reports that heterophile interference could be a significant factor.23 The authors demonstrate that of 264 confirmed HIV-negative samples falsely reactive with the Abbott assay, 95% (252) were nonreactive with the ADVIA Centaur assay. Treatments of the samples to block heterophile interference either eliminated or reduced the FP results when retested with the Abbott assay. The authors conclude the Abbott ARCHITECT HIV Ag/Ab Combo assay is more prone to FP results and suggest interference could be associated with heterophile antibody binding the monoclonal antibody against HIV-1 p24 used in the Abbott assay.

** Not available for sale in the U.S. for use on the ADVIA Centaur CP system.*
The ADVIA Centaur HIV assays are developed, manufactured and sold by Siemens Healthineers for Ortho-Clinical Diagnostics, Inc. and Grifols Diagnostic Solutions Inc.

Conclusion

The 4th gen HIV combo tests have enhanced the ability to detect infection in the brief Ag-positive/Ab-negative window. An increase in FP rates has been reported in general with adoption of 4th gen testing. The FP rate reported in the literature should be considered when selecting an HIV assay because different FP rates have been observed among commercially available assays.

Figure 1. HIV serological profile.[10-12]

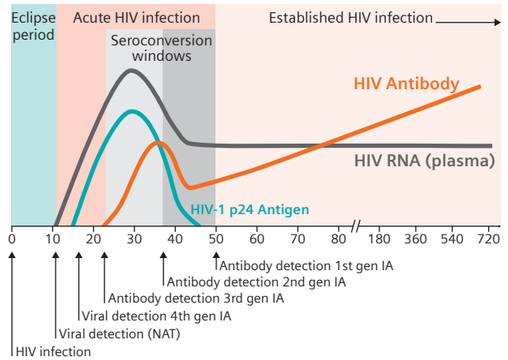

Table 1. HIV 3rd and 4th generation EIA and pooled nucleic acid test results by HIV infection category.[3]

Status	Result	RNA (N†)	ADVIA Centaur EHIV, 3rd gen (N†)	ADVIA Centaur CHIV, 4th gen (N†)	Abbott HIV Combo, 4th gen (N†)
No HIV evidence	Reactive	0	13	33	74
	Nonreactive	9435	9422	9402	9361
Established infection	Reactive	4	79	79	79
	Nonreactive	0	0	0	0
Preseroconversion (acute)	Reactive	6	0	2	4
	Nonreactive	0	6	4	2
Early seroconversion (acute)	Reactive	9	9	9	9
	Nonreactive	0	0	0	0

†If more than one sequential specimen was available for an individual, results for only the first specimen are given.

Table 2. Sensitivity and specificity of four FDA-approved HIV Ag/Ab screening assays using well-characterized specimens of known HIV status.[20]

	Sensitivity												Specificity		
	Overall			Established untreated			Established treated			Early infections					
Test	TP	FN	%	TP	FN	%	TP	FN	%	TP	FN	%	TN	FP	%
GS HIV Combo Ag/Ab	653	6	99.1	274	0	100	370	0	100	9	6	60	977	11	98.9
BioPlex 2200 Ag/Ab	653	6	99.1	274	0	100	370	0	100	9	6	60	974	14	98.6
ARCHITECT HIV Ag/Ab Combo	652	7	98.9	274	0	100	370	0	100	8	7	53.3	971	17	98.3
ADVIA Centaur HIV Ag/Ab Combo (CHIV)	653	6	99.1	274	0	100	370	0	100	9	6	60	977	11	98.9

TP = true positives; FN = fase negatives; TN = true negatives; FP = false positives.

Table 3. Reduction of FP rate for Abbott ARCHITECT repeat-reactive samples using a second combo assay, the Bio-Rad GS HIV Combo Ag/Ab EIA (total samples tested = 987,947).[21]

		Resolved HIV status		
		+	–	Total
Abbott only	+	507	1091	1598
	–	0	986,349	986,349
	Total	507	987,440	987,947

Sensitivity = 100%
Specificity = 99.9%
PPV = 31.8%
NPV = 100%

		Resolved HIV status		
		+	–	Total
Abbott and Bio-Rad	+	507	33	540
	–	0	987,407	987,407
	Total	507	987,440	987,947

Sensitivity = 100%
Specificity = 100%
PPV = 93.9%
NPV = 100%